COMPARISON OF RETENTION IN CARE RATES AMONG HIV-INFECTED OLDER PERSONS AND YOUNG ADULTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY AT A TERTIARY HOSPITAL IN HARARE, ZIMBABWE.

BY

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Thesis submitted in partial fulfilment of the Degree of

Masters in Medicine (Medicine)

University of Zimbabwe

DEPARTMENT OF MEDICINE

COLLEGE OF HEALTH SCIENCES

JUNE 2014
ABSTRACT

Objective: To evaluate differences in retention in care rates between older individuals and young adults initiated on HAART and to determine the baseline characteristics that are associated with retention in care.

Design: Retrospective cohort study using routinely collected clinic data

Setting: A public sector HIV adult facility at the Parirenyatwa Hospital Family Care Centre, Harare, Zimbabwe.

Participants: 444 HIV infected elderly patients (age 50 years and above) and young adults (age 25 to <50 years) who initiated HAART between 1 January 2009 and 31 December 2011.

Main outcome measures: Primary outcome: Retention rate among older individuals (≥50 years) compared to younger individuals(25-49 years).

Secondary outcomes: Factors associated with attrition.

Methods: Analysis of patient records was done. Survival analyses were performed using Kaplan-Meier method. Univariate analyses were done to determine factors associated with retention in care.

Results: Older individuals had a significantly lower retention in care rate than young adults(67.0% versus 81.8%) after 24 months on HAART in the final survival analysis(p<0.0001). Baseline CD4+ T-cell counts were significantly lower in the older age group(p=0.042) who also presented with more advanced WHO clinical stages 3 and 4(p<0.0001). Time from HIV diagnosis to HAART initiation was significantly shorter in older persons compared to younger individuals(31days versus 47.5days). In the older age group, baseline characteristics associated with attrition were WHO clinical stage 3and 4 OR 3.11 p=0.048[95%CI:1.96-4.05, CD4+ T-cell counts≤100cells/mm³ OR 2.27 p=0.041 [95% Cl: 1.82-3.22 ]and presence of at least one co-morbidity OR 2.07 p=0.028 [CI:1.71-6.02].

Conclusion: Retention in care was lower in older persons as compared to younger individuals. Older patients need to be tested for HIV and commenced on HAART early in order to maintain their continuity in care and prevent death.
DEDICATION

In loving memory of my late mother

Getrude Makanza

1962-2012
ACKNOWLEDGEMENTS

I express my sincere gratitude to the following individuals for their support towards the completion of this dissertation:

1. Dr Makadzange who was my supervisor.

2. The Department of medicine for their critique of the Project protocol and their advice at every stage of the research.

3. Fellow MMed Students for their constructive comments.

4. Prof Borok, Dr Ndhlouvu and Dr Ngwende for their much appreciated support in my time of loss.

5. The Parirenyatwa Hospital Clinical Director Mr S.Makarawo and the Family Care Centre Matron Nyandoro for granting the permission for me to conduct this research at the clinic.

6. Special thanks to my parents and siblings, for believing in me and my husband for his support and patience until the completion of this dissertation.

7. Above all, a very big thank you to God for the gift of life.
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>CDC</td>
<td>Centres for Disease Control and Prevention</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>IDU</td>
<td>Injection Drug Use</td>
</tr>
<tr>
<td>Log</td>
<td>Logarithm</td>
</tr>
<tr>
<td>LTFU</td>
<td>Loss to follow up</td>
</tr>
<tr>
<td>MSM</td>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>P</td>
<td>Probability</td>
</tr>
<tr>
<td>PGH</td>
<td>Parirenyatwa Group of Hospitals</td>
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<tr>
<td>PHFCC</td>
<td>Parirenyatwa Hospital Family Care Centre</td>
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PPD - Purified protein derivative

PPTCT - Prevention of Parent to Child Transmission

RNA - Ribonucleic Acid

SD - Standard Deviation

STI - Sexually Transmitted Infection

TB - Tuberculosis

WHO - World Health Organisation
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1. INTRODUCTION

1.1 Background

1.1.1 Epidemiology of adult HIV/AIDS

There are over 35.3 million people living with HIV infection worldwide (1). This global pandemic has been associated with high mortality rates. Since AIDS was first known in 1981, it has resulted in approximately 30 million deaths until 2009. Recent advances in both HIV treatment and prevention have resulted in significant improvement in mortality rates. AIDS related deaths have fallen worldwide by 30% since the peak in 2005.

Sub-Saharan Africa is disproportionately affected by the epidemic. Sub-Saharan Africa hosts 12% of the world’s population, and yet accounts for 70% of the global population of people living with HIV/AIDS, an estimated 23.5 million infected people. This was an increase in the prevalence from an estimated 22.5 million in 2009. The increase in the prevalence may be related to a decrease in AIDS related deaths in the region. There were 1.8 million deaths in 2005 and 1.2 million deaths in 2011. The adult prevalence rates of HIV infection are particularly high in Southern African countries, exceeding 20%, and 30% in Botswana and Swaziland respectively. The Zimbabwe Demographic Health Survey (ZDHS) reported a high adult HIV prevalence of 14.3% in 2010.
1.1.2 The role of Highly Active Antiretroviral Therapy (HAART)

Increasing access to HAART has resulted in major changes in mortality and life expectancy among individuals with HIV infection. The primary goal of HAART is to decrease HIV-related mortality and morbidity but it is now known to dramatically reduce transmission as well. Since its introduction in 1996, HAART has revolutionised the management of HIV disease by suppressing virologic replication and thereby improving survival of persons living with HIV/AIDS worldwide(2). However, in the early years of HAART, the majority of individuals in the developing world who required treatment for HIV infection were unable to access HAART because of its prohibitively high cost.

The introduction of free antiretroviral therapy roll out programs by governments and programs such as the Global Fund to Fight AIDS, TB and Malaria and World Health Organisation’s(WHO) “3 by 5” initiative, has led to dramatic improvements to access to HAART in the developing world. World coverage of HAART increased from 7% in 2003 to 42% in 2008.

In Zimbabwe, the National Antiretroviral Therapy (ART) program was initiated in 2004 and since that time the benefits of therapy have been noted. The scaling up of the ART programme is facilitated by identification and approval of ART-initiating sites using standardised assessment tools and simplified treatment guidelines that employ the public health approach as well as the family centred approach. There is evidence that even resource poor countries using a public health approach to HIV and AIDS care can achieve the same effectiveness with HAART as in more affluent settings.

Prior to 2010 only 50% of individuals could access care in Zimbabwe and by 2012, estimates suggest that at least 60% of individuals who require therapy according to
WHO treatment guidelines (WHO Stage 3 and 4, and CD4<350cells/mm³) were receiving HAART. This increased access to ART will mean that a growing number of individuals will be aging with HIV and on ART.

1.1.3 **Aging with HIV**

The WHO and most general practitioners and geriatricians define ‘elderly’ individuals as those aged ≥65 years. With regard to people living with HIV, the US Centre for Disease Control & Prevention (CDC) consider ‘elderly’ individuals to be those aged ≥50 years.

