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HIV Infection and Older Adults: a retrospective single-site cohort study from Johannesburg South Africa.

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A research report submitted to the University of Witwatersrand, Johannesburg in fulfilment of the degree of Master of Medicine 2017.

Declaration

I, India Lucy Claire Butler, declare that this research report is my own work which is being submitted for the degree of Master of Medicine. It has not been submitted before for any degree or examination at this or any other University.

Signed……

On this day the …….. of …….. 2017.

Publications and presentations

Data from this research project was accepted presented at the International Association of Gerontology and Geriatrics World Congress, San Francisco in July 2017.

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Dr Susan Coetzer presented at the International Association of Gerontology and Geriatrics World Congress, San Francisco in July 2017 on my behalf during my maaternity leave.

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List of Abbreviations

ADC AIDS-Defining Condition

AIC Alive and In Care

AIDS Acquired Immunodeficiency Virus

ALT Alanine Transaminase

ART Antiretroviral Therapy

AZT Zidovudine

BMI Body Mass Index

CD4+ Cluster of Differentiation 4 positive

CD8+ Cluster of Differentiation 8 positive

CI Confidence Interval

d4T Stavudine

EFV Efavirenz

GFR Glomerular Filtration Rate

Hb Haemoglobin

HIV Human Immunodeficiency Virus

ID Identity Document

LTFU Lost to follow up

MSM Men who have Sex with Men

NRTI Nucleoside Reverse Transcriptase Inhibitor

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor

NVP Nevirapine

OI Opportunistic Infection

PEPFAR President's Emergency Plan for AIDS Relief

PI Protease Inhibitor

PR Prevalence Ratio

TDF Tenofovir

TF Transferred

TLC Thembalethu Clinic

TB Tuberculosis

USAID United States Agency for International Development

VL Viral Load

WHO World Health Organization

1. Protocol with Extended Literature Review

1.1. Extended Literature Review

1.1.1. Background to HIV Treatment in South Africa

Human Immunodeficiency Virus (HIV) treatment in South Africa has had an inconsistent and controversial history. Presently South Africa is home to the largest number of HIV positive people and has the biggest antiretroviral program in the world. (1)

Apartheid created social and economic inequality in South Africa. This in addition to employment-related migration resulted in an environment that allowed infectious diseases such as HIV to thrive. (1)

The first few deaths from HIV or Acquired Immunodeficiency Syndrome (AIDS) in South Africa were in the 1980s but the prevalence rose sharply after independence in 1994. During the administration of President Thabo Mbeki that lasted from 1999 until 2008, there was much-criticised "AIDS denialism" as well as a delayed response to the increasing epidemic. Civil society challenged the government's policies in the high court and in 2002 the Constitutional Court compelled the state to provide nevirapine (NVP) for the prevention of mother-to-child transmission. Further expansion resulted in Antiretroviral Therapy (ART) initiation beginning at selected facilities, including the one under study, in April 2004. In 2009 President Jacob Zuma and the Health Minister Dr Aaron Motsoaledi tackled the legacy of the previous administration and up-scaled the response significantly. An expanded guideline was developed in 2010 that included safer medications and lowered thresholds for treatment. Further national guidelines were published in 2013 and 2015.(2) In the 2014/2015 financial year 6.3 million people in South Africa were living with HIV and 3.1million people were on ART. (SA Department of Health Fact Sheet)

1.1.2. Defining older persons with HIV

In developed countries the age of 65+ years is considered elderly. However, in the context of persons infected with HIV, age above 50 years , is regarded as "older". (3) This is due to several reasons. This age group has been identified as having different immunological and virological responses when initiated on ART. (4) Previous surveillance studies prior to 2007 used age 49 years as an arbitrary cut off and the over 50 age category was subsequently added and this division has been retained. (5) The premature ageing of HIV positive adults seems to support this lowered age threshold. (6) Premature physical frailty has been shown to be increased in HIV infected South African adults compared to HIV uninfected adults. This frailty was associated with female gender, low body mass index (BMI), older age and more advanced WHO stage diseases. Frailty is usually associated with increased age. (7) The premature ageing in HIV infected adults supports the lowering of the age considered older to 50 years. The World Health Organisation (WHO) has proposed a lower threshold to define an older person in Africa of 50-55 years of age although this is not standardised. (8)

1.1.3. Prevalence of HIV in older adults in South Africa and the scale of the problem

An increasing number of older adults are being diagnosed and living with HIV infection worldwide. The phenomenon is particularly marked in high-income countries where about a third of adults living with HIV are over the age of 50 years. In low- and middle- income countries the proportion has been estimated to be in the region of 10% in a 2013 report by Unaids. (9)

Within sub-Saharan Africa the countries of South Africa, Zimbabwe, Mozambique, Zambia and Nigeria have the highest prevalence of older adults with HIV. (10)

The number and proportion of elderly persons in South Africa is increasing. The mid year population calculation from 2015 estimates that the number of South Africans aged over 50 years to be over 8 million making up about 15.8% of the population.(11) In 2010 the number was about 7,5 million making up 14.9% of the population. (11)

In South Africa the prevalence of HIV infection among older adults remains high. South African National estimates from 2012 show that the average prevalence in those over 50 years old is 7.6% (95% CI 6.5-8.8).(12) The prevalence of HIV in patients aged over 50 years is predicted to double in the next 30 years, whereas the prevalence in the 15-49 year old age group is expected to halve. (13)

The incidence of HIV infection in adults over the age of 50 years in a high risk rural KwaZulu-Natal community in South Africa was found to be 0.5 per 100 person years. (5) HIV prevalence in this cohort of older adults was 9.5% in the year 2008 - higher than the national average. Protective associations for not having HIV infection in this cohort included marriage, older age and residing far from transport routes. (5)

The possible reasons for increased HIV prevalence in the over 50-year old age group in South Africa include: increased rate of new infections with older people having the same risk factors as younger people do, increased case finding due to the increasing awareness of this dimension of the HIV epidemic, increased survival on ART and a "shift" of the disease towards older age groups as the incidence in the younger age groups is reduced. (12)(14)(15)

Heterosexual transmission is the predominant mode of the spread of HIV infection in South Africa and intergenerational sex/age-disparate relationships between older men and younger women in return for financial gifts is a unique problem facing men in this age group. (12)(14)(15)

In a poor rural community in Agincourt, Mpumalanga Province of South Africa reasons for the vulnerability of older adults to HIV infection included risky sexual practices namely men with multiple sexual partners, extramarital partners, low celibacy among men and low condom usage, as well as the environmental and historical context. They noted factors such as migration for work leading to infidelity followed by back migration and infecting their wives, older men receiving pensions and having sexual relationships with younger

women in return for financial reward and lower libido of older women resulting in men seeking younger partners. Findings such as these may help to direct preventative interventions.(16)

1.1.4. The challenge of diagnosing HIV in older persons

The diagnosis of HIV infection may be delayed in this age group for various reasons. Lack of education about HIV is a barrier to detection in older adults as they are less likely to voluntarily test for HIV. (17) HIV education in South Africa does not reach over a third of older adults (62.2% exposure) and only 18% of males over age 50 are aware of their HIV status. Only 27.9% of males over age 50 and 21.2% of females over age 50 have accurate knowledge about HIV transmission compared to about 30% of people younger than the age of 50. (15)

