LONGITUDINAL ANALYSIS TO ASSESS THE CONTRIBUTION OF THE MULTI-MONTH SCRIPTING (MMS) REGIME ON ART OUTCOMES AMONG ADULT PERSONS LIVING WITH HIV IN ZIMBABWE

BY

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Abstract

Zimbabwe has a generalized HIV epidemic. Since 2015, the national ART program has been rolling out a suite of differentiated models of care in line with the 2013 WHO guidelines. One of the common models adopted by the country is Multi-Month Scripting (MMS) for stable ART patients. Insufficient evidence exists in the country around the contribution of MMS to patient level ART outcomes, almost two years after it was rolled nationally.

A retrospective cohort study was conducted at the five ART clinics in Chitungwiza. Secondary sources of data were used in the research. Longitudinal data analysis techniques were applied, including survival analysis.

Among the 305 ART patients with HIV/AIDS who initiated ART, there were five AIDS-related deaths; two within the first 6 months, two between the 42-48-month period and one in the 54-60-month period. Overall, the median survival time (53 months) was the same among MMS and non-MMS clients. The retention rates at 12, 24, 36, 48 and 60 months were 98%, 97%, 96% 91% and 87% respectively, and were not statistically different between MMS and non MMS clients. There was a statistically significant change in the CD4 counts (initial vs. follow up) for non-MMS clients. There were significant gains in weight among both MMS and non-MMS clients.

The outcomes of interest (weight, survival, retention and changes in CD4 cell count) were primarily associated with sex, age, WHO stage at initiation, receipt of Cotrimoxazole and level of education, among other factors, albeit at varying degrees of significance.

Two years into the roll out of MMS, this study suggests that there are no statistically significant differences in observed outcomes between clients on MMS and those not on MMS. More research is necessary to conclusively determine the contribution of each of the models of differentiated care to observed outcomes. However, the contribution of MMS to observed ART outcomes could as well be clinically significant. The factors associated with the clinical outcomes look similar to prior studies, albeit at varying levels of statistical significance.

Keywords: *HIV and AIDS, antiretroviral treatment, multi-month scripting, survival, retention, clinical outcomes, immunological outcomes, longitudinal analysis, survival analysis*

Declaration

I, Hamfrey Sanhokwe, declare that this work is original and is not submitted to any University for the award of any degree.

Student Signature …… Date …….

Supervisor Signature……..……Date ……

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I am forever indebted to the Almighty for the gift of life!

Dedication

This research master-piece is dedicated to my soul mate (Sheeba Murwira nee Sanhokwe); my beautiful daughters (Tatenda, Candice and Mufaro); my mom (Francisca Sanhokwe) and my late father (Founder Sanhokwe – May your soul rest in eternal peace dad!). Thank you all for being there for me!

Contents

List of Figures

List of Tables

List of appendices

List of acronyms

AGYW – Adolescent Girls and Young Women (15-24 years)

AIDS – Acquired Immuno Deficiency Syndrome

ART – Anti Retroviral Therapy

ARV – Anti Retro Viral

CD4+ - cluster of differentiation 4

CHAI – Clinton HIV and AIDS Foundation

CI – Confidence Intervals

DHS – Demographic and Health Survey

DMC – Differentiated Models of Care

FTR – Fast Track ART Refills

Global Fund – Global Fund to Fight HIV/AIDS, TB and Malaria

HAART – Highly Active Anti-Retroviral Therapy

HIV – Human Immuno Virus

HR - Hazard Ratio (AHR - Adjusted Hazard Ratio)

MMS – Multi-Month Scripting

MoHCC – Ministry of Health and Child Care

MRCZ - Medical Research Council of Zimbabwe

NAC – National AIDS Council

NASA – National AIDS Spending Assessment

OI – Opportunistic Infections

OSDM – Operational Service Delivery Manual

PEPFAR – Presidential Emergency Plan for HIV and AIDS Relief

PLHIV - People Living with HIV

PMTCT – Prevention of Mother to Child Transmission

TB - Tuberculosis

UNAIDS - Joint United Nations Programme on HIV/AIDS

VCT – Voluntary Counselling and Testing

WHO – World Health Organization

ZIMPHIA – Zimbabwe Population-based HIV Impact Assessment

CHAPTER 1

1.1 Introduction

This section provides context to the study. It details global epidemiology of HIV, epidemiology of HIV in Zimbabwe as well strategic plans/interventions for HIV in the country.

1.1.1 Global epidemiology of HIV

Acquired Immuno Deficiency Syndrome (AIDS), one of the major communicable diseases of all time, continue to be a major global public health issue. In 2016, there were an estimated 36.7 million people living with Human Immuno Virus (HIV)– the virus that causes AIDS - with a global HIV prevalence of 0.8% among adults (UNAIDS 2016, 2017). It is estimated that 30% of these same people do not know their HIV status (UNAIDS, 2017). The HIV burden has been further compounded by the high TB/HIV co-infection rate.

Ever since the first HIV case was diagnosed, it is estimated that 78 million people have become infected with HIV, while 35 million people have died of AIDS-related illnesses (UNAIDS, 2017). In 2016 alone, it is estimated that almost one million people died of AIDS-related illnesses (UNAIDS, 2017).

Evidence shows that most people living with HIV (PLHIV) are in low and middle-income countries (UNAIDS, 2017). It is estimated that 25.5 million of PLHIV are in Sub-Saharan Africa, with 19.4 million living in East and Southern Africa (UNAIDS, 2016).

At a global level, it is estimated that in 2016 alone, there were about 1.8 million new HIV infections, a decline from 2.1 million new infections recorded in 2015 (UNAIDS, 2017). Almost 44% of all new HIV infections globally, in 2016, were reported in Eastern and Southern Africa (UNAIDS, 2017). While there has been tremendous progress made across the 69 countries which witnessed a decline in new infections, UNAIDS notes that progress in combating viral transmission is still not happening fast enough to meet global targets (UNAIDS, 2017). A closer introspection of country specific data shows huge discrepancies in efforts to slow the spread of new infections. While some countries have achieved a decline of 50% or more in new HIV infections among adults over the last 10 years, some have made no measurable progress (UNAIDS, 2017). There are some countries that are still experiencing worrying increases in new HIV infections. For instance, since 2010, the annual number of new infection in the Eastern Europe and Central Asia region is estimated to have increased by an alarming 60% since 2010 (UNAIDS, 2017).

Previously there has been concern that the annual number of new infections, globally, among adults would remain static, as incidence rates failed to shift significantly between 2010 and 2015 (UNAIDS, 2017). However, new evidence shows a slightly more positive trend is emerging as new infections among adults are now estimated to have declined by 11% and 16% for the general population for the period 2010 and 2016 (UNAIDS, 2017).

While evidence shows that new HIV infections among children (0-14 years) globally have halved, from an estimated 300,000 in 2010 to 160,000 in 2016 (47%), stakeholders note that there is much more that needs to be done to improve knowledge and use of HIV testing services among adolescents and young adults (UNAIDS, 2017). This is because evidence points to increased risk among adolescent girls and young women (AGYW), with 59% of new infections in young people aged 15-24 occurring among this group (UNAIDS, 2017).

Despite the continued high levels of HIV infection, unprecedented gains have been made in the expansion of ART in resource-constrained settings. According to the United Nations Joint Programme for HIV/AIDS (UNAIDS), there were an estimated 18.2 million people [16.1 million – 19.0 million] accessing antiretroviral therapy in June 2016, up from 15.8 million in June 2015 and 7.5 million in June 2010 worldwide (UNAIDS, 2017). This was made possible through joint support between the international community and governments. For instance, at the end of 2016, US$ 19.1 billion was available for the AIDS response in low and middle-income countries. Domestic resources constituted 57% of the total resources for HIV in low- and middle-income countries in 2016. According to UNAIDS, an estimated US$ 26.2 billion will be required for the AIDS response in 2020 in low- and middle-income countries, with US$ 23.9 billion required in 2030 (UNAIDS, 2017). Evidence shows that expanded availability and access to ART have enabled millions of people to manage HIV infection as a chronic disease worldwide (Hazra et al, 2010; Lowenthal et al., 2014).

1.1.2 Epidemiology of HIV in Zimbabwe

According to the 2017 national HIV estimates, there are an estimated 1.2 million people living with HIV (National HIV and AIDS Estimates Report, 2017). Of these, almost 975,000 were on ART as of December 2016 (MoHCC National Program Report, 2016). Given a historical monthly initiation of between 4,000 and 6,000, this translates to ART coverage of approximately 80%. It is however, worth noting that in Zimbabwe, like other countries, has a "gendered epidemic" characterized by a disproportionately high burden among women (Gilbert and Selikow, 2011). Given the better health seeking behaviours of women, compared to men,

it is also not surprising to note that at least 60% of all those on ART in the country are women (ZNASP 2015-2018).

1.1.3 Strategic plans/interventions for HIV in the country

The National AIDS Council (NAC) of Zimbabwe was introduced in 1999, through an act of Parliament, to coordinate and facilitate the national multi-sectoral response to HIV (Bhat et al, 2016). In addition, the following strategic documents developed and rolled out to support the multi-sectoral response: The National Policy on HIV and AIDS (1999); the National HIV and AIDS Strategic Framework (2000-2004); the Zimbabwe National HIV and AIDS Strategic Plan (2006-2010; 2011-2015; 2015-2018). These policy documents, together with support from various arms of government and its stakeholders, resulted in the introduction of ART into the public sector in April 2004 and the subsequent scale up of HIV care and treatment services in Zimbabwe, towards universal access (Zimbabwe UNGASS Report, 2006).

As of June 2017, there were 1,400 ART initiation and follow-up sites in the Zimbabwe (MOH, 2017). It is important to note that the rapid scale up of ART in the country has been necessitated by policy shifts in the country which allowed for both decentralization of ART services and nurse-led ART initiation. Zimbabwe's success in scaling up ART is a reflection of strong political and institutional support for reducing HIV and AIDS-related mortality through expanding access to treatment services down to the primary care level. In addition, the AIDS levy, established in 2000, remains a sustainable, innovative, home grown domestic financing mechanism for HIV support in the country. Nonetheless, at least 85% of the total cost for the national HIV and AIDS response is externally funded through the Global Fund, PEPFAR, CHAI, among other donors (NASA, 2015).

As part of the continued efforts to scale up client focused ART program at a global level, WHO released guidance (the 2013 guidelines, followed by the 2016 guidelines) focused on differentiated models of care (DMC) (UNAIDS, 2017). DMC is meant to ensure that HIV services across the cascade reflect the preferences and expectations of various groups of people living with HIV, while enhancing service delivery.

In Zimbabwe, two models of differentiated care have been adopted for stable patients: adjusted appointment spacing through multi-month scripting (MMS) and community ART groups (CAGs). CAG members rotate in collecting medications at the facility for all members. MoHCC released an updated Operational and Service Delivery Manual for the Prevention, Care and Treatment of HIV in Zimbabwe (OSDM) in February 2017. This is the second edition

of the manual originally developed in 2015. It sets out 'how' to implement WHO's 2016 clinical guidelines, including differentiated service delivery (DMC) across the entire HIV cascade from prevention to suppression.

This study looks at the contribution of multi-month scripting (MMS) on antiretroviral therapy (ART) outcomes among adult (15+ years) PLHIV in Zimbabwe, focusing on the five health facilities in Chitungwiza. In the context of this study, MMS is defined as longer (at least three months) antiretroviral ART refills for PLHIV, as per the MoHCC guidelines.

The ART outcomes evaluated in this study are survival status (dead or alive), retention/ attrition, immunological response (change in CD4 count) and clinical outcomes (weight gain).

1.2 Background

In 2013, WHO released guidance on the then new HIV treatment guidelines. Embedded in that guidance were aspects on multi-month scripting (MMS) for stable ART patients (WHO, 2013). The Ministry of Health and Child Care subsequently authored the Operational and Service Delivery Manual (OSDM). The OSDM accompanied the MOHCC 2013 clinical guidelines to all Government health facilities.

Evidence gathered by WHO shows that MMS will reduce the burden at health facilities i.e. it frees both space and time among health care workers (WHO, 2013, 2017). At the same time, frees up resources at household levels, as patients no longer need to visit health centres at frequent intervals. Given the push to aggressively roll out MMS to all ART sites, it is imperative that evidence be collected on the contribution of MMS on ART outcomes among adult persons living with HIV in Zimbabwe.

Regular HIV medical appointments are an important opportunity to monitor adherence; side effects; clinical, immunological and virological failure. Mugavero et al.'s research (2009; 2014) demonstrated a significantly increased risk of mortality in patients who missed medical visits compared with patients who kept appointments. Retaining PLHIV in care remains a key global and national concern, especially in the era of increased drug resistance. Drug resistance is not only costly in terms of medical care but affects productivity too.

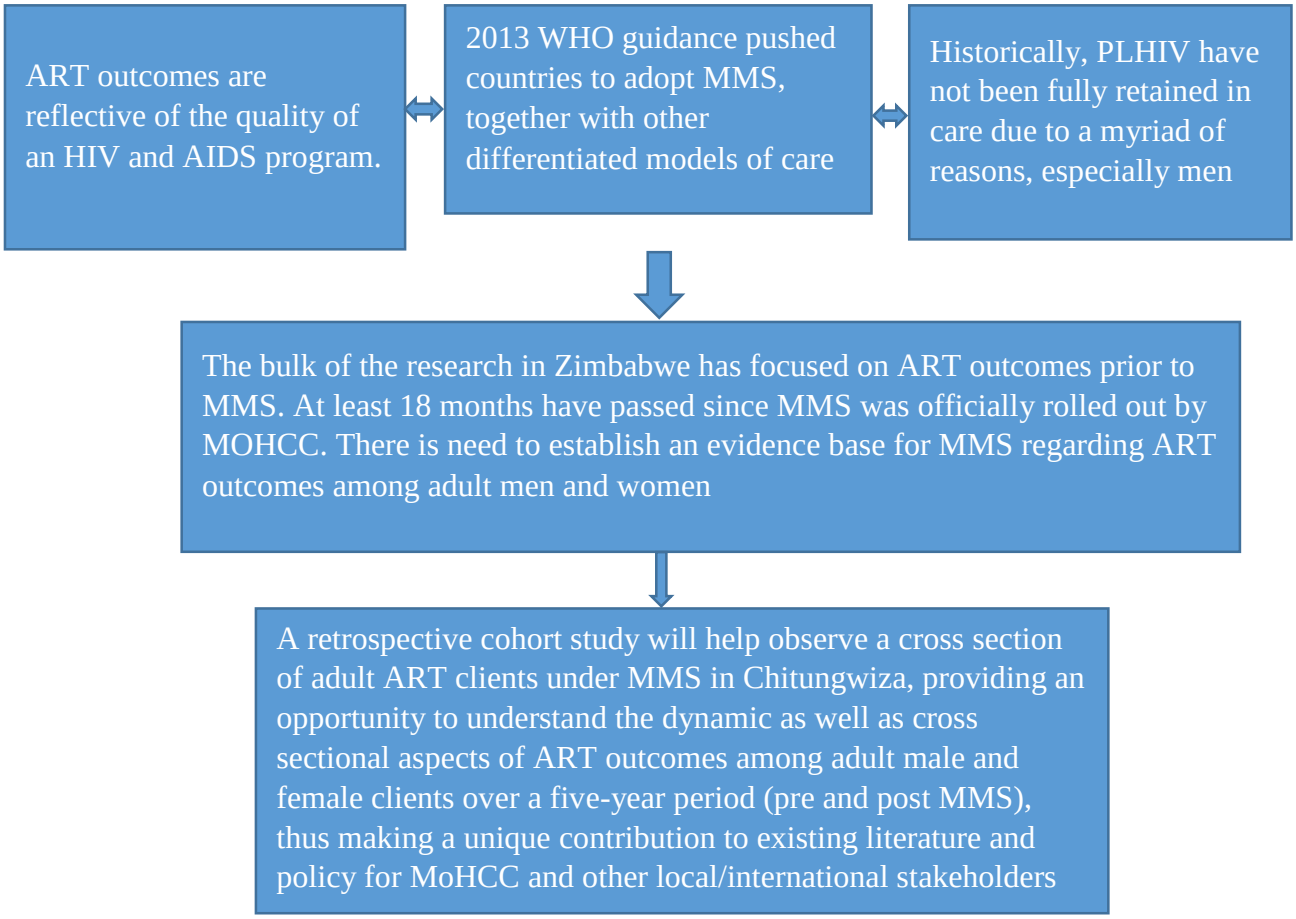
The 2016 MOHCC ART outcomes evaluation explored survival status, retention, immunological response and clinical outcomes. This study looked at the period October 2012 to January 2015, which is prior to the aggressive scale up and targeted facility support to pursue

MMS in most sites. Results showed ART retention at 3 months to be 95.5%. At 12 months, more than three quarters, 87.8% were retained in care while 82.8% were retained in care at 24 months (MoHCC ART Outcomes Report, 2016). The same report noted that consistently over the 24-month period females had better retention rates compared to males. The difference in retention rates by gender appeared to increase over time with 81.8% retention among males and 84.8% among females at 24 months. There is decrease in retention over time. This is consistent with previous ART outcomes evaluations in Zimbabwe. this study seeks to examine how ART outcomes after introduction of MMS. In addition, it also seeks to investigate factors associated with the observed ART outcomes in the country, pre-and post the MMS regime.

