FIRST-LINE AND SECOND-LINE ART TREATMENT FAILURE PREDICTION IN MALAWI: A SOFT COMPUTING MODELLING APPROACH

MASTER OF SCIENCE (INFORMATICS) THESIS

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UNIVERSITY OF MALAWI

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July, 2024.

DECLARATION

I the undersigned hereby declare that this thesis is my own original work which has not been submitted to any other institution for similar purposes. Where other people's work has been used acknowledgements have been made.

DUMISANI J. NDHLOVU

Full Legal Name

Signature

08 July, 2024

Date

CERTIFICATE OF APPROVAL

The undersigned certify that this Thesis represents the student's own work and effort and has been submitted with my approval.

Signature: _____ Date: _____

Dr Kondwani Godwin Munthali

Supervisor

DEDICATION

This work is dedicated to all health workers, all people living with HIV and to the Republic of Malawi.

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Firstly, I would like to thank my supervisor Dr Kondwani Godwin Munthali for his guidance in this research. Secondly, I would like to thank my work supervisors at Lighthouse Trust and the technical advisory from the M & E and Clinic departments. Thirdly, I would like to thank my friends, family, mum, brothers, and sisters for supporting me through my studies. Lastly and most importantly, I would like to thank God for giving me good health and grace throughout this research.

ABSTRACT

As part of routine care and treatment activities for people living with HIV and are on antiretroviral therapy (ART) treatment, health care providers conduct reviews on patients for possible ART treatment failure. However, due to the limited number of available experts and increasing number of treatment failure cases, it is not feasible to manually analyze patients for treatment failure. Most health facilities in Malawi use EMR systems to monitor patients' performance. This research aimed at finding an efficient and effective model to predict ART treatment failure by utilizing the data available in the EMR systems. An Artificial neural network binary classifier model was built to predict ART treatment failure for first- and second-line regimens. We used ethnographic methods to respond to qualitative objectives which were to establish ART treatment predictors and current algorithms that are followed in treatment failure determination. Participation and observations were employed and a total of 17 experts were interviewed. The methodology used, followed the CRISP-DM framework by first understanding the HIV treatment failure domain, the causes and factors associated with treatment failure, and how treatment failure is currently determined. Only correlated variables to the outcomes were considered in building the ANN prediction model. A random sample dataset of 10,000 patients was generated from the EMR system database. Out of these only 1,722 records had sufficient data and were used in the ANN modelling. SMOTE technique was used to balance the distribution of data on the target variable. A backpropagation ANN model was built using Python3, Sci-Kit Learn library, Keras and TensorFlow backend. The ANN model evaluation scored accuracy of 99.71% which shows that ANN model can be used to predict ART treatment failure outcome. The presented results have demonstrated in this research that it can be a viable technique to model treatment failure prediction using soft computing. The research recommends the model for treatment failure review process.

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ABBREVIATION AND ACRONYMS

AIDS	Acquired immunodeficiency Syndrome
ANC	Antenatal care
ART	Antiretroviral Therapy
ARV	Antiretroviral (drug)
CDC	Center for Disease Control
CRISP-DM	CRoss Industry Standard Process for Data Mining
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
EMR	Electronic Medical Record
ETV	Etravirine
HIV	Human immunodeficiency virus
IRNNS	Intelligent Rough Neural Networks
KS	Kaposi Sarcoma

LR	Linear Regression
MIQ	Machine Intelligence Quotient
MLP	Multi-Layer Perceptron
MoH	Ministry of Health
MPHIA	Malawi Population-Based HIV Impact. Assessment
NRTI	Nucleoside reverse-transcriptase inhibitor
NRTIs	nucleoside reverse transcriptase inhibitors
PI	protease inhibitor
PMTCT	Prevention of mother-to-child transmission
POC	point of care
RAL	Raltegravir
RTV	Ritonavir
SMOTE	Synthetic Minority Oversampling TEchnique
TAT	Turnaround Time
TB	tuberculosis
Tx	Treatment Failure

UNAIDS	United Nations Programme on HIV/AIDS
VL	Viral load
VL	viral load
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

There have been medical and scientific efforts to fight the human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS) pandemic for many years and still the cure has not been found. HIV is a virus which leads to AIDS, which causes failure of immune system hence allowing other opportunistic infections to affect the body and thrive (CDC, 2021). To restore immune function and reduce HIV-related adverse outcomes, people living with HIV take antiretroviral therapy (ART) (Danel et al., 2015). However, treatment failure takes away this advantage and leads to an increased morbidity and compromised quality of life in HIV patients (Ayalew et al., 2016). ART treatment failure is when ARV drugs are unable to control HIV infection (Aldous & Haubrich, 2009). Furthermore, studies have shown that ART treatment failure is now an emerging challenge in the fight against the HIV/AIDS pandemic (Chagomerana et al., 2018). Das & Sanyal (2020) also recognized that the crisis of healthcare resources such as healthcare workers and machines in our society are crucial issues and the crisis is well observed during outbreaks especially in low resource settings. Furthermore, ART Treatment failure and delay in switching to second-line regimen are major concerns in the treatment of HIV infected children in a resource limited setting (Haile & Berha, 2019).

Malawi is one of the low resource setting countries and treatment failure is determined manually by trained clinicians, hospital physicians and expert committees who follow a set of World Health Organization (WHO) and National ART guidelines.

This research aimed at modelling first- and second-line ART treatment failure prediction using Artificial Neural Networks (ANN) which is a component of soft computing techniques.

Soft computing is defined as a collection of methodologies that aim to exploit the tolerance for imprecision and uncertainty to achieve tractability, robustness, and low solution cost (Zadeh, 1994). It is used to solve complex problems which are uncertain, nonlinear, or time irreversible, such as human perception, biological evolution, and fuzzy reasoning. Soft computing is based on the human mind (Zadeh, 1994). Soft Computing techniques are widely used to solve problems in various fields in different branches of science and technology (Gupta & Shivani, 2021). Soft Computing is applied in the field of medical science a branch of science concerned with the research of the diagnosis, treatment and prevention of disease or condition (Das & Sanyal, 2020). In this research we looked at HIV treatment failure for people living with HIV and are on ART medication. Specifically, the research looked at First- and second-line ART treatment failure prediction by exploring the ANN soft computing modeling methods.

ART treatment is categorized into three regimen lines, namely: first, second and third-line and in each category line there are different drugs and drug combinations (MOH, 2016). Firstly, a diagnosed HIV patient is put on first-line drugs, but if the drugs are observed that they are not working accordingly, the patient is switched to second-line regimen and if the patient fails on second-line treatment, they are switched to third-line treatment (MOH, 2018). The drugs in second-line are more powerful than the first-line while the third-line drugs are more powerful than the second-line. The third-line regimens include newer generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) and boosted protease inhibitors (PIs) (Moorhouse et al., 2019). The third-line

regimen was recommended by the WHO to be made available in all countries from 2009, however only few can provide these regimens due to the high cost and complexity of implementation (Moorhouse et al., 2019).

The determination of treatment failure for patients on first-line is conducted by trained ART clinic providers who follow the National ART guidelines based on the WHO clinical, immunological, and virological criteria (WHO, 2017). Unlike the standard management of the first-line treatment failure, the second-line ART treatment failure is determined by higher cadre of ART providers (Moorhouse et al., 2019). In Malawi patients that are suspected to be failing on second-line ART treatment are referred to a committee of experts which reviews the cases across the country. For a patient to be reviewed, the primary care provider who is mostly a Clinician, fills in an application form[1] with patient's details and medical history summary which is then submitted to the committee known as the third-line expert ART committee (Heller et al., 2019).

The third-line ART committee exists to facilitate decision making when and after switching HIV patients that are on second-line regimen to third-line regimens (Heller et al., 2019). Applications come from all areas including in the most remote locations in Malawi. The process poses a challenge as most of the health facilities are located far apart in rural areas as well as urban areas. Additionally, the rural people are not getting proper treatment due to the lack of doctors and they are mostly committed to death due to improper diagnosis by the chock doctors (Das & Sanyal, 2020). Furthermore, Clinicians at the remote health facilities are often confronted with HIV patients with all the signs, suspected to be failing on their current treatment but they are forced to queue applications to expert committee to review and diagnose the patients. The process of applying to the expert committee usually takes long and waiting for results can be unbearable. In Malawi the mean turnaround time (TAT) from receiving an initial application until communication of the final recommendation is approximately two months (range of 21 to

[1] 3rd line ART application form (form is attached in the appendices)

166 working days) (Heller et al., 2019). The delay in diagnosing treatment failure for suspected patients can often be very distressing for both the patient and clinician managing the patient. In some cases the clinician responsible may be unsure whether it is necessary to apply for suspected treatment failure diagnosis as it is also reported that applications and samples from district level facilities total numbers were very low despite the district level staff undergoing training (Heller et al., 2019).

In developing countries, the use of Electronic Medical Records (EMR) is necessary to address the need for efficient delivery of services and informed decision-making especially at the local level where health facilities and practitioners may be lacking (Pulmano et al., 2016). Some health facilities providing HIV/AIDS patient care in Malawi have electronic medical record systems that are used to capture demographic data, vitals, clinic conditions, treatment, lab tests and results of the patients. The major objective of the installed EMRs is for monitoring and evaluation based on the national requirements (Douglas et al., 2010). The EMRs have patient adherence monitoring features and also includes most of the clinical data of the patient (Douglas et al., 2010). With all the data available the Clinicians and doctors in health facilities often assess patients based on WHO clinical and immunological criteria and the virological diagnosis criteria to determine ART treatment failure in the patients. Mostly, in similar kind of settings, sometimes clinical decisions are made based on doctors' intuition and experience rather than on the knowledge rich data hidden in the database (Saima et al., 2018). This practice leads to unwanted biases, errors and excessive medical costs which affects the quality of service provided to patients (Chang & Chen, 2009).

1.2 Study location

This research was conducted in Malawi, at the Lighthouse Trust Centers of Excellence (CoE) clinics. The clinics involved in this research are in HIV high burden cities in Malawi. Lighthouse Trust is a WHO recognized public trust working in close coordination with the Ministry of Health (MoH) to operate integrated HIV testing

services, treatment, and care clinics in Malawi (Phiri et al., 2004). The current Lighthouse's center of excellence clinics includes Bwaila Martin Preuss Center and Lighthouse Kamuzu Central Hospital clinic which are in Lilongwe, Umodzi Family Center located at Queen Elizabeth Central Hospital in Blantyre and Lighthouse Tisungane Clinic at Zomba Central Hospital in Zomba.

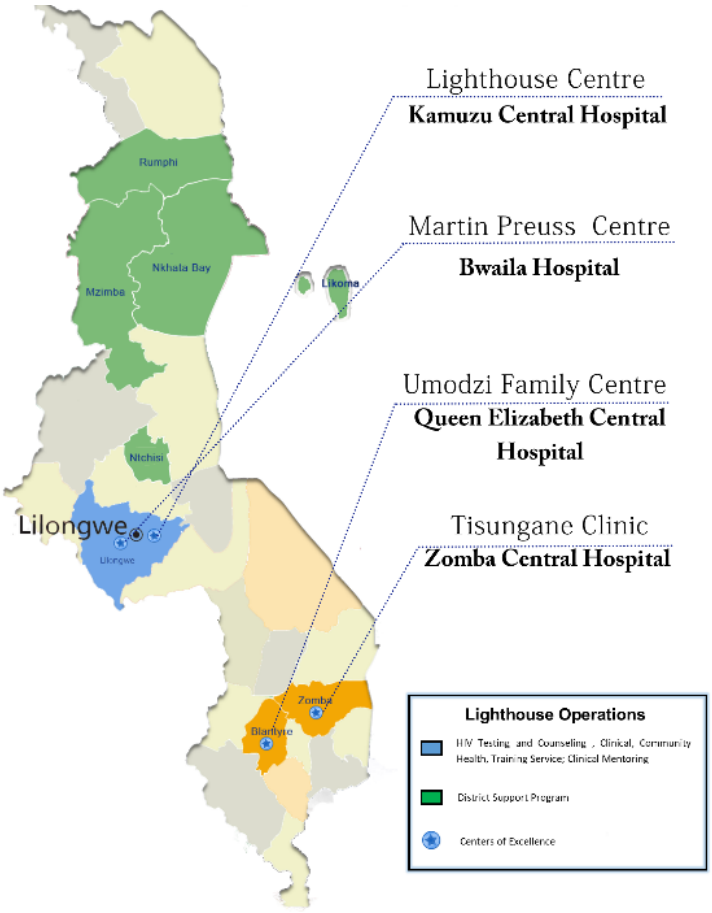


Figure 1: Map of Malawi showing Lighthouse Trust Operations (Lighthouse, 2020 Website)

1.3 Problem Statement

Most health facilities in Malawi have EMRS which capture vitals, clinic conditions, treatment, lab tests and results of the patients. Despite having this rich pool of data from

the EMRS, prediction of ART treatment failure for patients is still manually done. Overtime, the manual process has proven inefficient and ineffective model to predict and diagnose ART treatment failure in health facilities in Malawi.