The number of older (i.e. ≥50 years) patients living with HIV infection has increased greatly since the advent of HAART (3). Apart from patients who acquired HIV infection in their youth living into their 50s and longer, the average age at the time of infection has increased. As a result of these trends, global estimates suggest that by 2020, over 50% of individuals living with HIV/AIDS will be aged >50 years (4). In Sub-Saharan Africa, the proportion of HIV infected individuals >50 years is uncertain as most studies on HIV/AIDS focus on the young adults up to the age of 49 years. A study done in Kenya suggested that currently 17% of mortality among persons aged over 50 years may be HIV related (5).
1.1.4 Monitoring of HAART clinical outcomes

Retention in care is a requirement for optimal clinical outcomes in patients with HIV infection. After commencing HAART, retention in care allows ongoing use of ART, evaluation of the development of medication toxicities and recognition of the occurrence of treatment failure. Monitoring of adult HAART treatment outcomes is essential in evaluating the effectiveness of HAART. Poor retention in care is associated with poor adherence to medications increasing the risk for development of resistance to ART as well as morbidity and mortality. (7) Resistance limits future treatment options and increases mortality which is particularly pertinent in resource limited settings where the cost of resistance testing and second line and third line therapies limits their widespread use and availability.
1.2 LITERATURE REVIEW

**General HIV disease process**

HIV-1 is a lentivirus which is transmitted by direct contact with infected secretions or blood. Infection starts when the virus binds to CD4 and CCR5 or CXCR4 co-receptors to gain entry into target CD4+ T-cell. Transcription of RNA to DNA occurs within the cell by HIV reverse transcriptase and this is followed by integration of DNA into the host genome. Viral progeny are made by the host genome and released from the infected cell, with resultant destruction of the CD4+ T-cell. Acute seroconversion often manifests as a flu-like illness and includes fever, a rash, lymphadenopathy, pharyngitis, myalgias and malaise (8) (9). It lasts longer in some individuals and often resolves without medication (9). Antibodies to HIV are detectable 3 to 6 weeks post infection and this is followed by a variable latent infection period where the individual remains asymptomatic. The latent period is ultimately followed by the late stage of HIV infection known as AIDS.

**HIV Infection in ART naïve Older versus Younger Patients**

The natural history of HIV infection is generally unfavourable for older patients (10). Age has been found to be independently associated with faster clinical progression to AIDS or death among ART naïve adults compared with younger adults. Older individuals typically have higher viral set points than younger people, with HIV viral loads following seroconversion and throughout latent infection typically remaining 0.4-0.5 log₁₀ copies/mL higher than those in younger patients (11). CD4+ T cell counts are also 40 cells/mm³ lower in older HIV infected patients than younger patients and they also have a more rapid CD4 cell decline and advancement to AIDS and death (10).
Survival is poorer for older individuals with HIV infection compared with younger individuals. Egger and colleagues evaluated the prognosis of HIV infection in treatment naïve patients starting ART and found patients aged 50 years and older had a higher risk of clinical progression to AIDS or death(12). The CASCADE cohort of over 13,000 patients with known dates of seroconversion demonstrated that for every 10 years of increased age, there was a 32% increased risk of developing AIDS and a 47% greater risk of death independent of CD4 counts and HIV-RNA levels(13). Age at the time of infection also affects survival. In the analysis of two large HIV datasets, the median survival for those infected between the ages of 25-35 years was 11 years, compared to 6.6 years for those infected at 55 to 64 years(14). In another study, Butt and colleagues demonstrated that age 60 years and older at seroconversion was associated with shorter survival periods(15). These inferior outcomes are partly explained by faster rates of CD4 cell decline and also partly by higher rates of other co-morbid conditions in older individuals than in younger individuals at any given CD4 cell count(16).

**What aging and HIV do to the immune system**

The thymus is the site of T lymphocyte production and initial maturation. Aging is accompanied by thymic involution which becomes significant beyond the age of 45 years(17). Thymic output is minimal in individuals over 55 years of age and this is accompanied by a decline in naïve T cell production(18). There is diminished functionality of T lymphocytes and reduced memory T lymphocytes(19). HIV infection may also suppress production and function of naïve T lymphocytes(20) and
similarities between aging and the course of HIV infection suggest that HIV accelerates the aging process and perhaps also accelerates co-morbidities and frailty.

Chronic immune activation contributes largely to immunologic compromise in both HIV-infected patients and uninfected aging individuals. However, the mechanisms of chronic immune activation are different. Immune activation is due to recurrent infection in the HIV-infected individuals versus processes such as translocation of bacterial products across compromised mucosae and chronic cytomegalovirus infection in the HIV-uninfected.(21). Immunologic perturbations that are also shared by HIV-uninfected and HIV infected older individuals include inversion of the normal CD4+/CD8+ cell count ratio. In addition to the above , as a person ages there is increased expression of the CCR5 co-receptor and this could also hasten progression to AIDS(17).

**Clinical manifestations and Complications of HIV in Older Patients**

Older individuals have more frequent HIV associated clinical manifestations than younger individuals. HIV-associated dementia(HAD) and, to a lesser extent, HIV-associated oesophageal candidiasis and wasting are more frequent in older versus younger individuals(22). In a study of 144 184 persons with AIDS during the pre-ART era, HAD (specifically encephalopathy) was the AIDS-defining diagnosis in 19% of patients who were 75 years of age or older compared with 6% of patients aged 15-34 years(23). Another cross-sectional study of 202 HIV-infected patients showed that HAD occurred nearly twice as frequently in older (50 years and older) than younger HIV-infected individuals(20-39 years of age) despite similar baseline and nadir CD4 counts(24). In an adjusted analysis of the study above, the odds of having HAD was
3.26-fold greater among older individuals compared with younger persons (95% confidence interval [CI: 1.32-8.07]). However, the risk is associated with a lower nadir, but not current CD4+ T-cell count according to a recent report (25). One study suggested that blood flow in the brains of HIV-infected individuals was reduced to levels typically observed in persons 15-20 years older but this still needs to be confirmed by other studies (26). ART may reverse cognitive defects or reduce the rate of development of HIV dementia but milder forms of HAD appear to be refractory to treatment (27). Increased rates of depression and anxiety, which often are related to social isolation, poverty, substance use, and unemployment, also contribute to cognitive impairment in older HIV-infected individuals (28).

A South African study showed that older HIV-infected patients are more likely to develop co-morbid conditions such as non-AIDS defining malignancies, diabetes mellitus, hypertension, and liver, pulmonary, vascular, and renal disease than younger individuals (29). In a large cohort study the prevalence of ≥2 co-morbidities in 41 to 50 year old HIV-infected patients was similar to that in 51 to 69 year old uninfected individuals (30).
Offering HIV Tests to older persons

There is limited data on the rate of undiagnosed HIV infection among older individuals in Sub-Saharan Africa. The rate of undiagnosed HIV infection in the general population of persons 55 years of age or older in the United States is estimated to be 0.04% (42.5 cases/100 000 persons). However, this model excludes high prevalence areas such as California and Illinois. By contrast, a survey at 6 geographically dispersed Department of Veterans Affairs facilities showed seroprevalences of undiagnosed HIV infection of 0.7%, 0.5% and 0.1% among outpatients aged 55-64, 65-74, and 75 years of age and older respectively (31). The same study showed that patients with undocumented HIV infections were significantly more likely to be older than 55 years of age versus younger than 55 years of age (p=0.006) (31). In a study of hospitalised patients aged 60 years and above at time of death who had no history of HIV or AIDS, 6.2% of men and 8.9% of women were found to be HIV-seropositive, and over 60% of these HIV positive patients had no documented or identifiable risk factors (32).