1.3 Rationale for the study

The rationale for this study can better be presented visually as follows:

Figure 1: Graphic justification of the study



1.4 Research questions

Below are the key questions of the study:

1. Are there significant differences in ART outcomes among adult persons living with HIV, pre-and post the MMS regime?
2. What are the factors associated with ART outcomes, including survival status, retention, immunological response, clinical outcomes and adherence over time?

1.5 Aim and Objectives

1.5.1 Aim of the study

The overarching aim of the study is to assess the contribution of the multi-month scripting (MMS) regime on ART outcomes among adult persons living with HIV in Zimbabwe.

1.5.2 Specific Objectives

The specific objectives of the study are:

1. To assess changes in treatment outcomes (survival status, retention, immunological response, clinical outcomes) among HIV infected adults pre-and post the MMS regime using longitudinal data analysis techniques
2. To identify factors associated with ARV treatment outcomes among adult ART patients using the Cox proportional hazards model
3. To provide MMS-related recommendations to MOHCC and its stakeholders

1.6 Significance of the study

This study will provide finite details on the extent to which MMS has influenced patient level outcomes. The study design allows the researcher to look at the difference in outcomes from a "before/after" and a "with/without" perspective using longitudinal analysis techniques. Factors associated with these outcomes will be explored. This will be critical information for MoHCC and other countries as they pursue various differentiated models of care for ART clients.

1.7 Delimitations of study

The study was carried out in Chitungwiza, focusing on the MOHCC ART sites in this geographic unit, namely Chitungwiza Central Hospital, Seke North Clinic, Seke South Clinic, St Mary's Clinic and Zengeza Clinic. Chitungwiza provided an opportunity to look at MMS in greater detail given that most urban areas were the first to be targeted in roll out of MMS. In addition, it serves both an urban and peri-urban population. Given that ART was rolled out in

the five facilities, this presents an opportunity to look at outcomes over an extended period of time.

1.8 Limitations

Bias in data collection: Bias primarily resulted from the retrospective nature of the study and rates of missing data. The researcher minimized bias from the data abstraction team through training, supervision and adequate data cleaning. Furthermore, the database had built-in checks that would not accept clearly erroneous values. In addition, the fact that the study only focused on Chitungwiza, a predominantly urban area, limits the extent to which findings can be generalized.

CHAPTER 2 Literature review

2.1 Introduction

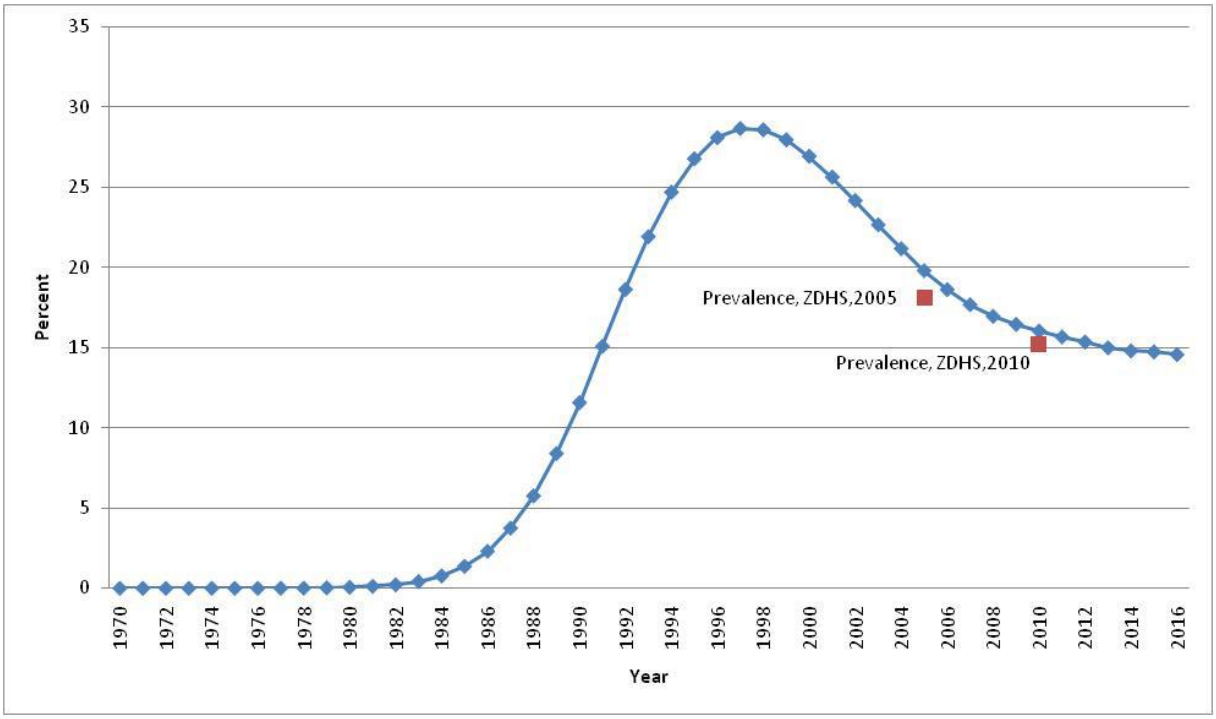
This section reviews some of the studies which have been conducted across the globe regarding the subject of interest, premised on the need to understand what has already been researched upon and the inherent therein. Embedded elements in this section include the following: the HIV and AIDS situation in Zimbabwe; WHO guidelines and differentiated models of care, differentiated models of care in the Zimbabwean context, meta-analysis of existing studies on the subject of interest (studies on MMS *vis a vis* ART outcomes, studies on factors associated with ART outcomes, similar studies in the context of Zimbabwe), as well as a conclusion to the section, focusing on significant findings from the literature review.

2.2 The HIV and AIDS situation in Zimbabwe

2.2.1 Historical trends on prevalence

The first AIDS case in Zimbabwe was reported in 1985. From 1985 to the mid-90s, the HIV prevalence rose sharply to reach a peak of 27.7% in 1997. It started declining thereafter, as shown in Figure 2 below.

Figure 2: Trends in adult HIV prevalence in Zimbabwe



Source: Zimbabwe National HIV Estimates 2015

The Zimbabwe Demographic and Health Survey (ZDHS) shows that the adult HIV prevalence declined by three percentage points from 18% to 15% over the five-year period between 2005/06 and the 2010/11. The 2015 ZDHS showed that the adult prevalence has further dropped to 13.8% (Zimbabwe National Statistics Agency and ICF International, 2005/06, 2010/11, 2015).

Overall, the HIV and AIDS epidemic in the country, like most Southern African countries, remains generalized, feminized and homogenous. The country continues to witness declines in new infection rates, prevalence and AIDS related morbidity and mortality (Zimbabwe Global AIDS Response Country Progress Reports, 2014, 2015). Of concern, however, is that there still exist areas of high HIV transmission, which include border districts, growth points, small scale mining areas, fishing camps and commercial farming settlements (HIV Hotspots Mapping Report 2014).

2.2.2 Trends in ART uptake

The government, through MoHCC, introduced antiretroviral therapy (ART) into the public sector in April 2004 (WHO, 2005). As of June 2004, there were about 6,000 PLHIV on ART in both the public and mainly the private sectors (WHO, 2005). Provision of ART in the public sector expanded thereafter. The number of PLHIV on ART doubled within nine months, between June 2004 and March 2015, to 12,000 (WHO, 2005). By November 2005, the number of PLHIV on ART had more than doubled again, to 23 000, with close to 15 000 receiving ART in public facilities (WHO, 2005). An unprecedented growth has occurred since then. As of December 2016, 975,000 PLHIV were on ART in Zimbabwe (in the public sector) out of an estimated 1.2-1.4 million PLHIV (2016 MoHCC Program Report). These numbers are supported by a decentralized network of about 1,400 ART initiation and follow-up sites in the country.

2.2.3 The current epidemiological status in the context of the 90*90*90

The 90*90*90 is an ambitious target by UNAIDS, premised on the need, by 2020, to have 90 percent of all PLHIV know their HIV status (first pillar of the HIV and AIDS); 90 percent of all PLHIV diagnosed with HIV receive sustained ART (second pillar of the HIV and AIDS cascade); and 90 percent of all PLHIV receiving ART have viral suppression (third pillar of the HIV and AIDS cascade). This is part of the global epidemic control agenda.

To help measure progress towards these ambitious targets, in 2015-16, the Government of Zimbabwe (GoZ), with support from the Centres for Disease Control (CDC), conducted the Zimbabwe Population Based HIV Impact Assessment (ZIMPHIA).

Evidence from the ZIMPHIA shows that prevalence of HIV among adults ages 15-64 years in Zimbabwe is 14.6 percent i.e. 16.7 percent among females and 12.4 percent among males. This corresponds to approximately 1.2 million PLHIV aged 15-64 years in Zimbabwe. The huge disparity in HIV prevalence by sex is most pronounced among young adults where HIV prevalence among 20-24-year olds is three times higher among females (8.5 percent) than males (2.7 percent).

The ZIMPHIA shows that 74.2 percent of PLHIV ages 15-64 years report knowing their HIV status i.e. 77.1 percent of HIV positive females and 69.7percent of HIV-positive males reportedly know their HIV status.

According to the same report, among adult PLHIV ages 15-64 years who know their HIV status, 86.8 percent self-reported current use of ART (to be confirmed through metabolite testing) i.e. 87.3 percent of HIV-positive females and 86.0 percent of HIV-positive males who knew their HIV status self-reported current use of ART.

Among PLHIV ages 15 to 64 years who self-reported current use of ART, 86.5 percent are virally suppressed: 87.9 percent of HIV-positive females and 84.1 percent of HIV-positive males who self-reported current use of ART were virally suppressed.

Overall, the above results show that the country is on track to achieve epidemic control. The focus now is continue strengthening activities and support services for certain vulnerable groups like AGYWs and men. Geographic focusing of services remains an important arm of the current strategy to successfully manage the epidemic in the country.

2.2.4 Differentiated models of care

According to Grimsrud A et al, 2016, differentiated models of care are a client-centered suite of approaches that simplify and adapt HIV services across the cascade, in ways that both serve the needs of PLHIV better and reduce unnecessary burdens on the health system. They are also meant to enhance patient level ART outcomes.

Since the launch of the 2013 WHO guidelines, there has been growing support for differentiated service delivery (DSD) of HIV care to increase service efficiencies and impact at patient level. According to Grimsrud A et al, 2016, DSD reflects the preferences and

expectations of various groups of people living with HIV (PLHIV), further supporting the concept of the right to health for PLHIV, where access and quality of services are key underpinnings of the concept. DSD is promoted by the latest World Health Organization (WHO) guidelines for preventing and treating HIV infection, building on the 2013 guidelines (WHO, 2016).

Current evidence shows that the inclusion of differentiated care catalyzes long-standing efforts to provide holistic and supportive care, particularly to underserved client groups.

Consequently, several countries in sub-Saharan Africa have incorporated differentiated models of care into their national guidelines; these include South Africa, Malawi, Swaziland, Zimbabwe, among others. Major donors, including the Clinton HIV and AIDS Initiative (CHAI), U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund, have promoted the adoption of differentiated models in several of countries, through targeted support to roll out reduced frequency of clinic visits and longer antiretroviral therapy (ART) refills (multi-month prescribing).

A few of the well-known models of differentiated care have focused on ART delivery to clients who are clinically stable. These have largely been implemented in high-prevalence countries in sub-Saharan Africa and include client-managed groups e.g. community adherence groups in Mozambique (International Treatment Preparedness Coalition, 2016); health care worker-managed groups e.g. adherence clubs in South Africa (AIDS Rights Alliance of Southern Africa, 2016); facility-based individual delivery e.g. ‘‘fast track’’ ART refills in Malawi (The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2016); and out-of-facility individual delivery (e.g. community drug distribution points in Uganda (Centers for Disease Control and Prevention, 2016).

Currently, most evidence in support of DSD to date comes from pilot programs for delivering ART to stable adults in high-burden countries in sub-Saharan Africa. Yet the WHO guidelines do not restrict DSD to this group. Grimsrud A et al (2016) pointed out that the net impact of the scale-up of differentiated models of care should be evaluated with clear indicators, including quality and outcomes of care.

2.2.5 Differentiated models of care in Zimbabwe

To enhance scale-up of ART in Zimbabwe like most other countries in the region, innovative and pragmatic models have been developed to optimize the efficiency of HIV service delivery in line with the WHO guidelines (MoHCC, 2016). For the country, two models of differentiated

care for PLHIV on ART have emerged for stable patients: adjusted appointment spacing through multi-month scripting and community ART groups (CAGs), where group members rotate in collecting medications at the facility for all members.

MoHCC released an updated Operational and Service Delivery Manual for the Prevention, Care and Treatment of HIV in Zimbabwe (OSDM) in February 2017. This is the second edition of the manual originally developed in 2015. It sets out 'how' to implement WHO's 2016 clinical guidelines (building on the 2013 guidelines embedded in the 2015 version), including differentiated service delivery across the entire HIV cascade from HTS to suppression. To accompany the manual, the Zimbabwe MoHCC also developed the Consolidated HIV and AIDS Job Aide that includes checklists, clinical algorithms and educational tools to support implementation.

2.2.6 Meta-analysis of existing studies on MMS

This section details some of the studies which have been conducted across the globe in relation to MMS. This is informed by objectives one and two of the study, focusing on contribution of MMS to ART outcomes and factors associated with the observed outcomes, pre-and post the MMS regime.

