LINKAGE AND RETENTION IN HIV CARE AND TREATMENT IN THE RWANDA NATIONAL HIV PROGRAM

Optimizing the Effectiveness for Individual- and Community-Level Outcomes in the Era of Pre-and on ART in Rwanda

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GENERAL ABSTRACT

Sub Saharan Africa (SSA) region carries the highest burden on HIV globally, with more than 75% of people living with HIV and 65% of global new HIV infections according to UNAIDS. Despite tremendous efforts made over the last decade to control HIV, especially with rapid scale up of Anti-Retroviral Therapy (ART), AIDS remain the main cause of deaths among youth 15-24 years old and only 50% of people living with HIV (PLHIV) in SSA access ART. The UNAIDS has recently recommended that 90% of people living with HIV get tested, 90% of them receive ART and 90% of those on ART suppress viral load with the ambition to end IDS by 2030.This goal could be only achieved with strong testing services, linkage to care and retention on sustainable and well tolerated regimen.

We systematically studied these questions using data from the entire Rwanda national HIV program and presented different studies and examples of successful policy implementation. Our first study assessed the HIV incidence from a longitudinal cohort study, the first ever implemented in Rwanda. Previously the country relied heavily on mathematical modelling to estimate incidence with several limitations. Findings suggested an estimated national incidence of 0.27 infections per 100 person-years, 50% higher than the UNAIDS Spectrum/EPP model estimated incidence; however, our study suggested that incidence was characterized by multiple breakouts. To understand the linkage and retention in care, we conducted two studies on HIV continuum of care and predictors of lost to follow up and mortality in Rwanda. We found a high proportion of patients entering care in Rwanda's HIV program retained with a low mortality and high proportion of PLHIV achieving viral suppression rates. Nonetheless, older age, low CD4 count at initiation and male sex were associated with disengagement from care and mortality on ART. The two studies also

provided new evidence that cascade of care is a non-linear pathway wherein patients have multiple opportunities to leave and re-engage in care. In line with the new era of treating all HIV+ regardless of CD4 count, we assess a phased approach implementation of the new policy in Rwanda and what is required to move from evidence to policy change and implementation considerations. We also assessed political, and financial implications especially required to implement the new HIV guidelines. The second part of this thesis evaluated treatment outcome for patients who failed first and second line ART available regimens, suggesting that overall, 92.5% of patients on second line ART in Rwanda were retained in care and 83% achieved viral suppression. Defaulting from care was significantly associated with more recent initiation of ART- PI based regimen, low CD4 cell count and HIV viral load at initiation of ART while Viral failure was associated with younger age, advanced disease and low CD4 count at initiation. Our study on outcomes from Rwanda's first national cohort of third-line ART indicated that, over 90% of all 55 patients ever started on third line ART achieved VL suppression. Only one patient died and all were retained in care; however, raised concerns of 10% of multi-drug resistant patients who have no other treatment options after failing third line ART. Finally, we assessed the magnitude of HIV among female sex workers (FSW), a group with alarming high prevalence (46%) and considered to be the bridge of HIV transmission in Rwanda. The study analysed a projected incidence of HIV among female sex workers and their male partners in Rwanda using a Markov model examining intervention effects. The study found significant success of current program interventions (ART, condom use) to reduce HIV incidence among FSW and also estimated that introduction of Prep expected in Rwanda in 2019, could prevent more new infections among FSW by 0.24%.

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CHAPTER 1. INTRODUCTION TO THE THESIS

1.1 Background

Morbidity and mortality among people living with HIV/AIDS (PLHIV) in Rwanda has decreased in recent years likely due to high coverage of antiretroviral therapy (ART), early treatment initiation and improvements in diagnosis and treatment of opportunistic infections (MoH/RBC-Rwanda 2016). The country's efforts to control HIV is further demonstrated by reductions in HIV incidence by approximately half in the last decade, as well as a decrease in annual deaths related to AIDS by 68%. The scale-up of ART in Rwanda has resulted in an increase of an additional approximate 25 years of life expectancy among PLHIV (Nsanzimana, Remera, Kanters, Chan, et al. 2015). Despite these achievements, several important challenges to ensuring care across the HIV care continuum remain. Many individuals are unaware of their HIV sero-status and as a result, miss the opportunity for linkage to HIV testing services and early treatment in case of an HIV positive test. Findings from a systematic review of treatment cohorts in Sub-Saharan Africa show that 41–54% of people are lost between testing and the assessment of eligibility for treatment, and 32% of those considered eligible for ART are lost between the assessment of eligibility and initiating ART (Rosen & Fox 2011). Once PLHIV start ART, about one quarter temporarily interrupt treatment and another quarter are lost within three years (Kranzer & Ford 2011). Among those lost, up to half (46%) may have died. A non-published retrospective study conducted in Rwanda on 8,580 adult clients who tested HIV positive in 80 heath facilities found that only 25% were linked to care within three months of their diagnosis and 50% of all newly tested HIV positive patients were lost to

follow-up (LTFU). The strategic efforts to improve linkage and retention are critical for Rwanda to achieve full control of the HIV epidemic.

1.2 The rationale for the studies reported in this thesis

We conducted studies to assess HIV incidence, linkage and retention in care across different ART regimens used in Rwanda. These projects addressed key issues related to HIV continuum of care and long-term retention in an entire national program using Rwanda as a case study to investigate engagement and retention in care. We have reported on patients' outcomes on first, second and third lines ART as well as modelled different scenarios to understand the role of female sex workers as a key mechanistic driver of the HIV epidemic in the country.

Apart from the research objectives described above, these projects provide important data for public health officials in Rwanda with respect to currently unknown individual and national programmatic features associated with poor linkage and/or retention to HIV care services in Rwanda. We believe that our findings will provide the Rwandan Ministry of Health with useful estimates for evaluating HIV services in Rwanda. Furthermore, as ART is provided on a rapidly increasing scale in low-income countries, it is becoming increasingly important to systematically characterize the individual and national programmatic features associated with retention in HIV care in low-income settings. This PhD thesis project will not only serve to improve aspects of the Rwanda HIV program requiring the most attention, but our results will, likewise, inform HIV programs in similar settings. This PhD thesis tackles critical stages of the national HIV program conducted by the student who is also the current Director of the Rwanda national HIV program and is charged with overseeing the implementation of the program. The government of Rwanda

highly recommends a combination of program implementation and academic rigor for greater precision in decision-making. This thesis is a great example of how the new initiative overcame barriers between researchers and program managers. This thesis combines data driven projects but also health policy development and implementation analysis that is unique for Rwanda's HIV program and could be replicated elsewhere.

CHAPTER 2. GLOBAL EPIDEMIOLOGY OF HIV

2.1 Status of the HIV epidemic

More than three decades ago, the first case of HIV was described in 1981 (Centers for Disease Control-USA 1981). Since then, more than 70 million people have been infected and about half have died due to HIV (UNAIDS 2017b). UNAIDS reported that in 2016, 36.7 [30.8-42.9] million people were HIV infected and 1.8 [1.6-2.1] million were newly infected, with approximately 1.0 million [830,000-1.2 million] AIDS related deaths worldwide. The prevalence of HIV globally is highest in Sub-Saharan Africa (SSA) where about 5% of the population are living with HIV (GBD 2015 HIV Collaborators 2016). Southern African countries are particularly affected, for example, Swaziland, Namibia, Botswana, Zambia, Zimbabwe and South Africa each have an HIV prevalence of more than 15% (UNAIDS 2017b). Other regions of the world have a relatively low prevalence compared to SSA; North Africa and the Middle East remain less affected with only 0.2% of people living with HIV (GBD 2015 HIV Collaborators 2016).

Although HIV is distributed across all continents new HIV infections continue to accumulate. The Sub-Saharan Africa region is most affected; encompassing nearly 65% of new global HIV infections in 2016. The global trend of new HIV infections has been flat over the years, but from 2010 to 2016, it has observed an 11% decline primarily in countries with high HIV burden (UNAIDS 2017b). There are significant differences in the number of new infections by gender and age with young women 15-24 years old having more infections than men of a similar age cohort.

Deaths attributed to HIV have declined by almost 50% over the last decade; a success attributed to the large scale up of anti-retroviral treatment (UNAIDS 2017b). Nonetheless,

AIDS remain the leading cause of death in Sub-Saharan Africa and among young women 15-24 in particular. The reduction of AIDS related deaths varied across regions: Eastern and Southern Africa marked a record of about 62% less deaths, while it was 52% in the Caribbean, 45% in Western, Central Europe and North America, 39% in Asia and Pacific island regions and 30% in Central Africa (UNAIDS 2017b). Notwithstanding the global decrease of AIDS related deaths, increases in mortality of approximately 48% were observed in the Middle East and North Africa and 38% in Eastern Europe and Central Asia (UNAIDS 2017b). The United Nations General Assembly in 2016 committed to achieve 500,000 fewer new HIV infections by 2020. However, achieving this goal by 2020 appears improbable given the slow trend of decline.

2.2 Global response to AIDS epidemic

HIV was once considered a death sentence in the 1990s before the start of anti-retroviral treatment. The first introduction of Highly Active Anti-Retroviral Therapy (HAART) in 1996, contributed importantly to reduce AIDS related deaths (GBD 2015 HIV Collaborators 2016). Following the creation of the UNAIDS in 1996, the United Nations started to consider HIV as a global health threat; later on, in 2003, the US President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFTAM) were created to mobilize necessary resources to tackle the AIDS epidemic (Harold Varmus 2013; TheGlobalFund 2013).

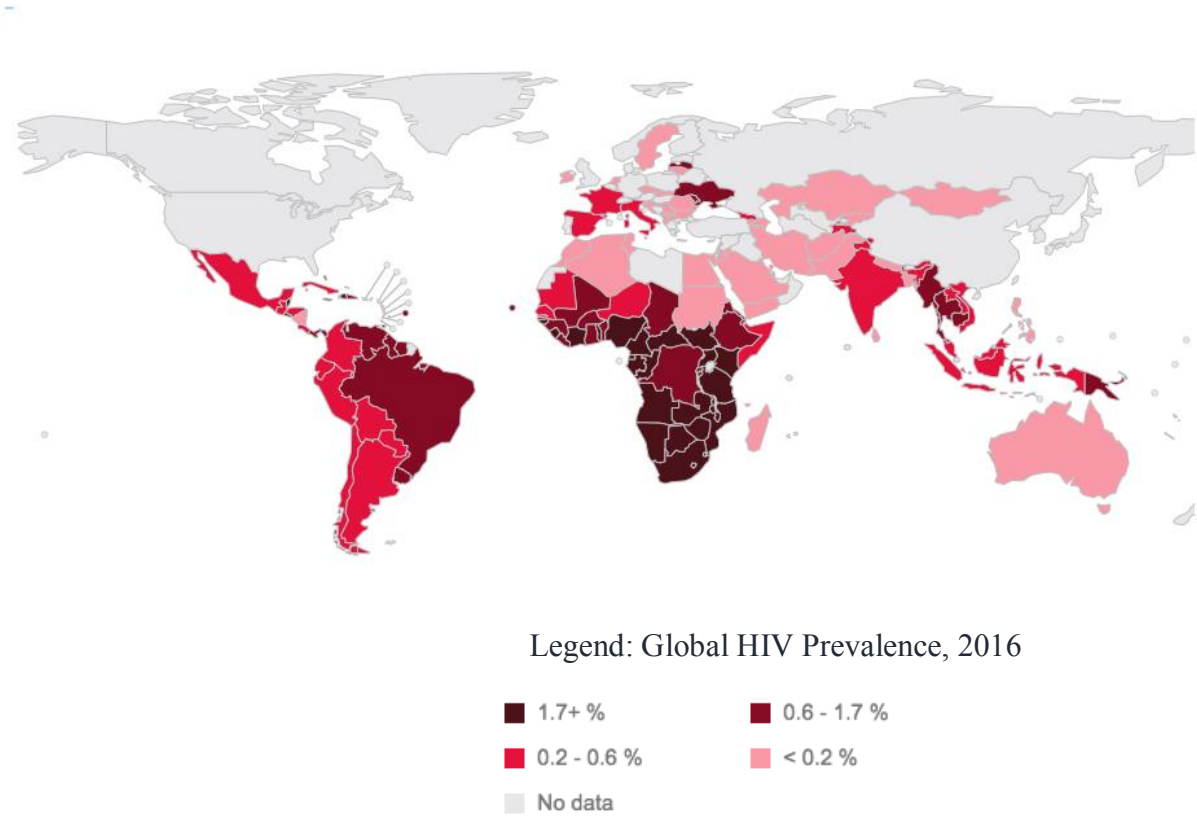
All these efforts led to a tremendous decline of HIV-related mortality in countries most affected especially in Sub-Saharan Africa. UNAIDS now promotes a concept of ending the AIDS epidemic by 2030 through a combination of preventative, education, treatment and research initiatives. Alongside these goals, UNAIDS launched, in 2015, the ambitious "90-

90-90" target to help end this disease (UNAIDS 2014), by controlling the AIDS epidemic in order to achieve overall positive social and health outcomes. The new strategy followed the previous strategy "getting to zero": Zero new HIV infections, zero AIDS related deaths and zero discrimination".

Through these ambitious targets, the new strategic overarching goal is to end AIDS by 2030, which articulates three key treatment targets to be achieved by 2030. These include:

- 90% of all people living with HIV knowing their status
- 90% of those diagnosed HIV+ have access to lifelong Anti-retroviral treatment
- and 90% of those on ART achieve viral load suppression below 1000 copies/mL

Figure 2-1: HIV Global epidemiology, UNAIDS, 2016



First target: 90% of all people living with HIV will know their HIV status (90% diagnosed) by 2020

The UNAIDS advisory board set this ambitious target based on progress made in some countries that could serve as an experience and best practice to be shared with those lagging behind. It was estimated that only 45% of people living in SSA were tested and knew their results, yet the plan aimed to achieve 90% within five years. The new target required the doubling of efforts and to change, considerably, the existing testing services across all populations and sub-populations. New necessary approaches include: self-testing, provider initiated counselling and testing, home based testing and aggressive community outreach campaigns. A significant challenge to this plan was to ensure that individuals know where to access the testing services, access them, be tested, receive results and acquire appropriate

care and treatment services in a timely manner. This requires improving risk perception, information seeking for services on the population side, enhanced accessibility to services and adherence tools and interventions, friendly policy environments and infrastructure strong monitoring platforms on the supplier side (Hargreaves et al. 2016).

Second target: 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy (90% on HIV treatment)

The global effort to scale up ART has been one of the most successful treatment interventions in medical history. From 2002-2012, two major programs changed the face of the disease, the Global Fund to fight AIDS, Tuberculosis and Malaria together with the United States President's Emergency Plan for AIDS Relief increased (mainly in Sub-Saharan Africa) access to lifesaving ART more than 100 fold (UNAIDS 2012b). Until 2016, CD4 count has been used as an indicator for ART initiation to stop the disease progression. However, the HIV Prevention Network trials (HPTN-052) (Cohen et al. 2011) and the Strategic Timing of Antiretroviral Treatment (The INSIGHT START Study Group 2015) clinical trials demonstrated that by providing ART as early as possible will prevent morbidity and mortality related to HIV and AIDS while also significantly reducing the transmission of HIV. Findings from this landmark trial confirmed the appropriateness of "treatment as prevention" or "Treat All" strategy, adopted in 2016 by the World Health Organization consolidated guidelines on the use of anti-retroviral drugs for treating and preventing HIV infection (WHO 2016).

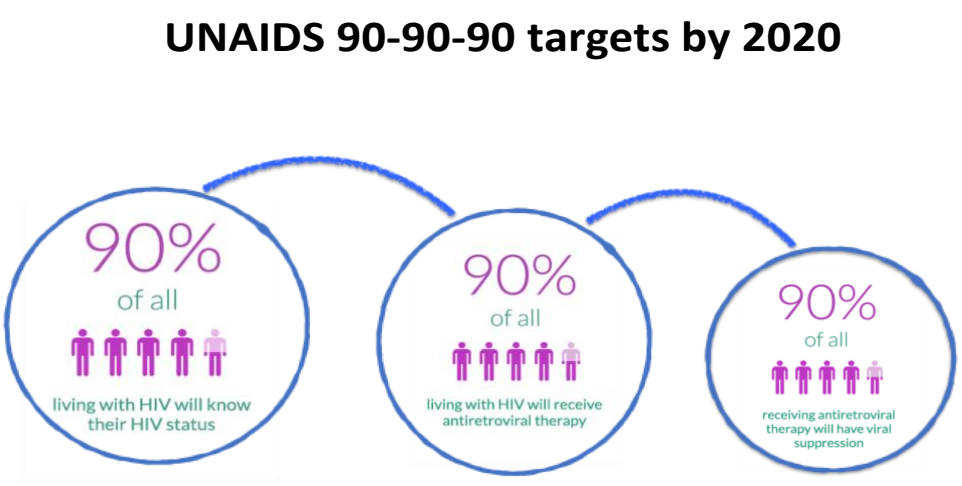
UNAIDS has used this evidence as a strong basis to set up the second 90 target – viewed as most likely to be achieved by 2020. For successful achievement of this target, countries were urged to increase ART coverage from 37% to 90% by 2020 by optimizing access to treatment services and retention in care - ensure uninterrupted supply chain for laboratory

and ARVs commodities - and creating a patient friendly environment in order to retain individuals in the programs for as long as possible (UNAIDS 2014).

Third target: 90% of all people receiving antiretroviral therapy will have viral suppression (90% suppressed)

When the 90-90-90 targets were launched, only 29% of people living with HIV had attained a level of HIV viral load suppression below 1000 copies/mL globally and the predicted VL testing scale up would only meet 57% of the needs by 2019 (UNAIDS 2015). Similar to the first 90, the third would require more investment in VL infrastructure and technology, strong monitoring to regularly check treatment success for re-engagement in care of those lost to follow up. Some countries demonstrated the feasibility of this target; for example, Rwanda achieved 83% of viral load suppression after more than 1 year on ART (Elul et al. 2013). In Latin America and the Caribbean, the median viral load suppression was 60% in 2013 (WHO 2014) yet, in other countries only one out of four HIV infected individuals on ART have a suppressed VL (UNAIDS 2016c).

Figure 2-2: UNAIDS 90-90-90 targets by 2020 to help ending AIDS by 2030



Adapted from UNAIDS 90–90–90 targets: An ambitious treatment target to help end the AIDS epidemic by 2030

6

2.3 Main challenges in HIV control

Global efforts to control HIV gained hope with the arrival of ART. However, new infections continue to rise in some parts of the world (North Africa and the Middle East). These regions continue to be the epicentre of the HIV epidemic and populations including, female sex workers, men having sex with men, and injecting drug users are viewed as the primary conduits of the epidemic in these regions and contribute more than 30% of HIV epidemic new infections in regions where condom use among youth is even sub-optimal. In addition, poor access to HIV services and inadequate health infrastructure and systems continue to be a major cause of stock depletion of essential medicines and ARVs in many parts of SSA (UNAIDS 2011).

Other regions have additional, localized challenges but across all, the issue of *sustainable financing* is a shared challenge. While in Asia, the Pacific Islands, and Eastern

Europe, HIV testing among people who inject drugs is a major challenge, violations of human rights and gender-based violence complicate delivery of preventive and treatment services in the Caribbean region and Latin America. In the United States, African-American men who have sex with men acquire HIV at a rate several times higher than those among other men who have sex with men. Western and Central Africa are particularly affected with other diseases (such as Ebola) in regions already heavily hit by recurrent humanitarian emergencies (seasonal shocks— drought, food insecurity, floods and disease outbreaks—and conflicts), which all influence the epidemic and threaten the response to HIV (Parpia et al. 2016).

CHAPTER 3: THE GENOCIDE AGAINST THE TUTSIS IN RWANDA AND ITS IMPACT ON RWANDA HEALTH SYSTEM.

3.1 Country background

In order to understand the epidemiology of HIV in Rwanda, it is important to understand the historical context of political and medical issues in the country. Rwanda is a land locked country located in the East African Region, bordered by Burundi in the south, Uganda in the north, Tanzania in the east and Democratic Republic Congo (DRC) in the west (Fig3). It is the most densely-populated country in the world with about 400 people per km^2. In the recent population and household census, the total population was 11,809, 295 in 2017 with a 2,39% projected annual increase. The life expectancy for both sexes was 66.6 years in 2017, which almost doubled in the last 20 years (Binagwaho et al. 2014). More than 80% of the population live in rural areas. The administration is divided into four provinces and the capital, Kigali City, hosts about 1,500,0000 people. The official languages recognized by the constitution are French, English and Kinyarwanda. Kiswahili is largely spoken in Rwanda, and the parliament is debating its recognition as a fourth language. 68% of the population above 15 years of age are literate; 72% among males and 65% among females (NISR-Rwanda 2015).

Figure 3: Geographical location of Rwanda in East-Central Africa.

3.2 The genocide against the Tutsi in 1994.

The roots of the genocide against the Tutsis in Rwanda in 1994 can be traced back a century ago. Following the 1884 Berlin Conference, Rwanda was assigned a German colony, which ended with the country's defeat during World War I. Subsequently, Belgium assumed reign over Rwanda-Urundi until 1962 when Rwanda achieved independence from Belgium with unprecedented ethnic tensions (Prunier 1998).

The two successive governments were dominated by Hutus extremists who fuelled systematic discrimination and violence against Tutsis minorities over 30 years. In October 1990, the Rwanda Patriotic Front (RPF) Tutsis dominated rebel army attacked Rwanda demanding return of refugees who had fled the country in post-colonial period. Periodic violence continued against Tutsis held hostage within Rwanda by the regime. On April 6th, 1994, unknown assailants shot the president of Rwanda Juvénal Habyarimana's plane as it prepared to land in Kigali from Tanzania for signature ceremony of peace negotiations with RPF. Immediately, an interim government was put in place and urged Hutus to exterminate

the Tutsis who were accused for the death of Habyarimana. Experts suggest that the killings may have been planned long before, with purchasing of machetes and ammunitions as well as the preparation of lists of Tutsis well in order across the country. This was testified by the speed of the targeted assassinations against the Tutsis and moderate Hutu political opponents.

The genocide against the Tutsis has been known as one of the worst humanitarian tragedies of the 20th Century. Over 100 days, one million people were killed~ an estimated 10,000 deaths every day. The genocide was put to an end when RPF army led by General Paul Kagame defeated the genocidal regime and took over the control of Rwanda in July 1994. In the aftermath of the genocide, Rwanda's infrastructure, human resources, and social cohesion were devastated by the genocide. Basic infrastructure was also destroyed. The majority of professional workers were either massacred, had participated in the killings themselves or fled to neighbouring countries. In this context, Rwanda became one of the poorest countries in the world (Binagwaho et al. 2014).

3.3 The genocide and health system in Rwanda

Health and education were among the most devastated systems in Rwanda during the genocide against the Tutsis. The end of the genocide was followed by a massive exodus of the population; with more than two million people having relocated into neighbouring countries – predominantly to Zaire (today known as DRC). This event was known as the great lakes humanitarian crisis, which resulted in a cholera epidemic and other communicable diseases in July 1994. The death toll due to cholera was 7000 per week and had contaminated all of Eastern Zaire (UNHCR 1997).

In Rwanda, less than 5% of the population had access to clean water and nearly 80 % of physicians had been killed or had fled the country. Health facilities were destroyed and supply chains for drugs and consumables were in ruins. Furthermore, infectious disease epidemics were also emerging. Meanwhile, funds to implement health initiatives were depleted. In an annual report in 1996, USAID estimated that, "70% of humanitarian assistance to Rwanda was channelled to refugees in DRC while the plight of survivors in Rwanda, especially women had been seriously neglected" (USAID 1996).

The newly formed government of Rwanda faced a serious challenge of rebuilding the country from scratch following a collapse of the economy. The Ministry of Health (MoH) decided in 1995 to reform the health sector resulting into excellent improvements regarding infant and child survival, maternal health, HIV, tuberculosis, and malaria control. Today, Rwanda is one of few African countries that achieved almost all the health-related Millennium Development Goals (MDGs) (Abbott, Sapsford & Binagwaho 2017) .

The new health system in Rwanda was built on an administrative structure that prioritized a strong decentralized system. The major coordinating bodies are the ministry of Health responsible for health strategies, policies and oversight of all health matters in the country and the "Rwanda Biomedical Center" who leads the implementation of all health policies and programs such as HIV/AIDS, malaria, tuberculosis, immunization and non-communicable diseases. The additional coordinating bodies; the national reference laboratory and its networks, the national blood transfusion centre, and the maternal, child and community health programs.

Approximately 80% of the health sector in Rwanda is public (55% is Government of Rwanda (GoR) owned and 22% are faith-based with GoR funding) and there are very few private clinics. The lowest level is a health post at the level of a cell, followed by a health

center covering a sector to a district hospital for each administrative district, with each of the five provinces served by a provincial hospital. The tertiary level is composed of three referral specialized hospitals and two University teaching hospitals. The country still lacks enough skilled personnel with only 525 physicians, 8273 nurses, and 240 midwives for more than 10 million people (MoH-Rwanda 2011).

To address the shortage of qualified healthcare workers, the ministry of health initiated and trained a team of 45,000 "Community Health Workers" three per village, who were elected by their peers in the communities. These workers play a major role in promoting maternal and child health, vaccination, and linkage to health facilities. As their experience and trust grew, they were trained to diagnose and treat empirical malaria and diarrhoea in the communities (Shapira et al. 2017).

Meanwhile, approximately 90% of the population is covered by community based health insurance program "mutuelle de santé", which subsidizes costs to medical services and other commodities. Initiated in 1999 to provide affordable basic services, the "mutuelle program" has successfully demonstrated that eliminating financial barriers to accessing healthcare and other social services improved health outcomes. The second major health system innovation was the implementation of Performance Based Financing (PBF) in 2001. The Government of Rwanda collaborated with two NGOs and the School of Public Health at the National University of Rwanda to experiment with the implementation of PBF. The PBF program provided payments to health workers to incentivize high-quality care and, in 2006, the program was scaled-up across the country with positive results (Logie, Rowson & Ndagije 2008).

The health care sector of Rwanda is facing a number of challenges. One of the most critical is the severe shortage of qualified medical staff. In 2010, a doctor-population ratio was 1 /16,001; nurse-population ratio was 1 / 1,291 with a target to reach 1 / 11,993 and 1 / 1,000 respectively by 2018 (MoH-Rwanda 2014).

Other issues included: insufficient medical equipment and a general dependency on foreign donor support, making it difficult for the country to establish a sustainable health care system. The health sector is currently heavily reliant on donor support (about 60% in 2016) and the government has been working on a medium- and long-term sustainable financing mechanisms.

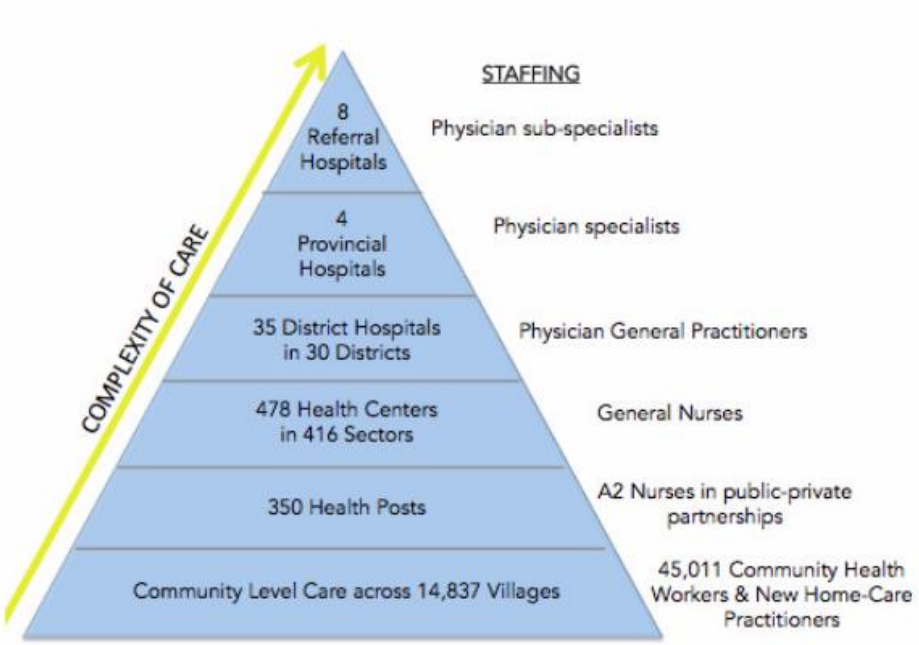


Figure 4: The pyramid of Rwanda health system

3.4 Overview of HIV epidemic in Rwanda and the national response.

The HIV program in Rwanda is coordinated under the Ministry of Health through its large implementing agency known as Rwanda Biomedical Center. The national program coordinates all activities related to HIV prevention and management under the National HIV Strategic Plan (NSP) which serves as a reference document to all sectors, donors and implementing partners. HIV interventions are highly decentralized and integrated in the health system in over 98% of health facilities across the country. Although the program has been cited as a good example of success, its past has been marked with several planning and implementation challenges that served as lessons learnt.

The first case of HIV in Rwanda was reported in 1983 at the Kigali Teaching Hospital (Van de Perre et al. 1984). By 1983, Rwanda was one of first countries in SSA most severely affected by the virus, with an HIV prevalence of 17.8% in urban and 1.3% in rural areas. The situation was exacerbated by the 1994 genocide against the Tutsis through widespread systematic sexual violence against women and girls. About 250,000 women had been systematically raped during the genocide and intentionally infected with HIV by their killers in the effort to torture and cause maximum pain (Donovan 2002). Nearly 5000 children were born to women who were raped and some were born HIV infected (African-Rights 2004). During a substantial historical population wave that followed the defeat of the genocide regime; infectious diseases including HIV were rampant and uncontained. An estimated 4 million people moved in and out of Rwanda between 1994-1996 at the height of the HIV epidemic.

In 1998, HIV prevalence in Rwanda was 27% among urban residents, 13% among semi-urban residents, and 7% among rural residents, during the same period when AIDS

related mortality was above 60%. In 1999, the Rwanda Ministry of Health began to scale up HIV testing services and Prevention of HIV transmission from Mother to Child (PMTCT). One year later, the universal ART treatment program begun in a few health facilities and under strict selection criteria for ART eligibility. The creation of GF and PEPFAR in 2003 increased considerably access to testing and ART. Today, there is an estimated 220,108 people living with HIV in Rwanda, including approximately 10,000 children below the age of 15 (Nsanzimana, Prabhu, McDermott, Karita, et al. 2015).

Most recent findings from the Rwanda Demographic and Health Survey, 2015 indicate that, HIV prevalence has remained stable at 3% in the last ten years (NISR-Rwanda 2014). Young women aged 18-19 years are ten times more likely to acquire HIV than young men of the same age. Results of the DHS showed that 3% of women and 2.2% of men are HIV positive. The prevalence differs by geographical area and age group. In urban areas, it is 6.2% while it is 2.2% in rural. The lowest HIV prevalence was found in the Northern Province (2.3%) and the highest in Kigali City (6.3%). The analysis of HIV prevalence data in 2010 and 2015 stratified by sex and age groups indicate that the HIV epidemic in Rwanda is evolving, as HIV prevalence shift over time towards older adult cohorts (Nsanzimana, Kanters, Remera, Forrest, et al. 2015).

The country is also experiencing a mixed HIV epidemic, with aspects of a generalized epidemic among the population at large and a more concentrated epidemic among key population groups (female sex workers and their clients, men who have sex with men, truck drivers, prisoners and HIV sero-discordant couples). HIV prevalence among female sex workers is particularly high at 45% nationally while it is 4% among men who have sex with men and 3% or less in all other categories. Other groups who are vulnerable to HIV

infections are people living with disabilities, refugees, orphans and other vulnerable children (MoH/RBC-Rwanda 2012).

The primary mechanism of HIV transmission in Rwanda is through unprotected sexual intercourse. Modes of Transmission (MOT) suggested in 2013 that heterosexual transmission account for 64% of new HIV infections, clients of sex workers for 19%, and sex out of marriage is estimated to account for approximately 10% of new infections (MoH/RBC-Rwanda 2012).

Female sex workers (FSWs) comprise an important sub-population in the epidemiology of HIV infection in Rwanda, as evidenced by a HIV prevalence amongst FSWs often being 10 to 20-fold higher than in the general population (Mutagoma et al. 2017). The Behavioural Surveillance Survey (BSS) conducted among FSWs in 2015 indicated that the total HIV prevalence among FSWs was 45%, with the highest rates in the City of Kigali (57%) and lowest in the Eastern province (34%). In 2012, the Rwanda Biomedical Center (RBC) conducted a study to estimate the size of the population of FSWs and found an estimated 12,278 FSWs, mostly concentrated in the capital city (Kigali) and two cities around the borders of the Democratic Republic of Congo (Rusizi and Rubavu) (Mutagoma et al. 2015). A study conducted in 2010 found that HIV incidence among a population of 397 FSWs in Kigali after 12 months was estimated at 3.5 per 100 person-years (Braunstein et al. 2009).

Over the last decade, the country updated its comprehensive HIV treatment guidelines raising the ART initiation CD4 cell count threshold from 200 cell/mm^3 in 2007, to <350 cells/mm^3 in 2009, and to <500 cells/mm^3 in 2013. The latest guidelines from 2016 recommend immediate start of ART (independent from CD4 cell count) ideally the same

day for all individuals with newly identified HIV+ (MoH/RBC-Rwanda 2013). The same guidelines suggest first, second and third line ART combinations to be built on:

- First line: Two nucleoside reverse transcriptase plus one non-nucleoside reverse transcriptase (2NRT+1NNRTI).
- Second line: Two nucleoside reverse transcriptase with one boosted protease inhibitor (2NRT+PI).
- Third Line: One integrase inhibitor plus a second generation of non-nucleoside reverse transcriptase plus boosted non-peptide inhibitor of protease (1NRTI+1NNRTI+PR).

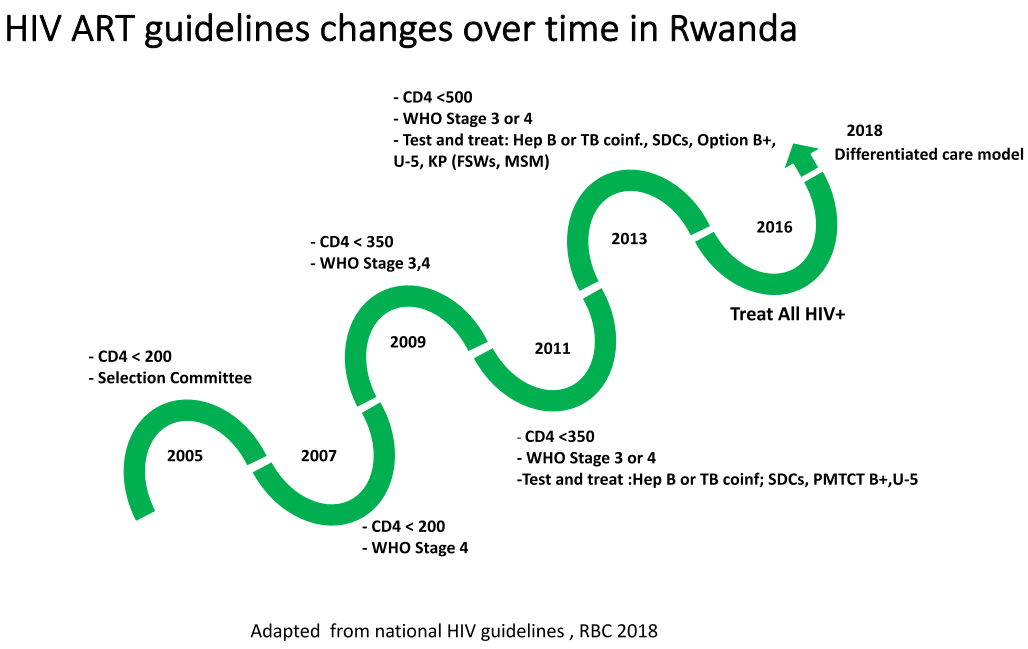


Figure 5: HIV guidelines changes overtime in Rwanda 2005-2018

While, we recognize the tremendous progress made to control the HIV epidemic in Rwanda over two decades, there are programmatic gaps along the cascade of care.

