OLD AGE HEALTH AND HIV IN A RURAL AREA WITH HIGH HIV PREVALENCE AND INCIDENCE:

WHAT IS THE IMPACT OF ENHANCED ACCESS TO ANTIRETROVIRAL TREATMENT?

A thesis presented for the degree of Doctor of Philosophy

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I, Portia Chipo Mutevedzi confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

The widespread roll-out of antiretroviral therapy (ART) has resulted in a decline of HIV-related deaths; as a result the HIV positive population is rapidly ageing with improved survival of HIV positive adults on ART. In sub-Saharan Africa, including South Africa, where older adults comprise a significant proportion of the total population, health services face the complexities of an ageing population and HIV. The aim of this PhD study is to inform understanding of issues relating to older adults, aged 50 years or more, HIV infection and ART, who are resident in Northern KwaZulu-Natal, South Africa.

Data from the cross-sectional Wellbeing of Older People Study (WOPS), including 422 older adults and nested within the demographic surveillance system, show that HIV positive older adults receiving ART for >1 year had less chronic morbidity than HIV negative older adults despite having higher IL6 and hsCRP levels.

To quantify the cause-specific morbidity burden at the time of initiating ART, data on 1 409 adults aged ≥16 years obtained from the ART Clinical Cohort show that chronic morbidity at time of ART initiation burden and HIV-associated morbidity was more common in older than younger (16-49 years old) adults.

Data from the HIV Treatment and Care programme, linked to an electronic Hospital Information database (n=8598 adults aged ≥16 years) show that older adults had a lower hospitalisation rate, but higher case fatality rates, than younger adults.

In the HIV treatment and Care programme, including 8846 overall, in the first year of ART, mortality was higher in older than younger adults, but rates in the two groups were similar thereafter. Older adults had a blunted immunological but superior virological response. All-cause mortality risk increased with a decline in CD4 cell count and unsuppressed viral load. Further detailed data from the ART Clinical Cohort showed that, in both age groups, the contribution of multiple co-morbidity to early mortality was high.

The results presented here contribute towards evidence required to understand issues surrounding the health of older adults in the context of high HIV prevalence and incidence with widespread availability and access to ART and provide knowledge required for evidence-based health planning for the ageing HIV cohort. The thesis concludes with a discussion of the implications for health service development and future research.

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95% CI	95% Confidence Interval
aHR	Adjusted hazard ratio
ALT	Alanine aminotransferase
aOR	Adjusted odds ratio
aPOR	Adjusted proportional odds ratio
apPOR	Adjusted partial proportional odds ratios
ART	AntiRetroviral Therapy
ARTemis	AntiRetroviral Therapy Evaluation and Monitoring Information System
AVERT	AVERTing HIV and AIDS
BMI	Body Mass Index
CD4	C(luster of) D(ifferentiation antigen) 4
GFR	Glomerular filtration rates
CGAIHS	Collaborative Group on AIDS incubation and HIV survival
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
hsCRP	high sensitivity C-reactive protein
IL1	Interleukin 1
IL6	Interleukin 1
IQR	Inter-quartile range
KS	Kaposi Sarcoma
NHLS	National Health Laboratory Services
OR	Odds ratio
p	p-value
PhD	Doctor of Philosophy
POR	Proportional odds ratio
pPOR	Partial proportional odds ratio

p-value	Probability value
SAGE	Study of global AGEing and adult health
STATS-SA	Statistics South Africa
STIs	Sexually Transmitted infections
TB	Tuberculosis
TNFα	Tumor Necrosis Factor- alpha
UCLA	University of California, Los Angeles
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
WHO	World Health Organisation
WOPS	Wellbeing of Older People Study

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1 Older adults and HIV infection

1.1 Introduction

The overall aim of this PhD study is to inform understanding of the issues relating to older adults and HIV infection and its treatment, using various data sources relating to older adults, aged 50 years or more, who are resident in an established demographic surveillance area in Northern KwaZulu-Natal, South Africa. The study area is characterised by high HIV prevalence and incidence, and since late 2004 substantial access to antiretroviral treatment (ART) in a public health programme delivered at primary health care level. Associations between chronic morbidity, HIV and ART status are explored, using data from a cross-sectional study nested within a longitudinal demographic surveillance area including HIV negative and positive (on ART or ART-naïve) older adults. Associations between health bio-markers (pro-inflammatory cytokines), morbidity and HIV are also investigated. Recognising that HIV positive older adults may face a dual burden of disease of chronic morbidities of ageing and HIV-related morbidity, this PhD study documents the morbidity burden in older HIV positive adults at the time of ART initiation, and compares their morbidity with that in younger (16-49 year old) adults. The PhD further quantifies the contribution of co-morbidities at time of ART initiation to subsequent morbidity and mortality, using data from an ART Clinical Cohort nested within the public sector HIV Treatment and Care Programme as well as linked data from the HIV treatment and care programme and an electronic patient information system at the only local district hospital. Finally this PhD examines outcomes of ART in older adults, including mortality, CD4 count reconstitution and viral suppression compared to younger adults using data from both the ART Clinical Cohort and the HIV Treatment and Care Programme.

Publication resulting from Chapter 1: Mutevedzi, P. C. and M. L. Newell (2011). "A missing piece in the puzzle: HIV in mature adults in sub-Saharan Africa." Future Virology 6(6): 755-767.

1.2 Background

The Human Immunodeficiency Virus (HIV) has caused the world's largest epidemic and Acquired ImmunoDeficiency Syndrome (AIDS), the disease caused by HIV, is one of the world's most serious health challenges (UNAIDS 2012). In low income countries in 2008 HIV/AIDS was the third leading cause of death, after lower respiratory infections and diarrhoeal diseases (WHO 2011). In 2011, 1.7 million people worldwide died from AIDS-related causes and 70% of these deaths were from sub-Saharan Africa (UNAIDS 2012).

According to the 2012 UNAIDS report on the Global AIDS epidemic, 34.0 million people globally were living with HIV at the end of 2011. The prevalence of HIV varies by country and region (UNAIDS 2012); sub-Saharan Africa remains most severely affected, accounting for 69% of the people living with HIV worldwide, and with nearly one in every twenty adults (4.9%) living with HIV (UNAIDS 2012). HIV prevalence in sub-Saharan Africa is five times higher than in the Caribbean and Eastern Europe and Central Asia and 25 times higher than in South, South-East and East Asia. HIV incidence is also highest in sub-Saharan Africa accounting for 71% of the adults and children newly infected worldwide in 2011. From the peak of the epidemic in 1999, worldwide, HIV incidence has been declining with the number of new HIV cases reported in 2011 (2.5 million cases) being 20% lower than the number reported in 2001 (UNAIDS 2012). In 25 countries across the world including Haiti, India, Thailand, Barbados, Ethiopia, Zambia, Malawi and Botswana, HIV incidence rates declined by 50% between 2001 and 2011. Across sub-Saharan Africa combined HIV incidence declined by 25% between 2001 and 2011 (UNAIDS 2012), with the estimated decline greater than 50% in countries such as Zimbabwe, Ghana, Gabon, Rwanda, Togo and Namibia. The incidence of HIV in South Africa, similar to that in Swaziland, Mozambique, Mali and Kenya, fell by between 26-49% (UNAIDS 2012).

Despite these declines in new HIV cases, HIV remains the largest epidemic in sub-Saharan Africa. South Africa has the largest number of people living with HIV in the world (UNAIDS 2010; UNAIDS 2011; UNAIDS 2013). In 2013, South Africa was home to 5.26 million people living with HIV in a population of 52 million; up from an estimated 4 million in 2002, and translating to one in every six people with HIV worldwide (STATS-SA 2010; UNAIDS 2010; UNAIDS 2012; STATS-SA 2013; UNPD 2013). Within South Africa, KwaZulu-Natal, the province within which this PhD study was conducted, has the highest HIV prevalence estimated in 2010 at 15.8% in adults aged 15-49 years old (UNAIDS 2013).

Southern Africa also has the continent's highest percentage of inhabitants aged 50 years and above with South Africa having the highest proportion owing to economic development and health care improvements (Kinsella and Ferreira 1997). In 2011, South Africa had 7.6 million people aged 50 years and above, increasing to 8.3 million (15.6% of the total population) in 2013 (STATS-SA 2013). Thus, this part of the world faces not only the burden of HIV, but also an increasing burden relating to the ageing of the population.

1.3 Burden of HIV in older adults

Definition of older adult

Growing old is a biological process that is also subject to how societies conceptualise it, making it difficult to state an exact age when a person becomes old, and there is no United Nations standard age cut-off (WHO 2002; WHO 2013; WHO 2013). Being old can be defined in various ways: chronological age, change in social role or change in physical capabilities (WHO 2002; WHO 2013). Similar to a number of other African countries, in South Africa the life expectancy at birth in 2010 was approximately 53.3 years for males and 55.2 years for females (STATS-SA 2010), and in this setting, by the time an adult reaches the age of 50 years, they are considered

an older adult. Female reproductive ages are well defined and reported to be from 15-49 years after which they move from being a "parent" to a "grandparent". In most African traditions, this confers the title "older" and adds respectability regardless of chronological age (WHO 2002). In the absence of a standard definition and age cut-off for older adult, most studies, reports and reviews have used 50 year as the start of older adulthood (Justice, Landefeld et al. 2001; WHO 2002; Abel and Werner 2003; Adeyemi, Rezai et al. 2008; Nguyen and Holodniy 2008; Negin, Wariero et al. 2010; Wallrauch, Barnighausen et al. 2010; Ward B, Hughes A et al. 2010; Hasse, Ledergerber et al. 2011; Scholten, Mugisha et al. 2011; Bendavid, Ford et al. 2012; Iwuji, Churchill et al. 2013). For uniformity and to enable comparisons with other studies, in this PhD older adults are defined as individuals aged 50 years and above.

1.3.1 HIV prevalence

The HIV epidemic substantially affects people aged 50 years and above; not only do older adults play an important role as caretakers of their adult HIV positive children and orphaned grandchildren but they themselves are increasingly likely to be HIV infected (WHO 2002; Schmid, Williams et al. 2009; Wallrauch, Barnighausen et al. 2010). The true burden of HIV in older adults is difficult to assess because HIV reporting mechanisms and estimates of epidemiological trends usually only encompass adults of reproductive ages (15-49 years) from antenatal screening and demographic health surveys (2008; UNAIDS 2008; Schmid, Williams et al. 2009; Negin and Cumming 2010; Negin, Wariero et al. 2010; UNAIDS 2010; UNAIDS 2012; STATS-SA 2013). At an international level, UNAIDS and other agencies that report on the state of the HIV epidemic have limited or no data on the number of HIV positive older adults in developing countries (STATS-SA 2006; Schmid, Williams et al. 2009; Negin, Wariero et al. 2010; STATS-SA 2010; UNAIDS 2010; UNAIDS 2012). Smaller studies have focused on high risk groups such as sex workers, drug users and migrants, driven by the need to monitor heavily affected groups of the population and provide critical data for monitoring the epidemic (Bendavid, Ford

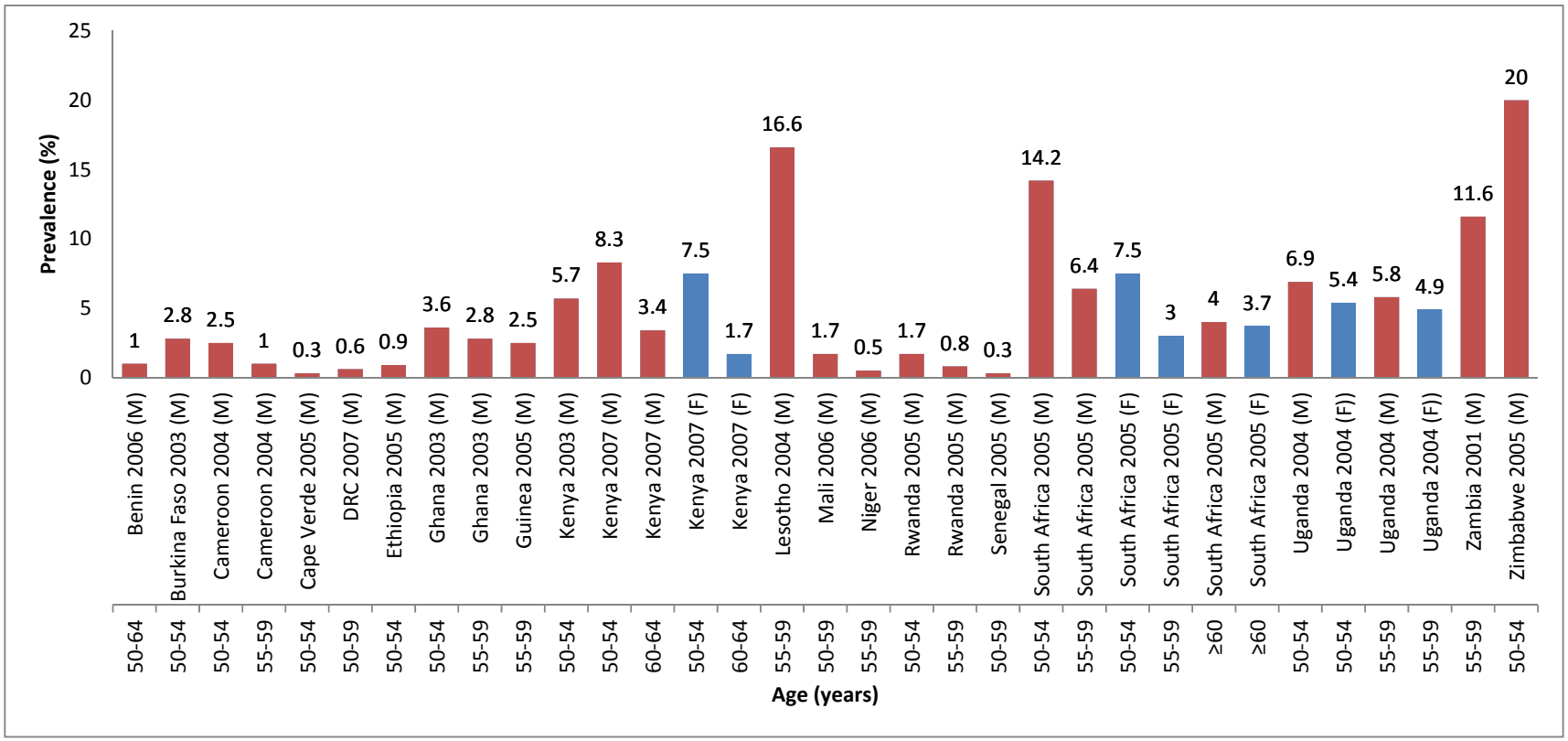
et al. 2012; Negin, Barnighausen et al. 2012). Another reason for the lack of HIV prevalence data in older adults is the fact that prior to widespread availability of antiretroviral therapy (ART), HIV and ageing were once mutually exclusive conditions; the HIV pandemic mostly affected younger adults who died before they had aged (Collaborative Group on AIDS incubation and HIV survival 2000; Babiker, Peto et al. 2001; Justice, Landefeld et al. 2001).

However, more recently, HIV in older adults has begun to receive some research attention and in 2006, UNAIDS reported on the total estimated global HIV prevalence in all adults aged 15 years and above, lifting the previous upper age limit of 49 years to include all ages (UNAIDS 2006). Still, within the UNAIDS report, most indicators such as continent specific prevalence, overall and place-specific incidence, condom use and multiple partners are reported for ages 15 to 49 years and exclude older adults. The Centers for Disease Control in the United States of America (USA) that collects, analyses and disseminates surveillance data on HIV infection from all 50 states within USA plus the District of Columbia and six USA dependent areas, reports that the proportion of HIV positive older adults aged 50 years and above in the USA increased from 20% in 2003 to 25% in 2006. In the same region, from 2008 to 2010, the number of older adults living with HIV increased from 250 958 to 306 934; and in 2010 older adults comprised 36% (306 934/872 990) of all people living with HIV (Centers for Disease Control 2011). In Europe the cumulative number of older adults living with HIV was 379 353 in 2010 (AVERT 2013).

In sub-Saharan Africa, the continent with the highest estimated HIV prevalence and incidence (UNAIDS 2010; UNAIDS 2012), data on HIV prevalence in older adults are limited. Available reports do not have a consistent age cut-off, with most only going up to age 59 years and being predominantly male in the older age groups (Schmid, Williams et al. 2009; Negin and

Cumming 2010; Peltzer, Phaswana-Mafuya et al. 2010), leading to difficulties in comparisons across settings as illustrated in Figure 1.1. A review that employed UNAIDS prevalence estimates derived from 43 Demographic Health Surveys in sub-Saharan Africa estimated that in 2007 sub-Saharan Africa had 3 million older adults living with HIV, or 14.3% of all HIV positive people worldwide (Negin and Cumming 2010). The study used data relating to people 15-49 years and the respective national population structures to extrapolate prevalence rates to those aged 50 years and above. Of the 43 surveys, 39 included people aged ≥ 50 years but only if they were men and the upper age limits ranged from 54-64 years; 18 had HIV prevalence data based on population-based HIV testing. From these, Mozambique, Nigeria, South Africa, Zambia and Zimbabwe had the highest HIV prevalence, accounting for 54% of all older HIV positive adult in sub-Saharan Africa (Negin and Cumming 2010). In rural Cameroon (2.6% in men and women aged 55-70 years), Ethiopia (5% in adults aged 50 years and above) and Tanzania (15% in older adults) estimated HIV prevalence among older adults is relatively low (Negin and Cumming 2010; Peltzer, Phaswana-Mafuya et al. 2010; Wallrauch, Barnighausen et al. 2010). In Kenya although the estimated HIV prevalence in those aged 50-54 was similarly low at 8%; the prevalence in this age group was twice as high as the prevalence in 15 to 24 year olds (Peltzer, Phaswana-Mafuya et al. 2010). In Kenya there is already evidence of increased HIV prevalence in older adults from two nationally representative Demographic and Health Surveys (in 2003 and 2008/9), from 5.7% to 8.3% in 50-54 years old males (Mills, Rammohan et al. 2010). For females there were no trend data available.

Figure 1.1: National HIV prevalence estimates in adults aged 50 years and above in sub-Saharan Africa



∞ Figure constructed using data from reference (Negin and Cumming 2010)

(M) – Males (red)

(F) – Females (blue)

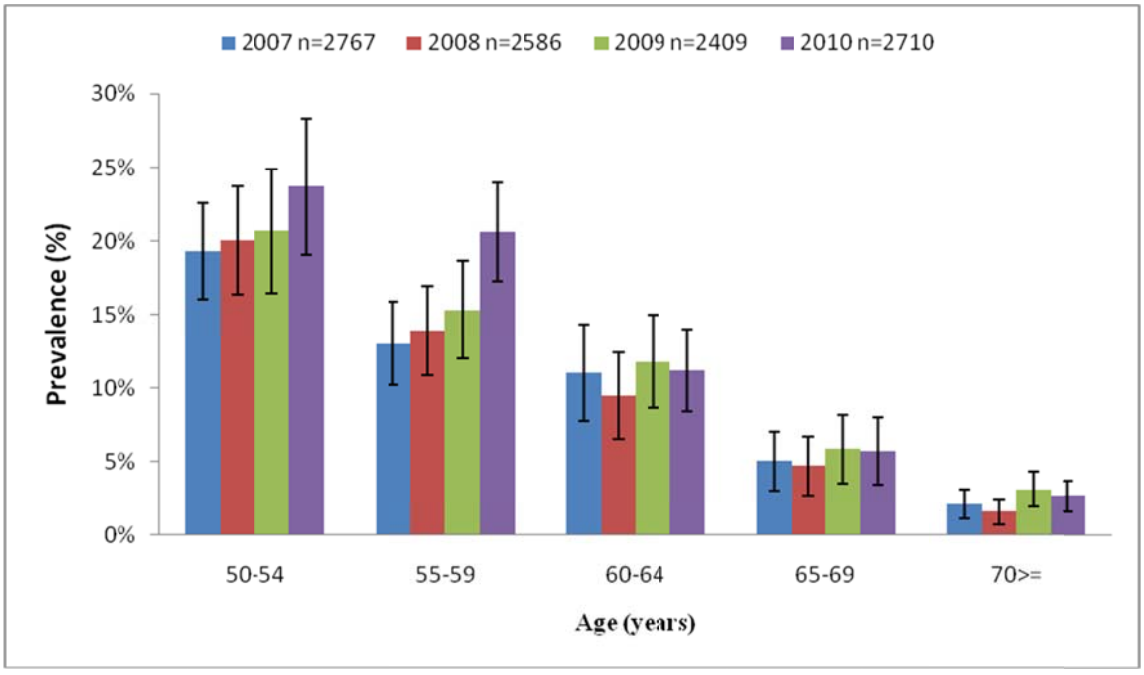
In South Africa, the country with the fourth highest HIV prevalence (17.8%) in the world in the 15-49 year old age group (UNAIDS 2010; UNAIDS 2012) and with the highest number of people living with HIV in absolute number terms (UNAIDS 2011), annual reports from Statistics South Africa (the organisation that reports on national population health and demographic statistics for South Africa) do not provide estimated HIV prevalence and incidence rates in people aged 50 years and above because their statistics are mainly based on antenatal surveys (STATS-SA 2006; STATS-SA 2010; STATS-SA 2013). In a national HIV survey between June 2008 and March 2009, conducted by the South African Human Sciences Research Council in collaboration with the Medical Research Council of South Africa and the Centre for AIDS Development, Research and Evaluation, estimated HIV prevalence was 10.4% and 10.2% in male and female 50-54 year old; 6.2% and 7.7% in 55-59 year old and 3.5% and 1.8% in ≥60 year old respectively (Shisana, Rehle et al. 2009). The survey was population-based, covering rural and urban areas of South Africa with a total sample size of 23 369 individuals aged two years and above. The sample was multi-stage stratified by province, settlement geography (geo-type) and predominant race group in each area. The sample was further stratified into census enumeration areas of 15 households each and in each household, one person was randomly selected in each of <2 years; 2-14years; 15-24 years and ≥25 years age groups. The results from the sample of 23 369 individuals was then weighted by age, race and province to give HIV prevalence and incidence rates representative of the general South African population. The response rate for HIV testing was 64% (Shisana, Rehle et al. 2009).

A year prior to this survey in 2007-2008, the WHO Study of global AGEing and adult health (SAGE), including a South African nationally representative cohort of 3 842 individuals aged 50 years and above, gave HIV prevalence estimates of 6.4% overall: 8.6% in those aged 50-59 years, 5.0% in those 60-69 years and 3.3% in those aged 70 years and above. The highest HIV

prevalence was in women aged 50-59 years (7.5%) and HIV prevalence was non-statistically significantly higher in rural (7.9%; 95% CI 5.2-10.6%) than urban areas (5.5%; 95% CI 3.8-7.2). KwaZulu-Natal, the area where this PhD was conducted, had the second highest HIV prevalence in older adults of 8.8% (Negin, Martiniuk et al. 2012). The SAGE cohort comprised of a population-based sample representative of the general population of people aged 50 years and above in South Africa, which was weighted during analyses to make the data nationally representative. The response rate for HIV testing was 75% (Negin, Martiniuk et al. 2012). Data from our own population in rural KwaZulu-Natal, using a longitudinal population-based HIV surveillance, comprising 2 684 older adults, estimated HIV prevalence of 9.5% in 2008, peaking in men aged 50-54 years (29.5%). HIV prevalence was high in women aged 50-54 years (17.3%) and in men (13.5%) and women (13.9%) aged 55-59 years. In older adults aged 70 years and above, 1.4% of men and women were HIV positive (Wallrauch, Barnighausen et al. 2010). Data used in the study included all adults aged 50 years and above and resident within a geographically defined well established surveillance area. The authors report that prevalence estimate calculations were adjusted for non-response by sex and age but did not explicitly state the response rate (Wallrauch, Barnighausen et al. 2010). Using that same rural longitudinal population-based HIV surveillance, we previously reported an increase in prevalence from 2007 to 2010 across all age groups from age 50 years (Figure 1.2) (Mutevedzi and Newell 2011). The increase in HIV prevalence was evident in both sexes.

Much of the increasing and substantial HIV prevalence among people over 50 year of age reflects longer longevity due to increasing availability and use of ART (Hontelez, de Vlas et al. 2012; Zaidi, Grapsa et al. 2013), but the risk of acquisition of new HIV infections in this age group should not be ignored.

Figure 1.2: HIV prevalence rates in adults aged 50 years and above over a 4 year period in rural KwaZulu-Natal, South Africa [adapted from (Mutevedzi and Newell 2011)]



1.3.2 HIV incidence

Data on HIV incidence rates in older adults are even more limited than prevalence estimates given that longitudinal HIV surveys commonly only follow younger adults aged 15-49 years and incidence reporting requires case-reporting systems which are largely absent in resource poor countries unlike in resource rich countries (Wallrauch, Barnighausen et al. 2010; Negin, Barnighausen et al. 2012). The Centers for Disease Control in the USA covering all 50 states within USA plus the District of Columbia and six USA dependent areas, reported that out of the 42 842 new HIV diagnoses in 2011, 7379 (17%) were aged 50 years and above (Centers for Disease Control 2011). This estimate is however limited by the fact that new HIV cases may have been acquired HIV prior to 50 years of age but not diagnosed and reported. Data from

the WHO Communicable Diseases Unit from central, eastern and western Europe shows an increase in new HIV cases from 2003 to 2007 from 10.4% to 12.9% in Western Europe, 8.2 to 9.3% in Central Europe and 1.8 to 3.7% in Eastern Europe (Lazarus and Nielsen 2010). This estimate is also limited by the fact that new HIV diagnoses do not necessarily reflect incidence cases. To accurately determine incidence rates in older adults, longitudinal studies that follow HIV negative cohorts are required.

One of the few reports on incidence in older adults in Africa, used prevalence rates from a meta-analysis of pooled data from five longitudinal community-based surveys participating in the Alpha network (Uganda- two sites; 1990 to 2005, Tanzania; 1994-2004, Zimbabwe; 1999-2004 and South Africa; 2004-5), to infer incidence rates. The study showed a primary prevalence peak in younger adults and a second lower prevalence peak in those aged 50 years and above and attributed the second prevalence peak to incident cases occurring in older adults (Zaba, Todd et al. 2008). The study does not explicitly measure incidence rates by age, making it difficult to determine the exact incidence rate in older adults. In the 2008/9 South African national population-based household HIV survey prevalence rates from previous surveys in 2002 and 2005 were compared with the 2008 estimates for individuals aged 14-20 and from this inferred a small decline in incidence, but HIV incidence in older adults could not be estimated on the basis of the same assumptions (Shisana, Rehle et al. 2009).

Although HIV incidence rates can be inferred from composite antibody tests, multiple cross-sectional surveys or other approaches (Barnighausen, Wallrauch et al. 2008; Zaba, Todd et al. 2008), to accurately measure HIV incidence, longitudinal cohorts of HIV negative populations prospectively recording HIV sero-conversions are the gold standard. In our study area, using a

longitudinal population-based survey, HIV incidence rate was estimated at 0.5 per 100 person years in older adults aged 50 years and above who were HIV negative in 2006 and were surveyed again before 2008. The incidence rate was higher in men (0.9 per 100 person years) than in women (0.4 per 100 person years) (Wallrauch, Barnighausen et al. 2010). The study consisted of 1 549 older adults contributing 1 575 person years at risk and 8 HIV incident cases (Wallrauch, Barnighausen et al. 2010). Due to lack of incidence trend data throughout sub-Saharan Africa, it is unclear whether HIV incidence rates are increasing.

Risk factors for HIV transmission

Transmission of HIV occurs when the virus enters the blood stream by direct contact or penetration of mucosal surfaces (Nguyen and Holodniy 2008). HIV infects CD4+ T lymphocytes and disease manifestations are largely a consequence of the decline in these CD4 cells causing immunosuppression (Pratt, Gascoyne et al. 2010). The most likely mode of HIV transmission in older adults is sexual activity. While in Europe and USA it is mainly transmitted through anal sex in Men who have Sex with Men (MSM), in Africa it is mainly through vaginal sex in heterosexuals (Manfredi, Calza et al. 2003; Schmid, Williams et al. 2009; Negin and Cumming 2010; Smith, Delpech et al. 2010). Several biological and behavioural factors predispose older adults to HIV infection; firstly the thinning of the vaginal wall after menopause increases the risk of sexual transmission and acquisition due to loss of vaginal mucosal integrity (Smith and Robinson 2002; Drew and Sharrard 2008). Secondly the association of ageing with increased expression of key T cell chemokine co-receptors which may facilitate viral entry into certain immune cells (Pratt, Gascoyne et al. 2010).

Behavioural factors also predispose older adults to HIV transmission; studies have suggested that risk of transmission and acquisition within the marriage may be high due to low condom use within the marriage relationship irrespective of extramarital relationships (Abel and Werner 2003; Negin and Cumming 2010; Peltzer, Phaswana-Mafuya et al. 2010; Schick, Herbenick et al. 2010). A study based on data from the 2005 South African national HIV prevalence and sexual behaviour survey consisting of 3 795 older adults reported that 40% reported being sexually active in the past month, 12.3% of whom had not used a condom at last sex act (Peltzer, Phaswana-Mafuya et al. 2010). The survey employed multi-stage stratified sampling technique to ensure that the sample was representative of rural and urban older adult populations within South Africa. In addition, a South Africa national survey with 21 000 individuals reported substantial numbers of multiple concurrent sexual partnerships with 7.5% of males aged 50 years and above reporting to be in such relationships in 2002, 9.8% in 2005 and 3.7% in 2008. The percentage of women aged 50 years and above in multiple concurrent relationships was low at 0.6% in 2005 and 0.8% in 2008 (Shisana, Rehle et al. 2009). In 2010 in rural South Africa, 152 of 1349 men (11.3%) and 96 of 2768 women (3.5%) reported having two concurrent sexual partners, although this study consisted of adults aged 16 years and above, about 13% were older adults (Miles, Barnighausen et al. 2011). Findings of low condom use and having more than one concurrent sexual partner in older adults have also been reported from Benin, Democratic Republic of Congo and Nigeria (Shisana, Rehle et al. 2009; Negin and Cumming 2010). This behaviour may also translate to high risk in acquiring sexually transmitted infection (STIs) more generally, which are known to increase the risk of HIV transmission in all age groups (Laga, Manoka et al. 1993; Abel and Werner 2003). In sero-discordant couples, where one partner is HIV positive and the other not, low condom use presents a transmission risk even in the absence of extramarital relationships (Grabar, Weiss et al. 2006; Schmid, Williams et al. 2009; Shisana, Rehle et al. 2009; UNAIDS 2010). However, results from the HPTN 052 trial showed that HIV transmission risk in sero-discordant couples is

very low if the HIV positive partner is on ART and has suppressed HIV viral load (Cohen, Chen et al. 2011; Reynolds, Makumbi et al. 2011). Lastly, practices of wife inheritance where the widow marries the deceased's relative are common in many parts of sub-Saharan Africa (Grabar, Weiss et al. 2006; Nguyen and Holodniy 2008; Schmid, Williams et al. 2009; Shisana, Rehle et al. 2009; Negin and Cumming 2010) and may likely increase risk of HIV transmission and acquisition. These factors raise concerns about increased risk of HIV infection in older adults.

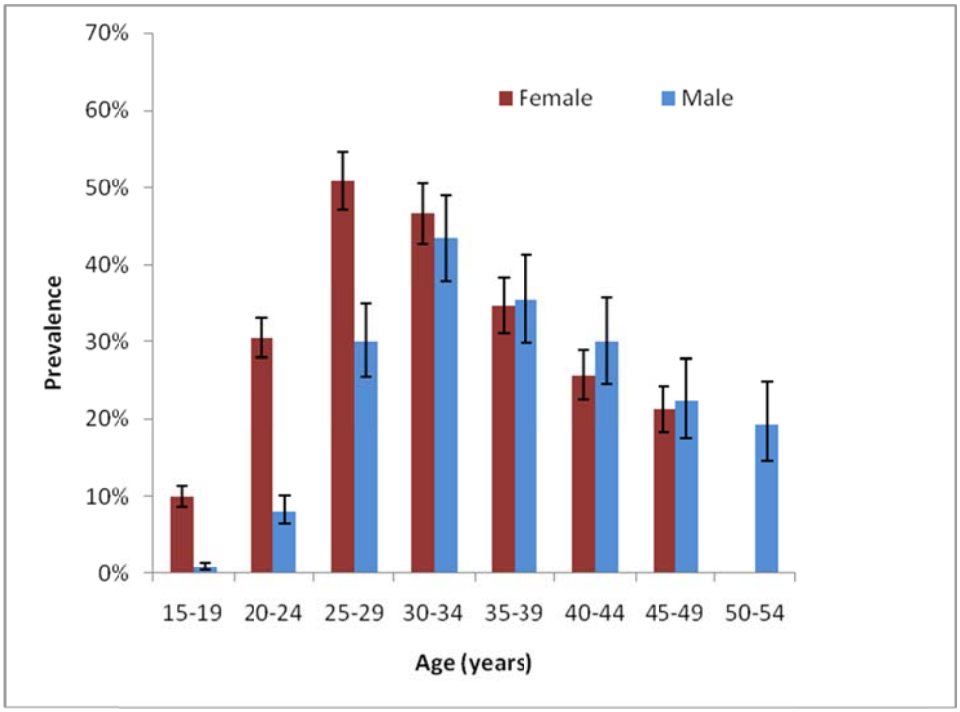
In sub-Saharan Africa it is generally, mistakenly, assumed that older adults are not sexually active (Kohli, Klein et al. 2006; Schmid, Williams et al. 2009; Shisana, Rehle et al. 2009; Negin and Cumming 2010; Negin, Barnighausen et al. 2012). However, in a Ugandan study of 750 HIV positive individuals aged 50 years and above, 40% reported to continue to be sexually active after being diagnosed with HIV (Funk, Odit et al. 2012). Similarly, a 2005 South African HIV prevalence and behaviour survey reported 41% and 36% of older adults being sexually active in the last 12 months and last month respectively (Peltzer, Phaswana-Mafuya et al. 2010). In the same report, although reported sexual activity declined with age, 9% of men and 3% of women still reported being sexually active at the age of 70 years and above. The results were based on self-reports and over- or under-reporting could have occurred. Further, older adults may have sexual partners considerably younger than themselves, with estimates ranging from 5 year age-gaps in women aged >40 years (Miles, Barnighausen et al. 2011) to as much as 20 year age-gaps in 17% of men aged 70 years and above and 6.4% of men aged 60-69 years (Peltzer, Phaswana-Mafuya et al. 2010), which raises concerns of increased HIV exposure risk in older adults by being sexually exposed to younger age groups with a much higher prevalence. Transmission in such cases is no longer driven only by the underlying HIV prevalence in older adults but also by that in the age group with which they mix sexually.

1.3.3 Increasing burden of HIV

The burden of HIV in older adults consists of two groups: firstly those who are infected with HIV at ages younger than 50 years who get onto ART and progress into the older adult age group and secondly those who acquire HIV after the age of 50 years. Although the considerable HIV incidence in older adults cannot be ignored, the burden of HIV in those aged 50 years and above is most likely largely driven by HIV positive individuals ageing (Manfredi, Calza et al. 2003; Grabar, Weiss et al. 2006; Nguyen and Holodniy 2008; Hontelez, de Vlas et al. 2012; Negin, Barnighausen et al. 2012). With the introduction of life-saving ART and the expansion of ART programmes, life expectancy is increasing (Bor, Herbst et al. 2013) with significant declines in mortality in both resource-rich and -poor settings. Survival is now expected to exceed 15-20 years from sero-conversion (Gebo 2008; Herbst, Cooke et al. 2009; Negin, Barnighausen et al. 2012; Bor, Herbst et al. 2013). A recent publication based on empirical data from a large HIV treatment cohort linked to surveillance data in our setting in rural KwaZulu-Natal reports an increase in life expectancy from 49.2 years in 2003 before the introduction of ART in South Africa, to 60.5 years in 2011: an 11.3-year gain (Bor, Herbst et al. 2013), which is in line with emerging data from other African countries, including Botswana, Uganda, Kenya and Zambia (Mermin, Were et al. 2008; Stover, Fidzani et al. 2008; UNAIDS 2010; UNAIDS 2012; UNPD 2013). Within the same rural KwaZulu-Natal setting in 2009 HIV prevalence peaked in women aged 30 to 34 years old and men aged 35 to 39 years old (Mutevedzi and Newell 2011) and if these peaks were to be sustained through provision of ART, in the next two decades, the peak will be in women aged 50 to 54 and men aged 55 to 59 years old. Evidence of this is already emerging depicted by the changing age pattern of HIV prevalence: whereas in 2004 HIV prevalence peaked in the ages 25-29 for women and 30-34 for men (Welz, Hosegood et al. 2007), in 2009 the prevalence peak for both sexes had shifted 5 years with the 2009 peak much broader (Figure 1.3 and 1.4) (Mutevedzi and Newell 2011). More recent studies show that the prevalence peak continues to shift towards the older age

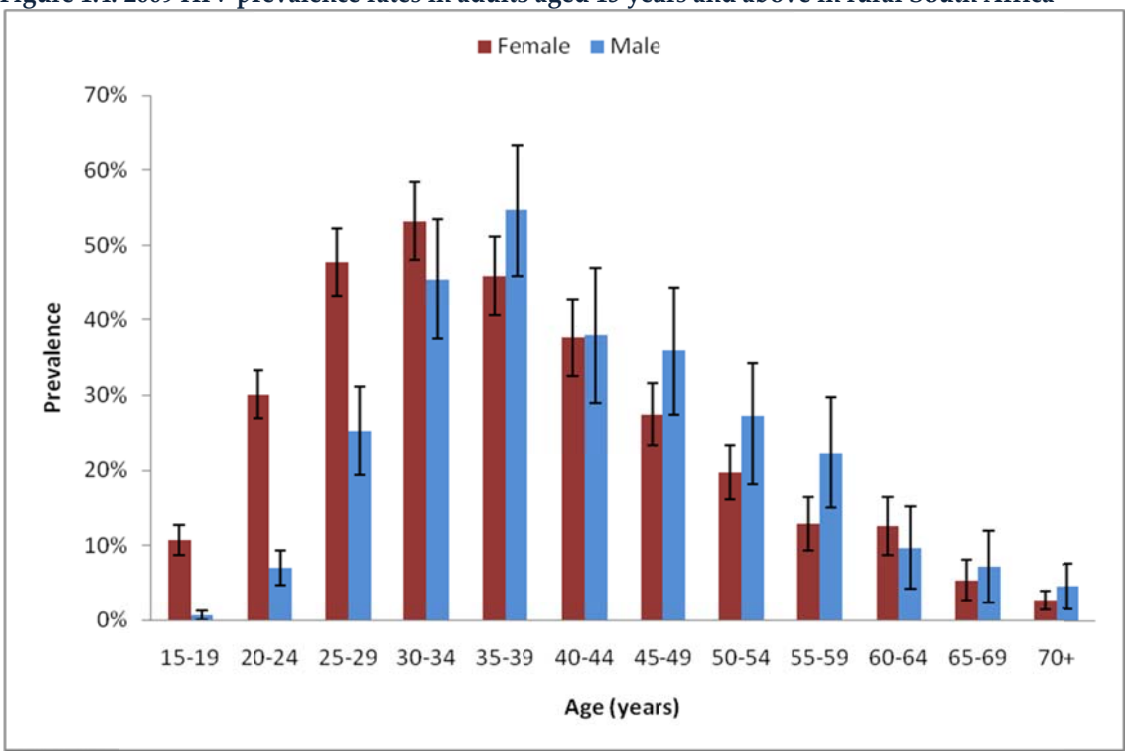
groups (Zaidi, Grapsa et al. 2013). A large modelling study using country specific HIV prevalence data, demographic composition, mortality rates, ART and circumcision coverage from 43 countries in sub-Saharan Africa used stochastic microsimulation models that simulated individuals in a dynamic network of sexual contacts under different trajectories of ART coverage expansion to predict age-specific HIV prevalence trends (Hontelez, de Vlas et al. 2012). The study projected that, assuming that 2011 ART provision levels are sustained, the total number of HIV positive older adults in sub-Saharan Africa will nearly triple from 3.1 million in 2011 to 9.1 million in 2040 whilst the HIV prevalence in those aged 15 to 49 years will decline by 2% likely changing the age composition of the HIV epidemic on the continent. In older adults in South Africa this translates to an increase in HIV prevalence from an estimated 11% in 2011 to 16% in 2040 (Hontelez, de Vlas et al. 2012).

Figure 1.3: 2004 HIV prevalence rates in adults aged 15 years and above in rural South Africa



This Figure was constructed using data from reference (Welz, Hosegood et al. 2007). Females aged 50 years and above, and men aged 55+, were not included in this HIV survey until after 2006

Figure 1.4: 2009 HIV prevalence rates in adults aged 15 years and above in rural South Africa



1.4 Older adults in ART programmes

Older adults now comprise a significant proportion of people enrolling in HIV treatment programmes in sub-Saharan Africa; a recent multicentre cohort study covering nine countries in sub-Saharan Africa reported that 1 977 (11%) of the 17 561 patients receiving ART were aged 50 years and above (Greig, Carrillo et al. 2012). In Uganda, 11% (2430/22 087) are aged 50 years and above (Bendavid, Ford et al. 2012). In South Africa, the country with the largest HIV treatment programme in the world, among 46 201 adults aged 16 years and above initiating ART between January 2002 and December 2009, within eight public sector ART sites participating in International Epidemiologic Databases to Evaluate AIDS (IeDEA), 7 486 (16%) were aged 45 years and above (Cornell, Schomaker et al. 2012). In another study of 45 383

patients aged 16 years and above initiating ART from 2003 to 2007 in 11 IeDEA sites within South Africa, when age was divided into quartiles; 11 350 (25%) of the cohort were older than 41.4 years when they initiated ART (Cornell, Technau et al. 2009). Closer to home in KwaZulu-Natal, (STATS-SA 2010; STATS-SA 2013), of the approximately 21 000 patients actively receiving therapy in a public sector ART programme in early 2013, 12% were 50 years or over at the time of ART initiation (www.africacentre.ac.za). Yet little is known in these settings about responses to ART in terms of morbidity, virological and immunological outcomes, and how these affect mortality following ART initiation. Cause-specific serious morbidity patterns and cause-specific mortality in older adults in sub-Saharan Africa are not often investigated making it difficult to improve clinical management of older people.

Across resource-rich and resource-limited settings, the introduction of ART in both older and younger adults has substantially reduced mortality and increased life expectancy (Hasse, Ledergerber et al. 2011; Herbst, Mafojane et al. 2011; Bendavid, Ford et al. 2012; Bor, Herbst et al. 2013; Zaidi, Grapsa et al. 2013) and HIV infection has become a chronic disease. HIV positive individuals aged 50 years and above on ART are likely to be faced with competing risks from ageing, co-morbid chronic diseases and drug toxicities and side effects resulting from concurrent treatment of HIV and non-HIV associated morbidities (Grabar, Weiss et al. 2006; Gebo 2008; Nguyen and Holodniy 2008; Gebo 2009; Negin and Cumming 2010; Onen, Overton et al. 2010). Associations of HIV-associated and non-HIV associated morbidity with ART and the impact of co-morbidities on HIV prognosis following ART initiation are largely unexplored in resource-poor African settings where introduction was ART significantly lagged behind that in resource-rich countries. Available data from developed countries suggest that life-long ART may increase the risk of age-associated chronic conditions (Manfredi, Calza et al. 2003; Grabar, Weiss et al. 2006; Kohli, Klein et al. 2006; Nguyen and Holodniy 2008; Kramer, Lazzarotto et al.

2009). However these authors acknowledge that the exact mechanisms leading to increased age-related chronic morbidity in HIV positive adults, occurring at younger ages than in HIV negative populations, are unknown and findings in this area are still debated. In HIV positive older adults who are likely to have age-related chronic morbidity, it is likely that co-morbidity both at time of initiating ART or during ART may have an impact on disease progression and mortality. Further prospective studies are needed to determine the impact of co-morbidity on ART outcomes of morbidity and mortality. Such studies may point towards interventions to reduce both morbidity and mortality in HIV positive older adults.

1.5 Morbidity burden in older adults

1.5.1 Non-HIV age-related chronic morbidities in the over-50s

Before discussing the associations between HIV with life-long ART and other chronic morbidities in older adults and possible complications thereof, it is necessary to understand age-associated chronic morbidities that occur in the absence of HIV. Progression through the life course entails biological and physiological changes. Compared to younger adults, older adults have modestly reduced hepatic mass, blood flow and metabolism through reduction in amount and function of Cytochrome P450 enzyme (Davies and Shock 1950). In addition there are age-associated reductions in renal mass, tubular secretion and glomerular filtration. These changes may result in sub-optimal clearance of toxins and drugs from the body especially in advanced ages (Davies and Shock 1950; Effros, Fletcher et al. 2008; Nguyen and Holodniy 2008). Ageing also alters the immune system; the number of B cell repertoire decreases and there is evidence of decreased B cell function. The ability of polysaccharide antigens to activate B cells for generation of effective antibody response for clinical protection also declines (Grabar, Kousignian et al. 2004; Nylor, Li et al. 2005; Effros, Fletcher et al. 2008; Nguyen and

Holodniy 2008; Gebo 2009; Gebo and Justice 2009). A United States-based study comprising of 156 individuals aged 18-88 years old suggested that by age 55 years, thymic function becomes significantly reduced (Nylor, Li et al. 2005). The study excluded individuals with serious diseases, such as a chronic inflammatory disease, cancer, a history of chemotherapy, advanced atherosclerotic disease or congestive heart failure, poorly controlled diabetes mellitus, or chronic obstructive pulmonary disease. Other studies have reported that cognitive function, gut absorption rate and bone density are also lower in older than younger adults, with the most impact in those aged over 65 (Grabar, Weiss et al. 2006; Gebo 2008; Nguyen and Holodniy 2008). These physiological changes may increase the risk of chronic morbidity such as heart disease, arthritis, diabetes and hypertension (Grabar, Weiss et al. 2006; Gebo 2008; Christensen, Doblhammer et al. 2009; Mayosi, Flisher et al. 2009). As such, the chronic morbidity burden of cardiovascular diseases, cancers, bone disorders, metabolic disorders is usually higher in those aged 50 years and above than in younger adults (Kahn, Tollman et al. 2006; Minh, Ng et al. 2008; Mayosi, Flisher et al. 2009; McElhaney and Effros 2009; Msyamboza, Ngwira et al. 2011; Negin, Martiniuk et al. 2012)

1.5.2 Interaction between HIV and non-HIV chronic morbidity

Studies suggest that across all age groups, HIV increases the risk of age-associated chronic conditions such as malignancies, metabolic disorders inclusive of diabetes and cardiovascular conditions. In a population of 77 025 HIV positive adults (median age 38 years) included in a prospective cohort, involving 61 French University hospitals, between 1992 and 1999, the risk of non-AIDS defining cancers prior to ART (1992 to 1995) was twice as high in HIV-positive men as in the general French male population. However the study showed no difference in cancer risk between HIV positive and negative women (Herida, Mary-Krause et al. 2003). Considering that HIV infection generally results in increased susceptibility to neoplasia by means of a

decrease in immunologic response to tumour cells and an increased susceptibility to oncogenic viruses (Pantanowitz and Dezube 2004), this lack of association in women is surprising and the authors hypothesize that this may be due to underreporting or competing mortality. A commentary on this French study suggested that the lack of difference in cancer risk was because women included in the French hospital study had lower cancer risk factors (lower social class, early age at first birth, high parity and low alcohol intake). The commentary also reported that as of 2004 there were only a limited number of published breast cancer cases in HIV positive women and suggested that HIV may have a protective effect on breast cancer (Pantanowitz and Dezube 2004). In the same French hospital study, the risk of lung cancer was twice as high in HIV-positive men and women compared to the general population. Similarly, in a study that linked the Swiss HIV Cohort Study and the Swiss cantonal cancer registries, high age standardised incidence ratios of Kaposi sarcoma, anal cancer, cervical cancer, liver cancer, lip, mouth, pharynx, lung and skin cancer were reported in HIV positive people compared to the general population. The Swiss study included 7304 HIV positive individuals aged 16 years and above contributing 28 836 person-years from 1985 to 2003 (Clifford, Polesel et al. 2005). In HIV positive patients only, the risk of cancer was the same during the ART era (1996 to 1999) as during the period prior to ART (1992-1995) (Herida, Mary-Krause et al. 2003). However, the lack of difference in cancer risk pre-ART and ART era might be a result of the short follow-up period (three years) in the ART phase.

Similar to cancer risk in HIV positive populations compared to the general HIV negative population, a review on cardiovascular risk and body fat abnormalities in HIV infected adults reported increased body-fat abnormalities and dyslipidemia in HIV positive adults possibly associated with increased diabetes. In HIV positive individuals with lipoatrophy, diabetes mellitus was observed in 7% compared to 5% in healthy controls matched by age and sex

(Grinspoon and Carr 2005). Rates of acute myocardial infarction between October 1996 and June 2004 in a cohort study in Boston, USA with 3 851 HIV positive (41% on ART) and 1 044 589 HIV negative individuals showed that the rate of acute myocardial infarction was twice as high in the HIV positive group as in those HIV negative. HIV positive individuals also had higher proportions of hypertension (21.2% versus 15.9%), diabetes (11.5% versus 6.6%) and dyslipidemia (23.3% versus 17.6%) than the HIV negative population (Triant, Lee et al. 2007). This Boston study included patients aged 18-84 years and the median age of participants was 38 years for those HIV positive and 39 years for those HIV negative. Although all studies mentioned above did not exclusively look at older adults, these results highlight that HIV positive people, have an increased risk of age-associated chronic morbidities. Findings of increased chronic morbidity risk in HIV positive adults of all ages might mean that in those HIV positive and aged 50 years and above, the burden of chronic morbidity may be higher still.

Indeed in sub-Saharan Africa, where the burden of HIV is high, older adults face a dual burden of disease from non-HIV chronic morbidities and HIV-associated morbidities (Andrew and David 2000; Rhee and Greenblatt 2008; Pardi, Nunes et al. 2009; Negin, Wariero et al. 2010). Irrespective of age, the distribution of chronic morbidity at population level is mainly driven by socioeconomic disparities that influence lifestyle risk factors such as smoking, exercise, alcohol, diet and stress levels (Bailis, Segall et al. 2003; Bradshaw, Groenewald et al. 2003; Lorant, Deliege et al. 2003; Kahn, Tollman et al. 2006; Lopez, Mathers et al. 2006; Mayosi, Flisher et al. 2009; Kyobutung, Egondi et al. 2010). Consequently, the largest morbidity burden is borne by poor communities in urban areas where these lifestyle risk factors are highly prevalent (Bailis, Segall et al. 2003; Bradshaw, Groenewald et al. 2003; Lorant, Deliege et al. 2003; Lopez, Mathers et al. 2006; Mayosi, Flisher et al. 2009). The UNAIDS Global HIV prevalence map shows HIV distribution follows the same pattern as that in chronic non-HIV

related morbidity of being higher in poor communities (UNAIDS 2010); meaning that populations prone to chronic morbidities may also face HIV. However for older adults, irrespective of lifestyle risk factors, the chronic morbidity burden is increased because of age. In a nationally representative South African survey of 3 795 rural and urban older adults of whom 5.8% were HIV positive, 50% and 38% of those positive reported at least one or two other illness respectively, in addition to being HIV positive (Peltzer, Phaswana-Mafuya et al. 2010). Similarly, in a report from a longitudinal demographic survey in Agincourt, rural South Africa, using verbal autopsy data to infer mortality rates in adults aged 50 years and above, of the deaths occurring between 1992 and 2000 in women aged 50 to 64 years old, 22% were due to stroke, 22% to diabetes, 16% to malignant neoplasms of the female genital organs and 27% to HIV/AIDS (Kahn, Tollman et al. 2006) .

A review on the burden of non-communicable diseases in South Africa utilising various data sources inclusive of the national burden of disease study, Statistics South Africa, the South African Demographic and Health Surveys, population-based demographic surveillance systems and other surveillance studies estimated that the chronic morbidity burden from cardiovascular diseases, diabetes mellitus, respiratory diseases and cancers in all age groups contributed 12% of the overall disease burden in a country with high HIV prevalence. Chronic morbidity burden was higher in older than younger adults. The authors suggested that prevention and treatment of non-communicable disease may be marginalised in South Africa because of the overwhelming burden of HIV and tuberculosis (Mayosi, Flisher et al. 2009). High non-HIV-related age-associated chronic morbidity in areas with high HIV prevalence leads to a population with dual burden of communicable and non-communicable diseases (Kahn, Tollman et al. 2006; Mayosi, Flisher et al. 2009) and is likely to impact on the future epidemiological trajectories of both HIV and chronic disease epidemics.

A study in a socio-economically poor community in Nairobi, including 2 072 adults aged 50 years and above reported poor health coupled with high HIV prevalence (Kyobutungi, Ezeh et al. 2009; Kyobutung, Egondi et al. 2010). The study used the WHO composite health score measure to estimate health status. The proportion of older adults below the median health score of 67.5 increased with age from 33% in those aged 50 to 59 years old to 79% in those aged 80 years and above (Kyobutung, Egondi et al. 2010). Similar to the African studies discussed above, cross-sectional and longitudinal studies from Europe and the United States of America report higher chronic morbidity including diabetes mellitus, cardiac diseases, hypertension, chronic kidney and liver disease, arthritis, depression and some cancers in HIV positive than negative older adults (Grabar, Weiss et al. 2006; Goulet, Fultz et al. 2007; National Institute of Ageing 2007; Christensen, Doblhammer et al. 2009; Mayosi, Flisher et al. 2009).

These studies begin to confirm the dual burden of infectious and chronic morbidity in HIV positive adults of all age groups in both resource-rich and -poor settings. However, what remains unknown is how the dual burden of morbidity associated and not-associated with HIV impacts on the success and efficacy of ART. The studies on morbidity burden highlighted above do not explore the potential direct benefits and harms of ART in HIV positive adults in reducing both HIV-associated morbidity and non-HIV associated chronic morbidity. Future studies estimating the morbidity burden in the context of HIV and ART must account for ART use and are important especially in older adults.

1.5.3 Health seeking behaviour

HIV positive adults of all ages on ART in sub-Saharan Africa are mandated to attend frequent clinic visits for ART collection. The South African HIV treatment guidelines stipulate that patients collect ART monthly (National Department of Health 2004; National Department of Health 2010; National Department of Health 2013). This means older adults who would otherwise not utilise health care services now have frequent access by virtue of being on ART, increasing opportunities for diagnosis and treatment of any other co-existing morbidity. Generally, the earlier a disease is diagnosed, the more likely it is that it can be cured or successfully managed (Suzman, Harris et al. 1992; WHO 1995; van der Hoeven, Kruger et al. 2012). To date there are no studies that have directly compared morbidity burden in HIV positive compared to HIV negative older adults taking into consideration HIV and ART status as a way of evaluating benefits of enhanced access to care via ART.

Availability of health care services and individuals' health care-seeking behaviour are likely to impact on morbidity burden and mortality because health care utilisation increases the chances of diagnosing and treating disease. For HIV positive individuals in HIV care receiving ART, contacts with health care facilities are increased compared to the HIV negative population as they have to frequently visit the clinic for ART collection and regular clinical monitoring. The South African HIV treatment guideline stipulate that patients visit the ART clinic monthly for ART collection and three-monthly for a nurse appointment (National Department of Health 2004; National Department of Health 2010; National Department of Health 2013). The most recent guidelines allow patients who are stable on ART with suppressed viral load to collect ART pills every other month, although in practice monthly visits remain the norm (National Department of Health 2013). ART-driven increased health care

utilisation in individuals that would otherwise not frequently utilise such services potentially confers a positive effect on the health of such individuals.

In resource limited settings in sub-Saharan Africa, most HIV services are placed in urban areas, but the majority of older adults, especially those post-retirement age, live in rural areas (Mills, Rammohan et al. 2010). Thus health care services may not be located where they are needed. A study in urban Kenya (East Africa) comprising of 276 women and 124 men aged 65 years and above of unknown HIV status showed that although 376 (93%) participants reported illness in the three months prior to the interview, from musculoskeletal, respiratory, sight and dental conditions, 63% of these perceived themselves as healthy and not requiring medical attention. Of those reporting illness on the day of the study interview, only 26% were on treatment whilst 73% reported that money hindered health care access. Participants criticised the fact that health care facilities were placed long distances apart making it difficult to reach them (Waweru, Kabiru et al. 2003). Similarly, in a household-based survey of 756 households in Nigeria with at least one household member aged 60 years and above, over 70% reported having either body pain, poor sight, depression, headaches, decreased mobility and weakness and fatigue, but more than two thirds (69%) had not visited a health facility for a medical check-up. In this study only 29% were aware of their health needs and poverty emerged as a barrier to health access (Abdulraheem 2007). Data from the Global Study on AGEing and adult health (SAGE) obtained from a nationally representative cross-sectional study with a response rate of 77% resulting in a sample size of 3 840 individuals aged 50 years and above in South Africa showed that only 1 919 (50%) of the participants had utilised outpatient care in the last year and of these only 1% did so for a routine medical check-up. The majority of participants (69%) utilised health care services because they had a chronic condition (Peltzer and Phaswana-Mafuya 2012), and those that did showed considerable level of dissatisfaction with

health services, especially those aged 55 years and above. The major reasons for dissatisfaction included long waiting times, staff attitudes, non-availability of medications, and staff shortages (Peltzer and Phaswana-Mafuya 2012). Issues relating to lack of facilities and financial and geographic barriers to health care access (Waweru, Kabiru et al. 2003; Ahmed, Tomson et al. 2005; van der Hoeven, Kruger et al. 2012), likely make older adults resort to self-treatment. As such, older adults participating in research from South Africa, Kenya and Bangladesh, self-reported that they preferred to seek no treatment or to self-treat for musculoskeletal problems, decreased mobility, general body pain and fever (Sarkisian, Hays et al. 2002; Waweru, Kabiru et al. 2003; van der Hoeven, Kruger et al. 2012). Low health care utilisation highlighted by these studies highlights a gap in health care that is probably not present in HIV positive older adults who have regular access to health care services via HIV treatment services.

1.6 Bio-markers of health in HIV infected older adults

Biomarkers are valuable markers of infection or disease whose levels within the human body may be an indication of increased morbidity risk or increased risk of future mortality. Since biomarkers are superior predictors of morbidity and mortality than self-reported health status (Goldman 2007; Neaton, Neuhaus et al. 2010; Armah, McGinnis et al. 2012), they are increasingly employed in monitoring health, identifying individuals with particular susceptibility to morbidities and evaluating therapeutic interventions (Harris, Ferrucci et al. 1999; Penninx, Kritchevsky et al. 2004; Kuller, Tracy et al. 2008; Population Reference Bureau 2008; Neaton, Neuhaus et al. 2010; Neuhaus, Jacobs et al. 2010). For example, cholesterol provides information on metabolic processes and future risk of coronary heart disease, body mass index (BMI) is an indicator of obesity, chronic metabolic disorders and fatty deposits (Population Reference Bureau 2008). Cytokines are released in response to trauma or infection

and their elevated presence has been linked to chronic morbidity (diabetes, arthritis, cardiovascular diseases and atherosclerosis) and increased mortality (Harris, Ferrucci et al. 1999; Bruunsgaard, Pedersen et al. 2001; Targher, Zenari et al. 2001; Penninx, Kritchevsky et al. 2004; Danesh, Kaptoge et al. 2008; Kuller, Tracy et al. 2008; Armah, McGinnis et al. 2012). Interleukin 1 (IL1) and Tumor Necrosis Factor-alpha (TNFα) are early mediators of the acute phase response; Interleukin 1 (IL16) is an anti-inflammatory and immune-regulatory cytokine which controls inflammatory responses and high sensitivity C-reactive protein (hsCRP) is an acute phase protein (Harris, Ferrucci et al. 1999; Bruunsgaard, Pedersen et al. 2001; Targher, Zenari et al. 2001; Bastard, Maachi et al. 2006). Although these markers are usually slightly elevated in older adults, they are further elevated in those with chronic morbidities and are predictive of increased risk of morbidities such as cardiovascular disease making inflammatory markers good indicators of health status even in the older age groups (Bruunsgaard, Pedersen et al. 2001; Targher, Zenari et al. 2001).

Uncontrolled HIV replication and associated immune activation increase levels of inflammation markers (Hober, Haque et al. 1989; Kuller, Tracy et al. 2008; Rodger, Fox et al. 2009; Neuhaus, Jacobs et al. 2010; Armah, McGinnis et al. 2012). These levels are likely to be higher during advanced stage HIV disease when immune activation is greatest. The Strategies for Management of Antiretroviral Therapy (SMART study), a large randomised control trial involving 5 472 HIV positive participants enrolled at 318 sites in 33 countries including the United states, Australia, Europe, North and South America and Austral-Asia and randomising individuals to continuous or CD4 guided interrupted ART, reported that high levels of IL6 were associated with advanced HIV-disease and with mortality after ART initiation which was largely thought to be due to cardiovascular disease (Kuller, Tracy et al. 2008). The SMART study also showed that interruption of ART increased IL6 levels and that these increases were

significantly associated with increased risk of death (Kuller, Tracy et al. 2008). Another large study in the United States (Veterans Ageing Cohort Study – VACS), including 1 525 HIV positive adults with a mean age of 52 years (standard deviation 8.2 years) and 843 HIV negative adults with a mean age of 54 years (standard deviation 9.3 years), reported higher levels of IL6 in HIV positive than in HIV negative individuals. Differences in median biomarker levels were most apparent when HIV was stratified by HIV RNA or CD4 cell count. IL6 levels were highest in advanced HIV disease when the HIV viral load was ≥ 500 copies/mL or when CD4 cell counts were less than 200cells/µL (Armah, McGinnis et al. 2012). In the SMART study, the increase in IL6 cytokine levels within a month of interrupting ART (Kuller, Tracy et al. 2008), suggests that HIV induces activation of inflammatory pathways and ART might dampen these effects thereby reducing cytokine levels (Neuhaus, Jacobs et al. 2010). However, HIV positive individuals always have elevated inflammatory markers (Armah, McGinnis et al. 2012) compared to HIV negative individuals, even after successful suppression of the HIV viral load (Neuhaus, Jacobs et al. 2010). The perpetually elevated cytokine levels may increase the risk of age-related chronic morbidities including cardiovascular diseases. Kuller at al. recommended further longitudinal studies assessing mortality and morbidity levels in patients on ART but with high IL6 levels (Kuller, Tracy et al. 2008) In a further SMART substudy, different classes of ART drugs were associated with different levels of inflammatory markers. Patients receiving a non-nucleoside reverse transcriptase inhibitor had higher median hsCRP levels than those on a protease inhibitor, whilst for those on nucleoside reverse transcriptase inhibitors, abacavir patients had higher levels of IL6 and hsCRP than those on any other nucleoside reverse transcriptase inhibitors (Neuhaus, Jacobs et al. 2010). Abacavir use has also been associated with increased risk of cardiovascular disease (Cutrell, Brothers et al. 2008) but there is controversy surrounding this association. A meta-analysis of published and unpublished data from 28 randomised control trials comparing abacavir-containing ART (4 376 participants) and non-abacavir-containing ART (4 857 controls) did not find an association between abacavir use

and increased risk of cardiovascular disease (Cruciani, Zanichelli et al. 2011). Another meta-analysis by the USA Food and Drug Administration (FDA) involving 26 randomised control trials also reported no association between abacavir use and cardiovascular disease (Ding, Andraca-Carrera et al. 2012). If the effect of ART on inflammatory marker levels varies by ART drug or regimen, then there is need for biomarker studies from across different settings where varying ART drug combinations are used for HIV treatment.

Whether the same phenomenon applies in African populations is unknown because there are very few studies in this area from African populations in Africa. A small study in South Africa including 80 HIV positive patients, the majority (60/80; 75%) of whom were ART- naive, reported higher levels of IL6 in HIV positive individuals with AIDS-associated co-infections of either tuberculosis, bacterial, viral or fungal infections than in 10 HIV negative controls (Cassol, Malfeld et al. 2010). The study also showed a non-statistically significant trend towards elevated IL6 levels in HIV positive individuals without co-infections. HIV positive patients in this study with WHO disease stage III or IV were stratified into three groups: on ART and ART-naive patients with (n=20) and without (40) opportunistic infections. For the HIV positive group, the median CD4 cell count was 135 for the ART-naive group and 386 for the HIV positive group and 20 (25%) had bacterial, viral or fungal co-infection inclusive of TB. The 20 HIV positive patients on ART had to have had undetectable viral load for at least 6 months. The eligibility criteria and the small size of the HIV negative control group limit the generalisability of this study's results. Despite these limitations, this study provides valuable knowledge in an area that is critically lacking studies. However, since the study was in younger adults with a mean age of 39 years in those HIV positive, the majority of whom were ART-naive, the study does not contribute towards understanding associations between HIV and ART status and

biomarkers in older adults. It is unclear if ART reduces cytokine levels to levels similar to HIV negative older adults.

Further, in older adults it remains unclear if elevated levels in the presence of ART are associated with chronic disease. All the above mentioned studies, except for the VACS study, (Armah, McGinnis et al. 2012) were limited by their inability to adjust for multiple co-morbid conditions such as diabetes and cardiovascular diseases that have been associated with elevated inflammatory markers. The association between elevated biomarkers in those HIV positive and increased co-morbidity burden are unknown (Armah, McGinnis et al. 2012). Possibly ART reduces inflammatory markers in older adults to levels that are not clinically significant and not associated with chronic morbidity, making these markers less efficient in identifying risk groups for disease in older HIV positive patients receiving ART. Studies are required in all settings to determine the associations between inflammatory markers and HIV status in the presence or absence of ART and associations between biomarkers and morbidity by HIV and ART status in older adults who due to age may already have elevated levels of inflammatory markers.

Obesity, irrespective of HIV status and age is a global concern due to its association with chronic health problems such as cardiovascular diseases, diabetes, stroke and arthritis (Cheymol 2000; Bastard, Maachi et al. 2006; Population Reference Bureau 2008). Similar to ageing, obesity is also characterised by elevation in inflammatory markers (Trayhurn 2005; Bastard, Maachi et al. 2006). HIV, irrespective of age and obesity status, is associated with increased prevalence of cardiovascular diseases, diabetes, strokes and arthritis (Barnighausen, Welz et al. 2008; Cornell, Technau et al. 2009; Larson, Bertozzi et al. 2011). Cytokine levels are

normally higher in obese individuals (Trayhurn 2005; Bastard, Maachi et al. 2006) and also in HIV positive individuals especially during advanced stage HIV disease (Hober, Haque et al. 1989; Kuller, Tracy et al. 2008; Rodger, Fox et al. 2009). High levels of obesity despite an HIV epidemic in the South African population have previously been reported (Barnighausen, Welz et al. 2008; Malaza, Mossong et al. 2012), which raises important questions relating to the association of elevated cytokine levels in this population of older adults. Considering the lack of knowledge in African populations on bio-marker levels that may identify increased risk of morbidity, studies focusing on how bio-marker levels and BMI relate to morbidity in African older adult populations, accounting for HIV and ART status will help determine which levels may be associated with morbidity.

1.7 HIV infection and ART in the older adult

1.7.1 HIV progression and mortality

Age at both infection and treatment commencement is a major determinant of disease progression and mortality for many diseases, including HIV infection, but the effect of age itself on other prognostic factors is not often studied directly (CGAIHS 2000; Collaborative Group on AIDS incubation and HIV survival 2000; Babiker, Peto et al. 2001; Nylor, Li et al. 2005; The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group 2008). A large study which pooled data from 38 studies in Australia and 14 countries in Europe and North America including 13 000 HIV positive adults aged 15-54 years, showed before the widespread use of ART, the risk of death increased by 50%, and of progression to AIDS increased by 33%, for each 10 year increase in age (CGAIHS 2000). Median survival was 10.9 years, 7.9 years, 6.1 years and 4.0 years for those sero-converting at ages 25-34 years, 45.54 years, 55-64 years and above 64 years. Time from HIV sero-conversion to AIDS also declined

from 9.8 years in those acquiring HIV aged 25-34 years to 6.3 years in those sero-converting aged 55-64 years (CGAIHS 2000). In the early ART era, death rates increased by 43% per ten-year increase in age at sero-conversion (Babiker, Peto et al. 2001). In a retrospective cohort in Maryland, United States with 906 ART-naive patients enrolled between February 1989 and January 2006 who went on to initiate ART between December 1995 and February 2006, 670 of whom were less than 40 years of age and 149 50 years and over, the survival time in older adults was half that in younger adults (25% of older and 25 % of younger adults died within 36 months and 59 months of initiating ART respectively) (Greenbaum, Wilson et al. 2008). Similarly in a cohort of 12 574 patients initiating ART within Europe and North America, with a median date of ART initiation of December 1997 [inter quartile range (IQR) June 1997 to July 1998], the risk of AIDS or death following ART initiation was 51% higher in those aged 50 years and above than in 17-29 year olds. The risk of death alone was three-fold higher in older than younger adults aged 17-29 years at ART initiation (Egger, May et al. 2002).

Pre-ART, in an analysis of pooled data from seven studies in five African countries and one study in Thailand , the median survival for adults aged 45 years and above was half (6 years) that in adults aged 25-34 years (11 years) (Todd, Glynn et al. 2007). The study included 3 823 sero-converters with age at sero-conversion ranging from 15 to 90 years, from three community population-based HIV surveys, two occupational clinics and three HIV clinics with sero-conversions observed from 1985 to 2003. The study used data based on South African miners obtained from an occupational clinic; a population that might not be generalisable to the general South African cohort. Despite this limitation, the study provides useful insight into the effect of age on HIV prognosis in Africa. Overall survival rates from sero-conversion were similar in East African sites (10.3 years) and South African miners (10.5 years) (Todd, Glynn et al. 2007). More rapid progression to AIDS and death in older adults compared to younger

adults may be due to modest immune response to infection and disease, age-related co-morbidities and decreased liver and kidney function that occurs with ageing.

Further to age accelerating HIV progression there are data suggesting that natural ageing or other chronic conditions may be negatively influenced by chronic HIV and ART (Effros, Fletcher et al. 2008; Kaplan, Sinclair et al. 2011; Onen and Overton 2011). The potential effect of HIV on health is exhibited by a number of immunologic abnormalities (immunosenescence) consistent with changes to the adaptive immune system seen in very old individuals (Deeks 2011). A study on 115 HIV-infected women and 43 age- and race-matched HIV uninfected controls reported that even in the absence of multiple classical risk factors for age-related conditions such as smoking and obesity, long-term infection with HIV may directly increase the risk of heart diseases (Kaplan, Sinclair et al. 2011). The authors hypothesized that this may be due to HIV promoting a permanent inflammatory state, causing accelerated ageing of the immune system possibly damaging blood vessels in ways that promote development of heart disease (Kaplan, Sinclair et al. 2011). However if this is the case then ART which leads to a decline in inflammatory markers should reverse the accelerated ageing effects posed by HIV infection. A review including an unknown number of manuscripts stratified into pre-defined categories of peer reviewed articles, systematic reviews and Centres for Disease Control and Prevention data, concluded that premature frailty was a manifestation of HIV-related accelerated ageing (Onen and Overton 2011). In this review, three studies reported that frailty prevalence in younger HIV infected adults (5% to 20%) was similar to prevalence of age-driven frailty in older adults which has been reported between 3-32%, possibly indicating the presence of HIV-driven premature ageing. Additionally, introduction of ART was associated with a decline in prevalence of frailty markers. Despite some literature advocating for accelerated ageing in individuals with HIV, of note is that ageing trajectories among those HIV-infected are largely

unknown in comparison to those age- and sex-matched but HIV-uninfected (Onen and Overton 2011). Accelerated ageing in HIV is currently topical, but there is no clear evidence of such a condition and the exact mechanisms of how HIV infection leads to chronic conditions of ageing remains unclear. Furthermore, there is no clear clinical definition of the frailty phenotype (Effros, Fletcher et al. 2008; Onen and Overton 2011).

Worldwide, data relating to age-driven HIV progression quantifying the contribution of age at ART initiation to decline in long term survival post-ART era are limited, and data on mortality outcomes by age are conflicting. Some African studies have reported an association between increasing age at ART initiation and increased risk of either AIDS or mortality (Toure, Kouadio et al. 2008; Lawn, Little et al. 2009; Tuboi, Pacheco et al. 2010; Gupta, Nadkarni et al. 2011), whilst other studies report similar mortality in younger and older adults receiving ART (Etard, Ndiaye et al. 2006; Stringer, Zulu et al. 2006; Brinkhof, Dabis et al. 2008; Brinkhof, Boulle et al. 2009). Assessing age as a continuous variable, two studies have suggested an association between increasing age and higher mortality on ART (Toure, Kouadio et al. 2008; Lawn, Little et al. 2009). Two studies analysing age as a categorical variable have reported significantly higher mortality for individuals aged greater than 50 years: the ART-LINC cohort, a collaboration of HIV treatment cohorts in lower-income countries, in an analysis of 7160 patients from 10 sites, reported a two-fold increased risk in all-cause mortality after 6 months on ART for those aged 50 years and above compared to 16-29 year olds (Tuboi, Pacheco et al. 2010). The study included patients aged 16 years and above initiating ART between 1996 and 2007 with at least three months of follow-up , and although the study included AIDS-defining conditions within the first 6 months of ART, causes of mortality were not available (Tuboi, Pacheco et al. 2010). In the South African Free State programme that followed-up 14 267 patients in a public sector ART programme for up to 20 months after enrolment into the

programme, 3 619 of whom had initiated ART between May 2004 and December 2005, there was 58% increased risk of mortality for older adults compared to 20-29 year olds, although the mortality in this analysis also included people dying before ART initiation (Fairall, Bachmann et al. 2008).

On the other hand, data from the International Epidemiological Databases to Evaluate AIDS (IeDEA), including ART programmes from Cote d'Ivoire, Malawi, South Africa and Zimbabwe, with 13 249 individuals contributing 1 177 deaths in 14 695 years of follow-up, reported no significant difference in mortality risk at 2 years after initiation of ART between patients aged 50 years and above and those aged 16 to 29 years at ART initiation (Brinkhof, Boulle et al. 2009). Similarly, other studies from sub-Saharan Africa including from South Africa, Zambia and Senegal have reported no clear association between age and mortality on ART, even with considerable sample sizes (Etard, Ndiaye et al. 2006; Stringer, Zulu et al. 2006; Brinkhof, Pujades-Rodriguez et al. 2009; MacPherson, Moshabela et al. 2009). Comparison across studies is complicated by the use of different age categories and different follow-up periods. Moreover these studies have included age as an explanatory variable rather than explicitly assessing mortality within and between younger and older ages.

A study by the Collaborative Group on AIDS incubation and HIV survival comparing mortality rates in HIV positive and HIV negative older adults showed that the excess mortality in HIV positive older adults is not accounted for by the increased mortality that comes with ageing (Collaborative Group on AIDS incubation and HIV survival 2000), indicating that there may be factors related to HIV infection and ART contributing to mortality in HIV positives. Rapid progression together with issues surrounding ART treatment complications (reduced

immunological response despite viral suppression) (Grabar, Weiss et al. 2006; Cuzin, Delpierre et al. 2007; Sabin, Smith et al. 2009; Schmid, Williams et al. 2009), possible drug-drug interactions and drug toxicities (Gebo 2006; Gebo 2008)) coupled with age-related co-morbidities (Manfredi, Calza et al. 2003; Tumbarello, Rabagliati et al. 2003) may surreptitiously drive increased mortality in older adults (Babiker, Peto et al. 2001; Gebo 2006; Goulet, Fultz et al. 2007; Bakanda, Birungi et al. 2011).

Cause-specific mortality and morbidity data are largely lacking in sub-Saharan Africa and registration systems do not record detailed mortality causes (Kahn, Tollman et al. 2006), making it difficult to determine the contribution of co-morbidities to increased mortality in patients aged 50 years and above. In a verbal autopsy study in rural Kenya, HIV-associated conditions were the cause of death in 27% of people aged 50 years and older and the leading cause of death up to the age of 70 years (Negin, Wariero et al. 2010). Other than this study, studies defining cause of death exclusively in adults aged 50 years and above by HIV status both pre- and post-ART are scarce and robust data are needed. From fifty studies in low and middle-income countries (38 (76%) from sub-Saharan Africa, 5 (10%) from Asia, 2(4% from the Americas and 5 (10% multi-regional) reported in a systematic review and meta-analysis, only 14 (28%) reported cause-specific mortality. These studies included young adults aged 16 to 49 years, the most common causes of mortality were TB (5% to 44%), wasting (5% to 53%), advanced HIV (20% to 37%) and chronic diarrhea (10% to 25%) (Gupta, Nadkarni et al. 2011).