2.5.1 Studies on MMS *vis a vis* ART outcome

Publicly available literature shows that at least two main studies have been conducted in the region, focusing primarily on MMS-related ART outcomes; one in South Africa and another one in Malawi. However, the researcher is also aware that some studies could have been conducted by not yet published.

A study in Malawi, conducted by Prust et al (2017), sought to assess the extent to which ART patients are differentiated premised on clinical stability. In addition, it also sought to describe the major characteristics and costs associated with the models of differentiated care offered in the country. This was a mixed methods study where interviews where the researchers interviewed 136 health care workers; reviewed of 75,364 patient clinical records; and conducted 714 observations of visit time and flow. The results show that, among ART patients, 77.5% (95% confidence interval [CI] 74.1–80.6) were eligible for differentiated models of care based on criteria for clinical stability from national guidelines. In addition, across the targeted facilities, 69% of patients were receiving MMS. In facilities offering fast track refills (FTRs) and CAGs, 67% and 6% of patients were enrolled in the models, respectively. Study results further show that the eligibility criteria were used inconsistently: 72.9% (95% CI 66.3–78.6)

of eligible patients and 42.3% (95% CI 33.1–52.0) ineligible patients received MMS. Results from the study further showed that patient travel and time costs were reduced by 67%. The computed unit costs of ART service delivery through the MMS, FTR and community ART groups (CAG) models were similar, accounting for a 10% reduction in the annual unit cost of providing care when compared with PLHIV on ART but not under these differentiated models of care. The report noted that MMS being was being implemented nationally and has already generated cost savings and efficiencies in Malawi for patients and the health system, but could be improved by more accurate patient differentiation.

This study, broad in scope of terms of clientele reach, provides an initial but crucial layer of analysis in terms of the targeting and reach of differentiated models of care. It provides important insights, especially related to inclusion/exclusion, which become important aspects as one explores the impact of the differentiated care. Lack of clarity on inclusion/exclusion "contaminates" the results and will likely dilute the net effect of differentiated care. Also, worth noting was the recognition from the researchers that *"future studies should investigate if the differentiated models lead to improvements in patient satisfaction or clinical outcomes that might justify their implementation*", a critical posture for this study.

For the study in South Africa by Williams & Wilkins in 2014 in South African, the focus was on adherence clubs (one form of differentiated models of care) and their impact on retention in care. The study recruited 1860 patients from 76 Adherence Clubs (ACs). As part of the study, over the holiday period, forty-two (42) adherence clubs were given four months of ART while thirty-four ACs were given 2 months of ART. Four (4) months after the final AC visit in 2012, the study results show that 4.0% had defaulted care overall [group A, 41 of 1054 (3.9%); group B, 33 of 806 (4.1%)]. Of note was that there was no difference in the risk of defaulting from an AC in group A who received 4 months of ART compared with group B who received 2 months of ART (risk ratio, 0.95; 95% confidence interval: 0.61 to 1.49; P = 0.82). In addition, the study results further show that no significant associations were observed between viral suppression and group (risk ratio, 1.06; 95% confidence interval: 0.63 to 1.81; P = 0.82). Between the last visit of 2012 and the first schedule visit of 2013, none of the club patients died.

The study escribed above begins to unpack some MMS-related outcomes like what this researcher is exploring. However, the study restricted itself to limited outcomes, over a short time period, and in limited settings.

2.5.2 Studies on factors associated with ART outcomes

Relatively a significant number of studies have been conducted in various settings to assess factors associated with ART outcomes, the majority of them prior to MMS. Below is a meta-analysis of such studies in the context of this research.

2.5.2.1 Factors associated with treatment failure

The United States' Department of Health and Human Services (2013) reported that treatment failure may occur in PLHIV due to various risk factors. These include poor adherence to treatment, poor absorption of ARVs, previous treatment failure, drug resistance, co-morbidities, drug toxicity and drug interactions, poor health prior to initiation of ART, as well as substance abuse (e.g. tobacco smoking or excessive alcohol consumption) leading to poor adherence. Other studies (Anude, Eze et al. 2013; Khienprasit, Sirisanthana et al. 2011; Ng'ang'a, Muttai et al. 2012; Crabtree-Ramirez, Villasis-Keever et al. 2010,) also seem to suggest that other factors such as advanced HIV disease, gender, ARV regimens low baseline CD4, age, and long periods on ART are strongly associated with treatment failure.

A study by Haile et al (2016) investigated the predictors of treatment failure among adult ART clients in the Bale Zone Hospitals, South Eastern Ethiopia. The study used a retrospective cohort study from four hospitals of Bale zone named Delomena, Robe, Goba and Ginir. Included in the study were 4,809 adult ART clients from these four hospitals. As a standard, adherence was measured by pill count method. The research used the Kaplan Meier curve to describe the survival time of ART patients. In addition, bivariate and multivariable Cox proportional hazards models were used to identify factors associated with treatment failure. The study results showed that male ART clients were more likely to experience treatment failure as compared to females [AHR = 4.49; 95% CI: (2.61±7.73)]. In addition, lower CD4 count (<100 m3/dl) at initiation of ART was found to be significantly associated with higher odds of treatment failure [AHR = 3.79; 95% CI: (2.46±5.84). Similarly, bedridden [AHR = 5.02; 95% CI: (1.98±12.73)] and ambulatory [AHR = 2.12; 95% CI: (1.08±4.07)] patients were more likely to experience treatment failure as compared to patients with working functional status. As expected, TB co-infected clients also had higher odds of experiencing treatment failure [AHR = 3.06; 95% CI: (1.72± 5.44)]. The study further showed that patients who developed TB after ART initiation had higher odds to experience treatment failure as compared to their counter parts [AHR = 4.35; 95% CI: (1.99± 9.54]. Having other opportunistic infections during ART initiation was also found to be associated with higher odds of experiencing treatment failure [AHR = 7.0, 95% CI: (3.19±15.37)]. Having fair [AHR = 4.99 95% CI:

(1.90±13.13)] and poor drug adherence [AHR = 2.56; 95% CI: (1.12±5.86)] were significantly associated with higher odds of treatment failure as compared to clients with good adherence.

Overall, the study by Haile et al (2016) shows two sets of variables: one with narrower confidence intervals (implying less variability) e.g. having a lower CD4 count, ambulatory status, TB coinfection and poor drug adherence. The other set of variables have wider confidence intervals (implying higher variability) e.g. bed ridden, developing TB after initiation, other OIs and fair drug resistance. This study explores some of the major factors being investigated in this study and provides critical insights into what to potentially expect. That it is a recent study adds value to what is being investigated in this study. However, the study report does not show whether these findings are reflective of a post MMS era or not. Nonetheless, other reviews done by this researcher show that Ethiopia has adopted the differentiated models of care.

2.5.2.2 Factors associated with survival

A retrospective study conducted by Ram Bajpai et al (2016) assessed the survival rates and factors associated with survival among adult PLHIV in Andhra Pradesh, India. This research piece used data from 139 679 PLHIV aged ≥15 years on ART, registered between 2007 and 2011. These were followed up through December 2013. The outcome of interest was death of the client. The Kaplan-Meier was used to estimate survival, while the Cox-regression models was used to explore the factors associated with survival.

The study results show that approximately 13% of those newly initiated on ART died during follow-up with 56% of all deaths occurring within the first three months. From the study, the CD4 count (adjusted hazard ratio of 4.88; 95% confidence interval of 4.36 to 5.46 for <100 cells/mm3 vs. >350 cells/mm3); functional status (adjusted hazard ratio of 3.05; 95% confidence interval of 2.82 to 3.30 for bedridden vs. normal), and body weight (adjusted hazard ratio of 3.69; 95% confidence interval of 3.42 to 3.97 for <45 kg vs. >60 kg) were strongly associated with the survival of HIV patients.

This study by Ram Bajpai et al (2016) shares a lot of methodological similarities with the study being undertaken by this researcher. This is exemplified by the following: a retrospective design, a relatively long follow up (which however is only half of what my study is looking at), and significantly larger sample size. It is also worth recognizing the narrower confidence intervals in this study (reflective of less variability owing to a large sample, among other factors). However, this study explores only a limited set out outcomes (primarily survival) in

comparison to what this study is investigating. Nonetheless, it provides a rich repository for the current study.

2.5.2.3 Factors associated with immunological and or virologic failure

Virologic failure remains one of the major ART outcomes for PLHIV on ART. Evidence shows that there is a myriad of factors associated virologic failure. These include, but not limited to the following: hazardous drinking of alcohol which affect adherence to ARVs (Chander, Lau et al. 2006); opportunistic infections during ART (Alave, Paz et al. 2013); previous exposure to ARVs before initiation of ART; advanced HIV disease (WHO clinical stage 4) (Huong, Bannister et al. 2011); change of ARVs due to toxicity; and baseline haemoglobin level less than 10g/dl (Anude, Eze et al. 2013). On the other hand, other studies indicated that sexual orientation of the patient (comparing heterosexual and non-heterosexual); marital and employment status (Datay, Boulle et al. 2010, Anude, Eze et al. 2013); patient's residence (whether urban or rural), pre-ART opportunistic infections, co-infection with Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), (Khienprasit, Sirisanthana et al. 2011).

In addition, other studies have also shown that nondisclosure of HIV status, history of Tuberculosis (TB), socioeconomic status/class, history of smoking at time of viral load testing, herbal medicine use at the time of viral load testing (Anude, Eze et al. 2013) and comorbidities (Chao, Tang et al. 2012) are associated with virologic failure.

While the HIV epidemic remains a "gendered one", studies done in Massachusetts General Hospital out-patient HIV clinic in the USA; in Clinicas de Porto of Brazil and in Chiang Mai University Hospital in Thailand showed that male gender was not associated with virologic failure (Khienprasit, Sirisanthana et al. 2011; Tuboi, Harrison et al. 2005; Robbins, Daniels et al. 2007). Similarly, a study done in Nigeria (Anude, Eze et al. 2013) and one done in a public HIV treatment program in Western Cape, South Africa (Datay, Boulle et al. 2010) showed that the male gender was not associated with virologic failure. However, a study done in the Americas (Mexico) showed different results i.e. the results showed that the female gender was marginally associated with virologic failure (Villasis-Keever et al. 2010).

2.5.3 Studies in the context of Zimbabwe

In a study by Mutasa-Apollo et al (2014), a retrospective review patient level data for adults ≥15 years initiated on ART from 2007 to 2009 was done. Bivariate analysis was done for rates of retention in care and changes in health status outcomes at 6, 12, 24 and 36 months respectively. The Cox proportional hazards models were used for determining factors

associated with attrition. The study results showed that rates of patient retention at 6, 12, 24 and 36 months were 90.7%, 78.1%, 68.8% and 64.4%, respectively. The results further showed that after ART initiation, the median weight gains at 6, 12, and 24 months were 3, 4.5, and 5.0 kgs whilst median CD4+ cell count gains at 6, 12 and 24 months were 122, 157 and 279 cells/μL respectively. The study further showed that the main factors associated with an increased risk of attrition included male gender (*AHR* 1.2; 95% CI, 1.1–1.4), baseline WHO stage IV (*AHR* 1.7; 95% CI, 1.1–2.6), lower baseline body weight (*AHR* 2.0; 95% CI, 1.4–2. 8) and accessing care from higher level healthcare facilities (AHR 3.5; 95% 1.1–11.2).

In 2015, an evaluation of treatment outcomes was undertaken by MoHCC. This study built on the 2010 ART outcomes evaluation (which only included adults >15 years and who were enrolled in ART care for at least three months prior to the study). In this current evaluation, its scope was extended to examine clinical outcomes of children, adolescents, adults and pregnant women enrolled in the national ART program at health facilities in Zimbabwe. Using a retrospective cohort analysis, the study collected key demographic, programmatic, clinical and biological information from patients enrolled in the ART program for 3 months or longer prior to the study. The study assessed mostly treatment outcomes of HIV-positive children (<15 years), adolescents, adults (≥15years) and pregnant women enrolled in ART care in Zimbabwe at 3, 6, 12 and 24-months post ART initiation. The study also sought to identify factors associated with poor outcomes including survival and retention at 3, 6, 12 and 24-months post ART initiation as well as describing contextual issues affecting treatment outcomes from the provider's perspective. All children, adolescents, adults and pregnant women initiated on ART at the sampled sites between 1 October 2012 and 31 January 2015 regardless of treatment outcome at the time of medical record abstractions were eligible for inclusion. The study used the Kaplan Meir to estimate survival, while logistic regression was used to explore factors associated with the outcomes of interest. This is in addition to the other bivariate and multivariate analysis techniques employed.

From the study, the results show that at the 95% CI, overall retention rates at 3,6,12 and 24 months were 95.4%, 92.4%, 87.7% and 83% respectively. Loss to follow up increased from 4% at 3 months to 16.2% at 24 months. Retention rates at 12 months were slightly higher among children at 83.8%. Retention in ART at 12 months among pregnant women was lower at 65% among those aged 10-19 years and 80% among those ≥20years of age. Among adult patients 0.5% had had a regimen change at 12 months and this gradually increased to 1.6% at 24 months. Regimen changes were more frequent among children aged 6 to 14 years where

2.7% had a regimen change at 12 months and 4.7% at 24 months. Among children aged <5years, 2.4% had a regimen change at 12 months and only 0.6% had a regimen change at 24 months. The most common reason for regimen changes was stock outs of ARVs. The retention rates at 3,6,9,12 and 24 months observed in this evaluation are higher than those reported in ART outcomes evaluations within Sub-Saharan Africa. They also higher than the rates reported in the Mutasa-Apollo et al (2014) study and the first MoHCC ART outcomes of 2010. In this evaluation, after weighting, there was no significant difference at 24 months between the proportions of males retained in care 83.3% compared to 82.2% women. However, similar evaluations undertaken in the SADC region have reported lower retention rates among males as well as higher mortality rates in the first 6 months of ART initiation. The proportion of pregnant women lost to follow up increased significantly from 3.4% at 3months to 30.3% at 12 months and remains relatively high with 27.6% reported as lost to follow up at 24 months.

The major factors associated with the major outcomes of interest mirrored those from the Mutasa-Apollo et al (2014) study and the 2010 ART outcomes study to a large extent. This study looked at the October 2012 to January 2015 ART cohort period. This is prior to the aggressive scale up of MMS in most sites. These studies form the basis on which this study is hinged upon. This should allow for some level of comparison.

2.5.4 Conclusion

It is clear from the above that in Zimbabwe, like the rest of Africa, several studies have been conducted around the subject of interest. However, there seems to be a general lack of MMS-specific information *vis a vis* ART outcome among adults. This, combined with the need to aggressively roll out the differentiated models of care, highlights the need for more knowledge in this area in order to create an evidence-base necessary to support implementation, hence the focus of this study.

CHAPTER 3: Methods

3.1 Introduction

This section outlines the approach to generating the data required for answering the research questions. In essence, it describes the study design and data sources including the following: data collection procedures; target population and sampling procedures, as well key variables for which data were collected. It also presents how the data will be presented and analysed. The ethical considerations are also laid out given that the data was collected from MoHCC facilities and that the study deals with human subjects.

3.2 Study Design and data sources

This is a retrospective cohort analysis of treatment outcomes. Data were abstracted from the OI/ART patient care booklets for clients initiated on ART between October 2012 and March 2013. MMS is the exposure variable, while the outcomes of interest are (clinical outcomes (weight gain, OIs, TB AEs); survival status, adherence; and retention.

