VIRAL LOAD DYNAMICS IN HIV-1 INFECTED SEX WORKERS IN THE SEX WORKER OUTREACH PROJECT (SWOP)-KENYA AFTER ART INITIATION

By;

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DECLARATION

I declare that this research is my original work and has never been submitted in any form as a credit for academic qualification to any learning institution.

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Signature: ………………………………….. Date: ……………………………

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DEDICATION

To, my parents Mr. & Mrs. Onchaga, Mr. & Mrs. Ochieng', my husband Mr. Antony Odhiambo and son Nathan, thank you for your moral support, May God bless you.

ACKNOWLEDGMENT

I give thanks to God Almighty, for He endowed me with wisdom, strength and perseverance while undertaking my research project.

To my family and friends thank you for your moral support, to the point of completion of my studies.

I am heartily thankful to my lecturers for their dedication and supervision and my colleagues, Mian Anatole and Henry Mwangiwhose encouragement and support enabled me develop an understanding of the subject, conduct the research study and to write my thesis.

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ABBREVIATIONS

FSW	Female sex workers
MSW	Male sex workers
PIWD	People who inject drugs
UNAIDS	United Nations programme on HIV and AIDS
WHO	World health organization
NACC	National AIDS Control Council
CD4	Cluster of Differentiation 4
RNA	Ribonucleic acid
LVCT	Liverpool voluntary counseling and testing
PCP	Pneumonocytis Carinii Pneumonia
ART	Antiretroviral Therapy
NASCOP	National AIDS and STI control programme
USA	United States of America
CDC	Centre for Disease Control
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
PLWH	People Living With HIV

ABSTRACT

Models have been developed to simplify complex processes for purposes of understanding them in order to solve a problem and make decisions. They are designed for a specific situation/process in manner that they reflect the reality. The main aim of this study was to model the viral load dynamics in HIV infected sex workers at SWOP after initiation of Antiretroviral Therapy.

This was a stochastic model using continuous time. The model structure comprised of four compartments- initiated into care, virally suppressed, virologically failed and viral load missing. A set of differential equations were defined to explain the transition process between the model compartments. HIV data for sex workers was obtained from SWOP city clinic to estimate the rates of transition between the compartments. For demographic rates, information from recent HIV reports in Kenya was used to define the parameters. Simulations were done to project the changes in model compartments within a period of 5 years. The net reproductive number was determined using the defined rate parameters, to set the threshold to control the incidence of virological failure among HIV positive sex workers in care.

The two year projection showed that after first two years (2019), for each patient initiated into care/ART, we have <1 patient in care achieving viral load suppression. In the five year projections, it was noted that after 2 years and 8 months, each patient initiated into care generates >1 virally suppressed patient. A similar trend was observed among male and female patients; however for the four year projection curve for male, the initiated into care curve and virally suppressed curve cross later than the female curves (after 3.5 years in males vs 2.5 years in females). To control the number of virological failure; it was determined that for one patient

initiated into care at least three patients in care should achieve viral suppression. From the simulation, it was noted that it would take the project at least 7 years to achieve this ratio.

The NHAS 90/90/90 model was successfully adapted; however the model can be improved further by adjusting the rates using accruing data from the project. The rates of initiation to care and viral suppression was lower in male than female sex workers, therefore SWOP should come up with tailored strategies to targeting undiagnosed HIV positive male sex workers to increase the number of HIV positive male sex workers with suppressed viral load. This will in turn reduce the rate of HIV transmission from infected male sex workers to susceptible people.

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

In 2016, approximately 36.7 million people were living with HIV infection globally yet only 60% were aware of their positive status. Further, less than ½ of these people living with HIV (PLWH) were on antiretroviral therapy (ART) but only 38% had achieved undetectable levels of HIV (UNAIDS, 2017).

UNAIDS/WHO set the 90-90-90 treatment targets in 2014 to ensure universal access to treatment for PLWH worldwide in achieving the goal to end the epidemic by 2030. (UNAIDS, 2014). It is expected that with the achievement of the three part target, at least 73% of PLWH worldwide will have full viral suppression by 2020. The 90-90-90 target requires that by 2020, 90% of all PLWH will have known their status (diagnosed), 90% of PLWH diagnosed put on sustained ART, and 90% of PLWH on ART will have fully suppressed viral load. To achieve the 90-90-90 target, a mathematical model was developed to guide the implementation of the HIV control and universal treatment programs in different jurisdictions. This model is a flexible interactive tool which can be used to simulate HIV dynamics projections and set up targets based transition rates between subpopulations of PLWH in different countries.

HIV burden, diagnosis/treatment coverage and barriers to early HIV diagnosis, timely initiation to ART and sustenance on treatment vary from one country to the other. For this reason it is useful to adapt the UNAIDS model using local data which is reflective of the local situation.

Kenya is ranked fourth worldwide in HIV epidemic jointly with Uganda and Mozambique. Latest HIV estimates report the HIV prevalence in Kenya at 5.9%, with 78,000 new infections by end of 2015. Out of 1.5 million PLWH, 59% were on ART (UNAIDS, 2015). For a long time Kenya's HIV epidemic was considered to be generalized, that's affecting all irrespective of age or gender but studies over the years have found that the infections are concentrated in certain groups of people commonly termed as Key Populations. They contribute 30% of annual new cases in Kenya (KASF, 2014/2015-2018/2019). Among the key populations are sex workers who carry a higher burden of the infection compared to the national HIV prevalence.

In 2011, approximately 30% of female sex workers and 40% of male sex workers respectively were living with HIV according to SWOP report. Despite the running of SWOP for seven years, the proportion reported to have been tested for HIV by 2015 was found to be very low; 18% among female sex workers (FSW), 12% among men who have sex with men (MSM) and 9% among people who inject drugs (PWID), compared to the 90-90-90 target (NACC, 2015). There is no available data on the estimated population of virally suppressed HIV-1 infected sex workers among those who are treatment; however in the general population the rate of viral suppression by 2016 was estimated at 38.8% (Cherutich et al, 2016).

As part of the ways to bring to an end the AIDS epidemic by 2030, WHO recommended a test and treat policy where any person diagnosed with the virus is supposed to receive Antiretroviral Therapy (ART) regardless of their CD4 count. HIV programs have adopted this policy in ensuring equitable access to HIV testing, treatment and general health care and have reported a significant improvement in the rates of HIV diagnosis, treatment and viral suppression. Sweden was the first country to achieve the 90-90-90 goal in the World, and in Africa, Rwanda (85-90-85), Zimbabwe at 74-87-86 and Malawi (73-89-91) were reported to be well on track according to UNAIDS data (2016)

Considering their inconsistent risk and weakness, key sex workers warrant a prioritized reaction to reduce HIV transmission. Since its initiation in 2008, SWOP under the Kenya AIDS control program has been working to provide a comprehensive HIV prevention, treatment and care package for sex workers as per the Kenya Ministry of Health guidelines. However the 90-90-90 targets cannot be reached without overcoming several factors such as persistence of stigma, discrimination and social exclusion that undermine the effective responses for sex workers. This calls for tailored approached and strategies that are developed in collaboration with the sex workers to achieve the HIV treatment goals for this population.

1.2 Problem statement

Despite the many HIV control programs running in Kenya, this gap between the current rates of viral suppression among those infected and the 90-90-90 target is an indicator that approaches being used to address this problem need to be reviewed. To effectively address this gap, it's important to understand the process in HIV care and management. Models have been developed to simplify complex processes for purposes of understanding them in order to solve a problem and make decisions. Models are designed for a specific situation/process in manner that they reflect they reflect the reality.

In this study the mathematical model established by NHAS (Kelly et al, 2016) to give HIV prevalence projections thus estimating the future demand for medical and support services at country level, was adapted. This was a compartmental model in which the process of transition between compartments was stochastic with continuous time. The population was divided into four compartments based on the care status: Abdool, (2010) added that undiagnosed in care/viral load>200, in care/viral load<200, and out of care (no viral load for 12 months) must be constant. In this model, national data for the general population (Georgia's 2014 HIV viral load data) was used to estimate the transition rates and project the expected number of people in the compartments by 2020.

This model defined using population average rates (*per capita* rate) which may not be a true reflection of the process in subpopulations such as sex workers, children etc. There has also been a change in the protocol for treatment of newly diagnosed HIV patients since 2014 with the introduction of the test and treat policy by WHO. With this policy, more HIV patients are initiated into ART early increasing the likelihood of having an increased number of treatment failure cases (Virologic failure). Therefore this subgroup of treatment failure should be considered when modeling viral load dynamics in patients on ART.

1.3 Justification

This model is specifically adapted to guide SWOP by using the available longitudinal HIV data for sex workers infected with HIV-1 in the database.

In addition to the compartments defined in the NHAS model, the virologic failure subpopulation was considered and the rates of transition were estimated using the available data. This model is useful to monitor and evaluate the progress of SWOP in regards to improving the health of HIV-1 sex workers and any other project working with key populations.

1.4 Objectives

1.4.1 Broad objective

To model the viral load dynamics among HIV-1 infected sex workers at SWOP-Kenya after initiation of Antiretroviral Therapy

1.4.2 Specific objectives

1. To estimate the rates of HIV diagnosis and initiation into care, viral suppression, virological failure and loss to follow-up

2. To define the set of differential equations explaining the change in model compartments

3. To estimate the net reproduction number to control the incidence of virological failure

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology of HIV/AIDS

With 36.7 million PLWH (UNAIDS, 2017), HIV/AIDS remains a major public health problem whose journey to eradication is still a long one. Adults constitute the majority of the PLWH in the world estimated at 34.5 million among them more half than being women (51.6%). In 2016, there were 1.8 million new infections (1.7 million adult cases). In Eastern and Southern Africa, carry half of the HIV/AIDS burden with an estimated 19.4 million PLWH. According to the Kenya Aids progress report 2016, it was estimated that 1,517,707 people were living with AIDS in Kenya, a prevalence of 5.9% with 77,647 new HIV infections and 35,821 AIDS related deaths (NACCK, 2016).

AIDS-related deaths in 2016 reached approximately 1 million where 89.0% were adults and the rest were children. AIDS- related illnesses is still the leading cause of many deaths among women of reproductive age (15–49 years) globally, they come second leading ground of death for young women aged 15–24 years in Africa (UNAIDS, 2017). Global scale-up of antiretroviral therapy has been the primary contributor to a 48% decline in deaths from AIDS-related causes, from a peak of 1.9 million in 2005 to 1.0 million in 2016 (UNAIDS 2017).