Despite a reported decline in HIV mortality in Africa by a study utilising verbal autopsy data within our population-based demographic surveillance system in rural KwaZulu-Natal (Herbst, Mafojane et al. 2011) and another utilising different data sources from across South Africa

(Mayosi, Flisher et al. 2009; Herbst, Mafojane et al. 2011), HIV still remains the major cause of death in both older and younger adults (Herbst, Cooke et al. 2009; Mayosi, Flisher et al. 2009; Negin, Wariero et al. 2010). These two studies did not investigate the likely variations in mortality causes between younger and older adults making it difficult to understand how age influences causes of mortality. Studies that quantify the effect of age on cause-specific mortality following ART initiation and associated risk factors will provide useful insight into the special needs to older adults receiving ART. Identification of risk factors may be useful to identify and target older adults at higher risk of mortality who may benefit from more intensive clinical monitoring and medical interventions. Such data are useful to inform interventions aimed at reducing co-morbidities and may lead to mortality reduction.

1.7.2 Association between co-morbidities and mortality on ART

Generally, co-morbidity patterns amongst persons of all ages with HIV are not well described (Goulet, Fultz et al. 2007), and even less so in Africa (Nguyen and Holodniy 2008; Negin and Cumming 2010; Greig, Carrillo et al. 2012; Negin, Barnighausen et al. 2012). Additionally, little is known about the contribution of co-morbidity to mortality on ART because data on causes of mortality are mostly incomplete in sub-Saharan Africa (Greig, Carrillo et al. 2012). Autopsies are rarely done and many deaths in rural areas go unreported (Herbst, Mafojane et al. 2011; Bradshaw, Dorrington et al. 2012). As such, the morbidity burden in older adults cannot be accurately inferred from mortality causes alone and the burden of morbidity and its impact on mortality remains under-estimated. Directly measuring morbidity is even more problematic due to limitations in diagnostics in resource-limited settings and the high costs of conducting longitudinal studies. Of data available from developed countries, studies comparing prevalence or incidence of single clinical events concur that there is high morbidity risk from cancers (Silverberg, Chao et al. 2009), diabetes mellitus (Butt, McGinnis et al. 2009),

myocardial infarction in HIV positive individuals compared to that in the general population (Lang, Mary-Krause et al. 2010). A limitation of these studies is that they have not examined the effect of multiple co-morbidities on HIV prognosis during ART. A recent large Swiss study with 8 444 participants, 2 233 (26%) aged 50 to 64 years and 450 (5%) aged 65 years and above, that estimated the prevalence of multiple co-morbidity of diabetes, cardio-vascular disease, osteoporosis and non-AIDS defining malignancies in a cohort of HIV positive adults aged 16 years and above, also did not assess the extent and consequences of multiple co-morbidity on ART outcomes but rather determined how much risk of multiple co-morbidity was due to poor immunologic and virological response. The study showed increased multiple co-morbidity in all adult patients with CD4 cell counts less than 200cells/μL and unsuppressed HIV load (Hasse, Ledergerber et al. 2011). Additionally the study reported higher multiple co-morbidities in older adults aged 50 years and above than those aged below 50 years. The authors acknowledged that a better comparison group for co-morbidities in older adults would have been HIV negative adults of a similar age (Hasse, Ledergerber et al. 2011).

Similar results were obtained from a study on 33 420 HIV positive and 66 840 HIV negative individuals from The Veterans Ageing Cohort Study (VACS) in the USA where levels of 11 co-morbid conditions were examined by HIV status and association with CD4 count and viral load (Goulet, Fultz et al. 2007). In the VACS, similar to the Swiss Study (Hasse, Ledergerber et al. 2011) although co-morbidity and multiple co-morbidity was higher in HIV positive older adults, the contribution of this co-morbidity to mortality was not explored and neither was the HIV positive group stratified by ART status. A small cross-sectional study in the USA including 122 HIV positive adults with a median age of 55 years reported multiple morbidity in older adults but again did not relate this morbidity to ART outcomes (Onen, Overton et al. 2010). These studies recommend further studies focusing on patterns of morbidity and multi-morbidity as HIV positive populations on ART survive for longer.

Of note is that the majority of morbidity studies quoted above are from Europe and America. Although it is possible that co-morbidity patterns in Africa may reflect what is observed in the USA and Europe, extrapolation of results should be cautiously done since morbidity is highly variable across socio-economic groups, gender, race and quality and availability of health care at national and local levels (Bailis, Segall et al. 2003; Bradshaw, Groenewald et al. 2003; Lorant, Deliege et al. 2003; Ahmed, Tomson et al. 2005; Lopez and Mathers 2006; Lopez, Mathers et al. 2006; Goulet, Fultz et al. 2007; Mayosi, Flisher et al. 2009). A study based in Abidjan, Cote d'Ivoire that compared HIV positive patients pre-and post-ART initiation in 608 patients with a median age of 31 years, reported a decline in all-cause morbidity with increased duration on ART. Additionally the authors note that morbidity on ART was affected by morbidity prior to initiating ART and recommended that when comparing HIV-morbidity and mortality rates, morbidity history should be taken into account (Seyler, Messou et al. 2007). However, the majority of studies looking at mortality on ART in older adults have not considered morbidity prior to ART initiation. This finding of pre-existing morbidity at the time of initiating ART influencing morbidity and mortality rates during antiretroviral therapy, in a cohort of younger adults with 75% of the cohort aged below 37 years raises important questions on outcomes in older adults who are likely to initiate ART with a large burden of pre-existing chronic conditions.

In South Africa there are limited data; in one national study which assessed the burden of a wide range of non-communicable diseases in the context of HIV and ART across urban and rural settings (Mayosi, Flisher et al. 2009) there was no clear distinction between older and younger age groups and it was unclear how morbidity was associated with ART and with ART outcomes. Rather, the study describes at a population level the burden of non-communicable diseases in the context of communicable diseases such as HIV and TB. Even in the absence of

HIV, in older adults the burden of TB coupled with non-communicable diseases of ageing is likely high given that increasing age is a well-recognised risk factor for TB (Narasimhan, Wood et al. 2013). Clearly there is need for more studies identifying and quantifying the morbidity causes and burden in adults aged 50 years and above in sub-Saharan Africa and its association with HIV and ART to not only inform which conditions to screen for, but also inform on health services integration, which is especially important in resource-poor settings where health systems are overstretched and prioritisation crucial in an effort to deliver essential health care. Determining the burden of chronic morbidity and associated factors in older adults at time of initiating therapy provides a basis for clinical management requirements for the general older adult population. Quantifying the contribution of cause specific co-morbidity to mortality following initiation of ART will underscore co-morbidities of importance which when successfully managed or prevented may result in reduced mortality both at individual and population level and improve quality of life in HIV positive older adults.

1.7.3 Other ART associated factors relevant to older adults

Multiple drug interactions and toxicities

The risk and severity of drug toxicities in older adults who may initiate ART on concurrent medication for other chronic conditions have been reported from Europe and the US (Grabar, Weiss et al. 2006; Gebo 2008; Nguyen and Holodniy 2008; Gebo 2009; Negin and Cumming 2010; Onen, Overton et al. 2010). The occurrence of pre-existing morbidities and decreased renal and liver function combined with effects of other chronic therapies raises concerns of potentially altered drug metabolism, drug-drug interactions and increased toxicities including diabetes, hepatotoxicity, renal insufficiency, dyslipidemia, neuropathy and lactic acidosis (Easterbrook and Meadway 2001; Justice, Landefeld et al. 2001; Gebo 2006; Grabar, Weiss et al. 2006; Kohli, Klein et al. 2006; Effros, Fletcher et al. 2008; Rhee and Greenblatt 2008).

Tuberculosis treatment regimens that contain Rifampicin are generally more effective than those that do not contain this drug. However, Rifampicin induces activity of the CYP3A4 enzyme, resulting in significant interactions with many of the anti-HIV drugs. These interactions mean that Rifampicin cannot be co-administered with any of the other approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors, due to alterations in levels of the drugs or side-effects such as liver toxicity and kidney failure. In older adults co-infected with TB, these drug-drug interactions may be profound. Nevirapine, the most widely used non-nucleoside reverse transcriptase in resource- limited countries when co-administered with Rifampicin in TB/HIV co-infected patients, significantly increases risk of hepatotoxicity (Boulle, Van Cutsem et al. 2008; NAM aidsmap 2013). A review of studies in older adults in developed countries show that combination ART drug toxicities affect virtually all organ systems (Christensen, Doblhammer et al. 2009), but few studies have studied safety and optimal dosage of ART specifically in older adults (Grabar, Weiss et al. 2006; Kohli, Klein et al. 2006).

Possible drug toxicities and complications from multiple co-morbidities in older adults highlight important questions relating to when to start treatment in older adults. The presence of both ART and other non-HIV medications for chronic conditions in older adults illustrates the need to closely monitor on an ongoing basis liver and renal function in older adults. The extent to which other co-morbidities and drugs interact with ART in sub-Saharan African populations and the impact on morbidity and mortality remains largely undocumented. It is possible that there is only limited interaction and that the benefits of ART in the presence of other drugs far outweighs the risks of side effects due to drug drug interactions. On the other hand there is concern about the introduction of ART coupled with other non-HIV medications in adults who may already have reduced liver and kidney function. Longitudinal studies in African settings monitoring morbidity and mortality trends in older adults who initiate ART with sub-optimal

kidney and liver function can help explain survival and morbidity of such older adult patients once they initiate ART.

The complexities discussed above highlight that the management of HIV positive older patients on ART may be more complicated than that of younger adults aged below 50 years. In sub-Saharan African treatment guidelines are tailored to cater for all adults aged 16 years and above without accounting for the special needs of older adults. Patient management is difficult in the absence of empirical data to guide clinicians on how to administer ART and monitor its effects in the older adults. Although guidelines may be available in resource rich countries, delivery of ART to HIV positive patients within the public sector in resource poor settings are guided by national and local HIV treatment guidelines. Available services for patient diagnosis and management within public sector HIV treatment programmes are in line with stipulated guidelines and this may limit clinicians' ability to conduct procedures that are outside the scope of existing guidelines.

1.7.4 Virological and immunological response to ART in older adults

Adherence to ART

Adherence to ART affects virological and immunological response to ART. A systematic review which utilised eleven electronic databases and all major conference abstract databases up till April 2006 to identify ART adherence studies of mixed populations in North America and sub-Saharan Africa (Dunbar-Jacob and Mortimer-Stephens 2001), included 31 studies from North America and 27 studies from sub-Saharan Africa (12 countries). The review reported ART adherence levels were higher in African countries with a pooled estimate of 77% adherence than in North America where the pooled estimate was 55% (at levels greater than 80%). Studies in this review included participants aged from 13 to 73 years and adherence levels

were not stratified by age making it difficult to determine adherence rates in older adults (Dunbar-Jacob and Mortimer-Stephens 2001). A limitation of this study is that fact that 71% of North American studies and 66% of the sub-Saharan African countries were based on self-reports of adherence. Closer to home using data from 4 674 adults aged 16 years and above initiating ART between August 2004 and March 2011 within our Hlabisa HIV treatment and care programme in rural KwaZulu-Natal, retention in care improved with each 10 year increase in age (Mutevedzi, Lessells et al. 2013). Despite our finding of better adherence in older adults, other authors have suggested that in older adults side effects of multiple drugs in those initiating ART with multiple co-morbidities may negatively affect adherence (Dunbar-Jacob and Mortimer-Stephens 2001; Tumbarello, Rabagliati et al. 2003; Silverberg, Leyden et al. 2007).

The association of age and immunological response to ART in older adults aged 50 years and above compared to younger adults have been well described by studies from Europe and North America and report poorer immunological response to ART in older adults than in those aged less than 50 years old (Grabar, Kousignian et al. 2004; Silverberg, Leyden et al. 2007; Greenbaum, Wilson et al. 2008; The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group 2008). Despite poor immunological response in older adults, these studies show better virological responses in older than in younger adults which have been attributed to possible better adherence to ART in older adults. Although the immunological and virological responses by age on ART have been widely explored, what remains unknown is how a blunted immune response, but with suppressed HIV, is associated with long-term mortality risk. None of the available studies have explored this association.

Immune restoration following initiation of ART can be divided into two phases: a redistribution of memory T lymphocytes in lymph nodes resulting in an initial rapid increase in CD4 cell counts, followed by a slower phase mainly involving accrual of naive T cells. Authors

have speculated that the increase in CD4 cell counts could be due to peripheral expansion of existing naive T cells and/or may be due to thymic production of new naive T cells, thus thymic involution in older adults, especially in those aged 65 years and above would attenuate the impact of ART-induced CD4 count reconstitution (Grabar, Weiss et al. 2006). The attenuation is likely to be more in the initial rapid phase, likely resulting in less ART efficacy in older than younger adults which may increase risk of early mortality in the older adult group during the initial phase of ART. Mortality difference by age is likely to change as HIV load is suppressed and CD4 cell counts in older adults gradually increase. Longitudinal studies examining the relationship between immunological and virological response in older adults compared to younger adults following ART initiation and how these changes affect mortality in those receiving ART will help to better understand the impact of age on response to ART and may begin to show whether older adults would benefit from earlier initiation of ART at higher CD4 cell counts than the current WHO recommended CD4 cell count threshold of 350 cells/μL (World Health Organization 2010).

1.8 Conclusion

The full benefits of provision of ART to all eligible individuals may only be realised if patients on ART also receive relevant prevention, diagnosis and treatment of the most important causes of severe morbidity that occurs on ART (Seyler, Messou et al. 2007; Bendavid, Ford et al. 2012; Negin, Barnighausen et al. 2012). Gaps in knowledge on morbidity and mortality patterns may perpetuate poor health provision for HIV positive older adults. Scientifically it is important to understand why and how chronic morbidities vary by HIV and age, to better understand the epidemiology of these conditions.

In conclusion, HIV in older adults has resulted in a burden of age-related chronic conditions in the presence of HIV-associated conditions. Interactions of these two in terms of treatment efficacy, side effects and ultimately morbidity and mortality in older age groups need to be investigated and understood as these outcomes place an additional burden on provision of efficient care in the both the private and public health sector especially in resource limited settings and should to be taken into account in health planning and health systems integration. HIV is a global threat (UNAIDS 2012), but aetiologies of patient outcomes are likely to be multifaceted and locally and regionally variable, demanding a tailored response(Easterbrook and Meadway 2001; Grabar, Weiss et al. 2006; Nguyen and Holodniy 2008). There is limited understanding of the relative contributions of age-associated differences in immunology, virology, access to treatment and susceptibility to co-morbid diseases and how these shape mortality patterns for older adults receiving ART in resource limited settings. Much of what we know from developed countries is likely not transferable to other settings with different patterns of the HIV epidemic, available ART therapies, risk factors for communicable and chronic conditions and mortality regimes.

Using data from an African population in rural Northern KwaZulu-Natal in South Africa, an area with high HIV prevalence and incidence and a large public sector HIV treatment and care programme, this PhD aims to contribute to knowledge in an area were data in sub-Saharan Africa are critically lacking, by addressing five objectives specifically targeted at understanding older adults' health in terms of cause-specific morbidity and mortality, accounting for HIV and ART status. Additionally this PhD will examine how bio-markers in older adults relate to older adults current health or future mortality. Finally cause-specific morbidity and mortality burden and risk factors in HIV positive older adults will be compared to that in younger adults aged

below 50 years so as to understand the complexities surrounding management of older adults receiving ART in older adults.

These findings will help identify health priorities for older adults in the context of high HIV and enhanced access to ART and will inform on whether older adults require intensive clinical management and follow up following commencement of ART, to optimise health benefits of ART. Early mortality causes in older adults will also underscore morbidities of importance that would require pro-active intensive screening, diagnosis, treatment and management. Data on associations between biomarkers and subsequent morbidity and mortality risk are useful in informing clinicians on high risk groups that may require close clinical monitoring to improve disease prognosis on ART. Quantifying the contribution of pre-existing co-morbidity and multiple co-morbidities, at time of initiating ART, on early mortality on ART will determine morbidities of public health importance that can be targeted to reduce mortality. Results from this PhD may inform on how health systems and services can be integrated for efficiency, accessibility and cost effectiveness to both the individual and for the government, to inform on resource allocation, demand forecasts and specific programme needs, especially in South Africa with the proposed implementation of the National Health Insurance (NHI) (National Department of Health 2011) from 2013 onwards.

2 METHODS

2.1 Aims and Objectives

The overall aim of this PhD is to quantify burden of chronic morbidity in older adults aged 50 years and above and investigate associations between chronic morbidity and HIV and ART status in a rural South African population characterised by high HIV prevalence and incidence with access to a large decentralised public sector HIV treatment and care programme (Barnighausen, Tanser et al. 2008; Tanser, Hosegood et al. 2008; Cooke, Tanser et al. 2010; Houlihan, Bland et al. 2010; Tanser, Barnighausen et al. 2013). Further, this PhD establishes associations of health biomarkers including pro-inflammatory cytokines with obesity, chronic morbidity and HIV and ART status. Since HIV positive older adults potentially face a dual burden of disease owing to chronic morbidities of ageing coupled with HIV-related morbidity, which may be exacerbated by ART, this study has a focus on HIV positive older adults and details morbidity in older HIV positive adults at the time of initiating ART. Finally this thesis quantifies the incidence of serious morbidity after initiation of ART in older adults, in comparison to that of younger adults aged 16 to 49 years old, and examines outcomes of ART including mortality, virological suppression and CD4 count reconstitution in older compared to younger adults.

The specific objectives are as follows:

I)

a. To quantify the morbidity burden in older adults and investigate associations between morbidity and HIV and ART status

Publication resulting from methods chapter: Mutevedzi, P. C., A. J. Rodger, et al. (under review). "Chronic morbidity in adults aged 50 years or older in rural South Africa: Validation of self-report." J Clin Epidemiol.

b. To establish associations of inflammatory cytokine levels of Interleukin 1 and 6 (IL1 and IL6), high sensitivity C-reactive protein (hsCRP) and Tumor Necrosis Factor- alpha (TNFα) with HIV, ART, obesity and morbidity

II) To describe and quantify the cause-specific morbidity burden in HIV positive older adults, at the time of initiating antiretroviral therapy, in comparison with younger adults

III)

a. To determine causes and rates of serious morbidity (resulting in hospitalization) following initiation of ART and the effect of age on such morbidity and to
b. To establish whether abnormal biomarker [haemoglobin (Hb), Alanine aminotransferase (ALT) and creatinine] levels at ART initiation are associated with subsequent increased morbidity risk.

IV) To quantify the effect of age on response to ART in terms of total mortality, viral suppression and CD4 count reconstitution after initiation of ART.

V)

a. To establish causes of early mortality (occurring in the first 3 months of initiating ART) following initiation of ART in older adults compared to younger adults,
b. To quantify the effect of baseline morbidity on early mortality risk

c. To ascertain whether levels of Hb, ALT and Glomerular Filtration Rates (GFR) at time of initiating ART are risk factors for early mortality.

2.2 Study setting and methodology

For purposes of this PhD, the PhD candidate conducted two studies namely the ART Clinical Cohort and the Wellbeing of Older People Study (WOPS) both nested within Hlabisa HIV Treatment and Care Programme and the Africa Centre Demographic Surveillance. In addition this PhD used data from three already established and existing prospective cohorts: one at a population level within a defined geographical area (Africa Centre Demographic Surveillance). The second cohort was of HIV positive patients receiving HIV treatment and care within a defined health sub-district (Hlabisa HIV Treatment and Care Programme) whilst the third one involved all patients hospitalised at the only district hospital within the Hlabisa health sub-district (Hlabisa Hospital Information System). The study specific methodologies are as follows:

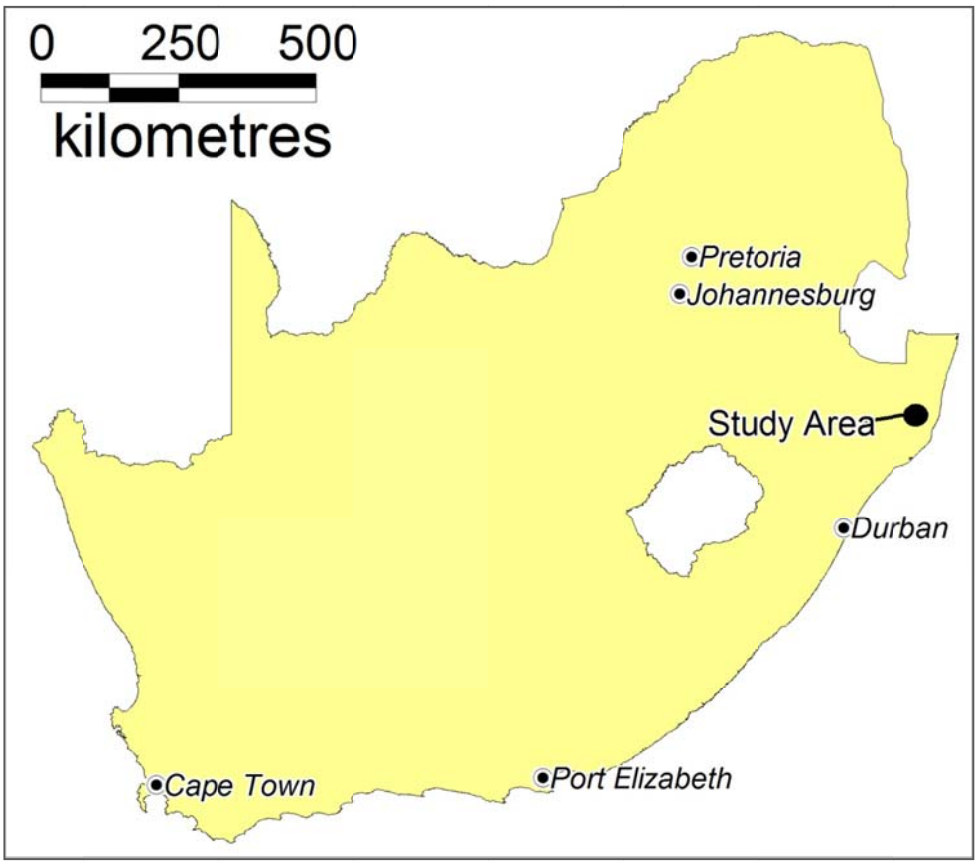
2.2.1 Africa Centre for Health and Population Studies (Africa Centre)

Setting

The Wellcome Trust-funded Africa Centre for Health and Population Studies hosts an ongoing Demographic Surveillance set up in 2000 to describe the demographic, social and health impact of the HIV epidemic in a population going through health changes and to monitor the impact of intervention strategies on the epidemic (Tanser, Hosegood et al. 2008). The Africa Centre Demographic Surveillance forms a longitudinal prospective population-based surveillance within a defined geographic area in rural northern KwaZulu-Natal (Figure 2.1). The Africa Centre surveillance area is predominantly rural, albeit with a township and an informal peri-urban settlement comprising less than 10% of the surveillance population. The area is

characterised by large variations in population densities ranging from 20 people/km^2 in the deep rural areas to 3 000 people/km^2 in an area near a major tarred road. Since the Africa Centre Demographic Surveillance inception, demographic, social and health data have been collected which in each surveillance round covers approximately 90 000 individuals in 11,000 households in an area of about 438 km^2 (Tanser, Hosegood et al. 2008); in each round approximately two-thirds of household members are resident within the surveillance area. In 2010 (the first full year for this PhD), there were 61 431 household members resident in approximately 11 500 households within the surveillance area; 13% of whom were aged 50 years and above (Nyirenda, Chatterji et al. 2012). According to the national health barometer, the surveillance area is located in one of the most economically-deprived districts in South Africa, with limited provision of health care services and essential housing amenities (Day, Barron et al. 2011; Tanser, Barnighausen et al. 2013). The principal sources of income are waged employment and state pensions (Tanser, Hosegood et al. 2008). Individuals enter the household surveillance cohort at birth or via migration into the area and exit through death. To account for complex patterns of cyclical migration, individuals are observed regardless of whether they reside permanently within the surveillance area, provided that they are members of a household under surveillance (Bor, Herbst et al. 2013).

Figure 2.1 Location of the study area within South Africa



Nested within the Africa Centre household surveillance system is an individual HIV surveillance (Barnighausen, Tanser et al. 2008; Tanser, Barnighausen et al. 2013), started in 2003. Eligibility to participate in the HIV surveillance was limited to women aged 15 to 49 years and men aged 15-54 years until the end of 2006. In 2007 this eligibility criteria was changed to include all individuals resident within the surveillance aged 15 years and above. The HIV surveillance cohort is an open cohort and any individual who migrates into the area immediately becomes eligible (www.africacentre.ac.za ; Welz, Hosegood et al. 2007; Barnighausen, Tanser et al. 2008; Tanser, Barnighausen et al. 2013).

Methodology

At time of this study, data within the household surveillance were collected 6-monthly on residency status of household members, births, marriages, deaths and migrations. Socio-economic status and employment were collected on an annual basis. Within the annual HIV surveillance, health information including dried blood spots for HIV testing is also collected (Table 2.1). Data collection is carried out by comprehensively trained fieldworkers with refresher trainings twice each year. The Africa Centre fieldwork training manual is available on the Africa Centre website (www.africacentre.ac.za). Data collection tools include validated questionnaires that are translated from English to the local language (Zulu). All Africa Centre surveillance questionnaires and 1% datasets are freely available on the same Africa Centre website.

Data obtained from Africa Centre Demographic Surveillance for completion of this work

All data from the Africa Centre demographic surveillance are entered in a dedicated surveillance database (ACDIS) which was used to identify eligible participants for the WOPS study. Additionally HIV status for all WOPS participants was obtained through linkage of ACDIS and Hlabisa HIV Treatment and Care Programme data.

Table 2.1: Data collected on participants in the Africa Centre surveillance

Data collected	Specific variables
Household demographics and socio-economic data	Owner and members of household, geographic location of household, household expenditure, asset ownership
Individual socio-economic data	Age, sex, household membership, education, employment, receipt of government grants
HIV status	VCT history, dried blood spot for HIV testing, VCT offered
Sexual behaviour	Pregnancy history, contraceptive use, sexual activity
Health	Health care utilisation, diagnosis of hypertension, diabetes, tuberculosis (TB)
Vital status	Births, deaths, migrations

2.2.2 Hlabisa HIV Treatment and Care Programme

Setting

The Africa Centre partners with the local Department of Health in a large ongoing public health HIV Treatment and Care programme, which is entirely devolved to 17 primary health care (PHC) clinics that are spread across the Hlabisa health sub-district as shown by the red crosses in Figure 2.2 and one district hospital located about 50kms from the Africa Centre (labelled in red font). While the surveillance area (yellow portion in Figure 2.2) covers only a proportion of the Hlabisa health sub-district, Hlabisa HIV Treatment and Care Programme covers the whole health sub-district of Hlabisa, an area with an estimated population of 228 000 people (Cooke, Tanser et al. 2010). Six of the primary health clinics are within the Africa Centre Demographic

Surveillance Area and about 40% of the total programme cohort resides within the Demographic Surveillance Area (Houlihan, Bland et al. 2010; Mutevedzi, Lessells et al. 2010; Tanser, Barnighausen et al. 2013). The programme is in line with other public sector HIV treatment programmes in South Africa and aims to deliver quality health care to HIV positive patients through delivery of ART and routine monitoring pre- and post-ART initiation (National Department of Health 2003). It supports the integration of HIV services into PHC, aiming to link treatment and care with prevention services.

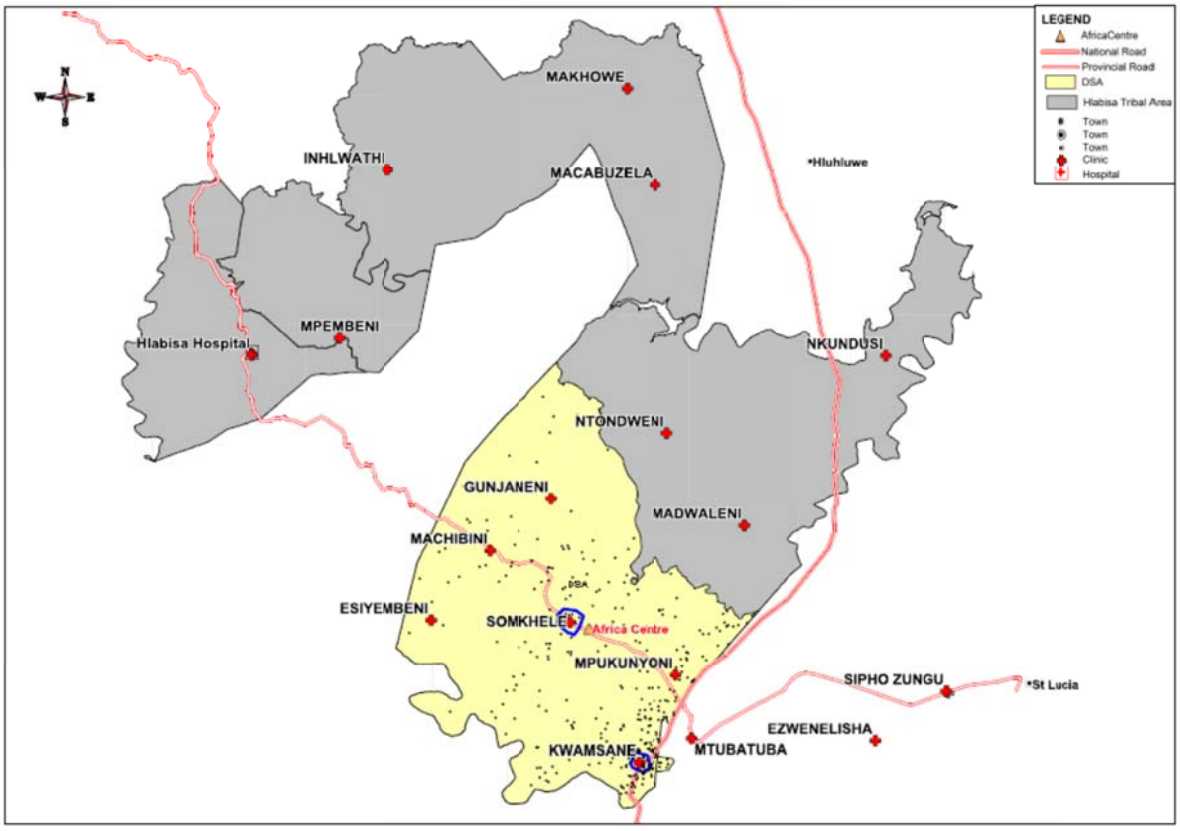
ART delivery within this programme has been rapidly scaled-up and by July 2011 an estimated 37% of all HIV positive adults in the area had been successfully started on ART which in number terms came to more than 20 000 patients by mid-2012 (Houlihan, Bland et al. 2010; Tanser, Barnighausen et al. 2013). Since inception of the programme in August 2004 ART initiation was a physician task; in mid-2012 this task was shifted to ART-trained nurses (National Department of Health 2010; National Department of Health 2013). Patient monitoring was always nurse- and counsellor-led and occurs at two and four weeks and at four-weekly intervals thereafter until a patient has a suppressed viral load and is clinically well when follow-up is every other month for life (Houlihan, Bland et al. 2010; Mutevedzi, Lessells et al. 2010; Tanser, Barnighausen et al. 2013). The programme adheres to South African National ART guidelines on HIV diagnosis, ART eligibility, screening, treatment regimens and follow-up which have evolved as follows:

- Between 2004 and April 2010: eligibility for adults based on CD4+ cell count <200 cells/µL (National Department of Health 2004)
- April 2010: CD4 threshold raised to 350 cells/µL for pregnant women and individuals with active TB infection (National Department of Health 2010)

- August 2011: eligibility criteria raised to 350 cells/µL for all HIV positive individuals (SANAC. 2011; National Department of Health 2013)
- In addition, irrespective of CD4 count threshold, ART was also recommended throughout for all individuals with WHO clinical stage 4 and since April 2010, for all individuals with drug-resistant TB.

Within the Hlabisa HIV Treatment and Care Programme, standard ART regimens are given according to the South African National HIV treatment guidelines and consist of two nucleoside reverse transcriptase (NRTI) and one non-nucleoside reverse transcriptase (NNRTI). Up till 2010, the NRTIs consisted of Stavudine, Abacavir, Lamivudine and Zidovudine whilst the NNRTIs consisted of Efavirenz and Nevirapine. In 2010, Stavudine was substituted with Tenofovir. As of April 2013, patients are initiated on a fixed dose combination pill consisting of Tenofovir, Emtricitabine and Efavirenz , unless contraindicated (National Department of Health 2004; National Department of Health 2010; National Department of Health 2013).HIV drug resistance testing is not routinely done under the South African National HIV treatment guidelines.

Figure 2.2: Geographic distribution of primary health clinics and hospital within Hlabisa health sub-district



Methodology

Hlabisa HIV Treatment and Care Programme currently has just over 58 000 HIV positive patients accessing HIV care and/or treatment; 27 000 (46.6%) of these have been initiated on ART and 20 600 (74.1%) are currently receiving ART in this programme. Approximately 14 500 (25%) are under pre-ART monitoring (www.africacentre.ac.za). Clinical data at ART initiation and during drug collection visits are captured onto clinic charts and subsequently entered into an electronic database (Houlihan, Bland et al. 2010). Laboratory test results are imported weekly directly from the South African National Health Laboratory Services database to the same electronic database. All clinical and laboratory data are entered in a database developed

and maintained at the Africa Centre (ARTemis database). Data collected are detailed in Table 2.2 below and all variables given in this table were used within this work.

Table 2.2: Data collected on patients initiated on ART in the Hlabisa HIV Treatment and Care Programme

Data collected	Specific variables
Basic detail	Age, sex, address, ID number, contact details, treatment clinic
Personal circumstances	Grants received, employment, education, number of dependants
TB record	TB history, TB treatment at initiation, new episodes of TB
ART record	WHO clinical staging, previous ART/PMTCT, ART regimen at initiation, changes in ART regimen during treatment
Laboratory data	Baseline and 6-monthly CD4 cell counts and HIV viral load, baseline haematology and biochemistry
Clinic visits	Monthly attendance and bi-monthly for patients stable on therapy
Vital status	Deaths, transfers out of the programme, loss to follow-up

2.2.3 ART Clinical Cohort

Setting

Since March 2010, the PhD candidate has been part of a team that established an ongoing prospective cohort nested within the larger Hlabisa HIV Treatment and Care Programme. The aims of the cohort were to:

- Determine the incidence of serious morbidity and mortality after the initiation of ART in a rural decentralised HIV treatment programme with a specific focus on TB, adverse drug events, frequency and causes of hospitalisation and changes in social circumstances

- Provide additional detailed information related to the HIV treatment and care programme such as factors associated with mortality, treatment failure and loss to follow up

- Based on study outcomes; make recommendations to improve clinical care of patients in this cohort and to inform other programme in similar settings

Findings are fed back to the Hlabisa HIV Treatment and Care Programme to improve clinical care of patients and are expected to provide valuable information for the provision of health to HIV positive individuals and their clinical management thereof.

The ART Clinical Cohort recruits all ART-naïve patients initiating antiretroviral treatment at two clinics, one of which is the largest clinic in the programme in terms of both resources and patient numbers and the other is a middle-sized clinic (marked with blue circles in Figure 2.2.). Cumulatively since ART Programme inception in August 2004, the largest clinic had 3 670 patients and the middle-sized clinic had 1 280 patients actively on ART as at 30 January 2013.

Patients who provide informed consent were eligible to participate; patients who are deemed too ill by the nurse to undertake the consent process were ineligible to participate. Ethics considerations and informed consent details are documented under Section 2.3. From the start of the Clinical Cohort (March 2010), 1545 patients had initiated ART at the two clinics. Approximately 1% (n=21) of patients initiating therapy declined participation in the Clinical Cohort due to work commitments and lack of time for study procedures. Of the 23 patients who were too ill to enrol, 17 patients went on to initiate ART at the district hospital and enrolled into the Clinical Cohort as down referrals from the hospital to the clinic, within a month of in-hospital ART initiation. By the end 2012, 1 518 patients aged 16 years and above had been enrolled into the Cohort (Figure 2.3). For the purposes of this PhD, patients initiating therapy before 1 August 2012 were included with follow-up until early 2013.

Sample size and Power considerations

STATA sample size and power calculation commands inclusive of sampsi and mvsampsi and stpower (http://www.stata.com), were used to estimate statistical power based on the Clinical Cohort sample size of 1409 patients. Sample sizes and proportions of the 1409 patients were as follows;

- 193 (13.7%) aged 50 years and above,
- baseline morbidity prevalence of 50.16% and 74.61% for young and older adults respectively,
- 59 deaths in the first 3 months of ART; 53 in young adults and 6 in older adults
- and an overall all cause very early mortality rate of 17.45 per 100 person years; 18.18 per 100 person years in young adults and 12.88% person years in older adults.

The calculations are presented below:

Test Ho: p1 = p2, where

p1 is the baseline morbidity prevalence in young adults

p2 is the baseline morbidity prevalence in older adults

From Clinical Cohort findings,

alpha = 0.0500 (two-sided)

p1 = 0.5016

p2 = 0.7461

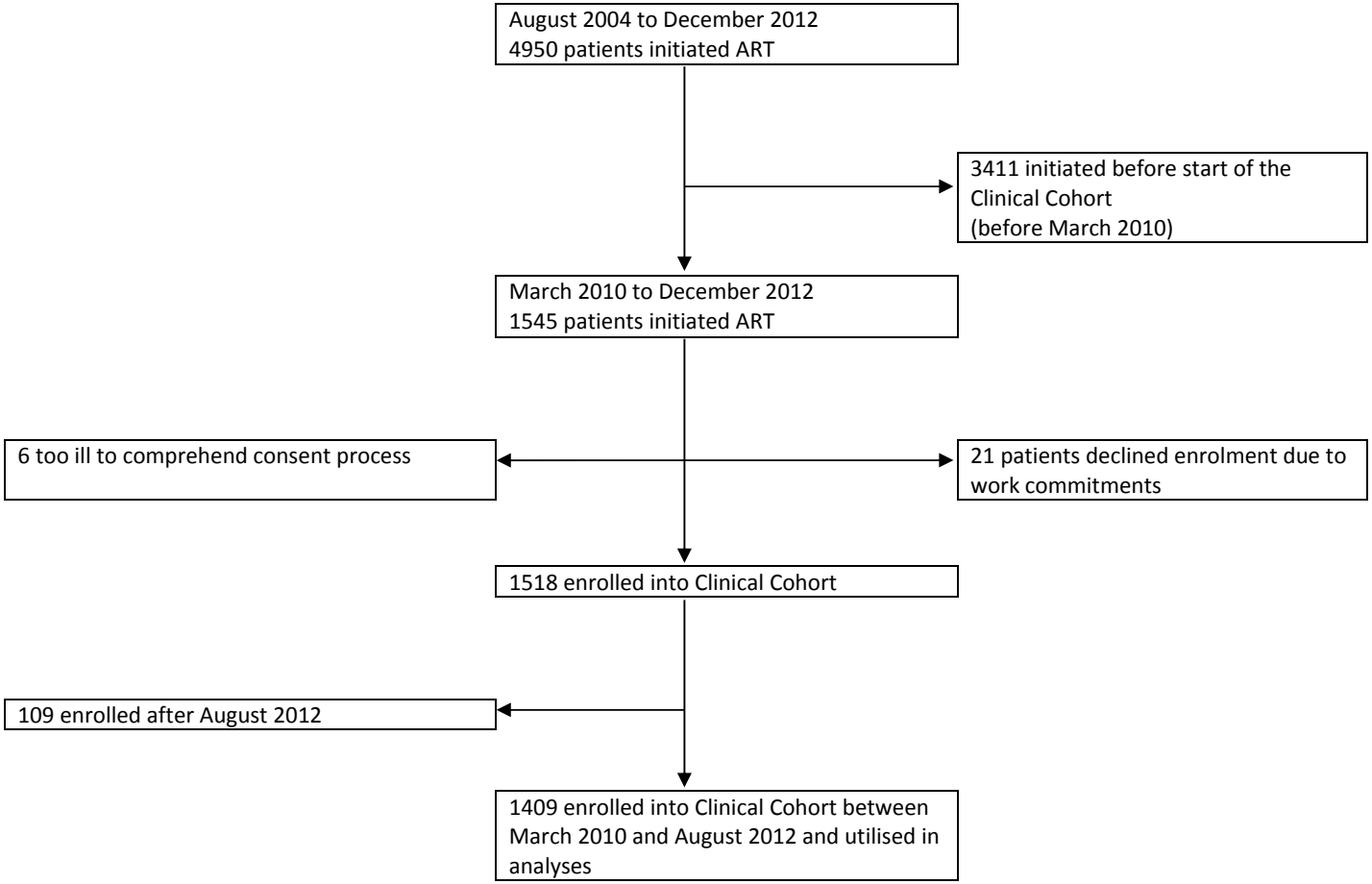
sample size for young adults = 1216

sample size for young adults = 193

Estimated power = >0.99

For differences in mortality causes in young compared to older adults, given the sample sizes, mortality numbers and rates listed above, the Clinical Cohort had only 38.66% power to detect statistically significant differences in mortality causes. For this reason these data were mainly used for descriptive purposes to document causes of mortality in young and older adults, an area where data are largely lacking.

Figure 2.3: Flow of patients enrolled and included in the Clinical Cohort analyses



Methodology

Two structured questionnaires are used to conduct interviews, one at baseline (Appendix 2.1) and the other during follow-up visits (Appendix 2.2) to systematically record and collate information on morbidity, ART-related factors including side effects, hospitalizations and in addition some limited data on demographics and social circumstances. These data are collected at ART initiation, two weeks post-ART initiation and then monthly thereafter during routine treatment collection visits (Table 2.3). If the patient has an unscheduled visit for any reason, that opportunity is taken to capture any morbidity events. Cause of death is ascertained through review of patient clinical files and through linkage with the local district hospital. ART outcomes of mortality, loss to follow-up and transfers out of the Hlabisa HIV Treatment and Care Programme are captured on a structured outcomes form (Appendix 2.3). Patients are defined as loss to follow-up if they miss three consecutive monthly clinic visits after which they are tracked first by telephone followed by a home visit if necessary. Transfers out comprise of patients who formally request to be transferred to other HIV treatment and care programmes outside the Hlabisa health sub-district.

Height is measured only at baseline, weight and blood pressure measurements are taken at baseline and at every monthly follow-up visit thereafter. Clinical examinations are conducted at each visit by trained nurses using standard national clinical guidelines (National Department of Health 2010; National Department of Health 2013). Morbidity data are collected at every visit and coded in line with WHO ICD10 coding guidelines. Similarly mortality data are ICD10 coded by cause of death. All data are collected by professional nurses with a nursing diploma or degree and registered with the South African Nursing Council. All cause of death is ascertained by an independent medical doctor through record review of available clinic and hospital records. Individuals enrolled into the cohort are already part of the Hlabisa HIV

Treatment and Care Programme attending clinics at monthly intervals and all ART Clinical Cohort interviews are conducted during patients' routine clinic visits hence there is no additional burden of clinic visits in those enrolled in the cohort.

Laboratory data (including CD4 cell counts and HIV plasma viral loads) are collected within the main Hlabisa HIV Treatment and Care Programme at ART initiation and then at 6-monthly intervals Standard haematology (haemoglobin, platelets and white blood cells) and biochemistry (creatinine, albumin, total bilirubin and alaninine transaminase) tests are done at ART initiation or when clinically indicated, and are then merged to the ART Clinical Cohort data. These tests are performed at a laboratory under the South African National Health Laboratory Services (NHLS), located at Hlabisa hospital. Test results are directly transferred, weekly, from the NHLS database into the Hlabisa HIV treatment and care ARTemis database. The ARTemis database was developed and is maintained by the Africa Centre, where it is also housed. No additional bio-specimens to those already collected in the main treatment programme are collected from ART Clinical Cohort participants. ARTemis data are then consolidated with ART Clinical Cohort data.

Patients who miss more than three consecutive monthly clinic visits are contacted by telephone followed by a home visit if necessary. Patients formally transferring out of the programme to access HIV care elsewhere are documented as such.

Table 2.3: Data collected on patients enrolled in the ART Clinical Cohort

Data collected	Specific variables
At ART initiation (Baseline visit)	
Basic detail	Age, sex, ID number, contact details, treatment clinic
Non-HIV related chronic morbidity	Chronic/ long term medications for HIV-unrelated morbidities
TB record	Previous TB episodes, pulmonary or extra-pulmonary, TB drug regimen and whether or not the treatment was completed. Current TB episode, pulmonary or extra-pulmonary, TB drug regimen
Current morbidity and WHO disease staging	Symptoms and diagnosis
Hospitalisation	Place of admission, date of admission, date of discharge, primary and secondary diagnosis
ART drug regimen	
Personal circumstances	Grants received, employment, education
During monthly follow-up visits	
Changes in drug regimen	Type of drug changes – single drug substitutions versus complete regimen change, reasons for drug change
Morbidity since the last clinic visit	Where care was sought and diagnosis given
Hospitalisation since the last visit	Place of admission, date of admission, date of discharge, primary and secondary diagnosis
Current morbidity	Symptoms and diagnosis
Mortality	Date of death and cause of death

2.2.4 Wellbeing of Older People Study

Setting

Also as part of this PhD, the PhD candidate conducted a cross-sectional study on 422 older individuals aged 50 years and above conducted between March 2010 and August 2010. This SAGE Well-being of Older People Study (WOPS) employed survey instruments adapted from the World Health Organization (WHO) Study on global AGEing and adult health (SAGE) (He, Muenchrath et al. 2012) and was carried out within the Africa Centre surveillance area on a multi-stage random sample of individuals aged 50 years and above between March-August 2010 (Nyirenda, Chatterji et al. 2012). The main aim of SAGE-WOPS was to investigate the direct and indirect effects of HIV on the health of older adults (Nyirenda, Chatterji et al. 2012). For sample selection, all older adults resident within the Africa Centre surveillance area falling into three categories namely; HIV positive on ART, HIV positive ART-naïve, and HIV-affected through co-residing with an HIV positive offspring (either alive or died within the last two years), were identified through existing Africa Centre population databases.

All contacted individuals, except four, agreed to participate in the study, giving a sample size of 422 individuals in total. Geographical typology of the randomly selected individuals as illustrated by the black dots within the yellow surveillance area in Figure 2.2 showed a distribution similar to the general distribution of the older adult population within the surveillance area (high population density along the main tarred roads and sparse density as you move further away from the main roads), suggesting the representativeness of the sample.

Sample size and Power considerations

Using the sampsi and the mvsampsi/mvsamp1i command in STATA (http://www.stata.com), the sample size of 422 would have no power limitations to detect differences in morbidity prevalence between HIV positive and HIV negative individuals. Stratifying HIV positives into on ART and ART-naive, the sample size would have 78% power to detect differences in morbidity prevalence between the HIV-negative and the HIV-positive population on ART but power would be limited to detect differences between HIV-negative and HIV- positive ART-naïve people:

	Current morbidity between those HIV negatives and HIV positives on ART	Current morbidity between those HIV negatives and HIV positive ART naive
alpha	0.05	0.05
P1	0.565	0.565
P2	0.389	0.505
Sample size n1	161	161
Sample size n2	108	109
Power	77.63%	13.27%

Where

p1 is the morbidity prevalence in HIV negative participants

p2 is the morbidity prevalence in ART stratified HIV positive participants

n1 is the sample size of HIV negative individuals

n2 is the sample size of ART stratified HIV positive individuals.

Using the mvsampsi command in STATA, a sample size of 422 would have 99% power to detect an effect size of 0.01 (i.e. morbidity prevalence difference of 0.1) in a multivariable model with 15 independent variables categories and lambda set at 0.9.

Methodology

The WOPS groups were defined as

- **Group 1**: Older persons who are HIV positive and on ART for more than a year
- **Group 2**: Older persons who are HIV positive waiting to initiate ART or who are on ART for less than 3 months
- **Group 3**: (i) an older person with an adult child who is HIV positive and is either waiting to receive ART or is receiving ART and (ii) or older persons who have lost an adult child due to HIV or other causes. Although in the main WOPS study group three was split into two groups, for this PhD the group is combined because the PhD researcher was interested in the HIV status of the 422 WOPS individuals. All older adults in group three who were also HIV positive were moved to either group one or two based on their ART status.

HIV positive older adults on ART for 3-12 months were excluded from the study to clearly distinguish ART experiences between HIV naive and HIV experienced older adults.

Eligibility

An eligible older adult, for all groups, at time of study had to:

- Fulfil the criteria for the group in which they are to be recruited as detailed above
- Be aged 50 years or older
- Be resident within the Africa Centre Demographic Surveillance Area

An eligible adult child for group 3, at time of study had to be:

- Under the age of 50 years but above 18 years
- HIV positive or deceased (from HIV related or non-HIV related cause)
- Resident within the Africa Centre Demographic Surveillance Area

Sampling frame

For all groups the primary entry point for selection for the study was the Hlabisa HIV Treatment and Care Programme clinics or the Africa Centre Demographic Surveillance and Hlabisa HIV Treatment and Care Programme databases. All older adults resident within the Africa Centre surveillance area who fulfilled the aforementioned circumstances were identified from the Africa Centre Demographic Surveillance database and the Hlabisa HIV Treatment and Care Programme database as this was a simpler and efficient route of identifying eligible participants for the study. There were 241, 117 and 804 eligible participants for groups 1, 2 and 3 respectively. From all eligible individuals, random samples of 150 participants each for the first two groups and 300 from the third group were generated. This selection included an additional 50% of potential households to accommodate refusals. All eligible individuals found at a visited household were invited to participate in the study. Enrolment in each group was done until the required numbers (100 for each of the first two groups, 200 in the third group) consenting to the questionnaire, blood draw and anthropometric measurements were reached. Persons too sick to participate (n=3); non-contacts (n=2) and those who refused participation (n=4) were excluded; in these cases replacements were selected from the respective eligible population. For the third group HIV status of older adults remained unknown and was only obtained from the Africa Centre HIV surveillance after WOPS study completion.

Recruitment

Eligible participants were visited in their households to seek consent for participation. Study procedures were administered if they provided informed consent. In households where we found more than one older person present, both of them enrolled. For households that had two surviving parents, preference was given to the male parent as the aim was to recruit at least 30% males and it was more common for households to have a female resident parent rather than a male one. In instances where there was more than 1 offspring in group 3, the index case was used for household identification.

Data Collection

All fieldwork was conducted by two professionally trained nurses, registered under the South African Nursing Council. Demographic and health information was collected through face-to-face interviews. Participants were asked if they had been ever diagnosed with a named chronic morbidity, the timing of the diagnosis (last 6 months; >6-12months; >12months) and whether or not, for that named condition, they had received treatment in the last 2 weeks and/or 12 months. In addition, weight and height were measured by trained nurses, who also collected blood specimens for laboratory measured biomarkers of lipid profile and cytokine levels (IL1, IL6, high sensitivity CRP (hsCRP) and TNFα).

A structured 16 page questionnaire and inclusive of health measurements (Appendix 2.4) were built upon existing validated instruments from the multi-country Study on Global Aging (SAGE) at the WHO (He, Muenchrath et al. 2012; WHO 2013; WHO 2013), ensuring alignment of the instruments with international standards. The questionnaire was translated into the local

isiZulu language and all interviews were conducted in isiZulu; a pilot study including 15 older adults was conducted to further validate the data collection instruments. A structured interview was followed for all participants with participants only answering the relevant questions as indicated by the skip patterns in the questionnaires. The interview time ranged from 45 minutes to 1hr 45minutes. The questionnaire was split into sections for ease of reading, understanding, completion and data capturing, namely:

- **Section 100:** Respondent and household characteristics
- **Section 200:** Health State Description
- **Section 300:** Chronic conditions and health service coverage
- **Section 400:** Health care utilization & risk factors and behaviours
- **Section 450:** Risk factors and preventive health behaviours
- **Section 500:** Health measurements
    - Anthropometrics, Performance Tests and Biomarkers
- **Section 600:** Care giving
    - Physical and nursing care to resident adults and children
    - Care-giving to adults (18 and above) who have died in the last 24 months
- **Section 700:** Care receiving
- **Section 800:** HIV experiences

Bio-measures – specimens and anthropometry

Health measurements of blood pressure, height and weight were taken before the questionnaire was administered. Venous blood samples were collected into EDTA and a serum storage (SST) blood tubes and used to determine biomarkers of pro-inflammatory cytokine levels (IL1, IL6, high sensitivity CRP (hsCRP) and TNFα) and lipogram profile (high density

protein, triglycerides and cholesterol). The specimens were stored appropriately and then shipped daily to a laboratory in Amanzimtoti about 300km from the study site for processing. The laboratory that processed specimens is accredited by the South African National Accreditation System (SANAS) and conforms to required good clinical and good laboratory practices (GCP and GLP respectively). Specific details on laboratory test assays used and lower detection limits for each assay are detailed in Chapter 3, Section 3.2.2.4.

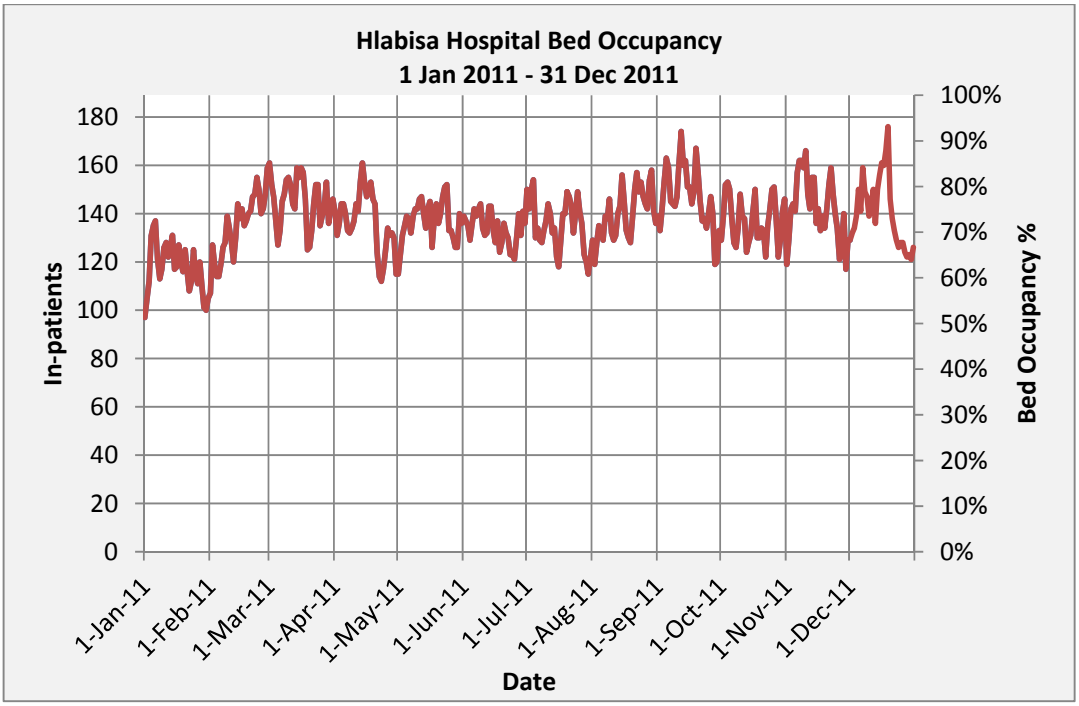
2.2.5 Hlabisa Hospital information system

To obtain hospitalisation data on patients accessing care within Hlabisa HIV Treatment and Care Programme, patient data are linked between Hlabisa HIV Treatment and Care Programme and an information system that was developed by the Africa Centre in mid-2010, at the only local district hospital (Hlabisa Hospital Information System). The aim of Hlabisa Hospital Information System is to obtain information pertaining to hospitalisation at the Hlabisa district hospital to help understand morbidity, mortality and health service utilisation within the Africa Centre study population and the Hlabisa Treatment and Care Programme. The Hlabisa Hospital Information System contains data on patient registration (name, date of birth, identity number, sex, address and nearest clinic), hospital admission (admission date, admitting doctor, admission ward, admission diagnosis, HIV and ART status), ward information (ward admission date, ward discharge date, responsible doctor, HIV and CD4 test results and special investigations and procedures) and hospital discharge (discharge date, discharge diagnosis, outcome, HIV status and ARV medication).

During 2011 the system recorded 5800 patients, 1029 (17.7%) of whom were aged 50 years and above giving an average bed occupancy of 73% (Figure 2.4). Admission diagnosis mainly

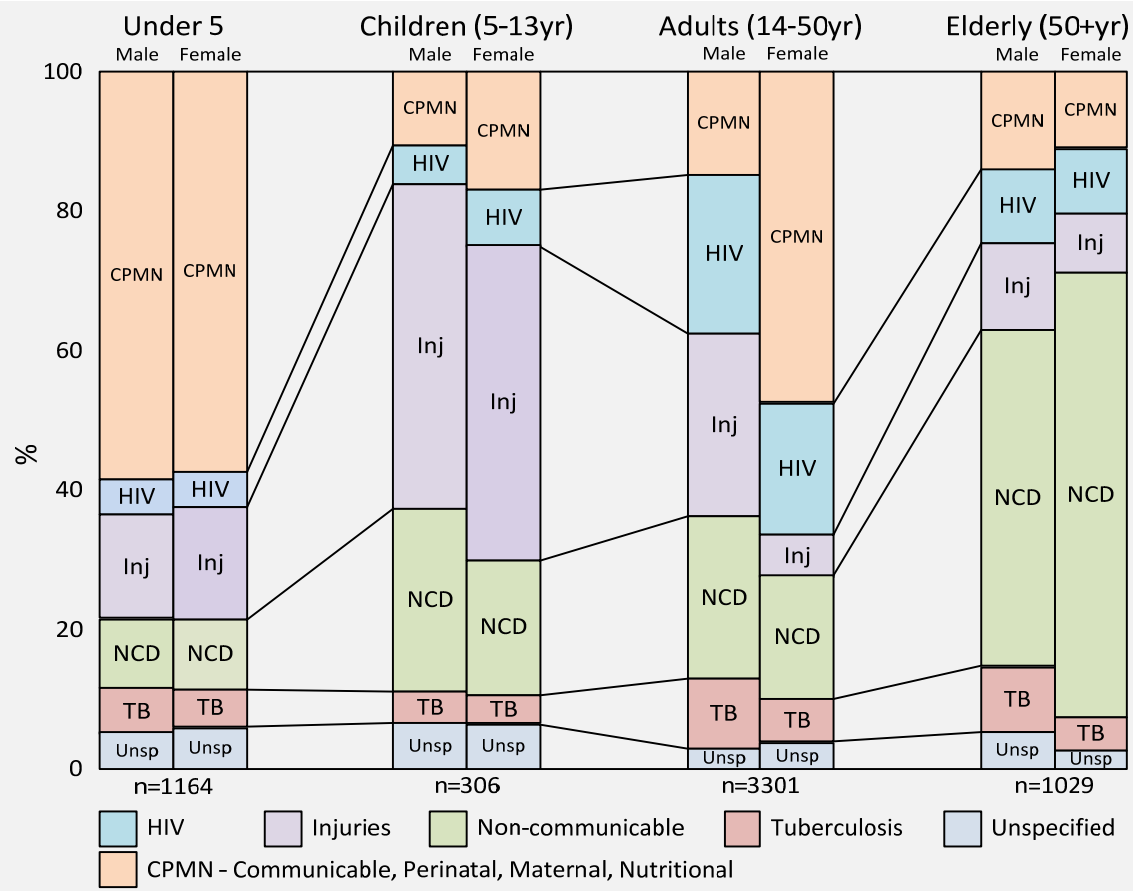
comprised of communicable, perinatal, maternal and nutritional conditions in young adults whilst for older adults majority of hospitalisation was due to non-communicable diseases (Figure 2.5). In the same year (2011) the overall hospital mortality rate was 10.9 per 100 discharges, which was higher in those aged 50 years (19.9 per 100 discharges) than in those aged 13-49 years (10.8 per 100 discharges) (Herbst and Bland 2011).

Figure 2.4: Hlabisa district hospital daily occupancy rate estimated through use of the hospital's information system (Herbst and Bland 2011)



Average Bed Occupancy =73%

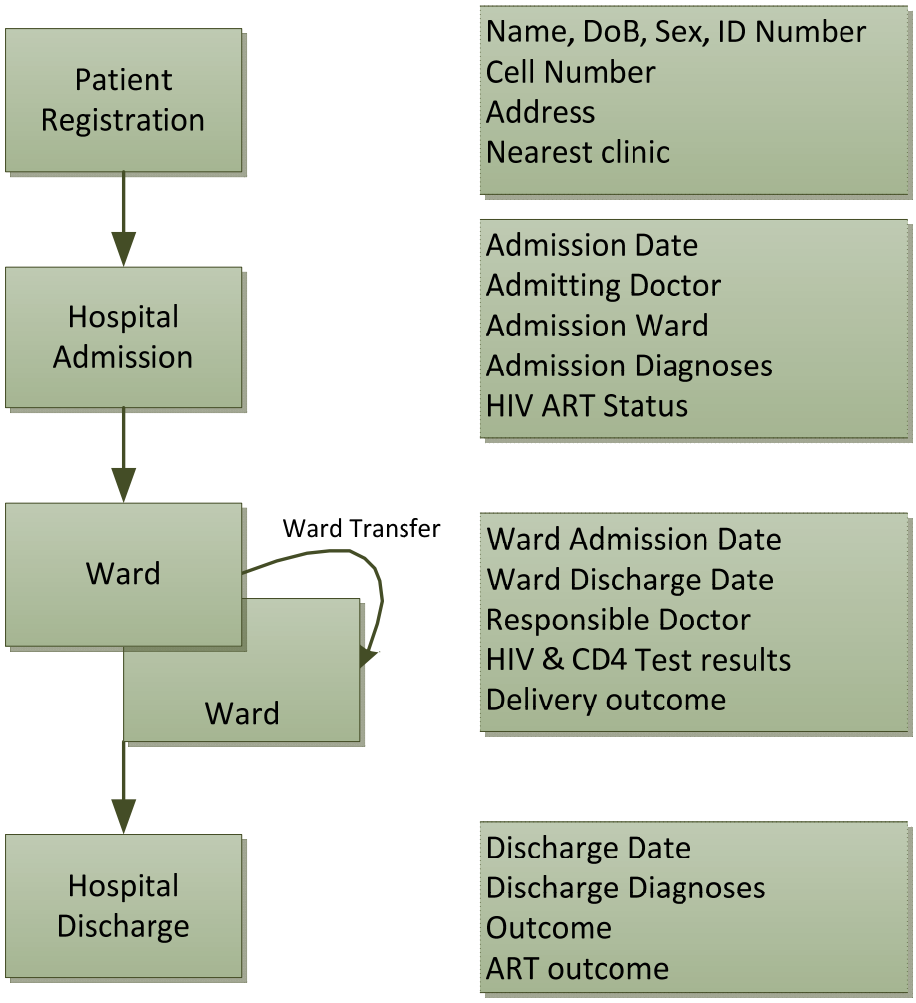
Figure 2.5: Age stratified distribution of primary discharge diagnosis for 5800 patients hospitalised in Hlabisa district hospital during 2011 (Herbst and Bland 2011).



Methodology

Patient data are collected by a professional nurse, with ICD-10 coding training, who reviews the recorded admission and discharge diagnoses, interacts with clinicians if needed, and assigns an ICD-10 code to each diagnosis. From the paper based system, admissions and discharge diagnoses are captured electronically on a daily basis by a dedicated clerk and the nurse professional nurse. Data are transferred to the Africa Centre on a weekly basis and clinically reviewed by two clinicians including a check of ICD10 codes allocation for the various diagnoses. The data collection process is illustrated below (Figure 2.6).

Figure 2.6: Data collection flow within the Hlabisa Hospital Information System



Key:
Cell number – cell phone number

HIV and CD4 test results recorded only when available or when patient is offered and consents to HIV testing

For purposes of this PhD, HIV status of patients from the Hlabisa Hospital Information System who were included in analysis was already known through the Hlabisa HIV Treatment and Care Programme.

The details of which data source and variables were employed for each specific objective are summarised in Table 2.4 below.

Table 2.4: Data sources and the sample sizes utilised for each PhD objective

Objective	Data sources	Study time-line	PhD sample size	Results Chapter	Publication appendix
To quantify the morbidity burden in older adults and investigate associations between morbidity and HIV and ART status and further establish associations of IL1, IL6, hsCRP, TNFα with HIV, ART, obesity and morbidity	• Wellbeing of Older People Study • Africa Centre household demographic surveillance • Africa Centre individual HIV surveillance	Mar 2010 - Aug 2010 Jan 2000 - ongoing Jan 2003 - ongoing	422	3	3.1
To describe and quantify the cause-specific morbidity burden in HIV positive older adults, at the time of initiating antiretroviral therapy, in comparison with young adults	• ART Clinical Cohort • Hlabisa HIV Treatment and Care Programme	Mar 2010 - ongoing Aug 2004 - ongoing	1 409	4	
To determine cause-specific incidence rates of serious morbidity following ART initiation and the effect of age on such morbidity and to establish whether abnormal biomarker [hemoglobin (Hb), Alanine aminotransferase (ALT) and creatinine] levels at ART initiation increase morbidity risk.	• Hlabisa HIV Treatment and Care Programme • Hlabisa Hospital Information System	Aug 2004 - ongoing May 2010 - ongoing	8 598	5	
To quantify the effect of age on response to ART in terms of total mortality, viral suppression and CD4 count reconstitution after initiation of ART	• Hlabisa HIV Treatment and Care Programme	Aug 2004 - ongoing	8 846	6	6.1
To establish causes of early mortality following ART initiation in older adults compared to young adults; quantify the contribution of baseline morbidity on early mortality risk and ascertain whether levels of Hb, ALT and Glomerular Filtration Rates (GFR) at ART initiation are risk factors for early mortality.	• Hlabisa HIV Treatment and Care Programme • ART Clinical Cohort • Hlabisa Hospital Information System	Aug 2004 – ongoing Mar 2010 – ongoing May 2010 - ongoing	1 409	7	

2.3 Ethics considerations

Both the ART Clinical Cohort and WOPS studies were approved and approvals continue to be renewed annually by the University of KwaZulu-Natal Bio-Ethics Review Committee (BREC), approval numbers BF110/09 and BF136/09 respectively. Africa Centre surveillance was approved in 2000 by this same committee, with annual re-certification (Ref Nos. E009/00 and BF233/09). For all studies and surveys, approval was first obtained from the local community through the Centre's Community Advisory Board and then from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. Individual written informed consent was obtained from all WOPS, ART Clinical Cohort and Africa Centre HIV surveillance participants. For the household surveillance verbal informed consent is obtained from the household informant who is preferably and in most cases the head of the household.

2.3.1 Ethical Conduct of the Study

All studies were conducted in an ethically sound manner in accordance with Good Clinical Practice (GCP) under the Helsinki declaration.

Informed Consent of Study Participants

All potential participants were provided with information on details of the study aims and methodologies, what participation entailed, how privacy and confidentiality would be maintained and time requirements for their participation. A detailed description of potential benefits and risks for each study was also provided. Informed consent was administered in the local Zulu language and at a level that the participant could comprehend. This process of informed consent was ensured by the ethics committee through approval of the consent documents to be found in

Appendix 2.5a and 2.5b for the ART Clinical Cohort and Appendix 2.6a and 2.6b for the Wellbeing of Older People Study.

Confidentiality of Study Participants

All data collected were anonymised through use of study numbers that could only be linked to an individual by study staff. Individual identifiers were excluded from all analysis datasets and participants were only identified through the study numbers. All interviews were conducted in areas that ensure privacy i.e. in a closed room at the clinics or an area identified by the participant in the participants' households. For WOPS groups 3 details of the HIV positive adult child were not divulged to any household member although the participant themselves at times openly volunteered the information.

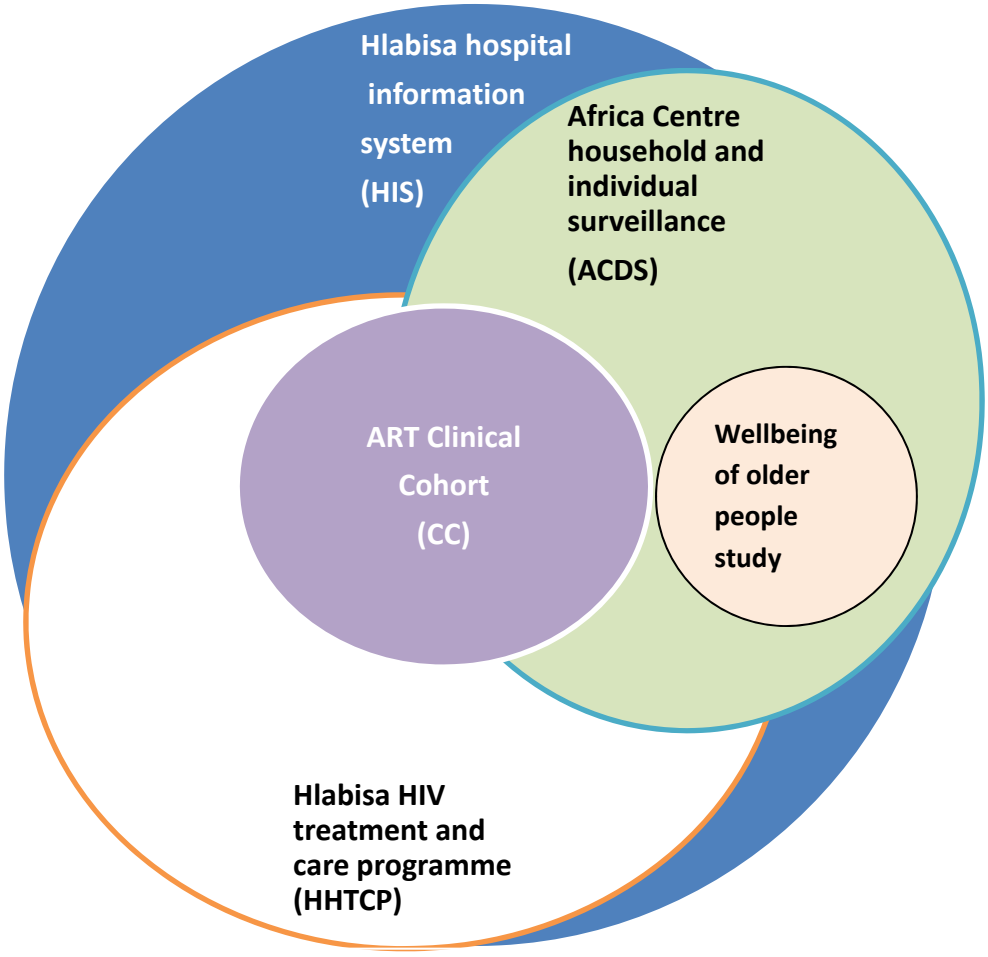
2.4 Linkage of data sources

All databases for the above mentioned surveys and studies are housed and maintained at the Africa Centre. The diagram below (Figure 2.6) demonstrates how these data sources are related and the extent of overlap between them.

About 40% of patients within Hlabisa HIV Treatment and Care Programme reside within the Africa Centre surveillance area and their information can be linked between the two databases. All patients within Hlabisa HIV Treatment and Care Programme accessing care at Hlabisa district hospital have been linked between the two databases and so have all Africa Centre surveillance participants accessing care at Hlabisa hospital. Since the ART Clinical Cohort is a subset of Hlabisa

HIV Treatment and Care Programme, all patients are linked to both the Africa Centre Demographic Surveillance and Hlabisa Hospital Information System via Hlabisa HIV Treatment and Care Programme. All WOPS participants reside within the surveillance area and can be linked to Hlabisa Hospital Information System and Hlabisa HIV Treatment and Care Programme via Africa Centre Demographic Surveillance.

Figure 2.7: Relationship of data sources utilised in this research



For all studies, in addition to study-specific participant anonymised identity numbers, the unique South African national identity number is collected for each participant. This is a number that is given by the South African Home Affairs Department to each South African citizen or permanent resident at birth or at naturalisation. This number in combination with other personal identifiers inclusive of but not limited to given names and surnames, nicknames, sex, age, date of birth, place of residency and mother's/father's name are used to link individuals across the different databases, after which the individual is identified as 'matched' between the different databases. The linkage system was set up by a specialised and dedicated database scientist with certain constraints that allows matching on an individual across different studies only after a number of set requirements are met. For example if between two data sources (Hlabisa HIV Treatment and Care Programme and Africa Centre Demographic Surveillance) ID numbers match but the name and surname are different the individual will not be identified as being the same individual participating in the Africa Centre surveillance and also accessing HIV care within the Hlabisa HIV Treatment and Care Programme. In such cases of inconsistencies (less than 5%) the case will be investigated by checking the full data spectrum of the two individuals across all four data sources until it is clear whether or not it is one or two individuals with that particular ID number. Additionally the source hard copy document for the ID number for both studies in question i.e. the patient clinic file for Hlabisa HIV Treatment and Care Programme and the Africa Centre surveillance questionnaire for Africa Centre Demographic Surveillance will be checked to ensure that there were no data entry errors at time of capturing the data into the system. All individuals successfully matched are captured as such under the "matched" variable as are those who were attempted but not matched. The reasons for failure to match are also documented under the comments section. Those that are not matched for example patients within Hlabisa HIV Treatment and Care Programme who are not part of Africa Centre surveillance system (members of

households located outside the Africa Centre surveillance area), are captured as 'not matched' under the "matched" variable within the respective parent database.

Analyses utilising linked Hlabisa HIV Treatment and Care Programme and Africa Centre Demographic Surveillance data have been successfully used before to answer different research questions pertaining but not limited to determining ART coverage within the surveillance area and socio-demographic determinants of retention in care prior to initiating ART (Cooke, Tanser et al. 2010; Houlihan, Bland et al. 2010; Mutevedzi, Lessells et al. 2010; Lessells, Mutevedzi et al. 2011; Tanser, Barnighausen et al. 2013).

2.5 Data management

For all studies, Microsoft SQL Server (MS SQL) databases are held and maintained by the Africa Centre according to already established and set data management guidelines (www.africacentre.ac.za). Participant confidentiality is maintained at all times during the strict document chain of custody. All data forms are captured by Africa Centre data capturing staff and securely filed. All databases contain appropriate quality control constraints to minimise data capturing errors and to maintain sensibility of data. For example all databases will not allow a weight of 300kgs or an age of 100 years unless verified by the interviewer to be correct then an exception is made to allow the database to save such data. Inconsistencies are also picked by the database system and flagged to the data capturer for rectifying before saving the data. Any forms found to have data queries at time of capturing are sent back to the interviewer for verification and rectification and the chain of custody is documented at each stage.

All data forms are stored in locked optiplan filing cabinets and databases were password protected and only available to core study staff.

2.6 Statistical analysis

For all objectives, baseline characteristics were described using medians and IQRs for continuous variables and proportions with 95% Confidence intervals for categorical variables. Median and proportions test inclusive of Kwallis2 test for equality of medians and χ^2 for equality of proportions were utilised. Specialised univariable and multivariable analyses for each study objective were dependent on the type of outcome and explanatory variables and are comprehensively detailed in results chapters 3 to 7 immediately prior to presenting the results for each objective. In summary, for cross sectional data ordinary, ordered and generalised ordered logistic regression techniques were used for assessment of associations. For longitudinal data analyses Kaplan-Meir time to event analysis and normal and time-stratified Cox regression techniques were employed to estimate event rates and establish rich factors respectively. For all analyses underlying assumptions were tested for and if found to be violated then the analysis method was substituted for a more fitting method. Comprehensive details of this are also documented in chapters 3 to 7 under analytical methods sub-headings and immediately before presenting the results. Unless otherwise stated all probability values were two-tailed with a threshold significance set at 0.05. All adjusted odds ratios and relative risks are presented with their respective 95% confidence intervals for all adjusted multivariable analysis.