CHAPTER 4. AIMS, OBJECTIVES, HYPOTHESIS AND METHODS

4.1 Overall objective of the present thesis

The overall purpose of this PhD project was to assess key epidemiological, individual and national programmatic features associated with the diagnosis of HIV (accurate estimates of HIV incidence), retention in HIV care during pre-ART period and linkage to ART and performance of individuals under the treatment programs in Rwanda. Results from the thesis projects will directly contribute to identifying programmatic gaps in the HIV care continuum and suggest interventions that can be applied to reduce the disengagement in HIV programs and to improve the performance of ART treatment programs. These interventions may be replicated in other similar countries with generalized HIV epidemics.

a. Specific aims

Specific aim 1: To generate key epidemiological parameters of the HIV epidemic in Rwanda allowing for better precision in planning and alignment of HIV program interventions.

Specific aim 2: To assess the clinical and immunological outcomes of HIV+ patients at different stages of the continuum of care in order to identify when patients are at greatest risk of disengagement in care; particularly, when evaluating treatment outcomes of patients on second- and third-line ART regimens in Rwanda.

Specific aim 3: To estimate the burden of HIV and its determinants among key populations and their connections to the general population in Rwanda.

CHAPTER 5. RWANDA HIV INCIDENCE HOUSEHOLD SURVEY: A NATIONAL OBSERVATIONAL COHORT STUDY

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5.1 Abstract

Background: In Rwanda, HIV prevalence among adults aged 15 to 49 years has been stable at 3% since 2005. The aim of this study was to characterize HIV incidence.

Methods: We conducted a nationally-representative, prospective HIV incidence survey for the period of 2013-2014 using two-stage sampling. We randomly selected 492 villages in the first stage and 14 households in the second stage, resulting in 14·222 respondents from 6·792 households. Participants completed a questionnaire and 14·140 were tested where 13·728 tested HIV negative, and were enrolled in the incidence cohort and re-tested and re-surveyed after 12 months.

Findings: Among 12·593 completers, 5965 were male (47·4%) and the mean age was 30 years. The majority 12,120 (88%) lived in rural areas; 4,826 (38%) were single and 7140 (57%) were married or cohabitating. Over the year, 35 participants sero-converted, resulting in an incidence of 0·27 per 100 person years (PY) (95% CI: 0·18-0·35); 0·21 per 100 PY (95% CI 0·10 – 0·32) among men and 0·32 per 100 PY (95% CI 0·19 – 0·45) among women. Findings were indicative of multiple breakouts, with 3 villages and 2 households having multiple sero-conversions. Incidence was higher among adults aged 36-45 years (0.37 per 100 person-years; aHR 4.5, 95% CI: 1.3-14.7), in Western province (aHR 5.9; 95% CI: 1.33-25.28) and in urban areas (aHR 3.1; 95% CI: 1.28-6.99).

Interpretation: Characterizing incident infections can help the national HIV program plan for prevention interventions tailored to those most at-risk.

Funding: Global fund to fight HIV, TB and Malaria, WHO/ Rwanda, UNAIDS/Rwanda and the Government of Rwanda.

Keywords: HIV, Incidence, household

5.2 Introduction

HIV remains a leading cause of death and disability globally (Wang et al. 2016). In 2015, there were 1·1 million HIV-related deaths, 2·1 million new HIV infections, and a total of 36·7 million people living with HIV (UNAIDS 2016c). The majority of the burden is in Sub-Saharan Africa, where 73% of deaths, 65% of new infections occur and 70% of people living with HIV live (UNAIDS 2016c). The global response to the epidemic has been impressive. As of 2015, 17 million people were receiving antiretroviral therapy (ART) and this contributed to an estimated 43% reduction in AIDS-related deaths since 2003 (UNAIDS 2016c). In 2016, the United Nations General Assembly agreed to fast-track the end of the HIV epidemic by achieving three global goals by 2020: (1) reduce new HIV infections to fewer than 500·000 globally; (2) reduce AIDS-related deaths to fewer than 500·000; and (3) eliminate HIV-related stigma and discrimination (Unite Nations. General Assembly. Human Rights Council 2008).

In Rwanda, HIV incidence peaked in the mid-90s and apparently started to decline after the implementation of population prevention measures including screening of donated blood, health education, and prevention services such as condoms. This decline was accelerated with the scale-up of ART nationally (Binagwaho et al. 2014). At the end of 2015, 160·000 people were receiving treatment and 86% of those on ART suppressed the virus in their blood (below 40 copies per mL) (Nsanzimana, Kanters, Remera, Forrest, et al. 2015). Reducing new HIV infections will require countries to understand incidence nationally, sub-nationally, and within different populations. HIV incidence remains the most informative measure towards understanding the nature of an HIV epidemic, such as where new infections are occurring and who are incurring the new infections. The World

Health Organization (WHO) recommends various methods to measure incidence (WHO/UNAIDS 2013). The gold standard is directly measuring incidence in a cohort of individuals who do not have HIV infection. While ideal, it is resource intensive and not always feasible. The most common alternative option for measuring incidence is mathematical modelling of data that affects incidence (e.g. HIV prevalence rates and risk behaviour). Some limitations of this approach are the robustness of the data used in modelling and the modelling methodologies (Hallett 2011). Modelling encompasses a much greater degree of uncertainty and room for error.

The national HIV control program in Rwanda had yet to conduct a national incidence cohort study since the initiation of ART scale-up in 2004. It has relied heavily on mathematical models from UNAIDS Spectrum/Estimation and Projection Package (EPP) for key indicators, including number of people living with HIV, incidence, AIDS related deaths and number of adults and children in need of ART (Stover, Brown & Marston 2012). These estimates are crucial for national planning, commodities quantification, policy directions and evaluations of interventions. However, the limitations of using national models for subnational planning persist, as many biases may be introduced in model assumptions and the national situation may not always represent what is happening at the local level (Stover et al. 2014). To inform national programming towards the end of the epidemic, Rwanda's Ministry of Health collaborated with The Global Fund to fight AIDS, Tuberculosis, Malaria and other partners to undertake the first study on national HIV incidence, the Rwanda HIV incidence survey. Thus, in order to have the most accurate and comprehensive HIV marker estimates, this study relied on the gold standard for measuring HIV incidence longitudinally in a cohort. Although there have been community-based

cohort studies in Eastern and Southern Africa (Wambura et al. 2007; Reniers et al. 2016; Lopman et al. 2009; Kranzer et al. 2008; Tanser et al. 2012) to our knowledge limited cohort studies (Justman et al. 2017) have been designed for measuring national incidence rates.

5.3 Methods

Sampling

We constructed a national prospective HIV incidence cohort by first conducting a nationally representative survey in 2013 and following all HIV negative individuals within that survey for one year through to 2014. The initial sampling survey was conducted in all five Rwandan provinces using two-stage sampling. In the first stage, we randomly selected 492 villages using probability proportional to the village size. In the second stage, 14 households per village were systematically selected. The sampled villages covered all five provinces of Rwanda and each of the 30 Districts of Rwanda, with 58 villages in urban areas and 434 in rural areas. The survey design considered the clustering of our data in the set-up and analysis of our data. Following the selection of villages, a comprehensive household listing activity was conducted within them; all households located in the selected villages were listed to construct a sampling frame. The study population included women aged 15-49 and men aged 15-59 living in sampled residential households. The sampling methods are the same as those used by the Rwanda demographic and health survey (RDHS).

We obtained a sample of 13·728 respondents from 6·792 households. The survey involved both individual interviews and blood sample collection. Two types of questionnaires were used for interviews. The household questionnaire helped identify

eligible participants for the interview in the selected household, according to age and usual resident of the household, as primary inclusion criteria. The individual questionnaire covered the following key topics: socio-demographic characteristics; sexual behaviour during the last 12 months; knowledge and attitudes towards HIV and related services; attitudes and use of condom; voluntary counselling and testing during the last 12 months; sexually transmitted infections during the last 12 months; male circumcision; exposure to HIV programs; and, contraceptive Methods. Both questionnaires were loaded onto Personal Digital Assistants that were used to conduct interviews.

Participants were also tested for HIV using rapid tests and ELISA. Those testing HIV negative were enrolled in the cohort and those testing HIV positives were only included in the baseline survey. The cohort was followed for 12 months from the time of first HIV test to the end point (last HIV test), with no special intervention or education. Two follow up visits were done, in February and May 2014 aimed to ensure that eligible participants are staying in the same villages and for collecting new addresses for the participants who resettled as well as ensuring that they were still willing to participate in the HIV incidence survey. All study participants regardless of the new HIV status were visited to avoid eventual social stigma related to the serological status, but only HIV negative participants were considered in the HIV incidence cohort. HIV incidence in the cohort prospective study was estimated as the number of HIV sero-conversions per 100 persons-years of follow-up. HIV incidence was the primary endpoint for our study.

HIV testing

All selected participants were enrolled after providing a signed consent form. HIV rapid tests were performed at the nearest health facility (HF)'s laboratory for swift return to the participants at baseline and at 12 months' follow-up. Respondents who agreed to provide a blood sample for HIV testing were provided with an HIV specimen result request voucher referring them to the nearest HIV counselling and testing centre to access their HIV-test results, while the HIV ELISA tests were done at the National Reference Laboratory (NRL) for confirmation. Respondents who tested HIV-positive were given counselling to be enrolled and followed up into HIV care and treatment services. Dried blood spot (DBS) specimens were collected by trained and qualified laboratory personnel through a finger-prick. Laboratory technicians collected and labelled three cryovials and the DBS specimens prepared at the (HF) laboratory each day were processed and tracked by recording specimen information on a specimen transportation manifest from the health facility laboratories and on receipt at the NRL in Kigali. All samples at baseline and end of follow up were tested using both (enzyme immunoassay (EIA) and rapid diagnostics according to the national HIV testing algorithm. At HF, HIV rapid test was performed on whole blood obtained by venipuncture using Colloidal Gold (Shanghai Kehua Bioengineering Co., Ltd, China) and Determine HIV-1/2 Ag/Ab (Alere, Japan) as screening tests and Uni-Gold HIV test (Trinity Biotech, Ireland) as confirmatory. For the survey testing results confirmation, the specimens were tested at the NRL using a 4th generation (Vironostika HIV-1/2 antigen/antibody, BioMérieux, France) as a screening and a 3rd generation (Murex HIV·1·2. O, Murex Biotech, Dartford, United Kingdom) HIV EIA second as a confirmation test in a serial testing algorithm. All blood specimens received from the field

were registered electronically against the respondent's identification number using a bar-code reader. Each specimen was assigned a unique laboratory number during the registration process and laboratory testing and storage in the repository was carried out against that number. The Emory University, Project San Francisco Lab in Kigali conducted the lab quality control whereby 10% positive and 5% negative specimens were re-tested using the same testing algorithm mentioned previously. Specimens with results discordant between two laboratories were resolved by repeating testing algorithm.

The specimens were stored at -80^{o}C prior to commencement of the testing. After testing was completed, results were added to the new survey data file. The unique random identification number originally assigned to each study respondent's questionnaire and venous blood sample served as the means for merging the survey and testing files.

Statistical analysis

The aims of the analyses were three-fold: 1) to estimate incidence after 12 months in the general population; 2) to understand where new infections were occurring and who were incurring the new infections; and 3) to understand which variables are associated with new HIV incidence. Data were collected using the structured questionnaire programed in the PDA (Personal Digital Assistance) and back up on daily basis in Rwanda Biomedical Centre Servers. Data editing and cleaning was conducted including checking of range, structure and internal consistency. Baseline, follow up and end points data were linked through the Participant ID.

Sampling weight was calculated based on a separate sampling probability for each sampling stage and for each sampling cluster. All analyses were weighted to adjust for the

complex sampling methods and non-response to achieve a national representative analysis. Weighted percentages were round up to the nearest whole number.

The incidence analysis was based on the 12·611(92%) participants who were found at the end point. For the purpose of better understanding HIV incidence, we used simple descriptive statistics and the Cox Proportion Regression, with 95% confidence interval. Incidence was calculated per 100 person-years. All analyses were conducted in Stata (Version 13). Furthermore, villages where new infections occurred were mapped using Arch GIS (Version 10.3) to understand more where new infections occurred. To determine if observed villages and households with multiple infections were to be expected or not, we derived probabilities of events as extreme or more extreme occurring using the Binomial distribution.

Role of the funding source

The main funder (Global fund to fight HIV, TB and Malaria), contributing more than 95% of the study budget had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Other funders (Government of Rwanda, WHO/Rwanda and UNAIDS/Rwanda), provided technical guidance in areas of study design, data collection and analysis and report writing. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics

The survey protocol was reviewed and approved by the Rwanda National Ethics Committee and the National Institute of Statistics of Rwanda.

5.4 Results

Participation and HIV prevalence.

The Rwanda HIV incidence survey had a high response rate. Out of 14·456 eligible participants from 6·792 sampled households, we obtained a sample of 14·222 respondents. This included 7·419 women and 6·803 men aged 15-59. Thus, the individual response rate was 98·4%. Blood samples for HIV testing were obtained for 14·140 (99·4%) of the 14·222 respondents.

Table 1 presents the demographic characteristics of the cohort as well as the prevalence estimates according to various subgroups. Of participants tested for HIV, 439 (3·0%; 95% [CI]: 2·6-3·4), were HIV sero-positive, which aligns very well with previous national prevalence estimates. It was higher among women at 270/7·678 (3·5%; 95% CI: 3·0-4·0) than men at 169/7·013 (2·4%; 95% CI: 2·1-2·8). HIV prevalence in urban areas was higher 92(5·6%) compared to 320 (2·6%) in rural areas. The difference in HIV prevalence by sex was also present in both urban and rural areas, where it was 59 (7·2%) among women in urban areas compared to 33 (4·0%) among men in urban areas. Similarly, it was 194 (3·0%) among women in rural areas compared to 126 (2·2%) among men in rural areas.

At the end of both follow-up visits, 12·593 out of 13·728, representing 91·7% of the baseline sample (excluding the participants who tested HIV-positive) participated in the endpoint data collection activities. By sex, the data collection activities were conducted for 6·628 (52·6%) women and 5·965 (47·4%) men. Among completers, the mean age was 30 years. The majority 12·120 (88%) lived in rural areas, 4·826 (38%) were single and 7·140 (57%) were married or cohabitating.

HIV incidence

Over the year of follow-up from November 5th, 2013 to November 15th, 2014; 35 cohort members sero-converted resulting in an HIV incidence of 0·27 per 100 person-years (95% CI: 0·18-0·36) in adults who had tested HIV negative at the baseline, as shown in *Table 2*. The incidence increased with age. Incidence was lowest in adults aged 26-35 years (0·21 per 100 person-years) and highest in adults aged 46-55 years (0·38 per 100 person-years). The incidence rate among young people aged 16-25 was 0·24 per 100 person-years; however, it should be noted that 12 of the 35 cases occurred in this age group and that 19 of 35 incident cases occurred among cohort members aged 30 or less. HIV incidence was higher among women than men; higher among the widowed, never married and the divorced relative to married couples; and was higher in urban areas relative to rural areas (*Table 2*).

We further explored the HIV incidence relationship with other variables. *Table 3* shows that the incidence was higher among adults aged 36-45 (aHR 4.5, 95% CI: [1.30 - 14.70]). Similarly, the western province was 5·9 times more likely to seroconvert (95% CI: [1.33 - 25.28]). The HIV incidence showed urban/rural variation with higher incidence in urban areas (aHR 3.1 95% CI [1.28 - 6.99]. It was 10-fold higher among those that experienced rape or forced sex (95% CI: [1.95 - 37.73]). Contrarily, being in relationship was less likely associated to sero-conversion (aHR 0.2, 95% CI [0.07 - 0.52]).

Figure 1 illustrates the map of Rwanda and distribution of new infection across the provinces. It also shows that with 17 infections a larger than expected number of infections occurring in the Western province, which does not represent a large portion of the overall population. A closer look at these cases finds that three villages experienced multiple

infections. Two pairs of cases also occurred within the same house, although one was a pair of brothers and the other was a mother and her daughter, so these were clearly not couples. Based on the number of participants, number of households and the estimated 0·27 per 100 person-years incidence rate, the probability is very low (0·0012) of observing two more such households. Similarly, the estimated probability of seeing two or more villages with three or more households with infections was 0·0001. Thus, these multiple cases within villages and households (accounting for nine infections) suggest that HIV outbreaks played a role in the spreading of HIV in Rwanda. The three villages are all located on the Northern shores of Lake Kivu, a large lake making up much of Rwanda's Western border. Those infected in the three villages tended to be farmers and there was no indication that any of them were migrant workers, such as fishermen. More generally, the results show that 60% of the new infections were in women while 40% were in men. Half of all new infections were among the never married (51·0%) while one third (33·6%) came from those in union. Also, though the divorced and widowed had higher incidence, they only contributed 15·43% of the overall HIV incidence.

5.5 Discussion

The first Rwanda HIV household incidence prospective survey suggests that remarkable improvements in the control of HIV have been made. However, new infections still occur with an estimated incidence of 0.27 infections per 100 person-years. For a long time, HIV incidence in Rwanda has been estimated using mathematical models and this research provides informative insights into the results of these models and the current state of the HIV epidemic in Rwanda.

The incidence in Rwanda is comparatively low in a region where wide variations occur across groups and demographics. It is, however, somewhat larger than may be expected in a country with a relatively stable prevalence of 3%. Other nearby countries have reported high incidence within different populations and at different times. This international geographic heterogeneity is consistent with findings from a recent systematic review that reported incidence ranged from 0·8-7·5% in Tanzania, 2·3-16 % in Kenya, 1·8- 17% in South Africa, and 0·5-9% in Uganda (Braunstein, van de Wijgert & Nash 2009). In the past, the incidence of HIV in Rwanda may have been underestimated by mathematical models by more than 50%; the estimates provided by this survey therefore provide more accurate data for future planning. According to EPP Spectrum model of UNAIDS (Stover et al. 2014; Stover, Brown & Marston 2012), the estimated incidence of HIV in Rwanda by 2014-2015 was 0·08% CI [0·05- 0·14%] and estimated number of new infections among adults and children was 7·342 [5·379–9·279] (MoH/RBC-Rwanda 2015a). These estimates were used by the national HIV program in strategic planning activities. However, questions of large confidence intervals and uncertainty of the model assumptions were regular discussions between country Monitoring and Evaluation team and the UNAIDS reference group (Stover, Brown & Marston 2012) . With these new results, suggesting slightly more than 14·000 new infections annually (0·27% incidence per 5·392·209 projected population aged 15- 49 years); the model estimates will likely be better adjusted to provide more accurate data for decision making. There is a necessity for follow-up surveys to determine the accuracy of our current findings. Given the coverage of ART in Rwanda, and relatively low HIV-associated mortality, this somewhat high incidence rate seems potentially inflated. Although youth did not have discernibly higher incidence, they make up a large

portion of Rwandan society and as a result account for most new infections. Efforts aimed at single young adults may help curb the current HIV incidence.

The incidence was largely driven by young adults and singles that account for more than half of all infections. This is probably due to low condom use among youth (51·1%), relatively low comprehensive knowledge (60%) about HIV among this particular group aged 14-25 (NISR-Rwanda 2014) . These results are particularly concerning given that HIV is a chronic disease that requires lifelong treatment. Another potential driver of incidence were local outbreaks. As noted, 26% of the seroconversions occurred among persons selected in three villages. We could not correlate the origin of the infection from individuals in those villages. Specifically, none appeared to have been migrant workers, none appeared to have engaged with sex workers and none appeared to be in discordant couples. Outbreaks are likely to be caused by acute infections, so these results possibly indicate that multiple sexual partnerships among young rural Rwandans is higher than reported in previous studies and that this plays a role in the spread of HIV infection in rural areas where condom use was also reported very low (NISR-Rwanda 2014).

We also noted that the HIV incidence was higher among adults in urban than in rural areas that stresses the importance of geographical locations to HIV dynamics. This observation has also been observed across the sub-Saharan African region (Braunstein, van de Wijgert & Nash 2009; MoH-Uganda 2004). The trend towards higher incidence in urban settings and the shift towards a growing urban population will require that we be extra vigilant moving forward with HIV care in urban settings. In South Africa, adults having multiple sexual partners had also higher HIV incidence (2·2%) compared to those who reported only one partner (1·4%) (Zuma et al. 2016). Previous estimates suggested that

most heterosexual HIV transmission in urban Zambia and Rwanda takes place within married and cohabiting couples (Dunkle et al. 2008); however, the risk of getting HIV is likely the result of extra marital relationships. Such a trend was not observed in our study; however, we did observe higher incidence among widowed, never married and divorced persons and these are more likely to have different casual partners than stable couples. Despite the evidence that male circumcision reduces the susceptibility to HIV (Bailey et al. 2007) we did not find a significance difference between circumcised and non-circumcised men.

There are strengths and limitations to consider in our analysis. This is the largest HIV household prospective incidence survey ever conducted in Rwanda, with high participation and retention rates. It enrolled a robust sample size weighted at national and provincial levels. The first limitation to this study is the small number of sero-conversions, which limited our ability to estimate risk factors with greater certainty and to adjust for confounding variables within analyses of risk factors. Second, because of a low number of infection events, it is possible that our study is biased by temporal trends that we were unable to examine in any post-hoc analysis. Follow-up incidence surveys will be necessary to ensure robust policy decision-making. Third, by only testing at the end of the year, it was not possible to discern the time of infection and as such estimate hazard ratios and other measures that could have been more informative. Additionally, though we conducted precise testing steps to eliminate false positives, recent protocols suggest a third high specific EIA serial confirmatory test. Fourth, although the retention rate was quite high, response rates to certain behavioural questions were relatively low. This at times made it difficult to use this information to better comprehend the results of this study. Fifth, given

the low number of infections, exploring differences between characteristics of infected and uninfected individuals is challenging and should be interpreted with caution. It is possible that not all participants answered all questions truthfully, particularly as questions relate to sexual behaviour.

Despite the progress made in HIV control globally, more data are needed to understand precisely the magnitude of the HIV epidemic in specific countries. This survey demonstrated that HIV new infections have been underestimated in previous measures using mathematical models. Reaching 90-90-90 global targets will require both resources and evidence for better decision making. As Rwanda has committed to ending AIDS by 2030, this study allows greater precision in decision-making.

5.6 Panel: research in context

Evidence before this study

Rwanda has a mature HIV epidemic with a stable 3% prevalence in the adult population for the past decade. Its HIV program has been successful at reaching impressive goals with respect to the HIV continuum of care and providing ART and care to those eligible. Despite a strong surveillance program, Rwanda has depended on mathematical models and programs to estimate the HIV incidence. We searched in Pubmed for studies containing the search terms "HIV incidence", "Household survey" and "longitudinal cohort" up to January 15th, 2017 and found only one study (Justman et al. 2017) on Swaziland HIV incidence measurement over 6 months' cohort follow up. We also found UNAIDS spectrum modelling from Rwanda for year 2015 estimating HIV incidence of 0·15 per 100 person-years (UNAIDS, Geneva aids info 2015).

Added value of this study

This study provides a nationally representative estimate of incidence as well as insights into the factors influencing incidence that was less than twice the 2015 UNAIDS EPP Spectrum estimates. The results were higher than those provided by mathematical models. The study also showed that non-married young adults were among the drivers of HIV incidence. Data also suggest that the nature in which new infections occur also involve outbreaks.

Implications to all available evidence

With increasingly complex HIV programs, better information is required for decision makers. Nationally representative prospective incidence surveys are feasible and could provide vital information to other HIV programs. Investing in primary data collection, such as incidence studies will likely have profound implications on modelling the epidemic.

Table 1: Patients characteristics and prevalence results from the Rwanda HIV incidence survey of 2013-2014

Background characteristics	Baseline characteristics		Prevalence	
	N (Weighted)	%	N (Weighted)	%
Overall	**14782**	**100**	**14691**	**3·0**
Age group				
15-19	3420	23·1	3407	0·4
19-24	2453	16·6	2435	1·0
25-29	2458	16·6	2437	2·1
30-34	2143	14·5	2125	4·4
35-39	1478	10·0	1469	5·0
40-44	1135	7·7	1130	7·2
45-49	987	6·7	982	6·4
50-54	407	2·8	405	6·0
55-59	301	2·0	300	4·8
Gender				
Female	7716	52.2	7678	3.5
Male	7066	47.8	7013	2.4
Marital status				
Single	6331	42·8	6281	1·1
Married/Cohabiting	7598	51·4	7561	3·7
Divorced/Separated /Widowed	853	5·8	849	11·1
Residence				
Urban	1927	13·0	1887	5·6
Rural	12855	87·0	12804	2·6
Province				
East	3373	22·8	2360	1·9
North	2362	16·0	3738	2·6
South	3739	25·3	3366	2·2
West	3286	22·2	3260	3·1
Kigali city	2022	13·7	1967	6·1
Education level				
No education	2160	14·6	2150	4·0
Primary	9426	63·8	9387	2·9
Vocational	269	1·8	268	5·6
Secondary	2542	17·2	2518	2·1
Highest education	385	2·6	368	3·1
Religion				
Other	461	3·1	453	6.2
Catholic	6511	44·0	6482	2.5
Protestant/Adventists	7479	50·6	7428	3.1
Muslim	332	2·2	328	6.9
Wealth index				
Lowest	2696	18·2	2684	3.1
Second	2842	19·2	2836	2.6
Middle	2813	19·0	2807	2.7
Fourth	3128	21·2	3109	2.9
Highest	3302	22·3	3255	3.6

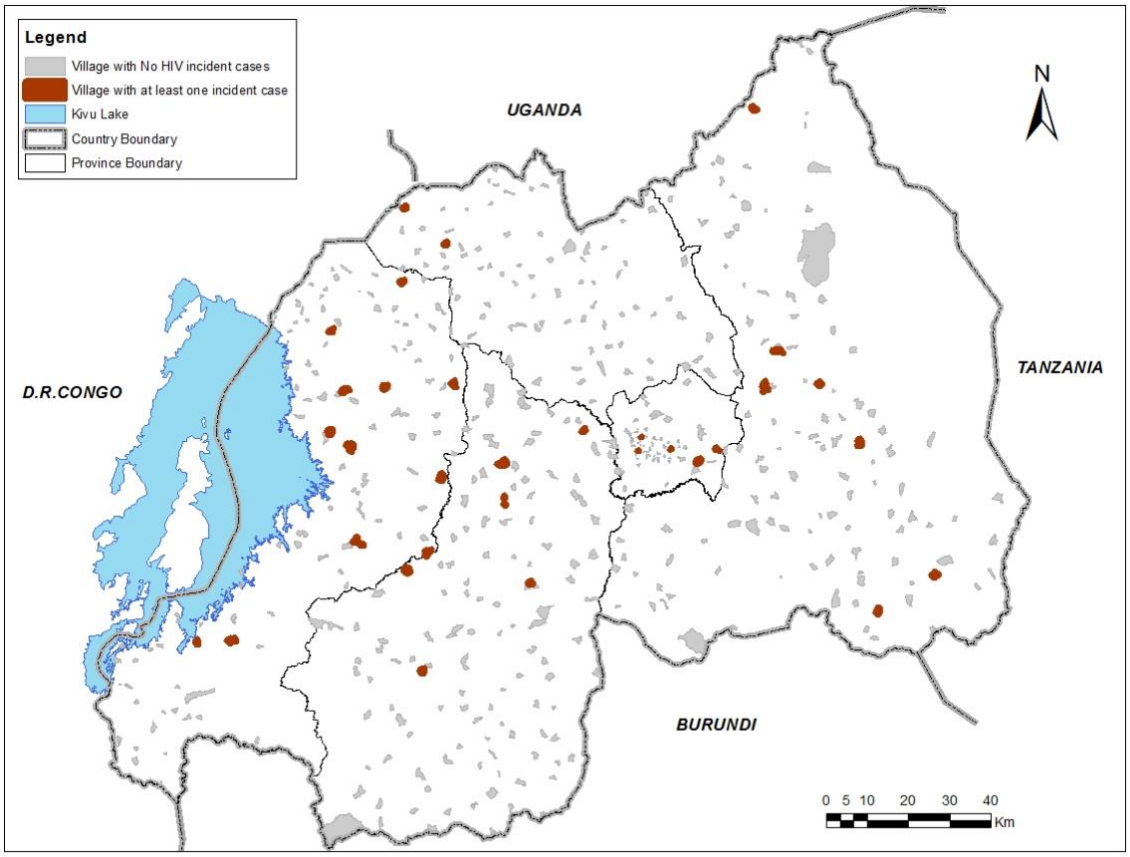
Table 2: HIV incidence by selected demographic characteristics and risk factors in the Rwanda HIV incidence survey cohort of 2013-2014

Demographic characteristics	N (Weighted)	HIV Incidence [95% CI] (per 100 person years)
Overall	**13056**	**0·27 [0·18 – 0·36]**
Age group		
16-25	5097	0·24 (0·11 – 0·37)
26-35	4163	0·21 (0·07 – 0·35)
36-45	2260	0·37 (0·12 – 0·62)
46-55	1270	0·38 (0·04 – 0·72)
56+	266	0·36 (0·00 – 1·08)
Sex		
Male	6182	0·21 (0·10 – 0·32)
Female	6874	0·32 (0·19 – 0·45)
Province		
North	2249	0.09 [0.03- 0.22]
South	3432	0.20 [0.05 - 0.37]
East	3000	0.14 [0.02 - 0.27]
West	2929	0.57 [0.31- 0.87]
Kigali	1409	0.40 [0.05 - 0.69]
Marital status		
Single	5007	0·35 (0·19 – 0·51)
Married	5266	0·14 (0·04 – 0·24)
Cohabiting	2132	0·20 (0·01 – 0·39)
Divorced	331	0·36 (0·00 – 1·01)
Widowed	320	1·30 (0·06 – 2·54)
Residence		
Rural	11636	0·22 (0·13 – 0·31)
Urban	1420	0·65 (0·23 – 1·07)
Had paying sex in the last 12 months		
No	13001	0·25 (0·16 – 0·34)
Yes	55	3·67 (0·00 – 8·64)
Circumcision status		
Not circumcised	4715	0·17 (0·05 – 0·29)
Circumcised	1464	0·34 (0·04 – 0·64)
Experienced rape/forced sex in the last 12 months		
No	8160	0·31 (0·19 – 0·43)
Yes	58	3·32 (0·00 – 7·93)
Had STIs during last 12 months		
No	12480	0·25 (0·16 – 0·34)
Yes	575	0·55 (0·00 – 1·15)
Currently pregnant		
No	6355	0·31 (0·17 – 0·45)
Yes	458	0·22 (0·00 – 0·65)

Table 3: Bivariate and Multivariate analysis

	Bivariate	Multivariate
	HR [95% CI]	**aHR [95% CI]**
Overall		
Age group		
16-25 (Ref)	1·0	1·0
26-35	0·8 [0·36-1·99]	2·0 [0·78 - 5·14]
36-45	1·4 [0·57-3·33]	4·49 [1·30 – 14·70]
46-55	1·3 [0·45-3·55]	3·70 [0·94 – 14·60]
Sex		
Male (Ref)	1·0	1·0
Female	1·4 [0·69-2·66]	1·14 [0·56 – 2·36]
Province		
North (Ref)	1·0	1·0
South	2·3 [0·49-11·25]	2·3 [0·48 – 11·06]
East	1·5 [0·28-8·29]	1·5 [0·27 - 8·05]
West	6·5 [1·49-27·97]	5·9 [1·33 – 25·28]
Kigali	4·1 [0·79-21·06]	1·7 [0·31 – 10·03]
Marital status		
Single (Ref)	1·0	1·0
Married/ Cohabitating	0·4 [0·19-0·82]	0·2 [0·07 – 0·52]
Divorced	0·8 [0·11-6·95]	0·3 [0·04 – 2·89]
Widowed	3·3 [1·11-9·63]	0·9 [0·22 – 4·04]
Residence		
Rural (Ref)	1·0	1·0
Urban	2·9 [1·37-5·96]	3·1 [1·28 – 6·99]
Experienced rape/forced sex in the last 12 months		
No (Ref)	1·0	1·0
Yes	10·9 [3·45-59·88]	10·2 [1·95 – 37·73]

Figure 1: Distribution of new HIV infection across Rwandan provinces



CHAPTER 6. HIV CONTINUUM OF CARE, PREDICTING LOST TO FOLLOW UP, AND MORTALITY IN RWANDA.

6.1 Summary

In order to understand the disengagement and defaulting from HIV care in Rwanda, we need to understand the different possible pathways from diagnosis to viral suppression, leakage and the possibility of returning into care at different time points. This phenomenon known as churning in and out of HIV care has been examined previously in Rwanda (Nsanzimana et al. 2014). Different reasons for leakage from care can be due to lost to follow up or mortality and the main predictor has been CD4 count. We conducted two studies to analyse the HIV continuum of care and predictors of attrition using routinely collected national data from multiple sources.

The findings summarised under this chapter were published as part of this PhD project preparatory work:

"HIV Care Continuum in Rwanda: A cross-sectional analysis of the national programme Published in The Lancet HIV 2015, Volume 2, No. 5, e208–e215, May 2015 http://dx.doi.org/10.1016/S2352-3018(15)00024-7"

and

"Effect of baseline CD4 cell count at linkage to HIV care and at initiation of antiretroviral therapy on mortality in HIV-positive adult patients in Rwanda: A nationwide cohort study published in The Lancet HIV, Volume 2, No. 9, e376–e384, September 2015 https://doi.org/10.1016/S2352-3018(15)00112-5"

6.2 Introduction

The scale-up of antiretroviral therapy (ART) for HIV treatment remains among the largest pharmacological interventions of all time (WHO/UNAIDS/UNICEF 2008, 2013). The benefits of ART extend beyond the individual, decreasing the likelihood of sexual transmission among those with undetectable plasma viral loads, as demonstrated by the HIV Prevention Trials Network (HPTN) 052 study (Cohen et al. 2011), and other observational and modelling analyses (Granich et al. 2009). In many regions, and, in particular, Sub-Saharan Africa, programs such as the US President's Emergency Plan for AIDS Relief (PEPFAR) (PEPFAR 2012) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) have increased access to treatment by more than 100-fold in less than a decade (UNAIDS 2012a). Despite the progress that has been made, HIV/AIDS continues to be a leading cause of death in Sub-Saharan Africa, with an estimated 1.2 million attributable deaths in 2011 (WHO 2012).

CD4 T-cell counts at the time of initiation of antiretroviral therapy (ART) is among the strongest predictors of mortality in patients with HIV (Sterne, Hernan & Ledergerber 2005; May, Sterne & Costagliola 2006; Mills, Bakanda & Birungi 2011; Braitstein et al. 2006).The World Health Organization (WHO) guidelines, 2013 recommend that ART be initiated for all people living with HIV who have CD4 cell counts of 500 cells/mm^3 or less, all HIV-positive pregnant women, all HIV-positive children younger than five years of age, all individuals with concomitant hepatitis B and chronic liver disease, and active tuberculosis, irrespective of CD4 cell count. However, despite these changes in global clinical guidance, CD4 counts at linkage to care and at ART initiation in Sub-Saharan Africa have not appreciably increased over the past decade (Siedner et al. 2015).

Previous evaluations of the prognostic value of CD4 cell counts on the survival of people living with HIV in sub-Saharan Africa are generally limited to an era with poor ART uptake, to small sample sizes and relatively low CD4 cell counts at ART initiation (Fox, Sanne & Conradie 2010; Gallant, Mehta & Sugarman 2013; May, Boulle & Phiri 2010; Mills, Bakanda & Birungi 2012); they have also been limited to evaluating the prognostic value of CD4 cell counts at ART initiation rather than also at clinical linkage with care. These and other studies concur that lower CD4 cell counts, particularly at initiation of ART are associated with worse survival (Cain, Logan & Robins 2011; Mills, Bakanda & Birungi 2012). Earlier linkage to clinical care may also have important benefits with respect to survival because it provides clinical and social support that may include health education, anti-infective and nutritional support prior to initiation of ART. Given that late ART initiation is most often the result of late clinical linkage and that the mechanisms by which clinical linkage and ART initiation affect survival are distinguishable, there is a need to understand the effect of CD4 cell counts at ART initiation, but also at linkage to care.