2.2 HIV/AIDS and Key Population

According to W.H.O, Key populations are people who are vulnerable to and most-at-risk for HIV. The include “men who have sex with men, transgender people, people who inject drugs and sex workers. Most-at- risk populations are disproportionately affected by HIV in most, if not all, epidemic contexts (Fettig et al, 2016). Estimates by the Joint United Nations Programme on

HIV/AIDS (UNAIDS) suggest that as many as 50% of all new HIV infections worldwide occur in people from key populations.

In Central Asia and Eastern Europe, people from key populations constitutes of for more than half of new infections – from 53% to 62%. Even in the sub-Saharan African countries with generalized epidemics that have carried out modes of transmission (MOT) analysis, the proportion of new infections in key populations is substantial, although it varies greatly – for example, an estimated 10% in Uganda, 30% in Burkina Faso, 34% in Kenya, 37% in Nigeria, 43% in Ghana and 45% in Benin.

Globally, gay men and other men who have sex with men accounted for 12% of new infections in 2015, while sex workers and people who inject drugs accounted for 5% and 8% of new infections, respectively. Furthermore, data reported by countries across the world show that HIV prevalence among key populations often is substantially higher than it is among than the general population (UNAIDS, 2017). In Kenya, HIV prevalence among key population is estimated as 29.3% for Sex Workers, 18.2% for men who have sex with men and 18.3% for people who inject drugs (NACCK, 2016).

2.3 Sex Workers

Female sex workers (FSWs) experiences a heavy HIV burden due to the risky sexual activities they are involved in (Shannon et al, 2014). In many countries expanding maximum access to HIV prevention, treatment, and care to sex workers has remained elusive (WHO, 2012). In a recent review and meta-analyses of HIV epidemics in developing countries, among the 26 countries with medium and high background HIV prevalence, 30.7% of FSWs were HIV-positive (Baral, 2012). It was found out that Two-thirds of LMIC did not keep data of HIV burden among FSWs, this is largely accredited to many of the same structural problems that often come up with barriers to HIV prevention, treatment and care (Alary, (2013). HIV prevalence among FSWs is in the world is 12%, with a range of 1.7% in the Middle East and North Africa to 36.9% in Sub-Saharan Africa. In that case, FSWs have a pooled odds ratio of HIV infection compared to women in the general population of 14 (Mountain et al, 2014). Thus, FSWs remain a key population for HIV prevention strategies. In ensuring high levels of ART uptake, FSWs would provide not only individual benefits to HIV-infected FSWs but also help in reducing HIV transmission at the population level (Alary et al, 2013).

2.4 HIV control

Many interventions have been introduced in on order to bring down transmission of HIV infections (Williams et al, 2011). However, promotions of behavior change programs have shown a confirmable effect on HIV incidence in only a few countries. Medical male circumcision is being promoted in many Africa countries to help in reducing the risk of HIV infection in men by 60% (Auvert et al, 2005). The vaginal microbicide containing tenofovir gel is also used to lessen the menace of HIV infection in women by 54%. Pre-exposure prophylaxis provides the same reduction in men who have sex with men Grant et al, (2010) indicates that condoms can be more effective, if used correctly and consistently, and some interventions with sex workers have resulted in high levels of condom use (Park et al, 2010), but the use of condoms in primary partnerships has still remained low (Foss et al, 2004);. The application of counseling and testing is effective in reducing risk behaviour among HIV-positive but not among HIV-negative. This intervention has succeeded is the use of ART to prevent mother-to-child transmission (MTCT) and in developed countries less than 2% of children born to HIV- positive mothers are themselves infected [15].

1.5 The Role of Antiretroviral Therapy

Antiretroviral therapy (ART) consists of a combination of drugs targeting the human immunodeficiency virus (HIV) lifecycle with the aim of stopping HIV replication and preserving or restoring immune function (Günthard et al, 2014). The most vital thing in on how best to manage HIV-1 infection by treating patients with antiviral drugs that suppresses HIV-1 replication to undetectable levels (Arts et al, 2012). The standard of HIV-1 care has evolved greatly to comprise management of cocklail of ARVs since the first HIV-1 specific antiviral drugs were provided as monotherapy in the early 1990s. The advent of combination therapy to treat HIV-1 infection was seminal in reducing the morbidity and mortality rates that is associated1 the infection (Collier et al. 1996). The mixture of antiretroviral therapy is aimed at suppressing the viral imitation and reduction of plasma HIV-1 viral load (vLoad) to below the limits of discovery.

UNAIDS Program Coordinating Board requested UNAIDS to aid country- and region-led efforts in order to come up with new targets for treating HIV cases to scale-up beyond the Year 2015. The world is now seeing powerful momentum coming up towards a new tale on HIV treatment. It is highly presumed that by the year 2020, over 90% of HIV+ people will know their status, and 90% of diagnosed cases will receive sustained antiretroviral therapy, while 90% of ARV patients will have viral suppression (UNAIDS, 2014).

In December 2013, close to 12.9 million people were getting ART in the whole world, while 37% of HIV+ adults were on antiretroviral therapy, but only 24% of HIV+ children received HIV treatment. However, it has been witnessed that considerable coverage gaps exists in

African, for instance treatment in 2013 ranged from 41% in Eastern and Southern Africa to 19% in North Africa. In Kenya, ART coverage is anticipated to be at 897,644 people (NACCK, 2016).

2.5 The Role of Mathematical Models in HIV Programme

Since HIV emerged in 1981, several studies, including mathematical modeling, have been devoted to understand the transmission of the infection. HIV models can be classified into two categories: population-level models and within-host models (Ogunlaran et al, 2016). Mathematical models cannot provide solutions to the pathogenesis of HIV infection or similar biological processes on their own; they can be combined with data as part of designed experiments to become an authoritative tool to help understand mechanisms in various complex systems (Adams et al, 2005). Data-oriented mathematical models can be used to stimulate further clinical and laboratory research. However, it is important to point out that while complex models are required to offer accurate descriptions of the underlying dynamics, they become only useful when compared to clinical data in any deliberations of mathematical modeling.

Research findings on the kinetics of virus and CD4+ T-cell populations carried out by use of mathematical models with data from different patients who are undergoing highly active anti-retroviral therapy (HAART) sustains the theory of very rapid and constant turnover of the viral and infected cell populations (Ho et al, 1995). These findings however contrasts with researchers' previous assumptions that the stable viral and CD4+ T-cell concentrations seen during the stage of clinical latency of chronic HIV infection were due to the lack of any vital viral replication. It can therefore be reported that both the viral and infected cell populations are turning over rapidly and incessantly. Then the only purpose of mathematical models can be said to approximate parameters since they are formulated to be associated with the infection like the death rate of infected cells or the viral production rate out of longitudinal data on virus load and T-cell counts (Alizon et al, 2012).

A mathematical model is also used to compare hypotheses, like when testing two hypotheses that are competing, for instance, when the virus growth is limited availability of target cells or by the immune response, it becomes possible for one to first estimate parameters for each model and then compare their likelihood assuming the most likely parameter values for each model (Bolker, 2008).

CHAPTER THREE

METHODOLOGY

3.1 Target population

The target population for this model is sex workers living with HIV. This population was subdivided according to viral load status. ‘Viral load’ is used to describe the amount of HIV in the blood of a HIV positive person. Viral load tests used to measure the amount of HIV’s genetic material in a blood sample describe the number of copies of HIV RNA in a millimetre of blood. In SWOP, once a sex worker is diagnosed with HIV, the viral load is measured and the patient started on first line ART. The viral load is checked after three months, then at least once a year thereafter to monitor the response to treatment.

Sex workers living with HIV were designated as diagnosed& ART initiated (not virally suppressed), in care/virally suppressed, in care/virologically failed or out of care/viral load missing (Viral load not updated in a period of 12 months).

A HIV positive person is considered as being virally suppressed if the viral load in the blood is <1000 copies/ml or below the lower detection limit (LDL) of a test according to the WHO guidelines for developing countries. It is expected that upon initiation into treatment, a patient’s viral load should fall to undetectable levels within three to six months of starting HIV treatment. When the ART fails to suppress and sustain a HIV infected person’s viral load to <1000 copies/ml with confirmation by repeat testing, the patient is considered as having virological failure or rebound.

3.2 Modelling method

A stochastic model with continuous time was constructed to simulate the viral load dynamics in the HIV-1 infected sex worker population. A stochastic model was chosen to incorporate the effect of fluctuations in response to ART on the viral load. Differential equations were defined to explain the stochastic process.

In this model, we suppose that only one event can occur at a specific point in time, therefore exponential distribution was used to estimate the time at which this event occurs. It was assumed that the probability of an event to occur at any point in time is constant; therefore a uniform distribution was used to generate the probability at which an event is supposed to take place. We assumed that as per the WHO test and treat policy, each patient diagnosed with HIV is immediately initiated into care.

3.2.1 Model structure

The model structure depends on the heterogeneity of the study population in terms of the outcome of interest. A compartmental model based on the virology status of the individuals was constructed as follows;

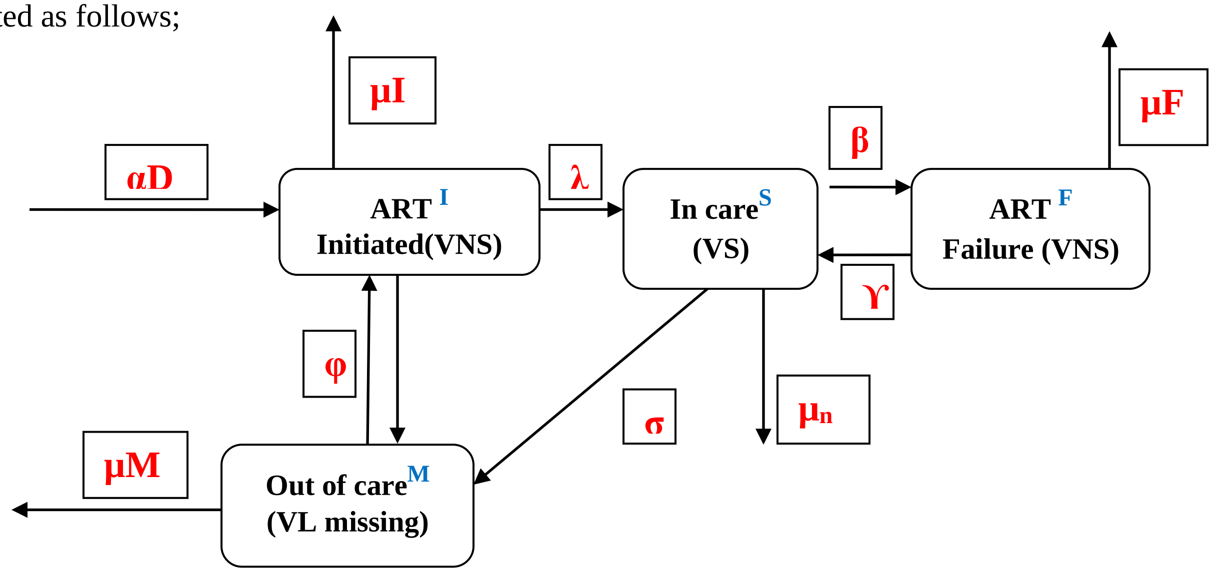

Figure 1: Viral load dynamics compartmental model

The model in **Figure 1** shows the transition process of a newly diagnosed HIV/AIDS sex worker from initiation into care/ART with viral load not suppressed (**I**), to viral load suppressed (**S**).

