National University of Rwanda
Université Nationale du Rwanda

www.nur.ac.rw

SCHOOL OF PUBLIC HEALTH
ECOLE DE SANTE PUBLIQUE

Outcomes of Adult patients on Antiretroviral Therapy from 2004-2010 in Rwanda

A dissertation submitted in partial fulfillment of the requirements for the award of a Master of Science in Field Epidemiology

By: Jean Pierre Nyemazi

Supervisor:
Professor Joseph NTAGANIRA

August, 2012

ACKNOWLEDGEMENTS

I would like to acknowledge the technical expertise and leadership of Prof. Joseph NTAGANIRA that brought this study to successful completion.

My deep appreciations go to the Honorable Minister of Health, Dr Agnes Binagwaho, for her leadership - mentorship role, encouragement and support that enabled me to undertake several research and capacity building opportunities,

To my colleagues within the Rwanda Biomedical Center and Field Epidemiology and Laboratory Training Program,

To Eric Remera, Dr Bass Chitou, Thierry for the data management support

Special thanks to my wife, Elise, my daughter, Lael,

Above, be praised the Lord,

ACRONYMS

AIDS	:	Acquired Immunodeficiency Syndrome
ART	:	Antiretroviral therapy
ARV	:	Antiretroviral
CI	:	Confidence Interval
CDC		Centers for Diseases Control
CTX	:	Cotrimoxazole
GFATM	:	Global Fund to fight AIDS Tuberculosis and Malaria
GoR	:	Government of Rwanda
HAART	:	Highly Active Antiretroviral Therapy
HIV	:	Human Immunodeficiency Virus
HMIS	:	Health Management Information Systems
IQ-Chart		IQChart Electronic Medical Records System
LTFU	:	Lost to Follow up
M&E	:	Monitoring and Evaluation
MOH	:	Ministry of Health
OI	:	Opportunistic Infection
OR	:	Odds Ratios
PEPFAR	:	US President's Emergency Plan for AIDS Relief
TB	:	Tuberculosis
TRAC Plus	:	Centre for Treatment and Research on AIDS, Malaria, TB and other Epidemics
UNAIDS	:	Joint United Nation Program on AIDS
VCT	:	Voluntary counseling and testing
VL	:	Viral Load
WHO	:	World Health Organization

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Introduction: Antiretroviral treatment (ART) programs in sub-Saharan Africa have scaled up rapidly since 2004. In Rwanda, the number of HIV infected individuals on treatment has increased from 870 patients in 2002 to 96,123 patients receiving ART in June 2011. We conducted this analysis to assess patient retention, immunological and clinical outcomes of adult patients using programmatic data gathered from IQ Chart in adults initiating ART from January 2004 to December 2010 in Rwanda.

Methods: We collected data from an Access database (IQCHART) and transferred them to STATA 11 for cleaning and analysis. We reviewed patient data from HIV-infected adult patients who had initiated ART at 121 IQ Chart sites in Rwanda between January 2004 and December 2010. We reported survival and retention in care, lost to follow up and death as well as CD4 count at ART initiation and at 6, 12, 24, 36, 48 months on ART. We calculated the change in CD4 count in months following ART initiation and we examined the relationship between our outcome variables and predictor variables.

Results: Out of 29,427 HIV-infected adults patients enrolled in our study, after 6, 12, 24 and 36 months, the overall HIV-infected adults patients who still alive in ART care were 95.9%, 94%, 91.6% and 89.9% respectively. There were 3.5% deaths after 6 months and after 12, 24 and 36 months of, the documented deaths were 4.6%, 5.8% and 6.4% respectively. The survival rates were estimates at 96.4% [95% CI: 96.2% - 96.6%], 94.6% [95% CI: 94.3% - 94.8%], 91.7% [95% CI: 91.4% - 91.9%] and 89.5% [95% CI: 89.2% - 89.9%] after 6, 12, 24 and 36 months after ART initiation. Male sex, lower CD4 at ART initiation, older age and not living with sexual partner were associated to higher mortality rates.

Conclusion: We found that patient retention on ART is very high and mortality is low in antiretroviral program in Rwanda. Furthermore, early ARVs initiation contributes in the end to improved patient's outcomes. However, older age, Low CD4 cell counts at ART initiation were associated with higher mortality rates.

Key words: HIV-infected Patient outcomes, Rwanda antiretroviral treatment program, Retention in care.

RESUME

Introduction: Les programmes antirétroviraux ont connue une expansion considérable depuis 2004 dans l'Afrique Sub-saharienne. Au Rwanda, le nombre de personnes infectées par le VIH sous traitement ARV est passé de 870 patients en 2002 à 96,123 en Juin 2011. En utilisant des données recueillies à l'aide d'un système de collecte données de routine, nous avons mené cette étude en vue de documenter le taux de rétention, l'évolution clinique et immunologique des patients adultes qui ont initiés le traitement antirétroviral de Janvier 2004 à Décembre 2010 au Rwanda.

Méthodologie: Nous avons recueilli des données à partir d'une base de données Access (IQCHART) et les a transférés en STATA 11 pour l'analyse. Il s'agit des données des patients adultes qui avaient initiés les ARVs entre Janvier 2004 et Décembre 2010 dans 121 sites utilisant IQ-Chart. Nous avons étudié la survie, mortalité ainsi que l'évolution immunologique des patients sous ARVs après 6, 12, 24, 36, 48 mois d'initiation du traitement antirétroviral. Nous avons calculé la variation de taux de CD4 au cours des mois qui suivent l'initiation aux ARVs et avons examiné les facteurs associés à la survie et à la mortalité des patients sous ARVs.

Résultats: Sur les 29 427 patients adultes infectés par le VIH inscrits dans notre étude, 95,9 pour cent, 94%, 91,6% et 89,9% restent dans le programme sous traitement, respectivement après 6, 12, 24 et 36 mois. La mortalité était de 3,5%, 4,6%, 5,8% et 6,4%, respectivement après 6, 12, 24 et 36. Les taux de survie est estimé à 96,4% [IC à 95%: 96,2 - 96,6%], 94,6% [IC à 95%: 94,3% - 94,8%], 91,7% [IC à 95%: 91,4% - 91,9%] et 89,5% [IC à 95% : 89,2% - 89,9%], respectivement après 6, 12, 24 et 36 après le début des ARVs. Le sexe masculin, le taux des CD4 bas à l'initiation, l'âge avancé et le fait de ne pas avoir le partenaire sexuel ont été associés à des taux de

mortalité plus élevés.

Conclusion : La rétention des patients sous ARV est très élevée et la mortalité est faible dans le programme de traitement antirétroviral au Rwanda. En outre, le programme national parvient à initier tôt le traitement ARV, ce qui contribue en fin de compte aux bons résultats du traitement antirétroviral. Cependant, l'âge avancée, faible taux de CD4 à l'initiation des ARV se sont révélés être associés à des taux de mortalité plus élevés.

Mots clés: Personnes infectées par le VIH, traitement antirétrovirale, Survie dans le programme de prise en charge du VIH/SIDA

1. INTRODUCTION

1.1. Definition of terms and concepts

- **Deceased:** A patient initiated on ART and who died on course of ART follow up an documented at sites
- **Transferred:** A patient transferred from ARV initiation site to another site for follow up and documented.
- **Lost to follow up:** A patient initiated on ART and who missed appointment for more than 3 months after the last appointment of drugs pick up
- **Alive in care:** A patient initiated on ART and having a last visit to the ART clinic in the three months preceding the date of data abstraction.
- **Retention**: Refers to ART patients who are alive and known to be receiving services at the clinic at the end of a follow-up period. This means that patients who are documented to have died, been lost to follow-up are considered non-retained.

1.2. Background

Worldwide, Access to antiretroviral therapy (ART) has rapidly expanded; as of the end of 2010, an estimated 6.6 million people were receiving ART in lower- and middle-income countries.

The HIV epidemic in Rwanda peaked in the late 1990`s with an overall prevalence of 13% in adults. This declined over the next decade with the national HIV prevalence currently estimated at 3% in the age group 15-49 years in 2010(1). Nationwide an estimated 200,000 people are infected with HIV. Rwanda was ranked among the ten best countries in world having achieved the universal access to antiretroviral therapy with eighty six percent of those in need actually receiving treatment(2)(3)

Considering much efforts and a lot of investment made in ART program in Rwanda, there is high expectation of achieving better patient retention and better patient outcome after ART initiation.

Limited studies and reports have been produced documenting the ART program in Rwanda and none has been conducted using routinely collected program data. In 2007, an evaluation of the national ART program conducted on 3,194 adults showed that 92% and 86% of patients respectively remained in care at their original site at 6- and 12-months after ART initiation. Furthermore, among the 49% and 35% of patients with available follow-up CD4 cell count data, median CD4 cell counts increased by 98 cells/µL and 119 cells/µL at 6 and 12 months after ART initiation, respectively.(4)

In 2010, a retrospective medical record review performed for a cohort of 1041 HIV+ adult patients initiating community-based ART showed that 92.3% were retained in care and the median CD4 T-cell count increase was 336 cells/µL (IQR 212-493) from median 190 cells/µL (IQR 116-270) at initiation. (5)

The sustainability, scalability and ultimately, long-term benefit from antiretroviral programs will be determined by the durability of patient in effective ART grogram. Targeted outcome evaluation therefore needs to be done that examines specific questions on how to maximize the durability of HIV virus suppression through proper retention on ART in the majority of patients treated in Rwanda.

1.3. Problem statement

Since 2002, Rwanda assured large-scale access to ARVs and observed a marked increase in uptake of ARVs almost hundred times to-date: from 870 patients in 2002 to 90,668 patients receiving ART in December 2010.(6)

Long-term retention of patients in Rwanda's rapidly expanding antiretroviral therapy (ART) programs for HIV/AIDS is essential for this programs' success and of vital importance to the health of the individual patient as well as to public health. The potential consequences of non-retention in highly active antiretroviral therapy (HAART) program include treatment failure or interruption and viral resistance in an individual

patient as well as transmission of resistant virus, all of which as earlier addressed, can limit future therapeutic options for the individual and the community.

1.4. Study rationale

With substantial emphasis placed on rapid implementation and service scale-up, there has been little opportunity to examine the retention and treatment outcomes of patients enrolled in ART program in Rwanda at large scale, especially using routinely collected program patient data widely available.

In this study, we aim to inform primarily Rwanda national ART program managers and the World with information on Patient retention in ART programs and associated factors to lower retention rate, thus triggers innovative approaches for services provision

1.5. Research questions

- What percentage of patients retained, Lost to follow up and dead at 6, 12, 24, 36 months after ART initiation?
- What are the immunological outcomes at 6, 12, 24, 36 months after ART initiation?
- What are the plausible factors associated to retention and mortality
- What is the estimated survival rate for the patients initiated on ART?

1.6. Study Objectives

1.6.1. General objective

To assess patient clinical and immunological outcomes of adult patients who were engaged in treatment in PEPFAR supported treatment centers between January 1st 2004 and December 31st 2011

1.6.2. Specific objectives

1. To evaluate the clinical outcomes of patients at 6, 12, 24, 36 months after ART initiation (survival, retention, mortality and Lost to follow up)

2. To evaluate the immunologic outcomes of patients at 6, 12, 24, 36 months after ART initiation (Median CD4 count cell rise on ARV treatment)
3. To determine the associated factors to clinical and immunological outcomes of patients on antiretroviral therapy

2. LITERATURE REVIEW

This chapter presents findings from the literature, providing snapshot information on current status of HIV epidemic in Rwanda and in the World; it also provides information on patient outcomes after initiation of antiretroviral therapy, highlighting the most common demographic and clinical characteristics of enrolled patients, factors that contribute to retention to care and outcomes. We performed a comprehensive literature review of published studies and reports via Pub Med, Hinari and other Health-related sciences websites, using the following key words: HIV-infected Patient outcomes, antiretroviral treatment, HIV in Sub-Saharan Africa.

2.1. The burden of HIV and AIDS

According to a report published by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2011, more than 34 million people were living with HIV, with more than 22 million people living in Sub-Saharan Africa. An estimated 6.6 million people were receiving ART in lower- and middle-income countries and 4.5 million in sub-Saharan Africa. This is only equals to 48.6% of those in needs.(2)

Rwanda, a country with a population of about 11 million, has an adult HIV prevalence (among women and men aged 15-49) of 3% in 2010, having remained unchanged since the 2005 Demographic and Health Survey(1). The median estimated number of adult infected with HIV in 2011 was 158,440 [136,140-179,960](3).

