CHAPTER 1: INTRODUCTION

BACKGROUND

HIV/AIDS is a global pandemic with 33.7 million people infected. In South Africa, the prevalence is about 20% (USAID, 2005). In the last decade, Antiretrovirals (ARVs), drugs used to treat HIV/AIDS have brought hope to so many people. In South Africa about 400,000 AIDS patients are on ARVs. For ARVS to be most effective patients have to take them continuously without breaks, and for life. Break in continuity of ARVs taking is a major problem in many Antiretroviral Therapy (ART) clinics in South Africa. The major consequences are resistance development, more expensive therapies and more laboratory tests, more side-effects, diet restrictions and consequent change in therapy schedules and hence failure to meet ART goals. This study attempts to establish, describe the extent of the problem and investigated the effects of these breaks in ART on the last CD4 as measure of treatment outcome.

This research report has five chapters. This chapter contains the introduction, statement of the problem, literature review and aims of the study. Chapter 2 describes the methodology, while Chapter 3 presents the results. Chapter 4 gives the discussion while Chapter 5 contains the conclusions drawn, recommendation and suggestions for further research.

Introduction

HIV/AIDS is a global pandemic with more than 33.7 million people living with HIV/AIDS by the end of 2007 (Global HIV/AIDS, 2007). Mortality is estimated to be 3.1 million. Up to 63% of these infections are believed to be in Sub-Saharan Africa with a mortality of 2.1 million. This represents 72% of all deaths in the world (New Vision, 2007). Over the last 5 years, use of Antiretrovirals (ARV's) in Southern Africa

has improved. By 2006, more than 1 million were receiving ARV's leading to reduced HIV-related morbidity and mortality (Lima, et al., 2007).

A significant number of these patients are receiving ARV's from public health facilities as majority are from the poor communities who may not have medical aid benefits or cannot afford private services. Currently, ARVs are the most effective mode of treatment for HIV/AIDS. For maximum benefit, ARVs are taken continuously without interruption. This has been shown to increase life expectancy of affected people by many years though the overall survival is not well known (Sungkanuparph, et al., 2008). However, since ARVs do not cure HIV/AIDS, they have to be taken for life time.

The challenge of taking medicines for life, without breaks in many chronic diseases is a major challenge. It is estimated that breaks in therapy for chronic diseases like hypertension, diabetes, and depression is common such that adherence ranges between 4 and 51% worldwide (WHO, 2003). Over a period of taking medicines a patients may break the continuity of taking these medicines. In some cases, where the patients develops side-effects or is not responding well to treatment, clinicians may cause a break in that therapy (Schroeder et al, 2004).

The South African government recommends monitoring of patients on ARVs at least on monthly basis, and at most 6 monthly. Some patients may not always cope with taking medicines continuously, in other words they may break the continuity of taking ARVs. Break in ART is a major problem in achieving ART goals (Bangsberg, et al., 2001).

Interruptions in therapy continuity may either be a clinician's decision or a patient's decision. A clinician may cause a break in therapy because of side-effects or unsatisfactory CD4 count response. Patients' decision to cause a break in therapy may be classified as patient-related, therapy-related and health-provider related. Patient-related factors include stigma, time management, and loss of faith in medicines, traditional beliefs, boredom and wellness. Therapy-related factors

include patient experiencing side-effects, frequency of medicines in a day, nature and type of tablets. Care-providers-related factors lead to reluctance in the patient to come for review or collect medicines. All these factors may lead to a break in the continuity of taking ARVs (William, 1997; Muko, et al., 2004; Kerr, et al., 2005).

The first break in ART the continuity was described in two ways; *when* the break occurred after starting the ARVs, and for *how long* the first break lasted. This way of describing the first break was the first of its kind.

This study is secondary data analysis of those patients who had breaks in taking antiretroviral therapy and was aimed at finding the extent of the problem, describing these breaks, investigate the associated factors and suggested possible solutions. Break in therapy was defined as not taking ARVs for more than 10 days as observed by patient not coming for a refill for more than 10 days..

Statement of the Problem

This study was a secondary data analysis of patients with break in continuity of taking ARV's by patients as this was a major problem in many ART clinics. Reasons for these breaks were seemed to be medical-decision-related or personal-decision-related (side-effects, un-ending therapy, wellness) and less effective adherence counseling. The major consequences are resistance development, more expensive therapies and more laboratory tests, more side-effects, diet restriction and consequent change in therapy schedules. This defeats the whole purpose of starting antiretroviral therapy whose aim is decrease morbidity and mortality. The overall consequences are loss of family members, economic and social consequences.