Compartment (**F**) represents Individuals in care but with virological failure and sex workers presumed out of care/ missing viral load (**M**) for 12 months.

A newly screened individual is initiated into ART (**I**) at the rate **α**and the viral load monitored; while in care, the individual can respond to treatment achieving viral suppression at the rate **λ**. Once viral suppression is achieved, an individual can develop treatment failure at rate **β** due to drug resistance or intolerance to ART regimen. The solution in this case is to change of course of treatment, after which the individual's viral load can become suppressed at rate **Υ**if response to new treatment is good. An individual in compartment **S** can disappear from care at rate **σ**and re-initiated into treatment at rate **φ**if they come back to care facility. **μ** represents the death ratein the concerned compartment and **μ_n**is death rate for an individual whose viral load is suppressed; the assumption in this model is that an individual whose viral load is suppressed lives a normal life therefore **μ_n** is estimated as the national population death rate.

The change in the population size in each compartment was described using a set of differential equations;

$$\frac{dI}{dt} = \alpha D - \mu I - \lambda I$$

$$\frac{dS}{dt} = \lambda I + \gamma F - \beta S - \sigma S - \mu_n S$$

$$\frac{dF}{dt} = \beta S - \mu F - \gamma F$$

$$\frac{dM}{dt} = \sigma S - \varphi M - \mu M$$

3.3 Data source

HIV/AIDS cohort data for sex workers from January, 2015 to August, 2017 was obtained from the SWOP City Clinic Database to estimate the model parameters. The following includes the data used to fit the model;

1) Annual number of sex workers screened for HIV/AIDS
2) Annual number of sex workers diagnosed with HIV/AIDS
3) Annual number of initiated into HIV treatment
4) Annual number of sex workers out of care for 12 months
5) Annual number of sex workers re-initiated into ART
6) Annual number of deaths due to HIV/AIDS among diagnosed
7) Annual number of deaths due to HIV/AIDS among individuals on ART treatment and virally suppressed
8) Total sex worker population in Nairobi County

The data was extracted from the SWOP database and stored in Microsoft Excel 2013. MATLAB R2013a software was used to solve the differential equations and obtain projections in each compartment.

3.4 Model quantification- Parameter estimation

3.4.1 Estimating mortality rates

In this model, it was assumed that all individuals who have not achieved viral suppression have the same date rate, with AIDS related illness being the main cause. To set up the mortality rate for sex workers initiated into care (**μI**), sex workers in care with virological failure (**μF**) and sex workers out of care/viral load missing (**μM**) the National AIDS related mortality rate was used.

Sex workers with suppressed viral load were assumed to have a healthy normal life as a HIV negative individual; therefore the National mortality rate was used as the mortality rate in this group.

3.4.2 Estimating the transition parameters (α, β, ϒ, λ, σ, φ)

The parameters representing the transition between two compartments **(α, β, ϒ, λ, σ, φ)** was estimated using annual cohort data from January, 2015 to August, 2017 extracted from SWOP city clinic database.

3.5 Model validation

Model validation was to be done using goodness of fit approach and graphical residual analysis. $R^2 \geq 0.7$ not less than 0.7 would be considered as a good fit between the model output and the data. Graphical analysis of the residuals is done to evaluate the distribution of the residual, which should be normally distributed with mean zero with fixed variance and should be unsystematic (not explained by any factor)

3.6 Prediction

Simulation was done to predict the change in the population size in each compartment for the next five years. The results from the prediction were used to make recommendations for the project (SWOP).

CHAPTER FOUR

RESULTS

4.1 Population characteristics

A total of 155 sex workers were diagnosed with HIV and started on HIV treatment at SWOP City clinic. This group was followed until August, 2017 to estimate the rate of change from detectable viral load to viral load suppression. 72.9% (113/155) of these sex workers were female. The age distribution among the male and female sex workers was similar as shown in Figure 2.

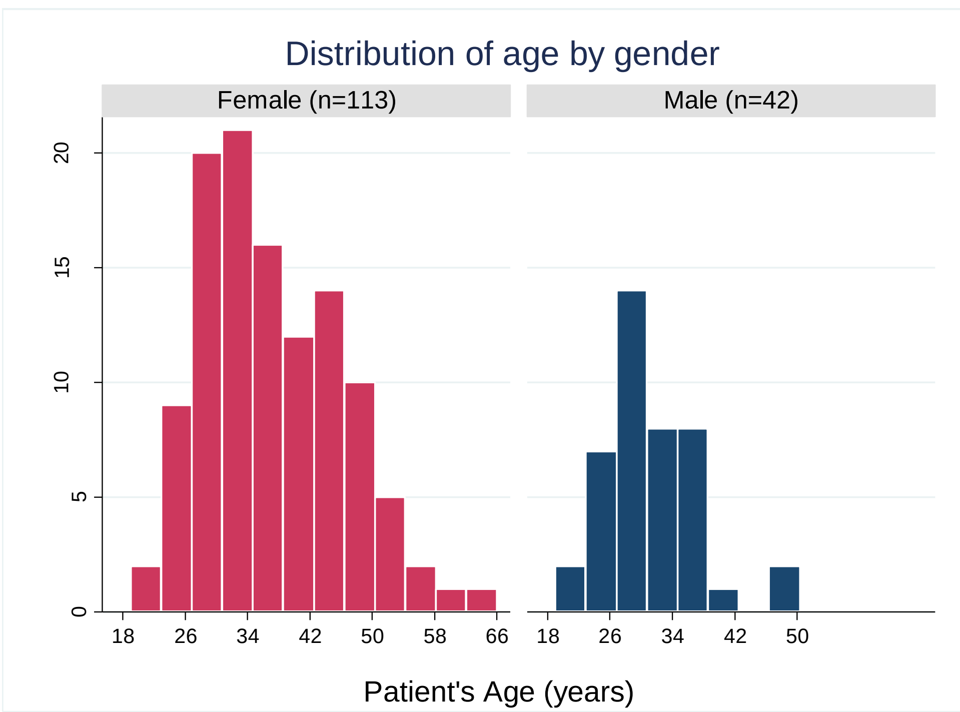

Figure 2: Patients' age distribution by gender

The distribution of age in female was right skewed with a mode at 31 years whereas among males the distribution was normal with a mean of 30.9 years.

The female patients were aged between 19 and 66 years with a mean age of 37.1 years (SD=9.1 years). The male patients were aged between 22 and 49 years with a mean age of 30.9 years (SD=6.0 years).

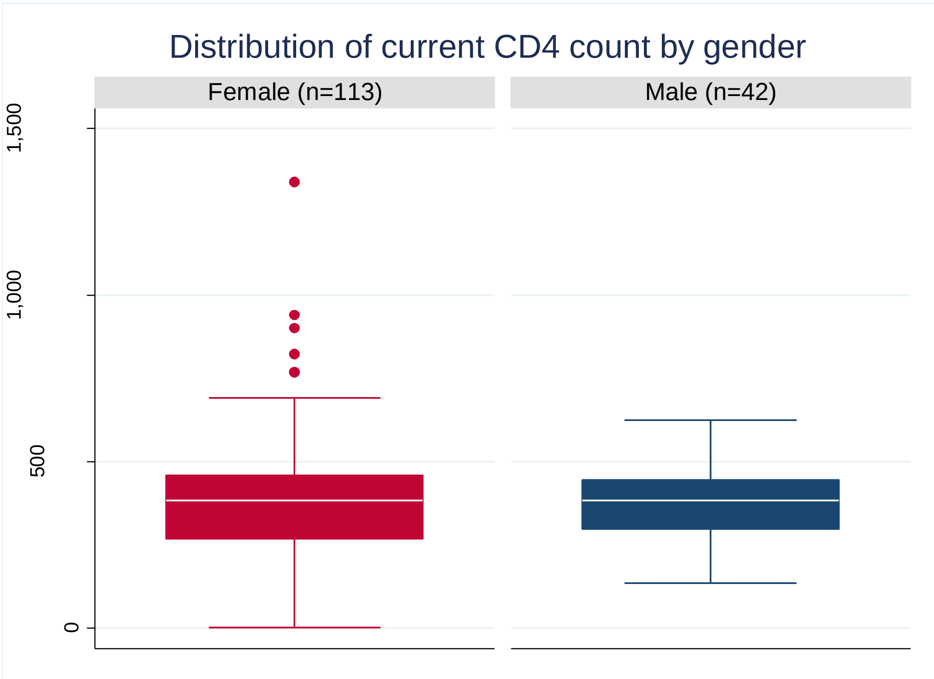

Figure 3: Distribution of patients' CD4 count by gender

The distribution of CD4 count was more spread among female patients than among males with extreme values >650 cells/ml.

4.2 Parameter estimation

4.2.1 Mortality rates

The mortality rates (**μI, μF, μM**) were estimated using the annual national AIDS related deaths and annual number of people living with HIV/AIDS as follows;

$$\mu I = \mu F = \mu M = \frac{Annual\ AIDS\ related\ deaths}{Annual\ estimate\ of\ PLWH} = 0.02$$

Where the estimated annual AIDS related deaths in 2016 was 36, 000 and estimated number of people living with HIV/AIDS was 1.6 million (UNAIDS, 2016).

The national mortality rate estimate for the general population in the year 2016 was used as the mortality rate among the sex workers who were virally suppressed (**μS**=6.8 per 1000 persons).

4.2.2 Compartment transition rates

The rate of diagnosis α was extracted from the NACC report on current HIV estimates in Kenya (2015). According to the report, HIV screening rate was estimated at 18% among female sex workers and 12% among male sex workers in 2015. The assumption is that, once a person tests positive for HIV, he/she is initiated into care as per the WHO policy of test and treat. Therefore α=0.18 for female sex workers and α=0.12 for male sex workers.