Medical practitioners and patients make assumptions on the risk of HIV infection among older individuals that may result in older people not undergoing routine HIV testing. Routine rather than risk based HIV testing is more relevant in the older persons as many of them are unaware of their risk factors for HIV or are reluctant to discuss the presence of risk factors with medical personnel (33). Some older patients may also have misconceptions about HIV infection (34).

Limiting HIV testing to persons with known risk factors fails to detect HIV infection in patients who do not report high-risk behaviours (35). A prospective study conducted
in a clinic specialising in sexually transmitted diseases demonstrated that screening only persons who report risk factors resulted in 74% of missed diagnoses(36).

In addition, clinical symptoms of HIV infection may mimic other common conditions found in the elderly resulting in missed opportunities for early diagnosis during visits to various health care centres. These often arise even in symptomatic patients because clinical HIV disease more often presents as encephalopathy and HIV wasting syndrome-conditions that mimic other illnesses associated with aging. However, even when hospitalised for what is ultimately found to be an HIV related condition, older persons are less likely to be tested for HIV infection, less likely to receive early treatment, and less likely to survive compared with younger counterparts(37). Locally, the number of older persons with undiagnosed HIV infection is unknown. The Zimbabwe Demographic and Health Survey (ZDHS) has not reported HIV testing or prevalence rates in the older persons aged 50 years and above.

**Timing of therapy**

The American Academy of HIV Medicine and the International AIDS Society-USA recommend consideration of earlier initiation of antiretroviral therapy in persons older than 50 or 60 years respectively, who have a CD4+ T-cell count >500cells/mm³. In the case of the American Academy of HIV Medicine, a >100cells/mm³ decline in CD4+ T-cell count in the previous 12 months, or risk factors for cardiovascular disease are indications for earlier initiation of HAART in the elderly(38). European AIDS Clinical Society makes no special recommendation for earlier initiation of antiretroviral therapy in older persons. Faster progression of untreated HIV infection,
immune senescence, co-morbidities which are exacerbated by CD4+ cell loss and inferior immune reconstitution provide a reasonable justification for initiating HAART at higher CD4 counts in the older than younger HIV infected patients. Unfortunately, the benefit gained by initiating therapy early is partially offset by age-related susceptibility to antiretroviral drug toxicities(39).

Treatment responses in Older versus Younger HIV-infected Patients

Clinical Response

Survival is improved in individuals on HAART irrespective of age. Although survival of all HIV infected patients has dramatically improved in the HAART era, time from acquisition of HIV infection to AIDS or death remains shorter in older patients(40). HAART provides substantial benefit to older patients(41). Nonetheless, in analyses that adjust for baseline CD4+ T-cell count, HIV-1 RNA and stage of disease, the risk of AIDS and/or death after the initiation of combination antiretroviral therapy remains greater in older versus younger patients(42). In a study by Sabin C.A. and colleagues which compared 55-59year olds to 30-39year olds, the risk of developing an AIDS defining condition was 18% higher in the former than in the latter and 32% higher in those 60years of age and older. In a retrospective chart review in Kenya the younger cohort had cumulative mortality of 6.8 %. The older cohort mortality was 10.6%. The relative risk of dying in the older cohort compared to the younger cohort was 1.43 p=<0.00001. A study in Uganda showed that non-elderly patients had significantly better survival than elderly patients (p<0.001)(5).
Retention in Care

A number of studies have been carried out in Africa focusing on retention in care rates in adult populations up to 49 years\(^\text{(44)}\). Little is known about retention in care rates of patients 50 years and older in Africa. Patient outcomes are mainly driven by clinical and immunological characteristics at HAART initiation\(^\text{(45)}\). A study performed in Kenya, Uganda and Zambia showed that baseline CD4 counts, WHO clinical stage and body mass index were predictive of patient outcomes at 12 and 24 months after HAART initiation but it did not state whether these varied across age strata\(^\text{(45)}\).

Virologic response

Studies in elderly individuals suggest that they respond to ART with more significant rates of virologic suppression compared with younger individuals\(^\text{(46)}\). Therefore, inferior clinical outcomes in older persons are not explained by poor virologic results. Rather, older individuals more often achieve virologic suppression\(^\text{(47)}\). These studies indicate that superior virologic outcomes are likely because of improved adherence to therapy among older patients versus younger patients\(^\text{(48)-(47)}\).

Immunologic response

Compared with younger persons, older patients who attain and maintain virologic control after the commencement of HAART have less robust CD4+ T-cell count recovery\(^\text{(49)}\). According to one study, for every 10-year increase in age, there is a 49% increased likelihood of having a CD4+ T cell count increase $<50\text{cells/mm}^3$ within 7-12 months of starting therapy and a 71% likelihood of not reaching CD4+ T-
cell count ≥500cells/mm³ after 5 years of antiretroviral therapy initiation (50). Another study showed that on average, for every 10-year increase in age, patients, with consistent virologic suppression gain 35 less CD4+ T cells/mm³ during the first year of therapy and 60 less CD4+ T cells/mm³ between 3 months post commencement of HAART and 4 years thereafter than younger patients (51). Impairment of immune reconstitution has also been reported in studies of patients who do not achieve sustained virologic suppression and in studies with mixed populations of patients who did or did not achieve virological suppression. The largest of such studies in mixed populations evaluated outcomes among 49,921 treatment naïve patients in 33 observational European cohort studies; 5,962 of these were aged 50 years and above. Analysis showed that persons aged 50 years and older were 7% less likely to demonstrate a CD4+ T-cell count increase ≥100cells/mm³ within the first 12 months of receiving antiretroviral therapy (52). Another large cohort which studied 5,090 The number of naïve CD4+ T cells at HAART initiation correlates with the extent of later CD4+ T-cell increases (53).
**Drug adherence**

Medication adherence is critical for successful treatment of HIV infection. Unlike treatment for other diseases, drug non-adherence causes multi-drug resistant HIV which compromises treatment options. Studies indicate that greater than 95% ART adherence therapy reduces the risk of developing drug resistant virus(54).

Studies suggest that older persons have better medication adherence but substance abuse and cognitive dysfunction may reduce adherence(55). Complex drug regimens, high pill burden, high medical costs, differing health beliefs, medication side effects, lack of social support and living alone may adversely affect adherence in the older persons in the same manner that they do in younger individuals(56).