In December 2010, 90,668 patients were receiving ART (This equals 84% of patients in need of ART in Rwanda). Despite this great achievement, there is a need of continued

program expansion considering the target for national ART coverage of 93% in 2012, which translates in an estimated 101,500 individuals receiving treatment.(6)

2.2. Strategies to optimize HIV treatment outcomes

To reduce the burden of HIV and AIDS, one is to optimize HIV treatment outcomes. It becomes complicated within the constraints of limited resources in sub-Saharan Africa. It calls for strategies that will have the greatest impact on the reduction of opportunistic infections, toxicities, and early mortality after antiretroviral therapy initiation as well improve adherence, clinical, immunological, and virologic responses, patient retention in antiretroviral therapy programs, and overall quality of life of people living with HIV/AIDS. Antiretroviral therapy scale-up needs to continue to grow exponentially to meet the need for universal access and keep pace with or exceed the new HIV infections. Expanding antiretroviral therapy to all those eligible requires evidence-based decisions about how, when, and where expansion should occur. (7)

Key strategies to optimize HIV treatment outcomes include,

i) Scaling up HIV testing to identify all in need of HIV treatment,

ii) Strengthening the links between HIV diagnosis and comprehensive HIV/AIDS care,

iii) Timely initiation of antiretroviral therapy,

iv) Optimal diagnosis and treatment of opportunistic infections and co-morbidities,

v) Investing in laboratory tests to support clinical monitoring of patients on antiretroviral therapy,

vi) Maximizing adherence to antiretroviral medication and retention of patients in HIV/AIDS care,

vii) Improving the health infrastructure, and increasing the human resources to handle the growing numbers of people in need of HIV treatment(8)

2.3. Performance of National HIV program in Rwanda

Rwanda's National Strategic Plan on HIV (NSP, 2009-2012) guides the HIV work in the country carried out by all sectors and partners. The allocation of funds to civil society and government entities to work to achieve the targets in the NSP are coordinated to align with the plan. The goals of the current NSP are by June 2013: (1) halving the incidence of HIV in the general population; (2) reducing morbidity and mortality among people living with HIV; (3) ensuring people infected and affected by HIV have the same opportunities as the general population.

Reduction of mortality and morbidity has been achieved through increased geographical coverage of ARV services, increased local capacity to do CD4 counts thereby realising treatment need and treatment failure quicker, higher degree of TB and HIV co-management and more active management of co-infection and co-morbidity. To respond to the limited number of Medical Doctors, 500 nurses were trained and certified to prescribe ARVS 1st line through task shifting policy adopted and implemented in Rwanda since 2010.(6)

Since 2002, Rwanda assured large-scale access to ARVs and observed a marked increase in uptake of ARVs almost hundred times to-date: from 870 patients in 2002 to 90,668 patients receiving ART in December 2010.(6) This total included 7,541 infants and children aged 0-14 (3 752 female and 3 789 male), as well as 83,127 aged 15 years and older (52,011 female and 31,116 male). In the HIV and AIDS in Rwanda 2010 Epidemiologic Update it is estimated that there were 110,030 people eligible for ARV treatment in 2010: 96,040 aged 15 years or greater and 13,990 aged 0-14 years.(3)

Using these nationally validated data, it is calculated that 84% of HIV-positive individuals eligible for ARV therapy in Rwanda are receiving this treatment. This percentage varies by age, with 53.9% of eligible individuals aged 0-14 years receiving ARV therapy, compared with 86.6% of eligible individuals aged 15 years and older.(3)

Universal access, that is, provision of ART to all patients who meet the eligibility criteria, continues to be a central priority of the Government of Rwanda (GOR). With the support

from the US President's Emergency Plan for AIDS Relief, the Global Fund to fight AIDS, Tuberculosis, and Malaria, and other sources, the GoR has launched a massive effort to control the HIV epidemic. The GoR response to HIV/AIDS has emphasized innovative technologies and programs to improve the care and treatment of people living with HIV/AIDS and the general population.

2.4. Patient retention and patient outcomes on antiretroviral therapy

Reporting treatment outcomes of patients enrolled in ART programs is important to demonstrate program effectiveness and to identify factors associated with poor outcomes for program improvement (9). A retrospective cohort study done in Ethiopia showed that out of a total of 86 deaths over 60 month period; 63 (73.3%) died during the first 12 months, 10 (11.6%) during the second year, and 10 (11.6%) in the third year of follow up (10). Routinely monitoring such results can benchmark program quality improvements and inform program planning.

In the paper published in 2007, the results from a systematic review of literature databases, conference abstracts, publications archives, and the gray literature between 2000 and 2007 for reports on the proportion of adult patients retained (i.e., remaining in care and on ART) after 6 month or longer in sub-Saharan African, non-research ART programs, with and without donor support, the weighted mean retention rates reported in ART programs in Sub-Saharan Africa were 79.1%, 75.0% and 61.6 % at 6, 12, and 24 months, respectively. There was no association between 6 month attrition rates and cohort size (p 0.32), attrition and baseline CD4 cell counts (p 0.72), proportion of women (p 0.23) or year of program initiation (p 0.40).(11)

A Malawi study published in 2008, studied the outcome of patients transferred to other facilities, which concluded that the probability of survival in patients transferring out was better than those who remained at the central hospital, suggesting that transfers occur after patients have stabilized on therapy and after the first three months when a large proportion of ART deaths occur. Furthermore the Malawi's study findings showed that, among all patients that were transferred out, 86% were alive and on ART, 5% dead and

4% lost to follow-up 120. There were also transferred out again amounting 5%. The proportion of transfer-out patients who died was significantly less than those who did not transfer out [OR 0.4, 95% CI 0.3–0.6], and of those transfer-out patients who did die, there was a significant trend towards later deaths compared with those who did not transfer out.(12)

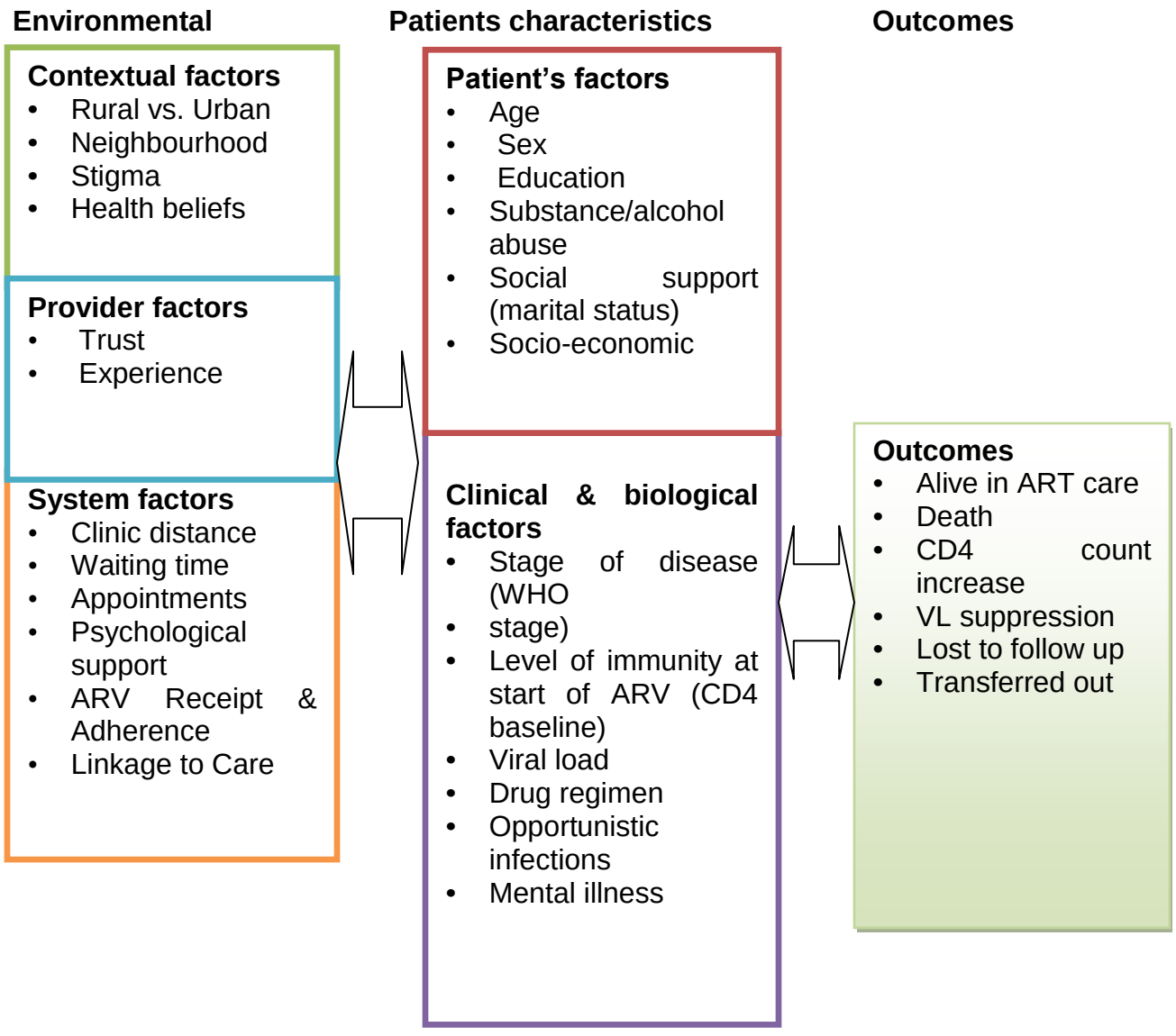
In 2007, an evaluation of the national ART program was conducted to assess retrospectively key clinical and immunological outcomes at 6- and 12-month among a nationally representative, stratified, random sample of 3,194 adults (≥15 years) who initiated ART from January 1, 2004 through December 31, 2005. At 6- and 12-months after ART initiation, 92% and 86% of patients, respectively, remained on ART at their original site. Female patients were more likely to remain alive and on ART at 6 months compared with similar male patients (AOR 1.50; 95% CI 1.14 to 1.98). Baseline CD4+ cell counts 50 cells/mm^3 were associated with lower likelihood of retention at 6 months (AOR 0.22: 95% CI: 0.06 to 0.89) and 12 months (AOR 0.25; 95% CI: 0.08 to 0.77). Among the 49% and 35% of patients with available follow-up CD4 cell count data, median CD4 cell counts increased by 98 /mm^3 (IQR 42–170) at 6 months and 119 cells/mm^3 (IQR 55–208) after 12 months on ART, relative to baseline. Female patients had median cell count increase at 6 months of 104 cells/mm^3 (IQR 44–178) compared with a median increase of 89 cells/mm^3 (IQR 35–150) for male patients (P = 0.005) and at 12 months of 122 cells/mm^3 (IQR 55–211) compared with 115 cells/mm^3 (IQR 54–200) for males (P = 0.35). In multivariate analysis, older age at ART initiation (AOR 0.88, per 10-year increment; 95% CI: 0.80 to 0.97) was associated with achieving a CD4+ cell count increase of $80 cells/$mm^3$ by 6 months on treatment.(4)

In 2010, a retrospective medical record review was performed for a cohort of 1041 HIV+ adult patients initiating community-based ART between June 1 2005 and April 30 2006 in Southeastern Rwanda. Key programmatic elements included free ART with direct observation by CHW, tuberculosis screening and treatment, nutritional support, a transportation allowance, and social support. Among 1041 patients who initiated community-based ART, 961 (92.3%) were retained in care, 52 (5%) died and 28 (2.7%)

were lost to follow-up. Median CD4 T-cell count increase was 336cells/mm^3 (IQR 212-493) from median 190cells/mm^3 (IQR 116-270 at initiation.(5)

2.5. ART patient outcome conceptual framework

The associated factors of patient remaining in ART care can be categorized in Environmental (Context, health system and provider factors), Patient factors (clinical, biological and socio-demographic factors)



3. METHODS

3.1. Study setting: National HIV and AIDS care program in Rwanda

Rwanda is an East African country with a population of approximately 11 million in 2012. It has a generalized HIV epidemic, and the national HIV prevalence was estimated to be 3% in 15-to-49-year-old adults (DHS2010). According to UNAIDS modeled estimates, there are currently 170,000 [140,000-190,000] HIV-infected individuals in Rwanda, as of year 2010, with 92,000 HIV-infected adults estimated to be on treatment.(3)

The first project to routinely offer ART in the public sector and on a district-wide basis in Rwanda was started in 2002 as a partnership between the Government of Rwanda, Global Fund and PEPFAR and one-UN. At that time, several local clinicians had already been involved in ART provision through clinical studies and private funding and were able to support this and subsequent initiatives.

