# Chapter 1

## 1.0 Introduction

### 1.1 Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome, a condition in humans in which progressive failure of the immune system allows life threatening opportunistic infections.[1] Globally 35.3 million (32.2 million-38.8 million) people were living with HIV at the end of 2013.[2] Approximately, 0.8% of adults of adult aged 15-49 years worldwide are living with HIV, although the burden of the epidermic continues to vary considerably between countries and regions.[2] Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults living with HIV, and accounting for 70.8% of the people living with HIV worldwide.[2] Zimbabwe has experienced a decreasing trend in HIV prevalence from 26.7% in 2002 to 15% in 2014.[3]

### 1.2 Human Immune-deficiency virus treatment failure

Human Immunodeficiency Virus (HIV) treatment failure can be defined by virological, immunologic or clinical measures. Virologically, HIV treatment failure is a repeated HIV Ribonucleic acid (HIV RNA) values above the lower limit of detection of a sensitive assay (usually 50 copies per mL).[4] The World Health Organization (WHO) guidelines define treatment failure virologically as viral load persistently (at least 2 results) above 5000 copies/ml. This is despite the patient taking antiretroviral therapy regimen. The implication would be that the medication is no longer effective to suppress viral replication in a patient.

The success of antiretroviral treatment is defined more specifically by viral suppression.[4] Therefore the standard of care should be to maintain an RNA level of below the limit of detection (generally<50 copies/mL). Based on this specific criterion, HIV RNA levels that are >50 copies/mL mean that Antiretroviral Therapy (ART) regimen is failing to suppress

viral load; hence the patient can be diagnosed with HIV treatment failure. Zimbabwe National Opportunistic Infections/Antiretroviral Therapy (OI/ART) program does not routinely measure viral load in patients and uses clinical and immunological measures for patient monitoring and diagnosis.[5]

**Working definition:**

1. Immunologically, HIV treatment failure is when CD4 count falls to below pre-therapy baseline or there is 50% fall from the treatment peak value (if known) or CD4 count levels are persistently (at least 2 results) below 100cells/$mm^3$.[6]
2. Clinically, HIV treatment failure is when there is a new or recurrent WHO stage 4 condition in a patient who has been on anti-retroviral therapy (ART) for at least 6 months.[6]

### 1.2 The importance of preventing HIV first line treatment failure

The development of HIV-1 treatment failure is not only a global clinical and public health concern but also a threat to ART expansion efforts in countries that use ART. This means that effort should be directed towards reducing it for better treatment outcomes. Preventing HIV first line treatment failure (virologic failure) is important for minimizing if not preventing disease progression and avoiding the development of antiretroviral resistance i.e. wild strains of Human Immunodeficiency Virus Drug Resistance (HIV DR).[4] Some measures which can adopted to prevent or reduce HIV treatment failure include perfect adhering to Anti retroviral Therapy (ART), . According to De Beaudrap P et al in 203 in Senegal; if a patient fails first line ART, the risk of that patient failing subsequent ART or developing HIV DR significantly increases.[6] Detecting virologic failure and intervening appropriately reduces mortality from HIV infection. Furthermore, early detection of virologic failure is an important HIV treatment cost reduction mechanism. The reduction in cost can be realized, for instance, through

avoiding second line drugs which are more expensive than first line drugs. The unit cost of ART is between US$153-US$400 per person per year in Zimbabwe.

### 1.3 Epidemiology of HIV treatment failure

A systematic review of the epidemiology of ART failure on a global scale by Gereti AM et al in 2007 noted that reported prevalence surveys showed inter-region and intra-region variability in part because of methodological differences.[7] Despite this variability, a collaborative study and meta-analysis of global trends of ART treatment failure in 2012 by Gupta RK et al found a significant increase in prevalence of treatment failure over time since ART roll out especially in regions of Sub-Saharan Africa.[8]

In the United States of America (USA) in 2004; a study on a random sample of 132 500 HIV infected adults, with HIV viremia of 500 copies/ml, an estimated 76% had failure to one or more antiretroviral drugs.[9] Further to this, the study found out that the odds of treatment failure were significantly higher among patients with a history of antiretroviral drug abuse, advanced HIV disease, higher plasma HIV viral load and lowest CD4 cell count by self report.

Inter-country variability in prevalence of HIV treatment failure is demonstrated in a study in France which, in contrast to USA, showed a lower prevalence. The follow up study in France on 1402 protease inhibitor-naive patients starting a highly active antiretroviral therapy regimen between July 1996 and March 1997 found out that 49.9% (n=700) had virologic failure.[10] In a Swiss HIV cohort study by Young J et al in 2011 to assess the efficacy, tolerability and risk factors for virologic failure of darunavir-based therapy for 130 treatment-experienced HIV-infected patients the rate of virologic failure at 48 weeks was 20%.[11]

Hammers S et al in 2008 conducted a study on six sub-Saharan African countries and determined 5.5% prevalence of HIV first line treatment failure.[12] A cross sectional study to determine the prevalence of HIV-1 treatment failure among reproductive aged women in Durban, Kwazulu Natal province, South Africa, was conducted by Horn S et al.[13] Of the 1073 valuable women, 37% (n=400) had HIV treatment failure.

Zimbabwe has experienced a decreasing trend in HIV prevalence from 26.7% in 2002 to 13.1 % in 2013.[3] While the prevalence of adult HIV is well documented; in contrary, the prevalence of HIV treatment failure is not well known at national level. In 2010, the National Drug and Therapeutics Advisory Committee (NDTAC) estimated that the percentage of patients who switched to HIV second line treatment was 1%.[5] As a proxy to HIV first line treatment failure; the 2009-2011 national HIV Drug resistance (HIV DR) survey reported an overall HIV DR prevalence of 6.3%.[14]

### 1.4 Study Setting: Zvishavane District

Zvishavane district is situated in Midlands Province in Zimbabwe. It has a population size of 72 513 according to 2012 Zimbabwe population census. The major economic activity in the area is mining; both formal and informal mining. The district experienced an increasing trend of Sexually Transmitted Infections (STIs) cases from 66 per 1000 population in 2002 to 97 per 1000 population in 2005.[15] According to the provincial health information STIs data, the district still records increasing trend of STIs and as of 2013, the rate is at 113 cases per 1000 population. In 2013 alone, the district recorded 4881 new STI cases, 35% (n=1721) of which were HIV positive cases.[16]

According to the provincial health information, the district has the highest prevalence of HIV first line treatment failure (**see figure 1**). The district is one of the 12 sentinel sites for the surveillance of HIV-1 drug resistance in Zimbabwe.[14] An operational research, through

genotyping, to determine the prevalence of HIV 1 drug resistance (HIV-1 DR) among all sentinel sites showed that the district had the highest prevalence of HIV-1 DR in Zimbabwe at 12.8%.[14] The district monitors HIV treatment failure using clinical and immunological measures.[5] However, it takes virologic measures irregularly.

### 1.5 Problem statement

HIV treatment failure is both a clinical and public health concern in terms of HIV treatment outcomes and cost of running HIV programs in Midlands Province. There are no national statistics on HIV-1 first line treatment failure. Below is a graph showing the prevalence of HIV first line treatment failure in districts of Midlands Province (**figure 1**).

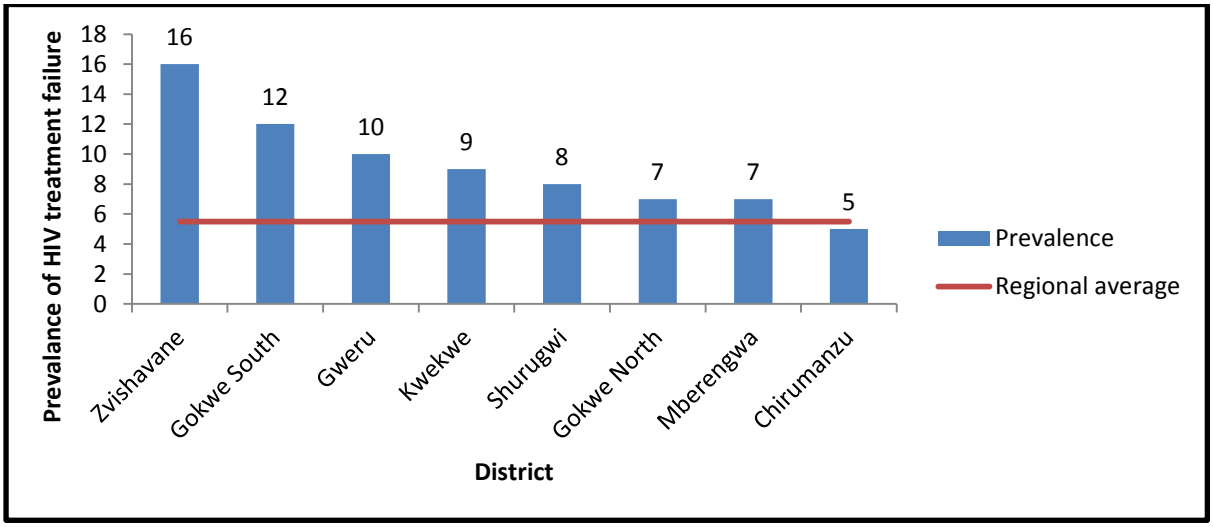


Figure 1: Distribution of HIV first treatment failure in districts of Midlands Province, 2014

Zvishavane district had the highest prevalence of HIV treatment failure at 16% (n=183) (**Figure 1**). This is well above the regional prevalence of 5.5%.[12] According to the 2013 Zimbabwe HIV Drug Resistance Early Warning Indicators (EWIs) survey report, Zvishavane district was the least performer to EWI 1 on time pill pick up.[17] Against a target of 90%, the district recorded 63% and 50% for adults and pediatrics respectively. While the district achieved 86%, which is above national target, on EWI 2 on retention in care, it fell short of national target on EWI 3 on pharmacy stock outs. Zvishavane is one of the 12 sentinel sites

for monitoring HIV DR and recorded the highest prevalence of HIV DR at 12.7%.[14] We, therefore sought to find out possible factors which could be contributing to HIV first line treatment failure in Zvishavane district.