HIV prevention and testing is not targeted towards older people in South Africa and health care workers (HCWs) may not suspect or test for the illness in this population, leading to missed or delayed diagnosis. (18)

International data shows that risk factors for HIV infection in older adults are inadequately assessed by healthcare practitioners and that risk factor assessment is unreliable in deciding who should be screened. (3) Misdiagnosis can occur due to an overlap of HIV infection with symptoms attributed to normal ageing or common medical conditions that may be present in older persons. As there is a higher mortality associated with late presentation, early detection of HIV in this older age group is important. An international guideline by the American Academy of HIV Medicine (written in 2011 for clinicians managing older patients with HIV) recommended routine HIV screening as a cost-effective, low risk intervention in settings where prevalence is greater than 0.1%. (19)

1.1.5. Immune changes with ageing

The immune system of older adults differs when compared to that of younger adults. “Immunosenescence” is the term used for the complex immunological changes associated with human ageing. These changes affect all components of the immune system and the net effect is that immunity becomes less efficient and

dysfunctional. Major changes across the different immune system components include: reduced innate immunity, reduced efficiency of mucosal and skin barriers, thymic involution, a shift in T cell repertoire to a CD8+ dominance, reduced B cell diversity and reduced B cell functioning. These changes result in increased clinical susceptibility to infections and malignancies, increased autoimmunity, potential reactivation of diseases such as shingles and tuberculosis, a reduced response to immunization and may contribute to the development of age-related chronic inflammatory diseases such as dementia and atherosclerosis as well as age-related syndromes such as frailty. (20) HIV infection leads to immunological changes very similar to changes seen in immunosenescence. The result is that older HIV infected patients will have immune deficits from HIV infection that are additive to the weaker immunity seen with ageing alone. (21) Furthermore, the immune restoration with successful ART in older patients is thought to be incomplete or delayed. (22)

1.1.6. Other age-related physiological changes

Physiological changes in body composition and age-related renal and liver dysfunction may alter drug pharmacokinetics and pharmacodynamics. This, together with the frequent presence of co-morbidities as well as other medications can potentially cause drug-drug interactions that lead to abnormal metabolism and increased toxicity of ART. (23) (22)

Older HIV infected adults have higher rates of medical co-morbidities when compared to HIV uninfected adults of the same age. (6) A wide range of diseases usually associated with ageing are occurring at a younger age in HIV infected patients on ART. (24) Examples of these so-called “HIV associated non-AIDS” co-morbidities include liver disease, cardiovascular disease, kidney dysfunction, osteoporosis, cognitive impairment, and non-AIDS related cancers. Multiple mechanisms have been suggested for the premature ageing of HIV infected adults. These include chronic inflammation, microbial translocation, oxidative stress and immunosenescence. (19) This means that while life-expectancy among those on ART has increased dramatically and rates of AIDS-defining conditions are lower, health has not been fully restored. The increased incidence

of HIV associated non-AIDS co-morbidities has resulted in HIV in the ART era becoming a complex chronic disease.

1.1.7. Clinical outcomes in HIV infected older adults

A pre-ART era study done in Canada showed that untreated older patients are more likely to present for the first time with AIDS, to progress faster to developing AIDS and to have a higher mortality than a younger HIV positive control group. (25) Older age at seroconversion is associated with an increased risk of death. Despite this, older adults have shown the most pronounced reduction in risk of death with ART compared to younger age groups. (26)

Pre-ART Southern African studies confirm that older age at the time of infection lead to faster progression to death. (27)

When compared to their younger counterparts, HIV infected older adults progress faster to AIDS and have reduced survival without ART. Therefore a North American guideline recommended earlier ART initiation in older HIV infected adults (<500 cells/mm3). (19) Reductions in HIV associated non-AIDS co-morbidities seen with earlier ART initiation also supports this strategy. (28) In South Africa a "test and treat" strategy has been adopted since 2016 (after this study period) where ART is initiated irrespective of CD4+ count. (29)

Mortality rates in older adults with HIV in South Africa in a large multi-centre cohort study were significantly higher than age-specific mortality rates of the general population. (8)

1.1.8. Immunological and virological outcomes in HIV infected older adults

Challenges in HIV infected older adults that have been identified in other studies include: more rapid progression to AIDS, greater disease co-morbidity, more treatment side effects with consequently reduced adherence, slower immune restitution and reduced life expectancy. (10)

A large multicohort study done in Europe showed that older patients have better or similar virological responses and better adherence to ART but poorer immunological responses when compared to younger patients. This may be related to functional immune impairment due to ageing. (30) South African data has confirm this observation. Older age groups were as likely to achieve viral suppression, however CD4+ increases 6 months after initiation of ART were impaired. (31) However, a retrospective observational study done in the United States of America showed that similar immunological outcomes can be achieved but over a longer time frame, in this case a median of 3.8 years. (22)

A large multi-centre South African cohort analysing patients with HIV commencing ART showed a diminished CD4+ count recovery and an increased risk of death with older age. However the virological response rate remained good despite older age and older persons had a lower risk of being lost to follow-up. (18)

1.1.9. Treatment issues in HIV infected older adults

The treatment of HIV infected older adults can be complex. Older HIV infected adults have higher rates of co-morbidities when compared to HIV uninfected adults of the same age. (28) Patients may be taking multiple non-ART medications with an increased potential for adverse drug interactions. The frequency of HIV drug-related toxicity is increased in older adults and patients aged over 60 are more likely to need either a switch or discontinuation of treatment due to drug toxicity. (22)(30) HIV infected older adults are more sensitive to medication side effects. (19) A potential increase in adverse drug events with tenofovir (TDF) and increased drug interactions and metabolic side effects with ritonavir-boosted protease inhibitors have led to some guidelines recommending cautious use of these drugs. (19) However, as no formal trials have been done, no “best regimen” has been identified and the treatment of older adults should be individualised. (19)

Older HIV infected adults may justify more specialised care than their younger counterparts in view of potential co-morbidities, polypharmacy and drug interactions and poorer reported outcomes despite ART. (18)

Older adults have a lower risk of non-adherence and treatment has been found to be successful despite the increased co-morbid conditions, cognitive impairment and higher likelihood of multiple other medications. (32)

1.2. Protocol

1.2.1. Research Question

As the HIV infected population ages and the incidence of newly diagnosed older adults appears to be increasing, clinicians will be challenged by "clinically old" HIV infected patients with multiple co-morbidities and complex medication prescriptions. Guidelines drawn up based on information from younger patients with lower rates of co-morbidity may not be appropriate for an older population. HIV infected older adults in South Africa may have unique demographic, epidemiological and social characteristics. There is a lack of data about this group. Research from other countries can guide clinicians in South Africa, but local research is vital to understand the particular needs of this population. The purpose of this study is to describe the cohort of HIV-infected older patients at Themba Lethu Clinic following initiation of ART and 12 months later. Treatment outcomes at 12 month follow up and any associations will also be described. This information will hopefully provide useful clinical information in order to inform treatment decisions in this population.