The rate of viral suppression, virological failure, transition from viral suppression to missing, transition from missing to care and from virology failure to virological suppression, were determined using the cohort data as follows;

λ (rate of transition from viral load not suppressed (I) to virally suppressed (S)

$$\boldsymbol{\lambda}_{\boldsymbol{aggregate}} = \frac{Annual\ number\ virally\ suppressed\ in\ 2016}{Annual\ number\ initiated\ into\ ART\ in\ 2015} = \frac{98}{155} = 0.63$$

$$\boldsymbol{\lambda}_{\boldsymbol{female}} = \frac{Annual\ number\ virally\ suppressed\ in\ 2016}{Annual\ number\ initiated\ into\ ART\ in\ 2015} = \frac{78}{113} = 0.69$$

$$\boldsymbol{\lambda}_{male} = \frac{Annual\ number\ virally\ suppressed\ in\ 2016}{Annual\ number\ initiated\ into\ ART\ in\ 2015} = \frac{20}{42} = 0.48$$

β (rate of transition from virology suppressed (S) to virology failure (F)

$$\boldsymbol{\beta}_{aggregate} = \frac{Annual\ number\ virology\ failed\ in\ 2017}{Annual\ number\ virally\ suppressed\ in\ 2016} = \frac{11}{98} = 0.11$$

$$\boldsymbol{\beta}_{female} = \frac{Annual\ number\ virology\ failed\ in\ 2017}{Annual\ number\ virally\ suppressed\ in\ 2016} = \frac{9}{69} = 0.13$$

$$\boldsymbol{\beta}_{male} = \frac{Annual\ number\ virology\ failed\ in\ 2017}{Annual\ number\ virally\ suppressed\ in\ 2016} = \frac{2}{20} = 0.1$$

ϒ (rate of transition from virology suppressed (S) to virology missing (F)

$$\boldsymbol{\Upsilon}_{aggregate} = \frac{Annual\ number\ virology\ missing\ in\ 2017}{Annual\ number\ initiated\ into\ care\ in\ 2015} = \frac{36}{155} = 0.23$$

$$\boldsymbol{\Upsilon}_{female} = \frac{Annual\ number\ virology\ missing\ in\ 2017}{Annual\ number\ initiated\ into\ care\ in\ 2015} = \frac{26}{113} = 0.23$$

$$\boldsymbol{\Upsilon}_{male} = \frac{Annual\ number\ virology\ missing\ in\ 2017}{Annual\ number\ initiated\ into\ care\ in\ 2015} = \frac{5}{42} = 0.12$$

The rate of transition from virology missing (F) to care/ART re-initiated was assumed to be equivalent to the rate of diagnosis [**φ=α]**

Using the defined parameters, the evolution of the subpopulations was modeled with the following set of differential equations;

$$\frac{\boldsymbol{d}}{\boldsymbol{dt}}\begin{bmatrix} I \\ S \\ F \\ M \end{bmatrix} = \begin{bmatrix} \alpha I\frac{N}{I} - \mu - \lambda & 0 & 0 & \varphi \\ \lambda & -\mu - \gamma - \sigma & \beta & 0 \\ 0 & \gamma & -\beta - \mu & 0 \\ \theta & \sigma & 0 & -\mu - \varphi \end{bmatrix} * \begin{bmatrix} I \\ S \\ F \\ M \end{bmatrix}$$

4.3 Projected change in model compartments

The set of differential equations were solved; projections were done based on the estimated parameters and presented graphically.

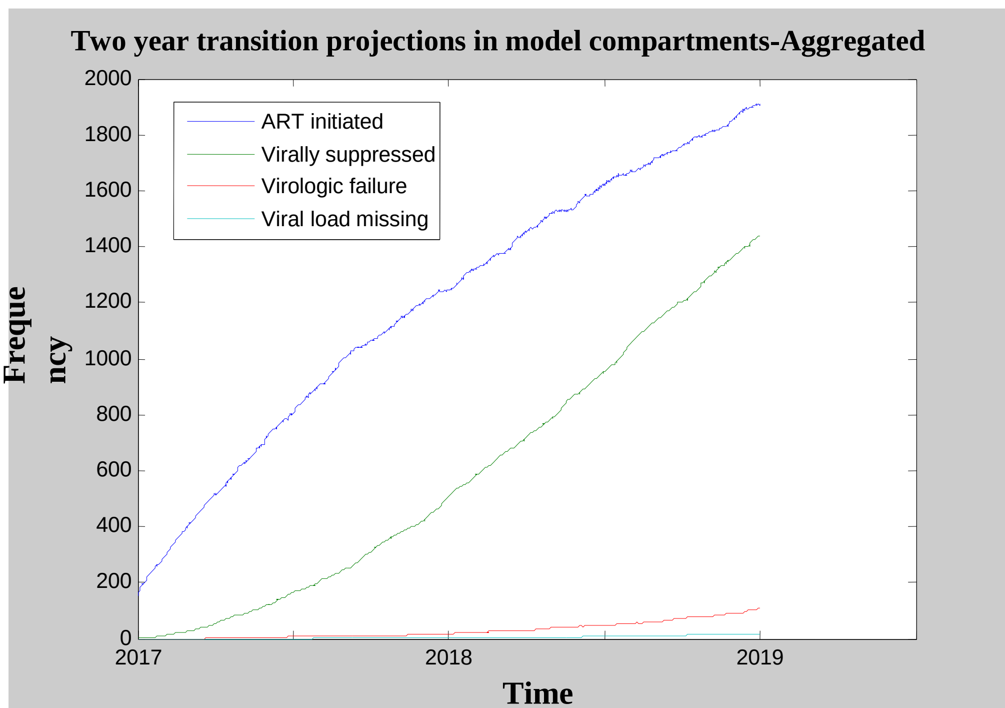

Figure 4: Two year transition projection in model compartments (All sex workers)

Using the set of rates ($\lambda = 0.63$, $\beta = 0.11$ $\sigma = 0.23$ $\Upsilon = 0.6$ $\varphi = 0.14$) and initial number of diagnosed/initiated into care=155 patients, there was a steady increase in the number of patients diagnosed and initiated into care and virally suppressed to about 1900 patients and 1400 patients by 2019, respectively. At any given point in time the number of diagnosed people initiated into care, was more than the number of patients who are virally suppressed by about 500 patients but the margin seemed to narrow as time approaches 2019. Starting with one patient with virological failure, the number increased gradually to about 100 patients in 2019. The patients lost to follow-up (viral load missing) remained low in the two year period.

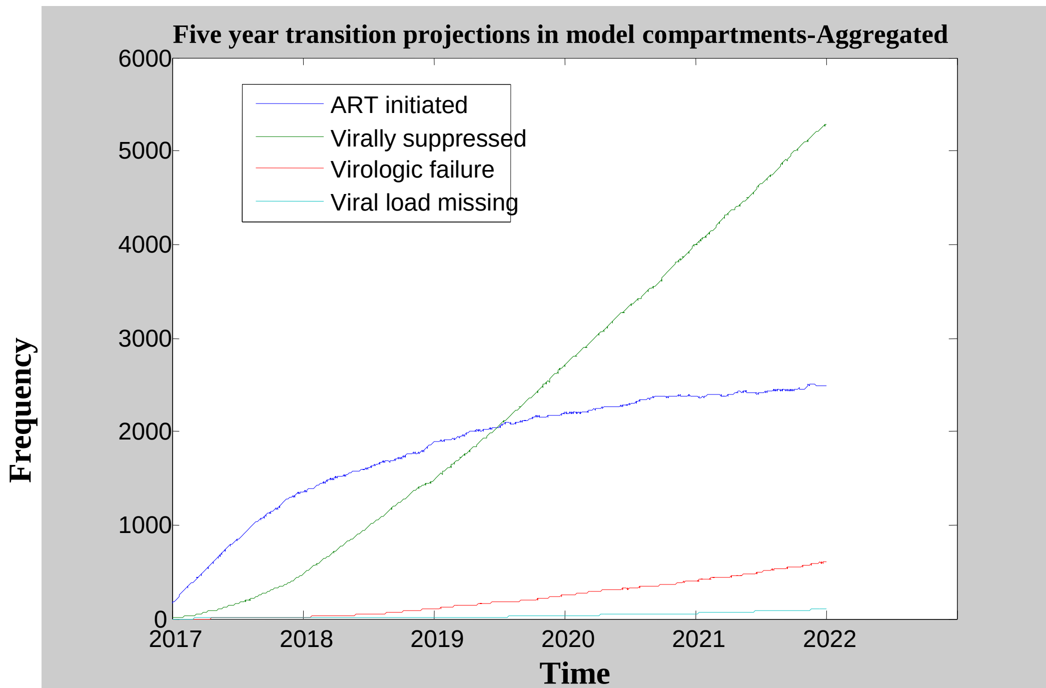

Figure 5: Five year projected transition in compartments (All sex workers)

Maintaining the status quo, there was a number of diagnosed/initiated into care tend to increase until 2019 after which the change tends to stabilize. Starting with 1 virally suppressed patient, the number in this compartment increases gradually up to 2018 to almost 200 patients, followed by a sharp increase for the next 4 years to about 5000 patients. In the first 2and half years, the number of patients initiated into care/ viral load not suppressed was more than the virally suppressed; after which the number patients virally suppressed exceeded the initiated into care.

The number of viral load missing increased gradually for the five years. The number of patients presumed to be out of care/viral load missing was very low throughout the five year period.

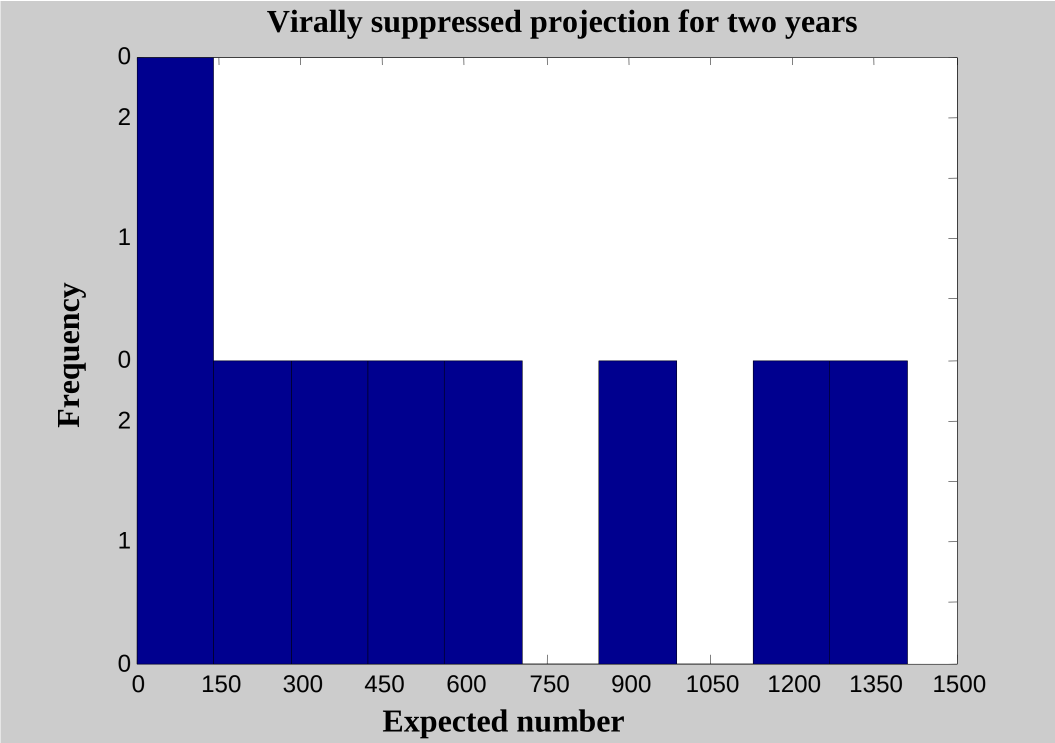

Figure 6: Histogram showing the expected cumulative number of virally suppressed patients between 2017 and 2019 at intervals of 3 months

For the first 6 months the expected cumulative of virally suppressed patients was 150 patients. Between the 6th month of 2017, and December, 2019, the expected number increased every three months up to about 1400 patients.