2.6.1 Definition of variables

All variables are defined in Chapters 3 to 7 under the specific objectives for which they pertain to, however those common to more than one objective are given below;

Morbidity was defined according to the data source from which it was derived

In WOPS

- *Self-reported chronic morbidity*: Based on responses to questions, "Have you been diagnosed with ...?" including heart disease (angina), arthritis, stroke, hypertension, chronic lung disease, asthma, cancer and diabetes.

- *Self-reported current chronic morbidity*: Based on responses to questions, "Have you been taking medication for ... in the last two weeks?" including heart disease (angina), arthritis, stroke, hypertension, chronic lung disease, asthma, cancer and diabetes.

Self-reported chronic morbidity has been validated against the WHO composite health score and against self-rated general health on day of WOPS interview. Results are presented in Chapter 3, Table 3.1 (page 119).

In the Clinical Cohort

Baseline morbidity was defined in three categories:

- Serious HIV-associated morbidity (WHO stage 3 or 4 HIV disease) - took into account all serious morbidity at time of initiating ART, classified according to WHO HIV disease staging classification as stage 3 or 4. Conditions classified as serious morbidity included:
  - >10% body weight loss, renal failure, anaemia, bacterial meningitis, oral candidiasis, chronic diarrhoea, cryptococcal meningitis, oesophageal candida, herpes, HIV

associated arthritis, HIV wasting, HIV associated malignancies, toxoplasmosis and PCP TB disease;

- Pre-existing chronic morbidity - was defined as chronic morbidities for which the patient was already receiving therapy at time of initiating ART i.e. chronic conditions diagnosed prior to initiating ART.

In the main Hlabisa HIV Treatment and Care Programme

- Serious morbidity defined as morbidity resulting in hospitalisation

Mortality was initially analysed as all-cause mortality which included all mortality that occurred after initiation of ART following which mortality was stratified into very early mortality referring to mortality occurring within the first 3 months of initiating ART and early mortality defined as mortality occurring between 3 months to 12 months after starting therapy.

In Africa Centre Demographic Surveillance

Wealth score - Household socio-economic status was determined using a wealth index, constructed using a set of assets a household owns, with ownership of each asset represented by a binary indicator. The wealth index of each household was derived in STATA (StataCorp, 2012) by principal component analysis (Colley and Lohnes 1971). Each household was assigned a wealth score, the distribution of these scores has mean zero and a standard deviation of one, which were then divided into quintiles. The first (lowest) quintile represents households with the least number of assets (poorest), whereas the fifth (highest) quintile represents households with the most

number of assets (very comfortable). Wealth quintiles were used as a proxy for socio-economic status.

Laboratory markers common to more than one objective included:

Within Hlabisa HIV Treatment and Care Programme, at time of initiating ART (baseline), haemoglobin levels, and liver and kidney function - based on laboratory measured levels of Alanine Aminotranferase (ALT), Creatinine and Glomerular Filtration Rates (National Department of Health 2003; National Department of Health 2004; National Department of Health 2010; National Department of Health 2013) For this reason the same markers were assessed in terms of their association with baseline morbidity. The threshold for determining abnormal levels was in line with previous published studies based on Hlabisa HIV Treatment and Care Programme data (Mutevedzi, Lessells et al. 2010; Mutevedzi, Lessells et al. 2011):

Laboratory marker	**Abnormal levels**	**Units**
Haemoglobin (Hb)	<8	g/dL
Alanine Aminotranferase (ALT)	>60 (2xupper limit of normal)	IU/ml
Glomerular filtration rate (GFR)	<60	ml/min/1.73m2
Creatinine	>120	µmol/L

Body Mass Index (indicator of obesity) was categorized as per WHO recommendations: underweight <18.5; normal 18.5-<25; overweight (pre-obese) 25-<30; obese 30-<40; morbidly obese 40+ (WHO 2012)

Hypertension was defined as systolic blood pressure >140 and/or diastolic pressure >90 mmHg (National Institutes on Health 1997)

2.7 Role of the researcher

2.7.1 Hlabisa HIV Treatment and Care Programme

Since August 2008, I have been one of two epidemiologists in charge of the Hlabisa HIV Treatment and Care Programme. My focus has been data collection and analysis relating to adult patients aged 16 years and above whilst the other epidemiologist focuses on children aged below 16 years. I have been responsible for the scientific component of the programme including patient data handling, analysis and publication. As co-investigator on use of routinely collected patient data within Hlabisa HIV Treatment and Care Programme for research purposes, my specific roles include compiling annual ethics recertification applications to the local ethics review board and regular monitoring of regulatory documents and liaison with the ethics board for ethics updates. Additionally I serve as a member of the Hlabisa HIV Treatment and Care Programme database management team, which regularly reviews data quality and assesses whether database structure and performance are optimal to meet required needs. I am also involved in the Africa Centre scientific committee comprising of multidisciplinary professionals, that monthly reviews the progress of the programme

I routinely monitor data collected during clinic visits from patients in the programme and provide regular feedback to the monitoring and evaluation team on data quality and possible areas of improvement. I also regularly provide the local Department of Health with research findings on mortality and morbidity based on the ART patient's data as well as updates on clinical and/or logistical issues arising.

I am part of a small team of researchers responsible for generation of scientific research questions relevant to HIV positive patients receiving care that can potentially be answered using Hlabisa HIV Treatment and Care Programme. I am responsible for extensive and in-depth data handling/cleaning and statistical data analysis using STATA to answer the research questions pertaining to outcome of patients receiving therapy within our context.

Data analysis of all Hlabisa HIV Treatment and Care Programme data presented in this analyses as well as preparation of various manuscripts, utilising Hlabisa HIV Treatment and Care Programme data, for publication in peer reviewed journals, at conferences and other scientific forums was my responsibility. My publications relevant to the background [Chapter 1 (Appendix 1.1)], methodology [Chapter 2 (Appendix 2.7)] and results [Chapter 3 (Appendix 3.1)] and [Chapter 6 (Appendix 6.1)] of this PhD are appended.

2.7.2 ART Clinical Cohort

As a co-investigator for the ART Clinical Cohort I was involved in obtaining ethics clearance from the local ethics review board and from the local department of health authorities and have been responsible for ensuring that the ethics recertification is renewed annually. Additionally I was responsible for the conception of the ART Clinical Cohort study in collaboration with senior researchers within the Africa Centre and collaborators based in London, United Kingdom. I

undertook a systematic review of the literature to develop a cohort data collection structure that would adequately address clinical issues relating to adult patients receiving ART. I also performed a comprehensive literature review to inform on serious conditions reportedly associated with HIV infection and ART, following which I then designed the questionnaires that are used for data collection within ART Clinical Cohort. During the questionnaire design phase, I worked closely with my supervisors and other clinicians at the Centre in an effort to ensure the tools were comprehensive, valid and reliable. I was also responsible for drafting informed consent documents including the participant information sheet and the consent form.

Once questionnaire design was completed, I was involved in setting up the study at the relevant clinics in close liaison with the clinic manager at each clinic as well as establishing document and data flow systems. I was responsible for recruiting nurses and data clerks for the study and training them in preparation for the study. As part of the training and to check for validity and reliability of the questionnaires and procedures, I managed a 3-week pilot phase of the study which included pilot interviews with patients at one of the clinics, checking the completed questionnaires and discussing them with the ART Clinical Cohort team members.

For database development, I worked closely with the Africa Centre senior database scientist who set up the database and ensured that the data-entry screens of the database not only captured all data collected within the questionnaires but were also user friendly.

Since recruitment of the first patient in March 2010, I have been responsible for management of the study including staff, data handling including data cleaning, consistency and completeness checks and generating query reports for quality control. I also conduct quality control checks on data collection and flow within the clinics. I update questionnaires as and when the need arises. In addition to manually checking each of the first 3 000 questionnaires in the study, as a way of

quality control, I also performed data capturing into the electronic database for the first 2 500 study questionnaires and manage the database on a daily basis.

I remain responsible for analysing the data and preparing manuscripts for publication

2.7.3 WOPS

I developed the protocol for the WOPS in close collaboration with co-investigators on this study; I also developed the financial budget for the study. I was responsible for submitting the protocol to the World Health Organisation (WHO) for funding approval and all liaisons with the relevant people at SAGE WHO including providing study updates on fieldwork, data management, finance and scientific output. I was involved with development of the study questionnaire and was directly responsible for development of all laboratory forms and manuals.

I was responsible for seeking ethics approval from both our local research ethics committee as well as from the local department of health authorities. Furthermore I was involved in obtaining approval from our local community advisory board whose function includes approving Africa Centre research studies as community appropriate before higher ethics approvals are sought.

Additionally it was my role to identify a suitable laboratory for processing study specimens, enter into a contract agreement with the lab as well as set up specimen flow processes and procedures to ensure specimen integrity is maintained from the time of specimen collection in the field to when the specimens are processes in the laboratory and results received at Africa Centre.

I was responsible for staff recruitment including developing job adverts, interviewing and selecting suitable candidates. In the setting up of the study, my tasks included getting all study documentation printed and purchasing all relevant field and laboratory equipment and ensuring

vehicle allocation for fieldwork and specimen transportation. Together with my co-investigator we delivered 2 weeks of comprehensive training to study nurses and my training sections included all health components, health and anthropometric measurements, specimen collection and management including all laboratory components of the study. For validity and reliability checks on all study tools, systems and logistics I oversaw a pilot study including 15 participants. All procedures including informed consent and questionnaire administration and anthropometric measurements were done except for collection of blood specimens. I was involved in checking the questionnaires to ensure accuracy, consistency and completion and feedback of pilot findings including delivering an additional training as informed by the pilot. Additionally I validated WOPS participants morbidity self-reports against those reported within Africa Centre Demographic Surveillance as a way of checking reliability of self-reports by older adults and this work is under peer review by the Journal of Clinical Epidemiology for publication (Appendix 2.7).

During the course of the study I was solely responsible for the management of the laboratory component of the study, quality control and quality assurance of laboratory documents, specimens and the results thereof including daily checks on laboratory results and referring any patients with urgent results to a doctor within the Africa Centre. Additionally I participated in checking all questionnaires completed to ensure research quality and standards as stipulated by Good Clinical Practice (GCP) are met.

Finally I was involved data handling and management for this study including data cleaning and analyses and publication of manuscripts in peer reviewed journal. Some of this work is detailed in Chapters 1; 2 and 4 of this work and is appended (Appendix 1.1, Appendix 3.1 and Appendix 6.1). I conducted all data cleaning and analyses for all analyses pertaining to this PhD.

2.7.4 Hlabisa Hospital Information System

I was not directly involved in the data collection process within Hlabisa Hospital Information System; however I was involved in reviewing the data for consistency and validity for all Hlabisa Hospital Information System patients including verification checks for all individuals linked to Hlabisa HIV Treatment and Care Programme and Africa Centre Demographic Surveillance. I was responsible for generating data specifications for analyses as well as data cleaning and analyses for all the results presented in this thesis.

3 Results: Morbidity burden in older adults - associations with HIV/ART status, cytokine levels (IL1, IL6, hsCRP and TNFα) and obesity

3.1 Introduction

Older people aged 50 years and above are at risk of chronic morbidity such as heart diseases, arthritis, diabetes and hypertension, associated with physiological changes with age(Grabar, Weiss et al. 2006; Gebo 2008; Christensen, Doblhammer et al. 2009; Mayosi, Flisher et al. 2009), but these conditions remain often undiagnosed particular in resource poor settings. The disease burden may be exacerbated by both HIV and antiretroviral therapy (ART)(Andrew and David 2000; Gebo 2006; Grabar, Weiss et al. 2006; Nguyen and Holodniy 2008; Rhee and Greenblatt 2008), suggesting worse health outcomes in HIV-infected than in HIV-uninfected adults. However, the association between HIV status and chronic morbidity, and possible benefit of regular access to general medical services within HIV treatment and care, remains little explored.

Certain biomarkers including cytokines are useful in predicting health outcomes (Goldman 2007) and are increasingly employed in monitoring health, identifying individuals at risk and evaluating therapeutic interventions (Penninx, Kritchevsky et al. 2004; Population Reference Bureau 2008). It is unknown whether such biomarkers reliably indicate morbidity risk in HIV positive older adults who may have elevated cytokine levels associated with both HIV and ageing (Chapter One, Section 1.6). Cytokines are released in response to trauma, infection or inflammation and sustained

Publication resulting from this chapter: Mutevedzi, P. C., A. J. Rodger, et al. (In press). "Decreased chronic morbidity but elevated HIV associated cytokine levels in HIV infected older adults receiving HIV treatment." PLoS ONE.

elevation has been linked to age-associated conditions and increased mortality (Harris, Ferrucci et al. 1999; Bruunsgaard, Pedersen et al. 2001; Targher, Zenari et al. 2001; Penninx, Kritchevsky et al. 2004).

Similar to HIV and ageing, obesity is linked to chronic health problems such as cardiovascular diseases, diabetes and arthritis (Cheymol 2000; Bastard, Maachi et al. 2006; Population Reference Bureau 2008) and is characterised by chronic low-grade inflammation (Trayhurn 2005; Bastard, Maachi et al. 2006). Understanding the associations of obesity, morbidity and HIV and ART status with cytokine levels is important, as cytokines are increasingly used to measure health risks and explain individual health status, in both HIV-infected and HIV–uninfected older adults.

In this chapter, data from a cross-sectional cohort of older people are used to address objective one by quantifying levels of chronic morbidity in HIV negative and HIV positive ART naïve and ART experienced older adults. Additionally this chapter ascertains associations of obesity and cytokine levels of IL1, IL6, hsCRP and TNFα with morbidity and HIV status in the presence or absence or ART.

3.2 Methods

Objectives

a. To quantify the morbidity burden in older adults and investigate associations between morbidity and HIV and ART status

b. To establish associations of inflammatory cytokine levels of Interleukin 1 and 6 (IL1 and IL6), high sensitivity C-reactive protein (hsCRP) and Tumor Necrosis Factor- alpha (TNFα) with HIV, ART, obesity and morbidity

3.2.1 Data sources

Africa Centre Demographic Surveillance

As detailed in Chapter 2, Section 2.2.1, demographic and health data have been collected by the Africa Centre on approximately 90,000 resident and non-resident members of 11 000 households in a geographically defined rural South African area in KwaZulu-Natal. Nested within this household surveillance is an annual HIV surveillance. On 1 January 2010, there were 61 431 resident household members of whom about 7,900 (13%) were aged 50 years or above (Welz, Hosegood et al. 2007; Barnighausen, Tanser et al. 2008; Tanser, Hosegood et al. 2008; Nyirenda, Chatterji et al. 2012).

Wellbeing of Older People Study

The SAGE Well-being of Older People Study employed survey instruments adapted from the World Health Organization (WHO) Study on global AGEing and adult health (SAGE) (He, Muenchrath et al. 2012; WHO 2013) and was carried out between March-August 2010 within the Africa Centre surveillance area on a multi-stage random sample of resident individuals aged 50+years (Nyirenda, Chatterji et al. 2012). Data collected, using a questionnaire to be found in Appendix 2.4, included:

Socio-economic demographics	sex, age, education, employment
Self-reported chronic morbidity	ever diagnosed, when diagnosed, current therapy

Life-style factors	smoking, alcohol
Venous blood specimen	laboratory testing of lipid profiles, IL1, IL6, hsCRP, TNFα
Anthropometric measures	weight and height
Vital signs	blood pressure

Information regarding HIV status was obtained from the Africa Centre HIV surveillance (nested within the Africa Centre demographic surveillance) and HIV treatment data from the Hlabisa HIV Treatment and Care Programme (Houlihan, Bland et al. 2010); data from these two sources can be linked through use of the unique individual South African national identity number, name and sex (Mutevedzi, Lessells et al. 2010; Lessells, Mutevedzi et al. 2011; Nyirenda, Chatterji et al. 2012) (Chapter 2 Section 2.4). From the Hlabisa HIV treatment and care programme, we identified HIV positive people and duration of therapy for those on ART. For those unknown to Hlabisa HIV treatment and care programme, HIV status from the HIV surveillance prior- and post-Wellbeing of Older People Study were used to infer HIV status of participants at time of the Wellbeing of Older People Study using the algorithm below:

- HIV negative before and after Wellbeing of Older People Study = HIV negative;
- HIV positive before and after Wellbeing of Older People Study = HIV positive;
- HIV negative within a year prior to Wellbeing of Older People Study and unknown after Wellbeing of Older People Study = HIV negative*;*
- HIV unknown before and after Wellbeing of Older People Study = unknown

3.2.2 Definition of variables

From Wellbeing of Older People Study

Self-reported current chronic morbidity: Based on responses to questions, "Have you been taking treatment for …… in the last 2 weeks?:

- Options were heart disease (angina), arthritis, stroke, hypertension, chronic lung disease, asthma, diabetes and cancer.

This question was only asked from all participants reporting ever been diagnosed by a health care professional with any of the aforementioned conditions.

BMI (indicator of obesity): Calculated from the weight and height measurements ascertained in Wellbeing of Older People Study categorized as per WHO recommendations since there are no separate set recommendations for native African populations (WHO 2012);

- Underweight: <18.5;
- Normal: 18.5-<25;
- Overweight (pre-obese): 25-<30;
- Obese: 30-<40 and
- Morbidly obese: 40+

Cytokines**:** Higher levels of cytokines have been reported to be associated with chronic inflammation and morbidity with the most effect in those with levels in the highest strata (Hober, Haque et al. 1989; Harris, Ferrucci et al. 1999; Bruunsgaard, Pedersen et al. 2001; Bastard, Maachi et al. 2006). Previous studies in western based populations have chosen various cut-off points, for

example dividing the continuous distribution into tertiles or quartiles (Harris, Ferrucci et al. 1999; Penninx, Kritchevsky et al. 2004; Rodger, Fox et al. 2009), log-transforming continuous levels (Penninx, Kritchevsky et al. 2004), taking the median (Harris, Ferrucci et al. 1999) or the lower cytokine detection limit (Puts, Visser et al. 2005) as cut-off. For CRP, values >3µg/ml have been used to indicate increased risk of heart disease whilst values >8.5 µg/ml appears to indicate clinically relevant inflammation (Puts, Visser et al. 2005). To ensure uniformity and comparability of result, in this study cut-off points for IL1, IL6, hsCRP and TNFα were similar to the ones mentioned above:

- IL1 (≤1.6, >1.6pg/mL);
- IL6 (≤1.56, >1.56-≤2.9, >2.9-≤5 and >5pg/mL);
- hsCRP (≤1, >1-3.9, >3.9-8.5, >8.5µg/mL) and
- TNFα (≤7.8, >7.8pg/mL).

Total cholesterol:high density lipoprotein (HDL) ratio*:* Higher ratios are associated with increased risk of cardiovascular disease (Bruunsgaard, Pedersen et al. 2001; Lemieux, Lamarche et al. 2001), however in South Africa, the decision to start pharmacological treatment is based on overall risk profile (age, smoking status, diabetes, family history of premature coronary heart disease, hypertension, symptomatic carotid arterial disease and peripheral arterial disease) rather than on lipid levels only (Davis 2011). In this analysis the following ratios are used

- Males: ratio1(<3.4), ratio2(3.4-<5), ratio3(5-<9.6), ratio4(≥9.6)
- Females: ratio1(<3.3), ratio2(3.3-<4.4), ratio3(4.4-<7.1), ratio4(≥7.1)

Age*:* categorised into tertiles based on age at Wellbeing of Older People Study interview

- 50-59 years

- 60-69 years
- 70+ years

Smoking and alcohol drinking status: classified as

- Past smoker/drinker;
- Current smoker/drinker;
- Never smoked/drank

From the Africa Centre HIV surveillance

HIV status: defined as

- HIV positive ART naive
- HIV positive and on ART for more than a year
- HIV negative
- HIV-unknown

From the Africa Centre demographic surveillance

Wealth score: stratified into five hierarchical quintiles were the first quintile represented the lowest socio-economic status and fifth quintile represented the highest socio-economic status (Chapter 2, Section 2.6.1).

From the Hlabisa HIV treatment and care programme

Duration of ART at time of the Wellbeing of Older People Study was determined as the difference between the date of ART initiation and the date of drawing eligible participants from the sampling frame.

- HIV positive ART naive older adults were the ones who were recorded in Hlabisa HIV Treatment and Care Programme as not having initiated ART when the participants eligible for the Wellbeing of Older People Study were sampled.
- Those, whose date of ART initiation with Hlabisa HIV Treatment and Care Programme was more than one year prior to Wellbeing of Older People Study sampling date, and had continuously received ART, were categorised as HIV positive and on ART.

To ensure that there was no contamination of the group comprising HIV positive ART naive participants (Group 2), the Wellbeing of Older People Study interviews for this group were conducted within a month of identifying eligible participants.

Wellbeing of Older People Study Laboratory procedures

All laboratory tests were conducted by a South African National Accreditation System (SANAS) certified laboratory (Global Clinical and Viral Laboratory). Tests were conducted using kits by BioVendor Research and Diagnostic Products, Czech Republic. Lower detection concentrations were 0.02ug/mL for hsCRP, 1.1pg/mL for IL1, 0.81pg/mL for IL6 and 5.0pg/mL for TNFα. Blood serum was used for determination of hsCRP, IL1 and TNFα levels and plasma for IL6.

3.2.3 Analytical methods

Baseline characteristics were described using medians and IQRs (equality of medians tested for using Kwallis2 test (Siegel and Castellan 1988)) for continuous variables and proportions with 95% CI for categorical variables. To assess the association of HIV and obesity with morbidity, ordinary logistic regression was employed. Because IL6 was categorized into an ordinal variable, ordered logistic regression (STATA bulletin 2000; UCLA 2012) assessed the association between IL6 , HIV and obesity. Ordered logistic regression takes into account the hierarchy in the dependent variable categories assuming proportional odds (POR) and results in a single equation estimating the relationship between predictor variables and all levels of the dependent variable. Due to violation of proportional odds assumption, associations of HIV and obesity with CRP were examined using generalized ordered logistic regression which estimates multiple equations over the different hsCRP levels without assuming proportional odds, producing partial proportional odds ratios (pPOR) (STATA bulletin 2000; Williams 2006). For IL1 (binary outcome) simple logistic regression was used. STATA 11.2 was used for all analyses (StataCorp LP).

3.3 Results

3.3.1 Baseline characteristics

Of the 422 Wellbeing of Older People Study participants aged 50 years and above, 161 (38%) were HIV negative, 108 (26%) were HIV positive with at least a year on ART, 109 (26%) were HIV positive ART-naïve and 44 (10%) had unknown HIV status but with characteristics (age, sex, cytokine, lifestyle factors and morbidity prevalence) similar to those HIV negative. Men comprised 25% of the 422 individuals (n=106). Median age for HIV negative individuals was 10 years older than for HIV positive and subsequent analyses were age-adjusted. As would be expected in this population

(Tanser, Hosegood et al. 2008; Nyirenda, Chatterji et al. 2012) and setting, few individuals reported current (n=48, 11.4%) or ever smoking (n=49, 11.6%) or current drinking (n=58, 13.8%) (Table 3.1). Only 24 older adults (5.7%) reported being employed and as such majority of the Wellbeing of Older People Study population (n=332, 79.4%) were dependent on the old age grant as a source of income.

Health care utilisation

Whilst nearly 90% of HIV positive older adults on ART reported to have utilised health care services more than six times in the 12 months prior to the date of interview by visiting a clinic or hospital, only 36.7% of those HIV negative and 61.5% of those HIV positive and not on ART reported similar health care utilisation frequency ($p>0.001$). Over a third of those HIV negative (37.9%) had only been to a clinic once or twice in the preceding 12 months whilst for those HIV positive that proportion was 3.7% and 11.9% for those on ART and ART-naive respectively (Table 3.1).

3.3.2 Self-reported morbidity

Of the 422 participants, 124 (29.4%, 95% CI: 25.0-33.8) reported never having been diagnosed with any chronic condition (Table 3.1) whilst 169 (40.1%, 95% CI: 35.4-44.7) and 100 (23.7%, 95% CI: 19.6-27.8) reported being diagnosed with one and two conditions, respectively; 29 (6.9%) individuals had more than two conditions. Significantly more HIV negative and HIV positive ART-naïve participants than HIV positive participants receiving ART reported current morbidity i.e. receiving therapy for either one of heart disease, arthritis, stroke, hypertension, asthma or diabetes (Figure 3.1) ($p=0.033$).

Correlation of self-reported chronic morbidity with the WHO composite heath score and with self-rated health on day of interview

Table 3.1 shows that similar to patterns of self-reported chronic morbidity across HIV/ART status strata, the WHO composite health score and self-rated health were higher in those HIV positive and on ART for over 12 months than in those HIV negative ($p<0.001$ for composite health score and $p=0.006$ for self-rated general health). Further analysis showed that in older adults reporting current morbidity 69.1% (95% CI; 62.8%-75.4%) were rated unhealthy using the WHO composite health score whilst 55.8% (95% CI; 49.1%-62.4%) of those reporting no current chronic morbidity were classified as unhealthy using the same WHO composite health score.

3.3.3 Anthropometry

BMI overall was high; and the median BMI was highest in those HIV negative compared to HIV positive (28.1 vs 25.3 ($p=0.057$)). Obesity was more frequent among HIV negative than among HIV positive on ART and ART-naïve (Table 3.1).

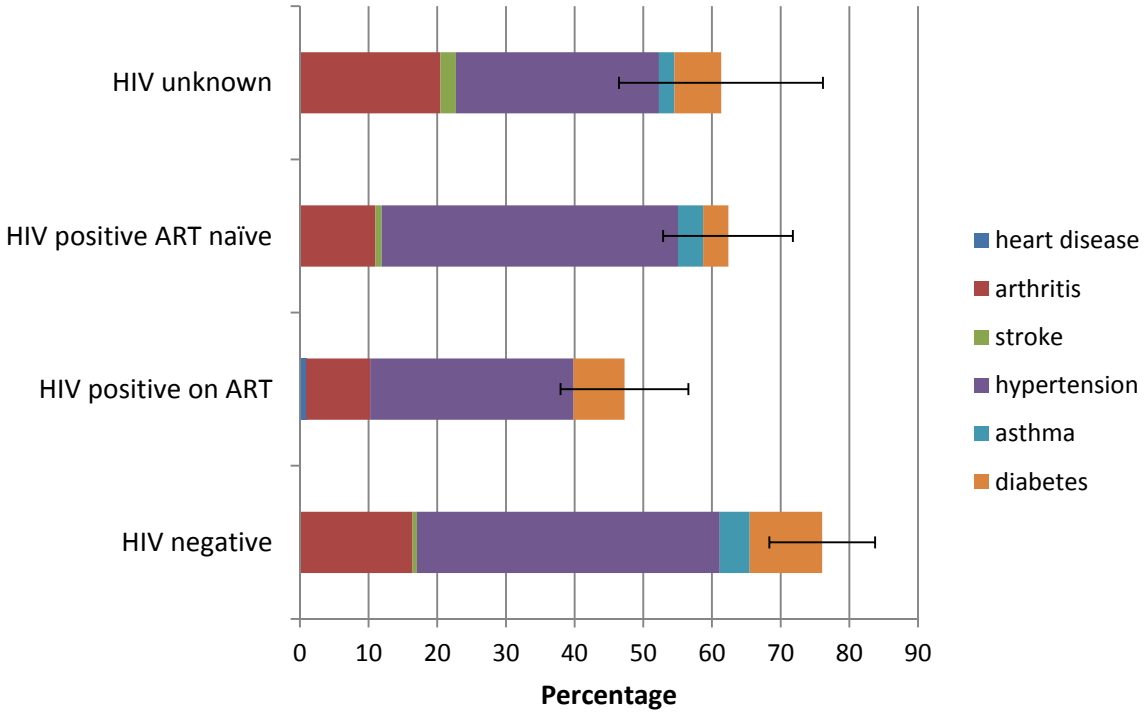
Table 3.1: Baseline demographic and clinical characteristics of 422 older adults stratified by HIV status

Characteristic		HIV negative (161)			HIV positive on ART (108)			HIV positive ART naive (109)			[a]Total (422)		p-value
		N / median	%	(95% CI)/IQR	N / median	%	(95% CI) /IQR	N / median	%	(95% CI)/ IQR	N / median	%/ IQR	
Sex	Male	30	18.6	(12.6-24.7)	36	33.3	(24.4-42.3)	30	27.5	(19.1-36.0)	106	25.1	0.05
Age at interview		68		61-75	57		53-62	53		51-60	60	53-69	<0.001
Employment	No	158	98.8	(97.0-1)	99	92.5	(87.5-97.5)	96	88.9	(82.9-94.9)	395	94.3	0.01
	Yes	2	1.3	(0-3.0)	8	7.5	(2.5-12.5)	12	11.1	(5.1-17.1)	24	5.7	
Main source of income	Grants	145	91.2	(86.8-95.6)	81	75.0	(66.8-83.2)	69	63.9	(54.8-73.0)	332	79.4	
	No source of income	7	4.4	(1.2-7.6)	9	8.3	(3.1-13.6)	18	16.7	(9.6-23.8)	36	8.6	<0.001
	Other	7	4.4	(1.2-7.6)	18	16.7	(9.6-23.8)	21	19.4	(11.9-27.0)	50	12.0	
BMI categories	Underweight	4	2.6	(0.1-5.1)	7	6.6	(1.8-11.4)	12	11.2	(5.2-17.2)	25	6.1	
	Normal	46	29.9	(22.6-37.1)	40	37.7	(28.4-47.0)	30	28.0	(19.5-36.6)	127	31.0	
	Overweight	45	29.2	(22.0-36.5)	37	34.9	(25.8-44.1)	35	32.7	(23.8-41. 7)	127	31.0	0.04
	Obese	48	31.2	(23.8-38.5)	17	16.0	(9.0-23.1)	24	22.4	(14.5-30.4)	105	25.6	
	Morbidly obese	11	7.1	(3.0-11.2)	5	4.7	(0.7-8. 8)	6	5.6	(1.2-10.0)	26	6.3	
Smoking	Never smoked	117	73.1	(66.2-80.0)	99	91.7	(86.4-96.9)	74	67.9	(59.1-76.7)	324	77.0	
	Past smoker	24	15.0	(9.4-20.6)	6	5.6	(1.2-9.9)	16	14.7	(8.0-21.4)	49	11.6	0.001
	Current smoker	19	11.9	(6.83-16.9)	3	2.8	(0-5.9)	19	17.4	(10.3-24.6)	48	11.4	

Alcohol	Never drank	94	58.75	(51.1-66.4)	82	75.9	(67.8-84.1)	64	58.7	(49.4-68.0)	269	63.9	
	Past drinker	41	25.63	(18.8-32.4)	14	13.0	(6.6-19.4)	33	30.3	(21.6-39.0)	94	22.3	0.01
	Current drinker	25	15.6	(9.96-21.3)	12	11.1	(5.1-17.1)	12	11.0	(5.1-16.9)	58	13.8	
Ever diagnosed with morbidity	No	38	23.6	(17.0-30.2)	39	36.1	(27.0-45.2)	29	26.6	(18.3-5.0)	121	28.7	0.12
	Yes	123	76.4	(69.8-83.00)	69	63.9	(54.8-73.0)	80	73.4	(65.0-81.7)	301	71.3	
Current morbidity	No	70	43.5	(35.8-51.2)	66	61.1	(51.9-70.4)	54	49.5	(40.1-59.0)	215	51.0	0.03
	Yes	91	56.5	(48.8-64.2)	42	38.9	(29.6-48.2)	55	50.5	(41.0-59.9)	207	49.1	
Morbidity in the last 12 months	No	52	32.3	(25.0-39.6)	52	48.2	(38.7-57.6)	48	44.0	(34.6-53.4)	173	41.0	0.04
	Yes	109	67.7	(60.4-75.0)	56	51.9	(42.4-61.4)	61	56.0	(46.6-65.4)	249	59.0	
Composite health score	Continuous	46.7		43.1-53.1	52.3		47.9-57.4	48.6		44.1-54.1	49.22	44.6-55.1	0.001
	Healthy	47	29.2	(22.1-36.3)	59	54.6	(45.2-64.1)	41	37.6	(28.5-46.8)	159	37.7	<0.001
	Unhealthy	114	70.8	(63.7-77.9)	49	45.4	(35.9-54.3)	68	62.4	(53.2-71.6)	263	62.3	
Self rated general health	Good/very good	65	40.4	(32.7-48.0)	64	59.3	(49.9-68.6)	42	38.5	(29.3-47.7)	193	45.7	0.006
	Moderate/bad/ very	96	59.6	(52.0-67.3)	44	40.7	(31.4-50.1)	67	61.5	(52.3-70.7)	229	54.3	
Health care facility use in the last 12 months	Not at all	6	3.7		0			0			9	2.1	
	1 to 2 times	61	37.9	(30.3-45.4)	4	3.7	(0.1-7.3)	13	11.9	(5.8-18.1)	98	23.2	<0.001
	3-6 times	35	21.7	(15.3-28.1)	6	5.6	(1.2-9.9)	29	26.6	(18.2-35.0)	83	19.7	
	>6 times	59	36.7	(29.2-44.1)	95	88.0	(81.8-94.1)	67	61.5	(52.3-70.7)	229	54.3	

- [a]total includes 44 participants with unknown HIV status (described in text)

Figure 3.1: Proportion with 95% confidence intervals of self-reported current chronic morbidity in 422 older adults stratified by HIV status



3.3.4 Cytokines

The distribution of laboratory measured IL1, IL6, hsCRP and TNFα for both HIV positive and HIV negative older adults showed little variation in terms of the median. HIV positive and HIV negative older adults had a similar median IL1 level of 1.6 pg/mL (Table 3.2). Although the medians were the same across groups, significantly more HIV-negative people had IL1 levels above 1.6µg/mL than those HIV positive ART-naive (p=0.003). For TNFα, only 7 (1.8%) participants had elevated levels, with medians similar across all HIV status strata (p=0.231) therefore variations in TNFα by

HIV sero-status was not assessed further. HIV positive older adults both on and not on ART had higher IL6 median levels compared to HIV negative individuals (Table 3.2). There was a trend towards highest hsCRP levels (>8.5pg/ml) in those HIV positive, with a statistically significant difference in HIV positive ART-naive compared to HIV negative.

Obese/morbidly-obese participants had increased hsCRP levels in both the median and categorized analyses. However IL1, IL6 and TNFα were not statistically significantly different across the different BMI strata (Table 3.2).

Table 3.2: Cytokine (IL1, IL6, CRP and TNFα) levels of 422 old adults stratified by HIV status and BMI levels

HIV status	HIV negative			HIV positive on ART			HIV positive ART naive			Total	
	Median/ N	% (IQR)	(95% CI)	Median/ N	% (IQR)	(95% CI)	Median/ N	% (IQR)	(95% CI)	Median/ N	IQR/(%)
IL1 (pg/mL)	1.6	(1.6-1.6)		1.6	(1.6-1.6)		1.6	(1.6-1.6)		1.6	1.6-1.6
<=1.6	123	83.1	(77.0-89.2)	100	92.6	(87.6-97.6)	94	96.9	(93.4-1.0)	353	(90.1)
>1.6	25	16.89	(10.8-23.0)	8	7.4	(2.4-12.4)	3	3.1	(0-6.6)	39	(10.0)
IL6 (pg/mL)	1.94	(1.6-2.6)		2.5	(2.0-3.1)		2.6	(2.0-3.2)		2.4	2.1-2.6
<=1.56	70	47.3	(39.2-55.4)	38	35.2	(26.1-44.3)	36	37.1	(27.4-46.8)	157	(40.1)
>1.56-2.9	20	13.5	(8.0-19.1)	24	22.2	(14.3-30.1)	19	19.6	(11.6-27.6)	68	(17.4)
>2.9-5	26	17.6	(11.4-23.7)	21	19.4	(11.9-27.0)	19	19.6	(11.6-27.6)	73	(18.6)
>5	32	21.6	(15.0-28.3)	25	23.2	(15.1-31.2)	23	23.7	(15.2-32.3)	94	(24.0)
CRP (µg/mL)	3.7	(2.5-4.1)		4.2	(3.5-5.8)		4.3	(2.6-6.5)		3.9	3.2-4.3
<=1	31	21.2	(14.6-27.9)	16	15.1	(8.2-22.0)	21	21.7	(13.4-29.9)	78	(20.1)
>1-3.9	52	35.6	(27.8-43.4)	33	31.1	(22.3-40.0)	25	25.8	(17.0-34.6)	122	(31.4)
>3.9-8.5	39	26.7	(19.5-33.9)	24	22.6	(14.6-30.7)	19	19.6	(11.6-27.6)	92	(23.7)
>8.5	24	16.4	(10.4-22.5)	33	31.1	(22.3-40.0)	32	33.0	(23.6-42.4)	96	(24.7)

BMI	**Normal**			**Overweight**			**Obese/ morbidly obese**			**Total**	
	Median/ N	% (IQR)	(95% CI)	Median/ N	% (IQR)	(95% CI)	Median/ N	% (IQR)	(95% CI)	Median/ N	
IL1 (pg/mL)	1.6	(1.6-1.6)		1.6	(1.6-1.6)		1.6	(1.6-1.6)		1.6	1.6-1.6
<=1.6	134	90.5	(85.8-95.3)	107	93.0	(88.4-97.7)	103	87.3	(81.2-93.3)	353	(90.1)
>1.6	14	9.5	(4.7-14.2)	8	7.0	(2.3-11.6)	15	12.7	(6.7-18.8)	39	(10.0)
IL6 (pg/mL)	2.5	(2.0-3.2)		2.5	(1.7-3.2)		2.08	(1.6-2.6)		2.4	2.1-2.6
<=1.56	58	39.2	(31.3-47.1)	47	40.9	(31.8-49.9)	51	43.2	(34.2-52.2)	157	(40.1)
>1.56-2.9	24	16.2	(10.2-22.2)	17	14.8	(8.3-21.3)	25	21.2	(13.8-28.6)	68	(17.4)
>2.9-5	26	17.6	(11.4-23.7)	28	24.4	(16.4-32.3)	17	14.4	(8.0-20.8)	73	(18.6)
>5	40	27.0	(19.8-34.2)	23	20.0	(12.6-27.4)	25	21.1	(13.8-28.6)	94	(24.0)
hsCRP (µg/mL)	2.5	(1.8-4.0)		3.2	(2.5-3.9)		6.15	(4.8-6.9)		3.9	3.2-4.3
<=1	46	31.3	(23.8-38.8)	17	14.9	(8.3-21.5)	13	11.2	(5.4-17.0)	78	(20.1)
>1-3.9	39	26.5	(19.4-33.7)	54	47.4	(38.1-56.6)	27	23.3	(15.5-31.0)	122	(31.4)
>3.9-8.5	27	18.4	(12.1-24.67)	20	17.5	(10.5-24.6)	43	37.1	(28.2-45.9)	92	(23.7)
>8.5	25	23.8	(16.9-30.7)	23	20.2	(12.8-27.6)	33	28.5	(20.2-36.7)	96	(24.7)

3.3.5 HIV status, obesity and morbidity

Logistic regression was used to determine the association of HIV status and morbidity and that of obesity and morbidity in the 422 Wellbeing of Older People Study participants aged 50 years and above; controlling for factors known to be associated with ill health (age, sex, smoking and wealth quintile). HIV positive older adults on ART were significantly less likely (OR=0.49, 95% CI 0.26-0.92; p=0.027) to report current morbidity than HIV negative adults (Figure 3.2). Cytokine levels were not significantly associated with current morbidity. In a model including an obesity marker (BMI) but not the ratio of total cholesterol:HDL , there was a borderline association between being obese/morbidly-obese and current morbidity (aOR=1.75, 95%CI: 1.0-3.0). However, including cholesterol:HDL ratio in the model, BMI lost its significance whilst higher levels of this ratio significantly increased the odds of current morbidity (Figure 3.2). Cholesterol:HDL ratio was associated with BMI, with normal BMI category having only 4.0% with ratio 4 whilst of those obese 11.7% had ratio4. Of the obese/morbidly-obese, only 10.8% had ratio 1 compared to 28.7% of those with normal BMI.

Sensitivity analysis

To adjust for age differences between HIV negative (median = 68; IQR 61-75 years) and HIV positive older adults on ART (median = 68; IQR 61-75 years) and ART naive (median = 68; IQR 61-75 years), all logistic regression models were age adjusted. In Table 3.3 adjusting for age as a three category variable, even though the odds of current morbidity in those HIV positive and on ART compared to those HIV negative increased slightly (0.44 vs 0.49) and the confidence interval widened, the finding of less current chronic morbidity in those HIV positive compared to those HIV negative persisted. To further assess whether the association between HIV status and morbidity

was largely driven by age differences rather than differences in HIV status and hence rule out residual confounding due to age, analysis was restricted to those aged 50 to 64 years old and further restricted to those aged 50-60 years old (Table 3.4). Considering older adults aged 50 to 65 years old, HIV positive older adults on ART had even less odds of morbidity compared to those HIV negative (0.37 compared to 0.49 in the regression including all 422 older adults). The confidence intervals were slightly wider in the analysis of those aged 50-65 years old due to the reduction in sample size from 422 to 248. Despite the sample size nearly halving in size, an association towards less current chronic morbidity in HIV positive older adults on ART compared to those HIV negative persisted. Restricting the analysis further to 199 older adults aged 50 to 60 years old, compared to those HIV negative, HIV positive individuals on ART still had less morbidity with an adjusted OR of 0.35 despite slightly wider confidence limits. The p-values in the restricted analyses were smaller than those from the complete dataset (0.027 vs 0.011 and 0.024 for the complete dataset, those aged 50-65 and those aged 50-60 respectively. In sum, reducing the age variations between the four HIV strata further confirms an even stronger differential in current chronic morbidity by HIV and ART status.

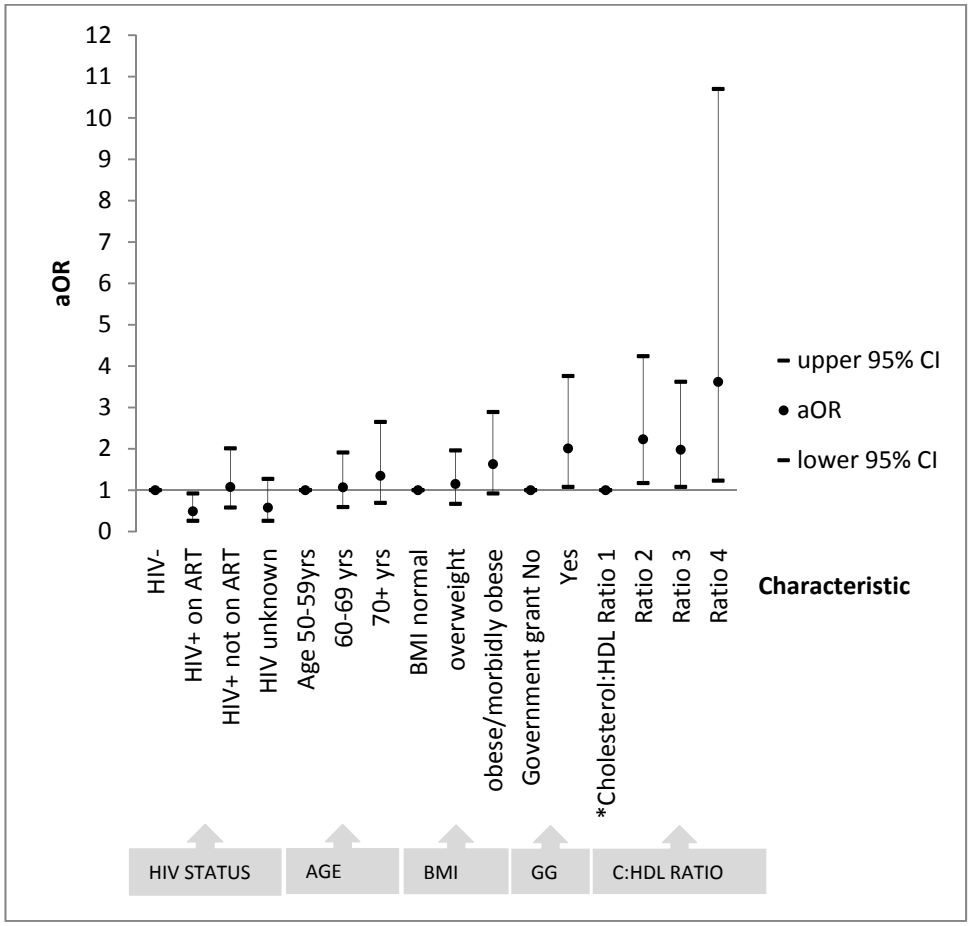
3.3.6 HIV status, obesity and cytokine levels

IL1

Across all HIV and ART strata, the median IL1 was 1.6pg/mL (IQR 1.6 pg/mL) with 39 (10%) of older adults having IL1 levels above this median. In a logistic regression adjusted for factors (age, gender, smoking and alcohol) likely to confound the association between HIV status and IL1 levels, compared to HIV negative, the odds of having IL1 levels >1.6pg/ml was lower by 65% (aOR=0.35, 95%CI: 0.13-0.94) for HIV positive on ART compared to HIV negative older adults. HIV positive ART-

naïve individuals also had reduced odds of elevated IL1 levels using the median IL1 (1.6 pg/mL) as the threshold for elevated levels (aOR=0.11, 95%CI: 0.24-0.54) and, respectively (Figure 3.3).

Figure 3.2: Logistic regression model of factors associated with current chronic morbidity in 422 older adults



Model adjusted for gender, smoking status and wealth score

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by the square of height in meters); GG, government grant; C:HDL ratio, ratio of total cholesterol:high density lipoprotein

*Ratio categories; Males: 1(<3.4); 2(3.4-<5); 3(5-<9.6); 4(≥9.6)

Females: 1(<3.3); 2(3.3-<4.4); 3(4.4-<7.1); 4(≥7.1)

Table 3.3: Factors associated with current morbidity before adjusting for age (second column) and after adjusting for age (fourth column)

Current morbidity	aOR unadjusted for age	95% C.I	Age adjusted aOR	95% C.I
HIV negative	1		1	
HIV+ on ART	0.44	0.25-0.79	0.49	0.26-0.92
HIV+ not on ART	0.98	0.55-1.73	1.08	0.58-2.01
HIV unknown	0.58	0.26-1.27	0.58	0.26-1.27
Age 50-59yrs			1	
60-69 yrs			1.07	0.59-1.91
70+ yrs			1.35	0.69-2.65
BMI normal	1		1	
overweight	1.13	0.66-1.93	1.15	0.67-1.96
obese/morbidly obese	1.60	0.90-2.83	1.63	0.92-2.89
Government grant No	1		1	
Yes	2.17	1.23-3.81	2.01	1.08-3.76
*Cholesterol:HDL Ratio 1	1		1	
Ratio 2	2.25	1.18-4.27	2.23	1.17-4.24
Ratio 3	1.98	1.09-3.62	1.98	1.08-3.62
Ratio 4	3.66	1.25-10.77	3.62	1.23-10.70

Both the age unadjusted and age adjusted models were adjusted for gender, smoking status and wealth score

Abbreviations: aOR, adjusted odds ratio from multivariable logistic regression; BMI, body mass index (measured as weight in kilograms divided by the square of height in meters); GG, government grant; C:HDL ratio, ratio of total cholesterol:high density lipoprotein

*Ratio categories; Males: 1(<3.4); 2(3.4-<5); 3(5-<9.6); 4(≥9.6)

Females: 1(<3.3); 2(3.3-<4.4); 3(4.4-<7.1); 4(≥7.1)

Table 3.4: Age restricted analyses of factors associated with current chronic morbidity in older adults

Current morbidity	50-65 years old only (n=248)				50-60 year old only (n=199)		
	Adjusted OR	95% C.I	p-value		Adjusted OR	95% C.I	p-value
HIV-	1				1		
HIV+ on ART	0.37	0.18-0.80	0.011		0.35	0.14-0.87	0.024
HIV+ not on ART	0.84	0.39-1.82	0.662		0.87	0.35-2.14	0.756
HIV unknown	0.39	0.11-1.38	0.143		0.42	0.09-1.95	0.266
Age (1 year increase)	1.02	0.96-1.10	0.479		1.04	0.95-1.15	0.398
BMI normal	1				1		
Overweight	1.3	0.65-2.60	0.459		1.09	0.50-2.38	0.823
Obese/morbidly obese	1.76	0.83-3.75	0.141		1.76	0.75-4.16	0.197
Government grant No	1				1		
Yes	1.81	0.94-3.49	0.078		1.77	0.90-3.45	0.096
*Cholesterol:HDL Ratio 1	1				1		
Ratio 2	2.01	0.92-4.76	0.08		2.09	0.82-5.34	0.124
Ratio 3	2.39	1.10-5.22	0.028		2.14	0.89-5.19	0.091
Ratio 4	6.75	1.66-27.5	0.008		5.57	1.07-29.13	0.042

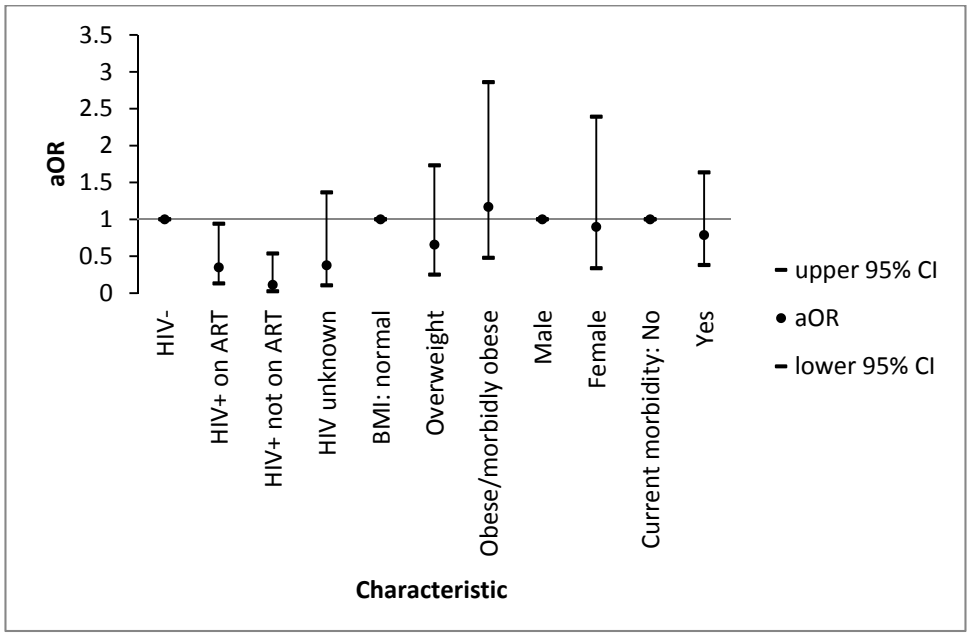
Both logistic regression models adjusted for gender, smoking status and wealth score

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by the square of height in meters); GG, government grant; C:HDL ratio, ratio of total cholesterol:high density lipoprotein

*Ratio categories; Males: 1(<3.4); 2(3.4-<5); 3(5-<9.6); 4(≥9.6)

Females: 1(<3.3); 2(3.3-<4.4); 3(4.4-<7.1); 4(≥7.1)

Figure 3.3: Logistic regression of factors associated with IL1 levels in 422 older adults



Model adjusted for age, smoking and alcohol status

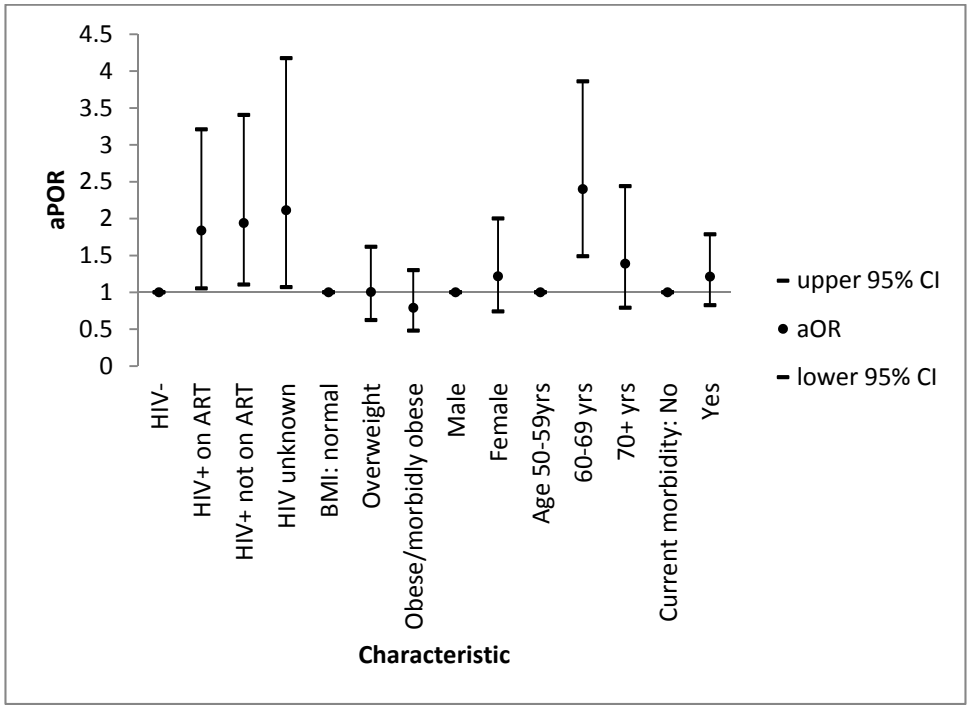
IL6

For all 422 older adults, the median IL6 was 2.4 (IQR 2.1-2.6) (pg/mL); 1.94 (IQR 1.6-2.6) (pg/mL) in the HIV negative group and 2.5 (IQR 2.0-3.1) (pg/mL) and 2.6 (IQR 2.0-3.2) for those HIV positive on ART and not on ART respectively. Accounting for the hierarchy of the IL6 levels using adjusted ordered logistic regression, compared to HIV negative, the proportional odds (aPOR) of having high IL6 levels was nearly twice as high in HIV positive individuals both on ART and ART naïve. This association was maintained from one level to the next IL6 level above ie from <=1.56 to >1.56-2.9 to >2.9-5 and finally to the highest level of >5. The proportional odds of having elevated IL6 levels (aPOR 2.40; 95%CI: 1.49-3.86) was higher in those aged 60-69 years than in those aged 50-59 years. For those aged 70+years the proportional odds of having IL6 levels in the highest strata

(>5pg/mL) was non-statistically significantly higher compared to those aged 50-59 years (aPOR=1.39; p=0.248) (Figure 3.4).

In both the adjusted regression model for IL1 and for IL6, Cholesterol:HDL ratio and BMI were not significantly associated with either of these two cytokine levels (IL1 p=0.675, IL6 p=0.681). Current morbidity was not statistically significantly associated with IL1 (aOR 0.79; 95% CI 0.38-1.64) Figure 3.3, IL6 (apOR 1.21; 95% CI 0.82-1.79) Figure 3.4 and hsCRP (appOR 1.00; 95% CI 0.99-1.02 – across all hsCRP levels).

Figure 3.4: Ordered logistic regression model for factors associated with IL6 levels in 422 older adults



Model adjusted for age, smoking and alcohol status

CRP

In descriptive statistics described above (Section 3.3.4), the 422 Wellbeing of Older People Study participants had a median hsCRP of 3.9 µg/mL. HIV infected adults on and not on ART had a higher median hsCRP and had a higher proportion of individuals within the highest hsCRP strata (above 8.5µg/mL). In a generalised ordered logistic regression model adjusted for sex, age, BMI, smoking and alcohol status, compared to HIV negative, HIV positive individuals on ART had more than twice the partial proportional odds (apPOR=2.30; p=0.004) of having slightly raised hsCRP levels (>1ug/mL), a level that is unlikely to be of clinical significance.

ART-naïve HIV positive individuals had more than double apPOR of having hsCRP levels (>3.9 ug/mL), a level that is indicative of increased cardiovascular disease risk (p=0.008). Assessing for factors associated with hsCRP levels > 8.5 µg/mL, HIV infection (both on and off ART) and having the highest ratio of cholesterol:HDL (>7.1 for females and >9.6 for males) were the only independent factors associated with these very high levels of hsCRP (>8.5ug/mL), levels that may signify clinically relevant inflammation with the likelihood being even higher in ART-naïve HIV positive participants (Table 3.3).

The association of BMI and hsCRP was also examined in this same generalised ordered logistic regression model whose results showed that although all BMI levels above normal increased the odds of having hsCRP levels likely to be of clinical significance (>1ug/mL), being obese/morbidly-obese nearly tripled the likelihood of having hsCRP levels, associated with increased cardiovascular disease risk, of >3.9ug/mL beyond which BMI was not associated with higher CRP levels (Table 3.3). Compared to those aged below 60 years, those aged 60-69years were twice as likely to have elevated hsCRP levels. Having cholesterol:HDL >7.1 for females and >9.6 for males was associated with three times more proportional odds of having elevated hsCRP levels across all CRP levels (Table 3.3).

Table 3.5: Generalised ordered logistic regression model for factors associated with elevated CRP levels in old adults n=422

CRP levels	Odds Ratio	P-value	95% Confidence interval	
<=1pg/mL				
HIV-	1			
HIV+ on ART	2.30	0.004	1.31	4.06
HIV+ ART naive	1.03	0.93	0.51	2.08
HIV unknown	0.83	0.61	0.42	1.66
BMI normal	1			
Overweight	2.54	0.005	1.33	4.85
Obese/morbidly obese	3.72	<0.001	1.81	7.63
Age 50-59years	1			
60-69 years	1.06	0.87	0.54	2.05
70+ years	1.27	0.41	0.73	2.21
>1-3_9pg/mL				
HIV-	1			
HIV+ on ART	2.30	0.004	1.31	4.06
HIV+ ART naive	2.30	0.008	1.25	4.24
HIV unknown	0.83	0.61	0.42	1.66
BMI normal	1			
Overweight	0.78	0.37	0.46	1.33
Obese/morbidly obese	2.78	<0.001	1.58	4.89
Age 50-59years	1			
60-69 years	2.09	0.009	1.21	3.61
70+ years	1.27	0.41	0.73	2.21
>3_9-8_5pg/mL				
HIV-	1			
HIV+ on ART	2.30	0.004	1.31	4.06
HIV+ ART naive	2.81	0.002	1.47	5.38
HIV unknown	0.83	0.61	0.42	1.66
BMI normal	1			
Overweight	0.80	0.48	0.43	1.48
Obese/morbidly obese	1.41	0.27	0.77	2.61
Age 50-59years	1			
60-69 years	1.43	0.23	0.80	2.57
70+ years	1.27	0.41	0.73	2.21
Across all levels of hsCRP				
[a]Cholesterol:HDL ratio 1	1			
Ratio 2	1.12	0.70	0.64	1.96
Ratio 3	1.47	0.16	0.86	2.53
Ratio 4	2.51	0.04	1.03	6.09

Adjusted for gender, current morbidity, smoking and alcohol status

[a]Ratio categories; Males: 1(<3.4), 2(3.4-<5), 3(5-<9.6), 4(≥9.6), Females: 1(<3.3), 2(3.3-<4.4), 3(4.4-<7.1), 4(≥7.1)

3.4 Key points

- 124/422 (29.4%; 95% CI: 25.0-33.8) reported never having been diagnosed with any chronic condition
- HIV-infected older adults on ART were significantly less likely (OR=0.49, p=0.027) to report current morbidity than HIV-uninfected adults
- Significantly more HIV-uninfected people had IL1 levels above 1.6µg/mL than those HIV-infected ART-naive (p=0.003), although the medians were the same across groups
- HIV-infected ART-naive older adults had higher hsCRP levels compared to HIV-uninfected
- Higher levels of Cholesterol:HDL ratio significantly increased the odds of current morbidity
- In adjusted regression, compared to HIV-uninfected, the proportional odds (aPOR) of having elevated inflammation markers of IL6 (>1.56pg/mL) was nearly doubled in HIV-infected individuals on (aPOR 1.84; 95%CI: 1.05-3.21) and not on (aPOR 1.94; 95%CI: 1.11-3.41) ART.
- Compared to HIV-uninfected, HIV-infected individuals on ART had more than twice partial proportional odds (apPOR=2.30;p=0.004) of having non-clinically significant raised hsCRP levels(>1ug/mL)
- ART-naïve HIV-infected individuals had more than double apPOR of having hsCRP levels indicative of increased heart disease risk (>3.9ug/mL;p=0.008).
- Being obese/morbidly-obese nearly tripled the likelihood of having hsCRP levels associated with increased cardiovascular disease risk (>3.9ug/mL)
- BMI was not significantly associated with IL1 and IL6 cytokine levels (IL1 p=0.675, IL6 p=0.681).

4 Results: Cause-specific morbidity at ART initiation in older adults

4.1 Introduction

Because HIV positive older adults face the prospect of both chronic morbidities of ageing and HIV-related morbidity, which may also be exacerbated by ART and multiple drug interactions (Chapter one, Section 1.5), a focus on this group is warranted to comprehensively document the morbidity burden in older HIV positive adults at the time of initiating ART. The management and determination of good clinical outcomes in HIV positive older adults after initiation of ART is likely to be associated with the prevalence of co-existing morbidities at time of initiating therapy. This chapter addresses objective two of this PhD by quantifying cause-specific morbidity burden in HIV positive older adults at time of initiating ART and investigates how this morbidity compares to that of young HIV positive adults aged below 50 years. A later objective of this PhD (Chapter 7) will quantify the contribution of morbidity at time of initiating ART, to mortality following ART initiation.

4.2 Methods

Objective

To describe and quantify the cause-specific morbidity burden in HIV positive older adults, at the time of initiating antiretroviral therapy, in comparison with younger adults

4.2.1 Data sources

ART Clinical Cohort

Since March 2010, a prospective clinical cohort nested within the larger Hlabisa HIV Treatment and Care Programme was established. Patients initiating ART at two of the largest primary health care clinics were enrolled into the cohort; less than 1% of patients declined the offer to participate due to work commitments and time constraints. Patients were reviewed monthly at the time of routine pill collection visits. Comprehensive details of ART Clinical Cohort study methodology are documented under the methods section of this thesis – Chapter 2, Section 2.2.3.2 and all study tools including data collection forms are to be found in Appendix 2.1 to Appendix 2.3. A summary of data collected at each monthly clinic visit are as follows;

- Demographic, socio-economic and morbidity data during patients' monthly clinic visits.
- A clinical examination conducted by professional nurses.
- Laboratory data (CD4 cell counts and viral loads) collected within the main Hlabisa HIV Treatment and Care Programme at ART initiation and 6-monthly thereafter are merged to the ART Clinical Cohort data.
- Anthropometric measures and vital signs
- Morbidity data coded in line with WHO ICD10 coding guidelines. Mortality data ICD10-coded by cause of death.
- All data collected by professional nurses; cause of death ascertained by an independent medical doctor.
- Data also collected if the patient makes an unscheduled visit for health related issues.

4.2.2 Definition of variables

Morbidity was defined in three categories:

- Serious HIV-associated morbidity (WHO stage 3 or 4 HIV disease) - took into account all serious morbidity at time of initiating ART, classified according to WHO HIV disease staging classification as stage 3 or 4. Conditions classified as serious morbidity included:
    - Severe weight loss, renal failure, anaemia, bacterial meningitis, oral candidiasis, chronic diarrheoa, cryptococcal meningitis, oesophageal candida, herpes, HIV associated arthritis, HIV wasting, HIV associated malignancies, pcp, urinogenital and neurologic conditions;
- TB disease;
- Pre-existing chronic morbidity - was defined as chronic morbidities for which the patient was already receiving therapy at time of initiating ART i.e. chronic conditions diagnosed prior to initiating ART.

BMI was categorized as per WHO recommendations (WHO 2012):

- underweight: <18.5;
- normal: 18.5-<25;
- overweight (pre-obese): 25-<30;
- obese/ morbidly obese: 30+

Age was categorised as <50 years and ≥50 years at time of initiating ART

Laboratory markers

In the Hlabisa HIV treatment and care Programme, at time of ART initiation (baseline), in addition to haemoglobin levels, patients liver and kidney function are evaluated based on laboratory measured levels inclusive of Alanine Aminotranferase (ALT), Creatinine and Glomerular Filtration Rates (National Department of Health 2003; National Department of Health 2004; National Department of Health 2010; National Department of Health 2013). These markers were assessed in terms of their association with baseline morbidity. The threshold for determining abnormal levels were kept in line with previous published studies based on Hlabisa HIV Treatment and Care Programme data (Mutevedzi, Lessells et al. 2010; Mutevedzi, Lessells et al. 2011);

Laboratory marker	**Abnormal**	**Units**
Hemoglobin (Hb)	<8	g/dL
Alanine Aminotranferase (ALT)	>60 (2xupper limit of normal)	IU/ml
Glomerular filtration rate (GFR)	<60	ml/min/1.73m2
Creatinine	>120	µmol/L

4.2.3 Analytical methods

Analysis included all adults (≥16 years) who were enrolled into the ART Clinical Cohort between March 2010 and July 2012 (inclusive). This time cut-off reflects the fact that the same dataset was used to assess the effect of baseline morbidity on very early mortality (occurring within the first 3 months of initiating ART) in Chapter 7, hence there was need to allow all patients a minimum

observation time of 6 months; 3 months in which very early mortality could occur and an additional 3 months to allow for reporting hence capturing the mortality events. Proportions and medians of categorical and continuous baseline characteristics respectively were described stratified by age at ART initiation i.e. young (<50 years) or older (≥50 years) adults. Differences in baseline characteristics between the two groups were assessed using the non-parametric equality-of-median test for continuous variables and proportions test for categorical variables. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (4-v MDRD) equation, without the ethnicity correction factor, as validated in a South African Population (Levey, Greene et al. 2000; van Deventer, George et al. 2008). Accounting for gender and baseline CD4 cell count, logistic regression was employed to quantify the association of age with chronic morbidity, TB morbidity and HIV-associated morbidity.

4.3 Results

4.3.1 Overall baseline descriptions

Over the 29 month period from March 2010 to July 2012 inclusive, 1 409 patients aged 16 years and above initiated therapy within the Hlabisa HIV Treatment and Care Programme at the two clinics where the ART Clinical Cohort was based. All patients were recruited into the ART Clinical Cohort; 21 adults (1%) declined participation. As such 1409 patients were enrolled into the ART Clinical Cohort, 425 (30.2%) male, median age 33 years and 193 (13.7%) aged 50 years and above at time of initiating ART. The proportion of males initiating therapy and the median age at ART initiation were similar to those within the main Hlabisa HIV Treatment and Care Programme (Cooke, Tanser et al. 2010; Houlihan, Bland et al. 2010; Mutevedzi, Lessells et al. 2010; Mutevedzi, Lessells et al. 2013).

Despite most patients initiating therapy with CD4 cell count <200cells/µl (National Department of Health 2010; National Department of Health 2013) (median 148; IQR 82-205) and just over 40% classified as having WHO diseases stage 3 or 4, the majority had a normal BMI; about 35.3% of ART Clinical Cohort participants were overweight or obese (Table 4.1). Based on laboratory measured haemoglobin (Hb), 66 patients (4.7%) were severely anaemic with Hb levels <8g/dL. Further, 127 patients (9.0%) had an estimated GFR<60 ml/min/1.73m2 whilst 62 (4.4%) had ALT levels greater than twice the upper limit of detection (>60 IU/ml) indicating poor kidney and liver functions respectively.

4.3.2 Pre-existing chronic morbidity

Based on report of currently taking medication for pre-existing chronic medication at time of initiating ART, 147 patients (10.4%) had one and 15 (1.1%) more than one pre-existing chronic morbidity. Specifically, 100 (65.79%) were on anti-hypertensive treatment, 14 (9.2%) had asthma, 12 (7.9%) epilepsy, 25 (16.5%) arthritis, 18 (11.8%) diabetes, 4 (2.6%) were on medication for psychiatric related conditions and 7 (4.6%) on other unspecified therapies. A total of 15 (1.1%) patients were on therapy for more than one pre-existing chronic morbidity (Table 4.1)

Table 4.1: Baseline demographic, clinical and laboratory description of 1409 patients enrolled in the ART Clinical Cohort

Characteristic	n	%	95% C.I
Sex (Male)	425	30.2	27.8-32.6
Age			
<50	1216	86.3	84.5-88.1
50+	193	13.7	11.9-15.5
BMI			
under weight	184	13.1	11.3-14.8
normal	703	49.9	47.3-52.5
overweight	303	21.5	19.4-23.7
obese/morbidly obese (20 were morbidly obese)	195	13.8	12.0-15.6
Missing	24	1.7	1.0-2.4
Blood pressure			
Normal	1162	82.5	80.5-84.5
Abnormal (>90/>140)	237	16.8	14.9-18.8
Pre-existing chronic morbidity treatment (yes)			
Asthma	14	9.2	
Epilepsy	12	7.9	
Arthritis	25	16.5	
Diabetes	18	11.8	
Hypertension	100	65.8	
Psychiatric	4	2.6	
Other	7	4.6	
Number of pre-existing chronic morbidity therapy			
0	1247	88.5	86.8-90.2
1	147	10.4	8.8-12.0
>1	15	1.1	0.5-1.6

WHO disease staging			
1&2	799	57.0	54.4-59.6
3&4	603	43.0	40.4-45.6
Concurrent TB therapy			
no	1117	79.8	77.7-82.0
Pulmonary	241	17.2	15.3-19.2
Extra-pulmonary	41	2.9	2.1-3.8
Hb			
Abnormal (<7)	66	4.7	3.6-5.8
Missing	68	4.8	3.7-6.0
CD4 count			
<50	216	15.4	13.5-17.3
50-200	821	58.4	55.9-61.0
>200	368	26.2	23.9-28.5
Glomerular filtration rate			
>=60	1222	86.7	85.0-88.5
<60	127	9.1	7.5-10.5
Missing	60	4.3	3.2-5.3
ALT			
<=60	1242	88.2	86.5-89.8
>60	62	4.4	3.3-5.7
Missing	105	7.5	6.1-8.8
ART regimen			
TDF+3TC+EFV	1,101	78.14	76.0-80.3
TDF+3TC+NVP	64	4.54	3.5-5.6
AZT+3TC+NVP	10	0.71	0.3-1.2
AZT+3TC+EFV	59	4.19	3.1-5.2
d4T+3TC+NVP	24	1.70	1.0-2.4
d4T/ABC+3TC+EFV	151	10.72	9.1-12.3

4.3.3 HIV-associated morbidity

HIV-associated morbidity took into consideration all serious HIV related morbidity and thus included all patients initiating ART with WHO HIV disease stage 3 or 4. Although nearly three-quarters of the cohort (n=1037, 73.8%) initiated therapy at CD4 cell counts below 200, 421 (30.0%) were asymptomatic (WHO stage 1) whilst 433 (30.7%) were classified as WHO disease stage 3 or 4. Of the 433 patients with HIV-associated morbidity at time of initiating ART, about half (n=216 49.9%) reported severe weight loss whilst 50 (11.6%) and 36 (8.3%) had oral candidiasis and chronic diarrhoea respectively. Twenty five (5.6%) had oesophageal candidiasis, 6 (1.4%) cryptococcal meningitis, 3 (0.7%) PCP and 3 (0.7 %) renal failure. HIV-associated morbidity at baseline by cause is presented in Table 4.2 below. Of the 282 patients enrolled into the cohort, 241 (85.5%) patients had pulmonary TB whilst 41 (14.5%) had extra-pulmonary TB (Figure 4.1 and Table 4.1).

4.3.4 Combined morbidity

Pre-existing chronic morbidity was defined as chronic morbidities for which the patient was already receiving therapy at time of initiating ART. HIV-associated morbidity took into account all serious morbidity at time of initiating ART, classified according to WHO HIV disease staging classification as stage 3 or 4. Assessing for pre-existing chronic, HIV-related and TB morbidity, 660 (46.8%) patients had no morbidity; 228 (16.2%) had TB only; 67 (4.8%) pre-existing chronic morbidity only; 337 (23.9%) HIV-associated morbidity only (Table 4.3). One individual had morbidity in all three categories and the rest had a combination of all three conditions as illustrated in the table below.

Table 4.2: Cause-specific prevalence of WHO HIV-disease stage III or IV morbidity at ART initiation

Morbidity cause	Number	Percentage	95 % Confidence Interval	
Bacterial meningitis	1	0.07	0	0.21
HIV associated arthritis	1	0.07	0	0.21
Neurologic	1	0.07	0	0.21
Renal failure	3	0.21	0	0.45
PCP	3	0.21	0	0.45
Cryptococcal meningitis	6	0.43	0.09	0.77
Herpes	7	0.5	0.13	0.86
Anaemia	8	0.57	0.17	0.96
HIV associated malignancies	11	0.78	0.32	1.24
Oesophageal candida	25	1.77	1.08	2.46
HIV wasting	25	1.77	1.08	2.46
Chronic diarrhoea	36	2.56	1.73	3.38
Urino-genital	40	2.84	1.97	3.71
Oral candidiasis	50	3.55	2.58	4.52
Severe weight loss	216	15.33	13.45	17.21
TB	249	17.67	15.68	19.67
None	727	51.6	48.98	54.21

Table 4.3: Overall morbidity burden at ART initiation in 1409 patients aged ≥16 years

Combined baseline morbidity	n	Percent (%)
None	660	46.84
HIV-associated only	337	23.92
TB only	228	16.18
Chronic only	67	4.76
HIV-associated & TB	32	2.27
HIV-associated & chronic	63	4.47
TB and chronic	21	1.49
All 3	1	0.07
Total	1,409	100.00

4.3.5 Baseline morbidity descriptions stratified by age at ART initiation

Of the 1 409 patients enrolled into the ART Clinical Cohort, 1216 (86.3%) were young adults whilst 193 (13.7%) were older adults aged 50+ years when they initiated ART. Although in both the older (≥50 years old) and young (<50 years old) adults majority of patients were female, there were significantly more males among the older (42.5%, 95% CI 35.5-49.5%) than the young adults (28.2%, 95% CI 25.7-30.7). About a third, 37.8%, of older adults and only 13.5% of young adults had blood pressure measurements suggestive of hypertension (systolic blood pressure 145

>140/diastolic pressure >90 mmHg). The proportion of older adults who were initiated on ART with a CD4 count of less than 50 cells/µl was significantly smaller for older adults (9.9%) than among young adults (16.2%; p=0.023), yet TB was more prevalent amongst younger adults: 220 (18.1, 95% CI 15.9-20.3) younger adults had pulmonary TB and 21 (10.9%, 95% CI 6.5-15.3) older adults. Extra-pulmonary TB was also more prevalent in younger (3.1%) than older adults (1.6%) although this difference did not reach statistical significance (p=0.225). Nearly four times as many older adults as younger adults had poor kidney function as approximated by glomerular filtration rate of <60(ml/min/1.73m2) (Table 4.4). The association of age with morbidity is detailed below within this Chapter in Section 4.3.9.

4.3.6 Baseline pre-existing chronic morbidity stratified by age

Pre-existing chronic morbidity at ART initiation included patients under medication for morbidities such as asthma, epilepsy, arthritis, diabetes and hypertension, with the most prevalent condition being hypertension (n=100, 65.8%). Of the 162 patients presenting with at least one pre-existing chronic morbidity, 15 (9.3%) were on therapy for more than one condition.

For all pre-existing chronic morbidity, older adults had higher proportions currently receiving therapy than younger adults, reaching statistical significance for arthritis, diabetes and hypertension as shown in Table 4.4. As such, 77 (6.3%; 95% CI 5.0-7.7%) of younger adults had one chronic condition whilst 70 (36.3%; 95% CI 29.5-43.1%) of older adults were on therapy for one named chronic condition. Four times as many older adults as younger adults had more than one chronic condition although this difference did not reach statistical significance likely due to the small numbers.