3.3 Study Population

A. Site Selection

Data were collected from all five MOHCC facilities in Chitungwiza; namely Chitungwiza Central Hospital, Seke North Clinic, Seke South Clinic, St Mary's Clinic and Zengeza Clinic. Retrospective data were abstracted from the OI/ART Patient Care Booklets for the period March 2013 to March 2017 for patients who were initiated on ART between October 2012 and March 2013.

B. Patient Inclusion Criteria

All HIV positive clients 15 years and older, who were initiated on ART between the October 2012 and March 2013, at the five ART sites in Chitungwiza, regardless of treatment outcome, were included in the study.

C. Patient Exclusion Criteria

Patients initiated on ART after March 2013 were excluded from the study as well as those without a documented ART initiation date were excluded from the study.

3.4 Sample size considerations

It is important to note that the study sought to detect the contribution of MMS on ART outcomes. In this regard, the study assumed the following:

- 50% of the adult patients were retained on ART over the course of the study period, 12 months after retention;
- that about 20% of the patients OI/ART Patient Care Booklets were missing; and that the design effect was 2.

This implied that the study needed to sample a minimum of 310 OI/ART Patient Care Booklets to generate 95% confidence intervals with +/-2.5% bounds around the proportion of interest.

The sample is distributed as follows (Table 1), per site, using probability proportional to size (as per their ART volume in June 2013):

Table 1: Sample size per health facility

Name of Health Facility	**Proportion**	**Sample size**
Chitungwiza Central Hospital	0.443371	137 (F=82; M=55)
Seke North Clinic	0.056729	18 (F=11; M=7)
Seke South Clinic	0.196021	60 (F=36; M=24)
St Mary's Clinic	0.127106	39 (F=24; M=15)
Zengeza Clinic	0.176786	56 (F=33; M=23)
Total	1	310 (F=186; 124)

3.5 Selection of individual ART records

All individuals on ART have OI/ART patient care booklets with unique identification numbers. The unique numbers, for the cohort of interest across the five sites, were entered into Microsoft Excel to generate a randomly ordered list of all patients at the site, as per the inclusion and exclusion criteria highlighted above. If a selected, eligible medical record is unavailable for review at the time of the site visit, ART clinical staff, who were present during the abstraction, will help determine whether it has been removed for patient tracing or other purposes (and therefore were retrieved where possible). Overall, a list of randomly identified OI/ART patient care booklets were selected until the quota of medical records for that site has been reached.

3.6. Variables collected during data abstraction

Below, in Table 2, is a construct of the key outcome variables for the study.

Table 2: The key outcome variables

Domain	**Variable**

Survival status	Dead or alive
Retention	Loss to follow up, on time pill pick up (active client)
Immunological/virological response	Change in CD4 count or viral load, treatment failure
Clinical outcomes	Weight gain, OIs

In addition to the key outcome data already described, a number of patient demographic and clinical data variables were abstracted during the evaluation. The data abstraction tool is documented in Appendix 1. A complete list of data to be abstracted is recorded below (Table 3):

Table 3: List of other variables to be abstracted

Domain	**Variable**
Demographic	Date of birth; Age at enrollment into HIV care; Sex; Residence at HIV care initiation; i.e. ward, town, and city; Marital status of the patient; Educational level reached at the time of enrollment into HIV care; Employment status at the time of enrollment into HIV care; and; Number of family members also in HIV Care at the time of enrollment into HIV care.
HIV Diagnosis information	Date of first HIV diagnosis recorded in the chart
Time Span of HIV Care	Date of HIV care initiation, ART initiation, and most recent ART visit
Source of referral	Referral source to HIV care
Pre-ART Care Information	WHO stage, weight, CD4 count at pre-ART care initiation; Opportunistic infections experienced before ART initiation; Was the patient prescribed Cotrimoxazole at HIV Care initiation; If female, was the patient

	screened for pregnancy; Was the patient screened for active tuberculosis prior to ART initiation and if so, what method was used?
ART Initiation Visit	Weight; Hemoglobin; CD4 count; Clinical stage; Cotrimoxazole prescription and ART Regimen at ART initiation
Most Recent ART visits	Weight; Clinical stage and Cotrimoxazole prescription at most recent visit
Key Events during ART	Since ART initiation is the patient alive and on ART or, has the patient; Stopped ART; Transferred out of care at that facility; Died; Been lost to follow-up. (For this study, an adult who is lost to follow-up were defined as an adult who is more than 90 days late for the last scheduled appointment with the health care provider or pharmacy); Defaulter. (For this study, an adult who has not come back to the clinic for less than 90 days for the last scheduled appointment with the health care provider or pharmacy) Where applicable, what was the reason for stopping ART; and what was the recorded cause of death
Regimen Changes and Drug Substitutions	Was the patient's regimen changed and, what was the reason for changing the regimen; Was a drug substituted and, what was the reason for the drug substitution?
Follow-up Information	Dates of all follow-up appointments and weights post ART initiation; Dates and values of all CD4 counts and hemoglobin levels after ART initiation
Adverse Events and Opportunistic Infections during ART	Occurrence of adverse events related to ART medication; Occurrence of opportunistic

	infections after ART initiation; Occurrence of WHO stage III & IV events while on ART
Counseling	Did the patient receive counseling prior to ART initiation, and at regular intervals during follow-up?
Adherence	Did the patient had any treatment interruptions

3.7 Recruitment of the data abstraction teams and capacity building

The student researcher recruited four data research assistants to work on the data abstraction. Before beginning data collection, all data abstractors underwent two-day training on the protocol, forms, and study procedures. This training was conducted at Parirenyatwa Group of Hospitals in Harare as per the MoHCC Directorate guidance. During training, the importance of maintaining confidentiality of the patients whose OI/ART Patient Care Booklets are reviewed was emphasized.

3.8 Chart abstraction

The following process was followed.

- One team of four data abstracters worked on this process as mentioned above. As per protocol, MOHCC Head Office, the Chitungwiza Central Hospital CEO, the Superintendent at CITIMED Chitungwiza Hospital and the Chitungwiza City Health Department were informed of the purpose and timing of the visit, including names of the data abstraction team.
- When the team arrived at the clinic, the abstractors met with and oriented one to two clinic staff about the objectives of the study and sought for any adult ART patient registers.
- The study numbers on each data extraction form are different to these unique identification numbers. In this way, there were no unique identifiers on any of the data abstraction forms that will allow data, collected on the form, to be linked with a specific patient attending the clinic.
- Where registers were not available, numbers were assigned to all adult ART patient OI/ART Patient Care Booklets for the purpose of sampling. Again, these numbers were not the same as the study numbers entered onto the data abstraction forms.

- Once numbers were assigned to all adult ART patient OI/ART Patient Care Booklets, Microsoft Excel was used to generate a list of randomly ordered ART OI/ART Patient Care Booklets at each site. The first sequential OI/ART Patient Care Booklets in the list were then be selected for review until the quota for the site is reached.
- Data was abstracted using the data abstraction tool (Appendix 1).
- A "study register" was created during chart review to document which records were not found or which were discarded due to one of the different exclusion criteria. The study register will not have any patient name. The study register was used to document the number of missing records at the facility and provide recommendations to the MoHCC at the end of the study.
- Feedback was given to the clinical staff at the end of the session based on the observations of the abstractors. Feedback focused on the importance of monitoring and evaluation of ART for quality promotion.
- The data was captured using tablets running on an ODK platform. After each site visit, all the data would be sync into a database managed by this researcher.

3.9 Data analysis

All analyses were performed using STATA/SE 12.0. Pre-analysis data management was performed to recode, encode, and create categories, destring, and categorize data values, respectively as necessary. Univariate analysis was conducted to come up with proportions, summary statistics, including point and dispersion estimates. The Wilcoxon matched –pairs signed-ranks test was applied to test for median difference between baseline CD4 and CD4 follow up, and baseline weight and follow-up weight, respectively.

The Kaplan Meier and Nelson-Aalen methods were used to model survivorship function curves for retention and survival stratified by selected independent variables. The log-rank test was performed to test the significance of the difference in retention and survival for selected categorical variables. Univariate and multivariate analysis was also performed using a linear regression, Poisson regression, and logistic regression for predictors of weight gain, immunological gain and retention, and parametric survival Weibull regression for predictors of survival, respectively. Since some variables were suffering from missingness and inadequacy, we performed missing description procedure in STATA to produce a table with the number of missing values, total number of cases, and percent missing for each variable. Once these variables were identified, they were registered for imputation, and chained

imputation approach applied for 80 imputation iterations. The data was then declared as imputation set and time-to event data, particularly for Cox Proportional Hazards Regression. Post estimation diagnosis was also performed to test the adequacy of all the models.

3.9.1 Controlling for confounding

The nature of the variables being investigated were all prone to confounding, hence the design which allowed for a longer follow up of clients (over a five-year period), allowing the researcher to explore both the "with/without" and "before/after" analysis.

3.10 Ethical considerations

Ethical approval was sought from the Medical Research Council of Zimbabwe (MRCZ) prior to the data abstraction process. To ensure confidentiality, no personally identifiable information relating to clients, such as patient name or clinic registration, number were collected during chart extraction. Data abstractors were trained on the importance of maintaining confidentiality. They all signed a confidentiality notes. All the data was kept by the principal investigator on a personal computer with a password-protected login screen.

3.11 Administrative approval

Clearance was sought from the MOHCC Head Office, the Chitungwiza Central Hospital CEO, the Superintendent at CITIMED Chitungwiza Hospital and the Chitungwiza City Health Department.

Chapter 4: Presentation, analysis and interpretation of data

4.1 Introduction

This chapter details the findings, analysis and interpretation of the data gathered whose two-pronged objectives were to help understand the contribution of the multi-month scripting (MMS) regime on ART outcomes among adult persons living with HIV in Zimbabwe as well as to explore the factors associated with the observed outcomes.

Data from 305 ART patient charts from the five health facilities in Chitungwiza was abstracted using Personal Digital Assistants (PDA) running on an Open Data Kit (ODK) platform. A minimum sample of 310 was anticipated. All the data was transferred to STATA/SE 12.0 for data analysis.

This chapter is organized into the following sections: demographic characterization of the sample; health related characteristics of the sample; treatment outcomes analysis, pre and post MMS; factors associated with the treatment outcomes; and discussion of results.

4.2 Sample description

This section provides a synopsis of the sample in terms of its demographic and health characteristics. This characterization is important as it will form the initial basis on which to answer the key objectives of this study.

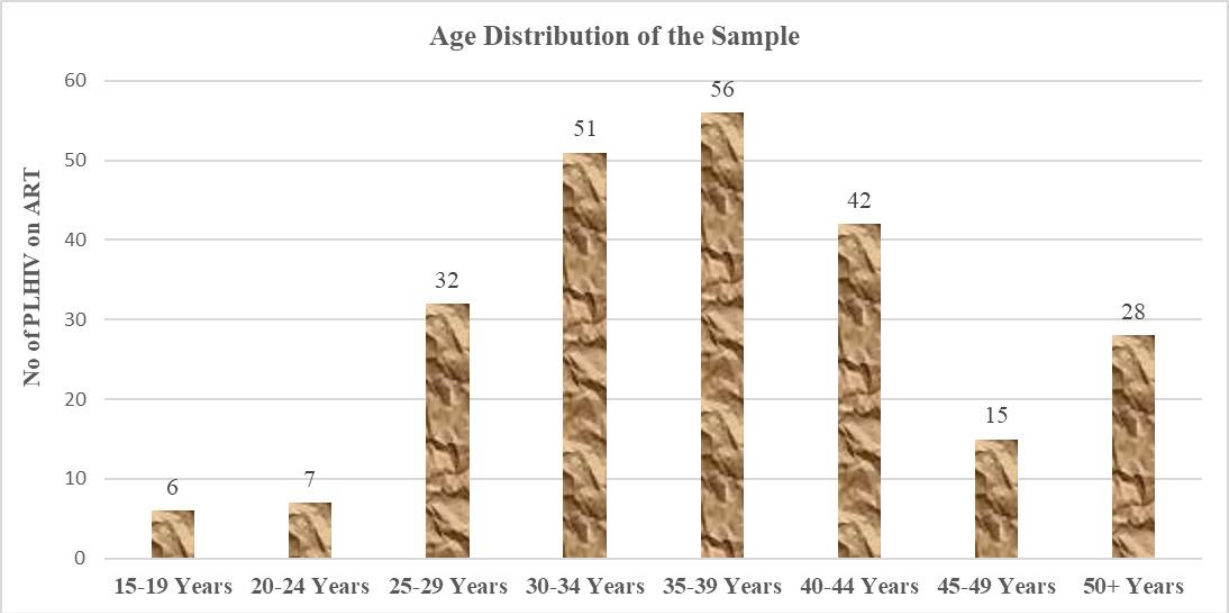
4.2.1 Demographic characterization of the sample

This section details the socio-economic characteristics of the study sample, expressed statistically, such as age, sex, education level and marital status.

4.2.1.1 Age and sex characterization

Overall, 76% of the sample was drawn from the age groups 25-49 years. While the data closely approximates a normal distribution, the left skewness is apparent i.e. more people on ART among the 25+ years compared to the less than 25 years), a feature synonymous with the status of the HIV epidemic in Chitungwiza in particular, and Zimbabwe in general.

Figure 3: Age distribution

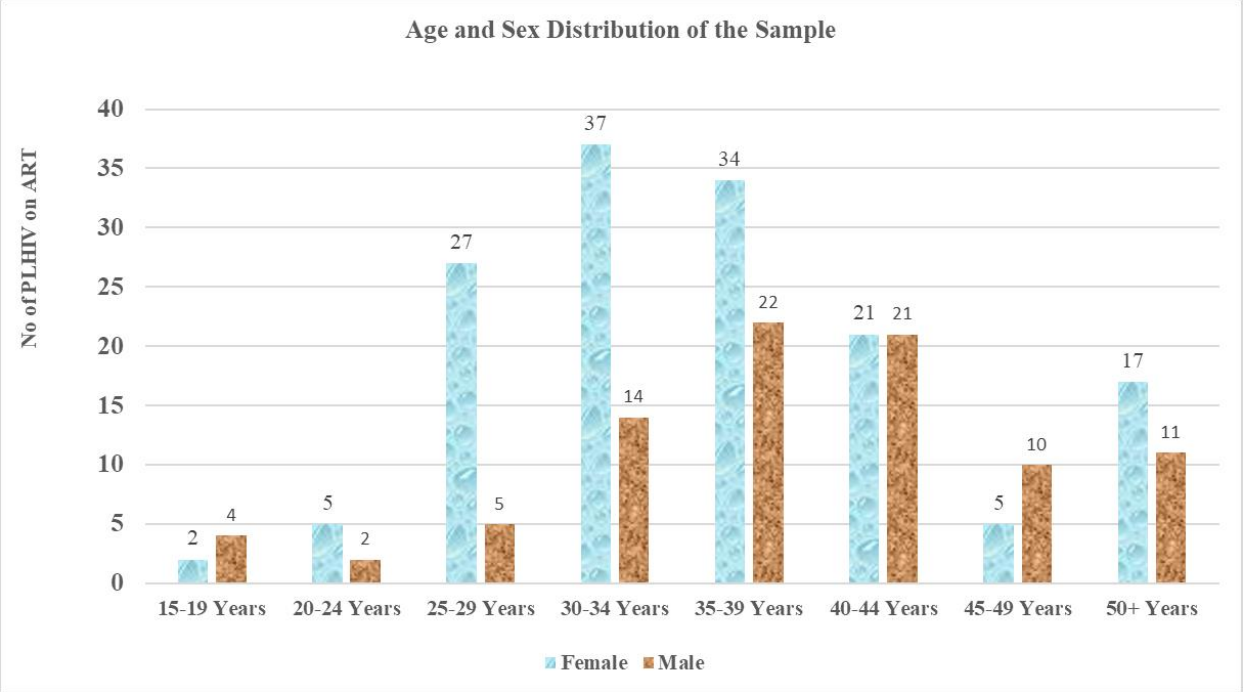


Source: Study survey data, 2017

The majority (24%) of the clients were in the 35-39-year age group, followed by the 30-34-year age group (22%) as shown in Figure 3 above.