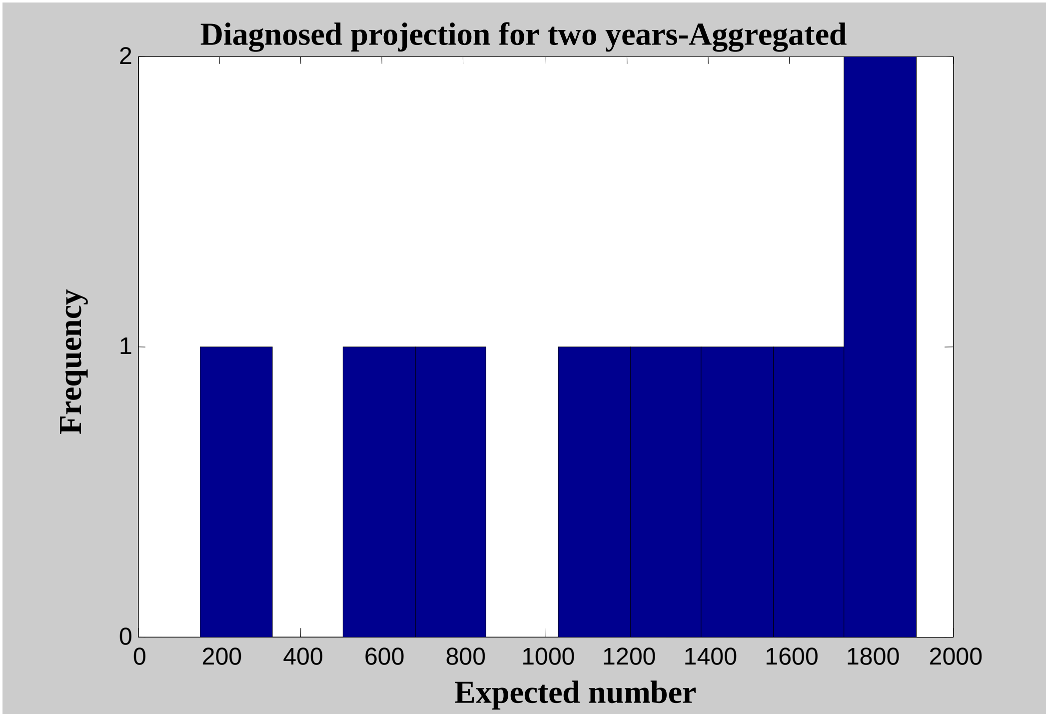

Figure 7: Histogram showing the expected cumulative number of patients initiated into care between 2017 and 2019 at intervals of 3 months

The expected cumulative number of diagnosed HIV patients initiated into care increased every three months from 200 in the first three months up to 1800 by December, 2019

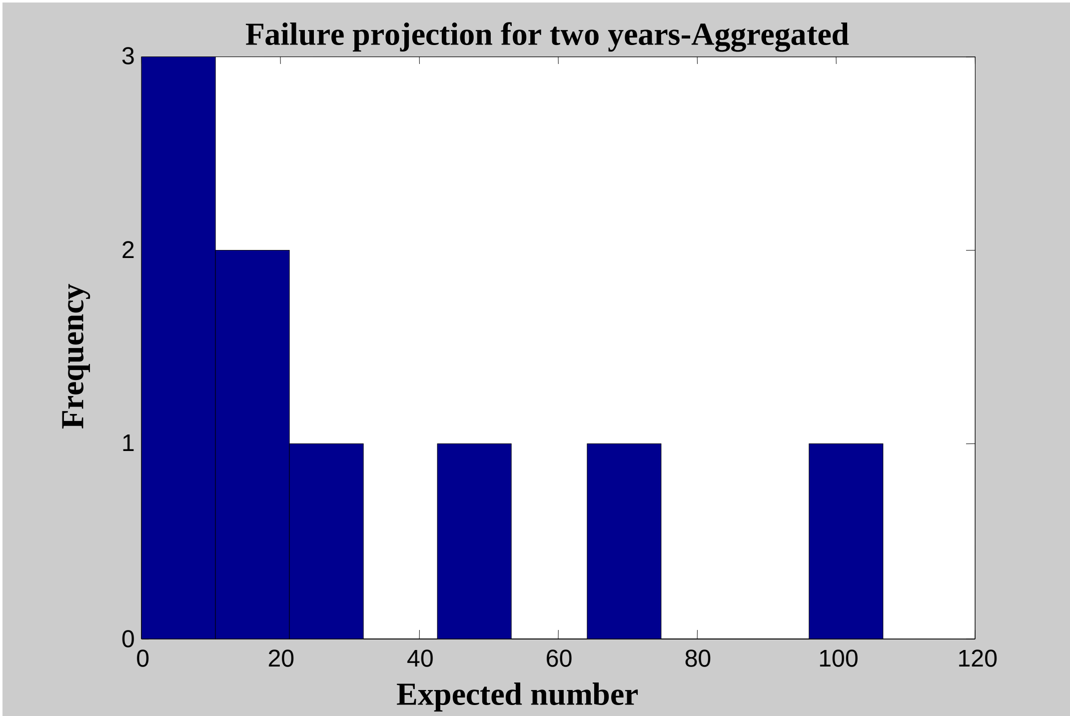

Figure 8: Histogram showing the expected cumulative number of patients with virological failure between 2017 and 2019 at intervals of 3 months

In the first 9months, the expected cumulative number of patients experiencing virological failure ranged between 0 and 10 patients; this number increased to about 110 patients by December, 2019.

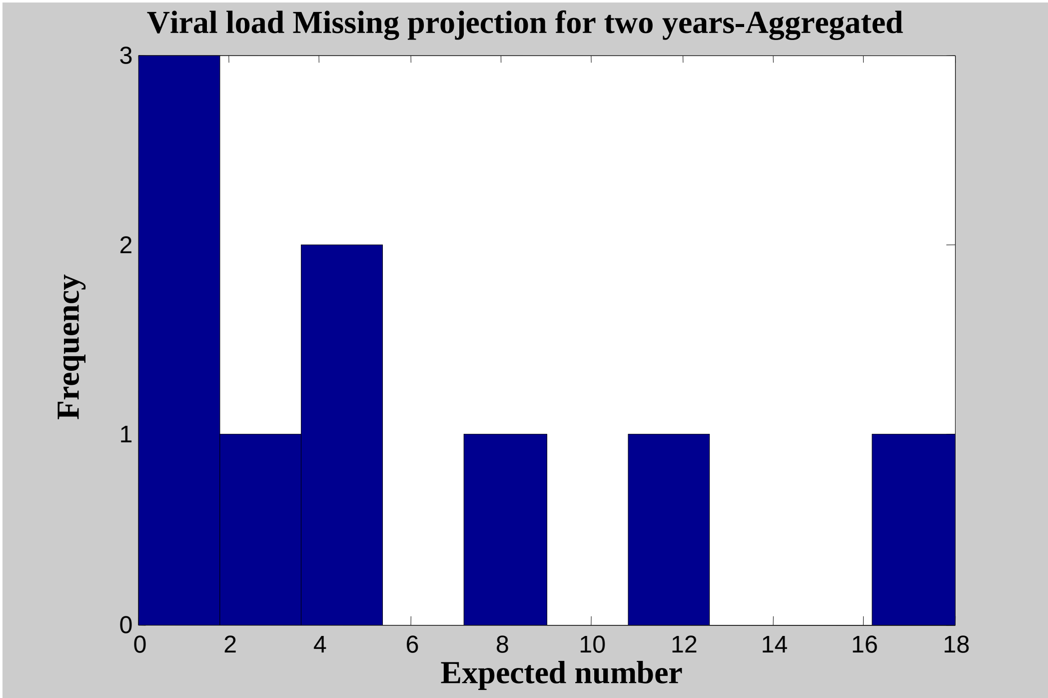

Figure 9: Histogram showing the expected cumulative number of patients with viral load missing between 2017 and 2019 at intervals of 3 months

For the first 9 months the expected cumulative number of patients likely to be lost to follow-up (viral load missing) ranged between 0 and 2 patients. By December, 2019, the number was expected to rise to about 18 patients.

Projections were done using the gender specific rates for comparison as shown in **Figures 10, 11, 12** and **13.**

Starting with a ratio of virally suppressed to ART initiated of 1:113, after one year the ratio increased to 5:13 and 15:19 after two years among female sex workers; This translates to a 43.5 times increase in ratio after 1 year and 89.2 times increase after two years (**see Figure 10**).

Among the males, starting with a ratio of virally suppressed to ART initiated of 1:42, after one year the ratio had increased to 5:20 followed by 15:31 increase at the end of two years; this translates to 10.5 times increase in the ratio after one year and 17.6 times increase after two years (**see Figure 11**).

The rate of increase in the number of patients who are virally suppressed with respect to the number initiated into care was higher among female compared to male.