We note that there was an increase of health facilities offering care and treatment services and in the same way patients increased. Since 2002, Rwanda assured large-scale access to ARVs and observed a marked increase in uptake of ARVs almost hundred times to-date from 870 patients in 2002 to 96,123 patients by June 2011 (6) in 336 health facilities offering care and treatment services.

The national care and treatment program continued to achieve strong results in the delivery of ART services to the population and services are equally distributed. The map bellow shows the location of our sites included in our study (PEPFAR supported sites).

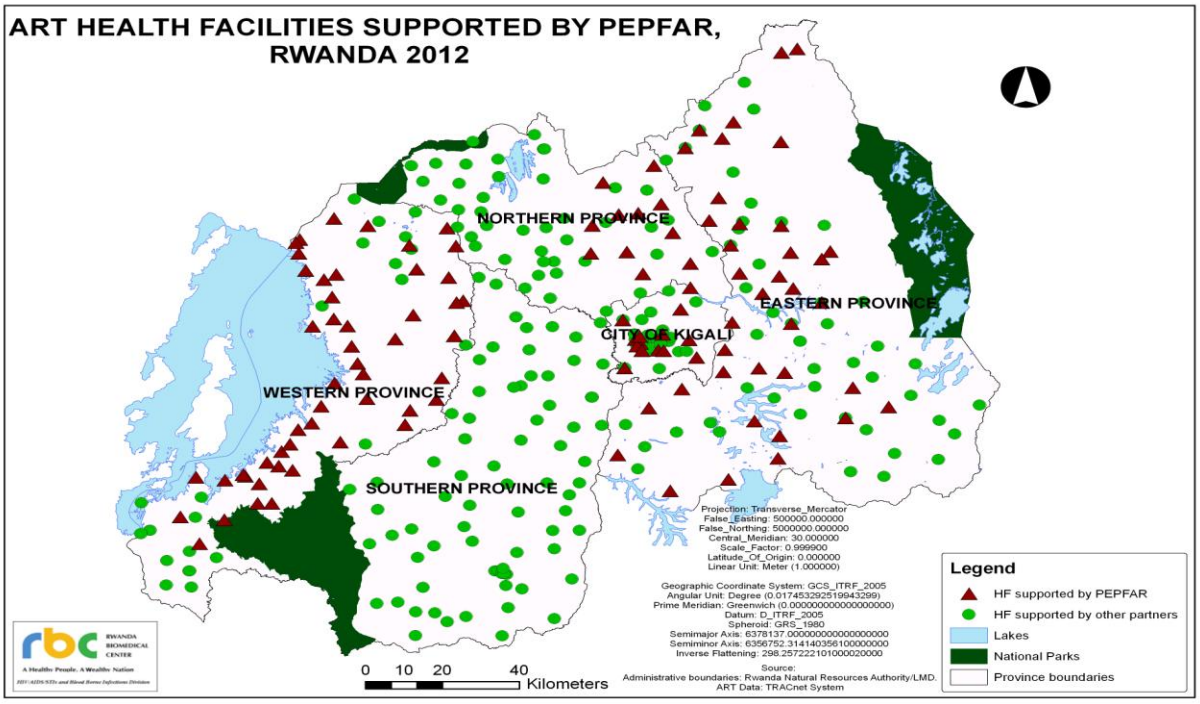


Figure 1 ART facilities in Rwanda, June 2012

3.1.1. National ART Initiation Criteria and Regimens

The first national ART guidelines for clinical providers were distributed in 2004–2005. At that time, adults were eligible for ART if they were as follows:

(1) HIV infected and classified according to WHO clinical stage 4, irrespective of CD4 cell count;
(2) WHO clinical stage 3 with a CD4 cell count, 350 cells per cubic millimeter; or
(3) WHO clinical stage 1 or 2 with a CD4 cell count, 200 cells per cubic millimeter

Other suggested criteria for initiation of ART included participation in adherence education and identification of a treatment supporter.

The recommended first-line regimen from 2004 to 2009 was stavudine or zidovudine with lamivudine (3TC) and either nevirapine or efavirenz.

During 2007–2008, eligibility criteria for ART initiation were modified. The threshold CD4 count for initiation of ART was increased from 200 to 350 cells per cubic millimeter, regardless of the WHO stage (1, 2, or 3); WHO stage 4 remained an indication for ART initiation regardless of CD4 count. Additionally, zidovudine with 3TC became the preferred first-line nucleoside reverse transcriptase inhibitors backbone combined with nevirapine or efavirenz.

In 2009, national guidelines were again revised to recommend tenofovir as the preferred first-line nucleotide reverse transcriptase inhibitor in combination with 3TC and either nevirapine or efavirenz. A second-line ART regimen of zidovudine, 3TC, and lopinavir/ritonavir is currently used. (7)

3.1.2. Routine Clinical and Laboratory Monitoring

At the time of ART initiation, routine baseline clinical and laboratory assessment of HIV-infected persons in Rwanda include weight, CD4 cell count, and WHO clinical staging. ART patients receive monthly clinical and psychological follow-up, including TB screening, adherence psychosocial support and weight measurements for the first 6 months, followed by routine clinical and CD4 evaluations at 6-month intervals. Pharmacy refill, continue on a monthly basis all along the treatment course. Before 2009, cotrimoxazole (CTX) prophylaxis was routinely provided to any patient with a CD4 cell count 350 cells per cubic millimeter; a diagnosis of active tuberculosis disease; or WHO clinical stage 4 criteria. During 2009, all patients with documented HIV infection were considered eligible for CTX regardless of CD4 cell count.

Patient outcomes are evaluated and recorded in patient files on regular basis. There are scheduled home visits that most of the time occur when poor adherence is suspected or in case of Lost to follow. A patient was defined as lost-to-follow-up (LTFU) if his last contact with the health facility for any reason (clinical follow-up, pharmacy refill, or laboratory monitoring) was more than 3 months for ART patients and if not known to have died or transferred to another treatment site. Deaths were recorded by each facility as they became known during hospitalization or from home visits after being identified as LTFU.

3.1.3. ART program information management system description

The ART program is successful when it shows its ability to deliver ARVs to those who need them using the scale-up approach and to ensure that patients stay well on treatment. In Rwanda, for this to occur, dedicated resources and processes have been expanded to establish and maintain harmonized monitoring and evaluation systems that will not only measure the effectiveness of ART programs and outcomes, but also inform the ongoing improvement and optimization of the clinical and management operations of scale-up.

In 2004, the Rwanda MOH and TRAC Plus began collecting limited aggregated ART program information using TRACnet, a web-based system. These data include the number of facilities providing ART and number of patient enrollment in the program with some clinical and demographic information. Standardized pre-ART and ART registers, medical records (the “dossier vert”), and pharmacy files are used by all sites providing HCT. On a monthly basis, every HCT site aggregates data for select indicators and submits a report into the TRACnet system. Indicators include number of patients on ART by gender, age category (adult vs. pediatric), and regimen (first vs. second line); number of patients on CTX prophylaxis; patients’ WHO stage at ART initiation; death; and LTFU.

The IQ-chart system is one component of a framework for the monitoring of the ART programme in Rwanda. Built on MS access platform, the system consists of multiple sheets that gather socio-demographic information, clinical, immunological, and biological and treatment information for individual patients. The system started to be used in PEPFAR supported sites from 2004 and over eighty percent of PEPFAR supported health care facilities use IQ-Chart in 22 PEPFAR supported Districts. Monthly reporting is universal across the sites and comprises cross-sectional patient and enrolment totals, the essential information required by managers to keep track of resource allocation and progress against targets.

However, while there has been an increased use of information systems for routine program data collection, they have not been widely used for program evaluation and monitoring of treatment outcomes.

The data we extracted were from 121 health facilities in the Western, Northern, Eastern provinces and Kigali City. Health facilities included one reference hospital, 17 district hospitals and 103 health centers.

3.2. Study Design

We reviewed patient data collected electronically from cohorts of HIV-infected adult patients (age 15 and above) who had initiated ART at one of the 121 IQ Chart sites in Rwanda between January 2004 and December 2010.

3.3. Study population

Our study population includes all adults patients (>15 years of age) initiated on ART between January 1st 2004 and December 31st 2010 and recorded in IQ-Chart. They are excluded in our study, all the patients age below 15 years and patients who initiated ART before January 1, 2004 or after December 31st, 2010. Thus, a total of 35,101 adult patients were eligible to be enrolled in our study.

In total 121 (35% of all the ART sites nationwide) using the IQ Chart (an Electro Medical Record to capture clinical and programmatic indicators for patient management and program monitoring purposes) were included in our study.

3.4. Sampling

All patients meeting inclusion criteria have been enrolled in our study.

3.5. Data abstraction and management

Standardized pre-ART and ART registers, medical records (the “dossier vert”), and pharmacy files are used by all sites providing HCT. Patients are entered into a register in the order in which they start ART. Each patient enrolled in HCT services is given a unique alphanumeric TRACnet identification code. The information recorded in the patient files, pharmacy cards and ART registers were entered into the IQ-chart system

where available, on regular basis. Built on MS access platform, the system consists of multiple sheets that gather socio-demographic information, clinical, immunological, and biological and treatment information for individual patients. The entered data is cross-checked on monthly basis and every time before reporting exercises. Quarterly cohort reports are provided a quarter in arrears to allow sites to complete the ascertainment of outcomes before reporting. The metrics captured in the system include gender, age category (adult vs. pediatric), marital status, regimen (first vs. second line); CTX prophylaxis; patients' WHO stage at ART initiation; outcomes (i.e. in care, transferred out, lost to follow-up, died) and biological information such as CD4 and Viral load.

3.6. Data analysis

3.6.1. Measurement of Outcomes

We evaluated ART program and patient outcomes using IQ-Chart stored data that captured demographic, programmatic, clinical, and immunologic indicators for all enrolled patients meeting the inclusion criteria.

Our measurement of outcomes	Operational definition
Retention in care	was measured as having a recent or last visit to the ART clinic in the three months preceding the date of abstraction
Mortality	Considered when a patient was recorded as dead in patient files and in the IQ-chart data base at the treatment sites.
Lost to follow up	When a patient was not found for more than 90 calendar days after the last appointment date and the status recorded in patient file

Immunological outcome (CD4 cell count rise)	Was evaluated by analyzing the trend of CD4 values at baseline and after 6, 12, 24 and 36 months on ART treatment.

3.6.2. Measurement of exposures

	Operational definition
Date at initiation	Time of ART initiation. Grouped in 2 categories: from 2004-2006 and from 2007-2010, based on major changes in national guidelines in regards to ARV initiation criteria in Rwanda). We had divided into 2 periods: the period before 2007, where the CD4 count threshold for ARV initiation was >200cells/mm^3 and the period after 2007 where the program initiates ARVs to all HIV-infected adults with CD4 cell count <350cells/mm^3
Age of the patient at ART initiation	Self-reported age at the time of enrolment (obtained by taking date at ART initiation minus date of birth)
Gender	A binary variable indicating the sex of the patient
Marital status	Marital status at time of ART initiation (living with a partner and non living with partner (single, divorced/separated, widowed)
CD4 count baseline	CD4 count measured at time of ART initiation
CD4 count follow up	CD4 count measured at specific points in the follow up after ART initiation

3.6.3. Statistical Analysis

We collected data from an Access database (IQCHART) and then transferred them to STATA [version 11] (STATA Corporation, College Station, TX, USA) for cleaning and analysis. In order to assess the patient outcomes on ART, we defined 3 major outcomes, alive/retention in care, dead and lost to follow up. As, the program expansion was expanding rapidly during the period covered by our review, we had a considerable number of patients who transferred their care to other health facilities. We excluded these patients from the analysis.

