Factors associated with 1st line ART failure among patients at Newlands Clinic, Harare 2011

By

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DECLARATION

I, the undersigned, hereby declare that the dissertation that I am submitting to the University of Zimbabwe, College of Health Sciences, is my own work. It has been prepared in accordance with the guidelines for the MPH dissertations for the University of Zimbabwe. I have not submitted it, in its entirety or in part, to any tertiary institution for any degree.

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Abbreviations and Acronyms

AIDS	–	acquired immune deficiency syndrome
AOR	–	adjusted odds ratio
ART	–	antiretroviral therapy
AZT	–	zidovudine
CD4	–	Cluster of Differentiation four
CI	–	Confidence interval
D4T	–	Stavudine
EFV	–	Efavirenz
HIV	–	Human immunodeficiency virus
HIVDR	–	Human immunodeficiency virus drug resistance
MRCZ	–	Medical Research Council of Zimbabwe
NVP	–	nevirapine
OI	–	opportunistic infection(s)
OIC	–	opportunistic infections clinic
OR	–	odds ratio
WHO	–	World Health Organisation
3TC	–	Lamivudine

Definition of terms

***First line ART regimen*:** The first combination of antiretroviral drugs a patient is given as treatment for HIV infection

Second line ART regimen: The second combination of antiretroviral drugs a patient is given as treatment for HIV infection after the first has failed.

***ART treatment failure*:** When the ART regimen a patient is receiving is no longer effective in preventing replication of the virus because drug resistance has developed

***Protective factor*:** A factor that reduces the likelihood of developing treatment failure

***Risk factor*:** A factor that increases the likelihood of developing treatment failure

ABSTRACT

Factors associated with 1st line ART failure among patients at Newlands Clinic, Harare

2011

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Introduction:

First line ART treatment failure occurs when drugs being administered for the treatment of HIV are no longer able to kill the virus i.e. virus would have developed resistance to the drugs. This study sought to determine factors associated with 1st line treatment failure among patients taking ART at Newlands clinic, Harare.

Materials and methods:

An unmatched 1:1 case control study was conducted at Newlands Clinic. Patients who had been on ART for at least 6 months were eligible for study participation. Questionnaires were used to collect data and a review of patient records was done.

Results:

A total of 464 participants were enrolled into the study. Median age of cases was 33.5 (Q1= 17, Q3 =45) and 37 for controls (Q1=27.5, Q3=37). Females represented 58.1% of study population and 41.9% were males. Median duration on ART for cases was 3.1 years (Q1=2.01, Q3=4.7 years) and 2.9 years for controls (Q1=1.96, Q3= 4.64). Independent risk factors associated with treatment failure were: Not being married (AOR= 1.8: 95% CI 1.01- 3.21), ART commencement by private doctor (AOR =

4.86: 95% CI 2.11- 11.2), WHO stage 3 / 4 at ART commencement (AOR=2.08: 95% CI 1.21- 3.57), poor adherence to treatment (AOR=1.73: 95% CI 1.01-3.21) and CD4 <50 at ART commencement (AOR=1.5: 95% CI 1.65- 8.20)

Discussion:

Late commencement of ART increases the risk of treatment failure. ART commencement by private doctors is a risk factor for failure due to poor patient preparation for ART at private surgeries. Unmarried people are less likely to have good adherence support and hence increased risk of failure.

Key words: First line ART, Treatment Failure, Newlands Clinic

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Chapter 1

Introduction

1.1 Global HIV epidemiology

Estimates of HIV prevalence vary in quality but give some idea of trends in different countries and regions. Of all regions in the world, sub-Saharan Africa is the hardest hit by HIV, containing around 70% of people living with HIV/AIDS. There are, however, recent signs of hope in Africa due to a slight reduction in the number of new HIV cases in the year 2009. Globally, in 2009, approximately 34 million people were living with HIV, 22.5 million in Sub-Saharan Africa. In 2009 there were an estimated 2.6 million (2.3 million – 2.8 million) people who became newly infected with HIV. In 33 countries, the HIV incidence has fallen by more than 25% between 2001 and 2009: 22 of these countries are in Sub-Saharan Africa. In Sub-Saharan Africa where the majority of new HIV infections continue to occur, an estimated 1.8 million people became infected in 2009.[1] Most countries in Asia have not seen explosive epidemics in the general population up to now but patterns of injecting drug use (IDU) and sex work are conducive to the spread of HIV so there is no room for complacency. Unpredictable epidemics among IDU in the former Soviet Union have the potential to spread into the general population. Some countries in Central America and the Caribbean have growing HIV epidemics with adult prevalence second only to sub-Saharan Africa.

1.2 HIV epidemiology in Zimbabwe

The first reported case of AIDS in Zimbabwe occurred in 1985. By the end of the 1980s, around 10% of the adult population was thought to be infected with HIV[2]. This figure rose dramatically in the first half of the 1990s, peaking at 26.5% in 1997. But since this time the HIV prevalence has declined, making Zimbabwe one of the first African nations to witness such a trend. According to government figures, the adult prevalence was 23.7% in 2001, and fell to 13.7% in 2010. The decline in the prevalence has been due to behavior change among men.[2] The main behavior change appears to have been a reduction in the proportion of men with casual sex partners, while condom use with non-regular partners has remained high since the 1990s. Zimbabwe initiated its national ART programme in April 2004, and since that time the benefits of such therapy have been widely documented.

1.3 Antiretroviral drug therapy

HIV and AIDS related diseases remain a major health burden despite the documented decrease in the prevalence of HIV and AIDS in Zimbabwe. The introduction of antiretroviral therapy (ART) has revolutionized the care and management of HIV and AIDS. Whilst ART does not cure HIV and AIDS, it dramatically reduces mortality and morbidity if used appropriately. Treatment with ART is for life.

In the past decade, rapid advances have been made in the management of HIV infection. Numerous clinical trials have shown greater virological effect of triple therapy over monotherapy or dual therapy[3]. The main treatment goals of clinicians

now are to reduce and maintain plasma HIV RNA levels below the limits of detection and to avoid drug resistance emergence and clinical failure[4]. The development of combination antiretroviral therapy (ART) has improved quality of life among HIV positive patients and has turned an infectious disease with an almost universally fatal outcome into a manageable chronic disease.

The global vision for treatment is first and foremost to extend life, and then to have evidence based global standard for ART. This is very important in low income settings like Zimbabwe and consists of one first line, one second line ART regimen and salvage therapy. The WHO global definitions of first and second line ART are:

***First line ART*:** The initial regimen prescribed for patients fulfilling national clinical and laboratory criteria for starting ART.

***Second line ART*:** This is the regimen used immediately after first line therapy has failed (Clinically, immunologically or virologically) [5].

1.4 Treatment Failure

There are three different definitions of treatment failure, clinical, immunological and virological. The WHO 2010 guidelines define them as follows:

- *Clinical failure* when there is new or recurrent WHO stage 4 condition in a patient who has been on ART for at least 6 months.
- *Immunological* failure when CD4 falls to below pre – therapy baseline or there is 50% fall from the on treatment peak value (If known) or CD4 levels are persistently (at least 2 results) below 100 cells/mm^3 : and

- *Virological failure* when plasma viral load is persistently (at least 2 results) above 5 000 copies/ml[3].

The Zimbabwe national OI / ART programme has adopted the WHO recommendations for diagnosis of ART treatment failure and currently approximately 1 % of ART patients have been switched to 2nd line treatment[6-7]. However the Zimbabwe national OI / ART programme uses only the Clinical and Immunological criteria for patient monitoring. No routine viral load measurement facilities are available in the national programme.

1.5 Monitoring of Patients on ART

The effectiveness of ART may be monitored by assessing clinical improvements, immunological function (CD4 lymphocyte count) and HIV viral load (VL). Where CD4 count testing is available, regular six-monthly testing should be conducted. With successful ART, the CD4 lymphocyte count increases. The rate of increase depends on the initial CD4 count. The VL usually decreases to undetectable levels within six months of greater than 95% adherence to ART. However, this response also depends on the initial pre-treatment VL. Clinical monitoring of ART effectiveness is ideally done at every clinic visit. The following indices suggest that the patient is responding to treatment:

- The patient feels better and has more energy to perform daily tasks.
- The patient is gaining weight
- There is improvement in symptoms and signs of the original presenting illness

The three methods of monitoring for ART effectiveness vary in their ability to diagnose treatment failure early. Based on pooled analysis of the size effects from two

randomized trials (HBAC and DART trials), clinical monitoring alone (compared to combined immunological and clinical monitoring or combined virological, immunological and clinical monitoring) resulted in increases in mortality, disease progression, unnecessary switches but no difference in serious adverse events.[7,8] However in one of these trials (HBAC trial), combined immunological and clinical monitoring was compared to combined virological, immunological and clinical monitoring, and resulted in no difference in mortality, disease progression, unnecessary switches or virological treatment failures.[7]

1.6 ART services at Newlands Clinic

Newlands clinic was established in January 2004 as a family treatment centre for HIV and AIDS. The clinic is situated in Newlands, Harare. It is a nurse based family-centred HIV clinic, using Zimbabwe HIV / AIDS national guidelines. The clinic was founded with a mandate to provide care and treatment for HIV infected people from vulnerable communities, orphans, widows, students and people working in essential services. The clinic uses a comprehensive approach to the care of HIV positive patients. Newlands Clinic was one of the first centres to offer 2nd line ART in Harare. Consequently some patients in need of 2nd line ART were referred from other Treatment centres in the city. As of 28 / 08 / 2011 the clinic was looking after 3 320 patients on ART and 286 (8.6%) are on 2nd line treatment.