Table 4.4: Baseline demographic, clinical and laboratory description of ART Clinical Cohort patients stratified by age at ART initiation

Characteristic	n	%	95% C.I	n	%	95% C.I
	YOUNGER ADULTS (1216)			OLDER ADULTS (193)		
Sex (Male)	343	28.21	25.67-30.74	82	42.49	35.49-49.49
BMI						
under weight	165	13.57	11.64-15.50	19	9.84	5.63-14.06
normal	618	50.82	48.01-53.64	85	44.04	37.01-51.07
overweight	254	20.89	18.60-23.18	49	25.39	19.23-31.55
obese/morbidly obese	157	12.91	11.02-14.80	38	19.69	14.06-25.32
mis	22	1.81	1.06-2.56	2	1.04	0-2.47
Blood pressure						
Normal						
Abnormal (>140/>90mmHg)	164	13.49	11.56-15.41	73	37.82	30.96-44.69
Hb (g/dL)						
Abnormal (<8)	62	5.10	3.86-6.34	4	2.07	0.06-4.09
mis	64	5.26	4.01-6.52	4	2.07	0.06-4.09
CD4 count						
<50	197	16.24	14.16-18.32	19	9.90	5.66-14.13
50-200	709	58.45	55.67-61.23	112	58.33	51.33-65.33
>200	307	25.31	22.86-27.76	61	31.77	25.16-38.38
Glomerular filtration rate (ml/min/1.73m2)						
≥60	1077	88.57	86.78-90.36	145	75.13	69.01-81.25
<60	81	6.66	5.26-8.06	46	23.83	17.80-29.87
miss	58	4.77	3.57-5.97	2	1.04	0-2.47
ALT (IU/ml)						
≤60	1062	87.34	85.46-89.21	180	93.26	89.72-96.81
>60	56	4.61	3.43-5.78	6	3.11	0.65-5.57
miss	98	8.06	0.98-6.27	7	3.63	0.98-6.27
Concurrent TB therapy						
no	951	78.21	75.88-80.53	166	86.01	81.10-90.92
Pulmonary	220	18.09	15.93-20.26	21	10.88	6.47-15.29
Extra-pulmonary	38	3.13	2.15-4.10	3	1.55	0-3.31
missing	7	0.58	0.15-1.00	3	1.55	0-3.31

Age stratified into young adults aged 16-49 years and older adults aged >50years

Table 4.5: Baseline prevalence of pre-existing chronic morbidity stratified by age at ART initiation

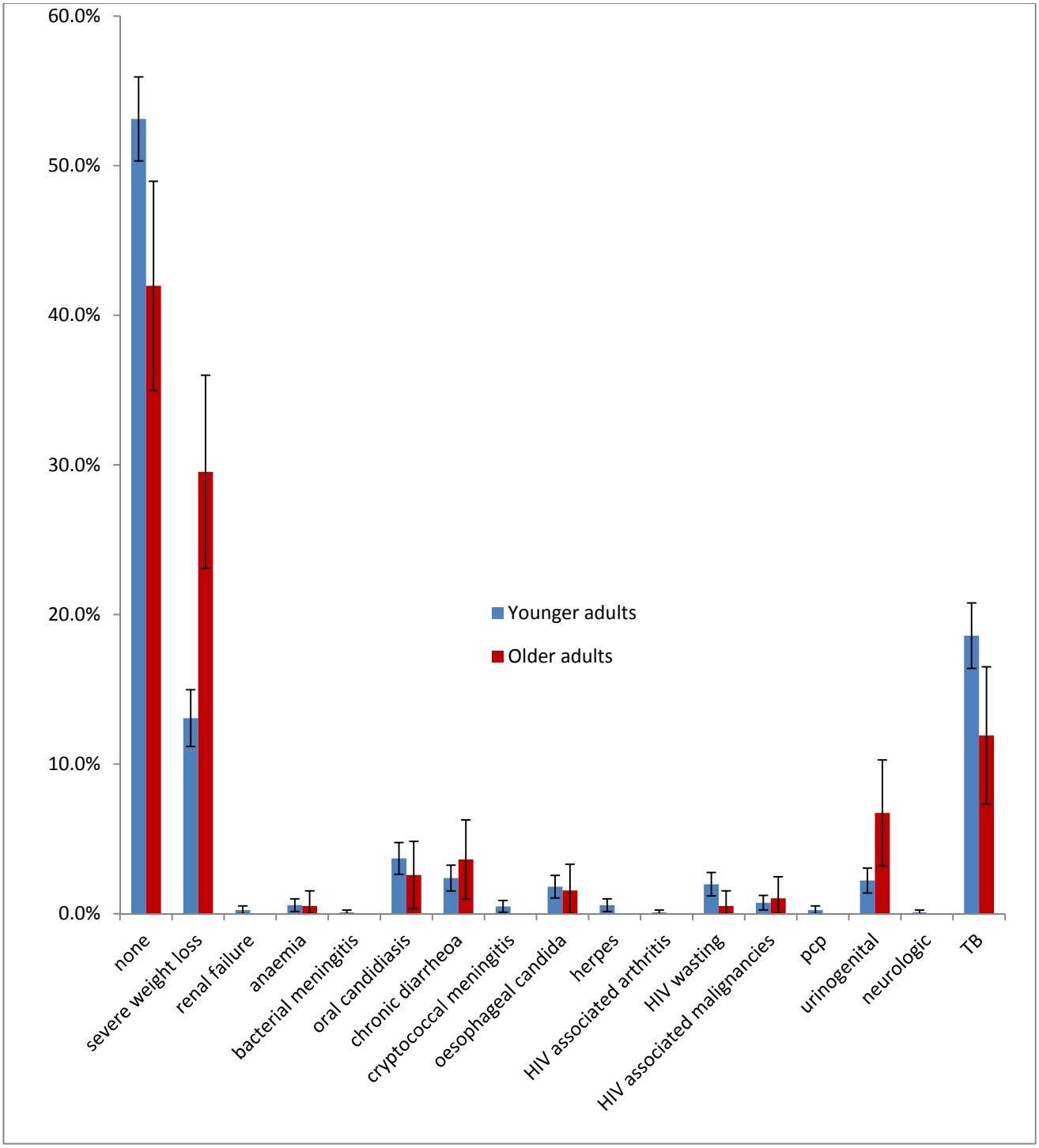
Characteristic	**n**	**%**	**95% C.I**	**n**	**%**	**95% C.I**
	YOUNGER ADULTS			**OLDER ADULTS**		
Pre-existing chronic morbidity						
Asthma	10	0.82	0.31-1.33	4	2.07	0.06-4.09
Epilepsy	9	0.74	0.26-1.22	3	1.55	0-3.31
Arthritis	14	1.15	0.55-1.75	11	5.70	2.42-8.98
Diabetes	4	0.33	0-0.65	14	7.25	3.58-10.93
Hypertension	48	3.95	2.85-5.04	52	26.94	20.66-33.22
Psychiatric	4	0.33	0-0.65	0	0	
Other	6	0.49	0-0.89	1	0.52	0-1.53
Number of pre-existing chronic conditions per patient						
0	1131	93.01	91.57-94.44	116	60.10	53.17-67.04
1	77	6.33	4.96-7.70	70	36.27	29.46-43.08
>1	8	0.66	0.20-1.11	7	3.63	0.98-6.27

Age stratified into young adults aged 16-49 years and older adults aged >50years

4.3.7 Baseline HIV-associated morbidity stratified by age

HIV-associated morbidity at ART initiation included patients with WHO HIV disease stage 3 or 4 (433 (30.7%)); 344 (28.3%; 95% CI 25.8-30.8%) in younger adults and 89 (46.1%; 95% CI 39.1-53.1%) in older adults. Figure 4.1 illustrates that younger adults initiated therapy with a wider spectrum of HIV-related morbidity than older adults albeit having a significantly smaller overall proportion of patients. In this cohort no older adults were diagnosed with bacterial or cryptococcal meningitis, herpes, renal failure, HIV-associated arthritis or PCP; although the prevalence was also very low in younger adults. For older adults, the most common HIV-associated morbidity was severe weight loss (29.5%; 95% CI 23.1-36.0%) whilst for younger adults TB (18.6%; 95% CI 16.4-20.8) was most prevalent.

Figure 4.1: Cause specific prevalence of HIV-associated morbidity at time of ART initiation stratified by age



Age stratified into young adults aged 16-49 years and older adults aged >50years

4.3.8 Age stratified co-morbidities at ART initiation

By virtue of older adults having a higher proportion presenting with either HIV-associated or pre-existing morbidity, only 75 (6.2%; 95% CI 4.8-7.5%) of younger adults compared to 46 (23.8% 95% CI 17.8-29.9%) of older adults had a combination of two morbidity types at time of initiating ART. Further analyses, stratifying HIV-associated morbidity into TB and other HIV-associated morbidity, revealed that morbidity differentials owing to age were mainly driven by differences in TB and pre-existing chronic morbidity rather than HIV-associated morbidity (Table 4.4). Older adults had a prevalence of 16.6% for chronic morbidity only, and 8.3% for TB morbidity only whilst younger adults the proportions were 3.3% for chronic morbidity only and 17.4% for TB morbidity ($p<0.01$). The differences in distribution of these two morbidities within the two age strata were the major reasons for the differences in the morbidity combinations presented in Table 4.6.

Table 4.6: Combined baseline morbidity burden highlighting differences by age at ART initiation

Characteristic	n	%	95% C.I	n	%	95% C.I
	YOUNGER ADULTS (1216)			**OLDER ADULTS** (193)		
None	606	49.8	47.0-52.6	49	25.4	19.2-31.6
HIV-associated only	282	23.2	20.8-25.6	50	25.9	19.7-32.1
TB only	212	17.4	15.3-19.6	16	8.3	4.4-12.2
Chronic only	40	3.3	2.3-4.3	32	16.6	11.3-21.9
HIV-associated & TB	31	2.6	1.7-3.4	1	0.5	0-1.53
HIV-associated & chronic	30	2.5	1.6-3.3	38	19.7	14.1-25.3
TB and chronic	14	1.2	0.6-1.8	7	3.6	1.0-6.3
HIV-associated & chronic & TB	1	0.1	0-0.24	-	-	-
Combined						
None	606	49.8	47.0-52.7	49	25.4	19.2-31.6
Only 1	534	43.9	41.1-46.7	98	50.8	43.7-57.9
Only 2	75	6.2	4.8-7.5	46	23.8	17.8-29.9
All 3	1	0.1	0-0.2	-	-	-

Age stratified into young adults aged 16-49 years and older adults aged >50years

4.3.9 Association of age with pre-existing chronic and HIV-associated morbidity

Pre-existing chronic morbidity and HIV-associated morbidity at ART initiation were combined into a composite morbidity variable whose association with age was determined through logistic regression. The resultant regression analysis, adjusting for gender and CD4 cell count at ART initiation showed that compared to younger adults, older adults had 3.09 times increased odds (95% CI 2.18-4.39) of presenting with any type of morbidity at baseline. Further investigation by assessing cause-specific co-morbidities categories(HIV-associated, pre-existing chronic or TB) showed that the excess odds of co-morbidity in older adults could be attributed to the very high odds of older adults having a pre-existing chronic morbidity (aOR 9.91; 95 % CI 6.77-14.49). Additionally, being an older adult was associated with increased odds of presenting with HIV-associated morbidity exclusive of TB (aOR 2.30; 95% CI 1.67-3.16). However compared to younger adults, older adults were 50% less likely to initiate ART whilst on TB therapy (aOR 0.50; 95% CI 0.31-0.80).

Table 4.7: Association of age with pre-existing chronic/HIV-associated/TB morbidity at ART initiation.

Morbidity type		aOR	95% C.I
HIV-associated	Young adults	1	
	Older adults	2.30	1.67-3.16
TB	Young adults	1	
	Older adults	0.50	0.31-0.80
Pre-existing chronic	Young adults	1	
	Older adults	9.91	6.77-14.49
HIV-associated / TB / Pre-existing chronic	Young adults	1	
	Older adults	3.09	2.18-4.39

Models adjusted for gender and CD4 cell count at time of initiating ART
Age stratified into young adults aged 16-49 years (reference) and older adults aged >50years

4.4 Key Points

- Baseline characteristics of patients enrolled into the cohort are similar to those reported in the larger Hlabisa HIV Treatment and Care Programme
- Despite nearly three-quarters of the cohort initiating therapy with CD4 cell counts below 200 and just over 40% classified as having WHO disease stage 3 or 4, the majority had a normal BMI
- 147 patients (10.4%) had one and 15 (1.1%) more than one pre-existing chronic condition; only 1 patient had a combination of non-HIV related chronic morbidity, HIV-associated morbidity and TB.
- HIV-related morbidity at baseline included severe weight loss, oral and oesophageal candidiasis, chronic diarrhoea, cryptococcal meningitis, PCP and renal failure
- Nearly four times as many older than younger adults had a low GFR of <60 (ml/min/1.73m2) suggestive of poor kidney function.
- Older adults had a higher proportion of patients initiating ART with pre-existing chronic morbidity but younger adults initiated therapy with a wider spectrum of HIV-related morbidity compared to older adults
- Only 75 (6.2%; 95% CI 4.8-7.5%) of younger adults compared to 46 (23.8% 95% CI 17.8-29.9%) of older adults had a combination of two morbidity types at time of initiating therapy - mainly driven by differences in TB and pre-existing chronic morbidity rather than HIV-associated morbidity
- A lower proportion of older adults than younger adults initiated ART whilst on TB therapy
- Older adults had a prevalence of 16.6% for chronic morbidity only, and 8.3% for TB morbidity only whilst younger adults had a proportion of 3.3% for chronic morbidity and 17.4% for TB morbidity ($p<0.01$).

- Accounting for sex and CD4 cell count, older adults had a three-fold increased odds (95% CI 2.18-4.39) of presenting with any one type of morbidity at baseline

5 Results: Cause-specific incidence rates of serious morbidity in older adults post-ART-initiation

5.1 Introduction

There is limited information regarding the outcomes of severe morbidity requiring hospitalisation for adults receiving ART in sub-Saharan Africa. Previous studies are based in resource- rich countries whilst the few that are from developing countries are mainly based in large urban hospitals, where morbidity patterns and outcomes may differ from those in more deprived rural areas. Understanding patterns of severe morbidity in patients receiving ART is essential for appropriate patient management and informs screening measures required to ensure morbidity is diagnosed and treated early.

In all HIV positive patients receiving ART, the risk and extent of side effects and drug toxicities, resulting in morbidity, may depend on the patients' kidney and liver function which also reflects the ability to metabolise and excrete ART drugs (Chapter 1.7). For this reason and in accordance with South Africa HIV treatment guidelines, unless the patient urgently requires therapy, before ART initiation, kidney and liver function efficiency is evaluated through Creatinine and Glomerular filtration rate (GFR) and Alanine aminotransferase (ALT) respectively. Haemoglobin (Hb) levels are also determined. However few studies especially in resource limited settings have determined how well these biomarkers can be used to determine future morbidity risk in patients initiating ART, as a way of identifying high risk groups requiring clinical interventions.

This chapter addresses objective three of this PhD which estimates overall and cause-specific rates of serious morbidity following initiation of ART and the effect of age at ART initiation on morbidity risk. Additionally it establishes whether abnormal biomarker (Hb, ALT, creatinine) levels at ART initiation may be risk factors of subsequent serious morbidity.

5.2 Methods

Objectives

a. To determine causes and rates of serious morbidity (resulting in hospitalization) following initiation of ART and the effect of age on such morbidity and to

b. To establish whether abnormal biomarker [haemoglobin (Hb), Alanine aminotransferase (ALT) and creatinine] levels at ART initiation are associated with subsequent increased morbidity risk.

5.2.1 Data sources

For analysis results presented in this chapter, data from the main Hlabisa HIV Treatment and Care Programme was linked to the Hlabisa hospital information system. To recap, Hlabisa hospital information system refers to an electronic database that captures information on all overnight hospitalisations at the district government hospital. Patients within Hlabisa health sub-district utilize this hospital; access to the regional government hospital, which is about 150 kms away from this district hospital, is mainly through referrals via the district hospital. Hlabisa hospital is the only district hospital within the Hlabisa HIV Treatment and Care Programme catchment area or health sub-district. It is thus highly likely that by linking into Hlabisa hospital information system, the

majority if not all hospitalizations of patients within Hlabisa HIV Treatment and Care Programme will be accounted for. Detailed descriptions of both Hlabisa HIV Treatment and Care Programme and Hlabisa hospital information system are within the methods Chapter under Section 2.2.2 and 2.2.5.

Since Hlabisa hospital information system was initiated around May 2010, the analysis for this study, done in February to March 2013, included all patients aged 16 years and above who initiated ART at 17 primary health care clinics between 01 June 2010 and 31 July 2012. Data were censored on 1 February 2013 to allow for sufficient time to capture early serious morbidity. Hospitalisation details were obtained by linking adults within Hlabisa HIV Treatment and Care Programme to the district hospital information system; both databases are hosted at the Africa Centre. Comprehensive details on data linkage are presented in Chapter 2 under Section 2.4.

ICD-10 was used to code all diagnosis at hospital admission, discharge or death.

5.2.2 Definition of variables

All morbidity was coded by a qualified nurse registered with the South African Nursing Council who was also trained in WHO ICD10 coding.

Serious morbidity was defined as any morbidity resulting in hospitalization for greater than 24 hours (one or more overnight stays).

Laboratory markers

Within the Hlabisa HIV treatment and care programme, at time of initiating ART (baseline), in addition to haemoglobin levels, patients liver and kidney function are evaluated based on

laboratory measured levels inclusive of Alanine Aminotranferase (ALT), Creatinine and Glomerular Filtration Rates (National Department of Health 2003; National Department of Health 2004; National Department of Health 2010; National Department of Health 2013); these same markers were assessed in terms of their association with baseline morbidity.

5.2.3 Analytical methods

Proportions and medians of categorical and continuous baseline characteristics respectively were described stratified by age at ART initiation i.e. younger (<50 years) or older (≥50 years) adults. Differences in baseline characteristics between the two groups were assessed using the non-parametric equality-of-median test for continuous variables and proportions test for categorical variables. Box plots were employed to illustrate duration of hospitalisation.

Overall and age-specific all-cause and cause-specific hospitalisation rates (HR) were estimated by Kaplan-Meier analysis. All observations started at time of initiating ART. For those hospitalised, observation ended at date of admission. Patients not seen for more than 180 days (nine months) from the date of database closure (16 January 2013) were classified as loss to care. Data were censored at earliest of loss to care, transferring out of the programme or last clinic visit. To ascertain the independent influence of age on risk of hospitalisation, a Cox regression model adjusted for age, sex and baseline clinical and laboratory markers, was used. Case-fatality rates were computed as the number of deaths per given cause of hospitalisation.

To assess the effect of missing baseline laboratory markers, the Cox regression model was run on the full data with missing values include as a missing category for each applicable variable after which a complete case model was run excluding patients with any missing observation.

5.3 Results

5.3.1 Baseline cohort descriptions

Overall

Between 1 June 2010 and 31 July 2012, 8 598 patients initiated ART; 2 626 (30.5%) male. Median age was 33 years (IQR: 27-41). Of the 8 598 patients, 962 (11.2%) were older adults aged 50+ years. Median CD4 count was 165 (IQR: 89-246) cells/µl and 1160 patients were on concurrent TB therapy at time of initiating ART. Approximately 3.2% (n= 273) had an Hb level <8g/dL. A small proportion of patients (43, 0.5%) had creatinine levels higher than 240µmol/L whilst 385 patients (4.5%) had ALT levels above 60 IU/L.

Age stratified baseline descriptions

The proportion of males initiating ART was much higher in older adults (43.2%, 95% CI 40.1-46.4%) than in younger adults (28.9%, 95% CI 27.9-30.0%). Interestingly, a lower proportion of older adults initiated ART with Hb levels <8 g/dL (1.6%, 95% CI 0.1-2.3%), CD4 cell count <50 cells/µL (10.6%, 95% CI 8.6-12.5%) elevated ALT levels >60 IU/mL (2.7%, 95% CI 1.7-3.7%) and a lower proportion was on concurrent TB therapy (10.9%, 95% CI 8.9-12.9%) compared to younger adults whose proportions were as follows: Hb levels less <8 g/dL (3.4%, 95% CI 3.0-3.8%), CD4 cell count

<50 cells/μL (14.6%, 95% CI 13.8-15.4%) elevated ALT levels >60 IU/mL (4.7%, 95% CI 4.2-5.2%) and proportion on concurrent TB therapy (13.8%, 95% CI 13.0-14.6%).

5.3.2 Hospitalisation incidence rate

Overall

A total of 675 patients (7.9%) were hospitalized over 8166 person years of follow-up, giving an estimated incidence rate of 8.3 (95% CI 7.7-8.9) per 100 person years. The rate of hospitalization was three-fold higher in the first 3 months subsequent to ART initiation (incidence rate (IR) 17.6 per 100 person years, 95% CI 15.8-19.6 compared to later periods (IR 5.4 per 100 person years, 95% CI 4.9-6.0). Additionally, patients initiating ART whilst concurrently taking TB medication were more likely to experience serious morbidity leading to hospitalisation than patients not on TB therapy: IR 13.0 95% CI 11.0-15.5 per 100 person years and IR 6.1 95% CI 4.2-8.9 for those on and not on TB therapy respectively. Although for both groups, incidence of serious morbidity was higher in the first 3 months compared to periods thereafter, for those initiating ART whilst on concurrent TB therapy, the IR was twice as high (IR 35.2; 95% CI 28.4-43.6) per 100 person years compared to those without TB (IR 15.3; 95% CI 13.5-17.4) per 100 person years. Post this period, the IR for those with TB was similar to that in patients without TB at around 5 cases per 100 person years.

Age stratified incidence of serious morbidity

Of the 675 patients hospitalized, 60 (8.9%) were aged 50+ years. Amongst younger adults, 615/7636 (8.1%; 95% CI 7.4-8.7%) were hospitalised during 7194.3 person years of follow up giving a hospitalization rate of 8.6 (95% CI 7.9-9.3) per 100 person years. Of older adults, 60/962 (6.2%;

91% CI 4.7-7.8%) were hospitalized during 972.4 person years of follow-up; hospitalization rate 6.2 (95% CI 4.8-7.9) per 100 person years (Table 5.1). Rates of serious morbidity resulting in hospitalization were non-statistically significantly higher in younger adults than in older adults, with slight overlap between the confidence intervals.

Table 5.1: Age-stratified hospitalisation rates in 8598 adults initiating ART aged 16 years and above

Cohort period	Person-time	Age group	Hospitalisations	Incidence Rate (per 100 person years)	95% CI	IRR	95% CI
0-3 months	1686.9	Younger	309	18.32	16.38-20.48	1	
	217.2	Older	26	11.97	8.15-17.58	0.65	0.44-0.97
>3months	5507.4	Younger	306	5.56	4.97-6.21	1	
	755.2	Older	34	4.50	3.22-6.30	0.81	0.57-1.15
Overall	7194.3	Younger	615	8.55	7.90-9.25	1	
	972.4	Older	60	6.17	4.79-7.95	0.72	0.55-0.94

Age stratified into young adults aged 16-49 years and older adults aged >50years

Since a considerable amount of hospitalisation in younger adults was due to pregnancy related issues such as infant deliveries and spontaneous abortions (126/615, 20.5%) which would not necessarily apply to older adults, removing pregnancy related conditions resulted in similar hospitalization rates in both age groups [(6.8, 95% CI 6.2-7.4 in younger adults and to 6.2, 95% CI 4.8-7.9 in older adults) per 100 person years]. After this adjustment hospitalisation rates in the

first 3 months of ART, were comparable for younger adults (14.9, 95% CI 13.2-16.9 per 100 person years) compared to older adults (12.0, 95% CI 8.2-17.6 per 100 person years).

5.3.3 Hospitalisation causes

Overall

Of the 675 serious morbidities that led to hospitalization, 231 (34.2%) was due to other non-infectious conditions (Figure 5.1). The majority of conditions within this category were pregnancy related- (126 (54.6%) followed by injuries with 29 cases (12.6%). Diseases of the circulatory system (10, 4.3%), eye and adnexa (2, 0.9%), musculoskeletal and connective tissue disorders (2; 0.9%), epilepsy (1, 0.4%), infections of the skin (15, 6.5%) and other (35, 15.2%) were also included in this category (Figure 5.2). TB was the second leading cause of hospitalisation with 155 (23.0%) patients having TB documented as cause of hospitalization at admission, 56 (36.1%) of whom had been diagnosed of TB and were receiving TB therapy at time of initiating ART. There were 22 cases of meningitis and 19 cases diagnosed at hospital admission as advanced HIV diseases including HIV wasting. Other causes of serious morbidity included malignancies, digestive and diarrheal conditions and respiratory infections, proportions of which are illustrated by Figure 5.1.

Age-stratified hospitalisation causes

Stratifying by age at ART initiation, younger adults had a wider spectrum of conditions leading to hospitalisation compared to older adults. All cases of malignancies, pneumocytosis and meningitis occurred in younger adults (Figure 5.3). It is worth noting that although a lower proportion of older adults had TB at time of initiating therapy, they had a higher proportion of cases diagnosed as TB at admission into hospital indicating likely unmasking of mycobacterial disease through

commencement of ART therapy. Fifty two of the 139 TB cases at admission (37.4%) in younger adults were on TB therapy whilst for older adults 4/16 (25%) were receiving TB therapy when they initiated ART. Older adults had a higher proportion of respiratory infections requiring hospitalisation than younger adults. For other non-infectious conditions (specific diseases prior listed) younger adults had a higher proportion compared to older adults (Figure 5.3). Small numbers of hospitalised older adults likely limited statistical power to detect significant differences in categories, except for non-infectious conditions, where differences by age were statistically significant. This difference was maintained even after removing pregnancy related conditions [(35.9%, 95% CI 32.1-39.7%) for younger adults vs (16.7%, 95% CI 7.1-26.2%) for older adults].

Figure 5.1: Causes of hospitalisation in adults aged 16 years and above following ART initiation determined through diagnosis made at time of hospital admission

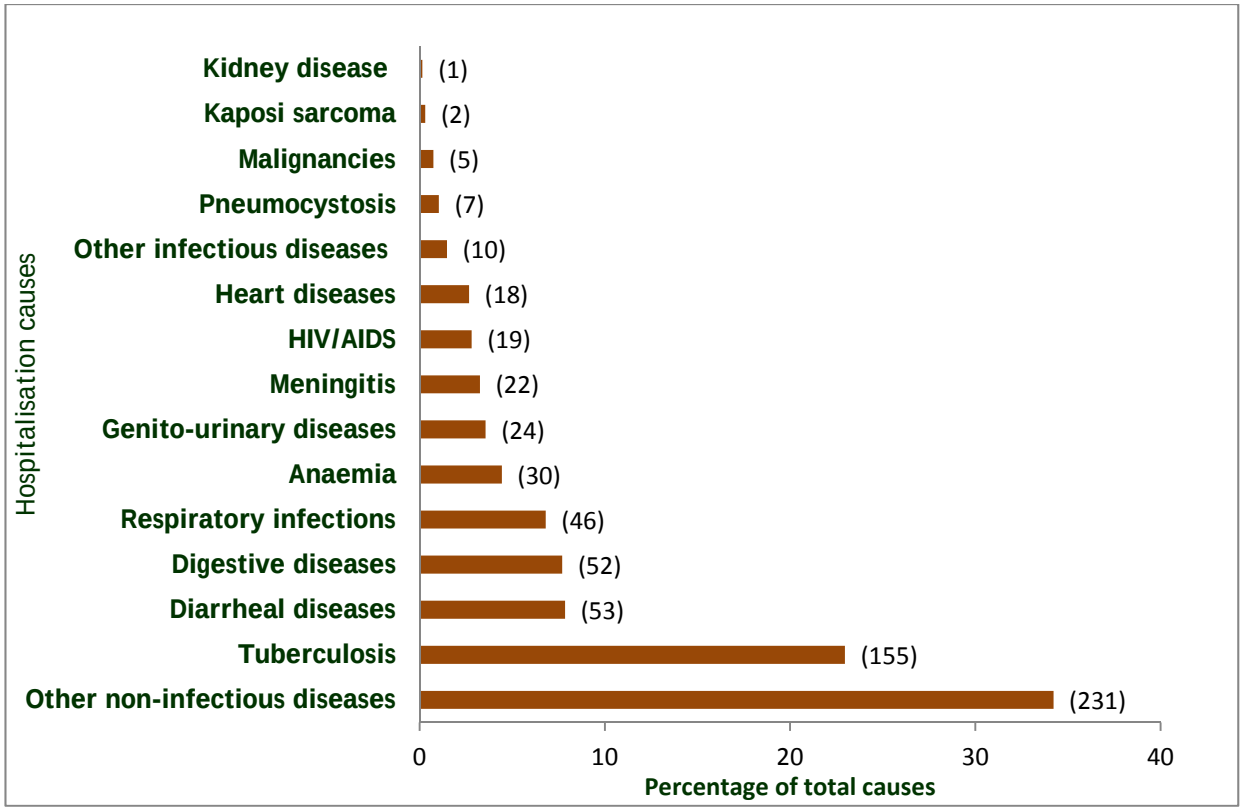


Figure 5.2 Conditions classified as other non-infectious diseases

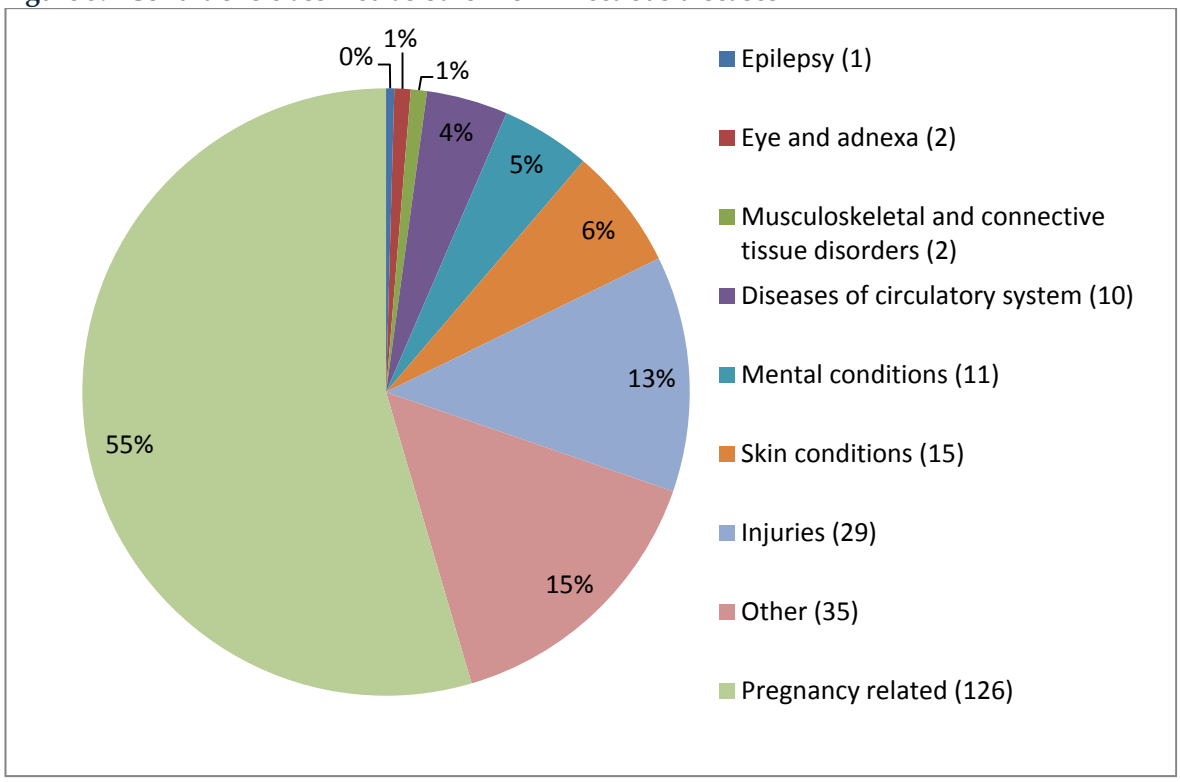
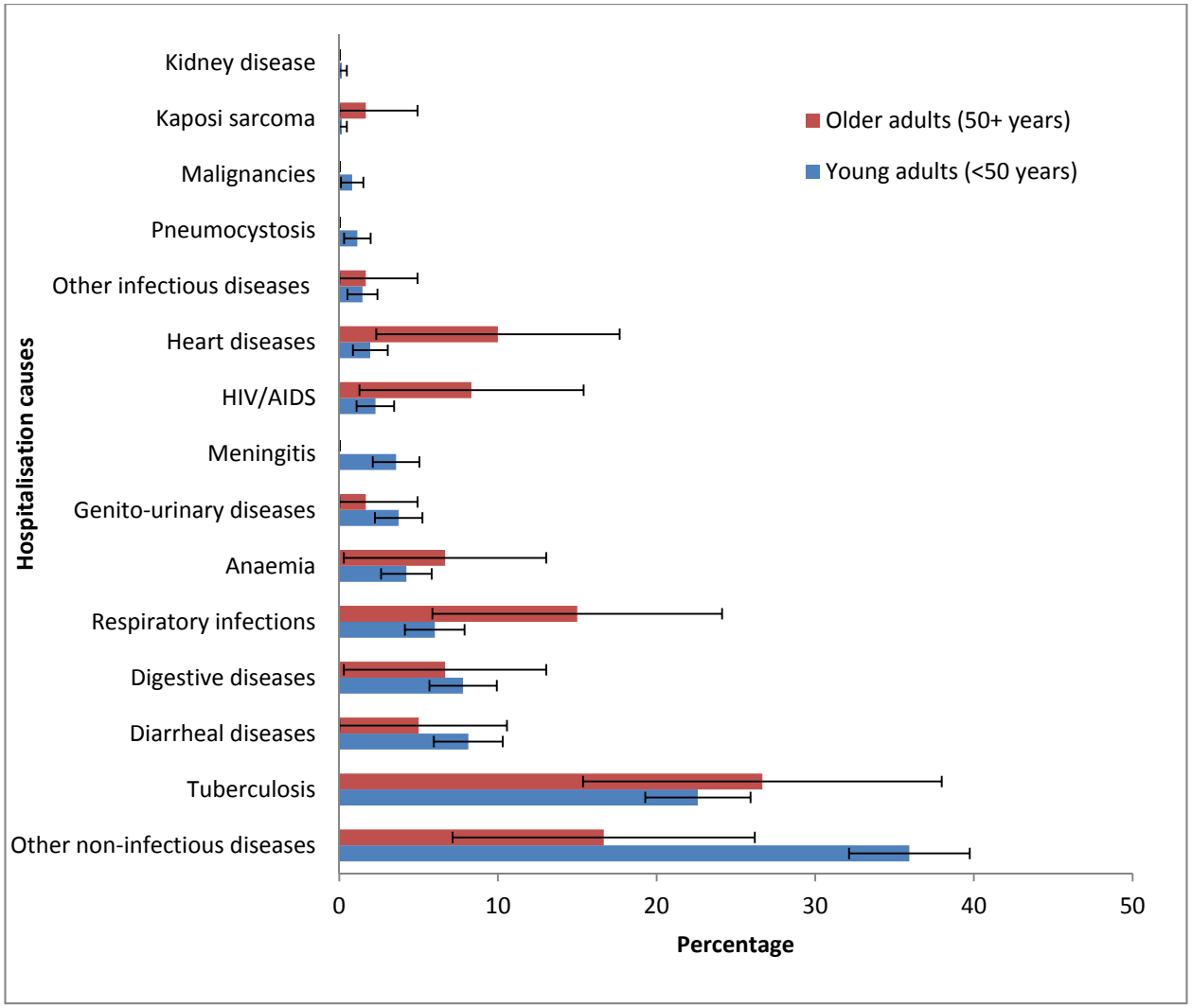


Figure 5.3: Age-stratified causes of hospitalisation following ART initiation determined through diagnosis made at time of hospital admission

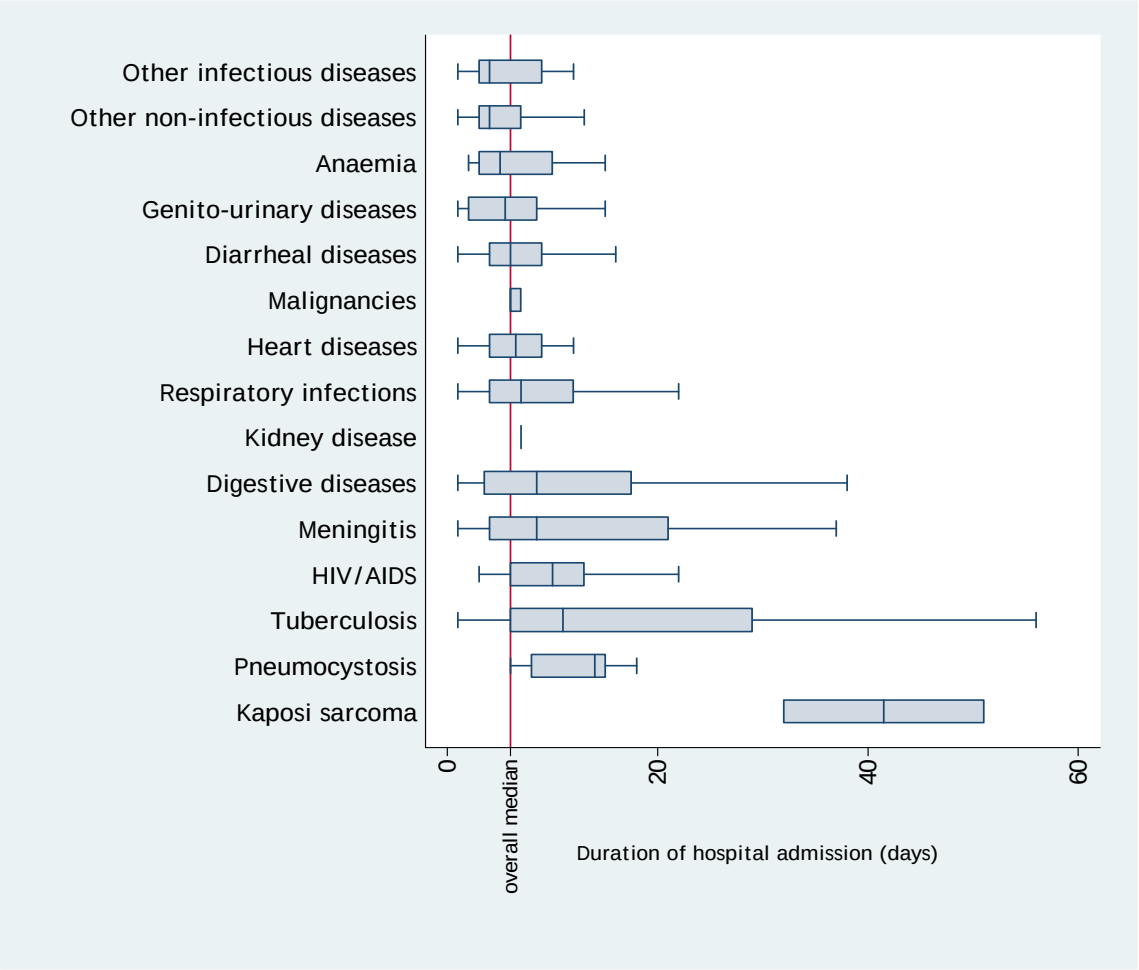


5.3.4 Duration of hospitalisation

The median duration of hospitalisation determined as the duration from date of admission to date of discharge/transfer to another health facility/absconding or death was 6 days; higher for older adults (median 8 days, IQR 4.5-13 days) compared to younger adults (median 6 days, IQR 3-12) p=0.002. Duration of hospitalization varied by cause of hospitalization with patients diagnosed

with more serious conditions such as Kaposi sarcoma, TB, advanced HIV/AIDS or pneumocytosis admitted into hospital for longer periods (Figure 5.4)

Figure 5.4: Duration of hospital admission stratified by morbidity type in patients receiving ART.

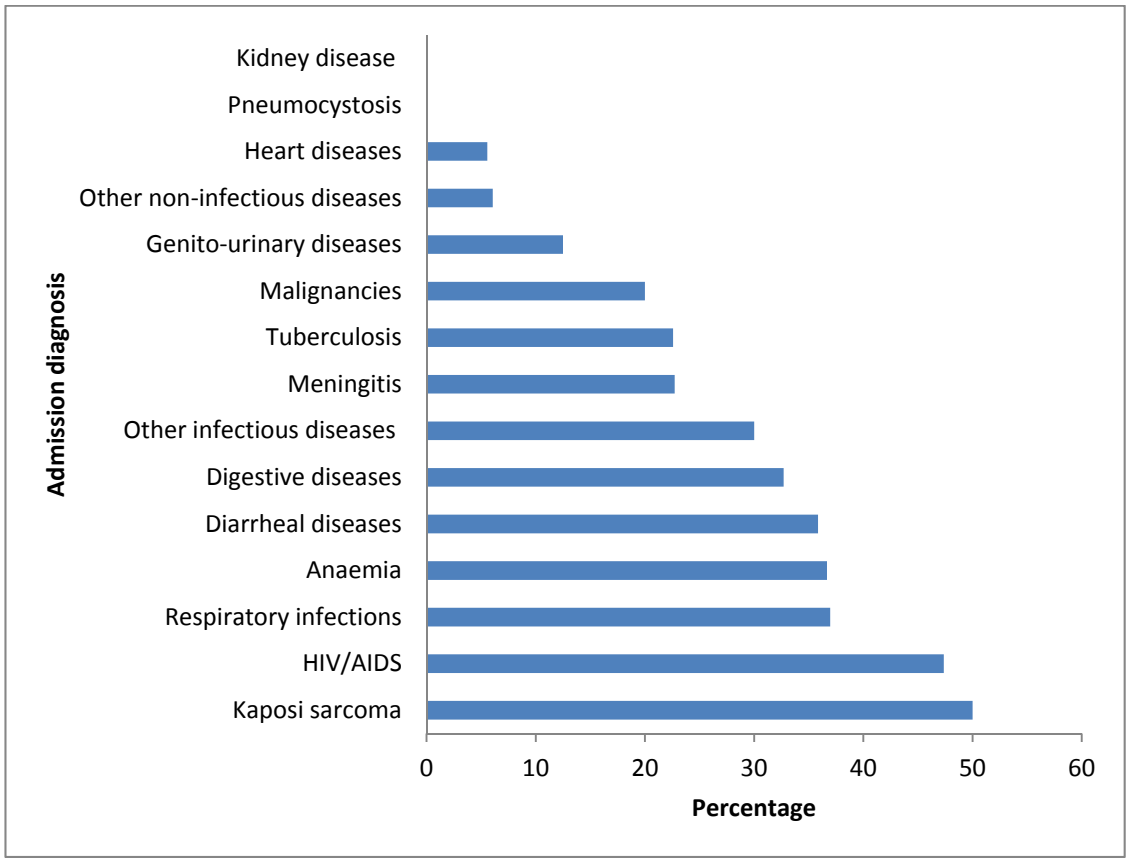


5.3.5 Hospitalisation outcomes

Of the 675 patients hospitalised following ART initiation, 529 (78.4%) were discharged home, 136 (20.2%) died, 5 (0.7%) were transferred to the regional hospital, 4 (0.6%) were in-patients at time of database closure and 1 (0.2%) had absconded from care. Although not statistically significant, older adults had higher in-patient mortality [16/60, 26.7% (95% CI,15.4-38.0%)] than younger adults [120/615, 19.5% (95% CI, 16.4-22.7%)].

Case-fatality rates (CFR)

Figure 5.5: Case-fatality rates stratified by the diagnosis given at hospital admission in patients receiving ART



Case-fatality rates were calculated as the number of deaths per each cause of admission. Common causes of hospitalisation such as genito-urinary diseases and other non-infectious conditions mainly consisting of pregnancy related conditions and injuries had relatively low case-fatality rates compared to rare conditions such as Kaposi sarcoma and advanced HIV/AIDS whose CFR were the highest at above 40% (Figure 5.5). TB was a common cause for hospitalisation and its CFR was considerably high at 23%. Differences in CFR by age at initiation were not explored due to the small numbers of patients dying in each morbidity category.

5.3.6 Effect of age on risk of hospitalisation

To assess whether older adults initiating ART had a higher risk of hospitalisation, a Cox regression model adjusted for baseline laboratory and clinical characteristics and gender was employed. From this analysis, compared to younger adults there was a trend towards lower risk of serious morbidity requiring hospitalization in older adults although this did not reach statistical significance (aHR 0.78, 95% CI 0.60-1.02) (Table 5.2). The statistically non-significant decreased risk of hospitalisation in older adults compared to younger adults was maintained even in an adjusted model excluding pregnancy related conditions (aHR 0.89, 95% CI 0.68-1.18).

5.3.7 Risk factors for hospitalisation

Adjusting for age at time of ART initiation, pregnant females were at higher risk of being hospitalized (aHR 1.34, 95% CI 1.05-1.72) than non-pregnant females. There were no significant differences in hospitalization risk in males compared to non-pregnant females. Worth noting is that in an adjusted model where serious morbidity excluded pregnancy related conditions, women

initiating therapy whilst pregnant were about half less likely to experience serious morbidity leading to hospitalisation (aHR 0.42 p<0.001) than non-pregnant women even after adjusting for age. In the same adjusted analysis, patients co-infected with TB at ART initiation had 41% increased risk of serious morbidity leading to hospitalisation (aHR 1.41 p=0.001) whilst those initiating therapy with advanced HIV as approximated by CD4 cell count less than 50cells/µl also had 60% increased risk of hospitalization (p<0.001). Anaemic patients (Hb <8g/dL) and those with low creatinine clearance as indicated by creatinine levels >240 µmol/L were at increased risk of hospitalization (Table 5.2).

Table 5.2: Risk factors for serious morbidity resulting in hospitalization following initiation of antiretroviral therapy

Variable	Adjusted hazard ratio	P>z	95% Confidence interval	
Sex: Females not pregnant	ref			
Males	1.08	0.392	0.91	1.28
Pregnant females	1.34	0.020	1.05	1.72
Age: <50 years	ref			
≥50 years	0.78	0.073	0.60	1.02
Concurrent TB therapy at ART initiation: No	ref			
Yes	1.41	0.001	1.15	1.72
Unknown	0.60	0.015	0.40	0.90
CD4 cell count (cells/µl): <50	1.59	0.000	1.30	1.94
50-200	ref			
>200	0.75	0.003	0.62	0.91
Missing	1.36	0.218	0.84	2.21
Hemoglobin (g/dL): ≥8	ref			
<8	2.80	0.000	2.09	3.76
Missing	1.06	0.743	0.76	1.47
Creatinine (µmol/L): ≤120	ref			
121-240	1.46	0.053	1.00	2.14
>240	3.97	0.000	2.15	7.34
Missing	1.85	0.007	1.18	2.90
Alanine transaminase (IU/L): ≤60	ref			
>60	0.99	0.973	0.70	1.41
missing	1.04	0.847	0.71	1.51

Sensitivity analysis

To account for missing baseline laboratory markers, two Cox regression models were used, one with only the complete cases (patients who had all laboratory markers measured and recorded) and the second one with all 8598 patients who initiated therapy within Hlabisa HIV Treatment and Care Programme between 1 June 2010 and 31 July 2012. Both regressions gave similar results in terms of the direction of the associations, the magnitude of the associations and the statistical significance levels. Hence conclusion described in the section immediately preceding this and given in Table 5.2 did not change once the missing categories were removed.

5.4 Key points

- Older adults initiate therapy early with higher CD4 counts, lower proportions with extremely low CD4 cell count (<50 cells/µl) and a lower proportion with extremely low haemoglobin levels than younger adults
- Rates of hospitalisation for patients receiving ART are high [8.3 (95% CI 7.7-8.9) per 100 person years]; rate of hospitalisation was three-fold increased in the first 3 months subsequent to ART initiation
- Patients initiating ART whilst concurrently taking TB medication were more likely to experience serious morbidity leading to hospitalisation (mostly due to TB) compared to patients not on TB therapy (IR 13.0 95% CI 11.0-15.5 per 100 person years and IR6.1 95% CI 4.2-8.9 for those on and not on TB therapy respectively). This was only the case in the first 3 months of ART.
- Rates of serious morbidity resulting in hospitalisation were non-statistically significantly higher in younger adults compared to older adults, with slight overlap between the confidence intervals.
- TB was the second leading cause of hospitalisation with 155 patients (23.0%); 56 (36.1%) of whom had been diagnosed with TB and were receiving TB therapy at ART initiation.
- Although a lower proportion of older adults had TB at time of initiating therapy, they had a higher proportion of cases diagnosed as TB at admission into hospital.
- Median duration of hospitalisation in older adults was 2 days longer than in younger adults. One in every 5 hospitalisation resulted in death; proportion was non-significantly higher in older adults.
- Case fatality rates were highest for Kaposi Sarcoma and advanced HIV/AIDS
- Patients initiating therapy with advanced HIV disease had a higher risk of hospitalisation.

6 Results: Association between age and mortality, viral suppression and CD4 count reconstitution after ART initiation

6.1 Introduction

Age is a major determinant of mortality for many diseases, including HIV infection, but the effect of age itself on other prognostic factors is not often studied directly (Babiker, Peto et al. 2001; The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group 2008). The excess mortality in the HIV positive older age group is not entirely accounted for by increased mortality that comes with ageing (Collaborative Group on AIDS incubation and HIV survival 2000), which would suggest that, in addition to age, there may be other factors contributing to mortality.

Since the wide-spread introduction of ART, there have been conflicting data on outcomes for older individuals (Chapter 1, Section 1.7.1). Some African studies have reported a positive association between increasing age and rapid HIV progression and subsequent mortality (Toure, Kouadio et al. 2008; Lawn, Little et al. 2009; Tuboi, Pacheco et al. 2010), while in other African studies there were no reported differences in mortality with varying age at ART initiation (Etard, Ndiaye et al. 2006; Stringer, Zulu et al. 2006; Brinkhof, Dabis et al. 2008; Brinkhof, Boulle et al. 2009). Whether rapid progression of HIV disease and high mortality are driven by older age or by later access to care by older persons (Grabar, Weiss et al. 2006) warrants further investigation.

Publication resulting from this results chapter: Mutevedzi PC, Lessells RJ, et al. (2011). "Association of age with mortality and virological and immunological response to antiretroviral therapy in rural South Africa" PloS One 6(7).

There is limited understanding of the relative contributions that age-associated differences in immunology, virology, access to treatment and susceptibility to co-morbid diseases have on long-term mortality outcomes (Danielson M E and C 2001; Grabar, Weiss et al. 2006; Silverberg, Leyden et al. 2007). Such gaps in knowledge may perpetuate poor health provision for HIV infected older people in resource-limited settings. The frequency of, and factors likely associated with, ART outcomes in older adults need to be studied to raise awareness and improve clinical management of older people on ART.

To narrow this gap in knowledge, this Chapter addresses Objective 4 of this PhD by quantifying the effect of age on response to ART in terms of total mortality, viral suppression and CD4 count reconstitution. Specifically, it assesses how mortality rates, immunological and virological responses following ART initiation compare between older and younger adults and how virological and immunological responses are associated with mortality risk using data from a large rural HIV Treatment and Care programme.

6.2 Methods

Objective

To quantify the effect of age on response to ART in terms of total mortality, viral suppression and CD4 count reconstitution after initiation of ART.

6.2.1 Data sources

Hlabisa HIV Treatment and Care Programme

The Hlabisa HIV Treatment & Care Programme is a partnership between the local Department of Health (DoH) and the Africa Centre for Health and Population Studies as described in Chapter 2, Section 2.2.1 and 2.2.2. The programme adheres to the national antiretroviral treatment guidelines which at the time of study (1st August 2004 to 31st October 2009) recommended initiation of ART for adults with WHO stage IV disease or CD4 cell count ≤200 cells/mm^3 (National Department of Health 2004). Co-trimoxazole was indicated for all individuals with CD4 count ≤200 cells/mm^3 or WHO stage 3/4. Guidelines have since been updated several times, as documented under Section 2.2.2.1.

First-line ART consisted of stavudine (d4T), lamivudine (3TC), and either efavirenz (EFV) or nevirapine (NVP). ART was initiated at primary health care (PHC) clinics (or at Hlabisa district hospital) by a physician; monitoring and ART dispensing was subsequently performed by nurses and counsellors. CD4 cell count and HIV viral load were measured every 6 months on ART.

6.2.2 Analytical methods

This analysis was solely based on data obtained within the Hlabisa HIV Treatment and Care programme and was not linked to any other data sources. Analysis included all adults (≥16 years) who initiated ART between 1st August 2004 and 31st October 2009, excluding patients already on ART who transferred into the programme from elsewhere. Analysis was stratified by age at initiation of ART (<50 years and ≥50 years). The <50 years age group was further stratified into 16-24 years and 25-49 years to assess for heterogeneity in overall outcomes and baseline descriptions. We assessed differences between the three groups in baseline clinical characteristics using the non-parametric equality-of-medians test for continuous variables and proportions test

for categorical variables. To evaluate kidney function at time of ART initiation, estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (4-v MDRD) equation, without the ethnicity correction factor, as validated in a South African population (Levey, Greene et al. 2000; van Deventer, George et al. 2008).

Kaplan-Meier survival analysis was used to assess and compare mortality between and within age strata. Data were censored at earliest of date of death, date of loss to follow-up, date of transfer out of programme, or 22nd April 2010. Loss to follow-up was defined as having missed three consecutive monthly pill collection visits (three months (90 days) without a clinic visit). To ascertain the independent influence of age on overall mortality, a Cox regression model adjusted for all significantly different baseline factors ($P<0.05$) was used to assess mortality hazard difference by age strata. The two bottom age strata (younger and mid-age groups) were combined in the analysis for determination of mortality risk factors because there were no statistically significant mortality outcome differences between the two groups. This is also consistent with previous analysis that assessed those aged below 50 years in comparison to those aged 50 years and above (Patterson, Napravnik et al. 2007; Schartz and Ogunmefun 2007; Negin and Cumming 2010; UNAIDS 2010). Studies including one from our Hlabisa HIV Treatment and Care Programme have reported very high mortality in the first three months of ART (Lawn, Myer et al. 2005; Boulle, Bock et al. 2008; Lawn, Harries et al. 2008; Lawn, Harries et al. 2010; Mutevedzi, Lessells et al. 2010), consequently stratified Cox regression with time split at 3 and 12 months post-ART initiation was used to determine risk factors for mortality in the periods 0-3 months (very early mortality), 3-12 months (early mortality), and >12 months post-ART initiation. For the two periods in the first year, analysis was further stratified by age to establish differences in mortality predictors between old and younger patients. For all Cox models, variables were included into the model one at a time and validity of the proportional hazards assumption was tested using the

score test based on scaled Schoenfeld residuals (Grambsch and Therneau 1994). All results are reported at 5% significance level.

Changes in CD4 cell counts in the 24 months following ART initiation were quantified using a piecewise linear model based on follow-up CD4 cell counts measured at six-monthly time points ± three months. For 909 and 504 patients with missing CD4 counts at 6 months and 12 months respectively the value was interpolated from their CD4 cell counts immediately before and after that time point. Viral load measurements were done at 6 and 12 months post-ART initiation hence virological response at one year was based on viral load measured between 6 and 15 months after ART initiation. The effect of sub-optimal virological response (defined as viral load ≥400 copies/ml) on mortality after the first year of ART was quantified in a Cox regression model adjusted for baseline variables and follow-up CD4 cell counts. For both viral loads and CD4 counts, where more than one measurement was available within the specified time period, the one closest to that time point was used.

Sensitivity analysis

To account for the effect of missing baseline and follow-up explanatory data, we assessed for any differences in mortality in those with missing observations compared to those with recorded observations. Where those with missing data had significantly different mortality rates, we maintained a category of the missing group within the respective variable in both the univariable and multivariable models exploring factors associated with mortality. This adjusted for any overestimation of the effect of measured/recorded variables on mortality in the absence of those with unmeasured/missing variables. To assess for the extent of loss to follow up bias; we

conducted sensitivity analyses where patients lost were considered dead. All analyses were performed with STATA version 11.0 (College Station, Texas, USA).

6.3 Results

6.3.1 Baseline patient characteristics

Between 1st August 2004 and 31st October 2009, 8846 adults initiated ART in the programme. Of these, 808 (9.1%) were aged 16-24 years, 7119 (80.5%) were aged 25-49 years and 919 (10.4%) were ≥50 years at time of ART initiation (range 16-83 years). Overall median baseline CD4 cell count was 119 cells/µl (IQR 58-174); slightly and non-clinically significantly higher for older adults (127, IQR 71-177) than in those aged 25-49 years (115, IQR 55-173). Older adults had the lowest proportion with CD4 cell count <50 cells/µl prior to ART initiation, significantly lower than those aged 25-49 (15.5%, 95% CI 13.2-17.9 for older adults vs 22.6%, 95% CI 21.6-23.6%) [Table 6.1 (page 182)].

6.3.2 Mortality rates

There were 997 deaths in 14 778 person-years of follow-up (72 deaths during 1 165.8 person years in adults aged 16-24 years; 790 deaths during 12 058.2 person years in adults 25-49 years and 135 deaths during 1 554.3 person years in older adults ≥50 years at ART initiation). The overall mortality rate was 6.75 per 100 person-years (95% CI 6.34-7.18). Table 6.2 shows the mortality rate was significantly higher for those ≥ 50 years old (8.69 per 100 person-years, 95% CI 7.34-10.28) than for younger adults aged 25-49 years old (6.55 per 100 person-years, 95% CI 6.11-7.02) and marginally higher than in those aged 16-24 years (6.18 per 100 person-years, 95% CI 4.90-

7.78). Overall, controlling for baseline characteristics (sex, WHO disease stage, baseline CD4 cell count, haemoglobin, weight and eGFR) there was a 32% increased mortality rate in patients aged ≥50 years (aHR 1.32, 95% CI 1.09-1.60, *P* = 0.004) compared to those aged 25-49. There were no significant differences in either overall mortality or time stratified mortality rates between those initiating aged 16-24 and those aged 25-49 [Table 6.2 (page 183)]

In all age groups, the majority of deaths (769 deaths, 77.1%) occurred in the first year after ART initiation, with mortality particularly high in the first three months after ART initiation (449 deaths, 45.0%). Figure 6.1 (Kaplan-Meier curve) illustrates mortality differences between the three age groups. Mortality rates were significantly higher for older adults (≥50 years) in the periods 0-3 months and 3-12 months post-ART initiation (Table 6.2) but there was no significant mortality difference after 12 months.

Figure 6.1: Kaplan-Meier plot of cumulative mortality probability after initiation of ART, stratified by age group

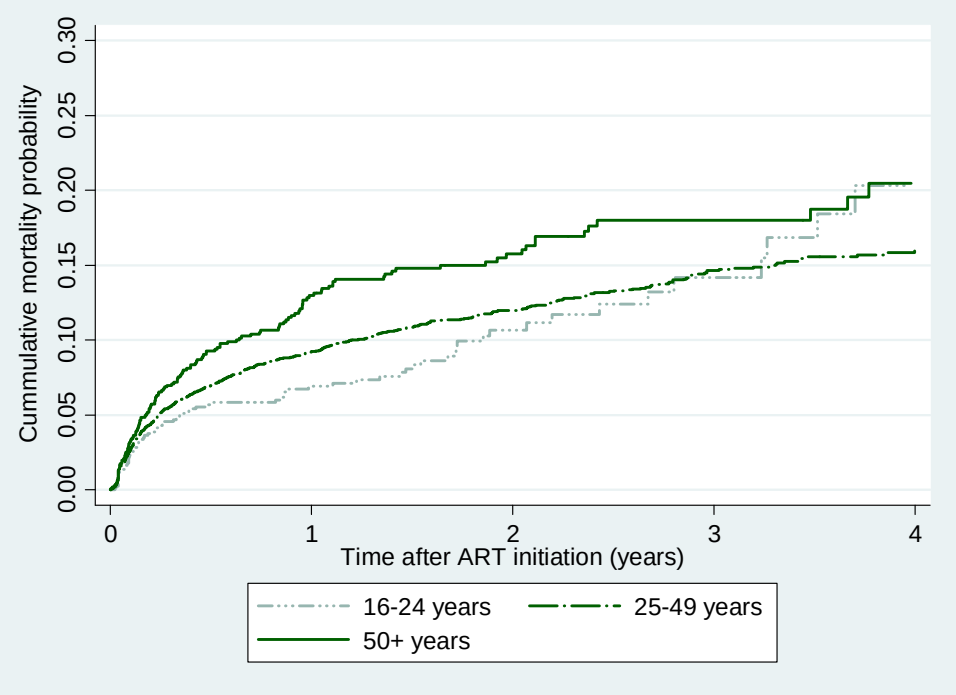


Table 6.1. Baseline characteristics for individuals initiated on ART August 2004 - October 2009 (n=8846), stratified by age at ART initiation

Variable	16-24 years			25-49 years			50+ years		
	N	% or median (IQR)	(95% CI)	*N*	% or median (IQR)	(95% CI)	*N*	% or median (IQR)	(95% CI)
Age	808	22 (21-24)		7119	35 (30-40)		919	54 (51-58)	
Male sex	107	13.2	10.9-15.6	2504	35.2	34.1-36.3	400	43.5	40.3-46.7
WHO stage 3 or 4	328	40.6	37.2-44.0	3435	48.3	47.1-49.4	420	45.7	42.5-48.9
Missing	357	44.2	40.8-47.6	2629	36.9	35.8-38.1	348	37.9	34.7-41.0
CD4 cell count, cells/µl									
Median (IQR)	777	133 (69-182)	125.7-144	6827	115 (55-173)	113-118	888	127 (71-177)	122-136
>200	118	15.2	12.7-17.7	764	11.2	10.4-11.9	114	12.8	10.6-15.0
150-200	220	28.3	25.1-31.5	1643	24.1	23.1-25.1	237	26.7	23.8-29.6
100-149	162	20.9	18.0-23.7	1449	21.2	20.3-22.2	221	25.0	22.0-27.7
50-99	139	17.9	15.2-20.6	1431	21.0	20.0-21.9	178	20.1	17.4-22.7
<50	138	17.8	15.1-20.5	1540	22.6	21.6-23.6	138	15.5	13.2-17.9
Viral load, log_{10} copies/ml	491	4.4	4.3-4.6	4313	4.4	4.4-4.4	542	4.5	4.4-4.6
Weight, kg (IQR)	704	56	54.7-57.1	6262	59.3	59-59.8	814	60	59.1-61
TB treatment	171	21.2	18.3-24.0	1581	22.2	21.2-23.2	175	19.0	16.5-21.6
Haemoglobin <8g/dL	76	9.4	7.4-11.4	576	8.1	7.5-8.7	44	4.8	3.4-6.2
Missing	110	13.6	11.3-16.0	914	12.8	12.1-13.6	101	11.0	9.0-13.0
***eGFR ≤60ml/min/1.73m^2**	30	3.7	2.4-5.0	854	12.0	11.2-12.8	311	33.8	30.8-36.9
Missing	93	11.5	9.3-13.7	725	10.2	9.5-10.9	86	9.4	7.5-11.2
Albumin <32 g/L	440	54.5	51.0-57.9	3764	52.9	51.7-54.0	474	51.6	48.3-54.8
Missing	98	12.1	9.9-14.4	767	10.7	10.1-11.5	93	10.1	8.2-12.1

CI, confidence interval; IQR, interquartile range

* eGFR, estimated glomerular filtration rate: calculated using 4-variable MDRD equation (without ethnicity correction)

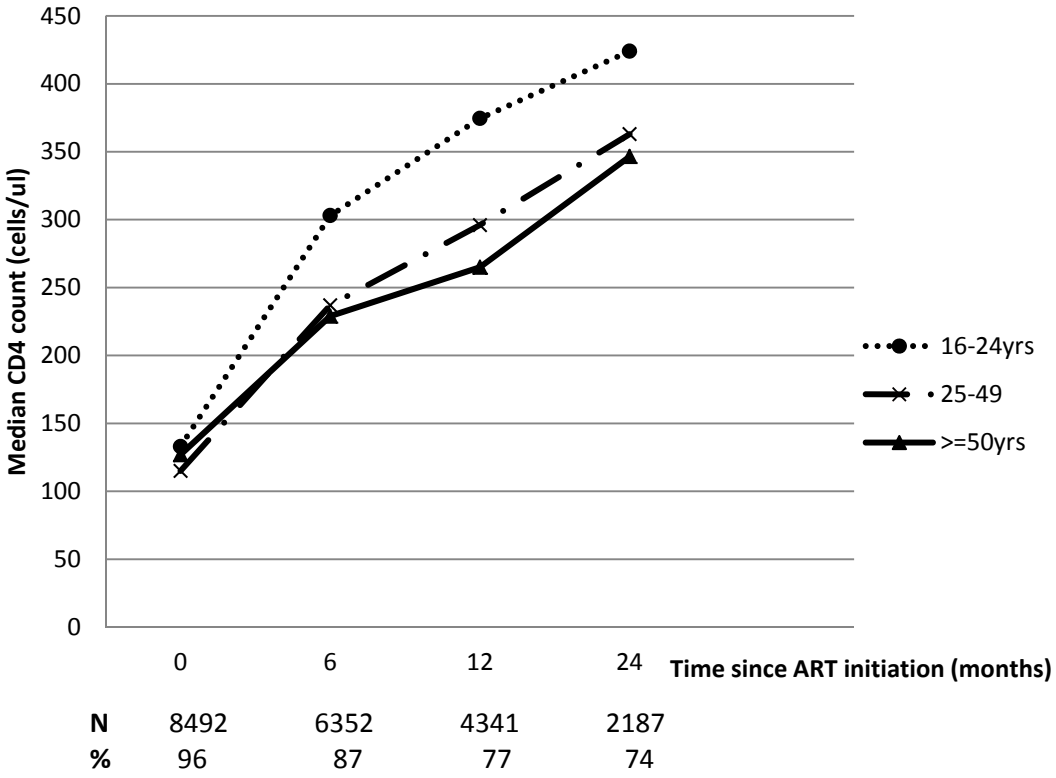
Table 6.2. Mortality rates following ART initiation stratified by age at initiation and cohort period time (N=8846)

Cohort period (months)	Person-time (years)	Deaths	Mortality rate	95% CI
		16-24 years		
0 - 3	186.3	32	17.2	12.1-24.3
>3-12	447.8	18	4.0	2.5-6.4
>12-24	340.9	13	3.8	2.2-6.6
>24	190.8	9	4.7	2.5-9.1
Total	1165.8	72	6.2	4.9-7.8
		25-49 years		
0 - 3	1675.7	358	21.4	19.3-23.7
>3-12	4166.9	251	6.0	5.3-6.8
>12-24	3478.1	111	3.2	2.7-3.8
>24	2737.5	70	2.6	2.0-3.2
Total	12058.2	790	6.6	6.1-7.0
		≥50 years		
0 - 3	217.6	59	27.1	21.0-35.0
>3-12	535.8	51	9.5	7.2-12.5
>12-24	445.1	15	3.4	2.0-5.6
>24	355.7	10	2.8	1.5-5.2
Total	1554.3	135	8.7	7.3-10.3
TOTAL	**14778.2**	**997**	**6.8**	**6.4-7.2**

6.3.3 Immunological response

Of the 2 977 patients alive and active attending drug collection clinic visits 12 months post- ART initiation, 2 187 patients (73.5%) had a recorded CD4 count. Although older adults initiated therapy with moderately higher median baseline CD4 cell count, their median CD4 cell count post-ART initiation was lower than for both groups of younger adults at each time point (Figure 6.2). Overall 16.6% had a poor immunological response (failed to achieve a CD4 count increase of ≥50 CD4 cells) in the first 6 months of therapy with the largest proportion being in those aged 50 years and above (19.6% vs 11.1% and 16.9% in 16-24 year olds and 25-49 years olds). Almost half of all those who initiated with CD4 cell count <50 cells/µl (45.2%) failed to attain a CD4 cell count >200 cells/µl at 12 months. The proportion of individuals with CD4 cell counts failing to reach the thresholds of 200 cells/ul and 350 cells/ul at specified time points post-ART initiation are displayed in Figure 6.3 and Figure 6.4 respectively.

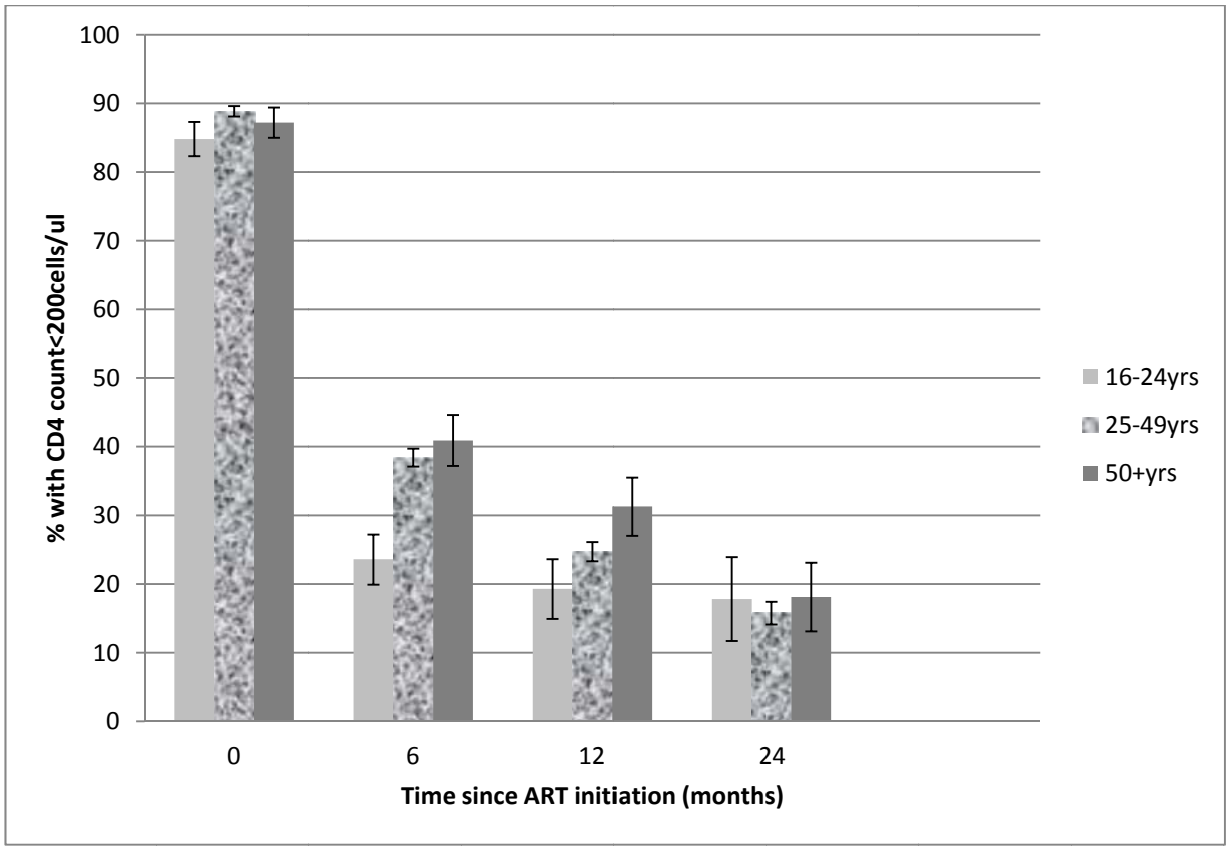
Figure 6.2: Median CD4 cell count (cells/µl) over time since ART initiation, stratified by age at ART initiation



N- Number with a recorded CD4 count at each time point

% - N as a percentage of the total number of people alive at active at the start of each time interval

Figure 6.3 Proportion of patients failing to achieve a CD4 count >200 cells/ul at pre-defined time points post ART initiation, stratified by age at initiation

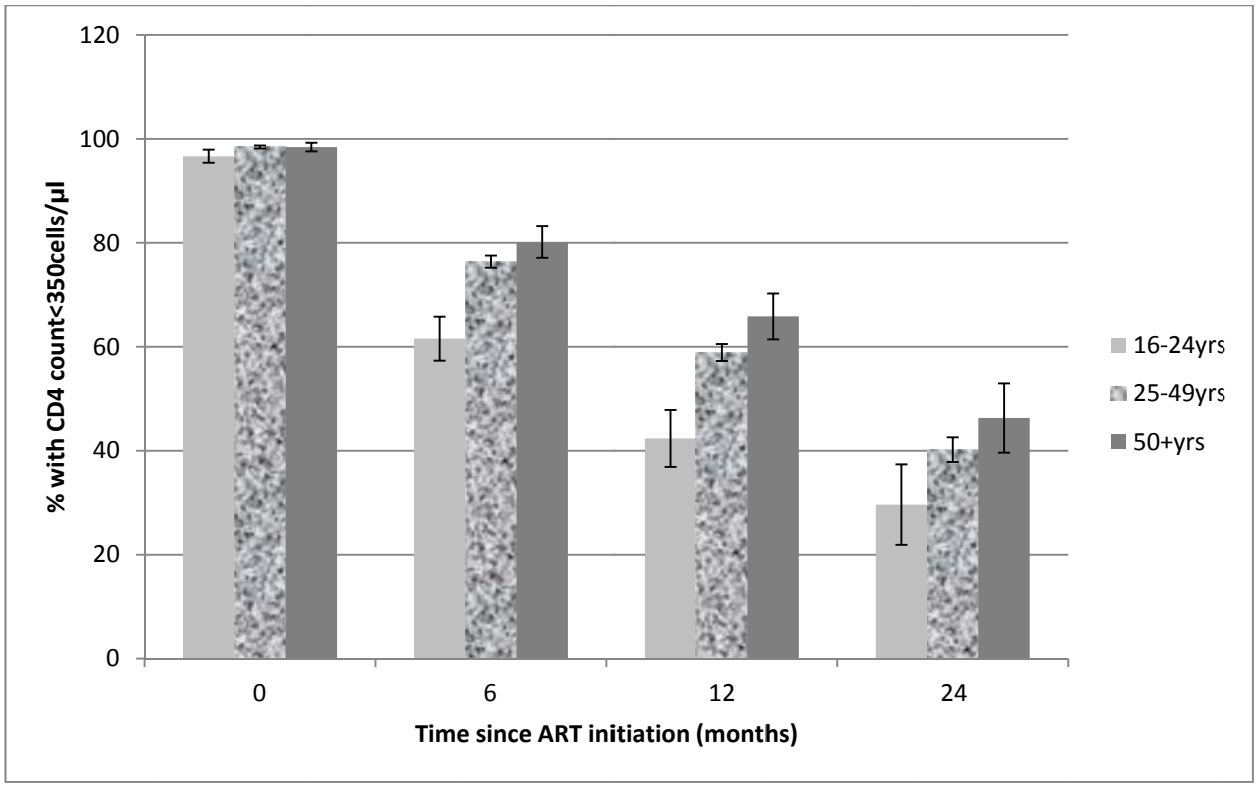


6.3.4 Virological suppression

From the 5 625 patients recorded as remaining under follow up at 12 months post-ART initiation, 3 809 (67.8%) viral loads were available for analysis. Most viral loads were missing because nurses forgot to collect blood specimens at the required times and viral load measurements were equally missing irrespective of age of patient or other clinical features of the patient (detailed in Section 6.3.6 on sensitivity analysis). Using viral load threshold of <400 copies/ml as an indicator of good virological response, 86.3% were classified as having a good virological response. A greater

proportion of older adults (90.1%, 95% CI 84.7-87.0) had a good response than younger adults (81.7%, 95% CI 77.4-86.1 and 86.2%, 95%CI 85.0-87.5 in 16-24 year olds and 25-49 year olds respectively).

Figure 6.4. Proportion of patients failing to achieve a CD4 count >350 cells/ul at pre-defined time points post ART initiation, stratified by age at initiation



6.3.5 Factors associated with mortality

0-3 months

Using age-stratified and time-split analysis, from the total 997 deaths, 449 occurred in the first three months after ART initiation (very early mortality) giving the highest period mortality rates of 20.9 and 27.1 per 100 person years in younger and older adults respectively (rate ratio 1.30; p=0.037). However, although mortality risk was significantly higher in the older age group, within

each age group, age was not independently association with mortality. There was strong evidence of an association between male sex, markers of advanced disease at initiation (CD4 cell count <50 cells/µl, higher log_{10} viral load, lower weight, and albumin <32g/L) and increased very early mortality in both age groups. In younger, but not in older, adults, there were additional associations with WHO stage 3/4, low haemoglobin, and renal impairment (Table 6.3).