Among Sub-Saharan African countries, Rwanda has made remarkable progress towards rebuilding a shattered health system in the two decades following the 1994 genocide (Farmer et al. 2013; Binagwaho et al. 2014). Rwanda began its ART scale-up in 2004 and by 2007 Botswana and Rwanda were the first two countries in Sub-Saharan Africa to reach universal ART coverage (defined as having ≥80% of eligible patients on treatment according to current guidelines). The Rwandan Ministry of Health has been consistently raising the CD4 cell count threshold for ART initiation aiming for treating all people living with HIV regardless of CD4 count (Nsanzimana 2014).

However, the successful delivery of ART to achieve universal coverage cannot be accomplished in the absence of a thoughtful and robust system of monitoring and evaluation that helps guide implementers through overcoming programmatic and logistical barriers. For example, poor engagement in care by HIV-positive individuals substantially limits the effectiveness of expanded access to ART.

Using the cascade of HIV care as a framework, the following two analyses aim to evaluate the Rwanda national HIV program by quantifying the engagement of HIV-positive individuals in care for the year 2013 and report factors associated with mortality in the ART and pre-ART stages and examine the predictive value of baseline CD4 cell count at clinical linkage to care and at ART initiation on mortality among HIV positive patients in Rwanda.

6.3 Methods 1: Quantifying disengagement in the HIV Continuum of care

Framework

The conventional model of the cascade of care fails to account for the cyclical aspects of engagement and re-engagement in care. Therefore, we extended this framework to better capture the multiple entries and exits of HIV-positive patients engaging in care in Rwanda. **Figure 1** displays this re-conceptualized framework. The stages of care include: being diagnosed, linking to care, initiating pre-ART, initiating ART and becoming virally suppressed. Additional stages may include being adherent to ART and being ART eligible. Currently, ART adherence is not assessed within the Rwandan national HIV-surveillance system, so it was not considered in these analyses. We do account for ART eligibility, but do not include it as a stage of the cascade.

Study Setting and Sources of Data

The prevalence of HIV in Rwanda remains stable at approximately 3.0% of the adult population (NISR-Rwanda 2014).The Ministry of Health (MoH), using the UNAIDS mathematical modelling program Spectrum (USAID 2009), estimates that there were approximately 252,670 HIV-positive Rwandans in 2013.

As no single data source can inform the entire cascade of HIV care in Rwanda, our study collated four principle data sources to quantify engagement in HIV care in Rwanda: the TRACnet database (Nsanzimana et al. 2012), electronic medical records (EMR), the IQ Charts, and an unpublished MoH study investigating linkage from diagnosis. The MoH study investigated 8598 newly diagnosed patients at 20 health facilities from 2010 through to 2011. Each source of data thus complements the other to capture each step in the cascade of HIV care in Rwanda.

The primary data source was the TRACnet database. Launched in 2003, TRACnet is a nation-wide surveillance database specific to HIV care. It captures data on all patients that are linked to HIV care; these data are aggregated at the health facility level and collected monthly. Data are captured at all of the over 500 health facilities providing HIV care in Rwanda, of which 465 provide ART delivery. Data are collected at the individual level prior to aggregation and TRACnet IDs are monitored to minimize double counting across clinics. We used TRACnet data for the year 2013, capturing 176,225 patients, to inform the Pre-ART and ART stages of the cascade of HIV care.

The secondary data source was the EMRs. Rwanda is currently in the process of converting to a national database of electronic medical records for all citizens, irrespective of HIV status. At present, these data remain stored locally at the health facility, rather than

centralized. Our team visited ten representative health facilities across all five provinces to extract EMR data on all HIV patients at those establishments (two facilities per province). The ten facilities captured individual-level data on 21,995 patients up to February 2014. These data capture many variables, including viral load measures, dates of diagnosis and linkage to care. We used EMR data to inform the viral suppression stage of the cascade of HIV care and transitions from and to that stage.

The final principal data source used for this analysis was the IQ Charts, a database of health indicators for all HIV patients receiving care at 110 of the 465 (24%) health facilities providing ART in Rwanda. These data are individual-level data that pertain to 87,613 patients spanning from 2004 – 2011 (approximately 50% of HIV patients receiving care). Health indicators include CD4 measurements, WHO disease stage, linkage date, dates of ART initiation and exit dates (including transfers, loss to follow-up and death). We used IQ charts to inform the probabilities of transitions between stages, as well as to draw inferences on mortality and loss to follow-up.

Variables and Definitions

Mortality and loss to follow-up (LTFU) were ascertained and recorded within hospital medical records and include deaths that occur outside of the health center setting. Family members and community often follow up with healthcare providers on unobserved deaths, and there are minimal deaths that remain unaccounted for among patients LTFU. Loss to follow-up is defined as failing to engage in care for three consecutive months. All pre-ART patients are prescribed monthly co-trimoxazole, and over the entire study period all patients are expected to see a healthcare provider and pick-up medication on a monthly basis.

To model factors associated with LTFU and mortality, we included age, sex, marital status, method of diagnosis (ANC, voluntary counseling and testing [VCT] or other), CD4 cell count at enrolment and at ART initiation, TB status, WHO disease stage, whether the health facility was religious, the type of health facility (health center or hospital) and the staff to patient ratio.

Analyses

We first calculated the proportions of individuals at each stage and the transition probabilities between stages of the cascade of HIV care. To determine factors associated with mortality, we fit Cox proportional hazards regression models, one for the pre-ART stage and another for the ART stage. Both CD4 cell counts and age were adjusted between models all other variables were baseline variables at enrolment. As three of the variables were at the facility level, a random effect for the health facility was added to create a hierarchical model. All tests were two-sided and conducted at the 0.05 significance level. All analyses were conducted in SAS 9.3 (Cary, North Carolina) and R 3.1.1 (Vienna, Austria). This study was approved by the Rwanda Health Research Committee.

6.4 Methods 2: Effect of CD4 cell count at enrolment and ART initiation on loss to follow-up and mortality

Study Design and Participants

This study was based on patient-level data sources of routinely collected data used by RBC for the purpose of research and surveillance: the IQ Charts database and EMR. Both IQ Charts and EMR contain demographic and clinical characteristics as well as longitudinal, HIV-specific clinical factors and vital statistics on HIV-positive patients enrolled in care. The records contain data on both pre-ART and ART periods of care. This

database contains patient information on all HIV-positive patients from 110 health facilities, representing 25% of ART providing health facilities in Rwanda. The sampled health facilities slightly over-represent rural settings; however, the patient sample appears to be representative as it is comparable to the overall HIV population as reported by TRACnet, the national surveillance database, with respect to mortality, loss to follow-up and other demographic and clinical variables.[20] We included patients aged 15 years or older with a known follow-up time (i.e., did not enter and exit the program on the same day) and who were linked to care or initiated ART between January 1997 and April 2014. There were fewer than 100 patients who initiated prior to 2003. For the first data set we additionally required that patients have a known ART initiation date (n = 345 excluded). The resulting dataset contains 50,147 patients having initiated ART of the estimated 205,000 persons living with HIV in Rwanda (Nsanzimana, Kanters, Remera, Forrest, et al. 2015).[20] The second dataset, not restricted to patients having initiated ART, included 72,061 patients.

Outcomes

The analyses were conducted using mortality and follow-up time. Follow-up time was measured from time of ART initiation to study exit for the primary analysis and from linkage to HIV care to study exit in the secondary analysis. Study exit was defined by one of four outcomes: end of study period, death, loss to follow-up, and transfer out to facilities outside of the study. Mortality data were ascertained in health facilities and through home follow-ups. Demographic variables considered for this analysis included sex and age at ART initiation (categorized by decade of life). Clinical variables included CD4 cell count (<50, 50-99, 100-199, 200-349, 350-499, 500+ cells/mm^3, unreported) at ART initiation,

year linkage, WHO disease stage (I, II, III, IV, or unknown), TB screening (positive, negative or unknown) and reason for diagnosis. Methods of diagnosis included voluntary counseling and testing (VCT), prevention of mother to child transmission (PMTCT) and other means; the other category includes provider initiated testing (PIT), which began in 2010, HIV associated hospitalizations, and testing initiated by indication of comorbidities. Year of linkage was dichotomized into a later era (2008 or later) and an early era (prior to 2008). This marks a distinct turning point in testing availability, patient behavior and ART guidelines (Nsanzimana, Remera, Kanters, Chan, et al. 2015). Outcomes were stratified by CD4 cell count at time of linkage to HIV care. Both CD4 cell count variables included an *unreported* category, 3825 at ART initiation and 667 at linkage. CD4 cell counts at ART initiation was set to missing if measured more than six months prior to ART initiation or more than two weeks following initiation. Lastly, we created a composite variable specifying whether patients had an indication to initiate ART other than CD4 cell count status. These reasons included having a WHO disease stage of III or IV at linkage to care, a positive TB screen, hospitalization as the reason for ART initiation or initiating ART through a prevention of mother-to-child transmission program. **Figure 1** summarizes the reasons for patients starting at CD4 cell counts of $\geq$500 cells/mm^3.

Statistical Analysis

We described data sources using summary statistics. The first analysis consisted of evaluating the association between CD4 cell counts at time of ART initiation and mortality, with a particular emphasis on the 500 cells/mm^3 and 350 cells/mm^3 CD4 cell count cut-offs. The second analysis evaluated the association between CD4 cell counts at time of linkage to care and mortality and related this to CD4 cell counts at ART initiation. Both

analyses used Cox proportional hazard regression models. In the first analysis, the composite indication variable was used as an effect modifier to CD4 cell count at ART initiation, with initiating between 200-349 cells/mm^3 without known additional indications for ART initiation as the reference category. The second analysis used similar models with CD4 cell count at linkage to care rather than CD4 cell count at ART initiation. In both models, time was used as an effect modifier as well. Models were fit to determine whether time was an effect modifier to all variables; however, the model with the triple effect modification between CD4, indication and time and no other modification had the best fit. All conditions for survival analysis were verified using tests based on the Schoenfeld residuals and all assumptions were met (Grambsch & Therneau 1994). Transfers are vigilantly recorded and verified in Rwanda and thus should be viewed as a non-informative censoring mechanism. For loss to follow-up a comparison of propensity score distributions for mortality between those lost to follow-up and those not suggested non-informative priors. Those lost to follow-up tended to be young and healthy.

All significance tests were 2-sided, and p-values of less than 0.05 were considered statistically significant. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina) and R version 3.1.1 (Vienna, Austria).

6.5 Results 1: Quantifying disengagement in the HIV Continuum of care

The complete results of our analysis on the cascade of HIV care in Rwanda are summarized in **Table 1a** that accompanies **Figure 1a**. **Table 1a** captures both the statistics of interest and identifies the data source for these statistics. The three following sub-sections describe and expand upon both.

Proportions of Patients at Each Stage of Cascade of HIV Care

The estimated number of HIV-positive individuals in Rwanda in 2013 was 252,670. This serves as the initial state for analyses related to the cascade of HIV care. Statistics in the middle of the cascade had the strongest evidence because they were observed, rather than estimated, through the TRACnet system. They are extremely precise and many steps were taken to minimize bias. Among HIV-positive Rwandans, 176,174 were retained in either pre-ART or ART care in 2013, accounting for 69.7% of all HIV-positive Rwandans. Further down the cascade, 129,405 (51.2%) HIV-positive individuals either initiated or already had initiated ART in 2013.

Statistics at the extremities of the cascade are estimated. Until recently, there was a single testing unit for viral monitoring within Rwanda, limiting the ability to monitor viral loads. Within the EMR database, 82.1% (95% confidence interval [CI]: 80.7-83.4%) of patients with viral loads were virally suppressed using a cut-off of 40 copies/ml (n=3,066). This translates into an estimated 106,371 virally suppressed HIV-positive individuals on ART (42.1% of all HIV-positive Rwandans) in 2013. At the front end of the cascade of HIV care, data on linkage to care are not captured by TRACnet. Using IQ charts, we estimated the percentage of patients that fail to be retained in care following linkage and those that die shortly after linkage (C2 and D1 in Table 1). Adding these values to the number of HIV-positive patients retained in care, we estimate that 183,515 (72.6%) HIV-positive individuals had linked to care. This excludes persons who engaged in care and died prior to 2013. Therefore, the percentages of HIV-positive individuals at each step of the 2013 cascade of HIV care were: 73% linked to care, 70% retained in care, 55% ART-eligible, 51% on ART and 42% virally suppressed.

Progression Towards Viral Suppression on ART

At linkage to HIV care, following staging, 70.4% of patients transitioned to pre-ART. Patients eligible for treatment at linkage were more often eligible due to low CD4 cell counts or opportunistic infections. Approximately 40% of accelerated ART initiation was through ANC according to 2011 data. In determining the percentage of patients eligible at linkage that entered Pre-ART, we used a one-month cut-off and found that 66% of patients that were ART-eligible at linkage initiated within a month. Healthcare providers suggest that many of the 34% of patients that are not put on treatment within a month can be explained by the fact that patients with co-infections (e.g., TB) are first placed on medications for the co-infection and stabilized prior to initiating ART. Data on this process do not exist at present. Using Spectrum, RBC estimates that 93% of all eligible patients were on ART, in accordance with 2013 Rwanda ART guidelines.

Exiting and Other Transitions

Among HIV-positive Rwandans receiving care, 304 (0.6%) patients died while in pre-ART and 1255 (1.0%) patients died while in ART. The mortality rate is lower in the ART period (Table 1a: D2 and D3) because there are many more people on ART and the length of time in pre-ART is often short. Loss to follow-up, at 3.9%, was higher within the pre-ART period than the ART period (2.2%), and even lower among patients that were virally suppressed (estimated at 1%).

The number of patients returning to care was 40% as large as the number of patients lost to follow-up in 2013, implying that the actual proportion of patients disengaged from care was actually lower than the 3.9% and 2.2% reported for Pre-ART and ART, respectively. Moreover, though lost to follow-up was larger in pre-ART than ART, rates

of return were higher in ART than pre-ART (**Table 1**: B4 and B5), suggesting that some disengage from pre-ART only to come back in time for ART.

Factors Associated with Mortality

Figure 2a and 3a presents the results of the Cox-proportional hazards regression models exploring the factors associated with mortality and LTFU within HIV care. Late initiation had an increasingly larger risk for mortality. None of the structural variables were significantly associated with mortality. More deaths were observed in hospitals with better capacity. However, this is due to confounding by indication because those centers with the best capacity (most trained medical staff per patient) are those to which the individuals with the poorest health are sent. Social support and being a woman were both protective in the Pre-ART period. Being diagnosed through a method other than VCT or ANC increased the risk of mortality because this category includes those diagnosed through hospitalization. Finally, the only age category that stood out was children, who had a higher mortality risk than all other age groups except those aged 50 years and older. Associations were similar in the ART time period compared to the Pre-ART time period. Children no longer stood out as having high mortality and diagnosis methods no longer appeared statistically significant. For LTFU, younger aged patients and male gender was associated with LTFU at both pre-ART and on ART.

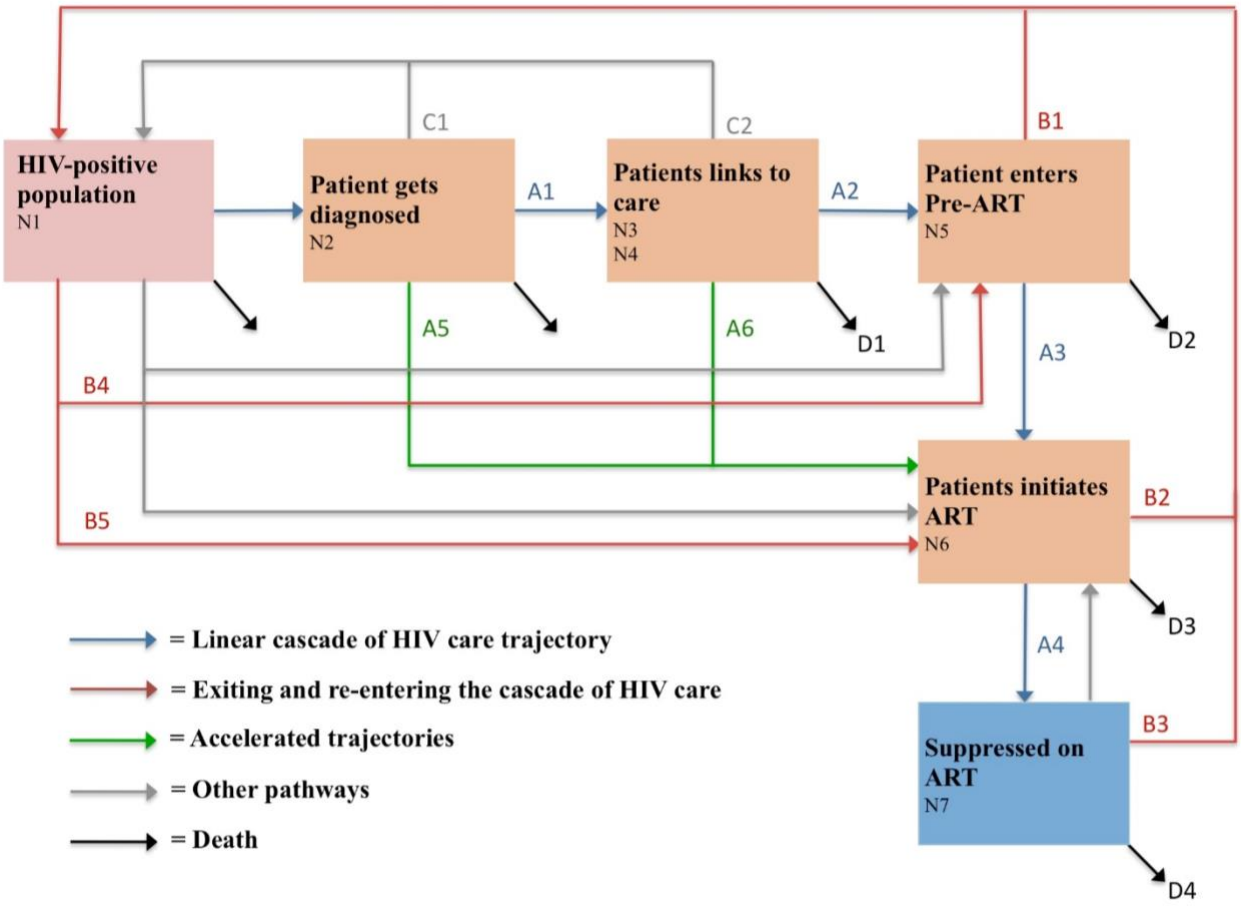
Table 1a: HIV care cascade 2013 statistics and transitions with data sources.

Label	Description	Statistic	Data Source
Stages of the Cascade of HIV Care			
N1	Estimated size of HIV positive population	252,670 **(100%)**	MOH estimate
N2	Number of total diagnoses	*Unknown*	*None*
N3	Number of patients that have linked to care	183,515 **(72.6%)**	TRACnet, not directly measured.
N4	Number of patients currently linked to care.	176,225 **(69.7%);** Currently 46,820 currently in Pre-ART	TRACnet, directly measured
N5	Number of patients in pre-ART	58,182 (23.0%) of which 46,820 (18.5%) at the end of 2013	TRACnet, directly measured
N6	Number of patients initiating ART	129,405 **(51.2%)**	TRACnet, directly measured
N7	Number virally suppression	106,371 **(42.1%)**	EMR estimate*
Progressing along the Cascade of HIV Care			
A1	From diagnosis to linkage to care	**50%** of diagnosed cases linked to within 3 months and **32.6%** were staged (*see A5*).	RBC/MOH Study
A2	From linkage to care to pre-ART initiation	**70.4%** of patients who linked to care initiated pre-ART.	IQ Charts
A3	From pre-ART to ART	**93.1%** of eligible patients on ART	RBC estimate using Spectrum
A4	From ART to viral suppression	**82.2%** of ART patients achieve viral suppression	EMR estimate*
A5	From diagnosis, directly to ART through antenatal care	**16.7%** of diagnosed cases linked to ART through ANC	RBC/MOH Study
A6	From linkage to ART in 2013	**26.5%** initiated ART within one month of linkage	IQ Charts
Churning, exiting and re-entering care			
B1	Loss to follow-up at pre-ART	**3.9% (2247)** of those in pre-ART lost to follow-up	TRACnet, directly measured
B2	Loss to follow-up on ART	**2.2% (2847)** of those on ART lost to follow-up, 1850 unsuppressed.	TRACnet, directly measured
B3	Loss to follow-up virally suppressed	**1.0% (997)** of virally suppressed patients on ART	EMR estimate
B4	Returning to pre-ART	**13.7%** of those lost to follow-up in pre-ART or later return to pre-ART	TRACnet, ratio of measurements

B5	Returning to ART	**26.3%** of those lost to follow-up in pre-ART or later return to ART	TRACnet, ratio of measurements
Other Pathways			
C1	Loss to follow-up at diagnosis	**50%** of diagnosed cases did not link within 3 months of diagnosis	RBC/MOH Study
C2	Loss to follow-up at linkage to care	**3.7%** of those linked to care lost after first visit	IQ Charts
Mortality			
D1	From linkage to care to death	**0.46%** die before being retained in care	IQ Charts 2004-2011
D3	From pre-ART to death	**9.7** deaths per 1000 person-years	TRACnet, 2013
D3	From ART to death	**6.5** deaths per 1000 person-years	TRACnet, 2013 and EMR 2006-2014
D4	From viral suppression to death	**3.6** deaths per 1000 person-years	EMR 2006-2014

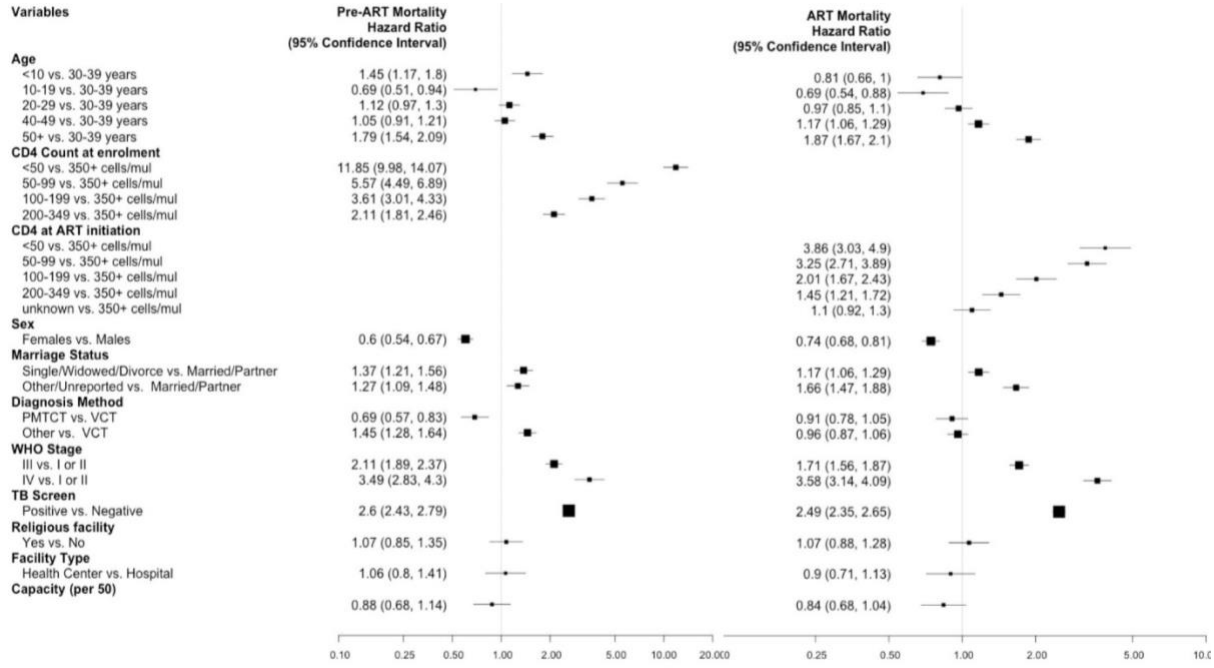
MOH: Ministry of Health; RBC: Rwanda Biomedical Center; EMR: Electronic Medical Records; ANC: Antenatal care. *Based on suppression among those with viral loads

Figure 1a: The cascade of HIV care through multiple trajectories



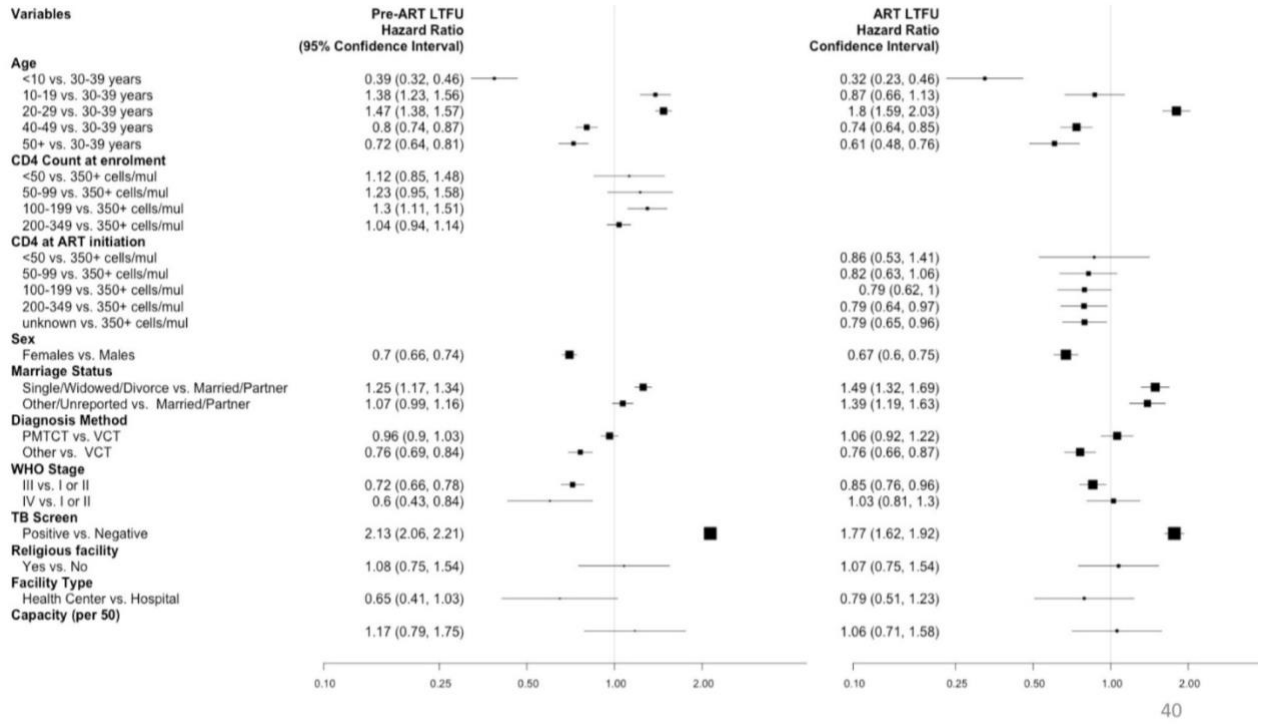
Legend: Statistics corresponding to each label (e.g. A1) are provided in **Table 1**. Other pathways (grey) include delayed engagement and virological failures. This is a simplification, as the red exit lines include individuals that will never re-engage in care and the grey entry lines include symptomatic persons who will engage in care without ever testing.

Figure 2a: Factors associated with mortality within the pre-ART and ART stages of the cascade of HIV care in Rwanda



Legend: VCT: voluntary counseling and testing; PMTCT: prevention of mother to child transmission.

Figure 3a. Factors associated with loss-to-follow-up within the pre-ART and ART periods of the cascade of HIV care in Rwanda



Legend: VCT: voluntary counseling and testing; PMTCT: prevention of mother to child transmission.

6.6 Results 2: Effect of CD4 cell count at enrolment and ART initiation on loss to follow-up and mortality

This analysis is based on data from 50,147 HIV-positive patients who initiated ART and 72,061 patients who were linked to care. **Table 1b** presents the demographic and baseline clinical characteristics of patients included in the primary and secondary analyses. The median age of patients at linkage to HIV care was 36 years (Interquartile range [IQR]: 30-43 years) and the median age at ART initiation was 37 years (IQR: 31-45 years). The median CD4 cell count at linkage to care was 256 cells/mm^3 (IQR: 145-383 cells/mm^3) and 233 cells/mm^3 (IQR: 139-316 cells/mm^3) at ART initiation. **Figure 1b** shows the characteristics of patients.

Table 2b displays the Cox proportional hazard results of the primary analysis among patients followed from time of ART initiation. Initiating ART in the early era of linkage into care (prior to 2008) compared to the later era (2008 or later) was significantly associated with mortality (Hazard Ratio [HR]: 1.54; 95% Confidence Interval [95% CI]: 1.19 – 2.00). Compared to ART initiation at a CD4 cell count of 200-349 cells/mm^3 with no other indication other than CD4 status to start ART, patients initiating treatment in the later era at a CD4 cell count ≥500 cells/mm^3 had a non-significant risk of death (HR: 0.73; 95% CI: 0.34 – 1.58). Among patients initiating ART without other indications, initiating ART in the later era at CD4 cell counts below 200 cells/mm^3 had significantly worse mortality outcomes compared to starting at 200-349 cells/mm^3 without other indications. For all CD4 strata, patients with an indication for ART initiation other than CD4 counts were at higher risk of mortality, with hazard ratio estimates ranging from 2.92 (95% CI: 2.37 – 3.75) among those initiating ART at 200-349 cells/mm^3 in the later era to 15.89 (95% CI: 12.39 – 20.36) among those initiating ART in the later era at 0-49 cells/mm^3. Risk of mortality was higher among men compared to women (HR: 1.37; 95% CI: 1.28 – 1.49), increased with age

with HR relative to age 30-39 years climbing from 0.69 for young adults to 2.00 among those aged 50 or more years ($p < 0.0001$) and was higher among persons without a partner (HR: 1.17; 95% CI: 1.06 – 1.28). Given that thousands of people die annually from HIV-attributable causes,[20] these results are also clinically significant.

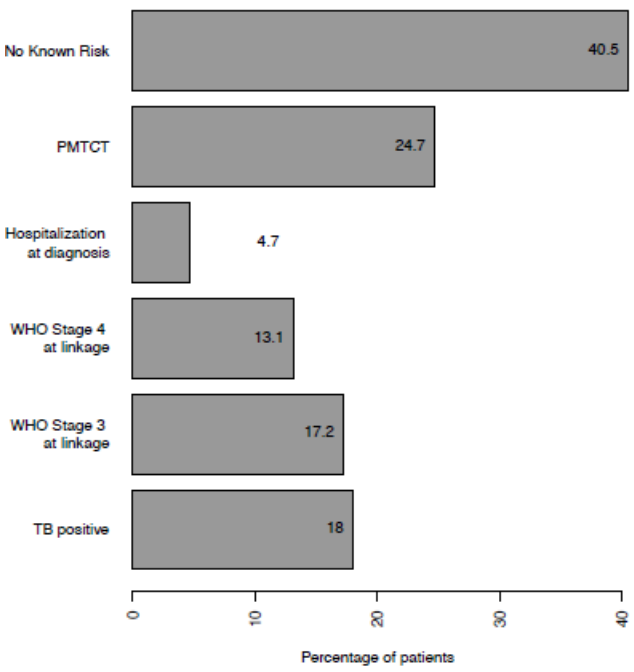
Results of the second analysis are displayed in **Table 3b.** When stratifying by indication status and adjusting for demographic differences, the lower CD4 cell count strata at either time of linkage to care or ART initiation in the late era were similarly associated to risk of mortality. For example, linking to care in the later era at 100-199 cells/mm^3 without any further indication was harmful compared to linking at 200-349 cells/mm^3 (HR: 1.37; 95% CI: 0.95 – 1.97), which was the same for initiating ART in this CD4 stratum (HR: 1.37; 95% CI: 0.92 – 2.04). However, these similarities were not true for higher CD4 strata. Compared to CD4 cell counts of 200-349 cells/mm^3, linking to care in the later era at ≥500 cells/mm^3 or more was protective (HR: 0.59; 95% CI: 0.48 – 0.73), while the observed effect of initiating ART in the later era at ≥ 500 cells/mm^3 was not distinguishable from chance alone (HR: 0.82; 95% CI: 0.21 – 3.20). Effects of gender, age and having a partner were similar in both analyses. **Figure 2b** presents Kaplan-Meier survival estimates across CD4 strata at linkage and ART initiation, separated by the presence or absence of other ART indications. The high CD4 stratum at linkage is more distinguishable.

Figure 3b displays the relationship between CD4 cell count at linkage to care and CD4 cell count at ART initiation. The red horizontal line indicates the 350 cells/mm^3 or lower threshold for immediate initiation of ART. Thus, points falling much lower than this threshold represent late initiators. Three features are apparent in the figure. First, a large portion of patients initiating below 350 cells/mm^3 enrolled in care at very similar CD4 levels, shown by the thick orange diagonal.

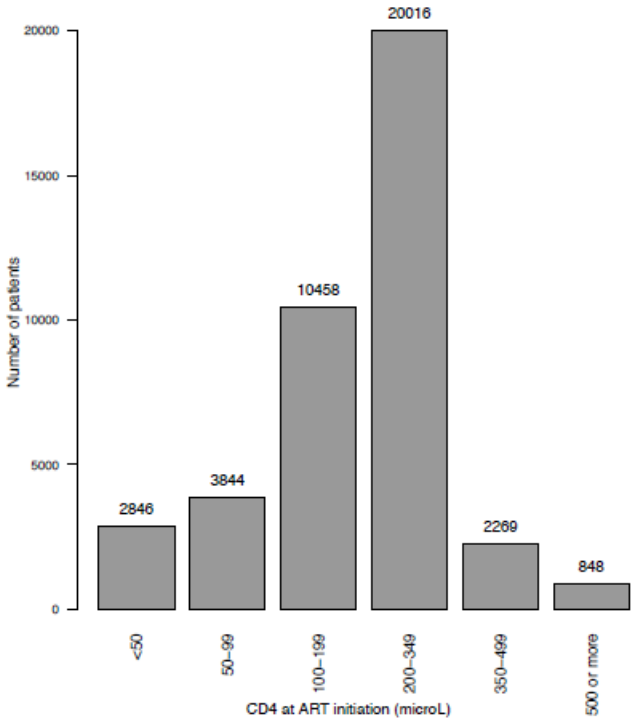
The second is the continuing diagonal above the 350 cells/mm^3 CD4 levels is less well populated and corresponds to immediate initiation due primarily to other indications for ART initiation. The third is the area below the 350 cells/mm^3 cut-offs and to the left of the first feature. This area suggests that in the delayed initiation of ART upon 350 and 500 cells/mm^3, considerably more patients initiate ART below 250 cells/mm^3. This is in part due to the frequency of CD4 testing as these are conducted every six months.

These features can be further described through some descriptive statistics of patients in pre-ART (patients linked to HIV care that are not yet on ART) and their transition to ART. For patients linking to care with CD4 cell counts below 350 cells/mm^3 the median time between linkage to care and ART initiation was 24 days (interquartile range [IQR]: 14 – 48 days). One of the features leading to longer delays in ART initiation was screening positive for TB. This is because these patients likely initiated treatment for TB prior to initiating ART. Among patients linking to care early, the median time between linkage and ART initiation was 311 days (IQR: 168 – 496 days). Finally, loss to follow-up within the pre-ART period was relatively low at 5.5 cases lost per 100 person-years, which is comparable to what has been reported for the entire country (Nsanzimana, Kanters, Remera, Forrest, et al. 2015).