Justification of Study

Since it is suspected that many patients had had a break in Antiretroviral therapy, these patients may not have been getting maximum benefits from therapy. This study attempted to establish the extent of the problem and investigated the effect of

these breaks on the last CD4 count. It was upon doing so, that effective and comprehensive corrective measures may be put in place. Any further delay in identifying the problem may have jeopardized chances of helping the patients. Resistance to antiretroviral therapy is costly in terms of life and resources, hence the need for such a study.. In addition, a study of this nature had not been done in South Africa.

Research question

What were some factors (demographic, clinical and laboratory factors) associated with failure, of more than ten days, to collect ARVs and what influence did these breaks in therapy have on the last CD4 count?

Null hypothesis

There was no association between break in antiretroviral therapy of more than ten days and the last CD4 count.

Literature Review

Antiretrovirals remain the current best available therapy for HIV/AIDS. However, they suppress viral multiplication but not completely eliminate the virus. Sustained viral suppression to cause improved immune function entails taking pills everyday, and for life without a break in the continuity of therapy. This may not be easy for some patients. Some patient's inevitably break this continuity and increasing the risk of therapy failure. When significant resistance of the virus to ARV's has developed, the viral load re-rises, destroying the immune system and opportunistic infections reappear. Serial measurements of viral load and CD4 count after many months of ART gives a good idea on progress of therapy and development of therapy failure (Nicca, et al., 2007).

Antiretrovirals are mainly in three classes. They work by blocking three different stages of the viral life-cycle. Taking of three types of ARV's per time, for life, and possibly facing side-effect raises chance of break in therapy continuity. Adherence is defined as taking of ARV's daily as prescribed without missing doses. Greater than 95% adherence is expected for ARV's to achieve best results (Nicca, et al., 2007). Recent studies have shown that different degrees of adherence have different effect on different classes of ARVs regarding resistance development. Resistance occurs at adherence of greater than >90% in patients a protease inhibitors, while for Non-nucleoside reverse transcriptase inhibitors, resistance occurs at moderate levels of adherence (Bangsberg, 2004).

When ARVs are started, viral load declines, within 4-8 weeks by at least 1 log as long as there is no break in taking of ARVs. Treatment success may be described as a decline in the viral load to less than 400 copies /ml ('undetectable') after commencement of therapy. If, while on treatment the viral load rises to greater than 1000 copies/ml treatment failure is suspected and adherence counseling is emphasised to the patient. If 3 months later the viral load is still above 1000 copies/ml, virologic failure is confirmed (Sungkanuparph, et al., 2006). CD4 count is more widely available than viral load because it is cheaper. After rising, it tends to start dropping when the viral load rises to over 10,000 copies/ml. Break in taking treatment continuously is the most important cause of rise in viral load and is associated with rapid deterioration to AIDS and death (Schrooten, et al., 2004).

A break in taking of ARVs may either be a medical decision by the clinician or personal decision by the patient. A clinician may stop ARVs because of side-effects (e.g. lactic acidosis, peripheral neuropathy) or when there is no satisfactory benefits from the regiment the patient is on e.g. when while already on ARVs, the CD4 count falls below the initial CD4 count. On the other hand, the patient may break the continuity of therapy because of stigma, time management, and reduced faith in medicines, traditional beliefs, boredom and wellness. Patient -related breaks may also be therapy-related as in patient experiencing side-effects, frequency of

medicines in a day, nature and type of tablets. Care-providers-related factors lead to reluctance in the patient to come and collect medicines. A break in continuity of therapy due patient decision is referred to as failure to adhere to therapy**.** Adherence is the correct taking of ARVs without a break. It remains one of most important challenges for both patients and the health-care providers. Adherence of more than 95% translates to not missing more than a days' dose in a month, or not more than 12 days in a year. Health-care providers only hope that patients are taking the medicines in their homes. The limited role of health-care providers, in this regard, is to emphasise on adherence during each visits. Breaks in ARVs taking continuity are well associated with rapid deterioration to AIDS (Ickovics & Meade, 2002; Overview Medication, 2006).