**Drug Toxicity and aging in HIV-Infected Patients**

Increased age is associated with decreased function of the hepatic cytochrome P450 enzyme system as well as decreased renal tubular secretion and glomerular filtration(57). Changes in body fluid compartments also influence drug pharmacokinetics by changing the drug volume of distribution. Decreased body weight and body water may increase drug levels with resultant increased toxicity and drug effects. Increased body adipose tissue acts as a depot for lipid-soluble drugs and can result in initial decreases in drug serum concentrations and drug effects followed by later toxicity(58). Further toxicity is caused by higher rate of polypharmacy in elderly which increases the likelihood of drug-drug interactions(59).

The relevance of these considerations is demonstrated by a study of 2 ART-naïve cohorts, one comprising HIV-infected patients aged 18-30 years and the other
comprising patients aged older than 45 years. All patients were on Stavudine, Emtricitabine and Lopinavir/ritonavir (60). In multivariate regression analyses, an age of 45 years was associated with increased trough levels of lopinavir due to age-related loss of cytochrome P3A4 activity. Also, a study of 508 treatment-naïve patients who initiated HAART found that the rate of treatment switches because of toxicity was 28% higher for every 10-year increase in age (61).
1.3 **Study justification**

Continuity of care at large public adult HIV/AIDS care clinics in resource limited settings are poorly described beyond the first year of HAART in older individuals. No Zimbabwean National HIV Treatment guidelines are available that distinctively address the management of the elderly HIV infected patient on HAART. Despite having a large HIV-infected elderly population and well established ART programme, few studies have been conducted describing the extent of retention in care among older persons on HAART. The recently conducted Zimbabwean study on retention in care only recruited patients aged 32-45 years(62).

The treatment cascade for older individuals is likely to be different from that for younger individuals. It is important that an understanding of HIV testing patterns, linkage to care, retention in care and successful outcomes on ART be well understood for elderly patients who have been successfully linked and initiated on ART.

This study was conducted in an endeavour to contribute to the existing body of knowledge on HAART outcomes in a resource limited setting which may help guide improvements in early diagnosis, treatment and care for individuals living with HIV/AIDS. It is anticipated that the study will also help to identify needs that may be peculiar to older individuals as compared to younger individuals with chronic HIV infection.
1.4 Research question

Do HIV-infected older individuals (age 50 years and over) have a lower retention rate compared to HIV-infected young adults (aged 25 to <50 years), in a clinic cohort of HIV-infected adults initiated on HAART between 1 January 2009 and 31 December 2011 at the Family Care Centre, Harare, Zimbabwe?

1.5 Primary Objective

To determine and evaluate differences in retention rates between older persons (age 50 years and over) and young adults (aged 25 to <50 years) 24 months after HAART initiation in a clinic cohort of HIV-infected adults initiated on HAART between 1 January 2009 and 31 December 2011 at Family Care Centre, Harare, Zimbabwe.

1.6 Secondary Objectives

- To describe demographic and clinical characteristics of participants at the time of initiation of HAART.
- To determine proportions and differences in retention in care rates between older persons and young adults 24 months after initiation of HAART.
- To determine what patient baseline demographic and clinical characteristics are associated with attrition in older persons and young adults 24 months after initiation of HAART.
1.7 **Hypothesis**

Older persons have lower retention rates 24 months after initiating HAART, with higher rates of loss to follow up than younger individuals due to:

- Late stage of presentation with a greater proportion presenting in WHO Clinical Stage 3 and 4.
- Lower baseline CD4 cell counts at presentation.
- High prevalence of co-morbidities.
2. RESEARCH DESIGN AND METHODS

2.1 Study design

A retrospective cohort study was performed.

2.2 Study setting

The study was performed at the Parirenyatwa Hospital Family Care Centre (PHFCC). This is a public sector HIV clinic at Parirenyatwa Group of Hospitals (PGH), a tertiary institution in the capital city of Harare, Zimbabwe.

Parirenyatwa Hospital Family care Centre (PHFCC) is one of the largest public ART programs in the country. Support for the clinic is from the Ministry of Health which provides staff, clinic resources including antiretroviral therapy, reagents for diagnostic tests such as CD4+ T-cell counts. Patients are referred to PHFCC from PGH medical wards and outpatients departments, Parirenyatwa Antenatal Clinic, Municipal primary care clinics, peripheral hospitals, general practitioners, private testing centres such as New Start Centre as well as patient self referral. These patients are managed by a team comprising of physicians, medical officers, registered general nurses, adherence counsellors, nurse aides, and pharmacists.

2.3 Sample size

The study cohort was selected based on systematic sampling of participants from 2 age group strata, age 25 to 49 years or 50 years and above.
Sample size was calculated to detect a minimum of 7% difference in retention in care between young and old adults assuming 80% power and a 2-sided test at an alpha level of 5% and a ratio of 3:1 in young to adult patients giving a minimum of 444 patients. This computation was performed in STATA 10 (STATA Corporation, College Station, TX) using the two-sample comparison of proportions method.

2.4 **Study participants**

2.4.1 **Inclusion criteria**

To qualify for entry into the study, the following criteria had to be met:

i. Age 25 years and above at time of HAART initiation

ii. Documented HIV infection

iii. Registration and HAART commencement at PHFCC between 1 January 2009 and 31 December 2011

iv. HAART naïve at clinic registration

v. At least 12 months of follow up data available after initiation of HAART

2.4.2 **Exclusion criteria**

The following criteria disqualified records from being entered into the study:

i. Age below 25 years

ii. Patients with prior ARV exposure

iii. Patients followed up on HAART for less than 12 months

iv. Inadequate baseline demographic and clinical data
The records of adult patients with documented HIV infection and aged 25 years and above, registered and commenced on HAART at PHFCC between 1 January 2009 and 31 December 2011 and meeting the above criteria were reviewed.

This period was chosen because of the better availability of CD4 counts and viral loads at PHFCC and the general improved health service provision with the official use of the United States Dollar in Zimbabwe in 2009. This was done in order to reduce confounders for poor outcomes.

The adult age group of 18-25 years was excluded due to age specific effects of adolescent and young adult HIV infection. All individuals enrolled in care at the clinic present with a verified documented HIV test result with HIV testing done at a recognised centre using the national testing algorithm.

2.5 Study Procedures

Systematic sampling of study participants’ charts was done with every 14th chart reviewed. Patient charts are ordered by date of registration to the clinic. If a participant did not meet the study criteria, the chart before or after that specific chart would be reviewed for recruitment. Data was extracted for each patient from handwritten medical files followed by Energy Plan electronic patient management system. Since the establishment of the clinic in 2005 patient records were stored handwritten on paper files. These were utilised until October 2012 when the electronic system became functional. Other information was also extracted from Pharmacy records. These data were not intended for research therefore no data quality checks were done on it at the time that the medical record was generated. Poor data quality in relation to missing information presented study limitations owing to the retrospective nature of the study.
A telephone interview was conducted with the next of kin of each patient whose outcome was not specified in the charts. This was done to ascertain whether the patient was alive or dead as relatives and next of kin rarely report deaths of PHFCC patients. If the patient was deceased the date of death and not the cause was requested (Appendix II). There were patients without contact numbers or whose telephones were unreachable, such patients’ outcomes were treated as lost to follow up (LTFU).