Figure 1b: Differences in characteristics and times of ART initiation with respect to initiating ART with CD4 above 500 cells/mm^3 between data sources



Panel A: Non-CD4 determinants of ART initiation



Panel B: Year of ART initiation

Figure 2b: Kaplan Meier curves for survival by CD4 cell count strata at linkage and at ART initiation and separated by presence or absence of other ART indications among 72,061 HIV positive Rwandans

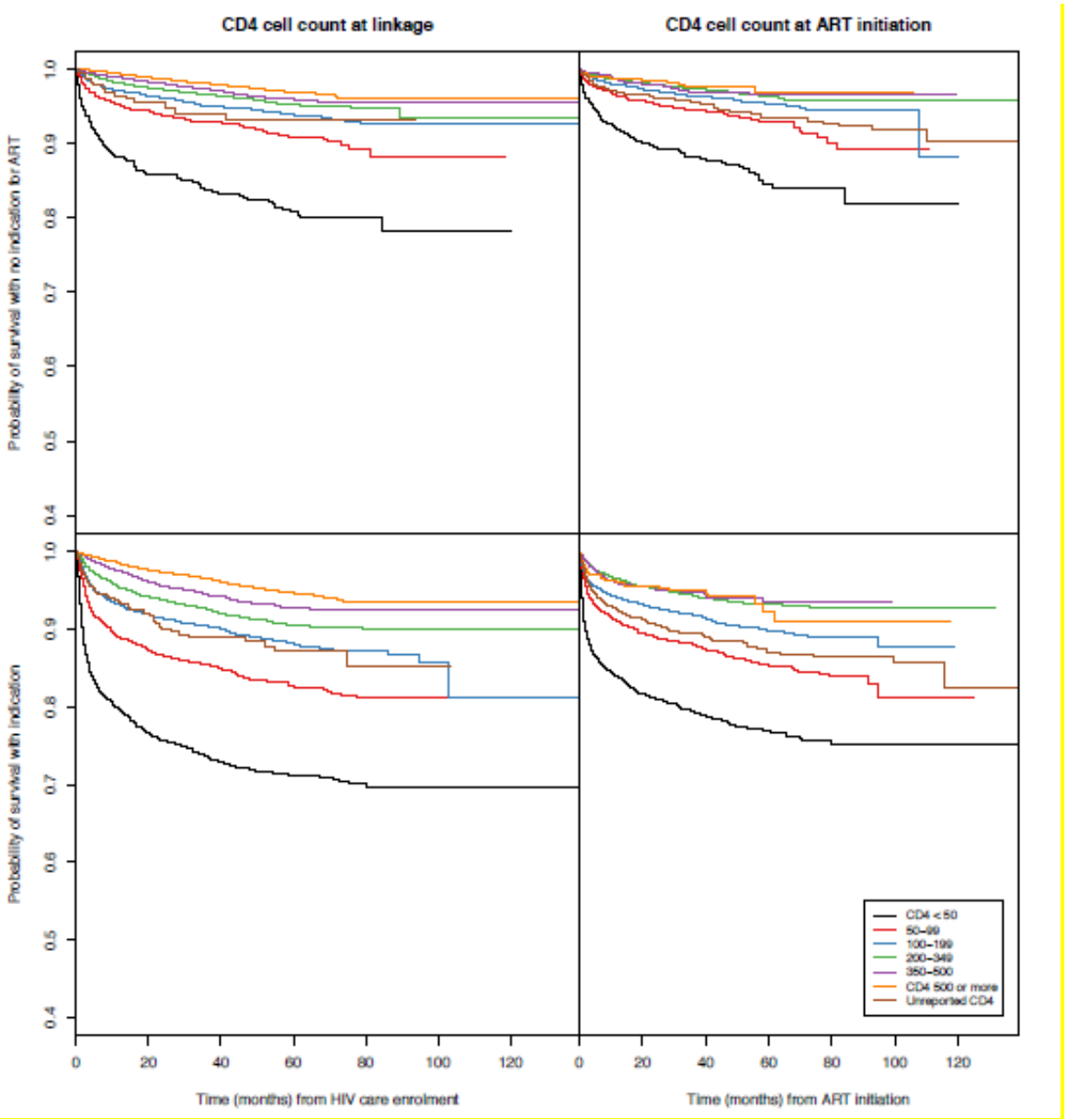
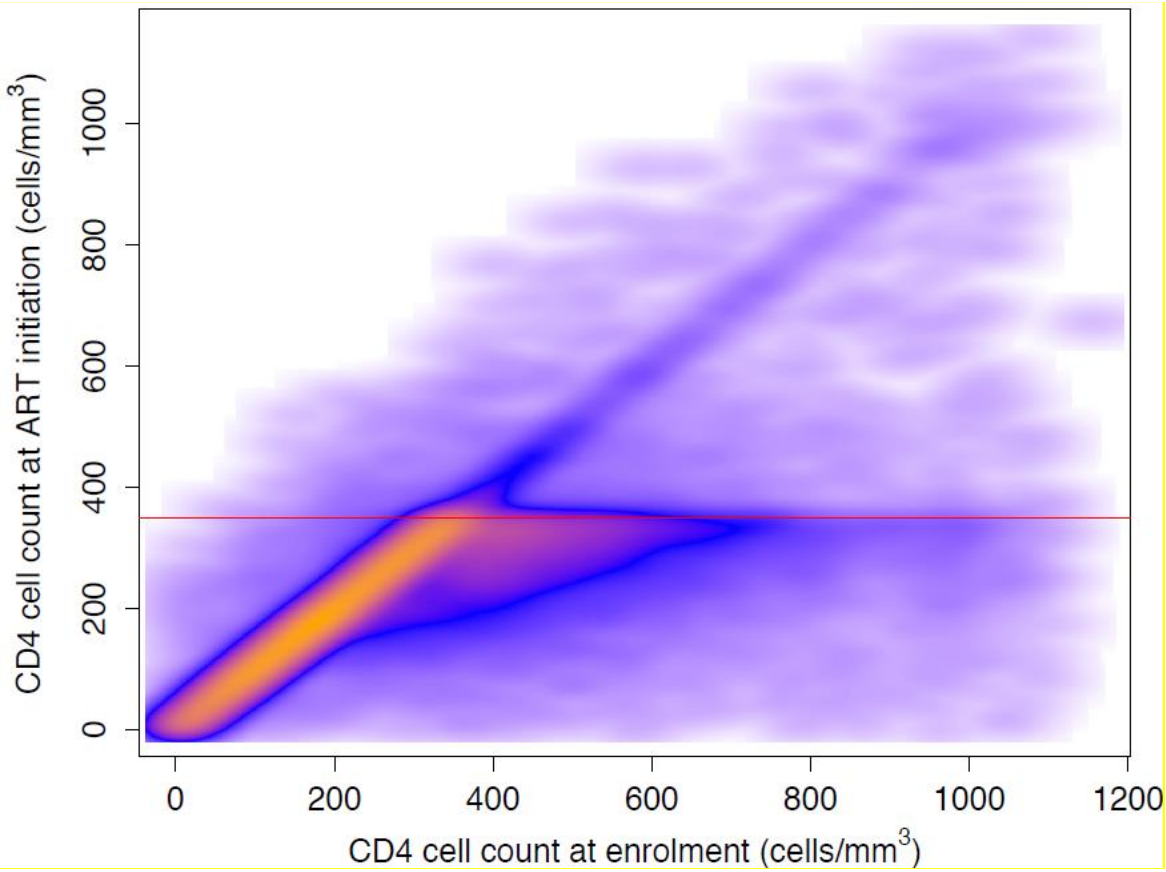


Figure 3b: Smoothed scatter plot relating CD4 cell counts at linkage to CD4 at ART initiation among 41,144 Rwandans who initiated ART between 2004 and 2011.



Legend: The intensity of color indicates the density of observations, with orange indicating thousands of observations in the immediate vicinity; blue indicating hundreds of observations and purple indicating few observations in the immediate vicinity. Among late presenters, most appear to initiate immediately. Among early linkers, there are two distinct lines, immediate starts and delayed starts. The area of concern is the non-negligible cluster of individuals who link above 350, yet delay initiation well below this level.

Table 1b: Demographic and clinical characteristics of patients linked to care and initiated ART in Rwanda

	Linkage to Care (IQ Charts and EMR) **n=72,061**	**ART initiation** (IQ Charts only) **n=50,147**
	Count (%) or Median (IQR)	
Age at linkage to HIV care	36 (30 – 43)	35 (28 – 42)
Age at ART initiation	37 (31 – 45)	--
Sex		
Male	18200 (36.3%)	26055 (36.2%)
Female	31947 (63.7%)	46006 (63.8%)
Marital Status		
Single/Widowed/Divorced	12731 (25.4%)	24086 (33.4%)
Married/Partner	25988 (51.8%)	34508 (47.9%)
Other/Unreported	11428 (22.8%)	13467 (18.7%)
Mode of diagnosis		
VCT	31997 (63.8%)	45897 (63.7%)
PMTCT	6691 (13.3%)	12880 (17.9%)
Hospitalization	2750 (5.5%)	2773 (3.8%)
TB Consultation	143 (0.3%)	241 (0.3%)
PIT	3310 (6.6%)	4254 (4.9%)
Other	5256 (10.5%)	6016 (8.3%)
Path to Treatment		
Immediate at linkage to care	--	17141 (23.8%)
PMTCT: Immediate at Dx	--	2689 (3.7%)
After a Pre-ART period	--	52231 (72.5%)
Exit Reason		
Transfer	11285 (22.5%)	14884 (20.7%)
Died	2949 (5.9%)	3917 (5.4%)
Lost	2167 (4.3%)	7034 (9.8%)
Other	498 (1.0%)	1309 (1.8%)
Censured at end of study	33248 (66.3%)	42953 (59.6%)
BMI at linkage to care	21.1 (19.2 - 23.1)	21.3 (19.5 – 23.3)
CD4 at linkage to care	256 (145 - 383)	394 (210 – 636)
CD4 at ART initiation	233 (139 - 316)	225 (136 – 305)
WHO disease stage		
I	19651 (39.2%)	34281 (47.6%)
II	13846 (27.6%)	18113 (25.1%)
III	14104 (28.1%)	15525 (21.5%)
IV	1734 (3.5%)	1721 (2.4%)
Unknown	812 (1.6%)	2421 (3.4%)
TB Screen		
Negative	39612 (79%)	53675 (74.5%)
Positive	8614 (17.2%)	12265 (17%)
Unknown	1921 (3.8%)	6121 (8.5%)

ART: antiretroviral therapy; Dx: diagnosis; PMTCT: prevention of mother to child transmission; VCT: voluntary counseling and testing; BMI: body mass index; EMR: electronic medical records.

Table 2b. Cox proportional hazards ratios for demographic variables and CD4 at ART initiation with and without indication to initiate ART other than CD4 cell count in Rwanda, 2004-2014

Variable	Hazard Ratio (95% CI)	Variable	Hazard Ratio (95% CI) Early era	Hazard Ratio (95% CI) Late era
Gender		**CD4 at initiation**		
Female	1.00 (--)	0-49 cells/mm^3, no indication	3.34 (2.45, 4.55)	7.84 (5.51, 11.17)
Male	1.37 (1.28– 1.49)	50-99 cells/mm^3, no indication	2.00 (1.49, 2.69)	2.58 (1.69, 3.95)
Age (years)		100-199 cells/mm^3, no indication	1.25 (0.99, 1.57)	1.51 (1.08, 2.13)
15-19	0.69 (0.49 – 0.96)	200-349 cells/mm^3, no indication	1.00 (--)	1.00 (--)
20-29	0.84 (0.74 – 0.96)	350-499 cells/mm^3, no indication	0.95 (0.62, 1.45)	1.13 (0.67, 1.9)
30-39	1.00 (--)	500+ cells/mm^3, no indication	0.91 (0.54, 1.52)	0.73 (0.34, 1.58)
40-49	1.20 (1.10 – 1.32)	0-49 cells/mm^3, with indication	5.91 (4.84, 7.21)	15.89 (12.39, 20.36)
50+	2.00 (1.81 – 2.21)	50-99 cells/mm^3, with indication	3.56 (2.89, 4.38)	8.3 (6.35, 10.86)
Marriage		100-199 cells/mm^3, with indication	2.71 (2.25, 3.27)	4.6 (3.55, 5.97)
Married/partner	1.00 (--)	200-349 cells/mm^3, with indication	1.86 (1.54, 2.25)	2.92 (2.27, 3.75)
Single/divorced/widowed	1.17 (1.06 – 1.28)	350-499 cells/mm^3, with indication	2.02 (1.46, 2.78)	2.68 (1.79, 4.01)
Other	1.08 (0.98 – 1.18)	500+ cells/mm^3, with indication	2.46 (1.68, 3.6)	2.44 (1.43, 4.15)
Era of enrolment into HIV care		Unreported	4.98 (4.05, 6.13)	1.41 (1.03, 1.95)
Prior to 2008	1.54 (1.19 – 2.00)			
2008 or later	1.00 (--)			

Table 3b: Survival analysis for time from linkage to HIV care and time from ART initiation among patients in the IQ Charts database in Rwanda, 2004-2011

	From time of linkage to care	From time of ART initiation
	Hazard Ratio (95% CI)	**Hazard Ratio** (95% CI)
Simple Unadjusted Models		
CD4 cell count at linkage/initiation*	4.82 (4.36 – 5.32)	4.90 (4.38 – 5.49)
<50 cells/mm^3	2.32 (2.07 – 2.59)	2.55 (2.25 – 2.88)
50-99 cells/mm^3	1.43 (1.29 – 1.58)	1.55 (1.39 – 1.72)
100-199 cells/mm^3	1.00 (--)	1.00 (--)
200-349 cells/mm^3	0.70 (0.63 – 0.79)	0.96 (0.75 – 1.22)
350-499 cells/mm^3	0.47 (0.42 – 0.52)	1.55 (1.15 – 2.11)
500+ cells/mm^3	1.62 (1.24 – 2.11)	7.59 (6.18 – 9.33)
Unknown		
Full Models		
Gender		
Female	1.00 (--)	1.00 (--)
Male	1.56 (1.27 – 1.67)	1.43 (1.32 – 1.56)
Age		
15-19	0.69 (0.52, 0.90)	0.78 (0.56 – 1.11)
20-29	0.93 (0.84, 1.02)	0.87 (0.77 – 0.99)
30-39	1.00 (--)	1.00 (--)
40-49	1.23 (1.14, 1.34)	1.28 (1.16 – 1.42)
50+	2.02 (1.84, 2.21)	2.05 (1.83 – 2.29)
Marital Status		
Married/Partner	1.00 (--)	1.00 (--)
Single/Div./Widow	1.43 (1.33 – 1.55)	1.31 (1.19 – 1.44)
Other	1.89 (1.74 – 2.05)	1.72 (1.55 – 1.91)
Era of enrolment into HIV care		
Prior to 2008	1.40 (1.07, 1.84)	1.45 (1.09, 1.92)
2008 or later	1.00 (--)	1.00 (--)

CD4 cell count at linkage/initiation* with/without other ART indication	**Early ART era**	**Later ART era**	**Early ART era**	**Later ART era**
0-49 cells/mm^3, no indication	6.3 (4.27, 9.31)	3.11 (2.24, 4.32)	7.22 (4.75, 10.98)	1.95 (1.43, 2.67)
50-99 cells/mm^3, no indication	4.01 (3.11, 5.18)	2.15 (1.37, 3.38)	1.95 (1.15, 3.3)	1.37 (0.92, 2.04)
100-199 cells/mm^3, no indication	1.97 (1.5, 2.6)	1.37 (0.95, 1.97)	1.21 (0.95, 1.55)	1.00 (--)
200-349 cells/mm^3, no indication	1.31 (1.05, 1.63)	1.00 (--)	1.00 (--)	0.8 (0.43, 1.47)
350-499 cells/mm^3, no indication	1.00 (--)	0.77 (0.55, 1.09)	0.8 (0.43, 1.47)	0.94 (0.41, 2.16)
500+ cells/mm^3, no indication	0.8 (0.63, 1.03)	0.53 (0.39, 0.72)	0.86 (0.32, 2.33)	0.82 (0.21, 3.20)
0-49 cells/mm^3, with indication	0.59 (0.48, 0.73)	15.2 (11.7, 19.6)	5.88 (4.78, 7.22)	15.7 (11.9, 20.5)
50-99 cells/mm^3, with indication	5.88 (4.88, 7.07)	7.27 (5.49, 9.63)		

100-199 cells/mm^3, with indication	3.29 (2.7, 4)	4.43 (3.38, 5.8)	3.5 (2.82, 4.34)	8.33 (6.23, 11.14)
200-349 cells/mm^3, with indication	2.26 (1.89, 2.71)	2.90 (2.21, 3.8)	2.6 (2.14, 3.15)	4.54 (3.42, 6.02)
350-499 cells/mm^3, with indication	1.91 (1.59, 2.29)	1.89 (1.4, 2.57)	1.85 (1.52, 2.25)	2.93 (2.24, 3.85)
500+ cells/mm^3, with indication	1.55 (1.26, 1.9)	1.18 (0.88, 1.58)	2.07 (1.45, 2.96)	2.43 (1.47, 4.02)
Unknown	1.16 (0.96, 1.41)	2.84 (1.51, 5.34)	3.95 (2.62, 5.97)	4.78 (2.65, 8.62)
	2.41 (1.74, 3.33)		9.78 (7.55, 12.67)	2.66 (0.84, 8.43)

* For models using time from linkage to care, the CD4 cell counts used are those at linkage to care, and for models using time from ART initiation, the CD4 cell counts are those at ART initiation.
ART: antiretroviral therapy; CI: confidence interval

6.7 Discussion

These analyses used the cascade of HIV care framework and CD4 count at ART initiation to evaluate the Rwanda national HIV program, quantify the engagement of HIV-positive individuals in care and predictive value of CD4 count on mortality among HIV positive patients. These results highlight the strengths of Rwanda's national HIV program, indicated by the high proportion of patients retained in care and the high proportion of treated patients with suppressed viral loads. Quantifying the cascade of HIV care for Rwanda has also highlighted areas where changes to the program and procedures of data monitoring may improve health outcomes; principally, the delay between positive diagnoses and engagement in HIV care and lack of data on the stages of the cascade of care from diagnosis to linkage to care. Overall, mortality and loss to follow-up in Rwanda were low in 2013. Nonetheless, findings on mortality were associated with late engagement in care (either with low CD4 counts or opportunistic infections), being male and not having a partner, suggestive of lower social supports. The proportion of treated HIV-positive individuals with suppressed viral loads compares with many programs in high-income countries, such as British Columbia, Canada (Nosyk et al. 2014).

A strong association between increasing survival outcomes with increasing CD4 cell count at time of linkage to HIV care was identified and, despite having a large sample and accounting for other mechanisms by which ART is initiated, found limited evidence of survival benefits through ART initiation at higher CD4 cell counts ($\geq$500 cells/mm^3) in comparison to initiating at 350 cells/mm^3. The limited evidence of survival benefits is in agreement with similar studies in developed settings, particularly in Sub-Saharan Africa. Given that many patients are still initiating ART at low CD4 counts (Siedner et al. 2015); the improved outcomes observed in persons entering

HIV care at high CD4 cell counts suggests that optimizing pre-ART and early uptake into HIV care services may better optimize clinical implementation.

There have been three major observational studies from developed settings examining the predictive value of CD4 cell count on mortality outcomes at time of ART initiation (Cain, Logan & Robins 2011; Sterne, Hernan & Ledergerber 2005; Kitahata et al. 2009). Nonetheless, smaller studies in Sub-Saharan Africa have also shown improved survival associated with ART initiation in the lower CD4 cell count strata (Mills, Bakanda & Birungi 2012). Our findings add to the evidence that despite improved survival in lower CD4 cell count strata, there is limited evidence to suggest this trend holds true in higher strata.

The observed improvement in survival outcomes in patients linking to care early indicate that a safe deferral strategy for ART initiation may be possible in regions where ART uptake remains poor so long as efforts are made to engage and retain patients in pre-ART care services. However, our study has demonstrated that in higher functioning health systems like Rwanda, patients can be linked and retained in care prior to the initiation of ART with good survival outcomes. The pre-ART program in Rwanda includes a variety of clinical and social support. Interventions to improve the retention of patients in pre and on ART care in low- and middle-income settings have been synthesized elsewhere (Govindasamy et al. 1903). In Rwanda, these may include a responsive national surveillance system (Kayibanda et al. 2011), universal health coverage (Lu et al. 2012), task shifting of healthcare providers (Shumbusho et al. 2009), performance-based financing (Zeng et al. 2014), strong donor support (Asiimwe, Rwiyereka & Kaufman 2010). Particularly strong access and availability to healthcare services, may explain the successful uptake of the program. This is best observed among the high proportion of men accompanying their female partners to

ANC. While this has been encouraged throughout most of Sub-Saharan Africa, the uptake in Rwanda (~85%) has been much higher than in other settings (on average ~45%) (Jennings et al. 2014). Lastly, Rwanda has demonstrated remarkable leadership and strong governance supporting an understaffed, under-resourced health system with observable population-level health improvements.

Nevertheless, linkage to clinical care from the point of testing remains low in Rwanda (Mugisha et al. 2014; Nsanzimana, Kanters, Remera, Forrest, et al. 2015), as in many Sub-Saharan African countries (Kranzer et al. 2010; Nsanzimana, Kanters, Remera, Forrest, et al. 2015) and a greater effort must be made to improve the integration of HIV testing, treatment and care services (Kranzer et al. 2010; Nsanzimana, Kanters, Remera, Forrest, et al. 2015).

These analyses do have limitations. One is that there is no single data source that can inform all stages of the cascade of HIV care and the health seeking pathways between them in Rwanda. We collated data sources in order to quantify engagement at each stage and predict mortality along the cascade. A lack of understanding of the cause of mortality prohibits this analysis from making conclusions on the attribution of HIV and AIDS along the cascade. However, the successful collation of several sources of data to demonstrate how nationwide routine surveillance and monitoring can be used to inform the proportion of engaged patients and mortality along the cascade of HIV care at the national level represents a strength of this study. Another strength of this study includes the nationally representative sample and large sample size. The current analysis is also based on a large number of patients with a CD4 cell count at ART initiation above 500 cells/mm^3 (1,534; 15.7%). An important limitation is the potential presence of measurement bias

with respect to indications for initiating ART. Our sample includes a majority of patients who began ART with very low CD4 cell counts, although these proportions have changed over time.

In summary, our study found that the cascade of care is a non-linear pathway wherein patients have multiple opportunities to leave and re-engage in care. Understanding the points at which individuals are most likely to leave care may improve large-scale delivery of care. We also found that initiating ART at a CD4 cell count of $\geq$500 cells/mm^3 was not importantly associated with improved survival, while linking to care at CD4 cell counts of $\geq$500 cells/mm^3 was strongly associated with increased survival. These results should contribute to the discussion that earlier linkage to care even with a delay in ART initiation may result in substantial reductions in mortality in Sub-Saharan Africa.

CHAPTER 7. PHASED IMPLEMENTATION OF SPACED CLINIC VISITS FOR STABLE HIV-POSITIVE PATIENTS IN RWANDA TO SUPPORT TREAT ALL

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Key words: antiretroviral therapy; differentiated care; Rwanda; stable patients; Treat All

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7.1 Abstract

Introduction: In 2016 Rwanda implemented "Treat All," requiring the national HIV program to increase antiretroviral (ART) treatment coverage to all people living with HIV. Approximately half of the 164,262 patients on ART have been on treatment for more than five years, and long-term retention of patients in care is an increasing concern. To address these challenges, the Ministry of Health has introduced a differentiated service delivery approach to reduce the frequency of clinical visits and medication dispensing for eligible patients. This article draws on key policy documents and the views of technical experts involved in policy development to describe the process of implementation of differentiated service delivery in Rwanda.

Discussion: Implementation of differentiated service delivery followed a phased approach to ensure that all steps are clearly defined and agreed by all partners. Key steps included: definition of scope, including defining which patients were eligible for transition to the new model; definition of the key model components; preparation for patient enrolment; considerations for special patient groups; engagement of implementing partners; securing political and financial support; forecasting drug supply; revision, dissemination and implementation of ART guidelines; and monitoring and evaluation.

Conclusions: Based on the outcomes of the evaluation of the new service delivery model, the Ministry of Health will review and strategically reduce costs to the national HIV program and to the patient by exploring and implementing adjustments to the service delivery model.

7.2 Introduction

Sub-Saharan Africa carries the highest burden of HIV, with approximately 70% of all people living with HIV worldwide living in the region. Despite major progress by governments, donors, and international and national implementing partners, access to antiretroviral therapy (ART) in Sub-Saharan Africa remains below the global average, with less than 50% of people living with HIV on ART, and coverage is considerably lower in some countries in the region (UNAIDS 2016c).

Rwanda is one of a few countries in Sub-Saharan Africa that has achieved high rates of HIV diagnosis and ART coverage, along with high rates of retention and medication adherence with viral suppression (Elul et al. 2013; NISR-Rwanda 2014). As of the end of June 2016, 164,262 people – 78% of all PLHIV in Rwanda – were receiving antiretroviral therapy. Retention in care is high, at 93% after 12 months on treatment, and viral suppression among those on ART and receiving a viral load is also high, at 86% at 12 months and 91.5% and 36 months post ART initiation (Lu et al. 2012). This progress is particularly remarkable given the backdrop of the 1994 genocide which left the health system in disrepair. In recent years, increased ART coverage has evolved with treatment guidelines recommending earlier initiation of ART (Binagwaho et al. 2014).

The successes of Rwanda's national HIV program are closely tied to a series of health system improvements made over the past 15 years, including a strengthened infrastructure, introduction of community-based health insurance, improved workforce skills, and training of community health workers to deliver preventive, diagnostic and therapeutic services at the village level (Group ISS 2015; WHO 2016; Binagwaho et al. 2014).

Despite successes, Rwanda faces new challenges and opportunities for increasing and sustaining access to antiretroviral therapy. In July, 2016 new guidelines were launched implementing "Treat All," under which all identified people living with HIV (PLHIV) would immediately begin ART irrespective of immunological or clinical status (WHO 2016). This new policy is expected to lead to major benefits in terms of reduced mortality, morbidity and new infections (TEMPRANO ANRS 12136 Study Group & The TEMPRANO ANRS STUDY GRP 2015; Group ISS 2015; Cohen et al. 2011), but challenges remain to national program to significantly increase the number of PLHIV receiving ART: there are more than 17,000 individuals who were in pre-ART care by June 2016. An estimated 10% increase in the number of PLHIV needing treatment in Rwanda following the shift to Treat All will add additional PLHIV who need continuous access to ART; With an annual HIV incidence of 0·27% (95% confidence interval: 0·18-0·36%), additional HIV positive individuals are anticipated to enter care each year (MoH-Rwanda 2015).

The national ART coverage target to reach 81% (the second "90" of the UNAIDS 90-90-90 targets) (UNAIDS 2014) of PLHIV on ART is expected to be achieved by the end of June 2017, with an estimated 92% of PLHIV enrolled in care and 82% on ART. Nevertheless, approximately half of the 164,262 patients on ART have been on treatment for more than five years, and long-term retention of patients in care is increasingly a major challenge for the national program. These two challenges of increasing enrolment and ensuring long-term retention have pushed the Ministry of Health of Rwanda to implement new operational strategies. These include reorganizing the existing patient flow and the frequency of clinical visits and the collection of medication from the pharmacy. Patient flow has been simplified by removing two steps - registration and vital signs regular checks at HIV clinic reception, clinic consultation for file records; the pharmacist at each

clinic has been trained to capture key information required before delivering ARVs at each pick up visit in a short time; and unnecessary visits have been removed such pre-treatment and regular counselling sessions.

Previous ART guidelines recommended clinic visits every three months for medical consultations, monthly medication pick up, monthly adherence counselling, and every three months visit for psychosocial support. The latest ART guidelines, issued in July 2016, recommend differentiating ART delivery, with spaced clinic visits and pharmacy pick up for patients who are stable on ART, with the anticipated outcomes of increasing efficiencies at the site level for the benefit of patients and clinical staff, leading to sustainable cost savings.

This article summarizes the sequential policy actions taken towards phased implementation of spaced clinic visits for stable patients in Rwanda.

7.3 Discussion

Implementation of spaced clinic visits, as outlined in Figure 1 and detailed below, has followed a phased approach to ensure that the key steps were defined and agreed by all partners.

Figure 1: Reconfiguring service delivery to reach "the Second 90"

Definition of scope

The first step was to convene a national technical consultation, which was held in August 2015. This immediately proceeded the meeting of the WHO guidelines development group in which the evidence supporting spaced clinic visits was presented (Nsanzimana et al. 2017). The national technical consultation included representatives from the WHO, UNAIDS, researchers from the University of Rwanda, School of Public Health, international researchers, members of the national HIV technical working group, the umbrellas of civil society organizations in the fight against HIV and health promotion, the network of people living with HIV, private and public health facilities under the leadership of the HIV control program of the Rwanda Biomedical Centre (RBC), an implementing body of the Ministry of Health. At this August 2015 consultation, Rwanda adopted its new Treat All policy, which changed ART eligibility to all HIV-positive persons regardless of CD4 count. Rwanda also adopted definitions of a "stable patient" who would

be eligible for greater spacing between clinic visits – a strategy termed "differentiated care" that is designed to reduce transport, economic and logistic burdens of clinic visits on healthy patients, and thus promote greater long-term retention in care.

It was recommended that for the first phase of the new service delivery model a stable patient would be defined as "a PLHIV >15 years old who has been on ART for 18 months with two viral load results of less than 20 copies/ml using Amplicor HIV-1 DNA test v1.5. and who is considered adherent (defined ≥ 90% adhering to taking their self-reported ART medication) under ART guidelines". Under this initial definition, up to 85% of all PLHIV on ART would be defined as "stable." The last viral load will be considered as recent if the results were reported at least after 2 months after blood collection for the test. All adult clients on 2nd and 3rd line treatments requesting to be part of the differentiated ART model, and fulfilling the eligibility criteria, are further evaluated and, if they show adequate adherence to treatment and viral suppression, are enrolled in the new ART model. Similarly, in accordance with other existing national guidelines, all members of key population groups can be included provided they meet the general eligibility criteria.

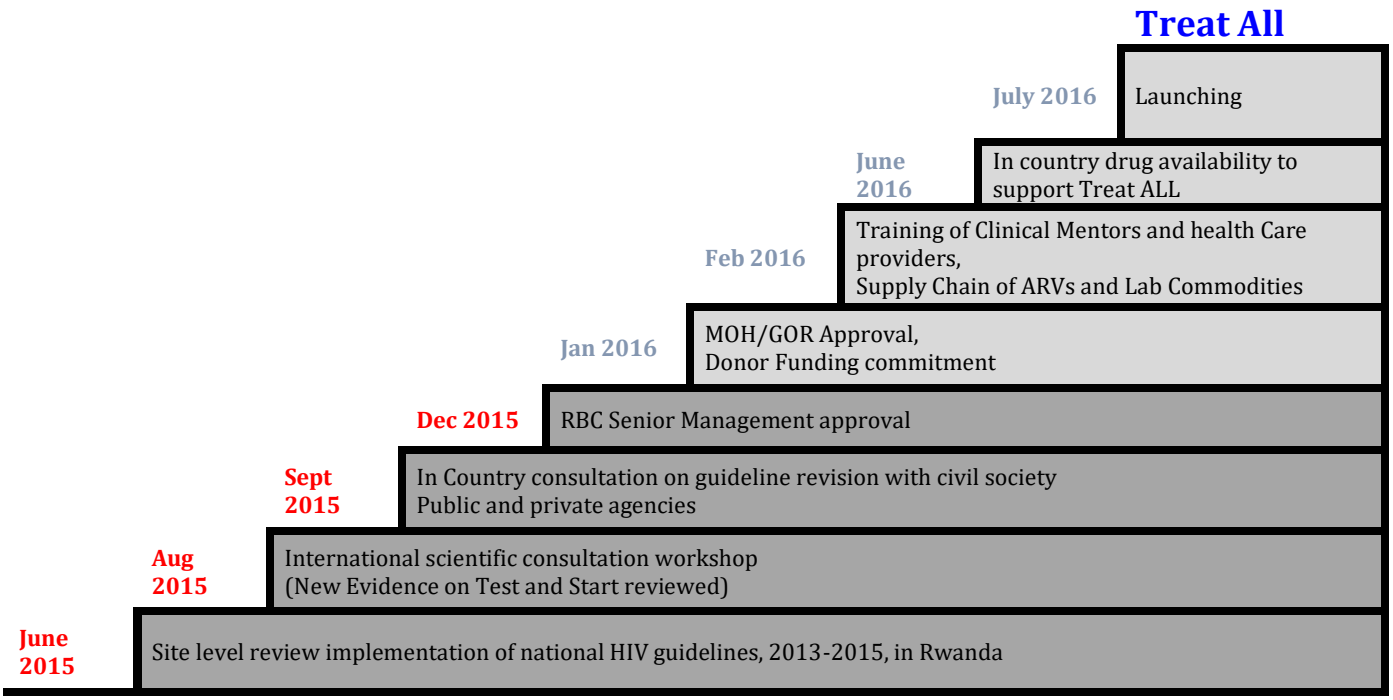
The following patients are currently considered non-eligible for the new model: all PLHIV clients on ART less than 18 months; patients on 2nd and 3rd line ART and not meeting adherence and viral load criteria; patients co-infected with NCDs such as diabetes, cancer, and heart disease in the intensive period of treatment until clinical symptoms are stabilized, pharmacy visit and laboratory visits will be coordinated with visits for their chronic conditions until patients is stabilized for that condition i.e. patients hospitalized or in acute phase management; malnourished PLHIV (calculated body mass index/ Height for Weight and excessive loss of weight below 10% of the normal value) in nutrition follow up services; all HIV positive clients who have TB and/or

hepatitis (C and B) co-infections until after six months of ARVs treatment; and children under 15 years of age defined by the national HIV guidelines as paediatric patients. Patients in this category will follow the standard ART guidelines: three monthly medical consultations, monthly medication pick up, monthly adherence counselling, and three monthly psychosocial support.

Definition of the Differentiated ART Model

With the introduction of the Treat All recommendations and the expanding availability of ART (Figure 2), it is anticipated that the majority of people will present to care earlier and require less intensive clinical care (UNAIDS 2016a). To reflect the different needs and preferences of different groups of PLHIV, and to reduce an unnecessary burden on the health system and multiple clinical visits for patients, the Rwandan national HIV program adopted a differentiated model for ART service delivery.

Figure 2: Implementation of "Treat All" in Rwanda



The model aims to delink clinical visits from ART refills visits for stable patients by decreasing patient clinical visits to once every six months and pharmacy pick-up for medication visits (both ARVs and OIs prophylaxis) to once every three months (Jain et al. 2014; Bemelmans et al. 2014). Pharmacy visits will be spaced from one to three months, and clinical visits from three to six months for patients defined as stable (Babigumira et al. 2011; Nakiwogga-Muwanga et al. 2014) . Further, the length of adherence counseling sessions prior to initiating ART for patients who present well will be reduced from three to one to allow a rapid ART initiation for the newly identified patients – within seven days and with the possibility of same-day start – consistent with recent evidence (Rosen et al. 2016; Pilcher et al. 2017; Mutasa-Apollo et al. 2017) (**Table 1**).

Table 1: "Standard of Care" vs. New Service Delivery Model

Group	Services	Standard of Care	New Service Delivery Model
Stable patients*	Clinical visits frequencies	3 months	6 months
	Medicine pick ups	1 month	3 months
	Counseling sessions (prior ART initiation)	3 sessions	1 session
	Peer support, CHWs	No	Yes
Specific populations: Pregnant women, Key populations, Children <15 years, 2nd, 3rd lines, and TB or HB/CV co-infection	Clinical visits	3 months	3-6 months (Case by case)
	Medicine pick ups	1 month	1-3 months (Case by case)
	Counseling sessions (prior ART initiation)	3 sessions	2 Sessions

*Stable patients are defined as: >15 years old, on ART for 18 months with two viral load results of less than 20 copies/ml, and evidence of adherence to ART

Preparation for enrolment in the new model

Selection of stable patients for the new ART model is anticipated to take a month. High volume sites will enrol patients in cohorts (i.e. groups of patients attending the clinics at the same time) and these facilities will take a maximum of three months to enrol all patients in cohorts. The clinics can organize a reasonable number of cohorts given total number of patients (20-30) per cohort.