### 1.6 Justification of the study

There are no studies that were done to determine factors associated with HIV first line treatment failure in Zvishavane district. In Zimbabwe, Chimbetete C and Tshimanga M in 2011 conducted a study on first line ART treatment at Newlands Clinic in Harare.[18] The study found out that not being married, commencement by private doctor, and WHO stage 3 or 4 at ART commencement were independent risk factors for HIV first line treatment failure. In other settings outside Zimbabwe studies have been done. However, factors associated with HIV first line treatment failure are not well defined. Treatment failure may progress into HIV DR, which is a wild strain of HIV. Conducting a study on factors associated with HIV first line treatment failure may generate evidence based interventions for reducing incidence of first line treatment failure which is a critical stage in curbing the burden of treatment failure.

### 1.7 Research question

What are the factors associated with HIV first line treatment failure in Zvishavane district?

## 1.9 Objectives of the study

### 1.9.1 Broad objective

To determine factors associated with first line HIV treatment failure in Zvishavane district.

### 1.9.2 Specific objectives

- To determine treatment related factors associated with first line HIV treatment failure in Zvishavane district, 2014.
- To determine health service factors associated with first line HIV treatment failure in Zvishavane district, 2014.
- To establish behavioral factors associated with first line HIV treatment failure in Zvishavane district, 2014.
- To determine participants' knowledge about factors associated with first line HIV treatment failure among study participants in Zvishavane district, 2014.

## 1.10 Definition of terms

### HIV treatment failure

Human Immune-deficiency virus (HIV) treatment failure is a repeated HIV Ribonucleic acid (HIV RNA) values (2 results) above the lower limit of detection of a sensitive assay (usually 50 copies per mL).[4]

### First line Regimen

Antiretroviral drug combinations of choice for patients who are put on treatment for the first time in Zimbabwe.[19] Some of these regimes include Tenolam (Tenofovir & Lamivudine), Zidovudine/Lamivudine/Nevirapine and Tenolam/Efavirenz.

### Second line Regimen

Antiretroviral drug combinations which are prescribed to patients who fail first line regimen.[19] Some of these regimens include Atazanavir/Lopinavir/Ritonavir, didanosine and abacavir

### Risk factor

An aspect that increases the likelihood of failing First Line HIV treatment.[20]

### Protective factor

An aspect that reduces the likelihood of failing HIV treatment.[20]

# Chapter 2

## 2.0 Literature Review

This chapter dealt with literature review based on global, regional and national overview of first line HIV treatment failure; and factors associated with first line HIV treatment failure.

## 2.1 Global Epidemiology of HIV treatment failure

The importance of understanding the prevalence of HIV treatment failure cannot be overemphasised considering that the whole world targets to end Human Immunodeficiency Syndrome (HIV/AIDS) by 2030 as specified in the Millennium Development Goal (MDG) 6.The prevalence of HIV treatment failure worldwide varies markedly from one region to another. The variation is explained by lack of a standard definition of HIV treatment failure.[4] A systematic review study on the epidemiology of antiretroviral therapy failure in HIV positive patients showed an inter-region and intra-region variability which can be explained in part by methodological differences.[7]

In the USA in 2004; a study on a random sample of 132 500 HIV infected adults, with HIV viremia of 500 copies/ml, an estimated 76% had failure to one or more antiretroviral drugs.[9] Further to this, the study found out that the odds of treatment failure were significantly higher among patients with a history of antiretroviral drug abuse, advanced HIV disease, higher plasma HIV viral load and lowest CD4 cell count by self report.

In North America in 2013, out of 42 790 individuals who received therapy, 16.7% (n=7159) experienced a second virologic failure.[21] The study showed that the risk of second virologic failure significantly decreased from 56 cases per 100 person years in 1996 to 16 cases per 100 person years in 2005 ($p < 0.001$). Concurring with this is a cohort study in America in 2014 which found a virologic failure of 13.5%.[22]

Inter-country variability in prevalence of HIV treatment failure is further demonstrated in a study in France which, in contrast to USA, showed a different prevalence. The follow up study in 2000 in France on 1402 protease inhibitor-naive patients starting a highly active antiretroviral therapy regimen between July 1996 and March 1997 found out that 49.9% (n=700) had virologic failure.[10] In a Swiss HIV cohort study by Young J et al in 2011 to assess the efficacy, tolerability and risk factors for virologic failure of darunavir-based therapy for 130 treatment-experienced HIV-infected patients the rate of virologic failure at 48 weeks was 20%.[11]

Li H and Zhong M conducted a study on the prevalence and mutations of HIV treatment failure from 2010 to 2011 among ART patients in the Yunnan province in China.[23] The study collected 664 plasma samples from which 609 pol sequences were derived in different cities during the study period. The prevalence of treatment failure was 45.1%. Bloch M et al conducted a cross sectional observational study in 2010, on triple class HIV antiretroviral therapy failure, on an Australian primary care setting found out that 5.1% (n=51) had triple class drug failure, 31.4% (n=16) of which had experienced virologic failure of each of the three main drug classes.[24]

**2.2 Regional Epidemiology of HIV treatment Failure**

Despite this variability, a collaborative study and meta-analysis of global trends of ART treatment failure by Gupta RK et al in 2012 found a significant increase in prevalence of treatment failure over time since ART roll out especially in regions of Sub-Saharan Africa.[8] Hammers T et al in 2008 conducted a study on six sub-Saharan African countries and determined 5.5% prevalence of HIV first line treatment failure.[12] A study in Ethiopia in 2012 found out that the prevalence of HIV treatment failure was 14.1%.[25] In contrary, a cross sectional study to determine the prevalence of HIV-1 treatment failure among reproductive aged women in South Africa by Horn S et al in 2013 found out that 37% had HIV treatment

failure.[13] Further intra-region variability is demonstrated in a study in Senegal which showed that the prevalence of HIV treatment failure was 25%.[26]

### 2.3 Epidemiology of HIV treatment failure in Zimbabwe

Zimbabwe has experienced a decreasing trend in HIV prevalence from 26.7% in 2002 to 13.1 % in 2013.[3] The decline is attributed to the roll out of national ART and behavior change programs since 2004. While the prevalence of adult HIV is well documented; in contrary, the prevalence of HIV treatment failure is not well known at national level. In 2010, the NDTAC estimated that the percentage of patients who switched to HIV second line treatment was 1%.[5] As a proxy to HIV first line treatment failure; the 2009-2011 national HIV DR survey reported an overall HIV DR prevalence of 6.3%.[14]

### 2.4 Factors associated with HIV treatment failure

While the scaling up of ART coverage is a positive development, there are fears of rapid and uncontrollable emergency of HIV-1.[27] Although HIV-1 drug failure is related to therapeutic strategies in the HIV-1-infected population, other factors substantially contribute to its development yet they are less well defined.[27] Until program managers understand risk factors for development of HIV treatment failure, it is difficult to implement effective interventions to reduce the incidence and prevalence antiretroviral failure. Defining risk factors for the development of HIV treatment failure is not only beneficial in terms of treatment outcomes but is also a basis of a risk insurance mechanism in terms of health financing bearing in mind that second line or third line treatment drugs are expensive.

Baseline viral load and CD4 can be some of the factors which may be associated with both virologic and clinical failure. This implies that interventions should target these indicators for better HIV treatment outcomes. Grabar S et al in 2000 conducted a study in France to determine predictors of virologic and clinical failure in patients receiving a protease inhibitor

as part of triple therapy.[10] After multivariate analysis, baseline CD4 cell count and viral load were found to be independent predictors of both virologic and clinical failure.

Consistent with this finding is Lambert-Niclot S et al in 2011 who conducted a study to determine virologic and clinical characteristics associated with virologic failure in HIV–infected patients switching to darunavir/ritonavir (DRV/r) monotherapy.[28] Using the logistic model, Viral Load (VL) >50 copies/mL was a predictive factor to virologic rebound (P = 0.042).

A case control study was conducted on factors Associated with First-Line Antiretroviral Therapy Failure amongst HIV-Infected African Patients in Kenya in 2012.[29] Using stratified Cox model, low baseline CD4 count < 50 /ml (Hazards Ratio (H.R) = 7.07, CI 4.92 - 10.15) and Zidovudine based ART (H.R 1.76, CI 1.25 - 2.48) and imperfect ART adherence (H.R = 2.77, CI 2.20 - 3.49). Participants who had a low baseline CD4 count were 7.07 times more likely to fail first line treatment than those with a CD4 count above CD4 $\geq$50/ml. Those who were on Zidovudine based ART were 1.76 times more likely to fail treatment than those on other regimens. Participants with imperfect adherence were 2.77 times more likely to fail treatment than those who had perfect adherence

Aldrovandi G et al in 2014 conducted a study on the prevalence of HIV DR among recently initiated adolescents to find out factors associated with HIV treatment failure.[30] The study found out that non exclusive factors associated with HIV treatment failure were sex with multiple partners, men who had sex with men, having sex under the influence of drugs/alcohol, exchanging sex for money, having an HIV infected partner, abuse of drugs, being a victim of sexual assault and having been recently infected with a sexually transmitted disease.