We computed proportions for categorical variables and means, standard deviations, and quartiles for the continuous variables. We examined the relationship between our outcome variables, being alive and retained in care, using the Pearson test. The Wilcoxon Signed Rank Test (a non-parametric statistical test for testing hypothesis on median) was used to assess whether the Median CD4 cell count rise in the different period statistically differed among population subjects. In addition, we estimated survival using Kaplan Meier curves stratified by CD4 cell values, age, sex and marital status at ART initiation. We assessed differences among group using the log rank test and logistic regression for categorical variables.

3.7. Ethical Considerations

This project involves no contact with human subjects and patients names were deleted in the dataset. Patients enrolled were given unique patient identifiers. To ensure patient confidentiality, no patient names is mentioned in the dataset. The data is stored in a password-protected electronic database housed at RBC which only study investigators and data managers at RBC have access.

4. RESULTS

4.1. Patient baseline characterstics at ART initiation

Thirty five thousands one hundred and one HIV infected adults aged 15 years and above initiated ART between January 2004 and December 2010 at the 121 participating sites supported by President Emergency Plan for AIDS Relief (PEPFAR). Seventy percent of them were initiated in the period between 2006-2009, where the National HIV program recorded its pick in the patient initiation on ARVs. The trend below describes the enrollement of HIV-infected adult in PEPFAR supported antiretroviral programs which also generally reflects the overall Rwanda ART program scale up. (Fig2)

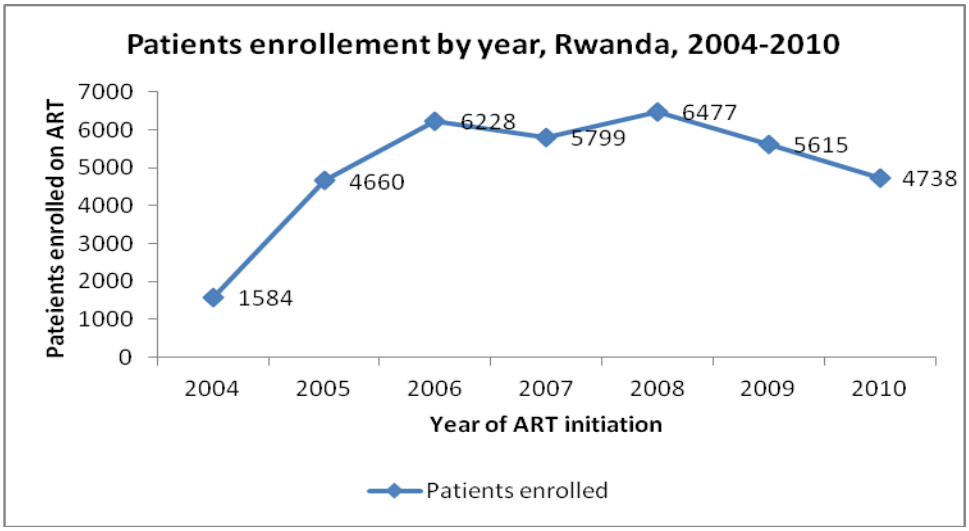


Figure 2 Trends HIV-Infected adults enrollment on ARVs from 2004-2010 in 121 study sites

Of these 35,101 adults patients, the median age was 36.3 years (IQR: 30.5-43.1) and mean age was 37.1 (SD± 9.56) at ART initiation and the majority were aged between 25-34 years (35.5%) and 35-44 years (36.4%). 22,301 (63.5%) of the enrolled patients were female and 12,800 (36.5%) were male patients. The female/male ratio equals 1.74.

Over Fifty five percent were documented as single, divorced, widowed or other, and 44.6% were documented as living with a sexual partner. (Table1).

CD4 levels were measured and recorded in 28,379 HIV-infected adults at ART initiation and overall median CD4 measured at baseline was 217cells/mm3 [IQR 131-298]. We observed that, a higher proportion (54.5%) of HIV-infected adults initiated on ARVs from 2004-2006 were having CD4 cell count at baseline in between 50-199 cells/mm3. these proportions significantly changed from 2007-2010; where the highest proportion (56.6%) of HIV-Infected adults were initiated ART on ARVs at CD4 cell count baseline in between 200-350cells/mm^3. This illustrates the change that occurred in 2007-2008 that instructed to increase the CD4 cell count threshold at baseline, from 200cells/mm3 to 350cells/mm3. Looking at the baseline characteristics at ART initiation, the 2 cohorts were statistically different (p<0.001). (Table1)

Table 1 Demographic and immunological characteristics of Adults Patients Ever Initiated on ART, by year of ART initiation, Rwanda, 2004-2010

Characteristics	Year of ART initiation		
	2004-2006	**2007-2010**	**Total**
N	**12,472**	**22,629**	**35,101**
Age*			
15 24 years	736 (5.9)	2143 (9.5)	2879 (8.2)
25 34 years	4136 (34.6)	8161 (36.1)	12477 (35.5)
35 44 years	5028 (40.3)	7748 (34.2)	12776 (36.4)
45 54 years	1997 (16.0)	3506 (15.5)	5503 (15.7)
55 and > years	395 (3.1)	1071 (4.7)	1466 (4.2)
Sex*			
Male	4215 (33.8)	8585 (38.0)	12800 (36.5)
Female	8257 (66.2)	14044 (62.0)	22301 (63.5)
Living with partner*			
Yes	4409 (35.4)	11237 (49.7)	15646 (44.6)
No	8063 (64.6)	11392 (50.3)	19455 (55.4)
CD4 baseline (CD4 cell count, in cells/mm^3)*			
<50	1009 (11.4)	1197 (6.1)	2206 (7.8)
51 199	4830 (54.5)	5804 (29.7)	10634 (37.5)
200 349	2793 (31.5)	11044 (56.6)	13837 (48.8)
350 499	146 (1.7)	1047 (5.4)	1193 (4.2)
500+	78 (0.9)	431 (2.2)	509 (1.8)

N	**8,856**	**19,523**	**28,379**

***Pvalue <0.001**

The differences in median CD4 at ARV initiation were observed by year off ART initiation: Before 2007, the overall median CD4 at ARV initiation was 164cells/mm3 [96 - 226] whereas in between 2008 – 2010, the median CD4 at ARV initiation is at 250cells/mm3 [158 – 314, (p<0.001)].

Considering CD4 baseline at ARVs initiation by sex, age and marital status, the findings suggested that HIV-infected female adults were initiated on ARVs early with median CD4 cell count of 227cells/mm^3 [IQR 141-304] compared to HIV-infected male adults who initiated with low median CD4 count of 198 cells/mm^3 [IQR 114-285] (p<0.001), the HIV infected adults living with sexual partners initiated early compared to non-living with partner with 227 cells/mm^3 [IQR 140-304] and 209 cells/mm^3 [IQR 124-292] median CD4 cell counts respectively (p<0.001). (Table2).

Table 2 Median CD4 count at ARV start date (baseline), by sex, cohorts, marital status and age

Patient characteristics	Median CD4 count at ARV start cells/mm^3 [IQR]
Over all Median CD4 at ART initiation (N=28,379)	**217 [131-298]**
ART start year: 2004-2006*	164 [96-226]
2007-2010	250 [158-314]
Sex*: Male	198 [114-285]
Female	227 [141-304]
Age group*: 15-24 years	250 [159.5-316.5]
25-34 years	222 [136-301]
35-44 years	204 [124-289]
45-54 years	212 [127-296]
55+ years	231 [139-298]
Marital status*: Living with partner	227 [140-304]
Not living with partner	209 [124-292]

***Pvalue <0.001**

Over all, we noted a trend increase of median CD4 baseline at ARVs initiation as the ART program in Rwanda matures, from median CD4 cell count of 126cells/mm^3 in 2004 to median CD4 cell count of 277cells/mm^3 in 2010. (Fig3)

This positive trend demonstrates the effective ART program in Rwanda with its ability to get HIV-infected adults in the their early stage of the disease and initiate them on ARVs which in long run contribute to better patients' outcome as will be shown later on.

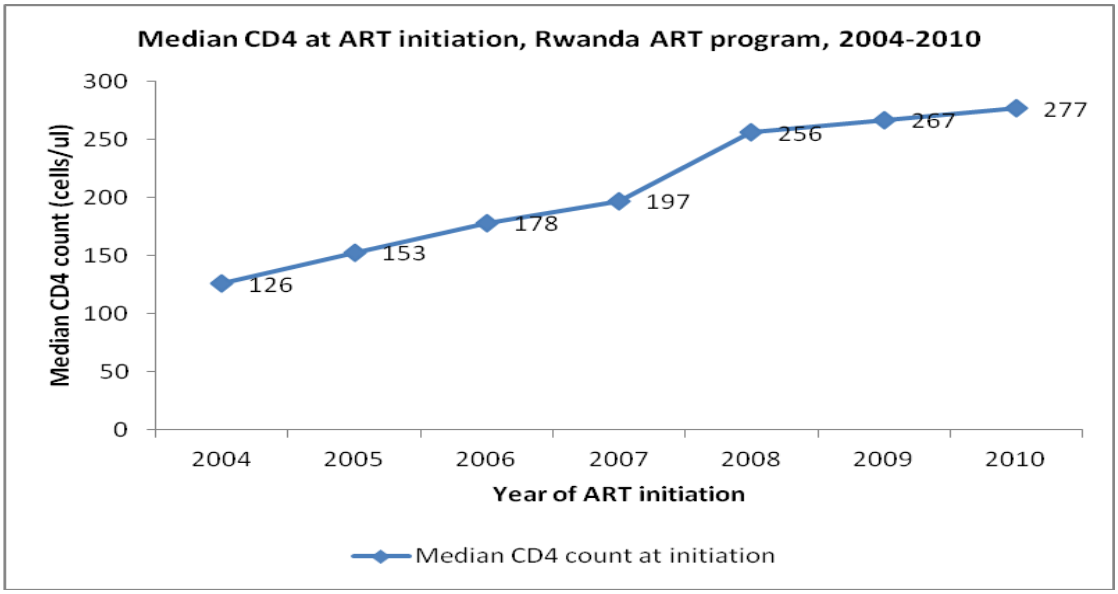


Figure 3 Evolution of median CD4 count baseline at ART initiation, Rwanda 2004-2010

4.2. Cell Response after 6, 12, 24 and 36 months of ART initiation

The first routinely scheduled follow-up CD4 cell count results was performed and recorded at 6 months after ART initiation for 24,417 patients and the median rise in CD4 cell count from baseline to this point was 135cells/mm^3 [IQR: 99-190]. Out of 20,829 patients who had 12 months CD4 cell count follow up, the median rise in CD4 cell count from baseline was 162cells/mm^3 [IQR: 122-222]. The follow-up CD4 cell count results performed and recorded at 24 months after ART initiation for 14,407 patients revealed the median rise in CD4 cell count from baseline to this point of 197cells/mm^3 [IQR: 159-262], and this rise was up to 221cells/mm^3 [IQR: 181-288], 36 months after ART

initiation for 9,009 patients who had CD4 cell count results performed and recorded at that point.