1.2.2. Objectives

a) To describe the characteristics of a cohort of HIV infected patients aged over 50 years at the time when ART was initiated and then 12 months later. The characteristics will include demographic, clinical, virological, laboratory and regimen details.
b) To measure the frequency of favourable and unfavourable treatment outcomes.
c) To identify any associations of a favourable or unfavourable outcome at 12 months in the older cohort.
d) To identify any associations with treatment complications as the secondary outcome.
e) To compare the characteristics and outcomes to a cohort of HIV infected patients aged between 18 and 40 years at the time when ART was initiated.

1.2.3. Study design and subjects

This is a retrospective observational study: analyzing data collected from a cohort of ART-initiated HIV infected patients attending Themba Lethu Clinic (TLC). Two groups will be considered- patients aged over 50 years when ART was initiated and patients aged between 18 and 40 years when ART was initiated. Patients aged between 41 and 49 years are usually excluded from similar analyses, due to physiological similarites to patients aged over 50 which might confound the results of comparisons based on age. (33)

Inclusions in the cohort for study are HIV infected adults, who are ART naïve at initiation, eligible for initiation and on first line ART regimens according to standard public-sector guidelines. The 2004 SA guideline recommended starting patients on ART if their CD4+ count was below 200 cells/mm^3 or if they had an AIDS-defining (WHO IV) condition. The usual regimen was Stavudine+Lamivudine+Efavirenz. (34) In April 2010 the guideline changed to Tenofovir instead of Stavudine and pregnant women and TB patients were initiated at CD4+ counts of <350cells/mm^3. (35) As of September 2011 the Guideline allowed initiation of all patients with CD4+ <350 cells/mm^3 althought this falls outside the study period. See **table 1** for details of alternative regimens. Exclusions from the study cohort are patients aged 41-49, patients "transferred in" from another site, patients who are participants in a drug trial, and patients initiated on ART outside of the study period.

Regimen	2004 Guidelines	2010 Guidelines
First-Line	d4T+3TC+EFV/NVP	TDF+3TC/FTC+EFV/NVP
Alternative First-Line		AZT+3TC/FTC+EFV/NVP
Second-Line	AZT+ddI+LPVr	AZT/TDF+3TC+LPVr

Table 1. South African public sector guideline recommendations for ART regimens in 2004 and 2010.

3TC: lamivudine, FTC: emtricitabine, EFV efavirenz, LPVr: lopinavir-ritonavir, NVP: nevirapine, TDF: tenofovir, d4T: stavudine, AZT: zidovudine. FTC can be used in place of 3TC. Second-line regimen in 2010 uses TDF if first-line regimen was d4T or AZT and AZT if first-line regimen was TDF.

1.2.4. Site

TLC is a public-sector HIV treatment site in Johannesburg, South Africa. The clinic is within Helen Joseph Hospital, a tertiary level urban teaching hospital affiliated to the University of Witwatersrand. TLC was established in 2004 and is administered by the South African Department of Health as a Comprehensive Care, Management and Treatment site. Right to Care is a non-governmental organisation which assists TLC via funding from the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR). TLC has about 30 000 HIV infected patients enrolled of which about 21 000 had been initiated on ART by 1 October 2011. (36)

1.2.5. Study period

Patients initiated on ART between April 2004 until April 2011.

1.2.6. Database

Data is collected and stored on TherapyEdge-HIV™: a patient management system. The data collected includes demographic, laboratory, medication and clinical data as well as clinic visits and drug pickups. The system is linked with the South African death registry if the patient has a valid national ID number. TherapyEdge-HIV™ is an electronic records collections system. Prior to 2007 data was collected on paper and entered onto the system by data-capturers, subsequently clinicians enter data at the time of clinical encounter with the patient. (36) Data is exported into SAS statistical analysis software where it is cleaned and the variables of interest are coded.

1.2.7. Patient characteristics to be described

Demographic: age, gender, education level, ethnic group.

Baseline clinical: clinical stage at initiation (WHO/CDC), non-ART medication associated with increased likelihood of toxicity (appendix 1), common non-ART medications which interact with ART (appendix 2), polypharmacy (>5 drugs) at initiation, TB at initiation, opportunistic infections other than TB at initiation, other AIDS-defining conditions at inititation, body mass index at initiation and at 12 months follow-up.

Laboratory parameters at ART initiation and 12 months follow-up:HaemoglobinALT CD4 count and VL

ART : ART regimen (NVP based, EFV based, PI based, D4T as NRTI, TDF as NRTI, AZT as NRTI, ABC as NRTI), year initiated on ART, and months on treatment.

1.2.8. Outcomes

Favourable primary outcomes are defined as: alive, in care with viral load suppressed (undetectable at 12 months after ART initiation) and good CD4+ response (increase by >100 cellms/mm^3 at 12 months after ART initiation).

Unfavourable primary outcomes are defined as: dead, lost to follow up, failure to achieve suppressed viral load (detectable viral load at 12 months after ART initiation) and failure to achieve an adequate CD4+ response (<100 cells/mm^3 increase at 12 months after ART initiation). Patients who have been transferred out to another clinic will be included here as they can no longer be followed up on the database.

Secondary outcome treatment complications include: changeing from first line to second line therapy, suspending ART due to toxicity, a single drug switch, toxicity noted in the records, suboptimal adherence, missed appointment or drug collection, and low self-reported adherence.

1.2.9. Statistical methods

Groups will be compared using the Willcox rank sum test for continuous variables and the Chi-squared test for proportions. Associations will be assessed using log-binomial regression models for primary and secondary outcomes to establish relative risk and 95% confidence interval. Multivariate analysis will be performed to adjust for confounders.

1.2.10. Limitations

Assessing the incidence of non-AIDS co-morbidities will not be possible as they are not captured. As the TLC pharmacy is minimally stocked with drugs other than ART and patients with many co-morbidities requring treatment are referred to different clinics in the hospital it will not be posssible to assess all

potential non-ART medications and potential interactions. The hospital records system is not linked to TLC and it will not be feasible to look at admission rates.

1.2.11. Ethics

Although TLC has blanket ethical approval for analysis of data from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, ethical approval for this study will be requested from the ethical review committee. Patient information will be confidential and data will be de-identified.

1.2.12. Timing

January 2012	Planning
February 2012	Planning
March 2012	Protocol
April 2012	Protocol
May 2012	Protocol
June 2012	Submission of protocol
July 2012	Permission
August 2012	Data collection and analysis
September 2012	Data collection and analysis
October 2012	Write up results
November 2012	Write up results
December 2012	Presentation

1.2.13. Budget

No funding will be needed as this is a retrospective review. Minor administrative costs will be covered by the author.

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2. Submissable Article

2.1. Abstract

2.1.1. Introduction

The number of Human Immunodeficiency Virus (HIV) infected adults aged over 50 years in South Africa is increasing. This study explored differences between younger and older HIV infected adults at initiation of antiretroviral treatment (ART) with regard to their baseline characteristics and compared their outcomes after 12 months of ART. Associations with the 12 month outcomes within the older group were then sought.

2.1.2. Methods

A retrospective review of a large single site cohort of treatment-naïve HIV-positive adult patients at initiation of ART was conducted. Patients aged 18-39.9 years were compared to patients aged over 50 years. Baseline characteristics and 12 month outcomes in the two age groups were compared using log-binomial regression.The older group was analysed separately using multivariate regression to find associations with 12 month outcomes.

