HIV prevalence and morbidity in older in-patients in a high HIV prevalence setting.

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DECLARATION

I, Vivendra Aroomugam Naidoo, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……..

Vivendra Aroomugam Naidoo

Signed ……. day of ……2019

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PRESENTATIONS ARISING FROM THIS PROJECT

1) September 2016: Wits Research Day and Post Graduate Expo – Poster presentation
2) November 2016: SoMCHAT (Soweto Matlosana SAMRC Collaborating Centre for HIV/AIDS and TB) Mini Conference – Oral presentation
3) June 2019: 9th SA AIDS Conference- Oral presentation

ABSTRACT

Introduction

Current understanding of the burden of human immunodeficiency virus (HIV) infection and chronic illnesses in patients aged 50 years and over is limited, especially in low- and middle-income countries. Antiretroviral therapy (ART) has increased life expectancy of HIV positive individuals, exposing them to age related chronic illnesses.

Objectives

To compare the demographic and disease profiles, including chronic illnesses of hospitalised patients aged 50 years and over by HIV status admitted to a regional hospital in South Africa.

Methods

Patients aged 50 years and older admitted on Sundays, Mondays and Thursdays to Tshepong Hospital Medical Wards from November 2015 to February 2016 were approached to participate. These days were selected as a representative sample of admissions without recruiting every day, as the principal investigator and assistant could not collect data daily due to other responsibilities. Socio-demographic data, laboratory results, anthropometric data, discharge diagnoses and HIV status were collected. Patient characteristics were stratified by HIV status and gender. The Kruskal-Wallis test was used to compare the continuous variables and p-values were obtained. Variables with p-value ≤ 0.05 were considered as significant.

Results

A total of 478 eligible patients were admitted over the study period and 151 participants were enrolled. Their median age was 61 years (IQR: 56-68 years); 89 were women (58.9%). Overall 47 (31.1%) were HIV positive, of whom 10 (6.6 %) were newly diagnosed at this admission. The HIV positive group was younger [median age 57.0 years (IQR: 53.0-62.0)] compared to HIV negative group [median age 64.3 years (IQR: 57.0-71.0 years)] (p-value<0.0001). The most common discharge diagnoses amongst all participants was acute gastroenteritis (11.5%) and community acquired pneumonia (11.5%). Hypertension and type 2 diabetes mellitus (T2DM) were the most common chronic illnesses in HIV negative, known HIV positive and newly diagnosed HIV positive participants respectively (Hypertension: 75.0%, 59.46% and 40.0%) (T2DM: 22.1%, 24.3%). Eighteen patients died during admission; 12 were HIV negative (p-value= 0.8617).

Conclusion

Almost a third of older patients admitted to hospital were HIV positive, whose leading cause for hospitalisation was infections. Although in the ART era, older patients have similar age-related chronic illnesses irrespective of HIV status.

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ABBREVIATIONS

ADC- AIDS–dementia complex

AGE- Acute gastroenteritis

AIDS- Acquired immunodeficiency syndrome

ART- Antiretroviral therapy

BMI- Body mass index

CAP- Community acquired pneumonia

COPD- Chronic obstructive pulmonary disease

COPD AE- Chronic obstructive pulmonary disease acute exacerbation

HIV- Human Immunodeficiency Virus

HIVAN- HIV-associated nephropathy

HIVAD- HIV-associated dementia

HDL- High density lipoprotein

LDL- Low density lipoprotein

MDR-TB- Multi-drug resistant tuberculosis

PHRU- Perinatal HIV Research Unit

SA-MRC- South African Medical Research Council

TB- Tuberculosis

VCT- Voluntary counselling and testing

WHO- World Health Organisation

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

Background

Current knowledge regarding the prevalence and incidence of HIV infection in patients aged 50 years and over (older patients), as well as their co-morbidity profile is sparse, especially in South Africa with the largest antiretroviral therapy program globally[1]. The South African antiretroviral treatment (ART) program started treating patients in 2004; therefore, it is likely that a substantial number of patients have survived to their sixth decade of life and beyond[2]. Moreover, older individuals are not immune to new infection with HIV[3,4].

Studies involving older individuals living with HIV infection, as well as the World Health Organisation (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS) reports on HIV infection and ageing, use an age cut off of 50 years and over to differentiate between older and younger individuals. This age cut off will be used in this study.

Klerksdorp/Tshepong Hospital Complex is a tertiary level hospital in the North West Province, rendering a wide range of specialist services to the province. The Internal Medicine Department is based at the Tshepong (West) Wing of the complex. The department has an admission ward and 5 medium-to-long stay wards, each of which can accommodate 36 patients. Assessment of medical admissions in 2014 suggests that approximately 40% of all patients admitted to the Internal Medicine wards are aged 50 years and over.

Statement of the problem

According to the Centre for Disease Control, out of 35 079 patients admitted to short-stay hospitals in United States in 2010, 9 483 were aged between 45-64 years (28.1%) and 13 591 were aged 65 years and older (38.7%) [5].

With the advent of ART and increased screening programmes, the number of people with HIV infection over the age of 50 years has increased. The prevalence of HIV infection in females in South Africa from 2012-2017 has increased from 14.8% to 20.2% in 50-54-year olds, 9.7% to 14.8% in 55-59-year olds, and 2.4% to 14.9% in individuals aged 60 years and older[6,7]. Amongst the male population, prevalence of HIV infection in South Africa from 2012-2017 has increased from 15.5% to 17.6% in 50-54-year olds, 6.2% to 14.9% in 55-59-year olds, and 4.6% to 8.2% in individuals aged 60 years and older[6,7]. As a result, the presentation of older patients to hospitals for admission has changed. The typical "diseases of the elderly" has been replaced by HIV infection related diseases. Due the complex interaction

between HIV, ART's and inflammatory and pathological disease processes, the disease and co-morbidity profile of older individuals is dramatically changing, resulting in new challenges.

A further challenge associated with HIV and older patients is polypharmacy. The prevalence of chronic disorders increases with age and as a result, older patients have a high pill burden. ART and long-term treatment therapy for many HIV associated diseases will further increase their pill burden. A retrospective chart review showed that HIV positive patients over the age of 60 years had a median of 13 concomitant medications (range 9-17) compared to a median of 6 in HIV negative patients [8]. This increase in pill burden in older HIV positive patients may result in reduced compliance and increased risk of relapse. A systematic review showed that mean dose compliance was 71% for single drug regimens and decreased as the number of daily doses increased[9]. However, they did not specify the mean age of the patients from all the studies reviewed. Non-compliance with treatment amongst older patients varies from 26-59% in patients aged over 60 years[10]. Older HIV positive patients have a higher risk of developing memory and depression problems which will further adversely affect treatment compliance[11,12].

Justification for the study

Many studies have been conducted comparing HIV positive patients aged 50 years and over to younger controls, but few international studies have been conducted comparing HIV positive and HIV negative patients aged 50 years and over, and none in South Africa. An understanding of the evolving disease and co-morbidity profile of older individuals in the era of ART will play a major role in preventative and therapeutic programmes, as well as hospital staffing and needs. This hospital-based study at Tshepong Hospital Department of Internal Medicine will provide valuable information regarding the disease profile of patients aged 50 years and over admitted to the medical admissions ward. Indeed, a review of the admissions register suggests that approximately 600 patients are admitted monthly to the Tshepong adult medical wards and of those patients; approximately 40% were aged 50 and over.

Literature Review

Ageing and old age are one of the most significant challenges facing medicine [13]. The ageing process is a major risk factor for underlying disease and disability[13]. Older people respond differently to therapies developed for younger adults, with less effectiveness and more adverse reactions [9]. Modern medicine and healthier lifestyles have increased the likelihood

that people will live longer and reach old age [13]. This rapidly increasing numbers of older people, often with age-related disorders, are predicted to overwhelm health care systems[13].

Ageing is a progressive process associated with declines in structure and function, impaired maintenance and repair systems, increased susceptibility to disease and death, and reduced reproductive capacity [13]. These include structural and functional changes, which may be primary ageing changes (sarcopenia, grey hair, increased peripheral vascular resistance) or age-related disease (dementia, osteoporosis, insulin resistance, hypertension) [13].

Old age is the major independent risk factor for chronic diseases and associated mortality including cardiovascular disease, cancers, and neurodegenerative disorders [13]. Older people have multiple comorbidities, usually in the range of 5–10 illnesses per person, resulting in acute illnesses not being treated in isolation, but a milieu of multiple comorbidities [13].