Miller V et al in 2000 conducted a study to analyse the immunological and virologic effects of treatment interruptions in HIV-1 infected patients with treatment failure.[31] Treatment interruption resulted in viral load increases (mean 0.7 $\log_{10}$ copies/ml, p=0.0001) and CD4 count decreases (mean 89 x $10^6$ cells/l, p=0.0001). Response to initiation of treatment fell with increasing viral load (Relative Hazard (RH) 0.33, P=0.001). A similar finding was made by Deeks SG et al in an intervention study in 2001.[32] The study found out that discontinuation of therapy for 12 weeks was associated with a median decrease in CD4 count of 128 cells/$mm^3$ and an increase in the plasma HIV RNA level of 0.84 log copies per milliliter. Drug susceptibility was associated with increases in plasma HIV RNA levels and decreases in CD4 cell counts.

Adherence to prescribed medication is a central feature to good clinical HIV care. In a study on predictors of self reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens in 2000, California, USA, it was found out that non adherence to combination antiretroviral therapy was common and associated with increased levels of plasma HIV.[33] High baseline plasma virus load was found to be significantly associated with treatment failure (multivariate hazard ratio [HR], 1.59; $p < .001$) in a 30 months long follow up study in British Columbia, Canada by Harrigan PR et al in 2005.[27]

Harrigan PR et al 2005 further found out that adherence was significantly associated with treatment failure on plasma samples with plasma virus loads (pVLs) >1000 copies/mL (estimated using prescription-refill data and/or untimed plasma drug-concentration measurements).[27] When compared with patients with low (0%-<20%) prescription-refill percentages, patients at an elevated risk of harboring drug-resistance mutations were those with relatively high but imperfect prescription refill percentages (80%-<90%; multivariate HR, 4.15; $p < .001$) and those with essentially perfect (⩾95%) refill percentages but with 2

plasma drug concentrations below the steady-state trough concentration minus 1 standard deviation (multivariate HR, 4.57; $P < .001$).

Sethi AK et al conducted a study on the association between adherence to antiretroviral therapy and human immunodeficiency treatment failure in the USA in 2000.[31] The study found out that a cumulative adherence of 70%–89%, a CD4 cell nadir of <200 cells/μL, and the missing of a scheduled clinic visit in the past month were independently associated with an increased hazard of viral rebound in 2004.[34]

A cross-sectional analysis of subjects in an observational prospective cohort was done in the US to examine the relationship between adherence, viral suppression and antiretroviral resistance in HIV-infected homeless and marginally housed people on protease inhibitor (PI) therapy by Bangsberg DR et al 2000.[35] Adherence was measured by periodic unannounced pill counts, electronic medication monitoring, and self-report; HIV RNA viral load; and HIV-1 genotypic changes associated with drug resistance. There was a substantial proportion of homeless and marginally housed individuals who had good adherence to PI therapy. A strong relationship was found between independent methods of measuring adherence and concurrent viral suppression.

A cross sectional correlational study was conducted in China by Molassiotis A et al in 2002 to assess adherence with antiretroviral medication in a sample of HIV patients in Hong Kong and identify predictors of adherence using self reports.[36] A high adherence rate was found in the 136 sample of predominantly Chinese patients. There were only 13.7% of patients who were classified as non adherent. Predictors of non adherence in the study included high self-efficacy, low tension anxiety scores, low intensity of nausea and vomiting ($R^2$=0.304). Additional factors included pain, numbness, age, disease stage, internal locus of control, fatigue and family support.

In conclusion, following is the summary of factors associated with HIV treatment failure among HIV positive patients on ART.[37]

**Patient-Related Factors:**

- Pre-existing (transmitted) drug resistance and suboptimal adherence.
- Higher pre-treatment or baseline HIV RNA level (depending on the specific regimen used)
- Lower pre-treatment or nadir CD4 T-cell count (depending on the specific regimen used)
- Co-morbidities (e.g. active substance abuse, psychiatric disease, neurocognitive deficits)
- Presence of drug-resistant virus, either transmitted or acquired
- Prior treatment failure
- Incomplete medication adherence and missed clinic appointments
- Interruption of or intermittent access to ART

**ARV Regimen-Related Factors:**

- Drug adverse effects and toxicities
- Suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs)
- Suboptimal virologic potency
- Prior exposure to suboptimal regimens (e.g., functional monotherapy)
- Food requirements and prescription errors
- High pill burden and/or dosing frequency

## 2.4. The Conceptual Framework

Based on review of literature done, below is a theoretical framework that will be applied in this study.

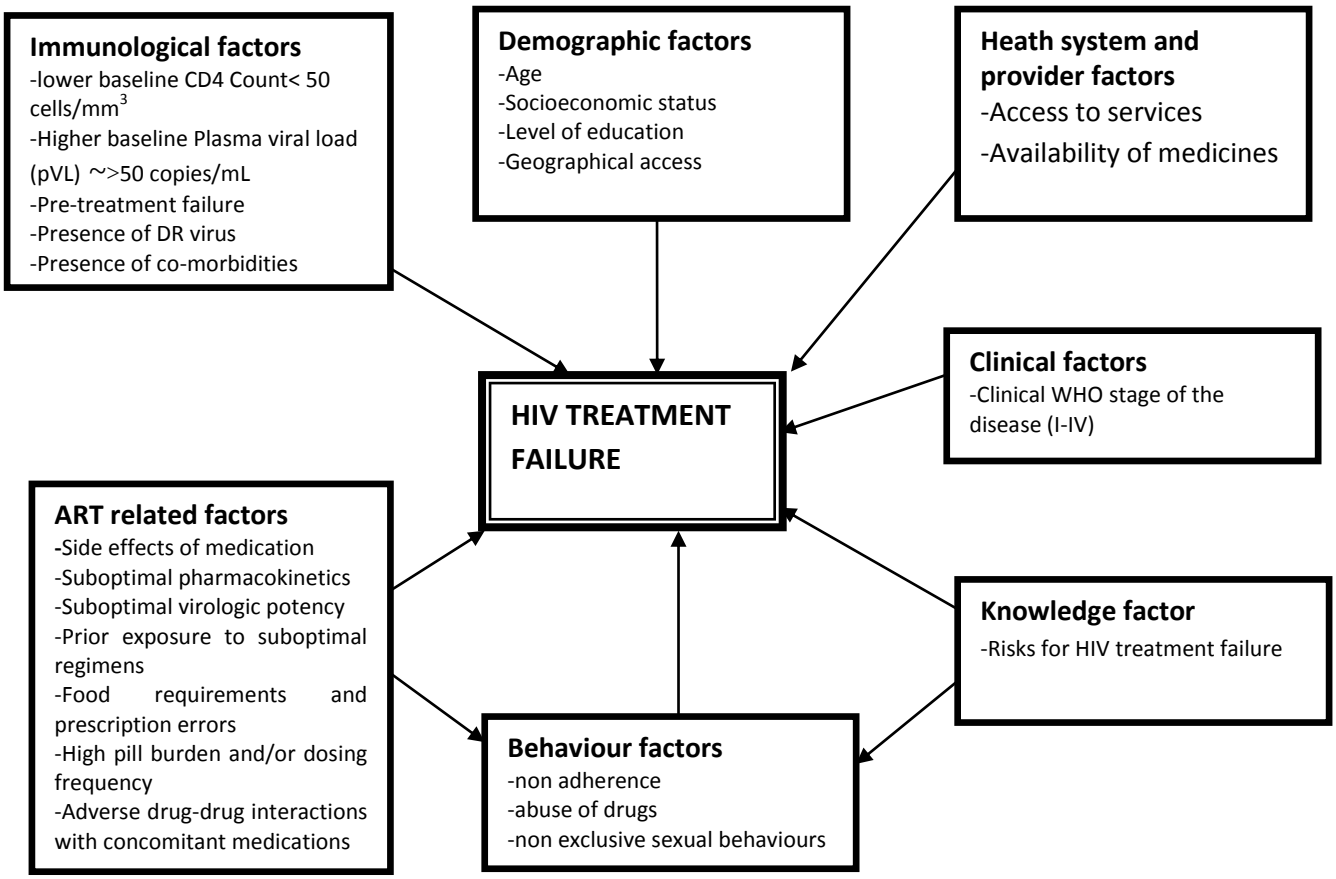


Figure 2: Theoretical Frame work on factors associated with First Line HIV treatment failure in Zvishavane District, 2014

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# Chapter 3

## 3.0 Research Methodology

This chapter looked at materials and methods for conducting the study. These included study type, sample size determination and data collection procedure and data analysis.

## 3.1 Study type

A 1:1 unmatched case control study was conducted.

**Case:** Was an HIV patient who was on first line ART for at least 6 months in Zvishavane district and switched to second line ART regimen because of treatment failure during the 2013/2014 period.