2.1.3. Results

The older cohort (n=1635) compared to the younger cohort (n=10726) had more males (47.2% vs 35.4%, prevalence ratio (PR) 1.52, p<0.05), smokers (12.9% vs 9.7%, PR 1.32, p <0.05) and overweight patients (26.0% vs 20.0%, PR 1.32, p <0.05) . Fewer older patients had secondary education (48.5% vs 84.5%, PR 0.24, p <0.05), tuberculosis (10.2% vs 15.3%, PR 0.67, p <0.05), other oppurtunistic infections (16.9% vs 23.3%, PR 0.70, p <0.05), World Health Organisation (WHO) stage III/IV disease (39.9% vs 43.2%, PR 0.89, p <0.05), haemoglobin <10g/dl (22.8% vs 28.4%, PR 0.77, p <0.05), alanine transaminase (ALT) >40U/l (17.1% vs 21.3%, PR 0.83, p< 0.05) and were in CD4+ count category <100cells/mm^3 (56.3% vs 59.9%, PR 0.71, p <0.05).

Mortality after 12 months of ART was higher in the older cohort (11.3% vs 7.5%, PR 1.48, p <0.05). Achievement of virological suppression at 12 months was higher in the older cohort (89.5% vs 86.5%, PR 1.28, p <0.05) but adequate response of CD4+ count (as defined as increase of >100cells/mm^3 at 12 months from baseline) was lower (62.8% vs 75.0%, PR 0.61, p <0.05). There was no difference in treatment complications between the groups.

Within the older cohort, associations with the 12 month outcome of death were: age >55years (PR 1.47, p<0.05), an AIDS-defininingcondition (PR 2.28, p <0.05), raised ALT (PR 1.53, p <0.05) and CD4+ <100cells/mm^3 (PR 2.15, p <0.05) at baseline. Associations with the outcome of favourable treatment response at 12 months were unemployment (PR 1.18, p <0.05) and raised ALT (PR 1.19, p <0.05). Associations with the outcome of presence of a treatment complication at 12 months were unemployment (PR 1.12, p <0.05), smoking (PR 1.20, p <0.05) and nevirapine use (PR 1.36, p <0.05) but secondary education was protective (PR 0.87, p <0.05).

2.1.4. Conclusions

HIV infected South African adults aged over 50 years differ in characteristics and outcomes compared to their younger counterparts and justify specialised management within HIV treatment facilities.

2.2. Introduction

South Africa is presently home to the largest number of Human Immunodeficiency Virus (HIV) infected people and the biggest antiretroviral program in the world. (1) In 2015 6.3 million people in South Africa were living with HIV and of those 3.1 million people were on antiretroviral treatment (ART). (SA Department of Health Fact Sheet) Persons infected with HIV and aged 50 years or more are considered "older". (2)(3)(4)(5) An increasing number of older adults are being diagnosed and living with HIV infection worldwide. In South Africa, the prevalence of HIV infection among older adults remains high Estimates from 2012 show that the average prevalence in those over 50 years old is 7.6% (95% CI 6.5-8.8). (6) In the next 30 years the prevalence of HIV infection in persons aged over 50 years is predicted to double in South Africa whereas the prevalence in the 15-49 year old age group is expected to halve. (7)

Possible reasons for rising HIV prevalence in the older age group in South Africa include: increased rate of new infections, improved case finding due to awareness of this dimension of the HIV epidemic, lengthened survival on ART and lastly, a "shift" of the disease towards older age groups as the incidence in the younger age groups is reduced. Heterosexual transmission is the predominant mode of spread in South Africa. (8)(6)(9)

Diagnosis of HIV infection may be delayed in the older age group. Lack of education about HIV is a barrier to detection in older adults as they are less likely to voluntarily test for HIV. (10) HIV education in South Africa does not reach over a third of older adults. (9) HIV prevention and testing is not targeted towards older people in South Africa and health care workers may not suspect or test for the illness in this population leading to missed or delayed diagnosis. (11)

"Immunosenescence" is the term used for the complex immunological changes associated with human ageing. These changes affect all components of the immune system and the net effect is that immunity becomes inefficient and dysfunctional. HIV infection leads to immunological changes very similar to

changes seen in normal ageing. Older HIV infected patients will have immune deficits from HIV infection that are additive to the weakened immunity of ageing.(12) Furthermore, immune restoration with ART in older patients is thought to be incomplete or delayed. (13)

Pre-ART international and Southern African studies confirm that older age at the time of HIV infection results in faster progression to death. (14)(15) Mortality rates in older adults with HIV on ART in South Africa in a large multicenter cohort study were significantly higher than age-specific mortality rates of the general population. (4)

A large multicohort study done in Europe showed that older patients have better or similar virological responses and better adherence to ART but poorer immunological responses compared to younger patients. (16) South African data confirm this observation. Older age groups were as (or more) likely to achieve viral suppression, but CD4+ increases after initiation of ART were impaired and mortality was increased.(17)(11)(4)

Treatment of HIV infected older adults can be complex. Older HIV infected adults have higher rates of co-morbidities when compared to HIV uninfected adults of the same age.(18) Patients may be taking multiple non-ART medications with the potential for adverse drug interactions. Physiological changes in body composition and age-related renal and liver dysfunction may alter drug pharmacokinetics and pharmacodynamics. This, and the frequent presence of co-morbidities and other medications potentially causing drug-drug interactions, can lead to abnormal handling and increased toxicity of ART. (19)(13) The frequency of HIV treatment drug-related toxicity is increased in older adults with patients aged over 60 being more likely to require either a switch or discontinuation of treatment due to drug toxicity.(13)(16) HIV infected older adults are more sensitive to medication side effects.(20)

This study's objectives were to compare the baseline demographic, clinical, laboratory and ART regimen variables and then the 12 month clinical, virological

and immunological outcomes as well as the prevalence of treatment complications in older versus younger HIV infected patients initiated onto ART. A further objective was to seek any associations with 12 month outcomes within the older cohort only.

2.3. Methods

2.3.1. Study design and setting

A single-centre retrospective cohort study of HIV-infected and ART-initiated patients attending Themba Lethu Clinic (TLC) in Johannesburg, South Africa was conducted. TLC is a public-sector HIV treatment site in Johannesburg, South Africa. The clinic is located within Helen Joseph Hospital, a tertiary level urban teaching hospital affiliated to the University of the Witwatersrand. TLC was established in 2004 and is administered by the South African Department of Health as a Comprehensive Care, Management and Treatment site. Right to Care is a non-governmental organisation which assists TLC via funding from the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR). TLC had about 30 000 HIV infected patients enrolled of which about 21 000 had been initiated on ART by 1 October 2011 since inception. (21)