The Wilcoxon signed-rank test was performed to determine the level of statistic significance of different median CD4 rise per age, sex, gender, cohort and marital status. Female patients had higher median cell count rise at 6 months of 144 cells/mm^3 (IQR 108–204) compared to median rise of 123 cells/mm^3 (IQR 91–168) in male patients, at 12 months of 173 cells/mm^3 (IQR 131–240) compared with 141 cells/mm^3 (IQR 110–186) for males, at 24 months of 215 cells/mm^3 (IQR 175–285) compared with 163 cells/mm^3 (IQR 136–208) for males and at 36 months of 244 cells/mm^3 (IQR 201–316) compared with 179 cells/mm^3 (IQR 112–222) for males (p<0.001). (Table3)

Table 3 Median CD4 cell count gain at 6, 12, 24 and 36 months after ART initiation

Patient characteristics	6 months Cells/mm3[IQR]		12 months Cells/mm3[IQR]		24 months Cells/mm3[IQR]		36 months Cells/mm3[IQR]	
Cohort*								
2004-06	122	[94-181]	159	[123-232]	224	[176-309]	260	[208-345]
2007-10	135	[101-302]	156	[123-231]	182	[148-261]	209	[164-287]
Sex*								
Male	123	[91-168]	141	[110-186]	163	[136-208]	179	[112-222]
Female	144	[108-204]	173	[131-240]	215	[175-285]	244	[201-316]
Living with partner*								
Yes	137	[99-191]	156	[119-222]	188	[153-255]	204	[166-279]
No	133	[99-189]	166	[124-223]	204	[164-268]	235	[193-296]
Age (years)*								
15-24	169	[115-257]	203	[143-302]	226	[169-343]	233	[182-353]
25-34	151	[113-207]	179	[135-244]	218	[179-285]	244	[202-317]
35-44	127	[94-172]	153	[118-206]	195	[154-248]	224	[181-279]
45-54	117	[91-169]	141	[106-183]	167	[133-224]	189	[161-240]
55+	107	[70-164]	129	[95-197]	148	[118-219]	155	[134-223]

*Pvalue <0.001

4.3. Adult patient outcomes at 6, 12, 24 and 36 months after ART initiation

Out of a total of 35,101 patients enrolled in our study, after 6- month cohort, 1,032 (2.9%) patients were transferred out to other health facilities, 1,041 (3.5%) patients died, 171 (0.6%) patients were lost to follow-up, and 32,857 (95.9%) patients were remaining in care. One year after ART initiation, 2,218 (6.3%) patients were transferred out to other health facilities, 1,347 (4.6%) patients died, 423 (1.4%) patients were lost to follow-up, and 27,657 (94.0) patients were remaining in care. Two years after ART initiation, 4,259 (12.1%) patients were transferred out to other health facilities, 1,697 (5.8%) patients died, 835 (2.8%) patients were lost to follow-up, and 26,895 (91.4) patients were remaining in care. Thirty six months after ART initiation, in total 5,674 (16.2%) patients were transferred to other treatment site, 1,086 (3.1%) were cumulatively lost to follow up and 1,891 (5.4%) were dead. (Table4).

Table 4 Adult Patient Outcomes at 6, 12, 24 and 36 Months (N=35,101)

Outcomes	6 months	12 months	24 months	36 months
Alive in care	28,215 (95.9)	27,657 (94.0)	26,895 (91.4)	26,450 (89.9)
Dead	1,041 (3.5)	1,347 (4.6)	1,697 (5.8)	1,891 (6.4)
Lost to follow up	171 (0.6)	423 (1.4)	835 (2.8)	1,086 (3.7)
Transferred out	1,032 (2.9)	2,218 (6.3)	4,259 (12.1)	5,674 (16.2)

The majority of death occurred in the first 6 and 12 months of ART initiation and decreased over time: Out of a total of 1,891 deaths over 36 month period; 1,041 (55%) died during the first 6 months, 306 (16.1%) between 6 and 12 months, 350 (18.5%) in the second year and 194 (10.2%) in the third year of follow up. We observed a reverse trend for lost to follow up where lost to follow up increased over time on ART: out of a total of 1,086 LTFU over 36 month period; 171 (15.7%) were lost during the first 6 months, 252 (23.2%) between 6 and 12 months, 412 (38.0%) in the second year and 251 (23.1%) in the third year of follow up. As our study covered the period of program

scale up, we noted a considerable proportion of transfers to other health facilities with a total of 16.2% of our total population were transferred after 36 months). (Fig4)

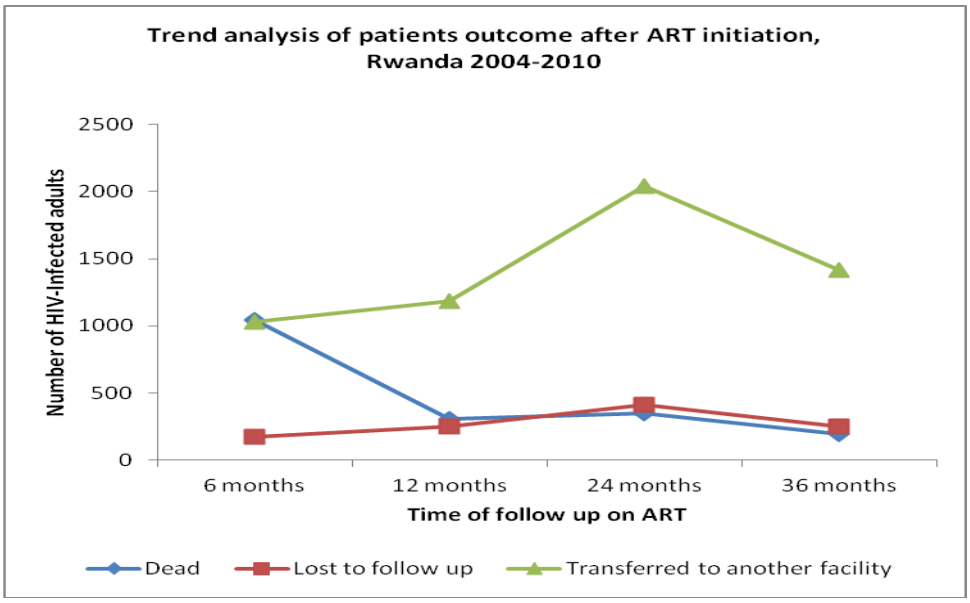


Figure 4 Trend analysis of HIV-infected outcomes after ART initiation in Rwanda, from 2004-2010

Excluding Transfers out in our analysis, six months after ART initiation, 28,215 patients (95.9%) were alive in care, 1,041 (3.5%) were dead, 171 (0.6%) were lost to follow up. Bivariate analysis showed that, female patients had better retention compared to male patients 96.5% vs. 94.7% (OR:1.5, 95%CI 1.37-1.72, p= 0.000), younger patients had better retention compared to old patients (OR:1.68, 95%CI 1.24-2.27, p= 0.001), patients not living with partner had lower retention compared to patients living with partner 95.1% vs. 96.8% (OR:0.63, 95%CI 0.56-0.72, p= 0.000), patients with higher median CD4 at ART initiation are more likely to be retained compared to patients starting ARV with CD4 count below 200 cells/mm^3. OR: 2.92, 95%CI 2.53-3.37, p= 0.000, for patients starting ARV with CD4 count between 200-349 cells/mm^3. (Table5)

One year after ART initiation, 27,657 patients (94.0%) were alive in ART care, 1,347 (4.6%) were dead, 423 (1.4%) were lost to follow up. Female patients had higher retention compared to male patients 94.9% vs. 92.5% (OR:1.47, 95%CI 1.33-1.62, p= 0.000), younger patients had better retention compared to old patients (OR:1.49,

95%CI 1.17-1.91, p= 0.001), patients not living with partner had lower retention compared to living with sexual partner 93.0% vs. 95.4% (OR:0.63, 95%CI 0.57-0.70, p= 0.000), patients with higher median CD4 at ART initiation are more likely to be retained compared to patients starting ARV with CD4 count below 200 cells/mm^3. OR: 2.41, 95%CI 2.14-2.70, p= 0.000, for patients starting ARV with CD4 count between 200-349 cells/mm^3. (Table5)

Twenty four months after ART initiation, 26,895 patients (91.4%) were retained in ART care 1,697 (5.8%) were dead, 835 (2.8%) were lost to follow up. Female patients had higher retention compared to male patients 92.5% vs. 89.5% (OR:1.45, 95%CI 1.34-1.57, p= 0.000), younger patients had better retention compared to old patients (OR:1.42, 95%CI 1.16-1.75, p= 0.001), patients not living with partner had lower retention compared to living with partner 89.7% vs. 93.4% OR:0.61, 95%CI 0.56-0.67, p= 0.000), patients with higher median CD4 at ART initiation are more likely to be retained compared to patients starting ARV with CD4 count below 200 cells/mm^3. OR: 2.03, 95%CI 1.85-2.34, p= 0.000, for patients starting ARV with CD4 count between 200-349 cells/mm^3. (Table5)

The number and proportion of patients retained in ART care after 36 months was 26,450 (89.9%), 1,891 (6.4%) were dead, 1,086 (3.7%) were lost to follow up. Female patients had higher retention compared to male patients 91.1% vs. 87.3% (OR:1.43, 95%CI 1.32-1.54, p= 0.000), younger patients had better retention compared to old patients (OR:1.37, 95%CI 1.13-1.67, p= 0.001), patients not living with partner had lower retention compared to living with sexual partner 88.0% vs. 92.1% (OR:0.63, 95%CI 0.58-0.68, p= 0.000), patients with higher median CD4 at ART initiation are more likely to be retained compared to patients starting ARV with CD4 count below 200 cells/mm^3. OR: 2.00, 95%CI 1.83-2.19, p= 0.000, for patients starting ARV with CD4 count between 200-349 cells/mm^3. (Table5)

The unadjusted analysis of patients characteristics at ART initiation against mortality showed significant risk differences between age group, gender, marital status and CD4

cell count. After 6 months of follow up, female were less likely to die compared to male (OR: 0.62, 95%CI: 0.54-0.69, p<0.001). The female gender was associated with lower mortality risk after 12, 24 and 36 months.

The patients not living with sexual partner had greater risk of death after 6 months compared to patient living with a sexual partner (OR: 1.51, CI: 1.33-1.72, p<0.001) and the trend remained the same after 12, 24 and 36 months on treatment.

Younger age was associated with lower risk of death compared to the old patients (55+ age group taken as reference) (OR: 0.45, 95%CI: 0.32-0.62, p<0.001). Similar results were observed after 12, 24 and 36 months of ART follow up.

Patients with higher median CD4 at ART initiation have lower risk of death compared to patients starting ARV with CD4 count below 200cells/mm^3. (OR: 0.29, 95%CI 0.24-0.34, p= 0.000, for patients starting ARV with CD4 count between 200-349 cells/mm^3). (Table6)

Table 5 Factors Associated with Retention at 6, 12, 24 and 36 Months after ART Initiation (N = 29,427), Rwanda 2004-2010

Baseline criteria	Retention												Total (N)
	6months			12months			24months			36months			
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	
Age group (years)													
15-24	1.68	1.24-2.27	0.001	1.49	1.17-1.91	0.001	1.42	1.16-1.75	0.001	1.37	1.13-1.67	0.001	2,392
25-34	1.87	1.46-3.39	0.000	1.99	1.53-2.31	0.000	1.85	1.55-2.21	0.000	1.87	1.59-2.20	0.000	10,337
35-44	1.69	1.32-2.15	0.000	1.79	1.46-2.20	0.000	1.90	1.60-2.27	0.000	1.90	1.61-2.24	0.000	10,819
45-54	1.36	1.05-1.77	0.019	1.45	1.16-1.80	0.001	1.55	1.28-1.87	0.000	1.60	1.33-1.90	0.000	4,631
55+	1	1	1	1	1	1	1	1	1	1	1	1	1,248
Sex													
Male	1	1	1	1	1	1	1	1	1	1	1	1	10,707
Female	1.5	1.37-1.72	0.000	1.47	1.33-1.62	0.000	1.45	1.34-1.57	0.000	1.43	1.32-1.54	0.000	18,720
Living with a sexual partner													
No	0.63	0.56-0.72	0.000	0.63	0.57-0.70	0.000	0.61	0.56-0.67	0.000	0.63	0.58-0.68	0.000	16,034
Yes	1	1	1	1	1	1	1	1	1	1	1	1	13,393
Baseline CD4 cell count													
<200	1	1	1	1	1	1	1	1	1	1	1	1	10,656
200-349	2.92	2.53-3.37	0.000	2.41	2.14-2.70	0.000	2.03	1.85-2.34	0.000	2.00	1.83-2.19	0.000	11,754
350-499	1.97	1.40-2.76	0.000	1.78	1.35-2.35	0.000	1.84	1.44-2.35	0.000	1.77	1.42-2.22	0.000	1,093
500+	1.39	0.89-2.18	0.139	1.33	0.92-1.94	0.132	1.03	0.77-1.39	0.817	1.11	0.83-1.47	0.473	446

Table 6 Factors Associated with Mortality at 6, 12, 24 and 36 Months after ART Initiation (N = 29,427), Rwanda 2004-2010