3-12 months

Three hundred and twenty deaths; 269 (12.8%) in younger and 51 (20%) in older adults occurred between 3-12 months (early mortality), mortality rates remaining higher in older compared to younger adults (9.5 vs 5.8 per 100 person years respectively; rate ratio 1.64, p=0.001). Low baseline CD4 cell count (<50 cells/µl) remained independently associated with mortality in those aged <50years, as did WHO stage3/4 disease and low albumin. For older adults the only factor independently associated with mortality in this period was haemoglobin <8g/dL. There remained a trend towards increased mortality risk with CD4 cell count <50 cells/µl and albumin <32g/dL but the low numbers of deaths in this period for older adults (n=51) likely limited statistical power (Table 6.3).

After 12 months

Factors associated with mortality after 12 months were explored in a single model incorporating all ages because of the similar mortality rates after 12 months of ART in both age strata. In the adjusted model (Table 6.4) mortality risk was not significantly different for older adults compared to younger adults (adjusted hazard ratio [aHR] 1.01, 95% CI 0.66-1.55). There was no longer any evidence of an association with baseline CD4 cell count, but a lower absolute CD4 cell count and a reduced increment at 12 months post-ART initiation were both associated with higher mortality.

Sensitivity analysis

Mortality rates did not differ significantly between those with complete baseline observations compared to those with missing observations. However, 116 (6.4%) of 1816 patients alive but with a missing viral load at 12 months subsequently died compared to 112 (2.9%) of 3809 with a recorded viral load ($P < 0.001$). While 103 (7.1%) of those alive but with a missing CD4 cell count at 12 months post-ART initiation died compared to 125 (3.0%) of those with a recorded CD4 count ($P < 0.001$), resulting in higher mortality risk in some of these missing categories (Table 6.3 and 6.4). Overall loss to follow-up was 12.9%; 11.6% and 6.5% in those aged 16-24 years, 25-49 years and older adults respectively ($p<0.01$). Despite these differences, the sensitivity Kaplan Meier and Cox regression analysis results did not differ significantly from those obtained using completely observed data.

Table 6.3. Independent risk factors for very early (0-3 months after ART initiation) and early (3-12 months) mortality, stratified by age at ART initiation (N=8846)

Variable	Very early mortality (0-3 months)		Early mortality (3-12 months)	
	<50 years (n=7927)	≥50 years (n=919)	<50 years (n=7154)	≥50 years (n=832)
Age (1yr increase)		0.9 (0.95-1.04)		1.0 (0.99-1.08)
25-49 years	1		1	
16-24 years	0.8 (0.54-1.34)		0.7 (0.45-1.19)	
Sex Male	1.6 (1.32-2.03)	1.8 (1.06-3.17)	1.4 (1.09-1.80)	1.3 (0.73 - 2.41)
WHO stage 3 or 4	1.8 (1.11-2.81)	NS	2.1 (1.19-3.57)	NS
CD4 cell count (cells/µl)				
>200	1.6 (0.96-2.52)	1.2 (0.35-4.05)	1.5 (0.90-2.51)	2.2 (0.83-5.82)
150-200	1	1	1	1
100-149	1.2 (0.79-1.88)	1.0 (0.37-2.86)	1.0 (0.65-1.68)	1.7 (0.70-4.26)
50-99	1.6 (1.05-2.33)	2.3 (0.97-5.67)	1.5 (0.97-2.31)	2.0 (0.79-4.87)
<50	2.4 (1.63-3.46)	2.6 (1.07-6.31)	2.8 (1.85-4.10)	2.0 (0.80-4.98)
Missing	2.1 (1.16-3.87)	4.0 (1.10-14.4)	1.8 (0.92-3.51)	0.3 (0.04-2.63)
Viral load (per $\log_{10}$ increase)	1.2 (1.03-1.34)	2.3 (1.52-3.43)	NS	NS
Weight (1kg increase)	0.9 (0.93-0.95)	0.9 (0.94-0.99)	0.9 (0.97-1.00)	NS
TB treatment*	1.6 (0.84-1.97)	0.9 (0.48-1.69)	1.1 (0.79-1.40)	1.4 (0.72-2.63)
Haemoglobin <8g/dL	2.1 (1.61-2.64)	NS	NS	4.2 (1.79-9.65)
eGFR ≤60 ml/min/1.73m^2†	1.7 (1.35-2.23)	NS	1.4 (1.00-1.98)	NS
Albumin <32g/L	3.6 (2.44-5.24)	2.6 (1.19-5.58)	2.2 (1.56-3.02)	1.5 (0.76-3.02)
missing	4.4 (1.88-10.19)	0.7 (0.42-10.58)	NS	NS

Cox regression models split by time under observation (person years) into very early mortality (0-3 months) and early mortality (3-12 months). Risk factors determined separately for age groups <50 years and ≥50 years
All values are adjusted hazard ratios with 95% confidence interval
NS, not significant in univariable model
*Concurrent TB treatment at time of ART initiation
†eGFR, estimated glomerular filtration rate

Table 6.4. Independent predictors of mortality after the first 12 months of ART (N=5625)

Variable	aHR	95% CI
Age 25-49 years	1	
≥ 50 years	1.01	0.66-1.55
16-24 years	1.35	0.86-2.14
Male sex	1.95	1.46-2.57
Baseline WHO stage 3/4	2.72	1.49-4.97
Missing	2.62	1.43-4.83
Baseline CD4 cell count (cells/µl)		
150-200	1	
100-149	0.80	0.51-1.25
50-99	1.11	0.72-1.71
<50	1.11	0.70-1.75
>200	0.65	0.38-1.13
Missing	0.46	0.20-1.06
Weight (1kg increase)	0.98	0.96-0.99
Albumin <32 g/L	1.77	1.27-2.47
CD4 increment at 6months (cells/µl)		
<50	1	
50-99	0.98	0.63-1.51
≥100	0.49	0.29-0.81
Missing	1.33	0.39-4.59
Absolute CD4 count at 6months (cells/µl)		
>350	1	
201-350	1.45	0.81-2.57
≤200	0.91	0.44-1.90
CD4 increment at 12months (cells/µl)		
<50	1	
50-99	0.41	0.23-0.73
≥100	0.46	0.24-0.88
Missing	6.15	1.69-22.38
Absolute CD4 count at 12months (cells/µl)		
>350	1	
201-350	0.81	0.43-1.54
≤200	1.49	0.73-3.03
Viral load at 12months (copies/ml)		
<400	1	
≥400	2.67	1.78-4.02
Missing	1.74	1.26-2.41

aHR, adjusted hazard ratio; CI, confidence interval

Risk factors determined through Cox proportional hazards regression techniques, assessing mortality after 12 months post ART initiation, conditional on being active on the treatment programme at 12 months.

6.4 Key points

- Older adults had the lowest proportion with CD4 cell count <50 cells/µl prior to ART initiation.

- The overall mortality rate was 6.75 per 100 person-years, significantly higher for older adults (8.69 per 100 person-years) than younger adults (6.18 and 6.55 per 100 person-years in those age 16-24 years and 25-49 years old respectively).

- In adjusted analysis, there was a 32% excess mortality risk in patients aged ≥50 years compared to those aged 25-49

- In all age groups, the majority of deaths occurred in the first year after ART initiation, with mortality particularly high in the first three months after ART initiation

- Despite baseline CD4 cell count being higher for older adults; their median CD4 cell count post-ART initiation was lower than for both groups of younger adults at each subsequent time point

- The largest proportion of patients with poor immunological response (failed to achieve a CD4 count increase of ≥50 CD4 cells) in the first 6 months of therapy was higher in older adults

- Almost half of all those who initiated with CD4 cell count <50 cells/µl (45.2%) failed to attain a CD4 cell count >200 cells/µl at 12 months post ART initiation

- Despite having poorer immunologic responses, a greater proportion of older adults (90.1%) than younger adults (81.7% and 86.2% in 16-24 year olds and 25-49 year olds respectively) had a good virological response

- Although mortality risk was significantly higher in the older age group, within each age group, age did not have an independent association with very early mortality

- In younger, but not in older adults, very early mortality was associated with WHO stage 3/4, low haemoglobin, and renal impairment

- Factors associated with mortality after 12 months were explored in a single model incorporating all ages because of the similar mortality rates in both age strata

- 12 months after initiating ART there was no longer any evidence of an association between mortality and baseline CD4 cell count, but a lower absolute CD4 cell count and a reduced increment at 12 months post-ART initiation were both associated with higher mortality after 12 months

7 Results: Contribution of morbidity and abnormal bio-measures to cause-specific very early mortality on ART

7.1 Introduction

Very early mortality in the first three months of antiretroviral therapy (ART) has consistently been reported to be higher in low- and middle-income countries than in Europe and North America, an observation only partly explained by lower CD4+ cell counts and more advanced clinical stage at time of ART initiation (Braitstein, Brinkhof et al. 2006; Boulle, Bock et al. 2008; Lawn, Harries et al. 2008; Mutevedzi, Lessells et al. 2010). Relatively little is known about specific causes of mortality or the influence of HIV-related and HIV-unrelated morbidities at the time of initiating ART. This knowledge is important to inform the design of programmatic strategies to reduce very early mortality and improve long-term prognosis.

This chapter presents results addressing Objective five of this PhD, aimed at establishing causes of very early mortality following initiation of ART in older adults, in comparison with younger adults. It quantifies the effect of baseline morbidity to very early mortality risk in both age groups and ascertains whether levels of Hb, ALT and GFR at ART initiation are indicators of increased very early mortality risk. These markers were of interest because treatment efficacy and mortality may depend on the patients' kidney and liver ability to metabolise and excrete ART drugs. For this reason and in accordance with South Africa HIV treatment guidelines, unless the patients urgently requires therapy, before patients initiate ART, kidney and liver function efficiency is evaluated

through laboratory measured Glomerular filtration rate (GFR) and Alanine aminotransferase (ALT) respectively. Haemoglobin (Hb) levels are also determined.

7.2 Methods

Objectives

a. To establish causes of early mortality (occurring in the first 3 months of initiating ART) following initiation of ART in older adults compared to younger adults,

b. To quantify the effect of baseline morbidity on early mortality risk

c. To ascertain whether levels of Hb, ALT and Glomerular Filtration Rates (GFR) at time of initiating ART are risk factors for early mortality.

7.2.1 Data sources

This analysis employed data collected within the ART Clinical Cohort which was established in March 2010 to provide amongst other things, specific morbidity and mortality causes in HIV positive patients receiving ART. The ART Clinical Cohort recruits patients that are initiating therapy at two of the 17 clinics within the Hlabisa HIV Treatment and Care Programme, details of which are in Section 2.2.3 of this thesis. Patients enrolled within this cohort did not systematically differ from those initiating elsewhere within the main Hlabisa HIV Treatment and Care Programme in terms of their baseline characteristics as detailed under Chapter 4 in Section 4.3.1 which describes baseline demographic, clinical and laboratory characteristics of patients at ART initiation. Analysis included all adults (≥16 years) who were enrolled into the ART Clinical Cohort between March

2010 and July 2012, allowing for 6 months of follow-up for all individuals included in the analysis. Data were censored at 31 January 2013.

7.2.2 Definition of variables

Very early mortality was defined as mortality within the first 91 days (3 months) of ART. In addition to specific ICD10 coding (Section 2.2.3.2), causes of mortality were broadly coded into system-specific categories such as genito-urinary, cardiovascular, haematological diseases, HIV/AIDS, TB and injuries. Broader categories were used as per Global Burden of Diseases classification, namely infectious and parasitic diseases; injuries; non-communicable diseases and unknown causes (Lopez and Mathers 2006; Lopez, Mathers et al. 2006).

Morbidity at ART initiation (baseline morbidity)

Specific details on baseline cause-specific morbidity differentials by age and how age at initiation is associated with baseline morbidity are presented in Chapter 3. In this chapter we employ the broad morbidity categories (none, HIV-associated only, HIV-associated and TB, HIV-associated and chronic, TB only) to quantify how presenting with certain morbidities at baseline influences mortality risk within the first 3 months of ART.

BMI categorized as per WHO recommendations (WHO 2012):

- Underweight: <18.5;
- Normal: 18.5-<25;
- Overweight (pre-obese): 25-<30;
- Obese/ morbidly obese: 30+

Laboratory markers

Within Hlabisa HIV treatment and care programme, at time of initiating ART (baseline) in addition to haemoglobin levels, patients liver and kidney function are evaluated based on laboratory-measured levels inclusive of Alanine Aminotranferase (ALT), Creatinine and Glomerular Filtration Rates (GFR) (National Department of Health 2003; National Department of Health 2004; National Department of Health 2010; National Department of Health 2013) and these same markers were assessed in terms of their association with baseline morbidity. The threshold for determining abnormal levels were kept in line with previous published studies based on Hlabisa HIV Treatment and Care Programme data (Mutevedzi, Lessells et al. 2010; Mutevedzi, Lessells et al. 2011):

Laboratory marker	**Abnormal**	**Units**
Hemoglobin (Hb)	<8	g/dL
Alanine Aminotranferase (ALT)	>60 (2xupper limit of normal)	IU/ml
Glomerular filtration rate (GFR)	<60	ml/min/1.73m2

7.2.3 Analytical methods

Proportions and medians of categorical and continuous baseline characteristics respectively were described stratified by age at ART initiation i.e. younger (<50 years) or older (≥50 years) adults. Differences in baseline characteristics between the two groups were assessed using the non-parametric equality-of-median test for continuous variables and proportions test for categorical variables. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable

Modification of Diet in Renal Disease (4-v MDRD) equation, without the ethnicity correction factor, as validated in a South African Population.

Overall and age-specific all-cause and cause-specific mortality rate in the first three months of ART were estimated by Kaplan-Meier analysis. Data were censored at earliest of loss to care, transferring out of the programme or last clinic visit. Patients not seen for longer than 180 days (nine months) from the date of database closure (16 January 2013) were classified as loss to care. To ascertain the independent influence of existing baseline co-morbidities on very early mortality, a Cox regression model adjusted for age, sex and baseline clinical and laboratory markers. Age-specific adjusted Cox regression models were used to examine whether the effect of baseline co-morbidities was age-specific.

7.2.4 Attributable early mortality risk due to baseline morbidity

Attributable risk (AR) is the difference in rate of early mortality in patients presenting with certain morbidities at baseline compared to those without. Attributable fraction ($AF_{exposed}$) refers to the proportion of cases following exposure whilst the etiologic fraction, also known as population attributable risk percentage (PAR%), is the reduction in early mortality incidence that would be observed at population level if the population was entirely unexposed compared with its current actual exposure levels. All definitions were in line with previously set definitions (Northridge 1995; Rothman and Greenland 1998). Although attributable risk measures may not replace relative measures of effect, they are essential in that, due to them being population based concepts, they provide a public health dimension to the appraisal of risks (Walter 1976). Identification of exposure with a high rate ratio would indicate a disease of public health priority, whereas a low exposure level at a population level would downgrade the disease. Despite attributable risk relying

on accurately measuring exposure status, its use is particularly relevant when the goal of a study is to estimate the amount or proportion of cases attributable to a certain risk factor and guides policy makers when it is time to take action (Northridge 1995).

Population attributable risk percentage (PAR%) was calculated as (Kelsey, Thompson et al. 1986)

$[(Rate_{total\ population}-Rate_{unexposed})/Rate_{total\ population}]*100\%$

And was expressed in terms of the rate ratio and exposure prevalence as

$P_{exposed}\ (RR-1)/[1+P_{exposed}\ (RR-1)]$

Where

RR=rate ratio

$P_{exposed}$= exposure prevalence

$(AF_{exposed})$ was calculated as

$Rate_{exposed}-Rate_{unexposed}/Rate_{exposed}$

7.3 Results

Between March 2010 and July 2012, 1 409 patients were enrolled into ART Clinical Cohort, 425 (30.2%) male, 193 (13.7%) aged 50 years and above at time of initiating ART. Most patients initiated therapy with a CD4 cell count <200 cells/µl (median 148; IQR 82-205) and just over 40% had WHO diseases stage 3 or 4. Based on laboratory-measured haemoglobin (Hb), 66 patients (4.7%) were severely anaemic with Hb levels <8g/dL. 127 patients (9.0%) had an estimated GFR<60

ml/min/1.73m2 whilst 62 (4.4%) had ALT levels greater than twice the upper limit of detection (>60 IU/ml). Baseline characteristics presented here mirror baseline characteristics within Hlabisa HIV Treatment and Care Programme as previously reported within this thesis (Chapter 7) and are also similar to previously published data from Hlabisa HIV Treatment and Care Programme (Mutevedzi, Lessells et al. 2010; Houlihan, Bland et al. 2011; Mutevedzi, Lessells et al. 2011; Lessells, Mutevedzi et al. In Press).

7.3.1 Mortality

Overall

At date of database closure (16 January 2013), 1 091 patients (77.4%) were actively on therapy, 89 (6.3%) had died, 100 (7.1%) were lost to follow up (LTFU) and a further 129 (9.2%) had formally transferred out of the programme. Truncating data at 3 months post-ART initiation, 1316 patients (93.4%) were actively on therapy, 59 (4.2%) had died, 24 (1.7%) were LFU and 10 (0.7%) had formally transferred out of the programme; indicating that most (66.3%) deaths occur immediately after initiating ART. Furthermore, within these first three months, most deaths were in the first month (33 of the 59 deaths; 66.1%).

Very early mortality rate

In the 1 409 patients initiated onto therapy and enrolled into the ART Clinical Cohort, 59 deaths (4.2%) occurred in the first 3 months of initiating ART after a total follow-up time of 338.14 person years; giving an estimated mortality rate in the first three months post-ART initiation of 17.45 per 100 person-years of observation (95% CI 13.52-22.52). Mortality was significantly higher in the

first month of ART than in the next 2 months: 29.13 (95% CI 21.13-41.80) and 11.45 (95% CI 13.52-16.81) per 100 person years respectively.

7.3.2 Cause-specific mortality rates

Using broad mortality causes categories, there were 44 infectious and parasitic mortality causes; mostly due to TB (n=24, 40.7%); cause-specific mortality rate in the first three months post-ART 7.1 (95% CI 4.8-10.6) per 100 person years and advanced stage HIV (n=15, 25.4%); cause-specific mortality rate in the first three months post-ART 4.4 (95% CI 2.7-7.4) per 100 person years. Cause-specific mortality from non-communicable diseases was 1.8 (95% CI 0.8-3.9) per 100 person years (n=6 deaths, 10.2%). Nine deaths (15.3%) were from unknown causes (Table 7.1). Specific ICD10 mortality causes per category are listed in Table 7.1 and Figure 7.1.

Table 7.1: Specific very early mortality causes falling within the non-communicable cause of death category

Broad ICD10 class	Specific conditions	Number of deaths
Genitourinary diseases	Acute renal failure, unspecified	1
Haematological disorders	Aplastic anaemia, unspecified	1
Cardiovascular diseases	Congestive heart failure	1
Digestive diseases	Hepatic failure, unspecified	2
Malignant neoplasms	Kaposi's sarcoma	1
Total deaths from non-communicable diseases		**6**

Infectious and parasitic diseases	**Tuberculosis**	o Drug resistant tuberculosis o Miliary tuberculosis, unspecified o Tuberculosis of lung, bacteriologically and histologically negative o Tuberculosis of lung, confirmed by culture only o Tuberculosis of lung, confirmed by sputum microscopy with or without culture o Tuberculosis of lung, without mention of bacteriological or histological confirmation o Tuberculous meningitis o Tuberculous pleurisy without mention of bacteriological or histological confirmation
	HIV/AIDS	o HIV disease resulting in Pneumocystis carinii pneumonia o HIV disease resulting in wasting syndrome o Unspecified HIV disease
	Meningitis	o Meningitis, unspecified
	Respiratory infections	o Pneumonia, unspecified
	Other infectious	o Candidal stomatitis o Cerebral cryptococcosis

Figure 7.1. Specific early mortality causes falling within the infectious and parasitic mortality causes

Interestingly, of the 24 deaths where the documented cause of death was TB and the 15 due to HIV/AIDS only 1 of each was amongst older adults (Table 7.2). Conversely, the mortality rate due to non-communicable diseases was higher for older than younger adults. All age-associated differences in cause-specific very early mortality rates failed to reach statistical significance most likely due to small numbers.

Of the 24 with TB documented as the cause of death within the first three months of therapy, 13 (54.2%) were on TB therapy at time of initiating ART whilst 11 (45.8%) were undiagnosed at ART initiation. Four (44.4%) of the 9 patients with an unknown cause of death were receiving TB therapy when they initiated ART. Just over half (8/15) of patients where the cause of death was HIV/AIDS were already severely underweight at initiation whilst a fifth (3/15) were asymptomatic when they initiated therapy. None of the 72 patients presenting for ART initiation with chronic morbidity only died within the first three months of ART. One patient who initiated ART whilst on TB and chronic (asthma) medication and presented with advanced HIV disease and wasting (WHO stage 4), survived the first three months of ART. Mortality in relation to this category could not be assessed further in regression analysis. Table 7.3 and Section 7.3.3 below detail the effect of baseline morbidity on very early mortality.

Table 7.2. Cause specific rates of mortality occurring in the first three months post-ART initiation stratified by age at ART initiation

Very early mortality cause		Number of deaths	Cause-specific mortality rates (per 100 person-years)	95% CI
HIV	Overall	15	4.44	2.67-7.36
	Young	14	4.80	2.84-8.11
	Old	1	2.15	0.30-15.23
TB	Overall	24	7.09	4.76-10.59
	Young	23	7.89	5.24-11.87
	Old	1	2.15	0.30-15.23
Other Infectious and parasitic conditions	Overall	5	1.48	0.71-4.12
	Young	5	1.71	0.71-4.12
	Old	-	-	-
Non-communicable conditions	Overall	6	1.77	0.80-3.95
	Young	5	1.71	0.71-4.12
	Old	1	2.15	0.30-15.23
Unknown	Overall	9	2.7	1.4-5.1
	Young	6	2.06	0.92-4.58
	Old	3	6.44	2.08-19.96
All cause	Overall	59	17.45	13.52-22.52
	Young	53	18.18	13.89-23.80
	Old	6	12.88	5.78-28.66

Age stratified into young adults aged 16-49 years and older adults aged ≥50 years

7.3.3 Effect of baseline morbidity on very early mortality

In multivariable analysis (Table 7.3), adjusting for age at ART initiation, sex, baseline laboratory (CD4 count, Hb, ALT and eGFR) markers and BMI, compared to no symptoms, initiating ART with HIV-associated morbidity increased risk of dying within the first three months of ART by

over five and half times (aHR 5.5; 95% CI 2.3-13.1. Initiating ART with HIV-associated morbidity coupled with either TB (aHR 5.65 p<0.01) or any chronic pre-existing morbidity (aHR 6.44 p<0.01) further increased the risk of mortality in the first three months of ART. Mortality risk in patients initiating therapy in the absence of any HIV-associated morbidity but with chronic morbidity only or chronic morbidity and TB did not statistically significantly differ from that in asymptomatic patients (Table 7.3)

Overall attributable risk

Categorizing baseline morbidity as a yes/no variable collapsing HIV-associated morbidity, pre-existing chronic morbidity and TB into a yes category, the ratio of early mortality incidence in those presenting for ART initiation with baseline morbidity to the incidence of early mortality in those without morbidity was high (6.7, 95% CI 3.04-17.51). Early mortality incidence attributable to baseline morbidity in those exposed was also high at 85.1% (95% CI 67.1-94.3%) as was the population-attributable risk percentage (75.0%) (Table 7.4).

Attributable risk by baseline morbidity status

Overall, assessing for exposure to baseline HIV-associate morbidity only (337/1409 patients (24%) presenting for ART initiation with HIV-associated morbidity only), early mortality incidence rate ratio was 2.9 (95% CI 1.7-4.9) with an attributable fraction of 0.65 (95% CI 0.39-0.80) in those exposed and an etiologic fraction (PAR%) of 29.7%. For those initiating with HIV-associated morbidity coupled with TB (32/1409; 2.3%), the early mortality rate ratio increased to 5.54. The attributable fraction in this group increased to 81.9% (95% CI 48.6-92.2%) but the PAR% was low at 8.3%. For those initiating with HIV-associated morbidity coupled with any pre-existing chronic morbidity (63/1409; 4.5%), all three measures were relatively low. Interestingly although the prevalence of TB at ART initiation was high in this cohort, the early

mortality incidence rate ratio between those with and without TB was low at 1.6 (95% CI 0.82-2.99). Early mortality attributable to baseline TB was not substantial (37.9%; 95% CI 0-66.5%) compared to baseline HIV-associated morbidity or baseline HIV-associated morbidity coupled with TB. The population-attributable risk of early mortality due to TB only was a modest 9.0%.

Age stratified attributable risk

Overall assessing for early mortality incidence and risk attributable to combined baseline morbidity (HIV-associated, pre-existing chronic and TB), in younger adults, the incidence early mortality rate ratio between those with morbidity and those without was still high at 6.8% (95% CI 3.05-17.83) with a PAR% of 74.0%. For older adults all 6 deaths that occurred within the first 3 months of ART were in patients with baseline morbidity and it was thus not possible to estimate the early mortality incidence rate ratio or the exposure- and population attributable risk.

Age stratified attributable risk by baseline morbidity status

Due to relatively small numbers of older adults in the Clinical Cohort (n=193; 13%), it was not possible to stratify PAR% by each baseline morbidity status (patients initiating with TB only or HIV-associated morbidity coupled with TB). However, for HIV-associated morbidity only the attributable fraction due to this morbidity was nearly double in older (93.4%; 95% CI 40.8-99.8%) than in younger adults (59.2%; 95% CI 26.0-77.1%). The PAR% was also higher for older adults (77.8%) than for younger adults (24.6%) and so were the rate ratios. However interpretation of these results is hindered by small numbers and very wide confidence intervals. The opposite was observed when looking at those patients initiating ART with both HIV-associated morbidity and pre-existing chronic morbidity. In this group, the early mortality incidence rate ratio was higher amongst younger (2.5; 95% CI 0.49-7.68) than older adults (0.8;

95% CI 0.02-7.32). The PAR% for both groups was similar with 3.4% for younger and 3.5% for older adults.

7.3.4 Effect of bio-measures on very early mortality

In adjusted analysis, patients initiating therapy with ALT levels greater than 60IU/ml, (twice the upper limit of normal (2xULN)), had triple increased risk of mortality (aHR 3.0; 95% CI 1.4-6.4) within the first 3 months of ART compared to patients with normal levels. The causes of death in the first three months of ART, in patients with elevated ALT levels were; 40% from TB, 10% from digestive related conditions and 50% from advanced HIV disease. Additionally, patients with a BMI in the underweight category were at increased risk of very early mortality compared to patients initiating therapy with normal BMI (aHR 2.6 p=0.002). Haemoglobin levels and glomerular filtration rates did not significantly increase mortality risk once differences in baseline morbidity, CD4 cell count, age and sex were accounted for (Table 7.3).

Table 7.3: Age-adjusted Cox regression model assessing the effect of morbidity and abnormal bio-measures on very early mortality in 1409 HIV positive individuals

Characteristic	Unadjusted hazard ratio	Age-adjusted hazard ratio	P>z	95% Confidence Interval
Age at ART initiation (years)				
<50		ref		
≥50		0.64	0.386	0.24-1.75
Sex Female	ref			
Male	0.84	0.87	0.646	0.49-1.55
CD4 count at initiation (cells/µl)				
<50	1.28	1.26	0.434	0.71-2.23
50-200	ref	ref		
>200	0.14	0.14	0.008	0.03-0.61
Hemoglobin (g/dl)				
>8	ref	ref		
≤8	1.18	1.16	0.731	0.50-2.69
missing	1.73	1.68	0.452	0.43-6.50
Estimated Glomerular Filtration Rate (ml/min/1.7m^2)				
≥60	ref	ref		
<60	1.13	1.23	0.57	0.60-2.50
Missing	1.02	1.02	0.977	0.26-4.03
Alanine aminotransferase (IU/ml)				
≤60 (2xULN)	ref	ref		
>60	3.07	2.95	0.006	1.35-6.43
Missing	1.36	1.34	0.586	0.47-3.82
Body Mass Index				
Normal	ref	ref		
Underweight	2.63	2.58	0.002	1.40-4.76
Overweight/obese/morbidly obese	0.56	0.57	0.213	0.24-1.38
Missing	3.81	4.01	0.062	0.93-17.25
Baseline morbidity				
none	ref	ref		
HIV-associated only	5.36	5.52	<0.001	2.33-13.06
HIV-associated and TB	5.80	5.65	0.005	1.68-18.98
HIV-associated and chronic	5.56	6.44	0.005	1.75-23.62
TB only	3.36	3.35	0.012	1.30-8.62
Chronic only/TB and chronic	1.20	1.35	0.782	0.16-11.22

Table 7.4: Very early mortality risk attributable to co-morbidities at time of initiating ART

	HIV-associated only		
	Exposed	***Unexposed***	***Total***
Number dead	27	32	59
	Point estimate	***95% CI***	
Incidence rate ratio	2.86	1.65-4.92	
Attributable fraction (exposed)	0.65	0.39-0.80	
Population attributable risk percentage (PAR)	29.75		
	HIV-associated and TB		
	Exposed	***Unexposed***	***Total***
number dead	6	53	59
	Point estimate	***95% CI***	
Incidence rate ratio	5.54	1.95-12.87	
Attributable fraction (exposed)	0.82	0.49-0.92	
Population attributable risk percentage (PAR)	8.33		
	HIV-associated and chronic		
	Exposed	***Unexposed***	***Total***
number dead	4	55	59
	Point estimate	***95% CI***	
Incidence rate ratio	1.46	0.38-3.96	
Attributable fraction (exposed)	0.32	-1.60-0.75	
Population attributable risk percentage (PAR)	2.14		
	TB only		
	Exposed	***Unexposed***	***Total***
number dead	14	45	59
	Point estimate	***95% CI***	
Incidence rate ratio	1.61	0.82-2.99	
Attributable fraction (exposed)	0.38	-0.22-0.67	
Population attributable risk percentage (PAR)	9.00		

7.4 Key points

- Similar to previously reported data within this PhD, mortality on ART was highest in the first 3 months of initiating therapy; most of which was in the first month of initiating therapy. There was a decline in mortality in the first three months post ART-initiation from 2010 onwards
- Using broad mortality causes categories, there were 44 infectious and parasitic mortality causes; mostly due to TB (n=24, 40.7%)
- Mortality from non-communicable diseases was low (n=6, 10.2%) and was higher for older than younger adults. 9 deaths (15.3%) were from unknown causes, also higher in older than younger adults
- Just over half (8/15) of patients dying due to HIV/AIDS presented for ART initiation with very advanced HIV disease (AIDS); a fifth (3/15) were asymptomatic at ART initiation.
- None of the 72 patients presenting for ART initiation with chronic morbidity only died within the first 3 months of ART, suggesting that HIV or complications of treatment for HIV are the driver for this very early mortality rather than the co-morbidities.
- In multivariable analysis, compared to asymptomatic patients, initiating ART with HIV-associated morbidity increased risk of very early mortality by over five and half times. At a population level, mortality incidence attributable to HIV-associated morbidity is about three-fold higher in older than younger adults.
- Initiating ART with HIV-associated morbidity coupled with either TB (aHR 5.65 $p<0.01$) or pre-existing chronic morbidity (aHR 6.44 $p<0.01$) further increased the risk of dying in the first 3 months on ART.
- For older adults the existence of pre-existing chronic morbidity does not significantly change very early mortality incidence as much as it does in younger adults as reflected by the rate ratio, PAR% and attributable fraction.

- Although the TB prevalence was high, its contribution to mortality is modest compared to the contribution of HIV-associated morbidity to mortality. Conversely, the prevalence of patients initiating therapy with both TB and HIV-associated morbidity was low (n=32; 2.3%) but mortality attributable to this morbidity is high at a population level indicating need for public health intervention.
- Although numbers are small, the effect of baseline morbidity on very early mortality in patients initiating ART is clear and points towards the need for early identification of eligible HIV infected people and timely ART- initiation prior to diseases manifestation
- Adjusting for possible confounders, patients initiating therapy with ALT levels greater than 60IU/ml a level twice the upper limit of normal (2xULN) had triple increased risk of very early mortality on ART; those classified as underweight by BMI were also at increased risk of mortality in the first three months on ART compared to patients initiating therapy with normal BMI (aHR 2.6 p=0.002).
- Haemoglobin levels and glomerular filtration rates did not significantly increase mortality risk once differences in baseline morbidity, CD4 cell count, age and sex were accounted for.

8 Discussion

Using data from an African population in rural Northern KwaZulu-Natal in South Africa, a setting with high HIV prevalence and incidence with a large public sector HIV treatment and care programme, this PhD contributes to knowledge on the health complexities surrounding HIV in older adults aged 50 years and above, an area were data in sub-Saharan Africa are critically lacking. This PhD fulfilled five aims specifically targeted at:

- determining older adults' health in terms of cause-specific morbidity and mortality and associated risk factors, accounting for HIV and ART status,
- assessing how biomarkers in older adults relate to their current or future morbidity, and mortality, and
- measuring the effect of age on cause-specific morbidity, mortality and virological and immunological response to ART by comparing HIV positive older adults aged 50 years and above to younger adults aged 16 to 49 years old,

Table 8.1 details the specific objectives and main findings from this PhD study.

Table 8.1: Specific objectives and associated findings

Objective	Chapter	Main findings
To quantify the morbidity burden in older adults and investigate associations between morbidity and HIV and ART status and further establish associations of IL1, IL6, hsCRP, TNFα with HIV, ART, obesity and morbidity	**3**	Compared to HIV negative adults aged 50 years and above: • HIV positive older adults receiving ART for over 1 year had less chronic morbidity • IL6 and hsCRP levels were higher in HIV positive older adults on ART and ART-naive • Obesity was common in both HIV negative and positive older adults and associated with elevated levels of IL6 and hsCRP
To describe and quantify the cause-specific morbidity burden in HIV positive older adults, at the time of initiating antiretroviral therapy, in comparison with younger adults	**4**	Compared to younger HIV positive adults aged 16-49 years: • Pre-existing (at time of ART initition) chronic morbidity burden was higher in older adults • HIV-associated morbidity was also higher in older adults at higher CD4 cell counts • TB prevalence was lower in older adults • Spectrum of morbidity causes was narrower in older adults
To determine cause-specific incidence rates of serious morbidity (resulting in hospitalization) following ART initiation and the effect of age on such morbidity and to establish whether abnormal biomarker [hemoglobin (Hb), Alanine aminotransferase (ALT) and creatinine] levels at ART initiation increase morbidity risk.	**5**	Compared to younger HIV positive adults aged 16-49 years: • Older adults had a lower hospitalisation rate but higher case fatality rates For both age groups: • Most hospitalisations were due to non-infectious conditions, followed by TB • Rates of serious morbidity were highest in the first 3 months of ART • Creatinine levels >240µmol/L and Hb levels <8g/dL increased hospitalisation risk

To quantify the effect of age on response to ART in terms of total mortality, viral suppression and CD4 count reconstitution after initiation of ART	**6**	Compared to younger HIV-positive adults aged 16-49 years: • Older adults had a blunted immunological but superior virological response • All-cause mortality risk in the first year of ART was higher in older adults, but similar after 1 year of ART In both age groups: • All-cause mortality risk increased with decline in time-updated CD4 cell count and unsuppressed viral load • Mortality was highest in the first 3 months of ART
To establish causes of early mortality (occurring in the first 3 months of ART) following ART initiation in older adults compared to younger adults, quantify the contribution of baseline morbidity on early mortality risk and ascertain whether levels of Hb, ALT and Glomerular Filtration Rates (GFR) at ART initiation are risk factors for early mortality.	**7**	Compared to younger HIV positive adults aged 16 to 49 years: • Mortality rate due to unknown was higher in older adults • Older adults had higher proportions of unknown mortality causes • For older adults pre-existing chronic morbidity did not significantly change very early mortality incidence to the extent it did in younger adults In both age groups: • The contribution of multiple co-morbidity to early mortality was high • ALT >60 IU/ml increased risk of early mortality

8.1 Morbidity burden in older adults, HIV and ART status and biomarkers of health

It will likely take years to untangle the extent to which non-AIDS defining conditions such as diabetes, cardiovascular disease and liver disease are independent co-morbid conditions or associates of HIV infection and treatment (Goulet, Fultz et al. 2007). The first step in addressing this question is to compare co-morbidity patterns between two groups, one of HIV positive and another of HIV negative individuals (Justice, Landefeld et al. 2001). The HIV negative comparison group must be socio-demographically similar to the HIV positive group, because co-morbidity and mortality are age, race, ethnicity, sex and socio-economically dependent (Bailis, Segall et al. 2003; Bradshaw, Groenewald et al. 2003; Lorant, Deliege et al. 2003; Lopez, Mathers et al. 2006; Goulet, Fultz et al. 2007). This PhD started by comparing the chronic morbidity burden in HIV positive adults aged 50 years and above to that in HIV negative adults also aged 50 years and above. To ensure appropriateness of the comparison group, both the HIV positive and negative groups comprised of older adults residing within the same defined geographic area with a largely homogenous rural community in terms of socio-economic status, ethnicity and availability and access to health care (Tanser, Hosegood et al. 2008; Houlihan, Bland et al. 2010; Nyirenda, Chatterji et al. 2012); the data used came from a cross-sectional study, of 422 older adults, nested within the Africa Centre demographic surveillance.

8.1.1 Morbidity burden in older adults by HIV and ART status

The PhD study presented here contributes to knowledge by being the first to demonstrate, in a rural African setting where ART delivery is devolved to primary health care level, the possibility of less current cause-specific chronic morbidity in HIV positive older adults receiving ART than in HIV negative adults of the same ages. This PhD shows

that controlling for factors known to be associated with ill health (age, sex, smoking and wealth quintile), whilst HIV positive ART-naive older adults had non-statistically significant higher odds of current morbidity, HIV positive older adults on ART for at least one year were significantly less likely (OR=0.49, p=0.027) to report current morbidity than HIV negative adults. A study from this setting previously reported a higher WHO composite health score [a health measure collating an individual's levels of difficulty in eight health domains (mobility, self-care, affect, vision, pain/discomfort, sleep/energy, interpersonal activities, and cognition)] in HIV positive than in HIV negative older individuals, not accounting for ART status (Nyirenda, Chatterji et al. 2012). The results presented here confirm this previous finding with more in-depth health measures and highlight differences by ART status. The previously reported higher composite health score amongst HIV positive individuals using the same study population reduces the possibility that chronic morbidity in HIV positive individuals remains undiagnosed or is misdiagnosed as HIV-related morbidity.

Data regarding the association of HIV and age-related morbidity, especially by ART status, in Africa are scarce. From resource-rich settings, some studies support the findings of this PhD whilst others do not. A few previous reports suggest that across all age groups, HIV increases the risk of age-associated chronic conditions such as malignancies, metabolic disorders inclusive of diabetes and cardiovascular conditions; in a population of 77 025 HIV-positive adults (median age 38 years) included in a prospective cohort, involving 61 French University hospitals, between 1992 and 1999, the risk of non-AIDS defining cancers prior to ART (1992 to 1995) was twice as high in HIV-positive men as in the general French male population (Herida, Mary-Krause et al. 2003). Similarly, in a study that linked the Swiss HIV Cohort Study and the Swiss cantonal cancer registries, high age-standardised incidence ratios of Kaposi sarcoma, anal cancer, cervical cancer, liver cancer, lip, mouth,

pharynx, lung and skin cancer were reported in HIV-positive people compared to the general population. The Swiss study included 7304 HIV positive individuals aged 16 years and above contributing 28 836 person-years from 1985 to 2003 (Clifford, Polesel et al. 2005).

Similar to cancer risk in HIV-positive populations compared to the general HIV-negative population, a study in Italy involving 2854 HIV-positive patients and 8562 controls with a mean age of 46 years reported higher prevalence of diabetes mellitus, cardiovascular disease, bone fracture and renal failure in those HIV-positive than in HIV-negative controls, with these conditions occurring at younger ages in the HIV-positive group (Guaraldi, Orlando et al. 2011). Rates of acute myocardial infarction between October 1996 and June 2004 in a cohort study in Boston, USA with 3 851 HIV-positive (41% on ART) and 1 044 589 HIV-negative individuals showed that the rate of acute myocardial infarction was twice as high in the HIV-positive group than in those HIV-negative. HIV-positive individuals also had higher proportions of hypertension (21.2% versus 15.9%), diabetes (11.5% versus 6.6%) and dyslipidemia (23.3% versus 17.6%) than the HIV-negative population (Triant, Lee et al. 2007). This Boston study included patients aged 18-84 years and the median age of participants was 38 years for those HIV-positive and 39 years for those HIV-negative. Besides these studies including young adults, morbidity differences by HIV status between these studies and this PhD may be largely driven by the fact that in this PhD, HIV-positive older adults were stratified by ART status hence highlighting possible benefits of ART and illustrating that immune reconstitution after ART may have morbidity limiting effects.

In line with results of this PhD, a small USA-based study with 122 HIV positive patients, 92% of whom were receiving ART, with high rates of virological suppression, reported similar morbidity prevalence in both HIV negative and positive older adults and lower than expected cardiovascular co-morbidity in the HIV positive group which the authors attributed to aggressive management of modifiable atherosclerotic risk factors within the US (Onen, Overton et al. 2010). In another study (VACS) recruiting from 8 sites in the United States of America, data from 1525 HIV positive (75% on ART) and 843 HIV negative adults showed that those who were HIV positive had less prevalent cardiovascular diseases, hypertension, diabetes and renal disease compared to HIV negative adults, although the cohort was younger with a mean age of 53 years (Armah, McGinnis et al. 2012). In another VACS study, utilising data from 33 420 HIV positive adults of whom 31% were aged 50 years and above, older HIV negative patients were more likely to suffer from hypertension, diabetes and pulmonary disease than HIV positive older adults. HIV positive older adults were not stratified by ART status making it difficult to assess morbidity differences by ART status (Goulet, Fultz et al. 2007). The authors further acknowledged that although single morbidity rates were higher in HIV negative older adults, multi-morbidity was more common in HIV positive older adults.

In line with finding of lower morbidity burden in HIV positive older adults on ART, reported in this PhD, a cross-sectional study comprising 500 older adults in Ugandan reported comparable health scores for HIV negative and positive older adults (Scholten, Mugisha et al. 2011). It is possible that in the Ugandan study, health status was similar in HIV positive and negative older adults because unlike in this PhD where specific morbidity causes were assessed, the Uganda study used the WHO composite health score, a score that is subjective since it measures individual's self-reported levels of difficulty in eight health domains (mobility, self-care, affect, vision, pain/discomfort, sleep/energy,

interpersonal activities, and cognition. In addition, the Uganda study did not stratify the HIV positive group into those receiving ART and those ART-naive thus the superior health in older adults receiving ART might have been masked by the poor health in those HIV positive but waiting to receive ART.

It is likely that in our population morbidity in HIV-infected older adults receiving ART is reduced through regular screening and treatment during frequent routine HIV clinic visits. Our study confirms significantly higher health care utilisation rates in those HIV positive than HIV negative with the proportions being even higher in those on ART. Whilst nearly 90% of HIV positive older adults in our WOPS study on ART reported to have utilised health care services for more than 6 times in the 12 months prior to the date of interview, only 36.7% of those HIV negative and 61.5% of those HIV positive and not on ART reported similar health care utilisation frequency ($p>0.001$). In resource limited settings, older people (50+years) with chronic morbidity such as heart diseases, arthritis, diabetes and hypertension, are likely to remain undiagnosed due to issues relating to financial and geographical access to health services (Waweru, Kabiru et al. 2003; Ahmed, Tomson et al. 2005; van der Hoeven, Kruger et al. 2012) . Previous studies report that older adults prefer to seek no treatment or to self-treat (Sarkisian, Hays et al. 2002; Waweru, Kabiru et al. 2003; van der Hoeven, Kruger et al. 2012) due to financial constraints, lack of health facilities; even when available, a negative attitude of health workers towards the care of the older adults (Gjorup, Henrick et al. 1987; Waweru, Kabiru et al. 2003; Ahmed, Tomson et al. 2005) could possibly result in late diagnosis and poor prognosis irrespective of HIV status (WHO 1995; Waweru, Kabiru et al. 2003). Despite HIV positive older adults potentially facing a larger morbidity burden than HIV negative adults, the potential benefit of enhanced access to care for HIV positive older adults who regularly utilise health care services for HIV related services remains poorly quantified. Generally, the

earlier a disease is diagnosed, the more likely it is that it can be successfully managed (Suzman, Harris et al. 1992; WHO 1995; van der Hoeven, Kruger et al. 2012). Thus, it is conceivable that once initiated on ART, which requires frequent attendance at health care facilities, HIV positive older adults potentially receive better detection and management of chronic pre-existing conditions than HIV-negative older adults who may have limited contact with health care services.

Results from previous studies discussed above on morbidity and health care utilisation, together with results from this PhD, begin to point towards improved health and less morbidity in HIV positive older adults receiving ART than in HIV negative individuals aged 50 years and above. These results also provide evidence that comparison of co-morbidity levels between younger and older adults may be misleading as younger adults nearly always have less morbidity than older adults. The results from this PhD show health benefits of enhanced access to care even in this rural African area with mostly lower socio-economic status, poorer health care services, limited and lower cost ART regimens with more side effects and where access to ART was only substantially scaled-up relatively recently. These results underscore the need of extending health care services to HIV negative older adults, which need to go beyond mere provision at fixed clinics. Bringing health services to older adults through regular community chronic disease screening would ensure health care reaches all older adults in need, and could translate to considerable health benefits even for HIV negative older adults who might not be keen on utilising health care services based at fixed clinics. Indeed the South African government, in response to continued poor health outcomes in rural areas with limited health resources, is currently piloting the feasibility of district specialist health teams to facilitate community based health care delivery (Ministerial-Task-Team 2011; Motsoaledi 2011; Nathan and Rautenbach 2013)

8.1.2 Cytokine levels (IL6, IL1, hsCRP and TNFα) by HIV and ART status and their association with chronic morbidity

To determine the levels of cytokine markers in HIV positive and negative older adults who may have raised cytokine levels due to age and explore how these cytokines are associated with chronic morbidity, this PhD used data from a cross-sectional study of 422 adults aged 50 years and above to show that, compared to HIV negative older adults, HIV positive older adults on ART for over a year had nearly twice the odds of having elevated IL6 levels and more than twice the odds of elevated hsCRP levels, indicating immune inflammatory response. This PhD is to my knowledge the first to assess how in an African black population, controlling for age differences across HIV strata, cytokine levels differ by HIV and ART status and how these levels are associated with chronic morbidity during ART.

Similar results of elevated cytokine levels in HIV positive adults have been reported from studies in resource-rich countries, however most of these studies did not have an HIV negative comparison group (Hober, Haque et al. 1989; Kuller, Tracy et al. 2008; Rodger, Fox et al. 2009). Among those that did (Reingold, Wanke et al. 2008; Neuhaus, Jacobs et al. 2010; Armah, McGinnis et al. 2012), few explored the association between elevated levels and chronic morbidity in adults receiving ART. Furthermore only a few specifically focused on older adults; a study using blood specimens from the large (n=5472) Strategies for Management of Antiretroviral Therapy (SMART) study, based in 33 countries, reported high levels of IL6 and hsCRP at study entry and also observed that in those already on ART, IL6 levels increased in the first month of interrupting ART (Kuller, Tracy et al. 2008), indicating that ART may have a lowering effect on levels of inflammatory markers

(Neuhaus, Jacobs et al. 2010). This PhD shows that compared to HIV negative older adults, HIV positive older adults had higher IL6 and hsCRP levels. However within the HIV positive group, IL6 and hsCRP levels were lower in those on ART for more than one year than in ART-naive older adults. Consistent with these findings from this PhD, the VACS, in the United States including 1525 HIV positive adults (75% of whom were on ART), with a median age of 52 years, and 843 HIV negative adults, with a median age of 54 years, reported higher levels of IL6 in the HIV positive than in the HIV negative group even when the HIV viral load was unsuppressed (≥ 500 copies/mL) or when CD4 cell counts were less than 200 cells/µL (Armah, McGinnis et al. 2012). A study utilising 494 participants from the SMART study, 5386 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) study and 3231 participants in the Coronary Artery development in Young Adults (CARDIA) study, aged between 33 and 76 years, reported results similar to those of this PhD of elevated hsCRP levels and IL6 levels even after HIV RNA levels were successfully suppressed, although they did not further investigate how these levels were associated with chronic morbidity (Neuhaus, Jacobs et al. 2010). Results from this latter study were limited by the fact that it did not have a true HIV negative comparison group because the study compared individuals known to be HIV positive from the SMART study to those of unknown HIV status from the MESA and CARDIA studies and assumed that the participants from the two latter studies were likely to be HIV negative (Neuhaus, Jacobs et al. 2010). While these studies were not exclusively focused on older adults, these results together with this PhD's results begin to highlight the possibility of decrease in inflammatory markers once patients initiate ART. This PhD further shows that, levels of IL6 remained elevated in those HIV positive even though HIV negative adults had higher prevalence of co-morbid conditions.

In sub-Saharan Africa, biomarker studies are rarely done due to high costs associated with such studies and limited laboratory facilities for biomarker testing, and therefore a small South African study with 80 HIV positive adults and 10 HIV negative controls that assessed the association between IL6 and HIV is of interest; reported findings were in line with those in this PhD, of high IL6 levels in those HIV positive (Cassol, Malfeld et al. 2010). The limitations of this study include the age of the participants, the small numbers and the fact that the study mainly consisted of HIV positive patients with advanced HIV disease and that the possible influence of ART was not allowed for.

In contrast to what is found in this PhD, elevated biomarkers in the VACS study were strongly associated with co-morbidity whilst in this PhD study biomarkers of IL6, IL1 and hsCRP were not significantly associated with chronic morbidity inclusive of heart disease, hypertension, diabetes, arthritis, stroke, asthma and cancer. Reasons for this difference might lie in the fact that the VACS study included younger adults (median age for the HIV positive group was 52 years and for the HIV negative group 54 years) or possibly in ART-regimen driven differentials because different ART drugs have different cytokine lowering effects. Another possible explanation of the lack of association between cytokine levels and morbidity in this PhD might be due to the small sample size (n=422) of my PhD's Wellbeing of Older People Study which provided data for this specific objective. Despite these limitations and variations between studies the results of this PhD show that cytokine levels in the presence of ART, even if not as low as those in HIV negative individuals, are not associated with chronic morbidity.

Although some studies have reported association between elevated cytokine levels and increased cardiovascular and diabetes morbidity (Trayhurn 2005; Bastard, Maachi et al.

2006), it remains unknown whether elevated cytokine levels result in morbidity or whether an immune inflammatory response due to morbidity results in elevated cytokines. Results from this PhD of lower morbidity in HIV positive older adults on ART, but not in ART-naïve HIV positive older adults, than in HIV negative older adults irrespective of high HIV-associated cytokine levels, together with those from the SMART and VACS studies (Kuller, Tracy et al. 2008; Armah, McGinnis et al. 2012), suggest that even in the absence of co-morbid conditions, cytokine levels in HIV positive older adults do not return to pre-HIV infection levels despite ART. Cytokine levels may thus not be ideal markers for chronic morbidity in such populations. In support of this suggestion, a study reported that after adjusting for underlying co-morbidity there remained an association between HIV and elevated biomarkers even in patients receiving ART (Armah, McGinnis et al. 2012) highlighting the possibility of HIV driven elevation independent of other co-morbidity. This PhD makes an important contribution by not only supporting the previous few reports of elevated cytokine markers in HIV positive older adults, but additionally showing that these elevated levels in the presence of ART are not associated with increased chronic morbidity. It would be beneficial for future studies to quantify inflammatory levels that would clinically signify morbidity and morbidity risk for the different HIV and ART statuses.

8.1.3 Association of obesity with morbidity and cytokine levels in older adults

Obesity is linked to chronic health problems such as cardiovascular diseases, diabetes, stroke and arthritis (Cheymol 2000; Bastard, Maachi et al. 2006; 2008) and, similar to ageing, is characterised by chronic low-grade inflammation (Trayhurn 2005; Bastard, Maachi et al. 2006). Understanding how bio-marker levels and body mass index (BMI) relate to morbidity in this rural older adult population will inform guidelines regarding the

clinical management of this group. Results from this PhD show that in this population with high obesity levels, it is the ratio of total cholesterol:HDL, a marker of cardiovascular disease risk, that is associated with high morbidity rather than BMI per se. In an analysis adjusted for this ratio, BMI ceased to be an independent factor for morbidity, with the odds of morbidity nearly quadrupling in individuals within the highest ratio quartile possibly suggesting that total cholesterol:HDL ratio may be a stronger indicator of morbidity than BMI.

Although BMI was not associated with morbidity when accounting for total cholesterol:HDL ratio, being obese/morbidly obese was associated with high hsCRP levels suggestive of increased inflammation and cardiovascular disease risk, similar to studies from developed countries (Trayhurn 2005; Bastard, Maachi et al. 2006). Literature from African populations is scarce. These results highlight that although obesity was not directly associated with morbidity in this population, it was associated with elevated bio-markers whose persistently high levels may ultimately result in disease, especially for those HIV positive and ART-naive, as older adults continue to age with high body mass indices.

Strengths and limitations

Data for this PhD objective here discussed (Section 8.1), was obtained from a cross-sectional study that was nested within the Africa Centre Demographic Surveillance Area which included 422 resident HIV positive and negative older adults aged 50 years and above. Eligible participants were identified through linkage of the Africa Centre surveillance and the Hlabisa treatment and care programme database. A random sample of older adults from all eligible participants was invited to participate in the study. The

study design confers certain limitations; the cross-sectional nature means causality cannot be assumed from associations, and possible relationships need to be further elucidated in longitudinal cohort studies. Although the role of survivor bias cannot be ruled out, if the observed reduced reported morbidity in HIV positive older adults receiving ART was purely due to survivor bias we would also expect an even larger morbidity decrease amongst the HIV positive ART-naïve group, but instead this PhD shows non-statistically significantly higher morbidity in HIV positive older adults not on ART compared to those HIV negative.

Comparison of morbidity by HIV and ART status in this PhD study may have been biased by age differences between HIV negative (median = 68; IQR 61-75 years) and HIV positive older adults on ART (median = 57; IQR 53-62 years) and ART-naive (median = 53; IQR 51-60 years). To fully account for these differences, all logistic regression models were age-adjusted. Although the odds ratio for the association between HIV status and current chronic morbidity weakened when the analysis was adjusted for age, there still remained a statistically significant association between being HIV positive on ART and reduced odds of morbidity. To rule out residual confounding due to age, secondary analyses was restricted to those aged below 65 years old (50-64 years) and further restricted to those aged 50-60 years old. In both analyses the finding of less chronic morbidity in those HIV positive on ART than in HIV negative individuals not only persisted but even strengthened suggesting an even stronger differential in current chronic morbidity by HIV and ART status after reducing the age variations between the four HIV strata.

Although data were self-reported, it was assumed that any unreliability of self-reports occurred equally across groups resulting in non-differential bias which does not affect

validity of our results. This assumption was based on the fact that there is no evidence supporting the likelihood of over-reporting current morbidity amongst HIV negative, but not among infected, individuals. Studies that have examined health seeking behaviour in older adults document that reports of being unwell and seeking health care are dependent on the awareness, interpretation and experience of symptoms (Ahmed, Tomson et al. 2005) and it would thus be more likely to expect HIV positive individuals to over-report than HIV negative individuals because of their knowledge of the underlying HIV infection and considering that they would have been made aware of existing morbidity during their HIV clinic visits. Furthermore, both HIV positive and HIV negative participants were identified from the community via the longitudinal demographic surveillance rather than from health care facilities and this would have reduced selection bias. Although the WOPS sample size of 422 adults aged 50 years and above is small, limiting the extent to which the study could detect differences between groups, the fact that despite this there were significant differences between HIV positive participants receiving ART and those HIV negative possibly points towards an even larger morbidity difference had a larger sample size been used. As such the sample size issue does not nullify these results but rather confirms the strength of existing associations between morbidity prevalence and HIV-infection and ART.

8.2 Cause-specific morbidity burden at ART initiation in older and younger adults

To further explore associations of ART and co-morbidity in HIV positive older adults and determine whether these older adults have special HIV management needs over and above those of younger HIV infected adults (aged 16 to 49 years old), the second objective of this PhD determined age stratified pre-existing chronic morbidity and WHO

stage III and IV HIV-associated morbidity burden at time of initiating ART. Knowledge of co-morbidities at time of initiating HIV therapy in older adults is useful in projecting subsequent clinical management needs. Moreover, the management and determination of good clinical outcomes of HIV positive older adults after initiation of ART is likely dependent on prevalence of co-existing morbidities at time of initiating therapy. These data are useful in developing evidence based interventions for morbidity and consequently mortality reduction.

Objective two of this PhD aimed at quantifying cause-specific morbidity burden in older compared to younger adults aged 16 to 49 years used data from the ART Clinical Cohort. The ART Clinical Cohort was nested within the main Hlabisa HIV treatment and care programme, and recruited adults aged 16 years and above initiating ART at two of the largest primary health care clinics within the Hlabisa HIV treatment and care programme. In the ART Clinical Cohort similar to the Hlabisa HIV treatment and care programme, just over 10% of adults who initiated ART during the study period were aged 50 years and above. In the Hlabisa HIV treatment and care programme, standard ART regimens are given according to the South African National HIV treatment guidelines and consist of two nucleoside reverse transcriptase (NRTI) and one non-nucleoside reverse transcriptase (NNRTI). Up till 2010, the NRTIs consisted of Stavudine, Abacavir, Lamivudine, Zidovudine and Stavudine whilst the NNRTIs consisted of Efavirenz and Nevirapine. In 2010, Stavudine was substituted with Tenofovir. As of April 2013, patients are initiated on a fixed dose combination pill consisting of Tenofovir, Emtricitabine and Efavirenz , unless contraindicated (National Department of Health 2004; National Department of Health 2010; National Department of Health 2013).

Results of this objective demonstrated that, compared to younger (16-49 year old) HIV positive adults, both pre-existing chronic morbidity burden at time of ART initiation and HIV-associated WHO stage 3 or 4 morbidity were higher in older adults, even though they presented for ART initiation with CD4 cell counts higher than in younger adults. Whilst older adults had a higher burden of co-morbidity and multiple morbidity than younger adults, the spectrum of morbidity causes was narrower for older than younger adults. The prevalence of TB was lower in older adults.

Whilst evidence from high-resource settings has suggested that older adults present with more advanced disease (Grabar, Kousignian et al. 2004; Sabin, Smith et al. 2004; Grabar, Weiss et al. 2006; Iwuji, Churchill et al. 2013), the findings from this PhD from both the main treatment programme and the ART Clinical Cohort suggest the opposite with a significantly lower proportion of older adults initiating ART with CD4 cell count <50 cells/µl than in younger adults. The most striking clinical difference between older and younger adults at baseline in the main Hlabisa HIV Treatment and Care Programme and in the ART Clinical Cohort was the higher proportion of renal dysfunction at baseline in older than younger adults, with over a quarter of older adults having an estimated glomerular filtration rate (eGFR) of ≤60 ml/min/1.73m^2. Consistent with the observed decline in GFR with age in other cohorts (Hasse, Ledergerber et al. 2011), this alerts us to the high frequency of renal disease in this setting which is not always detected with serum creatinine measurements alone (Franey, Knott et al. 2009). However despite older adults having a lower proportion with CD4 cell count <50 cells/µl at time of initiating ART and a higher median CD4 cell counts, older adults had a higher burden of WHO HIV disease stage 3 or 4 morbidity, raising important questions on when to initiate ART in older adults. Results from this PhD indicate that older adults require ART at CD4 cell count thresholds

higher than those for younger adults to ensure they get onto ART before development of opportunistic infections.

In Africa, there is limited understanding of age-related chronic morbidity burden in HIV positive older adults requiring ART (Negin and Cumming 2010; Bendavid, Ford et al. 2012; Greig, Carrillo et al. 2012; Negin, Barnighausen et al. 2012) and how this morbidity impacts on HIV prognosis on ART. Reports from the USA and Europe (Justice, Landefeld et al. 2001; Gebo 2008; Rhee and Greenblatt 2008) indicate that use of ART in older adults may be complicated by multiple chronic co-morbidities and co-administered non-HIV medicines. This PhD study using data from the ART Clinical Cohort including 1409 HIV positive patients aged 16 years and above at time of commencing ART shows that, irrespective of age, of the 11.5% with pre-existing non-AIDS-related chronic morbidity, 66% had hypertension, 16% had arthritis, 12% had diabetes, 8% had epilepsy, 9% had asthma whilst 3% had psychiatric conditions. Stratifying by age at ART initiation, older adults had higher proportions of patients with pre-existing non-AIDS-associated chronic morbidity at time of initiating ART than younger adults: only 6 % (95% CI 5-8%) of younger adults had one chronic condition whilst 36% (95% CI 30-43%) of older adults were on therapy for one named chronic condition with four times as many older adults as younger adults having more than one chronic condition. Similar to findings from this PhD, in a Swiss HIV cohort, co-morbidity and multi-morbidity of non-AIDS diseases especially diabetes mellitus, cardiovascular disease and osteoporosis became more important in care of HIV infected persons as the age of the patients increased. In the Swiss cohort diabetes was common in older adults but this was after a median of 6 years on ART rather than at ART initiation (Hasse, Ledergerber et al. 2011). Also comparable to results from this PhD, the VACS study recruiting from 8 sites in the United States of America comprising 33,420 HIV positive patients of whom 31% were aged 50 years and above,

reported the majority of older adults, irrespective of HIV status, had at least one morbidity; multiple morbidity was common in those HIV positive (Goulet, Fultz et al. 2007). Although assessing individuals aged 65 years and above and not at the time of initiating ART, a study in east Africa also confirmed high prevalence of hypertension, diabetes and arthritis in older adults irrespective of HIV status (Waweru, Kabiru et al. 2003). Similar to this PhD, a study from Botswana reported increased risk of non-AIDS defining morbidity amongst HIV older adults receiving antiretroviral therapy compared to younger HIV positive adults (Wester, Koethe et al. 2011). These studies including this PhD highlight the high burden of non-AIDS associated co-morbidity in older compared to younger HIV positive individuals but comparability of the findings in this PhD of high pre-existing chronic co-morbidity at time of initiating ART is limited by the fact that the reference time point in the other studies is not necessarily at time of initiating ART.

This PhD study reports that compared to younger adults, not only did older adults present for ART initiation with more pre-existing chronic co-morbidity and multiple co-morbidities, 46% of older adults compared to 28% in younger adults had WHO HIV disease stage 3 or 4 morbidity. However, despite younger adults having less co-morbidity than older adults, younger adults had a wider spectrum of HIV-associated morbidity at time of initiating therapy whilst for older adults severe weight loss was the most frequent HIV-associated morbidity. In the ART Clinical Cohort, no older adults were diagnosed with either bacterial or cryptococcal meningitis, herpes, renal failure, HIV-associated arthritis or PCP; prevalence of these conditions was also very low in younger adults. Because the disease spectrum is narrower for older adults, integration of health services to effectively manage older HIV positive adults may be less cumbersome as they only need to deal with a limited range of diseases. Health care staff complement and diagnostic equipment required is also likely more specific and limited than that which would be required to deal

with a wide spectrum of conditions seen in younger adults. However the disease spectrum in older adults with prolonged exposure to ART may differ from baseline morbidity and community based care health workers would be useful monitoring morbidity changes in older adults on ART.

TB prevalence in older patients was half that in younger adults (8% compared to 17%). Whether this is due to a true low TB prevalence or under-diagnosing due to clinicians alluding TB symptoms to other morbidities of ageing remains unknown and requires further studies. It could be that TB presentation is different in older adults or that symptoms are less frequently attributed to TB in this group leading to missed diagnoses and mortality (Negin and Cumming 2010; van Duin 2012). To understand this association further, this PhD work quantified how much of mortality in the first three months of ART was due to TB and how much of hospitalisation on ART was also due to TB in older adults. High levels of unknown causes of mortality in the first 3 months of ART and considerably high numbers of older adults hospitalised due to TB as reported in Section 5.3.3 and 7.3.2 of this thesis point towards this low TB prevalence in older adults at ART initiation being more due to misdiagnosis than a true low prevalence. It is possible that TB presentation in older adults is often alluded to respiratory problems often common in older adults and this finding alerts clinicians of the need for more vigorous TB screening using more sensitive TB screening methods in this age group. By virtue of these older adults having multiple co-morbidities vigilant screening of co-morbidity should be prioritised in older adults to accurately diagnose and treat co-morbidity prior to initiating ART.

Strengths and limitations

Results of this PhD study, although not as large as other studies such as the SWISS cohort, VACS and SMART studies, show a similar high burden of co-morbidity and multiple morbidity in older adults compared to younger adults. Over and above these studies, this PhD gives a clear presentation of the burden and causes of morbidity in older adults at the time when they initiate ART. These data are important to clinicians by highlighting conditions that they should be aware of that are likely to interact or interfere with ART and helps direct health services integration by highlighting common morbidities in older HIV positive adults who also require ART. Unlike in this PhD, the main limitation of the large SWISS, VACS and SMART studies was that they could not prospectively screen patients for morbidity diagnoses or conduct medical chart reviews due to the high costs associated with such an approach. Within the ART Clinical Cohort set up for purposes of this PhD, morbidities were systematically screened for monthly when the patients came for pill collection visits and morbidity was coded using ICD10 coding guidelines (WHO 2010). Medical charts were also reviewed for morbidity and mortality causes ensuring that morbidity and mortality were comprehensively captured. In addition patients missing two consecutive monthly clinic visits were tracked to ascertain mortality and morbidity within that group. The morbidity results from this PhD study based on data from the ART Clinical Cohort are likely generalisable to other HIV positive older adults from comparable African settings as their characteristics were similar to those in the main Hlabisa HIV treatment and care programme, which were also largely similar to those of other HIV treatment cohorts from similar settings (Houlihan, Bland et al. 2010; Mutevedzi, Lessells et al. 2010; Tanser, Barnighausen et al. 2013; Lessells, Mutevedzi et al. In Press).

The main limitation of this Clinical Cohort is the relatively small sample size of 1409 individuals limiting power to detect age driven differences in rare conditions. The follow-

up time was also relatively short limiting the time required to observe clinical events. For this reason a large proportion of the morbidity results were descriptive and the logistic regression models could only use broad mortality groups. The Clinical Cohort is still enrolling patients and follow-up is also accruing to enable more detailed future analyses.

8.3 Age and cause-specific serious morbidity rates during ART

Not only does age modify co-morbid conditions and their management, but complexity is added by the fact that older patients have decreased renal and liver function; combined with effects of ART and other chronic therapies this may lead to toxicities and serious morbidity such as diabetes, hepatotoxicity and renal insufficiency (Justice, Landefeld et al. 2001; Gebo 2008; Rhee and Greenblatt 2008). In Africa, there is limited understanding of serious morbidity patterns in HIV positive older adults once they initiate ART. In resource-limited settings serious morbidities leading to hospitalisation place a huge burden on human and financial resources within the health sector and appropriate planning is required, based morbidity frequency and severity, for adequate health service provision. To reduce the gap in knowledge, the third objective of this PhD used linked data from the Hlabisa HIV treatment and care programme and the Hlabisa district hospital, the only hospital within the Hlabisa health sub-district within which the treatment and care programme in located, to determine differences in serious morbidity rates and causes following ART initiation by age at ART initiation.

Using data from 8 598 HIV positive patients receiving ART in the main Hlabisa HIV Treatment and Care Programme, contributing 675 patients hospitalisations over 8 166 person years of follow-up, the estimated hospitalisation rate was 8.3 (95% CI 7.7-8.9) per 100 person years in adults aged 16 years and above receiving ART. Studies from Africa

systematically documenting morbidity in patients receiving ART are limited and as such it was difficult to compare these results to other African settings. A study in Cote d'Ivoire in West Africa with 608 patients followed prior to ART initiation, 187 of whom went on to initiate ART, reported a high rate of severe morbidity (40.6 per 100 person years); a rate that is nearly five times higher than the estimate in this PhD. This difference in morbidity rate might be because in the Cote d'Ivoire study severe morbidity was defined as any WHO stage 3 or 4 disease regardless of whether or not the morbidity resulted in hospitalisation and the cohort also included patients pre-ART (Seyler, Messou et al. 2007). A recent study from an urban hospital in Gauteng province and a rural hospital in Mpumalanga province in South Africa, including 3 906 patients aged 18 years and above, pre- and post-ART reported high rates (534/3 906, 14%) of hospitalisations over a median follow-up time of 13.1 months) (Meyer-Rath, Brennan et al. 2013). Comparison of this estimate with that from this PhD is complicated by the different measurement scales employed by the two studies and by the fact that only 4% of the Meyer-Rath et al. study group were receiving ART. Similar hospitalisation rates to those reported from this PhD study were reported in a Swiss HIV positive cohort of 8 444 patients although 15% of these were not on ART (Hasse, Ledergerber et al. 2011).

In this PhD, in all patients regardless of age, the rate of hospitalisation was higher (three-fold higher) in the first three months (17.6 per 100 person years) subsequent to ART initiation than later. Similar findings of higher hospitalisation immediately following ART initiation have been reported from urban and rural South Africa (Meyer-Rath, Brennan et al. 2013), looking at all cause-hospitalisation. Results from the HIV Swiss Cohort assessing AIDS-related opportunistic illnesses occurring after ART initiation also showed decreasing rate of morbidity with increased time on ART, with the highest rate of AIDS-related illnesses in the first three months of ART (7.7 per 100 person years)(Ledergerber, Egger et

al. 1999). All adult patients initiating ART whilst concurrently taking TB medication were more than twice as likely to experience serious morbidity leading to hospitalisation than patients who initiated ART not on TB therapy. The difference in serious morbidity risk by TB status was only significant in the first three months of ART, showing that Tuberculosis-associated immune reconstitution inflammatory syndrome (TB IRIS) may be a large contributor to early serious morbidity. The results obtained here are useful by highlighting the need for close TB monitoring within the first few weeks of ART to diagnose and manage TB IRIS.

This PhD estimates hospitalisation rate higher in younger adults than older adults because a large number hospitalisations was actually due to women under the age of 50 years being hospitalised for pregnancy related conditions inclusive of infant deliveries and a few miscarriages. This finding is as would be expected in any population irrespective of HIV status. Interestingly, after excluding pregnancy related conditions, the rate of serious morbidity resulting in hospitalisation was similar between younger and older adults. Even allowing for clinical, laboratory and socio-demographic characteristics at ART initiation in regression analysis, although not statistically significant, there was a trend towards lower odds of hospitalisation (including and excluding pregnancy related conditions) in older than younger adults on ART. The finding within this PhD of lower morbidity in older adults is contrary to reports in the Swiss Cohort where hospitalisations were higher in older adults than younger adults. However in the Swiss cohort, 15% of patients were not receiving ART and those on therapy had been on it for considerably longer periods than in our cohort, with a median time on ART of six years (Hasse, Ledergerber et al. 2011). This PhD's finding of lower hospitalisation rates in older adults is surprising considering older adults had higher baseline co-morbidity than younger adults and also had higher mortality than younger adults during the early phase of ART. For older adults, half of deaths in the

first three months on ART were due to unknown causes. Taken together with the higher case fatality rates in older than younger adults, these results support the fact that older adults are less likely to seek care when unwell (Sabin, Smith et al. 2004; Welz, Hosegood et al. 2007; Franey, Knott et al. 2009). Delayed health care seeking coupled with the large burden of co-morbidities at time of initiating ART and blunted immunological response would inevitably lead to a higher mortality rate in older adults counteracting the benefits of ART.

In this PhD, excluding pregnancy related conditions , for both younger and older HIV positive adults on ART, the most frequent causes of serious morbidity resulting in hospitalisation were non-infectious conditions comprising of injuries (12.6%), diseases of the circulatory system (4.3%), eye and adnexa (1%), musculoskeletal and connective tissue disorders (1%), epilepsy (0.4%) and infections of the skin (6.5%). Similar to results of injuries being a common cause of hospitalisation in this PhD, a previous study reported that injuries were a common cause of hospitalisation in HIV positive South Africans both pre-ART and post-ART, although the analysis was not age stratified (Meyer-Rath, Brennan et al. 2013). In contrast, in a Swiss HIV cohort where 32% (n= 2683) of the cohort were aged 50 years and above, most morbidity was of bacterial pneumonia, strokes, myocardial infarctions, diabetes and non-AIDS malignancies, with the risk (Hasse, Ledergerber et al. 2011). Several contextual factors that may have led to differences in morbidity reported in the Swiss cohort compared to that reported in this PhD; the risk of morbidities due to TB and injuries varies extensively between the two settings. Morbidity varies by gender and whilst in the Swiss cohort a large proportion comprised of men who have sex with men (MSM), in this PhD cohort the majority were women in heterosexual relationships which might explain differences between these two studies. The fact that although analysis for the Swiss cohort covers 2008 to 2010, ART therapy had been available for much longer

periods and patients initiated therapy at much higher CD4 count threshold (Hasse, Ledergerber et al. 2011), may have given rise to differences in morbidity epidemiology between the two settings.

TB was the second leading cause of serious morbidity in patients on ART in this PhD whilst about 3% of admissions were due to meningitis, in agreement with previous reports from urban Cote d'Ivoire (Seyler, Messou et al. 2007) and from rural and urban South Africa (Meyer-Rath, Brennan et al. 2013). Further, adults with TB at ART initiation had an increased risk of hospitalisation and so did patients initiating therapy with advanced disease as approximated by baseline CD4 cell counts<50cells/µl, highlighting the contribution of advanced HIV disease and co-morbidity to poor prognosis even after initiation of ART. Similar to baseline morbidity, younger adults had a wider spectrum of hospitalisation causes than older adults because infectious diseases were mainly concentrated in the younger age groups, whilst chronic morbidity mainly affects the older populations (Murray and Lopez 1997; Lopez and Mathers 2006; Lopez, Mathers et al. 2006; Mayosi, Flisher et al. 2009). A similar disease spectrum, mainly consisting of bacterial and parasitic conditions in younger adults was reported in a relatively small study of 723 adults in an urban African setting (Seyler, Messou et al. 2007). Our results shows considerable serious morbidity in older adults due to respiratory infections similar to findings from an urban Kenya in East Africa, although the Kenya study included participants aged 65 years and above of unknown HIV status (Waweru, Kabiru et al. 2003). In 3 906 HIV patients aged 18 years and above in rural and urban South Africa, the mean length of admission was 8.7 days (Meyer-Rath, Brennan et al. 2013), about 3 days more than that reported in this PhD. The increased duration of admission might have been due to the fact that the Meyer-Rath study included patients pre-ART. Older adults had a longer admission duration and case-fatality rates were higher for older than younger

adults; a finding that may be related to age-associated immune decline. In both age groups, conditions such as Kaposi sarcoma and advanced HIV/AIDS had the highest case fatality rates.

Results presented here show that there is high serious morbidity following ART initiation, mainly driven by advanced stage HIV and TB. Medical interventions, particularly intensive screening and treatment for TB and cryptococcal infection should be implemented and evaluated to improve understanding of the epidemiology of these infections particularly in older adults (Lawn, Harries et al. 2010). Considering the high costs associated with hospital admissions of HIV positive patients (Meyer-Rath, Brennan et al. 2013), it would be beneficial to initiate ART in HIV positive individuals early, irrespective of age. In South African the ART immunologic eligibility criteria was increased from 200 to 350 cells/µL in August 2011 and it would be interesting to assess serious morbidity patterns from August 2011 in comparison to those prior to August 2011 to quantify realised benefits on health and hospitalisation costs averted .

8.4 Older age and ART outcomes of mortality, virological suppression and CD4 count reconstitution

8.4.1 All-cause time stratified mortality

To address objective four, this PhD used data from a large rural HIV treatment programme in South Africa, with a comprehensive tracking system for patients lost to follow-up, to assess mortality rates and differences in two population groups defined by age. In this analysis of 8846 adults with 997 deaths, overall mortality risk was 32% higher for those who initiated ART aged 50 years and above compared to those initiating at age 25-49

years. Although consistent with previous reports from non-African and African urban settings (Fairall, Bachmann et al. 2008; Tuboi, Pacheco et al. 2010; Greig, Carrillo et al. 2012; Iwuji, Churchill et al. 2013), results here show that this mortality difference is restricted to the first year of ART, following which mortality rates in older adults are no longer statistically significant different from those in younger adults despite an only modest CD4 count reconstitution in the older age group. Similar to findings from this PhD work, previous studies from Europe and North America (Grabar, Kousignian et al. 2004; Silverberg, Leyden et al. 2007; Greenbaum, Wilson et al. 2008; The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group 2008) have reported poorer immunological but better virological responses in older compared to younger adults but have not explored how these may relate to mortality rates in older age groups receiving ART.