Sixty percent of the respondents were females. As shown in Figure 4 below, there are apparent age-sex specific differences worth mentioning. For instance, the majority of the females included in the study were in the 30-34-year age group, while for men the data shows a seemingly bimodal distribution for 35-39 and 40-44-year age groups.

Figure 4: Age and sex distribution



Source: Study survey data, 2017

4.2.1.2 Marital status and level of education

As shown in Table 4 below, overall, 64% of the clients were married (79% of males compared to 59% females), while 18% were widowed (26% of women compared 7% men). Almost 10% were divorced (13% women compared to 4% men), and a further seven percent were single (same percentage among both males and females).

Table 4: Marital status and level of education

Demographic Variable	**Female ART Clients**			**Male ART Clients**			**Overall Sample**	
Marital Status	Number	Percent		Number	Percent		Number	Percent
Divorced	24	13%		5	4%		29	10%
Married	99	54%		96	79%		195	64%
Single	13	7%		9	7%		22	7%
Widowed	47	26%		9	7%		56	18%
Unknown Status	0	0%		3	2%		3	1%
Total	**183**	**100%**		**122**	**100%**		**305**	**100%**
Level of Education								
None	2	1%		1	1%		3	1%
Primary	27	15%		10	8%		37	12%
Secondary	123	67%		95	78%		218	71%
Tertiary	2	1%		1	1%		3	1%
Unknown Level	29	16%		15	12%		44	14%
Total	**183**	**100%**		**122**	**10%**		**305**	**100%**

Source: Study survey data, 2017

The majority (71%) of the clients attained a secondary level of education. By sex, more males (78%) than females (67 %) reached secondary level of education. On the contrary, more females than males (15% vs. 8%) attained a primary level of education. Only one percent of both males and females reached tertiary level. In addition, only one percent did not have any level of education.

4.2.2 Health related characteristics of the sample

This section provides the HIV and AIDS related characteristics of the study sample, expressed statistically, such as referral source for HIV care and treatment, WHO staging, CD4+ cell count at initiation, prior ART exposure, as well as exposure to opportunistic infections prior to ART initiation.

There are different conduits to accessing HIV care and treatment services. As shown in Table 5 below, overall, the majority (58%) of the clients were diagnosed of HIV in voluntary counseling and testing settings and consequently referred for HIV care and treatment. In addition, 28% of the clients were diagnosed of HIV when they had been hospitalized and subsequently referred for HIV care and treatment.

There are differences among males and females in this regard. More males (71%) than females (49%) were diagnosed and referred for HIV care and treatment through VCT. In addition, more males (8%) than women (3%) were diagnosed of HIV and referred for HIV care and treatment services through TB Clinics. On the other hand, more females (34%) than males (19%) were diagnosed of HIV and referred for HIV care and treatment through hospitalization. Among females, the PMTCT and obstetrics units were also important entry points to HIV diagnosis and subsequently care and treatment.

Table 5: Clinical characteristics of the sampled male and female clients

Referrla source for HIV care and Treatment	Female ART Clients			Male ART Clients			Overall Sample	
VCT	89	49%		87	71%		176	58%
TB Clinics	5	3%		10	8%		15	5%
PMTCT	13	7%		0	0%		13	4%
Obstetrics Unit	10	5%		0	0%		10	3%
Hospitalization	62	34%		23	19%		85	28%
Home	1	1%		0	0%		1	0%
Other	3	2%		2	2%		5	2%
Total	183	100%		122	100%		305	100%
WHO Stage at Initiation	Number	Percent		Number	Percent		Number	Percent
Stage I	55	30%		20	16%		75	25%
Stage II	73	40%		40	33%		113	37%
Stage III	49	27%		59	48%		108	35%
Stage IV	6	3%		3	2%		9	3%
Total	183	100%		122	100%		305	100%
CD4+ Cell Count Done								
Yes	42	23%		29	24%		71	23%
No	141	77%		93	76%		234	77%
Total	183	100%		122	100%		305	100%
Pre-ART Exposure								
HAART	39	21%		21	17%		60	20%
PMTCT	7	4%		0	0%		7	2%
SD NVP	4	2%		1	1%		5	2%
None	133	73%		100	82%		233	76%
Total	183	100%		122	100%		305	100%
Exposure to OI prior to ART initiation								
TB	9	5%		21	17%		30	10%
Other OI	36	20%		16	13%		52	17%
None	138	75%		85	70%		223	73%
Total	183	100%		122	100%		305	100%

Source: Study survey data, 2017

In resource constrained settings like Zimbabwe, the WHO Clinical Staging and Disease Classification System (revised in 2007) has been readily utilized by clinicians when determining the need or otherwise for initiating a client on ART. The classification has been used in complementarity with CD4 cell count measurements where available. The system classifies HIV disease progression on the basis of clinical manifestations that can be recognized and treated by clinicians with varying levels of HIV expertise and training.

As shown in Table 5 above, all clients had a documented WHO Stage. Overall, 37% of the clients initiated were in Stage 2. A further 35% were in Stage 3, while 25% were in stage 1 as shown in the same table. By gender, 48% of males were initiated in WHO Stage 3, while a further 33% were initiated in WHO Stage 2. On the other hand, 40% and 30% of the women

were initiated in WHO Stages 2 and 1 respectively. In 2013, access to point of care CD4 machines was constrained to some extent, thus for most facilities, the determination to initiate was significantly influenced by the WHO stage of the client as determined by the nurse.

Of the total sample, 23% did not have a CD4 count done (42/183 women and 29/122 men) as shown in Table 6 above. In 2012/13, where point of care CD4 counts was done, ART initiations were restricted to those with a CD4 cell count of 350 cells/µL or less. The exceptions to this rule were pregnant women as well as those who were TB-HIV co-infected regardless of sex. The proportion of those with/without a documented CD4 result was the same for both males and females. The average CD4 count at initiation was 334 cells/µL for females and 289 cells/µL for males.

One of the characteristics of most ART programs is re-initiation. As shown in Table 6 above, 24% of all the clients "initiated" in this cohort had prior ART exposure. The majority were females (27%), while among males 18% had a prior exposure.

Twenty-seven percent of the sampled clients had been exposed to opportunistic infections prior to initiation. Among men, TB was more common, while "other" OIs were common among women as shown in Table 6 above.

4.3 Treatment outcomes analysis

This section provides a synopsis of the treatment outcomes over time.

4.3.1 Survival

As shown in Table 6 below, the incidence rate (failure or mortality rate) was, on average, 19 per 1000 across the age groups. It was highest, at 20 per 1000, among the 40-44 year olds and lowest among the 25-29-year age group. The median survival time is 53 months (out of a possible 60) as shown below. The median survival time is lowest in the 15-19-year age group and highest in the 20-24 and 50+ year age groups.

Table 6: Survival time data by age, sex and MMS status

Variable	Time at risk	Incidence rate	Number of subjects	Survival Time		
Age Group				25%	50%	75%
15-19 years	311	0.0192	6	51	51	53
20-24 years	375	0.0187	52	53	54	55
25-29 years	1699	0.0182	32	52	53	56
30-34 years	2686	0.019	51	52	53	55
35-39 years	2952	0.019	56	51	53	55
40-44 years	2028	0.0197	42	52	52	55
45-49 years	782	0.0191	15	51	52	55
50+ years	1383	0.0188	28	52	54	55
Total	**12216**	**0.019**	**237**	**52**	**53**	**5**
Sex						
Male	6121	0.0191	121	51	53	55
Female	9440	0.0193	183	51	53	55
Total	15561	0.0192	304	51	53	55
MMS						
No	5541	0.0195	108	51	53	55
Yes	10020	0.0191	196	51	53	55
Total	**15561**	**0.0192**	**304**	**51**	**53**	**55**

Source: Study survey data, 2017

By sex, the incidence rate is similar i.e. 19 per 1000 as shown in Table 6 above. Similarly, the median survival time is the same, at 53 months as shown in the same table. As shown in Table 6 above, the incidence rate (19 per 1000) and median survival time (53 months) does not differ by whether one is on MMS or not. Survival time is also the same at both the 25^{th} and 75^{th} percentile too.

As shown in Table 7 below, there were two failures (deaths) in the first six months after ART initiation (rate of 1.1038, 95% CI: 0.28-4.41). In addition, there were 2 deaths in the 42-48-month period (rate of 1.1869436; 95% CI: 0.2968518-4.745921). There was also one death in the 54-60-month period (rate of 5.4317824; 95% CI: .0.7655624-38.58191).

Table 7: Survival by period

Cohort	Person-time	Failure	Rate	95% Confidence Interval	
0-6 months	1812	2	1.104	0.276	4.413
6-12 months	1788	0	.	.	.
12-18 months	1782	0	.	.	.
18-24 months	1772	0	.	.	.
24-30 months	1766	0	.	.	.
30-36 months	1760	0	.	.	.
36-42 months	1744	0	.	.	.
42-48 months	1685	2	1.187	0.297	4.746
48-54 months	254	0	0	.	.
54-60 months	184	1	5.434	.	.
Total	**15561**	**5**	**0.321**	**0.766**	**38.582**

Source: Study survey data, 2017

A further interrogation of the data shows that four of the five deaths occurred among clients with no TB as shown in Table 8 below. However, as shown in the same table, the survivor function (probability of surviving beyond time, t,) was higher among clients without TB compared to those diagnosed with TB.

Table 8: The survival function by TB status

No TB	Beginning Total	Fail	Surviivor Function	Standard Error	95% Confidence Interval	
6 months	271	1	0.9964	0.0036	0.9744	0.9995
12 months	271	0	0.9964	0.0036	0.9744	0.9995
24 months	269	0	0.9964	0.0036	0.9744	0.9995
36 months	267	0	0.9964	0.0036	0.9744	0.9995
48 months	247	2	0.9887	0.0065	0.9654	0.9963
60 months	4	1	0.9768	0.0135	0.9285	0.9926
Diagnosed with TB						
6 months	29	1	0.9667	0.0328	0.7861	0.9952
12 months	29	0	0.9667	0.0328	0.7861	0.9952
24 months	28	0	0.9667	0.0328	0.7861	0.9952
36 months	28	0	0.9667	0.0328	0.7861	0.9952
48 months	27	0	0.9667	0.0328	0.7861	0.9952
60 months	1	0	.	.	.	.

Source: Study survey data, 2017

4.3.2 Retention

For retention, the incidence rate (attrition rate) was, on average, 18 per 1000 as shown in Table 9 below. It was highest among the 40-44-year age group (18.2 per 1000) and lowest among the 25-29-year age group (16.5 per 1000). The median retention time was 53 months

as shown in the same table. Median retention time was lowest in the 15-19-year age group compared to the other age groups.

Table 9: Retention over time, by age, sex, MMS status and TB status

Variable	Time at risk	Incidence rate	Number of subjects	Survival Time		
Age Group				25%	50%	75%
15-19 years	311	0.0161	6	51	51	53
20-24 years	375	0.0187	52	52	53	54
25-29 years	1699	0.0165	32	52	53	56
30-34 years	2686	0.0179	51	52	53	55
35-39 years	2952	0.0176	56	52	54	55
40-44 years	2028	0.01182	42	52	53	55
45-49 years	782	0.0179	15	52	52	55
50+ years	1383	0.0174	28	51	54	55
Total	**12216**	**0.0176**	**237**	**52**	**53**	**5**
Sex						
Male	6121	0.0168	121	52	53	55
Female	9440	0.0175	183	52	53	55
Total	15561	0.0172	304	52	53	55
MMS						
No	5541	0.0175	108	51	54	55
Yes	10020	0.0171	196	52	53	55
	15561	0.0172	304	52	53	55
TB						
No TB	14110	0.0172	274	52	53	55
Diagnosed with TB	1451	0.0172	30	52	53	55
Total	**15561**	**0.0172**	**304**	**52**	**53**	**55**

Source: Study survey data, 2017

As with survival, the median retention time was the same between males and females, at 53 months, and so were the incidence rates (17 per 1000) as shown in Table 10 above. Similarly, the data shows no differences in the median retention time between ART clients diagnosed with TB and those with no TB, see Table 10 above. A look at the data by MMS status shows that the median retention time, among clients on MMS was 53 months, compared to 54 months among clients not on MMS, see Table 9 above.

Below is a summary of retention rates at 6, 12, 24, 36, 48 and at 60 months. As shown in Table 10 below, at 12 months, the retention rate was 98%, dropping to 97% at 24 months. The

retention rate drops marginally to 96% at 36 months, before taking a dive to 91% at 48 months. At 60 months, the retention rate is 87% as shown in Table 11 below.

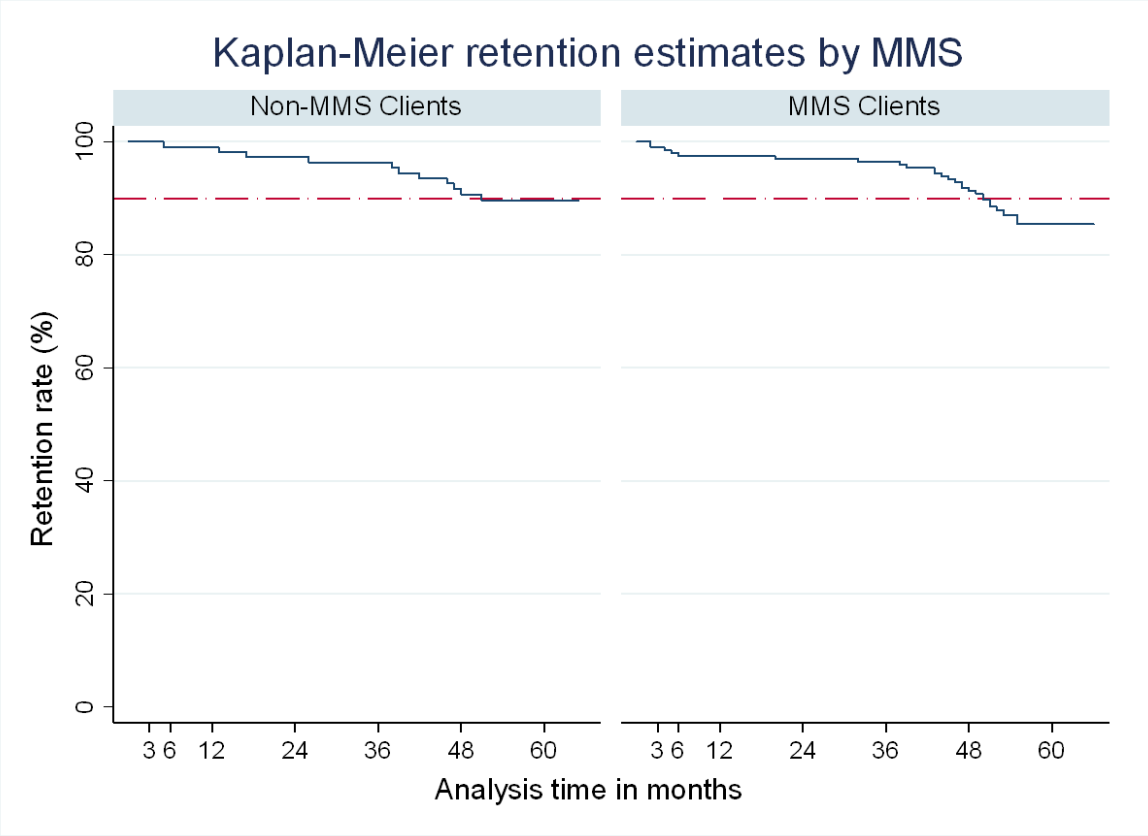
Table 10: Retention rates over time

	Total	Fail	Survivor Function	Standard Error	95% Confidence Interval	
6 months	299	6	0.9803	0.008	0.9566	0.9911
12 months	299	0	0.9803	0.008	0.9566	0.9911
24 months	296	3	0.9704	0.0097	0.9439	0.9845
36 months	294	2	0.9638	0.0107	0.9356	0.9798
48 months	273	16	0.9107	0.0164	0.8725	0.9379
60 months	4	9	0.8697	0.0214	0.8211	0.9059

Source: Study survey data, 2017

The retention rates do not differ significantly between MMS and non-MMS clients. The retention rates are shown below in Figure 5. The red line shows the 90% retention level.