1.4 Research Motivation

As stated in the background, the current procedures to classify treatment failure are prone to human errors, delayed detection of first- and second-line ART treatment failure which leads to increased risk of morbidity and mortality of people living with HIV. A research conducted by Calmy et al., (2007) found that the timing and accuracy of identifying treatment failure in resource limited settings is fundamental but challenging. In the case of the former, a delayed detection of treatment failure may increase drug toxicity, drug resistance and associated mutations accumulations, increased morbidity, and mortality. In the latter, misclassification of treatment failure also causes problems that include premature switch to and use of valuable advanced regimens, which are costly and may represent the last available regimen (Gilks et al., (2006). Thus, the fight against increased risk of morbidity and mortality among people living with HIV needs concerted effort that pool in information accurately and in timely manner.

1.5 Research Objectives

The main objective of the research was to develop a first- and second-line ART treatment failure prediction model using soft computing techniques. To meet the main objective the research specifically aimed to:

- Identify the factors associated with first- and second-line treatment failure among people living with HIV and are on treatment.
- Determine first- and second-line treatment failure prediction algorithms.
- Build an ANN model for predicting first- and second-line treatment failure.

1.6 Research questions

The main research question is to find how we can develop first- and second-line ART treatment failure prediction model using soft computing techniques using the available data sets and experts working in the HIV healthcare service in Malawi. The research sub questions in this research included:

- What are the factors that are associated with first- and second-line treatment failure among people living with HIV and are on treatment?
- How is first- and second-line treatment failure determined?
- How can the first- and second-line ART treatment failure prediction be modeled?
- What is the accuracy of using the soft computing model comparing with the current procedures used to determine first- and second-line ART treatment failure?

1.7 Research Hypothesis

The research hypothesizes that soft computing cannot be used to model ART treatment failure prediction.

1.8 Thesis document structure

This thesis commences with an introductory chapter, which sets the stage for the research. The subsequent sections include a comprehensive literature review, a detailed methodology, a presentation of findings and discussion, and ultimately, a conclusion chapter. Additionally, this document includes a references section and appendices, which follow the conclusion.

CHAPTER 2

LITERATURE REVIEW

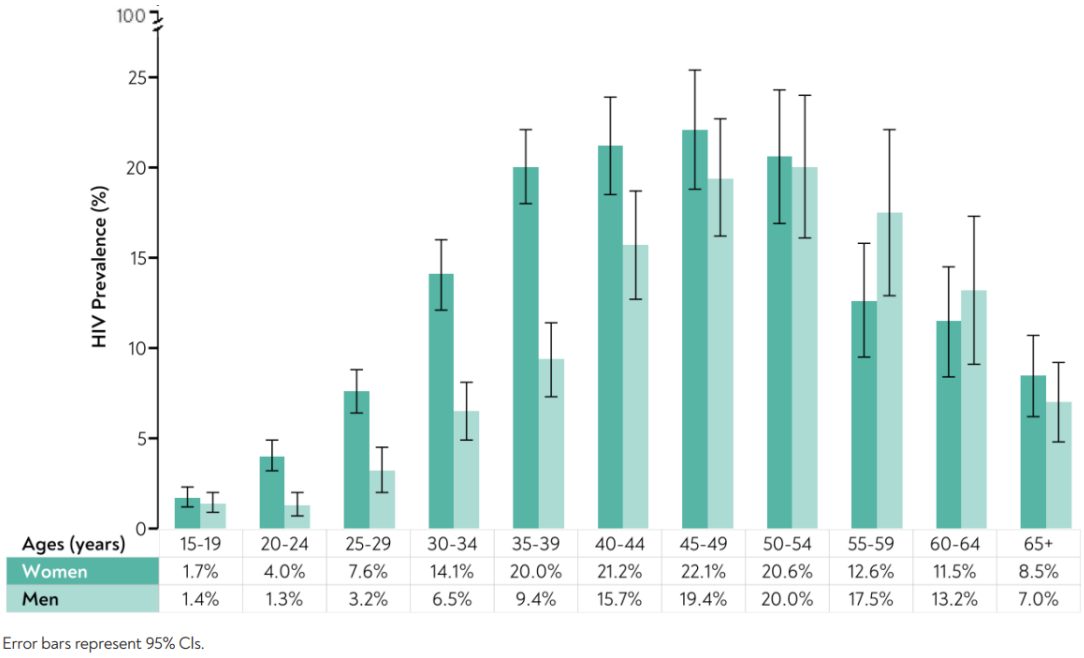
This chapter reviews relevant literature used in this research in terms of theories, study approaches and application of soft computing in the field of healthcare. Soft computing techniques are widely used to solve problems in various fields in different branches of science and technology. In healthcare, soft computing techniques have been used extensively in medical diagnosis, detection, and evaluation of medical conditions and treatment cost estimation. In this research we reviewed literature on HIV/AIDS domain and the application of soft computing techniques.

2.1 HIV/AIDS situation in Malawi

Although national HIV prevalence decreased from 12 percent in 2004 to 10.6 percent in 2010, Malawi continues to face a severe epidemic (MPHIA, 2018). The 2020 to 2021 population survey assessing HIV in Malawi showed progress toward epidemic control, but still the country has one of the highest HIV prevalence in the world despite the impressive progress in controlling its HIV epidemic in recent years. The survey found that HIV prevalence among adults was 8.9% indicating that approximately 946,000 adults were living with HIV in Malawi.

HIV prevalence by age and sex presented in Figure 2 showed that among adults (ages 15 years and older), HIV prevalence ranged from 1.7% among older adolescent girls aged 15 to19 years to 22.1% among women aged 45 to 49 years, and from 1.4% among older adolescent boys aged 15 to 19 years to 20.0% among men aged 50 to 54 years.

HIV prevalence showed that it was twice as high among women than among men in each 5-year age group between ages 20 and 39 years (MPHIA, 2022).



Ages (years)	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
Women	1.7%	4.0%	7.6%	14.1%	20.0%	21.2%	22.1%	20.6%	12.6%	11.5%	8.5%
Men	1.4%	1.3%	3.2%	6.5%	9.4%	15.7%	19.4%	20.0%	17.5%	13.2%	7.0%

Error bars represent 95% CIs.

Figure 2: HIV Prevalence, by Age and Sex (Source: MPHIA, 2022)

The 2022 MPHIA report also showed that Viral Load Suppression (VLS) prevalence among adults (ages 15 years and older) living with HIV varied by age but not by sex. Among women aged 15 to 24 years and 25 to 34 years (73.2% and 82.6%, respectively) VLS rates were considerably lower than among women aged 35 to 44 years and 45 to 54 years (91.4% and 95.9%, respectively). There was a similar pattern among men, where the prevalence of VLS among those aged 15 to 24 years and 25 to 34 years (75.0% and 74.0%, respectively) was lower than among those aged 45 to 54 years (91.7%) and men aged 65 years and older (94.7%).

2.2 ART Treatment failure

People living with HIV take ART to restore immune function and reduce HIV-related adverse outcomes (WHO, 2017). But treatment failure takes away this advantage and leads to an increased morbidity and compromised quality of life in HIV patients (Ayalew et al., 2016). ART treatment failure is when an ARV regimen is unable to control HIV infection (Aids Info, 2010).

The WHO describes treatment failure in three main ways which include clinical failure, immunological failure, and virological failure but viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure. If viral load is not routinely available CD4 count and clinical monitoring should be used to diagnose treatment failure (WHO, 2017). In Malawi misclassification of ART failure occurs frequently using WHO clinical and immunological criteria of ART failure for poor settings (Oosterhout et al., 2009). A viral load test confirming ART failure is therefore advised to avoid unnecessary switching to higher regimens.

According to Chagomerana et al., (2018) ART failure is now an emerging challenge in the fight against the HIV/AIDS pandemic. Chagomerana et al., (2018) found that among HIV-infected pregnant women who had been receiving ART for at least 6 months at the first ANC visit under the PMTCT Option B+ program at Bwaila Hospital from June 2015 to Dec 2017, the prevalence of treatment failure was 7.6%. CD4 cell count was strongly associated with treatment failure. The research recommended that women who are failing on ART should be identified early for adherence counseling and may require switching to an alternative ART regimen. Detection of treatment failure early in pregnancy among women who are already on therapy is essential for achieving maximal prevention of mother-to-child transmission (PMTCT).

2.2.1 First, and second-line ART treatment failure

Malawi's 2018 national ART guidelines recommended regimens based on two nucleoside reverse transcriptase inhibitors (NRTIs), combined with a non-NRTI, mainly efavirenz (EFV), as first-line ART and a combination of two NRTIs with a ritonavir (RTV) boosted protease inhibitor (PI) as second-line ART. The national guidelines have a provision for third-line ART which contains ritonavir-boosted darunavir (DRV), raltegravir (RAL) and etravirine (ETR), but the process of switching patients from second-line to third-line was not defined (Heller et al., 2019).

Additionally, WHO (2017) recommends that monitoring individuals receiving ART is important to ensure successful treatment, identifying adherence problems and determining whether and which ARV regimens should be switched in case of failure in ART treatment. Before 2010, WHO guidelines on ARV recommended using clinical outcomes and CD4 count for routinely monitoring the response to ARV drugs. However, the value of viral load testing as a more sensitive and an early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings. Viral suppression is the desired outcome of ART to maintain viral load below the level of detection of available assays which is less than 50 copies per ml. Using the virological criterion, a patient with viral load of at least 1000 copies per ml on two consecutive VL measurements in three months and has adherence support to treatment following the first VL test is said to be failing on treatment (WHO, 2017).

A study by Enderis et al. (2019) established that poor adherence to treatment and low baseline CD4 cell count were the significant predictors of treatment failure in Ethiopia with a 4.1% prevalence of first-line ART failure. The failure mostly occurred in patients with poor drug adherence and those who were delayed starting ART till their CD4 cell count became very low (Enderis et al., 2019). In Uganda, low peak CD4 count, shorter duration on first-line ART, d4T based regimen, and low baseline BMI, unemployment

and formal educational level were significantly associated with increased treatment failure (Babo et al., 2017). The research further found that adherence and alcohol uptake increased the risk of treatment failure (Babo et al., 2017). These studies proposed a retention of patients on their initial first-line regimen with appropriate follow up and improving their socioeconomic status through various livelihood initiatives should be strengthened on one hand and a patient tailored ART adherence counseling among young patients and alcohol users on the other.

Furthermore, given the high cost of second and third-line regimens compared with first-line ART it is essential to assess the effectiveness of these regimens to ensure optimal use of resources (Garone et al., 2013).

2.2.2 Establishment of third-line antiretroviral therapy

In 2013, WHO made recommendations that national programmes should develop policies for third-line ART in countries that have financial constraints that limit the adoption of third-line regimens (WHO, 2017). In Malawi third-line ART is accessed through a national committee that assesses eligibility and makes individual regimen recommendations (Heller et al., 2019; Moorhouse et al., 2019). The committee was formed in 2016 under the guidance of the Ministry of Health department of HIV/AIDS (Heller et al., 2019). During the establishment of the committee, it was learned that there was a shortage of applications coming from district level staff despite the district level staff having training in the third-line ART decision making. The researchers therefore recommended that further attention and training is needed to develop a more efficient up and down referral system that can effectively capture those suspected of second-line treatment failure and connect them with the appropriate management. Despite Heller et al., (2019) recommendations, Malawi still has a critical shortage of health care workers and in some cases task shifting is applied to cover up some service provision to stable patients in the ART treatment care (Tweya et al., 2012). Heller et al., (2019) also observed a low number of samples drawn from patients from the districts for testing

during eligibility and ART treatment failure diagnosis in the research period. This was attributed mainly to the patients not being available when a request for a sample collection was made later by the committee and the turnaround time (TAT) for VL monitoring. The mean TAT from receiving the initial application until communication of the final recommendation was 50 working days (range 21 -166 days) (Heller et al., 2019).

2.3 Use of Electronic Medical Records systems in low resource countries.

As outlined, in developing countries EMR systems are necessary to address the need for efficient delivery of services and informed decision-making, especially at the local level where health facilities and practitioners may be lacking (Pulmano, Regina, and Estuar, 2016). Douglas et al., (2010) indicated that point of care (POC) EMR system combines healthcare delivery and data collection processes into one activity, with the added intention of providing enhanced decision support to clinicians during the patient encounter. Some of the early implementation of EMR was to solve drug procurement and distribution challenges which were faced in many resource-poor countries and are a major reason for lack of access to medicines. It was thought that with many countries scaling up antiretroviral therapy (ART), it is vital to avoid interrupted drug supplies, which would lead to drug resistance and treatment failure, by ensuring rational drug forecasting and timely procurement to prevent drug stock-outs (Harries et al., 2007). Mtonga et al., (2020) further showed the significance of electronic interventions for dispensaries in limited resource settings globally. However, the researchers also stated that strong user value propositions are needed to ensure continued usage.