Immunity appears to play an important role in regulating the mechanisms of ageing and the development of the diseases of ageing[14-16]. The immune system in older adults have a number of changes, including a reduced number and function of hematopoietic stem cells, a reduced number of circulating naive T cells and increased proinflammatory cytokines including interleukin (IL)-6 and TNFα[14]. The "ageing phenotype", including the immunosenescence is due to the imbalance of inflammatory and anti-inflammatory mechanisms with the development of a state of "inflammageing"[15]. This is due to chronic antigen stimulation in the course of life and the resultant oxidative stress that involves the production of oxygen free radicals and toxic products[15]. There is subsequent "remodelling" and the "up-regulation" of pro-inflammatory cytokines (including IL-6), which has been implicated in the development of fragility[14.15]. Inflammageing is a risk factor for the development of infectious diseases, cardiovascular disease, chronic kidney disease, diabetes mellitus, cancer, depression, dementia and sarcopenia[15,16]. The number of T cells decreases due to age-related atrophy of the thymus. B cells overproduce autoantibodies, resulting in age-related increase in autoimmune diseases and gammopathies[13]. Older people are considered to be immunocompromised with a reduced response to infection (absence of fever, no leukocytosis) and increased mortality[13].

A supplement to the UNAIDS report on the global AIDS epidemic in 2013 reported that since 2007, the global proportion of adults aged 50 and over living with HIV has increased, with the current worldwide number estimated at 3.6 million[4]. They also report that 10% of the population living with HIV in low- and middle-income countries is aged 50 years and

older[17]. The supplement to the UNAIDS reports that the increase in prevalence of HIV in older individuals is due to three primary reasons[4]:

1. Success of ART prolonging the lives of HIV positive individuals
2. Decrease incidence of HIV in younger individuals, shifting the burden of disease
3. People aged 50 years and over exhibit the same risk factors for acquiring HIV infection as younger people (sexual intercourse with multiple partners, low condom use)

An estimated 100 000 people aged 50 years and over acquire HIV infection every year in low- and middle-income countries, with 74% of these living in sub-Saharan Africa[3]. The South African national HIV prevalence, incidence and behaviour survey reported that more than 50% of individuals aged 50 and over had sex 1-4 times in the last 30 days, with more than one fifth saying they had sex 5-9 times in the same time period[6].

People aged 50 years and over have the same risk factors for acquiring HIV infection as younger people, and may be at increased risk through the following biological and behavioural mechanisms[3,4,7]:

- Postmenopausal women have thinning of the vaginal wall
- Knowledge of condoms is lower
- Usage of condoms is six times less than adults aged 15-49 years

Trends in the United States of America

A supplemental report from CDC found that the HIV prevalence in the United States of America has increased from 2011 through 2015; at the end of 2015, 450 579 older adults were living with diagnosed HIV infection and a prevalence of diagnosed HIV infection of 406.5[18].

A UNAIDS report estimates that in high-income countries, approximately 30% of adults with HIV are aged 50 years and over[4].

Trends in Africa and developing nations

There were an estimated 2.9 million people aged 50 years and over living with HIV in low- and middle-income countries in 2012. It is the first time since the beginning of the HIV epidemic that 10% of the adult population in these countries are aged 50 years and over[4].

Sub-Saharan Africa has the highest burden of HIV among older adults (approximately 2.5 million) while the Middle East and North Africa (14 000) and the Caribbean (33 000) had the lowest number of older adults infected with HIV[19]. The reasons for the difference in the number of older adults with HIV infection between the regions is not clear, but all the regions show an increase in HIV infection in older adults[19].

An analysis of a scale up programme looked at the prognosis of 10 031 adult patients who started ART between 2004 and 2007 in Ivory Coast, Malawi and South Africa[20]. They found that 7% of the patients enrolled were aged 50 years and older. This sub-group of the study population also had the highest probability of death within the first year of starting ART. It was postulated that it may be due to differences in patients' age, but subsequent studies have shown that age this is a weak association[21] and the reason for this difference in mortality is unclear.

With the roll out of ART and increased screening programmes, the number of people living with HIV over the age of 50 years has increased[2]. The rapid and large upscale of ART in sub-Saharan Africa (SSA) and resulted in improved life expectancy and quality of life[3]. Provision of ART has decreased AIDS-related deaths, with 42% fewer AIDS-related deaths in 2017 compared to 2010 in the eastern and southern Africa, and a 34% reduction worldwide[22]. In South Africa[17,23], life expectancy for males born without HIV has increased from 61.1 years in 2002 to 64.7 years in 2014, while in females; it has risen from 67.1 years to 71.0 years. The life expectancy for males born with HIV has increased from 51.1 years in 2002 to 59.1 years in 2014[17,23]. Similarly, in females, the life expectancy if born with HIV has risen from 55.7 years in 2002 to 63.1 years in 2014[17,23]. Out of an estimated population of 55 million, approximately 8.9 million individuals are aged 50 years and over[17]. Mills et al showed that life expectancy for patients starting ART has increased, with patients starting at age 35 years having an additional life expectancy of 27.9 years, and patients starting at age 50 years having an additional 20 years[24]. This means that the number of individuals living with HIV infection will extend to the sixth decade and beyond. The increase in life expectancy of HIV positive individuals to age 50 years and over will result in the "unmasking" of the burden of non-communicable diseases which was previously hidden by the high rates of HIV-related deaths[3].

Mid-year population estimates published in 2014 showed that of the number of persons living with HIV in South Africa has increased from approximately 4.09 million in 2002 to 5.51

million by 2014 and the prevalence of HIV is increasing in individuals aged 50 years and over[23]. The total number of HIV/AIDS related deaths has declined between 2002 and 2014 (43.6% to 31.1%)[16]. These findings suggest that there currently are, and will be an increasing percentage of the population aged 50 and over who are HIV infected and possibly on ART.

Hontelez et al estimates that the number of HIV positive individuals aged 50 years and over in Sub-Sharan Africa will nearly triple over the next 2 decades to up to 9.1 million in 2040[3]. With increased ART use and a decrease prevalence of HIV infection amongst individuals aged 15-49 years old, there will be a dramatic shift in the age profile of people living with HIV. A survey (*South African National HIV Prevalence, Incidence, Behaviour and. Communication Survey)* conducted in 2017, showed that the prevalence of HIV infection in individuals aged 50-64 years had risen to 17.2%[7]. A cross-sectional biomarker survey in the rural South African Agincourt Health and Sociodemographic Surveillance site in 2010 showed HIV prevalence was 35% among men aged 55-59 years and 27% among women of the same age. HIV prevalence was 20% among men aged 60-64 years, and 17% among men aged 65-69 years, while among women in the same age groups it was 13% and 10%, respectively[25]. Interestingly, ART provision only started in 2007 in this area, which suggests that many of the individuals aged 50 years and older acquired HIV infection at a younger age[25]. The reason for the higher rate of HIV infection in males is not clear, but it may be due to behavioural differences, such as men having multiple sexual partners and engaging in greater risk-taking behaviour.

Findings from death notifications for 2013 in South Africa showed that HIV Infection was the 3rd most common underlying natural cause of mortality (5.1%), moving up from 7th place in 2011[26]. Amongst the 45-64-year age group, HIV infection ranked as the 4th most common underlying cause of natural death (5%), while in the 65 and older age group, HIV infection did not rank in the top 10[25]. For both the 45-64-year age group and the 65 years and older age group, diabetes mellitus and cardiovascular related disease ranked in the top 10 leading underlying natural cause of death[26]. While the findings are not definitively stated for aged group 50 years and older (due to WHO classification of age groups), there is evidence of HIV infection as well as endocrine and cardiovascular co-morbidities in the older persons[26].

Co-morbidity profile

Older patients who are HIV infected may present with an AIDS defining illness, or may present with co-morbidities common in older individuals and are picked up through voluntary testing programmes[27-29]. A longitudinal, historical cohort study in Milan, Italy, enrolled 159 older patients (aged 50 years and over) and 118 controls[30]. The results found a similar number of older HIV positive patients and younger HIV positive controls who presented with AIDS defining illnesses. They also found no difference in the number of cases and controls with co-morbid conditions, but did find that co-morbidities in the older patients were cardiovascular, endocrine and metabolic disorders, whereas those in the younger controls were liver-related. In a retrospective study of newly diagnosed HIV positive patients from 2006–2011 in New York, 30.7% of patients presented with AIDS defining illnesses, with a similar spectrum of illnesses in the older and younger groups[28].