2.5.1 Data capturing

All charts remained on the premises. Data was abstracted onto a paper-based questionnaire by the principal investigator then entered into Epi Info database. Discrepancies were then resolved by referring back to the paper questionnaires before the final dataset was cleaned prior to data analysis.

2.6 Study variables

Age, gender, marital status and address were the four demographic variables measured in this study cohort. The patient’s age (in completed years) at HAART initiation was calculated as the difference in years between the HAART initiation date and the birth date. This was further stratified into the age groups of young adults (25 to <50 years) and the older adults (aged 50 years and above). All study participants were analysed according to their age group at HAART initiation.

Baseline Weight, WHO Clinical Stage and baseline CD4 count are variables that were also assessed for association with retention in care. Time from HIV diagnosis
to HAART initiation, Opportunistic infections e.g. TB and Non-communicable co-morbidities e.g. HPT, DM at presentation were also assessed.

CD4+ T-cell counts were measured at assessment before HAART initiation and scheduled every 24 weeks thereafter. These were computed in counts(cells/mm³) and were further categorised into either CD4+ T-cell counts ≤100, >100-≤200, >200-≤300, >300-≤400 and >400cells/mm³. Weight was measured in kilograms(kg) and categorised into ≤50kg, >50 - ≤75kg and >75kg. For purposes of this study, baseline parameters were the nearest measurement taken within 3 months before initiation of HAART or one week after HAART initiation date.

Participants with WHO Stage 3 or 4 disease were categorised as having clinically advanced disease and the study participants with WHO stage 1 or 2 disease were categorised as having non-clinically advanced disease.

2.7 Follow-up

Follow up was from the date of HAART initiation to date of occurrence of an end point such as death, transfer to a peripheral centre or loss to care. Those patients whose death dates could not be ascertained but only the month was remembered the death date was taken as the last day of that particular month. Patients who did not experience the above end points were followed up to 24 months after commencement on HAART.

2.8 Outcome factors

The primary study outcomes were:

i. Retention in care at 24 months

ii. Death from any cause.
Secondary outcomes: Factors associated with retention in care

Retention in care was determined by assessing if patients either returned to the clinic for follow up or prescription refill or by telephone calls. In this setting, patients are usually given two to three months of antiretroviral medications before returning to the clinic for follow-up. Hence loss to follow up (LTFU) was considered if subjects had not returned for review or drug pick up for at least 6 months. Attrition included deaths and LTFU. Known transfers to continue ART at other centres were not classified as attrition.

2.9 Ethical considerations

The study protocol was approved by the Joint Research Ethics Committee (JREC). For those patients whose clinical records were eventually analysed, no consent was obtained due to the nature of the study (retrospective cohort). The study did not involve treatment or interventions.

All charts remained on the premises. To minimise the risk of violation of privacy and loss of confidentiality number codes were used instead of patient names or medical record numbers. Data was stored in a password protected computer. Coded subject information was kept separate from the spreadsheet linking codes to subject identity. For the purposes of this study, only the Principal Investigator and Co-investigators had access to identifying information.

On the telephone interviews with the patient’s relatives or next of kin, there was strictly no mention of the patient’s diagnosis or therapeutic interventions. Only
information on whether the patient was alive or dead was requested. If the patient was deceased, their date of death and not its cause was requested for. Such information was not obtained from minors. Those who declined to give such information were not pressurised to do so.

There were no physical risks to the study patients and investigator as this is a retrospective chart review. There was no direct benefit to the study patients but information gathered may improve management of other patients in future.

2.10 **Statistical analyses**

Data analysis was performed in STATA version10 statistical package and it consisted of standard statistical methods

2.10.1 **Descriptive statistics**

Baseline demographic and clinical characteristics were described according to the age strata. Mean (standard deviation) or median (inter-quartile range) were used to summarise continuous variables if data were normally or non-normally distributed respectively. Categorical and discrete random variables were reported as frequencies (n) and percentages (%). Pearson’s Chi-square test was used to perform two way comparisons for the frequency and baseline categorical variables whilst the Fisher’s exact test was applied when any of the cells had expected values less than 5. The Student’s t-test was used to compare normally distributed baseline continuous variables.
2.10.2 **Inferential statistics**

In the primary analysis, Kaplan-Meier plots stratified by age group were compared by the log-rank test. Assessment of individual patient data was discontinued after 730 days (96 weeks) or at the cohort specific close of the database, whichever occurred first. The Log rank test for equality of survival functions was used to determine whether there was a statistically significant difference at 5% significance level, in the retention in care between the two age groups.

In the secondary analysis, logistic regression was used to determine baseline variables associated with retention in care at 24 months after initiation of HAART. Univariate analyses were also performed.
3. RESULTS

3.1 Cohort recruitment

During the period of 1 January 2009 to 31 December 2011, 6,231 patients were initiated on HAART at PHFCC. A total of 1005 charts were reviewed and 561 patients did not meet the criteria because they either were not commenced on HAART, were followed up for less than 12 months, had missing baseline and/or repeat CD4 counts or were aged less than 25 years. The final data set comprised of 444 adults, 333(75%) young adults and 111(25%) older persons.

3.2 Baseline demographic characteristics

The mean age of the study cohort was 41 years (SD±11.8 years). Young adults presented for HAART initiation at a mean age of 35.4 years (SD±6.8years) while the older age group presented at a mean age of 57.7 years (±7.1years). In the combined study sample, there were 175(39.4%) male and 269(60.6%) female participants. The older age group was predominantly male (55.9%) with females dominating the younger age group (66.1%). The commonest marital status was being married in the combined study cohort 237(53.3%) followed by being widowed in the older age group 38(34.2%) and single in the young adult age group 55(16.5%).

Demographic characteristics of the study cohort at HAART initiation are described in Table 1 below.
**Figure 2**: Flow diagram of participant selection

- 6231 Number of patients registered between 1 January 2009 and 31 December 2011

- 1005 Number of patient charts reviewed on systematic sampling

- 561: Number of patients not meeting inclusion criteria

- 444 Patients who met inclusion criteria
Table 1: Demographic characteristics of the combined and age-stratified study cohort at initiation of HAART

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=444)</th>
<th>Young adults (n=333)</th>
<th>Older persons (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years, mean (SD)</td>
<td>41 (+/- 11.8)</td>
<td>35.5 (+/- 6.8)</td>
<td>57.7 (+/- 7.1)</td>
</tr>
<tr>
<td><strong>Gender n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>175 (39.4)</td>
<td>113 (33.9)</td>
<td>62 (55.9)</td>
</tr>
<tr>
<td>Female</td>
<td>269 (60.6)</td>
<td>220 (66.1)</td>
<td>49 (44.1)</td>
</tr>
<tr>
<td><strong>Marital status n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>237 (53.3)</td>
<td>188 (56.5)</td>
<td>49 (44.1)</td>
</tr>
<tr>
<td>Single</td>
<td>59 (13.3)</td>
<td>55 (16.5)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Divorced</td>
<td>49 (11.0)</td>
<td>32 (9.6)</td>
<td>17 (15.3)</td>
</tr>
<tr>
<td>Widowed</td>
<td>88 (19.8)</td>
<td>50 (15.0)</td>
<td>38 (34.2)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>11 (2.5)</td>
<td>8 (2.4)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td><strong>Address n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harare high density</td>
<td>191 (43.0)</td>
<td>148 (44.4)</td>
<td>43 (38.7)</td>
</tr>
<tr>
<td>Harare medium density</td>
<td>88 (19.8)</td>
<td>65 (19.5)</td>
<td>23 (20.7)</td>
</tr>
<tr>
<td>Harare low density</td>
<td>68 (15.3)</td>
<td>46 (13.8)</td>
<td>22 (19.8)</td>
</tr>
<tr>
<td>Outside Harare</td>
<td>64 (14.4)</td>
<td>45 (13.5)</td>
<td>19 (17.1)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>8 (1.8)</td>
<td>6 (1.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Harare Avenues</td>
<td>25 (5.63)</td>
<td>23 (6.9)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>
3.3 **Baseline clinical characteristics and laboratory parameters**