The TB/HIV EMR system in Malawi includes registration of demographics, anthropometric measurements, management of laboratory samples and results (Smear microscopy of sputum, CD4 count, viral load etc.), HIV testing, TB diagnosis, WHO HIV clinical staging condition, family planning services, clinical review and drug dispensation. Other co-morbidities and infections such as diabetes, cancer, meningitis, and malaria are also documented during clinical reviews. Its fundamental purpose,

according to Douglas et al., (2010), was to provide a complete set of automated reports for Monitoring and Evaluation (M&E) based on national requirements.

Currently the TB/HIV EMRs deployed in health facilities in Malawi do not have a component for predicting treatment failure for patients both on first- and second-line regimens. In terms of volumes, Lighthouse Trust in Lilongwe, serves over 28,000 patients living with HIV and these have millions of observations which are recorded to fulfill the fundamental purpose of the EMR (Sande et al., 2020);(Tweya et al., 2016); (Douglas et al., 2010). In addition, with advancement of the information age, data mining is increasingly being used in clinical practice (Yang et al., 2020). In a study that looked at analysis of big data to personalized medicine, they suggested that major investments should be made in the fields of bioinformatics, biomathematics, and biostatistics to develop translational analyses of omics data captured through health information systems to make best use of high throughput technologies. The researchers further suggested that new generations of multi-talented scientists and multidisciplinary research teams are required to build accurate complex disease models and to permit effective personalized prevention, diagnosis, and treatment strategies (Alyass et al., 2015).

Since the current EMRs do not have treatment failure prediction models, health care providers conduct manual reviews on patients for possible treatment failure by following the national HIV/ART guidelines and sometimes the treatment failure detection takes very long (Heller et al., 2019). Thus, long term treatment complications like delayed detection of treatment failure from adherence problems and drug resistance lead to increased opportunistic infections, morbidity, and mortality (Calmy et al., 2007). Calmy et al., (2007) found that the timing and accuracy of identifying treatment failure in resource limited settings is fundamental but challenging. In the case of the former, a delayed detection of treatment failure may increase drug toxicity, drug resistance and associated mutations accumulations, increased morbidity, and mortality. In the latter, misclassification of treatment failure also causes problems that include premature switch

to and use of valuable advanced regimens, which are costly and may represent the last available regimen (Gilks et al., (2006).

2.4 Soft Computing

Soft computing is a group of methodologies consisting of Artificial Intelligence (AI) based computational techniques that provide fast and cost-effective solutions for complex real-life problems (Gupta & Shivani, 2021). It is an approach to computing, which parallels the ability of the human mind to reason and learn in an environment of uncertainty and imprecision (Zadeh, 1994). It is tolerant of imprecision, uncertainty, partial truth, and approximations which is unlike the conventional (hard) computing like logistic regression (Venugopal, Srinivasa, and Patnaik, 2009).

Soft computing systems are turning out to be promising tools that can provide massive advantages. For example, soft computing systems are used in agricultural engineering, healthcare and biomedical applications, crime forecasting, data mining, image processing, industrial machineries, pattern recognition and many others (Gupta & Shivani, 2021). In addition, Soft Computing is applied in the field of medical science a branch of science concerned with the research of the diagnosis, treatment and prevention of disease or condition (Das & Sanyal, 2020).

The main soft computing techniques include Fuzzy Logic and Artificial Neural Networks, and includes other techniques like Support Vector machines, Evolutionary computing, Machine learning and probabilistic Reasoning (Kurhe, Satonkar, Khanale, & Ashok, 2011). Rough Sets Theory (RST) is another significant component of soft computing (Chaturvedi, 2008). These tools are used independently as well as jointly depending on the type of domain applications. The integration of RST with ANNs has also attracted growing attention as a means of building more efficient and intelligent systems (Bello and Verdegay, 2012). Generally, employment of soft computing

techniques leads to systems which have high Machine Intelligence Quotient (MIQ) (Venugopal et al., 2009).

2.4.1 Fuzzy logic

Fuzzy logic technique is based on the degree of truth instead of just assigning either true or false to variables. The fuzzy logic involves three main processes which include the process of fuzzification, applying of rules and defuzzification (Gupta & Shivani, 2021). In the fuzzification process, crisp values are taken as inputs and assigns them membership values. The fuzzy inputs are then taken in the application of rules usually the IF-THEN rules are applied to obtain the fuzzy output function. In the last process, it involves converting the fuzzy output functions into crisp values (Dzitac & Sorin, 2021). In terms of application of the fuzzy logic, it can be used as an explanation model for the characteristics of other black box models like the neural network (Khan et al., 2013). Some of the disadvantages of this technique is that it has low speed and long running time (Khan et al., 2013).

2.4.2 Artificial neural network (ANN)

Artificial Neural Networks (ANN) is called neuro computing which involves the research of a group of interconnected nodes called neurons. The ANN is inspired by the biological nervous system, such as how the brain processes information (Gupta & Shivani, 2021). A typical ANN has three layers which include input, hidden and output layer and it is configured for a specific application, such as pattern recognition or data classification, through a learning process. Furthermore, ANN can be applied to problems that do not have algorithmic solutions or problems for which algorithmic solutions are too complex to be found. Put differently, ANN is an efficient approach in problems where input and output variables do not have clear relationships between them (Khan et al., 2013). Tangri et al., (2014) demonstrated that ANN outperformed Logistic regression (LR) models in predicting survival in peritoneal dialysis patients and Chang & Chen, (2009),

experimenting on classifying six major skin diseases, found that neural network model had the highest accuracy in prediction. Based on the accuracy of the results, the AI classification technology can serve as important and useful references in diagnosis for physicians to avoid unnecessary medical waste and enhance health care quality (Chang & Chen, 2009).

There are different types of ANNs based on their structure and these include: single layer perceptron, multilayer perceptron, backpropagation net, hopfield net and kohonen feature map. Multi-layer perceptron (MLP) is recognized as the best ANN used in classification and the back-propagation algorithm in MLP is the solution of choice for many machine learning tasks. Back propagation is a method to adjust the connection weight to compensate for each error found during learning and this algorithm is a fast algorithm compared to other algorithms (Durairaj & Meena, 2011).

ANN has three main learning paradigms which include supervised learning, unsupervised learning and reinforcement learning (Sharma, 2013). Supervised learning takes in a set of paired inputs and desired outputs and the learning process is to produce the desired output for each input. Among the three paradigms, the supervised learning is mostly used in classification problems (Yang et al., 2020).

2.4.3 The Rough Sets Theory

Rough Sets theory (RST) proposed by Zdzislaw Pawlak in 1982 (Pawlak, 1982) is an efficient and excellent mathematical technique that produces useful mathematical foundations for developing automated computational systems that can help understand and make use of imperfect knowledge (Shen & Jensen, 2007). In comparison with traditional techniques, RST gives the optimal result from the analysis process without loss of information in original set. RST consists of classification, reduction, rule generation and feature selection methods (Jeyarani et al., 2018) and it has advantages in data analysis since it is based solely on the original datasets and does not require any

external information. Furthermore, it does not require any assumptions to be made about the data, and it can be used for analyzing both qualitative and quantitative features (Durairaj & Meena, 2011).

Researchers have found that a hybrid rough sets theory and Artificial neural networks model perform much better than using independent components of the soft computing methodologies. A study done by Durairaj & Meena, (2011) showed that the proposed hybrid architecture was very efficient for medical data analysis in significantly lesser processing time. In the research RST was used as a tool to reduce the input to ANN and improve the classification and prediction of semen quality. The researchers recommended that future models should incorporate some additional biological information in the spermatological data which was used in their research.

2.5 Data Modelling Framework

Despite efforts made to introduce various methods for managing data mining (DM) projects, Moss & Atre (2003) argued that several common pitfalls occurring in DM projects can be summarized as a lack of methodology for project development. In addition, Becker & Ghedini (2005) stated that in practice data mining projects are still approached in an unstructured and ad hoc manner. Generally, studies have shown that utilizing process models in data science is perceived as beneficial. Saltz et al., (2018) argues that there are many reasons data science teams should use a well-defined process to manage and coordinate their efforts, such as improved collaboration, efficiency, and stakeholder communication. Unfortunately, based on the researcher's survey results, most data science teams used an ad hoc project management approach. In fact, 82% of the data scientists surveyed did not follow an explicit process (Saltz et al., 2018).

CRoss Industry Standard Process for Data Mining (CRISP-DM) presented in Figure 3 below, is a popular process in practice and in research (Nadali et al., 2011). It is a robust framework for guiding data mining processes (Wirth & Hipp, 2000). CRISP-DM is an

attempt to provide industrial standards for the practice of DM and it comprises of six phases: business understanding, data understanding, data preparation, modeling, evaluation and deployment (Nadali et al., 2011).

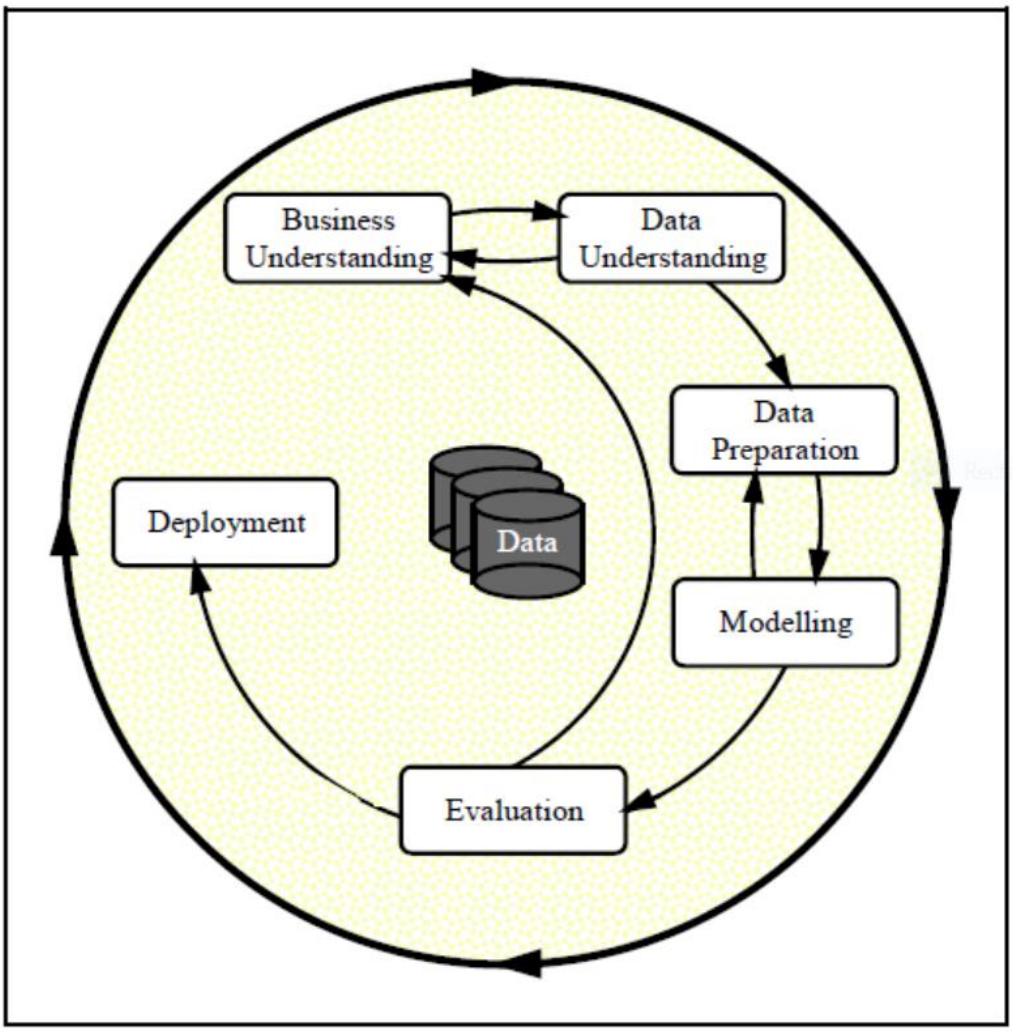


Figure 3: CRoss Industry Standard Process for Data Mining (CRISP-DM) Phases

CHAPTER 3

METHODOLOGY

This chapter contains the research design, modelling and research approach, data collection and analysis techniques and methods which were used in this research.

3.1 Research Design

There are three main research designs that can be applied in a research, these includes: qualitative, quantitative, and mixed method (Creswell, 2009). Qualitative method explores and understands the meaning individuals or groups assign to human or social problem (Creswell, 2009). This approach allows the researcher to collect data in the participant's setting and makes interpretation of the meaning of data. Quantitative method examines relationships among different variables and statistical procedures are used to analyze data. The mixed method is an approach that combines both qualitative and quantitative methods depending on the type of data to be collected (Creswell, 2009). Given the above, this research adopted a mixed approach.

This research used the ethnographic approach to answer all qualitative research objectives. Ethnographic research is a qualitative method where researchers observe and/or interact with a study participant in their real-life environment. Ethnography approach is usually used to support in design modelling to deepen the understanding of the design problem (Baskerville & Myers, 2015). In this research, observations, document reviews and semi structured interviews were conducted.