Figure 5: Kaplan Meier retention estimates



Source: Study survey data, 2017

4.3.3 Immunological response

This section details changes in CD4 cell counts, comparing the initial values *vis a vis* values collected at the end of the follow up period, and assessing the level of statistical significance using the paired t test.

As shown in Table 11 below, among male ART clients, there was a statistically significant difference/change in the initial and final follow up CD4 counts for the all the clients on ART (mean difference between initial CD4 count and final follow up CD4 count is statistically significantly different from zero) i.e. p = 0.0178

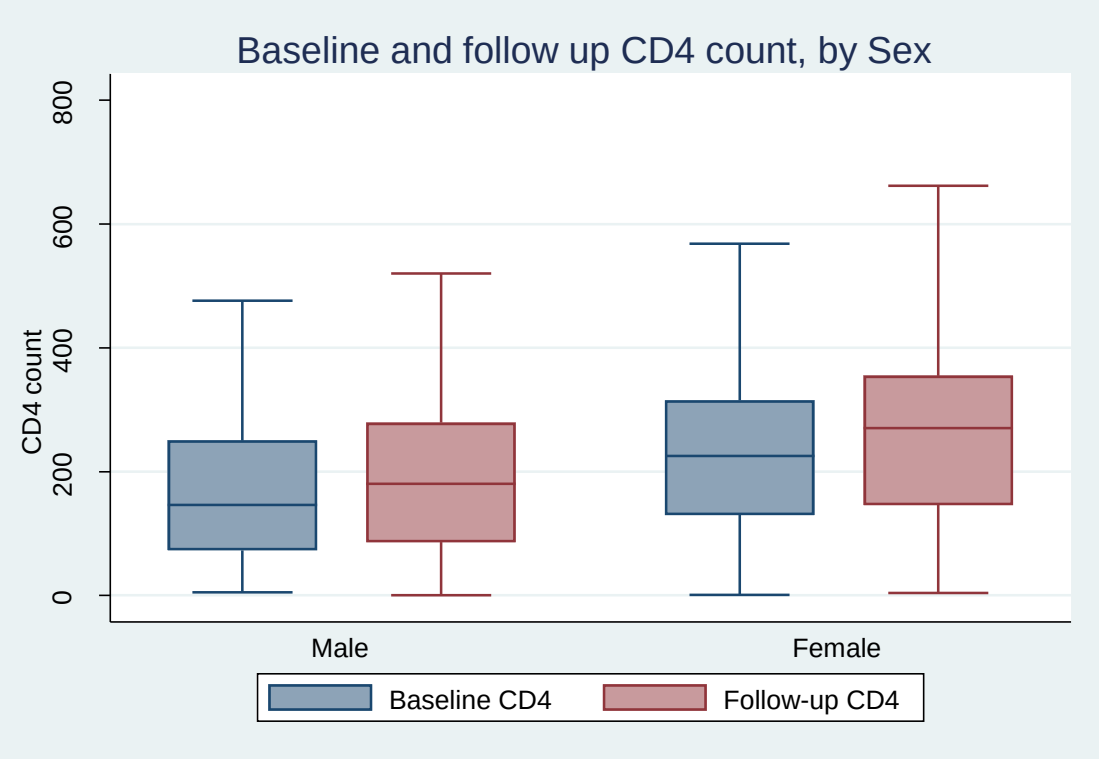
Table 11: Comparing the changes in CD4 count at initiation with the final follow up CD4 count for male ART clients using the paired t test

Variable	**Initial_CD4 Mean(sd)**	**Final_ CD4Mean(sd)**	**Mean difference**	**P value**
All Clients - CD4 count(Cells/mm$^{3)}$	163.6 (112.2)	202.4 (191.9)	38.87(156.3)	0.0178
Females - CD4 count(Cells/mm$^{3)}$	229.4667 (48.4242)	276.0427 189.1483)	46.576 (163.7603)	0.0007
Male- CD4 count(Cells/mm$^{3)}$	163.5574 (112.1684)	202.428 (191.8836)	38.87059 (156.2586)	0.0178

Source: Study survey data, 2017

Similarly, among female ART clients, there was a statistically significant improvement in the CD4 counts i.e. p= 0.0007, see Table 11 above. The pictorial view for both males and females is also presented graphically in Figure 6 below.

Figure 6: Changes in CD4 cell count by sex

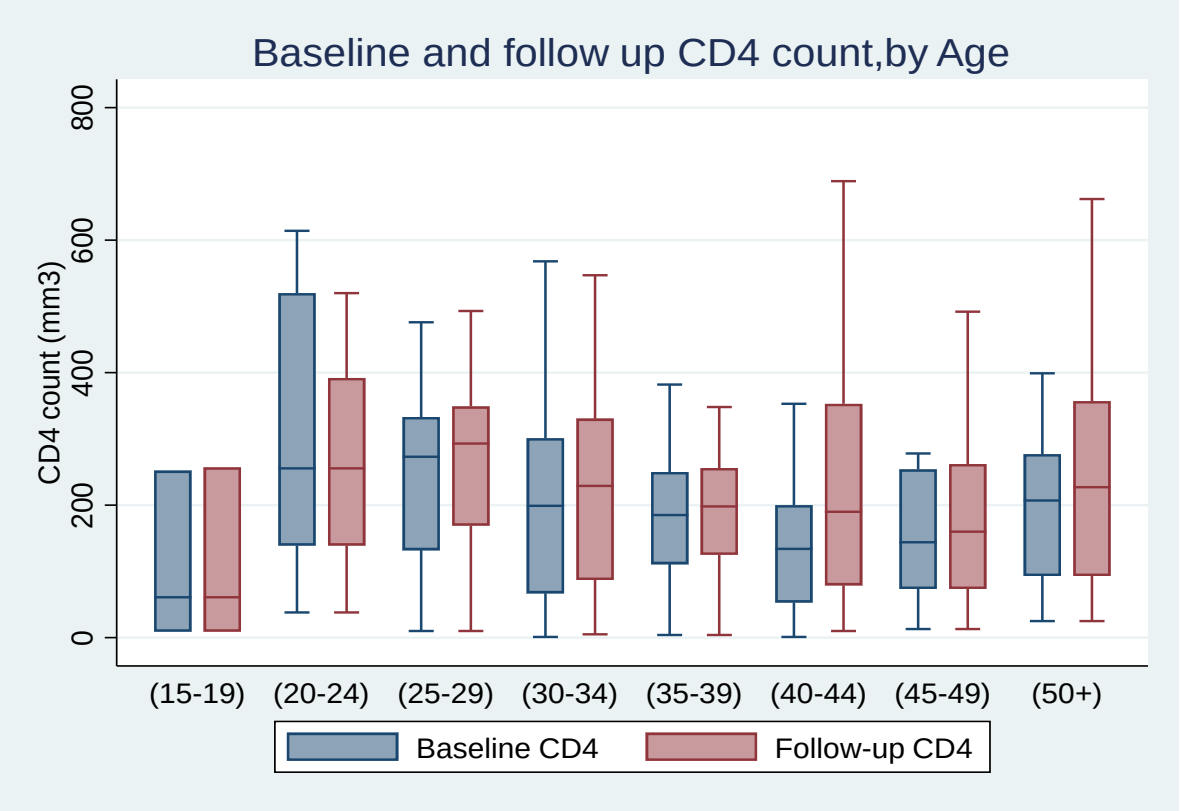


Source: Study survey data, 2017

By age, the data shows that among the 15-19 year olds there was no statistically significant difference in mean CD4 changes at initiation *vis a vis* at final follow up i.e. $p = 0.4226$. The picture is true for the 20-24-year age group too. This is typical of adolescent clients, hence the reason they have CD4 counts done every six-month (note change in policy).

The picture begins to change from 25-29-year-old age groups going up i.e. the mean difference between initial CD4 count and final follow up CD4 count is statistically significantly different from zero, see Figure 7 below.

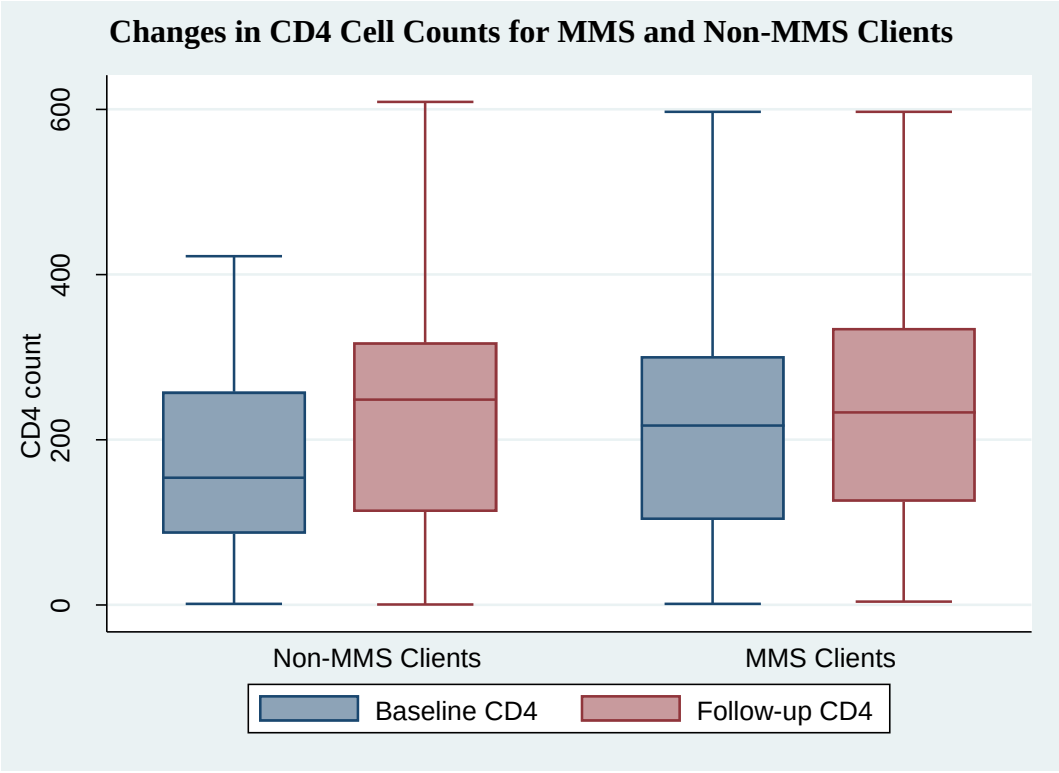
Figure 7: Changes in CD4 counts by age



Source: Study survey data, 2017

In addition, clients who were not MMS showed a statistically significantly change in their CD4 counts i.e. p= 0. 0014.The picture is similar to that of clients on MMS i.e. p = 0.0066, also see Figure 8 below.

Figure 8: Changes in CD4 cell count by sex



Source: Study survey data, 2017

When further stratified by TB status, as shown in Table 12 below, ART clients without TB showed a statistically significant change in their CD4 count i.e. p=0.0001 compared to clients diagnosed with TB i.e. p= 0.1878. ART clients diagnosed with TB did not show significant gains in CD4 counts i.e. p = 0.1878 as shown in Table 12 below.

Table 12: Comparing the changes in CD4 count at initiation with the final follow up CD4 count for ART clients with and without TB using the paired t test

Variable	Initial_CD4 Mean(sd)	Final_ CD4Mean(sd)	Mean difference	P value
Clients without TB - CD4 count(Cells/mm$^{3)}$	212.3291 (140.2014)	258.0432 (195.8688)	45.71406 (166.5312)	0.0001
Clients with TB - CD4 count(Cells/mm$^{3)}$	116.4286 (90.36624)	137.6667 (116.8509)	21.2381 (71.35959)	0.1878

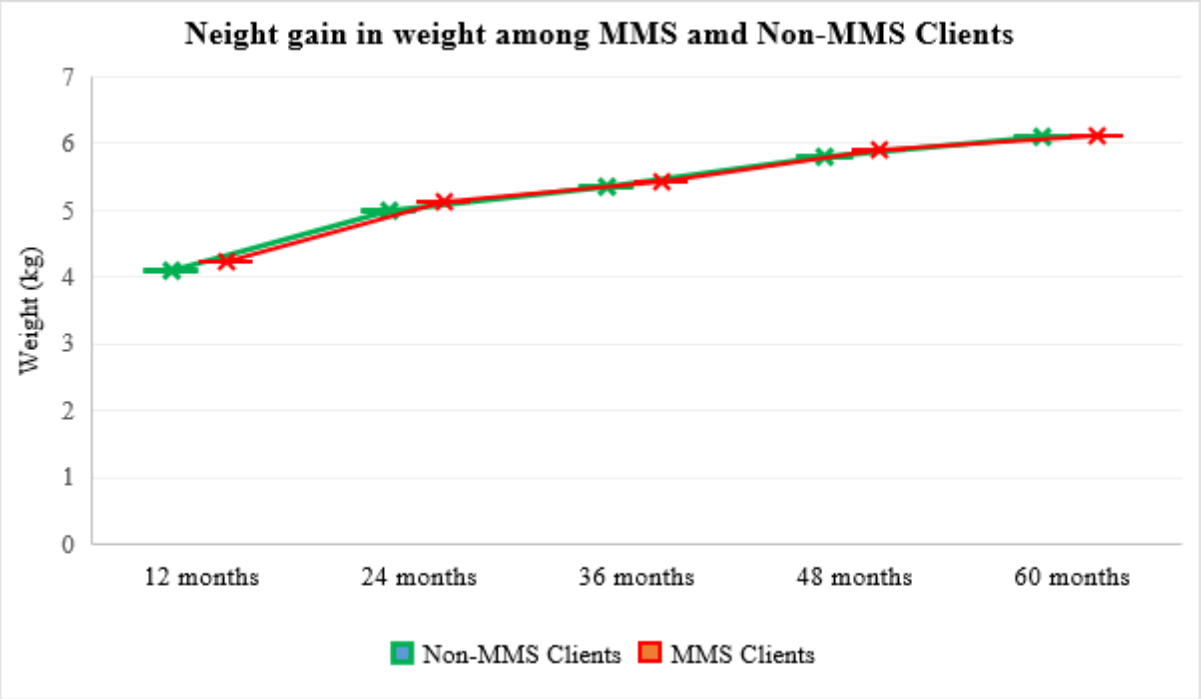
Source: Study survey data, 2017

4.3.4 Clinical response

Overall, the median weight gains at 12, 24, 36, 48 and 60 months were 4.2, 5.1, 5.4, 5.9 and 6.1kgs respectively among MMS clients as shown in Figure 8 below. For MMS clients, the

median weight gains at 12, 24, 36, 48 and 60 months were 4.1, 5, 5.34, 5.8 and 6.1 kgs respectively The results were not statistically different between MMS and non-MMS clients ($p>0.05$).