Patients receiving ART at Newlands Clinic are monitored for treatment success clinically, virologically and immunologically. On every monthly visit patient is seen by a nurse well experienced in ART provision. Monthly weights and height in children are done as standard of care. Immunological monitoring (CD4 count) is done

every 6 months. An estimation of viral load is done every 6 months using P24 antigen tests. The criterion for diagnosing treatment failure at Newlands Clinic is primarily based on elevated P24 antigen levels above 5 pg on at least two readings. Poor adherence to treatment is excluded before switch to 2nd line ART

1.7 Problem Statement

Newlands Clinic currently manages 3 320 ART patients of which 286 (8.6%) have failed 1st line ART and are receiving 2nd line treatment. According to the Zimbabwe national ART guidelines, second line ART regimens should be based on a protease inhibitor and two other drugs from the nucleoside or nucleotide reverse transcriptase class. The protease inhibitor being used for 2nd line ART is ritonovir boosted Lopinavir (Alluvia). Second line treatment is associated with more side effects than 1st line ART, chiefly metabolic complications. Examples of metabolic complications of 2nd line ART include development of diabetes mellitus, lipid derangements leading to cardiovascular disorders such as myocardial infarction and gastrointestinal disorders such as diarrhoea. The ART regimen for 2nd line treatment has a greater pill burden than the 1st line regimen. In adults the 1st line regimen typically has 2 pills a day whereas that for 2nd line typically has 6 pills a day. The increased pill burden may impact negatively on the patient's adherence to medication. Second line regimen for the Zimbabwe ART programme costs at least six times the cost of first line ART. Predictors of 1st line ART treatment failure in a heterogeneous patient population like Newlands Clinic in Zimbabwe are not known. Data on predictors of ART treatment failure is mainly from clinical trials whose patient populations differ greatly from treatment programme patients.

1.8 Justification of study

Since initiation of the Zimbabwe national OI / ART programme in 2003, emphasis has been on increasing access to 1st line treatment. Universal access to ART in the country has almost been achieved since all districts in Zimbabwe now offer ART services. However, as the OI / ART programme in the country matures, patients are beginning to fail 1st line treatment and would need to switch to more expensive and toxic 2nd line regimens. It is crucial that the predictors of ART failure be identified so as to inform programme managers and clinicians on how best treatment failure may be avoided. Patients need to be educated on risk factors for treatment failure to enable them to maximise on the benefits of 1st line regimens. Furthermore, evidence shows that late diagnosis of treatment failure among patients enables the virus to develop cross resistance to other antiretroviral drugs in the same drug class or different classes. Development of drug resistant virus may also lead to transmission of HIVDR within the population with serious public health consequences. The results of this study will assist in providing much needed evidence on predictors of ART failure and hence evidence based interventions will be possible to enable care givers to prevent development of treatment failure and its consequences.

1.9 Research question

What are the risk factors for developing 1st line treatment failure among HIV infected patients receiving ART at Newlands Clinic, Harare, Zimbabwe?

1.10 Broad objective

To assess the factors associated with 1st line ART treatment failure among patients receiving ART at Newlands Clinic.

1.11 Specific objectives

- To assess the demographic characteristics associated with 1st line treatment failure.
- To identify patient related factors associated with treatment failure.
- To assess drug related factors leading to 1st line failure
- To assess health service related factors associated with 1st line failure
- To assess pre-treatment factors associated with 1st line failure

Chapter 2

2.0 Literature Review

2.1 ART Drug resistance

The emergence of HIV drug resistance (HIVDR) is inevitable, given HIV's high replication and mutation rates and the need for life long antiretroviral therapy. To maintain the effectiveness of first- and second- line antiretroviral regimens, WHO recommends that countries develop a national strategy for HIVDR prevention and assessment.[9]

ART inhibits the function of essential viral proteins such as reverse transcriptase and protease. Mutations resulting in changes in the amino acid sequence at key sites in the target proteins reduce the activity of antiretroviral drugs. This is known as ART drug resistance. Failure to achieve virological suppression on an ART regimen leads to development of drug resistant mutant virus which rapidly becomes the predominant population if the antiretroviral drugs are continued eventually leading to treatment failure.[10]

Most ART drug resistance is induced or secondary resistance which means that the patient was infected with drug sensitive HIV and resistance mutations developed following the use of ART. The commonest cause for developing secondary drug resistance is poor adherence to prescribed ART.[11] Primary resistance occurs when the patient is infected with HIV that has already developed resistance to one or more antiretroviral drugs in the absence of ART exposure. Surveys in developed countries

show that 5% to 20% of patients have primary resistance to one or more antiretroviral classes. The prevelance of primary resistance in Southern Africa is currently very low, but likely to increase with the burgeoning use of ART.[12]

2.2 Diagnosing Treatment Failure

As antiretroviral therapy (ART) becomes more available in resource-limited settings, treatment failure and the need for second- and third-line ART will increase commensurately. It is estimated that between 5% and 20% of patients who begin ART will fail therapy within four years, despite good adherence and therapeutic drug levels. Second- and third line ART is expensive and complex and switching from a first-line regimen should not be done prematurely. In upper- and middle-income settings, treatment failure is usually diagnosed when there is evidence of virologic failure; that is, when viral replication, as measured by plasma viral load increases. This technology however, is not widely available in sub-Saharan Africa, and other methods of diagnosing treatment failure are under consideration. One such method is monitoring for immunological failure, which is, using a decline in CD4 cells to diagnose treatment failure. According to World Health Organization (WHO) guidelines, a decreasing CD4 count is a surrogate marker for treatment failure and should trigger a switch in ART, particularly if the cell count is <200 cells/µL.[13]

In an evaluation of the clinical and CD4 criteria of diagnosing ART failure in South Africa, the authors noted that: WHO clinical and CD4 criteria have poor sensitivity and specificity in detecting virological failure. The low specificities and positive predictive values mean that individuals with adequate virological suppression risk being incorrectly classified as having treatment failure and unnecessarily switched to

second-line therapy. Virological failure should be confirmed before switching to second-line therapy.[14]

Despite the enormous progress made in scaling up antiretroviral therapy (ART) in sub-Saharan Africa, many challenges remain, not least of which are the identification and management of patients who have failed first-line therapy. Less than 3% of patients are receiving second-line treatment at present, whereas 15-25% of patients have detectable viral loads 12 months or more into treatment, of whom a substantial proportion might have virological failure. The development of new diagnostic tools for ART failure, in particular a point-of-care HIV viral-load test, combined with simple and inexpensive second-line therapy, such as boosted protease-inhibitor monotherapy, could revolutionise the management of ART failure in resource-limited settings.[15]

Diagnosis of treatment failure in a clinic setting in resource limited settings like Zimbabwe is a challenge to the treating physician. Initial antiretroviral therapy regimens should be changed after evaluating adherence and pharmacologic or other reasons for virologic failure and confirming the increase in viral load.[16]

2.3 Factors associated with ART treatment failure

Data on 4 143 patients from 5 observational cohorts in Europe and North America who were started on initial 3 drug regimens between 1996 and 2002 indicate that the annual rate of virologic failure declined from 40% to 25% during the period. Risk of virologic failure was lower among patients who were older, had lower baseline viral load and who had an absence of an AIDS diagnosis and among men who reported having sex with men as a risk factor[17].

Several studies suggest that the median time to failure of ART is approximately 1.6 years. Lack of adherence- whether due to toxicity, poor tolerability, or inconvenient dosing frequency or food interactions is a major cause of virologic failure.[18]

Other factors that may lead to development of ART treatment failure include the use of drug combinations that are not sufficiently potent or that are antagonistic e.g. triple combination of abacavir, lamivudine and tenofovir.[19]

Virological failure may also occur due to low-level mutant populations of circulating virus archived in reservoirs in the body. Clonal analysis may demonstrate mutations not identified by population genotyping or phenotyping. Some patients fail to respond to antiretroviral therapy due to drug toxicity or intolerance.[20]

In an analysis of treatment outcomes in a Ugandan cohort done in 2007, several risk factors for treatment failure were identified. Risk factors for virological failure (>1000 copies/ml) were poor adherence, Tuberculosis diagnosed after ART initiation, sub therapeutic NNRTI concentrations, general clinical symptoms and lower weight than at baseline. About 14% of patients had low ARV plasma concentrations. Digestive symptoms and poor adherence to ART were risk factors for low ARV plasma concentrations.[21]

In a study to determine the predictors of clinical and virological failure in patients receiving a triple therapy including protease inhibitors results showed that after a median follow up of 12 months, 49.9% had virological failure. In the multivariate analyses, baseline CD4 cell count and viral load were found to be independent predictors of both virological and clinical failure. Neither the type of the first protease inhibitor taken nor previous antiretroviral therapy experience was associated with risk

of clinical progression. For virological failure, the use of saquinavir was associated with an increased risk of treatment failure compared with indinavir.[22]

In a retrospective analysis conducted of HIV infected patients followed in an urban clinic various predictors of ART failure were identified. Baseline characteristics associated with treatment failure in the multivariate model were poor adherence, absolute CD4 count less than 100 / mm^3, less than 12 months of viral suppression, nucleoside only regimen, prior virologic failure and having missed more than 1 clinic visit per year. More than one quarter of patients had treatment failure over a 2 year period.[23]

An analysis of the predictors of virologic failure in HIV infected adults receiving first line ART in 8 provinces of China demonstrated several risk factors of 1st line ART failure. In a multivariate model, treatment given at locations other than country level hospitals was less likely to achieve viral suppression with greater risk for inadequate virologic response found at village clinics, township hospitals and public clinics. Patients receiving didanosine based regimens were more likely to experience an inadequate virologic response than those receiving lamivudine based regimens.[24]

According to the USA guidelines on treatment of adults and adolescents infected with HIV, risk factors for ART failure are listed as: Previous AIDS diagnosis, high baseline HIV viral load, lower pre-treatment or nadir CD4 count, presence of drug resistant virus, co morbidities (e.g. depression and substance abuse), drug adverse effects and toxicities, provider experience, Suboptimal pharmacokinetics (variable absorption, metabolism or, theoretically, penetration into reservoirs; food/fasting requirements, adverse drug-drug interactions with concomitant medications) and Suboptimal potency of the antiretroviral regimen.[25]

In a Ugandan study to assess for predictors of long term viral failure among Ugandan children and adults treated with ART, the researchers found that children were almost twice as likely to have viral failure compared with adults. In adults, the sole independent predictor of viral failure was treatment with stavudine (D4T), lamivudine (3TC) and nevirapine (NVP) versus zidovudine (AZT), 3TC and Efavirenz (EFV). In children, independent predictors of viral failure were male gender, baseline CD4% less than 5 and treatment with D4T/3TC/ NVP versus ZDV/3TC/ EFV.[26]

Around a third of women who take single dose nevirapine develop drug resistant HIV, which can make subsequent treatment involving nevirapine and efavirenz (a related drug) less effective. Studies have shown that drug resistance resulting from single dose nevirapine tends to decrease over time; if a mother waits at least six months before beginning treatment then it may be less likely to fail. Nevertheless, in some cases the drug resistant HIV persists for many months in some parts of the body, even if it cannot be detected in the blood, and this may undermine the longer term effectiveness of treatment. [27-29]

Among babies infected with HIV and exposed to single- dose nevirapine, around half have drug resistance at 6-8 weeks old. Other infants may become infected with drug resistant HIV through breastfeeding. [30]

In summary, development of resistance to antiretroviral drugs is a common cause of failure. There are many factors that increase the likelihood of treatment failure such as:

- Inadequate adherence (e.g. missed dose, wrong dose, wrong time intervals between doses and food / fasting requirements not observed.)