Observations were conducted at the Lighthouse clinics with the researcher immersed in the day-to-day activities of clinic workers and experts.

The ethnographic approach was used to gather data to identify the factors associated with treatment failure; solicit all the required procedures, algorithms and guidelines that are used to detect ART treatment failure; and gather general perceptions toward use of soft computing modelling in predicting treatment failure. With consent from participants this research audio recorded responses of participants which were later translated and transcribed for analysis.

Purposive sampling was used to select study expert participants involved in ART treatment at Lighthouse Trust Centers of Excellence (CoE) Clinics located in the HIV high burden cities in Malawi. A sample size of 17 was reached while observing the concept of saturation.

3.2 Modelling approach

This research utilized a data driven modelling (DDM) technique in the development of the artificial neural network prediction model. Data driven methods are methods that extract knowledge and insights from datasets, which are typically large, and use this acquired knowledge to forecast new outputs (Venugopal et al., 2009). Furthermore, this research utilized a CRISP-DM process model which is an industry- independent process model for data mining. CRISP-DM is a process framework for designing, creating, building, testing, and deploying machine learning solutions. The framework consists of six iterative phases which include Business Understanding, Data Understanding, Data Preparation, Modelling, Evaluation and Deployment (Hui et al., 2019).

3.2.1 Data extraction and Preprocessing

In the CRISP-DM framework, business understanding stage is primarily concerned with understanding business requirements (Hui et al.2019). Key activities in this stage included engaging with stakeholders, observing business processes, and studying relevant documentation. The final patient data was extracted from the EMR databases and was presented in comma-separated values (CSV) file tabular format. The data set included many variables including the available variables gathered in the qualitative findings. Data extraction from OpenMRS EMR databases was achieved by writing MySQL scripts.

During the data extraction a randomized sampling technique was conducted for the data which was used in the modelling treatment failure process. Firstly, a random sample of 10,000 patients was extracted from the HIV patients EMR database. Secondly, extraction of patient observations of these patients was limited to records between 2017 to 2022. A period of latest 5 years was chosen to have reliable and up to date available data. In addition, this research considered all patients with treatment failure outcome regardless of the chosen period, these were extracted from the system in addition to the 10,000 patients. The final dataset after data preprocessing was 1,722 total number of patients and this was the data which was used to build the ANN model. The following diagram Figure 4 summarizes the data extraction process and presents the final patient fact table which was extracted into CSV file format.

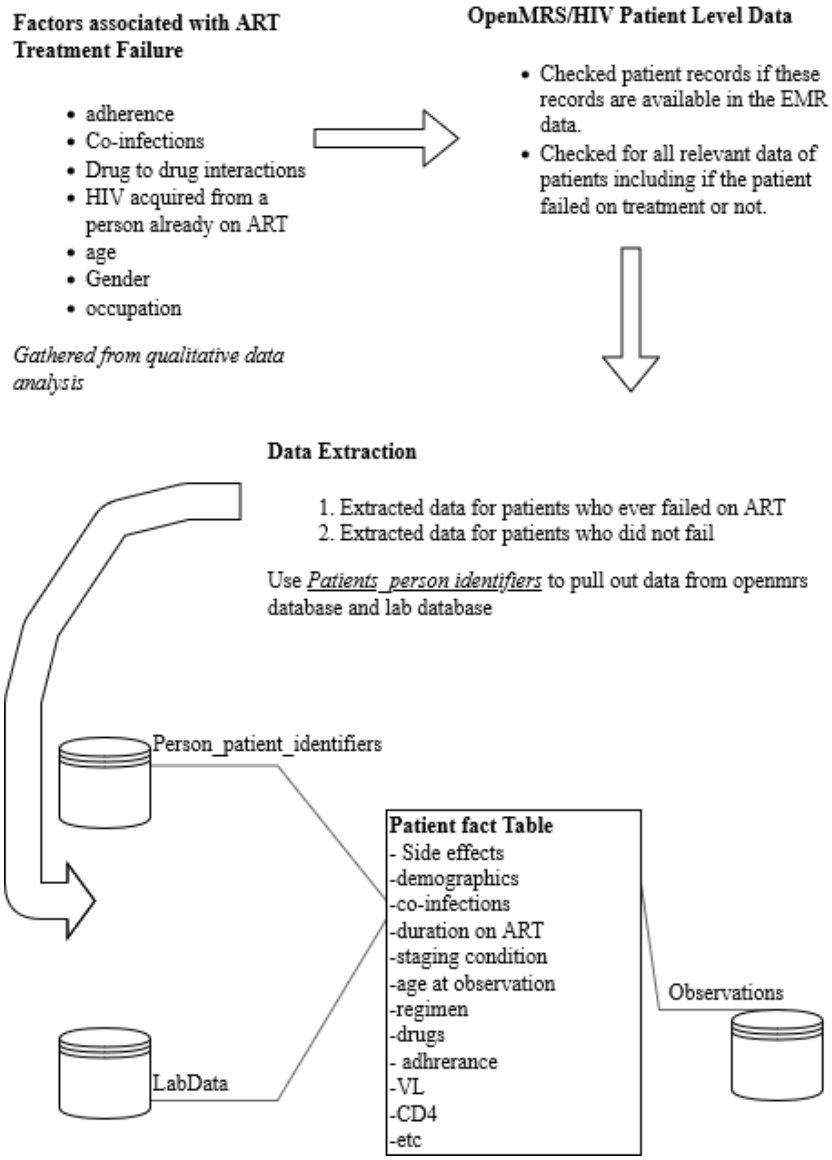


Figure 4: Data extraction flow process

Following this stage in the CRISP-DM framework is the data understanding stage, which examines the quality of datasets by applying statistical and data visualization techniques (Hui et al.2019). In this stage, distribution charts and heat map correlation matrices between variables were employed.

The data preparation stage involved removing features with zero variance. A correlation matrix was used to select relevant variables that contribute most to the prediction variable. All feature variables were correlated with the target feature, and based on the correlation values, only features with correlation of above 0.3 were chosen. A Pearson correlation threshold of 0.3 was chosen because correlation of above 0.3 is a significant correlation and this threshold was eliminating a lot of insignificant variables (Sabilla et al., 2019). The feature selection process was conducted to reduce overfitting, improve accuracy, and reduce training time. Thus, in the process of feature selection data analysis, attributes were reduced, which implies that some redundant attributes that do not play any role in distinguishing an object from the others, are eliminated without any information loss. This research employed a two-dimension (2D) reduction data preprocessing algorithm. The 2D reduction data preprocessing reduced data both horizontally and vertically. Horizontal reduction implied attribute reduction and vertical reduction implied the deletion of conflicting objects. The vertical reduction in this research deleted only redundant objects. Furthermore, during preprocessing, discretization process was also performed on the original dataset. Discretization is a process of converting continuous attributes into categorical variables in an information system. Typically, Machine Learning algorithms accept only numerical inputs (Potdar et al., 2017), hence, during data preprocessing we used encoding techniques to encode all categorical variables into numerical values which included duration in months on ART, BMI, Age and HIV staging condition. This research employed Synthetic Minority Over-sampling Technique (SMOTE) to balance the data among the outcome variable classes.

3.2.2 Building ANN Model

Artificial neural network, developed in python 3, was used in this research by employing back propagation (BP) techniques. The back propagation neural network algorithm is a multi-layer feedforward network trained according to error back propagation algorithm and is one of the most widely applied neural network models (Durairaj & Thamilselvan, 2013). In addition, TensorFlow, Keras and Sklearn tools are used to build the Artificial

Neural Networks prediction model in this research as backend applications. Keras is a model-level library, providing high level building blocks for developing deep-learning models and it is widely used. TensorFlow as it is widely used mostly scalable and mostly production ready open-source tool developed by Google. The above were chosen because these are widely used and there is a huge community for support.

At the configuration level, a patient can either be in a state of treatment failure or no treatment failure, reducing the ANN classification to a binary problem. A sequential model was used in this research since the project required plain stack layers with exactly one input tensor and one output tensor. The input was fed to the input layer, the neurons perform a transformation on this input using the weights and biases. We used the ReLu and Sigmoid activation functions when building the model to be able to learn the complex patterns from the data. A ReLu activation function is a nonlinear activation function which does not activate all the neurons at the same time. ReLu function, used in the hidden layers to perform an efficient computation, is presented as: $f(x)=max(0,x)$ where x is an input value. All output values from this function are values above 0 and all values that are negative they are automatically resulted to 0. A sigmoid is another nonlinear activation function which transforms values between 0 and 1, represented as: $f(x) = 1/(1+e^{-x})$ where x is an input value. This function was used to give out binary output of 0 and 1. We further used the *adam* optimizer which is a powerful tool for improving accuracy and speed of the ANN and we used a *binary_crossentropy* as loss function for the binary classification ANN model. The ANN model was further configured to use the accuracy metric to describe how the model performed across the classes. Batch size was 60 and number of epochs was 120. Using sklearn library, a train-test split was used on the final dataset with test size data set configured to 20% (0.2) of the input dataset. The following table summarizes the ANN configuration used to predict ART treatment failure as a binary classification.

Table 1: ANN model configuration

Item	Configuration
Model Type	Sequential()
Number of layers	5
Input shape on input layer	Total number of variables after feature selection process =17
Activation function on input layer and Activation function on hidden layer	Relu
Activation function on output layer	Sigmoid
Optimizer	Adam
Loss function	binary_crossentropy
Metrics	Accuracy
batch_size	60
Epochs	120
Training Data and test data set	Test size of 20% of the data randomly selected

In building the model the preprocessed data from data preparation phase was passed on to the next phase where training, testing, validation and then prediction of the unknown outcome cases was performed. The training subset was used to adjust the connection weights in the ANN model. A confusion matrix was used to evaluate the performance of the model by visualizing and summarizing the performance of a classification algorithm (Singh et al., 2021). To deploy the model, we serialized it into a JSON file and the model training weights were saved into a HDF5 file for testing purposes.

3.2.3 ART Treatment prediction model conceptual framework

Conceptually, data was sourced from the medical database with the variables listed under HIV data and lab data. It was then preprocessed and fed into the ANN model as training, validation, and testing data. Finally, the ANN gave an outcome of treatment failure when

test data is passed into the model. Figure 5 below, is a diagram that summarizes the conceptual framework.

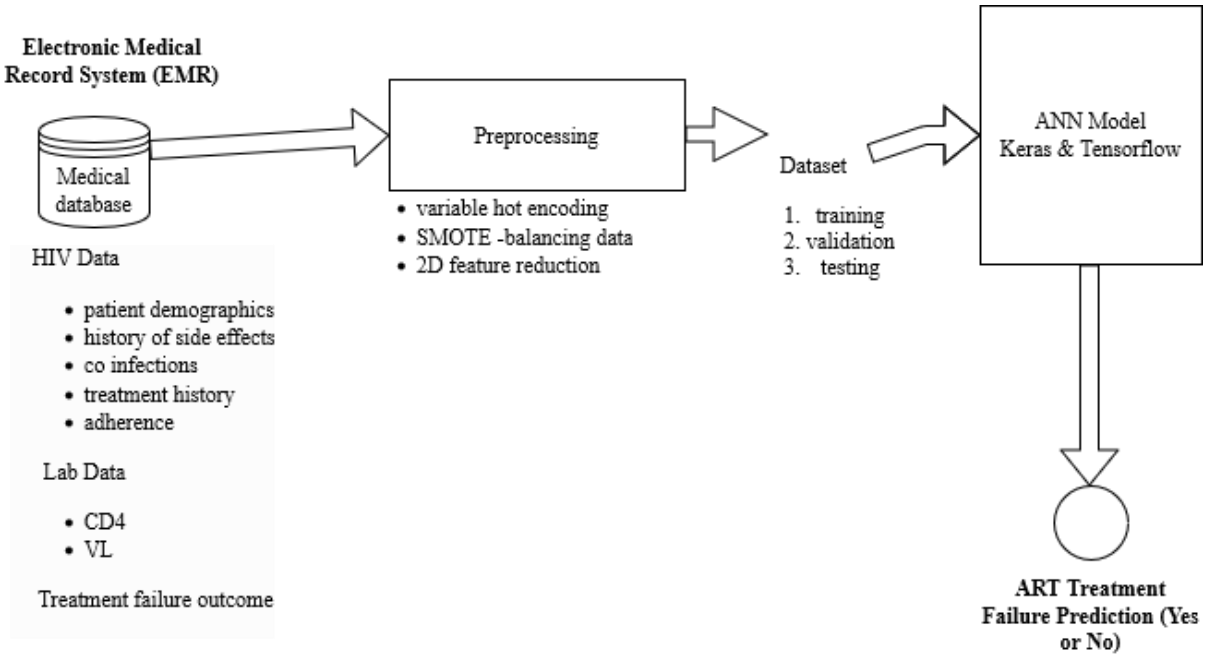


Figure 5: ART Treatment prediction model framework

3.3 Data Sources and Analysis

The primary data included a range of viewpoints on factors that contribute to ART treatment failure, knowledge on what the participants currently use to determine ART treatment failure and the whole process that they follow. It was collected from clinicians, HIV experts, and artifacts through interviews and observations. The research also collected perceptions of the users, finding out if they would trust the developed model to run on its own. For secondary data, the research extracted HIV data from the EMR databases related to ART treatment failure diagnosis and document analysis.