2.3.2. Inclusion criteria, outcomes and definitions

Study subjects were included if they were HIV infected non-pregnant adults, ART naïve at initiation, eligible for initiation and on first-line ART regimens according to standard public-sector guidelines. The time frame included patients initiated on ART from 1 January 2004 until 10 October 2011. The study encompassed two treatment guideline periods. If treatment was initiated before 1 April 2010 then patients with CD4+ count of <200cells/mm^3 or World Health Organisation (WHO) stage IV status (irrespective of CD4+ count) were eligible for treatment under the 2004 guideline. If treatment was initiated from 1 April 2010 onwards then patients with CD4+ <200cells/mm^3 or CD4 <350cells/mm^3 diagnosed with Tuberculosis (TB) or WHO stage IV status (irrespective of CD4+ count) were

eligible for treatment under the 2010 guideline. The cohort was divided into two age groups namely patients aged 50+ years and patients aged between 18 and 39.9 years. Patients aged between 40 and 49.9 years were excluded due to physiological similarites that might confound the results of comparisons based on age. (22)

The following outcome measures after 12 months of ART were used:

1. Status at 12 months: Alive and in Care (AIC) vs Dead, Lost to Follow Up (LTFU) or Transferred out (TF out).
2. Treatment response at 12 months (within those that were AIC): A favourable outcome was defined as both viral load (VL) suppressed (<400copies/ml at 12 months) and CD4+ count increased by >100cells/mm^3 from baseline at 12 months versus an unfavourable outcome (one or both of those criteria not being met).
3. Treatment complication at 12 months (within those that were AIC): the presence of any treatment complication at 12 months (indicated by the following surrogate measures: regimen change, single drug switch, drug toxicity variable noted, VL at 6m > 400copies/ml, missed medical appointment, missed drug pickup or low self-reported adherence) versus the absence of of any treatment complication.

LTFU was defined as 3 months late for a scheduled appointment without a later visit. Clinic counsellors attempted to trace patients who were LTFU and some deaths were identified this way. Deaths were further ascertained within the LTFU group by cross checking with the South African Vital Registration records using the patient's South African national identity (ID) number if known. (23)(24) Patients were seen monthly for the first 6 months after initiation then every 2nd month unless there was a clinical reason for more frequent visits. Laboratory monitoring of CD4+ count and VL is done every 6 months. (23)

Treatment non-naïvety at initiation was defined if a variable indicative of treatment naïve status was negative, if baseline VL was suppressed suggestive of prior treatment or in patients not meeting standard criteria for initiation

according to the South African National Department of Health Guidelines of that time.

Polypharmacy was defined as >5 non-ART medications. Non-ART drugs associated with toxicity or a drug interaction are listed in the appendices. (20)

2.3.3. Data collection and statistical analysis

Data was collected and stored on TherapyEdge-HIV™ (*version 3.2 for Windows*, Topsfield, MA, USA: Therapy Edge Inc. ABL S.A. 2005): a patient management system. The data collected included demographic, laboratory, medication and clinical data as well as clinic visits and drug pickups. The system is linked with the South African death registry if the patient has a valid national ID number. TherapyEdge-HIV™ is an electronic records collections system. Prior to 2007 data was collected on paper and entered onto the system by data-capturers, subsequently clinicians entered data at the time of clinical encounter with the patient. (21) Data was exported into SAS Software (*version 9.3 for Windows,* Cary, NC, USA: SAS Institute Inc. 2002-2010) where it was cleaned and the variables of interest were coded.

The first part of this study was a comparison of the older cohort to the younger cohort. Comparisons of the demographic, clinical and laboratory variables as well as ART regimens and non-ART medications at the time of initiation (baseline) variables were done using log-binomial regression. Continuous variables were categorised into clinically meaningful categories.

The second part of the study was to compare the prevalence of the following outcomes after 12 months of ART in the different patient groups: status, treatment response and treatment complication presence.
The older and younger groups were compared for each of the outcomes, using log-binomial regression.

The third part of the study measured the associations between demographic, clinical and laboratory characteristics as well as ART regimens and non-ART

medications at baseline and outcome variables within the older cohort only. For each of the outcomes, the groups were initially compared with each of the independent variables, using log-binomial regression. Subsequently a multivariate analysis was done adjusting for known confounders identified from existing data: gender, baseline haemoglobin (Hb), baseline body mass index (BMI). (17) Before commencing multivariate analysis, bivariate correlation analysis was conducted among the independent variables to explore potential confounding relationships that should be accounted for in the multivariate analysis. Phi coefficients were determined between two dichotomous variables and Cramer's V between two categorical variables. There were no strongly confounded variables (phi coefficient or Cramer's V > 0.50).

Data analysis was carried out in SAS Software (*version 9.4 for Windows,* Cary, NC, USA: SAS Institute Inc. 2002-2010). The 5% significance level was used.

2.4. Results

2.4.1. Patient selection

The master data set was created on the 10th of October 2012. There were 21 536 records within the data time frame range and with age and initiation date variables available. A further 9175 records were excluded as outside the age ranges 18-39.9y and 50y+, pregnant, not treatment naïve or not on standard first-line treatment regimens at initiation, leaving 12361 records for analysis.

2.4.2. Baseline characteristics

An overview of the baseline demographic, clinical, laboratory and regimen characteristics is provided in Table 1. The median age of the younger cohort was 32.8 years (IQR 29.0-36.1) and of the older cohort was 54.1 years (IQR 51.8-57.6). Both populations were predominantly female but the older population had a higher proportion of males than the younger population (47.2% vs 35.4%, p <0.05). Fewer in the older population had a background of secondary education (48.5% vs 84.5%, p <0.05).The percentage of those unemployed at the time of initiation was the same. Self-reported alcohol usage was similar in both

groups.The older population reported more smoking (12.9% vs 9.7%, p <0.05). A smaller proportion of the older cohort had TB (10.2% vs 15.3%, p <0.05) or other opportunistic infections (OI) (16.9% vs 23.3%, p <0.05) at initiation of ART. The proportion of those with other AIDS-defining conditions (ADC) was similar between the two age groups. Fewer older patients were classified as WHO stage III or IV at initiation compared to the younger patients (39.9% vs 43.2%, p <0.05). A similar proportion were underweight (BMI <18.5) but a larger proportion of the older cohort were in the overweight category (having a BMI >25.0kg/m^2) (26.0% vs 20.0%, p <0.05). Fewer older patients were anaemic with Hb <10g/dl (22.8% vs 28.4%, p <0.05) and fewer had raised alanine transaminase (ALT) >40U/l as a marker of liver disease (17.1% vs 21.3%, p <0.05) when compared to the younger group. A smaller proportion of the older cohort had a low baseline CD4+ category of <100cells/mm^3 (56.3% vs 59.9%, p <0.05). Fewer older patients were initiated on nevirapine (NVP) (3.7% vs 12.1%, p <0.05) as the non-nucleotide reverse transcription inhibitor (NNRTI) component compared to efavirenz (EFV). A larger number were initiated on either zidovudine (AZT) (5% vs 3.7%, p <0.05) or tenofovir (TDF) (22.1% vs 19.6%, p <0.05) as the nucleoside reverse transcriptase inhibitor (NRTI) alternatives to stavudine (d4T). The proportion of patients initiated after April 2010 when the treatment guideline changed was higher in the older cohort (27.2% vs 20.4%, p <0.05). The number of patients in the older cohort taking non-ART drugs associated with toxicity approached statistical significance (11.7% vs 10.2%, p 0.06). A lower proportion of the older cohort were taking non-ART drugs associated with a drug interaction (19.6% vs 22.6%, p<0.05). The proportions of polypharmacy were similar.