- Drug side effects and toxicity leading to poor adherence
- Baseline patient factors (e.g. high pre-treatment viral load, Low CD4 count, prior AIDS diagnosis and presence of drug resistant virus)
- Drug-drug interactions between the antiretroviral drugs and other concomitantly administered drugs.
- Suboptimal potency of the antiretroviral regimen.

2.4 Managing treatment failure

It is important to confirm treatment failure, using the appropriate definitions of virologic and immunologic failure. A single abnormal result should be rechecked after 4-6 weeks. Identifying the cause of failure is important before deciding to switch to the second line antiretroviral regimen.[31]

The decision on when to switch from first-line to second-line therapy is critical. If the decision is made too early the months and years of potential survival benefit from any remaining first-line effectiveness is lost, if it is made too late, there will be accumulation of resistance to mutations. The effectiveness of second-line therapy may be compromised and the patient is put at additional and appreciable risk of death.[32, 33]

When available and affordable, resistance testing has emerged as a valuable tool for the clinician in the strategic management of antiretroviral therapy. Correct use of resistance testing may help limit the development of drug resistance and cross resistance and guide the optimal sequencing of antiretroviral agents during the many years of therapy required to maintain the health of the infected individual.[34]

Chapter 3

3.0 Research Methodology

3.1 Study design

An unmatched 1: 1 case control study was done to determine risk factors for developing 1st line treatment failure among patients on ART.

3.2 Study setting

The study was carried out at Newlands Clinic, Harare.

3.3 Study Population

Patients receiving ART at Newlands Clinic who have been on ART for at least 6 months were eligible for the study.

3.4 Working definitions

For the purpose of this study cases and controls were defined as follows:

A ***case*** was a patient who has failed 1st line ART after taking the regimen for at least 6 months and had been switched to 2nd line ART because of treatment failure.

A ***control*** was a patient who has been on first line ART for at least 6 months and has not failed 1st line treatment. Patient was still receiving 1st line ART.

3.5 Sample size determination

According to a study done by Roos E. Barth and others in 2010 on ART treatment outcomes in South Africa, they found out that one of the predictors of treatment failure was gender i.e. males were more likely to experience treatment failure compared females and it was statistically significant (O.R. 1.74; C.I.; 1.2-2.3)[35.] Using the Statcalc function of Epi info, exposure being defined as a male on treatment and the disease defined as treatment failure. Exposure in the "not ill" group was males on treatment who had successful treatment outcomes (24%). Using an odds ratio of 1.74, 95% confidence interval and 80% power, minimum required sample size was calculated to be 266 cases and 266 controls.

3.6 Sampling Procedure

Patients on second line ART at Newlands Clinic were randomly selected using lottery method if they fulfilled the inclusion criteria.

Controls were randomly selected using lottery method from patients who were on 1st line ART.

Recruitment of participants was done daily during period of data collection. The clinic attendance register was the sampling frame for controls. Selection of patients was limited to those who would have attended their scheduled clinic visits.

3.7 Inclusion and exclusion criteria

Inclusion criteria

- A patient receiving ART at Newlands Clinic
- Patients should have received ART for at least 6 months
- Patient has consented to participate in the study
- For children under 18, consent was acquired from parent / guardian

Exclusion criteria

- Patient who has been on ART for less than 6 months
- Patient who has denied to consent for study participation
- Patients on 2nd line ART due to drug adverse effects or pregnancy
- Patients who have failed 1st line ART but have not yet been switched to 2nd line

3.8 Study Variables

Dependent variables: Treatment failure to 1st line ART

Independent variables: Pre treatment factors, treatment / drug related factors, patient related factors and health service related factors.

Pre treatment variables

- Baseline WHO stage (Stage 1,2,3 or 4)
- Baseline CD4 count
- Baseline Haemoglobin level
- Baseline neutrophil count
- Past history of TB

Treatment / Drug related variables

- First line ART regimen
- Duration of 1st line ART
- Diagnosis of drug related adverse effect
- TB treatment

Patient related variables

- Gender
- Age
- Adherence levels
- Other comorbidities
- Disclosure of HIV status
- Previous exposure to ART

Health service related variables

- Place of 1st line ART commencement
- Pre ART counselling received
- On going ART counselling received

3.9 The Conceptual Framework

The following logic framework was used in this study to guide on the factors associated with 1st line treatment failure which were identified from literature review.

Fig 1: The Logic Framework – Factors associated with ART failure at Newlands Clinic

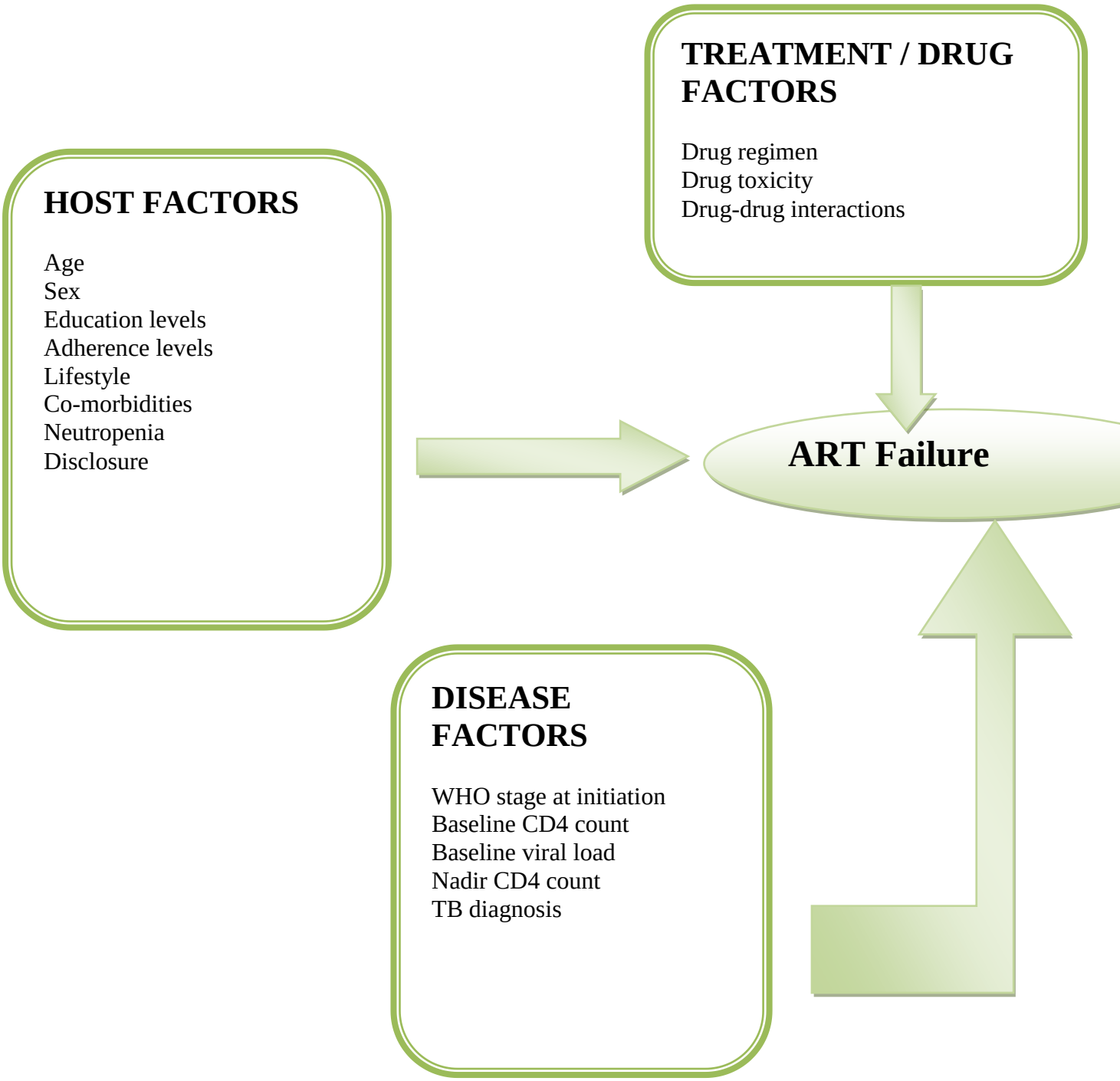


Table 1: Operationalisation of variables, Newlands Clinic, 2011

Variable	Operationalization (outcome variables)
Pre treatment factors	Proportion with CD4 <50 at baseline Proportion with CD4 between 50 and 200 at baseline Proportion with CD4 >200 at baseline Proportion with HB>10g at baseline Proportion with grade 3 & 4 neutropenia Proportion with WHO stage 1 & 2 at baseline Proportion with WHO stage 3 & 4at baseline
Treatment/drug related variables	Proportion who received D4T/3TC/NVP 1st line Proportion who received AZT/3TC/NVP 1st line Duration of 1st line ART Proportion who develop ART adverse effects on 1st line
Health service Related factors	Proportion who commenced ART at government facility Proportion who commenced ART at private general practitioner Proportion who commenced ART at Newlands Clinic
Patient related factors	Proportion who are male / female Proportion who are 0-13yrs, >13-18yrs & >18yrs Proportion who at any one time had adherence < 95% Proportion who have disclosed their HIV status to a treatment buddy

	Belonging to support group Alcohol use Other drugs e.g. antihypertensive , cancer drugs etc

A review of records was done to assess laboratory investigations and results. The laboratory results that were reviewed in the records were baseline CD4 counts, baseline Haemoglobin level and baseline neutrophil count. Furthermore a review of records assessed adherence levels and baseline WHO clinical stage.

3.10 Data Collection

Interviewer administered questionnaires were used among cases and controls to gather information on the factors associated 1st line ART failure at Newlands Clinic. Pretesting of questionnaires was conducted at Mazowe street OI clinic.

3.11 Data analysis

Epi-info 3.5.1 was used to analyze data and generate odds ratios, p values and 95% confidence intervals. Bivariate analysis was done to identify factors associated with failure of first line ART. Stratified analysis and multivariate analysis were done to check for confounding and effect modification.