Figure 8: Changes in weight gains at 12, 24, 36, 48 and 60 months for MMS and Non-MMS clients



Source: Survey data, 2017

4.4 Factors associated with the observed treatment outcomes

This section details the factors associated with the four outcomes of interest, namely retention, weight gain (clinical outcome), changes in CD4 cell count (immunological outcome) and survival.

4.4.1 Factors associated with retention

Table 13 below provides a synopsis of factors associated with retention. As shown in Table 13 below, the odds of females being retained in care were 1.91 times that of men. Similarly, the odds of being retained in care among clients in WHO Stage II was 3.067 times that of women in Stage IV. In addition, the odds of being retained in care among clients who received Cotrimoxazole was 1.887 times that of clients who did not receive it as shown in Table 13 below.

Table 13: Predictors of retention

Covariates	Odds Ratio	Std. Err.	t	P>t	95% Confidence Interval	
Sex						
Female	1.91	0.694	1.78	0.075	0.937	3.891
Age						
(25-29)	0.371	0.083	-4.41	0	0.239	0.576
WHO stage						
II	3.067	0.84	4.09	0	1.792	5.247
Cotrim						
Yes	1.887	0.221	5.42	0	1.5	2.374
ART regimen						
Lamivudine+stavudine+nevirapine	0.256	0.102	-3.44	0.001	0.118	0.557
_cons	3.309	1.244	3.18	0.001	1.584	6.912

Source: Study survey data, 2017

4.4.2 Factors associated with clinical outcomes (weight gain)

Table 14 below gives a synopsis of the key factors associated with weight gain (the clinical outcome of interest) using a linear regression model. As shown in Table 14 below, for every unit increase in female(s), we expect a 1.313-unit increase in weight, holding all other variables constant (CI: 0.347-2.279). For every unit increase in widows, we expect a 3.322-unit decrease in weight, holding all other variables constant. Similarly, for every unit increase in PLHIV with no education, we expect 1.724 decrease in weight. In addition, for every unit increase in the PLHIV aged 25-29 years, we expect a 4.303 decrease in weight. See table 14 below for the full set of significant factors. The old ART regimen is also associated with failure to gain weight (coefficient of -1.269; CI: -2.4—0.138).

Table 14: Predictors of weight gain (clinical outcome of interest)

Covariates	Coefficient	Std. Err.	t	P>t	[95% Confidence Interval	
Sex						
Female	1.313	0.368	3.57	0.018	0.347	2.279
Age						
(25-29)	-4.303	1.147	-3.75	0.015	-7.315	-1.29
(30-34)	-4.95	1.297	-3.82	0.014	-8.358	-1.542
Marital status						
Widowed	-3.322	1.534	-2.17	0.086	-7.351	0.706
Level of education						
None	-1.724	0.596	-2.89	0.037	-3.29	-0.158
ART regimen						
Lamivudine+stavudine+nevirapine	-1.269	0.431	-2.95	0.035	-2.4	-0.138
_cons	65.554	0.46	142.58	0	64.346	66.762

Source: Study survey data, 2017

4.4.3 Factors associated with immunological outcomes (CD4)

Table 16 below provides a synopsis of the factors associated with positive changes in CD4 count among ART clients 15+ years old. The IRRs are the incidence rate ratios for the Poisson model which are obtained by exponentiating the Poisson regression coefficient. The IRR is the estimated rate ratio for one-unit increase in CD4, given the other variables are held constant in this model. If a widowed person living with HIV were to increase their CD4 by one point, his/her rate ratio for CD4 is expected to decrease by a factor of 0.68. This is statistically significant (CI: 0.57-0.81). The picture is the same for single persons (IRR=0.54; CI:0.36-0.80); received Cotrimoxazole (IRR=0.69; CI: 0.63-0.76); on MMS (IRR=0.77; CI:0.64-0.92).

Table 15: Predictors of positive changes in CD4

Variable	IRR	Std. Err.	t	P>|t|	95% Confidence Interval	
Widowed	0.68	0.06	-4.22	0.00	0.57	0.81
Single	0.54	0.11	-3.06	0.00	0.36	0.80
Secondary Education	0.00	0.00	-17.61	0.00	0.00	0.00
WHO_stage_4	1.71	0.12	7.54	0.00	1.48	1.96
Received Cotrimoxazole Prophylaxis	0.69	0.03	-8.00	0.00	0.63	0.76
On MMS	0.77	0.07	-2.79	0.01	0.64	0.92
ART_lamivudine tenefovir efavirens	1.59	0.31	2.37	0.02	1.08	2.33
ART_zidovudine lamivudine nevirapine	1.52	0.12	5.45	0.00	1.31	1.76

Source: Study survey data, 2017

Clients in WHO stage IV are expected to have a rate of 1.71 times greater for loss in CD4 than clients in stage 1, while holding other variables constant (IRR=1.71; CI:1.48-1.96). The other significant variables are as appears in Table 15 above.

4.4.4 Factors associated with survival

Table 16 below details the factors associated with survival. Using the Weibull regression for predictors, the data shows that women were 96% more likely to survive than male (HR=0.04; CI:0.01-0.22). Similarly, those who received Cotrimoxazole were 90% more likely to survive than those who did (HR=0.10; CI:0.03-0.31) As shown Table 16 below.

Table 16: Predictors of survival

Variable	Haz. Ratio	Std. Err.	t	P>|t|	95% Confidence Interval	
Sex_woman	0.04	0.04	-3.78	0.00	0.01	0.22
Received Cotrimoxazole Prophylaxis	0.10	0.06	-3.98	0.00	0.03	0.31
Age group_25-29 years	7.28	7.21	2.01	0.05	1.05	50.69
Age group_30-34 years	0.00	0.00	-21.30	0.00	0.00	0.00
Age group 35+ years	0.00	0.00	-22.35	0.00	0.00	0.00
University level	0.11	0.06	-3.84	0.00	0.04	0.34
Who_stage_1	0.07	0.07	-2.58	0.01	0.01	0.52
Who_stage_2	0.00	0.00	-23.94	0.00	0.00	0.00
ART_lamivudine tenefovir nevirapine	0.00	0.00	-18.38	0.00	0.00	0.00
ART_zidovudine lamivudine nevirapine	0.00	0.00	-16.02	0.00	0.00	0.00

Source: Study survey data, 2017

PLHIV with university level were dying at a rate that was 89% lower than those without any education (HR=0.11; CI:0.04-0.34), while clients in WHO stage I were dying at a rate that was 93% lower than those in Stage IV (HR=0.07; CI: 0.01-0.52). The hazard of dying was significantly higher in the 25-29 year olds compared to the 15-19 year olds (HR=7.28; CI: 1.05-50.69), albeit with a wider confidence interval. Other important factors are detailed in the same table.

4.5 Discussion of results

This research explored ART outcomes and analysed the factors associated with these outcomes among clients living with HIV/AIDS who were on ART in the five MoHCC facilities in Chitungwiza.

Among the 305 ART clients with HIV/AIDS who initiated ART, there were five AIDS-related deaths; two within the first 6 months, two between the 42-48-month period and one in the 54-60-month period. Overall, the median survival time (53 months) was the same among MMS and non-MMS clients. Survival time was also the same at both the 25^{th} and 75^{th} percentile. Women were 96% more likely to survive than male (HR=0.04; CI:0.01-0.22). Similarly, those who received Cotrimoxazole were 90% more likely to survive than those who did (HR=0.10; CI:0.03-0.31). PLHIV with university level were dying at a rate that was 89% lower than those without any education (HR=0.11; CI:0.04-0.34), while clients in WHO stage I were dying at a rate that was 93% lower than those in Stage IV (HR=0.07; CI: 0.01-0.52). The hazard of dying was significantly higher in the 25-29 year olds compared to the 15-19 year olds (HR=7.28; CI: 1.05-50.69), albeit with a wider confidence interval. Most studies have shown the disparity between men and women on survival and these results just confirm this known fact. These results also point to the dilemma facing clinicians –challenges with adolescents and young

people (*vis a vis* adults) regarding survival, adherence and even retention to an extent. Clients who were initiated in WHO Stage II had a lower risk of attrition compared to those initiated while in Stage III and IV, thus conforming findings from earlier studies. For instance, in the study by Mutasa-Apollo et al (2014), the main factors associated with increased risk of failure to survive included male gender (*AHR* 1.2; 95% CI, 1.1–1.4), baseline WHO stage IV (*AHR* 1.7; 95% CI, 1.1–2.6), lower baseline body weight (*AHR* 2.0; 95% CI, 1.4–2. 8) and accessing care from higher level healthcare facilities (AHR 3.5; 95% 1.1–11.2).

The retention rates at 12, 24, 36, 48 and 60 months were 98%, 97%, 96% 91% and 87% respectively, and were not statistically different between MMs and non MMS clients. These results are higher than those from the 2016 MOHCC ART outcomes evaluation which showed ART retention at 3, 12 and 24 months to be 95.5%, 87.8% and 82.8% respectively. The results are also higher in comparison to a retrospective study by Mutasa-Apollo et al (2014), which showed retention at 6, 12, 24 and 36 months as 90.7%, 78.1%, 68.8% and 64.4%, respectively. The differences could partially be explained by time the studies were undertaken and cohorts being investigated which are all different. In addition, the country's ART program has witnessed significant investments meant to enhance clinical outcomes for ART patients e.g. investments in nurse mentors at facility level, capacity development of health care workers, motivation grants (salary top ups through Global Fund), deployment of community cadres (peer navigators and health care workers) and patient follow-up resources (through both PEPFAR, Global Fund and World Bank) which all help facilitate an effective ART program.

Overall, the median weight gains at 12, 24, 36, 48 and 60 months were 4.2, 5.1, 5.4, 5.8 and 6.2kgs respectively. The results were not statistically different between MMS and non-MMS clients. The results are similar to the study by Mutasa-Apollo et al (2014) (for adults ≥15 years initiated on ART from 2007 to 2009) where the median weight gains at 6, 12, and 24 months were 3, 4.5, and 5.0 kgs. The results show that for every unit increase in female(s), we expect a 1.313-unit increase in weight, holding all other variables constant (CI: 0.347-2.279) i.e. women are likely to gain weight than men. In addition, for every unit increase in widows, we expect a 3.322-unit decrease in weight, holding all other variables constant i.e. widows were likely not to gain weight compared to those in marriage. Similarly, for every unit increase in PLHIV with no education, we expect 1.724 decrease in weight i.e. PLHIV with no education were less likely to gain weight than those with tertiary education. In addition, for every unit increase in the PLHIV aged 25-29 years, we expect a 4.303 decrease in weight i.e. women aged 25-29 years were less likely to gain weight than the 15-19 year olds.

There was a statistically significant change in the CD4 counts over time for non-MMS clients compared to MMS clients. ART clients diagnosed with TB did not show significant changes in CD4 cell counts. The results also showed that there was no statistically significant difference in mean CD4 count among the 15-19 year olds. As highlighted earlier, this is typical of adolescent clients, hence the reason they have CD4 counts done every six-month, yet for adults, once a client is deemed stable, the CD4 or viral load is to be done once a year. For factors associated with changes in CD4 cell count, the results show that if a widowed person living with HIV were to increase their CD4 by one point, his/her rate ratio for CD4 is expected to decrease by a factor of 0.68. This is statistically significant (CI: 0.57-0.81). The picture is the same for single persons (IRR=0.54; CI:0.36-0.80); received Cotrimoxazole (IRR=0.69; CI: 0.63-0.76); on MMS (IRR=0.77; CI:0.64-0.92). Clients in WHO stage IV are expected to have a rate of 1.71 times greater for loss in CD4 than clients in stage 1, while holding other variables constant (IRR=1.71; CI:1.48-1.96).

The findings of this study may be inconclusive as it was limited by several factors. First, the analysis does not take into account the time-varying nature of some behaviours (e.g. high-risk behaviours), and how these may be related to the ART outcomes of interest. Secondly, this study only captures the status quo of ART clients provided at specific sites in Chitungwiza and cannot therefore account for care received in other settings, especially the more rural settings. Third, the study analysis does not address other factors that may contribute to such outcomes as retention and immunological response, such as time varying covariates like changes in risk behaviour or quality of life. Fourth, the study did not take into account and or control the obvious contribution of other MoHCC related interventions aimed at enhancing the clinical outcomes e.g. roving ART teams.

Nonetheless, the study findings suggest the need for more research to conclusively determine the contribution of each of the models of differentiated care. There is evidence on the economic benefits of MMS. The fact that it saves on time and space at health facilities is also well documented.

CHAPTER 5: Summary, conclusions and recommendations

This research sought to assess the contribution of MMS to ART outcomes among PLHIV on ART, while exploring factors associated with the observed ART outcomes.

The study results show that the median survival time was the same among MMS and non-MMS clients. The retention rates were not statistically different between MMs and non MMS clients. There was a statistically significant change in the CD4 counts (initial vs. follow up) for non-MMS clients. There were significant gains in weight among both MMS and non-MMS clients. Similarly, the difference between MMS and non-MMS clients was insignificant. The factors associated with the four outcomes of interest are similar to factors explored in related studies.

Two years into the roll out of MMS, the study results do not point to a statistically significant contribution of MMS to observed clinical outcomes. However, the contribution of MMS to observed ART outcomes could as well be clinically significant. The factors associated with the clinical outcomes look similar to prior studies, albeit at varying levels of statistical significance.

Premised on the above, the researcher advocates for the following:

1. An expanded research, covering a wide spectrum of sites, especially the rural sites, to help understand more the actual net effect of MMS, beyond the documented financial and other resource benefits of MMS
2. Conduct an evaluation of the various models of differentiated care individually, and in tandem with others, to assess the net effect of these differentiated models of care, controlling for other factors (e.g. other interventions already in place to enhance patient level ART outcomes).

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Appendix 1: Statement of intent to maintain confidentiality for the data abstraction process

I ……, will always maintain the confidentiality of the patients, whose OI/ART Patient Care Booklets are reviewed, and the health workers, who are interviewed, as part of this evaluation. At no time will I disclose the names of patients whose OI/ART Patient Care Booklets are reviewed, or any information within the OI/ART Patient Care Booklets. OI/ART Patient Care Booklets will be reviewed in a private location. If there are questions related to the chart review, these will be discussed with the facilitator in a private location. No names will be written on the data abstraction forms or on the interview sheets.

Signed by: …….