**Control:** Was an HIV patient in Zvishavane district who was on first line ART, had been on first line ART for at least 6 months and had not failed first line ART.

## 3.2 Plan for reducing potential biases

***Ascertainment bias:***

There was a possibility that controls that failed first line HIV treatment, but not yet diagnosed, could have been recruited into the study. This could have reduced the strengths of associations. This was reduced by recruiting controls that had been on ART for at least 6 months and were not diagnosed with first line HIV treatment failure according to national guidelines.

***Recall bias:***

There was a possibility that cases (diagnosed with first line HIV treatment failure) and controls (did not have first line HIV treatment failure) could have remembered or reported exposure information in different ways. This could have overestimated the strengths of associations as cases are more likely to remember exposure information than controls. To

reduce this bias, ascertainment of exposure was done through checking medical records where possible.

***Interviewee bias:***

The study assessed reported adherence. Participants could have overestimated their adherence levels. This could have threatened internal validity of this study. To reduce this bias, medical records were checked to ascertain adherence.

### 3.4 Study setting

The study was conducted on all health facilities offering ART in Zvishavane district, Midlands Province, Zimbabwe.

### 3.5 Study population

HIV positive patients had received ART in Zvishavane district for a period of at least 6 months.

### Key informants

These were HIV programme managers and had specific knowledge about HIV programme in Zvishavane district. They included Zvishavane District Medical Officer (DMO), Zvishavane District Matron, Zvishavane District Nursing Officer (DNO) Zvishavane district Health Information Officer (HIO) and Zvishavane District HIV focal person.

### 3.6 Records Review

Patients' files in health facilities in Zvishavane district and notes (cards) were reviewed in the study to:

- Identify baseline CD4 count when HIV first line treatment was given
- Indentify baseline WHO clinical HIV stage when First Line HIV treatment was given

### 3.7 Permission and Ethical considerations

Permission to conduct the study was obtained from:

- Provincial Medical Director (PMD), Midlands
- Zvishavane District Medical Officer (DMO)
- Health Studies Office (HSO)
- Medical Research Council of Zimbabwe (MRCZ)
- Joint Research Ethics Committee (JREC)

Written informed consent was obtained from study participants. Consent of parents or legal guardians for those participants that could not legally consent (<18 years) was obtained. No names or addresses of participants were used in the study. Confidentiality was maintained throughout the study. Participation was voluntary and there were no financial gains for participating in the study.

### 3.8 Inclusion criteria and exclusion criteria

#### 3.8.1 Inclusion Criteria

- HIV positive patients of all age groups had been receiving antiretroviral therapy in Zvishavane district for at least 6 months
- HIV positive patients who had either failed first line treatment and were on second line ART or had been on first line ART for at least 6 months and had not failed treatment.

#### 3.8.2 Exclusion criteria

- Patients in Zvishavane district who declined to participate in the study.
- Patients who were on second line ART due to side effects or pregnancy

### 3.9 Sample size determination

#### 3.9.1 Primary participants

Sample size was calculated using Stat Calc and based on a study by Wakibi SN et al "Factors associated with non-adherence to highly active antiretroviral therapy in Nairobi, Kenya."[38] Assumptions were that non-adherence to antiretroviral therapy was a significant risk factor for HIV treatment failure with an odds ratio of 2.40. Exposure of controls to adherence was 18%. A 1:1 unmatched case control study, 95% confidence interval and 80% power, was conducted. A minimum sample size of 111 cases and 111 controls was calculated. Assuming a 10% non response rate in the study by Wakibi SN et al, the minimum total sample size was 246. Therefore the minimum calculated sample size was 123 cases and 123 controls.

#### 3.9.2 Sample size for records

Each participant's records were reviewed, giving a total of 246 records.

#### 3.9.3 Sample size for key informants

Five key informants as defined in section 3.3 were included in the study.

### 3.10 Sampling

The OI/ART register which captures and highlights patients on first line or second line treatment was used to sample participants into the study

#### 3.10.1 Cases

Cases were randomly recruited from OI/ART register into the study using the lottery method. Names of participants were written on pieces of paper and blindly picked by the researcher until a sample size of 123 cases was reached

#### 3.10.2 Controls

Controls were randomly selected from OI/ART attendance register

### 3.10.3 Key informants

Key informants were purposively sampled into the study to provide information on HIV program in Zvishavane district in terms of inputs, processes, outputs and outcomes.

### 3.10.4 Records Review

A desk review of records for all 123 cases and 123 controls was done

## 3.11. Pretesting data collection Instruments

### 3.11.1 Interviewer administered semi structured questionnaire

- The questionnaire was pretested in Gweru district for test retest reliability to check inter-rater agreement.

## 3.12 Data collection

### 3.12.1 Primary participants

A pre-tested interviewer administered, semi-structured, questionnaire was used to collect data from cases and controls. Checklists were used to identify baseline CD4 count and baseline clinical WHO HIV clinical stage of HIV.

### 3.12.2 Key Informants

An interview guide for key informants was used to elicit information on the district's HIV program; from inputs, processes, outputs and outcome. Checklists were used to assess resource availability.

## 3.13 Data analysis

Questionnaires were checked for completeness and internal consistence before being created in Epi info version 5.3.1 for data analysis. Stratified analysis was done to control for confounding and effect modification. Forward stepwise logistic regression analysis was done

to determine independent factors associated first line HIV treatment failure. Qualitative data was sorted and analyzed thematically.

# Chapter 4

## 4.0 Results

This chapter focuses on data presentation and analysis on socio-demographics, factors associated failing first line HIV treatment and patient knowledge on first line HIV treatment failure in Zvishavane district.

## 4.1 Socio-demographic characteristics of study participants

A total of 123 cases and 123 controls were recruited into the study. Table 1 illustrates socio-demographic characteristics of study participants.

**Table 1: Socio-demographic characteristics of study participants, Zvishavane district, Midlands Province, Zimbabwe, 2014**

| Variable | Category | Cases n=123 (%) | Controls n=123 (%) | P value |
|---|---|---|---|---|
| Sex | Males | 70 (57) | 61 (50) | 0.25 |
| | Females | 53 (43) | 62 (50) | |
| Age in years | <20 | 18 (15) | 13 (11) | |
| | 20-29 | 43 (35) | 39 (31) | |
| | 30-39 | 32 (26) | 43 (35) | |
| | >39 | 30 (34) | 28 (23) | |
| Median age in years | | 30 ($Q_1$=22, $Q_3$=39) | 32($Q_1$=25,$Q_3$=38) | 0.68 |
| Marital status | Single | 44 (36) | 18 (15) | 0.16 |
| | Married | 47 (38) | 58 (47) | |
| | Divorced | 16 (13) | 35 (28) | |
| | Window | 16 (13) | 12 (10) | |

| | | | | |
|---|---|---|---|---|
| Place of residence | Urban | 82 (67) | 79 (64) | 0.41 |
| | Rural | 35 (28) | 41 (33) | |
| | Outside Zimbabwe | 6 (5) | 3 (3) | |
| Highest level of Education | None | 3 (2) | 1 (1) | 0.31 |
| | Primary | 27 (22) | 26 (21) | |
| | Secondary | 88 (72) | 81 (66) | |
| | Tertiary | 5 (4) | 15 (12) | |
| Religion | Orthodox | 37 (30) | 30 (24) | 0.53 |
| | Pentecostal | 39 (32) | 56 (45) | |
| | Traditional | 19 (15) | 13 (11) | |
| | Muslim | 1 (1) | 1 (1) | |
| | None | 27 (22) | 23 (19) | |
| Employment Status | Formally employed | 43 (35) | 71(58) | 0.03 |
| | Informally employed | 29 (24) | 17 (14) | |
| | Unemployed | 51 (41) | 35 (28) | |

Cases and controls were statistically comparable in terms of socio-demographic characteristics except on employment where cases were more likely to be unemployed.

### 4.2 Commodities Availability Status, Zvishavane District, Midlands Province, 2014

Commodities availability status was assessed in Zvishavane district (Table 2).

Table 2: Commodities Availability, Zvishavane District, Midlands Province, 2014

| **Item** | | **History of stock outs** | **Current stock** (Tabs) | **Required minimum stock** (Tablets) | **Out of stock** (Tabs) | **Comments** |
|---|---|---|---|---|---|---|
| **Drug code** | **Drug Name** | | | | | |
| **1st line antiretroviral drugs** | | | | | | Mostly available |
| TDF/3TC | Tenolam (Tenofovir & Lamivudine) | - | 18124 | 1167 | - | Excess in stock |
| NVP | Nevirapine | - | 28665 | 11330 | - | Excess in stock |
| AZT/3TC/ NVP(300/150mg) | Zidovudine/ Lamivudine/ Nevirapine | 09/07/14-15/07/14 | 2166 | 162 | - | Currently Excess in stock. Patients bought in private sector during stock outs |
| AZT/3TC (60/30mg) | Zidovudine/ Lamivudine | 19/06/14-15/07/14 | 259 | 153 | - | Currently excess in stock. Patients bought in private sector during stock outs |
| TDF/3TC/ EFV 300/600mg | Tenolam/ Efavirenz | - | 3239 | 2394 | - | Excess |
| **2nd line antiretroviral drugs** | | | | | | Relatively less available |
| ATV/LNV$_r$ 300/100mg | Atazanavir/ Lopinavir/ Ritonavir | Often in Stock outs | 37 | 326 | 289 | The drug is in short supply in the country (Rationing done) |
| DD1400 | Didanosine | 27/06/14-15/07/14 | 17 | 7 | - | Currently excess in stock. Patients had to buy in private sector during stock outs |
| DDI 1250 | Didanosine | - | 2 | 23 | 21 | In short supply (Rationing done) |
| ABC 600/300mg | Abacavir | - | 58 | - | - | - |
| ABC 300mg | Abacavir | 18/07/14 to date | 0 | 29 | 29 | Was still by the time the study ended on 05/08/14 |
| **CD4 count machines** | | The district has 1 machine which had a breakdown on 28/07/14 and was not functional | | | | The machine was still non functional by the time the study ended on 05/08/14 |