Baseline criteria	Mortality												Total (N)
	6months			12months			24months			36months			
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	
Age group (years)													
15-24	0.45	0.32-0.62	0.000	0.41	0.30-0.54	0.000	0.32	0.25-0.42	0.000	0.29	0.22-0.37	0.000	2,392
25-34	0.43	0.33-0.58	0.000	0.39	0.31-0.49	0.000	0.34	0.28-0.41	0.000	0.30	0.25-0.36	0.000	10,337
35-44	0.55	0.42-0.70	0.000	0.50	0.40-0.62	0.000	0.43	0.36-0.52	0.000	0.40	0.34-0.48	0.000	10,819
45-54	0.70	0.54-0.92	0.000	0.66	0.52-0.83	0.000	0.59	0.48-0.72	0.000	0.55	0.46-0.67	0.000	4,631
55+	1	1	1	1	1	1	1	1	1	1	1	1	1,248
Sex													
Male	1	1	1	1	1	1	1	1	1	1	1	1	10,707
Female	0.62	0.54-0.69	0.000	0.63	0.57-0.71	0.000	0.63	0.57-0.70	0.000	0.63	0.57-0.69	0.000	18,720
Living with a sexual partner													
No	1.51	1.33-1.72	0.000	1.52	1.35-1.70	0.000	1.60	1.44-1.76	0.000	1.56	1.41-1.72	0.000	16,034
Yes	1	1	1	1	1	1	1	1	1	1	1	1	13,393
Baseline CD4 cell count													
<200	1	1	1	1	1	1	1	1	1	1	1	1	10,656
200-349	0.29	0.24-0.34	0.000	0.32	0.28-0.37	0.000	0.34	0.30-0.39	0.000	0.35	0.32-0.40	0.000	11,754
350-499	0.42	0.29-0.62	0.000	0.45	0.32-0.63	0.000	0.42	0.31-0.57	0.000	0.44	0.33-0.60	0.000	1,093
500+	0.60	0.36-0.99	0.046	0.57	0.36-0.90	0.018	0.61	0.40-0.92	0.017	0.60	0.40-0.88	0.010	446

4.4. Predictors of adult patient outcomes at 6, 12, 24 and 36 months after ART initiation

4.4.1. Retention

A multivariate analysis was performed adjusting for gender (Male vs. female), age at ART initiation (15-24 years of age vs. other age group), CD4 count (Median CD4 count at baseline <200cells/mm^3 vs. other groups) at ART initiation, and marital status (not living with partner vs. living with partner) and yield following results:

After 6 months of ART initiation, female patients were more likely to be retained in care compared to male patients (AOR 1.46; 95% CI: 1.26–1.69, p<0.001) patients not living with partner had lower odds to be retained (AOR 0.68; 95% CI: 0.59–0.79, p<0.001), patients with median CD4 of 200-349 at ART initiation were more likely to be retained compared to patients with lower CD4 cell count at initiation (AOR 3.44; 95% CI: 2.92–4.06, p<0.001).

Twelve months after, female patients were more likely to be retained in care compared to male patients (AOR 1.48; 95% CI: 1.41–1.71, p<0.001) patients not living with partner had lower odds to be retained (AOR 0.61; 95% CI: 0.54 – 0.69, p<0.001), patients with median CD4 of 200-349 at ART initiation were more likely to be retained compared to patients with lower CD4 cell count at initiation (AOR 2.53; 95% CI: 2.24 – 2.85, p<0.001).

Twenty four months after, female patients were more likely to be retained in care compared to male patients (AOR 1.56; 95% CI: 1.41 – 1.71, p<0.001) patients not living with partner had lower odds to be retained (AOR 0.59; 95% CI: 0.53 – 0.65, p<0.001), patients with median CD4 of 200-349 at ART initiation were more likely to be retained compared to patients with lower CD4 cell count at initiation (AOR 2.08; 95% CI: 1.89 – 2.30, p<0.001).

Thirty six months after, female patients were more likely to be retained in care compared to male patients (AOR 1.53; 95% CI: 1.40 – 1.68, p<0.001) patients not living with partner had lower odds to be retained (AOR 0.61; 95% CI: 0.55 – 0.66, p<0.001), patients with median CD4 of 200-349 at ART initiation were more likely to be retained compared to patients with lower CD4 cell count at initiation (AOR 1.98; 95% CI: 1.80 – 2.17, p<0.001). (Table7)

Table 7 Predictors of retention at 6, 12, 24 and 36 Months after ART Initiation (N = 29,427)

Predictors	Retention			
	6 Months	12 Months	24 Months	36 Months
Sex				
Female*	1.46(1.26–1.69)	1.48(1.32–1.66)	1.56(1.41–1.71)	1.53(1.40–1.68)
Male	1	1	1	1
Living with partner				
No*	0.68(0.59–0.79)	0.61(0.54–0.69)	0.59(0.53–0.65)	0.61(0.55–0.66)
Yes	1	1	1	1
CD4 cell count at baseline*				
>200	1	1	1	1
200-349*	3.44(2.92–4.06)	2.53(2.24–2.85)	2.08(1.89–2.30)	1.98(1.80–2.17)
350-499*	2.34(1.58–3.45)	1.90(1.43–2.51)	1.90(1.49–2.43)	1.76(1.40–2.20)
500+**	1.56(0.93–2.59)	1.38(0.94–2.02)	1.05(0.78–1.42)	1.08(0.81–1.45)

*P value <0.001, ** Pvalue >0.001

4.4.2. Mortality

Multivariate analysis adjusting for gender (Male vs. female), age at ART initiation (15-24 years of age vs. other age group), CD4 count (Median CD4 count at baseline <200 cells/mm^3 vs. other groups) at ART initiation, and marital status (not living with partner vs. living with partner) showed that; after 6 months of ART initiation, female patients had lower risk of death compared to male patients (AOR 0.68; 95% CI: 0.59 to 0.79, p<0.001) patients not living with partner had higher risk of death (AOR 1.47; 95% CI: 1.27 to 1.69, p<0.001), patients with median CD4 of 200-349 at ART initiation had lower risk of death (AOR 0.29; 95% CI: 0.25 to 0.34, p<0.001).

Twelve months after, female patients had lower risk of death compared to male patients (AOR 0.70; 95% CI: 0.61 to 0.79, p<0.001) patients not living with partner had higher risk of death (AOR 1.51; 95% CI: 1.32 to 1.70, p<0.001), patients with median CD4 of 200-349 at ART initiation had lower risk of death (AOR 0.32; 95% CI: 0.28 to 0.37, p<0.001).

Twenty four months after, female patients had lower risk of death compared to male patients (AOR 0.68; 95% CI: 0.61 to 0.77, p<0.001) patients not living with partner had higher risk of death (AOR 1.60; 95% CI: 1.42 to 1.80, p<0.001), patients with median CD4 of 200-349 at ART initiation had lower risk of death (AOR 0.35; 95% CI: 0.31 to 0.40, p<0.001).

Thirty six months after, female patients had lower risk of death compared to male patients (AOR 0.69; 95% CI: 0.61 to 0.77, p<0.001) patients not living with partner had higher risk of death (AOR 1.57; 95% CI: 0.90 to 2.13, p<0.001), patients with median CD4 of 200-349 at ART initiation had lower risk of death (AOR 0.37; 95% CI: 0.33 to 0.42, p<0.001). (Table8)

Table 8 Predictors of Mortality at 6, 12, 24 and 36 Months after ART Initiation (N = 29,427)

Predictors	Mortality			
	6 Months	12 Months	24 Months	36 Months
Sex				
Female*	0.68(0.59–0.79)	0.70(0.61–0.79)	0.68(0.61–0.76)	0.69(0.61–0.77)
Male	1	1	1	1
Living with sexual partner				
No*	1.47(1.27–1.69)	1.51(1.32 –1.70)	1.60(1.42–1.80)	1.57(0.90–1.13)
Yes	1	1	1	1
CD4 cell count at baseline*				
<200*	1	1	1	1
200-349*	0.29(0.25–0.34)	0.32(0.28-0.37)	0.35(0.31–0.40)	0.37(0.33–0.42)
350-499*	0.43(0.29–0.62)	0.45(0.32–0.63)	0.43(0.35-0.94)	0.47(0.35–0.63)
500+**	0.64(0.38–1.06)	0.60(0.37–0.96)	0.67(0.44-1.01)	0.67(0.45–1.00)

*P value <0.001, ** Pvalue >0.001

4.5. Survival analysis of patient initiated on ART and associated factors

We plotted the Kaplan-Meier survival estimates which showed that retention into ART care were 96.4% [95 CI: 96.2% - 96.6%] at 6 months, 94.6% [95 CI: 94.3% - 94.8%] after 1 year, 91.7% [95 CI: 91.4% - 91.9%] at 2 years and 89.5% [95 CI: 89.2% - 89.9%] at 3 years. This corresponds to monthly attrition rates of 3.4 in the first 6 months of HAART, which reduces in the following years. (Fig6)

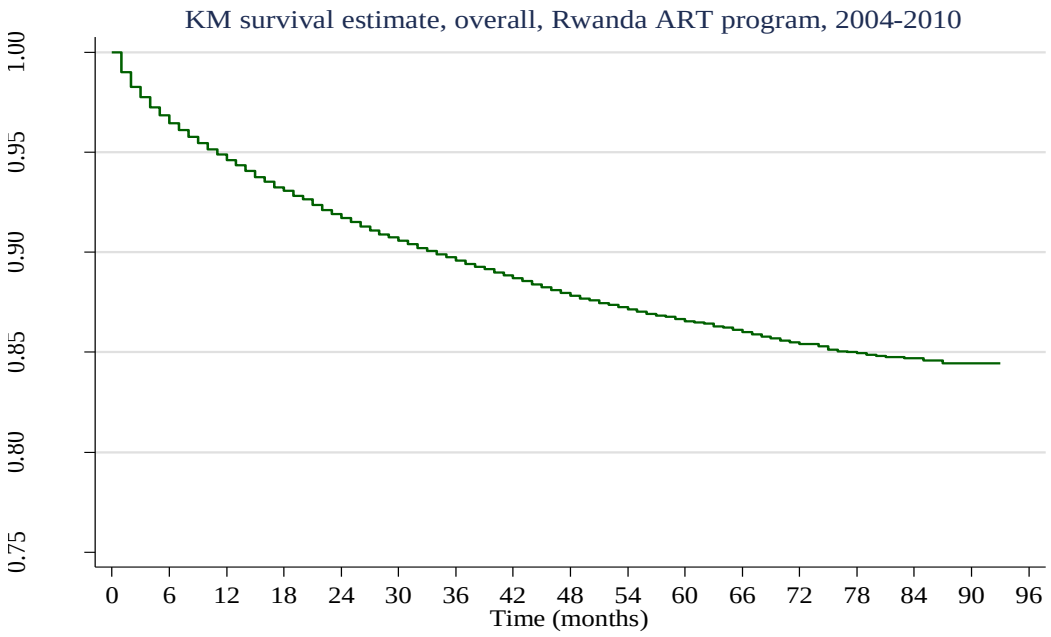


Figure 4 KM survival estimate, overall, Rwanda ART program, 2004-2010

Stratified by age, sex, CD4 cell count at baseline and marital status, the 55 years and plus group was associated with lower survival rate in ART care after 6, 12, 24 and 36 months of ART initiation compared to the younger age group ($p< 0.001$). The survival rate after 6, 12, 24 and 36 months of ART initiation was significantly higher in female patients compared to male patients. ($p<0.001$). It was also higher in patients living with partner compared to non living with partner. ($p= 0.000$). And it was lower among patients with baseline CD4 count ≤ 50 cells/mm3 compared to those with baseline CD4

count above 200cells/mm3. (p= 0.000). The low CD4 count at ART initiation is associated with lost to follow up or death among patients on ART.

Crude survival curves for alive in ART care by socio-demographic and biological characteristics are shown in Figures 7 to Figure 10.