Place: ……..……

Date: ……..……

Witness 1: ……..……

Appendix 2: Data abstraction operational procedures

OI/ART Patient Care Booklets used for the routine collection of data on adult patients at ART sites will be reviewed and should provide all the data needed for completion of the data abstraction form. However, the following challenges are anticipated:

- A chart of a selected adult ART patient, who is recorded in the ART register, cannot be located, even after requesting assistance from attending clinic staff. In this situation, numbers of missing OI/ART Patient Care Booklets must be recorded. The next chart on the randomly ordered list of ART OI/ART Patient Care Booklets will then be selected for inclusion in the study.
- Different sites may be using different standard ART OI/ART Patient Care Booklets. If certain data, which are not essential for routine adult ART care and are not routinely requested by the standard ART chart, but are requested by the data abstraction form, the box labelled "not collected" should be ticked on the data abstraction form. Certain data, will be regarded as mandatory for basic adult ART care. Regardless of whether the data are requested in the standard ART chart or not, if the data are missing from the chart and requested by the data abstraction form, the box labelled "missing" should be ticked.
- For dates of follow-up appointments, patient weights at these appointments, and all CD4 counts, it may not be possible to record specific outcomes at precise 6 months follow up visits as some patients will not be able to attend appointments on these specific dates. Therefore, attempts will be made to collect data on all follow-up visits as well as the weights at these visits. If a patient has more than 27 follow-up visits a separate data abstraction form should be completed until all weights, dates of follow-up visits, and CD4 counts, are collected.
- All weights should be recorded in kilograms, Hemoglobin levels in grams/deciliter.
- If the patient being reviewed has not missed the most recent appointment it will be documented as alive and on therapy, if missed it most recent appointment by less than 90 days, it will be considered as defaulter. If the patient has been transferred out, died, or stopped therapy since the most recent visit, as documented in the file or register, this fact along with the date should be recorded in the data abstraction tool. If the patient has missed his/her most recent appointment by more than 90 days, this patient should be documented as "lost to follow up".

Appendix 3: Data abstraction tool

ADULT ART Site Code:_ _ _ _ **ADULT** Study ID: _ _____ _ _
Abstractor's Name:_____ Date of Abstraction _ _/_ _ /_ _ _ _

A. DEMOGRAPHIC INFORMATION		
1. Date of birth:	/ / (D D M M Y Y Y Y)	☐ Missing
2. Age at enrollment into HIV Care	_ _ years	☐ Missing.
3. Sex:	☐ Male ☐ Female	☐ Missing
4. Residence at ART initiation:	District :_____	☐ Missing
	Commune/village:_____	☐ Missing
	Suburb :_____	☐ Missing
Partner Information – Most Recent		
5. Marital Status of Patient	☐ Married ☐ Widowed	☐ Missing.
	☐ Divorced ☐ Single	☐ Not collected
	☐ Other……..	
Education, Employment, Family Information – Most Recent		
6. Patient education level at time of enrollment into HIV Care	☐ None ☐ Primary school ☐ Secondary school	☐ Missing
	☐ Other…… ☐ University	☐ Not collected
7. Is the patient employed at the time of enrollment into HIV Care?	☐ yes ☐ No	☐ Missing
		☐ Not collected
8. How many biological children has this patient ever had?		☐ Missing
	……	☐ Not collected
B. HIV DIAGNOSIS		
9. Date of first **diagnosis of HIV-infection recorded in the chart**:	/ / D D M M Y Y Y Y	☐ Missing
10. Result of HIV test	☐ HIV-1 ☐ HIV-2	☐ Missing
	☐ HIV-1/HIV-2 dual	☐ Not collected
C. TIME LINE		

11. Date of HIV Care initiation at this facility.	/ / ☐ Missing D D M M Y Y Y Y
12. Date of ART initiation at this facility.	/ / ☐ Missing D D M M Y Y Y Y
13. Date of most recent visit.	/ / ☐ Missing D D M M Y Y Y Y
D. SOURCE OF REFERRAL	
14. Referral source to HIV care/treatment **(choose one)**	☐ VCT Center ☐ PMTCT ☐ Outpatient Depart. ☐ Adult ward ☐ TB clinic ☐ Maternal Obst. Unit ☐ Hospitalization ☐ Self-referral ☐ Home Based C. ☐ Other Adult ART clinic ☐ Others:_____
15. Is this a patient newly enrolled in HIV Care and ART, or a patient transferred in from another clinic?	☐ New Patient ☐ Transfer in ☐ Missing ☐ Not collected
16. If patient is a "transfer in", list the dates of HIV Care Initiation and ART initiation at previous facility.	**HIV Care Initiation:** / / DD MM YYYY ☐ Missing **ART Initiation:** / / DD MM YYYY ☐ Missing **Regimen initiated at previous facility**_____
E. PRE-ART CARE INFORMATION	
17. Stage at HIV Care initiation	☐ A ☐ B ☐ C ☐ I ☐ II ☐ III ☐ IV ☐ Missing
18. Weight at HIV Care initiation	_ _ . _ kg ☐ Missing
19. CD4 count at HIV Care initiation	_ _ _ _ cells/mm^3 ☐ Missing ☐ Not collected / / ☐ Missing D D M M Y Y Y Y
20. Prescribed CTX?	☐ Yes ☐ No ☐ Missing
20.b. Prior ART exposure?	☐ None ☐ HAART (transfer in) ☐ SD NVP ☐ PMTCT combination therapy ☐ Missing
21. If female, which of the following screening methods for pregnancy were performed prior to ART?	☐ Date of last period ☐ Pregnancy at start of ART documented ☐ Pregnancy test ☐ Other..... ☐ N/A (male) ☐ Missing ☐ No test requested
22. Was patient pregnant at time of initiation of ART?	☐ Yes ☐ No ☐ Missing ☐ N/A (male)
23. What screening method was used to screen patient for active TB?	☐ Chest Radiograph ☐ Sputum microscopy ☐ Patient on TB Rx at start of ART ☐ Skin testing ☐ Method for screening missing ☐ No test requested
24. Was this patient screened for Hepatitis B?	☐ Yes ☐ No ☐ Missing ☐ Not collected

F. ART INITIATION VISIT

25. Weight	_ _ . _ kg ☐ Missing	
26. Hemoglobin	_ _ . _ g/dl ☐ Missing	/ / (D D M M Y Y Y Y) ☐ Missing
27. CD4 count	_ _ _ _ cells/mm³ ☐ Missing	/ / (D D M M Y Y Y Y) ☐ Missing
28. Viral Load	_ _ _ _ _ _ _ copies/ml ☐ Missing	/ / (D D M M Y Y Y Y) ☐ Missing
29. Clinical Stage recorded	☐ A ☐ B ☐ C ☐ I ☐ II ☐ III ☐ IV ☐ Missing	
30. Which of the following OI's occurred prior to ART ? (Most recent episode, if many recorded).	☐ Crypto mening / / ☐ Active TB / /	
	☐ Other_____ / / ☐ Other_____ / /	
	☐ Other_____ / / ☐ Other_____ / /	
31. Prescribed Cotrimoxazole?	☐ Yes ☐ No ☐ Missing	

31.b. What was the initial ART regimen prescribed at this facility? (Choose from the list below) (Most patients will be receiving 3 drugs, BUT, if documentation of less or more drugs is present, please tick all that apply.

NRTI	NNRTI	PI's and Boosted PI's	FDC
☐ **Zidovudine** (AZT)	☐ **Nevirapine** (Viramune, NVP)	☐ **Lopinavir** (Lop)	☐ **Virolans** (d4T/3TC/Nevirapine)
☐ **Lamivudine** (3TC)	☐ **Efavirenz** (EFV)	☐ **Nelfinavir** (NFV)	☐ **Combivir** (AZT/3TC)
☐ **Stavudine** (d4T)		☐ **Ritonovir** (Rit)	☐ **Triomune, Triviro, Stalanev** (d4T/3TC/NVP)
☐ **Abacavir** (ABC)		☐ **Saquinavir** (Saq)	☐ **TZV** (ABC/3TC/ZDV)
☐ **Didanosine** (Videx, ddI)		☐ Lopinavir/ritonovir(Lop/r)	☐ **Other, specify:**
☐ **Tenofovir** (TDF)		☐ Nelfinavir/ritonovir (Nfv/r)	_____
		☐ Indinavir/ritonovir (Ind/r)	☐ **Missing**
		☐ Saquinavir/ritonovir (Saq/r)	

G. MOST RECENT VISIT

32. Date of most recent visit.	/ / (D D M M Y Y Y Y) ☐ Missing
33. Weight	_ _ . _ kg ☐ Missing
34. Clinical Stage recorded	☐ A ☐ B ☐ C ☐ I ☐ II ☐ III ☐ IV ☐ Missing
34.b. Most recent viral load	_ _ _ _ _ _ _ copies/ml ☐ Missing / / ☐ Missing
35. Prescribed Cotrimoxazole?	☐ Yes ☐ No ☐ Missing
36. If female, which of the following screening methods for pregnancy were performed at the most recent visit?	☐ Date of last period ☐ Pregnancy documented ☐ Pregnancy test ☐ Other…… ☐ N/A (male) ☐ Missing
37. If Female, did she ever become pregnant since ART initiation?	☐ Yes ☐ No ☐ Missing ☐ Not documented ☐ N/A (male)

H. KEY EVENTS DURING ART

38. Since ART initiation, the patient has (choose one): **Comments**_____	☐ **Continued; patient is currently on ART**	
	☐ **Stopped ART**	**A)** / / ☐ **Missing** D D M M Y Y Y Y TILL **B)** / / ☐ **No restart** D D M M Y Y Y Y
	☐ **Transferred out** (officially documented)	/ / ☐ **Missing** D D M M Y Y Y Y
	☐ **Died**	/ / ☐ **Missing** D D M M Y Y Y Y
	☐ **Been lost to follow up.**	/ / ☐ **Missing** D D M M Y Y Y Y

39. If patient **stopped ART**, what was the reason?	**Reason**	**Date**	**Specify**
	☐ **Developed Active TB**	_ _ / _ _ / _ _ _ _	
	☐ **Drug toxicity/intolerance**	_ _ / _ _ / _ _ _ _	**Neur/Rash/Hep/Lipo /other/unknown**
	☐ **IRIS**	_ _ / _ _ / _ _ _ _	
	☐ **Other**.....	_ _ / _ _ / _ _ _ _	.....
	☐ **Unknown**		

40. If patient died, what was the cause of death documented?	☐ **Respiratory (not pulmonary TB)** ☐ **Acute diarrhea** ☐ **Chronic diarrhea** ☐ **TB (pulm + extra pulm)** ☐ **IRIS** ☐ **Other**..... ☐ **Unknown**

I. REGIMEN CHANGES

41. If regimen changed, give **content, starting date, and reason for regimen change** (1=Immunological failure, 2=virological failure, 3=clinical failure, 4=other, please specify), or tick: ☐ **NO regimen change**

(a) 2nd line: _ _ _/_ _ _/_ _ _	/ / ☐ **Missing** D D M M Y Y Y Y	_____(1/2/3/4) ☐ **Missing**
(b) 3rd line: _ _ _/_ _ _/_ _ _	/ / ☐ **Missing** D D M M Y Y Y Y	_____(1/2/3/4) ☐ **Missing**

J. DRUG SUBSTITUTIONS

42. If a drug was substituted, give **content, starting date, and reason for substitution** (1 = Toxicity, 2 = pregnancy, 3 = suspicion of pregnancy, 4 = active TB, 5 = new medicine available, 6 = break in supply of a drug, 7 = other, please specify)

Regimen	**Substitutions**	**Dates** D D / M M / Y Y Y Y	**Reason**
1st line	**1st Sub**_ _ _/_ _ _/_ _ _	/ / ☐ **Missing**	_____(1-7) ☐ **Missing**
	2nd Sub_ _ _/_ _ _/_ _ _	/ / ☐ **Missing**	_____(1-7) ☐ **Missing**

2nd Line	1st Sub _ _/_ _/_ _ _	/ /	☐ Missing	_____(1-7) ☐ Missing
	2nd Sub_ _/_ _/_ _ _	/ /	☐ Missing	_____(1-7) ☐ Missing
3rd Line	1st Sub _ _/_ _/_ _ _	/ /	☐ Missing	_____(1-7) ☐ Missing
	2nd Sub_ _/_ _/_ _ _	/ /	☐ Missing	_____(1-7) ☐ Missing

K. FOLLOW-UP INFORMATION

43. Please record the dates of all visits and weights of the patients at these visits

Visit	DD MM YY	Missing?	weight	Weight Missing?	Visit	DD MM YY	Missing?	Weight	Weight missing?
1st	_ _/_ _/_ _	☐	_ _. _	☐	9th	_ _/_ _/_ _	☐	_ _. _	☐
2nd	_ _/_ _/_ _	☐	_ _. _	☐	10th	_ _/_ _/_ _	☐	_ _. _	☐
3rd	_ _/_ _/_ _	☐	_ _. _	☐	11th	_ _/_ _/_ _	☐	_ _. _	☐
4th	_ _/_ _/_ _	☐	_ _. _	☐	12th	_ _/_ _/_ _	☐	_ _. _	☐
5th	_ _/_ _/_ _	☐	_ _. _	☐	13th	_ _/_ _/_ _	☐	_ _. _	☐
6th	_ _/_ _/_ _	☐	_ _. _	☐	14th	_ _/_ _/_ _	☐	_ _. _	☐
7th	_ _/_ _/_ _	☐	_ _. _	☐	15th	_ _/_ _/_ _	☐	_ _. _	☐
8th	_ _/_ _/_ _	☐	_ _. _	☐	16th	_ _/_ _/_ _	☐	_ _. _	☐

L. CD4, Hb, ALT

44. Please record the dates of ALL CD4 counts, Hemoglobin levels, and ALT values and the dates of the tests.

Post ART initiation	CD4 count cells/mm^3	Date dd mm yy	Hb g/dl	Date dd mm yy	ALT U/l	Date dd mm yy
1st	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
2nd	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
3rd	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
4th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
5th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
6th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
7th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
8th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
9th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /
10th	_ _ _ _ cells/mm^3	/ /	_ _. _ g/dl	/ /	_ _ _ _	/ /

M. ADVERSE EVENTS AND OI's WHILE ON ART

45. Which of the following adverse events occurred during ART and were presumed to be due to ART?	☐ Severe rash	/ /	☐ Hepatitis	/ /
	☐ Neuropathy	/ /	☐ Lipodystrophy	/ /
	☐ Anemia	/ /	☐ IRIS	/ /
46. Which of the following OI's occurred during ART ? (Give date of 1st episode, if many recorded).	☐ Crypto meningi	/ /	☐ Active TB	/ /
	☐ Other_____	/ /	☐ Other_____	/ /
	☐ Other_____	/ /	☐ Other_____	/ /

N. COUNSELING – Did Patient receive:

47. Pre-ART counseling	☐ Yes	☐ No	☐ Not collected	☐ Missing
48. Counselling at ART initiation	☐ Yes	☐ No	☐ Not collected	☐ Missing
49. Counselling during follow-up	☐ Yes	☐ No	☐ Not collected	☐ Missing

O. PHARMACY REGISTER

50. What date were medicines first collected?	/ / DD MM YYYY	☐ Missing
51. What date were medicines most recently collected from the pharmacy?	/ / DD MM YYYY	☐ Missing
52. Between the above two dates, # of days LATE medicines collected:	_ _ _ _ days late in total.	