A study by Negin *et al* using data from the WHO's Study of global AGEing and adult health (SAGE) conducted South Africa in 2007–2008 found that 29.6% of HIV infected individuals aged 50 years and older had 2 or more chronic conditions, compared to 8.8% of individuals aged 18–49 years[31].

Pathological effects of HIV

In addition to HIV-related opportunistic infections and malignancies, there are several clinical syndromes that affect the various organ systems[32,33]:

Cognitive, motor and behaviour dysfunction can manifest at any time during HIV-infection and is termed AIDS–dementia complex (ADC) or HIV-associated dementia (HIVAD) [32,.33], with the prevalence ranging from 20% to 69% in various series[34].

Numerous haematological abnormalities occur with HIV infection. The cause is multifactorial, but HIV infection of lymphocytes, monocytes and macrophages cause alterations of cytokine production that adversely affect the regulation of haematopoiesis[32,33].

Gastro-intestinal disease is the most frequent complication of HIV infection. At least one third of patients experience oesophageal disease during their illness, while up to 50% of patients will experience diarrhoeal disease[32].

Emphysematous lung disease is more common in HIV positive patients even after adjusting for smoking. Diaz *et al* found the incidence of emphysema was 15% in HIV positive smokers compared to 2% in HIV negative smokers, with a higher percentage of cytotoxic lymphocytes found in HIV positive smokers in alveolar lavage[35]. Respiratory symptoms are more common

in HIV positive individuals, with chronic cough and expectoration (47%) and breathlessness during exercise (33.9%) commonly reported[36]. Airflow limitation and low pulmonary diffusing capacity is also found in HIV positive patients and findings persists even with virological suppression[36]. The exact mechanism related to this is unclear[37,38].

Han *et al* conducted a single-centre cross-sectional study in South Africa and in this study, HIV-associated nephropathy (HIVAN) was found in 25 (83%) patients. Seven patients had persistent microalbuminuria and were biopsied, with six (86%) showed HIVAN[39]. There are numerous nephropathies that can occur with HIV, including HIV associated nephropathy (HIVAN). Renal biopsies from autopsy studies demonstrated histological features of HIVAN in 6.9% of HIV-infected people, which increased to 12% when only looking at African patients[32,33].

The pathogenesis of cardiovascular disease in HIV infected individuals of any age is multifactorial. The HIV virus has many pathological effects that alter cardiovascular risk factors such as[40]:

- Abnormal lipid metabolism and subsequent reduced levels of HDL cholesterol, LDL cholesterol and an increase in triglyceride levels
- The exact mechanism of insulin resistance is unknown. It has been demonstrated that excess free fatty acid due to altered lipolysis reduces insulin sensitivity in peripheral tissue, resulting in impaired glucose metabolism
- Increased truncal adiposity, related to ageing, male gender and ethnicity, as well as fat redistribution secondary to HIV infection and ART confer a higher risk for insulin resistance
- Atherogenesis stimulated by HIV infected monocyte macrophages results in accelerated vascular disease
- Vasculitis in small, medium and large vessels related to leucocytoclastic vasculitis increase the risk of development of hypertension at a younger age
- HIV infected patients may develop coagulation abnormalities (increased levels of D-dimer, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, or deficiency of protein S and protein C) which may be related to CD4 cell count, concurrent infections and neoplasms, as well ART

This, in combination with pathophysiological changes associated with ageing, accelerates the pathogenesis of cardiovascular disease and its associated risk factors. Cardiac morbidity

associated with HIV is estimated at 6-7% in Europe and USA, with a mortality of 1-6%[39]. HIV myocarditis represents an important cause of dilated cardiomyopathy, with a prevalence of up 3.6%[40]. On autopsy, 25% of HIV-infected patients have been shown to have dilated cardiomyopathy and up to 52 % have myocarditis[33,33].A large study conducted at Johns Hopkins University suggested that patients with HIV-associated cardiomyopathy have a poor prognosis with a hazard ratio for death of 4.0, which increased to 5.9 when adjusted for demographic and hemodynamic characteristics[41].

Combined effects of HIV infection and ageing

Rates of certain AIDS-defining cancers have declined with the advent of ART, but this burden is now complicated by an increase in non-AIDS-defining cancers[42]. There is increase risk in selected malignancies (liver, cervical, anal, Hodgkin's lymphoma), potentially due to premature ageing caused by HIV-related inflammation and immunosenecence [42].

Hypertension, diabetes, chronic glomerulonephritis and obstructive uropathy due to infectious diseases are the most common causes of chronic kidney disease in Sub-Saharan Africa[41]. An increased risk of renal disease especially HIVAN is found more commonly among individuals of African ancestry[42]. Similarly, studies from Zambia and Botswana found high rates of renal insufficiency at time of ART initiation amongst HIV infected individuals[43,44]. Some ART and medications used in the prophylaxis and treatment of opportunistic infections are also nephrotoxic. Ageing in HIV positive patients is an independent risk factor for the development of renal disease, with studies in Africa finding an association between renal dysfunction and older age in HIV positive patients without co-morbidities that may predispose to renal dysfunction (type 2 diabetes, hypertension)[43-46].

Studies in Sub-Saharan African shows pooled prevalence of depressive symptoms and major depression at 31.2% and 18% respectively[47]. Depression can lead to challenges in ART adherence. There has been an increased prevalence of less severe HIV-related cognitive disorders, including HIV-associated neurocognitive disorder (HAND), particularly among older individuals with HIV/AIDS. Ageing independently increases the risk of neurocognitive disorders[42]. Mental processes may be negatively impacted by either ageing, HAND or their combined impact on cognitive dysfunction. There is a two-fold higher prevalence of cognitive impairment amongst individuals aged 50 year and over with HIV infection compared with those 35 years of age and younger[48,49].

Chronic respiratory diseases represent a growing health burden. In South Africa, non-neoplastic conditions include chronic obstructive pulmonary disease, asthma and lung disease secondary to occupational exposure[50]. In high-income countries, there is a higher rate of non-communicable respiratory diseases amongst older individuals with HIV infection than younger individuals[50]. Findings from the Veterans Administration Ageing cohort showed an increase risk of chronic non-malignant pulmonary diseases in HIV infected individuals compared with age-matched HIV negative controls[52].

Bone mineral density loss is well associated with ageing. Premature osteopaenia and osteoporosis have been described in HIV infected individuals regardless of age, with rates three times higher than HIV negative individuals[42]. The mechanisms by which HIV infection and ART causes reduced bone mineral density has not been clearly defined. Current evidence suggest that bone loss associated with initiation of most ART regimens is due to an increased remodelling rate, resulting in bone microstructure changes[53]. Some protease inhibitors cause stimulation of osteoclastogenesis and inhibition of osteoblast function, and zidovudine has also been shown to stimulate osteoclastogenesis[53]. Tenofovir can cause renal tubular dysfunction, and is associated with the rare Fanconi syndrome and hypophosphataemic osteomalacia[53]. Efavirenz has been associated with an increased risk of vitamin D deficiency[53]. Chronic immune reconstitution, as a result of ART initiation, causes raised circulating levels of proinflammatory, proresorptive cytokines[53].

Physiological effects of ART

The Milan cohort study found that the older patients had a higher risk of abnormal blood tests (glucose, cholesterol profile, serum creatinine) than younger controls after 48 weeks of ART[30]. They also found a higher incidence of new co-morbidities in the older case group. No clear reason could be established for this (e.g. lower CD4 cell count, high viral load etc) and may have been the result of adverse effects of ART and natural senescence.

A literature review by Chalwa et al, found that patients on long term ART had associated decline in bone mineral density with certain nucleotide reverse transcriptase inhibitors, increase fracture risk with tenofovir, increased risk of chronic kidney disease, increased incidence of diabetes mellitus, and increased incidence of myocardial infarction, especially with protease inhibitors[54].

Prolonged use ART has been associated with an increased risk of adverse cardiovascular events, increased levels of cholesterol, low and very low-density lipoproteins and

abnormalities in glucose metabolism. These adverse events are particularly noticed with protease inhibitors, as well as certain nucleoside and non-nucleoside reverse transcriptase inhibitors[55].

Proximal tubular cell dysfunction can be caused by tenofovir exposure, which may be associated with acute kidney injury or chronic kidney disease[56]. Patients may develop Fanconi syndrome (partial or complete), with or without a reduction in glomerular filtration rate (GFR)[56].