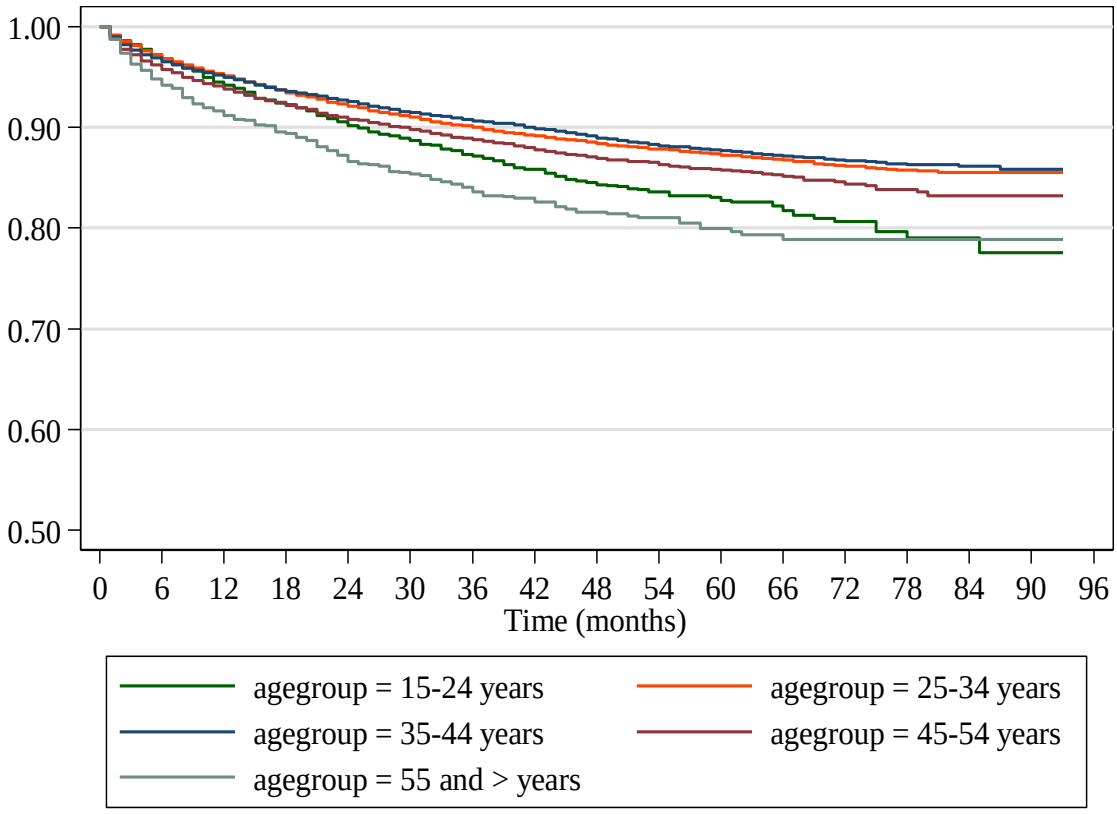


Figure 5 Survival estimates by age at ART initiation, Rwanda 2004-2010

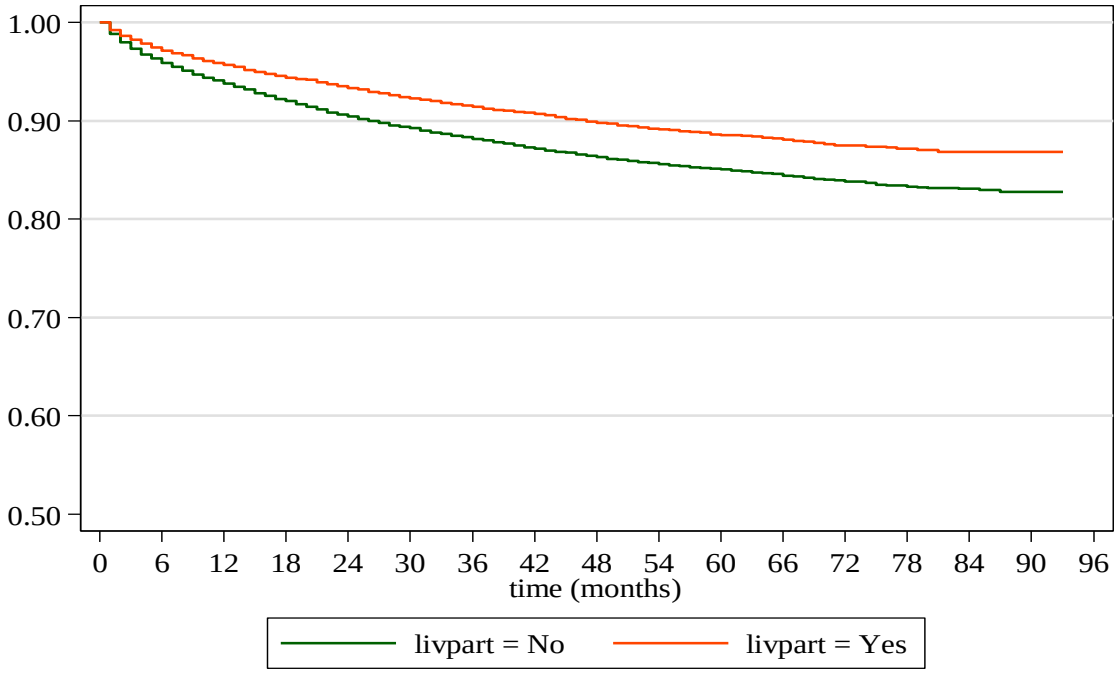


Figure 6 Survival estimates by marital status at ART initiation, Rwanda 2004-2010

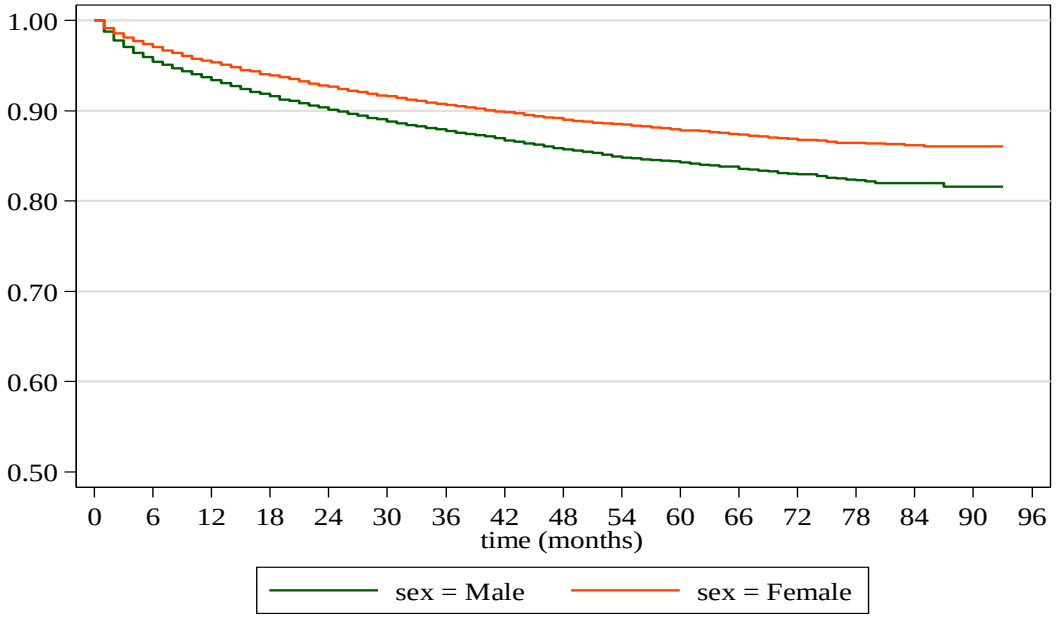


Figure 7 Survival estimates by sex, Rwanda 2004-2010

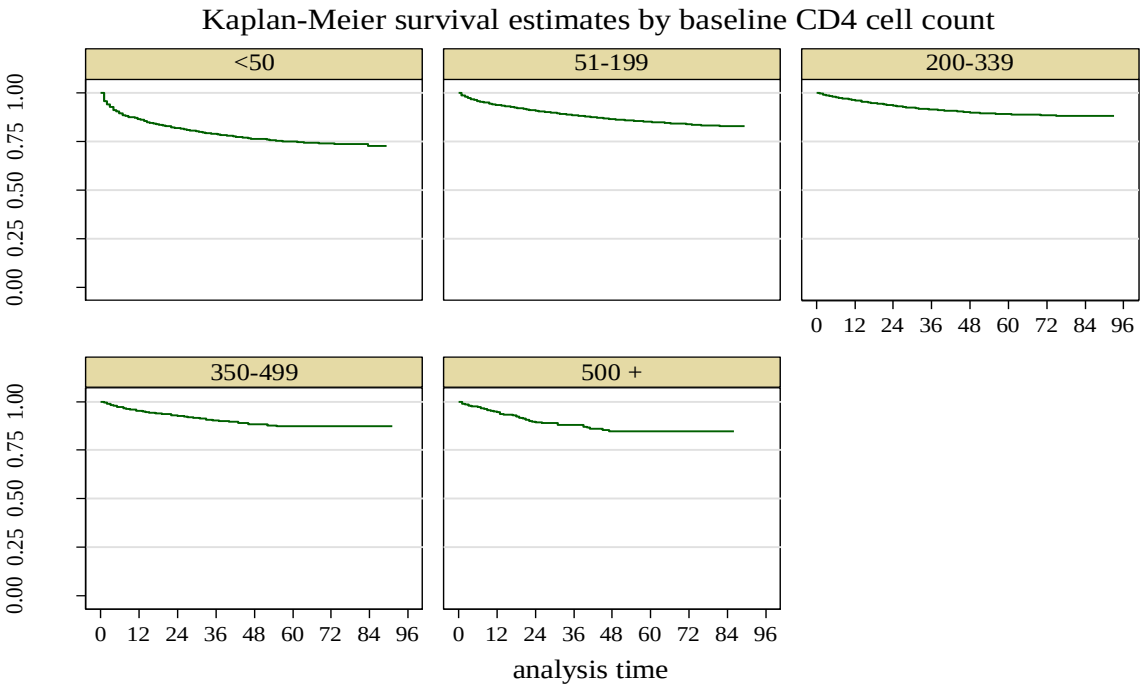


Figure 8 Survival estimates by CD4 count baseline, Rwanda 2004-2010

5. DISCUSSION

5.1. Clinical outcomes

Using routinely collected patient data, our study aimed at assessing HIV-infected adults retention and outcomes in Rwanda after 6, 12, 24 and 36 months of ARVs initiation. We found that almost 90 percent of patients initiating ART were alive and in care at 36 months in 121 assessed clinics. These clinics represent fully one-third of patients on ART in Rwanda, and this represents the largest series to data from the country.

On course of our study, we experienced the effect of the programme expansion which was at higher pick in the period of 2005 to 2009. Thus, we had documented several patients transferred to other health facilities (16.2 percent) and we did not further study them due to lack of follow up information. However, through literature review, we learnt that, Malawi researchers studied the outcome of patients transferred to other facilities and showed that, among all patients that were transferred out, 86% were alive and on ART, 5% dead and 4% lost to follow-up, and there were also transferred out again amounting 5%. Suggesting better outcome for patients who were transferred to other facilities compared to ones remaining at the initiation sites. The better outcomes for the patients transferred to other facilities were partly due the fact that, the patients are in most of the cases transferred after first 3-6 months where most of the deaths and lost to follow up occur, and after the patients become old and adhere to the program.(12)

The majority of death occurred in the first 6 and 12 months of ART initiation and decreased over time, from 55% in the first 6 months of ART to 16.1%, 18.5% and 10.2% after 12, 24 and 36 months respectively. This is likely due to the severity of HIV disease at ART start, but also probably due the IRS which in most of the cases occurs in the first 2 months of ART initiation and predominantly in patients who initiated at very advance disease stage. Other causes might be the intolerance or side effects to ARV drugs. A study done in Ethiopia also concluded with similar results.(10) We observed a reverse trend for lost to follow up where lost to follow up increased over time on ART: from 15.7% in the first 6 months to 23.2% between 6 and 12 months, 38.0% in the second year and to 23.1% in the third year of follow up. As our study covered the period of

program scale up, we noted a considerable proportion of transfers to other health facilities with a total of 16.2% of our total population were transferred after 36 months)

Out of 29,427 HIV-infected adults patients enrolled in our study, after 6, 12, 24 and 36 months, the overall HIV-infected adults patients who still alive in ART care were 95.9 percent, 94 percent, 91.6 percent and 89.9 percent respectively. There was 3.5 percent death after 6 months and after 12, 24 and 36 months of, the documented deaths were 4.6 percent, 5.8 percent and 6.4 percent respectively. The following factors were independently associated with retention and mortality: Gender, CD4 cell count baseline, marital status and age.

In a similar study conducted in Rwanda in 2005, the reported retention rate after 6 months was 91.9% and 85.9% after one year(4). However, the data show comparable results with a community based ART program treatment in East Province of Rwanda which reported retention after 2 years of 92.3%(5).