The research used iterative and unstructured ethnographic data analysis technique to analyze qualitative data. Ethnography involved an inductive and iterative process, where

data collection and analysis happened simultaneously, without the need to gather all the data. The ethnographic approach used in this research did not follow a linear trajectory. Data collected from semi structured interviews was analyzed by finding repeating themes, coding the emergent themes with keywords and phrases; grouping the codes into concepts hierarchically; and then categorizing the concepts through relationship identification. In identifying the factors contributing to treatment failure quantitative analysis of the available data sets of clients/patients that have known treatment failure outcomes was done to compliment the findings in the qualitative approach. Patterns were observed, and classifications were made based on the correlation of the variables to the treatment failure outcome. Lastly, a comparative analysis of the outcomes from the current prediction methods with the developed model outcomes was performed.

This research used Python statistical data analysis libraries for all quantitative objectives. All data was presented on comma separated values (CSV) files which are easy to create, human readable and easy to work with across data processing platforms. We used pandas, numpy, matplotlib, sklearn, statsmodels, imblearn, keras, tensorflow, and seaborn libraries to load, transform the data, build ANN model, and generate descriptives such as tables and graphs. Python programming was done in the Spyder IDE.

3.4 Ethical consideration

The research dutifully upheld confidentiality and privacy according to ethical guidelines of the University of Malawi Research Ethics Committee (UNIMAREC). There was no risk posed to participants in the research. This research was conducted with written consent to the organization that was approached to supply data. Patient identifiers in the data sets were removed. This study also maintained participant anonymity during data collection, which was preceded by obtaining informed consent from all individuals involved. Names of participants were not recorded in the research information sheet notes. This research used a central data repository server during the modeling process.

The research utilized a secondhand desktop which had Linux server operating system and MySQL database management server installed on it. The server was protected with an encrypted password both on operating system and application level. The server was not connected to a public network, and it was physically secured in a protected server room. Periodically data from the server was backed up to an external drive. All the backed-up data in the external drive was in the deidentified and anonymized format. The files on the external drive were in a compressed format protected with an encrypted password.

CHAPTER 4

RESULTS AND DISCUSSION

This chapter presents results and discussion of the research obtained through the analysis described in the methodology.

4.1 First- and second-line treatment failure among people living with HIV and are on treatment.

ART treatment failure has been defined as *"... when the patient is taking the medication, but the virus/ viral load is increasing and not dropping and clinically when the patient is developing advanced HIV signs while taking medication…".* The research highlights the use of the Malawi national HIV/ART guidelines in determining treatment failure using trained ART service providers " ...*we usually follow the national HIV guidelines and currently we are using the 2019 issued guidelines*". Despite the training, the participants indicated challenges in following the guidelines due to the introduction of Dolutegravir (DTG) drugs which belonged to both first- and second-line regimens. Therefore, most ART experts are only able to perform first-line and non DTG based regimen patients' treatment failure assessment. A few others, trained in DTG based regimens and second-line drug resistance assessment techniques, can determine the corresponding treatment failure. In either case, the research identified three types of assessments used to determine treatment failure: clinical, immunological, and virological, the most common being the virological. To qualify for virological assessment, a patient must have at least one viral load (VL) result as shown in the Figure 6 flow diagram.

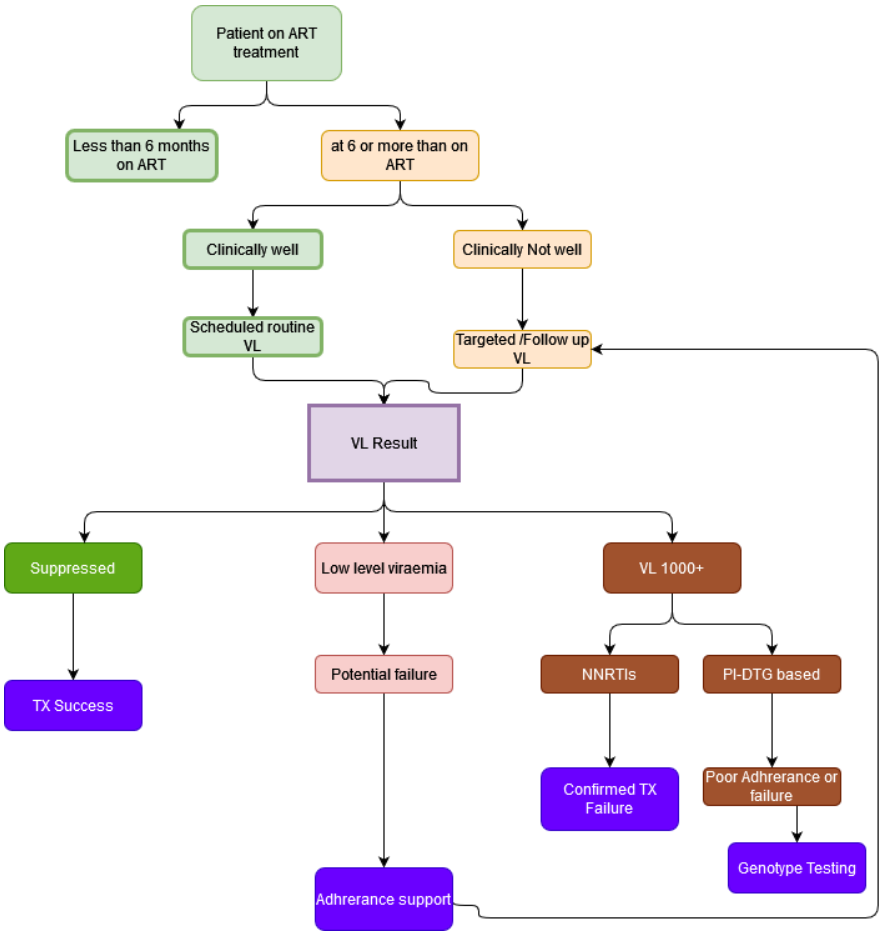


Figure 6: Current first- and second-line treatment failure prediction algorithms using VL

While the assessment heavily relies on availability of VL, the research reveals that VLs are not usually available to the patients instantly after a sample is collected. In many cases this results in delays for alternative care for the patients if they are determined to be failing on ART treatment. When VL is available the assessment is done only for patients who have been on ART for more than six months. Once the result is presented, if the result shows undetectable HIV load, the patient is classified as virally suppressed and he/she is considered as a treatment success. When the VL result shows low-level viraemia the patient is only classified as a potential treatment failure as that patient is suspected not to be adherent on the current prescriptions and then he/she is put on

adherence counselling and the VL testing is repeated after some time at a targeted or follow up VL testing. Only when a patient has VL result of 1000+ copies is considered as treatment failure for patients on NNRTI regimen and for all patients on PI or DTG based regimen these patients are examined further with advanced genotype resistance testing which was not nationally available.

Independent of the assessment type, there are several causal factors that lead to treatment failure. The expert analysis results show that a patient is more likely to fail from ART treatment if they are not adherent to medication than from any other causal factor. The patient record quantitative data analysis supports this finding as shown in Figure 7 where most of the patients that were adherent to treatment had a positive treatment outcome of not failing on ART as opposed to the poorly adherent patients. The results further show that poor adherence results, first, from alcohol, drugs, and smoking practices as people tend to forget to take medication.

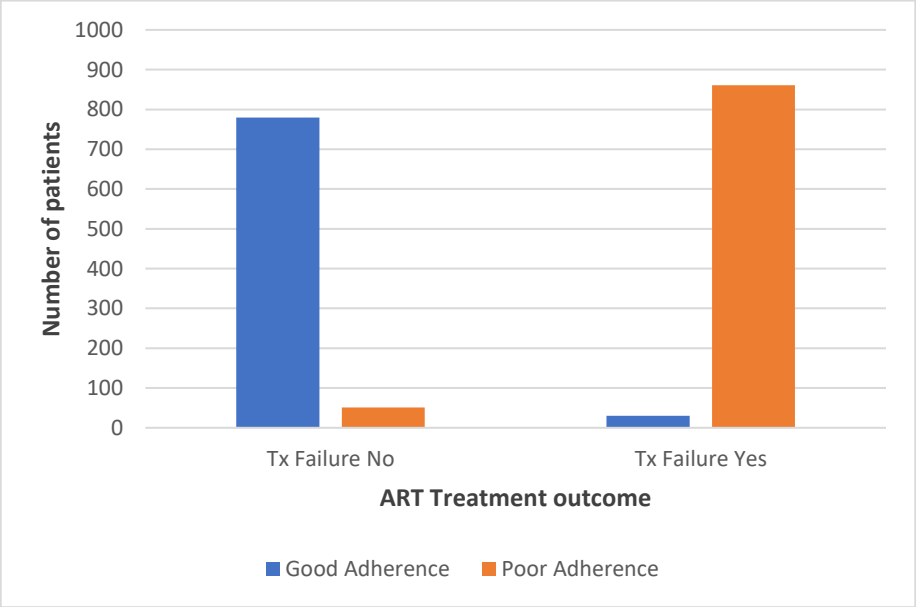


Figure 7: ART Treatment Failure by Adherence to ART

Secondly, poor adherence to ART was influenced by age of patient, where younger people and children were commonly seen to miss drugs as compared to adults. As shown

in Figure 8, ART treatment failure was most prevalent in the ages between 0 to 35 years putting the patients in this age bracket at higher risk of treatment failure as compared to the older age groups. Specifically, most patients between the age group of 20 to 35 years old failed treatment while more than half in the age group of 40 to 65 years did not experience treatment failure.

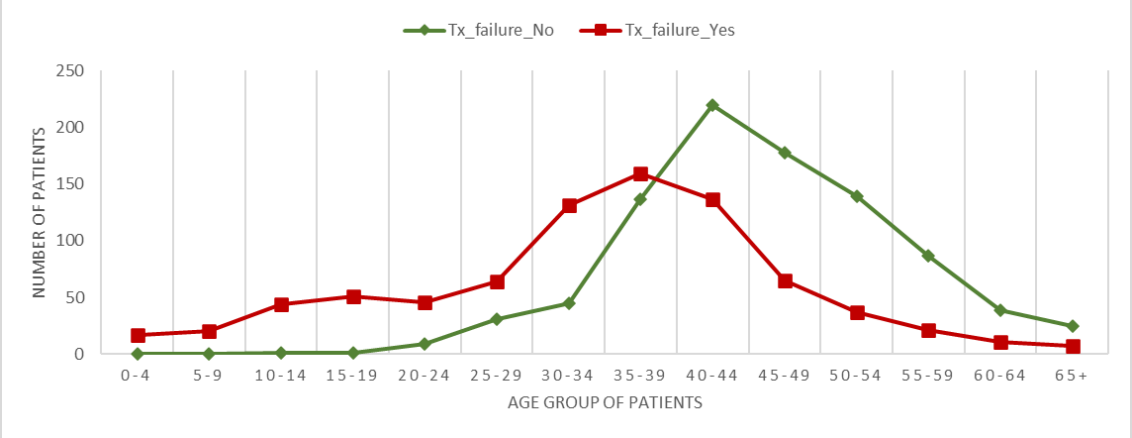


Figure 8: Treatment failure distributed by Patient Age Group

It was also noted that gender and occupation of the patient contributed to poor adherence where males and travelling occupations, such as transporters and businesspersons respectively, were likely to adhere poorly to ART treatment. However, this expert analysis is not concretely supported by the patient record data which shows that both males and females have an even chance of failing on ART treatment. Figure 9 below, summarizes the distribution of treatment failure against gender.

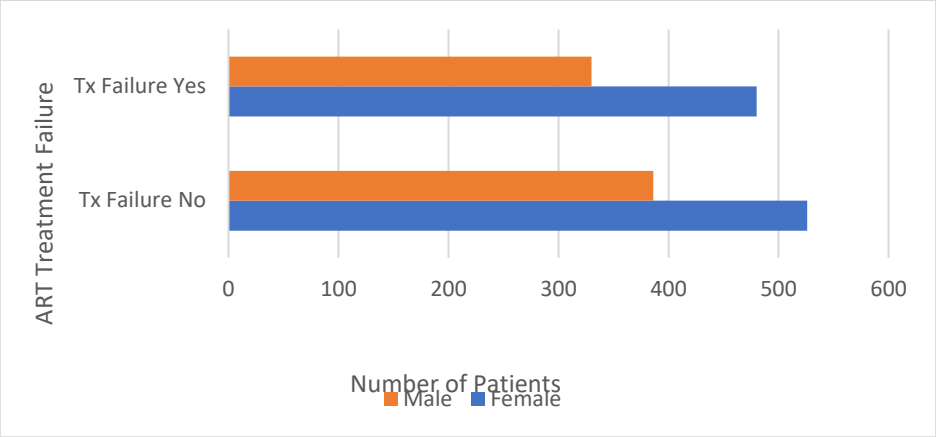


Figure 9: Treatment failure distributed by Gender

The second casual factor of treatment failure was drug to drug interaction in that some drugs, for instance for TB, reduced the efficiency of the ART. This relates to the co-infection factor in which patients developed other conditions like liver failure, malabsorption, and pregnancy. The co-infectious diseases include TB, KS, Cryptococcus Meningitis which usually drop the immunity of the body and CD4 count resulting in failure for the body to fight and suppress HIV as indicated by Aldous & Haubrich (2009) and Siraj et al., (2021). Lastly, the expert analysis revealed that treatment failure was prevalent in patients who acquired the HIV from a person who was already on ART treatment and was resistant to the ARVs. Table 2 summarizes the factors associated with first- and second-line ART treatment failure.