At HAART initiation, the vast majority of patients had advanced disease, as evidenced by their WHO clinical stage 3 and 4 and CD4 counts below 200cells/uL. By WHO clinical staging, 50% and 24.32% were in stages 1 and 2 in the younger and older age groups respectively, versus 50% and 75.68% in stages 3 and 4 ($p<0.0001$). Proportions of CD4+ T-cell counts also differed significantly in the two age strata with 40.5% of older persons having counts below 100cells/mm$^3$ compared to 26.1% in the younger adults ($p=0.042$). Median Time from HIV diagnosis to HAART initiation was 47.5 days in the young adults and 31 days in the older age group ($p=0.006$). Baseline weights and Previous Tuberculosis were not significantly different between the older and young adults. Hypertension was recorded in charts of 9.91% of the older adults compared with 2.10% of young adults and the difference was statistically significant ($p<0.0001$). The number of participants with diabetes was not significantly different in the two age groups. Table 2 below summarises baseline clinical and laboratory parameters.
Table 2: Comparison of baseline clinical and laboratory characteristics in the older and young adults age groups

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>All n=444</th>
<th>Young adults n=333</th>
<th>Older n=111</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from HIV diagnosis to HAART initiation (days)</td>
<td>42(19-152)</td>
<td>47.5(19-167)</td>
<td>31(18-100)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Median(range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline weight (Kg)</td>
<td>n = 425</td>
<td>n=322</td>
<td>n=103</td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>36(8.47)</td>
<td>25(7.76)</td>
<td>11(10.68)</td>
<td>0.284</td>
</tr>
<tr>
<td>&gt;50- ≤75</td>
<td>318(74.82)</td>
<td>247(76.71)</td>
<td>71(68.93)</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>71(16.71)</td>
<td>50(15.53)</td>
<td>21(20.39)</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count (cells/uL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100</td>
<td>132(29.73)</td>
<td>87(26.13)</td>
<td>45(40.54)</td>
<td></td>
</tr>
<tr>
<td>&gt;100-≤200</td>
<td>143(32.21)</td>
<td>113(33.93)</td>
<td>30(27.03)</td>
<td></td>
</tr>
<tr>
<td>&gt;200-≤300</td>
<td>119(26.80)</td>
<td>94(28.21)</td>
<td>25(22.52)</td>
<td>0.042*</td>
</tr>
<tr>
<td>&gt;300-≤400</td>
<td>43(9.68)</td>
<td>34(10.21)</td>
<td>8(7.20)</td>
<td></td>
</tr>
<tr>
<td>&gt;400</td>
<td>7(1.58)</td>
<td>5(1.50)</td>
<td>3(2.70)</td>
<td></td>
</tr>
<tr>
<td>Baseline WHO Stage†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Advanced disease</td>
<td>Advanced disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>193(43.47)</td>
<td>166(49.85)</td>
<td>27(24.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250(56.43)</td>
<td>167(50.15)</td>
<td>84(75.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>P&lt; 0.0001</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18(4.05)</td>
<td>7(2.10)</td>
<td>11(9.91)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>426(95.95)</td>
<td>326(97.90)</td>
<td>100(90.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>P&lt;0.0001</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiabetesMellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10(2.25)</td>
<td>6(1.80)</td>
<td>4(3.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>434(97.75)</td>
<td>327(98.2)</td>
<td>107(96.40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.268</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>73(16.44)</td>
<td>50(15.02)</td>
<td>23(20.27)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>371(83.56)</td>
<td>283(84.98)</td>
<td>88(79.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.160</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Less clinically advanced (WHO clinical stage 1 and 2) and clinically advanced (WHO Stage 3 and 4)

*Variable statistically significant at alpha level of 0.05
Figure 3: CD4+ T-cell counts at baseline entry into care by age group. Older participants presented with marked immunosuppression as compared to younger participants.
Figure 4: WHO clinical stage by age group

Figure 5: Prevalence of infectious and non-infectious co-morbidities among study participants by age group
3.4 Patient follow-up

The primary study outcome was retention in care among older participants as compared with younger participants.

Telephone contact and sms messaging is generally recommended as a method of ensuring that patients on long-term ART remain in care and are appropriately followed up. We used telephone contact to determine patient outcome among participants who were clearly no longer retained in care as defined by a clinic visit within the last 6 months. Telephone numbers were documented in the chart for 346(77.9%) and the availability of telephone contacts was comparable between the different age groups(77.4% versus 79.3%). 66.2% of participants in the young adult age group were successfully contacted per phone whilst 47.8% were contacted in the older age group. The reasons for failing to contact participants included number no longer in use, patient unknown to the phone owner and number not reachable.

3.5 Retention in care

Retention in care among study participants was evaluated. At 24 months, of the 444 participants who had been enrolled in care for at least 12 months, 323(72.75%) were still retained in care, while 121(27.25%) were either deceased, transferred or lost from care. Of the 444 participants recruited, 49(11%) were transferred to clinics and hospitals nearest to where they live after at least 12 months in care. The outcome of the 395 who were not transferred was determined and 23(5.8%) had died and 49(12.4%) were lost to follow up while 323(81.8%) were retained in care. Retention in care was substantially and significantly higher among the younger age group than the older age group (p<0.0001).
The median duration of follow-up of the study cohort was 23 months [IQR 21.5 – 24.0 months], calculated as time to a.) death, b.) transfer, c.) LTFU, d.) last review or drug pick-up (for those retained in care). The total duration of follow-up was 814 patient-years. The median duration of follow-up for the 121 patients not retained in care at the end of the follow-up period of 24 months was 16.9 months [IQR 13.8 – 19.6 months].
Table 3: Distribution of all patient outcomes

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Young</th>
<th>Older</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retained in care</td>
<td>323(72.75)</td>
<td>258(77.48)</td>
<td>65(58.56)</td>
<td></td>
</tr>
<tr>
<td>Not retained in care</td>
<td>121(27.25)</td>
<td>75(22.52)</td>
<td>46(41.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>444(100)</td>
<td>333(100)</td>
<td>111(100)</td>
<td></td>
</tr>
</tbody>
</table>

*Transfers to other hospitals were censored from the survival analysis.