Table 1. Baseline demographic, clinical, laboratory and regimen characteristics at the time of ART initiation.

Variable	18-39.9 years n (%) **n=10726**	Over 50 years n (%) **n=1635**	Prevalence Ratio (95% Confidence Interval)	p-value
Age Median (IQR)	32.8 (29.0-36.1)	54.1 (51.8-57.6)		
Male gender	3801 (35.4)	771 (47.2)	1.52 (1.39-1.66)	<0.05
Education level secondary or higher	6749 (84.5)	602 (48.5)	0.24 (0.22-0.27)	<0.05
Missing	2739	393		
Unemployed	5878 (54.8)	860 (52.6)	0.93 (0.85-1.01)	0.10
Alcohol user	1113 (11.5)	152 (10.3)	0.89 (0.76-1.05)	0.17
Missing	1070	156		
Smoker	936 (9.7)	191 (12.9)	1.32 (1.15-1.15)	<0.05
Missing	1082	157		
Tuberculosis at initiation	1633 (15.3)	167 (10.2)	0.67 (0.57-0.78)	<0.05
Missing	20	0		
Other opportunistic infection at initiation	2502 (23.3)	276 (16.9)	0.70 (0.62-0.79)	<0.05
Other AIDS defining condition at initiation	162 (1.5)	29 (1.8)	1.15 (0.82-1.61)	0.42
WHO Stage III/IV	4635 (43.2)	652 (39.9)	0.89 (0.81-0.97)	<0.05
Body Mass Index (BMI) <18.5	1864 (22.4)	272 (20.4)	0.98 (0.86-1.12)	0.78
BMI 18.5-24.9	4797 (57.6)	715 (53.6)		
BMI >25.0	1669 (20.0)	347 (26.0)	1.32 (1.18-1.49)	<0.05
Missing	2396	301		
Haemoglobin <=10.0 g/dL	2528 (28.4)	321 (22.8)	0.77 (0.69-0.87)	<0.05
Missing	1812	230		
Alanine Transaminase >40 U/L	1796 (21.3)	237 (17.1)	0.83 (0.73-0.95)	<0.05
Missing	1859	249		
Baseline CD4+ 0-100 cells/m^3	5590 (59.9)	827 (56.3)	0.71 (0.54-0.93)	<0.05
Missing	1389	165		
Regimen contains nevirapine (vs efavirenz)	1294 (12.1)	60 (3.7)	0.31 (0.24-0.40)	<0.05
Regimen contains zidovudine (vs stavudine)	395 (3.7)	82 (5.0)	1.36 (1.11-1.66)	<0.05
Regimen contains tenofovir (vs stavudine)	2106 (19.6)	361 (22.1)	1.16 (1.04-1.29)	<0.05
Guideline period after 1 April 2010 (vs before April 2010)*	2184 (20.4)	444 (27.2)	1.38 (1.25-1.53)	<0.05
Non-ART drugs associated with toxicity**	1097 (10.2)	192 (11.7)	1.14 (0.99-1.31)	0.06
Non-ART drugs associated with drug interaction**	2422 (22.6)	320 (19.6)	0.85 (0.76-0.96)	<0.05
Polypharmacy (>5 non-ART medications) noted**	6232 (58.1)	962 (58.8)	1.03 (0.94-1.13)	0.57

* The South African National Department of Health ART guidelines changed on this date from 1st line stavudine-containing regimens to first line tenofovir-containing regimens.

** These drugs are listed in the Appendix.

2.4.3. Outcomes after 12 months of ART

An overview of the treatment outcomes after 12 months of ART is provided in Table 2. A higher proportion of the older patients were dead (11.3% vs 7.5%, p <0.05) compared to the younger patients. There was no difference in LTFU. A higher proportion in the older group were transferred out (6.2% vs 4.3%, p <0.05). In the older group proportionally fewer had a favourable response to treatment (54.1% vs 63.8%, p <0.05). This was due to less having adequate CD4+ restoration (62.8% vs 75.0%, p <0.05); however more older patients had a suppressed VL (89.5% vs 86.5%, p <0.05). The proportion of those with a treatment complication was similar in both age groups (54.6% vs 53.9%, p 0.66).

Table 2. The outcomes after 12 months of ART

	Category	18-39.9 years	Over 50 years	Prevalence Ratio (95% Confidence interval)	p-value
Baseline: n		**10726**	**1635**		
Status	Alive	8265 (77.1)	1189 (72.7)		
	Dead	807 (7.5)	185 (11.3)	1.48 (1.29-1.71)	<0.05
	Lost to follow-up	1193 (11.1)	160 (9.8)	0.94 (0.81-1.10)	0.43
	Transferred out	461 (4.3)	101 (6.2)	1.43 (1.19-1.72)	<0.05
Alive: n		**8265**	**1189**		
Treatment response	CD4+ Δ >100cells/m^3	4746 (75.0)	587 (62.8)	0.61 (0.54-0.69)	<0.05
	Missing	1935	255		
	VL suppressed	5685 (86.5)	869 (89.5)	1.28 (1.05-1.56)	<0.05
	Missing	1695	218		
	Unfavourable: VL>=400 and/or change_CD4 <=100	2183 (36.2)	412 (45.8)		
	Favourable: VL<400 and ch_CD4>100	3840 (63.8)	486 (54.1)	0.71 (0.63-.080)	<0.05
	Missing	2242	291		
Treatment complication*	Absent	3810 (46.1)	540 (45.4)		
	Present	4455 (53.9)	649 (54.6)	1.02 (0.92-1.04)	0.66

* Surrogate variables for treatment complications were regimen change, single drug switch, drug toxicity noted, VL at 6m unsuppressed, missed medical appointment, missed drug pickup and low self reported adherence

2.4.4. Multivariate analysis of associations with 12 month outcomes

An overview of the associations with 12 month outcomes in the older cohort is provided in Table 3. Baseline variables associated with an increased risk of death that persisted after multivariate analysis were age category of older than 55 years compared to age of 50 to 55 years (PR 1.47, p <0.05), the presence of another AIDS defining condition (not an OI or TB) at initiation (PR 2.28, p <0.05), baseline ALT >40 (PR 1.53, p <0.05) and baseline CD4+ <100 cells/mm^3 (PR 2.15, p <0.05). Initiation with a NVP-containing regimen approached significance (PR 2.04, p 0.06) but the numbers on NVP were small. Factors associated with a favourable response to treatment that persisted after adjusted regression analysis were: being unemployed (PR 1.18, p <0.05) and baseline ALT >40U/l, (PR 1.19, p<0.05). Age older than 55 years approached statistical significance as being negatively associated with a favourable response to treatment (PR 0.87, p 0.06). Associations with the presence of a treatment complication after multivariate analysis included: being unemployed (PR 1.12, p <0.05), smoking at initiation (PR 1.20, p <0.05) and taking a NVP containing regimen (PR 1.36, p<0.05). An education level of secondary school or higher (PR 0.87, p<0.05) appeared to be protective.

Table 3. Adjusted* multivariate regression done on the group older than 50 years showing associations with 12-month outcomes.