Immunological response to ART

Two prospective studies have suggested that older HIV positive patients have a lower baseline CD4 cell count compared to younger controls[55,57]. Both studies also found that the older patients' immunological improvement paralleled that of the controls, but never reached the same level[55,57]. This shows that older HIV positive patients may present with advanced disease due to their low CD4 cell count, but will show good recovery if started on ART early.

Study Aim

To determine the demographics and disease profile of patients aged 50 years and over admitted to the adult medical wards at Tshepong Hospital for the period 1 August 2015 to 31 October 2015

Objectives

1. To determine the reason for admission and comorbidity profile of patients aged 50 years and over to the Medical wards at Tshepong Hospital during the period 1 August 2015 to 31 October 2015
2. To determine the HIV infection prevalence amongst patients aged 50 years and over admitted to the Medical wards at Tshepong Hospital
3. To compare the disease and co-morbidity profile of HIV negative and HIV positive patients aged 50 years and over admitted to the Medical wards at Tshepong Hospital
4. To determine the CD4 cell count of newly diagnosed HIV patients aged 50 years and over to the Medical wards at Tshepong Hospital
5. To determine the CD4 cell count, viral load and ART regimen of known HIV-infected patients aged 50 years and over admitted to the Medical wards at Tshepong Hospital

Methodology

Study Design

The study is a cross sectional study with patients recruited in a prospective manner.

Study setting

The study will be conducted at the Medical admission ward and adult Medical wards at Tshepong Hospital. The hospital has a total of 382 beds, of which 216 are for medical patients and 98 are at the multi-drug resistance/extremely-drug resistance tuberculosis centre. The bed occupancy rate ranges from 90-96%. The hospital provides 24-hour level one services for Matlosana district, level two services for Dr Kenneth Kaunda district and level three services for the whole of the North West Province.

Study Period

The study will be conducted from the 1 August 2015 to 31 October 2015.

This study start date is chosen in order to begin the study as soon as possible after the anticipated approval from the ethics committee and the appointment of a study assistant. The study period is chosen as the minimum amount of anticipated time needed to recruit the required number of patients.

Study population

In keeping with international studies, the older age group will be defined as 50 years and over, as opposed to the traditional definition of elderly being 65 years and older. Therefore, all patients aged 50 and over admitted to the Internal Medicine department during the study period are eligible for the study

Sampling

Approximately 600 patients are admitted per month to the adult Medical wards, of which 240 (40%) are aged 50 years and older. Therefore, over the study period, approximately 600 patients will be aged 50 years and older. A 10% error at 95% confidence intervals is wanted, therefore a sample size of 200 patients aged 50 years and over is required.

In order to collect the desired number of patients for the study, patients admitted every Sunday, Monday and Thursday from the beginning of the study period that are aged 50 years and older will be approached for participation in the study. Data will only be collected every

Monday, Tuesday and Friday due to logistic, clinical and academic responsibilities precluding daily data collection. A day is defined as starting at 7am on the pre-determined date to 7am the following day, starting from 1 August 2015.

Inclusion criteria:

1. Age 50 years and older admitted to the Medical Ward with a medical diagnosis
2. Known HIV status by the time of discharge/death

Exclusion criteria

1. Informed consent not obtained to for participation in the study
2. Refused or unable to obtain consent for voluntary counselling and testing for HIV

Measurements and data sources

The measurement tool for data collection will be data capture sheets. The source data will be patient interviews, patient records, and supporting documents.

During the study period, the intake register in the Medical admissions ward will be reviewed on data collection days, and all patients meeting the age criteria for the study will be noted. These patients will be approached and written informed consent to participate in the study will be obtained. The following variables will be collected at the first interview:

1. Demographic information: age, gender, source of income, housing and patient's caregiver will be asked
2. Admission diagnosis as per admission form
3. Co-morbidities which the patient self-reports as well as those listed in patients records
4. HIV status if the patient is aware of their status. The patient must have been tested within the last 4 weeks for an HIV negative status to be accepted due to the window period of HIV infectivity.
5. If the patient is HIV positive, information regarding the age of diagnosis, ART status, and duration on ART will be collected, as well as if they have defaulted ART before
6. Tobacco history: number of cigarettes (including pipes and roll up cigarettes) per day and the duration of years smoking
7. Alcohol use: type, quantity and frequency of consumption and volume consumed

8. The patient's weight, height, hip circumference and waist circumference will be measured according to methods outlined in the WHO STEPwise approach to surveillance (STEPS) programme[58]
9. Admission haemoglobin and creatinine levels

Patients will be followed up until time of discharge/death and the following information will be collected:

1. Whether the patient was discharged home or demised during hospitalisation as per medical records
2. Diagnosis at time of discharge/death as per patient's medical records
3. HIV status if not known and patient has accepted routine, hospital offered voluntary counselling and testing (VCT) (Annexure A). This will be obtained from the patient's medical records, as patients are routinely offered VCT and the result documented in the patient's notes
4. If the patient is diagnosed with HIV, a routine (baseline) CD4 cell count is taken on all patients as part of patient work up and eligibility for ART. This result is documented in the patient's records and will be obtained from there or the barcode with the result will be used.
5. If the patient is known HIV positive, a routine CD4 cell count and HIV viral load is collected unless one is available from the last 6 months in the patients, in order to asses compliance and effectiveness of ART
6. Any information not fully obtained during the first interview

<u>Limitations and bias of the study</u>

- The variables collected in the study are recorded by different people at different times and there may be an information bias
- Incomplete information in patients' files
- Recall bias of patients

The following steps will be taken in order to limit bias:

- Consultant notes will be used to capture diagnoses and co-morbidities
- ICD-10 coding will be used to capture diagnoses
- Patients reported co-morbidities will be checked against patient records and vice-versa

- Efforts will be made to check and follow up all blood results

Data Processing and Data analysis

The patients' names will not be entered into the data sheet- rather study numbers will be used. De-identified data will be collected for each patient and the results will be compared within the patient population. Comparison of continuous variables will be done by the Student t-test and categorical data by the Chi-squared test. The statistical significance will be calculated at the 95% confidence interval.

Ethical Considerations

All information will be collected anonymously in the data sheet using unique study numbers and patient confidentiality will be respected. Permission to conduct the study will be obtained from the Human Research Ethics Committee of the University of the Witwatersrand and the Hospital Management.

HIV testing is offered voluntarily to all patients at Tshepong Hospital (Annexure A). If they test positive, a routine CD4 cell count is done. If a patient is HIV positive and does not have a documented CD4 cell count or viral load from the last 6 months, these investigations are routinely done. Therefore, these variables which form part of the study will not be beyond routine investigations offered to patients and not incur any extra costs.

Consent will be obtained from the Head of the Department of Internal Medicine as well as the CEO of Klerksdorp/Tshepong Hospital Complex. Signed consent will be obtained from each patient. Individual numbers will be assigned to each patient sequentially.

Confidentiality will be ensured with subject identifiers rather than personal names. Limited access to data (Principal Researcher, supervisors) will further ensure confidentiality.

Time Schedule

Task	**Time Required**	**Deadline**
Submission for assessor group meeting		29 May 2015
Present protocol to assessor group	30 minutes	17 June 2015
Submit application for ethical clearance		July 2015

Refine protocol, data capture sheet and analysis model with supervisor	± 2 hours	July 2015
Study preparation • Finalise tools • Data collection • Data analysis and results	±6 months	July 2015- December 2015
Submit data analysis and results write-up to supervisor and an outline of what will be included research article		Mid-February 2016
Supervisor feedback	±3 hours	End February 2016
Article writing	3-4 weeks	End March 2016
Submit first draft of research report to supervisor		End March 2016
Prepare research article for submission	3-4 weeks	End May 2016
Submit research article for examination		June 2016
Disseminate article on approval		September 2016

<u>Funding</u>

Study Preparation

Home office	0
Stationary, photocopies	750
Travel	500
Study Nurse	±20 000
Subtotal	21250

The R20 000 will be used to employ a study nurse to aid in obtaining informed consent and with patient interview. Funding will be obtained from a small developmental grant through the Perinatal and HIV Research Unit (PHRU) from the South African Medical Research Council (SAMRC), which is offered to Master of Medicine candidates who do their research at Klerksdorp/Tshepong Hospital Complex.