Table 2: First- and second-line treatment failure causal and indirect factors

	Causal factor	**Documented in EMR?**	**Indirect factors**
1	Poor adherence	Yes	Alcohol, drugs, and smoking practices; Age; Occupation; and Gender
2	Drug to drug interactions.	Yes	
3	HIV acquired from a person resistant to ART treatment	No	
4	Patient with other conditions	Yes	
5	Co-infection with other diseases	Yes	

4.2 First- and second-line treatment failure prediction

As established, the national guidelines, while they suffice, they are less efficient in identifying ART treatment largely due to insufficient human capacity and capital on one hand and time insensitive on the other. Notwithstanding, there is huge pool of patient data to derive meaningful insights from patient HIV data sets to complement the experts in determining ART treatment failure.

To begin with, we randomly sampled 10,000 patient records within a 5-year period of 2017 to 2022 and 898 patient records with ART treatment failure from the ART EMR. Out of the former, a total of 912 records were carried forward for patients having been on ART for at least 6 months and had all variables complete with data (e.g., adherence, coinfections, side effects, age etc.). In the case of the latter 810 records were carried forward for patients who had complete variables. This gave a total of 1,722 records of patients with complete data and a known ART treatment failure outcome with variables. Beyond these, some of the discarded records had errors ranging from numerical values entered as text, missing CD4 and VL data as it was largely paper-based waiting to be updated into the openmrs database. As a result, CD4 and VL data was not used in this research.

This research found that using ANN model to predict ART treatment failure was possible even when the data did not have treatment failure determining variables like the VL and CD4 count used in the current determination/ prediction algorithms which are considered and recommended by the MoH guidelines and the WHO.

This research gathered that the dataset had a lot of variables and to ensure that only relevant variables were considered, this research was able to select the relevant ones. From a total of 41 features found in the hot encoded data set only 17 were selected through the feature selection process and all features with zero variance and correlation value of less than 0.3 were removed.

Table 3 provides the full list of the variables that were used. Additionally, to missing data, the ART EMR showed that 38% of patients who were registered on second-line and third-line did not have treatment failure record. The ART EMR had a total of more than 29,000 patients who were on first-line regimen and 1,439 patients who were on second-line and third-line regimen and only 62% of these were registered as treatment failure. The expectation is that most of the patients that were switched from first-line to second-line ART treatment failed before they were switched to the higher level. About 98.7% of the 898 patients that were recorded to have failed on ART had complete data. Groenwold (2020) agrees with this research finding that most electronic health records have a lot of missing data and to help to solve this problem in prediction modeling, the researcher suggests that utilizing synthetic data could help. Synthetic data can be generated from the available data variables to come up with values of missing data.

4.3 Building ANN prediction model

This study demonstrates the feasibility of using ANN model to predict ART treatment failure, even in the absence of traditional determinants like VL and CD4 count, which are used in the current determination/ prediction algorithms which are considered and recommended by the MoH guidelines and the WHO. Through feature selection, the study identified the most relevant variables from the dataset, narrowing down the initial 41 features to 17 key predictors, and excluding those with zero variance or a correlation value below 0.3.

Table 3: ART EMR Variables

	Variable	Description
Demographics	Male	Gender for male
	Female	Gender for female
	HIVStage_at start	WHO HIV staging condition at initiation
	Age_grp_initiation	Age group of patients at ART initiation
	Age_grp_now	Age group of patients at observation date.
	Breastfeeding_now	Breastfeeding patient at time of observation
	Pregnant_now	Pregnant at time of observation
	BMI_now	The BMI measure at time of observation
History of side effects	Peripheral_Neuropathy	Peripheral Neuropathy side effect or condition
	Jaundice	Jaundice condition
	Lipodystrophy	Lipodystrophy condition
	Kidney failure	Kidney failure condition
	Psychosis	Psychosis condition
	Gynaecomastia	Gynaecomastia condition
	Anemia	Anemia condition
	Weightloss	Patient losing weight severely
	Fever	Having fever
	Diarrhea	Having diarrhea
	Vomiting	Patient vomiting
Co-infections	Have_TB	Patient has TB
	Have_KS	Patient having Kaposi's sarcoma
	Cryptococo_meningitis	Patient having Cryptococcus meningitis
	Liver_failure	Patient having liver failure
Treatment history	PI_DTG_based	Protease inhibitor and dolutegravir ART regimen/ drugs
	NNRTI_based	Non-nucleoside reverse transcriptase inhibitors regimen/drugs
	Months_on_tx	Months on treatment
	TB_treatment	TB treatment
Adherence	GoodAdherence	Have good adherence
	PoorAdherence	Have poor adherence
Lab	CD4	CD4 count is a test that measures how strong your immune system is
	VL	The amount of HIV in a sample of blood
Outcome	Tx_failure	Treatment failure. Yes = patient failed on ART treatment and No = patient did not fail, or patient is assumed to be healthy.

The Figure 10 below presents a heatmap with variables that were selected on the condition that they showed significant correlation to the outcome variable.

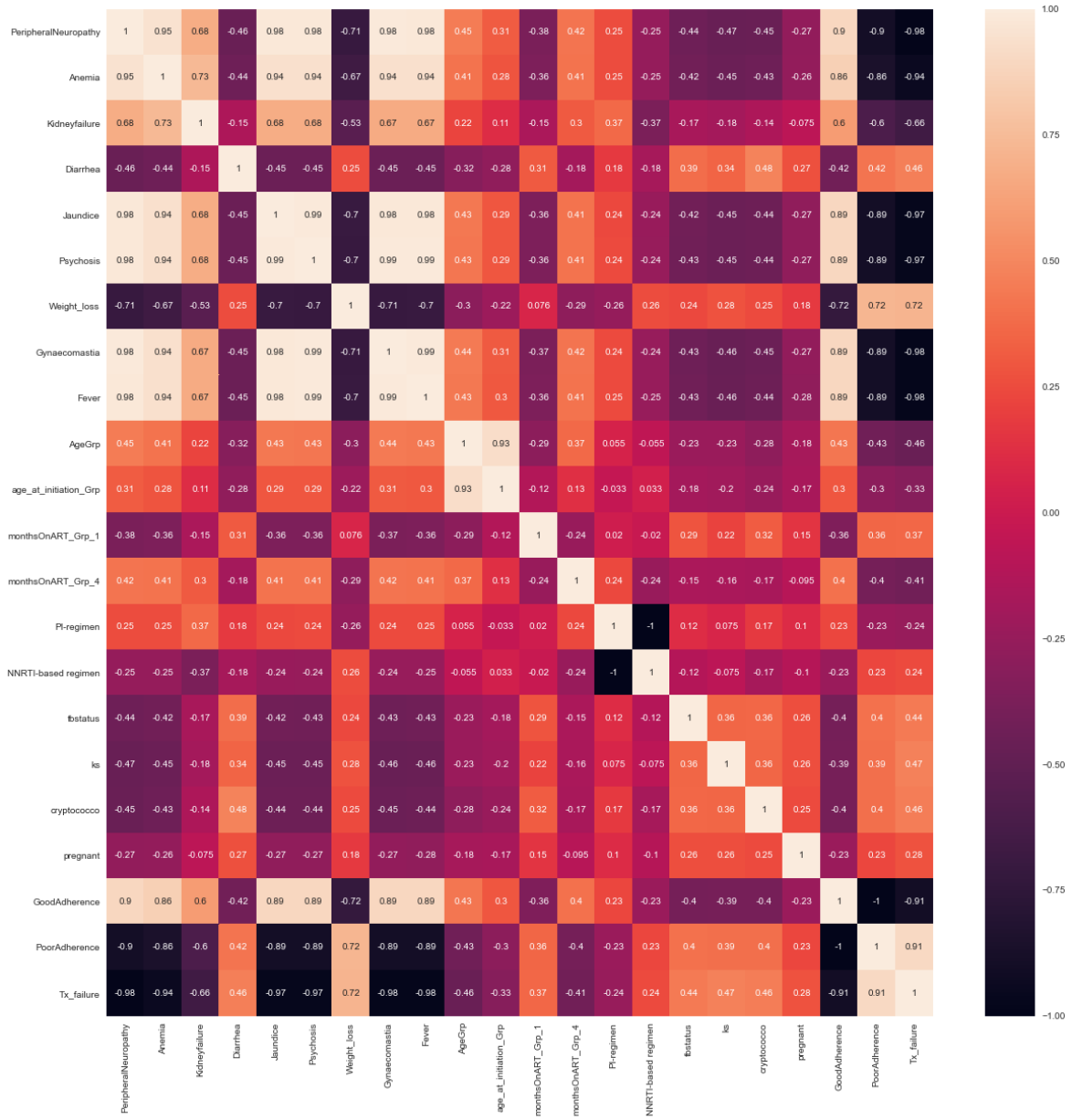


Figure 10: Heatmap presenting correlation for selected features

In Table *4* we present correlation for variables against the outcome treatment failure variable. The table shows that poor adherence and weight loss showed very strong positive correlation to treatment failure. Poor adherence and Good adherence variables had inverse correlations to treatment failure and Good adherence was dropped from the model input variable as it did not add any new information to the model. The table also

shows that having coinfections of KS, Cryptococcus, TB and being on ART treatment for more than 6 months but less than 12 showed moderate positive correlation to treatment failure meaning that patients with these conditions and in these categories were at moderate risk to fail on ART treatment. Being on ART treatment for over 72 months had a moderate negative correlation to treatment failure. Age at ART initiation showed that as the age groups were advancing the correlation showed a moderate negative behaviour against treatment failure. Children in the age group of 0 to 4 years showed a moderate negative correlation to treatment failure. The heat map Figure 10 also reveals that some of the variables were also influencing each other and from these only one from the associated variables was kept in the model as an input variable without changing the behaviour of the model outcome. Psychosis and Jaundice, Peripheral Neuropathy, Gynecomastia, and fever seemed to have high correlations to each other respectively. This presented an optimal model which had 14 variables from a pool of 17 variables.

Table 4: Correlation between the Input Variables vs Treatment Failure

	-1	
Peripheral Neuropathy	-0.98	
Gynecomastia	-0.98	
Fever	-0.98	
Jaundice	-0.97	
Psychosis	-0.97	Strong negative correlation
Anemia	-0.94	
Kidney Failure	-0.66	
Age Group 5 years (1- 4)	-0.46	
Months On ART in Group 4 (Over 72 months)	-0.41	
Age at initiation group	-0.33	Moderate correlation
Months On ART Grp 1 (Over 6 months < 12 months)	0.37	
TB Status	0.44	
Diarrhea	0.46	
Cryptococcus	0.46	
KS	0.47	
Weight Loss	0.72	
Poor Adherence	0.91	Strong positive correlation
	1	

In the model evaluation, since the model produces estimates of the outcome variable in the range of 0 and 1, a function to round the estimates was made to round everything that had estimates above 0.5 to 1 and those below to 0. The evaluation of the model then was run, and it was found that the accuracy metric of the model was 99.71% and loss of 0.0716. This shows that the model performed well. The table below further presents the evaluation results for the model.

Table 5: Precision, recall, f1-score values

	Precision	**Recall**	**F1-score**
0	1	1	1
1	0	1	1
Accuracy			1
Macro avg	1	1	1
Weighted avg	1	1	1

Table 5 shows the accuracy, precision and f1 score for the model. The metrices show that the model performed well in the classification problem, for instance the f-score of 1 indicates that the model has perfect precision and recall.

The training versus the validation loss curves in Figure 11 below shows that the model was well fitted. The curves also showed that the loss kept on improving with increasing number of epochs set for the model.

The training accuracy versus the validation accuracy in Figure 12 also shows that the model is generalizable as the gap between the curves is minimal and the scores are high and improving with increasing number of epochs set for the model.