	Dead		Favourable treatment response		Presence of treatment complication	
Variable	Prevalence Ratio (95% Confidence Interval)	p-value	Prevalence Ratio (95% Confidence Interval)	p-value	Prevalence Ratio (95% Confidence Interval)	p-value
Age at initiation >55 years	1.47 (1.08-2.00)	<0.05	0.87 (0.76-1.00)	0.06	0.95 (0.85-1.06)	0.39
Education level secondary or higher	0.91 (0.62-1.35)	0.65	1.09 (0.94-1.27)	0.23	0.87 (0.76-0.99)	<0.05
Unemployed	1.19 (0.87-1.65)	0.27	1.18 (1.03-1.33)	<0.05	1.12 (1.01-1.26)	<0.05
Alcohol user	1.08 (0.64-1.84)	0.77	1.16 (0.95-1.42)	0.15	1.12 (0.94-1.32)	0.22
Smoker	0.77 (0.45-1.36)	0.38	0.96 (0.77-1.21)	0.74	1.20 (1.03-1.40)	<0.05
First regimen contains nevirapine	2.04 (0.97-4.31)	0.06	1.26 (0.84-1.89)	0.26	1.36 (1.07-1.72)	<0.05
First regimen contains zidovudine	0.92 (0.37-2.31)	0.86	0.71 (0.43-1.19)	0.20	0.95 (0.67-1.34)	0.76
First regimen contains tenofovir	0.68 (0.42-1.09)	0.11	1.09 (0.93-1.27)	0.30	0.91 (0.79-1.06)	0.23
Guideline period after April 2010	0.72 (0.47-1.11)	0.14	1.06 (0.91-1.24)	0.44	1.00 (0.88-1.14)	0.96
Non-ART drug associated with toxicity	0.96 (0.63-1.48)	0.86	0.96 (0.80-1.15)	0.67	0.96 (0.82-1.13)	0.64
Non-ART drug associated with drug interaction	0.94 (0.64-1.37)	0.73	0.95 (0.81-1.11)	0.52	0.95 (0.82-1.09)	0.46
Polypharmacy noted	1.26 (0.88-1.80)	0.21	1.04 (0.90-1.19)	0.62	1.00 (0.89-1.13)	0.96
Tuberculosis at initiation	0.71 (0.41-1.23)	0.22	0.92 (0.73-1.16)	0.49	0.95 (0.78-1.15)	0.59
Other opportunistic infection at initiation	0.80 (0.52-1.22)	0.30	1.05 (0.88-1.25)	0.60	1.00 (0.85-1.17)	0.97
Other AIDS defining conditon at initiation	2.28 (1.30-4.01)	<0.05	0.69 (0.33-1.40)	0.30	0.94 (0.61-1.47)	0.80
Baseline ALT >40 U/l	1.53 (1.06-2.22)	<0.05	1.19 (1.02-1.40)	<0.05	0.98 (0.83-1.14)	0.76
Baseline CD4+ 0-100 cells/m^3	2.15 (1.48-3.13)	<0.05	1.08 (0.67-0.73)	0.75	0.85 (0.63-1.16)	0.32

* Adjusted for gender, baseline haemoglobin, baseline clinical stage of HIV infection as per the World Health Organization staging system, and baseline body mass index.

2.5. Discussion

In this study we found that South African older adults initiated onto ART were a demographically and clinically distinct population with different outcomes when compared to younger adults. They should be considered as a separate group within HIV treatment facilities for more specialised care as well as integrated chronic disease management.

The higher proportion of males in our study has been shown in other South African cohorts and mirrors prevalance data. (25) (6) Reasons for this were previously explored in a rural setting in Mpumalanga Province. These men were found to have riskier sexual practices such as multiple sexual partners,

extramarital partners, low celibacy rates and low condom usage. There is a historical contextual component including factors such as migration for work leading to opportunities for infidelity, this was followed by back migration in later life and men then infecting their wives. Older men received pensions and may have had sexual relationships with younger women in return for financial reward (colloquially called "Blessers"). Older women reported lower libido and this resulted in men seeking younger partners. Findings such as these may help to direct preventative interventions.(26) Men who have sex with men (MSM) could be contributing to the increased numbers; however heterosexual spread still predominates in the South African setting. (9)

The lower education levels of the older group relates to the historical legacy of apartheid that resulted in the segregation of races under the Bantu Education Act of 1953. The curriculum for non-white people was of a lower standard, teachers were poorly paid and unqualified, resources were comparatively limited and education was not free. This lasted from 1954 until 1980.

The increased proportion of smokers is important to note as smoking has multiple health implications in HIV positive people including increased vascular and respiratory illnesses and higher associated mortality. In our study, smoking was associated with the presence of a treatment complication. (27) Assistance with smoking cessation could be an important part of health promotion in this age group; however the prevalence of smoking in our cohort was still lower than the national average. (28)

The older group had a lower prevalence of TB, OIs and advanced WHO stage disease at baseline. There was a lower proportion in the CD4+ count 0-100cells/mm^3 category. They had a higher proportion in the BMI category >25kg/m^2. This seems to indicate better health status at initiation and is contrary to resource rich settings where studies show that older HIV infected adults presented with more advanced disease. (15) Outcomes in terms of mortality and immunological response to treatment were worse in older patients than their younger counterparts. This has also been shown in other South

African studies. A large South African multi-centre study of the Kheth'Impilo cohort conducted across both urban and rural areas showed that a lower proportion of older patients (in this study >55 years) had CD4+ counts of <50cells/mm^3, WHO stage IV disease and TB treatment at baseline. They also showed that viral suppression was greater in older patients compared to younger patients and that the CD4+ response was slower and lower in the older cohort with increased mortality in the older cohort. (4) Although, despite better baseline health markers and better virological suppression, older age results in poorer treatment outcomes. This phenomenon may only be in the short term - an effect not looked at in our study. In the Hlabisa HIV Treatment and Care Programme in Kwazulu Natal older age was significantly linked to higher early mortality (particularly in the first 3 months of treatment) in the face of higher initiation CD4+ counts. However after 12 months of treatment this difference was no longer noted regardless of CD4+ response. They also found better virological response to ART but poorer immunological responses compared to younger adults. (15) The authors of that study proposed that the leveling out of mortality after 12 months may represent survivor bias, better virological response to ART and improved access to health care for other chronic illnesses. (15)

The increased number of older patients initiated after 2010 compared to before reflects the trend of increased older persons with being diagnosed with HIV. (6)

HIV-associated non-AIDS comorbidities such as liver disease, cardiovascular disease, kidney dysfunction, osteoporosis, cognitive impairment, frailty and non-AIDS cancers are common in older HIV infected adults. Although HIV is known to exacerbate chronic illnesses and chronic inflammation, in a rural South African community, access to general chronic illness screening for HIV positive patients attending clinics established for HIV treatment may have actually reduced morbidity due to regular contact with health care services that they would otherwise not have. (29). Ideally older HIV infected adults should be screened for other age-related chronic illnesses as part of holistic HIV care. Services should be

integrated to avoid the need to attend several separate clinics for treatment of other chronic illnesses.