Health care-provider-related factors include positive and supporting relationship between medical staff and the patient, perceived competence of staff, non-judgmental approach if a patients breaks the taking of medicines, unreliable services e.g poor communication, lack of information about services, expensive services and shortage of basic medications (Godin, et al., 2005). *Condition-related factors* are mainly the physical and psychological effects of a chronic incurable disease (Singh, et al*.,* 1996). *Therapy-related factors* include side-effects of ARVs, taste and frequency of taking medicines and difficult-to-follow regimens (Murphy, et al., 2004**;** Schönnesson , et al., 2006). Socio-demographic or psychosocial factors are generally not the main determinants leading to breaks in therapy though some studies have showed that higher economic status, male sex, better patient literacy have been associated with better adherence (Wolf, et al*.,* 2005). Psychosocial factors include forgetting to take pills, problems in fitting in personal daily programs, embarrassment to collect medicines, associated side-effects, medication type and faith in efficacy of the medicines (Olubusoye & Meshesha, 2008). Alcohol, active drug use and mental disorders are also associated with poor adherence (Harzke, et al., 2004; Ingersoll, 2004; Uldall, et al, 2004; Hosek, et al*.,* 2005; Begley, et al., 2008).

Interventions to minimize break in therapy are classified as modified DOTS (Directly Observation Therapy Strategy), behavioral and affective intervention and cognitive interventions. This refers to giving enough information about the importance of taking ARV's daily so that the person's attitude and behavior accepts ARV's as part of their lives. These interventions may either be individualized, or where there are so many patients on ARV's due to high prevalence of HIV, as the case in South Africa, careful patient preparation prior to therapy is most appropriate (Heyer & Ogunbanjo, 2006).

After extensive search, there were literally no studies to the best of my knowledge which have described the first break in therapy and *when* it occurred, and for *how* long this first break lasted. Available literature describes treatment interruption which may be structured (STI) or unstructured. Other literature extensively discusses adherence and its determinants. These interruptions were planned and agreed upon between clinician and patients. The advantages included reduced risk of side-effects. However STI were banned because of the danger of resistance development. When treatment is interrupted the viral load rebounds over a few months and the CD4 count progressively drops, though the rate is unpredictable but the AIDS disease progresses. These interruptions are even more risky when the CD4 counts are very low (Gulick, 2002; Youle, M., 2002; Chesney, M.A., 2000).

From clinical experience omitting taking of medications for more than three days in a month and twelve days in a year has negative effects on the treatment outcome as it increases the chances of treatment failure. The proxy marker of success ART is the rising CD4 count done at six monthly intervals and the undetectable viral load. Though the CD4 count is used to monitor ART, it is less informative than CD4/CD8 ratios. Since CD4 counts are done at specific time intervals, a survivals analysis would provide more useful information.

Aim

The aim was to investigate the last CD4 count levels in patients who had a more than ten days break in the taking of Anti-Retrovirals, at the largest HIV/AIDS clinic in Johannesburg, South Africa from 2004 to 2008.

Objectives

The objectives were;

1. To describe the first break in ARV therapy continuity in terms of *when* the first break occured and the *length* (in days) of the first break in therapy.
2. To determine the demographic, clinical and laboratory factors associated with the first break in therapy, and
3. To investigate the association between first break in ARVs continuity and last CD4 count.

CHAPTER 2

METHODOLOGY

The previous chapter of this report started with the introduction and went on to describe briefly the problem with antiretroviral therapy and also the break in the continuity of taking therapy. The chapter further stated the aim of the study and its justification.

This chapter describes the methodology of the study. This includes description of the study population and data set, study design, sampling strategy, and sample size. A description of variables, limitations, and plan for utilization and dissemination of results, ethical issues, data management and statistical analysis are also presented.

Study population

The population under study was patients within the city of Johannesburg who were receiving Antiretroviral therapy services at *Themba Lethu* clinic, which is the largest HIV/AIDS clinic in Johannesburg. The clinic, located at Helen Joseph Hospital, started in 2004 and provides care to about 15,000 HIV-positive patients of whom 11,000 were on ARV's as of June, 2008. They comprised adults of either sex. Only adults above 18 years were included. A larger proportion of these patients were females. Unemployment was high. ARVs and other health services were provided at no charge. These patients were reviewed on specific scheduled days, although those who were not scheduled were also attended to.