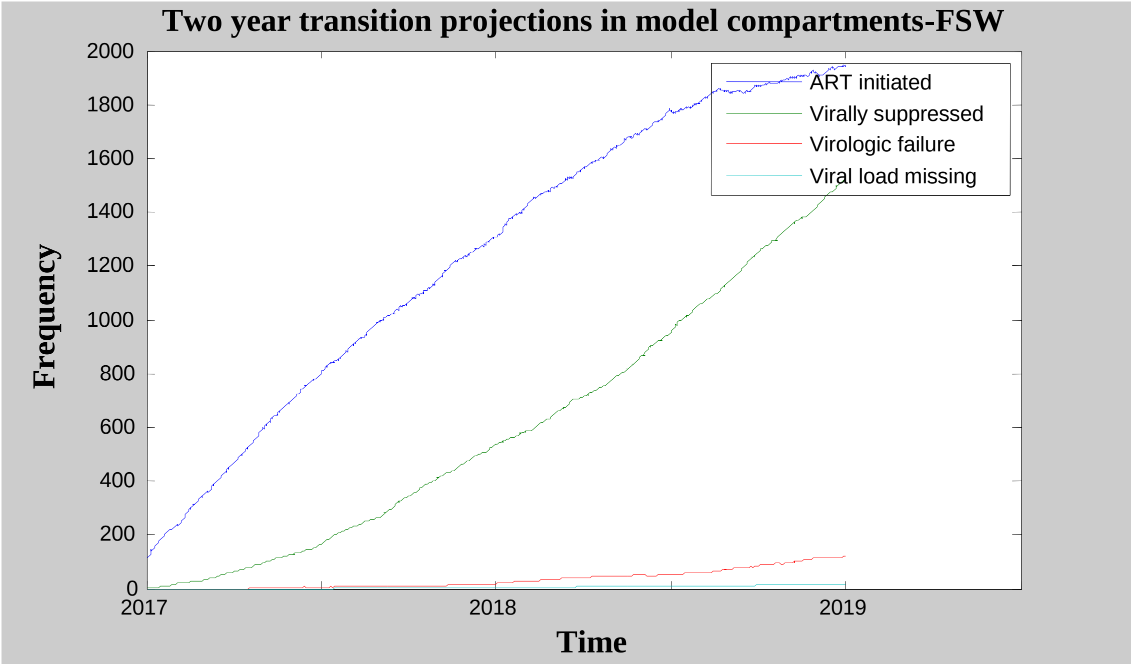

Figure 10: Two year projections in model compartments using rates specific for female sex workers

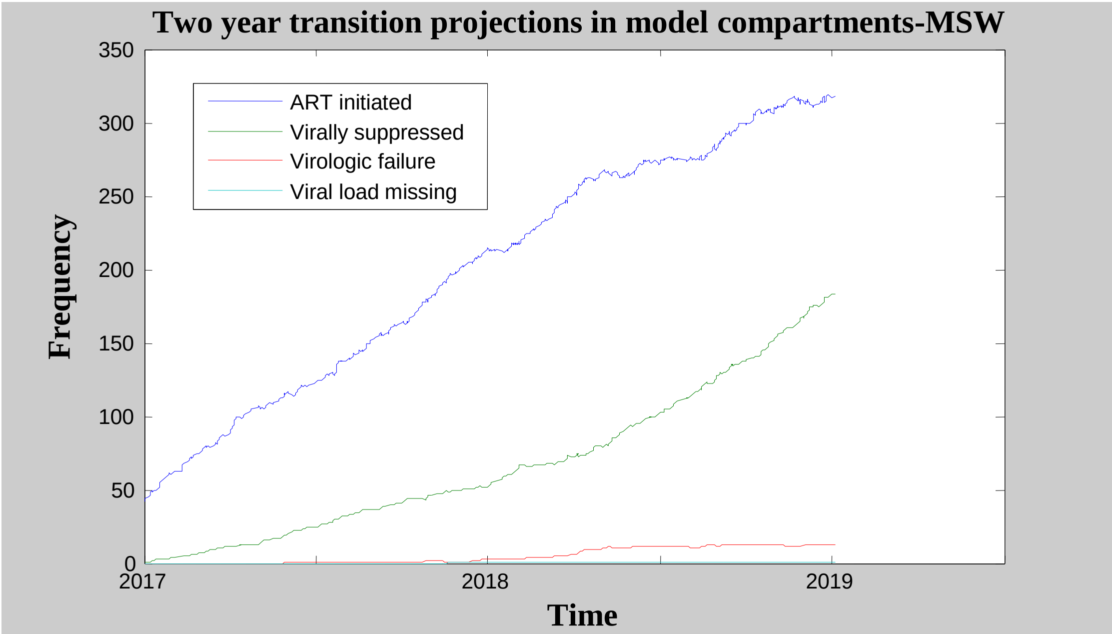

Figure 11: Two year projections in model compartments using rates specific for male sex workers

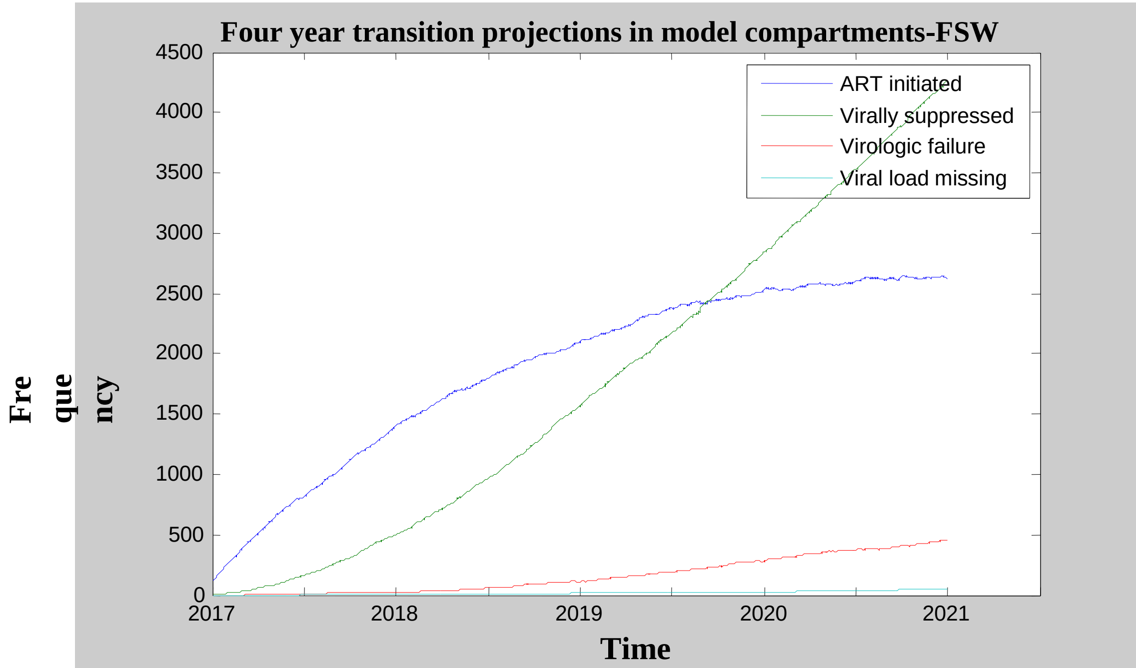

Figure 12: Four year projections in model compartments using rates specific for female sex workers

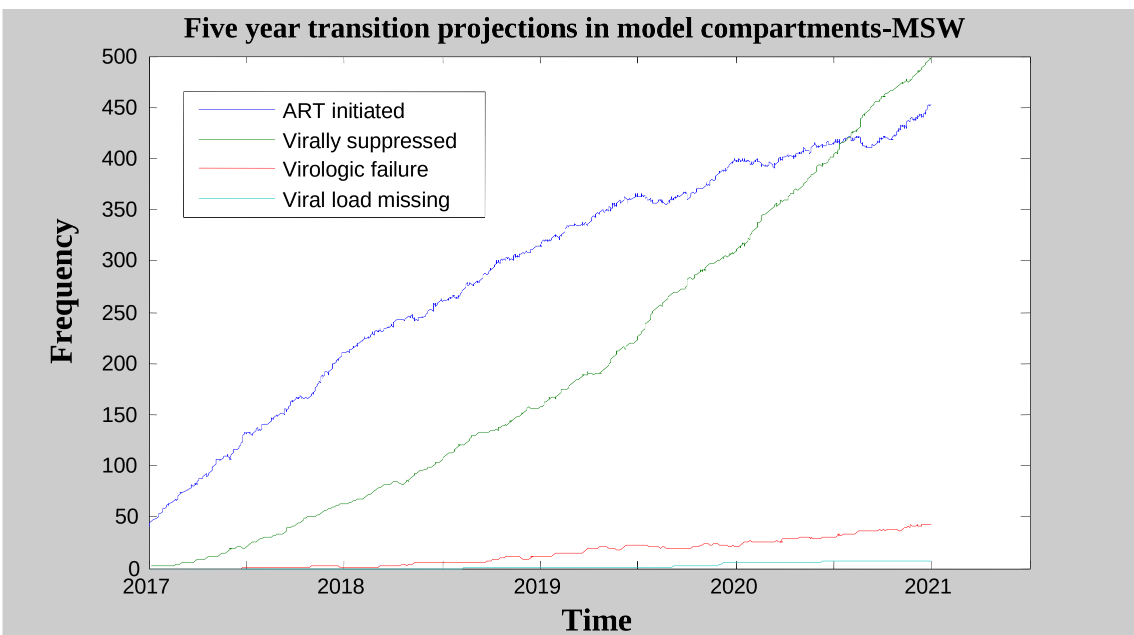

Figure 13: Four year projections in model compartments using rates specific for male sex workers

4.4 Estimation of the net reproductive number

The primary goal of SWOP is to ensure that at least 90% of HIV patients in care achieve viral suppression and maintain their viral load below detectable levels for as long as possible. If this is scenario, we should have observed an increasing trend in the viral suppression curve (cumulative frequency in the virally suppressed compartment)and a decreasing trend in the other three curves (other compartments). As observed in Figure 5, despite the increasing trend in the viral suppression curve, an increasing trend in the failure compartment was pronounced. To ensure a continuous and sustained increased in the viral suppression compartment, the virology failure needs to be controlled. Mathematically this implies that;

$$\frac{d\boldsymbol{S}}{d\boldsymbol{t}} = \boldsymbol{\lambda I} + \boldsymbol{\gamma F} - \boldsymbol{\beta S} - \boldsymbol{\sigma S} - \boldsymbol{\mu_n S} < 0$$

$$\boldsymbol{\lambda I} + \boldsymbol{\gamma F} - (\boldsymbol{\beta} - \boldsymbol{\sigma} - \boldsymbol{\mu_n})\boldsymbol{S} < 0$$

$$\boldsymbol{\lambda I} + \boldsymbol{\gamma F} < (\boldsymbol{\beta} - \boldsymbol{\sigma} - \boldsymbol{\mu_n})\boldsymbol{S}$$

$$\frac{\boldsymbol{\lambda I} + \boldsymbol{\gamma F}}{(\boldsymbol{\beta} - \boldsymbol{\sigma} - \boldsymbol{\mu_n})\boldsymbol{S}} < 1$$

Considering number of treatment failures (F) are come from the patients initiated into care/ART (I), then $\boldsymbol{F} < I$and,

$$\boldsymbol{\lambda I} + \boldsymbol{\gamma F} < \lambda I + \gamma I$$

Therefore,

$$\frac{(\boldsymbol{\lambda} + \boldsymbol{\gamma})\boldsymbol{I}}{(\boldsymbol{\beta} - \boldsymbol{\sigma} - \boldsymbol{\mu_n})}\frac{\boldsymbol{I}}{\boldsymbol{S}} < 1$$

Substituting the equation above with the calculated rates; we obtain,

$\mathbf{3.12}\frac{I}{S} < 1$**,** therefore; for 1 patient initiated into care, 3 patients are expected achieve viral suppression in order to control the number in the virological failure compartment.