In our study a higher proportion in the older cohort were taking drugs associated with a drug toxicity and there were similarly high rates of polypharmacy across the two groups. Despite this, treatment complications were not increased. This contradicts international data but correlates with other South African studies. (13) Loss to follow up was lower and viral rebound and a regimen switch were less likely in older patients in a South African multi cohort public sector study. (4) This suggests that despite increased likelihood of co-morbid conditions, cognitive impairment and multiple other medications, older South African patients are compliant with and tolerate standard ART regimens with a lower risk of non-adherence and treatment is successful.

The reasons for the higher number of older patients transferred out of care compared to younger patients were not clear from our study. We speculate that transfer was requested in order to be closer to employment or their home. Some of the older group may have been retired and living in the rural areas. Some may have been transferred out as they were clinically stable. Some may have had reduced mobility or ability to access public transport.

LTFU rates were no different between the two groups and TLC has active tracing methods for patients that are LTFU and also the ability to check against South African vital registries in order to avoid underestimating mortality, a technique not used in other similar studies. This improved the accuracy of the outcome status of dead. (24) (4)

Within the older cohort, age 55+ years was associated with death. Unsurprisingly very low CD4+ count at initiation as well as the presence of an AIDS defining condition was associated with increased risk of death. Baseline elevation of ALT was also associated with death and liver disease has a poor prognosis in HIV-infected patients. (30) The almost significant association of the drug NVP with death should be interpreted cautiously as the numbers on NVP were extremely small. In the absence of child-bearing potential, NVP was generally used for

persons with cognitive or psychiatric illness or night shift workers. This may have caused a selection bias. In a similar study NVP was associated with increased likelihood of a regimen switch. (4) Unfortunately renal dysfunction was not analysable due to a large amount of missing data. This would have been relevant in view of the use of TDF and a high proportion of baseline renal dysfunction among older HIV infected adults in other studies like the Hlabisa cohort. (15)

Unemployment was associated with a favourable response to treatment and this seems surprising. The majority of the older group were under 60 years which is below the age of eligibility for old age pensions, however they may have had access to disability pensions and unemployment is a prerequisite to qualify for these benefits. The association of increased ALT levels with a favourable response to treatment is also counter-intuitive (increased baseline ALT was also associated with a higher risk of death) but is perhaps explained by more frequent clinical monitoring and favouring or avoiding certain medication regimens in the presence of liver dysfunction (e.g NVP avoidance in liver disease). Age of 55+ years showed a negative association with a favourable treatment outcome in keeping with previous research. (4)

Higher education levels were protective against treatment complications. This may have been due to improved understanding of the treatment and better access to healthcare. The presence of a treatment complication was associated with unemployment and smoking. Unemployment could represent a lower functional status. Smoking has previously been shown to affect ART efficacy adversely. (27) NVP-use was also associated with a treatment complication. This association has been described in other studies and warrants further examination. (4)(27)

Our study has several limitations including large amounts of missing data, in particular non-ART medication as well as laboratory data. Non-ART drugs and co-morbidities may not have been accurately captured due to operational issues as the HIV clinic and ART pharmacy does not record or supply many of the

medications for other chronic medical conditions and these are prescribed and dispensed through a separate system. Unfortunately, due to the large amount missing and concern regarding selection bias, renal function in terms of glomerular filtration rate data was non-interpretable. This would have been highly relevant in the context of older adults taking TDF. We did not have access to a functional score, pertinent in older patients in view of the heterogeneity of health. Although this is a large study undertaken in a real life setting, it only encompasses one centre and its findings may not be applicable to those that are not urban-dwelling South Africans. The time frame of 12 months is a further limitation as the CD4+ restitution may have been further improved over a longer time period. We did not analyse early (3 months) and later outcomes as has previously been done and this may have given additional information. (15)

2.6. Conclusion

It is important to consider the unique characteristics of the increasing numbers of HIV positive older adults in South Africa. Educational and health campaigns should be directed to older persons specifically. Clinicians need to maintain a high index of suspicion and test for HIV in this age group. Sexual risk campaigns around HIV prevention should be tailored to this older age group, particularly men. Presenting to health care for HIV treatment should be used as an opportunity to screen and treat for smoking, obesity and other non-communicable diseases within integrated health services. ART initiation in the older person should be expedited in view of higher mortality despite a clinically well patient and slower immune restitution and the move towards 'test and treat' in South Africa is likely to benefit this older group provided the diagnosis is made early. The use of NVP in older patients might require caution and further study. Closer monitoring of treatment is advised. An awareness of polypharmacy and non-ART medications associated with toxicity or drug interactions is important to reduce potential adverse effects. Consideration should be given to eligibility criteria for social/disability grants for those that are unemployed and not old enough to qualify for a pension.

Compliance and VL suppression is as good in the older age group but CD4+ response is slower or attenuated. Older adults have different characteristics and needs. Special guidelines should be considered.

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3. Appendices

3.1. List of medications used in the TLC cohort that are associated with an increased risk of adverse side effects in HIV infected adults (19)

Drug Class	Type	Examples
Anticholinergic	Antihistamines	chlorpheniramine maleate, loratadine, promethazine
	Muscle relaxants	baclofen, orphenadrine
	Anti-parkinsons	biperidin
	Antiemetics	prochlorperazine
	Antispasmodics	hyoscine methylnitrate, hyoscine-n-butyl bromide
	Antidepressants	amitriptyline, amitriptyline HCL, imipramine, paroxetine,
	Antipsychotics	chlorpromazine HCL, fluphenazine HCL
	Antimuscarinics	
Sedative	Benzodiazepines	alprazolam, chlordiazepoxide, clonazepam, diazepam, oxazepam,
	Other sedatives	phenobarbital, zolpidem tartrate
Baroreceptor	Alpha-blocker	doxazosin mesylate
	Beta-blocker	atenolol, propranolol HCL,
Analgesics	Opioids	pethidine HCL, hydrocodone bitartrate, morphine sulphate, oxycodone HCL

3.2. List of medications used in the TLC cohort that commonly interact with ART (19)

Drug class	Antiretroviral	Examples
Anti TB	PI/NNRTI	rifampicin
Antibiotic	PI/NNRTI	clarithromycin
Statin	PI/NNRTI	simvastatin, atorvastatin, pravastatin
Antiepileptic drugs	PI/NNRTI	phenytoin, phenobarbital, carbamazepine, lamotrigine, valproic acid
Antihypertensive	PI/NNRTI	nifedipine, amlodipine, diltiazem, felodopine
Corticosteroid	PI/NNRTI	Dexamethasone
Benzodiazepines	PI/NNRTI	midazolam, alprazolam, diazepam
Respiratory	PI	salmeterol, sildenafil, fluticasone
Migraine	PI/NNRTI	ergotamine tartrate
Antidepressant	PI	Amitriptyline
Miscellaneous	NNRTI	warfarin, atovaquone
Miscellaneous	PI	colchicine, atovaquone,

PI- Protease Inhibitor
NNRTI- Non-Nucleoside Reverse Transcriptase Inhibitor

3.3. Letter of ethics approval from Wits

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr India Butler

CLEARANCE CERTIFICATE	**M121004**
PROJECT	HIV Infection and Older Adults
INVESTIGATORS	Dr India Butler.
DEPARTMENT	Internal Medicine/Div of Geriatric Medicine
DATE CONSIDERED	26/10/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 26/10/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Brent Tipping

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...