Table 4: Distribution of outcomes of patients considered in the survival analysis (transfers excluded)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Outcome</th>
<th>n(%)</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retained in care</td>
<td>Attrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td>LTFU</td>
<td></td>
</tr>
<tr>
<td>Young adults</td>
<td>258(86.58)</td>
<td>12(4.03)</td>
<td>28(9.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Older persons</td>
<td>65(67.01)</td>
<td>11(11.34)</td>
<td>21(21.65)</td>
<td>97(100)</td>
</tr>
<tr>
<td>Total</td>
<td>323(81.77)</td>
<td>23(5.82)</td>
<td>49(12.41)</td>
<td>395(100)</td>
</tr>
</tbody>
</table>

Table 5: Distribution of outcomes of patients not retained in care by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Patients not retained in care</th>
<th>n(%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transferred</td>
<td>Attrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dead</td>
<td>LTFU</td>
</tr>
<tr>
<td>Young adults</td>
<td>35(46.05)</td>
<td>12(15.79)</td>
<td>28(38.16)</td>
</tr>
<tr>
<td>Older persons</td>
<td>14(30.43)</td>
<td>11(23.91)</td>
<td>21(45.65)</td>
</tr>
</tbody>
</table>
Figure 6: Kaplan-Meier survival estimate of the study cohort

Figure 7: Kaplan-Meier survival estimates by age group (p<0.0001)
3.6 Factors associated with attrition (death and LTFU).
In the univariate analysis of the older age group, attrition was substantially and significantly associated with WHO clinical stages 3 and 4, OR 3.11 p=0.048 [95% CI: 1.96-4.05], Baseline CD4+ T-cell count ≤100 cells/mm³ OR 2.27 p=0.041 [95% CI: 1.82-3.22] and having at least 1 baseline co-morbidity OR 2.07 p=0.028 [95% CI: 1.71-6.02]. The odds of attrition in the older persons was substantially but not significantly increased with respect to baseline weight kg ≤50 kg OR 1.92 p=0.0460 [95% CI: 0.62-2.94] and prior tuberculous infection OR 2.23 p=0.112 [CI: 0.83-6.00].
In the young adults, attrition was associated with baseline WHO stage 3 and 4 OR 2.09 p=0.04 [95% CI: 1.13-4.24]. The common comorbidities were epilepsy, diabetes, hypertension, heart failure or psychiatric illness.
Table 5: Univariate analysis of factors associated with attrition (LTFU and death)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young adults</th>
<th>Older age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p-value</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>Female</td>
<td>1.02</td>
<td>0.955</td>
</tr>
<tr>
<td>WHO Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less advanced</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Advanced</td>
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4 DISCUSSION, LIMITATIONS, STUDY BIAS AND MISSING DATA

4.1 Discussion

This study has demonstrated a global retention in care rate of 81.77% between 12 and 24 months on HAART. This is higher than the retention rates demonstrated by the recent Zimbabwean retrospective study that showed a 24 months retention in care rate of 68.8% in patients commenced on HAART between 2007 and 2009 (62). However, that was a multicentre study which included patients followed up for less than 12 months when the highest mortality after starting antiretroviral therapy is observed in most countries in Sub-Saharan Africa (63). Regional and global estimates from data reported from national ART programmes of 54 countries in Sub-Saharan Africa suggested a lower retention on ART of 66.8% at 24 months in (63). A systematic review of 33 cohorts in 13 countries in Sub-Saharan Africa showed variable retention in HAART programs in different stations with the best reporting a 24 month retention rate of 85% and the worst 46% (64). The rates found in our study may underestimate retention rates given that we considered loss to care in patients who did not have contact telephone numbers and those whose telephones were unreachable.

There was a significant difference in retention rate at 24 months among older persons of 67.01% compared to the younger age group of 86.58% (p<0.0001). There have been variable findings among African studies on retention in care with some demonstrating older age to be a determinant of poor outcomes (65) and others showing no association between older age and retention in care (66). However, in most of these studies, age was stratified into age groups younger than 50 years and patients older than 50 years were totally excluded.
The general death rate in the current study was 5.82% with 11.34% in the older age group compared to 4.03% deaths in the young adults respectively. This is in keeping with studies done in the western world where it was proven that increasing age is associated with attrition (67) (15) (68). This is in contrast with a study done in West Africa where younger age was associated with a higher attrition risk $aHR=1.10$ (95% CI:1.03—1.19) another one done in Zambia where age greater than 50 years was associated with better retention rate of 78% than in those aged less than 50 years old. Mortality rates are closely associated with advanced HIV disease states at ART initiation (69)(70) The causes of death could not be ascertained in our study as families of patients who die elsewhere rarely report deaths of PHFCC patients and asking for details of cause of death per phone would not be justified ethically as this may risk unintended disclosure of HIV status to the deceased participant’s next of kin.

We found that LTFU was also higher in the older age group (21.65%) compared to the younger age group (9.40%). Increased rates of loss to follow up in the elderly may be accounted for by silent relocation to peripheral hospitals that are closer to the participants’ rural home which is often the preferred residence for elderly Zimbabweans. Significant LTFU has been documented to be largely due to death and non-documented transfers in some African studies (71)(69).

This study also sought to describe baseline characteristics of the 444 study participants and their association with attrition. Most participants had markers of advance disease at HAART initiation; 63.4% had CD4+ T-cell count≤200 cells/mm³ and 56.4% were in WHO clinical stage 3 and 4. Other African countries have reported similarly advanced disease at presentation (72)(73)(74) Baseline WHO clinical stage 3 and 4 were significantly different between the age strata ($p<0.0001$)
and was associated with attrition in the older age group. This was similar to findings in a study done in Zambia, Uganda and Kenya which found worse baseline WHO stage as a predictor of outcome at 24 months post HAART initiation (45). They also found that baseline CD4 count and BMI were factors that were predictive of outcomes. In the current study, baseline CD4 counts were significantly different in the two age groups and older participants were overly represented in the low CD4+ T-cell strata. Baseline CD4+ T-cell counts <100 cells/mm³ increased the risk of attrition in the older age group OR 2.27 p=0.041 [1.82-3.22]. Several studies have been done in the US on T cell dysfunction in aging and in HIV infection and these seem to strongly suggest that at baseline, older individuals have lower CD4 cell counts (17)(20).

Baseline weight was evaluated for association with attrition. Baseline weight less than 50 kg substantially but not significantly increased the risk of attrition in the older persons OR 1.92 p=0.460 [CI: 0.62-2.94]. It would have been worthwhile assessing body mass index rather than weights but this was not possible without height measurements which are not routinely done for adults in the clinic. BMI monitoring is important as this may be a complication of antiretroviral treatment with potential of resulting in serious cardiovascular complications.

Hypertension was significantly more common in the older than younger age group (9.91 versus 2.10%) but these rates were both lower than the national prevalence of Hypertension in the general population of 35% in women and 24% in men (75). A South African cohort study demonstrated higher prevalences of co-morbid conditions which also arise at an earlier age in HIV positive patients compared to the general population (29) (30). Co-morbid conditions have been found to contribute to accelerated progression of HIV disease and death (16).
hypertension at PHFCC may be due to absence of routine BP checks at the clinic as well as lower reporting of non HIV conditions in PHFCC as much as they would in a general medical clinic. However, having at least 1 non-HIV co-morbidity was a significant predictor of poor outcome in this study with an odds ratio of 2.07[95% CI: 1.71-6.02].