Health providers at health facility level will use patient registers and patient charts to classify patients receiving ART in different categories including: patients eligible for the new model; patients non-eligible for new model; and special considerations (pregnant and breastfeeding women, adolescents, patients with non-communicable diseases (NCDs), patients with other co-infections, and other considerations to be addressed on a case-by-case basis).

Health providers, supported by clinical mentors, will coordinate routine clinical consultations, planned medicine pickup with laboratory visits to reduce visit frequencies for patients. During the preparation phase, health providers will register stable patients (those eligible for the new spacing model) who have the same day visits and group them as a cohort. These patients/cohorts will be required to attend clinic on the same day to receive the same services.

Patients eligible for new ART delivery model are required to participate in one to two education and counselling sessions. During these sessions, health providers assess willingness to participate in the model, explain the benefits and risks related to the model, and summarize how the model works (how patients will be seen - either separately or in groups; coordination for different visits; community providers' interventions; when patients move from one location to another, and so on). If eligible patients are pregnant women, adolescents, or patients with any chronic diseases that have a different consultation schedule, education sessions are adapted to a particular group, focusing on challenges for that specific group and how ART model will be aligned with the exiting conditions.

In parallel, support has been provided to community HIV services platforms to improve linkage and retention in treatment and adherence for all PLHIV including children born to key populations. At the community level, community healthcare workers and volunteers refer children to health facilities for HIV services. Facilities also work with community structures, including support groups and peer educators, for adherence support promotion, and retention in care.

Considerations for specific populations

Pregnant or breastfeeding mothers on ART will require different follow-up and health providers need to coordinate their clinical and pharmacy visits with ANC or PMTCT visits on a quarterly basis. A different frequency of clinic visits for pregnant women is used from the

beginning of pregnancy until the end of the breastfeeding period. At the end of breastfeeding period, pregnant and breastfeeding mothers who meet all other eligibility criteria can then be enrolled in the new ART model. However, follow up of exposed and infected new born and younger children remains a special case requiring more regular contact with health services, both at the clinic and in the community.

Due to school routines and other competing priorities, adolescents at schools are scheduled for pharmacy and clinical visits every three months, timed with school break periods. All adolescents in school continue in this model until the end of their secondary education and at least 19 years of age. After this time, they are transitioned to the spacing model as adult patients provided all other eligibility criteria are met. Adolescent out of school are be considered on a case-by-case basis based on virological, adherence and socio-economic criteria.

Engagement of implementing partners

Civil society and the private sector have been engaged to provide inputs through a civil society organization (CSO) consultation held in February 2016. This meeting engaged numerous community partners and their constituencies, including the NGO umbrella groups for health CSOs and PLHIV, as well as the CCM Secretariat, UNAIDS, and MOH/RBC. A second consultation was held during a mid-term review of the national ART program in June 2016. During this process, civil society groups and implementing partners were encouraged to voice concerns on the new ART and service delivery model. Concerns were raised about implementation considerations: Increase of lost to follow up while contacts to clinics will be spaced- quality of household storage of drugs and associated losses or misuse.

In mid 2016 the RBC conducted a series of consultative meetings and workshops with health care providers, clinical mentors, district pharmacy directors, local leaders and community

health workers. The objective of this consultation process was to seek support and feedback for the implementation of the new service differentiated model. During these consultations, experience sharing from the providers helped RBC to refine implementation steps including for example, the need to increase the storage space at the District Pharmacies.

Securing political and financial support

The recommendations from the technical working group were presented to the Minister of Health, Minister of State for Public health and Primary Health Care, and the Permanent Secretary for Health, for agreement in December 2015. Following this, a costed plan was presented to US President's Emergency Plan for AIDS Relief (PEPFAR) to request US$4 million one-time additional central funding to cover the transition to three-month drug pick-ups nationally for stable patients and the related supply chain monitoring in order to increase the national buffer stock to support the rollout of the three-month drug pick-ups. PEPFAR approved US$3.67 millions of this request in June 2016 during PEPFAR's Country Operational Plan (COP) review meeting.

Since 2005, the funding allocation for commodities in Rwanda is done by using a "common basket" mechanism; largely depending on external donor contributions. Under the Coordinated Procurement and Distribution System (CPDS) all actors in quantification, procurement and distribution from government, bilateral and multilateral partners meet regularly to estimate the needs and submit their report to Resource Management Committee (RMC) of the CPDS. The RMC requests financial contributions from each partner. In 2016, Of the total needs for ARVs, laboratory commodities and drugs for opportunistic infections prophylaxis and treatment; PEPFAR contributed 26 million USD (not including the central funding amount), the Global Fund contributed 19 million USD while the government of Rwanda has been investing in supporting infrastructure, running costs and personnel for HIV supply chain systems.

Forecasting drug supply

The national HIV Quantification Committee drafted a supply plan for all ARV drug needs in Rwanda in December 2015. The quantification exercise was supported with the use of *Quantimed*, a quantification software tool developed by USAID's Strengthening Pharmaceutical Systems Project (Management Sciences for Health 2006), took into account the implementation of " Treat All " in July 2016, and the required levels of buffer stock to transition to spaced clinic visits and dispensing for stable patients. It was estimated that 196,933 patients would be started on ART in 2017. In order to implement the three-month drug supply policy within the supply chain system as early as possible, a one-time procurement of additional products was determined to be necessary to top up all health facilities so they have the required stock to administer to patients. Based on procurement and supply chain systems, it was estimated to consider six month's supply time for these additional quantities to be in place before the launch of the new guidelines.

Implementation of the three-month drug supply policy will occur as soon as the buffer stock was in place at facility level. In line with current practices within the national supply chain system, health facilities will calculate and order additional quantities necessary for subsequent orders. Additional shipments are needed for procurement to meet the demand on the national commodities supply due to the change in the service delivery model to three-month drug pick-ups. The cost of the entire ARV procurement needed to cover the transition was calculated at $US 3,677,180 USD. It was estimated that additional extra cost on other supply chain expenditures is minimal and could be managed within existing budget.

Ongoing monitoring of the supply chain on at least a quarterly basis will be put in place to adjust future shipments, monitor stock status, and avoid situations of expiry or stock out of medications. A full review of the implementation of the new policy and its effect on the distribution

and storage system by the new supply chain mechanism is planned within the first quarter of rollout. Outputs from this review will inform future decisions regarding inventory control and distribution and procurement, as well as the national quantification of commodities, in order to realize cost savings and ensure commodity security. Based on all of these factors, the implementation of the 3-month drug pick-ups is, planned to start in December 2016.

Revision of ART guidelines

The revision of comprehensive HIV guidelines in Rwanda is carried out every two years based on most recent evidence available and priorities for the country and is a broadly consultative process involving experts from national technical working groups, implementing partners, bilateral and multilateral funding partners involved in HIV response in Rwanda, and external experts. The revision and approval of the 2016 guidelines was concluded with the endorsement by the Ministry of Health. A nationwide training of health care providers was undertaken over a three-month period to ensure that at least two nurses in each of the 500 health centers in Rwanda were trained to implement the new guidelines. Trainings consisted of an overview on basics in HIV testing, treatment, and follow up, the benefits of the Treat All strategy, and evidence supporting differentiated service delivery and how best it can be implemented according to the country context. The trainings combined both expert presentations and groups discussions. At the end of each session, participants were encouraged to suggest improvements in the implementation plan. In addition, RBC has established clinical mentorship teams (1 nurse and 1 doctor) who received advanced training in HIV management, located at each district hospital and supporting all health centers in the catchment area. These teams provide continuous education and skills transfer to the nurses responsible for managing ART. At the end of each training, participants received a written

summary of the guidelines and the Ministry of Health issued an official letter to implement the new changes.

Dissemination and Implementation

Each health centre was tasked to assess the number of stable patients and clinical services implementing partners will contact sites regularly to ensure that all sites are implementing the new service delivery model according to the national guidelines. Health centers are supported by clinical mentors to identify stable patients ahead of implementation. Implementation will be phased to allow for adaptation as necessary. Starting in October 2016, stable patients having an appointment will be asked to come back after 6 months and will be told to keep coming monthly for their drug pick-ups only until the three-month drug pick-ups are aligned with the patient's new clinical visit schedule pending additional drugs for three months pick-ups are expected to arrive in December 2016. These two appointments are conducted in different offices and drug pick up at pharmacy takes approximately five minutes while clinical visit in a consultation room is estimated to 20 minutes per patient. With an estimated average of ten consultations a day per health care provider, the spacing of clinical visits is expected to result in the following benefits: reduced burden on the clinics; increased time and quality of care for cases that need more clinical investigation; reduced frequency of travel for patients; and reduced likelihood of inadvertent disclosure of status as clients will spend less time in clinic services.

On December 1, 2016 patients with appointments for ARVs will receive three month's supply if classified as stable and will be asked to come back one week before the end of their three-month stock. The transition to three-month drug pick-ups is expected to rollout over the course of three months so that at the end of the three-month period, beginning in December 2016, all stable patients will be receiving three months of drugs and will align one of every two three-month drug

pick-ups with one of the six-clinical visits (**Table 2**). During this period, special support will be needed to make adjustments in case issues arise.

Table 2: Roll out of 3-month ARV pick-ups for stable patients

	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17
Group A	3 months			3 months		
Group B	1 month	3 months			3 months	
Group C	1 month	1 month	3 months			3 months

Expected challenges include: stock outs (while additional bolus funding has been added to increase the buffer stock, adding an additional layer into the supply chain is a potential cause of stock out); loss to follow up (a potential negative effect of less frequent clinic contact); sharing of pills between patients; and issues of home storage of ARVs and confidentiality. To mitigate these anticipated challenges, a quantification and distribution team has been established and tasked to meet every two weeks to monitor implementation and report regularly to the leadership of the RBC and MoH for real time changes and decisions making. The technical working group will continue to discuss the role of community workers in implementation of the new model in the framework of peer support to the network of people living with HIV.

Implementation of the new model will be adaptive so that on a quarterly basis, changes may be incorporated according to information and data received during implementation. For example: three-month pick-ups may be better implemented in rural settings than in urban areas given high patients mobility in urban areas; if this is found to be the case, a two-month pick up may be proposed for such areas.

Monitoring and Evaluation

The National HIV program with support from PEPFAR through CDC and WHO has established a technical group in strategic information to design how the new model will be evaluated on technical performance and financial reporting. Rwanda has a good M&E infrastructure for HIV with the TRACNet database that has been operating since 2004 and has recently been successfully integrated into Health Management Information System (HMIS). Since 2010 The TRACNet/HMIS has an interoperability system with Electronic Medical Record (EMR) and captures most of HIV individual patient data from testing to enrolment and follow up, covering 305 health facilities out of 500 existing in Rwanda. These systems will provide key data to track progress in the implementation of Treat All and outcomes of the new service delivery (Nsanzimana, Remera, Kanters, Forrest, et al. 2015). Enhanced indicators will be included such as number of patients that came for clinical visits and drug pick-ups will be added in existing M&E systems. Financial indicators will be included based on visit and pick-up indicators, including case load of health workers and time spent to consult the patient.

7.4 Conclusions

Based on the success of the new service delivery model, the Ministry of Health will review and seek to further strategically reduce costs to the national HIV program and to the patient by exploring and implementing adjustments to the service delivery model. For example, moving to 12-month clinical visits and six-month prescription drug refills, and expanding the definition of "stable patient" to be more inclusive and reach more PLHIV. These and other modifications such as viral load results turnaround time, adherence measurement to the service delivery model will seek to support the continued delivery of ART as part of the national HIV program while maintaining quality.

CHAPTER 8. RETENTION IN CARE AMONG HIV+ PATIENTS ON SECOND LINE ART IN RWANDA: A NATIONWIDE REPRESENTATIVE SAMPLE

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Key Words: HIV, second-line antiretroviral therapy, treatment failure

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8.1 Abstract

Background: Currently, there is limited evidence on the effectiveness of second-line antiretroviral therapy (ART) in Sub-Saharan Africa. To address this challenge, outcomes of second-line protease inhibitor (PI) based ART in Rwanda were assessed.

Methods: A two-stage cluster sampling design was undertaken. 49 of 340 health facilities linked to the open-source electronic medical record (EMR) system of Rwanda were randomly sampled. Data sampling criteria included adult HIV positive patients with documented change from first to second-line ART regimen. Retention in care and treatment failure (viral load above 1000 copies/mL) were evaluated using multivariable Cox proportional hazards and logistic regression models.

Results: A total of 1688 patients (60% females) initiated second-line ART PI-based regimen by 31st December 2016 with a median follow-up time of 26 months (IQR 24-36). Overall, 92.5% of patients were retained in care; 83% achieved VL < 1000 copies/ml, 2.8% were lost to follow-up and 2.2% died. Defaulting from care was associated with more recent initiation of ART- PI based regimen, CD4 cell count <500 cells/mm^3 at initiation of second line ART and viral load > 1000 copies/ml at last measurement. Viral failure was associated with younger age, WHO stage III&IV at ART initiation, CD4 cell count <500 cells/mm^3 at switch, atazanavir based second-line ART and receiving care at a health center compared to hospital settings.

Conclusions: A high proportion of patients on second-line ART are doing relatively well in Rwanda and retained in care with low viral failure rates. However, enhanced understandings of adherence and adherence interventions for less healthy individuals are required. Routine viral load measurement and tracing of loss to follow-up is fundamental in resource-limited settings, especially among less healthy patients.

8.2 Background

According to the 2016 estimates of the Joint United Nations Program on HIV/AIDS (UNAIDS), 36.7 million people lived with HIV globally, and approximately half were on antiretroviral therapy (ART) (UNAIDS 2016c, 2016b). Sub-Saharan Africa (SSA), in particular, accounts for more than 80% of the global population of people living with HIV (PLHIV) (Kharsany & Karim 2016). Since the introduction of ART in 1996, there have been substantial declines in morbidity and mortality related to HIV (Kharsany & Karim 2016; Haas et al. 2015). Despite this achievement, a considerable number of people have failed to maintain a sustained virological and immunological response to ART (Biset Ayalew M, Kumilachew D, Belay A, Getu S, Teju D, Endale D, Tsegaye Y 2016).

The World Health Organization (WHO) recommends the use of a two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) backbone and a non-nucleoside/nucleotide reverse transcriptase inhibitor (NNRTI) as a first-line ART; and, in the off chance of treatment failure, proposes a switch to a second-line regimen composed of a ritonavir-boosted protease inhibitor (PI/r) with two NRTIs (WHO 2016). The number of PLHIV switching from first- to second-line ART regimens is increasing and this shift is related to several factors. Primarily, non-adherence to medication, as a result of, adverse events or non-continuous medication access was reported in many studies as the key cause of treatment failure (Hosseinipour et al. 2013). Additionally, as ART scale-up in SSA and elsewhere was initiated in 2004 (Kharsany & Karim 2016; Haas et al. 2015), more PLHIV began receiving treatment. Unavoidably, even under optimal circumstances, treatment failures will occur overtime, resulting in an increase in the number of individuals in requiring second-line ART. Other factors, such as increased resistance

testing, improved adverse events detection and enhanced country access to affordable medications will also likely contribute to improved accessibility to second-line ART (Haas et al. 2015).

Since the launch of second-line regimens in SSA, outcomes of large-scale national ART programs were assessed only in a few studies (Laurent et al. 2011; Nsanzimana, Kanters, Remera, Forrest, et al. 2015; Wilhelmson et al. 2016; Sherr et al. 2009; Bartlett & Shao 2009; Shao & Williamson 2012). Botswana and Rwanda are two countries in SSA achieving the highest ART coverage >80% (UNAIDS 2016c, 2016b). Of the estimated 220,000 PLHIV in Rwanda, 175,398(80%) were receiving ART by December 2016 (Nsanzimana, Kanters, Remera, Forrest, et al. 2015). Rwanda, for example, has demonstrated a high rate of patients on first-line ART (>90%) (Nsanzimana, Kanters, Remera, Forrest, et al. 2015). Similarly, the number of patients on second-line ART in Rwanda has also increased substantially in the last decade from 388 patients in 2007 to 7,390 by the end of December 2016, representing ~4% of all patients on ART. Given this progression, the purpose of this study is to assess the outcomes associated with the rapid expansion of second-line ART access in Rwanda (WHO 2006).

8.3 Methods

Study design and data sources

By the end of 2016, a total of 553 health facilities were offering HIV treatment in Rwanda. Among them, 513 had enrolled 7390 patients on second-line ART. Since the open-source electronic medical record (EMR) system was available in only 340 of the 553 health facilities, this constituted our sampling frame. A two-stage cluster sampling design was undertaken to randomly select 49 of the 340 eligible sites where all patients were considered for analysis.

A comprehensive list of health facilities providing second-line ART in Rwanda was compiled using the Health Management Information data hosted at the Rwanda Biomedical Center. This list formed the basis of our first sampling frame, which consisted of our randomly selected sample of health facilities. We restricted our selection to health facilities that had a fully functioning EMR system. There were no other expected differences with health facilities that were in the process of EMR roll out. Our stratification was balanced, enabling equal opportunity for the inclusion of urban, rural, small and big sites.

Our data source consists of electronic medical records. After selecting 49 sites, we determined the data sampling criteria to include all adult patients (aged 15years or older) on second-line ART. The total number of patient data used for the study was 1,689, representing ~25% of the total patients on second-line regimen in Rwanda. Since Rwanda is currently in the process of transferring HIV related data sources to a national electronic database, some data are still stored locally. Two authors (DS, VN) visited all 49 health facilities and extracted data backups from EMR local servers using *mysql* software and exported them to STATA version 14 to conduct the analyses.

Study population and definitions

Our study included patients aged 15 years or older, who had switched to second-line ART as of 31st December 2016. First-line ART regimens were composed of one NNRTI plus two NRTIs and second-line regimens were PI-based, in accordance with national guidelines. Two key possible reasons for change may be due to first-line treatment failure (virological and/or immunological) or the result of adverse-effects to any compound in first-line combinations or prior exposure to antiretroviral drugs. We defined *virological failure* as having a viral load (VL) > 1000 copies/mL after at least 12 months on first-line ART with self-reported good adherence to medication (>90%

no dose missed). Viral load failure was used as an approach to confirm *treatment failure*. The VL suppression threshold of < 1000 copies/mL and *undetectable VL* < 20 copies/mL were in accordance with the 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (WHO 2016).

We defined *retention* as alive and in care on second-line ART at the time of data collection (31st December 2016) and with no met criteria for loss to follow-up (having missed contact with the health facility during 3 consecutive months). Deaths were assessed using recorded medical data in the EMR, which included deaths that occurred outside of the health facilities. Deaths were recorded within the national mortality registry. Both viral suppression and loss to care (the reverse of retention) served as the outcomes. The explanatory variables for this analysis were all measured at the initiation of first line ART and included demographic variables (age, sex, marital status, body mass index (BMI), clinical variables (TB screening status, CD4 cell count, WHO stage, viral load, date of ART initiation, type of ART regimen), and health facility-level variables (type of health facility: district hospitals, health centers and referral hospitals).

Statistical analyses

Data are presented as medians and interquartile ranges (IQRs) for continuous variables and frequencies and percentages for categorical variables. Fisher's exact test was used to assess the association between outcome of interest (retention and viral load suppression) and each predictor. We used multivariate Cox proportional-hazards regression to analyse time to discontinuation (loss to follow-up or death) on second-line ART. The regression model included the following covariates: age, gender, CD4 cell count strata, WHO clinical stage, ART regimens, viral load, and type of health facilities at the time of first ART. The overall dataset contained only one case of missing value which was not considered for retention outcome. We controlled all different

antiretroviral backbones and PI based combinations for each individual patient to assess differences in ART formulations vis-à-vis retention and viral suppression.

The proportional hazard model test was used to ensure that the proportional assumption was met. For model selection, we used Aikaike Information Criteria (AIC) to identify the model that best-balanced parsimony and minimized residuals.

To model virological suppression, multiple logistic regression was used to analyse viral load suppression using the latest viral measurements. Finally, we calculated the probability of a subject not being suppressed given a set of predictors in order to obtain adjusted coefficients. The coefficients were expressed as adjusted odds ratios (OR). The model diagnostics were performed to assess the goodness of fit using Hosmer and Lemeshow test, deviance, and Pearson's Statistics. All analyses were conducted using STATA statistical software, version 14.

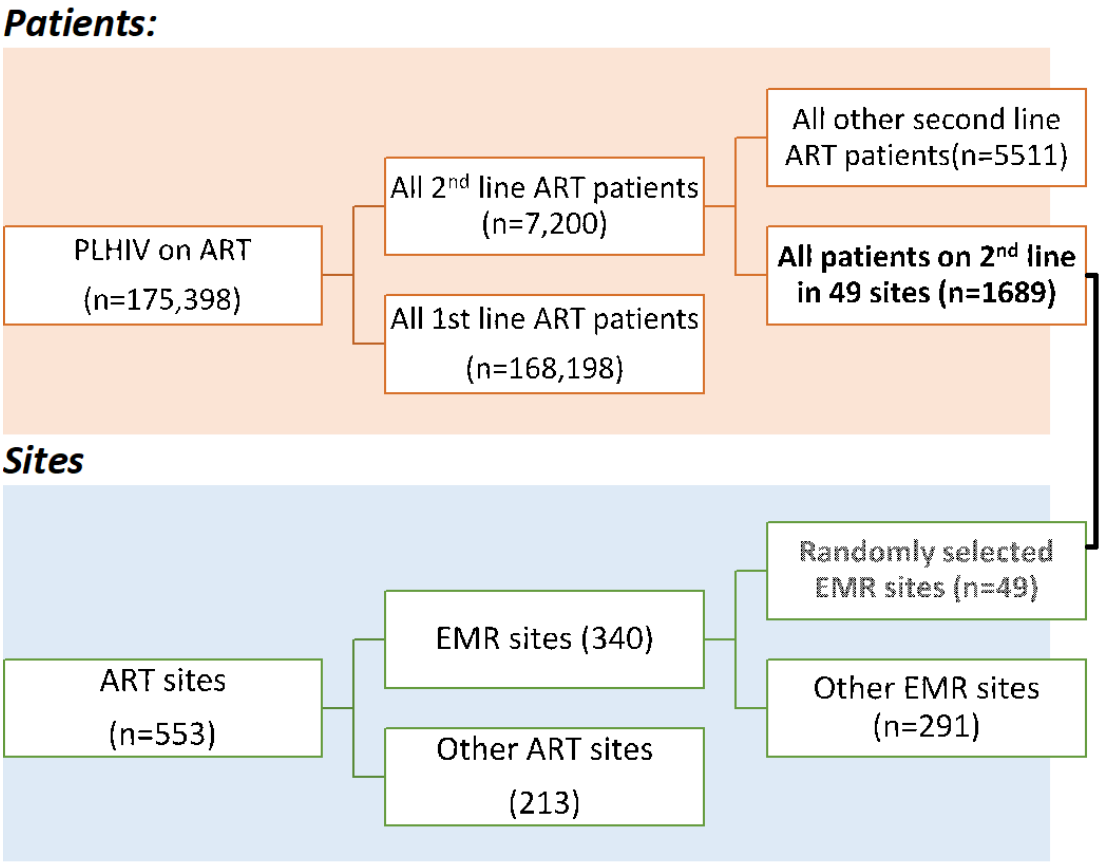
Ethical approval

Data used for this study were anonymized, routinely collected program data maintained by the Rwanda Biomedical Centre, Division of HIV/AIDS, STIs and Other Blood Borne Infections. The use of routine program data was approved by the Rwanda National Ethics Committee. The Rwanda Ministry of Health also granted approval for data access and use to the principal investigator (SN) for the purposes of improving program performance in Rwanda.

8.4 Results

Among the 181,921 (82.7%) individuals on ART in Rwanda (Nsanzimana, Kanters, Remera, Forrest, et al. 2015), 174,252 (95.8%) received first-line ART and 7,625 (4.2%) received second-line ART by 31st December 2016 (Shearer et al. 2017). Figure 1 presents a flow diagram of the second line ART Rwanda study sites and the patient selection process.

Figure 1: Flow diagram of Second line ART in Rwanda study sites and patients selection process



EMR: Electronic Medical Record system; ART: Antiretroviral; PLHIV: People Living with HIV

In our analysis, 1688 eligible patients were included, all of which had initiated second-line ART in 49 randomly selected health facilities representing ~25% of all patients on second-line ART nationwide. **Table 1** presents the baseline characteristics of the selected patients. There were more women (60%) in the sample.

Table 1: Baseline characteristics of patients on second-line ART in Rwanda stratified by retention and viral suppression

Characteristics	Total	Retained	Defaulting from care		Viral load suppression (copies/ml)		
		Alive	LTFU	Died	Total	<= 1000	> 1000
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
Median age (IQR)	41 (33,49)						
Age category(year)							
15-29	327 (19)	300 (92)	24 (7)	3 (1)	327 (19)	242 (74)	85 (26)
30-39	426 (25)	390 (92)	28 (7)	8 (2)	426 (25)	344 (81)	82 (19)
40-59	841 (50)	785 (93)	35 (4)	21 (2)	842 (50)	718 (85)	124 (15)
60+	94 (6)	87 (93)	2 (2)	5 (5)	94 (6)	84 (89)	10 (11)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
Sex							
Female	1031 (61)	952 (92)	55 (5)	24 (2)	1032 (61)	866 (84)	166 (16)
Male	657 (39)	610 (93)	34 (5)	13 (2)	657 (39)	522 (79)	135 (21)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
Marital status							
Single	344 (20)	309 (90)	27 (8)	8 (2)	344 (20)	259 (75)	85 (25)
Married/Cohabitating	648 (38)	602 (93)	30 (5)	16 (2)	649 (38)	540 (83)	109 (17)
separated/Divorced	98 (6)	89 (91)	7 (7)	2 (2)	98 (6)	86 (88)	12 (12)
Widowed	226 (13)	214 (95)	6 (3)	6 (3)	226 (13)	198 (88)	28 (12)
Missing	372 (22)	348 (94)	19 (5)	5 (1)	372 (22)	305 (82)	67 (18)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
ART Initiation period							
2009 and before	1062 (63)	1004 (95)	34 (3)	24 (2)	1063 (63)	892 (84)	171 (16)
2010-2012	502 (30)	447 (89)	44 (9)	11 (2)	502 (30)	400 (80)	102 (20)
2013-2016	123 (7)	110 (89)	11 (9)	2 (2)	123 (7)	96 (78)	27 (22)
Total	1687 (100)	1561 (93)	89 (5)	37 (2)	1688 (100)	1388 (82)	300 (18)
TB Screening							
Negative	1458 (86)	1356 (93)	75 (5)	27 (2)	1459 (86)	1213 (83)	246 (17)
Positive	151 (9)	138 (91)	8 (5)	5 (3)	151 (9)	111 (74)	40 (26)
N/A	79 (5)	68 (86)	6 (8)	5 (6)	79 (5)	64 (81)	15 (19)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
Body mass index							
Normal weight	964 (57)	894 (93)	50 (5)	20 (2)	965 (57)	783 (81)	182 (19)
Underweight	186 (11)	165 (89)	13 (7)	8 (4)	186 (11)	144 (77)	42 (23)
overweight & Obese	538 (32)	503 (93)	26 (5)	9 (2)	538 (32)	461 (86)	77 (14)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
Median CD4 (IQR)	418 (248, 618)						
> 500 cells/mm^3	638 (38)	606 (95)	26 (4)	6 (1)	638 (38)	599 (94)	39 (6)
<= 500 cells/mm^3	1050 (62)	956 (91)	63 (6)	31 (3)	1051 (62)	789 (75)	262 (25)

Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
WHO stage							
Stage 1-2	1042 (62)	971 (93)	51 (5)	20 (2)	1042 (62)	881 (85)	161 (15)
Stage 3-4	623 (37)	570 (91)	36 (6)	17 (3)	624 (37)	489 (78)	135 (22)
missing	23 (1)	21 (91)	2 (9)	0 (0)	23 (1)	18 (78)	5 (22)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
Second-line ARV regimen							
LPV/r +dual NRTI	1097 (65)	1011 (92)	55 (5)	31 (3)	1098 (65)	920 (84)	178 (16)
ATV/r + dual NRTI	591 (35)	551 (93)	34 (6)	6 (1)	591 (35)	468 (79)	123 (21)
Total	1688 (100)	1562 (93)	89 (5)	37 (2)	1689 (100)	1388 (82)	301 (18)
Median VL (IQR)	20 (20, 100)						
Viral load results							
<= 20 copies/mL	1056 (63)	1002 (95)	43 (4)	11 (1)			
21-1000 copies/mL	331 (20)	303 (92)	20 (6)	8 (2)			
> 1000 copies/mL	301 (18)	257 (85)	26 (9)	18 (6)			
Total	1688 (100)	1562 (93)	89 (5)	37 (2)			
Retention							
Retained					1562 (93)	1305 (84)	257 (16)
Not retained					126 (7)	82 (65)	44 (35)
Total					1688 (100)	1387 (82)	301 (18)

VL: viral load; TB: tuberculosis; BMI: body mass index; ART: antiretroviral therapy; WHO: World Health Organization; ATV/r: ritonavir boosted atazanavir; LPV/r: ritonavir boosted lopinavir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitors; IQR: interquartile range; LTFU: lost to follow-up.

The median age range was 35 - 44 years and approximately 38% of patients had initiated ART at WHO stage 3 or 4. The majority of patients (64%) had initiated second-line ART prior to 2010 resulting in median follow-up time of 26 months (IQR 24 - 36).

In total, 1562/1688 (92.5%) individuals were retained in care, 126 (7.5%) were loss to follow-up and 37 (2.2%) had died. Retention appeared to be lowest among those aged 25 -34 years, and among singles, and the least healthy. Retention was 89.0% in individuals who were underweight and 90.7% among patients screened positive for tuberculosis, and 90.4% among those with CD4 cell counts below 350 cells/mm^3 at initiation of ART.

In all 1688 individuals, at least one viral load result was available, regardless of whether patients had subsequently defaulted from care. Of these, 1387 of 1688 (83%) individuals were virologically suppressed (<1000 copies/ml) at last follow-up, whereas 1056 (63%) achieved undetectable viral loads (<20 copies/ml). Viral failure with VL > 1000 copies/mL was found in 301 of 1689 (18%) individuals. Of all those retained in care, a higher proportion were virologically undetectable at the time of the last available viral load test result compared to those lost to care (64% vs 43%). Virological failure was also higher among those who were lost to care (35% vs 16%). Retention in care was 94% for those who were virologically suppressed and 85% for those who were not suppressed.

Hazards for defaulting from care

The predictors of defaulting from care are presented in **Table 2**.

Table 2: Predictors of attrition and virological failure on second-line ART

Predictors	Multivariate analysis			
	Defaulting from care		Virological failure	
	Adjusted hazard ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Age category (years). Reference category Age 40-59 *				
15-29 years	0.85 (0.42, 1.71)	0.654	2.22 (1.46, 3.38)	<0.001
30-39 years	1.03 (0.58, 1.81)	0.930	1.45 (1.03, 2.05)	0.032
60+ years	1.87 (0.80, 4.38)	0.147	0.74 (0.36, 1.53)	0.421
Sex *				
Male vs. female	0.87 (0.53, 1.43)	0.585	1.07 (0.80, 1.43)	0.644
Marital status. Reference category single *				
Married/Cohabitating	0.48 (0.26, 0.90)	0.023	0.96 (0.64, 1.45)	0.857
Separated/Divorced	0.69 (0.24, 1.96)	0.487	0.56 (0.27, 1.14)	0.110
Widowed	0.57 (0.24, 1.34)	0.197	0.71 (0.40, 1.26)	0.242
Missing	0.31 (0.15, 0.65)	0.002	1.02 (0.68, 1.54)	0.916
ART initiation. Reference category 2009 and before *				
2010-2012	2.43 (1.47, 4.01)	0.001		
2013-2016	2.49 (1.00, 6.18)	0.049		
TB Screening. Reference category TB negative +				
Positive	1.26 (0.64, 2.49)	0.504	1.40 (0.92, 2.13)	0.117
No screening	3.04 (1.49, 6.22)	0.002	1.01 (0.54, 1.88)	0.979
BMI category. Reference category recommended weight +				
Underweight BMI<	1.94 (1.05, 3.57)	0.034	0.99 (0.66, 1.50)	0.965
Overweight BMI >	1.23 (0.73, 2.06)	0.432	0.80 (0.59, 1.09)	0.155
CD4 Category +				
< 500 copies vs. > 500 cells/mm^3	2.12 (1.20, 3.75)	0.009	5.40 (3.75, 7.77)	<0.001
WHO Stages. Reference category Stage 1-2 *				
Stage 3-4	1.22 (0.77, 1.96)	0.399	1.56 (1.18, 2.06)	0.002
Missing	0.49 (0.06, 3.73)	0.489	1.36 (0.46, 3.99)	0.574
Second-line regimen +				
ATV/r + 2 NRTI vs. LPV/r + 2 NRTI	0.52 (0.29, 0.93)	0.027	1.48 (1.12, 1.95)	0.005
Viral load suppression +				
> 1000 copies/mL vs <1000 copies/mL	2.95 (1.83, 4.76)	<0.001		
Health facility types +				
HC vs. RH/PV	0.93 (0.52, 1.65)	0.799	1.55 (1.11, 2.17)	0.010
DH vs. RH/PV	1.23 (0.68, 2.22)	0.496	0.92 (0.63, 1.34)	0.653

variable measured at initiation of ART, + variable measured at switch to second line ART.
CI: confidence interval; DH: district hospital; HC: health centre; PH: provincial hospital; RH: regional hospital; TB: tuberculosis; BMI: body mass index; ART: antiretroviral therapy; WHO: World Health Organization; ATV/r: ritonavir boosted atazanavir; LPV/r: ritonavir boosted lopinavir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitors.
BMI categories: underweight=< 18.5 kg/m^2, normal weight=18.5-24.9 kg/m^2, overweight& obesity =25 kg/m^2 or greater

These included ART initiation period from 2010-2012 and from 2013-2016 relative to 2009 or earlier (adjusted hazard ratios [HR] 2.43, 95% confidence interval [CI] 1.47 - 4.01 and HR 2.49, 95% CI 1.00-6.18), CD4 cell count < 500 cells/mm^3 vs CD4 cell count > 500 cells/mm^3 at initiation (HR 2.12, 95% CI 1.20 - 3.75), lopinavir/ritonavir (LPV/r) vs. atazanavir/ritonavir (ATV/r) based second-line regimen (HR1.91, 95% CI 1.08 - 3.40) and viral load > 1000 copies/ml vs < 1000 copies/ml at latest measurement (HR 2.60, 95% CI 1.71 - 3.94). In addition to these clinical variables, being married or cohabitating with a partner, relative to being single, was protective of defaulting from care (HR 0.48, 95% CI 0.26-0.90).

Risk factors for virological failure

The following risk factors were associated with virological failure in multivariate analysis: Age groups 15-29 years and 30-39 years compared to age group 40-59 years (adjusted odds ratios (OR): 2.22, 95% CI 1.46 - 3.38 and OR 1.45, 95% CI 1.03 - 2.05), CD4 cell count <500 cells/mm^3 vs. CD4 count > 500 cells/ mm^3 at ART initiation (OR 5.40, 95% CI: 3.75 - 7.77), WHO stage III & IV care compared to WHO stage I and II at program enrolment (OR, 1.56, 95% CI 1.18 - 2.06), ATV/r compared to LPV/r based second-line regimen (OR 1.48, 95% CI 1.12 - 1.95) and receiving care at a health center relative to regional or provincial hospital (OR 1.55, 95% CI 1.11 - 2.17).

8.5 Discussion

Our study is the first to report on retention and viral load outcomes using a national representative sample of second-line ART patients in Rwanda. We found that, overall, a high proportion of patients were retained in care after a median follow-up of 26 months. The estimated 92.5% retention was higher than that reported in previous studies in similar settings (Wilhelmson et al. 2016; Assefa et al. 2011). High retention in care in the Rwanda HIV program was also previously reported (Nsanzimana, Kanters, Remera, Forrest, et al. 2015; Ndahimana et al. 2016). Several possible reasons for high rates of retention in care include the highly decentralized health system that provides easy to access HIV services (98% of health facilities in Rwanda offer integrated, comprehensive HIV services). Further, there is a strong network of PLHIV that supports peer adherence to medication including home visits, awareness and education activities in the communities. In addition, Rwanda has a robust electronic monitoring and surveillance system that allows early warning signs of lost to follow-up, which initiates home visits by health care providers. Finally, health care seeking behavior in the Rwandan PLHIV population is high (Nsanzimana, Kanters, Remera, Forrest, et al. 2015).