3.12 Ethical Considerations

Permission to proceed with the study was sought from the Chairman of Newlands Clinic research unit. Clearance was obtained from Medical Research Council of Zimbabwe (Approval Number: MRCZ/B/ 227).

The aim of the study was explained to all the potential participants and it was explained to them that they were free to withdraw from the study at any time and no penalty would be imposed on them if they decided to do so. Informed written consent was obtained from the study participants to whom the research objectives, procedure

and benefits were explained. For participants aged below 18 years informed written consent was obtained from their parents or guardians and assent was obtained from the minor participants. Confidentiality was assured and maintained throughout the study as names were not used on participants' study records.

3.13 Dissemination of Study Results

Results were disseminated to clinic staff at Newlands Clinic. Results were yet to be disseminated to the Ministry of Child and Welfare at the time of submission. It is hoped that the results of this study will assist health care workers in identifying patients who are at risk of failing 1st line ART treatment. Identifying patients at risk of treatment failure early will enable timely intervention by health care workers were possible so as prolong effectiveness of 1st line ART.

Chapter 4

4.0 Results

4.1 Socio-demographic characteristics of study participants

We managed to enroll 232 cases and 232 controls. Reasons for failure to achieve desired sample size were:

1. Thirty seven patients on 2nd line ART regimen were not eligible for study participation because they had not failed 1st line ART.
2. Two patients on 2nd line ART denied consent to participate in the study.
3. Fifteen patients on 2nd line did not visit the clinic during period of data collection.

55% of cases were females and 45% were males. 61.2% of controls were females and 38.8% were males. The majority of study participants (76.3%) had received at least one year of secondary level education and there was no significant difference between the cases and controls. Only 32.8% of participants were in a marriage relationship. The other 67.2% were single, divorced or widowed.

The demographic characteristics of participants are summarised in Table 2 below.

Table 2: Demographic characteristics of participants, Newlands Clinic, 2011

Variable	Case	Control	p-value
Sex			
Male	104	90	0.113
Female	128	142	
Residence			
High density	113	173	0.101
Low density	98	53	
Rural	14	0	
Other	7	6	
Marital Status			
Divorced	21	18	0.232
Married	58	94	
Single	110	75	
Widowed	43	45	
Educational level			
None	0	2	0.567
Primary	54	54	
Secondary	142	140	
Tertiary	36	36	

4.1.1 Age distribution of participants, Newlands Clinic, 2011

The median age was 33.5 (Q1=17: Q3= 45) for cases and 37 (Q1=27.5: Q3=44) for controls. There was no significant age difference between the cases and controls. The majority of study participants (78.44%) were above the age of 18 years. Table 3 below summarises the age distribution of study participants.

Table 3: Age distribution among participants, Newlands Clinic, 2011 (n=464)

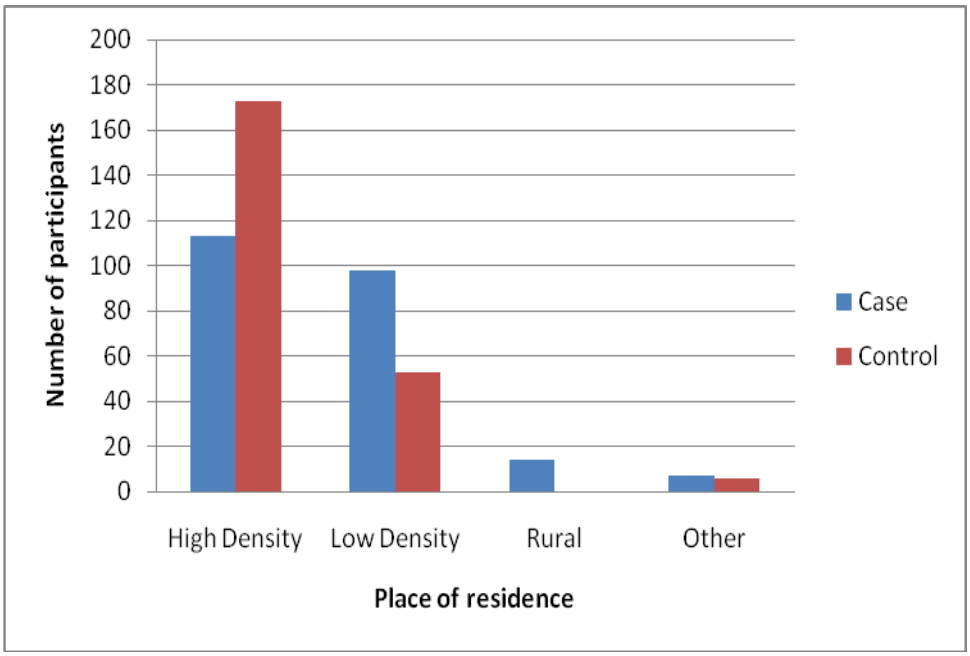
Age group in years	Case (%)	Control (%)	Total (%)
0-13	26 (5.60)	18 (3.88)	44 (9.48)
>13-18	36 (7.76)	22 (4.74)	58 (12.50)
>18	170 (36.64)	192 (41.38)	362 (78.02)
Total	**232 (50)**	**232 (50)**	**464 (100)**

$X^2 = 6.6$ P = 0.03

4.1.2 Place of residence of the participants, Newlands Clinic, 2011

The majority of study participants (61.6%) live in the high density residential areas of Harare. The 'other' category included participants who live in farming compounds and mining areas and these constituted 2.8% of study population. Fig 2 summarises the place of residence for study participants.

Fig 2: Place of residence of the participants, Newlands Clinic, 2011

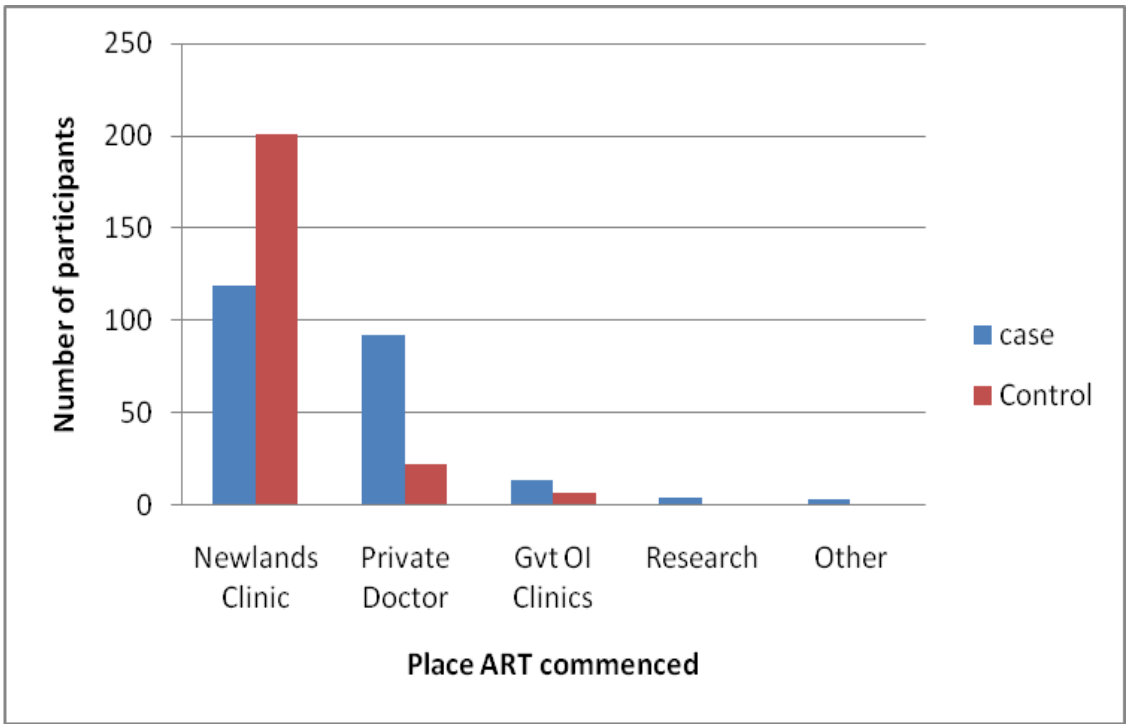


$X^2 = 40.58$ P value = 0.101

4.1.3 Place of ART commencement of participants, Newlands Clinic, 2011

The majority (69.97%) of study participants commenced their ART at Newlands Clinic. Other centres for participant ART initiation were, private doctors (24.57%), Government OI clinics (4.53%), research centres (1.08%) and 0.86% commenced ART at other places. Fig 3 highlights participants' place of ART commencement.

Fig 3: Place of ART commencement of the participants, Newlands Clinic, 2011



$X^2 = 69.97$ P value = 0.0000

4.2 Baseline participant characteristics.

The study participants' baseline CD4 count, neutrophil count, haemoglobin, WHO clinical stage and initial first line regimen were established.

4.2.1 Baseline CD4 count for participants, Newlands Clinic, 2011

There was a significant difference in the baseline CD4 counts among cases and controls. The median baseline CD4 count among cases was 88 (Q1=37: Q3=130) and among controls was 165 (Q1=91: Q3=336). Cases hence commenced ART earlier than controls. Table 4 shows baseline CD4 count for cases and controls.