4.5 Projection of patient population size initiated into care and virally suppressed compartments at a point in time

Using the estimated rate parameters from the cohort data, the estimated number of patients initiated into care by July, 2019 (2 years) is 1,925 whereas the population size of virally suppressed at the same period is estimated at 1,470; giving a ratio of 1 patient initiated into care for 0.7 virally suppressed patients (**see Figure 14 & 15**).

After 5 years (July, 2022), the population size among initiated into care was estimated at 2,525 and 5,300 among virally suppressed. This translates to a ratio of 1 initiated into care for 2.1 virally suppressed patients (**see Figure 16 & 17**).

In July, 2024 (after 7 years), we expect to have 2,575 patients initiated into care and 8,100 patients virally suppressed. This gives a ratio of 1 initiated into care for 3.14 virally suppressed patients (**see Figures 18 & 19**).

Maintaining the current rates of transition, it will take 7 years from now to obverse a decreasing trend in the number of viral load failure among patients in care.

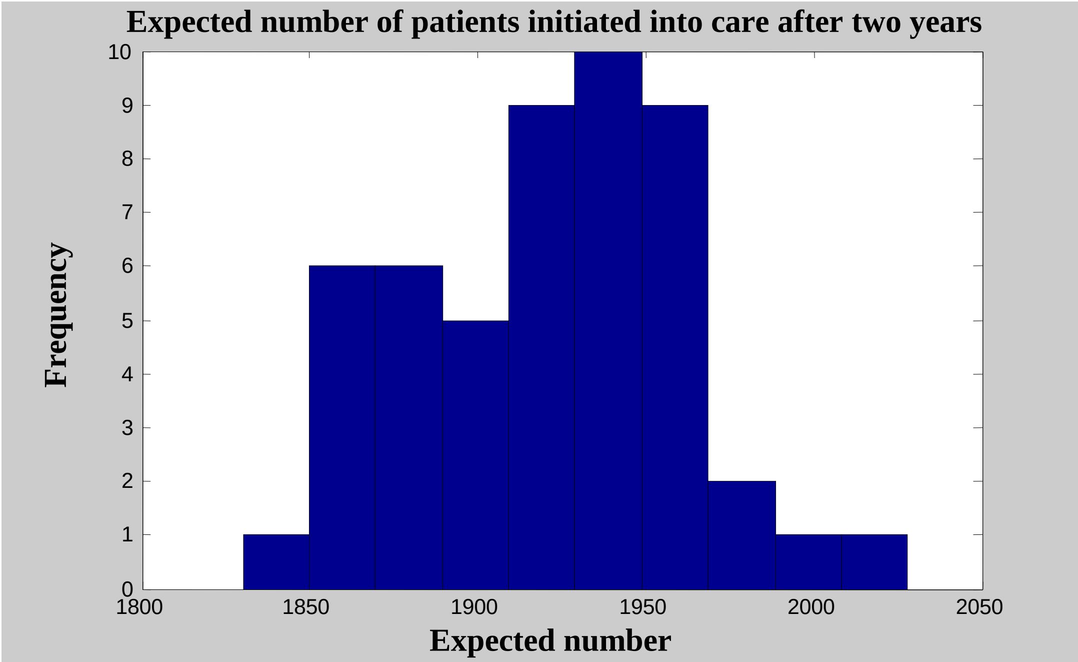

Figure 14: Projected population size of initiated to care compartment after two years

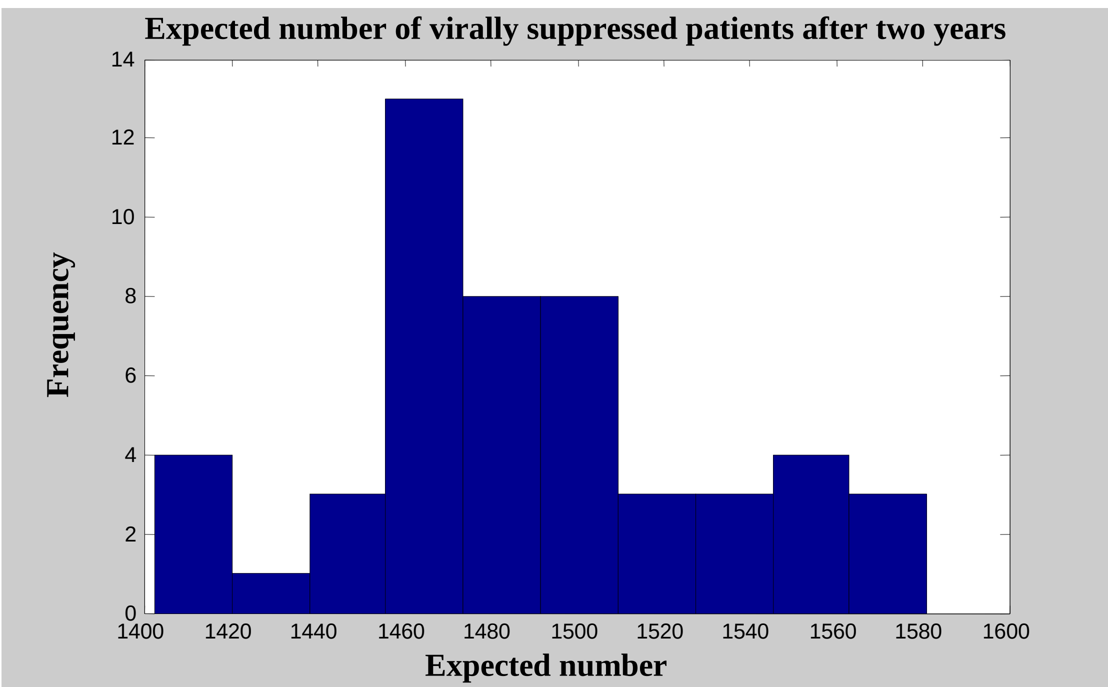

Figure 15: Projected population size in viral load suppressed compartment after two years

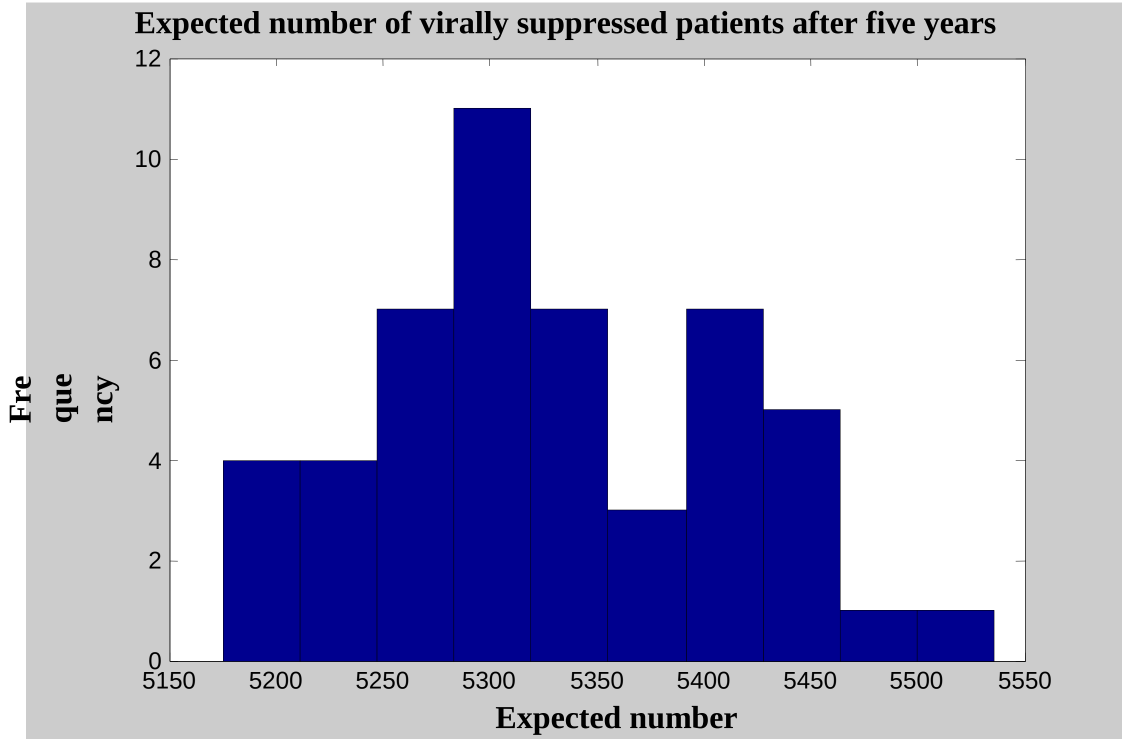

Figure 16: Projected population size in viral load suppressed compartment after five years