Zvishavane district had first line drugs stock outs of Zidovudine/Lamivudine/Nevirapine from 09/07/14 to 15/07/14 and Zidovudine/Lamivudine from 19/06/14 to 15/07/14. The district experienced second line stock outs of Didanosine (DD1400) from 27/06/14

to15/07/14 and Abacavir (ABC 300mg) from 18/08/14 (Abacavir (300mg) was still out of stock when the study ended on 05/08/14). Atazanavir/Lopinavir/Ritonavir is often out of stock and the current stocking level below minimum by 289 tablets. Didanosine (DD1250) current stocking levels were below the required minimum by 21 tablets. Patients bought medication from the private sector during stock outs or low stocking levels. The district rationed drugs among patients during low stocking levels. Other drugs assessed were above minimum stocking levels and/or had no history of stock outs. The district has 1 machine which had a breakdown on 28/07/14 and was still not functional when the study ended on 05/08/14.

### 4.3 Treatment Related Factors Associated with First Line HIV Treatment Failure, Zvishavane District, Midlands Province, Zimbabwe, 2014

Treatment related factors associated 1st line HIV treatment failure were analyzed (Table 3).

**Table 3: Treatment Related Factors Associated with 1st Line HIV Treatment Failure, Zvishavane District, Zimbabwe, 2014**

| Factor | | Cases n=123 (%) | Controls n=123 (%) | Odds Ratio 95% CI |
|---|---|---|---|---|
| Baseline CD4 Count of <50 cells/mm$^3$ | Yes | 43 (35) | 15 (12) | 3.87* |
| | No | 80 (65) | 108 (88) | 2.01-7.45 |
| Clinical WHO Stage 3 or 4 at ART initiation | Yes | 82 (67) | 50 (59) | 2.92* |
| | No | 41 (33) | 73 (41) | 1.74-4.91 |
| Baseline CD4 Count of <100 cells/mm$^3$ | Yes | 81 (67) | 51 (41) | 2.82* |
| | No | 42 (33) | 72 (59) | 1.68-4.74 |
| Duration of Treatment of >3 Years on ART | Yes | 39 (32) | 27 (22) | 1.64 |
| | No | 84 (68) | 96 (78) | 0.94-2.94 |
| Presence of co-morbidities | Yes | 68 (55) | 59 (48) | 1.34 |
| | No | 55 (45) | 64 (52) | 0.81-2.21 |
| Experiencing drug side effects | Yes | 68 (55) | 59 (48) | 1.34 |
| | No | 55 (45) | 64 (52) | 0.81-2.21 |

Significant treatment related risk factors associated with first line treatment failure were baseline clinical WHO Stage 3 or 4 (OR=2.92, CI 1.74-4.91), baseline CD4 Count of <100 cells/mm$^3$ (OR=2.82, CI 1.68-4.74) and baseline CD4 Count of <50 cells/mm$^3$ (OR=3.87, CI 2.01-7.45).

### 4.4 Health Service Related Factors Associated with First Line HIV Treatment Failure, Zvishavane District, Midlands Province, Zimbabwe, 2014

Health service related factors associated with first line HIV treatment failure were determined (Table 4).

**Table 4: Treatment Related Factors Associated with First Line HIV Treatment Failure, Zvishavane District, Zimbabwe, 2014**

| Factor | | Cases n=123 (%) | Controls n=123 (%) | Odds Ratio 95% CI |
|---|---|---|---|---|
| Drug Stock outs | Yes | 70 (57) | 33 (27) | 3.60* |
| | No | 53 (43) | 90 (73) | 2.11-6.15 |
| Long patient waiting Time | Yes | 66 (54) | 39 (32) | 2.49* |
| | No | 57 (46) | 84 (68) | 1.48-4.19 |
| Had at least one individual counseling on ART adherence | Yes | 90 (73) | 109 (89) | 0.35* |
| | No | 33 (27) | 14 (11) | 0.18-0.69 |
| Initiated at a private institution | Yes | 17 (14) | 11 (9) | 1.63 |
| | No | 106 (86) | 112 (91) | 0.73-3.65 |
| No money for transport | Yes | 23 (19) | 17(14) | 1.46 |
| | No | 100 (81) | 108 (86) | 0.74-2.89 |
| Lack of privacy at facility | Yes | 2 (2) | 1 (2) | 2.02 |
| | No | 121 (98) | 122 (98) | 0.18-22.54 |
| No money for consultation | Yes | 3 (2) | 2 (2) | 1.51 |
| | No | 120 (98) | 121 (98) | 0.25-9.21 |
| Busy schedule at attend OI/ART Clinics | Yes | 16 (13) | 15 (12) | 1.08 |
| | No | 107 (87) | 108 (88) | 0.51-2.29 |

Significant risk factors for HIV first line treatment failure were long patient waiting time (OR=2.49, CI 1.48-4.19) and drug stock outs (OR=3.60, CI 2.11-6.15). Receiving at least one individual counseling on ART was a significant health service related protective factor associated with first line HIV treatment failure (OR=0.35, CI 0.18-0.69).

### 4.5 Behavior Related Factors Associated with First Line HIV Treatment Failure, Zvishavane District, Midland Province, 2014

Table 5 illustrates an analysis output for behavior related factors associated with first line HIV treatment failure in Zvishavane district

**Table 5: Behavior Related Factors Associated with 1st Line HIV Treatment Failure, Zvishavane District, 2014**

| Factor | | Cases n= (%) | Controls n= (%) | Odds Ratio 95% CI |
|---|---|---|---|---|
| Poor adherence (<80 adherence) | Yes | 96 (78) | 42 (34) | 6.86* |
| | No | 27 (22) | 81 (66) | 3.89-12.09 |
| Drinking alcohol | Yes | 32 (26) | 18 (15) | 2.05* |
| | No | 91 (74) | 105 (85) | 1.08-3.90 |
| Disclosure of HIV status | Yes | 102 (83) | 115 (93) | 0.34* |
| | No | 21 (17) | 8 (7) | 0.14-0.80 |
| Having previously undergone Prevention | Yes | 10 (17) | 22 (33) | 0.41* |
| of Mother to Child Transmission process | No | 49 (83) | 44 (67) | 0.17-0.96 |
| Smoking | Yes | 21 (17) | 12 (10) | 1.90 |
| | No | 102 (83) | 111 (90) | 0.89-4.07 |
| Taking ART before initiation by a Doctor | Yes | 10 (8) | 8 (6) | 1.27 |
| | No | 113 (92) | 115 (94) | 0.48-3.34 |
| Smoking | Yes | 21 (17) | 12 (10) | 1.90 |
| | No | 102 (83) | 111 (90) | 0.89-4.07 |
| Sexually active | Yes | 100 (81) | 98 (80) | 1.11 |
| | No | 23 (19) | 25 (20) | 0.59-2.08 |
| Practice safer sex | Yes | 74 (73) | 76 (77) | 0.80 |

| | | | | |
|---|---|---|---|---|
| | No | 28 (27) | 23 (23) | 0.42-1.51 |
| Have sex with at least 2 people per month | Yes | 13 (13) | 10 (10) | 1.33 |
| | No | 86 (87) | 88 (90) | 0.55-3.20 |
| Having a sexual partner on ART | Yes | 68 (67) | 77 (79) | 0.56 |
| | No | 33 (33) | 21 (21) | 0.30-1.06 |
| Males | Yes | 70 (57) | 61 (50) | 1.34 |
| | No | 53 (43) | 62 (50) | 0.93-2.56 |

Significant risk behavior related factors associated with first line HIV treatment were poor adherence (<80% adherence) (OR= 6.86, CI 3.89-12.09) and drinking alcohol (OR=2.05, CI=1.08-3.90). Significant protective factors were disclosure of HIV status (OR=0.34, CI 0.14-0.80) and having previously undergone Prevention of Mother to Child Transmission (PMTCT) (OR=0.41, CI 0.17-0.96).

### 4.6 Determinants of Poor Adherence (<80%) to First Line HIV Treatment, Zvishavane District, Midlands Province, 2014

Determinants of poor adherence were analyzed (Table 6).

**Table 6: Determinants of Poor Adherence (<80%) to First Line HIV Treatment, Zvishavane District, Midlands Province, 2014**

| Factor | | <80% adherence n= 138(%) | ≥80 adherence n= 138 (%) | Odds Ratio 95% CI |
|---|---|---|---|---|
| Drug stock outs | Yes | 89 (64) | 40 (37) | 3.09* |
| | No | 49 (36) | 68 (63) | 1.83-5.21 |
| Married | Yes | 54 (39) | 51 (47) | 0.72 |
| | No | 84 (61) | 57 (53) | 0.43-1.19 |
| Male | Yes | 80 (58) | 51 (47) | 1.54 |
| | No | 58 (42) | 57 (53) | 0.93-2.56 |

Drug stock outs was significantly associated with poor adherence (<80% adherence) to HIV treatment (OR=3.09, CI 1.83-5.21).