Table 4: Baseline CD4 counts among participants, Newlands Clinic, 2011

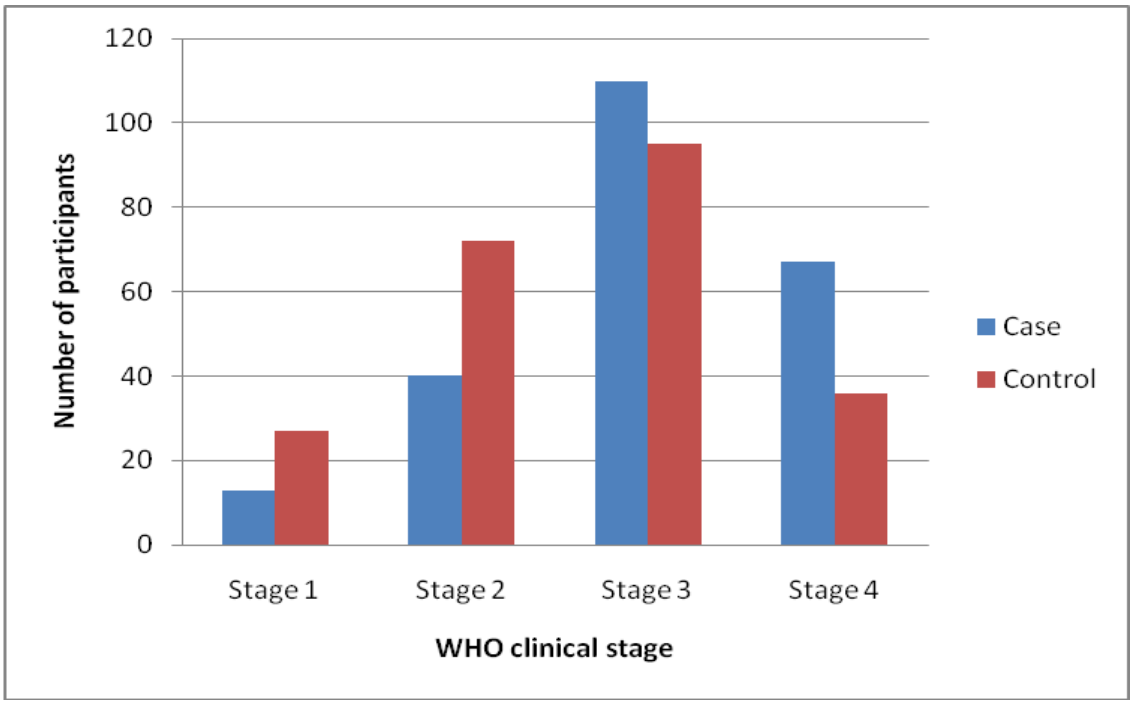
Baseline CD4 count (Cells / mm^3)	**Case (%)**	**Control (%)**	**Total (%)**
0-50	76 (16.38)	23 (4.96)	99 (21.34)
51-200	119 (25.65)	121 (26.08)	240 (51.73)
201-350	24 (5.17)	83 (17.89)	107 (23.06)
Above 350	13 (2.80)	5 (1.08)	18 (3.88)
Total	**232 (50)**	**232 (50)**	**464 (100)**

Among the study participants, 21.3% commenced ART very late with severe immunosuppression i.e. CD4 counts of 50 and below.

4.2.2 WHO stage at ART commencement

Majority of study participants (67%) had suffered an AIDS defining illness i.e. stages 3 and 4 conditions at the time of ART initiation. The proportion of patients who commenced ART after developing signs or symptoms suggestive of mild immunosuppression (WHO stage 2) was 24.4%. Only 8.6% of participants were commenced on ART before developing HIV associated symptoms or signs i.e. WHO stage 1. Fig 4 shows distribution of WHO clinical stages at ART commencement.

Fig 4: WHO stage at ART commencement (n=464)



$X^2 = 26.88$ P value = 0.001

4.2.3 Initial ART regimen at treatment commencement

The majority of patients (78%) were commenced on a first line regimen of stavudine, lamivudine and nevirapine. The 'other' ART combinations at treatment commencement were very diverse ranging from monotherapy, dual drug therapy and protease inhibitor based first line ART. Five patients were commenced on Tenofovir as part of their 1st line drug combination. It was noted that not all patients were commenced on ART according to Zimbabwe national ART guidelines. Some patients started ART before national guidelines were formulated and others commenced treatment outside Zimbabwe. Table 5 shows frequencies of 1st line ART regimens among study participants.

Table 5: ART regimen at treatment commencement

ART Regimen	**Case n=232**	**Control** **n= 232**
D4T / 3TC / NVP	109 (82.6)	171 (74.3)
AZT / 3TC / NVP	22 (9.6)	45 (19.6)
AZT / 3TC / EFV	3 (1.3)	4(1.7)
D4T / 3TC / EFV	2 (0.9)	3(1.3)
Other ART combinations	13 (5.7)	7(3.0)

4.2.4 Baseline Neutrophil count and Haemoglobin level

There was no significant difference in the baseline Haemoglobin (HB) between cases and controls. The median baseline HB was 11.2 (Q1=9.4: Q3=12.4) for cases and 11.6 (Q1=10.3: Q3=13) for controls. No significant difference was noted in the baseline neutrophil count between cases and controls. The median baseline neutrophil count for cases was 1.6 (10^3/ mm^3) (Q1=1.2: Q3= 2.2) and 1.7 for controls (Q1=1.28: Q3= 2.5).

4.3 Duration of first line antiretroviral therapy

There was no difference in the duration of 1st line ART among the cases and controls. The median duration of 1st line treatment among the cases was 2.95 (Q1=2; Q3=4.02) and that for controls was 3.06 (Q1=2.03; Q3= 5.0). Among the study participants, the longest duration on 1st line ART was noted to be 10.5 years. Table 6 shows time on 1st line ART for participants.

Table 6: Duration of first line ART among participant, Newlands Clinic, 2011

Time on 1st line ART in years	Case n=232	control n=232
0-1	10 (4.3)	1(3.1)
>1-3	118 (50.9)	101 (44.1)
>3-5	80(34.5)	64 (27.9)
>5	24 (10.3)	57 (24.9)

4.4 Drug adverse effects

Drug adverse effects were very common among the study participants. The table below highlights the drug adverse effects suffered. The most common side effect reported was peripheral neuropathy suffered by 68 cases and 51 controls. A total of 97 cases and 83 controls suffered drug adverse effects as indicated in table below.

Table 7: Drug adverse effects on 1st line among participants, Newlands Clinic, 2011

Adverse effect	Cases (232)	Controls (232)
Peripheral Neuropathy	73	46
Lipodystrophy	12	14
Rashes	7	5
Anaemia	5	7
Vomiting	6	4
Steven Johnson syndrome	2	3
Drug hypersensitivity	1	1
Hepatotoxicity	1	1
Confusion	0	1
Pancreatitis	0	1

4.5 Chronic medical conditions among participants, Newlands Clinic, 2011

Commonest chronic medical condition among study participants was noted to be hypertension. Table 8 below summarises the chronic medical conditions among the study participants.

Table 8: Chronic medical conditions among participants, Newlands Clinic, 2011

Chronic medical condition	Cases (232)	Controls (232)
Hypertension	27	21
Asthma	2	4
Diabetes mellitus	3	1
Epilepsy	2	1
Arthritis	2	0
Depression	1	0
Psychosis	1	0
Renal impairment	1	0

4.6 Risk factors for failing 1st line ART among Newlands Clinic patients

Analysis for factors associated with failing 1st line ART was conducted through bivariate analysis. This resulted in the identification of factors that increased the likelihood of developing treatment failure.

4.6.1 Patient related factors

We compared risk of failure between participants less than 18 years of age to those greater than 18 years. Results showed that those less than 18 years old were 2.38 (95%CI:1.10-2.75) times more likely to fail 1st line than those above 18 years.

On comparing participants who are married to those who are not (i.e. single, divorced or widowed), those not married were 2.04 (95%CI: 1.38-3.04) times more likely to fail than those who are married.

Participants who were receiving medication for other chronic medical illness besides HIV were 2.05 (95%CI: 1.19-3.54) times more likely to fail than those who are not suffering from other illnesses.

Participants who had insufficient food at home whist on 1st line ART were more likely to fail than those who did not have food shortages. Their risk of failure was increased by 1.18 times. (95%CI: 0.78-1.86)

Missing clinic appointments was a predictor of treatment failure as those who admitted to missing their scheduled appointments were 1.18 times more likely to fail than those who did not.

In our study, particapants' adherence to antiretroviral drugs was assessed by a review of their electronic medical records. At every clinic visit, nurses document drug adherence levels as assessed by pill counts. Poor adherence was defined as adherence of less than 95%. The participants who had documented poor adherence were 4.97 (95%CI: 3.09-8.00) times more likely to fail ART than those whose adherence levels have been good.

Table 9: Patient related factors associated with treatment failure, Newlands Clinic, 2011

Exposure		Cases	Controls	OR	Confidence Interval
Poor adherence	Yes	96	30	**4.97**	(3.09; 8.00)
	No	136	202		
Age < 18 years	Yes	62	40	**1.74**	(1.10; 2.74)
	No	170	192		
Drinking Alcohol	Yes	202	193	1.33	(0.79; 2.2)
	No	30	39		
Sex	Male	104	90	**1.28**	(1.04; 3.38)
	Female	128	142		
Disclosure of status	No	33	27	0.75	(0.75; 2.05)
	Yes	199	205		
Treatment partner	No	97	104	0.88	(0.61; 1.20)
	Yes	135	128		
Insufficient food	Yes	174	181	0.82	(0.53; 1.27)
	No	58	51		
Sexually active	Yes	143	120	**1.4**	(1.01; 2.13)
	No	89	112		
Safe sex practiced	No	17	3	**8.50**	(2.4; 17.01)
	Yes	72	108		
Chronic medical illness	Yes	43	24	**2.05**	(1.19; 3.54)
	no	189	208		
Hypertension	Yes	27	21	1.3	(0.72; 2.41)
	No	205	211		

Married	No	174	138	**2.04**	(1.38; 3.04)
	Yes	58	94		
Physical Exercise	No	95	67	**1.71**	(1.16; 2.53)
	Yes	137	165		

4.6.2 Health service factors associated with 1st line ART failure

Patients who did not receive any counselling at the commencement of ART had a very high risk of failing their treatment as compared to patients who received counselling (OR = 10.53). Patients who commenced ART at a private doctor did not do as well as patients who commenced ART at other institutions (OR= 6.27). Other significant health service factor for treatment failure was having difficulties in accessing ART. Of the patients who reported difficulties in accessing ART, 85% commenced their treatment at a private doctor. Among patients who commenced treatment at private doctors, 51.8% did not receive pre-ART counselling. Table 10 below summarises health service risk factors for ART treatment failure.

Table 10: Health service related risk factors for treatment failure, Newlands Clinic, 2011

Exposure		Cases	Controls	OR	Confidence Interval
ART commencement by private doctor	Yes	92	22	**6.27**	(3.76; 10.46)
	No	140	210		
Difficulties in accessing ART	Yes	38	9	**5.6**	(2.55; 12.28)
	No	194	223		
ART counselling received	No	58	7	**10.53**	(4.68; 23.65)
	Yes	174	225		
Individual counselling received	No	98	104	0.82	(0.61; 1.21)
	Yes	134	128		
On-going counselling	No	30	38	0.84	(0.74; 2.08)
	Yes	202	194		

4.6.3 Pre-treatment related factors for 1st line ART failure

Starting antiretroviral treatment late was associated with a high risk of treatment failure. Those initiating ART at a CD4 count less than 50 cells / mm^3 were 4.77 times more likely to fail than those commencing ART at CD4 above 50 cells / mm^3. ART initiation at CD4 count less than 100 cells / mm^3 was associated with a 2.77 times risk of failure than those initiating at a CD4 above 100 cell / mm^3. Initiating ART after diagnosis of WHO 3 or 4 conditions was associated with a 2.51 times risk of treatment failure compared to ART initiation while in WHO stage 1 or 2. Baseline haemoglobin of less than 10g/dl and baseline neutrophil count less than 1 were not

associated with treatment failure. Table 11 below summarises association between baseline factors and treatment failure.