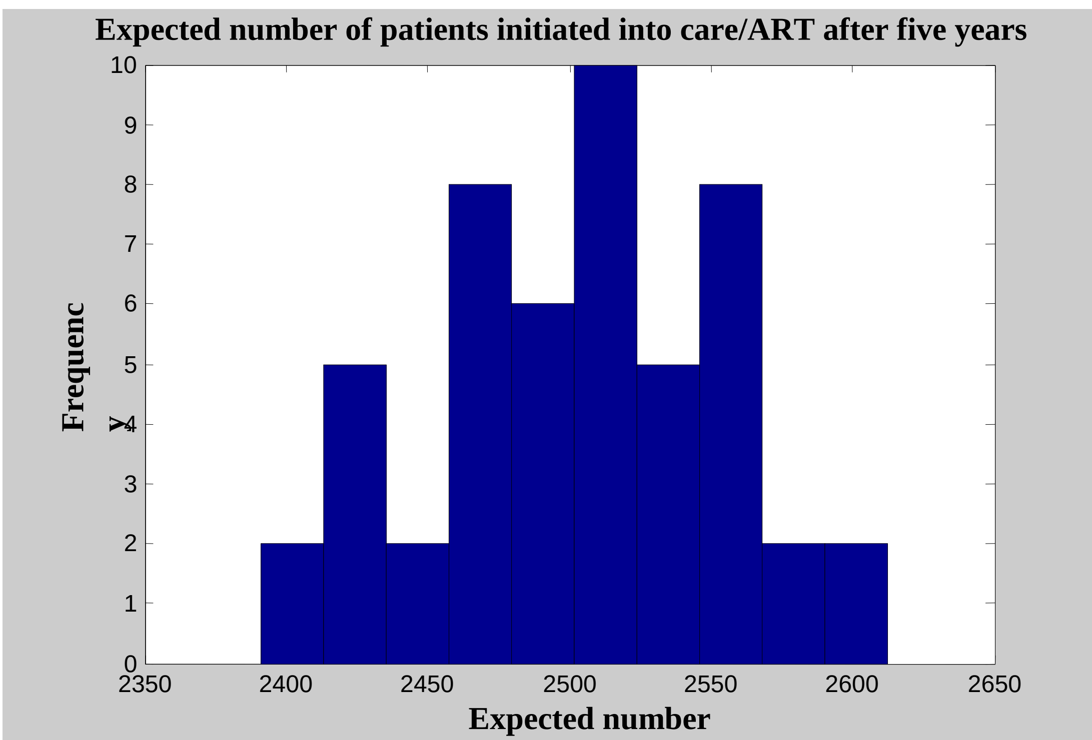

Figure 17: Projected population size of initiated to care compartment after five years

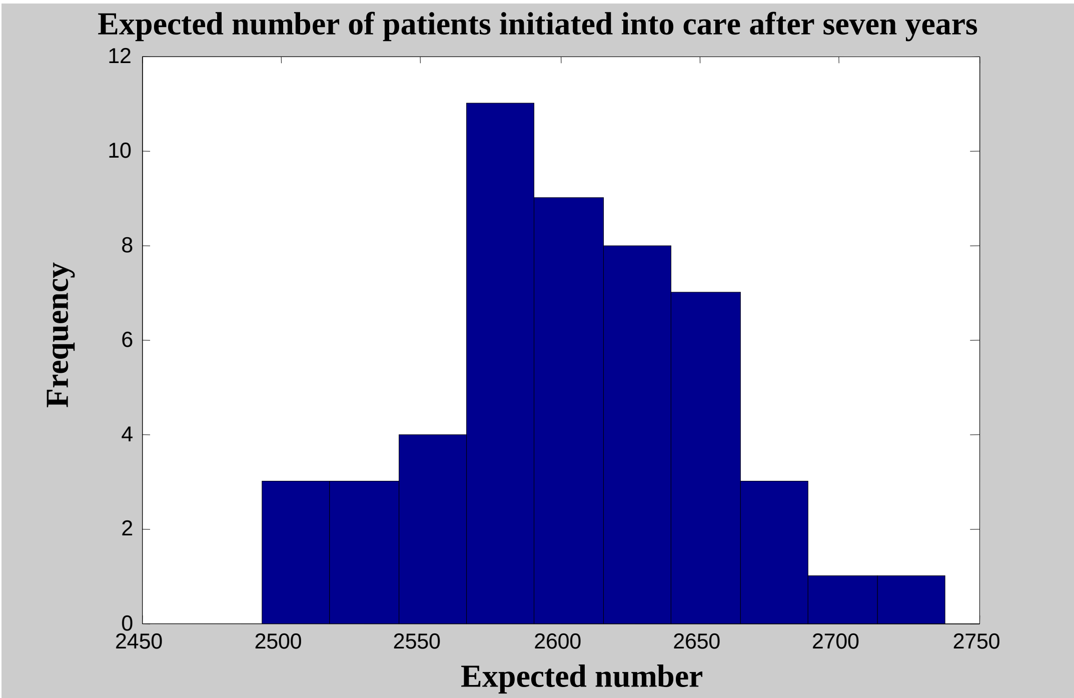

Figure 18: Projected population size of initiated to care compartment after seven years

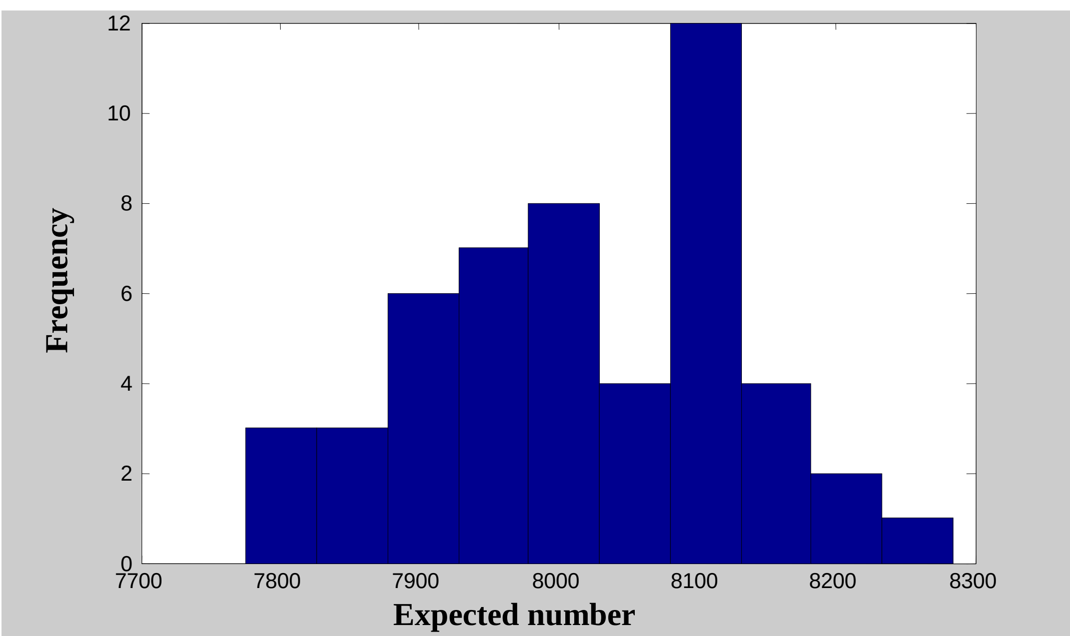

Figure 19: Projected population size in viral load suppressed compartment after seven years

CHAPTER FIVE

DISCUSSION

Mathematical models have proved to be a useful tool in the study of biological and biochemical systems. They have been extensively used to make HIV prevalence and incidence projections and to set up thresholds to guide HIV control programs. Several models have been constructed to describe the dynamic process of HIV transmission, testing and treatment response. Mathematical models can be adapted to a specific population by taking account of the heterogeneity of the population; this is achieved by fitting the models to the available longitudinal (follow-up) data of the target population (Zhimin et al, 2016).

In this study the NHAS Mathematical model described by Kelly (2016) was adapted and calibrated using the HIV viral load data for sex workers initiated into care in 2015 at SWOP City clinic. The aim of this model was to describe mathematically the viral load transition process in patients initiated into care and determine the net reproduction number to control the number of patients with virology failure. Achievement and sustenance of suppressed viral replication is the primary goal of ART; viral suppression prolongsthe survival of people living with HIV/AIDS leading to an increase their number in the populationand reduces new infections by lowering transmission (Rivadeneira et al, 2014).

The study population comprised of male and female sex workers; the two subpopulations presented similar characteristics in terms of age and CD4 counts. With regards to the rates of transition between compartments, only the rate of virological failure was almost equal in the two groups ($\boldsymbol{\beta_{female}=0.13}$ vs $\boldsymbol{\beta_{male}=0.1}$). This finding is consistent with the results of studies done in a rural HIV clinic in Coastal Kenya(Hassan et al, 2014) and in a semi urban HIV clinic (Wamicwe et al, 2012) investigating the predictors for HIV-1 virologic failure in patients attending the facilities. In both studies, the both studies the risk of HIV virologic failure was statistically not different between male and female patients. The rate of viral suppression was higher in female compared to male sex workers (**λ_{female}=0.69** vs **λ_{male} =0.48**). Considering the fact that the rate of failure is similar for both male and female, more female are likely to have sustained viral suppression compared to male.

Simulation was done to project the changes in the subpopulations maintaining the rates estimated from the data. The two year projection showed that after first two years (2019), for each patient initiated into care/ART, we have <1 patient in care achieving viral load suppression. In the five year projections, it was noted that after 2 years and 8 months, each patient initiated into care generates >1 virally suppressed patient. A similar trend was observed among male and female patients; however for the four year projection curve for male, the initiated into care curve and virally suppressed curve cross later than the female curves (after 3.5 years in males vs 2.5 years in females)

The net reproductive number was determined to set the threshold to ensure a decrease in the number of virological failure. Using the rates obtained from the data, for one patient initiated into care at least three patients in care should achieve viral suppression. Simulation was done to evaluate the time at which this ratio will be achieved under the same conditions; it would take the project at least 7 years to achieve this ratio and observe a decreasing trend in the number of virological failure.

CONCLUSION

The study successfully adapted the NHAS mathematical model to SWOP; in view of the difference in rates of initiation to care and viral suppression between male and female sex workers, SWOP should come up with tailored strategies to targeting male sex workers to increase the number of HIV positive male sex workers with suppressed viral load. This will in turn reduce the rate of HIV transmission from infected male sex workers to susceptible people.

The estimated period of 7 seven years to observe a decreasing trend in virologic failure can be reduced by adjusting the different rates of transition. Further studies should be conducted to investigate the factors affecting the rate parameters between different compartments.

There's need to improve on HIV data reporting for all sex workers in care, especially the group of patients that are lost to follow-up.

This model is applicable to SWOP; optimization should however be done at least every two years to reflect the reality of the project.

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APPENDIX: ETHICAL APPROVAL

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Ref. No.KNH/ERC/R/42

20th March 2017

Dr. Joshua Kimani
Co-Investigator
UNITID
College of Health Sciences
University of Nairobi

Dear Dr. Kimani

Re: Approval of Annual Renewal – Use of clinical data care database by the University of Nairobi/University of Manitoba Research team to evaluate HIV prevention, care and treatment in Kenya (P258/09/2008)

Refer to your communication dated March 10, 2017.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol P258/09/2008.

The approval dates are 18th February 2017 - 17th February 2018 .

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH- UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN-Ethics & Research Committee for each batch of shipment.

Protect to discover

g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

Kindly ensure that the study is renewed annually within the period required by KNH-UoN ERC.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Principal, College of Health Sciences, UoN
The Director CS, KNH
The Chairperson, KNH-UoN ERC

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