Report Preparation and Write-up

Home office	0
Stationary, photocopies, printing	2000
Travel	500
Subtotal	2500

Grand total:R 23 750

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Annexure A

Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

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HAST PROGRAMME
DR KENNETH KAUNDA DISTRICT

HIV CONSENT AND TEST RESULTS FORM

Patient details	
Name and surname	
ID no / DOB	
Age	
Physical address	
File no	
Facility	
Date of visit	

PRE TEST COUNSELING

	Yes	No
Pre test counseling offered		
Test accepted and written consent obtained		

TESTING

HIV test used	Rapid	ELIZA
Batch no for test kits (screening & confirmatory)	Screening test kit batch no:	
	Confirmatory test kit batch no:	
Test conducted by - Name & Surname :		
Results issued by – Name & Surname		

POST TEST

	Yes	No
Post test counseling offered		
Results issued		
Referral to support group – if yes state name and location of the support group		
Patient / guardian (Name & Surname)		
Witness (Name & Surname)		

Healthy Living for All
DR KK HIV TEST AND RESULTS FORM 2012

CHAPTER 2: SUBMISSIBLE ARTICLE

HIV prevalence and morbidity in older in-patients in a high HIV prevalence setting.

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- **Authors' contributions:** Vivendra A Naidoo was the project leader and primary author. Neil Martinson and Ebrahim Variava assisted with study conception and design, and editing of the manuscript. Katlego Mothlaoleng and Wendy Mqakelana assisted with data acquisition. Pattamukkil Abraham and Kennedy Otwombe assisted with data analysis and interpretation.

- **Disclaimer:** The views expressed in this article are that of the author(s) and not an official position of the North West Department of Health, Tshepong Hospital, PHRU, SA MRC or the University of the Witwatersrand

- **Source(s) of support:** PHRU and SA MRC Soweto-Matlosana for providing funding towards the study assistants.

- **Summary:**
    - Number of words (excluding abstract and references): 3153
    - Abstract word count: 260
    - Pages: 20 (Twenty)
    - Tables: Five (5)
    - Figures: Two (2)

- **Tweet for the journal Twitter profile:** HIV in older individuals

ABSTRACT

Introduction

Current understanding of the burden of human immunodeficiency virus (HIV) infection and chronic illnesses in patients aged 50 years and over is limited, especially in low- and middle-income countries. Antiretroviral therapy (ART) has increased life expectancy of HIV positive individuals, exposing them to age related chronic illnesses.

Objectives

To compare the demographic and disease profiles, including chronic illnesses of hospitalised patients aged 50 years and over by HIV status admitted to a regional hospital in South Africa.

Methods

Patients aged 50 years and older admitted on Sundays, Mondays and Thursdays to Tshepong Hospital Medical Wards from November 2015 to February 2016 were approached to participate. These days were selected as a representative sample of admissions without recruiting every day, as the principal investigator and assistant could not collect data daily due to other responsibilities. Socio-demographic data, laboratory results, anthropometric data, discharge diagnoses and HIV status were collected. Patient characteristics were stratified by HIV status and gender. The Kruskal-Wallis test was used to compare the continuous variables and p-values were obtained. Variables with p-value ≤ 0.05 were considered as significant.

Results

A total of 478 eligible patients were admitted over the study period and 151 participants were enrolled. Their median age was 61 years (IQR: 56-68 years); 89 were women (58.9%). Overall 47 (31.1%) were HIV positive, of whom 10 (6.6 %) were newly diagnosed at this admission. The HIV positive group was younger [median age 57.0 years (IQR: 53.0-62.0)] compared to HIV negative group [median age 64.3 years (IQR: 57.0-71.0 years)] (p-value<0.0001). The most common discharge diagnoses amongst all participants was acute gastroenteritis (11.5%) and community acquired pneumonia (11.5%). Hypertension and type 2 diabetes mellitus (T2DM) were the most common chronic illnesses in HIV negative, known HIV positive and newly diagnosed HIV positive participants respectively (Hypertension: 75.0%, 59.46% and 40.0%) (T2DM: 22.1%, 24.3%). Eighteen patients died during admission; 12 were HIV negative (p-value= 0.8617).

Conclusion

Almost a third of older patients admitted to hospital were HIV positive, whose leading cause for hospitalisation was infections. Although in the ART era, older patients have similar age-related chronic illnesses irrespective of HIV status.

Introduction

Anti-retroviral treatment (ART) has had an immediate and dramatic improvement in prognosis, quality of life and longevity of HIV-infected individuals. Provision of ART has decreased AIDS-related deaths, with 42% fewer AIDS-related deaths in 2017 compared to 2010 in the eastern and southern Africa, and 34% reduction worldwide[1]. This, together with the introduction of universal test and treat strategies for HIV, has led to an increase in the number of people with HIV infection over the age of 50 years. Indeed, it is estimated that there are 32 million adults 50 years and older globally, 13% who are is HIV-infected, representing 3.6 million people[2]. The majority (2.9 million) live in middle- and low-income countries, where they represent 10% of the population [2]. Moreover, an estimated 100 000 people aged 50 years and over acquire HIV infection every year in low- and middle-income countries, with 74% living in sub-Saharan Africa[2]. More than 2 million people aged 50 and older living in sub-Saharan Africa are HIV infected, which accounts for 60% of all people living with HIV over the age of 50[3].

Immunity appears to play an important role in the regulation of the mechanisms of ageing and the development of the diseases of ageing[4-6]. The immune system in older adults undergoes a number of changes, including a decrease in the number and function of hematopoietic stem cells, reduced circulating naive T cells and increased proinflammatory cytokines[4]. The "ageing phenotype", including the immunosenescence is due to the imbalance of inflammatory and anti-inflammatory mechanisms with the development of a state of "inflammageing[5]. The "up-regulation" of pro-inflammatory cytokines (including IL-6) has been implicated in the development of fragility[4,5]. Inflammageing is a risk factor for the development infectious diseases, cardiovascular disease, chronic kidney disease, diabetes mellitus, cancer, depression, dementia and sarcopenia[5,6].

Another concern for older patients is that of polypharmacy and a high pill burden. The prevalence of chronic disorders increases with age, with 30% of the people aged 50 years and over in South Africa having two or more chronic co-mordities[7]. Non-adherence increases with age, and with an increase in the frequency and number of medications[8,9]. The estimated number of people aged 50 years and over on ART in South Africa is 753,020, representing approximately 76.7% of all those living with HIV in this age group[10]. Anti-retroviral treatment, as well as long term treatment or maintenance therapy for many HIV associated diseases, will further increase that burden, which may reduce adherence. Drug interactions

may increase side effects and may affect ART efficacy[11]. Moreover, older HIV infected patients have a higher risk of depression and memory and cognitive loss, which further affects treatment adherence[12,13].

Ageing populations increase health utilisation, and the demographic profile of patients with severe illness has implications not only for individuals and their quality of life, but also for health services[7].

This study aimed to determine the HIV prevalence, demographics and disease profile of patients aged 50 years and over admitted to the adult medical wards at Tshepong Hospital.

Research methods and design

Study design, setting and population

We conducted a prospective study of in-patients aged 50 years and older, admitted to the medical wards at Tshepong Hospital in Matlosana, South Africa. The study was conducted from November 2015 to February 2016.

Approximately 600 patients are admitted per month to the adult Medical wards, of which 240 (40%) are aged 50 years and older. Therefore, over the study period, approximately 600 patients will be aged 50 years and older. A 10% error at 95% confidence intervals is wanted, therefore a sample size of 200 patients aged 50 years and over is required.

All patients aged 50 years and older admitted to adult internal medicine wards on Sundays, Mondays and Thursdays during the study period were approached to participate in the study. Due to logistic, clinical and academic responsibilities, the principal investigator and study assistant were unable to collect data daily. These days were selected to ensure that the sample population would be representative of patients admitted over the weekend (Sundays), early in the week (Mondays), and towards the end of the week (Thursdays) and for convenience. Patients were excluded when informed consent could not be obtained or HIV testing declined. We extracted daily tallies of all potentially eligible patients for the duration of the study from the ward admission register.

Demographic data (age, gender, source of income, housing and patient's caregiver), co-morbidities (either newly diagnosed or present at time of study enrolment), HIV status (either known or newly diagnosed) and habits (tobacco and/or alcohol use) was captured. If patients were HIV positive, their most recent CD4 cell count and viral load results were obtained.