Our study identified key factors associated with defaulting from care: initiating at higher viral loads, low CD4 cell count, less clinical engagement, and time of treatment switch. Other studies from SSA and Asia have investigated predictors of attrition in care (Ajose et al. 2012; Wilhelmson et al. 2016; Boettiger et al. 2015; Hosseinipour et al. 2010; May Myat Win et al. 2011). Across many settings, loss to follow-up on second-line patients was significantly higher among those with low CD4 cell count at baseline, and previously undiagnosed treatment failure on a first-line regimen (Wilhelmson et al. 2016; Boettiger et al. 2015; Fox et al. 2010; Hosseinipour et al. 2010; May Myat Win et al. 2011; Kanters et al. 2017; Laker et al. 2014; Ongubo et al. 2017;

Smith, Jeganathan & Ray 2006; Jobanputra et al. 2015). Other findings in similar settings reported that advanced disease at initiation was associated with attrition on second-line ART, and is likely the result of mortality (Johnston et al. 2012), as well as higher viral load and age (Boettiger et al. 2015). Studies from Malawi (Hosseinipour et al. 2010), Thailand (May Myat Win et al. 2011) and South Africa (Fox et al. 2010) reported that adherence was the major determinant of treatment failure.

In this study, viral suppression rate (VL< 1000 copies/mL) among second-line patients in Rwanda was estimated to be 83%. This rate is consistent with similar results observed in other resource limited settings with an average of 80% viral suppression after 12 months on second-line ART (Ajose et al. 2012; Wilhelmson et al. 2016). Results obtained from this study are generally consistent with other studies in developing countries. For example, the pooled proportion of virological failure in a recent systematic review and meta-analysis on second-line ART in low- and middle-income countries was 23.1%, 26.7% and 38.0% at 12, 24 and 36 months, respectively (Ndahimana et al. 2016). In many settings, virological failure was observed in the first 6 months following second-line ART start (Ndahimana et al. 2016). However, the reported results had large variations between studies and comparison of treatment failure might be difficult due to different cut offs used for viral load suppression across countries.

Patients who were lost to care were more likely to be viraemic than patients who were retained in care – a finding observed also by others (Stinson et al. 2014). This has important implications for evaluating progress towards the UNAIDS 90-90-90 targets. For instance, assessing virological suppression (the third 90) only among patient retained in care will overestimate success unless losses to care are taken into account.

In Rwanda, a previous study reported that only 23% of patients presenting virological failure (> 1000 copies/mL) had drug resistance mutations suggestive of third line ART, though 77% with high viral load could still remain on efficacious second-line therapy (Ndahimana et al. 2016, 2015). This reinforces the need for intensive adherence for patients presenting suboptimal viral load suppression before switching to costly and complicated salvage therapies. The same challenge was also reported in other resource-limited countries (Ajose et al. 2012; Jobanputra et al. 2015; Ndahimana et al. 2015).

The HIV program in Rwanda has made major shifts since 2009, when no new drug classes were available for cases of virological failure (20). The new recommendation was implemented in 2013, when LPV/r based regimens were replaced by ATV/r based regimens. In our analysis, patients who started anti-retrovirals after 2010 had better retention on ART, yet no better VL outcomes.

For this study, we controlled the distributions of backbones for both LPV/r and ATV/r. There was equal distribution of zidovudine, tenofovir and abacavir for each PI-based combination; lamivudine was maintained across all second-line regimens as per national guidelines. Patients treated with ATV/r were significantly more likely to experience virological failure. A recent systematic review of six randomized controlled trials on the comparative efficacy of second-line ART did not find a difference in efficacy between LPV/r or ATV/r plus two NRTIs and LPV/r with raltegravir. Although ATV/r had a greater numerical efficacy compared to LPV/r, differences were not statistically significant (Kanters et al. 2017). Another study conducted in Uganda (Laker et al. 2014) compared LPV/r and ATV/r in patients failing first line ART (2NRTI+1NNRTI) and confirmed comparable potency and efficacy. Being on LPV/r was twofold associated with defaulting from care, which could be due to the higher pill burden and adverse gastro-intestinal

drug reactions associated to LPV/r causing low adherence to medication (Al-Dakkak et al. 2013). A recent study in Malawi among patients receiving ATV/r also reported that bilirubin levels predicted VL failure (Ongubo et al. 2017). ATV/r prescription with related increased bilirubin has been associated with high interpatient disparities with hyperbilirubinemia and jaundice resulting into premature discontinuation of atazanavir and subsequently impact on virological outcome (Smith, Jeganathan & Ray 2006).

A major strength of our analyses is the relatively large sample size corresponding to 25 % of all people living with HIV on second-line ART in Rwanda. We also used routinely reported data that reflects more precisely the everyday life of patients. In addition, we had few missing data and all our patients had at least one viral load measured in the last 12 months on ART. Data were collected from a diverse population of patients in large, medium and small sites. In addition, we managed to successfully demonstrate how nationwide routine surveillance open MRS data could be used to inform on patients' retention and viral load suppression.

Our study also has several limitations. First, the data was collected from an open electronic medical record system for which individual patient-level data were routinely reported. As such, not all desired variables were available – most importantly adherence to HIV medication and outcomes among those lost to care. Second, we could not distinguish reasons for switching to second-line ART other than virological failure. Third, the sampling population only included 340 of the 513 health facilities with second-line patients. Thus, there is a risk of selection bias innate to the data availability. Finally, as with all observational studies, confounding through unmeasured covariates need to be considered when interpreting the reported associations.

8.6 Conclusions

In conclusion, our study suggests that patients on second-line ART within Rwanda are doing relatively well, with high levels of retention in care and viral suppression. A better understanding of adherence and adherence interventions for those that are less healthy is required. Importantly, routine viral load measurement and tracing of loss to follow-up is fundamental in resource limited settings in order to minimize the risk of treatment failure.

8.7 Declarations

Ethics approval and consent to participate

The use of the routine program data was approved by the Rwanda National Ethics Committee. The Rwanda Ministry of Health had also granted approval for data access and use to the principal investigator (SN).

CHAPTER 9. TREATING MULTICLASS-RESISTANT HIV+ PATIENTS IN RWANDA USING A PUBLIC HEALTH APPROACH

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This paper has been submitted to scientific journal for review

9.1 Abstract

Background: In Rwanda, third line ART has been introduced in 2012 for all patients with virological failure on first (NRTIs) and second line (PI) based regimens. We aimed to characterize the outcomes of these patients over 5 years on integrase inhibitors based treatment.

Setting: Rwanda has a mature HIV epidemic, with 3% prevalence and 82% of all people living with HIV receiving ART. Individual patient data were collected from medical records in all health facilities offering this therapy.

Methods: We collected data from all individuals who ever started third line anti-retroviral therapy between June 2012 and September 2017 in Rwanda and calculated the proportion of patients achieving viral suppression at 12 and 24 months on therapy. Genotyping was conducted in all patients at baseline.

Results: In total, 53 Patients started third-line ART and were followed for a median of 43 (IQR 29-54). Overall, 93.3% and 90.9% achieved VL less than 1000 copies/ml after 12 and 24 months respectively. The regimen was well tolerated with 8.8% of participants experiencing severe adverse events and 90.9% self-reported good adherence. The majority of patients were susceptible to raltegravir and ritonavir boosted darunavir.

Conclusion: Overall, our findings demonstrate the feasibility of providing third-line ART in a routine program in resource limited setting; however, it raises concerns about patients who failed all available treatment options.

9.2 Introduction

The World Health Organization (WHO) recommends the use of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens in first-line antiretroviral therapy (ART) against HIV, boosted protease inhibitor (bPI)-based regimens in second-line ART, and integrase inhibitors in third-line ART (WHO 2016) . While the vast majority (≥90%) of the 16 million individuals currently receiving ART are on first- and second-line regimens, the number of people requiring third-line regimens continues to rise (WHO 2016). Most developing countries do not currently provide third-line ART because of limited data and high cost. We report outcomes from Rwanda's national HIV program, one of the first cohorts providing third-line ART in sub-Saharan Africa.

9.3 Methods

Rwanda's Ministry of Health has been providing eligible HIV patients with ART since 2004. By September 2016, 92% of 214,000 individuals with HIV were receiving ART on first-line and 4% on second-line ART, as depicted in figure 1. A total of 553 health facilities were offering HIV treatment in Rwanda. Among them, 23 had enrolled 53 patients on third-line ART using an open electronic medical record (EMR) system implemented in Rwanda since 2010. We included in our analysis all patients ever started third-line anti-retroviral therapy between June 2012 and September 2017 in Rwanda national HIV program. Our data source was electronic medical records. Two authors (ER, MR) visited all the third line health facilities and extracted data backups from EMR local servers using mysql software and exported them to STATA version 14 to conduct the analyses.

According to the national HIV guidelines, patients were provided with third line ART following virological failure on second-line regimens and selection of antiretroviral drugs based on genotyping results using Stanford HIV drug resistance database (Rhee et al. 2003). National

guidelines consider virological failure as two viral load results above 1,000 copies/mL separated by at least three months and a behavioural adherence intervention. We calculated the proportion of patients achieving viral suppression after third-line initiation regardless of the time treatment was initiated, using simple statistics for 95% CI to assess the difference between outcome variables and independent variables. Patients were censored at date of death, date stopping ART, or on September 30, 2017. We also calculated accumulated drug resistance mutations, self-reported adherence and treatment-limiting adverse events.

This study received approved by the Rwandan National Ethics Committee for analysis and publication of routine program implementation activities under Rwanda Biomedical Center.

9.4 Results

By end of September 2017, 53 patients were enrolled on third line of ART. The median age was 43 years (IQR 29-54) and 56.6% were female. Patients were on first-line ART for a median period of 44 (IQR 24-75) months and on second line ART for 46 (IQR 30-59) months. Patients were followed for a median of 36 (IQR 13-47) months on third-line ART. The median CD4 cell count at start of third-line was 196 cells/µL (IQR 75-329) and the median viral load decreased from 52,600 copies/ml at the initiation to 20.85 copies/ml for the latest viral load. Viral load results were obtained for 51 patients at baseline, 30 patients had at 12months, while 22 patients achieved 24 months on third line ART.

Overall, 93.3%, 90.9% of all patients achieved VL less than 1000 copies/ml after 12 months (N=30) and 24 months(N=22) on third line ART respectively. Only one patient died and no lost follow up. The proportion of patients with high viral load >1000 copies decreased from 82,3% at baseline to 6,7% at 12 months and 9.1% after 24 months on ART (**figure 2)**. Similarly, the median BMI increased from 20.4 [IQR: 15.9-24.6] to 22 [IQR: 19.6 - 25.8].

Genotyping was conducted in 83.8% of all patients across all reverse transcriptase and protease inhibitors prior to initiation of third line ART; 96.5%,63.4% and 75.8% of patients had two or more resistance mutations to NRTIs, NNRTIs and PIs respectively. 75.47% and 77.36% had at least one mutation on NRTI and NNRTI respectively. Overall, the majority of patients were susceptible to raltegravir and darunavir/ritonavir. All patients received a combination of boosted darunavir, raltegravir, etravirine and in addition +/- 2 NRTIs. Adherence was assessed in 44 patients at initiation of third line ART and 40 (90.9%) self-reported good adherence to medication. Overall, 93.3 % and 90.9% of patients achieved viral suppression < 1000 copies/mL at 12 and 24 months respectively (**Figure 2**); Overall the regimen was well-tolerated, with 8.8% of participants experiencing a treatment-limiting adverse events, including skin rash, gastro intestinal intolerance and hepatotoxicity.

9.5 Discussion

Our report exemplifies one of the first evaluations of third-line ART in Sub-Saharan Africa. We included in our analysis all patients who ever initiated third line ART in Rwanda. We found that overall viral suppression after 12 and 24 months was high given that these patients had already experienced failure on multiple various regimen. The reported 90.9% of patients achieving viral load less than 1000 copies/ml after 12 months was marginally higher than previously reported elsewhere (Meintjes et al. 2015; Mata-Marín et al. 2015; Prasitsuebsai et al. 2017). Our findings on virological suppression are consistent with other studies on multiclass resistant treatment outcomes using raltegravir, darunavir and etravirine in developed and developing countries as reported in South Africa, France, Mexico, and Thailand (Fagard et al. 2012; Mata-Marín et al. 2015; Prasitsuebsai et al. 2017; Meintjes et al. 2015). Our study identified that close to 10% of multi-drug resistant patients had virological failure after more than two years on third line ART.

Although, there is limited data available on virological failure in third line therapy; our findings are consistent with other studies with an average rate of virological failure ranging from 10-40% mainly due to poor adherence (Mata-Marín et al. 2015; Prasitsuebsai et al. 2017; Charpentier et al. 2012).

In this cohort, genotyping resistance testing was done in all patients who had failed second line PI based therapy to inform third line regimen selection. The majority of our patients were susceptible to raltegravir and darunavir, although etravirine (NNRTI second generation) has included in the national guidelines as part of third line combination; the possibility of resistance to etravirine after failing first generation of NRTI has been reported previously (Charpentier et al. 2012; Cotte et al. 2009; Scherrer et al. 2009) and merits further research. Overall, our findings demonstrate the feasibility of providing third-line ART in a routine program setting in contrast of clinical trials; however, it raises important questions about the future treatment options for patients failing available treatment in the context of resource-limited backgrounds. Important limitations of our study are related to the small number of patients on third line ART. In addition, this was retrospective analysis using routinely available data and thus we were not able to measure key factors that may have influenced treatment outcome.

9.6 Acknowledgments

The delivery and implementation of HIV services in Rwanda is supported by the Government of Rwanda and the Global Fund to Fight HIV/AIDS, TB, and Malaria. We thank Dr. Byiringiro Vianney and Madeleine Uwungutse for helping with the onsite extraction of medical records data. Preliminary results from this survey were presented at the Conference on Retrovirus and Opportunistic Infections (CROI) 2018, Boston, MA, USA. Abstract no 511.

Table1: Characteristics of study participants alive on third line antiretroviral therapy in Rwanda.

Characteristic	Baseline value	End point value (as of December 2017)
Current Age (yr)		
Median	43	
Interquartile range	29-54	
Female sex – n (%)	30 (56.6%)	
Education – n (%)		
No school	9 (21.43%)	
Primary school	24 (57.14%)	
Secondary school or more	9 (21.43%)	
Marital status – n (%)		
Married	29 (54.72%)	
Divorced-widowed	10 (18.87%)	
Single	14 (26.46%)	
HIV clinical stage at ART initiation– n (%)		
Stage 1	11 (20.75%)	
Stage 2	8 (15.09%)	
Stage 3	20 (37.74%)	
Stage 4	14 (26.42%)	
CD4 T-cell count at ART Initiation– cells/mm3		
Median	196	-
Interquartile range	75-329	-
Body-mass index (Initial)– kg/m2		
Median	20.4	23.1
Interquartile range	15.9-24.6	19.7-30.1
Body-mass index (current)– kg/m2		
Median	22.04	
Interquartile range	19.6 - 25.81	
First-line regimen used – n (%)		
TDF- Based	5 (9.43)	
AZT-Based	24 (45.28)	
D4T Based	18 (33.96)	
Others	6 (11.32)	
Second-line regimen used – n (%)		
2NRTI+LPV/r	37 (69.81)	
2NRTI+ATV/r	7 (13.21)	
Others	3 (5.66)	
N/A	6 (11.32)	

Third-line regimen used – n (%)		
DRV/r+RAL+ETV	31 (58.49)	
2NRTI+ DRV/r+RAL	13 (24.53)	
2NRTI+ DRV/r+RAL+ ETV	1 (1.89)	
Other PI + RAL + ETV	8 (15.09)	
Others		
Major NRTI mutations*		
None	13 (24.53)	
At least one	40(75.47)	
Major NNRTI mutations*		
None	12 (22.64)	
At least one	41(77.36)	
Major protease mutations*		
None	19 (38.00)	
At least one	34 (62)	
All three mutations combined		
None	11 (20.75)	
At least one	42 (79.24)	
Median Viral load	52.600 copies /ml (IQR: 7,380-153,000).	20.85copies/ml (IQR:<20 - 5320)

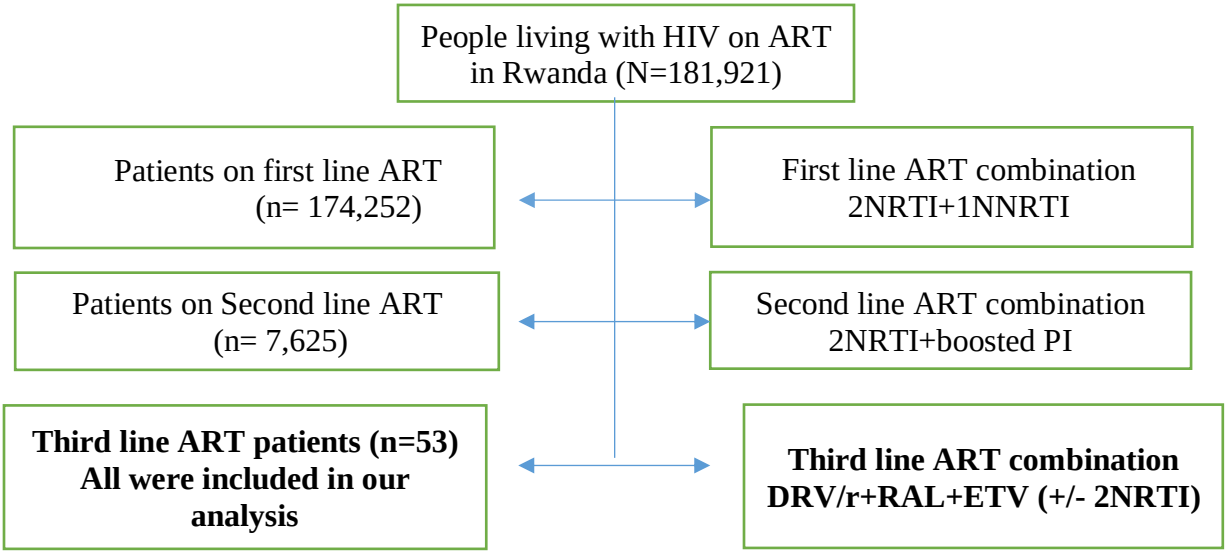
**Mutations were classified as major based on International Antiviral Society guidelines [6].*

Major NRTIs mutations (on the genotyping test result, thymidine analogue mutations are not specified rather nucleoside reverse transcriptase inhibitor mutations):
M46I, I54V, V82A, V75M, E44D, Y115F, G190A, M230L, F77L, I50V, L74I, F116Y.

Major NNRTIs mutations:
V118I/wt, K45I, K101H, Y188L, K311N, V2921I, K103N, A98G, V106I, V108I, Y181I, H221Y, G190A, Y318F, E138A, V179I, V189I, F227L.

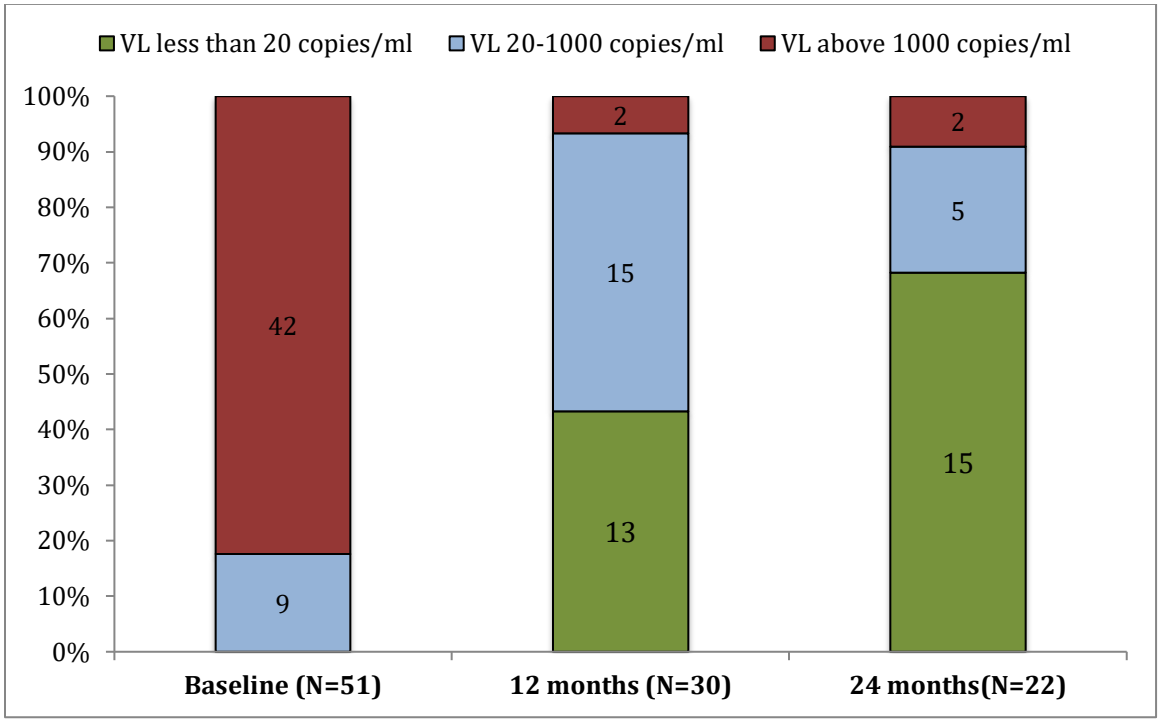
PIs major mutations:
L10F/wt, I13V/wt, I15V, M36I, K55R/wt, H69K, A71T, I93L, L33F, L24I, G73S, K20R, L63D, L38W, R41K, I64V, E35D, M46I, L24I, E35D, I93L, K20J, M461MV, G16E, K20R, H69K, K70R, T74S, L89I, K45R, E47A, M61I, I62V, E25D, I13V, I85V.

Figure 1: Flow of Patients on ART by regimen in Rwanda.



ART: Antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase; NNRTI: Non-Nucleoside Reverse Transcriptase; DRV: Darunavir; ETV: Etravirine; RAL: Raltegravir.

Figure 2. Viral load suppression at baseline,12 and 24 months on third line ART



CHAPTER 10: PROJECTED PREVALENCE AND INCIDENCE OF HIV AMONG FEMALE SEX WORKERS AND CLIENTS IN RWANDA: A MARKOV MODEL EXAMINING INTERVENTION EFFECTS

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10.1 Abstract

Background: Female sex workers (FSWs) and their clients are drivers of HIV epidemic in the Sub-Saharan African region. FSW have high prevalence rates of HIV and may engage in unprotected sex with multiple partners. Rwanda has identified FSWs as a key population to implement effective prevention strategies for HIV infection and for immediate antiretroviral therapy (ART) of infected FSW. Prevention strategies include education, access to male condoms, antiretroviral therapy for infected FSWs and pre-exposure prophylaxis (PrEP) for uninfected FSWs. Given constrained resources for HIV in Rwanda, it is important to understand how the incidence and prevalence of HIV among the FSW community is affected by different prevention efforts.

Methods: To estimate the effects of targeted prevention strategies on the HIV epidemic for FSWs and sex clients, we developed a dynamic Markov model to estimate the prevalence and incidence of HIV for FSWs and the residual community in Rwanda. Promotion of condom use as well as the expected widespread introduction of PrEP in 2019 were also incorporated. We considered the following six states: 1) HIV negative; 2) undiagnosed HIV; 3) diagnosed HIV without ART; 4) on ART with suppressed and 5) unsuppressed viral load; and 6) death. Our Markov model used national level demographic data, sexual sero-behavior data of the three populations, HIV associated morbidity and mortality to estimate the incidence and prevalence of HIV starting at 2017 with a time horizon of 10 years.

Findings: We observed the HIV epidemic being controlled with the current HIV treatment and prevention strategies that are in place at the national level. These efforts also prevented a spike in the HIV incidence and prevalence among FSWs and their male partners. Introduction of testing and improved ART coverage further mildly reduced prevalence among FSWs and sex clients,

whereas a worst-case scenario in coverage and testing had an opposite effect. A 30% improvement in condom use among FSWs reduced HIV prevalence by 6-7% over 10 years among FSWs and sex clients. Improvement in condom use among the general population reduced the prevalence by 0.24%. Lastly, introducing PrEP among female sex workers in 2019 with increasing coverage would reduce the incidence of HIV among FSWs by 50% in 2027.

Interpretation: Implementation of different prevention strategies offer differing preventive effects. The findings of our study have implications to other countries in Sub-Saharan Africa with concentrated HIV epidemic in FSWs.

10.2 Introduction

Female sex workers (FSWs) are a key population in the Sub-Saharan African HIV epidemic as they have a high prevalence of HIV, may engage in unprotected sex, and may have multiple partners. While there is some regional variation, the estimated HIV prevalence in the FSW population is 10- to 20-fold higher than in the general population (WHO 2011). In Rwanda the HIV prevalence among FSWs is estimated to be approximately 50% (Ngugi et al. 2012). In response, Rwanda has developed in the last two decades, a strong national response to control its HIV epidemic, including the FSW population (MoH/RBC-Rwanda 2012). It has made impressive achievements in HIV care through progressive treatment guidelines and reduced the number of new HIV infections by 50% and the overall number of AIDS related deaths by 78% from 2004 to 2014 (MoH/RBC-Rwanda 2012). The national prevalence of HIV has been stable at 3% as of 2013 (Nsanzimana, Kanters, Remera, Forrest, et al. 2015). However, the country still faces challenges with high concentrations of HIV in the FSW population; 46% of these women are estimated to be HIV positive (MoH/RBC-Rwanda 2015b), and HIV incidence among this population is 3.5% per 100 person-years (95% CI: 1.6, 5.4), compared with the general population incidence rate (0·27 per 100 person-years, 95% CI 0·18-0·35) (Nsanzimana et al. 2017; Braunstein et al. 2009). Given that FSWs are more likely to have multiple sexual partners and may engage in unprotected sex, targeted interventions within this community may yield important public health benefits.

Rwanda has specified efforts to test and treat HIV+ FSWs with antiretroviral therapy (ART) regardless of CD4 counts, in an effort to reduce HIV transmission (MoH/RBC-Rwanda 2012). Targeted efforts include an intensive prevention package for FSWs. Mobile services and outreach activities have been implemented to reach FSW populations regardless of their location or work environment (MoH/RBC-Rwanda 2012). At the facility level, services such as HIV counselling

and testing, family planning and sexual reproductive health services, STI screening and treatment, and condom provision are offered to FSWs (MoH/RBC-Rwanda 2012). Outreach involves hotel and bar-based services, street services, and opportunities to engage FSWs involved in incidental transactions (MoH/RBC-Rwanda 2012). Health care providers receive training to minimize stigma faced by FSWs and prevent avoidance for accessing health care services (MoH/RBC-Rwanda 2012). In addition, implementation of pre-exposure prophylaxis (PrEP) targeted at FSWs is currently being considered for the next revision of HIV and AIDS National Strategic Plan for the year 2019. This targeted intervention of PrEP along with the other efforts to increase utilization of other HIV services and ART coverage for FSWs will likely result in reduced likelihood of HIV transmission.

It is therefore vital to understand how the incidence and prevalence of HIV will be affected by Rwanda's specific initiatives for FSWs. Given constrained resources for HIV treatment and prevention services, it is important to estimate the prevalence and incidence rates of HIV over time for strategic planning. Using nationally representative and FSW specific data in Rwanda (Mutagoma et al. 2015; Nsanzimana et al. 2017; Nsanzimana, Remera, Kanters, Forrest, et al. 2015; Nsanzimana, Kanters, Remera, Forrest, et al. 2015; Nsanzimana, Remera, Kanters, Chan, et al. 2015), we developed a dynamic Markov model to estimate the prevalence and incidence rates of HIV amongst FSWs and sex clients over the next 10 years. In this study, we estimated the effects of ART, PreP and condom use based prevention strategies on the HIV epidemic in Rwanda. In particular, we examine the evolution of incidence and prevalence in the FSW population, male clients and in the overall population.

10.3 Methods

Model structure

We developed a nationwide dynamic Markov model (Aalabaf-Sabaghi 2007) for transmission of HIV from 2017 to 2027 to estimate the incidence and prevalence of HIV among FSWs, sex clients, and the general population in Rwanda. Our model includes national level demographic data, sexual and sero-behavioral information of the three populations, HIV associated morbidity, all-cause mortality, and HIV-related mortality. We considered the HIV transmission, testing patterns, adherence to ART, and their likelihood for viral suppression for FSWs, their male partners, and the general population. Finally, as introduction of PrEP to FSWs is expected in Rwanda by year 2019, the model assumes and captures an expected 40% PrEP up-take in FSW by the end of 2019 with a gradual increase to 80% PrEP use in the year 2027.

For each population, our Markov model considered the following six states: 1) HIV negative; 2) undiagnosed HIV+; 3) HIV+ virally suppressed on ART; 4) HIV+ not virally suppressed on ART; 5) HIV+ without ART; and 6) death. Here, state four represents a setting where under current ART regimen viral suppression is not achieved, and state five represents a setting where the patient has discontinued ART for the duration of the cycle. **Figure 1** displays the transition pathways between the six states. In addition, we retained transitions in from one population to another, remaining in the same state. That is, in each cycle some transition is accounted for from belonging to the general population and to engaging in sex work or buying sex, and some FSWs and clients disengaging from having paid sex and moving back to the general population risk scheme for acquiring HIV. A time horizon of 10 years was considered starting in 2017. Cycle duration was set to one year and transition probabilities derived accordingly.

Model parameterization

Population sizes movement between populations

The size of the three considered populations were obtained from recent nationwide surveys and are presented in **Table 1** (individual calculations for numbers in **Table 1** are outlined in **Supplementary Table 1**). The model also assumes an annual growth rate of 2.4% (UNAIDS 2016a) in Rwanda's population, as well as separate mortality rates for HIV negative individuals, undiagnosed or non-virally suppressed HIV+ individuals, and virally suppressed HIV+ individuals on ART (see **Supplementary Table 2**). Movement of individuals between the different population groups were considered as follows: We assumed that 47,644 active FSWs reside in Rwanda. We assumed that on average FSW would remain active for 10 years before retiring and, as a base case, that the number of FSWs would remain constant over the next 10 years (relative to country population growth). Identical entry and exit rates were assumed for male clients. For scenario analyses where the size of the FSW population was allowed to vary over time, the size of the sex client population was modified accordingly by holding number of sexual encounters and sex clients per FSW constant (the same as assumed for the base case, see below) and mathematically solving for number of sex clients.

Transmission between populations

We assumed HIV transmission occurs between FSWs and clients as well as between sex clients and their life time partners in the general population. We did not assume FSWs transmit directly to the general population. We assumed an average number of 52 sex clients per year per FSW, as well as an average number of 2.5 exposures (sexual acts) per client. HIV transmission probabilities were calculated using the equations provided in the Supplement (see section HIV transmission probabilities). This equation incorporates the size of each population, the HIV

prevalence in the client group, the average number of sexual exposures for each group, condom use or use of PreP, the risk of HIV transmission per sexual intercourse (unprotected and protected), and the type of intercourse (anal vs vaginal). The values assumed for these parameters are presented and justified in **Supplementary Table 2**.

Transmission between populations

The transition probabilities for the six states (**Figure1)** are presented and justified in **Supplementary Table 2**. These are derived from multiple nationwide surveys and longitudinal studies conducted in Rwanda (References provided in the appendix). In addition, general and Rwanda specific estimates of likelihood of adherence to ART is incorporated. The model was programmed in *R v.3.4.2,* and figures were produced using the *ggplot* package.

Model validation

We validated our model using data collected from 2010 (MoH/RBC-Rwanda 2010) and 2015 (MoH/RBC-Rwanda 2015b) on the prevalence for FSWs and the general population. The estimated HIV prevalence among FSWs were 51% in 2010 and 45% in 2017 (see **Supplementary Figure 1**). The HIV prevalence among clients was estimated to be 10% in 2015. The estimated national HIV prevalence has remained constant at approximately 3% over the past decade.

Analysis

We recorded the evolution of annual HIV prevalence and incidence from 2017 to 2027 in our Markov model. For each analysis, 1,000 simulations with multinomial allocations of people to different Markov states each year were performed. Base case scenario input parameters are all presented in **Table 1** as well as in **Supplementary Table 1** and **Table 2** as described in the methods section. We considered worst and best-case scenario analysis for key parameters related to testing behavior and ART coverage, condom use and PrEP uptake, as well as growth or decline

in the FSW population. The considered parameters and the assumed worst and best-case estimates are presented in **Table 2**.

10.4 Results

Model calibration is presented in Supplementary Figure 1. The projected 2015 prevalence estimates were nearly identical to the 2015 survey estimates.

Base case 2027 projections

The overall incidence rate of HIV (per 1000 person-years) over time in Rwanda is illustrated in **Figure 2**. With the current HIV testing and ART coverage, the annual overall population incidence rate decreases from 2017 (1.45 per 1000 person-years) to 2027 (1.17 per 1000 person-years). With the introduction of PrEP in 2019 the annual incidence decreases further with a notable additional decrease in 2020, and a continuing decrement to 1.05 per 1000 person-years) in 2027. The number of people living with HIV increases from 344,594 in 2017 to 394,869 by year 2027 (**Figure 3**), which corresponds to a 1.37% annual growth (note, the general population growth rate is 2.4%). With the current HIV testing and ART coverage, the annual incidence of FSWs living with HIV remains stable over the 10-year period. With the introduction of PrEP, the incidence among FSW decreases from 46.5 per 1000 years in year 2017 to 11.8 per 1000 years (**Figure 4**). The number of HIV positive FSWs decreased from 21,469 in 2017 to 15,006 in 2027 (see also **Supplementary Figure 2**). Among sex clients, incidence decreases from 19.5 per 1000 person-years in 2017 and 12.2 per 1000 person-years in 2027. The number of male partners infected with HIV rises from 24,631 to 26,183, corresponding to an annual growth of 0.6% (i.e., only a quarter of the annual overall population growth). The evolution of the number and proportion of FSWs and sex clients living with HIV in the base case scenario are presented in **Supplementary Figures**

2 and 3. Overall evolution of proportion of FSWs and sex clients in each of the six states for the base case scenario are presented in **Supplementary Figure 4.**

Scenario analysis

Table 2 presents the worst-case and best-case scenarios for 2027 prevalence estimates for the selected scenario analysis parameters. **Figure 5** presents the tornado diagrams illustrating each of the three populations' sensitivities to changes in the explored parameters (i.e., magnitude of change in results under the worst and best-case scenarios). For the parameter of testing and treatment, we observed the following trends: Increased testing for FSWs was associated with a small reduction in HIV among sex clients. Increased testing of the general population and national coverage of ART were associated with a reduction in HIV prevalence among FSWs and the latter was also associated with a reduction in sex clients. Finally, improved adherence to ART had a moderate impact on HIV prevalence in both FSWs and the general population, but a worsening in ART adherence was associated with a larger negative effect with increased HIV prevalence. Changes in testing or ART related parameters, however, never exceeded 1%. For use of condoms, the best-case scenario for increased use among FSWs reduces the prevalence by 7.76% (36.43% vs 28.67%) among FSW population and by 6.21% (18.66% vs 12.45%) among sex clients. In the worst-case scenario with decreased condom use among FSWs, however, the models estimate a 3.4-4.3% increase in HIV prevalence in both populations. An increase in condom among FSWs reduces the prevalence in the overall population by 0.1%. The best-case scenario of increased condom use in the general population leads to 0.17% absolute decrease in HIV prevalence in the overall population (i.e. a 6.4% relative reduction) but does not affect the prevalence among FSWs or male partners. Similarly, a worst-case reduction in condom use in the general population is associated with an increase in prevalence. The best-case scenarios for PrEP use among FSW results

in a 1.53% reduction in prevalence among FSW, whereas in the worst-case scenario a 2.95% increase in HIV prevalence can be expected. Best case scenarios for condom use and PrEP use yields the largest reduction in prevalence overall, and no further reduction is observed from added HIV testing, ART coverage and adherence under this scenario. However, in the worst-case scenarios for condom use and PrEP further increase in HIV prevalence will result if combined with worst case scenarios for HIV testing, ART coverage and adherence.