Table 11: Pre-treatment related risk factors for treatment failure, Newlands Clinic, 2011

Exposure		Cases	Controls	OR	Confidence Interval
CD4 < 100 cells /mm^3	Yes	115	60	**2.74**	(1.87; 4.02)
	No	106	163		
CD4 < 50 cells /mm^3	Yes	67	17	**4.77**	(2.79; 8.15)
	No	154	206		
WHO stage	3/4	175	131	**2.51**	(1.68; 3.78)
	1/2	52	98		
Baseline Neutrophil count	<1	35	31	1.19	(0.71; 1.98)
	>1	191	196		
Baseline Haemoglobin (g/dl)	<10	24	33	0.73	(0.44; 1.23)
	>10	201	191		

4.6.4 Treatment / Drug related factors for ART treatment failure

A first line ART regimen containing stavudine (D4T) was associated with a 1.63 times increased risk of failure when compared to none D4T containing regimens. Patients who reported suffering from peripheral neuropathy were at 1.44 times increased risk of treatment failure than those who did not. Having changed ART drugs while on 1st line was noted to be a significant factor for treatment failure. Participants who once received mono or dual ART therapy were 16.9 times more likely to fail than

those who did not. Treatment duration was not associated with treatment failure. Table 12 highlights the drug and treatment related factors for ART treatment failure.

Table 12: Drug / Treatment related risk factors for treatment failure, Newlands Clinic, 2011

Exposure		Cases	Controls	OR	Confidence Interval
Duration of 1st line ART	>3yrs	104	124	0.71	(0.49; 1.02)
	<3yrs	128	108		
Adverse effects of ART	Yes	135	149	0.78	(0.54; 1.14)
	No	97	83		
Peripheral Neuropathy	Yes	67	51	**1.44**	(1.08; 2.19)
	No	165	181		
Received ART for PMTCT	Yes	6	11	0.59	(0.21; 1.64)
	No	226	221		
TB treatment during ART	Yes	184	196	0.70	(0.43; 1.13)
	No	48	36		
D4T in1st line drug regimen	Yes	194	176	**1.63**	(1.02; 2.58)
	No	38	56		
Changed 1st line drugs	Yes	107	83	**1.60**	(1.10; 2.32)
	No	125	149		
Received Mono / Dual ART therapy	Yes	16	1	**16.9**	(2.23; 30.50)
	No	216	231		

4.6.5 Stratified Analysis

WHO stage stratified by baseline CD4 count

Variable	Case	Control	OR	95%CI
CD4 < 100 cells /mm^3				
WHO stage at ART commencement				
Stage 3 & 4	102	45		
Stage 1 & 2	19	21	**2.51**	(1.23-5.11)
CD4>100 cells /mm^3				
WHO stage at ART commencement				
Stage 3 & 4	66	83		
Stage 1 & 2	30	78	**2.06**	(1.22-3.51)

Crude OR = 2.65

Adjusted (MH) OR = 2.20 (1.4-3.3)

A baseline CD4 count of less than 100 cells /mm^3 confounded the relationship between baseline WHO stage and 1st line ART treatment failure.

After adjusting for baseline CD4 count, patients who had baseline WHO stage 3 & 4 were 2.20 times more likely to fail treatment than those in WHO stage 1 & 2.

Baseline WHO stage stratified by gender

Variable	Case	Control	OR	95%CI
Sex = Female				
WHO stage at ART commencement				
Stage 3 & 4	95	79		
Stage 1 & 2	33	61	**2.22**	(1.32-3.73)
Sex = Male				
WHO stage at ART commencement				
Stage 3 & 4	82	52		
Stage 1 & 2	20	38	**3.00**	(1.57-5.70)

Crude OR = 2.52

Gender modified the relationship between baseline WHO stage and treatment failure. Males with a baseline WHO stage of 3 & 4 had a higher risk of failing 1st line ART than females.

WHO stage at baseline stratified by age group

Variable	Case	Control	OR	95%CI
Age < 18 years				
WHO stage at ART commencement				
Stage 3 & 4	48	25		
Stage 1 & 2	14	15	**2.06**	0.85-4.93
Age > 18 years				
WHO stage at ART commencement				
Stage 3 & 4	129	108		
Stage 1 & 2	39	84	**2.62**	1.65-4.14

Crude OR = 2.52

Age modified the relationship between baseline WHO stage and treatment failure. Those aged over 18 years who had baseline WHO stage 3 & 4 were more likely to fail 1st line ART than those aged less than 18 years with a baseline WHO stage 3 & 4.

4.6.6 Logistic Regression Analysis

Further multivariate analysis (step wise logistic regression analysis) was performed in order to estimate the measures of association while simultaneously controlling for a number of other and confounding variables. All variables whose p-values were less than 0.25 in the bi-variate analysis were included in the logistic regression model. The model was started off with a single variable then variables were added one by one. Variables which had a p-value greater than 0.05 were removed from the model until all the possible variables had been added to the model and significant factors determined. The adjusted odds ratios and 95% confidence intervals that were obtained from the final model are presented in the following table.

Table 13: Independent factors associated with treatment failure, Newlands Clinic, 2011

Risk factor	AOR	Conf. Interval	p-value
Not married	1.80	1.01; 3.21	0.037
Poor adherence	1.73	1.05: 3.43	0.029
ART commenced by Private doctor	4.86	2.11; 11.2	0.000
WHO stage 3 & 4 at ART commencement	2.08	1.21; 3.50	0.007
CD4 < 50 at ART commencement	1.5	1.65; 8.20	0.001
Duration of 1st line > 3 years	**0.54**	**0.32; 0.93**	**0.029**

Independent risk factors for developing treatment failure were identified as:

1. Not being married
2. Poor adherence to treatment
3. Antiretroviral drugs commenced at a private doctor's surgery
4. Being in WHO stage 3 and 4 at initiation of ART
5. Starting ART with a CD4 count less than 50 cells /mm^3.

Having been on ART for more than 3 years was identified as a significant protective factor against developing 1^{st} line ART failure.

Chapter 5

5.0 Discussion

5.1 Risk factors for ART treatment failure

In this study, risk factors for treatment failure on 1st line ART at Newlands Clinic were identified. These factors included baseline patient characteristics, stage at which patient commences treatment and to the type of ART drugs being used. The independent risk factors identified were, poor adherence to treatment, commencing ART at private doctor, not being married, CD4 count less than 50 cells /mm^3 at ART commencement and baseline WHO stages 3 and 4. Our results were able to show a variety of potentially actionable clinical characteristics that identify HIV positive patients at increased risk of treatment failure. From these results, it shows that if ART is administered early i.e. before patients develop WHO stage 3 & 4 conditions or their CD4 count falls to less than 50, treatment failure may be avoided in most of the patients on antiretroviral treatment.

Before a patient is commenced on antiretroviral therapy, it is essential that they be adequately prepared for this life-long drug therapy. ART treatment necessitates a change in life style and social habits. Poor patient treatment may lead to poor drug adherence by patients, increasing the likelihood of treatment failure. In Zimbabwe, patients who are commenced on ART at government OI clinics undergo intensive counselling sessions to prepare them for good ART adherence. At Newlands Clinic, patients are allocated a full hour of ART counselling before initiating therapy. In contrast, patients who are commenced on ART by a private doctor do not receive similar levels of counselling. Most private clinics are not dedicated to HIV treatment and hence experience in HIV management is lower among private doctors. Most

training in HIV management has targeted clinicians in the government hospitals and very little training has been offered to private practitioners. In the American HIV management guidelines, poor provider experience in ART management is identified as a risk factor for treatment failure.

Furthermore, patients who commenced ART from private doctors are likely to have had treatment interruptions associated with financial barriers of securing therapy and competing financial demands such as food, accommodation and school fees. These treatment interruptions have been evaluated in other studies lead to virological rebound and drug resistance, may explain the elevated risk of treatment failure among our study participants who commenced treatment at a private doctor.[36]

Patients who reported difficulties in accessing ART had a high risk of treatment failure on univariate analysis. These patients are likely to have commenced ART at private institutions since at Newlands Clinic and Government OI clinics drugs are provided for free and no stock outs are experienced. These difficulties in accessing ART could have led to unstructured treatment interruptions consequently development of viral drug mutations.

In our study, poor adherence was identified as a risk factor for developing treatment failure. Although reported adherence is subject to measurement error and we cannot exclude that some patients over reported their level of adherence during clinic visits, our findings are consistent with that of numerous other studies that identified poor adherence as a predictor of treatment failure. Parienti et al [37] found that patient reported adherence was associated with none nucleoside reverse transcriptase inhibitor (NNRTI) resistance in a resource rich setting and Spacek et al[38] found that

patient reported treatment interruptions was associated with virological failure in Uganda . The long half life of NNRTI may lead to effective monotherapy during period of treatment interruption (poor adherence). Monotherapy with NNRTI enables the virus to develop drug resistant mutations leading to resistance to the NNRTI. Re-introduction of triple therapy means that the patient will effectively be on dual therapy which in itself is prone to development of resistance, subsequently leading to treatment failure. The message to individuals who are on antiretroviral therapy is that long-term viral suppression will only be achieved with near perfect adherence.

Patients who are not married were at a greater risk of treatment failure. Marriage provides an increased social and adherence support. The spouses become a readily available treatment buddy. When both partners in a marriage are on ART, adherence becomes very good as they take medications at the same time and remind each other of importance of good adherence. This explains the low risk of failure in marriage participants.

This study revealed that late commencement of ART is a risk factor for treatment failure. Patients who commenced ART after developing AIDS related illness (WHO stage 3 & 4), and those who had low baseline CD4 counts of below 50 cells / mm^3 had a significantly higher risk of treatment failure.