Anthropometric data recorded on admission included weight, height, hip circumference and waist circumference. Weight and height were obtained on participants who were able to stand and mobilise, as no bed weighing scales were available. Admission haemoglobin and creatinine concentration, hospital outcome, as well outcome diagnoses (categorised according to ICD-10 Version: 2016) were also extracted from clinical records.

We defined discharge diagnosis as diagnoses listed on patients' discharges summaries, which were determined by the treating physician. In those participants who died, the most likely cause of death was determined by death report forms completed at daily mortality meetings. Medical conditions were considered comorbid if patients reported that they were taking or told that they required long term medical treatment for an illness(es).

Data Analysis

Data was entered into a RedCap^{TM} database after review and validation by a physician (VAN). Frequencies and percentages were calculated for categorical variables. As the data was not normally distributed, median and interquartile range (IQR) were determined for continuous variables. Where pertinent, patient characteristics were stratified by HIV status and gender. The Kruskal-Wallis test was used to compare the continuous variables and p-values were obtained. Variables with p-value ≤ 0.05 were considered as significant. Analysis was conducted using SAS Enterprise Guide 7.1.

Ethical Considerations

Ethical clearance was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (clearance certificate number: M150739). Permission to conduct research was obtained from the Klerksdorp/Tshepong Hospital Complex and the North West Department of Health.

Results

We enrolled 151 patients (approximately 31.6% of eligible patients; and approximately 40.0% of all admissions over the study period). By extrapolation of overall admission and demographic trends, we estimate that a total of 1197 patients 50 years and older were admitted during the study period of whom 478 were admitted on Sundays, Mondays and Thursdays. There was a higher than anticipated number of patients who were unable to provide consent. The calculated sample size required was 200 patients, but due to logistical, clinical and academic responsibilities, we were only able to enrol 151 patients. Patients

not enrolled either declined consent for study participation and/or HIV testing or were unable to provide consent due to their medical illness (delirium, dementia, or cerebrovascular accident).

The median age in our cohort was 61.0 years (IQR: 56.0-68.0 years). Forty-seven patients were HIV positive (31.1%), 37 (78.7%) were previously diagnosed as HIV positive and 10 (21.0 % of all HIV positive participants) were newly diagnosed on current admission. The HIV positive group was younger; their median age of 57.0 years (IQR: 53.0-62.0) compared to HIV negative group with a median of 64.3 years (IQR: 57.0-71.0 years) (p-value<0.0001). Overall 89 patients (58.9%) were women. Of the 47 HIV positive patients, 28 (59.6%) were female. The median age of the female HIV positive patients was 57.0 years (IQR: 54.0-62.0 years) and the median age of the males was 56.0 years (IQR: 53.0-60.0 years) (p-value= 0.8350).

Body mass index (BMI) was calculated on admission in patients who were able to stand and have their weight measured. BMI was lower amongst the HIV positive patients, particularly those who were newly diagnosed (Table 1). The differences in BMI was not statistically significant (p-value=0.3030). Waist circumference was obtained from patients who were able to be appropriately positioned to measure it. Waist circumference was obtained from 85 patients (64 HIV negative patients, 16 patients known HIV positive and 5 newly diagnosed HIV positive patients). The median waist circumference amongst all participants was 88.0 cm (IQR: 79.0-102.0 cm). Amongst the known HIV positive patients, the median waist circumference was 83.0cm (IQR: 73.0-96.3 cm); newly diagnosed positive patients had a median waist circumference of 79.0 cm (IQR: 78.0-84.0 cm); and in the HIV negative patients, the median waist circumference was 90.0 cm (IQR: 79.8-105.3 cm). The differences in waist circumference between the three groups were not statistically significant (p-value= 0.1025).

Twenty-three (15.2%) of study patients consumed alcohol, of whom, seventeen (73.9%) were HIV negative. Sixty-one (40.4%) of patients self-reported tobacco use, with 46 (75.4%) being HIV negative.

The median haemoglobin was 12.4 g/dL (IQR: 10.4-13.9 g/dL). The value was lowest amongst the newly diagnosed HIV positive patients (11.4 g/dL) which was statistically significant (p-value= 0.0056). The median creatinine was 87.0 µmol/L (IQR: 72.0-132.0

µmol) and highest amongst the known HIV positive patients (101.5 µmol/L). However, this was not statistically significant (p-value= 0.2435)

Overall, 131 patients were discharged (86.8%), 18 patients died in hospital (11.9%) and two (1.3%) were lost to follow up (discharge summaries and death reports not traceable during follow up period).

Most (78.8%) patients were reliant on immediate or extended family for care, with only 17.2% of patients independently caring for themselves. A large proportion (59.6%) of patients received social grants as their sole source of income. Twenty-two (15.1%) of study patients were still working and 13.0% were receiving a pension.

A large proportion of patients stay in formal housing structures (brick/concrete house-80.8%; apartment/flat-3.3%). Only one patient stayed in a care facility for the elderly.

HIV infection

Participants newly diagnosed with HIV infection (10/47) had a lower CD4 cell count of 209.0 cells/µL (IQR= 120.0-379.0 cells/µL) than those previously diagnosed with HIV infection which was 256.0 cells/µL (IQR= 102.0-471.0 cells/µL) (p-value= 0.8204).

Most HIV positive patients (33/37) were receiving ART (89.2%), for a median duration of 2.6 years. Two patients were on ART for less than six months, five patients for between six and twelve months and 25 patients for more than one year. The duration on ART could not be determined for one patient and three patients had not yet initiated ART; one patient had defaulted previously (Table 2).

The leading ART regimen received was tenofovir-emtricitabine-efavirenz fixed dose combination (84.8%), with only three patients (9.1%) on a protease-inhibitor containing regimen. Twenty-nine patients had a viral load available, and of these, only 14 (48.3%) patients were virally suppressed (viral load of <20 copies/mL), with the majority (11) on ART for more than one year.

There was no statistically significant difference in the creatinine of HIV positive participants when comparing those on ART to those not on ART (p-value= 0.7245).

Chronic illnesses

Overall, hypertension was the most common chronic illnesses (68.9%), followed by type 2 diabetes mellitus (T2DM) (21.2%) and chronic obstructive pulmonary disease (COPD)

(13.9%). Other chronic illnesses included chronic cardiac disease: atrial fibrillation, valvular heart disease (5.3%), epilepsy (5.3%), cerebrovascular accident (4.0%) and thyroid disorders (hypothyroidism and hyperthyroidism) (3.3%). The morbidity profile amongst the three subgroups showed a similar distribution (p-value= 0.9290) (Figure 1, table 3).

Of patients with COPD, 17 patients reported prior (58.8%) or current (41.2%) tobacco smoking, with 12 patients (70.6%) having a smoking history of ten pack years or more. Five COPD patients were HIV positive; none had a smoking history of ten pack years or more.

Twenty-nine patients had both hypertension and T2DM (19.2% of all participants). Of those, eight were known HIV positive and the remainder were HIV negative.

Discharge/death diagnoses

The most common discharge diagnosis amongst all patients was acute gastroenteritis (AGE) and community acquired pneumonia (CAP) (both 11.5%). Five (3.3%) patients with AGE and two (1.3%) patients with CAP had acute renal dysfunction. Acute exacerbation of COPD (COPD AE) (9.9%), uncontrolled hypertension (9.2%) and congestive cardiac failure (7.6%) were the next most common diagnosis. Hyperglycaemia accounted for 5.3% of admissions (seven participants), with two being admitted with hyperglycaemic emergencies. Cerebrovascular events (transient ischaemic attacks and cerebrovascular accidents) and cor-pulmonale accounted for 4.6% of admissions. Figure 2 shows the distribution of admissions for each subgroup as a percentage of all patients, and table 3 show the distribution of admissions broken down each subgroup (p-value= 0.4100).

Of the 18 patients who died, 6/47 (12.7%% of HIV-infected patients) were HIV positive and 12/104 (11.5%) were HIV negative (p-value= 0.8617). One (0.7%) was newly diagnosed with HIV, with a CD4 cell count of 10.0 cells/µL. In the five patients who died with known HIV infection, the median CD4 cell count was 106.0 cells/µL (IQR 26.0-137.0 cells/µL) and the median viral load (available for four out of the five patients) was 148 086.0 copies/mL (IQR 17.0-1 384 647.0 copies/mL). Two of the five patients were virally suppressed. In HIV positive patients, the most likely causes of death were: intra-abdominal malignancy (one patient), AGE (two patients, of whom one had renal dysfunction), pneumocystis pneumonia (one patient), CAP with associated renal dysfunction (one patient) and Steven-Johnson's syndrome (one patient). In the HIV negative patients, the most common causes of death were: AGE (two patients of whom one had renal dysfunction), congestive cardiac failure (three patients), tuberculosis (two patients) and COPD AE (one patient).