The ratio of male to female in the younger age group of 1:1.67 mirrors the sex ratio in general population of Zimbabwe and in most studies on adult HIV infection(45) (62) (71). The reversal of sex ratio in the older age group may imply that older men have more risky sexual practices with younger women and contract HIV more than older women. In addition health seeking behaviours may be important contributors with older women possibly seeking medical attention less readily than older men. Older women may also have less perceived risk of HIV infection than older men.

Older persons had a significantly shorter HIV diagnosis to HAART initiation time than their younger counterparts (32 versus 47.5 days) but this added no risk to attrition in both age strata on the univariate analysis. This may have been due to the relatively lower CD4+ T-cell counts among the older participants as compared to the older participants. In addition there was a greater proportion of older patients presenting with AIDS defining WHO Stage 3 and 4 illnesses which immediately made them eligible for HAART unlike the younger age group who at times were registered and treatment deferred until they became eligible for HAART.
4.2 Study limitations, study bias and missing data

Nature of study

There are limitations in all retrospective studies.

Verification of the outcome of interest-death, could not be done through the Registrar General’s office because of logistical reasons. Some cellular networks were not reachable hence inflating the number of participants lost to care.

There was lack of information on laboratory data and co-morbid disease states. Co-morbidities such as epilepsy, hypertension and diabetes mellitus are not routinely managed at the PHFCC so limited information was recorded in the patient charts.

It was a big limitation that we could not reliably distinguish between LTFU and death. Characteristics associated with non attendance suggest death a major part of it. It was also not possible to look at drug adherence in this retrospective study.

Financial and Time constraints

It would have been worthwhile making door to door follow up on those patients who could not be contacted on the telephone as this could have reduced the number of patients lost to follow up. However, this would have included huge investments on time and transport costs.
4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusion

The study demonstrates a lower retention in care rate of 67.01% in the elderly compared to 86.58% in younger counterparts after 24 months on HAART. The three baseline variables associated with increased risk of attrition in the older age group were baseline weight less than 50kg, advanced WHO clinical stage at presentation and having non-HIV related co-morbidities. It draws attention to the unique presentation of older individuals to HAART programs in Zimbabwe, as well as other non-AIDS co-morbidities they have which may affect clinical outcomes. As the number of elderly patients enrolled and eligible for HAART continues to rise, older individuals need to be tested for HIV and commenced on HAART early in order to maintain their continuity in care and prevent HIV progression and death. In addition serious attention needs to be put into the management of co-morbidities such as diabetes, obesity and hypertension.
4.2 Recommendations

a) A prospective study

A study to determine the treatment cascade among elderly individuals in Africa is desperately needed. The delayed presentation with high WHO clinical stages and the high rates of attrition are concerning as they suggest that treatment cascade for elderly individuals may be steeper with greater drop-offs along the cascade than among younger individuals.

b) Setting up of follow up of PHFCC patients

Currently no defaulter tracing is offered by the clinic. In order to improve retention in care and hence continuity on HAART and survival, there is need for the government to consider community defaulter tracing for elderly patients who may not have adequate social support. This may be done through telephone calls or home visits.

c.) Offering HIV testing to all elderly patients aged 50 years and above despite perceived low HIV risk.

Routine HIV testing should be provided to all adults in Zimbabwe. Testing should be done at least annually for all adults irrespective of age. This would catch more older individuals at less advanced WHO clinical stages and result in improved outcomes on ART as well as decrease the risk of attrition from care.
d.) Incoorperating treatment of co morbidities in the HIV clinic.

In the PHFCC Routine BP, glucometer and height readings were not taken from 2009 to 2011 as these were assumed to be checked at the main hospital. However, patients attending PHFCC only were experiencing missed opportunities for diagnosis of the neglected non-communicable diseases such as hypertension, diabetes and obesity (BMI>30kg/m²). Blood pressure is now being measured and continuation of these routine readings plus at least one height measurement would be beneficial especially in the elderly population whose HIV treatment is often complicated by these co morbidities.

e.) Community awareness

Community awareness programmes are recommended to educate the public on HIV infection among the elderly and decrease the common misconception that HIV infection rarely occurs in the elderly.
REFERENCES


6. Life expectancy at birth, total (years) | Data | Table [Internet]. [cited 2014 May 25]. Available from: http://data.worldbank.org/indicator/SP.DYN.LE00.IN/countries/1W


APPENDIX I

DATA COLLECTION SHEET

Study ID: ................. Date of Chart Review: ...../...../.....

PHFCC Registration Date: ....../...../..... Contact details Yes/No

Demographics

Gender: Male /Female Date of Birth: ....../...../.....

Age at Clinic Registration: ........years

Address: ...................................... Marital status... M S D/Sep W Unknown

HIV testing

Date of HIV test: ....../...../.....

Place of HIV test.......................... Reason for HIV test...........................................

Baseline visit

Weight............ (kg) Height............ (m) BMI............ (kg/m²) WHO Stage: 1 2 3 4

BL CD4........... (cells /μl) Date....../...../.....

Prior Tuberculosis YES/ NO

HAART history

Time from HIV test to HAART initiation............. (weeks)

Initial Regimen.......................................................... Start Date: ....../...../....
**HAART Switch 1**

Reason: PPTCT  Side effects  Drug interactions  Treatment failure  Unknown
Date: ....../....  Regimen: ..............................

**HAART Switch 2**

Reason: PPTCT  Side effects  Drug interactions  Treatment failure  Unknown
Date: ....../....  Regimen: ..............................

**HAART Switch 3**

Reason: PPTCT  Side effects  Drug interactions  Treatment failure  Unknown
Date: ....../....  Regimen: ..............................

**Repeat CD4 counts**

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**New TB dates:** ....../....

**Viral loads**

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</table>
Date of last visit: ..../..../....        Outcome: Alive / Dead / TF / Unknown
APPENDIX II

THE TELEPHONE INTERVIEW

This is a description of the telephone interview done with the patient or patient’s relative or next of kin as a way of finding out the outcome (death) of the study patients.

The researcher rang the telephone or mobile number that was recorded in the patient’s clinical records. On getting a response the researcher specifically asked for the person recorded as next of kin to whom the researcher introduced self and asked if they did not mind being asked a few personal questions.

If they answered in the affirmative, then the researcher would ask about the whereabouts of the study patient. The spontaneous answer was “akashaya” if the patient was deceased, then the researcher would ask for the date of death then conclude the conversation by conveying condolences and thanking them.

If the patient was alive and present the researcher did not make efforts to talk to them. If the study patient answered the phone the conversation would be concluded by thanking them for letting the researcher know their whereabouts.

If a minor answered the call, the researcher would ask for the adult person present, no information was obtained from minors.

No diagnosis or therapeutic interventions were mentioned on the phone.

Those who refused to be interviewed were not pressurised, instead the researcher thanked them all the same.