### 4.7 Patients Knowledge of First Line HIV Treatment Failure, Zvishavane District, 2014

Table 7 illustrates an assessment of patients knowledge of first line HIV treatment failure was assessed.

**Table 7: Patients Knowledge of First Line HIV Treatment Failure, Zvishavane District, 2014**

| Knowledge Indicator | | Cases n=123(%) | Controls n=123(%) | OR 95% CI |
|---|---|---|---|---|
| ART should be taken for the rest of my life | Yes | 112 (91) | 114 (93) | 0.8 |
| | No | 9 (7) | 9 (7) | 0.32-2.01 |
| The time at which the medication is taken | Yes | 108 (88) | 116 (94) | 0.43 |
| will influence its effectiveness | No | 15 (12) | 7 (6) | 0.17-1.11 |
| Missing doses and/or taking them late or | Yes | 105 (85) | 108 (88) | 0.81 |
| incorrectly determines if treatment works | No | 18 (15) | 15 (12) | 0.39-1.69 |
| For my medicine to work best, I should not | Yes | 104 (85) | 105 (85) | 0.94 |
| miss a dose, nor take it late or incorrectly | No | 19 (15) | 18 (15) | 0.47-1.89 |
| Drug resistance develops when my ART | Yes | 67 (54) | 80 (65) | 0.64 |
| are missed and/or taken late or incorrectly | No | 56 (46) | 43 (35) | 0.39-1.07 |

Both cases and controls had good knowledge of first line HIV treatment failure. There was no statistical difference in knowledge levels between cases and controls

### 4.8 First Line HIV Treatment Outcome Status and Poor adherence (<80% adherence) stratified by taking alcohol, Zvishavane district, 2014

Poor adherence (<80% adherence) was stratified by drinking alcohol to control for confounding or effect modification (Table 8).

**Table 8: First Line HIV Treatment Outcome Status and Baseline WHO Stage 3 or 4 Stratified by Gender, Zvishavane district, 2014**

| **Covariate** | | Poor adherence (<80% adherence) | | **Stratum Specific OR (95% CI)** | **Chi Square for Interaction p-value** |
|---|---|---|---|---|---|
| | | Case | Control | | |
| **Crude OR**=6.86 95% CI 3.89-12.30, **Adjusted OR (MH)=** 6.54 95% CI 3.69-11.58 | | | | | |
| **Drinking Alcohol** | **Yes** | 28 | 24 | 7.00<br>1.73-28.30 | 0.01 |
| | **No** | 68 | 33 | 6.45<br>3.45-12.08 | |

Crude OR (COR=6.86, 95% CI 3.89-12.30) falls within stratum specific ORs (6.45, 7.00). The effect of poor adherence (<80% adherence) was modified by whether participants drank alcohol or not.

### 4.8 Independent Risk Factors Associated with First Line HIV Treatment Failure, Zvishavane District, 2014

Forward stepwise logistic regression was conducted to determine independent risk factors associated with first line HIV treatment failure (Table 8).

**Table 8: Independent Risk Factors Associated with First Line HIV Treatment Failure, Zvishavane District, 2014**

| Variable | Adjusted OR | 95% C.I | P-value |
|---|---|---|---|
| Poor adherence (<80% adherence) to ART | 5.14 | (2.75-9.62) | <0.05 |
| CD4 Count of <50 cells/$mm^3$ | 3.25 | (1.47-7.16) | <0.05 |
| Drug stock outs | 3.02 | (1.20-6.98) | <0.05 |
| Baseline WHO Stage 3 or 4 | 1.95 | (1.05-3.61) | 0.03 |

Independent risk factors associated with first line HIV treatment failure were poor adherence to ART (AOR=5.14, CI 2.75-9.62), drug stock outs (AOR=3.02, CI 1.20-6.98), CD4 Count of <50 cells/$mm^3$ (AOR=3.25, CI 1.47-7.16) and baseline WHO Stage 3 or 4 (AOR=1.95, CI 1.05-3.61).

### 4.10 Results from Key Informants

Five key informants were interviewed. These included the Zvishavane District Medical Officer (DMO), Zvishavane District Matron, Zvishavane District Nursing Officer (DNO) Zvishavane district Health Information Officer (HIO) and Zvishavane District HIV focal person. They reported that the district experienced occasional first and second line drug stock outs in Zvishavane district (Table 9 above). There are 1640 patients on ART and there are 20 health workers in district trained in HIV program management. There are HIV manuals and guidelines for HIV management in all 20 ART initiating sites in the district. The district has adequate information, education and communication materials for HIV management and these were being distributed to the community. Zvishavane is an HIV DR sentinel site and the prevalence of HIV DR in the district is 12.8%.

# Chapter 5

## 5.0 Discussion

Poor adherence to ART was an independent risk factor associated with first line HIV treatment failure in Zvishavane district (AOR=5.14, CI 2.75-9.62). This was the most risk factor in this study. This is plausible considering that drug pick up was untimely the district coupled with occasional drug stock outs. Charles et al reported similar results in their case control study in Kenya. They reported that imperfect ART adherence was a significant risk factor for first line HIV treatment failure (OR = 2.77, CI 2.20 - 3.49). Significant determinant of ART adherence was drug stock outs (OR=3.09, CI 1.83-5.21). This could mean that when drugs are out of stock and patients are advised to buy from the private sector, they do not afford them leading to poor adherence. Stocking drugs above required minimum levels is necessary to reduce first line HIV treatment failure. The public health message which can be drawn from this result is that imperfect adherence leads to viral rebound and hence treatment failure.

Drug stock outs were an independent risk factor for HIV first line treatment failure in Zvishavane district (AOR=3.02, CI 1.20-6.98). This, according to HIV DR report of 2013, has happened against least performance of the district in Midlands Province on EW1 on "on time pill pick up."[2] The district experienced occasional drug stock outs of both first line and second line drug regimens, with instances where stocks fell below required minimum stocking levels. This leads to drugs rationing among patients to the limit stocking levels can sustain and/ or patients buy them from the private sector. Patients reported that they cannot afford to buy drugs from the private sector. They end up not accessing medication, becoming non adherent and consequently failing HIV treatment. The implication is that sustained suppression of viral load requires facilities to have sufficient stocks. This means that one way

of reducing HIV first line treatment failure is by ensuring that drug stocks are above minimum required stocking levels in Zvishavane district.

This study demonstrated that CD4 count of <50 cells/mm$^3$ (AOR=3.25, CI 1.47-7.16) and baseline WHO Stage 3 or 4 (AOR=1.95, CI 1.05-3.61) were independent risk factors for first line HIV treatment failure in Zvishavane district. Several studies have shown similar findings.[12,16,26,31]Chimbetete C and Tshimanga M who found out that CD4 count of <50 cells/mm$^3$ (AOR=1.5, CI 1.25-8.20) and baseline WHO Stage 3 or 4 (AOR=2.08, CI 1.21-3.50) were independent risk factors for first line HIV treatment failure at Newlands clinic in Harare.[16] What can be drawn from this is that if an HIV positive patient is commenced on ART at WHO stage 3 or 4 and /when CD4 is low, viral load may not be successfully suppressed leading to HIV treatment failure. For better treatment outcomes interventions should focused on identifying HIV before it advances.

Drinking alcohol was a significant risk factor for HIV treatment failure in Zvishavane district (OR=2.05, CI=1.08-3.90). This means patients who fail first line HIV treatment in Zvishavane district drink alcohol. Alcohol compromises effectiveness of medication leading to treatment failure. Strategies to address this problem should be incorporated in lessons that are conducted during OI/ART clinics. Males were 1.34 times more likely to fail first line treatment than females though the association was not statistically significant. Other studies have shown significant associations.[16] The dissimilarity could be attributed to improvement in turn out for men for care in the district. PMTCT offers a window of opportunity for early identification of the disease and treatment before risk factors such viral load, CD4 count and clinical WHO stages have worsened.

Long patient waiting time was a significant risk factor for first line HIV treatment failure in Zvishavane district (OR=2.49, 1.48-4.19). Similar findings were found by Miller et al in South Africa.[39] The study found out that patient waiting time was a significant institutional factor for defaulting treatment. OI/ART clinics are done twice per week on specific dates in respective ART initiating sites/facilities in Zvishavane district. The district has over 1000 patients on ART, a number that overwhelms health staff leading to long waiting period for reviews and resupplies. Patients do not come and/or delay to come for resupply, which causes them to miss their doses, to avoid long waiting periods.

Disclosure of HIV status to family/friends was a significant protective factor for first line HIV treatment failure in Zvishavane district (OR=0.34, CI 0.14-0.80). Ramadhani HO et al in 2007 found similar results in Tanzania that disclosure of HIV status to family members and others was protective against virologic failure (AOR =0,10. P=0.04).[40] Those patients who do not disclose their HIV status could be finding it hard to perfectly adhere to treatment because they do not have the necessary support. Imperfect adherence would lead to HIV treatment failure. This means that encouraging disclosure among patients on ART should be an integral part of HIV management to reduce failure.