Tuberculosis (TB) was diagnosed in six patients. Three patients had drug sensitive TB, of whom two were HIV negative. Three patients had multi drug resistant TB (MDR-TB) and of these, two were HIV positive (one newly diagnosed HIV positive). Of the two patients with TB disease who died, one had MDR-TB and one had drug sensitive TB. Both patients who died were HIV negative.

Table 5 demonstrates the number of AIDS defining and associated conditions diagnosed in the HIV positive patients, both known and newly diagnosed HIV positive.

Discussion

In our study, almost one third of patients admitted to Internal Medicine wards were HIV positive. In HIV positive older patients admitted to hospital, the most common diagnoses at discharge were co-infections. Worryingly, for the achievement of 90-90-90 targets[14], less than half the HIV infected older receiving ART were virally suppressed.

Non-infectious chronic illnesses (hypertension and T2DM) were common in both HIV positive and HIV negative patients. Similar to other studies, chronic illnesses are common in HIV infected individuals[3,15,16]. HIV infection may be coincidental and can be an additional risk factor for cardiovascular disease and malignancy, or may contribute directly to diagnosis[17,18].

As in keeping with other studies, the median age of HIV positive patients was 57.0 years, with a 75th percentile of 62 years[19]. Older HIV positive individuals have a higher mortality, especially seven months to 5 years after starting ART[19], while the average life expectancy for males starting ART at aged 60 years is 10.1 years and 14.4 years for females[20], which may account for no HIV positive patients over the age of 75 years in our study group.

An interesting finding in our study was the median age difference of 7.3 years between the HIV negative group (median age of 64.3 years) and the HIV positive group (median age of 57.0 years), which was statistically significant (p-value<0.0001). The HIV positive patients were significantly younger, yet had similar chronic illnesses to the HIV negative patients. This may be due to accelerated ageing and progression of chronic diseases in HIV infection and with ART use[17,19,21].

There is limited data available on mortality rates of patients aged 50 years and over, specifically with HIV infection, as most mortality studies in older patients use 60 years as the minimum age of enrolment. In comparison to available studies, the overall mortality rate of

11.9% is similar to other studies[22]. The mortality rate between our HIV negative and HIV positive group of patients was similar of (11.8% and 12.8% respectively). The mortality rate amongst HIV positive patients was higher compared to a study conducted in Cape Town, but they did not analyse in-hospital mortality rates by age[19].

Comorbid hypertension, T2DM with raised abdominal circumference fulfil criteria for Metabolic Syndrome, which we found in 17 of study participants; which increase the risk for cardiovascular disease[23]. With the pro-inflammatory state of HIV infection, this risk may be accelerated[17].

Renal disease, as evaluated by creatinine of greater than 90 µmol/L, was more severe in the older HIV positive participants admitted to hospital. Tenofovir, AGE, CAP, diabetes and hypertension[24,25] likely contributed to renal injury.

COPD was present in all three sub-groups of patients (15.4% in HIV negative participants; 8.1% in known HIV positive patients and 20% in newly diagnosed patients). COPD was the most common ICD-10 sub-category of patients amongst high acute health services users in Canada aged 50 years and over[26]. This study however did not look at HIV status. Of the patients with COPD 17 reported current or tobacco use. All the HIV positive patients had a smoking pack year history of less than 10. Emphysematous lung disease is more common in HIV positive individuals even after adjusting for smoking[27-30], a risk that persists even after virological suppression[20, 31]. Smoking prevalence amongst HIV positive individuals is as high as 34%[32], therefore encouraging smoking cessation is an important intervention.

AGE and CAP was the joint most common discharge diagnosis. There were a similar number of patients in all three groups who had CAP (8.1% in the known HIV positive group; 10.0% in the newly diagnosed HIV positive group; 11.8% in the HIV negative group). AGE showed a similar occurrence in all three groups (HIV negative- 10.8%; known HIV positive- 18.9%; newly diagnosed HIV infected- 10.0%). All five participants with renal dysfunction were HIV positive (one newly diagnosed with HIV infection) and had AGE. Patients with acute renal dysfunction exposed to tenofovir tend to have more severe renal abnormalities[25.] Two percent of HIV negative patients were asthmatic, with none being present in HIV positive patients. There is limited literature comparing discharged diagnoses of HIV positive and HIV negative patients, but a study conducted in Canada looking at use of acute health services by patients aged 50 and over found diseases of the respiratory, circulatory and digestive system amongst its' top 5 diagnostic categories- similar to our study[26]. A cross-sectional of HIV

positive patients in Brazil had a study population, where 15.7% of the patients were aged 50 years and over, found that after opportunistic infections, community acquired pneumonia and gastro-intestinal infections were the most common causes of hospitalisation[33].

Three of our study patients had MDR-TB, which accounts for 50% of all TB cases in our study. This is higher than the national prevalence (2.1% among new tuberculosis cases)[34], but it did not take account all TB cases diagnosed during the study period.

Few studies from high HIV burden settings have reported on the burden of disease in older in-patients, but it is becoming increasingly important as the HIV population is becoming older[2,9,35-41], to understand the dynamics and challenges associated with treating this group of patients

Limitations

Only 31.6% of eligible patients were recruited. The calculated sample size required was 200 patients, but due to logistical, clinical and academic responsibilities, we were only able to enrol 151 patients. This was a single centre study with a small sample size, recruited over a short period and not including an entire year. The study was limited to the public sector in a single district and may not necessarily be generalised to the entire population of South Africa. Due to the study period, seasonal differences could have been missed, as it was carried out over four consecutive months only. Incomplete record keeping regarding time and dates of admission resulted in the inability to gain an accurate assessment of the number of eligible study participants. Similarly, laboratory results relied on routinely collected data which was not always available. We were unable to obtain anthropometric measurements on all study participants. Our estimates of mortality in the groups is likely an underestimate and may be affected by misclassification bias as those not able to provide consent were excluded the study.

Conclusion

In our study, HIV infection in older patients was common, with just under one third of patients having HIV infection. Older patients have similar age-related non-infectious chronic illnesses and causes for hospitalisation, irrespective of HIV status. Non-infectious chronic illnesses are common in both HIV negative and positive patients, with up to 25% of all patients having T2DM and 68% suffering from hypertension. Non-infectious chronic illnesses were found at a younger age in our HIV positive patient cohort (median age

difference of 7.3 years younger), and screening for these conditions should be considered at least 5 years earlier than current recommendations for HIV negative individuals.

Infectious illnesses are the most common reason for admission in older patients, regardless of HIV status.

Individuals may only be diagnosed with HIV infection at an older age and this population group also at risk for acquiring HIV infection. Therefore, HIV prevention and screening programmes should also be targeted at older individuals.

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Competing interests

None

Authorship contributions

VAN was the project leader and primary author. NAM and EV assisted with study conception and design, and editing of the manuscript. KM and WM assisted with data acquisition. PA and KO assisted with analysis and interpretation of data.