Data Set Description and Data collection

The *primary data* set was longitudinal data from *Themba Lethu* ART clinic. The period covered was from March 2004 to July, 2008. This data was abstracted from the *Therapy Edge* database. Only data which was required for this study was abstracted. There data was not linked to any names of patients. There were about 15,

892 patients, of which 10,788 were on ARV's and 5,104 were not on ARVs. When patients were started on ARVs they were seen every two weeks for the first 1 month and monthly for the first 3 months. Thereafter, the reviews were two monthly up to the 6th months of therapy. After the 6th month, patients were seen at three months intervals. The first review was for collection of ARVs and tolerability of ARVs evaluation and adherence counseling. The second review was to monitor tolerability of ARVs and also for collection of ARVs. This type of review was repeated monthly for the first three months. Thereafter, it was bi-monthly until the 6th months. At this stage, patient review was similar to previous monthly reviews except that the CD4 count was also done.

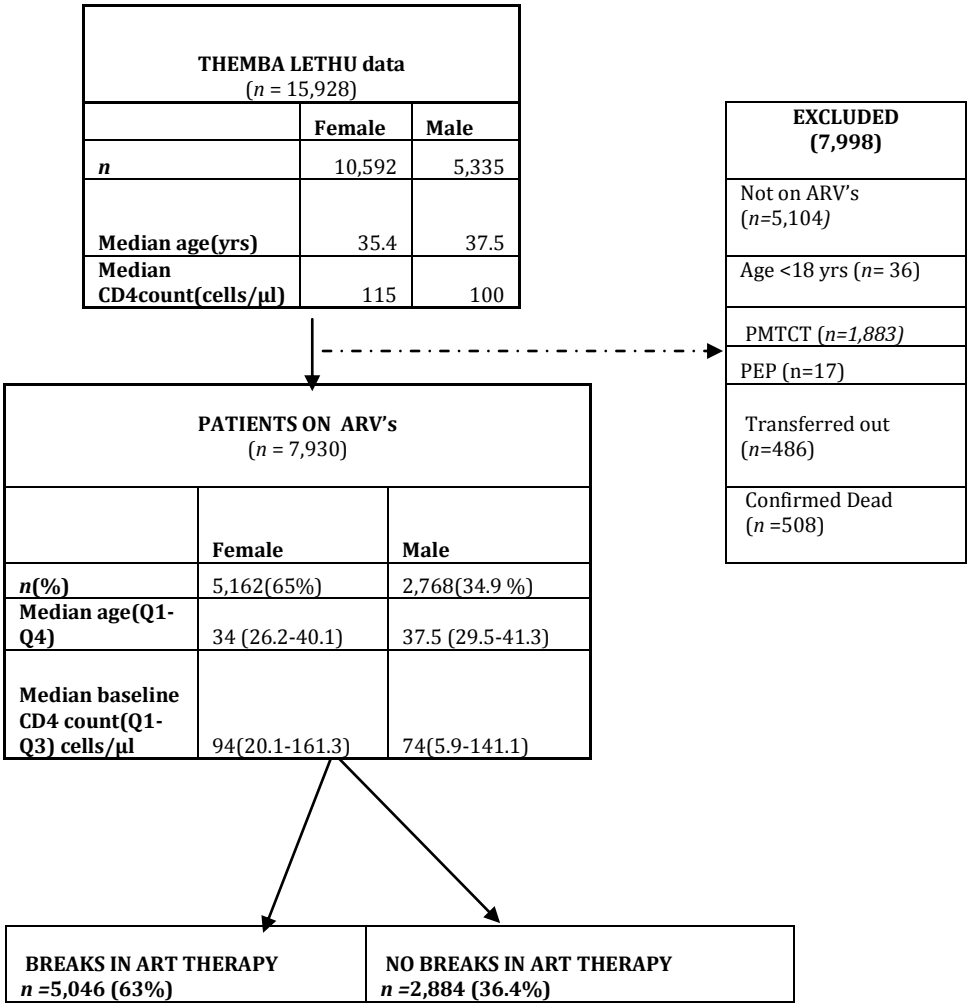
Demographic data which included Name of patient, age, Sex, residential address, employment status was collected at the initiation of ART and updated whenever necessary e.g. when patient changes job or residence. Clinical data which included weight of patient, height of patient, WHO staging of HIV disease, presence of opportunistic infection e.g. tuberculosis, and HIV complications were collected mostly during the initial visit. During reviews a set of standard questions were asked with an aim of detecting opportunistic infection e.g. Pulmonary Tuberculosis. Laboratory data included kidney function tests, Liver function tests, haemogram and whether female patient is pregnant. Data were collected on all the visits in the first 6 months, except for CD4 count which is collected at initiation of therapy and at 6 monthly intervals. Viral load was collected at initiation of therapy and whenever clinical needs dictated, e.g. suspected ARVs resistance.