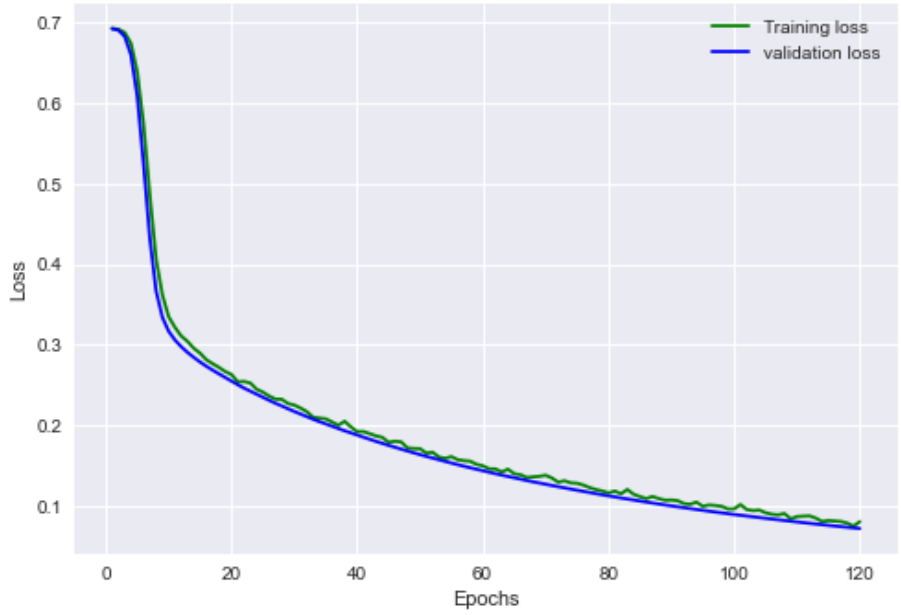


Figure 11: Training versus validation loss curves

Figure 12: Training versus validation accuracy curves

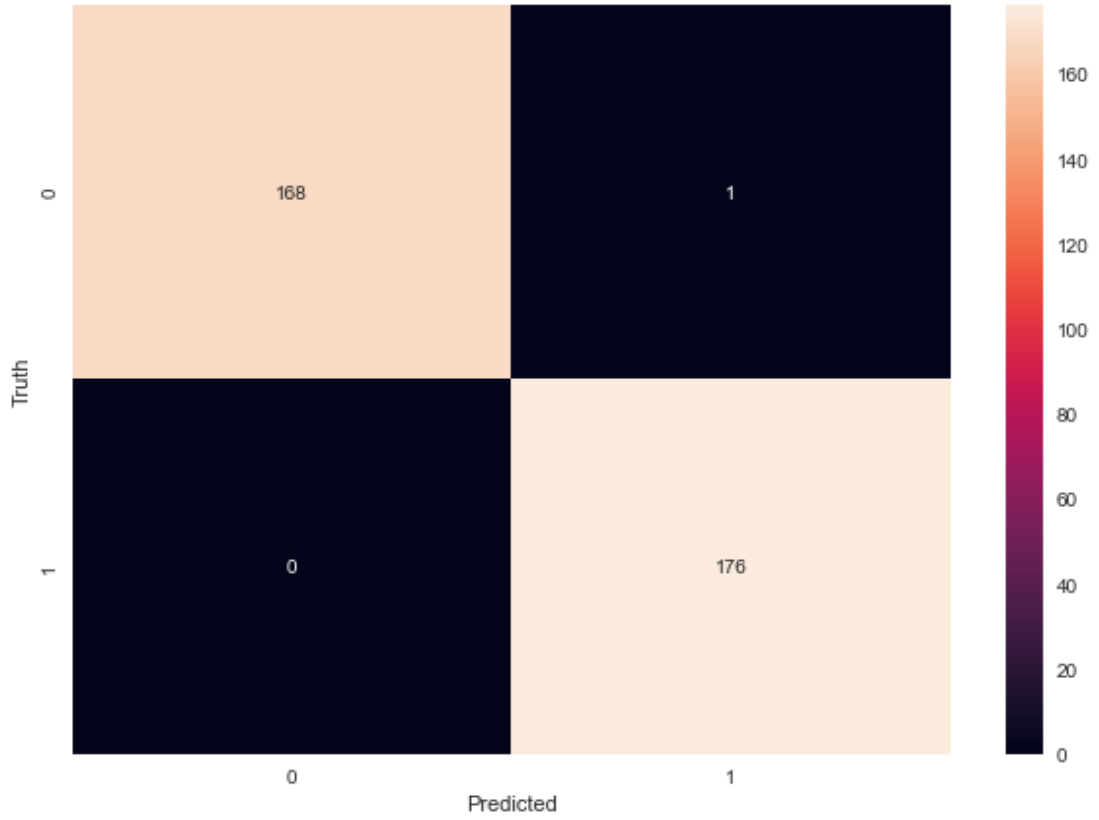


Figure 13: Confusion Matrix showing performance of the built model

From the confusion matrix Figure 13 above, it shows that the model only misclassified one patient as treatment failing patient from the test data during the model testing process. The model was able to predict all patients that did not have treatment failure accurately. This means that the model could be trusted, and it could be possible that the patient who has been misclassified by the model is a true classification of the outcome since the followed manual algorithms are also depended on humans who are prone to making errors in the process of reading and diagnosing the outcomes.

The Table 6: Print out random 10 actual outcomes versus predicted values is the output from the test process of the model. The table shows 10 test random patients comparing the actual outcomes and predicted outcomes. With reference to the test results of the

model, the model was able to predict 100% accurately. This also added on the evidence that the ANN model was able to predict accurately on the outcomes of treatment failure.

Table 6: Print out random 10 actual outcomes versus predicted values

Patient Record number	Actual outcome	Prediction
719	0	0
607	0	0
766	0	0
546	0	0
1064	0	0
1144	0	0
1634	1	1
1080	0	0
1105	0	0
623	0	0

Lastly, this research interviewed participants to see if they would trust the modeled prediction system to be implemented to run in a real environment. Most of the participants were of the view that the system should not be implemented to run independently in the real-life environment. One of the participants mentioned that

> "*Trust would come after testing the system several times and validating with examples of real-life cases and if the system will be able to predict or give expected outcomes. This system should only help the health care provider and the system should be helped by the provider to input the required data requirements"*.

This research gathered that users preferred not to have the system run on its own without a medical person giving it the required parameters.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

In summary, the primary aim of this research was to create a predictive model for first- and second-line Antiretroviral Therapy (ART) treatment failure using soft computing techniques, leveraging available datasets and expertise from HIV healthcare professionals in Malawi. Using soft computing techniques, an Artificial Neural Network, a pragmatic framework has been proposed to predict the detection of treatment failure in patients living with HIV and are on ART. The presented results have been demonstrated in this research that it can be a viable technique to model treatment failure prediction using soft computing. Even with some of the missing predictors, the model has demonstrated that with the minimal available variables the prediction model was able to predict treatment failure in patients who were on ART. The research also found that users preferred not to have the system run on its own without a medical person attending to it, with this finding the research recommends that the presented prediction model can be used alongside the medical personnel working in the field of ART treatment care.

Furthermore, since this research relied on ART experts and access to HIV patient level data to provide theoretical information and patient information used in modeling prediction. The data which was gathered and used for modelling may not be generalizable to the entire nation since the data was only gathered from Lighthouse Trust clinics.

This was considered a limitation in this research and further recommendations from this research is to use national ART data to model ART treatment failure for Malawi. Additionally, the scope of this research did not include the discussion on efficiency of different soft computing models, and we therefore recommend that efficiency of different soft computing models be researched further.

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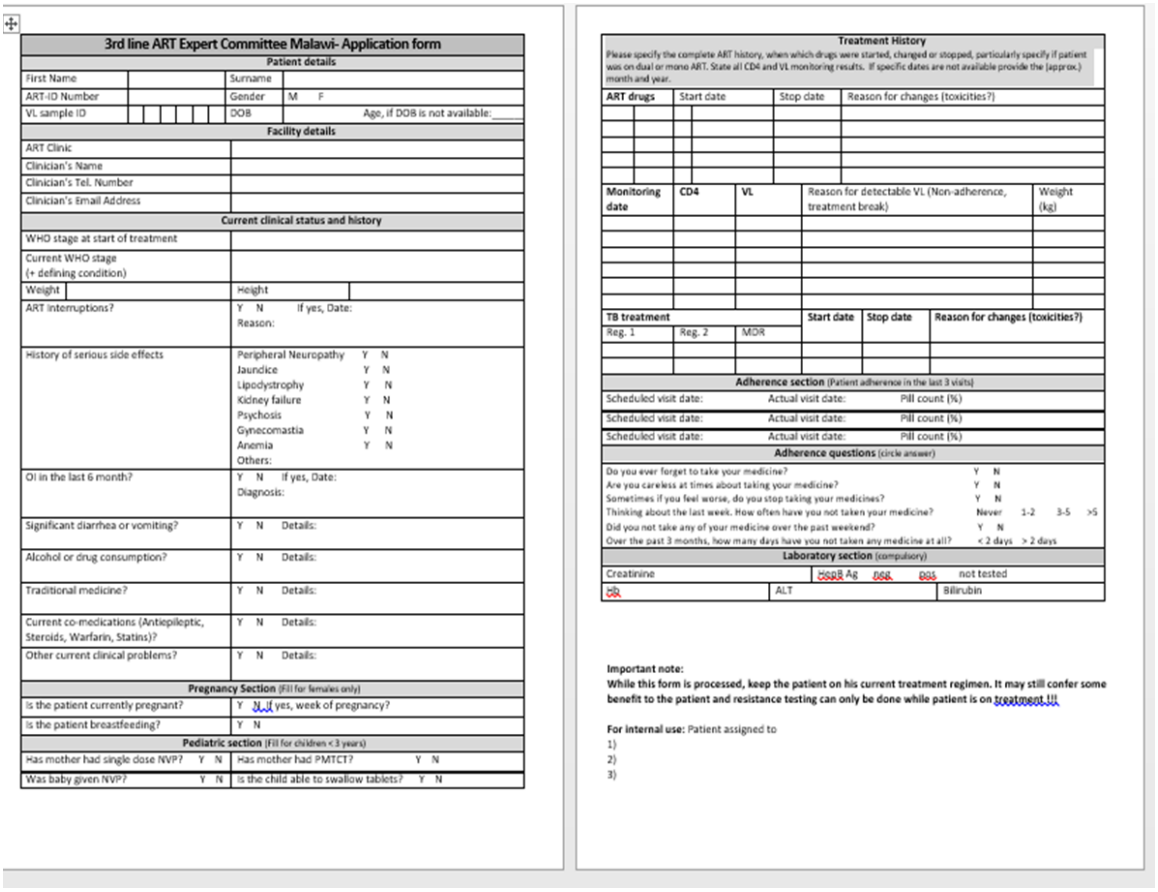
APPENDICES



3rd line ART Expert Committee Malawi- Application form

Patient details

First Name		Surname	
ART-ID Number		Gender	M F
VL sample ID		DOB	Age, if DOB is not available:____

Facility details

ART Clinic	
Clinician's Name	
Clinician's Tel. Number	
Clinician's Email Address	

Current clinical status and history

WHO stage at start of treatment	
Current WHO stage (+ defining condition)	
Weight	Height
ART interruptions?	Y N If yes, Date: Reason:
History of serious side effects	Peripheral Neuropathy Y N Jaundice Y N Lipodystrophy Y N Kidney failure Y N Psychosis Y N Gynecomastia Y N Anemia Y N Others:
OI in the last 6 month?	Y N If yes, Date: Diagnosis:
Significant diarrhea or vomiting?	Y N Details:
Alcohol or drug consumption?	Y N Details:
Traditional medicine?	Y N Details:
Current co-medications (Antiepileptic, Steroids, Warfarin, Statins)?	Y N Details:
Other current clinical problems?	Y N Details:

Pregnancy Section (Fill for females only)

Is the patient currently pregnant?	Y N If yes, week of pregnancy?
Is the patient breastfeeding?	Y N

Pediatric section (Fill for children <3 years)

Has mother had single dose NVP? Y N	Has mother had PMTCT? Y N
Was baby given NVP? Y N	Is the child able to swallow tablets? Y N

Treatment History

Please specify the complete ART history, when which drugs were started, changed or stopped, particularly specify if patient was on dual or mono ART. State all CD4 and VL monitoring results. If specific dates are not available provide the (approx.) month and year.

ART drugs	Start date	Stop date	Reason for changes (toxicities?)

Monitoring date	CD4	VL	Reason for detectable VL (Non-adherence, treatment break)	Weight (kg)

TB treatment			Start date	Stop date	Reason for changes (toxicities?)
Reg. 1	Reg. 2	MDR			

Adherence section (Patient adherence in the last 3 visits)

Scheduled visit date:	Actual visit date:	Pill count (%)
Scheduled visit date:	Actual visit date:	Pill count (%)
Scheduled visit date:	Actual visit date:	Pill count (%)

Adherence questions (circle answer)

Do you ever forget to take your medicine?	Y N
Are you careless at times about taking your medicine?	Y N
Sometimes if you feel worse, do you stop taking your medicines?	Y N
Thinking about the last week. How often have you not taken your medicine?	Never 1-2 3-5 >5
Did you not take any of your medicine over the past weekend?	Y N
Over the past 3 months, how many days have you not taken any medicine at all?	< 2 days > 2 days

Laboratory section (compulsory)

Creatinine	HepB Ag	neg.	pos. not tested
Hb	ALT		Bilirubin

Important note:
While this form is processed, keep the patient on his current treatment regimen. It may still confer some benefit to the patient and resistance testing can only be done while patient is on treatment !!!