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Figures and Tables

Table 1. Characteristics of patients aged 50 years and over admitted to the medical wards

	All patients	Known HIV-positive	Newly diagnosed HIV positive	HIV negative
Number, n (%)	151	37 (24.5%)	10 (6.6%)	104 (68.9%)
Age (years)	61.0 (56.0-68.0)	57 (53.0-62.0)	56.5 (53.0-59.5)	64.0 (57.0-71.0)
Range	50.0-90.0	50.0-74.0	51.0-64.0	50.0-90.0
Age by groups (n)				
50-54	35	13	4	18
55-59	33	9	3	21
60-64	29	8	3	18
65-69	20	4	0	16
70-74	18	3	0	15
>75	16	0	0	16
Gender				
Females, n (%)	89 (58.9)	22 (59.5)	6 (60.0)	61 (58.6)
Haemoglobin (IQR) (g/dL)	12.4 (10.4-13.9)	11.6 (8.9-13.0)	11.5 (10.6-12.6)	12.8 (10.8-14.5)
Creatinine (umol/L)	87.0 (72.0-132.0)	101.5 (76.5-157.0)	82.5 (59.5-232.8)	86.5 (73.3-118.5)
No of participants from who anthropometric measurements were obtained	85	16	5	64
BMI (kg/m^2)	24.8 (20.2-30.8)	23.2 (18.3-29.7)	19.7 (19.5-22.3)	25.0 (21.6-31.9)
Waist circumference (cm) by gender				
Males	85.5 (79-95)	78 (71-79.75)	78 (78-78)	88 (81-98)
Females	92 (79-105)	91 (77-102.5)	81.5 (77.5-84.75)	95 (79-107.5)

Results reported as median values and interquartile range, unless otherwise stated
BMI- Body Mass Index

Table 2. Demographics, CD4 cell count and viral loads of known HIV positive patients aged 50 years and over admitted to the medical wards

	All patients	Males	Females
Number	37	15	22
Age (years)	57.0 (53.0-62.0)	56.0 (53.0-61.0)	57.0 (53.3-62.8)
Number on ARV (%)	33 (89.2%)	13 (86.7%)	20 (90.9%)
Duration on ARV			
Less than 6 months	2	0	2
6-12 months	5	3	2
More than 1 year	25	10	15
Unknown	1	0	1
CD4 cell count (cells/uL)	256.0 (102.0-472.0)	247.0 (126.0-473.0)	264.0 (72.0-451.0)
Virally supressed* (Viral load <20 copies/mL) n (%)	14/29 (48.3%)	4/10 (40.0%)	10/19 (52.6%)
Viral load (copies/mL)* n (%)			
<50	16 (55.2%)	5 (50%)	11 (57.9%)
50-1000	2 (6.9%)	1 (10%)	1 (5.3%)
>1000	11 (37.9%)	4 (40%)	7 (36.8%)

*From viral loads available on 29 participants
Results reported as median values and interquartile range, unless otherwise stated
ARV- Anti-retroviral treatment

Table 3. Common chronic illnesses of patients aged 50 years and over admitted to the medical wards grouped by HIV status

	Overall n (%)	HIV negative n (%)	Known HIV positive n (%)	Newly diagnosed n (%)
Hypertension	104 (68.9)	78 (75.0)	22 (59.46)	4.00 (40.0)
Type II diabetes mellitus	32 (21.2)	23 (22.1)	9 (24.32)	0.00 (0.0)
COPD	21 (14.0)	16 (15.4)	3 (8.11)	2.00 (20.0)
Epilepsy	8 (5.3)	6 (5.8)	2 (5.4)	0 (0)
Cardiac disease	8 (5.3)	6 (5.8)	1 (2.70)	0 (0)
Cerebrovascular accident	6 (4.0)	5 (4.8)	1 (2.70)	0 (0)
Thyroid disease (hypothyroidism, hyperthyroidism)	5 (3.3)	4 (3.9)	1 (2.70)	0 (0)

COPD- Chronic obstructive pulmonary disease

Table 4. Discharge diagnoses of patients aged 50 years and over admitted to the medical wards grouped by HIV status

	Overall n (%)	HIV positive n (%)	Newly diagnosed HIV positive n (%)	HIV negative n (%)
Acute gastroenteritis	15 (11.5)	5 (15.6)	1 (11.1)	9 (10.0)
Community Acquired Pneumonia	15 (11.5)	2 (6.3)	1 (11.1)	12 (13.3)
Uncontrolled hypertension	12 (9.2)	1 (3.1)	0 (0)	11 (12.2)
Acute exacerbation COPD	13 (9.9)	2 (6.3)	1 (11.1)	10 (11.1)
Congestive cardiac failure	10 (7.6)	1 (3.1)	2 (22.2)	7 (7.8)
Urinary tract infection	8 (6.1)	4 (12.5)	1 (11.1)	3 (3.3)
Cor Pulmonale	6 (4.6)	0 (0)	1 (11.1)	5 (5.6)
Hyperglycaemia	7 (5.3)	1 (3.1)	0 (0)	6 (6.7)
Cerebrovascular event	6 (4.6)	2 (6.3)	0 (0)	4 (4.4)

COPD- Chronic obstructive pulmonary disease

Table 5. WHO AIDS defining and associated conditions of HIV positive patients aged 50 years and over admitted to the medical wards

	Discharged (n=41)	Demised (n=6)
Tuberculosis	3	-
Herpes Zoster	1	-
Molluscum Contagiosum	1	-
Oral Candidiasis	-	1
***Pneumocystis jiroveci* pneumonia**	-	1
Acute gastroenteritis	6	2
Community Acquired Pneumonia	3	1

CHAPTER 3: APPENDICES

3.1 Data Collection Sheet

Study Number: _____

Gender: □Male □Female **Date of birth (DD/MM/YYYY):**_____ **Age:** ____

Date of admission (DD/MM/YYYY): _____

Outcome: □ Discharge □ Death

Date of death/discharge (DD/MM/YYYY): _____

Admission diagnosis:

1. _____ ICD 10:_____
2. _____ ICD 10:_____
3. _____ ICD 10:_____

Final Diagnosis (at discharge/death):

1. _____ ICD 10:_____
2. _____ ICD 10:_____
3. _____ ICD 10:_____
4. _____ ICD 10:_____
5. _____ ICD 10:_____

Primary care giver

□Self □Spouse/Partner □Children □ Grandchildren □Neighbour/Friend
□Other: _____

Source of income

□Work □Pension □Social Grant □Other:_____

Housing

□ Brick/concrete house □Apartment/Flat □ Traditional hut/dwelling □ Garage
□ 1 room □ Shack □ Homeless
□ Home for the elderly □Other: _____

Other co-morbidities

□ Diabetes Mellitus Type I	□ DM Type II	□ Hypertension
□ Asthma	□ COPD	□ Kidney Disease
□ Heart Disease	□ Liver Disease	□ Thyroid Disease
□ Psychiatric Condition	□ CVA	□ Malignancy
□ TB		

Other:

HIV

□ Known HIV positive □ Newly Diagnosed Positive □ Negative □ Refused testing

If newly diagnosed

CD4 count:_____ □ No CD4 available

If known HIV

Age of diagnosis: _____

Currently on ART: □Yes □No

If on ART, initiation date (MM/YYYY): _____

If not on ART: □ Defaulted □ Never on ART

Date of default (MM/YYYY): _____

Re-initiated on ART: □ Yes □ No

CD4 count:_____ □ No CD4 available

Viral load:_____ □ No viral load available

Alcohol use

Do you drink alcohol □ Yes □ No

How often do you drink alcohol:

□Daily □Weekly □Occasionally (less than twice a month)

What do you drink:

□ Cans (330ml) □ Cans (500ml) □ Quartz (750ml) □ Tot (whiskey) □ Glass (wine)

How many do you drink:

□ 1 □2 □3 □4 □5 or more

Smoking history

Have you ever smoked tobacco □Yes □No

(Tobacco includes pipes, hand rolled cigarettes)

If yes, how old were you when you started smoking: _____

Are you still smoking □ Yes □No

If no, how old were you when you stopped smoking: _____

How many cigarettes do/did you smoke per day: _____

Anthropometry

- Waist circumference (cm) :_____ □ Unable to obtain
- Hip circumference (cm) :_____ □ Unable to obtain
- Height (cm) :_____ □ Unable to obtain
- Weight (kg) :_____ □ Unable to obtain
- Body mass index (kg/m^2) :_____ □ Unable to calculate

Haemoglobin: _____

Creatinine: _____

3.2 Ethics clearance certificate

R14/49 Dr Vivendra Aroomugam Naidoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150739

NAME: (Principal Investigator)	Dr Vivendra Aroomugam Naidoo
DEPARTMENT:	Internal Medicine Tshepong Hospital, Klerksdorp, North West
PROJECT TITLE:	Disease Profile of Patients Aged 50 Years and Older Admitted to Tshepong Medical Wards between 01 August 2015 and 31 October 2015
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Neil Martinson and Ebrahim Variava
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/09/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.3 Change of title approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

12 September 2018
Person No: 0601305R
TAA

Dr VA Naidoo
P O Box 2648
Lenasia
1820
South Africa

Dear Dr Vivendra Naidoo

Master of Medicine: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine** has been approved:

From:	**Disease profile of patients aged 50 years and older admitted to Tshepong Medical Wards between 1 August 2015 and 31 October 2015**
To:	**HIV prevalence and morbidity in older in-patients in a high HIV prevalence setting**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

3.4 “Turnitin” Report

Document Viewer

Turnitin Originality Report

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