10.5 Discussion

Our findings highlight a number of key components for containing and reducing the HIV epidemic in Rwanda. First, a continued promotion of ART based prevention strategies, particularly in high-risk group like FSWs, is essential to stabilize the incidence and prevalence. Equally relevant, any worsening in these parameters would have severe negative consequences. Second, the expected introduction of PrEP will likely have a substantial impact on the incidence and prevalence of FS and clients and to a minor extent in the general population. Most notably, the incidence of HIV among FSWs is expected to halve over the next 10 years with the introduction of PrEP in 2019.

After implementing the test-and-treat strategy in 2016 Rwanda has observed drastic improvements in several HIV related outcomes. The national ART coverage and testing has increased considerably in the last decade. The overall number of people who are now aware of their HIV status and treated with ART has also improved. In combination, these measures have led to a stabilization of the overall HIV prevalence in Rwanda. Meanwhile, the annual percentage increment in overall number of people living with HIV (2.1%) is superseded by the annual population growth rate, resulting in a slight decrease in the overall prevalence. It appears that the continuing epidemic may largely be driven by the concentrated epidemic of HIV among FSWs

and their clients. However, it is important to recognize that accomplishments that with "treat all HIV FSW" policy implemented in Rwanda since 2013; without that, both the incidence and prevalence among FSWs and their male partners would have experienced a drastic upsurge.

As Rwanda prepares to plan for its fourth edition of its National Strategy Plan for HIV/AIDS, it recognizes the necessity for a continued focus on FSWs. Efforts to increase the testing of HIV in FSWs and ensuring lifelong ART in HIV positive FSW with provision at diagnosis will need to be continued, along with efforts to improve consistent condom use. Our model clearly shows that the latter will have a substantial effect on HIV prevalence in the FSW and general population. Promoting condom use among FSWs will dramatically reduce prevalence among sex clients over the next 10 years. Finally, the planned introduction of PrEP to FSWs in 2019 will have a substantial effect on the FSW population as the incidence of HIV drops drastically after its (modelled) introduction and continues to decline steeply. The individual prophylactic efficacy of increased testing and ART coverage, condom use, and PreP uptake among HIV negative FSWs hold much promise, and in the long run, may be the long-term strategy to control the HIV epidemic in Rwanda.

Our model and analyses have several strengths and limitations. Our model capitalized on access to rich up-to-date nationwide Rwandan specific data sources and interaction with the Ministry of Health officials who were available to provide the local context. As a result, the majority of transition probabilities are directly informed by data with high internal validity. This stands in contrast to many Markov models, where scattered data from several countries typically necessitate questionable assumptions to derive transition probabilities. The utilized data, however, are all cross-sectional and not representative of the local sub-populations of FSWs that may have different geographical challenges and constraints. There was also limited information on

behaviours of sex clients, and as a result, it was necessary to indirectly model these via the links to FSWs and the general population. To estimate the HIV transmission probabilities for our Markov model, we had to rely on self-reported data on sexual behaviors, which are likely subject to some bias. Lastly, our model did not include other key risk populations (e.g. men who have sex with men, male sex workers, and sero-discordant couples) in Rwanda.

Continuing to improve the quality and access of existing prevention and treatment interventions along with the new investment in PrEP in FSWs will likely have the largest public health impact on the HIV epidemic. While HIV care in Rwanda has been among the best in sub-Saharan Africa in terms of expanding ART coverage through investments in HIV infrastructure, it will require tremendous continued efforts. Introducing PrEP will require more resources, and this needs to be complemented and supported with other aspects of the HIV treatment cascade. Improving access and adherence to ART and condom use, along with achieving 80% coverage of PrEP are ambitious targets. Such efforts will require multi-sector response and coordinated participation and actions across all groups of stakeholders in Rwanda. Health care providers will need to receive continued training to minimize stigma and discrimination faced by FSWs in order to ensure that they will not avoid accessing key health care services such as regular HIV testing, PrEP, and ART. As well, economic empowerment and opportunities with educational support are also likely required for this key population to control the concentrated HIV epidemic (WHO 2011). Despite the progress made in containing the HIV epidemic in Rwanda, the concentration of the HIV epidemic remains high in marginalized groups such as FSWs. There have been limited investigations on FSWs. Future research that needs to be prioritized include FSWs' ability to negotiate condom use with their clients and ways to increase diagnostic testing of HIV and other STIs in FSWs. Existing barriers that affect FSWs' acceptability and adherence to ART and PrEP

should be explored and addressed to remove barriers that are institutionalized. This study has demonstrated the need for continued efforts to improve and expand the quality of existing HIV services (e.g. more testing and ART), as well the potential gain of adopting a targeted intervention strategy such as PrEP in FSWs and other key drivers of the HIV epidemic not only in Rwanda, but also in other Sub-Saharan African countries.

Table1: Sizes of the three populations and number of individuals within each state for each population

Parameter	Base value	Lower bound	Upper bound	Source
FSW population				
HIV- (State 1)	24,300	13,340	48,950	BBSS SW Rwanda 2015[5]
Undiagnosed HIV (State 2)	2,691	2,318	3,053	BBSS SW Rwanda 2015[5]
HIV+ with viral suppression on ART (State 3)	11606	4478	39236	BBSS SW Rwanda 2015[5]
HIV+ without viral suppression on ART (State 4)	2513	970	8496	BBSS SW Rwanda 2015[5]
HIV+ not on ART (State 5)	3,890	1,894	10,266	BBSS SW Rwanda 2015[5]
Total size	47,644	25,000	111,000	ESPHS Rwanda 2011[15]
Male partners population				
HIV- (State 1)	159,300	38,070	--	BBSS SW Rwanda 2015[5]
Undiagnosed HIV (State 2)	2,301	550	--	BBSS SW Rwanda 2015[5]
HIV+ with viral suppression on ART (State 3)	10,126	2,420	--	UNAIDS 2016[12]; Nsanzimana 2015[4]
HIV+ without viral suppression on ART (State 4)	2,193	524	--	UNAIDS 2016[12]; Nsanzimana 2015[4]
HIV+ not on ART (State 5)	3,080	736	--	UNAIDS 2016[12]
Total size	177,000	42,300	177,000	ESPHS Rwanda 2011[15]
Overall population				
HIV- (State 1)	11,589,295	11,559,295	11,609,295	NISR 2015[4]; UNAIDS 2016
Undiagnosed HIV (State 2)	20,000	18,182	22,727	UNAIDS 2016[12]
HIV+ with viral suppression on ART (State 3)	131,520	113,436	146,316	UNAIDS 2016[12]; Nsanzimana 2015[4]

Parameter	Base value	Lower bound	Upper bound	Source
HIV+ without viral suppression on ART (State 4)	28,480	24,564	31,684	UNAIDS 2016[12]; Nsanzimana 2015[4]
HIV+ not on ART (State 5)	40,000	22,000	62,000	UNAIDS 2016[12]
Total size	11,809,295	--	--	NISR 2015[4]

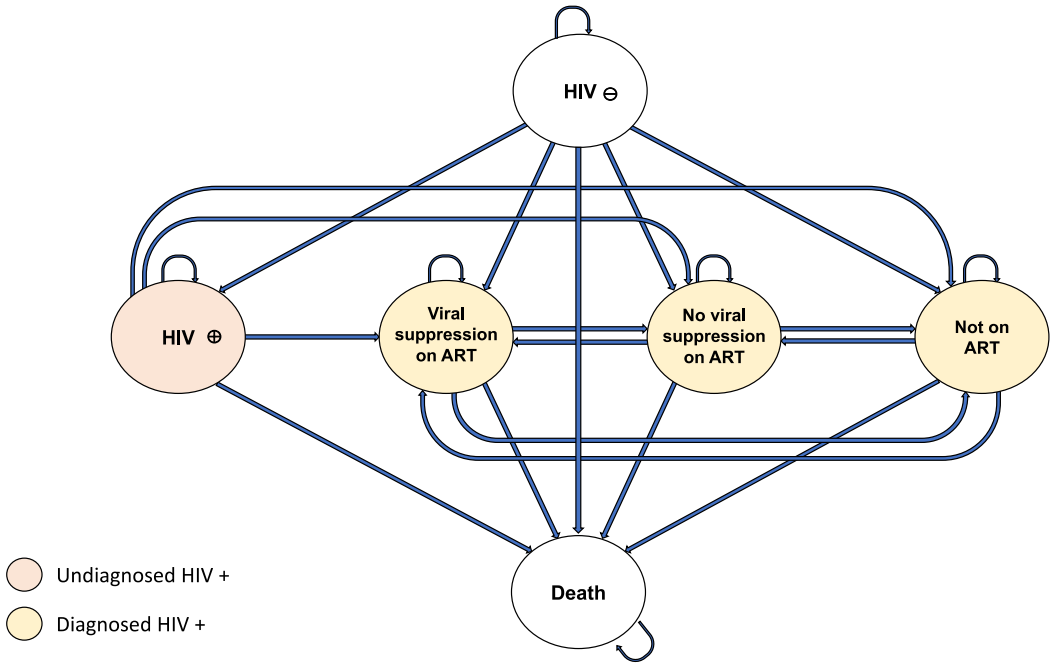
Table 2: Different scenario analyses on ART, condom and PrEP, and changes in the number of FSWs.

Description	Input			Output: Prevalence (%) at Year 2027								
				Female sex workers (FSWs)			Male partners			Overall population		
	Base case	Worst case	Best case	Base case	Worst case	Best case	Base case	Worst case	Best case	Base case	Worst case	Best case
Scenario 1: Changes in testing and treatment for ART												
A) Probability of HIV test for SW	0.71	0.50	0.90	36.43	36.43	36.43	18.66	18.75	18.60	2.64	2.64	2.64
B) Probability of HIV test for general population	0.46	0.30	0.80	36.43	36.75	36.06	18.66	18.61	18.69	2.64	2.64	2.63
C) % of national coverage of ART	0.80	0.60	0.90	36.43	36.68	36.32	18.66	18.79	18.59	2.64	2.64	2.63
D) % of consistent adherence to ART	0.90	0.74	0.95	36.43	37.41	36.01	18.66	19.74	18.17	2.64	2.69	2.61
E) Parameters above combined	--	--	--	36.43	37.87	35.48	18.66	19.91	18.06	2.64	2.70	2.60
Scenario 2: Changes in condom and PrEP use												
A) % of consistent condom use for SWs*	0.45-0.55	0.30-0.40	0.75-0.85	36.43	40.70	28.67	18.66	22.06	12.45	2.64	2.69	2.54
B) % of consistent condom use for General population	0.30	0.2	0.45	36.43	36.46	36.39	18.66	18.69	18.62	2.64	2.76	2.47
C) % of consistent PrEP use for SWs*	0.40-0.80	0.20-0.60	0.50-0.90	36.43	39.38	34.90	18.66	18.88	18.54	2.64	2.65	2.63
D) Parameters above combined	--	--	--	36.43	44.69	28.13	18.66	22.45	12.40	2.64	2.83	2.36
Scenario 3: Changes in number of FSWs												

A) Probability of women entering as a sex worker	0.0004	0.0008**	0.0002***	36.43	24.52	44.73	18.66	17.00	19.65	2.64	2.63	2.64
Combined scenarios												
A) Scenarios 1 and 2 combined	--	--	--	36.43	47.86	28.13	18.66	24.56	12.34	2.64	2.93	2.35
B) Scenarios 1, 2, and 3 combined	--	--	--	36.43	54.07	46.50	18.66	22.29	8.77	2.64	3.15	2.51

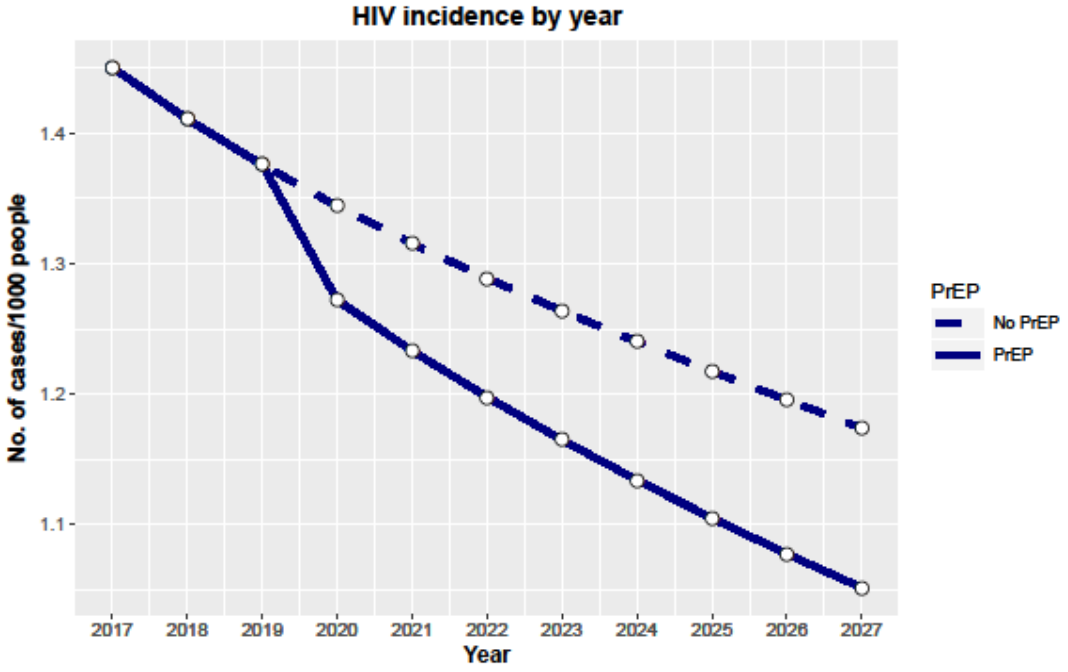
Prevalence (%) at year 2017: FSW = 45.1%; MP = 15.7%; Overall population = 2.9%
** Intervals represent starting point (2017) and end point (2027) assuming a linear increase over 10 years*
***2x times more young girls choosing to enter sex work assumed as the worse case*
****1/2 times less young girls choosing to enter sex work assumed as the best case*

Figure 1: Model structure for HIV transmission



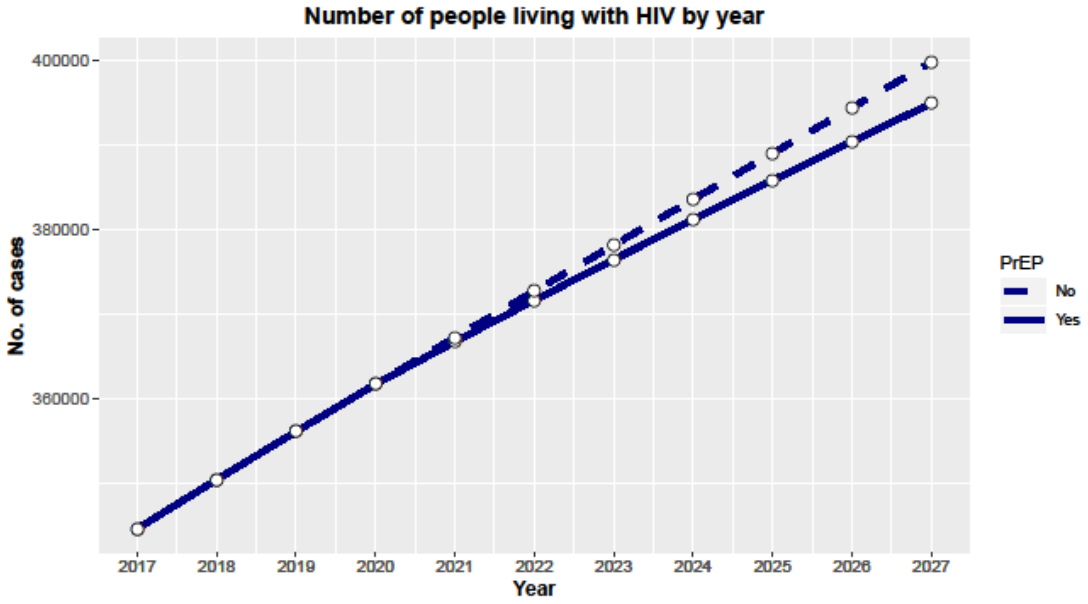
Acronyms: HIV, human immunodeficiency virus; ART, antiretroviral therapy; "+", positive; and "- ", negative

Figure 2: Overall HIV incidence over time with or without PrEP



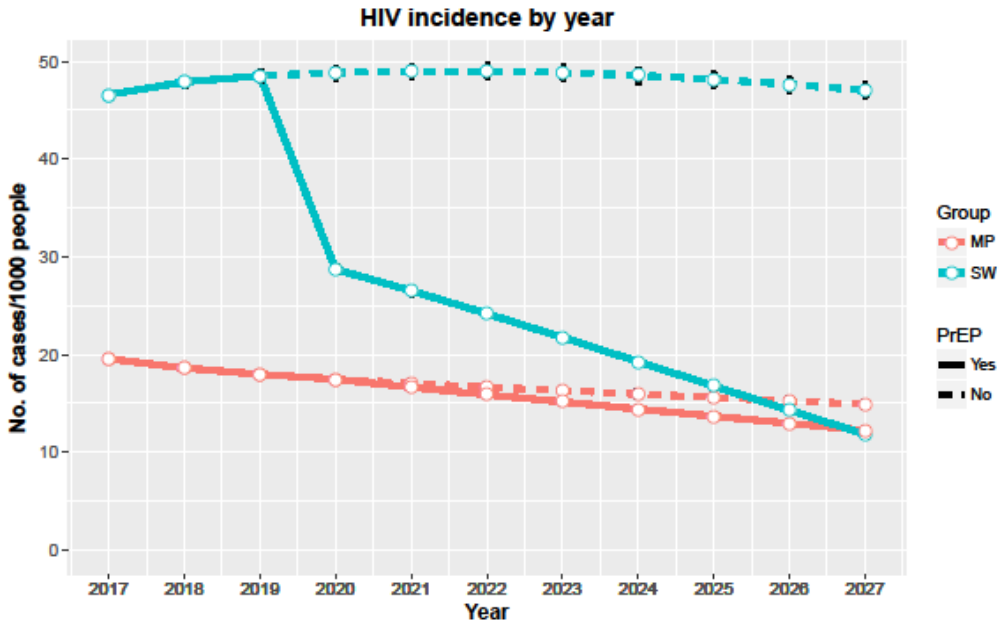
Acronyms: PrEP, pre-exposure prophylaxis

Figure 3: Number of overall population living with HIV



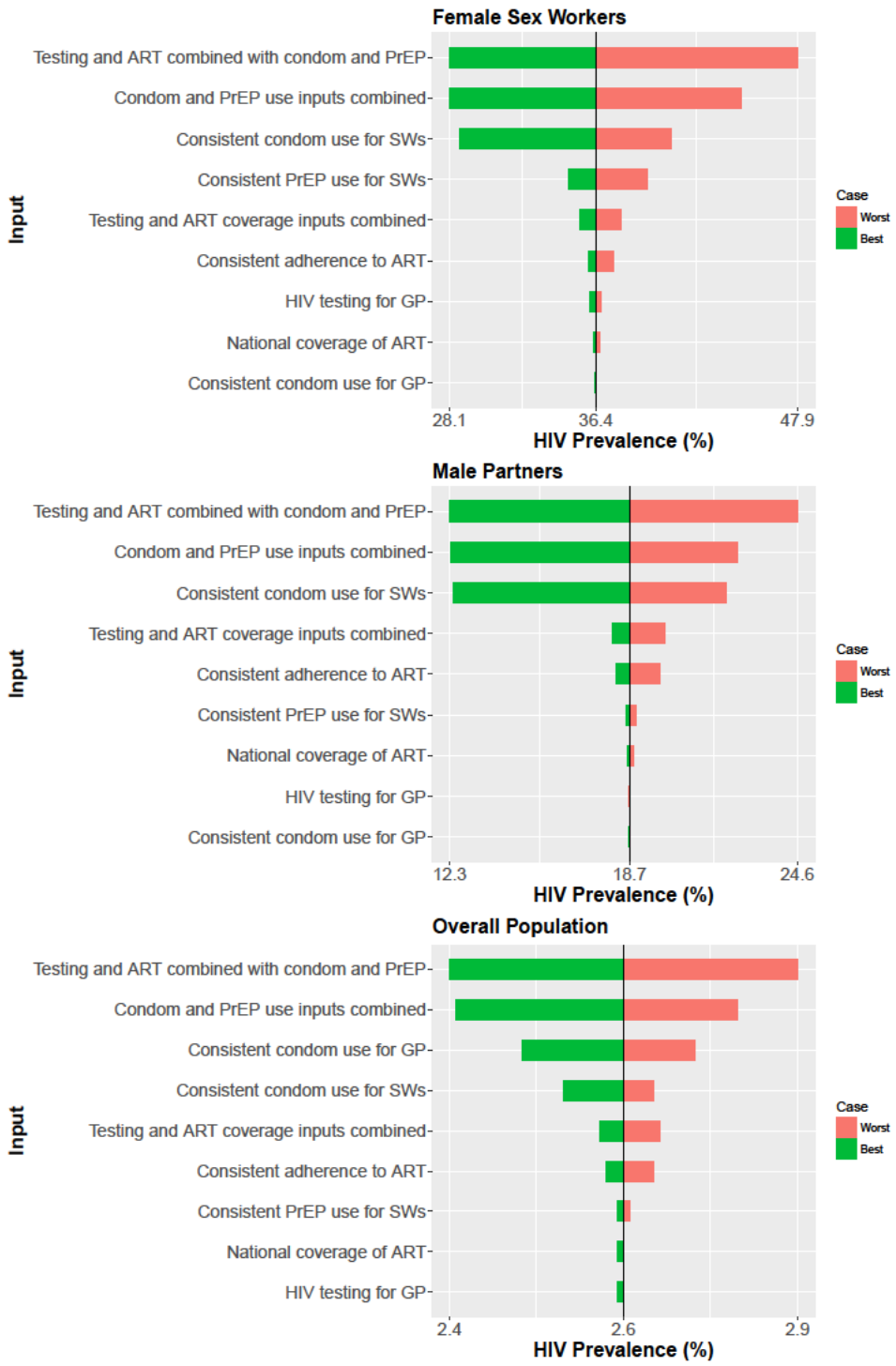
Acronyms: PrEP, pre-exposure prophylaxis

Figure 4: Incidences of HIV among FSWs and male partners over time with or without PrEP



Acronyms: PrEP, pre-exposure prophylaxis; MP, male partners; SW, female sex workers

Tornado diagrams for each population illustrating model sensitivity to worst-case/best-case changes on tested parameters.



Acronyms: PrEP, pre-exposure prophylaxis; MP, male partners; SW, female sex workers; GP, general population; ART, antiretroviral therapy

CHAPTER 11. GENERAL DISCUSSION OF THESIS

This thesis provides further evidence on linkage and retention to HIV care services in the Rwanda national HIV program. In this section, we synthesize and discuss main findings from studies presented in different chapters with implications for HIV control in Rwanda. We made recommendations for national HIV program improvement and future research to fill the gaps identified in this project. The present PhD project studied key areas of the entire national HIV program, focussing on parameters of HIV diagnosis and linkage to care, evaluation of clinical outcomes on first, second and third lines ART, and explorers the main drivers of the epidemic. The added value of the PhD project is in driving successful policy change from a deep exploration of the program's data.

In the aftermath of the genocide against the Tutsis in 1994, no one would expect a country like Rwanda to overcome several challenges related to the tragedy. As we described before (chapter 3), despite the situation, the program scaled up rapidly around main programs areas outlined in the national strategic plan on HIV and AIDS in a multisector response approach such as community awareness, HIV testing services, treatment and linkage to care, retention and adherence, evidence based to inform policy changes and ensuring uninterrupted supply of medicines.

After 2 decades, the program results were impressive, with more than 80% of people living with HIV accessing medication, new infections estimated decline more than 50% and AIDS related deaths dramatically reduced by 78% and consequently life expectancy among people living with HIV increased by 25 years. In addition, the country implemented strong data systems. Our main objectives were to identify the main programmatic gaps and fix them using deep analysis of routinely reported data.

11.1 Parameters of HIV diagnosis and linkage to care

Knowledge of HIV burden in Rwanda was not fully understood as demographic and health surveys conducted previously in 2005, 2010, and 2015 assessed only HIV prevalence and risk factors which limited proper policy decision making. Knowledge of HIV epidemic required better understanding of where and to whom HIV new infections, are coming from; measuring incidence provides an entry point to care and this stage was critical information the country needed. We therefore assessed for the first time the incidence of HIV in Rwanda in a longitudinal household survey (chapter 5). Our findings showed an estimated national incidence of 0.27 infections per 100 person-years (Nsanzimana et al. 2017). The incidence was comparatively lower than in other countries in the Eastern and Southern Africa (Braunstein, van de Wijgert & Nash 2009) , but the incidence was 50% higher than the UNAIDS Spectrum/EPP model estimated incidence of HIV in Rwanda (MoH/RBC-Rwanda 2015a). Surprisingly the overall prevalence of HIV assessed in DHS has been reported stable at 3% for more than a decade (Chapter 4). At several occasions, policy makers and scientists debated on such unchanged figure that could be only possible with a balanced mortality and new infections yet this was not fully studied. Two studies conducted in the preparatory phases of this PhD complimented this discussion providing new evidence on trajectory pathways of PLHIV from diagnosis, linkage to care, lost to follow up and deaths in the national program for pre-ART and on ART patients (chapter 6).

These studies provided more accurate data to understand the HIV epidemiology in the country, the importance of early diagnosis and linkage to care and informed future mathematical

model estimates and updated situation of HIV epidemic in Rwanda for better program planning. Concerning the areas of improvement identified in these studies. We found that the incidence of HIV was significantly driven by young adults and singles (chapter 5) who accounted for more than half of all new infections. Similarly, this paradox among adolescents was observed almost for all stages of the cascade of care (chapter 6) examining the transition probabilities of the HIV continuum of care in a cross-sectional analysis of the national program. Further in multi drug experienced patients, adolescents had sub-optimal adherence on first and second line therapy (chapter 9) suggesting that adherence interventions should be targeting this group in particular. Our results on measuring incidence showed that breakouts appear to be key contributor to HIV epidemic in Rwanda. Quantifying HIV incidence and prevalence is the first step to measure the HIV cascade of care.

A high proportion of patients entering care in Rwanda HIV program were retained and achieve high viral suppression rates (82%). The mortality was low both in pre-ART (0.6%) and on ART (1%) stages. Main risk factors for mortality include older age, CD4 count at initiation and male sex (Chapter 6). The issue of men adherence and retained in care in Rwanda was underestimated previously, while many countries struggled to achieve couple counselling and testing during antenatal care, Rwanda was the first country to achieve the highest proportion (85%) of males accompanying their wives for pregnancy tests in antenatal care. These studies demonstrated a real need for special programs targeting men and adolescents such as health clubs already tested in some US-PEPFAR supported countries.

In the pre-ART era, CD4 count have been used to measure treatment outcomes, we evaluated the effect of baseline CD4 cell count at linkage to HIV care and at initiation of antiretroviral therapy on mortality in HIV positive adult patients in Rwanda in a nationwide cohort

study (Chapter 6). Our results showed a strong association between mortality and increasing CD4 cell count at time of linkage to care. Although CD4 has been used previously used as a basis for initiation of ART, the benefits of early start of ART regardless of CD4 cell count were reported in different studies and clinical trials to inform new WHO guidelines (Mills, Bakanda & Birungi 2011; Cohen et al. 2011).

Our findings supported the changes in the Rwanda ART guidelines, in 2015 to treat all HIV+ regardless of CD4 cell count expected to substantially reduce mortality among people living with HIV in Sub-Saharan Africa. Nevertheless, surveillance of CD4 cell counts at HIV diagnosis and initiation of ART will still remain important to monitor whether more individuals are tested earlier and retained in care. Countries will need to build adequate capacity and quality of testing to meet the viral load requirements for monitoring treatment outcomes.

HIV program in Rwanda considered moving away from CD4 threshold even before WHO guidelines recommendations (chapter 9). The strategy was to shift to "treat all" particular groups of people in particular all pregnant women and children under five years of age in 2010. Key populations such as those with, HIV-TB, HIV- chronic hepatitis B and C co-infected patients in 2013 and finally widely adopted in 2015 to all people living with HIV. There is a need for innovative approaches to engage people and retain them in care under optimal adherence that requires real time program data, and adaptation of interventions to the need of patients as well as increased funding to HIV programs in Sub-Saharan Africa. Policy development and implementation do not always happen at the same track especially in resource limited settings.

Our policy study provided an example of different steps for consideration from guidelines adoption to implementation in the newly adopted recommendation in Rwanda to initiate ART for all HIV+ clients. The study detailed phased implementation of spaced clinic visits for stable HIV-

positive patients in Rwanda to support treat all. We described key policy developments and implementation of comprehensive differentiated service delivery such as definition of scope in national and international scientific consultations, categorization of patients to patients to transition from monthly to quarterly medicine pick-ups and clinical visits change from quarterly to bi-annual. We also assessed political, and financial implications especially for additional commodities required to implement the new guidelines. Our analysis resulted into a cost plan for additional $4 million to increase national commodities buffer stock which was funded by the United States President's Emergency Plan for AIDS Relief (PEPFAR).

Results from a systematic literature review conducted to assess the impact of reduced frequency of clinic visits and medication pick-up on antiretroviral treatment outcomes suggest that less frequent clinical visits led to better retention in care with no differences in virological and mortality outcomes comparing less and frequent visits (Mutasa-Apollo et al. 2017).

These findings compliment the Rwanda decision to implement a nationwide differentiated service delivery model whereby medical clinics for stable patients changed from quarterly to only twice a year and drug pick-ups from monthly to quarterly. Accelerating initiation to ART has been associated with better health outcomes. Not only treat all HIV+ is beneficial, immediate initiation could reduce the risk of lost to follow up and mortality among those with advanced disease and those at high risk of transmitting the virus (Ford et al. 2018; Ford & Nsanzimana 2016). These findings informed WHO and Rwanda ART guidelines recommendation on accelerated ART initiation, including the possibility of same day ART start.

Our data driven and policy analysis studies provide greater value to understand the HIV situation in Rwanda towards achieving UNAIDS 90-90-90 targets. However, our first cascade of care presented in chapter 6 was analysed at the beginning of this PhD project; it would be

worthwhile to examine what happens after 3 years since the current PhD's goal was to suggest improvements to the national HIV program where greatest needs are. The latest updates on HIV cascade of care for Rwanda is depicted in figure 1.

The UNAIDS suggested that by 2020, 90% of all people living with HIV should know their HIV status, 90% of those diagnosed should have access to ART and 90% of all people on ART should maintain viral suppression (the 90-90-90 targets) (UNAIDS 2014). These targets were based on the fact that the benefits of early initiation outweigh reasons for delay (Cohen et al. 2011) (The INSIGHT START Study Group 2015) (TEMPRANO ANRS 12136 Study Group & The TEMPRANO ANRS STUDY GRP 2015). As many countries struggled to implement strategies to reach the targets with only 66%, 77% and 82% achievements to first, second and third 90 respectively(UNAIDS 2017a). Rwanda has almost achieved each of those and now raising the bar to 95-95-95 by 2023 (MoH/RBC-Rwanda 2016). Of 224,664 people estimated living with HIV in Rwanda in 2018 (UNAIDS EPP 2018), 88% have been identified through comprehensive combination of strategies targeting key populations, pregnant women and their partners, and sero-discordant couples; implementation of HIV index testing for partners and family members of newly identified PLHIV and most recently launched HIV self-testing and HIV case based surveillance. These transformations contributed greatly to achieve almost the first 90, known as the hardest to reach and consequent linkages to ART and viral suppression may be affected. Nonetheless, the country has to find 26,644 HIV+ people not yet diagnosed and link them to care in addition to those who will continue to be newly identified HIV+.

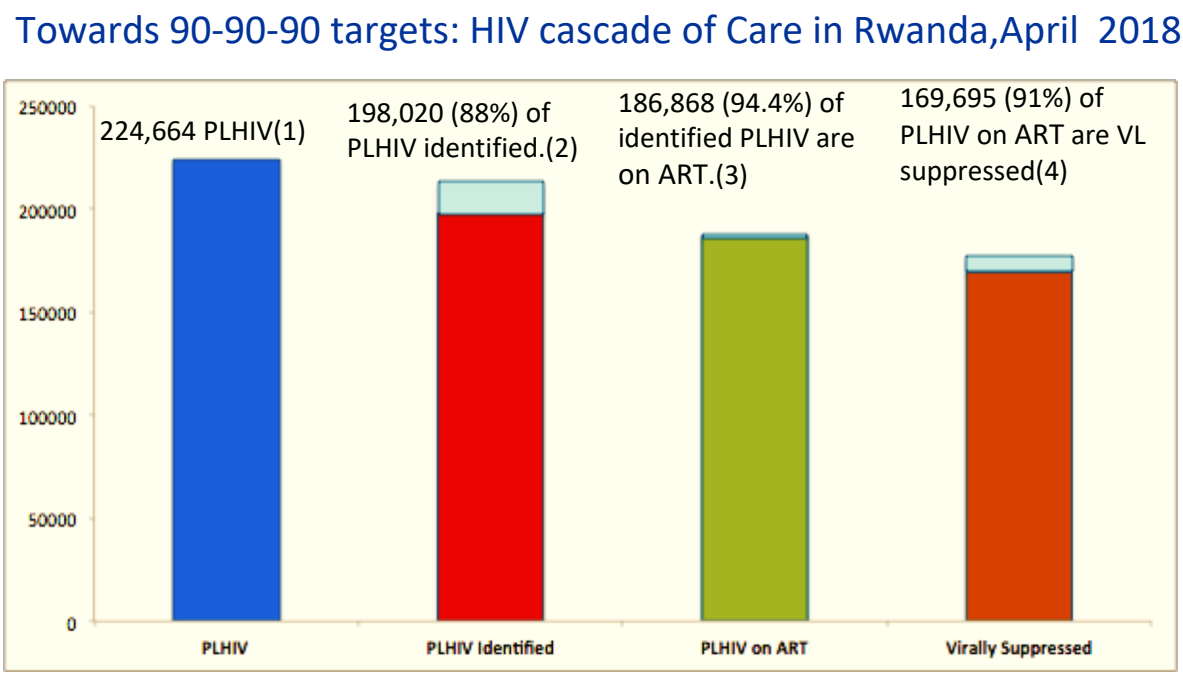
Rwanda is a successful example of ART services scale up; 94.4% of all identified PLHIV in Rwanda are on antiretroviral therapy as of April 2018. This resulted from the policy change in 2016 recommending a test and treat approach in the national guidelines, eliminating CD4

eligibility thresholds totally. The country currently provides ART to 186,868 patients, representing ~94.4% of infected individuals diagnosed in care, a significant increase from 153,000 patients ~73% of infected individuals in 2015 (Nsanzimana, Kanters, Remera, Forrest, et al. 2015). Despite these, children and adolescents aged 15-24 years are disproportionally reached with lower than 70% tested for HIV and 80% initiated on ART compared to adults. National program strategies need to be refocussed in particular to these groups to avoid that there are overshadowed by the overall rate of achievements. More granular data will be required not only to initiate more people on ART but also to achieve long term good adherence with largely known benefits (Ford et al. 2010; Carrieri et al. 2003), The national HIV guidelines in Rwanda published in 2016 suggest a same day ART initiation to reduce lost to follow up between testing and care; New evidence is now available about clinical benefits and feasibility of same day ART initiation (Kok et al. 2015).

Rwanda also achieved the third 90; Of all PLHIV on ART in Rwanda, 91% achieved VL less than 1000 copies/Ml. The last 90 requires innovative strategies and laboratory infrastructure to maintain adherence and retention in care and to reduce lost to follow ups. Rwanda HIV program uniqueness in this field relied on strong access to viral load turn-around time which has been improved through the implementation of a decentralized sample referral and transportation system linking health facilities to the nine VL testing hubs and the use of a web based Laboratory Information System. The investments made by the country improve warehousing and supply chain efficiencies and strengthen laboratory network capacity to manage laboratory stock. Consequently, viral load testing access has been multiplied nine folds in the last five years.