Several studies have demonstrated that commencing ART late is associated with higher risks of mortality or treatment failure. Egger et al estimated the risk of AIDS or death according to baseline CD4 count, plasma HIV concentration, and age and disease stage. In their results, the authors concluded that the 3 year risk of AIDS (treatment failure) or death in patients who started ART at a low CD4 count was

greatly increased.[39] Other studies have demonstrated that deferring treatment to lower CD4 counts is associated with a more rapid clinical progression.[40,41]

In a study to assess the relationship between baseline CD4 cell counts as a predictor of the duration of highly active antiretroviral therapy, the authors noted that: lower baseline CD4 cell count was associated with increased risk of viral rebound. Risk of viral rebound was independently associated with baseline CD4 count and changes of CD4 count from baseline.[42]

A study done at Chirazulu District of Malawi by Ferradini et al showed that WHO stage four; male sex and baseline CD4 count lower than 50 cells / mm^3 were independent determinants of poor survival among patients on ART. They also showed that self reported poor adherence (<80%) in the preceding 4 days was the best predictor of detectable viral load (treatment failure).[43]

In our study, males had a greater risk of failing than females. This finding is consistent with other studies which have identified male gender as a risk factor. Roos E. Bath et al in a study done in South Africa to determine risk factors for treatment failure reported that males were more likely to experience treatment failure than their female counterparts[35.] On average, males commence treatment later than females. Most ART treatment centres in the country have more females than males. This delay partly explains why males are at a greater risk of treatment failure. Furthermore, lifestyle habits of males are less promotive of good treatment adherence. More males drink alcohol than females.

Dual or monotherapy for the treatment of HIV is inferior to 3 drug combination ART. Seventeen participants in our study received dual or monotherapy for varying periods

of time. The treatment failure risk in these participants was very high. Most likely they received these combinations early on in the HIV pandemic before guidelines for the use of triple drug combinations had been developed. Several studies have demonstrated the inferior efficacy of dual or monotherapy regimens when compared to triple therapy. World-wide HIV treatment guidelines promote the use of triple drug combinations.

In this study presence of other chronic medical illnesses was identified as a significant risk factor for ART treatment failure. The increase in the risk of treatment failure can be explained by the increase in the total number of pills that the patient has to take daily. Studies to determine predictors for adherence for patients who are on ART have identified increased pill burden as a significant risk factor. In a study to determine factors affecting adherence to antiretroviral therapy, it was noted that: The principle factors associated with none adherence to drugs appear to be patient – related, including substance and alcohol abuse. However, other factors noted in the study included inconvenient dosing frequency and increased pill burden.[44]

Risk of treatment failure was significantly increased among patients who are sexually active. This risk was higher among those who admitted to having unsafe sex. When a patient fails treatment, the drug resistant virus that would have been generated can be transmitted sexually if unsafe sex is practiced, this in turn leads to treatment failure in the sexual partner.

In our study patients who admitted to drinking did not have a significant higher risk of treatment failure than those who do not. However other studies have demonstrated

that consumption of alcohol is a risk factor for ART treatment failure. It has been reported that patients who drink alcohol are likely to have poor adherence to ART when compared to patients who do not. In a study to determine factors associated with poor adherence in a rural South African setting, poor adherence among was seen in those who used consumed alcohol regularly. In the same study 50.8% 0f patients who suffered medication side effects reported poor adherence.[45] Alcohol consumption in this study was not a risk factor possibly because the levels of drinking alcohol by the participants had no effect on their drug adherence levels.

Participants less than 18 years of age were more likely to fail treatment than those above 18 years. This finding is consistent with other studies which have showed that treatment failure is more likely to occur in the paediatric than adult patients.[46]
Children are less likely to have excellent adherence to medication because of the need of a motivated care giver to assist with medication taking. Furthermore, children are more likely than adults to receive inadequate dosing of treatment as there is need to constantly recalculate their drug doses due to weight gain associated with growing up.

In our study, although diagnosis of ART toxicity was not a significant risk factor for treatment failure, patients who were diagnosed with peripheral neuropathy were more likely to fail ART. Patients who had stavudine as part of their 1st line ART regimen were also at a significant high risk of failure. Stavudine use is associated with development of peripheral neuropathy in a majority of patients. Development of peripheral neuropathy is likely to lead to poor adherence to medication and hence lead to treatment failure. In a study to identify variables predictive of none adherence to highly active antiretroviral therapy (HAART) and to assess whether self-reported

symptoms or medication side effects are related to adherence, authors concluded that patient reported symptoms and medication side effects were significantly associated with adherence to HAART.[47]

5.2 Protective factors for ART treatment failure

In our study, the only significant protective factor against developing ART failure was having been on ART for greater than 3 years. Patients who have been on 1st line ART for more than 3 years are likely to have adapted well to taking ART and have good adherence. This result also demonstrates the fact that if ART is taken well, patients are likely to do well on their 1st line combination for a long time.

5.3 Study limitations

Our study was a case control study and some participants could not accurately answer some of the questions. Recall bias could have affected some of the study findings. Information on baseline CD4 count, haemoglobin, WHO stage and neutrophil count was missing in some patients and hence affected risk factor analysis.11 cases and 9 controls had missing baseline CD4 count. 3 cases and 5 controls had missing WHO stage. 6 cases and 5 controls had missing baseline neutrophil count. 7 cases and 8 controls had missing baseline haemoglobin. The minimum required sample size was not achieved and this too could have affected risk factor analysis.

5.4 Conclusion

This study demonstrated numerous risk factors for development of antiretroviral treatment failure. Late initiation of treatment for HIV infection predisposes to treatment failure. Factors that negatively impact patient's adherence to treatment were shown to increase likelihood of treatment failure. The independent risk factors for developing treatment failure were identified as: Poor adherence to treatment, commencing ART by private doctor, WHO stages 3 & 4 at ART commencement, not being married and CD4 less than 50 at baseline. The risk factors for treatment failure identified in this study are potentially avoidable and it is possible to retain 1st line ART for a long time and avoid the more expensive 2nd line ART. Having been on ART for more than 3 years was a significant protective factor against treatment failure.

5.6 Recommendations

1. The AIDS and TB unit in the ministry of health should seek to partner the private medical sector in the management of HIV infection. Private Doctors should be invited to the numerous trainings that the ministry is offering government clinicians in HIV management. Furthermore the ministry should pursue possibility of providing free antiretroviral drugs to patients being managed in the private sector so as to prevent treatment interruptions.
2. The Ministry of Health and Child Welfare should ensure that every health centre in the country must be able to offer HIV testing and free CD4 counts. This measure will go a long way in enhancing early diagnosis and treatment of HIV infection.
3. Health care providers must routinely, at every clinic visit, monitor the patient's adherence to antiretroviral medication. Interventions to improve adherence should be promptly introduced among those identified to be poorly adhering to treatment. ***(Ministry of Health and HIV clinicians)***
4. The use of Stavudine in the management of HIV infection should be avoided since one of its major side effect, peripheral neuropathy, may affect adherence eventually leading to treatment failure. ***(Ministry of Health)***

Chapter 6

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Questionnaire

Good morning/afternoon. My name is Dr Cleophas Chimbetete, I am an MPH Officer. I am carrying out a study on the prevalence and risk factors of 1st line ART treatment failure amongst patients receiving ART at Newlands Clinic. I would like to ask you a few questions about the subject if you are willing to participate in the study. I would assure you that any information you provide will be treated as confidential and will be used to improve the management of ART patients in Zimbabwe.

May I proceed? *(Participant to complete consent form)*

Circle the appropriate responses or use the space provided for written responses.

Status Case / Control

Demographic Characteristics of patient

1. Sex M/F
2. Age …..
3. Area of residence
    a) High density
    b) Low density
    c) Rural
    d) Other, specify
4. Marital status
    a) Single
    b) Married
    c) Divorced
    d) Widowed

5. Level of education

    a) None

    b) Primary

    c) Secondary (at least 1 year)

    d) Tertiary

Pre treatment / Health service related factors

6. When did you test HIV positive? …..

7. What was / is duration on 1st line ART? ….. Years

    ……Months

8. Where was ART commenced?

    a) Government OI clinic

    b) Private Doctor

    c) Newlands Clinic

    d) Research centre

    e) Other, (specify) ……

9. Did you receive ART counseling before commencement of treatment?

    A. Yes

    B. No

    If no skip to question 10.

10. How many ART counseling sessions did you receive?

    A. One

    B. Two

    C. Other, (specify)

11. Did you receive any individualized counseling?

    A. Yes

    B. No

Adherence assessment (Interviewer to verify with records on adherence levels of participant)

12. Have you disclosed your status to any of your family members? Y / N

13. How many doses of ART have you missed in the last month?

    a) None

    b) 1- 4

    c) More than 4

14. Have you missed any clinic appointments ever since ART commencement? Y/N

15. Are you part of a treatment support group? Y/N

16. Do you receive ongoing treatment counseling when you come to the clinic? Y/N

17. Do you have someone who helps you to remember your drugs (treatment buddy)? Y / N

18. Have you faced any problems in accessing ART? Y/N

If no, skip question 19

19. What are the problems you have faced in accessing ART?

……..

Drug related factors

20. What ART drugs where you commenced on for 1st line treatment?

    A. AZT / 3TC / NVP

    B. AZT / 3TC / EFV

    C. D4T / 3TC / NVP

    D. D4T/ 3TC / EFV

    E. Other, (specify) ……..

21. Have you suffered any adverse effects of ART drugs? Y / N

    If no, skip question 22

22. What adverse effects have you suffered?

    A. Peripheral neuropathy

    B. Anemia

    C. Nausea and Vomiting

    D. Lipodystrophy

    E. Other, (specify) …….

23. Did you change any of your 1st line ART drugs? Y / N

    If no, skip question 24

24. Why did you change ART drugs?

    A. Developed side effects

    B. Commenced on TB medication

    C. Other, (specify) …….

25. Did you ever receive ART as a single drug or dual drug regimen? Y / N

    If no, skip question 26

26. How long did you receive mono / dual therapy?

    A. Less than 1 week

    B. 1-2 weeks

    C. More than 2 weeks

27. While on ART, have you received TB treatment? Y / N

28. Have you received antiretroviral drugs for PMTCT? Y / N

    If no, skip question 29

29. What drug regimens have you received for PMTCT?

    A. Single dose nevirapine in labour

    B. NVP in labour + 1 week of AZT and 3TC

    C. AZT during pregnancy + NVP in labour + 1 week of AZT and 3TC

    D. AZT alone

    E. Others (specify)

Clinical History

30. Have you been hospitalized while on 1st line ART? Y / N

31. Have you suffered from any opportunistic infection while on 1st line ART? Y / N

    If no, skip question 32

32. What opportunistic infection have you suffered from?

    A. Tuberculosis

    B. Meningitis

    C. Oral sores

    D. Other, (specify)

Sexual History / lifestyle factors

33. Are you sexually active? Y / N

    If no, skip question 34 and 35

34. Do you have a regular sexual partner? Y / N

35. Do you practice safe sex at all times? Y / N

36. Do you take alcohol? Y / N

37. Do you exercise regularly? Y / N

38. While on 1st line ART, have you ever had problems in obtaining sufficient food? Y / N

Comorbidities

39. Do you suffer from other chronic medical conditions? Y / N

If no, skip question 40

40. What chronic medical conditions do you suffer from?

    A. Hypertension

    B. Diabetes mellitus

    C. Others (specify)

Patient record review

1. Baseline WHO stage …….
2. Baseline CD4 counts at ART commencement…….
3. Baseline HB……..
4. Baseline Neutrophil count……
5. Documented adherence problems Y / N

Consent forms

English

Factors associated with 1st line Antiretroviral Therapy treatment failure in patients receiving ART at Newlands clinic

Introduction

You are invited to participate in a research Study of determining factors associated with 1st line ART failure among patients receiving treatment at Newlands Clinic. You are selected as a potential participant because you are receiving treatment at Newlands Clinic. We ask that you read this form and ask any questions that you may have before agreeing to be in the study.