This PhD study shows that despite older adults having a lower proportion of individuals achieving good immunological response in the first year on ART, their mortality rate as a group, after 12 months on ART, was similar to that observed in the younger adult group. This finding coupled with the fact that older adults had a higher proportion of individuals achieving optimal viral suppression, might imply that in older adults, the degree of CD4 count reconstitution may matter less once HIV has been suppressed. Previous studies have postulated that excess mortality in older adults compared to younger adults may be largely driven by higher levels of non-AIDS related chronic morbidity in this age group (Wester, Koethe et al. 2011; Greig, Carrillo et al. 2012). The results from this PhD study of no significant mortality difference by age after a year of ART might be an indication that after a considerable time of ART, through frequent screening, diagnosis and treatment of this chronic morbidity, the negative effects of co-morbidity on mortality are less significant.

Despite older adults having 32% increased risk of mortality compared to younger adults, in both age groups the highest mortality rates were in the first three months of ART, which is in line with data previously published from this and other programmes (Lawn, Myer et al. 2005; Braitstein, Brinkhof et al. 2006; Lawn, Myer et al. 2006; Boulle, Bock et al. 2008; Mutevedzi, Lessells et al. 2010). Very early (first three months following ART initiation) and early mortality (between three and six months post-ART initiation) was higher in older than younger adults, although older adults had a significantly lower proportion of patients presenting for ART initiation with CD4 counts less than 50cells/µL. High early mortality mainly associated with advanced disease and a blunted immunologic response in older adults raises an important question of whether older adults should initiate ART at higher CD4 count threshold than younger adults and calls for interventions to encourage early presentation for ART. The benefits of initiating ART early are well recognised and remain the reason why CD4 cell count thresholds for ART eligibility continue to be reviewed and increased.

In South Africa, since August 2011 the CD4 cell count threshold for ART eligibility was increased from 200 to 350 cells/µl for all HIV positive individuals. It is worth noting that very early mortality rates within Hlabisa HIV Treatment and Care Programme between 1 August 2004 to 31 October 2009 were higher (30.1 per 100 person years) than rates obtained in the ART Clinical Cohort from 1 March 2010 to 31 July 2012 (17.5 per 100 person years). This difference may be attributed to earlier initiation of ART reducing very early mortality risk associated with advanced HIV. This finding is not only peculiar to this study but a recent publication utilising data from the main Hlabisa HIV Treatment and Care Programme including 19 747 adults aged 16 years and above initiating ART from

August 2004 to July 2012 shows significant declines in early mortality with increase in CD4 count threshold for ART initiation (Lessells, Mutevedzi et al. In Press).

In HIV positive older adults compared to HIV positive younger adults, extremely high mortality rates in the first year of ART suggests that strategies to reduce this early mortality need to be implemented and evaluated with a degree of urgency and that the needs of older adults, over and above those of younger adults, should be considered within these strategies (Lawn, Harries et al. 2010). It would be useful to understand better the current patterns of testing and health care usage amongst older adults so that appropriate age-specific interventions can be developed. In HIV positive adults aged 16 years and above during pre-ART care, we have previously shown lower rates of retention in older adults than younger adults (Lessells, Mutevedzi et al. 2011). With the known association between older age and more rapid CD4 decline, it is necessary to explore alternative care strategies such as community-based follow-up (May, Wood et al. 2009).

Integrated chronic disease management delivered through community-based follow-up fits in well with the proposed re-engineering of primary health care systems in South Africa in an effort to manage the high burden of chronic conditions such as hypertension, diabetes and cardiovascular diseases coupled with HIV and TB (Ministerial-Task-Team 2011). The South African Minister of Health in his parliamentary speech in 2011 acknowledged that health systems in South Africa were stretched and overburdened by HIV and TB and recognised a growing epidemic of chronic conditions, he therefore suggested that primary health care systems needed to be re-engineered to ensure integrated efficient health care systems not only at health facility levels but also in schools, community halls and in households, ensuring a strong referral system with local

hospitals (Motsoaledi 2011). It would be of interest to see whether more intensive follow-up either at health facility level or community level by community health workers impacts on mortality for individuals at high-risk of death in the first few months of ART. For the community-based health care delivery to work efficiently, cause-specific morbidity burden in different age groups should be well understood.

8.4.2 Virological suppression and CD4 count reconstitution

This PhD used data from the Hlabisa HIV treatment and care programme involving 8846 adults; 808 (9.1%) aged 16-24 years, 7119 (80.5%) aged 25-49 years and 919 (10.4%) aged 50 years and above at time of ART initiation, and showed that at 12 months, approximately one-quarter of patients in the cohort had CD4 cell count ≤200 cells/µl with the largest proportion and the least immunological response in those aged 50 years and above and this was associated with increased risk of death subsequently. Larger CD4 count increases were significantly associated with reduced mortality risk irrespective of the time updated absolute CD4 count. In addition, previous absolute CD4 cell thresholds (CD4 cell count at six months after ART initiation) were not associated with mortality although CD4 count increments of greater than 100 cells/ul at this stage decreased mortality risk beyond a year on therapy. This may possibly imply that as long as there is an immune response greater than a certain threshold, the influence of the absolute CD4 cells count on mortality becomes minimal and non-significant.

Although younger adults demonstrated superior immunological responses compared to older adults, virological suppression was achieved more frequently in older than younger adults. This finding has been previously reported (Grabar, Kousignian et al. 2004; Silverberg, Leyden et al. 2007; Greenbaum, Wilson et al. 2008; The Collaboration of

Observational HIV Epidemiological Research Europe (COHERE) study group 2008; Onen, Overton et al. 2010; Hasse, Ledergerber et al. 2011), but the novel finding that this PhD work presents is the fact that the effect of inferior immunological responses on mortality in older adults waned when HIV was suppressed. Incomplete virological suppression was associated with a nearly three-fold increased risk of mortality after the first year on therapy. The increased mortality risk in older adults associated with poorer immunologic response may thus have been counteracted by the reduced risk associated with superior virological response resulting in equal mortality risk in both age groups after one year of ART. Superior virological suppression in older adults may be due to better adherence within this group as previously published data from Hlabisa HIV Treatment and Care Programme has shown that the risk of disengaging from HIV care decreases with increasing age (Mutevedzi, Lessells et al. 2013). Additionally, the fact that these older adults are seen every month by health care personnel when they come to collect ART drugs may mean that, with prolonged ART use, age driven morbidities are diagnosed early and better managed, waning the effect of age on mortality.

Strengths and limitations

The study population used for this fourth objective of the PhD is similar to that from many rural public health HIV treatment programmes and therefore results presented here are likely generalisable to similar settings in sub-Saharan Africa. The large cohort size and high mortality rates have enabled this analysis (Mutevedzi, Lessells et al. 2010). A major strength of the Hlabisa HIV Treatment and Care Programme is the comprehensive tracking system for patients lost to follow-up which ensures that deaths are ascertained contemporaneously, unlike in many other programmes where patients lost to follow up are not pro-actively tracked to ascertain death (Brinkhof, Pujades-Rodriguez et al. 2009),

giving us confidence that mortality rates reported here are representative of the true population mortality rates.

Data obtained from the Hlabisa HIV Treatment and Care Programme have limitations as a retrospective analysis of routine programmatic data; some analyses were hampered by missing results particularly for follow-up CD4 cell counts and viral loads which was addressed by interpolation of missing CD4 cell counts. The immunological deficiency in older adults compared to younger adults, especially at six months post-ART initiation, might have been under-estimated given the higher early mortality in the older age group in the very early phases of ART. CD4 cell count changes are influenced by survival bias, as individuals with the worst immunological response are more likely to have died. Although analyses controlled for multiple biological variables in determining factors associated with mortality, there might still be residual confounding by socio-economic characteristics, adherence levels or other unmeasured variables.

8.5 Causes of early mortality on ART and the contribution of pre-existing co-morbidity at ART initiation

Cause of death could not be ascertained within the main Hlabisa HIV Treatment and Care Programme; only 42 of 997 deaths (4.2%) could be attributed to a specific cause. However, the high number of deaths immediately after ART initiation suggests that this mortality is still driven largely by HIV disease. Similar to our Hlabisa HIV Treatment and Care Programme, cause of mortality data are not systematically sought in HIV treatment cohorts within Africa. A large mortality analysis including 17 561 patients from 17 HIV programmes in 9 African countries acknowledges the major limitation of not being able

to report on cause of death (Greig, Carrillo et al. 2012). To bridge this gap in knowledge the final objective of this PhD study used data from the ART Clinical Cohort to determine causes of early mortality following initiation of ART; analysis confirms that irrespective of age, a quarter of all deaths in the very early phase post-ART initiation were due to advanced HIV. Just over half of HIV positive adults on ART dying due to HIV/AIDS presented for ART initiation with very advanced HIV disease (AIDS). Further, the leading causes of very early mortality were infectious and parasitic diseases, mainly TB, which was responsible for just over 40% of the very early deaths.

Research in similar settings has also shown mortality in the first year of ART to be caused predominantly by infectious diseases related to immunosuppression with TB consistently shown to be the leading cause of death across all age groups followed by cryptococcal disease and other infectious diseases (Lawn, Myer et al. 2005; Etard, Ndiaye et al. 2006; Castelnuovo, Manabe et al. 2009; MacPherson, Moshabela et al. 2009). This PhD adds additional information to existing knowledge by showing that although mortality due to TB was high irrespective of age, TB mortality rate was higher in younger adults than in older adults. This PhD also highlights that similar to findings from a study in Kenya there is considerable AIDS-associated mortality in older adults (Negin, Wariero et al. 2010).

A recent publication from the same setting as this PhD using population level verbal autopsy data from the Africa Centre reported mortality causes, based on the Global Burden of Diseases Classification, in the general population which were similar to those reported in this PhD study (Herbst, Mafojane et al. 2011). HIV and TB remained important mortality contributors followed by non-communicable diseases (Figure 8.1 and Figure 8.2). This was true in both the HIV- positive cohort presented in this PhD and in the

population-level verbal autopsy study. At a population level, injuries made a considerable contribution to mortality, especially in younger men (Herbst, Mafojane et al. 2011) but not in the PhD study, likely due to the fact that the PhD study focused on mortality in the first 3 months of initiating ART and the age groups included. To highlight the difficulties and limitations in assigning causes of death in resource limited settings such as the Africa Centre, in both these studies, a considerable proportion of deaths were classified as unknown, being even higher in older adults than young adults. This is because even when deaths occur in health facilities autopsies are very expensive and rarely done. Even before death, there are diagnostic challenges in accurately ascertaining morbidity causes hence limiting the extent to which mortality causes may be accurately assigned.

Unlike in European cohorts (Hasse, Ledergerber et al. 2011) where non-communicable diseases were reported as the major cause of mortality, in our setting non-communicable diseases were a minor cause of very early mortality in both younger and older adults. Mortality due to non-communicable diseases, although not frequent, was non-statistically significantly higher in older than younger adults, similar to reports elsewhere (Hasse, Ledergerber et al. 2011). None of the 72 HIV positive individuals presenting for ART initiation with chronic morbidity only died within the first 3 months of ART, highlighting that it is still the HIV driving very early mortality. However, deaths due to unknown causes remain a significant contributor to mortality in the initial phase of ART, more so for older adults than younger adults, possibly due to the fact that cause of death maybe more difficult to ascertain in older adults who may have more co-morbidities. Also, in diseases such as bacterial pneumonia, some classic signs such as chest pain and fever are less frequent with increasing age (van Duin 2012).

Figure 8.1 Very early mortality causes in an HIV positive cohort following ART initiation (based on the Global Burden of Disease Classification) – results from this PhD study

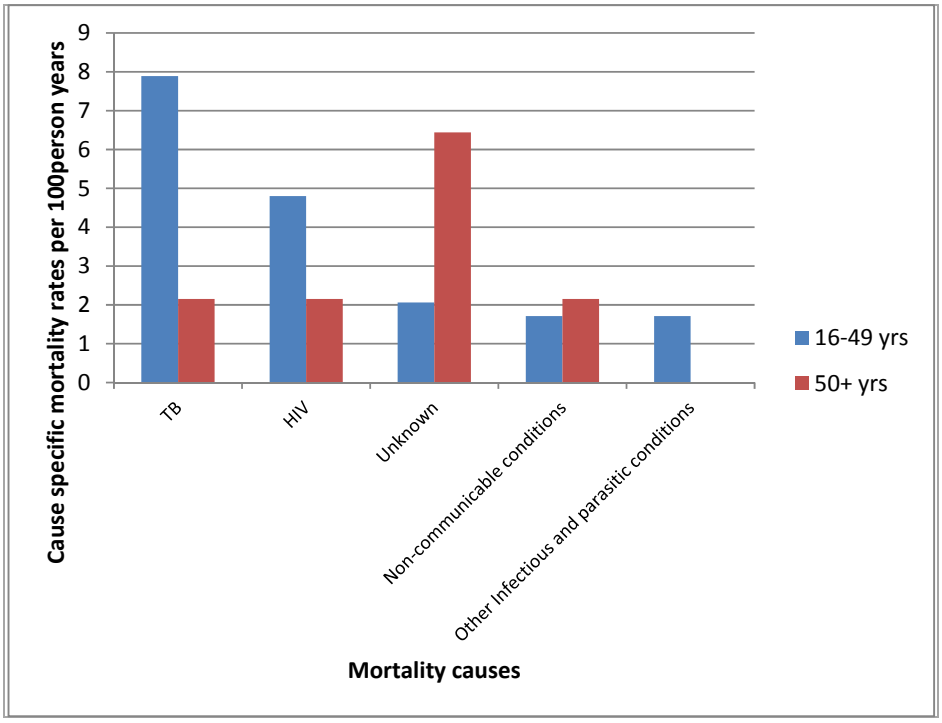
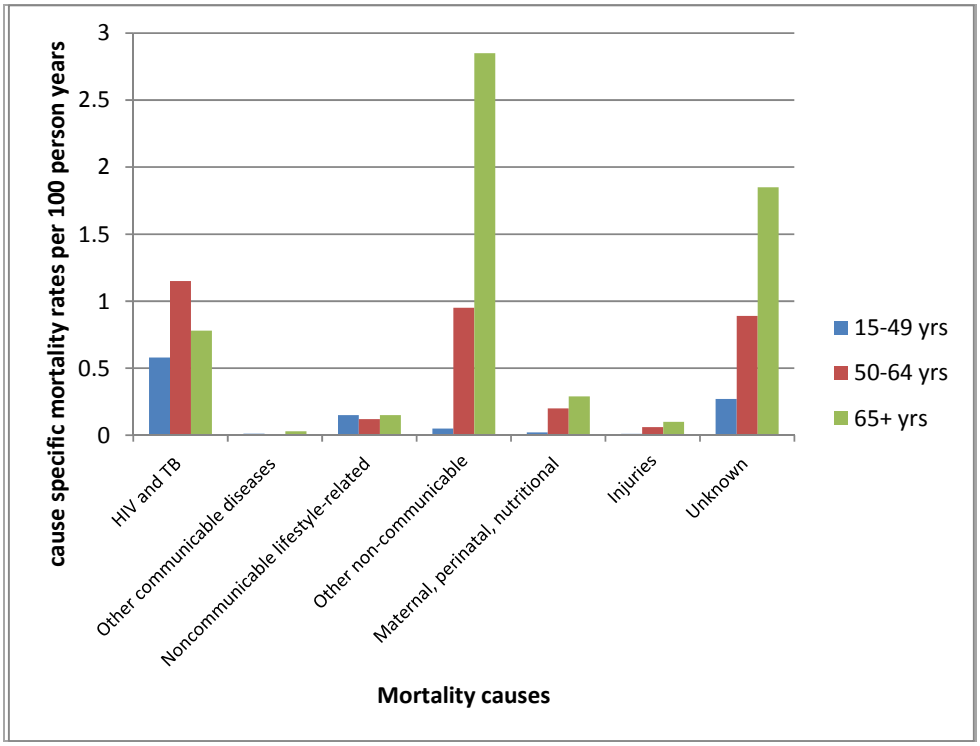


Figure 8.2 Cause specific mortality rates in the general population in rural KwaZulu Natal (based on the Global Burden of Disease Classification)



Data for figure obtained from (Herbst, Mafojane et al. 2011)

Strengths and limitations

In addition to prior mentioned strengths and limitations of the Clinical Cohort (Section 4.3.9), the reduction in very early mortality rates with the increase in CD4 cell count threshold for ART eligibility resulted in fewer early deaths (Lessells, Mutevedzi et al. In Press), limiting statistical power to detect mortality cause differences by age. The ART Clinical Cohort is still enrolling HIV positive adults initiating ART and was expanded in early 2013 to cover an additional 5 clinics, in an effort to increase sample size. Comparison of socio-demographic and clinical characteristics of patients initiating ART within the main treatment programme and those enrolled in the Clinical Cohort showed no differences, giving us confidence that the results from the Clinical Cohort are largely comparable to the main treatment programme as a whole.

8.5.1 The contribution of baseline morbidity to very early mortality

The extent to which co-morbidities before or at ART initiation and drugs used in their treatment affect the rate and risk of death subsequent to initiating ART remains largely undocumented, especially in sub-Saharan Africa. Most studies discussed above report prevalence or incidence of morbidity after ART initiation, and fail to address the impact of co-morbidity at start of ART on efficacy of ART, information which would be useful in providing estimates of how much benefit there is in initiating HIV positive individuals early on ART, both at patient and population level. Results from this PhD show that after adjustment for differences in age, sex, baseline laboratory markers (CD4 count, Hb, ALT and eGFR) and BMI, the risk of dying within the first three months of ART was five and half times higher in older adults with HIV-associated morbidity than in older adults initiating ART without HIV-related symptoms, Whilst initiating ART with HIV-associated morbidity coupled with either TB modestly increased mortality risk, initiating ART with AIDS-

associated morbidity coupled with any chronic pre-existing morbidity significantly increased mortality risk in the first three months of ART.

Using Attributable fraction ($AF_{exposed}$) analysis which refers to the proportion of cases that develop due to exposure, and etiologic fraction also known as population attributable risk percentage (PAR%) which refers to the reduction in early mortality incidence that would be observed if the population was entirely unexposed compared with its current actual exposure levels, the ratio of early mortality incidence in those presenting for ART initiation with baseline morbidity to the incidence of early mortality in those without morbidity was extremely high. For older and younger individuals initiating ART with any type of morbidity, very early mortality attributable to this morbidity was 85% with an etiologic fraction of 75%. Although it is impossible to eliminate morbidity in any given population irrespective of HIV status, initiating HIV positive individuals onto ART early before development of multiple co-morbidities may significantly reduce mortality rates in this population.

Mortality in adults initiating ART with WHO stage 3 or 4 HIV disease and concurrent TB is largely driven by TB co-infection with a mortality incidence rate ratio (mortality in those with HIV and TB co-morbidity compared to those without) of 5.5 and with 82% of mortality in this group being due to the HIV and TB co-morbidity. Although the mortality risk in adults initiating ART with WHO stage 3 or 4 disease was lower than in those with HIV and TB co-morbidity, initiating ART in adults before WHO stage 3 or 4 HIV disease develops, would avoid more early deaths than initiating ART before TB co-infection develops [population attributable risk percent (etiologic fraction) of HIV and TB co-morbidity was 8.3% compared to 30% due to WHO stage 3 or 4 HIV disease]. Thus, even if

at an individual patient level it would be beneficial to initiate TB patients onto ART before their HIV disease progresses, at a population level it would be more beneficial to initiate all HIV positive adults of all age groups onto ART early whilst still asymptomatic irrespective of their TB status.

The first study for this PhD (Mutevedzi, Lessells et al. 2011) provided evidence of extremely high mortality rates in the first three months of receiving ART, and reported higher mortality rates than observed using later data from within the ART Clinical Cohort. The ART Clinical Cohort was implemented about six months (March 2010) after the South African HIV treatment guidelines were expanded with higher CD4 count eligibility thresholds for those pregnant and with TB co-infection. About five months after the implementation of the ART Clinical Cohort these guidelines were again updated to a higher threshold for all irrespective of TB and pregnancy status, following which significant very early mortality declines were observed not only within the ART Clinical Cohort but within the whole HIV Treatment programme (Lessells, Mutevedzi et al. In Press). Further investigation of this decline showed that mortality within the first three months of ART started with the initial changes in guidelines for adults aged 16 years and above with TB and those pregnant but only became statistically significant after the threshold was increased for all HIV infected adults (Lessells, Mutevedzi et al. In Press). The differences in population level benefits may partly be explained by the differences in total numbers exposed to either HIV associated morbidity or both HIV associated morbidity and TB as well as the differences in the mortality rate ratios in those exposed against those not exposed. More importantly the decline in very early mortality was higher for older than younger adults, indicating an even bigger benefit of earlier initiation of ART in this group.

Chronic morbidity in itself did not significantly increase very early mortality, which is not surprising considering that, as discussed above, infectious diseases are a more frequent cause of mortality compared to chronic illnesses. Low hospitalisation rates from chronic morbidity have been reported in this PhD study and in another study on native African older adult population (Waweru, Kabiru et al. 2003), suggesting that in HIV positive adults, infectious diseases are more important than chronic morbidities. To date there has been little evidence in this setting of drug toxicities as a cause of serious morbidity, but this may change with increased and prolonged exposure to ART and other chronic morbidity treatments. For this reason it remains important to not only pro-actively screen for chronic morbidities but to also monitor liver and kidney function especially for all adults receiving lifelong ART with other co-morbid chronic conditions.

Worth noting and in line with previous studies that have called for earlier initiation in older than younger adults (Gebo 2006; Patterson, Napravnik et al. 2007; Silverberg, Leyden et al. 2007; Gebo 2008; Rhee and Greenblatt 2008; The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group 2008; Onen, Overton et al. 2010; Greig, Carrillo et al. 2012; Iwuji, Churchill et al. 2013), both the attributable risk of mortality due to advanced HIV disease and the etiologic fraction were about double in older compared to younger adults, suggesting that for older adults, even after initiating ART, it becomes more difficult to restore immune function and reverse the effects of HIV compared to younger adults. Concurring with this finding, as discussed below (Section 8.9) results from this PhD work also show blunted immune response in older adults, especially in the early phases after initiation of ART.

Although previous analyses of data from this same population showed that, compared to older, younger age was associated with higher TB incidence in the first three months of ART (Houlihan, Mutevedzi et al. 2010), it could be that TB presentation is different in older adults or that symptoms are less frequently attributed to TB in this group leading to missed diagnoses and mortality (Negin and Cumming 2010(van Duin 2012)). In line with this argument, results from this PhD work show that although older adults are less likely to be on TB therapy at time of initiating ART, they are more likely to be hospitalised due to TB after initiation of therapy. Further, irrespective of age at ART initiation, 46% of deaths within the first three months of ART were due to TB which was not diagnosed and treated at time of initiating ART, whilst just under half of deaths due to unknown causes were in adults who were receiving TB therapy when they initiated therapy. This was despite all TB suspects, identified through a highly sensitive and not very specific TB screening algorithm, were tested for TB by X-ray and culture before initiating therapy. The contribution of immune reconstitution inflammatory syndrome (IRIS) to early mortality remains unclear; a recent meta-analysis, using data from diverse settings across high-, middle- and low-income settings, suggested that IRIS might be responsible for 21% of all deaths after ART initiation (Muller, Wandel et al. 2010). Within this PhD work, those on concurrent TB therapy when they initiated ART had a serious morbidity incidence rate twice as high as that in those without TB. Although older adults were less likely to be on concurrent TB therapy at ART initiation, the risk of hospitalisation due to TB was higher in this age group. Whether the incidence and presentation of IRIS is different in older adults requires further study with cohorts of large sample sizes.

8.6 Morbidity and mortality risk related to abnormal bio-markers (Hb, ALT, creatinine and GFR) at ART initiation

Lifelong exposure to any chronic medication may result in kidney and liver toxicities due to drug side effects and suboptimal drug clearance (Effros, Fletcher et al. 2008). Since kidney and liver function declines with age (Davies and Shock 1950; Effros, Fletcher et al. 2008), the risk of drug toxicities and side effects is increased in older adults, necessitating vigilant monitoring of liver and kidney toxicities through laboratory markers of Alanine Transaminase (ALT)and creatinine and Glomerular Filtration Rates (GFR) correlates of liver and kidney function respectively (Davies and Shock 1950; Effros, Fletcher et al. 2008; Onen, Overton et al. 2010; Hasse, Ledergerber et al. 2011). However studies utilising these bio-markers are rare, especially in populations from resource-limited countries because these tests are expensive to conduct and require specialised laboratories. For this reason and to contribute to the limited knowledge base, this PhD used data from the main Hlabisa HIV treatment and care programme and the ART Clinical Cohort to ascertain whether levels of ALT and GRF at ART initiation predict risk of serious morbidity (part of objective three) and early mortality (part of objective five). Adjusting for age and sex, CD4 cell count at ART initiation and TB co-infection, adults with poor creatinine clearance (creatinine levels >240 µmol/L) were at increased risk of hospitalisation as were anaemic adults (Hb <8g/dL). Elevated ALT levels did not significantly increase risk of hospitalisation. Accounting for differences in age, sex, pre-existing co-morbidity and baseline CD4 cell count, adults initiating ART with ALT levels greater than 60IU/ml a level (twice the upper limit of normal) had a three-fold increased risk of dying within the first 3 months of ART. However, in this PhD, although sub-optimal glomerular filtration rates were a risk factor for serious morbidity requiring hospitalisation, its association with very early mortality risk was statistically non-significant once differences in baseline morbidity, CD4 cell count, age

and sex were accounted for, suggesting that liver function may be a more important independent risk factor of mortality.

Similar to results from this PhD, others have reported increased mortality risk associated with elevated levels of creatinine, GFR and ALT; recent results from the D.A.D study reported increased mortality risk in adults with sub-optimal liver function approximated through elevated ALT levels (Sabin, Ryom et al. 2013) as did a smaller cohort of 885 HIV positive women and 425 HIV negative controls in four urban areas in the USA, where high creatinine levels were associated with increased mortality in the HIV positive women (Gardner, Holberg et al. 2003). Further, a study on 3 137 HIV positive Ghanaian adults reported high prevalence of renal dysfunction (measured through estimated glomerular filtration rates) pre- and post-ART, which was associated with increased risk of mortality (Sarfo, Keegan et al. 2013).

In this PhD study, high morbidity and mortality risk in adults with sub-optimal liver and kidney function identified a group of individuals requiring enhanced monitoring and management of potential side effects to ensure success of ART. Results from this PhD confirms that diagnosis and management of sub-optimal liver and kidney function should be a priority in HIV infected adults, especially in older adults and illustrate a group of adults who would potentially benefit from alternative drug regimens that have low toxicities. The South African HIV treatment guidelines introduced Tenofivir a couple of years ago instead of Stavudine (National Department of Health 2010; National Department of Health 2013). Given the reports from the Swiss HIV cohort, Centres for AIDS Research Network of Integrated Clinical Systems and EuroSIDA (Luetkemeyer, Havlir et al. 2010) of decreased renal efficiency (reduced GFR) following initiation of Tenofivir-

containing ART caution may be necessary in the use of Tenofovir, especially in older adults who are more likely to present for ART initiation with low GFR levels. In the ART Clinical Cohort, individuals were not followed from time of sero-conversion to ART eligibility and it is therefore difficult to say determine if kidney and liver disease were a consequence of HIV infection.

Strengths and limitations

This PhD presented data from routine care of HIV positive adults aged 16 years and above within a public sector HIV treatment and care programme and has limitations. Data on creatinine and ALT measurements were incomplete mainly because the samples for these evaluations had not been taken when the individual came for the visit, issues relating to specimen quality or misplacement of results. Although it was not possible to ascertain the exact reason for missing measurements of ALT, creatinine and GFR , it is likely that missingness was at random given that the both explanatory and outcome variables were similar in those with missing and with complete observations. To account for missing values within variables, all analyses were conducted as both complete case analyses as well as including the missing categories, the results of which gave similar conclusions from both scenarios.

The results presented here are generalisable to HIV positive populations receiving ART from settings such as this, as discussed above and previously (Mutevedzi, Lessells et al. 2010; Houlihan, Bland et al. 2011; Bor, Herbst et al. 2013; Tanser, Barnighausen et al. 2013; Lessells, Mutevedzi et al. In Press), adults receiving therapy within the Hlabisa HIV Treatment and Care programme had characteristics similar to adults in other public health sector HIV programmes from resource-limited settings. Although the ART Clinical Cohort

had limited statistical power to detect differences in rare conditions, the cohort itself was representative of the treatment programme as a whole. The ART Clinical Cohort data were sufficient to describe and explore morbidity issues surrounding HIV treatment and outcomes and provides a platform for future larger cohort studies with more statistical power. Also worth noting is that the small sample size does not nullify our findings but rather confirms strong associations that were evident even with these limited sample sizes.

8.7 Conclusion

In conclusion, results from this PhD study have shown that HIV positive adults over 50 years of age who were on ART for at least a year have a lower chronic (non-HIV related) morbidity burden than HIV negative adults in this age group, despite elevated inflammatory markers. This reduction in morbidity is only evident in HIV positive older adults on ART; indeed HIV positive, ART-naive older adults have a non-statistically significant higher morbidity burden than in HIV negative adults. These findings could suggest benefit of enhanced access to health care in HIV positive older adults who utilise health care services every month for ART pill collection visits. It also suggests that providing health care services to older adults through community mobile clinics may improve the health of HIV negative adults who would otherwise not access health care services.

However, although HIV positive older adults had less chronic morbidity than HIV negative adults of similar age, compared to younger HIV positive adults older adults have a higher morbidity burden of both AIDS defining and chronic non-AIDS defining illnesses at the point of initiating ART. This would indicate that even at point of requiring therapy, with

advanced HIV disease, older adults already have special clinical needs over and above those of younger adults. Clinicians need to be cognisant of this fact and both health service providers and older adults would benefit from having age- specific HIV management guidelines. Results here also show that although older adults have superior virological suppression following ART initiation than younger adults, they have only a modest increase in absolute CD4 cell counts after initiating antiretroviral therapy. This finding together with the high co-morbidity and morbidity at higher CD4 cell counts compared to younger adults and the high early mortality in older adults largely driven by AIDS-related morbidity at ART initiation highlights the need to consider timely initiation of ART in older adults; the recently expanded treatment eligibility criteria in South Africa may improve the health of older adults.

This PhD study finds higher rates of multiple morbidity in older than younger adults; health care providers need to vigilantly screen for co-morbidity in older adults prior to prescribing ART and take cognisance of possible drug interactions between ART and other prescribed non-AIDS related medications so as to minimise drug interactions that may increase liver and kidney toxicities, side effects or reduce efficacy of their co-administered drugs. Considerable levels of reduced kidney function in older adults and of reduced liver function (approximated by glomerual filtration rates/creatinine levels and alanine transaminase respectively) associated with increased risk of serious morbidity and mortality following ART initiation, in this PhD, indicates the need for frequent monitoring of kidney and liver function. In South Africa since April 2013, HIV positive adults are initiated on a fixed dose combination pill consisting of Tenofovir, Emtricitabine and Efavirenz, unless contraindicated, and if clinicians do not diligently screen for and detect kidney and liver problems, ART may result in harm especially in older adults.

This PhD reports mortality attributable to AIDS-associated morbidity at ART initiation is high for both younger and older adults and highlights the need for enhanced clinical monitoring of individuals initiating ART with advanced HIV disease to reduce high early mortality. Additionally, in the absence of WHO stage 3 or 4 HIV disease, non-HIV related chronic morbidity alone does not significantly increase mortality risk compared to individuals initiating ART without any type of morbidity. These results suggest that although co-morbidity complicates successful antiretroviral therapy, HIV itself remains the major driver of very early mortality following initiation of therapy as such early initiation of ART would be the most effective intervention for early mortality reduction and further monitoring of HIV positive patients aged 50 years and above initiating therapy under the revised South African eligibility criteria will give useful insights on and quantify realised benefits.

TB remains a challenge in mortality and morbidity of HIV positive patients receiving ART. For older adults, complexity is added by findings from this PhD work showing that even though older adults are less likely to on TB treatment at ART initiation and are less likely to be hospitalised due to TB, their mortality due to TB is significantly high indicating potential diagnostic issues – misdiagnosis, under-diagnosis. Older adults would benefit from vigilant TB screening even in the absence of classical TB symptoms.

Obesity levels are high even in HIV positive individuals and considering its associated with decreased absorption of some ART drugs, for HIV positive individuals it is essential to maintain a healthy weight. Community based interventions on lifestyle modification campaigns focusing on exercise and healthy eating habits can go a long way in reducing obesity and associated problems.

High prevalence of non-AIDS morbidity in HIV positive older adults shows that this group would benefit from integration of HIV and age-related chronic morbidity services and alludes to the high cost of maintaining good health in older adults due to multiple morbidity and calls for more vigorous primary health prevention campaigns and interventions to reduce the risk and incidence of both HIV- and non-HIV related morbidity.

The ageing of the HIV infected cohort requires greater efforts to integrate the needs of older adults into responses to the HIV epidemic as we move into the future and to specifically address the needs of older adults in HIV treatment delivery. Meeting the complexities of geriatric care for HIV infected adults in the future will further challenge overwhelmed health systems and will require that health systems be integrated and optimally efficient. Aids2031, a group established by UNAIDS to chart the actions needed to address the trajectory of the HIV epidemic, has emphasized the need for a shift in the response from crisis management to sustained strategic response (Larson, Bertozzi et al. 2011). The results presented here contribute towards evidence required to understand issues surrounding the health of older adults in the context of high HIV prevalence and incidence with widespread availability and access to ART and provides knowledge required for evidence based health planning for the ageing HIV cohort.

8.8 Recommendations for future studies

The results from this PhD provide data that can be utilised to inform on future studies to firstly understand mechanisms and processes leading to increased morbidity in older adults at an individual level and secondly to improve the health care delivery for older adults at a population level.

At an individual level, now that results from this PhD have indicated that ART is associated with decreased levels of inflammatory markers, levels of which remain higher than those in HIV negative older adults, there is need for studies evaluating whether at these low levels morbidity risk is still significant and to assess which ART drugs in this setting are most effective in reducing cytokine levels. Within the current South African treatment guidelines it would be difficult to conduct such studies by collecting blood specimens for determining bio-marker levels using patients within existing treatment cohorts because since April 2013 patients are initiated on a fixed dose combination pill consisting of Tenofovir, Emtricitabine and Efavirenz, making it difficult to tease out the effects of individual drugs. Differences in effectiveness of ART in reducing inflammatory marker levels are best explored using randomised multi-arm studies and such studies can be embedded within future trial evaluating efficacy of ART regimens. Such trials can also assess the efficacy and benefits of a cytokine lowering pill coupled with ART, in morbidity and mortality reduction in older adults.

There is ongoing debate on whether HIV causes accelerated ageing and existing reports are conflicting. An age-matched case-control study comparing frailty markers between HIV positive and HIV negative individuals would be useful in contributing to knowledge in this area.

To elucidate the relationship of HIV, co-morbidity and cytokines requires longitudinal biomarkers studies of large cohorts with long follow up periods carefully documenting clinical events with frequent blood specimen collection to measure the rates of incident morbidity at different levels of cytokines in HIV positive and negative older adults. Studies designed this way enable capturing of infrequent events and provides bio-marker levels prior to and post disease hence showing with levels relate to morbidity and by so doing

establish the temporal relationship between morbidity or mortality and cytokine levels. The ART Clinical Cohort set up for purposes of this PhD, nested within a large HIV treatment programme will continue to collect morbidity events that will be useful in understanding age-driven long term HIV prognosis in the presence of ART. Moreover data from such studies can be used to explain mechanisms in HIV induced immune activation and how ART modifies these mechanisms hence inform on possible interventions that can be implemented to reduce levels of inflammatory markers in high risk groups.

Although biomarkers such as cytokines and lipid profiles are more precise and accurate measures of health and are better able to detect disease than a diagnosis based on clinical signs and symptoms, their use in clinical practice is limited by the fact that there are still many unknowns in terms of how HIV modifies levels or function of these biomarkers. It remains largely undetermined how different biomarker levels translate to disease in those HIV-positive. Biomarker levels are population dependent and there is thus a need to determine what is normal in different populations before biomarkers can be successfully used to determine health in routine clinical practice. In resource-limited settings use of biomarkers is hugely limited by the expense associated with setting up required laboratories and conducting the biomarker evaluations themselves.

At a population level, results of high co-morbidity and multiple morbidities in HIV positive older adults show that health services integration makes delivery and receipt of health care services easier and more efficient as consultation for multiple conditions can be done by one nurse/doctor in one room. Future randomised control trials where the control group receives the current standard of care, are required to evaluate different health service delivery modes are useful to guide the implementation of integrated health systems delivery. These interventions can also be used to evaluate the benefits of mobile

community clinics conducting chronic morbidity and TB screening and the use of community health workers in improving the health of older adults and promoting adherence to treatment. Such studies will begin to explain why for older adults, there is lower morbidity and better health in those HIV positive than HIV negative.

Population attributable risk calculations from this PhD show that initiating patients early irrespective of TB status, results in considerable mortality reduction at a population level. This result coupled with the recent findings of the benefits of ART in HIV prevention highlights the need for early therapy. However, several African cohorts have reported increased retention-in-HIV-care problems as HIV treatment cohorts grow. With HIV treatment resistance highly associated with sub-optimal treatment adherence, this necessitates multi-arm randomised interventions to assess treatment delivery models at multiple CD4 cell count thresholds that are not only cost effective but also promote and sustain high retention levels in HIV care.

Closer to home, this PhD has established an association between obesity and high inflammatory marker levels whose perpetually high presence may lead to disease. Future community based projects that provide different modes of weight management and healthy life style techniques such as providing necessary seeds and equipment for gardening and funding the establishment of community netball or soccer teams, are needed to evaluate whether such interventions can reduce the obesity epidemic in this rural South African community.

To address some of the limitations of WOPS 1 including the 10 year age difference between the HIV-negative and HIV-positive groups and the cross-sectional nature of the

study, a WOPS 2 study is currently enrolling all WOPS 1 older adults and an additional 100 individuals to increase the sample size and replace those who have died in the HIV positive ART-naive group. The data from the two WOPS rounds (2010 and 2013) will be used to further confirm morbidity differences by HIV and ART status and to rule out the role of survivor bias in explaining lower morbidity in HIV positive older adults on ART. These data will also be used to assess patterns of health care utilisation by HIV status and how this influences chronic morbidity.

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Appendices

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Visit Date Y Y Y Y M M D D	Clinic **K M C**
SA ID No.	Gender Female **O** Male **O**
First names	Surname
Date of birth Y Y Y Y M M D D	Clinical cohort number

Interviewer name	

Clinical cohort number						

Clinical cohort number	Visit Date
	Y Y Y Y M M D D

1. **ANTHROPOMETRY AND VITAL SIGNS** (*take the following measurements)*

Weight ☐☐☐.☐kg Height ☐☐☐cm Blood pressure ☐☐☐/☐☐☐

All the questions on this form are about the patient named above. Try to obtain the relevant information as far as possible from the file or relevant clinic card(s) i.e. TB or PMTCT card. Where information from these sources is unavailable, vague or conflicting clarification should be sought through direct interviewing of the patient.

2. **REFERRALS**

2a. When did you have your first positive HIV test? Y Y Y Y M M

2b. When did you have your first CD4 count? Y Y Y Y M M

2c. What made you have an HIV test?

PMTCT **O** TB Clinic **O** Hospital **O**

Private doctor **O** Main government clinic **O** Clinical trial/study **O**

Other **O** → Specify

2d. Have you ever had a negative HIV test? Yes **O** → *2e* No **O** → *Section 3* Don't know **O** → *Section 3*

2e. When was this test done? Y Y Y Y M M

3. **DRUGS** (*tick all that apply)* - obtain information from patient file if not in file then ask the patient

3a. Besides the HIV related drugs, are you on any other chronic/long term medication?

Yes **O**→ *Q3b* No **O**→ *Section 4* Don't know **O**→ *Section 4*

3b. For which disease? *(tick all that apply)*

Epilepsy ☐ Diabetes ☐ Hypertension ☐

Arthritis ☐ Psychiatric ☐

Other ☐ → Specify

4. **TB –** obtain information from TB card. If information is not recorded on the card or the card is missing then ask for the information from the patient.

4a. Have you previously been treated for TB? Yes **O** No **O** Don't know **O**

4b. Only complete the table below if patient has answered YES in 4a above. For past TB episodes record year only if actual date is not recorded on TB card and the patient does not remember. *(tick the one that applies)*

Date past TB treatment started						**TB site**		**Regimen**			**Treatment completed**	
						Pulmonary	**Extra-pulmonary**	**1**	**2**	**DKN**	**Yes**	**No**
Y	Y	Y	Y	M	M	**O**	**O**	**O**	**O**	**O**	**O**	**O**
Y	Y	Y	Y	M	M	**O**	**O**	**O**	**O**	**O**	**O**	**O**

4c. Are you on TB treatment currently? Yes **O** No **O** Don't know **O**

Clinical cohort number						

4d. Only complete the table below if patient has answered YES in 4c above.

Date current TB treatment started								TB site		Regimen			
								Pulmonary	Extra-pulmonary	1	2	MDR	XDR
Y	Y	Y	Y	M	M	D	D	O	O	O	O	O	O

5. CURRENT MORBIDITY- obtain information from patient file if unavailable then ask from the patient. The presence of clinical symptoms/signs and the systems associated with those symptoms/signs should be determined by the nurse.

5a. Do you have clinical symptoms/signs at this visit? Yes **O** No **O→***5e*

5b. Complete the table below regarding **(A)** the system to which the current symptoms are linked, **(B)** whether the current illness is a new condition or is related to an existing condition, **(C)** the symptoms, and **(D)** symptom code. The basis of diagnosis can be both symptoms and lab/investigations.

Φ Nurse must determine which system the symptoms are linked to and the likely diagnosis. A lab diagnosis is one based on lab tests performed on the patient's biological specimen(s). Symptoms diagnosis is one based on presenting clinical signs and symptoms. Systemic includes sweat, fever and poor appetite.

(A) SYSTEM LINKED TO SYMPTOMS *(tick all that apply)*	**(B)** CONDITION		**(C)** SYMPTOMS	**(D)** SYMPTOM CODES				
	New	Existing					•	
Musculoskeletal ☐	**O**	**O**					•	
							•	
Ear/nose/throat ☐	**O**	**O**					•	
							•	
Neurological ☐	**O**	**O**					•	
							•	
Gastrointestinal ☐	**O**	**O**					•	
							•	
Oral (teeth +mouth) ☐	**O**	**O**					•	
							•	
Respiratory ☐	**O**	**O**					•	
							•	
Cardiovascular ☐	**O**	**O**					•	
							•	
Genitourinary ☐	**O**	**O**					•	
							•	
Eyes ☐	**O**	**O**					•	
							•	
Lymph nodes ☐	**O**	**O**					•	
							•	
Systemic ☐	**O**	**O**					•	
							•	
Skin ☐	**O**	**O**					•	
							•	
Other ☐	**O**	**O**					•	
							•	

Clinical cohort number							

5c. Diagnosis	Code	Basis of diagnosis *(tick all that apply)*	
		Clinical signs/ symptoms	Lab / investigations
	.	☐	☐
	.	☐	☐
	.	☐	☐

5d. Are you being admitted to hospital for the current illness reported above? Yes **O** No **O**

5e. What is the clinical staging of this patient? I **O** ii **O** iii **O** iv **O**

Specify reason for staging →

5f. In the past 6 months have you been admitted to hospital? Yes **O**→*5g* No **O**→*Section 6*

5g. Diagnosis | Code . |

6. SOCIO-ECONOMIC STATUS – obtain information through direct interviewing of the patient

6a. Are you employed? *(tick one only)*

Yes, casual work **O** Yes, formal work **O** Never employed **O**

No, but was employed previously **O**

6b. Are you a recipient of a social security grant?

Yes **O** No **O**→ *Section 7*

Applied **O** → Y Y Y Y M M D D

6c. What type of social security grants do you receive? *(tick all that apply)*

Care dependency ☐ For how many children? ☐☐ Old age ☐

Child support ☐ For how many children? ☐☐ Disability ☐

Foster care ☐ For how many children? ☐☐

7. HIV STATUS DISCLOSURE – obtain information through direct interviewing of the patient

7a. Have you disclosed your HIV status to anyone?

Yes **O**→*Q7b* No **O**→ *section end* Refused to answer **O**→ *section end*

7b.To whom have you disclosed your HIV status? *(tick all that apply)*

Partner/Spouse ☐ Parent ☐ Church member ☐

Child ☐ Sibling ☐ Neighbour ☐

Friend ☐ Other ☐ → Specify

Interviewer name and code				

Clinical cohort number: ☐☐☐☐☐☐

Visit Date: Y Y Y Y M M D D

1. ANTHROPOMETRY AND VITAL SIGNS (*take the following measurements)*

Weight ☐☐☐.☐kg Blood Pressure ☐☐☐/ ☐☐☐

All the questions on this form pertain to the patient named above. Try to obtain the relevant information as far as possible from the file or relevant clinic card(s) i.e. TB or PMTCT card. Where information from these sources is unavailable, vague or conflicting clarification should be sought through direct interviewing of the patient.

2. ART DRUGS - obtain information from patient file if not in file then ask the patient

2a. Have your ART drugs been changed since your last clinic visit? Yes **O**→*Q2b* No **O** →*Section 3*

2b.What type of drug change was this? Single drug substitution **O**→*Q2c* Complete regimen change **O**→*Q2d*

2c.

Which drug was removed?	Which drug was added?

2d. Which drugs are you on now?

Drug 1	d4T	**O**	TDF	**O**	AZT **O**	ABC	**O**
Drug 2	3tc	**O**	ddI	**O**		FTC	**O**
Drug 3	NVP	**O**	EFV	**O**	LPVr **O**	ATVr	**O**

2e. What were the reasons for changing the drug? *(Tick all that apply)*

Treatment failure ☐ TB ☐ Pregnancy ☐

Psychiatric illness ☐ Other ☐ → Specify

Adverse events ☐ → Specify

3. MORBIDITY SINCE THE LAST CLINIC VISIT – obtain information for this section through direct interviewing of patient

3a. Have you suffered from any illness since your last clinic visit? Yes **O**→*Q3b* No **O**→*Section 5*

3b. Which of the following did you consult for the illness mentioned above? *(Tick all that apply)*

Clinic ☐ Private doctor ☐ Traditional healer ☐

Hospital OPD ☐ Did not consult ☐→ *Section 5* Health facility admission ☐→*Section 4*

Other ☐ → Specify

3c. What was the diagnosis given from the consultation above? Code ☐☐☐.☐

3d. What was the diagnosis in Q3c. above based on? *(tick all that apply)*

Clinical signs/symptoms ☐ Laboratory/investigations ☐

Clinical cohort number:	Visit Date:
	Y Y Y Y M M D D

4. ADMISSION DETAILS obtain information for this section through direct interviewing of patient
(Only complete section 4 if patient reported hospital admission in Q3b above.)

4a. In which health facility were you admitted?																			
4b.	**Disease**								**Code**					**Basis of diagnosis** *(tick all that apply)* Clinical signs/symptoms		Laboratory /investigations	
Main diagnosis												•		☐		☐	
Other diagnosis												•		☐		☐	
Admission date	Y Y Y Y M M D D								Discharge date	Y Y Y Y M M D D									

4c. Which of the following was the main diagnosis most likely to be related to? *(tick all that apply)*

New disease ☐ ART Drug reactions ☐ Worsening existing disease ☐

Other ☐ → Specify

5. CURRENT MORBIDITY - obtain information from patient file, if unavailable then ask the patient. The system associated with symptoms should be determined by the nurse.

5a. Do you have clinical symptoms at this visit Yes **O** No **O**→Section 6

5b. Complete the table below regarding **(A)** the system to which the current symptoms are linked, **(B)** whether the current illness is a new condition or is related to an existing condition, **(C)** the symptoms, and **(D)** symptom code. The basis of diagnosis can be both symptoms and lab/investigations.

(A) SYSTEM LINKED TO SYMPTOMS *(tick all that apply)*	**(B)** CONDITION New	Existing	**(C)** SYMPTOMS	**(D)** SYMPTOM CODES
Musculoskeletal ☐	**O**	**O**		•
Ear/nose/throat ☐	**O**	**O**		•
Neurological ☐	**O**	**O**		•
Gastrointestinal ☐	**O**	**O**		•
Oral (teeth +mouth) ☐	**O**	**O**		•
Respiratory ☐	**O**	**O**		•
Cardiovascular ☐	**O**	**O**		•
Genitourinary ☐	**O**	**O**		•
Eyes ☐	**O**	**O**		•
Lymph nodes ☐	**O**	**O**		•
Systemic ☐	**O**	**O**		•
Skin ☐	**O**	**O**		•
Other ☐	**O**	**O**		•

5c. Diagnosis	Code					Basis of diagnosis *(tick all that apply)* Signs/ symptoms	Lab /investigations
1.				•		☐	☐
2.				•		☐	☐

Clinical cohort number: | Visit Date: Y Y Y Y M M D D

5d. Is the current illness likely to be related to ART drugs i.e. adverse drug reactions?

Yes **O** No **O** Don't know **O**

5e. Are you being admitted to hospital for the current illness reported above? Yes **O** No **O**

6. TB - obtain information from TB card. If information is not recorded on the card or the card is missing then ask for the information from the patient.

6a. Have you had any of the following symptoms since your last clinic visit? *(tick all that apply)*

Night sweats ☐ Cough ☐ Rapid weight loss ☐ None ☐

Other ☐ → Specify

6b. Have you been started on TB treatment since the last visit?

Yes **O** No **O** →*section 7* Don't know **O**→ *section 7*

6c. Complete the table below as fully as possible regarding the TB diagnosis reported above in 6b.

Date TB treatment started	TB site		Regimen				BASIS OF DIAGNOSIS	
	Pulmonary	Extra-pulmonary	1	2	MDR	XDR	Signs/symptoms	Lab/Investigations
Y Y Y Y M M	O	O	O	O	O	O	☐	☐

7. GRANTS - obtain information through direct interviewing of the patient

7a. Have you received a social security grant since your last clinic visit?

Yes **O** No **O**→*end*

Applied **O** → Y Y Y Y M M D D

7b. What type of social security grants do you receive? *(tick all that apply)*

Care dependency ☐ For how many children? ☐☐ Old age ☐

Child support ☐ For how many children? ☐☐ Disability ☐

Foster care ☐ For how many children? ☐☐

Interviewer name and code

Clinical cohort number:	**Completion Date:**
	Y Y Y Y M M D D

1. DEATH

1a. Who/what is the source of information?

Informant **O** Hospital records **O** Tracking team **O**

Physician's report **O** Clinic record **O**

1b. Date of death Y Y Y Y M M D D

1c. What was the cause of death?

Immediate cause

Underlying cause

Associated cause (a)

(b)

(c)

2. LOSS TO FOLLOW-UP

∞Loss to follow-up is missing 3 or more consecutive monthly clinic visits.

2a. Date of last clinic visit Y Y Y Y M M D D

2b. What was the reason for not attending clinic visits?

Employment **O** Dissatisfied with service **O** Moved away **O**

Death of caregiver **O** Decided to stop treatment **O**

Other **O** → specify

Clinical cohort number:	Completion Date:
	Y Y Y Y M M D D

3. TRANSFER OUT

⚯Transfer out is completely moving out of the Hlabisa HIV treatment and care programme to receive ART elsewhere i.e. outside the sub district or to another HIV care programme within the sub district.

3a. Date of last clinic visit Y Y Y Y M M D D

3b. What was the reason for transferring out?

Employment **O** Dissatisfied with service **O** Moved away **O**

Other **O** → specify

Interviewer name C O D E

Wellbeing of Older People Study (WOPS),
Somkhele, South Africa
in collaboration with the WHO
Study on Global Ageing and Health (SAGE)

WOPS ID	Respondent's DSID	Respondent's BSID
Interviewer code	Respondent's Name Surname, First name(s)	BS Owner
Date of Interview Y Y Y Y / M M / D D	Household Head	Location/Isigodi:
Start time of interview H H : M M	Date of Birth Y Y Y Y / M M / D D	Age Sex: Male ○ Female ○

Section 1: Respondent and household characteristics

101	What is your relationship to the head of this household?	
102	What is your current marital status?	
103	What is your highest level of education attained? ***(Tick only one)***	Grade or No formal education ○ Less than 1 year ○ Adult education only ○ Certificate ○ Diploma ○ Bachelors degree ○ Honours/Masters+ ○ Don't know ○
104	Are you currently in employment?	Yes ○ No ○
105	What is the main source of drinking water for members of this household? ***(Tick only one)***	Piped - inside house ○ Piped - public tap/kiosk ○ Borehole ○ Well (non-borehole) ○ Rainwater ○ Protected spring ○ Flowing river/stream ○ Dam/Stagnant water ○ Other, specify _____
106	What type of toilet facilities do members of your household mainly use? ***(Tick only one)***	Flush toilet ○ VIP ○ Ordinary Latrine ○ Bucket/Chemical toilet ○ No facilities (bush) ○ Neighbour's latrine ○ Other, specify _____
107	What type of fuel does your household mainly use for cooking? ***(Tick all mentioned)***	Electricity from generator ☐ Gas (LPG) ☐ Electricity from solar energy ☐ Wood ☐ Electricity from grid ☐ Coal / charcoal ☐ Kerosene/paraffin ☐ Other, specify _____
108	Is your house connected to an electricity grid?	Yes ○ No ○
109	Does anyone in your household have any of the following in good working condition….? ***(Tick all mentioned)***	Bicycle ☐ Gas cooker ☐ Radio ☐ Fridge/freezer ☐ Mobile/cellular telephone ☐ TV ☐ Video recorder/DVD player ☐ Sofa/sofa set ☐
110	Does your household have any of the following domestic animals/fowl? ***(Tick all mentioned)***	Cows ☐ Goats ☐ Pigs ☐ Chickens/ducks ☐ Rabbits ☐ Other, specify_____
111	[Please tell me] which of these sources is your main source of household income, by that I mean from which source does most of the money used in this household come from? ***(Tick only one)***	Earnings from selling or trading ○ Income from rental property ○ Wages, salary from job ○ Government grants ○ No source of income ○ Other, specify _____
112	Compared to 3 years ago would you say your financial situation is better or worse?	Better ○ About the same ○ Much worse ○

Section 2: Health State Description

Interviewer to read: Now we will ask questions specifically about your health. The first questions are about your overall health, including both your physical and your mental health.

201	In general, how would you rate your health today?	Very Good ○ Good ○ Moderate ○ Bad ○ Very Bad ○
202	Overall, in the last 30 days/month, how much difficulty did you have with work or household activities?	None ○ Mild ○ Moderate ○ Severe ○ Extreme/cannot do ○
203	How was your health during the last two weeks? ***If 'Very Good' or 'Good' skip to Q205***	Very Good ○ Good ○ Moderate ○ Bad ○ Very Bad ○
204	What signs of illness did you experience in the last two weeks? ***Tick all that respondent mentions then read the others and tick all that apply***	Diarrhoea ☐ Itchy skin ☐ Herpes zoster ☐ Night sweats ☐ Vomiting ☐ Incontinence ☐ Feeling very weak ☐ Not able to sleep ☐ Confused ☐ Painful wounds ☐ Pain in the body ☐ Cough, chest pain ☐ Fever ☐ Could not eat because of nausea ☐ Could not eat because of pain when swallowing Others Specify _____

Interviewer to read: I would like to review the different functions of your body. When answering these questions, I would like you to think about the **last 30 days/ month**, taking both good and bad days into account.
When I ask about difficulty, I would like you to consider **how much difficulty** you have had, on an average, in the past one month, while doing the activity in the way that you usually do it. By **difficulty, I mean** requiring increased effort, discomfort or pain, slowness or changes in the way you do the activity. Please answer this question taking into account any assistance you have available (answer this question the difficulty you might have when you do it without assistance).

Mobility

	Overall in the last 30 days/month … ***Read and show scale to respondent***	1. None	2. Mild	3. Moderate	4. Severe	5. Extreme/cannot do	6. N/A
205	….. how much difficulty did you have with moving around?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
206	… how much difficulty did you have in vigorous activities (digging in the garden, lifting heavy objects such as a bag of potatoes)? (Vigorous activities require hard physical effort and cause large increases in breathing or heart rate)	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○

Self Care

207	….. how much difficulty did you have with self-care, such as bathing/washing or dressing yourself?	1. ○	2. ○	3. ○	4. ○	5. ○
208	….. how much difficulty did you have in taking care of and maintaining your general appearance (for example grooming, looking neat and tidy)	1. ○	2. ○	3. ○	4. ○	5. ○
209	…..how much difficulty did you have in staying by yourself for a few days (3 to 7 days)?	1. ○	2. ○	3. ○	4. ○	5. ○

Pain and discomfort

210	….. how much of bodily aches or pains did you have?	1. ○	2. ○	3. ○	4. ○	5. ○
211	….. how much bodily discomfort did you have?	1. ○	2. ○	3. ○	4. ○	5. ○
	If Q210 AND Q211 are 'NONE' skip to Q213					
212	…..how much difficulty did you have in your daily life because of your aches pain or discomfort?	1. ○	2. ○	3. ○	4. ○	5. ○

Cognition

	Read responses	1. None	2. Mild	3. Moderate	4. Severe	5. Extreme/cannot do
213	….. how much difficulty did you have with concentrating or remembering things?(e.g. cooking, bathing).	1. ○	2. ○	3. ○	4. ○	5. ○
214	…..how much difficulty did you have in learning a new task (for example, learning how to get to a new place)?	1. ○	2. ○	3. ○	4. ○	5. ○

Interpersonal activities

215	….. how much difficulty did you have with personal relationships or participation in the community?(eg attending ceremonies, meetings)	1. ○	2. ○	3. ○	4. ○	5. ○
216	…..how much difficulty did you have in dealing with conflicts and tensions with others (e.g. family/community matters)?	1. ○	2. ○	3. ○	4. ○	5. ○
217	….. how much difficulty did you have with making new friendships or maintaining current friendships?	1. ○	2. ○	3. ○	4. ○	5. ○
218	…..how much difficulty did you have with dealing with strangers?	1. ○	2. ○	3. ○	4. ○	5. ○

Sleep and energy

219	….. how much of a problem did you have with sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning or sleeping too much?	1. ○	2. ○	3. ○	4. ○	5. ○
220	…..how much of a problem did you have due to not feeling rested and refreshed during the day?	1. ○	2. ○	3. ○	4. ○	5. ○

Affect

221	... how much of a problem did you have with feeling sad, low or unhappy?	1. ○	2. ○	3. ○	4. ○	5. ○
222	…..how much of a problem did you have with worry or anxiety (having the experience receiving bad news and having fast heart beating)	1. ○	2. ○	3. ○	4. ○	5. ○

Vision

(If respondent normally wears glasses or contact lenses, should ask the following Qs as "Since starting to wear glasses/contact lenses….".)

223	Have you ever had your eyes examined by a medical professional? If yes, when was the last time? ***Interviewer: Enter years or months ago. Enter "00" if less than 1 year or 1 month ago.***	YES ○ NEVER ○ DON'T KNOW ○ If Yes when, years ☐☐ months ☐☐
224	Do you use eyeglasses or contact lenses to see far away (for example across the street)?	YES ○ NO ○
225	Do you use eyeglasses or contact lenses to see up close (for example at arms length, like when you are reading)?	YES ○ NO ○

226	…. how much difficulty did you have in seeing and recognizing an object or a person you know across the road (from a distance of about 20 metres)? ***INTERVIEWER: Indicate a spot that is similar distance for each respondent.***	1. ○	2. ○	3. ○	4. ○	5. ○
227	…..how much difficulty did you have in seeing and recognizing an object at arm's length (for example, sorting beans, groundnuts or rice)? ***If Q226 & Q227are 'None' skip to Q229***	1. ○	2. ○	3. ○	4. ○	5. ○
228	…..how much difficulty do you have fulfilling daily tasks because of not seeing properly? (e.g. cooking, washing)	1. ○	2. ○	3. ○	4. ○	5. ○

Subjective wellbeing

Interviewer to read: Now, we would like to ask for your thoughts about your life and life situation. We want to know how you feel about your health and quality of life.

229	Do you have enough energy for everyday life? ***Read and show scale to respondent***	Completely ○	Mostly ○	Moderate ○	A little ○	None at all ○
		1. Very Satisfied	2. Satisfied	3. Neither satisfied nor dissatisfied	4. Dissatisfied	5. Very dissatisfied
230	How satisfied you are with your health?	1. ○	2. ○	3. ○	4. ○	5. ○
231	How satisfied you are with your self?	1. ○	2. ○	3. ○	4. ○	5. ○
232	How satisfied you are with your ability to perform your daily living activities?	1. ○	2. ○	3. ○	4. ○	5. ○
233	How satisfied you are with your personal relationships?	1. ○	2. ○	3. ○	4. ○	5. ○
234	How satisfied you are with the conditions of your living place?	1. ○	2. ○	3. ○	4. ○	5. ○
235	Taking all things together, how satisfied are you with your life as a whole these days?	1. ○	2. ○	3. ○	4. ○	5. ○
236	How often have you felt that you were unable to control the important things in your life? **Read responses**	Never ○	Almost never ○	Sometimes ○	Fairly often ○	Very often ○
237	How often have you found that you could not cope with all the things that you had to do? **Read responses**	Never ○	Almost never ○	Sometimes ○	Fairly often ○	Very often ○
238	How would you rate your overall quality of life? **Read responses**	Very Good ○	Good ○	Moderate ○	Bad ○	Very Bad ○

Functioning assessment

These next questions ask about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs. Think back over the last 30 days and answer these questions thinking about how much difficulty you had doing the following activities.

INTERVIEWER: *For each question, please tick only one response.*

	In the last 30 days/month, how much difficulty did you have … ***Read responses***	1. None	2. Mild	3. Moderate	4. Severe	5. Extreme/cannot do	6. NAD
239	… in sitting for long periods?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
240	… in walking 100 metres?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
241	… in standing up from sitting down?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
242	… in standing for long periods?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
243	... with climbing one flight of stairs without resting?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
244	… with stooping, kneeling or crouching?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
245	…picking up things with your fingers (such as a coin from a table)?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
246	… in taking care of your household responsibilities?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
247	… in joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
248	… concentrating on doing something for 10 minutes?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
249	… in walking a long distance such as a kilometre?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
250	… in bathing/washing your whole body?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
251	… in getting dressed?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
252	… in your day to day work?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
253	… with carrying things?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
254	… with moving around inside your home (such as walking across a room)?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○

		1. None	2. Mild	3. Moderate	4. Severe	5. Extreme/cannot do	6. NAD
255	… with eating (including cutting up your food)?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
256	… with getting up from lying down?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
257	… with getting to and using the toilet?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
258	… with getting where you want to go, using private or public transport if needed?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
259	… getting out of your home?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
260	In the last 30 days/month, how much have you been emotionally affected by your health condition(s)?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
261	Overall, how much did these difficulties interfere with your life?	1. ○	2. ○	3. ○	4. ○	5. ○	6. ○
262	Besides any vision (eyeglasses, contact lenses) or hearing aids, do you use any other devices (such as a cane, walker, or other) for any difficulties you experience?						Yes ○ No

Depression

Interviewer to read: Now I would like to ask you questions about your feelings of sadness or depression

263	Have you ever been diagnosed with depression? ***If 'NO' SKIP to Q266***	Yes ○ No ○
264	During the last 2 weeks have you been taking any medications or other treatment for it? (Other treatment can include attending therapy or counselling sessions.)	Yes ○ No ○
265	During the last 12 months have you been taking any medications or other treatment for it?	Yes ○ No ○
266	During the last 12 months, have you had a period lasting several days when you felt sad, empty or depressed?	Yes ○ No ○
267	During the last 12 months, have you had a period lasting several days when you lost interest in most things you usually enjoy such as personal relationships, work or hobbies/recreation?	Yes ○ No ○
268	During the last 12 months, have you had a period lasting several days when you have been feeling your energy decreased or that you are tired all the time?	Yes ○ No ○
	INTERVIEWER: IF ANY ONE OF Q266, Q267 OR Q268 IS "YES", CONTINUE TO Q269. IF ALL 3 ARE "NO", GO TO Q301	
269	Was this period [of sadness/loss of interest/low energy] for more than 2 weeks?	Yes ○ No ○
270	Was this period [of sadness/loss of interest/low energy] most of the day, nearly every day?	Yes ○ No ○
271	During this period, did you lose your appetite?	Yes ○ No ○
272	Did you notice any slowing down in your thinking?	Yes ○ No ○
273	Did you notice any problems falling asleep?	Yes ○ No ○
274	Did you notice any problems waking up too early?	Yes ○ No ○
275	During this period, did you have any difficulties concentrating; for example, listening to others, working, watching TV, listening to the radio?	Yes ○ No ○
276	Did you notice any slowing down in your moving around?	Yes ○ No ○
277	During this period, did you feel anxious and worried most days?	Yes ○ No ○
278	During this period, were you so restless or jittery nearly every day that you paced up and down and couldn't sit still?	Yes ○ No ○
279	During this period, did you feel negative about yourself or like you had lost confidence?	Yes ○ No ○
280	Did you frequently feel hopeless - that there was no way to improve things?	Yes ○ No ○
281	During this period, did your interest in sex decrease?	Yes ○ No ○
282	Did you think of death, or wish you were dead?	Yes ○ No ○
283	During this period, did you ever try to end your life?	Yes ○ No ○

Section 3: Chronic conditions and health service coverage

Interviewer: Now I would like to read you questions about some health problems or health care needs that you may have experienced, and the treatment or medical care received

		HEART DISEASE Angina/angina pectoris	ARTHRITIS	STROKE	HYPER-TENSION	CHRONIC LUNG DISEASE	ASTHMA	DIABETES	CANCER
301	Have you ever been diagnosed with/told you have?	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No
302	How long ago was the diagnosis?	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months ○ 7-12 months ○ >12 months ○	0-6 months 7-12 months >12 months
303	Have you been taking medications or other treatment for……. during the last 2 weeks?	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No
304	……. during the last 12 months?	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○	Yes ○ No

Interviewer: Now I would like to ask you about some health symptoms you may have experienced, and the treatment or medical care received

Heart Disease/Angina

305	During the last 12 months have you experienced discomfort, pain, or heaviness in chest, arm, or breastbone when walk uphill or in a hurry?	Yes ○ No ○
306	During the last 12 months/year have you experienced any pain or discomfort in your chest when you walk at ordinary pace on level ground?	Yes ○ No ○ ***If Q305 & 306 are 'NO'*** →***Q3***
307	What do you do if you get the pain or discomfort when walking? ***(Tick only one)***	Stop/slow down ○ Carry on walking ○ Take pain relief medicine then carry on ○
308	If you stand still, what happens to the pain or discomfort?	Relieved ○ Not relieved ○
309	Have you experienced these symptoms in the last 2 weeks?	Yes ○ No ○
310	Have you been seeing a doctor or other health worker for these symptoms?	Yes ○ No ○
311	During the last 12 months/year have you seen a traditional healer for these symptoms?	Yes ○ No ○
312	Are you currently taking any herbal or traditional remedy for your symptoms?	Yes ○ No ○

Arthritis

313	During the last 12 months/year have you experienced pain, aching, stiffness or swelling in or around joints (arms, hands, feet) not related to injury & lasted for more than a month?	Yes ○ No ○
314	During the last 12 months/year have you experienced any stiffness in the joint in the morning after getting up from bed or after a long rest?	Yes ○ No ○ ***If Q313 & 314 are 'NO'*** →***Q3***
315	How long does this stiffness last?	30 mins or less ○ More than 30 mins ○
316	Does this stiffness go away after exercise or movement in the joint?	Yes ○ No ○
317	Have you experienced these symptoms in the last 2 weeks?	Yes ○ No ○
318	Have you experienced back pain during the last month? On how many days if yes?	Yes ○ Days_____ No ○
319	Have you been seeing a doctor or other health worker for these symptoms?	Yes ○ No ○
320	During the last 12 months/year have you seen a traditional healer for these symptoms?	Yes ○ No ○
321	Are you currently taking any herbal or traditional remedy for your symptoms?	Yes ○ No ○

Stroke

322	Have you ever suffered from sudden onset of paralysis or weakness in your arms or legs on one side of your body for more than 24 hours?	Yes ○ No ○
323	Have you ever had, for more than 24 hours, sudden onset of loss of feeling in one side of your body, without anything having happened to you immediately before?	Yes ○ No ○

Hypertension

324	During the last 12 months have you seen a traditional healer for raised blood pressure (hypertension)?	Yes ○ No ○ ***If 'NO'*** ⟶ ***Q327***
325	Are you currently taking any herbal or traditional remedy for your raised blood pressure (hypertension)?	Yes ○ No ○
326	Do you currently eat any special food for your raised blood pressure (hypertension)? Name the food, if yes	Yes ○ FOOD _____ No ○

Chronic Lung Disease

327	During the last 12 months/year have you experienced any shortness of breath while at rest or while awake?	Yes ○ No ○
328	During the last 12 months/year have you experienced any coughing or wheezing for 10 minutes or more at a time?	Yes ○ No ○
329	During the last 12 months/year have you experienced any coughing up sputum or phlegm for most days of the month for at least 3 months?	Yes ○ No ○ ***If 327 to 329 are 'NO'*** → 3
330	These symptoms that you say you experienced, have you experienced them in the last 2 weeks?	Yes ○ No ○
331	Have you been taking any medications or other treatment for your symptoms during the last 2 weeks?	Yes ○ No ○
332	Have you been taking any medications or other treatment for your symptoms during the last 12 months?	Yes ○ No ○
333	In the last 12 months/year have you had a tuberculosis (TB) test?	Yes ○ No ○
334	Have you had blood in your phlegm or have you coughed blood?	Yes ○ No ○

Asthma

335	During the last 12 months/year have you experienced any attacks of wheezing or whistling breathing?	Yes ○ No ○
336	During the last 12 months/year have you experienced any attacks of wheezing that came on after you stopped exercising or some physical activity?	Yes ○ No ○
337	During the last 12 months/year have you experienced any feeling of tightness in your chest?	Yes ○ No ○
338	Have you woken up with a feeling of tightness in your chest in the morning or any other time?	Yes ○ No ○
339	Have you experienced shortness of breath that came on without obvious cause when you were not exercising or doing some physical activity?	Yes ○ No ○
340	***Go to Q344 if Q335, 336, 337, 338 & 339 are all 'NO'*** Have you experienced any of these symptoms you describe in the last 2 weeks?	Yes ○ No ○
341	Have you been seeing a doctor or other health worker for these symptoms?	Yes ○ No ○
342	During the last 12 months/year have you seen a traditional healer for these symptoms?	Yes ○ No ○
343	Are you currently taking any herbal or traditional remedy for your symptoms?	Yes ○ No ○

Diabetes

344	During the last 12 months/year have you been taking insulin or other blood sugar lowering medications?	Yes ○ No ○
345	During the last 2 weeks have you been taking insulin or other blood sugar lowering medications?	Yes ○ No ○
346	Have you been following a special diet, exercise regime or weight control program for diabetes during the last 2 weeks?	Yes ○ No ○

Cataract/Eye problems

347	In the last 5 years were you diagnosed with a cataract (cloudiness in the lens of the eye) in one or both of your eyes?	Yes ○ No ○ ***If 'NO'*** → ***Q349***
348	In the last 5 years have you had eye surgery to remove this cataract(s)?	Yes ○ No ○
349	In last 12 months have you experienced cloudy or blurry vision?	Yes ○ No ○
350	In last 12 months have you experienced vision problems with light, such as glare from bright lights or rings around lights?	Yes ○ No ○
351	Have you ever gone to the clinic because of eye problems?	Yes ○ No ○

Oral Health

352	Have you lost all your natural teeth?	Yes ○ No ○
353	During the last 12 months have you had any troubles with your mouth and/or teeth (this includes problems with swallowing)?	Yes ○ No ○ ***If 'NO'*** → ***Q357***
354	Have you received medication or treatment from a dentist during the last 12 months for mouth/teeth problems?	Yes ○ No ○
355	In last 12 months have you seen a traditional healer for your mouth/teeth problems (including problems with swallowing?	Yes ○ No ○
356	Are you currently taking any herbal or traditional remedy for your problems with mouth or teeth?	Yes ○ No ○

Injuries

357	During the last 12 months did you have an injury?	Yes ○ No ○ ***If 'NO'*** → ***Q400***
358	How did the injury happen? Was it an accident?	It was an accident ○ Someone else caused it deliberately (intentional) ○ I did it to myself (self-inflicted) ○
359	Did you receive medical treatment for the injury	Yes ○ No ○
360	Did you suffer a physical disability as a result of being injured?	Yes ○ No ○
361	In what way were you physically disabled? ***(Tick only one)***	Unable to use hand/arm ☐ Difficulty using hand/arm ☐ Walk with a limp ☐ Loss of hearing ☐ Loss of vision ☐ Weakness/shortness of breath ☐ Inability to remember things ☐ Inability to chew ☐ OTHER _____
362	What caused the injury? ***(Tick all mentioned)***	Fall ○ Stabbed ○ Gun shot ○ Fire or burn ○ Near-drowning ○ Poisoning ○ struck/hit by person/object ○ Animal bite ○ Electric shock ○ OTHER, SPECIFY _____

Section 4: Health care utilization & risk factors and behaviours

400	During the last 4 weeks, did you suffer from one of the following diseases or symptoms: ***Read the symptoms and record*** ***If no symptoms skip to 405***	Fever / malaria Yes ○ No ○ Gastro-intestinal problems (e.g. diarrhoea) Yes ○ No ○ Coughing/ respiratory problems Yes ○ No ○ Skin conditions such as (LOCAL NAMES) Yes ○ No ○ Trouble with mouth and/or teeth or swallowing Yes ○ No ○ Other Specify _____
401	For those symptoms, what did you do….? ***Tick all that apply***	Used own herbal medicine ☐ Took medicine (self treatment) ☐ Visited a government health centre /public clinic ☐ Admitted to a government hospital ☐ Did nothing about the symptoms ☐ Saw a traditional healer/ herbalist ☐ Visited the Pharmacy/chemist/shop ☐ Visited a private or missionary health clinic ☐ Admitted to a private or missionary hospital ☐ Other Specify _____
402	Where did you go first? ***Tick only one***	Traditional healer / herbalist /shrine ○ Government health centre /public clinic ○ Government hospital ○ Others Specify _____ Pharmacy/chemist/shop ○ Private or missionary health clinic ○ Private or missionary hospital ○
403	Did you have to pay for consultation and/or drugs?	Yes ○ No ○ ***If 'NO' → Q405***
404	Who paid for the consultation and/or drugs?	Son/daughter ○ Spouse ○ Self ○ Other relative ○ Insurance ○ Was free ○ Other Specify _____
405	During the last 12 months, how often have you visited a clinic or hospital?	Not at all ○ Once or twice ○ Three to six times ○ More than six times ○ Don't know ○
406	When you visit the clinic or hospital how long, do you usually have to wait before it is your turn to be seen by a nurse or doctor?	Not long ○ Quite long ○ Very long ○
407	When you visit the clinic or hospital, do the health professionals usually give you enough time to explain to them what your health problem is?	Always ○ Sometimes ○ Never ○
408	When you visit the clinic or hospital, do the health professionals usually take the time to explain your health problem and treatment in a way that you understand?	Always ○ Sometimes ○ Never ○
409	Overall, are you satisfied with the services?	Satisfied ○ Indifferent ○ Dissatisfied ○
410	Do you ever go to traditional healers for treatment?	Yes ○ Never goes to traditional healer ○ ***If 'Never….' skip to Q412***
411	What are the reason(s) that you go to the traditional healers for treatment? ***Tick all that apply***	Closer distance ☐ Traditional healers are cheaper ☐ Traditional healers allow you to pay in goods ☐ Traditional healers will wait for your payment ☐ Traditional healers give better treatment ☐ Other Specify _____ ☐

Health centre/clinic, hospital stays

412	Were you ever hospitalized in the last year? If so, how many times?	Yes ○ If 'Yes', Number of admissions _____ No ○ ***If 'NO' skip to Q450***
413	What type of hospital was it the last time you were hospitalized?	Public hospital ○ Private hospital ○ Charity or church run hospital ○ Old people's home or long term care facility ○ Other Specify _____
414	Which reason best describes why you were last hospitalized?	Specify reason hospitalized _____
1= communicable diseases, infections, malaria, infection TB, HIV; 2= nutritional deficiencies 3= acute conditions, (diarrhoea, flu, headaches, fever, cough and others); 4= injury; 5= surgery; 6= sleep problem; 7= occupational /work related condition/injury; 8= chronic pain in joints/arthritis (joints, back, neck); 9= diabetes or related complications; 10= problems with heart including unexplained pain in chest; 11= problems with mouth, teeth, swallowing; 12= problems with breathing; 13= high blood pressure, hypertension; 14= stroke/ sudden paralysis of one side of body; 15= generalized pain(stomach, muscle or other nonspecific pain); 16= depression, anxiety; 17= cancer; 87= other, specify		
415	Who paid for this hospitalization?	Son/daughter ○ Spouse ○ Self ○ Other relative ○ Insurance ○ Was free ○ Other, Specify _____

Section 4.5: Risk factors and preventive health behaviours

Tobacco use

450	Have you ever smoked tobacco or used smokeless tobacco?	Yes ○ No ○ ***If 'NO' skip to Q454***
451	Do you currently use (smoke, sniff or chew) any tobacco products such as cigarettes, cigars, pipes, chewing tobacco or snuff?	Yes, daily ○ Yes, but not daily ○ No, not at all ○ ***If 'Yes, not daily' OR 'No, not at all' SKIP TO Q454***
452	For how long have you been smoking or using tobacco daily?	Number of years _____
453	On average, how many cigarettes or pipes do you smoke or use each day?	Number of cigarettes _____

Alcohol

454	Have you ever consumed a drink that contains alcohol (such as beer, spirits, wine, etc.?)	Yes ○ No ○ ***If 'NO' skip to Q458***
455	Have you consumed alcohol in the last 30 days/month?	Yes ○ No ○ ***If 'NO' skip to Q458***
456	During the past 7 days, how many standard drinks of any alcoholic beverage did you have each day?	Number of drinks _____
457	In the last 12 months,/year how frequently [on how many days] on average have you had at least one alcoholic drink?	Less than once a month ○ 1 to 7 days per month ○ 1 to 4 days per week ○ 5 or more days per week ○

Nutrition

458	In the last 12 months, were you ever hungry, but didn't eat because you couldn't afford enough food?	Yes ○ No ○ ***If 'NO' skip to next section***
459	In the last 12 months, how often did you eat less than you felt you should because there wasn't enough food?	Every week ○ Every month ○ Almost every month ○ Some months, but not every month Only in 1 or 2 months ○ Never ○

Section 5: Anthropometric measurements

Interviewer to read: Now we would like to ask you to participate in a few tests to determine your health status. We would like to measure a few things, like your blood pressure, your weight a height etc. We will start with taking your blood pressure.