The improvement in patients' outcomes could be attributed to the improvement of access and quality of care provided in Rwanda. From 2004, The Government of Rwanda with Partners, mainly the Global Fund and US Government started to provide ARV drugs and services for free. Too much emphasis was put to train care providers in HIV care and to avail drugs and other medical consumables at District Hospitals and Health Centers. With all the above measures, we note the access to ART treatment that tremendously improved. The number of sites providing ART increased from 86 in 2005 to 336 in 2011 and number of patients initiated on ART passed from 19,308 in 2005 to 90,668 in December 2010. In 2007, the National HIV programme revised the treatment guidelines that instructed health care providers to start ART at the CD4 threshold of less than 350cells/mm^3, thus enrolling patients in disease early stage, which improved the response to ARV therapy and reduction of AIDS-related mortality. The other important change linked to that was to avail drugs combination based on NNRTIs and INNRTIs. In 2009, the National guidelines were further reviewed to include Tenofovir-based regimen as first line regimen.

The patients' outcomes in Rwanda are far better compared to the other sub-Saharan African countries. Similar studies conducted in Ethiopia reported that health facilities in Ethiopia were able to retain 80%, 74% and 68% of their patients after 6, 12 and 24 months on ART, respectively(13), similarly in South Africa, Malawi, West Africa and generally in Sub-Saharan Africa(11)(12)(14)(15)(16)(17) .

The majority of our patients were female and this reflects the national figures where women are predominantly on ART in Rwanda. Moreover women were significantly associated with early treatment initiation, better survival rate and lower mortality rates compared to HIV-infected males on ART. We observed that female were more likely to be retained in ART care after 3 years compared to male patients. The association remained obvious after we controlled for other hypothetical confounding factors such as age, CD4 baseline and marital status. The similar results were identified in a study conducted in Mozambique, but with much lower retention results compared to our findings(9)(18)

Patients living with partner had better outcome compared to non living with partner 91.92% vs. 88.42% ($p<0.001$). Our finding emphasizes the importance of a third person in HIV care and treatment which was previously not well documented in other studies, besides community based ART program(5). The National program emphasizes on having the third person commonly known as ''parrain'' who support the infected –patient in adherence and timely consultation of HIV services.

Similarly to other conducted studies, our findings confirmed that, the HIV-Infected patients with age above 55years was associated with lower retention compared to younger patients.(5) The reasons might be the late diagnosis and poor response to ARV drugs or underlying diseases or health problems that we were not able to control in our study.

The survival rate estimate is very high in Rwanda compared to other countries. This was partly due above cited criteria including early initiation to antiretroviral treatment in Rwanda HIV-infected adults.(13)(17)(20)(21)

5.2. Immunological outcomes

The study findings show an incredible improvement in ART program in Rwanda over the years of implementation. It is of great importance to note that, we have seen a tremendous increase in CD4 baseline at ARVs initiation from the median CD4 count to start ART of 126cells/mm^3 in 2004 to the median CD4 cell count of 277cells/mm^3 in 2010. The national program has recorded unprecedented achievement in early enrollment of patients to ART drugs. Actually, Rwanda ART program is among the first programs that have high median CD4 cell count at ARV initiation which justifies its higher retention and lower mortality.(10)(19). This achievement can be attributed to a successfully pre-ART program where all clients tested HIV infected are encouraged to enroll in Pre-ART program where the enrolled HIV infected people receive regular quarterly CD4 control and clinical follow up on top of cotrimoxazole prophylaxis. At the same time they receive psychosocial support and continue to be prepared for ARV treatment.

After one year on treatment, patients with higher median CD4 at ART initiation had better outcome compared to ones with lower CD4 baseline at ART initiation 96.1% for patients starting ARV with CD4 count between 200-350cells/mm^3 vs. 82.6% for patients starting ARV with CD4 count below 200cells/mm^3(AOR 0.29; 95% CI: 0.25 to 0.34, p<0.001). This finding was highlighted in the previous study done in Rwanda which reported that baseline CD4+ cell counts, 50cells/mm^3 were associated with lower likelihood of retention at 6 months (AOR 0.22: 95% CI: 0.06 to 0.89, p<0.01) and 12 months (AOR 0.25; 95% CI: 0.08 to 0.77, p<0.01)(4). Other studies in Sub-Saharan Africa showed comparables findings in regards to the association of CD4 cell count at Baseline with patients outcomes (10)(20)

The purpose of ART treatment is to improve the patient life status by increasing the immunological status and suppression of Virus. In our study we found that, the median CD4 increase after 6, 12, 24 and 36 months of ART initiation were 135cells/mm^3 [IQR: 99-190], 162cells/mm^3 [IQR: 122-222], 197cells/mm^3 [IQR: 159-262], and 221cells/mm^3 [IQR: 181-288] respectively. Female patients had higher median cell count increase at

6, 12, 24 and 36 months compared to male patients. This was due in part to the fact that, female enroll earlier n treatment compared to male patients and are likely to improve their immunological status more rapidly.(4)

5.3. Study Strengths and Limitations

The limitation of this study is that routinely collected data have a certain error factor, with potential transcription errors as data elements are entered from patient charts into electronic data base. There may also be errors in medical record completion, with potential for missing data. Another limitation is that it is not clear whether transfers out are actually transferred in at another site, or whether they are similar to those who are lost-to-follow-up.

As well, these 121 sites in 17 districts (out of 30 national districts), so are not nationally representative.

A key advantage of these data is that routinely collected data represents routine health care practice, and could be more reflective of the actual situation and that this is the largest EMR system in Rwanda, covering more than 35% of all the HIV-infected adults on ART in Rwanda.

6. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

Reporting treatment outcomes of patients enrolled in ART programs is important to demonstrate program effectiveness and to identify factors associated with poor outcomes for program improvement. Using routinely collected data, we found that 95.9%, 94.0%, 91.4% and 89.9% of patients initiating ART were alive and in care at 6, 12, 24 and 36 months respectively, in 121 surveyed clinics. These clinics represent fully one-third of patients on ART in Rwanda, and this represents the largest series to data from the country. We estimated high survival rate of patients enrolled on antiretroviral therapy in Rwanda.

The majority of death occurred in the first 6 and 12 months of ART initiation and decreased over time, from 55% of the total deaths that occurred in the first 6 months of ART to 16.1%, 18.5% and 10.2% after 12, 24 and 36 months respectively.

Furthermore, we found that, an improved Rwanda ART program which enrolls patients within the early stage of the disease (median CD4 baseline of 217cells/mm^3 [131–298]) which contributed in the end to better patient's retention rates. Older age, Low CD4 cell counts at ART initiation and not living with sexual partner were negatively associated with lower retention and increased risk of death.

6.2. Recommendations

The ART program in Rwanda has done well in terms of early initiation of patients on antiretroviral therapy and remarkably achieved greater results. However throught our study we noted the following that need immediate attention of the National HIV program:

HIV-infected males adults are less enroled in the program and have the increased risk of death with poor immunological improvement compared to females. This needs to be studied in deep to assess the reasons, mainly causes of late initiation on ARVs and having the increased risk of death. In the meantime, special programs including

mesaging and sensitization should be developed and focus on the male population, to improve their enrollemnt rate and baseline conditions.

Single, Divorced and separated HIV-infected patients tend to have lower retention rate and increased risk of death. The program should emphasize on its policy of having a third person (Body) for adherence and psychosocial support, specifacally for those groups. Using community health workers and other health systems in place, special messages and programs should be designed to foster services delivery to these group of people.

We recommend the program to strentgthen the referral system in order to track the patients transferred to other health facilities and make sure they are enrolled and continue treatment.

7. REFERENCES

1. Rwanda Demographic and Health Survey. 2011; (December).

2. The UNAIDS. GLOBAL REPORT. 2010.

3. Mwumvaneza M, Hinda R, Nyankesha E, Mugwaneza P, Sebaziga G, Koleros A. HIV and AIDS in Rwanda. 2010;2015(Table 1).

4. Lowrance DW, Ndamage F, Kayirangwa E, Ndagije F, Lo W, Hoover DR, et al. Adult clinical and immunologic outcomes of the national antiretroviral treatment program in Rwanda during 2004-2005. Journal of acquired immune deficiency syndromes (1999) [Internet]. 2009 Sep 1;52(1):49–55.

5. Rich ML, Miller AC, Niyigena P, Franke MF, Niyonzima JB, Socci A, et al. O PERATIONAL R ESEARCH : C LINICAL S CIENCE Excellent Clinical Outcomes and High Retention in Care Among Adults in a Community-Based HIV Treatment Program in Rural Rwanda. 2012;59(3):35–42.

6. Rwanda Annual Report on HIV and AIDS, 2010-2011 1. 2011;2010–1.

7. Ministère de la Sante. Guide de Prise en Charge des Personnes Infectées par le VIH au Rwanda. 2009;

8. Nakanjako D, Colebunders R, Coutinho AG, Kamya MR. Strategies to optimize HIV treatment outcomes in resource-limited settings. AIDS reviews [Internet]. 2009;11(4):179–89.

9. Auld AF, Mbofana F, Shiraishi RW, Sanchez M, Alfredo C, Nelson LJ, et al. Four-year treatment outcomes of adult patients enrolled in Mozambique's rapidly expanding antiretroviral therapy program. PloS one [Internet]. 2011 Jan [cited 2012 Jul 27];6(4):e18453.

10. Biadgilign S, Reda A a, Digaffe T. Predictors of mortality among HIV infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. AIDS research and therapy [Internet]. ???; 2012 Jan [cited 2012 Aug 11];9(1):15.

11. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS medicine [Internet]. 2007 Oct 16 [cited 2012 Jul 17];4(10):e298.

12. Yu JK-L, Tok T-S, Tsai J-J, Chang W-S, Dzimadzi RK, Yen P-H, et al. What happens to patients on antiretroviral therapy who transfer out to another facility? PloS one [Internet]. 2008 Jan [cited 2012 Aug 11];3(4):e2065.

13. Assefa Y, Kiflie A, Tesfaye D, Mariam DH, Kloos H, Edwin W, et al. Outcomes of antiretroviral treatment program in Ethiopia: retention of patients in care is a major challenge and varies across health facilities. BMC health services research [Internet]. BioMed Central Ltd; 2011 Jan [cited 2012 Jul 30];11(1):81.

14. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Tropical medicine & international health : TM & IH [Internet]. 2010 Jun [cited 2012 Jul 12];15 Suppl 1(june):1–15.

15. Ekouevi DK, Balestre E, Ba-Gomis F-O, Eholie SP, Maiga M, Amani-Bosse C, et al. Low retention of HIV-infected patients on antiretroviral therapy in 11 clinical centres in West Africa. Tropical medicine & international health : TM & IH [Internet]. 2010 Jun [cited 2012 Jul 17];15 Suppl 1(june):34–42.

16. Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van Rie A. Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. Journal of the International AIDS Society [Internet]. 2009 Jan [cited 2012 Aug 11];12:38.

17. Koole O, Kalenga L, Kiumbu M, Menten J, Ryder RW, Mukumbi H, et al. Retention in a NGO Supported Antiretroviral Program in the Democratic Republic of Congo. PloS one [Internet]. 2012 Jan [cited 2012 Jul 30];7(7):e40971.

18. Tweya H, Gareta D, Chagwera F, Ben-Smith A, Mwenyemasi J, Chiputula F, et al. Early active follow-up of patients on antiretroviral therapy (ART) who are lost to follow-up: the “Back-to-Care” project in Lilongwe, Malawi. Tropical medicine & international health : TM & IH [Internet]. 2010 Jun [cited 2012 Jul 13];15 Suppl 1(june):82–9.

19. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Tropical medicine & international health : TM & IH [Internet]. 2010 Jun [cited 2012 Jul 12];15 Suppl 1(june):1–15.

20. Deeks SG, Eron JJ, Brooks JT, Rourke SB, Ph D, Gill MJ, et al. NIH Public Access. 2010;360(18):1815–26.

21. Chan AK, Mateyu G, Jahn A, Schouten E, Arora P, Mlotha W, et al. Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. Tropical medicine & international health : TM & IH [Internet]. 2010 Jun [cited 2012 Jul 30];15 Suppl 1(june):90–7.