Data were cleaned, sorted and coded in STATA 10. Descriptive statistics were used to help summarise the data. For categorical variable proportions and percentages were used while for continuous variables mean, median and standard deviations were used to describe the data. Key variables were examined for errors and corrected (Cleaning data, 2003). Analysis was done in STATA 10.

Data available for this study was secondary data from *Therapy age* database. This is the database for the cohort of patients on ARVs at Themba Lethu clinic. The data is

safely stored in SAS. After permission from the hospital and ethical clearance from the Wits University Ethic Committee data was made available for analysis. THE data was transferred to STATA 10 through software called Datatrans 11. Firstly, all data was in 'wide' and not 'longitudinal' format. All efforts to collect time-series data proved futile. This made it impossible to analyse time-series information, for instance six-monthly CD4 counts. Secondly, only data on first break in the continuity of therapy was available. There was no information on all other breaks. What was available was cumulative days of not coming to collect ARVs.

Figure 2.1: Diagram showing the process of exclusion of patients on ARV's at Themba *Lethu clinic*, 2004-2008



Study design

The study used secondary data from a of longitudinal (cohort) study of patients on Antiretroviral therapy. The *Inclusion criterion* for analysis was; Adults 18 years and above, either sex and patients with a CD4 count less than 350 cells/µl at initiation of ARV therapy.

The *exclusion criterion* was; all the patients not on ARVs, patients on antiretrovirals for Prevention-of-Mother-to-Child transmission (PMTCT), those on Post –Exposure-Prophylaxis(PEP), transfer-outs and the confirmed dead.

A break was said to have occurred if a patient did not come for more than 10 days to collect medicines after the scheduled date. The days were calculated by subtracting the 'actual day of coming to clinic' from the 'scheduled appointment date'. 10 days was used instead of 7 because of some patients who missed their Friday appointments were rescheduled for the next Monday.

The patients who had not missed any scheduled appointments were the control (comparison) group.

The break under study was the first break in antiretroviral therapy and was described in two ways; the time taken, in days, from initiation of ARVs up to when the first break in taking ARVs occurred, and the length of the first break. Time on therapy before the first break was the period, in days, from the day the patient started ARVs to the time the interrupted therapy of more than 10 days occurred for any reason. This period was categorized into 6 monthly intervals; 0-<6 mo, 6-<12, 12-<18 mo, 18-<24 mo and >24 months.

Length of first break was the period, in days, from the time the ARVs were interrupted for more than 10 days, for any reason, to the time the patient resumes taking ARV. The categories were 10-30, 31-60, 61-120, 121-180. These were based

on the expected scheduled appointments. Those who has missed appointments for that 180 days were listed as confirmed loss-to-follow-up and were excluded.

Patients on PEP only took ARVs for 1 month, while those on PMTCT took Nevirapine as a single dose, hence their exclusion from the study. Patients who had a break in therapy more than 180 days were also excluded as these were considered as confirmed loss to follow-up.

Sample size and Sampling Strategy

Based on the inclusion and exclusion criteria the total sample size for analysis was 8,316 patients of whom 5,428 (65%) had a break in the continuity of taking ART while 2,888(35%) had no break in the continuity of taking ART. All patients who met the criterion were included in the study for analysis.

Variables

The predictor variable was the break in the continuity of taking ARVSs, described as 'duration on ART before the first break' and 'length of the first break'.

The main outcome variable was the last CD4 count (cells/µl). The range was 0 to 1200 cells/µl. Medians and inter-quartile ranges were used to describe this variable. Key variables that were investigated for association with last CD4 count were: Sex (Male/female); Age (Years) at initiation of therapy; Baseline BMI (Kg/m^2); Baseline CD4count (cells/µl) and Baseline hemoglobin (mg/dl); Employment status(Yes/No); Clinical WHO staging of HIV/AIDS (I, II, III or IV); Tuberculosis at initiation of ART (yes/No); Milliary Tuberculosis at initiation of ART(Yes/No); Total Incidence (episodes) of Tuberculosis after ART (0,1,2, 3); Peripheral neuropathy at the initiation of ART (Yes/No); Total Incidence (episodes) of peripheral neuropathy after ART (0,1,2).