Having at least one individual counseling session on ART at ART commencement was a significant protective factor for HIV first line treatment failure in this study (OR=0.35, CI 0.18-0.69). While this indicates that institutions are providing this service, it means counseling is effective in reducing HIV treatment failure in Zvishavane district. Several studies have shown similar findings. In consistent with this finding Chimbetete C and Tshimanga M found that not receiving ART counseling on ART commencement was a significant risk factor for HIV treatment failure (OR=10.53, CI 4.68-23.65). Similar findings

were made in Harare.[16] What this could indicate is that if people are provided with counseling, adherence to ART could improve thereby reducing HIV treatment failure.

Having previously undergone Prevention of Mother to Child Transmission (PMTCT) (OR=0.41, CI 0.17-0.96) was a significant reinforcing factor associated with first line HIV treatment failure in this study. This could suggest that PMTCT provides an opportunity for early detection and treatment of HIV thereby reducing treatment failure for mothers. Therefore, PMTCT programs should be regarded as one additional strategy to reduce HIV treatment failure by public health practitioners.

Being initiated on ART by a private doctor was not a significant risk factor for first line HIV treatment failure in Zvishavane district (OR=1.63, CI 0.73-3.65). This contrary to findings in Harare by Cleopas C and Tshimanga M who found out that being initiated by a private doctor was a significant risk factor for HIV first line HIV treatment failure (OR=6.27, CI=3.76-10.46).[16] This difference could be accounted for by differences in study settings. There more private health care services in Harare than they are in Zvishavane. Very few patients use private service in Zvishavane.

Being male was associated with failing first line HIV treatment (OR=1.34, 081-2.22) and being non adherent (OR=1.54, 95% 0.93-2.56) but not statistically significant in this study. This is contrary to findings in South Africa by Roos et al who found out that being male was significantly associated failing treatment. The difference could be attributed to differences in sample size. There were more males who were cases in the latter study. However, it important note that men are associated with non adherence and hence treatment failure. Therefore there is an opportunity for reducing HIV treatment failure programs target to improve health seeking behaviors in men.

Having a sexual treatment partner was protective though not statistically significant (OR=O.56, CI 0.30-1.06). Though not significant, this could mean that partners encourage each other to adhere to ART. Sexual partners should be encouraged to disclose their HIV status and support each other to reduce failure of ART in Zvishavane district.

There was a significant difference in terms of employment status between patients who failed first line treatment and those who did not. Those who failed first line treatment were more likely to be unemployed relative to those who did not. This could mean that those who are not employed could be having challenges accessing ART in case of drug stock outs. OI/ART program should prioritize these vulnerable people when drug levels are below required minimum stocking levels.

### 5.1 Strengths of the study

The study was able to examine multiple etiologic factors for first line HIV treatment failure in Zvishavane district.

### 5.2 Limitations of the study

Controls that failed first line HIV treatment but not yet diagnosed could have been recruited into the study thereby reducing the strengths of associations. This was reduced by recruiting controls that had been on ART for at least 6 months and were not diagnosed with first line HIV treatment failure. There was a possibility for recall bias which relates to differences in ways exposure information was remembered or reported by cases that were diagnosed with first line HIV treatment failure, and by controls that were not. Cases could have more likely reported more exposures than controls thereby overestimating the strengths of associations. Ascertainment of exposure, where possible, was done through checking medical records. This study assessed reported adherence. There was a potential for cases to overestimate their

adherence levels. This could have threatened internal validity of this study. Ascertainment of some exposure variables was done through checking medical records where possible to reduce this bias.

### 5.3 Possible areas of research

There are areas that were beyond the scope of this study and were therefore not answered. We suggest an AIDS and TB program evaluation in Zvishavane district to explain poor performance outcomes of the program.

# Chapter 6

## 6.0 Conclusions and Recommendations

### 6.1 Conclusions

First line HIV treatment failure affected all age groups in Zvishavane district. Multiple etiological factors were associated with first line HIV treatment failure in Zvishavane district. Poor adherence, drug stock outs, CD4 Count of <50 cells/$mm^3$ and baseline WHO Stage 3 or 4 were demonstrated to be independent risk factors for HIV first line treatment failure in the district. Providing counseling, disclosing HIV status and receiving PMTCT were significantly protective in Zvishavane district. Patients on ART in Zvishavane district have good knowledge of first line HIV treatment failure. Results of the study provided guidance to AIDS/TB program managers to reduce first line HIV treatment failure in Zvishavane district

### 6.1 Recommendations

1. To routinely monitor adherence to ART: **District HIV/AIDS focal Coordinator**

   -Use self reports number of days for which ART was prescribed

   -Use pharmacy reports

   -pill counts and routine CD4 count measures

2. To conduct outreach campaigns on HIV Testing and Counseling to detect HIV/AIDS early. **Midlands Provincial Health Promotion Officer, Zvishavane District Medical Officer.**
3. To increase OI/ART clinic days in health facilities to reduce patient waiting time for reviews and resupplies and reduce workload per day on health workers-**Zvishavane District Medical Officer.**
4. To maintain essential drug stocking levels beyond required minimum levels in Zvishavane district-**National Pharmacy Director, Midlands Provincial Pharmacist and the District Pharmacist.**

5. To include health education on effects of drinking alcohol when a patient is on ART during early morning lessons on HIV/AIDS during OI/ART clinic days-**District Health Promotion Officer/Sister in Charge, Zvishavane District.**
6. To incorporate benefits of disclosure on HIV/AIDS during routine lessons and counseling sessions on patients on ART-**Zvishavane District: Matron/Counselor.**

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## Annex 1A

**Consent Form for study participants**

Factors Associated with HIV First Line Treatment failure in Zvishavane District, Midlands Province, 2014

**Principal Investigator** : Takura Matare

**Phone** : 0773819667

**Introduction**

You have decided to take part in the research study named above. The study will collect your information on demographic factors and risk factors for first line treatment failure. This consent form gives you information about the collection, storage and future use of data collected from you. Please ask if you have any questions. You will be asked to sign or make your mark on this form to indicate whether or not you agree to participate in the study. You will be offered a copy of this form to keep and will keep the other form for at least 3 years.

**Your participation is voluntary**

Participation in the study is completely voluntary. You may decide to withdraw from the study any time during the study and this will not affect your health care.

**Purpose**

The study seeks to determine factors Associated with HIV First Line Treatment failure in Zvishavane District, Midlands Province, 2014

**Data collection procedures**

Data will be collected using an interviewer administered questionnaire and checklists

**Data storage**

Completed questionnaires and checklists will be kept under lock and key for at least 3 years after which they may be destroyed.

**Risks and/or discomforts**

There are ethical risks related to storing your information. It is possible that if others find out information about you in the questionnaire, it could cause you problems of stigmatization. To minimise this risk your information will be strictly put under lock and key. Information collected from you will be used only for academic purposes.

**Potential benefits**

There are no immediate benefits to you from having your information stored. You and others could benefit in the future from research done on you.

**Confidentiality**

To keep your information private, your name will not be written on the questionnaire.

a) I agree to participate in the study on "**Factors Associated with HIV First Line Treatment failure in Zvishavane District, Midlands Province, 2014"**

_____ _____ _____ _____

Participant Signature or Mark Date Researcher's Signature Date

If you have any questions concerning this research beyond those answered by the investigator, including questions about the future researches, your rights as the source of data; or if you feel that you have been treated unfairly and would like to talk to someone other than a this data collector, please feel free to contact Dr G. Shambira on +263 4 791631 or the Medical Research Council of Zimbabwe on telephone (04) 791792 or (04) 791193. You may also want to visit the MRCZ offices located at the National Institute of Health Research premises at corner Josiah Tongogara and Mazowe Street in Harare.

## Annex 1B

**Fomu Rechibvumirano**

Factors Associated with HIV First Line Treatment failure in Zvishavane District, Midlands Province, 2014

**Principal Investigator** : Takura Matare

**Phone** : 0773819667

**Nhanga nyaya**

Mabvuma kupinda mutsvakiridzo yataurwa pamusoro apo. Tvakiridzo iyi ichatora humbowo pamusoro pehupenyu hwenyu uye zvikonzero zvingaita kuti murwere asashandirwa zvakanaka nemushonga unotanga kupiwa pachirwere chemukondombera (HIV/AIDS). Chibvumirano ichi chinokupai humbowo maererasno nekutorwa kwenyaya yeupenyu hwenyu, machengeterwo aichaitwa uye mashandisirwe aichaitwa muneramangwana. Kana muine mubvunzo makasununguka kubvunza henyu. Muchakumbirwa kunyora runyoro rwenyu kutaridza kuti muri kubvuma kana kuramba kupinda mutsvakiridzo iyi. Muchasara nebepa rine chibvumirano ichi uye isu tichasarawo nerimwe ratichachengeta kwemakore matatu.

**Isarudzo yenyu kupinda/kana kurega kupinda mutsvakiridzo iyi**

Kupinda mutsvakiridzo iyi hakumanikidzwi. Makasununguka kubuda mutsvakiridzo iyi nguva ipi zvayo tiri mutsvakiridzo yacho kunyange manga mambobvuma pekutanga uye kubuda mutsvakiridzo iyi hakukanganisi kurapwa kwenyu kwamanga muchiwana nguva dzose.