INTERVIEWER: Ask the respondent to release the arm and relax.

501	**Time 1:** Systolic ☐☐☐	Diastolic ☐☐☐	Pulse rate ☐☐☐
	INTERVIEWER: Ask the respondent to release the arm and relax. Wait for one minute before time 2. Do not ask the respondent questions.		
502	**Time 2:** Systolic ☐☐☐	Diastolic ☐☐☐	Pulse rate ☐☐☐
	INTERVIEWER: Again, remind the respondent to relax and wait.		
503	**Time 3:** Systolic ☐☐☐	Diastolic ☐☐☐	Pulse rate ☐☐☐

504	***Interviewer: Can respondent stand up?***	Yes ○ No ○

Interviewer to read: I would now like to measure how tall you are. To measure your height I need you to please take off your shoes. Put your feet and heels close together, stand straight and forward standing with your back, head and heels touching the wall. Look straight ahead

505	Measured height in centimetres	Height ☐☐☐	Not able to measure ○ refused ○

Now we want to measure your weight – could you please keep your shoes off and step on the scale.

506	Measured weight in kilograms	Weight ☐☐•☐	Not able to measure ○ refused ○

Section 6: Care giving

Interviewer read: Now we would like to talk about people who live with you here in your household (resident); we mean those who share meals and usually stay here for at least four months a year. Please include people who may presently be in an institution due to their health (for example, in hospital) for a short time. Lets start by talking about resident adults (18+ years) to whom may have provided care.

6.1: Physical, nursing care and financial assistance to resident adults and children

			Care giving to adults (18 years and above)	Care giving to children (less than 18 years)
601	Are you providing any physical or nursing care to any *adults/children* resident in your household? ***Interviewer: First ask Q601 to Q613 for care giving to adults and then start again from Q601 to Q613 for care giving to children***		Yes ○ No ○ ***If 'NO' skip to Q604*** If Yes how many? ___	Yes ○ No ○ ***If 'NO' skip to Q604*** If Yes how many? ___
602	Do you provide any care/ assistance such as with….?	Bathing (washing one's body) Eating (assistance with eating but not cooking) Dressing (putting on or taking off clothing) Toileting (getting to and using the toilet) Moving around (within or outside dwelling) Incontinence (help with hygiene problems) Preparing and giving medicines Taking care of wounds	Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Had no medicines ○ Yes ○ No ○ Had no wounds ○	Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Had no medicines ○ Yes ○ No ○ Had no wounds ○
603	Do you provide any physical assistance such as…?	Buying food Agricultural work Fetching water Cooking Taking to clinic or traditional healer Other	Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Specify_____	Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Specify_____
604	Are there any *adults/children* often sick and need care and treatment?		Yes ○ No ○ ***If 'NO' skip to Q611***	Yes ○ No ○ ***If 'NO' skip to Q611***
605	Can you tell me for what the *adults/children* need care and treatment for? ***If not 'HIV/AIDS RELATED' skip to Q607***		HIV/AIDS related ○ Health related reason, ○ Specify _____ Other reason, ○ Specify _____ Don't Know ○	HIV/AIDS related ○ Health related reason, ○ Specify _____ Other reason, ○ Specify _____ Don't Know ○
606	***Interviewer: Ask only If HIV/AIDS is mentioned in Q605*** How many *adults/children* with HIV infection do you take care of? ***If more than one adult or child needs care and treatment, ask the next questions about the adult or child in most need of care and treatment***		___	___
607	Do you know the kind of treatment/medication (NAME) needs? ***DO NOT PROBE: Tick only one.***		ARV treatment ○ TB treatment ○ Knows it is for AIDS, but not name ○ Other, Specify _____	ARV treatment ○ TB treatment ○ Knows it is for AIDS, but not name ○ Other, Specify _____

			Care giving to adults (18 years and above)	Care giving to children (less than 18 years)
608	Does (NAME) need to take daily medication/ treatment from the clinic?		Yes ○ No ○ ***If 'NO' skip to ➔ Q611***	Yes ○ No ○ **If 'NO' skip to ➔ Q611**
609	Do you need to remind (NAME) to go for their medical appointments and/or to take their medicines/(ARV)? ***(Interviewer: only mention ARV if ARV was mentioned in Q607)***		Yes ○ No ○	Yes ○ No ○
610	Do you accompany (NAME) going to the clinic/ hospital for follow up and /or ARV or TB treatment resupply? ***(Interviewer: ask only if ARV or TB is mentioned in Q607)***		Yes ○ No ○	Yes ○ No ○
611	Do you provide (NAME) with financial assistance such as……? ***Read and tick all that apply*** ***If all answers are <u>NO</u> skip TO Q613***	Paying for medicines Paying doctor or clinic or hospital fees Paying for food Paying for clothing Paying for transportation Paying for school expenses (of sick person's children) Other SPECIFY _____	Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○	Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○ Yes ○ No ○
612	Before (NAME) became ill, was s/he contributing to your household in cash or in kind or labour?		Yes ○ No ○	Yes ○ No ○
613	Overall, how difficult would you say it is for you to provide care, physical assistance or financial assistance to *adults/children*?		Very difficult ○ A little difficult ○ Not difficult ○	Very difficult ○ A little difficult ○ Not difficult ○

6.2 Care-giving to adults (18 and above) who have died in the last 24 months (2 years)

614	Has any adult resident member(s) of this household died in the last 24 months? ***Interviewer: If 'NO' deaths skip to Q701***	Yes ○ No ○ Number of deaths if Yes |_|_|_|
615	Of the resident adults who died in the last 24 months, how many were contributing an income/in cash or in kind to the household?	Number of adults contributing |_|_|_|
616	Were any of the persons who died the main income earner for your household?	Yes ○ No ○ Don't know ○
617	Did you provide care to any of the adults who died in the last 24 months? ***Interviewer: if provided care to more than one adult member, ask the next questions about the most recent death.***	Yes ○ No ○ ***If 'NO' go to Q701***
618	What is the NAME and SEX of the person who died?	Name: _____ Sex: Male ○ Female
619	How old was (NAME) when they died?	Age in years |_|_|_|
620	What was your relationship to (NAME)?	Relationship type |_|_|_|
621	For how long was s/he sick before he/she died? ***If less than one month skip to Q625***	Number of months |_|_|_|
622	Where was (NAME) living during the time s/he needed care?	Outside DSA ○ Inside the DSA ○
623	Did you stay/live with (NAME) during his/her sickness?	Yes ○ No ○ ***If 'No' skip to Q625***
624	How long did you stay/live with (NAME) during the time s/he needed care?	Number of Months |_|_|_| Number of Days |_|_|_|

6.3 Assessment of satisfaction with care-givers role

Interviewer read: Now I am going to ask whether you faced some problems related to your health and well-being the time you provided care and support to adult resident members who died in this household in the last 24 months			
625	During the time that you provided care how much difficulty did you have with…..? ***(Read responses and tick all that apply)***	Having enough energy to do extra work Taking care of your own ailments (if exist) Knowing the correct care to give for health problems Visiting family and relatives and friends Sharing feelings about care giving responsibility Knowing how to protect yourself from getting the illness/ disease Stigma or problems as a result of or associated with illness or death	Very much ○ some ○ None ○ Very much ○ some ○ None ○ Very much ○ some ○ None ○ Very much ○ some ○ None ○ Very much ○ some ○ None ○ Very much ○ some ○ None ○ Very much ○ some ○ None ○
626	Did the care you gave to adult household members give you the following …? ***(Read and tick all that apply)***	A chance to keep busy and occupied A chance to do things that makes use of your abilities A chance to feel a sense of accomplishment despite the difficulties A chance to do something useful for your sick household member	Yes ○ somewhat ○ No ○ Yes ○ somewhat ○ No ○ Yes ○ somewhat ○ No ○ Yes ○ somewhat ○ No ○

Section 7: Receiving care

Interviewer to read: Now we will continue asking questions about the assistance and care you might have needed and received.

FINANCIAL ASSISTANCE

701	Do you receive financial assistance for……? ***Read and record all that apply*** ***If all answers are 'NO' skip to Q705***	Paying for medicines Yes ○ No ○ Paying doctor or clinic or hospital fees Yes ○ No ○ Paying for food Yes ○ No ○ Paying for clothing Yes ○ No ○ Paying for transportation Yes ○ No ○ Paying school expenses (for offspring) Yes ○ No ○ Other SPECIFY _____
702	Who is/are the provider(s) of this financial assistance to you? ***Record all answers given***	Spouse ☐ Son/daughter ☐ Grandson/daughter ☐ Sibling ☐ Other relative ☐ Community ☐ Neighbour/ Friend ☐ Government ☐ Church ☐ Insurance ☐ Other Specify _____
703	For how long have you been receiving this assistance?	Years ☐☐☐ Months ☐☐☐
704	Overall, how difficult would you say it has/ had been to receive financial assistance?	Very difficult ○ A little difficult ○ Not difficult ○
705	In the past, before you became ill, were you contributing to the household in cash or in kind or labour?	Yes ○ No ○ ***If 'No' Skip to Q707***
706	Were you the main provider of cash or labour for the household?	Yes ○ No ○

GOVERNMENT GRANTS

707	Are you receiving any government grant meant for your use? ***Tick only one. If 'No, none' Skip to Q709.***	Yes, Care Dependency ○ Yes, Disability ○ Yes, Old Age Pension ○ No, none ○ Other Specify _____
708	On what do you mainly use this grant you receive? ***Tick only one***	Own upkeep ○ Care and support another household ○ Household expenses ○ Given to adult member of household ○ Other Specify _____
709	Are you receiving any government grant on behalf of some other member of your household? ***Record all answers given***	Yes, Care Dependency ☐ Yes, Disability ☐ Yes, Old Age Pension ☐ Yes, Foster Care ☐ Yes, Child Support ☐ No, none ☐ Other Specify _____

PHYSICAL ASSISTANCE

710	Do you receive physical assistance such as……? ***Read and tick all that apply*** ***If all answers to Q710 are 'NO' skip to Q713***	Buying food Yes ○ No ○ Agricultural work Yes ○ No ○ Fetching water Yes ○ No ○ Cooking Yes ○ No ○ Going to clinic or traditional healer Yes ○ No ○ Other SPECIFY_____

711	Who is/are the provider(s) of this assistance to you? ***TICK ALL THAT APPLY***	Parent ☐ Spouse ☐ Son/daughter ☐ Grandson 16+ ☐ Grand daughter 16+ Grandson under 16 ☐ Granddaughter under 16 ☐ Community volunteer ☐ Neighbour ☐ Government ☐ Church ☐ Sibling ☐ Friend ☐ Other Specify _____
712	For how long have you been receiving this assistance?	Years ☐☐☐ Months ☐☐☐

NURSING CARE AND SUPPORT

713	Do you know your HIV Status?	Yes ○ No ○
714	Do you need care, support and/or treatment?	Yes ○ No ○
715	Are you receiving any care, support and/or treatment?	Yes ○ No ○ ***If 'No' Skip to Q717***
716	Could you tell us why you need care, support and/or treatment? ***Do <u>not</u> read the response categories. Tick only one.*** ***Complete next section as well if 'HIV/AIDS related' is mentioned***	HIV/AIDS related ○ TB related ○ Health related reason, Specify _____ Other reason, Specify _____ Don't know ○ Refused ○
717	Do you receive care/assistance with...? ***Read and record all that apply***	Bathing (washing one's body) Yes ○ No ○ Eating (assistance with eating but not cooking) Yes ○ No ○ Dressing (putting on or taking off clothing) Yes ○ No ○ Toileting (getting to and using the toilet) Yes ○ No ○ Moving around (within or outside dwelling) Yes ○ No ○ Hygiene problems (bowel and bladder control) Yes ○ No ○
a.	Do you receive care/assistance with...?	Preparing and taking medicines Yes ○ No ○ Had no medicines ○

718	Overall how satisfied are you with the care/assistance you have received?	Satisfied ○ Indifferent ○ Not satisfied ○
719	Overall, how difficult would you say it has been for you to arrange this care/assistance?	Very difficult ○ A little difficult ○ Not difficult ○
720	Is there anything else you would like to tell us about the care/assistance you have received?	Yes ○ No ○
a.	**Record verbatim:**	

Interviewer: If 'HIV/AIDS related' was mentioned in Q716 Go to Q801, otherwise thank the respondent and end interview.

Section 8: HIV Experiences

EXPERIENCES OF LIVING WITH HIV/AIDS (only for respondents who know they are HIV infected)

Interviewer read: Now I would like to continue asking questions for this study about your health but the questions we will ask are now related to HIV and ARV treatment. We are asking the questions to get a better understanding about how this HIV affects older people but also the experience older people have with the ARV treatment.

801	How long ago did you learn that you have HIV?	Years ☐☐ Months ☐☐
802	How was your health at the time you tested HIV positive?	Good Moderate Bad ***IF 'Good' Skip to Q804***
803	For how long had you been sick before you learnt that you have HIV?	Years ☐☐ Months ☐☐
804	Since knowing that you have HIV, have you changed residence?	Yes No ***If 'NO' SKIP TO 806***
805	Did you move dwellings because of ….? ***Read and record all that apply***	Needed care Yes No Fail to pay rent Yes No Stigma Yes No Feeling better Yes No Other (specify)_____
806	During the last 3 months how would you say your health was?	Good Moderate Bad ***IF 'Good' Skip to Q808***
807	What signs of illness did you experience during the last 3 months? ***Read responses and tick all that apply***	Diarrhoea ☐ Itchy skin ☐ Herpes zoster ☐ Night sweats ☐ Vomiting ☐ Incontinence ☐ Feeling very weak ☐ Not able to sleep ☐ Confused ☐ Painful wounds ☐ Pain in the body ☐ Cough, chest pain ☐ Fever ☐ Could not eat because of nausea ☐ Could not eat because of pain when swallowing Others Specify _____
808	Before taking ARVs did you need any personal / nursing care?	Yes No Not yet on ARVs ***If 'Not yet on ARVs' End interview***
809	How long ago did you start ARVs treatment?	Years ☐☐ Months ☐☐ Weeks ☐☐
810	Do you experience any of these problems with taking the ARVs? ***Read and record all that apply***	Has side effects ☐ Sometimes forgets ☐ Needs certain kinds of food ☐ Other specify_____
811	Did you experience any serious side effects after starting ARV such as..? ***Read and record all that apply*** ***If did not experience <u>any</u> side effects, Skip to Q815***	Skin conditions Yes No Yellow eyes Yes No Muscle weakness Yes No Pain in the muscle Yes No Nausea/ vomiting Yes No Diarrhoea Yes No Hallucinations Yes No Bad dreams Yes No Self hate Yes No Fears Yes No Sadness Yes No Unreasonable/irritable Yes No Other specify_____
812	How many weeks did these side effects last?	Weeks ☐☐
813	Are you still experiencing these side effects?	Yes No
814	Have you changed ARVs because of side effects?	Yes No
815	Has your health improved since taking ARVs?	Very much Same as before Is worse
816	Does anyone living in the household ever remind you to take ARVs on time? ***Tick only one***	Daily or almost daily Several times a week Only once in a while Rarely or never At first but not now Other Specify _____
817	Does anyone accompany you when you go for follow up visits?	Yes, always Yes, sometimes Only when feeling sick No ***If 'No' End intervie***
818	Who usually accompanies you for follow up (and or resupply) visit?	Family member Friend Community volunteer

End time of interview ☐☐ Hours ☐☐ Mins

End of interview. Thank the respondent.

Introduction

We are inviting you to participate in a clinical cohort of patients on antiretroviral treatment that is being conducted by the Africa Centre. A cohort means a 'group of individuals'. The 'cohort' or group of individuals included in this study are patients who are on antiretroviral treatment (ART) in the Hlabisa HIV Treatment and Care Programme.

This document gives you information about the study that will be discussed with you. Once you understand the study, and you agree to take part, you will be asked to sign a consent form, or make a mark on the form in front of a witness.

Explanation of what we are trying to do.

In the HIV Treatment and Care Programme we already collect some clinical data, for example information on when people start on their ART, when they were last seen at clinic, what their latest CD4 count is. This information helps us to ensure that we are looking after patients well in the programme. These data are stored in a database at the Africa Centre; only certain people in the programme have access to this information in order to protect patients' details. We wish to extend our data collection to include additional information about patients' health, including any illnesses, hospital admissions, and weights.

Who will take part?

All HIV-infected patients starting on ART in the Hlabisa HIV Treatment and Care Programme attending Kwamsane and Somkhele clinics will be invited to take part in this study.

What does it mean to be involved in this study?

If you agree to participate in this study, you will be interviewed by a research nurse whenever you are visiting the clinic for your routine treatment collection or for consultation due to ill health. If you miss one ore more clinic visits you will be contacted by the research nurse to ask you about your health and why you have not been collecting your treatment. If you are admitted to hospital, the research nurse may conduct a follow up visit to obtain information

about your admission and may ask you a few questions relating to your admission. This information will also be recorded on research questionnaires.

Is there any risk of being in the study?

There are no risks involved to your health in participating in this study. The only foreseen discomfort is extra time spent at the clinic (approximately 20 minutes) whilst being interviewed by the research nurse. All possible steps will be taken to ensure the confidentiality of your medical records.

Is there any benefit by being in the study?

People being followed in this clinical cohort may experience better clinical care than those not in the cohort. With each clinic visit, you will have the opportunity to see the research nurse who will be able to assist with any queries you may have. We will also ensure that you have had all necessary tests carried out and that you understand the results of these (e.g. routine CD4 counts and viral loads). We will also refer you for additional help if you require it – for example, if you need help with a grant application an appointment will be made with the social worker.

What if I do not want to take part?

Taking part in this study is entirely voluntary. If you decide not to take part, or decide to take part and later withdraw from the study, you will not be penalised. You will continue to receive care in the ART programme and at the clinic.

Who will have access to this information?

The information that is collected will be kept confidential. Only the clinical cohort study researchers and staff will have access to this information and results. The name or identity of the study participants will not be revealed. The study results will be made known to the Hlabisa hospital management and clinic based staff without revealing the identity of the individuals who participated in the study. The results will also be made known to the Department of Health in KwaZulu-Natal and at the national level.

Who can you contact for more information about this study?

If you need more information or if there is something you do not understand concerning this study, you can contact the following people:

Dr Ruth Bland, Project Principal Investigator

Africa Centre for Health and Population Studies

035 550 7500.

Or

Mr Mduduzi Mahlinza, Head of Community Liaison Office

Africa Centre for Health and Population Studies

035 550 7500

Or

The Biomedical Ethics Committee

Private Bag X54001, Durban, 4000

Telephone: +27 (0)31 – 260 4769

Fax: +27 (0)31 – 260 4609

E-mail: BREC@ukzn.ac.za or ramnaraind@ukzn.ac.za

I..... agree to be part of the **Clinical ART Cohort**. The study has been explained to me and I fully understand the information written in the study information sheet. I understand the implications of joining the study, and that I may be asked additional information regarding my health during each study visit.

I understand that the study research nurse will contact me if I miss scheduled visits and, if I am admitted to hospital, may visit me to collect additional information about my illness and hospital stay. I also give permission for the research staff to look at my clinic file and clinic card.

I understand that I may leave the study at any time and I will not be discriminated for doing so. I will continue to use the ART clinic and be given appropriate care as usual.

Signature of the study participant:..... date:...../...../.....

Signature of the caregiver:.....date:...../...../.....

Witness signature :.....date:...../...../.....

INFORMATION DOCUMENT – **English Version**

TITLE OF THE RESEARCH STUDY:
Wellbeing of Older People Study (WOPS)

Greetings:

INTRODUCTION:
You are being invited to take part in the research study named "Wellbeing of Older Peoples Study (WOPS)", being conducted by the Africa Centre.

This document gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign the consent or make your mark in front of a witness. You will be given a copy to keep.

Please note that:

- **Your participation in this research is entirely voluntary;**
- **You are free at any point not to answer any question you do not want to;**
- **You may decide not to take part or to withdraw from the study at any time.**

WHAT ARE WE TRYING TO LEARN IN THIS STUDY?
The main aim of this study is to describe the household duties, mental and physical health and social circumstances of older people aged 50 years and above. In this study physical health refers to body illnesses such as arthritis, diabetes or hypertension; mental health refers to conditions like depression; social health relates to your ability to having friends, church or family members who you can talk to about your problems and joys. We will also look to see if the health mentioned above is different in people who have Human Immunodeficiency Virus (HIV) and those who do not have HIV themselves but have a child with HIV. The study will ask questions that will help to see what happens when a child gets ill from HIV or when a child dies from HIV or other causes. We also want to see how antiretroviral drugs (ART) which are given to some HIV patients affect the wellbeing of the family.

This study will look at old people because they are the ones who usually look after their children and grandchildren. It will also look at the elderly because only a few studies have looked at people in this age group. We need to know more about the difficulties that old people face in this time of HIV so that these people receive help that best suits them. To be able to do this, the study will ask questions about who brings money into the home, who looks after the small children for example bathing the children and cooking for them. It will also ask questions on illnesses of the body and illnesses of the mind and who is available for you to talk to about your problems. For elderly people who have experienced death of an adult child in the last 2 years (24months), they will be asked how this has affected the household in terms of money, health or having more people to look after.

The results obtained here will be used to identify what problems the elderly people are facing. This information will be made available to government departments such as the Department of Health, Department of Social Welfare so that they know what help the elderly people should receive.

WHO WILL TAKE PART IN THIS STUDY?
The study will recruit people who are aged 50 years and above who take part in the Africa Centre Demographic Surveillance and live in the Mpukunyoni area. The study will have in total 400 male and female participants. The 400 will be chosen at random from the Africa Centre Surveillance and the Hlabisa

HIV Treatment and Care programme records to make sure that everyone who is eligible has an equal chance of participating in the study. 200 will be randomly selected from people aged 50 years and above who have been on ART for less than three months or more than one year in the Hlabisa HIV Treatment and Care programme and participate in the Africa Centre demographic surveillance system. 100 older people will be randomly selected from eligible elderly people who have an adult child who is in the Hlabisa HIV Treatment and Care programme and been on ART for less than three months or more than one year. The last 100 will be those who have lost a child aged between 18 and 49 years through death, in the last 2 years.

However when potential participants are invited to take part in the study, details contained in the surveillance system or treatment programme will not be divulged to the study participant or household members. Participants HIV status will not be disclosed by any field staff member. Questions pertaining to HIV will be asked only to people who know their HIV status and are willing to respond to the questions.

Participation in this study is completely voluntary. Participants can refuse to answer any questions at any time if they feel uncomfortable answering the questions. Withdrawal from the study can be done at any time without penalties.

WHAT WILL IT MEAN TO TAKE PART IN THE STUDY?

If you agree to take part in the study, you will be asked a set of questions about your mental and physical health. You will be asked questions about whether or not you look after small children and who brings money into your household. You will also be asked questions on how easy it is for you to get someone to talk to about your concerns and whether or not you have someone taking care of you. If you fall into the group that has lost a child in the last 2 years then you will also be asked about the cause of death, how this death has affected you in terms of money to look after the family and additional people to take care of.

In addition, your blood pressure, weight and height will be measured. A blood specimen of 10ml (two teaspoons) will be drawn from your arm and will be used to assess your risk of stress, diabetes, anaemia and heart diseases. From your blood only these tests will be done; we will **NOT DO** any HIV tests. Anybody who would want an HIV test will be referred to a local health facility or any of our free counselling and testing facilities.

The test we would like to do can unfortunately only be done in a laboratory. Therefore these specimens will be transported to the Global Clinical Viral laboratory in Durban where the tests will be done. On these specimens only the study number will be used as an identifier. Your name and surname will not be used to ensure confidentiality.

We also ask your permission to store your blood sample in the Africa Centre laboratory in Durban and analyse it later in other research projects that we may have. All this information will be stored on a very secure computer database. We will also ask your permission to use your stored blood samples for additional analyses in the future, provided that such analyses are approved by the Ethics Committee.

To ask all questions and to take all measurements will take about an hour and a half in total. About half way through the interview, the nurse will ask you if you want a break for a short while and continue or if you would like the nurse to come back another day to complete the interview. If you would like to continue on another day, it will have to be within a week of the date of the first session.

Participation in the study is voluntary. Answering the questionnaire is voluntary. The blood sample and taking of weight, height and blood pressure are also voluntary and you are free to refuse to have any of this done.

IS THERE ANY RISK BEING IN THE STUDY?

There are no major risks in this study. The only discomfort may be the pain from the needle prick for blood draw but this will soon go away without any scaring. The interviewer is a nurse who is trained to take blood.

There are, unfortunately, potential risks. Questions on illness and death of a member of the household may cause you to be sad or distressed. However if this happens, the nurse conducting the interview will be able to refer you for counselling and medical advice. In cases of serious distress and with your consent the nurse can either refer you to the clinic or offer you transport to get to the nearest clinic. In line with procedures in other studies at the Africa Centre we would be able to refer you to existing services either at the Africa Centre or within the Department of Health. The Africa Centre collaborates with the Department of Health in terms of providing staff capacity including doctors, a psychologist and a social worker and facilities in the HIV Treatment and Care programme. Any of these staff members and the Department of Health staff will be willing to assist you at any of the 17 primary health care clinics in the Hlabisa sub-district.

There is also a minimal potential risk of accidental falls as during the interview you may be asked to stand up to do some measurements such as height and weight. The team of nurses have been thoroughly trained to minimize such risks.

WHAT ARE THE BENEFITS TO BEING IN THE STUDY?

There are many advantages to knowing your health status:

Through the interview, blood pressure, weight and height measurements we will be able to inform you of your health status and refer you to the necessary health facility. In cases where the nurse finds your health to be in a critical condition the nurse will transport you to the nearest clinic where you can receive medical attention. You will also have the opportunity to speak to a trained nurse about your health and how best you can live a healthy lifestyle.

You may also be referred to a social worker if it is determined for instance that you are not receiving a government grant you should be receiving.

If you wish to know more about HIV, you can see an HIV counsellor in any of the department of health clinics. Through ongoing counselling we hope to contribute to the reduction of stigmatization in the community.

Your participation in this study will help us better understand the challenges older people face in this community. With this information we can advise the local, provincial and national authorities to improve older people's health and wellbeing in your community. Since this is a study being done in other African countries such as Uganda, your participation will contribute to understanding the experiences of not only older people in this community but in the other countries as well.

WHAT IF YOU DO NOT WANT TO TAKE PART?

Taking part in the study is voluntary. You are free to refuse to answer the questionnaire and to have your blood sample taken. You are free to refuse to answer any questions that you are not comfortable

with. You are also free to refuse to have blood pressure, height and weight measurements taken. However, if you do not want to answer any questions or you do not want to give blood or have any of your measurements taken then we would like you to say this at the beginning.

WHO WILL SEE THE INFORMATION THAT WE COLLECT?

The University of KwaZulu-Natal Research Ethics Committee may look at the information from the study to check that procedures are being correctly and safely followed but they will maintain absolute confidentiality. At the end of the study, we will inform the Africa Centre Community Advisory Board (CAB) about the general results of the study but not results for any individual. General results will also be presented to you and the community at specially arranged meetings. Scientists from the Africa Centre will analyze the results and may write about the results of the study in scientific journals to share the information we learn with people in your community and in other parts of the world.

REIMBURSEMENTS OR TOKENS FOR PARTICIPATION?

In line with Medicines Control Council (MCC) of South Africa which states that reimbursement should be offered for any additional costs for clinic visits to take part in a research study, we will NOT offer any reimbursement in this study. There are no additional costs due to participation in this study since all visits will be conducted either at home or when you come to the clinic to collect your medicine. You will not be required to make any additional clinic visits.

However, as a token of appreciation for your participation you will receive a snack packet consisting of a loaf of bread, fruit and juice during the interview.

Contact details of BREC Administrator or Chair for reporting of complaints/problems:

Biomedical Research Ethics, Research office, University of KZN, Private Bag X54001, Durban, 4000
Telephone: +27 (0)31 260 4769 / 260 1074
Fax: +27 (0)31 260 4609
Email: BREC@ukzn.ac.za or ramnaraind@ukzn.ac.za

WHO TO CONTACT IF YOU WANT TO KNOW MORE, OR IF YOU HAVE A PROBLEM AT ANY TIME?

If you need more information or there is something you do not understand concerning this study, you can contact the following people:

Mr Mduduzi Mahlinza, Head of Community Liaison Office
Africa Centre for Health and Population Studies
035 550 7686

Or Makandwe Nyirenda and Portia Mutevedzi (Co-investigators)
Africa Centre for Health and Population Studies
035 550 7500.

You may also wish to use our toll free phone number (0800-203695) to reach our Community Liaison Office or the study investigators, at no cost to you.

I..... agree to be part of the **Wellbeing of Older People Study (WOPS)**. The study has been orally explained to me and I fully understand the information written in the study information sheet. I understand the implications of joining the study and that I will be asked for a venous blood sample in addition to being interviewed. I also understand that my weight, height and blood pressure will be measured. **YES** ☐ **NO** ☐

In addition I do understand that if I am found to be ill at the time of the home visit, I may be referred for further health management. **YES** ☐ **NO** ☐

It has been explained to me and I fully understand that information relating to me previously collected in the Africa Centre Surveillance or in the Hlabisa HIV Treatment and Care programme may be used together with the information collected in this study.

YES ☐ **NO** ☐

I also understand that all the information collected will be kept confidential and that all information will be anonymised and my name or any other personal identifier will not be used in any of the analyses. **YES** ☐ **NO** ☐

I understand that joining the study is completely voluntary and also understand that even if I join the study, I am free to withdraw from the study at any time and I will not be discriminated or penalized in any way for doing so. **YES** ☐ **NO** ☐

I consent to have my blood specimen stored for use by Africa Centre researchers for additional tests in the future provided that such tests are approved by the Ethics Committee.

YES ☐ **NO** ☐

_____ _____

Signature of Participant **Signature of research nurse**

_____

Date of consent

Contact the Africa Centre community liaison office on 035-550-7686 if you have any question or concerns pertaining to the study.

Chronic morbidity in adults aged 50 years or older in rural South Africa: Validation of self-report

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Abstract

Objective

To investigate the reliability of self-reports within a cross-sectional study (WOPS) compared to self-reports within a longitudinal population-based survey (AC-surveillance) for diabetes and hypertension in older adults (50+years) in rural South Africa and their agreement with measured HbA1c and BP respectively.

Design

A nested cross-sectional study within a longitudinal population-based survey

Methods

Kendall's concordance coefficient and Kappa-statistic assessed concordance. Bland-Altman plots evaluated inter-survey agreement between AC-surveillance and WOPS.

Results

Agreement between self-reports of ever been diagnosed within the two data sources was high: 86.9% and 74.1% of individuals reporting ever been diagnosed with hypertension and diabetes respectively in WOPS reported the same in AC-surveillance. Similarly self-reports of recent treatment had high consistency comparing WOPS with AC-surveillance giving a low Blant-Altman mean bias for hypertension (0.078) and diabetes (0.005). Responses to timing of diagnosis in WOPS had low agreement with those in AC-surveillance. Hence, comparing agreement measures of ever been diagnosed to those of timing of diagnosis; Kappa and Kendall's W statistics declined from 0.69 to 0.21 and 0.29 to 0.07 respectively for diabetes and from 0.68 to 0.002 and 0.63 to 0.16 respectively for hypertension.

Conclusions

Our results confirm validity of self-reported diabetes and hypertension prevalence but not recent diagnosis, and indicate appropriateness of using self-reported measures in resource-limited settings.

Key words: self-reported health, validation, gycoxylated Hb (HbA1c), diabetes, hypertension

Running title: validation of self-reported morbidity

Word count: Main body 4350; Abstract 211

What is new?

- Validations of self-reported morbidity have mainly been done in Western countries and such data is lacking in resource-limited settings where accuracy of self-reports from local and national surveys remains unknown
- Our study in rural South Africa shows that despite low education in older adults, their self-reports of ever been diagnosed with either hypertension or diabetes are consistent across different data sources in the same setting.
- However, consistency markedly declines when asked to account for the timing of diagnosis, which would possibly imply that although self-reports reliably approximate disease prevalence, they may be less useful in approximating disease incidence in older adults.
- Low correlation between bio-measures of HbA1c for diabetes and blood pressure for hypertension with self-reported diagnosis may be due to normal readings in patients established on therapy; however correlation is good amongst those reporting to never having been diagnosed with either hypertension or diabetes.
- Our results potentially confirm validity of self-reported diabetes and hypertension morbidity, and show the appropriateness of using self-reported measures in resource-limited settings to assess disease burden and health care need.

Introduction

The use of self-reports, by researchers and health specialists in epidemiological studies and national health surveys, to determine burden of disease and population health is increasing globally due to the high cost of conducting clinical diagnostic studies(1-4). However, self-reported measures may be prone to bias (1,3,5,6), especially in old aged adults with possible short term memory limitations (2,6-8). Almost all self-reported health validation studies, comparing self-reports to other measures of morbidity from the same population, have been carried out in Western populations. Validation of self-reports in resource-rich settings such as Britain (England, Wales, Scotland), Finland, America (Boston), Canada and Netherlands (Amsterdam) (1-3, 7, 9-11) may not be generalizable to resource-poor communities, because accuracy of self-reports is not only influenced by the disease under investigation (1, 2, 5, 9) but also by population under consideration (3) and patient characteristics such as educational level and psychological distress (1, 5, 7, 8) which are directly influenced by socio-economic status (12,13). However despite the lack of setting-specific validation, self-reported morbidity surveys have become widely used in developing countries (1). It is therefore important to validate self-reported health in African settings. Further, studies to date have not directly looked at validity of self-reported timing of morbidity diagnosis, although some health surveys and studies report morbidity incidence based on self-reported data.

Although the validity of self-reported measures of health is said to be influenced by underlying socio-cultural factors and perceptions of health and its meaning may vary between individuals and within individuals over time(1, 5, 14), consistency between multiple self-reported morbidity measures and clinical bio-measures may be an indicator of stability and reliability of health responses (2,9,10). Most validation studies compare patients' self-reports with hospital, clinic or doctor information (1,2,7,9,10). However, bio-measures, such as HbA1c for diabetes and measured blood pressure (BP) for hypertension

could be useful objective disease markers (11) and could be valid gold standards against which to validate self-report but their use is largely and essentially limited by the fact that they do not accurately account for patients who are established on therapy and may have normal bio-measures as a consequence.

In this study we aimed to investigate the stability and reliability of self-reports comparing those obtained in a cross-sectional study and a longitudinal population-based survey within the same 12 month period , for two important health conditions (diabetes and hypertension) in older adults aged 50 years and above in a rural setting in South Africa. Additionally, we validate in the cross-sectional survey self-reported diabetes and hypertension through agreement with measured HbA1c and BP respectively. We also assess stability of self-reports when used to estimate timing of diagnosis.

Methods

Africa Centre Surveillance

Since 2000, individual and household data have been collected within a bi-annual (and tri-annual since 2012) demographic and health surveillance in a circumscribed area including approximately 11 000 households and 90 000 individuals per round. The surveillance area of approximately 435 km^2 is predominantly rural with a small urban segment around a local township(15,16). On 1 January 2010, 61 431 of the approximately 90 000 household members were resident within the surveillance area, 13% of whom were aged 50 years or above (15).

Data collected during the surveillance rounds from a key informant include demographic, social and health data (16). In addition, self-reported morbidity data on hypertension, diabetes, mycobacterium tuberculosis (TB) and other morbidities are collected using standardized women's and men's general

health questionnaires in a nested annual, individual HIV and health surveillance among resident adults identified from the household surveillance. Validated instruments used in both the household and individual surveillances can be obtained from the Africa Centre for Health and Population Studies (AC) website (www.africacentre.co.za).

The SAGE Well-being of Older People Study (WOPS)

The WOPS study employed instruments adapted from the World Health Organisation (WHO) Study on global AGEing and adult health (SAGE) (17,18) and was carried out within the AC-surveillance area between March-August 2010. WOPS used a shortened version of the SAGE questionnaire and was partially harmonized with a similar study in Uganda(19). The main aim of WOPS was to investigate the direct and indirect effects of HIV on the health and wellbeing of older adults and participants were categorized as HIV-infected or HIV affected (see below). For selection of study participants, stratified random sampling was employed where the first sampling stage involved using the AC-surveillance to identify eligible participants for the four specified strata followed by random sampling of 100 participants within each stratum of eligible individuals resulting in a study sample of 400 older adults in total. Criteria for each stratum were as follows:

- Stratum one, HIV-infected participants who had been on ART for a year or longer;
- Stratum two, HIV-infected participants on ART for three months or less or waiting to initiate treatment. Stratum one and two are HIV-infected.
- Strata three and four, participants with an adult offspring who was either HIV-infected or had died of HIV-related causes. Stratum three and four are defined as HIV-affected.

Details of the main WOPS study have been detailed elsewhere (15). The study included a comprehensive questionnaire collecting demographic information and health status. Participants were asked if they had

ever been diagnosed with hypertension or diabetes, among other conditions. If the response was "yes" then they were further asked for timing of diagnosis. They were also asked whether or not, for that named condition, they were on treatment in the last 2 weeks or had been in the last 12 months. The second component comprised of anthropometric measurements including BP whilst the third entailed collection of two 5mls blood specimens for laboratory measured bio-measures inclusive of gycosylated heamoglobin (HbA1c) for diabetes diagnosis. HbA1c is a measure of percentage of heamoglobin molecules in the blood that are bound to glucose and provides an integrated measure of glucose levels in the blood for the 2- to 3-month period prior to test (1,20).

WOPS interviewers were different from AC-surveillance interviewers and whilst the WOPS study had a specific focus on health aspects in older adults, the AC- surveillance sought to collect general household and individual demographic and health data. However, the specific questions on chronic morbidity were similar in the two data sources:

WOPS :

- "Have you ever been diagnosed with…?",
- "How long ago was the diagnosis?" (last 6 months; >6 months-12 months; >12 months) and
- "Have you been taking medications or other treatment for…?"

AC-surveillance: questions asked annually

- "Have you been diagnosed with … in the last 12 months?" and
- "Are you receiving treatment for …?"

Although all individuals within WOPS were also members of the household surveillance, not all of them were part of the individual surveillance which only collects information on a subset of the overall

demographic surveillance members. Until 2007 the AC individual surveillance was limited to women less than 50 years and men less than 55 years; the analysis presented here is limited to the 207 (51.75%) of the 400 WOPS sample who had consented to be part of the AC-surveillance at least once.

The aim of this analysis was to evaluate the reliability (consistency in self-reported morbidity between different data sources) of self-reported hypertension or diabetes through assessment of agreement amongst self-reports in WOPS and AC-surveillance in 2010 and agreement with bio-measures. Additionally we measured agreement in WOPS between laboratory measured levels of HbA1c and interviewer measured BP to self-reports of either having been diagnosed with diabetes or hypertension respectively, recently (in the last 12 months) or in the past, as well as having been on treatment in the last 12 months from date of interview.

Variables

Ever been diagnosed: self-reported diagnosis of either hypertension or diabetes irrespective of timing

Recent diagnosis: self-reports of having been diagnosed in the last 12 months from date of interview for both WOPS and AC surveillance.

Past diagnosis: self-reports of having been diagnosed but not in the last 12 months.

Recent treatment: receiving treatment for either of hypertension or diabetes in the last 12 months

Measured morbidity from hypertension or diabetes: an abnormal (as defined below) measurement of either HbA1c or systolic, diastolic and overall BP.

- Threshold of 7 was used for determining abnormal HbA1c levels (diabetes) with <7 considered as normal (1,20-22).

- Systolic BP>140 mmHg and diastolic BP>90 mmHg, based on an average of three recordings at the time of interview, was considered abnormal (hypertension) (23).
    - Pre-hypertensive stages (systolic BP of 120-140 mmHg and diastolic BP of 80-90 mmHg) (23) were grouped with normal BP in line with NIH guidelines stating that pre-hypertension is not a disease category(23).
    - Hypertensive stage 1 (systolic BP of 141-159 mmHg and diastolic BP of 91-99 mmHg) and stage 2 (systolic BP of ≥160mmHg and diastolic BP of ≥100mmHg)(23) were combined into one category.

All individuals within WOPS with abnormal HbA1c and BP levels were referred to a doctor within the primary health care service for further assessment.

Analytical methods

To assess validity and reliability of self-reported diabetes and hypertension through estimating levels of concordance (agreement) between reported morbidity in WOPS and AC-surveillance as well as between WOPS self-reports and measured bio-measures, a number of statistics were employed. Kendall's coefficient of concordance (Kendall's W) and the Kappa statistic (24-27) were used to assess for concordance. Whilst Kappa gives a quantitative measure of the magnitude of agreement, informing on precision and reliability of the measures, its use is limited by the fact that it is affected by prevalence of the finding under consideration. Kendall's W makes no assumptions regarding the nature of the probability distribution and can handle any number of distinct outcomes. Bland-Altman plots were used to assess whether the bias and precision between the different self-reports were comparable. The Bland-Altman method calculates the mean difference between two methods of measurement (the 'bias') and 95% limits of agreement. Ideally the bias should be 0 so the closer to 0 the bias is, the better the agreement (precision) between the two methods. The 95% limits of agreement are used for visual

judgment of the degree of agreement; the smaller the range between the two limits, the better the agreement between the two methods (28-30). Although all methods employed take into account the fact that there is no gold standard between the different data sources and the true value of the measured quantity and the true state of the reported morbidity remains unknown (28,31), they each have limitations (24,29-31). We chose not to calculate sensitivity, specificity and predictive values because of the lack of a true gold standard and although several validation studies use medical records as a gold standard for calculating these measures, most of them acknowledge that medical records are not an ideal gold standard and cannot be assumed to be accurate (2,9,32,33).

For all coefficients except Bland-Altman, 0 represents no concordance whilst 1 represents complete agreement and precision. All results are reported at 5% significance level. STATA 11.2 was used for all analyses.

Ethics approval

The AC-surveillance was approved in 2000, and the HIV and Health surveillance in 2003, by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, with subsequent annual re-certification (Ref Nos. E009/00 and BF233/09). For the WOPS study, approval was first obtained from the local community through the community advisory board and then from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref No. BF136/09). In addition, SAGE and related sub-studies have been approved by WHO's Ethical Review Board and are reviewed annually. Individual written informed consent was obtained from all WOPS participants and from all AC individual surveillance participants. Verbal informed consent was obtained from the surveillance household informant.

Results

Overall, 207 older adults participated in both WOPS and the 2010 AC individual surveillance, with a median age of 61 years (IQR 53-70); 43 (20.8%) were males. Only 20 (9.7%) had received secondary education or higher and 104 (50.2%) had no formal education. The majority of individuals' source of income was through the old age social security grants (n=178; 85.9%).

Overall morbidity

Hypertension

In WOPS, a total of 112/207 (54.1%) older adults reported ever having been diagnosed with hypertension, reported prevalence in AC-surveillance at 107 (51.7%) was similar. Whereas in WOPS few participants (6/112, 5.4%) reported having recently been diagnosed (in the last 12 months), in AC-surveillance 52/107 (48.6%) reported their diagnosis as recent ($p<0.001$). In both surveys, most participants reporting ever been diagnosed also reported receiving therapy in the last 12 months prior to date of interview: 78.5% in AC-surveillance and 89.3% in WOPS. Numbers reporting diagnosis and recent treatment are presented in Table 1.

Diabetes

A total of 28/207 (13.5%) older adults in WOPS and 27/207 (13.0%) in AC-surveillance reported ever having been diagnosed with diabetes. Recent diagnosis was under-reported in WOPS; only 4/28 (14.3%) reported recent diagnosis, whilst in AC-surveillance 13/27 (48.1%) reported recent diagnosis. Most participants ever diagnosed had received therapy in the last 12 months (approximately 78% in each) (Table 1).

Bio-measures within WOPS

Blood pressure

Hypertensive individuals

For systolic BP, 41 (19.9%) had stage 1 hypertension and 33 (16.0%) had stage 2. On diastolic BP, 33 (16.0%) and 16 (7.8%) had stage 1 and 2 hypertension. Only 46 (22.3%) participants had normal systolic and diastolic BP. Eighty-eight older adults (42.7%) had abnormal systolic and diastolic blood pressure measurements.

Pre-hypertensive individuals

Of the 71 participants who were pre-hypertensive on systolic BP, 34 (47.9%) reported to have ever been diagnosed with hypertension; 30 (88.2%) of whom reported to recently gone on therapy. Thirty-seven (60.66%) of the 61 older adults who were pre-hypertensive on diastolic BP reported ever been diagnosed with hypertension; 34 (91.9%) of whom reported receiving therapy.

Glycoxylated Hb

The majority of older adults had normal HbA1c levels (181, 91.4%). Of the 17 (8.6%) participants with high HbA1c levels (median 10; IQR:7.9-11.7; range 7-15), 14 (82.4%) reported to have ever been diagnosed with diabetes, all of whom had received therapy in the 12 months before date of interview. The 3 participants with abnormal HbA1c reporting never having been diagnosed with diabetes had levels of 7, 10.5 and 11. Of the 9/207 patients (4.3%) who refused blood samples for HbA1c measurements, 2 reported to have ever been diagnosed with diabetes whilst 1 was on diabetes therapy.

Correlation of self-reported morbidity in WOPS and AC-surveillance

Agreement between AC-surveillance and WOPS self-reports of ever been diagnosed with either hypertension or diabetes was high: 86.9% of individuals reporting ever been diagnosed with hypertension in AC-surveillance reporting the same in WOPS and 74.1% of individuals reporting ever been diagnosed with diabetes in WOPS reporting the same within AC-surveillance. Similar to questions of ever been diagnosed, questions relating to recently being on treatment had high consistency between the 2 studies with 90.5% and 81.0% of those reporting recent hypertension and diabetes treatment respectively in AC-surveillance reporting the same in WOPS. Agreement was equally high in individuals reporting no morbidity with over 80% of participants who report never been diagnosed and not on treatment in AC-surveillance reporting the same in WOPS. As such, we observe high values of Kappa and W (Tables 2 and 3) and low mean difference (bias) on the Blant-altman plots (Figures 1 and 2) for questions pertaining to ever diagnosed or recent treatment. For diabetes the inter-survey agreement was even higher than for hypertension.

For both conditions, agreement was good as highlighted by the high Kappa and Kendall's W statistics and low mean bias on the Blant-Altman plot, when participants were asked questions about ever being diagnosed but not when they were asked to recall the timing of diagnosis. Tables 2 and 3 show high concordance values for questions relating to ever diagnosed and low for recent diagnosis (asking the participants to recall whether the diagnosis was in the last 12 months or more than 12 months ago). Responses to timing of diagnosis (when diagnosed) in WOPS had low agreement with those in AC-surveillance. Hence, comparing agreement measures of ever been diagnosed to those of timing of diagnosis; Kappa and Kendall's W statistics declined from 0.69 to 0.21 and 0.29 to 0.07 respectively for diabetes and from 0.68 to 0.002 and 0.63 to 0.16 respectively for hypertension

(Tables 2 and 3). For both, recent diagnosis was under-reported in WOPS; 98% of individuals reporting recent hypertension diagnosis in AC-surveillance report in WOPS that their diagnosis was not recent whilst for diabetes 84% report their diagnosis as being recent in AC-surveillance but not in WOPS.

Correlation of WOPS reported morbidity and bio-measures collected at time of interview

Agreement between self-reports of ever been diagnosed with or recent therapy for hypertension and measured morbidity was generally low as shown by the higher median bias and wider limits of agreement and the low Kendall's test for concordance (Table 4). For self-reported diabetes compared to measured HbA1c, the Blant-Altman median bias was 0.02 for recent therapy indicating considerable agreement between the two measures. Agreement between self-reported morbidity and bio-measures was considerably higher for those reporting no morbidity than amongst those reporting morbidity diagnosis or treatment; with 66% and 98% of those reporting no hypertension and diabetes morbidity also having normal bio-measure levels. However a considerable number of participants reporting morbidity who were receiving therapy had normal bio-measure levels. Overall, there was better agreement between self-reported health in WOPS and self-reported health in AC-surveillance than between self-reported and measured morbidity within WOPS (Tables 2-4). Bland-Altman plots mean differences (Table 4) confirm this finding as shown by the wider limits of agreement when assessing for self-reported health and bio-measures. This is even more apparent with hypertension.

For both conditions, over half of individuals reporting recent treatment still had abnormal bio-measures, whilst nearly half of individuals reporting ever been diagnosed had normal bio-measures (Table 4).

Discordant pairs

Assessing for agreement on questions relating to recent diabetes treatment in WOPS and AC-surveillance, 9 individuals gave discordant responses. Of these, 4 had high HbA1c readings. Fourteen were discordant on recent diagnosis and 15 on ever diagnosed with diabetes; 6 and 4 had high HbA1c levels respectively. For hypertension, 32 were discordant on reports of recent treatment; 13 (40.6%) had abnormal BP readings. Thirty three were also discordant on ever been diagnosed.

Diagnosed not on therapy

Twelve older adults in WOPS had been diagnosed with hypertension but reportedly had not received any treatment in the last 12 months. Of these 4 (25%) had an abnormal BP reading; 3 of whom had stage 2 hypertensive readings and were aged below 65 years. Six individuals of those diagnosed with diabetes reported not to have been on therapy in the last 12 months, all of whom had normal HbA1c levels.

Discussion

Most national health surveys that provide data for health resources planning and allocation are based on self-reported data(1, 2), although validation of self-reports remains limited in developing countries. Because the validity of these data sources has not been well established in such settings, there may be a risk of inappropriate and inadequate health resource allocation. Our study seeks to address this gap by estimating the reliability of self-reported hypertension and diabetes morbidity through assessment of agreement between self-reports within a longitudinal demographic surveillance system and those within a cross-sectional study with additional comparisons to objective health measures of HbA1c for diabetes

and blood pressure for hypertension. Data obtained from both studies was within the same time period (2010)

Results from both surveillance and WOPS show high levels of self-reported hypertension (51.7%; (95%CI:44.8-58.6%) in AC-surveillance vs 54.1% (95%CI:47.3-61.0%) in WOPS) and diabetes (13.0% 95%CI:8.4-17.7% in ACDSS and 13.5% (95%CI:8.8-18.2%) in WOPS). In both studies, self-reported hypertension prevalence had a lower 95% margin of 44% and diabetes prevalence of 8.4%. These estimates are in line with previous studies, in this age group, from this and other similar settings (34, 35) and higher than that reported in European populations(36) and in a Malawian nationwide survey that also included individuals 25-49 years old (37).

Previous results from developed countries have generally reported good or reasonable agreement between self-reports and health practitioner records for conditions such as diabetes but less agreement for conditions with less clear diagnostic criteria such as hypertension (2,3,7,9). It is of interest to note that self-reported prevalence from both AC-surveillance and WOPS were highly concordant for both conditions, confirmed by the low bias (median difference) and the narrow confidence intervals observed from the Blant-Altman plots. These results provide some confidence in older adults self-reports of ever diagnosed morbidity even in populations with low education status. Previous reports have suggested that self-reports may vary depending on the questionnaire and interview employed (8,9). We find substantially consistent self-reports although there were minor differences in questionnaire sentence structure between AC-surveillance and WOPS. We would thus suggest that self-reports can be used for to assess burden of disease and health care needs. However, although our data on self-report of having ever been diagnosed seem reliable (based on an individual's responses of ever been diagnosed with a specific condition or recently receiving treatment in two different surveys), this was not the case for self-report of recent diagnosis and disease incidence cannot be reliably determined for this group of adults

in this setting based on self-report. This is not surprising with previous studies elsewhere indicating that the date an event happened is generally a poor cue in recalling an event (8) and that self-reports from questionnaires administered within a short time period post-visiting the health care provider had good agreement with medical records from that specific visit (38) implying that time frame of events may possibly hinder the accuracy of self-reports. These results suggest the need for alternative data sources and research strategies when assessing for morbidity incidence. Data from longitudinal studies, linkage with hospital or clinic records, or population surveillances may better address such questions.

Similar to results from a validation study in Taiwan, conducted using data from a national survey (1), and two longitudinal studies in the Netherlands (2,3), prevalence estimates in our study using HbA1c were similar to those obtained through self-reports (13.5%; 95% CI:8.8-18.2% in WOPS and 8.6%; 95% CI:4.6-12.5% using measured HbA1c). However contrary to studies from Uganda, Taiwan and the Netherlands (1,3,19,39) which reported substantial underestimation of hypertension prevalence based on self-reports, our study shows non-statistically significant higher hypertension estimates from self-reports compared to measured BP (54.1%; 95% CI:47.3-61.0 in WOPS and 42.7%; 95% CI:35.9-49.5% using measured BP). This is likely to be due to the fact that once subjects have been diagnosed and put on therapy, markers of hypertension revert back to normal levels and these individuals would then be classified as disease-free using bio-measures. As such and in line with previous reports (3) we note relatively low concordance between either reported ever been diagnosed or recently receiving therapy and measured bio-measures. For diabetes however, agreement between self-reported diabetes and bio-measures was higher because HbA1c levels in diabetics remain slightly elevated even during therapy. Although bio-measures perform well in indicating disease state in newly diagnosed individuals(20) our study highlights a problem of validating self-reports against bio-measures in patients well established on therapy, a fact often overlooked in studies that validate self-reports using bio-measures (1,3). Despite this, bio-measures may be a powerful tool in monitoring treatment success in patients receiving therapy

as we would expect individuals on recent treatment to normalise bio-marker levels. The fact that over half of patients receiving hypertension therapy still had bio-measures that were above the normal threshold might be an indicator of treatment failure or adherence problems in these older adults and identifies individuals requiring additional clinical monitoring. However for diabetics it is hard to get HbA1c measure completely back to normal, because if their sugars get too low to achieve normal levels they end up having hypoglycemic episodes; even with good control HbA1c levels are likely to remain slightly outside the normal range. A recent systematic review of diabetes in sub-Saharan Africa reported similar high levels of inadequate glucose control amongst previously diagnosed diabetics (35) whilst a Ugandan study reported 44% of older adults on anti-hypertensive treatment still having high BP (19) .

The high concordance between normal HbA1c and self-reports of never having been diagnosed with diabetes reported in this study makes this bio-marker an excellent tool for disease screening. Results from a community-based study in the Netherlands also reported excellent specificity for both hypertension and diabetes using measured BP and fasting glucose respectively (3).

The community-based nature of our study minimized selection bias that normally occurs in validation studies that recruit participants in health facilities or within health programmes, thus selecting patients with favourable health seeking behavior who may differ from individuals with limited access and/or utilization of health facilities. Our results show that even if specific health questions are asked by different people using questionnaires with questions that are structured slightly different, self-reports obtained may be valid as long as they are not strictly time bound.

Our study has certain limitations; the sample size is limited but this is a common phenomenon with validation studies. Secondly although both surveys were conducted in 2010, the reference period in the questions of the last 12 months were based on the date of interview and could have differed between the two studies. However, this bias is likely minimal because whilst AC-surveillance was from January to

December 2010, WOPS was from March to August in the same year and the non-overlapping time interval was minimal. There was no real gold standard to measure self-reports against since both studies were self-reported and accuracy of bio-measures is limited when assessing for individuals established on therapy. We therefore could not directly estimate sensitivity and specificity of self-reported health. Of note is that although most validation studies use medical records as a gold standard for estimating sensitivity and specificity of self-reports, authors acknowledge that medical records are not an ideal gold standard and are not necessarily accurate themselves (2,9,32,33). The lack of a gold standard does not limit the soundness of our validation results because agreement between multiple self-reports may approximate the validity and reliability of the report. Further, another study within our surveillance area has previously shown that health self-assessments strongly predicted mortality within 4 years of follow-up in both HIV-infected and HIV-uninfected individuals (40) suggesting that the surveillance may serve as a good comparator for validating WOPS self-reports.

Author contributions

PC Mutevedzi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: Mutevedzi, Rodger, Newell

Acquisition of data: Mutevedzi, Nyirenda

Analysis of data: Mutevedzi, Newell

Interpretation of data: Mutevedzi, Rodger, Newell

Drafting the manuscript: Mutevedzi, Newell

Revising it critically for important intellectual content: Mutevedzi, Rodger, Nyirenda, Newell

Final approval of the version to be published: Mutevedzi, Rodger, Nyirenda, Newell

Conflict of interest

All authors declare no conflict of interest

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The sponsor had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data and preparation, review or approval of the manuscript

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Table 3: Prevalence of self reported hypertension and diabetes morbidity in AC surveillance and WOPS (N=207)

	AC surveillance			WOPS		
	n	%	95% Confidence interval	n	%	95% Confidence interval
Hypertension ever diagnosed (Yes)	107	51.7	44.8-58.6	112	54.1	47.3-61.0
Hypertension past diagnosis (Yes)	55	51.4	41.5-61.2	106	94.6	88.7-98.0
Hypertension current diagnosis (Yes)	52	48.6	38.8-58.5	6	5.4	2.0-11.3
Hypertension current treatment (Yes)	84	78.5	69.5-85.9	100	89.3	82.0-94.3
Diabetes ever diagnosed (Yes)	27	13.0	8.4-17.7	28	13.5	8.8-18.2
Diabetes past diagnosis (Yes)	14	51.9	31.9-71.3	24	85.7	67.3-96.0
Diabetes current diagnosis (Yes)	13	48.2	28.7-68.1	4	14.3	4.0-32.7
Diabetes current treatment (Yes)	21	77.8	57.7-91.4	22	78.6	59.0-91.7

Table 2: Concordance/precision of self reported hypertension morbidity in WOPS and AC surveillance (N=207)

		WOPS					
		Ever been diagnosed with hypertension		Recent diagnosis of hypertension		Recent hypertension treatment	
AC surveillance		***No***	***Yes***	***No***	***Yes***	***No***	***Yes***
No	n	81	19	150	5	98	24
	%	81.0	19.0	96.8	3.2	80.3	19.7
Yes	n	14	93	51	1	8	76
	%	13.1	86.9	98.1	1.9	9.5	90.5
Kendall's W		0.63		0.16		0.63	
Kappa		0.68		-0.02		0.69	
95% Conf. interval		0.58-0.78		-0.08-0.05		0.59-0.79	
%Observed agreement		84.06		72.95		84.47	
95% Conf. interval		78.35-88.76		66.35-78.87		78.78-89.13	

Table 3: Concordance/precision of self reported diabetes morbidity in WOPS and AC surveillance (N=207)

		WOPS					
		Ever been diagnosed with diabetes		Recent diagnosis of diabetes		Recent diabetes treatment	
AC surveillance		***No***	***Yes***	***No***	***Yes***	***No***	***Yes***
No	n	172	8	191	2	181	5
	%	95.6	4.4	98.9	1.0	97.3	2.7
Yes	n	7	20	11	2	4	17
	%	25.9	74.1	84.6	15.4	19.1	80.9
Kendall's W		0.29		0.07		0.25	
Kappa		0.69		0.21		0.77	
95% Conf. interval		0.54-0.82		-0.05-0.48		0.62-0.91	
%Observed agreement		92.75		93.69		95.65	
95% Conf. interval		88.33-95.89		89.45-96.60		91.91-97.99	

Table 4: Concordance/precision of self reported hypertension and diabetes morbidity in WOPS and measured biomarkers (N=207)

	WOPS							
	Ever diagnosed with hypertension		Recent hypertension treatment		Ever diagnosed with diabetes		Recent diabetes treatment	
BP/HbA1c measure	***No***	***Yes***	***No***	***Yes***	***No***	***Yes***	***No***	***Yes***
Normal n	63	32	71	36	169	3	174	3
%	66.3	33.7	66.4	33.6	98.3	1.7	98.3	1.7
Abnormal n	55	56	47	52	12	14	7	14
%	49.6	50.5	47.5	52.5	46.2	53.9	33.3	66.7
Kendall's W	0.43		0.44		0.23		0.22	
Kappa	0.17		0.19		0.61		0.71	
95% Conf. interval	0.03-0.30		0.06-.032		0.43-0.79		0.34-0.88	
%Observed agreement	57.77		59.71		92.42		94.95	
95% Conf. interval	50.71-64.60		52.67-66.47		87.81-95.70		90.91-97.55	
Blant-Altman mean difference	0.112		0.053		0.045		0.02	
95% limits of agreement	-1.15-1.37		-1.19-1.30		-0.49-0.58		-0.42-0.46	

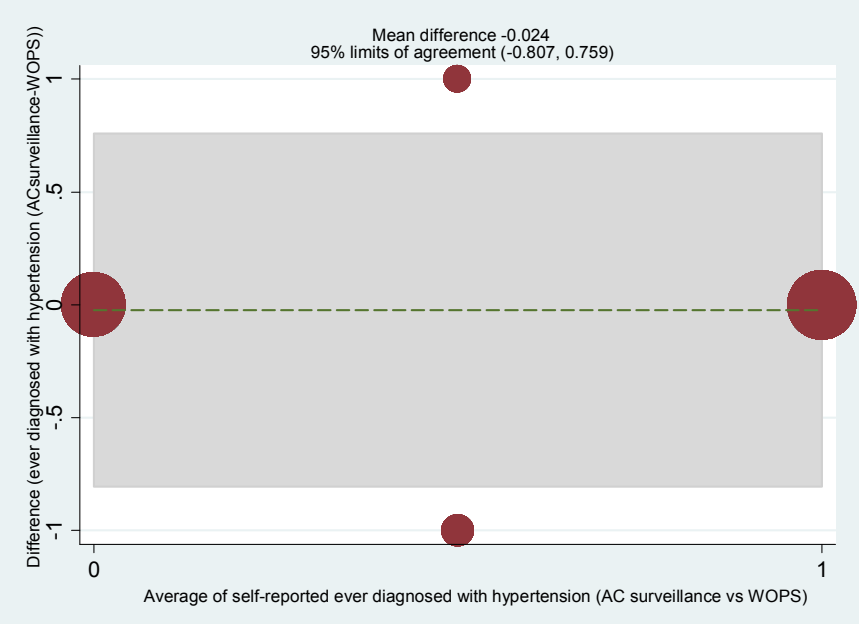

Figure 2a: Blant-Altman Plot comparing self-reported ever diagnosed with hypertension

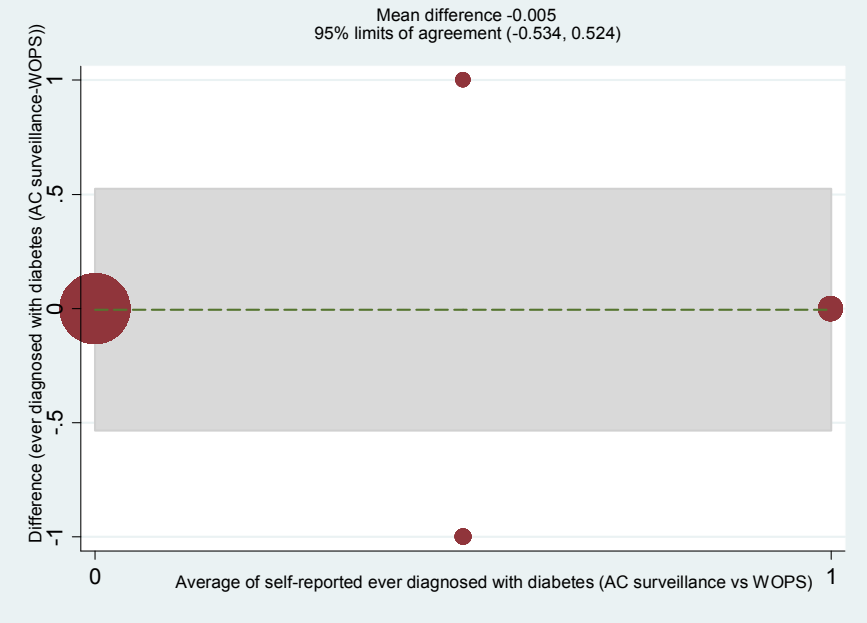

Figure 1b: Blant-Altman Plot comparing self-reported ever diagnosed with diabetes

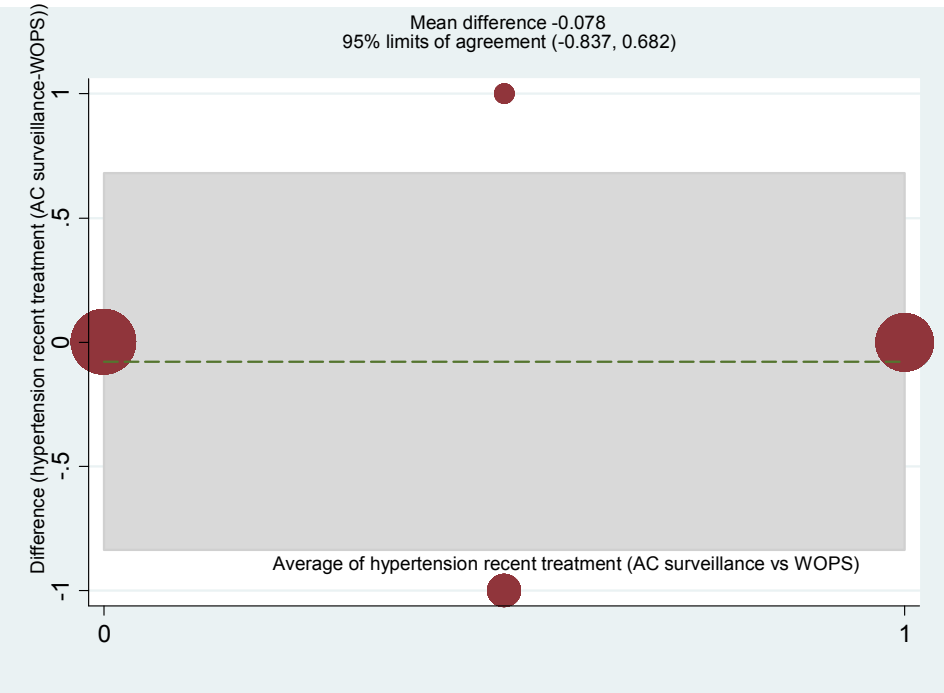

Figure 2a: Blant-Altman Plot comparing self-reported recent hypertension treatment

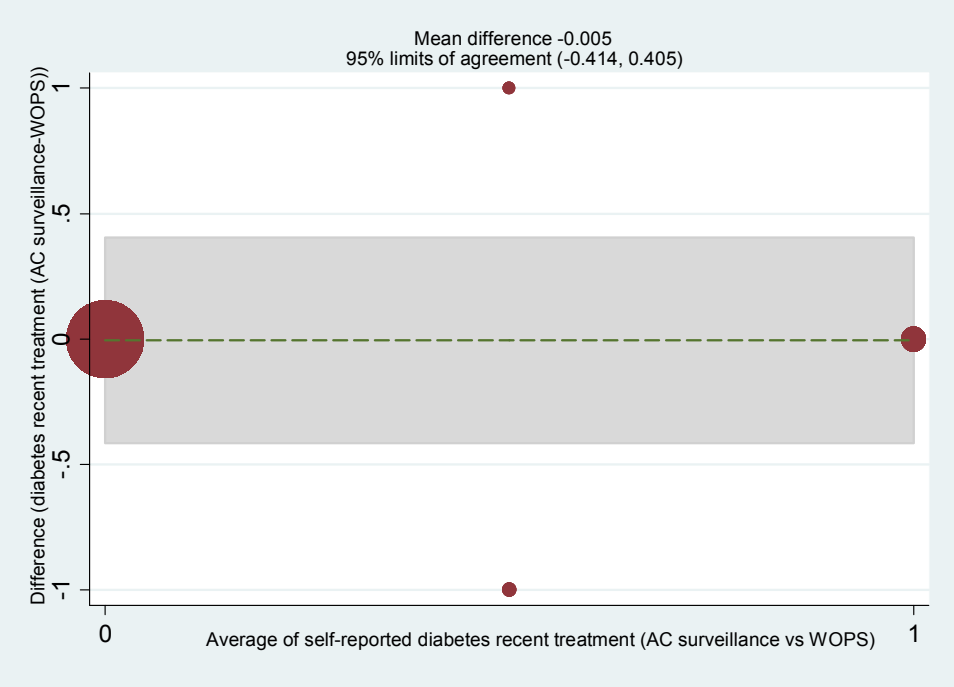

Figure 2b: Blant-Altman Plot comparing self-reported recent diabetes treatment

Decreased chronic morbidity but elevated HIV associated cytokine levels in HIV-infected older adults receiving HIV treatment: Benefit of enhanced access to care?

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Key words: chronic morbidity; HIV; antiretroviral therapy (ART); older adults; cytokines, BMI

Short title

Morbidity & cytokines by HIV/ART status

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Abstract

Background

The association of HIV with chronic morbidity and inflammatory markers (cytokines) in older adults (50+years) is potentially relevant for clinical care, but data from African populations is scarce.

Objective

To examine levels of chronic morbidity by HIV and ART status in older adults (50+years) and subsequent associations with selected pro-inflammatory cytokines and body mass index.

Methods

Ordinary, ordered and generalized ordered logistic regression techniques were employed to compare chronic morbidity (heart disease (angina), arthritis, stroke, hypertension, asthma and diabetes) and cytokines (Interleukins-1 and -6, C-Reactive Protein and Tumor Necrosis Factor-alpha) by HIV and ART status on a cross-sectional random sample of 422 older adults nested within a defined rural South African population based demographic surveillance.

Results

Using a composite measure of all morbidities, controlling for age, gender, BMI, smoking and wealth quintile, HIV-infected individuals on ART had 51% decreased odds (95% CI:0.26-0.92) of current morbidity compared to HIV-uninfected. In adjusted regression, compared to HIV-uninfected, the

proportional odds (aPOR) of having elevated inflammation markers of IL6 (>1.56pg/mL) was nearly doubled in HIV-infected individuals on (aPOR 1.84; 95%CI: 1.05-3.21) and not on (aPOR 1.94; 95%CI: 1.11-3.41) ART. Compared to HIV-uninfected, HIV-infected individuals on ART had >twice partial proportional odds (apPOR=2.30;p=0.004) of having non-clinically significant raised hsCRP levels(>1ug/mL); ART-naïve HIV-infected individuals had >double apPOR of having hsCRP levels indicative of increased heart disease risk(>3.9ug/mL;p=0.008).

Conclusions

Although HIV status was associated with increased inflammatory markers, our results highlight reduced morbidity in those receiving ART and underscore the need of pro-actively extending these services to HIV-uninfected older adults, beyond mere provision at fixed clinics. Providing health services through regular community chronic disease screening would ensure health care reaches all older adults in need.

Introduction

Older people (50+years) are at risk of chronic morbidity such as heart diseases, arthritis, diabetes and hypertension, associated with physiological changes with age[1-4], but these conditions remain often undiagnosed particular in resource poor settings. The disease burden may be exacerbated by both HIV and antiretroviral therapy (ART)[3,5-8], suggesting worse health outcomes in HIV-infected, especially those on ART, than in HIV-uninfected adults. Generally, the earlier a disease is diagnosed, the more likely it is that it can be cured or successfully managed. However, the association between HIV status and chronic morbidity, and possible benefit of regular access to general medical services within HIV treatment and care, remains little explored. Evidence on differential morbidity by HIV status from two studies was conflicting [9,10] and neither study include specific age-related morbidities in their outcome measure.

Certain biomarkers are useful tools for predicting clinical events[11] and are increasingly employed in monitoring health, identifying individuals at risk and evaluating therapeutic interventions[12,13]. Cytokines are released in response to trauma, infection or inflammation and sustained elevation has been linked to age-associated conditions and increased mortality[13-16]. Cytokines of interest in chronic conditions of older age include Interleukin- 1 and 6 (IL1 and IL6), Tumor Necrosis Factor alpha (TNFα), and C-Reactive Protein (CRP)[14-17]. Little is known on the association of HIV and ART status with cytokine levels and age-related chronic morbidity.

Obesity is linked to chronic health problems such as cardiovascular diseases, diabetes and arthritis[12,17,18] and, similar to ageing, is characterised by chronic low-grade inflammation[17,19]. Cytokine levels, as inflammation, trauma or infection markers, are thus normally higher in obese[17,19] and HIV-infected individuals with advanced disease[20,21]. It is critical to understand the associations of

obesity with cytokine levels increasingly used to measure health risks and explain individual health status, in both HIV-infected and HIV–uninfected older adults.

We use data from a cross-sectional cohort of older people in a high HIV prevalence area to examine levels of chronic morbidity in HIV-infected and uninfected older adults and subsequent association of HIV and ART status with selected cytokines and BMI.

Methods

Ethics Statement

For the WOPS study, approval was first obtained from the local community through the Centre's Community Advisory Board and then from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref No. BF136/09). AC surveillance was approved in 2000 by this same committee, with annual re-certification (Ref Nos. E009/00 and BF233/09). Individual written informed consent was obtained from all WOPS and AC HIV surveillance participants.

Setting and data collection

Since 2000, demographic and health data have been collected by the Africa Centre (AC) on approximately 11 000 households in a geographically defined South African area. On 1 January 2010, there were 61 431 resident household members of whom about 7,900 (13%) were aged 50 years or above [9,22-24]. Within the household surveillance is a nested annual HIV surveillance, in which dried blood spot specimens are collected from eligible adults, for anonymized HIV testing[22-24].(www.africacentre.ac.za).