For internal use: Patient assigned to
1)
2)
3)

Figure 14: 3rd line ART application form

Study information sheet

STUDY INFORMATION SHEET

RESEARCH TITLE: MODELLING FIRST AND SECOND LINE ART TREATMENT FAILURE PREDICTION USING SOFT COMPUTING TECHNIQUES

CONTACTS	
RESEARCH ETHICS COMMITTEE	PRINCIPLE INVESTIGATOR
The Chairman, University of Malawi Research Ethics Committee (UNIMAREC), Chancellor College, P.O Box 280, Malawi. Zomba. Email: unimarec@cc.ac.mw	Mr. Dumisani J. Ndhlovu C/O The Lighthouse Trust, P.O BOX 106, Lilongwe, Malawi. Email: j.dumisani7291@gmail.com ; Phone: +265 999635514

INTRODUCTION

Thank you for taking the time today to meet with me. My Name is **Dumisani Ndhlovu**. I am a student at the University of Malawi currently studying Master of Science in Informatics. I am here to collect data for my research study which intends to Model

prediction for ART treatment failure using Soft computing techniques. Here is my introduction letter from school for your perusal.

Specific objectives of the research:

1. To identify the factors associated with first- and second-line treatment failure among people living with HIV and are on treatment
2. To identify the current algorithms which are used to determine first and second line treatment failure
3. To build an artificial neural networks model for prediction of first- and second-line treatment failure
4. To compare the outcomes of the current procedures used in establishing first- and second-line treatment failure to the predicted outcome based on the developed model

My goal is to capture a wide range of viewpoints that can usefully inform my academic research study. Your answers will be kept confidential and will not be used for any purpose other than in a report that will help in achieving the objectives of the research.

The interview should last about an hour. Participation is voluntary and you can choose not to take part. You can also choose to refuse to answer any questions you are uncomfortable with or do not want to answer. I would like you to feel free to be open and honest in your responses. Your responses will be appreciated and will contribute substantially to the development of a prediction model of ART treatment failure using soft computing techniques which I believe it maybe a solution to some of challenges that may exist.

Consent form

Figure 15: Consent forms

STUDY INFORMATION SHEET

RESEARCH TITLE: MODELLING FIRST AND SECOND LINE ART TREATMENT FAILURE PREDICTION USING SOFT COMPUTING TECHNIQUES

CONSENT

Before we begin, do you have any questions about the purpose of the study or what will happen to the information? If it's ok, I would like to audio record the interview for note-taking accuracy. The only people who will have access to the recordings and interview notes are project researchers, who have taken a strict oath of confidentiality. In this study I will not record your name on the information sheet as well as the audio to ensure anonymity. The recording will also be pitched to ensure we maintain anonymity with voice recognition. I would like also to request you that you should not mention actual names of patients in your examples when giving out responses.

Do I have your permission to conduct this interview? *Yes* *No*

Do I have your permission to record this interview? *Yes* *No*

Respondent Name: _____ Signature: _____

Form Number	
Interviewer Name	
Interview Date	
Interview Time	
Respondent Profession	
Location (We use anonymized locations e.g Hospital 1, 2, 3 &4)	

Qualitative data collection tool

I. English version

Figure 16: English

STUDY INFORMATION SHEET

RESEARCH TITLE: MODELLING FIRST AND SECOND LINE ART TREATMENT FAILURE PREDICTION USING SOFT COMPUTING TECHNIQUES

QUESTIONS

- To identify the factors contributing to first- and second-line treatment failure among people living with HIV and are on treatment
    1. How involved are you in HIV patients/clients care and treatment?
    2. In your own words how can you describe what it means by first and second line treatment failure in HIV patients?
    3. What are the causes of first line treatment failure among people living with HIV and are on treatment?
    4. What are the causes of second line treatment failure among people living with HIV and are on treatment?
- To identify the current procedures that are used to determine first and second line treatment failure diagnosis and prediction
    1. How do you diagnose or predict first and second line ART treatment failure in HIV patients?
    2. Step by step what are the steps that you follow when determining or predicting ART treatment failure in HIV patients?
    3. Do you follow these steps? Why?
    4. Is it possible for you to share or refer me to documents that guides you to determine treatment failure in HIV patients?
    5. What do you say are the limitations of using these algorithms to diagnose and predict treatment failure?
    6. Is it possible for you to share the challenges you have faced or currently face when diagnosing or predicting first line ART treatment failure?
- To build first- and second-line ART treatment failure prediction using soft computing techniques

1. Do you think a computer software if developed can be able to determine and predict ART treatment failure accurately?
2. What do you think would be required before developing a computer program like this one?
3. Would you trust the outcomes of the predictions from the software?

II. Chichewa version

STUDY INFORMATION SHEET

DZINA LA KAFUKUFUKU: KUFUNA KUPEZA NJIRA YOLOSERA YA KULEPHERA KWAMAGWIRIDWE AMANKWALA AMA ARV POGWIRITSA NTCHITO NJIRA ZA MA KOMPYUTA.

CONTACTS	
OPEREKA CHILOLEZO CHAKAFUKUFUKUYI	**Mwini Kafukufuku**
The Chairman, University of Malawi Research Ethics Committee (UNIMAREC), Chancellor College, P.O Box 280, Malawi. Zomba. Email: unimarec@cc.ac.mw	Mr. Dumisani J. Ndhlovu, C/O The Lighthouse Trust, P.O BOX 106, Lilongwe, Malawi. Email: j.dumisani7291@gmail.com ; Foni: +265 999635514

POYAMBA

Zikomo kwambiri chifukwa chopatula nthawi lero kuti mukumane ndi ine. Dzina langa ndi **Dumisani Ndhlovu**. Ndine wophunzira ku sukulu yakachendede yochedwa University of Malawi pano ndikuphunzira Master of Science yokhuzana ndizama kompiyuta. Ndili pano kuti ndisonkhanitse mfundo ya kafukufuku wanga yemwe akufuna kulosera za akulephera kwamagwiridwe amankhala ama ARV pogwiritsa ntchito njira za ma kompiyuta. Ichi ndichi kalata chochokera ku sukulu cho tsimikizira kuti ndine wophunzira wawo.

Zolinga zaka fukufukuyi

1. Kufufuza zifukwa zomwe zimapangitsa kuti anthu amene ali ndi kachilombo ka HIV omwe akumwa mankhwala kuti asamangwire bwino ntchito bwino mthupi.
2. Kuwona ndondomeko zomwe zikugwiritsidwa ntchito po lotsela kusiya kugwira ntchito kwa mankhwala ama ARV.
3. Kupanga njira yolotsela komaso kudziwa za kulephera kogwira ntchito kwa ma ARV mthupi pogwiritsa ntchito njira zofewa zama kompyuta.
4. Kuyerekeza zotsatira za njira zomwe zikugwiritsidwa ntchito pakukhazikitsa kulephera kwa mankhwala oyamba ndi mzere wachiwiri ndi zomwe zalotseledwa pogwiritsa ntchito njira zofewa zama kompyuta

Cholinga changa ndikugwira malingaliro osiyanasiyana omwe angadziwitse bwino maphunziro anga pakafukufukuyu. Mayankho anu adzasungidwa mwachinsinsi ndipo sazagwiritsidwa ntchito pazifukwa zina kupatula ripoti lomwe lithandiza kukwaniritsa zolinga za kafukufukuyi.

Mafunsowa akhala pafupifupi ola limodzi ndi kufusa mafuso sikupitirila ola limodzi. Kutenga nawo mbali ndikosakakamiza ndipo mutha kusankha kuti musatenge nawo mbali. Muthanso kusankha kukana kuyankha mafunso aliwonse omwe simumasuka nawo kapena amene simukufuna kuyankha. Ndikufuna kuti mukhale omasuka kuyankha momasuka. Mayankho anu adzayamikiridwa ndipo athandiza kwambiri pakupanga mtundu wa kuneneratu kwa kulephera kwa chithandizo cha ma ARV pogwiritsa ntchito

njira za kompyuta za soft computing zomwe ndikukhulupirira kuti mwina ndi yankho ku zovuta zina zomwe zingakhalepo.

STUDY INFORMATION SHEET

DZINA LA KAFUKUFUKU: KUFUNA KUPEZA NJIRA YOLOSERA YA KULEPHERA KWAMAGWIRIDWE AMANKWALA AMA ARV POGWIRITSA NTCHITO NJIRA ZA MA KOMPYUTA.

KUPEPHA CHILOLEZO

Tisanayambe, kodi muli ndi mafunso okhudzana ndi cholinga cha phunziroli kapena zomwe zidzachitike muchidziwitso? Ngati zili bwino, ndikufuna kujambula kuyankhulana kumeneku kuti ndikapita kumenendachokera ndikhoza kubwerelamo pamene sinavetse bwino. Anthu okhawo omwe angapeze zojambulidwa ndi zolemba zake ndi akatswiri ofufuza basi, omwe adachita malumbiro osunga zinsinsi za mukafukufuku ameneyu. Mukafukufukuyi sindilemba dzina lanu papepala lazidziwitso komanso pamawu kuti ndiwonetsetse kuti mutsadziwike kuti ndinu mumayankha mafunso. Zojambulazo zidzapangidwanso kuti tiwonetsetse kuti simukudziwika ndi kuzindikirika mawu. Ndikufunsanso kuti musatchule mayina enieni a odwala muzitsanzo zanu popereka mayankho.

Kodi ndili ndi chilolezo chofunsa mafunso? *Inde* *Ayi*

Kodi ndili ndi chilolezo chojambula kuyankhulana uku? *Inde* *Ayi*

Dzina Laoyankha Mafunso: _____Signature: _____

Nambala ya fomu	

Dzina la ofunsa	
Tsiku lofusa	
Nthawi yofusa	
Bungwe kumene oyankha amagwira	
Ofesi ya oyankha Mafuso	
Malo	

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MAFUSO

- Kufufuza zifukwa zomwe zimapangitsa kuti anthu amene ali ndi kachilombo ka HIV omwe akumwa mankhwala kuti asamangwire bwino ntchito bwino mthupi.
    1. Kodi mumatenga nawo mbali bwanji pa kasamalidwe ka amene ali ndikachilombo ka HIV?
    2. M'mawu anu kodi mungafotokoze bwanji tanthauzo la kulephera ndi chithandizo chokwanira cha regimeni woyamba ndi wachiwiri kwa odwala omwe ali ndi HIV?
    3. Kodi zoyambitsa kulephera kwa kagwiridwe ka mankhwala a regimeni yoyamba yama ARV muthupi la omwe akumwa mankhwalawa ndi chani?
    4. Kodi zoyambitsa kulephera kwa kagwiridwe ka mankhwala a regimeni yachiwiri yama ARV muthupi la omwe akumwa mankhwalawa ndi chani?

- Kuwona ndondomeko zomwe zikugwiritsidwa ntchito po lotsela kapena kudziwa kwa kusiya kugwira ntchito kwa mankhwala ama ARV a legimeni yo yamba komaso yatchiwiri.
    1. Mumazindikira bwanji kapena mumalosela bwanji kuti mankwala asiya kugwira ntchito muthupi mwa amene akumwa mankhwala a regimeni yoyamba komaso yachiwiri yama ARV?
    2. Gawo ndi sitepe ndi magawo ati omwe mumatsatira mukamaganizira kapena kulosela kwa kulephera kwa magwiridwe ama ARV kwa omwe ali ndi kachirombo ka HIV?
    3. Kodi mumatsatira izi? Chifukwa chiyani?
    4. Kodi ndizotheka kuti mugawane kapena munditumizire ku zikalata zomwe zikukuwuzani kuti mupeze kulephera kwa magwiridwe ama mankhwala kwa omwe ali ndi kachirombo ka HIV?

5. Mukuti ndichani chavuta chimene mukuchidziwa kuti chingalepherese kuti ndondomeko iyi komaso njira iyi kuti ikhale yosadalilika?
6. Kodi ndizotheka kuti muzigawana zovuta zomwe mwakumana nazo kapena zomwe mukukumana nazo pofufuza kapena kuneneratu za kulephera kwa mankhwala a ART?

- Kupanga njira yolotsela komaso kudziwa za kulephera kogwira ntchito kwa ma ARV mthupi po gwiritsa ntchito njira zofewa zama kompyuta.
    1. Kodi mukuganiza kuti pulogalamu ya pakompyuta ngati itapangidwira ikhoza kudziwa ndikuganiza molondola pa kulephera kwa mankhwalawa?
    2. Kodi mukuganiza kuti chidzafunika chiyani musanapange pulogalamu yamakompyuta ngati iyi?
    3. Kodi mungakhulupilire zomwe zatsimikizika kuchokera pulogalamuyo?