**Chinangwa**

Tsvakiridzo iyi iri kutsvaka zvinhu zvingaita kuti mutadze kushandirwa zvakanaka nemushonga weHIV/AIDS unotanga kupiwa vanhu pekutanga muZvishavane district, 2014

**Matorero atichaita humbowo hwenyu**

Tichashandisa bepa rine muchibvunzo yamuchakumbirwa kupindura nemachekilisiti.

**Machengeterwo achaitwa humbowo hwenyu**

Tichachetengera humbowo hwenyu mukadhibhodhi matichange tichigara takakiya kwemakore matatu. Mushure mezvo tichaparadza humbowo uhu.

**Njodzi kana kushungurudzika mutsvakiridzo iyi**

Pane zvinonogona kusakusununguraí zvingaitika patinenge takachengeta humbowo hwenyu. Zvinogona kuitika kuti umwe munhu anogona kuwona humbowo hwenyu zvingaita kuti

magariro enyu mudunhu ange ane kushungurudzika. Kudzivirira izvi tichachengetedza zvakanyanya humbowo hwenyu. Humbowo hwenyu tichahushandisa kune zvekudzidza chete.

**Zvingakuyamuraiwo pakupinda mutsvakiridzo iyi.**

Hapana kuyamurika kwamunoita pakupinda mutsvakiridzo iyi munguva yamunenge muri mutsvakiridzo asi imwi nevamwewo munogona kuzoyamurika mune ramangwana.

**Kuchengetedzwa kwenyaya yenyu kuti isainda kisaburitswa**

Kuchengetedza chimiro chenyu, zita renyu haridiwi pabepa rine mubvunzo yamuchapindira.

a) Ndinobvuma kupinda mutsvakiridzo inonzi "**Factors Associated with HIV First Line Treatment failure in Zvishavane District, Midlands Province, 2014"**

_____ _____ _____ _____

Siginecha(runyoro renyu) Zuva Siginecha yemutsvakiridzi Zuva

Kana muine mibvunzo yamusina kugutsikana nemhinduro kana yamungada kubvunza umwe munhu asiri mutsvakiridzi uyu, kuda ingava maererano nedzimwe tsvakiridzo dzingada kuzoitwa, kodzero dzenyu kana kuti mukafunga kuti hamuna kubatwa zvakanaka nokudaro munoda kubvunza umwe munhu makasunguka kubata Dr G. Shambira on +263 4 791631 or kana Medical Research Council of Zimbabwe (MRCZ) on telephone (04) 791792 or (04) 791193. Mungada kushanyira MRCZ hofisi iri pa National Institute of Health Research premises pa corner Josiah Tongogara and Mazowe Street muguta re Harare.

## Annex 2

**Interview Guide for Key Informants**

Clinic/hospital name _____

**Part A: Demographic characteristics**

1. What is your job title/ position? _____

   Sex (*observe only)* [ ] Female [ ] Male

2. How long have you been in your current position? _____

3. What is your marital status? [] Single [] married [] divorced [] widowed

4. What is your Religion? [] Orthodox [] Traditional [] Pentecostal [] Muslim [] None

5. What is the highest level of education you attained? [] Never went to school [] Primary

   [] Secondary [] Tertiary

6. What is your profession? _____

**Part B: HIV program management**

7. Do you experience any first line drug stock outs at your facility? [ ]Yes [ ] No
8. Do you experience any second line drug stock out at your facility? [ ]Yes [ ] No
9. Do you experience CD4 machine breakdowns at your facility? [ ]Yes [ ] No
10. Are the health workers (nurses, doctors, counselors) in your district trained in HIV program management? [ ]Yes [ ] No

    If yes, what proportion of health workers (nurses, doctors, nurse aids, EHPs) were trained in your district? _____

11. Do you have manuals for HIV management in the units in your district? [ ] Yes [ ] No (ask for the manual and also confirm when at the study site)
12. Do you have HIV management guidelines booklet in all your clinics?
    [ ] Yes [ ] No
13. Does your district have information, education and communication materials for HIV management (Confirm presence)? [ ]Yes [ ] No
14. If yes, have these been distributed to the community? [ ] yes [ ] no
15. What do you think could have given rise to HIV first line treatment failure in your district?

    _____

    _____
16. In your opinion what do you think should be done to prevent HIV first line treatment failure? [ ] Provide HIV health education to the community
    [ ] having regular surveillance meetings
    [ ] other specify_____

_____Thank you for your time_____

## Annex 3

**Questionnaire for cases and controls, Zvishavane district**

**Questionnaire no_____ Health Facility_____**

Participant's signature_____ Date_____

**Part A: Socio-demographic data**

Status of respondent: [] Case [] Control

1. What is your age? (Completed years)_____
2. Sex [] Female [] Male
3. What is your marital status? [] Single [] married [] divorced [] widowed
4. What is the highest level of education you attained? [] Never went to school [] Primary [] Secondary [] Tertiary
5. What is your Religion? [] Orthodox [] Traditional [] Pentecostal [] Muslim []None
6. Are you employed? [] Yes [] No_____
7. What is your profession? _____
8. How long has it been since you were diagnosed with HIV infection?[] less than 1 year [] 1-3 years [] 4-6 years [] more than 6 years
9. Have you had HIV-related previous hospitalisations? Yes [] No []
   If Yes, what year? _____
10. If yes, please specify the reason for hospitalisation: _____
11. Is your family aware of your HIV status? Yes [] No [] Don't Know []
12. Are your friends aware of your HIV status? Yes [] No [] Don't Know []

**Part B: Drug history**

1. List any other medicines you are on besides ART_____ (confirm with records)
2. List any other supplements you are on if applicable_____
3. List any previously medicines used_____ (Confirm with records

**Part C: Knowledge about HIV first line treatment failure**

The following statements are attempts to capture your knowledge about taking ART

1. ART should be taken for the rest of my life Yes [ ] No [ ]
2. The time at which the medication is taken will influence its effectiveness. Yes [ ] No [ ]
3. Missing doses and/or taking them late or incorrectly will determine if the treatment works Yes [ ] No [ ]
4. For my medicine to work best, I should not miss a dose, nor take it late or incorrectly Yes [ ] No [ ]
5. Drug resistance develops when my ART are missed and/or taken late or incorrectly Yes [ ] No [ ]

**Part D: Behavior factors for developing HIV first line treatment failure**

*Reported adherence*

1. Which of the following reasons represent or would represent a major problem to you when you are taking medication? (Multiple responses are allowed)

   [] Number of pills [] Fear of side effects [] Having side effects [] Frequency of dosing [] Interference with daily schedule [] Privacy to take medication not available [] Fear of disclosure of HIV status [] Other Please specify: _____

2. Did you miss any of your treatment during the last four days? Yes [] No []
3. Were you late for any of your intakes by >2 hours during the last 4 days? Yes [] No []
4. Did you miss any of your treatment last week-end? Yes [] No []
5. In general, would you say you take your treatment? (A visual analog scale)

Never ⟷ Always

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

*Non exclusive behaviors*

6. Have you ever taken ARVs without being initiated by a medical staff Yes [] No []
7. Is your partner aware of your status? Yes [] No []
8. Are you sexually active? Yes [] No []
9. Do you practice safe sex? Yes [] No []
10. Have you had sex with more than one partner in the previous month Yes [] No []
11. Do you drink alcohol Yes [] No []
12. If Yes, How much alcohol? _____ pines, how often? _____
13. Do you smoke marijuana Yes No [], If yes, how often? _____
14. If you are a female, have you ever taken PMTCT? Yes [] No []

**Part E: Health system and provider factors**

1. Where do you stay Urban [] Rural [] Other [], specify_____
2. Where were you initiated? Government of Zimbabwe health Facilities [] Private sector [] Other [], specify_____
3. Do you face challenges accessing drugs from your health facility? Yes [] No []
4. If yes, specify them [] Transport to the Health Facility [] Drug Stock outs

5. If yes, how do you them miss your medication because of these challenges?

   Yes [] No []

6. How often do you miss your medication because of these challenges? _____

_____

*Thank you for participating in the study*

## Annex 4

**Checklist for clinical, immunological and adherence data**

Checklist No._____ Name of Health Facility_____

Date of review_____

**Immunological data**

**CD4 count**

CD4 count at ART initiation_____ Date_____

**Presence of co-morbidities**

At initiation Yes [] No [], If Yes, specify _____

**Clinical factors [WHO Clinical HIV stages: 1-4]**

WHO Clinical HIV stage at initiation_____ Date _____

## Annex 5

**Checklist for assessing availability of commodities at the health facility (entire period)**

Clinic name_____ Date of review_____

| Item | History of stock outs | Current stock | Required minimum stock | Out of stock | Comments |
|---|---|---|---|---|---|
| **1st line antiretroviral drugs** | | | | | |
| 1. | | | | | |
| 2. | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |
| 6. | | | | | |
| **2nd line antiretroviral drugs** | | | | | |
| 1. | | | | | |
| 2. | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |
| 6 | | | | | |
| **CD4 count machines** | | | | | |

## Annex 6

**Project finance-Budget**

| **Item** | **Unit Cost (USD)** | **Quantity** | **Total cost (USD)** |
|---|---|---|---|
| Fuel | 1.49 | 80L | 111.20 |
| Bond paper | 5.00 | 1 | 5.00 |
| Pen | 0.20 | 4 | 1.0 |
| Allowances (PHO) | 30.00 | 2 days | 60.00 |
| Accommodation (PHO) | 50.00 | 1 night | 50.00 |
| Grand total | | | 227.00 |