Study

This study is being by Dr C. Chimbetete who is studying for a Masters in Public Health degree with the University of Zimbabwe as part of requirements for the degree programme.

Study Procedures

If you agree to participate in this study, we will ask you some questions relating to your illness history and treatment. We will review your treatment records for analysis. The study will not influence your medical follow up. Your medical follow will continue as normal if you decide not participate in this study.

Risks and Discomforts

The study has no risks

Benefits and Compensation

The benefits to study participation are that this may help improve the treatment for you and other people in future. There are no payments for involvement in the study

In the event of injury

There is no foreseeable study related injury

Confidentiality

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. No information with your name will leave the clinic. Your name will not occur on any of the records.

Voluntary Participation

Participation in this study is voluntary. Your decision whether or not you participate in this study will not affect your current or future relation with Newlands Clinic

Offer to answer any question

Before signing this form please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think about it.

Contacts and questions

The researcher conducting this study is Dr. C. Chimbetete. You may ask any questions you have now, or if you have questions later, you are encouraged to contact him at Newlands Clinic, at 56 Enterprise Road, Newlands, Harare.

Telephone 776433

Authorisation

You are making a decision whether or not to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all questions answered and have decided to participate. All pages will be stamped to indicate form validity as approved by MRCZ.

If you have any questions or concerns regarding the study and would like to talk to someone other than the investigator, including questions about the research, study questions, your rights as a research participant or research related injuries, or if you

feel you have been treated unfairly and would like to talk to some one other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe on Telephone 791792 or 791193

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Name of participant…….. (Please Print)

Signature of participant (Parent/guardian) ……..

Date ……. Time ……..

Signature Investigator/ Research Staff …….

Parental consent

AUTHORIZATION

You are making a decision whether or not to allow your child to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered and have decided to allow your child to participate.

The date you sign this document to enroll your child in this study, that is, today's date, MUST fall between the dates indicated on the approval stamp affixed to each page. These dates indicate that this form is valid when you enroll your child in the study but do not reflect how long your child may participate in the study. Each page of this Informed Consent Form is stamped to indicate the form's validity as approved by the MRCZ.

_____ _____

Name of Parent (please print) Date

_____ _____

Signature of Parent or legally authorized representative Time

_____

Relationship to the Subject

_____ _____

Signature of Witness Signature of Research Staff

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research subject or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe on telephone 791792 or 791193.

For children 12 years old to 17 years old – to read and sign below

My participation in this research study is voluntary. I have read and understood the above information, asked any questions which I had and have agreed to participate. I will be given a copy of this form to keep.

_____

Name of Subject

_____

Signature of Subject

Consent form

Shona

FACTORS ASSOCIATED WITH 1ST LINE ANTIRETROVIRAL FAILURE AT NEWLANDS CLINIC, HARARE, ZIMBABWE.

Mavambo

Munokokwa kupinda muongororo yatinoda kuita ye "Factors associated with 1st line ART failure at Newlands Clinic." Makasarudzwa kupinda muongororo iyi nekuti muri kurapwa pa Newlands Clinic. Tinokukumbirai kuti muwerenge fomu iri mugobvunza mibvunzo yamungave nayo musati mabvuma kupinda muongororo iyi. Ongororo iyi irikuitwa na Dr C. Chimbetete vachishanda neve Newlands Clinic.

Donzo reongororo

Chinangwa chechirongwa ichi ndechekuti tiongorore zvikonzero zvinoita kuti mishonga ye 1st line ART isashanda zvakanaka muvanhu varikunwa ART.

Maitirwo eongororo

Mukabvuma kupinda muongororo iyi tichakubvunzayi mibvunzo inoenderana nehutano hwenyu uye matorero amunoita mishonga yenyu. Tichaongorora magwaro ehurwere hwenyu kana mwana wenyu. Ongororo iyi haineyi nemarapirwe amunoitwa. Kurapwa kwenyu hakuzosiyane kana mukasapinda muchirongwa ichi.

Matambudziko eongororo

Hapana matambudziko atinofungidzira kuti achavapo kana mapinda muongororo iyi.

Mubairo / muripo

Mubairo wekuva muchirongwa ichi ndewekuti ongororo iyi inotarisirwa kubatsira marapirwo evanhu vanorarama neutachiwana weHIV.

Kukuvara muchirongwa

Hapana kukwara kwevanenge vapinda muchirongwa ichi.

Kuchengetedzwa kwemashoko (Confidentiality)

Magwaro echirongwa ichi achachengetedzwa kuti asaonekwe nevasiri muchirongwa ichi. Hapana magwaro kana zvimwe zvinemazita enyu zvichatorwa kubva pa Newlands Clinic. Zita renyu harinyorwi paongororo iyi.

Kupinda muongororo pasina kumanikidzwa (Voluntary participation)

Kupinda muchirongwa ichi hakumanikidzwi. Sarudzo yenyu kurega kana kuva muchirongwa hakukanganisi marapirwo enyu amagaroitwa kana ukama hwenyu panguva ino kana inoyevera.

Kubvunza mibvunzo

Musati masaina fomu iri sunungukai kubvunza mibvunzo pane zvamusina kunzwisisa. Munogona totora nguva muchimbofunga nezvazvo.

Vamunogona kuona kana mune mibvunzo

Mukuru arikuita ongororo iyi ndi Dr C. Chimbetete. Munogona kubvunza kana mune pamunoda kunzwisisa izvezvi kana imwe nguva inotevera pa Newlands Clinic, 56 Enterprise Road, Newlands, Harare.

Telephone 776433

Tendero (Authorisation)

Muri kufunga kuti mapinda muongororo here kana kuti kwete. Kusaina kwenyu kunoreva kuti maverenga mukanzwisisa zvakanyorwa pamusoro uye mibvunzo yenyu yapindurwa uye mabvuma kuva muongororo.

Kana mune mibvunzo nezveongororo iyi uye munoda kutaura nemumwe asiri Mukuru wechirongwa ichi uye kana muchida kunzwa nezve kodzero dzenyu muongororor. Kana mukaona kuti hamuna kubatwa zvakanaka sunungukai kuona kana kufonera veMedical Research Council off Zimbabwe panhamba dzefoni; 791792 kana 791193.

Mutsara wemvumo

Ndaverenga / ndatsanangurirwa nezvechirongwa ichi ndikapiwa mukana wekubvunza mibvunzo ndikatsanangurirwa zvinogutsa.

Ndinobvuma kuti magwaro ehurwere hwangu ashandiswe muongororo iyi.

Zita…….. (Please Print)

Kusaina ……..

Date ……. Nguva ……..

Kusaina Kwamuongorori …….

Parental consent (Shona)

KUBVUMIDZA

Makutora danho rekuti mwana wenyu apinde kana kusapinda mu*research* ino. Kusaina kwenyu pafomu rino kunoreva kuti maverenga zviri pafomu rino mukazvinzwisisa, mibvunzo yamanga muinayo yese yapindurwa uyezve mabvuma kuti mwana wenyu apinde mu*research* ino.

Zuva ramunosaina fomu rino pakupinda kwemwana wenyu mu*research*, rinova zuva ranhasi, rinofanirwa kunge riri pakati pemazuva akatarwa pachidhindo chiri papeji yoga yoga. Mazuva iwayo anoratidza kuti fomu rino richine basa panguva inopinda mwana wenyu mutsvagiridzo asi hazviratidze kuti nguva yaangangopinda mu*research* yakareba zvakadii. Peji yoga yoga yefomu rino ine chidhindo chekuratidza kuti fomu rino richine basa sekutenderwa kwarakaitwa neMRCZ.

_____ _____

Zita remubereki kana mumiriri wemubereki (NYORAI ZVINOWONEKA)

Dheti

_____ _____

Kusaina kwemubereki kana mumirириri wemubereki Time

_____

Ukama nemwana

_____ _____

Kusaina kwehwitinesi Kusaina kwemunyori

MUCHAPIHWA KOPI YEPEPA RAMASAINA KUTI MUGOCHENGETA

Kana muine mibvunzo pamusoro pe*research* ino kana fomu ramasaina iri kunze kweyamapindurwa kare nemunyori, kusanganisira zvetsvagiridzo, kodzero dzenyu pakupinda mu*research* kana nezvekukuvara kunokonzerwa nekupinda mu*research* uyezve kana muchiwona kuti hamuna kubatwa zvakugutsai muchida kukurukura nemumwe munhu asiri muchikwata chevari kuita *research* ino sunungukai kufonera veMedical Research Council of Zimbabwe panhamba dzinoti 791792 or 791193

Vana vane makore ari pakati pegumi nemaviri kusvika pagumi nemanomwe – verenga ugosaina pasi

Kupinda kwangu mu*research* ino ndekwekuzvipira. Ndaverenga ndikanzwisisa zvakanyorwa pamusoro, ndabvunza mibvunzo yese yandanga ndiinayo uyezve ndabvuma kupinda mu*research.* Ndichapiwa kopi yefomu rino kuti ndigorichengeta.

_____

Zita remwana

_____

Siginecha yemwana