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The SAGE Well-being of Older People Study (WOPS) employed survey instruments adapted from the World Health Organization (WHO) Study on global AGEing and adult health (SAGE)[25,26] and was carried out within the AC surveillance area on a multi-stage random sample of individuals aged 50+years between March-August 2010[9]. The main aim of SAGE-WOPS was to investigate the direct and indirect effects of HIV on the health of older adults[9]. For sample selection, all resident older adults falling into 3 categories namely: HIV-infected on ART, HIV-infected ART-naïve, and HIV-affected through co-residing with an HIV-infected individual, were identified through existing AC population databases. From all eligible individuals, random samples of 150 participants each for the first two groups and 300 from the third group were generated; participants were contacted through a home visit and enrolled into the study if they were willing and provided informed consent. Enrolment in each group was done until the required numbers (100 for each of the first two groups, 200 in the third group) were reached, giving a total of 400 participants. For purposes of this study individuals were grouped into mutually exclusive groups by their HIV/ART status. All contacted individuals agreed to participate in the study, and 22 individuals consented to the questionnaire and anthropometric measures only and not to blood collection, giving a sample size of 422 individuals in total. Participant HIV status was not disclosed during the WOPS interview. Geographical typology of the randomly selected individuals showed a distribution similar to the general distribution of the older adult population within the surveillance area, suggesting the representativeness of the sample.

Demographic and health information was collected through face-to-face interviews. Participants were asked if they had been ever diagnosed with a named chronic morbidity, timing of diagnosis (last 6 months; >6-12months; >12months) and whether or not, for that named condition, they had received treatment in the last 2 weeks and/or 12 months. In addition, weight and height were measured by trained nurses, who also collected blood specimens for laboratory measured biomarkers of lipogram profile and cytokine levels (IL1, IL6, high sensitivity CRP (hsCRP) and TNFα).

Information regarding HIV status was obtained from the HIV surveillance and the Hlabisa HIV Treatment and Care Programme (HHTCP)[27]; data from these two sources can be linked through use of the unique individual South African national identity number, name and sex[9,28,29]. HIV status information was subsequently updated after completion of the SAGE-WOPS interviews, as appropriate. From the HHTCP, we identified HIV-infected people and duration of therapy for those on ART. For those unknown to HHTCP, HIV status from the HIV surveillance prior- and post-WOPS were used to infer HIV status of participants at time of the WOPS study using the algorithm below:

- HIV-uninfected before and after WOPS = HIV-uninfected;
- HIV-infected before and after WOPS = HIV-infected;
- HIV-uninfected within a year prior to WOPS and unknown after WOPS = HIV-uninfected (*with an incidence rate of 0.5; (95% CI: 0.3-1.0) per 100 person years in adults 50+ years[30] we would expect at most only 1 individual of the 51 participants to have seroconverted within the year)*; and
- HIV unknown before and after WOPS = unknown

Variables

Self-reported current chronic morbidity: Based on responses to questions, “Have you been taking treatment for …… in the last 2 weeks?", including heart disease (angina), arthritis, stroke, hypertension, chronic lung disease, asthma and diabetes. This question was only asked from all participants reporting ever been diagnosed by a health care professional with any of the aforementioned conditions.

BMI(indicator of obesity): categorized as per WHO recommendations: underweight: <18.5; normal: 18.5-<25; overweight (pre-obese): 25-<30; obese: 30-<40; morbidly obese: 40+[31].

159 *Cytokines*: Although within the continuum of circulating cytokines, higher levels of cytokines are
160 associated with chronic inflammation and morbidity, there is no defined cut-off point beyond which
161 morbidity starts to increase. Consequently previous studies have chosen arbitrary cut-off points,
162 employing a range of cut-offs from dividing the continuous distribution into tertiles and
163 quartiles[13,15,20] , log-transformed continuous levels[13], median cut-off[15] or the lower cytokine
164 detection limit [32]. For CRP, values >3µg/ml have been used to indicate increased risk of heart disease
165 whilst values >8.5 indicate clinically relevant inflammation[32]. For this study we adopted cut-off points
166 within range of existing studies, for uniformity and comparability of results. Categories were as follows;

167 IL1 (≤1.6, >1.6pg/mL); IL6 (≤1.56, >1.56-≤2.9, >2.9-≤5 and >5pg/mL); CRP (≤1, >1-3.9, >3.9-8.5,
168 >8.5µg/mL) and TNFα (≤7.8, >7.8pg/mL).

169 *Total cholesterol:high density lipoprotein (HDL) ratio (ratio of bad to good cholesterol):* Higher ratios are
170 associated with increased cardiovascular disease risk[14,33].

171 • Males: ratio1(<3.4), ratio2(3.4-<5), ratio3(5-<9.6), ratio4(≥9.6)
172 • Females: ratio1(<3.3), ratio2(3.3-<4.4), ratio3(4.4-<7.1), ratio4(≥7.1)

173

174 ***Laboratory procedures***

175 All laboratory tests were conducted by a South African National Accreditation System (SANAS) certified
176 laboratory (Global Clinical and Viral Laboratory). Tests were conducted using kits by BioVendor Research
177 and Diagnostic Products, Czech Republic. Lower detection concentrations were 0.02ug/mL for hsCRP,
178 1.1pg/mL for IL1, 0.81pg/mL for IL6 and 5.0pg/mL for TNFα. Blood serum was used for determination of
179 hsCRP, IL1 and TNFα levels and plasma for IL6.

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Analytical methods

Baseline characteristics were described using medians and IQRs (equality of medians tested for using Kwallis2 test[34]) for continuous variables and proportions with 95% CI for categorical variables. To assess the association of HIV and obesity with morbidity, ordinary logistic regression was employed. Because IL6 was categorized into an ordinal variable, ordered logistic regression[35,36] assessed the association between IL6 , HIV and obesity. Ordered logistic regression takes into account the hierarchy in the dependent variable categories assuming proportional odds (POR) and results in a single equation estimating the relationship between predictor variables and all levels of the dependent variable. Due to violation of proportional odds assumption, we examined associations of HIV and obesity with CRP using generalized ordered logistic regression which estimates multiple equations over the different CRP levels without assuming proportional odds, producing partial proportional odds ratios (pPOR)[36,37]. For IL1 (binary outcome) simple logistic regression was used. STATA 11.2 was used for all analyses (StataCorp LP).

Results

Of the 422 older WOPS participants, 161 (38%) were HIV-uninfected, 108 (26%) were HIV-infected with at least a year on ART, 109 (26%) were HIV-infected ART-naïve and 44 (10%) had unknown HIV status with characteristics similar to those HIV-uninfected. Men comprised 25% of the 422 individuals (n=106). Median age for HIV-uninfected individuals was 10 years higher than for HIV-infected hence all analyses were age adjusted. As would be expected in this population and setting, few individuals reported currently or ever smoking or drinking (Table 1).

Self-reported morbidity

Of the 422 participants, 124 (29.4%; 95% CI: 25.0-33.8) reported never having been diagnosed with any chronic condition (Table 1) whilst 169(40.1%; 95% CI: 35.4-44.7) and 100(23.7%; 95% CI: 19.6-27.8) reported diagnosis with one and two conditions, respectively; 29(6.9%) individuals had more than two conditions. Significantly more HIV-uninfected and HIV-infected ART-naïve participants than HIV-infected participants receiving ART reported current morbidity i.e. receiving therapy for either one of heart disease, arthritis, stroke, hypertension, asthma or diabetes (Figure 1) (p=0.033). Specific current morbidities are illustrated using Figure 1.

Anthropometry

Median BMI was highest in those HIV-uninfected compared to HIV-infected (28.1 vs 25.3 (p=0.057)); obesity was more frequent among HIV-uninfected than among HIV-infected on ART and ART-naïve (Table 1).

Cytokines

Overall, there was little variation in median IL6 by HIV status (Table 2). For TNFα, only 7(1.8%) participants had elevated levels, with medians similar across all HIV status strata (p=0.231) therefore TNFα was not assessed further. Significantly more HIV-uninfected people had IL1 levels above 1.6µg/mL than those HIV-infected ART-naive (p=0.003), although the medians were the same across groups (Table 2). There was a trend towards highest CRP levels (>8.5pg/ml) in those HIV-infected, with a statistically significant difference in HIV-infected ART-naive compared to HIV-uninfected. Obese/morbidly-obese participants had increased CRP levels in both the median and categorized analyses (Table 2).

HIV status, obesity and morbidity

Controlling for factors known to be associated with ill health (age, sex, smoking and wealth quintile), HIV-infected older adults on ART were significantly less likely (OR=0.49, p=0.027) to report current

morbidity than HIV-uninfected adults (Figure 2a). Cytokine levels were not significantly associated with morbidity. In a model including obesity marker (BMI) but not ratio of good:bad (HDL) cholesterol, there was borderline association between being obese/morbidly-obese and current morbidity (aOR=1.75; 95%CI: 1.0-3.0). However, including cholesterol:HDL ratio in the model, BMI lost its significance whilst higher levels of this ratio significantly increased the odds of current morbidity(Figure 2a). Cholesterol:HDL ratio was associated with BMI, with normal BMI category having only 4.0% and those obese 11.7% with ratio4. Of the obese/morbidly-obese, only 10.8% had ratio 1 compared to 28.7% of those with normal BMI.

HIV status, obesity and cytokine levels

IL1

Adjusting for lifestyle factors (smoking and alcohol), age and gender, compared to HIV-uninfected, the odds of having IL1 levels >1.6pg/ml was lower by 65% (aOR=0.35; 95%CI: 0.13-0.94) and 89% (aOR=0.11; 95%CI: 0.24-0.54) for HIV-infected on ART and HIV-infected ART-naïve, respectively (Figure 2b).

IL6

In adjusted ordered logistic regression, compared to HIV-uninfected, the proportional odds (aPOR) of having low IL6 levels was nearly twice as high in HIV-infected individuals both on ART and ART naïve. The proportional odds of having elevated IL6 levels (aPOR 2.40; 95%CI: 1.49-3.86) was higher in those aged 60-69 years than in those aged 50-59 years. A non-significant increased odds was observed in individuals aged 70+years (aPOR=1.39; p=0.248) (Figure 2c).

Cholesterol:HDL ratio and BMI were not significantly associated with IL1 and IL6 cytokine levels (IL1 p=0.675, IL6 p=0.681).

CRP

Compared to HIV-uninfected, HIV-infected individuals on ART had more than twice the partial proportional odds (apPOR=2.30; p=0.004) of having slightly raised hsCRP levels(>1ug/mL-levels that have been associated with non-clinically significant inflammation) whilst ART-naïve HIV-infected individuals had more than double apPOR of having hsCRP levels indicative of increased cardiovascular disease risk (>3.9 ug/mL) (p=0.008). HIV infection and cholesterol:HDL ratio 4 were the only independent factors associated with very high levels of hsCRP (>8.5ug/mL – levels that may signify clinically relevant inflammation); the likelihood was even higher in ART-naïve HIV-infected participants(Table 3).

Although all BMI levels above normal increased the odds of having hsCRP levels>1ug/mL, being obese/morbidly-obese nearly tripled the likelihood of having hsCRP levels associated with increased cardiovascular disease risk (>3.9ug/mL) beyond which BMI was not associated with higher CRP levels(Table 3). Compared to those aged below 60 years, those aged 60-69years were twice as likely to have elevated hsCRP levels. Having cholesterol:HDL ratio4 was associated with three times more proportional odds of having elevated hsCRP levels across all CRP levels(Table 3).

Current morbidity was not associated with cytokines levels.

Discussion

Older HIV-infected adults face both chronic conditions of ageing and HIV[1,4,38,39], with data suggesting that HIV treatment may exacerbate chronic conditions associated with aging[2,3,6,40]. There is lack of reliable data in Africa regarding associations of HIV, obesity and age-related morbidity especially comparing morbidity by HIV and ART status. This study contributes to knowledge by being the first to demonstrate, in a rural African setting, the possibility of less current chronic morbidity in HIV-

infected older adults receiving ART compared to HIV negatives. Could this be due to access to ART and/or health services?

We previously reported a higher WHO composite health score [a health measure collating an individual's levels of difficulty in eight health domains (mobility, self-care, affect, vision, pain/discomfort, sleep/energy, interpersonal activities, and cognition)] amongst HIV-infected than in HIV-uninfected individuals, not accounting for ART status[9]. We now confirm this previous finding with more in-depth health measures and highlight differences by ART status. The fact that we previously report a higher composite health score using the same study population reduces the possibility that chronic morbidity in HIV-infected individuals remains undiagnosed or is misdiagnosed as HIV-related morbidity. It is likely that morbidity in HIV-infected older adults receiving ART is reduced through regular screening and treatment during frequent routine HIV clinic visits.

Although elevated cytokine levels have been associated with increased cardiovascular and diabetes morbidity[17,19] it remains unknown whether the elevated cytokine levels result in morbidity or immune inflammatory response due to morbidity results in elevated cytokines. Our finding of lower morbidity in HIV-infected adults receiving ART and of the increased odds of elevated hsCRP and IL6 levels in this group may suggest that these cytokines may be associated more with chronic HIV rather than with other existing chronic morbidity. Compared to those HIV-uninfected, HIV-infected individuals on ART had nearly twice the odds of having elevated IL6 levels and more than twice the odds of elevated hsCRP levels, indicating immune inflammatory response. Similar elevated cytokine levels in HIV-infected adults have been reported from studies in resource-rich countries focused on HIV-infected people only, however these did not make comparisons with HIV-uninfected adults nor explored the association with

ageing-morbidity[20,21]. Our study is the first to assess how in an African black population, controlling for age differences across HIV strata, cytokine levels differ by HIV and ART status and how these levels associate with chronic morbidity during ART. Although previous studies, not accounting for HIV status, report higher morbidity in individuals with elevated cytokine levels, they acknowledge that clinical mechanisms and significance of this phenomenon remains unclear[13-16].

Our results of lower morbidity in HIV-infected on ART, but not HIV-infected ART-naïve, than in HIV-uninfected older adults irrespective of high HIV-associated cytokine levels, may highlight the likelihood that even in the absence of co-morbid conditions, cytokine levels in HIV-infected adults do not return to pre-HIV infection levels despite ART and cytokine levels may not be ideal markers for chronic morbidity in such populations. Some studies have suggested that soluble cytokine receptors released in response to elevated cytokine levels, are more stable in circulation over time and hence might be more reliable markers of chronic inflammation than cytokines[13]. Longitudinal studies are needed to elucidate associations between HIV status and cytokine levels and how these relate to incident chronic morbidity and to explain mechanisms leading to morbidity decline in HIV-infected older adults on ART and to explain mortality differentials from chronic morbidity by HIV status. Within lifelong exposure to ART, vigilant monitoring of liver and kidney toxicities is required as these would negate the realized benefits.

Our results show that in this population with high obesity levels, it is the ratio of bad:good fat (cholesterol) ratio, a marker of cardiovascular disease risk, that is associated with high morbidity rather than BMI per se. In an analysis adjusted for this ratio, BMI ceased being an independent factor of morbidity, with the odds of morbidity nearly quadrupling in individuals within the highest ratio quartile possibly suggesting that total cholesterol:HDL ratio may be a stronger indicator of morbidity than BMI.

316 Although BMI was not associated with morbidity when accounting for the ratio of bad:good fat, being
317 obese/morbidly obese was associated with high hsCRP levels suggestive of increased inflammation and
318 cardiovascular disease risk. Studies from developed countries have also shown increased inflammatory
319 response in obese people[17,19] but literature from African populations is scarce.

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321 Our results underscore the need of extending health care services to HIV-uninfected older adults, which
322 need to go beyond mere provision at fixed clinics. Bringing health services to older adults through
323 regular community chronic disease screening would ensure health care reaches all older adults in need,
324 and could translate to considerable health benefits.

325

326 Our cross-sectional study has limitations, and we cannot assume causality in our associations but
327 highlight possible associations which could be further elucidated in longitudinal cohort studies. Although
328 we cannot rule out the role of survivor bias, if the observed reduced reported morbidity in HIV-infected
329 receiving ART was purely due to survivor bias we would also expect even larger morbidity decreases
330 amongst the HIV-infected ART naïve group, which is not the case. Although our data was self-reported,
331 we assumed that any unreliability of self-reports occurred equally across groups resulting in non-
332 differential bias which does not affect validity of our results. This assumption was based on the fact that
333 there is no evidence supporting the likelihood of over-reporting current morbidity amongst HIV-
334 uninfected, but not infected, individuals. It is likely that HIV-infected individuals may over-report
335 morbidity due to their knowledge of the underlying HIV infection. Furthermore both HIV-infected and
336 HIV-uninfected participants were identified from the community via the longitudinal demographic
337 surveillance system rather than from health care facilities, and thus would have reduced selection bias.
338 Although our sample size is small, limiting the extent to which we could detect differences between

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groups, the fact that despite this we were able to detect significant differences between HIV-infected participants receiving ART and those HIV-uninfected possibly points towards an even larger morbidity difference had we used a larger sample size with tighter confidence intervals. As such the sample size issue does not nullify our results but rather confirms the strength of existing associations between morbidity prevalence and HIV-infection and ART.

Author contributions

PC Mutevedzi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: Mutevedzi, Rodger, Newell

Acquisition of data: Mutevedzi, Nyirenda

Analysis of data: Mutevedzi, Newell

Interpretation of data: Mutevedzi, Rodger, Newell

Drafting the manuscript: Mutevedzi, Kowal, Newell

Revising it critically for important intellectual content: Mutevedzi, Rodger, Kowal, Nyirenda, Newell

Final approval of the version to be published: Mutevedzi, Rodger, Kowal, Nyirenda, Newell

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Table 1: Baseline demographic and clinical characteristics of 422 older adults stratified by HIV status

Characteristic		HIV-uninfected (161)			HIV-infected on ART (108)			HIV-infected ART naive (109)			[a]Total (422)		p-value
		N / median	%/ IQR	95% CI	N / median	%/ IQR	95% CI	N / median	%/ IQR	95% CI	N / median	%/ IQR	
Sex	Male	30	18.6	(12.6-24.7)	36	33.3	(24.4-42.3)	30	27.5	(19.1-36.0)	106	25.1	0.05
Age at interview		68		61-75	57		53-62	53		51-60	60	53-69	<0.001
Marital status	Married	40	24.8	(18.1-31.6)	36	33.3	(24.4-42.3)	33	30.6	(21.8-39.3)	120	28.5	
	Never been married	32	19.9	(13. 7-26.1)	33	30.6	(21.8-39.3)	43	39.8	(30.5-49.1)	116	27.6	<0.001
	Divorced/widowed	89	55.3	(47. -63.0)	39	36.1	(27.0-45.2)	32	29.6	(21.0-38.3)	185	43.9	
Employment	No	158	98.8	(97.0-1)	99	92.5	(87.5-97.5)	96	88.9	(82.9-94.9)	395	94.3	0.01
	Yes	2	1.3	(0-3.0)	8	7.5	(2.5-12.5)	12	11.1	(5.1-17.1)	24	5.7	
Main source of income	Grants	145	91.2	(86.8-95.6)	81	75.0	(66.8-83.2)	69	63.9	(54.8-73.0)	332	79.4	
	No source of income	7	4.4	(1.2-7.6)	9	8.3	(3.1-13.6)	18	16.7	(9.6-23.8)	36	8.6	<0.001
	Other	7	4.4	(1.2-7.6)	18	16.7	(9.6-23.8)	21	19.4	(11.9-27.0)	50	12.0	
BMI categories	Underweight	4	2.6	(0.1-5.1)	7	6.6	(1.8-11.4)	12	11.2	(5.2-17.2)	25	6.1	
	Normal	46	29.9	(22.6-37.1)	40	37.7	(28.4-47.0)	30	28.0	(19.5-36.6)	127	31.0	
	Overweight	45	29.2	(22.0-36.5)	37	34.9	(25.8-44.1)	35	32.7	(23.8-41. 7)	127	31.0	0.04
	Obese	48	31.2	(23.8-38.5)	17	16.0	(9.0-23.1)	24	22.4	(14.5-30.4)	105	25.6	
	Morbidly obese	11	7.1	(3.0-11.2)	5	4.7	(0.7-8. 8)	6	5.6	(1.2-10.0)	26	6.3	
Smoking	Never smoked	117	73.1	(66.2-80.0)	99	91.7	(86.4-96.9)	74	67.9	(59.1-76.7)	324	77.0	
	Past smoker	24	15.0	(9.4-20.6)	6	5.6	(1.2-9.9)	16	14.7	(8.0-21.4)	49	11.6	0.001
	Current smoker	19	11.9	(6.83-16.9)	3	2.8	(0-5.9)	19	17.4	(10.3-24.6)	48	11.4	
Alcohol	Never drank	94	58.75	(51.1-66.4)	82	75.9	(67.8-84.1)	64	58.7	(49.4-68.0)	269	63.9	
	Past drinker	41	25.63	(18.8-32.4)	14	13.0	(6.6-19.4)	33	30.3	(21.6-39.0)	94	22.3	0.01
	Current drinker	25	15.6	(9.96-21.3)	12	11.1	(5.1-17.1)	12	11.0	(5.1-16.9)	58	13.8	
Composite health score	continuous	46.7		(43.1-53.1)	52.3		47.9-57.4	48.6		(44.1-54.1)	49.22	45-55	0.001
	Healthy	47	29.2	(22.1-36.3)	59	54.6	(45.2-64.1)	41	37.6	(28.5-46.8)	159	37.7	<0.001
	Unhealthy	114	70.8	(63.7-77.9)	49	45.4	(35.9-54.8)	68	62.4	(53.2-71.6)	263	62.3	
Ever diagnosed with morbidity	No	38	23.6	(17.0-30.2)	39	36.1	(27.0-45.2)	29	26.6	(18.3-5.0)	121	28.7	0.12
	Yes	123	76.4	(69.8-83.00)	69	63.9	(54.8-73.0)	80	73.4	(65.0-81.7)	301	71.3	
Current morbidity	No	70	43.5	(35.8-51.2)	66	61.1	(51.9-70.4)	54	49.5	(40.1-59.0)	215	51.0	0.03
	Yes	91	56.5	(48.8-64.2)	42	38.9	(29.6-48.2)	55	50.5	(41.0-59.9)	207	49.1	
Morbidity in the last 12 months	No	52	32.3	(25.0-39.6)	52	48.2	(38.7-57.6)	48	44.0	(34.6-53.4)	173	41.0	0.04
	Yes	109	67.7	(60.4-75.0)	56	51.9	(42.4-61.4)	61	56.0	(46.6-65.4)	249	59.0	

- [a]total includes 44 participants with unknown HIV status (described in text)

Table 2: Cytokine (IL1, IL6, CRP and TNFα) levels of 422 old adults stratified by HIV status and BMI levels

HIV status		HIV negative		HIV positive on ART		HIV positive ART naive		Total
		Median /N	% (95% CI)/(IQR)	Median/ N	% (95% CI)/(IQR)	Median/ N	% (95% CI)/(IQR)	Median/N (IQR/95%CI)
IL1		1.6	(1.6-1.6)	1.6	(1.6-1.6)	1.6	(1.6-1.6)	1.6 (1.6-1.6)
	<=1.6	123	83.1 (77.0-89.2)	100	92.6 (87.6-97.6)	94	96.9 (93.4-1.0)	353 (90.1)
	>1.6	25	16.89 (10.8-23.0)	8	7.4 (2.4-12.4)	3	3.1 (0-6.6)	39 (10.0)
IL6		1.94	(1.6-2.6)	2.5	(2.0-3.1)	2.6	(2.0-3.2)	2.4 (2.1-2.6)
	<=1.56	70	47.3 (39.2-55.4)	38	35.2 (26.1-44.3)	36	37.1 (27.4-46.8)	157 (40.1)
	>1.56-2.9	20	13.5 (8.0-19.1)	24	22.2 (14.3-30.1)	19	19.6 (11.6-27.6)	68 (17.4)
	>2.9-5	26	17.6 (11.4-23.7)	21	19.4 (11.9-27.0)	19	19.6 (11.6-27.6)	73 (18.6)
	>5	32	21.6 (15.0-28.3)	25	23.2 (15.1-31.2)	23	23.7 (15.2-32.3)	94 (24.0)
CRP		3.7	(2.5-4.1)	4.2	(3.5-5.8)	4.3	(2.6-6.5)	3.9 (3.2-4.3)
	<=1	31	21.2 (14.6-27.9)	16	15.1 (8.2-22.0)	21	21.7 (13.4-29.9)	78 (20.1)
	>1-3.9	52	35.6 (27.8-43.4)	33	31.1 (22.3-40.0)	25	25.8 (17.0-34.6)	122 (31.4)
	>3.9-8.5	39	26.7 (19.5-33.9)	24	22.6 (14.6-30.7)	19	19.6 (11.6-27.6)	92 (23.7)
	>8.5	24	16.4 (10.4-22.5)	33	31.1 (22.3-40.0)	32	33.0 (23.6-42.4)	96 (24.7)
BMI		Normal		Overweight		Obese/ morbidly obese		Total
		Median /N	% (95% CI)/(IQR)	Median/ N	% (95% CI)/(IQR)	Median/ N	% (95% CI)/(IQR)	Median/N (IQR/95%CI)
IL1		1.6	(1.6-1.6)	1.6	(1.6-1.6)	1.6	(1.6-1.6)	1.6 (1.6-1.6)
	<=1.6	134	90.5 (85.8-95.3)	107	93.0 (88.4-97.7)	103	87.3 (81.2-93.3)	353 (90.1)
	>1.6	14	9.5 (4.7-14.2)	8	7.0 (2.3-11.6)	15	12.7 (6.7-18.8)	39 (10.0)
IL6		2.5	(2.0-3.2)	2.5	(1.7-3.2)	2.08	(1.6-2.6)	2.4 (2.1-2.6)
	<=1.56	58	39.2 (31.3-47.1)	47	40.9 (31.8-49.9)	51	43.2 (34.2-52.2)	157 (40.1)
	>1.56-2.9	24	16.2 (10.2-22.2)	17	14.8 (8.3-21.3)	25	21.2 (13.8-28.6)	68 (17.4)
	>2.9-5	26	17.6 (11.4-23.7)	28	24.4 (16.4-32.3)	17	14.4 (8.0-20.8)	73 (18.6)
	>5	40	27.0 (19.8-34.2)	23	20.0 (12.6-27.4)	25	21.1 (13.8-28.6)	94 (24.0)
hsCRP		2.5	(1.8-4.0)	3.2	(2.5-3.9)	6.15	(4.8-6.9)	3.9 (3.2-4.3)
	<=1	46	31.3 (23.8-38.8)	17	14.9 (8.3-21.5)	13	11.2 (5.4-17.0)	78 (20.1)
	>1-3.9	39	26.5 (19.4-33.7)	54	47.4 (38.1-56.6)	27	23.3 (15.5-31.0)	122 (31.4)
	>3.9-8.5	27	18.4 (12.1-24.67)	20	17.5 (10.5-24.6)	43	37.1 (28.2-45.9)	92 (23.7)
	>8.5	25	23.8 (16.9-30.7)	23	20.2 (12.8-27.6)	33	28.5 (20.2-36.7)	96 (24.7)

Abbreviations: BMI: body mass index (measured as weight in kilograms divided by the square of height in meters), IL1: Interleukin 1, IL6: Interleukin 6, hsCRP: high sensitivity C-reactive protein, ART: antiretroviral therapy

Table 3: Generalised ordered logistic regression model for factors associated with elevated CRP levels in old adults n=422

CRP levels	Odds Ratio	P-value	95% Confidence interval	
<=1pg/mL				
HIV-				
HIV+ on ART	2.30	0.004	1.31	4.06
HIV+ ART naive	1.03	0.93	0.51	2.08
HIV unknown	0.83	0.61	0.42	1.66
BMI normal				
Overweight	2.54	0.005	1.33	4.85
Obese/morbidly obese	3.72	<0.001	1.81	7.63
Age 50-59years				
60-69 years	1.06	0.87	0.54	2.05
70+ years	1.27	0.41	0.73	2.21
>1-3_9pg/mL				
HIV-				
HIV+ on ART	2.30	0.004	1.31	4.06
HIV+ ART naive	2.30	0.008	1.25	4.24
HIV unknown	0.83	0.61	0.42	1.66
BMI normal				
Overweight	0.78	0.37	0.46	1.33
Obese/morbidly obese	2.78	<0.001	1.58	4.89
Age 50-59years				
60-69 years	2.09	0.009	1.21	3.61
70+ years	1.27	0.41	0.73	2.21
>3_9-8_5pg/mL				
HIV-				
HIV+ on ART	2.30	0.004	1.31	4.06
HIV+ ART naive	2.81	0.002	1.47	5.38
HIV unknown	0.83	0.61	0.42	1.66
BMI normal				
Overweight	0.80	0.48	0.43	1.48
Obese/morbidly obese	1.41	0.27	0.77	2.61
Age 50-59years				
60-69 years	1.43	0.23	0.80	2.57
70+ years	1.27	0.41	0.73	2.21
Across all levels of hsCRP				
[a]Cholesterol:HDL ratio 1				
Ratio 2	1.12	0.70	0.64	1.96
Ratio 3	1.47	0.16	0.86	2.53
Ratio 4	2.51	0.04	1.03	6.09

Adjusted for gender, current morbidity, smoking and alcohol status

[a]Ratio categories; Males: 1(<3.4), 2(3.4-<5), 3(5-<9.6), 4(≥9.6)

Females: 1(<3.3), 2(3.3-<4.4), 3(4.4-<7.1), 4(≥7.1)

Abbreviations: BMI: body mass index (measured as weight in kilograms divided by the square of height in meters), IL1: Interleukin 1, IL6: Interleukin 6, hsCRP: high sensitivity C-reactive protein, ART: antiretroviral therapy

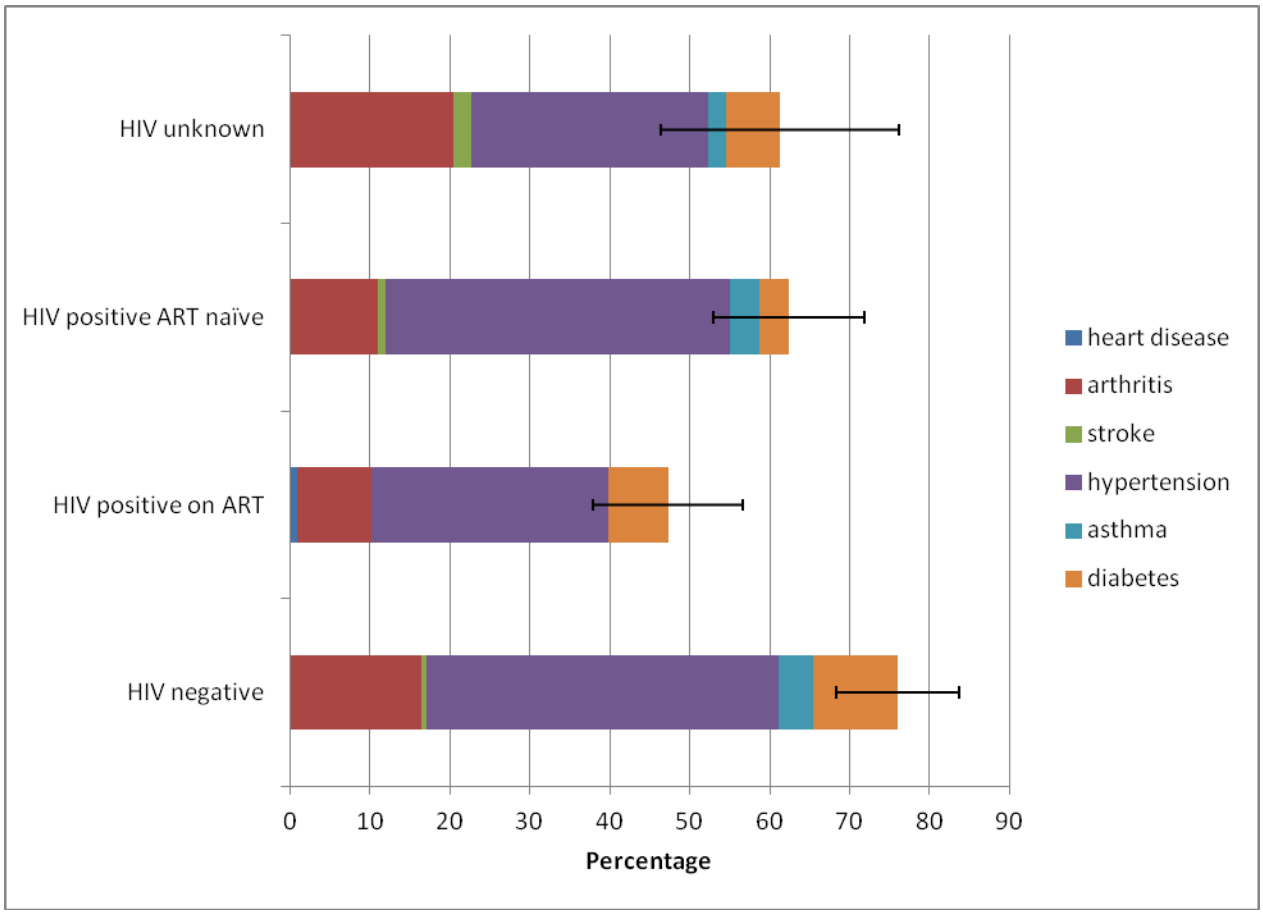

Figure 1: Proportion with 95% confidence intervals of self-reported current chronic morbidity in 422 older adults stratified by HIV status

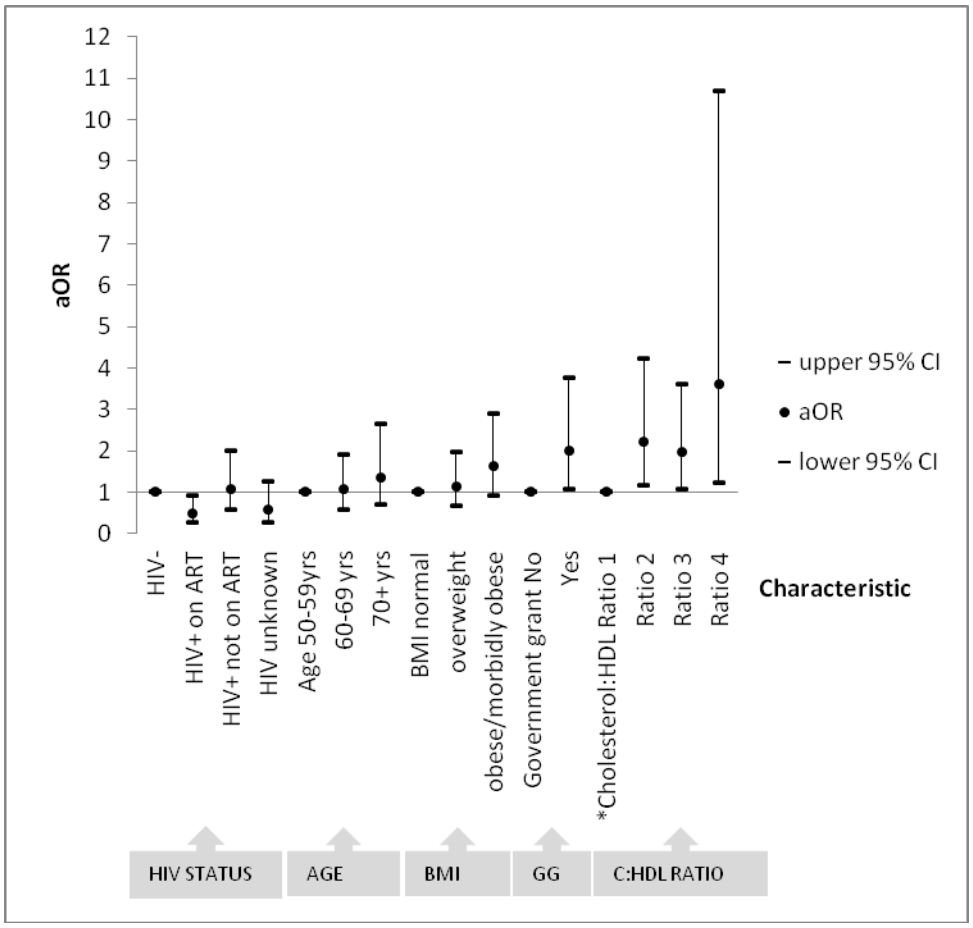

Figure 2a: Logistic regression model of factors associated with current chronic morbidity in 422 older adults

Model adjusted for gender, smoking status and wealth score

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by the square of height in meters); GG, government grant; C:HDL ratio, ratio of total cholesterol:high density lipoprotein

*Ratio categories; Males: 1(<3.4); 2(3.4-<5); 3(5-<9.6); 4(≥9.6)

Females: 1(<3.3); 2(3.3-<4.4); 3(4.4-<7.1); 4(≥7.1)

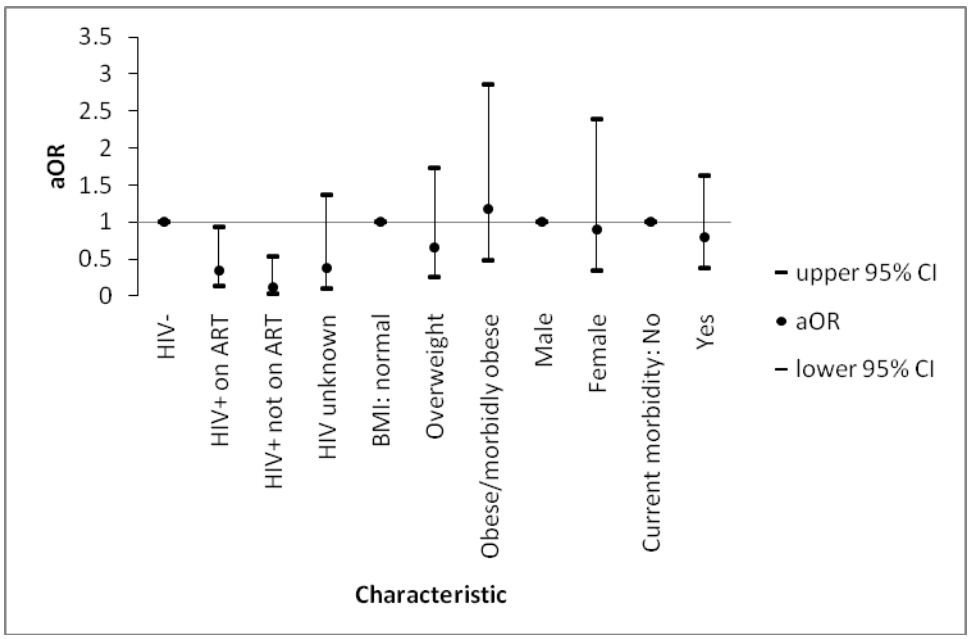

Figure 2b: Logistic regression of factors associated with IL1 levels in 422 older adults

Model adjusted for age, smoking and alcohol status

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by the square of height in meters

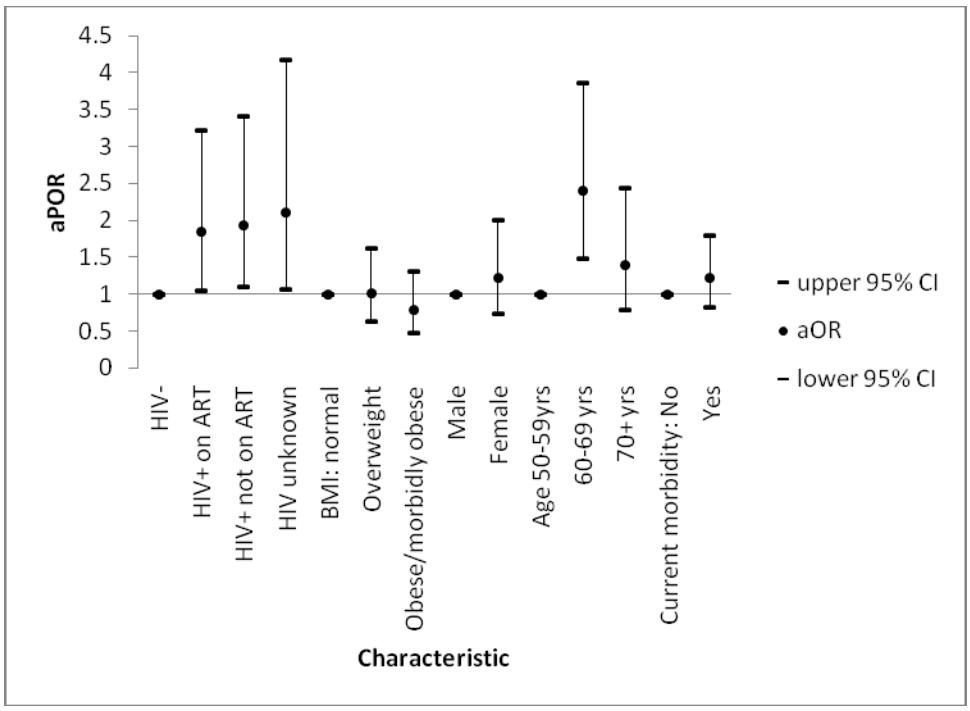

Figure 2c: Ordered logistic regression model for factors associated with [a]IL6 levels in 422 older adults

[a]Four IL6 levels: (≤1.56; >1.56-≤2.9; >2.9-≤5 and >5)pg/mL

Model adjusted for smoking and alcohol status

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by the square of height in meters)

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PLoS one

Association of Age with Mortality and Virological and Immunological Response to Antiretroviral Therapy in Rural South African Adults

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Abstract

Objective: To assess whether treatment outcomes vary with age for adults receiving antiretroviral therapy (ART) in a large rural HIV treatment cohort.

Design: Retrospective cohort analysis using data from a public HIV Treatment & Care Programme.

Methods: Adults initiating ART 1st August 2004 - 31st October 2009 were stratified by age at initiation: young adults (16–24 years) mid-age adults (25–49 years) and older (≥50 years) adults. Kaplan-Meier survival analysis was used to estimate mortality rates and age and person-time stratified Cox regression to determine factors associated with mortality. Changes in CD4 cell counts were quantified using a piecewise linear model based on follow-up CD4 cell counts measured at six-monthly time points.

Results: 8846 adults were included, 808 (9.1%) young adults; 7119 (80.5%) mid-age adults and 919 (10.4%) older adults, with 997 deaths over 14,778 person-years of follow-up. Adjusting for baseline characteristics, older adults had 32% excess mortality (p = 0.004) compared to those aged 25–49 years. Overall mortality rates (MR) per 100 person-years were 6.18 (95% CI 4.90–7.78); 6.55 (95% CI 6.11–7.02) and 8.69 (95% CI 7.34–10.28) for young, mid-age and older adults respectively. In the first year on ART, for older compared to both young and mid-aged adults, MR per 100 person-years were significantly higher; 0–3 months (MR: 27.1 vs 17.17 and 21.36) and 3–12 months (MR: 9.5 vs 4.02 and 6.02) respectively. CD4 count reconstitution was lower, despite better virological response in the older adults. There were no significant differences in MR after 1year of ART. Baseline markers of advanced disease were independently associated with very early mortality (0–3 months) whilst immunological and virological responses were associated with mortality after 12months.

Conclusions: Early ART initiation and improving clinical care of older adults are required to reduce high early mortality and enhance immunologic recovery, particularly in the initial phases of ART.

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Introduction

Older adults (≥50 years old) comprise a significant proportion of people enrolling in HIV treatment programmes in sub-Saharan Africa yet outcomes after initiation of antiretroviral therapy (ART) for this group have not been well described. Older adults have generally been neglected in addressing the global HIV epidemic [1]. Indeed, reporting mechanisms and estimates of epidemiological trends usually only encompass adults aged 15–49 [2]. UNAIDS estimated that globally there were 2.8 million adults aged 50 years and older living with HIV in 2005 [3]. Data from our surveillance programme in rural KwaZulu-Natal estimates overall HIV prevalence rate at 9.5% and incidence of 1% in adults aged 50 years and older [4]. In a verbal autopsy study in rural Kenya, HIV was the cause of death in 27% of people aged 50 years and older and was the leading cause of death up to the age of 70 years [5].

Age is a major determinant of mortality for many diseases in the absence of HIV and ART [6]. In the pre-antiretroviral therapy (ART) era, data from sub-Saharan Africa showed that older age at seroconversion was associated with more rapid progression to death [7,8,9,10]. Since the introduction of ART, there have been conflicting data on outcomes for older individuals. Assessing age as a continuous variable, two studies have suggested an association

between increasing age and higher mortality on ART [11,12]. Two studies analysing age as a categorical variable have reported significantly higher mortality for individuals aged >50 years: the ART-LINC cohort in an analysis of 7160 patients from 10 sites reported a two-fold increased risk in overall mortality for those ≥50 years compared to 16–29 year olds [13]; while in the South African Free State programme there was 58% increased risk of mortality for adults >50 years compared to 20–29 year olds, although the mortality also included people dying before ART initiation [14]. Other studies including a 7 year cohort in Senegal have reported no clear association between age and mortality on ART [15,16,17,18,19]. Comparison across studies is complicated by the use of different age categories. Moreover these studies have included age as an explanatory variable rather than explicitly assessing mortality within and between younger and older ages. ART outcomes including mortality, immunological and virological response may potentially be influenced by age [20,21] hence it is important to understand treatment outcomes to inform on appropriate HIV management in older adults. We aim to explicitly assess how mortality rates following ART initiation compare between older and younger adults and the factors associated with mortality in each age category using data from a large rural HIV Treatment and Care cohort and to quantify immunological and virological responses in different age groups.

Methods

Ethics statement

Written informed consent was obtained from all participants in the programme to allow use of anonymised routine clinical data in research. Ethical approval for retrospective analysis of these data was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE066/07) and the Research Office of the KwaZulu-Natal Department of Health.

Hlabisa HIV Treatment and Care Programme. The Hlabisa HIV Treatment & Care Programme is a partnership between the local Department of Health (DoH) and the Africa Centre for Health and Population Studies (www.africacentre.ac.za). The details of the programme have been previously described [22,23].

The programme adheres to the national antiretroviral treatment guidelines which at the time of study recommended initiation of ART for adults with WHO stage IV disease or CD4 cell count ≤200 cells/mm^3 [24]. Co-trimoxazole was indicated for all individuals with CD4 count ≤200 cells/mm^3 or WHO stage 3/4. First-line ART consisted of stavudine (d4T), lamivudine (3TC), and either efavirenz (EFV) or nevirapine (NVP). ART was initiated at primary health care (PHC) clinics (or at Hlabisa district hospital) by a physician; monitoring and ART dispensing was subsequently performed by nurses and counsellors. CD4 cell count and HIV viral load were measured every 6 months on ART.

Data acquisition. Clinical information at baseline and at monthly clinic visits after initiation of ART is transferred from standardised clinic records to a centralised Microsoft® Access database. A comprehensive tracking service operates whereby patients who are more than one week late for their clinic visit are contacted by telephone and, if necessary, visited at home by a tracker nurse. Information pertaining to death after initiation of ART is therefore obtained either by the clinic staff or tracker team through communication with family members, other clinic staff, or hospital staff. Cause of death is recorded if known but not systematically sought within the routine programme. Laboratory results (CD4 cell count and HIV viral load) are regularly updated from the National Health Laboratory Service (NHLS) laboratory at a district hospital (Hlabisa Hospital). CD4 counts were analysed using the Beckman Coulter EPICS® XL flow cytometer (Beckman Coulter, Inc.). Viral load was measured at a provincial laboratory using the NucliSens EasyQ® HIV-1 assay (bioMérieux), with a lower detection limit of 25copies/ml.

Data analysis. Analysis included all adults (≥16 years) who initiated ART between 1st August 2004 and 31st October 2009, excluding patients on ART who transferred into the programme from elsewhere. Analysis was stratified by age at initiation (<50 years and ≥50 years), a classification which ensured consistency with previous reports [21]. The <50 years age group was further stratified into 16–24 years and 25–49 years to assess for heterogeneity in overall outcomes and baseline descriptions. We assessed differences between the three groups in baseline clinical characteristics using the non-parametric equality-of-medians test for continuous variables and proportions test for categorical variables. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (4-v MDRD) equation, without the ethnicity correction factor, as validated in a South African population [25,26].

Kaplan-Meier survival analysis was used to assess and compare mortality between and within age strata. Data was censored at earliest of date of death, date of loss to follow-up, date of transfer out of programme, or 22nd April 2010. Loss to follow-up was defined as three consecutive months without a clinic visit. To ascertain the independent influence of age on overall mortality, a Cox regression model adjusted for all significantly different baseline factors ($P<0.05$) was used to assess mortality hazard difference by age strata. The two bottom age strata (young and mid-age groups) were combined in the analysis for determination of mortality risk factors because there were no statistically significant mortality outcome differences between the two groups. This is also consistent with previous analysis that have assessed those aged below 50 years as one group in comparison to those aged 50 years and above [27,28,29,30]. Stratified Cox regression with time split at 3 and 12 months post-ART initiation was used to determine risk factors for mortality in the periods 0–3 months (very early mortality), 3–12 months (early mortality), and >12 months post-ART initiation. For the two periods in the first year, analysis was further stratified by age to establish differences in mortality predictors between old and young patients. For all Cox models, variables that were associated with mortality at 15% significance level were individually included into the model and model goodness-of fit assessed. Validity of the proportional hazards assumption was tested using the score test based on scaled Schoenfeld residuals [31]. All results are reported at 5% significance level.

Changes in CD4 cell counts in the 24 months following ART initiation were quantified using a piecewise linear model based on follow-up CD4 cell counts measured at six-monthly time points ± three months. For 909 and 504 patients with missing CD4 counts at 6 months and 12 months respectively the value was interpolated from their CD4 cell counts immediately before and after that time point. Of the 2977 patients alive and active 12 months post ART initiation, 2187 patients (73.5%) had a recorded CD4 count.

Virological response at one year was based on viral load measured between 6 and 15 months after ART initiation. The effect of suboptimal virological response (defined as viral load ≥400 copies/ml) on mortality after the first year of ART was quantified in a Cox regression model adjusted for baseline variables and follow-up CD4 cell counts. For both viral loads and CD4 counts, where more than one measurement was available within the specified time period, the one closest to that time point was used.

Sensitivity analysis. To account for the effect of missing baseline and follow-up explanatory data, we assessed for any

differences in mortality in those with missing observations compared to those with recorded observations. Where those with missing data had significantly different mortality rates, we maintained a category of the missing group within the respective variable in both the univariable and multivariable models exploring factors associated with mortality. This adjusted for any overestimation of the effect of measured/recorded variables on mortality in the absence of those with unmeasured/missing variables. To assess for the extent of loss to follow up bias, we conducted sensitivity analyses where patients lost were considered dead. All analyses were performed with STATA version 11.0 (College Station, Texas, USA).

Results

Patient characteristics

Between 1st August 2004 and 31st October 2009, 8846 adults initiated ART in the programme. Of these, 808 (9.1%) were aged 16–24 years, 7119 (80.5%) were aged 25–49 years and 919 (10.4%) were ≥50 years at time of ART initiation (range 16–83 years). Overall median baseline CD4 cell count was 119cells/μl (IQR 58–174). Older adults had the lowest proportion with CD4 cell count <50cells/μl prior to ART initiation and the highest median CD4 count was amongst those aged 16–24 years (Table 1).

Mortality

There were 997 deaths in 14,778 person-years of follow-up (72 in adults aged 16–24 years; 790 in adults 25–49 years and 135 in adults ≥50 years at ART initiation). The overall mortality rate was 6.75 per 100 person-years (95% confidence interval [CI] 6.34–7.18), significantly higher for ≥50 year old adults (8.69 per 100 person-years, 95% CI 7.34–10.28) than younger adults (6.18 per 100 person-years, 95% CI 4.90–7.78 and 6.55 per 100 person-years, 95% CI 6.11–7.02 in those age 16–24 years and 25–49 years old respectively). Overall, controlling for baseline differences (sex, WHO disease stage, baseline CD4 cell count, haemoglobin, weight, eGFR, education and employment) there was 32% excess mortality risk in patients aged ≥50 years (aHR 1.32, 95% CI 1.09–1.60, $P = 0.004$) compared to those aged 25–49. There were no significant differences in either overall mortality or time stratified mortality rates between those initiating aged 16–24 and those aged 25–49 (Table 2).

In all age groups, the majority of deaths (769 deaths, 77.1%) occurred in the first year after ART initiation, with mortality particularly high in the first three months after ART initiation (449 deaths, 45.0%). Figure 1A (Kaplan-Meier curve) illustrates mortality differences between the two age groups. Early mortality rates were significantly higher for older adults (≥50 years) but there was no significant mortality difference after 12 months (Table 2).

Immunological response

Despite baseline CD4 cell count being higher for older adults; their median CD4 cell count post-ART initiation was lower than for both groups of younger adults at each time point (Figure 2A). Overall 16.6% had a poor immunological response (failed to achieve a CD4 count increase of ≥50 CD4 cells) in the first 6 months of therapy with the largest proportion being in those aged

Table 1. Baseline characteristics for individuals initiated on ART August 2004 - October 2009 (n = 8846), stratified by age at ART initiation.

Variable	16–24 years			25–49 years			50+years		
	N	% or median (IQR)	(95% CI)	*N*	% or median (IQR)	(95% CI)	*N*	% or median (IQR)	(95% CI)
Age	808	22 (21–24)		7119	35 (30–40)		919	54 (51–58)	
Male sex	107	13.24	10.90–15.58	2504	35.17	34.06–36.28	400	43.5	40.32–46.73
WHO stage 3 or 4	328	40.59	37.21–43.98	3435	48.25	47.09–49.41	420	45.70	42.48–48.92
Missing	357	44.18	40.76–47.61	2629	36.93	35.81–38.05	348	37.87	34.73–41.00
CD4 cell count, cells/μl									
Median (IQR)	777	133 (69–182)	125.7–144	6827	115 (55–173)	113–118	888	127 (71–177)	122–136
150–200	220	28.31	25.14–31.48	1643	24.07	23.05–25.08	237	26.69	23.78–29.60
100–149	162	20.85	17.99–23.71	1449	21.22	20.25–22.19	221	24.89	22.04–27.73
50–99	139	17.89	15.19–20.59	1431	20.96	20.00–21.93	178	20.05	17.41–22.68
<50	138	17.76	15.07–20.45	1540	22.56	21.57–23.55	138	15.54	13.16–17.93
>200	118	15.19	12.66–17.71	764	11.19	10.44–11.94	114	12.84	10.64–15.04
Viral load, log_{10} copies/ml	491	4.38	4.26–4.56	4313	4.40	4.36–4.43	542	4.53	4.43–4.63
Weight, kg (IQR)	704	56	54.7–57.1	6262	59.3	59–59.8	814	60	59.1–61
TB treatment	171	21.16	18.34–23.98	1581	22.21	21.24–23.17	175	19.04	16.50–21.58
Haemoglobin <8 g/dL	76	9.41	7.39–11.42	576	8.09	7.46–8.72	44	4.79	3.41–6.17
Missing	110	13.61	11.25–15.98	914	12.84	12.06–13.62	101	10.99	8.97–13.01
***eGFR ≤60 ml/min/1.73 m^2**	30	3.71	2.41–5.02	854	12.00	11.24–12.75	311	33.84	30.78–36.90
Missing	93	11.5	9.3–13.7	725	10.2	9.5–10.9	86	9.4	7.5–11.2
Albumin <32 g/L	440	54.46	51.02–57.89	3764	52.87	51.71–54.03	474	51.58	48.34–54.81
Missing	98	12.13	9.88–14.38	767	10.7	10.05–11.49	93	10.12	8.17–12.07

CI, confidence interval; IQR, interquartile range.
*eGFR, estimated glomerular filtration rate: calculated using 4-variable MDRD equation (without ethnicity correction).
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Table 2. Mortality rates following ART initiation stratified by age at initiation and cohort period time (N = 8846).

Cohort period (years)	Person-time (years)	Failures	Mortality rate	95% CI
16–24 years				
0–0.25	186.34	32	17.17	12.14–24.28
>0.25–1	447.76	18	4.02	2.53–6.38
>1–2	340.94	13	3.81	2.21–6.57
>2	190.76	9	4.72	2.45–9.07
25–49 years				
0–0.25	1675.67	358	21.36	19.26–23.70
>0.25–1	4166.90	251	6.02	5.32–6.82
>1–2	3478.11	111	3.19	2.65–3.84
>2	2737.47	70	2.56	2.02–3.23
≥50 years				
0–0.25	217.64	59	27.11	21.00–35.00
0.25–1	535.77	51	9.52	7.23–12.53
>1–2	445.10	15	3.37	2.03–5.59
>2	355.74	10	2.81	1.51–5.22
TOTAL	**14778.19**	**997**	**6.75**	**6.34–7.18**

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50 years and above (19.6% vs 11.1 and 16.9 in 16–24 year olds and 25–49 years olds respectively). Almost half of all those who initiated with CD4 cell count <50 cells/μl (45.2%) failed to attain a CD4 cell count >200 cells/μl at 12 months. Proportions with CD4 cell counts below 200 cells/μl at specified time points post ART initiation are displayed in Figure 2B.

Virological suppression

From the 5625 patients recorded as active at 12 months post-ART initiation, 3809 (67.8%) viral loads were available for analysis. Overall 86.3% had a good virological response (<400 copies/ml). A greater proportion of older adults (90.1%, 95% CI 84.7–87.0) had a good response compared to younger adults (81.7%, 95% CI 77.4–86.1 and 86.2%, 95%CI 85.0–87.5 in 16–24 year olds and 25–49 year olds respectively).

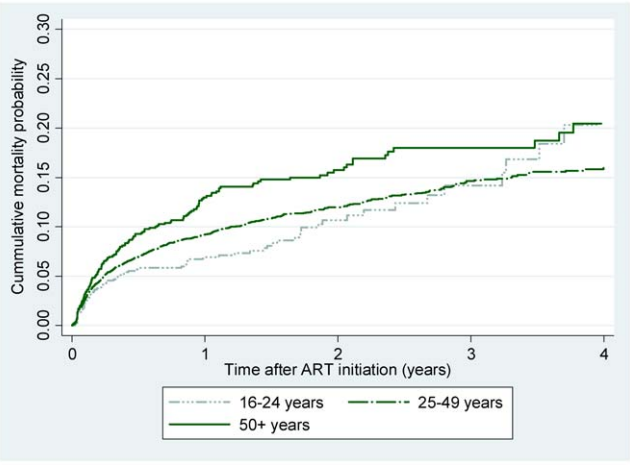

Figure 1. Age and mortality risk post ART initiation. Kaplan-Meier plot of cumulative mortality probability after initiation of ART, stratified by age group at time of ART initiation.
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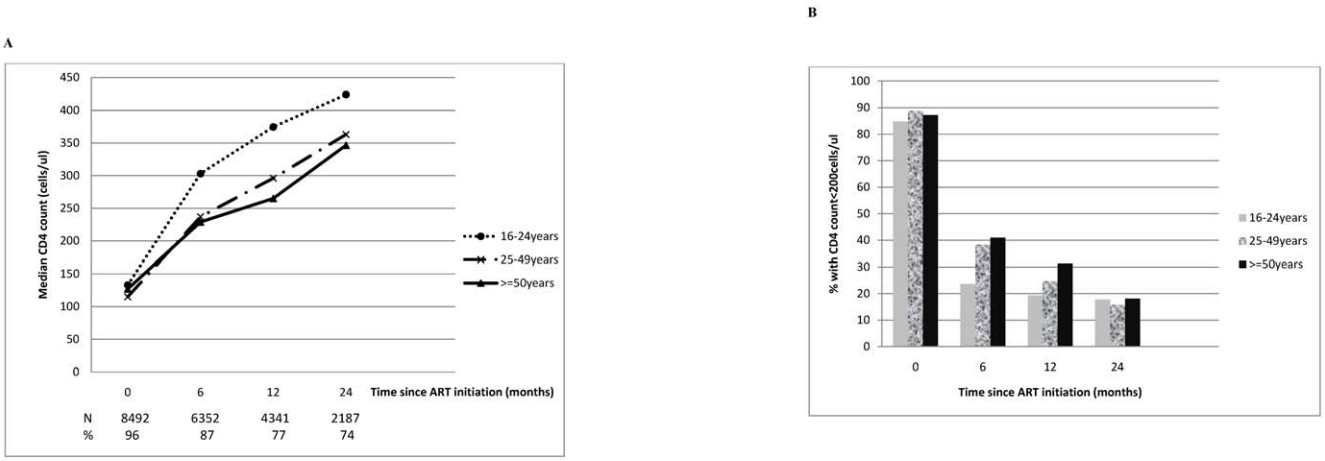
Factors associated with mortality

0–3 months. Using age stratified and time split analysis, from the total 997 deaths, 449 occurred in the first three months after ART initiation (very early mortality) giving the highest period mortality rates of 20.9 and 27.1 per 100 person years in younger and older adults respectively (P = 0.037). However, although mortality risk was significantly higher in the older age group, within each age group, age did not have an independent association with mortality. There was strong evidence of an association between male sex, markers of advanced disease at initiation (CD4 cell count <50 cells/μl, higher $\log_{10}$ viral load, lower weight, and albumin <32 g/L) and increased very early mortality in both age groups. In younger adults, but not in older adults, there were additional associations with WHO stage 3/4, low haemoglobin, and renal impairment (Table 3).

3–12 months. Three hundred and twenty deaths; 269 (12.8%) in younger and 51 (20%) in older adults occurred between 3–12 months (early mortality), mortality rates remaining higher in older compared to younger adults (9.5 vs 5.8 per 100 person years respectively; p = 0.001). Low baseline CD4 cell count (<50 cells/μl) remained independently associated with mortality in those aged <50years, as did WHO stage3/4 disease and low albumin. For older adults the only factor independently associated with mortality in this period was haemoglobin <8 g/dL. There remained a trend towards increased mortality risk with CD4 cell count <50 cells/μl and albumin <32 g/dL but the low numbers of deaths in this period for older adults (n = 51) likely limited statistical power (Table 3).

After 12 months. Factors associated with mortality after 12 months were explored in a single model incorporating all ages because of the similar mortality rates in both age strata. As such in the adjusted model (Table 4) mortality risk was not significantly different for older adults compared to younger adults (adjusted hazard ratio [aHR] 1.01, 95% CI 0.66–1.55). There was no longer any evidence of an association with baseline CD4 cell count, but a lower absolute CD4 cell count and a reduced increment at 12 months post ART initiation were both associated with higher mortality.

In all models there was no statistically significant association between mortality and either education or employment.



N- Number with a recorded CD4 count at each time point
% - N as a percentage of the total number of people alive at active at the start of each time interval

Figure 2. Age and immune response to ART. A. Median CD4 cell count (cells/μl) over time since ART initiation, stratified by age at ART initiation. B. Proportion of patients failing to achieve a CD4 count >200 cells/ul at pre-defined time points post ART initiation, stratified by age at initiation.
doi:10.1371/journal.pone.0021795.g002

Table 3. Independent risk factors for very early (0–3 months after ART initiation) and early (3–12 months) mortality stratified by age.

Variable	Very early mortality (0–3 months)		Early mortality (3–12 months)	
	<50 years (n = 7927)	≥50 years (n = 919)	<50 years (n = 7154)	≥50 years (n = 832)
Age (1yr increase)		0.99 (0.95–1.04)		1.03 (0.99–1.08)
25–49 years	1		1	
16–24 years	0.79 (0.54–1.34)		0.73 (0.45–1.19)	
Male sex	1.64 (1.32–2.03)	1.84 (1.06–3.17)	1.40 (1.09–1.80)	1.33 (0.73–2.41)
WHO stage 3 or 4	1.77 (1.11–2.81)	NS	2.06 (1.19–3.57)	NS
CD4 cell count (cells/μl)				
150–200	1	1	1	1
100–149	1.22 (0.79–1.88)	1.03 (0.37–2.86)	1.04 (0.65–1.68)	1.73 (0.70–4.26)
50–99	1.57 (1.05–2.33)	2.34 (0.97–5.67)	1.50 (0.97–2.31)	1.97 (0.79–4.87)
<50	2.38 (1.63–3.46)	2.60 (1.07–6.31)	2.76 (1.85–4.10)	2.00 (0.80–4.98)
>200	1.56 (0.96–2.52)	1.19 (0.35–4.05)	1.50 (0.90–2.51)	2.19 (0.83–5.82)
Missing	2.12 (1.16–3.87)	3.97 (1.10–14.4)	1.80 (0.92–3.51)	0.30 (0.04–2.63)
Viral load (per $\log_{10}$ increase)	1.16 (1.03–1.34)	2.28 (1.52–3.43)	NS	NS
Weight (1kg increase)	0.94 (0.93–0.95)	0.96 (0.94–0.99)	0.99 (0.97–1.00)	NS
TB treatment*	1.59 (0.84–1.97)	0.90 (0.48–1.69)	1.05 (0.79–1.40)	1.38 (0.72–2.63)
Haemoglobin <8g/dL	2.06 (1.61–2.64)	NS	NS	4.15 (1.79–9.65)
eGFR ≤60 ml/min/1.73m^2†	1.73 (1.35–2.23)	NS	1.41 (1.00–1.98)	NS
Albumin <32g/L	3.58 (2.44–5.24)	2.56 (1.19–5.58)	2.17 (1.56–3.02)	1.52 (0.76–3.02)
missing	4.38 (1.88–10.19)	0.67 (0.42–10.58)	NS	NS

Cox regression models split by time under observation (person years) into very early mortality (0–3 months) and early mortality (3–12 months). Risk factors determined separately for age groups <50 years and ≥50 years.
All values are adjusted hazard ratios with 95% confidence interval.
NS, not significant in univariable model.
*Concurrent TB treatment at time of ART initiation.
†eGFR, estimated glomerular filtration rate: calculated using 4-variable MDRD equation (without ethnicity correction).
doi:10.1371/journal.pone.0021795.t003

Table 4. Independent predictors of mortality after the first 12 months of ART (N = 5625).

Variable	aHR	95% CI
Age 25–49 years	1	
≥50 years	1.01	0.66–1.55
16–24 years	1.35	0.86–2.14
Male sex	1.95	1.46–2.57
Baseline WHO stage 3/4	2.72	1.49–4.97
Missing	2.62	1.43–4.83
Baseline CD4 cell count (cells/μl)		
150–200	1	
100–149	0.80	0.51–1.25
50–99	1.11	0.72–1.71
<50	1.11	0.70–1.75
>200	0.65	0.38–1.13
Missing	0.46	0.20–1.06
Weight (1 kg increase)	0.98	0.96–0.99
Albumin <32 g/L	1.77	1.27–2.47
CD4 increment at 6months (cells/μl)		
<50	1	
50–99	0.98	0.63–1.51
≥100	0.49	0.29–0.81
Missing	1.33	0.39–4.59
Absolute CD4 count at 6months (cells/μl)		
>350	1	
201–350	1.45	0.81–2.57
≤200	0.91	0.44–1.90
CD4 increment at 12months (cells/μl)		
<50	1	
50–99	0.41	0.23–0.73
≥100	0.46	0.24–0.88
Missing	6.15	1.69–22.38
Absolute CD4 count at 12months (cells/μl)		
>350	1	
201–350	0.81	0.43–1.54
≤200	1.49	0.73–3.03
Viral load at 12months (copies/ml)		
<400	1	
≥400	2.67	1.78–4.02
Missing	1.74	1.26–2.41

aHR, adjusted hazard ratio; CI, confidence interval.
Risk factors determined through Cox proportional hazards regression techniques, assessing mortality after 12 months post ART initiation, conditional on being active on the treatment programme at 12 months.
doi:10.1371/journal.pone.0021795.t004

Sensitivity analysis

Mortality rates did not differ significantly between those with complete baseline observations compared to those with missing observations. However 116 (6.4%) of 1816 patients alive but with a missing viral load at 12 months subsequently died compared to 112 (2.9%) of 3809 with a recorded viral load ($P<0.001$), whilst 103 (7.1%) of those alive but with a missing CD4 cell count at 12 months post ART initiation died compared to 125 (3.0%) of those with a recorded CD4 count ($P<0.001$), resulting in higher mortality risk in some of these missing categories (Table 4).

Overall loss to follow-up was 12.9%; 11.6% and 6.5% in the 16–24 yrs, 25–49 yrs, and ≥50 yrs age groups respectively ($p<0.01$). Despite these differences, the sensitivity Kaplan Meier and Cox regression analysis results did not differ significantly from those obtained using completely observed data.

Discussion

We used a large rural HIV treatment programme in South Africa, with a comprehensive tracking system for patients lost to follow-up, to assess mortality rates and differences in three population groups defined by age. In this analysis of 8846 adults with 997 deaths, overall mortality risk was 32% higher for those who initiated ART at age ≥50 years compared to those initiating at age 25–49. Although consistent with previous reports from urban African settings [13,14] we show that this mortality difference is only evident in the first year of ART, following which mortality rates in older adults are no longer different from that in younger adults despite only modest CD4 count reconstitution in the older age group. Previous studies from Europe and North America [32,33,34,35] have also reported poorer immunological but better virological responses in older compared to younger adults but have not explored how these may relate to mortality rates in older age groups receiving ART. Our study shows that despite older adults having a lower proportion of individuals achieving good immunological response in the first year on ART, their mortality rate as a group, after 12 months on ART, was similar to that observed in the younger adult group. This finding coupled with the fact that older adults had a higher proportion of individuals achieving optimal viral suppression, might imply that in older adults, the degree of CD4 count reconstitution may matter less once HIV has been suppressed. Mortality was not significantly associated to either education or employment probably because in this population there is not much heterogeneity in socio-economic variables and everyone is poor [22].

The majority of people enrolled in HIV care and treatment programmes in sub-Saharan Africa are younger adults, consistent with prevalence patterns [37]. In this programme, just over 10% of adults who initiated ART during the study period were ≥50 years old. The higher proportion of males is contrary to the treatment programme in general but is consistent with local prevalence data that shows more males being infected later in life hence expected to access care much later than females [4,23]. Whilst evidence from high-resource settings has suggested that older adults present with more advanced disease [33,38,39], our data suggest the opposite with a higher median CD4 cell count and lower proportion with CD4 cell count <50 cells/μl in older adults. The most striking clinical difference between the groups at baseline was the higher proportion of renal dysfunction at baseline, with 37% of older adults having an estimated glomerular filtration rate (eGFR) of ≤60 ml/min/1.73 m^2. Consistent with the observed decline in GFR with age, this alerts us to the high frequency of renal disease in this setting which is not always detected with serum creatinine measurements alone [40].

In all age groups, the highest mortality rates were in the first three months of ART in line with data previously published from this and other programmes [23,41,42,43,44]. Very early and early mortality was higher in older adults, although older adults presented for ART initiation with higher CD4 counts than younger adults. High early mortality mainly associated with

advanced disease coupled with blunted immunologic response in older adults raises an important question of whether older adults should initiate ART at higher CD4 count threshold compared to younger adults and calls for interventions to encourage early presentation for ART. Older adults may also potentially benefit from enhanced clinical care during initial phases of ART.

The high number of deaths immediately after ART initiation suggests that this mortality is still driven largely by HIV disease itself. However, for older adults, the higher mortality may be explained by higher prevalence of non-HIV conditions such as cardiovascular diseases and diabetes. Unfortunately we were unable to ascertain the cause of death since this information within the programme was extremely limited, with only 42 of 997 deaths (4.2%) attributed to a specific cause. However, research in similar settings has shown mortality in the first year of ART to be caused predominantly by infectious diseases related to immunosuppression with tuberculosis consistently shown to be the leading cause of death across all age groups followed by cryptococcal disease and other infectious diseases [18,19,44,45]. Although in previous analyses we showed that younger age was associated with higher TB incidence in the first three months of ART [36], it could be that TB presentation is different in older adults or that symptoms are less frequently attributed to TB in this group leading to missed diagnoses and mortality [46]. The contribution of immune reconstitution inflammatory syndrome (IRIS) to early mortality remains unclear; a recent meta-analysis, using data from diverse settings across high-, middle- and low-income settings, suggested that IRIS might be responsible for 21% of all deaths after ART initiation [47]. Whether the incidence, presentation or mortality attributable to IRIS is higher in older adults requires further study.

Our study demonstrates that at 12 months, approximately one-quarter of our cohort had CD4 cell count $\leq$200 cells/μl with the largest proportion and the poorest immunological response in those aged $\geq$50 years and this was associated with increased risk of subsequent death. Larger CD4 count increases were significantly associated with reduced mortality risk irrespective of recent absolute CD4 count. In addition previous absolute CD4 cell thresholds (CD4 cell count at 6 months after ART initiation) were not associated with mortality although CD4 count increments of greater than 100 cells/μl at this stage decreased mortality risk beyond a year on therapy. This may possibly imply that as long as there is an immune response greater than a certain threshold, the influence of the absolute CD4 cells count on mortality becomes minimal and non-significant. Despite younger adults demonstrating superior immunological responses, they had inferior virological suppression, a finding that supports previous observations [32,33,34,35], and was associated with a nearly threefold increased risk of mortality after the first year on therapy. Hence the increased risk in older adults associated with poorer immunologic response may have been counteracted by the reduced risk associated with superior virological response resulting in equal mortality risk in both age groups after one year of ART. Although it is possible that this lack of mortality difference may be due to limited statistical power, there are also possible reasons why this may be; the fact that these older adults are seen every 30 days by health care personnel when they come to collect ART may mean that they have a better chance of early diagnosis of age driven morbidities and better clinical management of new and existing morbidities hence limiting the effect of age on mortality. Babiker et al previously suggested that the effect of age on mortality could be attenuated in the HAART era if there was proportionately a reduction in mortality in older age groups. As older adults are at higher risk of HIV mortality primarily due to a faster decline in CD4 cell counts, HAART associated increases in CD4 could have a larger impact in reducing mortality in an older population [6].

Our study population is similar to that from many rural public health HIV treatment programmes and therefore our results are likely generalisable to similar settings in sub-Saharan Africa. The large cohort size and high mortality rates have enabled this analysis [23]. A major strength of our programme is the comprehensive tracking system for patients lost to follow-up which ensures that deaths are ascertained contemporaneously, unlike in many other programmes [48], giving us confidence that our mortality rates are representative of the true population mortality rates.

Our study has certain limitations as a retrospective analysis of routine programmatic data; we were hampered by missing results particularly for follow-up CD4 cell counts and viral loads which we attempted to address by interpolation of missing CD4 cell counts. The blunted immunological response in older adults compared to younger adults might have been underestimated because CD4 cell count changes are influenced by survival bias, i.e. individuals with the worst immunological response are more likely to have died. Although we controlled for multiple biological variables in determining factors associated with mortality, there might still be residual confounding by adherence levels or other unmeasured variables.

Extremely high mortality rates in the first year of ART, more so for older adults suggests that strategies to reduce this early mortality need to be implemented and evaluated with a degree of urgency and that the needs of older adults should be considered within these strategies. Medical interventions, particularly intensive screening and treatment for TB and cryptococcal infection should be implemented and evaluated to improve understanding of the epidemiology of these infections in older adults [49]. Better understanding of the current patterns of testing and health care usage amongst older adults will inform on appropriate age-specific interventions. Making HIV services more acceptable for this age group might get them into HIV care at an earlier stage. We have previously shown lower rates of retention in pre-ART care for older adults [50]; with the known association between older age and more rapid CD4 decline, it is necessary to explore alternative care strategies, which might include integration with other chronic disease management or community-based follow-up [51]. Further work is ongoing within our programme to determine the causes of death and the burden of co-morbidities in the older population. Future work is required to evaluate whether more intensive follow-up impacts on mortality for individuals at high-risk of death in the first few months of ART.

Discussion around older adults and the HIV epidemic in sub-Saharan Africa often only focus on the indirect impact of the epidemic. Our finding of higher mortality on ART for older adults compared to younger adults adds to the evidence base pointing to a substantial direct effect of HIV on older adults' health. As we move into the next phase of ART scale-up the challenges of HIV in older people will need to be addressed with more purpose.

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Author Contributions

Responsible for study design, data analysis, and drafting the manuscript: PCM RJL. Assisted with data interpretation, and revision of the manuscript: AR. Provided critical oversight throughout the process of study design, data analysis, and manuscript preparation: MLN. Wrote the manuscript: PCM RJL. All authors approved the final version of the manuscript.

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