Adapting care to the needs of individual patients such as children and adolescents will be necessary to improve viral suppression in a longer term. Strengthening genotyping capacity will be required to precisely know when to switch before accumulation of resistance mutations.

Figure 1: HIV Cascade of Care in Rwanda, adapted from national HIV progress report, April 2018.

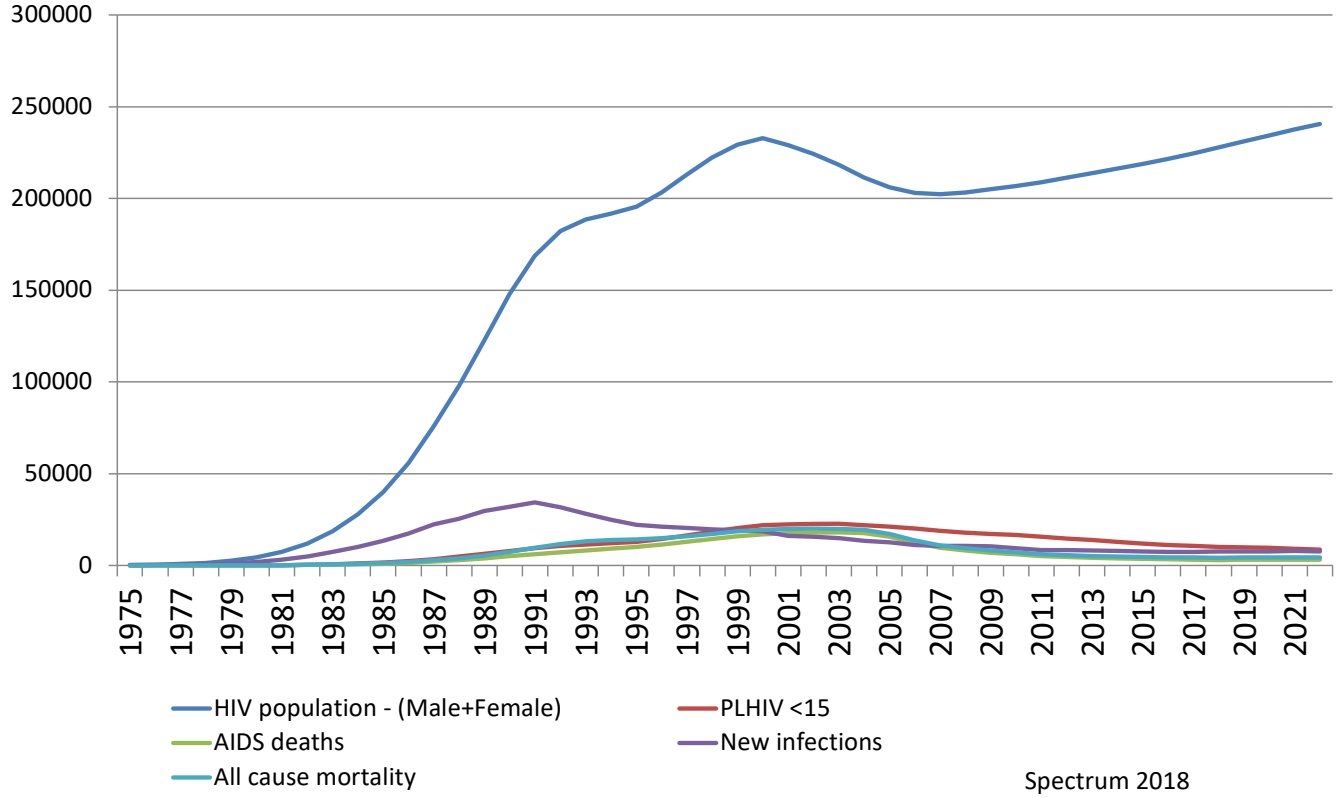


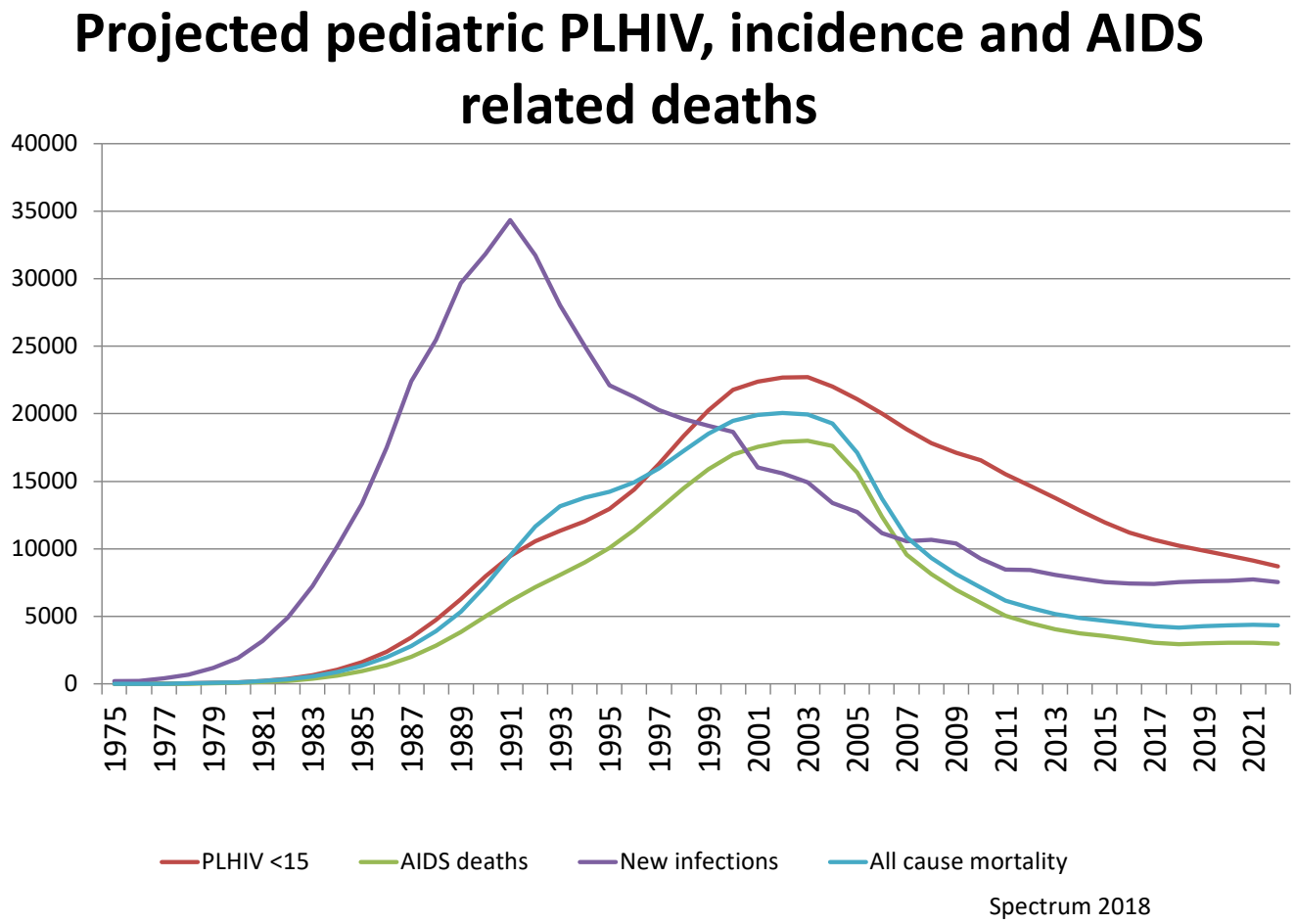
Data sources:
* *1 .EPP Spectrum 2018*
* *2 Estimated using EPP Spectrum, DHS and HMIS*
* *3. Health Management Information System of the MoH*
* *4 Source: PEPFAR Supported sites*

Adapted from Rwanda national HIV progress report, RBC: April, 2018

Figure2: Projected people living with HIV, incidence and AIDS related deaths in Rwanda, 2018

Projected PLHIV, incidence and AIDS related deaths in Rwanda





The trend and current state of HIV epidemic in Rwanda summarised in figure 2.

Since the first case of HIV in Rwanda, in the early 1980s, the Government demonstrated efforts and commitment in fighting the HIV-AIDS epidemic. Concrete HIV interventions and services were implemented after the genocide against the Tutsis in 1994. Significant changes in incidence, number of PLHIV on ART and reduction of AIDS related deaths were observed with the support of Global Fund and PEPFAR, in 2004. The prevalence of HIV remained constant for the last decade, the analysis of HIV prevalence data in 2010 and 2015 stratified by sex and age groups indicate that, HIV epidemic in Rwanda is aging as the highest prevalence shift overtime to

the right; consequently the number of adults living with HIV on ART continue to rise; however, HIV+ children below 15 years old declined significantly in accordance to reduced transmission of HIV from mother to child from 10.9% in 2004 to 1.5% in 2018 (MoH/RBC 2017) giving a hope for an AIDS free generation in Rwanda.

What makes Rwanda HIV program unique could be explained by:

First, a highly decentralized and integrated HIV clinical service ~98% of health centers in Rwanda provide comprehensive HIV services. As a geographically small, but densely populated and homogenous, Rwanda has eliminated many barriers to accessing care by offering localized clinical services. Offering decentralized services reducing the travel burden to clinical services has been shown to be among highest predictors of retention in care (Govindasamy, Ford & Kranzer 2012)

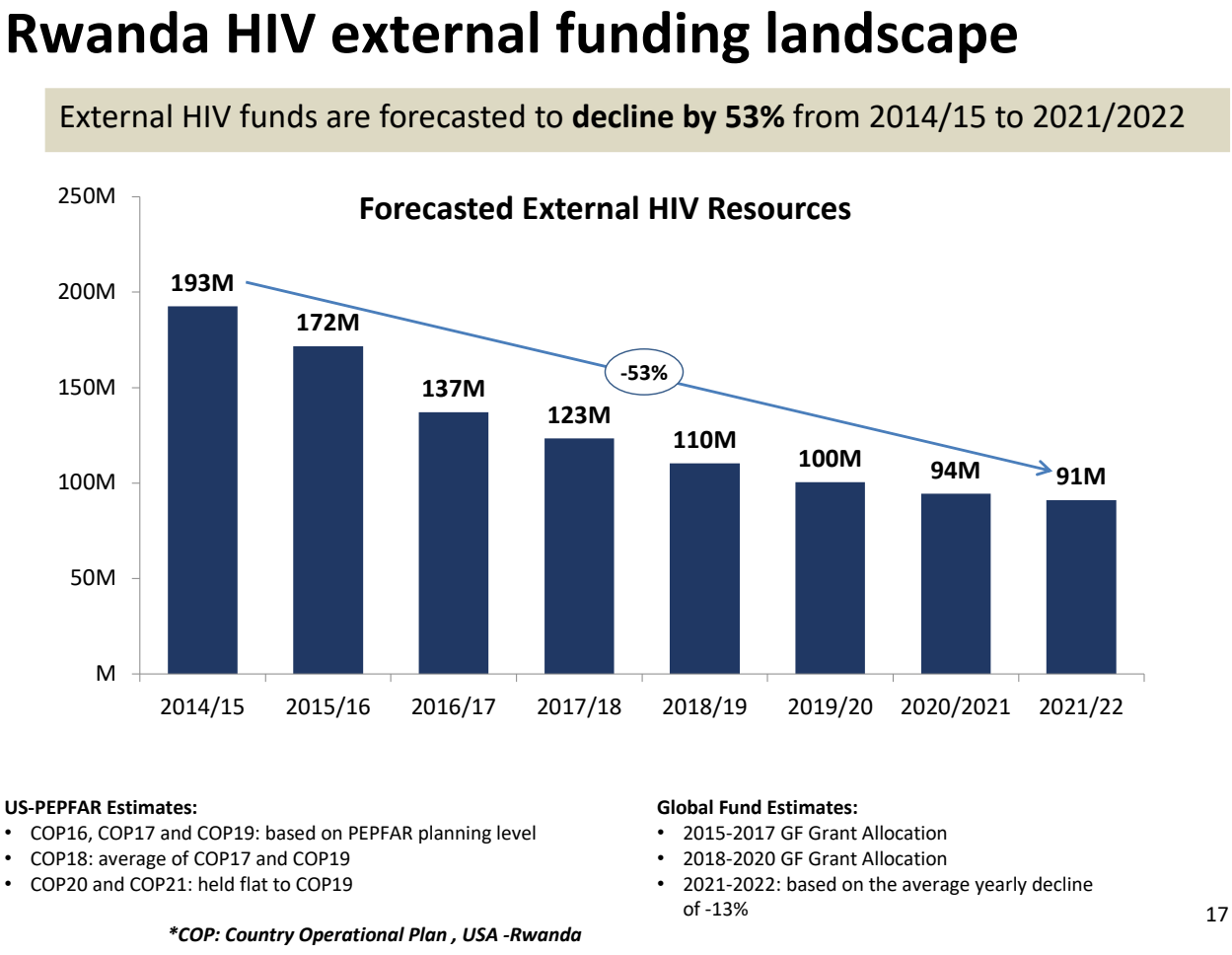
Second, the country's leadership from top to down has implemented performance-based contracts for central and local leaders, health and non-health professionals. These contracts serve as direct commitment and hold accountable all leaders to achieve set indicators. HIV among other country's priorities benefited significantly from this initiative.

Third, a program with a robust data surveillance systems for HIV care service including Health Management Information System, Electronic Medical record and health commodities supply chain systems; For example, laboratory information system provides quantification information and minimizes laboratory commodities stock outs. Strong routine centralized surveillance systems are key to examining the progress of any program for better patients care (Diaz et al. 2005; Koenig et al. 2017).

Remaining challenges relies on early monitoring, prevention and management of HIV drug resistance; HIV prevalence among female sex workers and similar key populations remaining very

high. In addition, HIV program in Rwanda is highly depending on external resources to combat HIV. Significant decline in funding (figure 3) demonstrated an urgent need for the country to develop a sustainable funding plan to diversity sources of means otherwise, significant gains may be lost if not sustained. The next mile could be even more resources and innovations demanding.

Figure3: Rwanda HIV external funding declining



11.2 Clinical outcomes on second and third line ART

Having analysed critical gaps in HIV diagnosis and linkage to care is essential to understand how optimal individual patient adherence to ART is important to prevent treatment failure and disengagement from care.

Treatment outcome data for patients on salvage therapy is scarce in resource limited settings (WHO 2016).

We assessed the treatment outcome for patients who failed first and second line ART available regimens.

Our nationwide study assessing retention in care and treatment failure for patients on second line ART suggested that overall, 92.5% of patients on second line ART in Rwanda were retained in care; 83% achieved VL < 1000 copies/ml, 2.8% were lost to follow up and 2.2% died. This study is the first to analyse outcome of patients on second line ART in Rwanda with a national representative sample.

Although our results show high proportion of patients achieving good retention in care and low failure on second line ART, these rates are lower compared to those of patients on first line ART (chapter 6). Defaulting from care was significantly associated with more recent initiation of ART- PI based regimen, CD4 cell count <500 cells/mm3 at initiation of second line ART and viral load > 1000 copies/ml at last measurement while Viral failure was associated with younger age, WHO stage III&IV at ART initiation, CD4 cell count <500 cells/mm3 at switch, atazanavir based second-line ART and receiving care at a health center compared to the hospital. Similar results were obtained in other surveys with an average of 80% viral load suppression and virological failure ranging from 23%-28% (Ajose et al. 2012).

These results strongly suggest the need for regular viral load monitoring and adherence support especially to patients likely to default from care across all stages of treatment cascade and all regimen transitions. The study on outcomes from Rwanda's first national cohort of third-line ART indicated that, over 90% of all 55 patients ever started on third line ART achieved VL

suppression less than 1000 copies/ml. Only one patient died and all were retained in care (chapter 7) Our results were comparable to data reported in other similar cohorts (Meintjes et al. 2015).

Regrettably, close to 10% of multi-drug resistant patients had virological failure for all available treatment options in Rwanda raising critical concerns for financial accessibility of further regimen in resource limited countries. Poor adherence is most of the time associated with treatment failure and drug resistance (Levison et al. 2012; Wallis et al. 2011).

In our study, more than 70% of the patients had accumulated at least one mutation on NRTI and NNRTI, however the majority were still susceptible to raltegravir and darunavir/ritonavir. Similar studies reported comparable treatment outcome on a third line combining darunavir/ritonavir, and raltegravir, recommending that this can be used as a standardized third-line regimen (Chimbetete et al. 2018; Rawizza et al. 2013; Meintjes et al. 2015) . The selection of a proper regimen depends most of the time on expert opinion based on available evidence, which is very dynamic. The Rwanda National HIV guidelines recommend the use of darunavir/ritonavir+raltegravir+etravirine in addition to a two NRTI based backbone for treatment of patients who failed previous protease inhibitors and/or NNRTIs. Given that this is the most expensive treatment combination available in the country; while an average cost on first line is 100 USD per patient per year; average cost per patient per year on second line is 500USD; the cost on third line is 6 times more , ranging between 3000-3500 USD per patient per year (MoH-Rwanda 2018; Management Sciences for Health 2006).

Failing these regimens critically has both financial and clinical implications for management of these patients in a resource limited context. The Rwanda national HIV program heavily depend of donor support, the main funding partners are Global fund and US-PEPFAR; more than 50% decline in funding was observed over a five-year trend and expected to continue;

Rwanda's gross national income is 700 USD per capita it ranks 159 in UNDP's Human Development Index 2016 (World Bank,2015) and significant financial barriers remain to achieve a sustainable HIV response in the near future.

There is a strong need for the Ministry of Health of Rwanda to develop a diversified source of funding including increased domestic investment, more efficiencies and innovations to sustain the HIV program.

Our analysis guided the national HIV program to select second line regimen in the new Rwanda ART guidelines version 2017 (MoH/RBC-Rwanda 2017).

11.3 Key drivers of HIV epidemic in Rwanda

HIV prevalence in the general population in Rwanda is 3% and HIV annual incidence ~ 0.27% (chapter 5); Female sex workers represent the only group with an alarming high prevalence with almost one out of two sex workers are HIV infected (Household community survey reference). The magnitude and dynamics of sex work in Rwanda's HIV program is not well understood due to the fact that the national programme data collection tools do not allow for easy identification of sex workers when in contact with facilities due to stigma and confidentiality reasons; though it is an important group in the society. The study on national household incidence (Chapter 5) revealed that people engaged in sexual activities had also six times more risk to acquire HIV. Although the Rwandan constitution criminalizes sex work, this group continue to be considered as a bridge to HIV transmission from sex workers to their male sexual clients and to the general population. The national HIV strategic Plan considers FSW as key population but needed to assess which interventions could be implemented to reduce the transmissions.

Although the impact of sex work on the rate of new HIV infections varies widely in Sub-Saharan Africa, it impacts significantly on the HIV/AIDS epidemics in a number of countries in this region. For example, FSWs, their clients, and the sexual partners of clients made up a third of all new HIV infections in Ghana in 2009, 10% of all new HIV infections in Uganda, and 14% of HIV infections in Kenya in the same year (Bórquez et al. 2016).

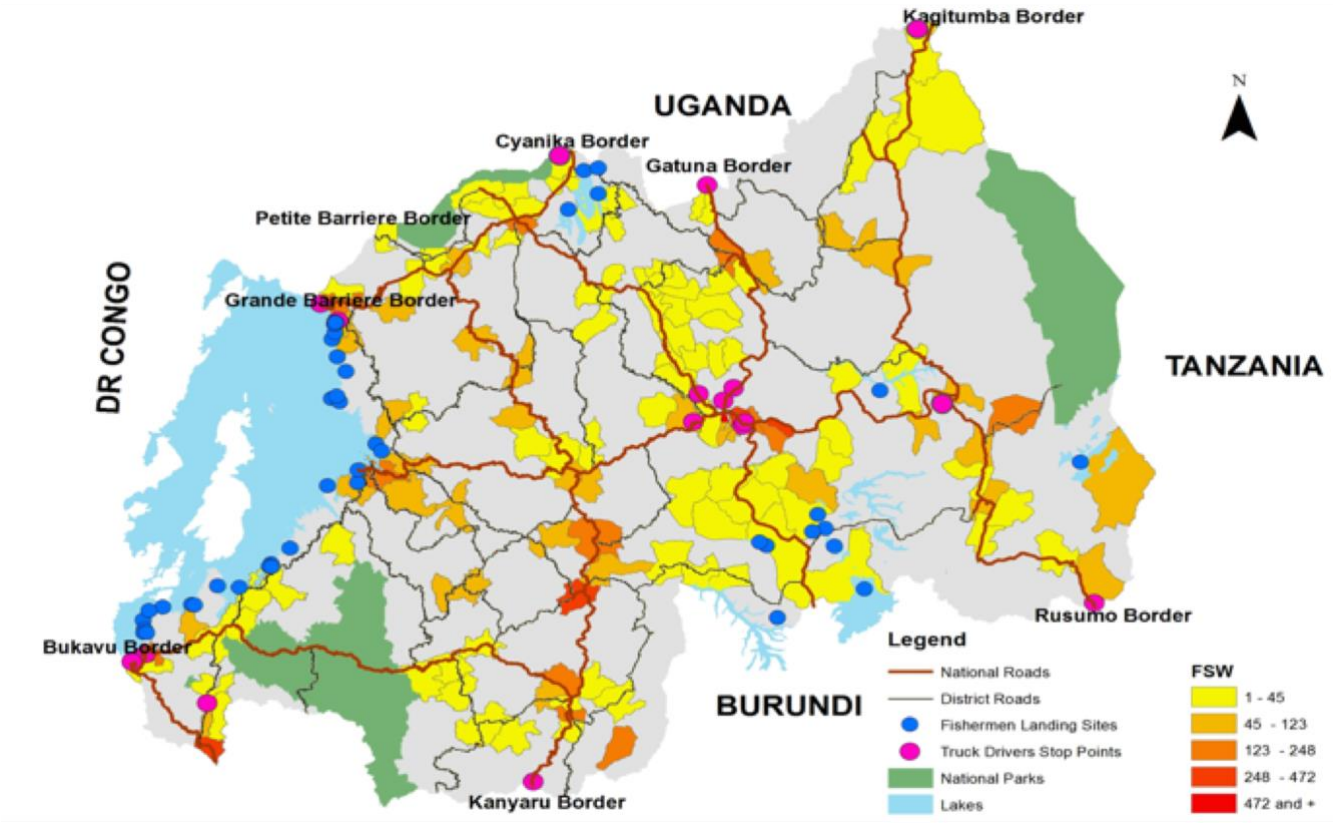
Our projected analysis of incidence of HIV among female sex workers and their male partners in Rwanda using a Markov model examining intervention effects (Chapter 8) provided important data for future strategic planning. The study found significant success of current program interventions (ART, condom use) to reduce HIV incidence among FSW, increased coverage that could result into 6-10% reduction on HIV prevalence every year. We also estimated that introduction of Prep expected in Rwanda in 2019, could prevent more new infections among FSW by 0.24%. Our findings will have greater impact in the development of the Rwanda National Strategic Plan 2018-2023 as FSW remains the key driver of new HIV infections in the country. There is a need to examine barriers and facilitators at different levels of care, which influence entry into and engagement in the continuum of health services for FSWs in Rwanda.

Similarly, our analysis has implication to strategic planning in other countries with concentrated epidemic in key populations such as FSW, MSM. Using Markov model to this analysis was motivated by its wide success in health economy; it has the advantage for combining different stages of transition probabilities. The majority of transition probabilities were directly informed by data with high internal MoH validity. Our model main limitation includes self-reported data on sexual behaviors, which are likely subject to some bias; the model did not include other key risk populations (e.g. men who have sex with men, male sex workers, and sero-discordant couples) in Rwanda.

All other projects were either research studies, routine program data analysis or policy implementation; In this project, we preferred to conduct this model to predict the future of HIV among FSW which was highly needed by the Rwanda Ministry of Health. Follow up project ongoing include a cohort of HIV negative FSW that will be tested for HIV after 12 months, we expected that results from this survey also will contribute to respond to this important question.

As illustrated in the figure below; the relationship between female sex workers, male clients of sex workers and general population in Rwanda is worrying due to the role of this network in the continuous transmission of HIV. The presented mapping of key populations locations could facilitate precision of interventions according to where the highest needs are; for example, western province that accounted for more new infections (chapter 5) has a concentrated number of fishermen; the same province shares 2 main border areas with DRC where truck drivers and sex workers are also represented in high proportions. The capital of Rwanda, Kigali has HIV prevalence three times higher than other provinces (Chapter 5) and estimated to host more than 3000 active sex workers in several hot spots and truck drivers stop points (Mutagoma et al. 2015).

Key populations hotspots in Rwanda, 2017



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11.4 Policy implications

Despite the reported high performance of Rwanda national HIV program, our project identified several areas of improvement in strategic planning, program implantation, monitoring, evaluation and strategic information towards the country commitment to achieve 90-90-90 UNAIDS global targets by 2030

Our first study on HIV incidence and prevalence underlines challenges associated with breakouts of new HIV infections and significant number of growing infections among youth and

singles. This reality implies new strategies in the testing and condom use program area. Majority of the individuals possibly driving infections didn't know they are HIV+ though testing services are free of charge across the country. The country should put in place new strategies for individuals who are hard to reach with existing testing and linkage to care services. Our findings revealed also that mathematical modelling such as UNAIDS Epi Spectrum estimating HIV indicators in most countries could have been underestimating the rates of HIV in different countries. The models should be recalibrated to reflect this paradox of outbreaks. Countries could plan nationwide household HIV incidence surveys for better precision without relying only on estimates.

Our studies on HIV care continuum in Rwanda and effect of baseline CD4 count on mortality demonstrated the need to focus on males, adolescent and less healthy HIV–positive patients in national strategic planning. Furthermore, continuum of care is not a single trajectory pathway, individuals re-engage and disengage from care at different stages, the national program and beyond should be aware of these multiple pathways to improve timely linkage and retention in care.

In our different project studies; treatment outcome for first, second and third line regimens demonstrate increasing treatment failure by regimen respectively; rigorous and innovative medical and laboratory monitoring should be introduced to maintain individuals on successful treatments without unnecessary changes to second and third lines in resource limited context. However, resource limited countries do not systematically implement drug resistance testing before initiation and switching of ART regimen, consequently, patients maintained on a failing treatment are at great risk to accumulate drug resistance mutations. Therefore, the World Health Organization guidelines need to strongly recommend regular and systematic drug resistance testing especially for patients who are not suppression viral load. Although we reported a high rate of retention in

care in Rwanda, the national program has to put more efforts to retain those at high risk to disengage from care. The UNAIDS 90-90-90 targets should be updated to reflect those defaulted from care who are potentially at risk of treatment failure.

HIV epidemic in Rwanda is largely driven by the condensed epidemic of HIV among FSWs and their male partners. As the Country develops its National HIV Strategic Plan 2018-2023, it should focus more on interventions targeting FSWs and their networks such as testing, linkage to care, improve consistent condom use and introduction of PreP among HIV negative FSW. As presented in Chapter 3 and Chapter 11; The city of Kigali has a substantial HIV prevalence among general population (6% Vs 3%) and FSW (52% vs 46%) probably due to the population migration and legacy of post genocide effects; In this context, a specific strategy for Kigali city to combat HIV is highly recommended.

11.5 Recommendations for further research

1. Due to the importance of high HIV prevalence among FSWs in Rwanda; follow up studies to our model are needed to determine HIV incidence and associated factors to increase program precision in decision making. This PhD project already initiated this follow up study which is at early stage of implementation. This prospective follow-up over 12 months of a cohort of female sex workers (FSW) in Kigali will provide key data on behavioural determinants of linkage and retention in care and estimation of HIV incidence among a cohort of HIV-negative female sex workers in Kigali, the capital of Rwanda.
2. Given that the HIV epidemic in Rwanda is driven by key populations, there is a need to further investigate patients' trajectories in different stages of care especially for key and priority populations (FSWs, MSM, Adolescents, Males).

3. As Rwanda get closer to achieving UNAIDS 90-90-90- targets by 2020, we recommend an operational study to assess the progress towards achieving this goal after implementation of “treat all” and differentiated service delivery model

CHAPTER 12. OVERALL CONCLUSION OF THE THESIS

We conducted this project to identify gaps in the entire national HIV program and recommend clinical and public health interventions to improve the country’s program. Our findings reflected in seven studies, demonstrated a high performance of HIV program in Rwanda, with a relatively stable prevalence; improved cascade of care across different treatment regimens. Nonetheless, several gaps were highlighted with increasing needs to focus on key and priority populations; adolescents, males and delayed linkages to care should be prioritized to maintain a sustainable and cost-effective program. Further, due to increased number of patients failing available treatment options, strengthening viral load and genotyping testing should be prioritized to maximize patients’ treatment outcomes and prevent future epidemic of HIV drug resistance.

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ANNEX - CURRICULUM VITAE

CURRICULUM VITAE, July 2018
Sabin Nsanzimana
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Summary:

Sabin Nsanzimana is trained as a Medical Doctor, with a Master degree in Clinical Epidemiology from National University of Rwanda and Epidemiology PhD from Basel Institute for Clinical Epidemiology and Biostatistics and Swiss Tropical and Public Health Institute, University of Basel, Switzerland. Currently He serves as the Director of National HIV program for Rwanda and Division Manager for HIV/AIDS and Viral Hepatitis in the Institute of HIV Disease Prevention and Control-Rwanda Biomedical Center for the last 9 years; with 12 years' experience in HIV, TB and hepatitis program design, implementation, and operational and clinical trial research with a focus on HIV cascade of care in Rwanda national HIV program; He has senior-level coordination of a variety of health projects , operations research, and extensive experience in leading partnership programming with government, NGOs, community based organizations, and civil societies. Dr Sabin is also part of African Scientists fellows and serves as faculty member for Global Health Delivery with Rwanda MoH, Harvard Medical school; Lecturer at the Global Health Equity University and a collaborator to the Institute of Health Metrics (IHME), Global Burden of Diseases (GBD); University of Washington. He previously contributed to develop the 2013, 2015, 2017 and 2018 WHO ART guidelines as a member of Guidelines development group (GDG). He has been leading the development of comprehensive HIV guidelines for Rwanda since 2008. Over more than a decade, Dr Sabin led the development of national strategic plans and grant negotiations from

several bilateral and multilateral organizations such as Global Fund, PEPFAR, oneUN, BMGF, and research organizations (NIH, CDC…)

In addition, he has published more than 100 research articles in peer review journals and book chapters. He speaks fluently French, English, Swahili, and Kinyarwanda.

Organization: Institute of HIV Disease Prevention and Control – Rwanda Biomedical Centre
Ministry of Health.

a. NAME: NSANZIMANA, Sabin, MD, MSc, PhD; Director of Rwanda National HIV Program and Head of HIV/AIDS, STI and Viral Hepatitis Division.

b. DEGREES:

PhD, Epidemiology, Basel Institute for clinical epidemiology and biostatistics and Swiss Tropical & Public Health Institute, University of Basel 2015-2018

Master of Sciences. Clinical Epidemiology, University of Rwanda
2012

Diploma, HIV specialist, Interuniversity Diploma, University of Burkina Faso 2009

Advanced HIV management. Institute of Human Virology University of Maryland, USA
2011

Medical Doctor, General Medicine and Surgery, National University of Rwanda
2006

BA, Human Biology, National University of Rwanda
2003

Latin and Sciences (Biology Chemistry), Junior seminary Virgo Fidelis 1998

Selected Additional Training

Faculty, Global Health delivery 2014

Global Health Delivery Course, Harvard University Faculty in Training
2012

Rwandan Ministry of Health and Harvard School of Medicine
Certificate of Advanced Management of HIV/AIDS,
2011

International Physician Exchange Program, University of Maryland
Inter-University Diploma on HIV/AIDS Global Management --
2006

University of Pierre Marie Curie and University of Brescia
Certificate of English Proficiency
2000
EPLM (School of Modern Languages), National University of Rwanda

c. EMPLOYMENT HISTORY

Director, National HIV Program and Head of HIV/AIDS, STI and viral hepatitis Division, Institute of HIV Disease Prevention and Control (IHDPC) – Rwanda Bio Medical Center	2009-present
Lecturer, University of Global Health Equity, Kigali-Rwanda	2016-present
Deputy Director General & **Head of the institute** for HIV and Diseases (TB, Malaria, epidemics, NCDs, Mental health) prevention and control	2012
Coordinator, Treatment and Control of Diseases TWG	2010-present
Technical Country Counterpart for Rwanda, East African Community EALP Program	2009-present
Coordinator, National HIV care and treatment Technical Working Group (TWG), HIV/AIDS – PEPFAR Steering Committee	2008-present
Director, HIV/AIDS and STIs, Treatment and Research for AIDS, TB, Malaria and other epidemics (TRACPlus) Center, Rwanda Bio Medical Center	2010-2011
Coordinator, HIV/AIDS Care and Treatment Department, Rwanda Bio Medical Center	2008-2010
HIV/AIDS Drugs and Commodities **Supply Chain Analyst**, HIV/AIDS and STI Unit/TRACPlus	2008
Clinical Mentorship **Program Coordinator**, HIV/AIDS and STI Unit/TRACPlus, UNICEF Kigali	2007-2008
Clinical Medical Doctor -- Surgery and Gyneco-Obstetrics, Kigali Teaching Hospital; Internal Medicine, Ruhengeri District Hospital; Pediatrics Department, King Faisal Hospital	2006-2007

d. HONOURS

International Association of Providers of AIDS Care –Honoree (IAPAC - 150)	2016
Letter of appreciation for HIV Achievements in Rwanda by Mr. Bill Gates, USA	2014
Certificate of Compassion and Courage in the HIV Fight in Rwanda, Institute of Human Virology, University of Maryland, USA	2011
Letter of Appreciation, Professor Michel Kazatchine, Executive Director of Global Fund, Geneva Switzerland	2010
Letter of Acknowledgement to dedication for pediatric HIV, by HE Bill Clinton.	2008
Post Graduate Award for Academic Excellence, Student Financing Agency, Rwanda	2007

e. SCHOLARLY AND PROFESSIONAL ACTIVITIES

Memberships

African Scientific Institute (ASI) fellow, 2015

WHO TB/HIV task force, member, 2015

WHO ART Operational Guidelines Development Group member ,2013- 2018

Faculty Member, International Association of Providers of HIV Care (IAPAC)

Global Burden of Diseases (GBD) expert, IHM, University of Washington, USA

Member, International AIDS Society

Faculty, Global Health Delivery Team, Rwanda – Harvard Medical School

Member, International Physician Exchange Program – University of Maryland

Member, EST African Community on Regional Multisector Technical Working Group (TWG) on the Control and Prevention of HIV/AIDS, Sexually Transmitted Infections (STIs) and Tuberculosis

Member, Country Coordinating Mechanism (CCM) Rwanda, Global Fund to Fight AIDS, Tuberculosis and Malaria

Member, Rwanda Medical Association

Member, Health Sector Senior Management Team

Member, Rwanda Bio Medical Centre Senior Management Team

f. SELECTED PUBLICATIONS (from over 100 peer reviewed publications)

Papers in Refereed Journals

Is hepatitis C elimination possible in sub-Saharan Africa? The case of Rwanda
Neil Gupta, **Sabin Nsanzimana**, 6 April 2018. https://doi.org/10.1016/S2468-1253(18)30089-XGet rights and content. The Lancet Gastroenterology & Hepatology, Volume 3, Issue 5, May 2018, Pages 289

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https://doi.org/10.1177/0956462418761695

Household survey of HIV incidence in Rwanda: a national observational cohort study Nsanzimana, Sabin et al. The Lancet HIV, Volume 4, Issue 10, e457 - e464, 2017

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The mental health of HIV-positive adolescents .Mary Fabri · Charles Ingabire · Mardge Cohen · Geri Donenberg ·**Sabin Nsanzimana.**The Lancet Psychiatry 08/2015; 2(8):e21. DOI:10.1016/S2215-0366(15)00291-6

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