Statistical Analysis

Descriptive and inferential statistics were done partly in SAS but mainly in STATA v10. All analyses were conducted at 5% significance level.

Descriptive Analysis

Descriptive statistics such as median and standard deviation were used to describe continuous variables. Proportions and percentages were used to describe categorical variables. Continuous variables were Age (Years) at initiation of therapy, Basal Metabolic Index (BMI) (Kg/m^2), Baseline CD4 count (cells/µl), Baseline hemoglobin (mg/dl), duration (months) on therapy before the first break and length (days)of the first break. For all variables median and inter-quartile range were used to describe since they had a non-Gaussian distribution.

Categorical variables were Sex (Male/female), Age (years) at initiation of ART (<25-29, 30-35, 40-44, 45-49, 50-54, >55 yrs), Employed (Yes/No), Baseline CD4 count (cells/µl) categories (0-49, 50-99,100-149, 150-199>200). WHO staging of HIV/AIDS (I, II, III or IV), Tuberculosis at initiation of ART (Yes/No), Total Incidence (episodes) of Tuberculosis after ART initiation (0 (None),1,2 or 3), Peripheral neuropathy at the initiation of ART (Yes/No), Total Incidence (episodes) of peripheral neuropathy after ART initiation (0,1,2) Milliary Tuberculosis at initiation of ART(Yes/No), break in continuity of therapy (Yes/No), when the first break occurred after starting therapy (months)(<6, 6->12, 12-<18, 18-<24, ≥24mo.) and length (days) of break (<30, 30-<60, 60-<90, 90-<120, 120-<180, >180 days). Proportions and percentages were used to describe these variables.

Inferential Analysis

The break in the continuity of taking ARVS was described in details in two ways namely*:* Period (Time taken) before the first break and length of the first break.

Period (Time taken) before the first break:

Fisher's exact test was used to compare the difference in time taken before the first break in therapy between males and females, for different age groups, CD4 categories and employment status. In this case, the period taken before the break in the continuity of taking ARVs was categorised in months. Chi-square test was used to determine its association with Sex, age-groups, CD4 categories and employment status. Spearman's correlation was used determined the relationship between the period before the first break and Baseline CD4, Baseline BMI.

To determine which baseline factors (demographic, laboratory and clinical factors) were associated with the period before the first break in therapy (since this period had been categorized into 6 monthly intervals) multiple logistic regression was used to do this. The factors studied were Sex (Male/female); Age (Years) at initiation of therapy; Baseline BMI (Kg/m^2); Baseline CD4 (cells/µl) and Baseline hemoglobin (mg/dl); Employed (Yes/No); WHO staging of HIV/AIDS (I, II, III or IV); Tuberculosis at initiation of ART (yes/No); Milliary Tuberculosis at initiation of ART(Yes/No); Total Incidence (episodes) of Tuberculosis after ART (0,1,2, 3); Peripheral neuropathy at the initiation of ART (Yes/No); Total Incidence (episodes) of peripheral neuropathy after ART (0,1,2). Interactions which were statistically significant were incidence of peripheral neuropathy while on ART/baseline BMI, previous peripheral neuropathy/baseline hemoglobin, Age at initiation of therapy/incidence of tuberculosis after initiation of ART, baseline hemoglobin/incidence of tuberculosis. These were thus included in the final equation.

Length of the first break

Fisher's exact test was used to compare the difference in time taken before the first break between males and females, for different age groups, CD4 categories and employment status. In this case, length of the first break was categorized. Chi-square test was used to determine its association with Sex, age groups, CD4 categories and employment status. Spearman's correlation was used to determine the relationship between length of first break and Baseline CD4 and baseline BMI. Multiple logistic regressions was used to determine the relationship of length of first break in therapy(since it was categorized into intervals of 30 days) and baseline demographic, laboratory and clinical factors as mentioned above. Interactions between previous pneumonia, baseline hemoglobin, baseline BMI and WHO stage with length of first break were analysed.

Association of break in the continuity of therapy and the last CD4 count

To determine the association of duration before first break and the last CD4, multiple linear regressions was used. Demographic, laboratory, and clinical factors under study were checked for confounding and interactions. The following association were investigated; last CD4/incidence of peripheral neuropathy after ART initiation, baseline Cd4/employed, baseline Cd4/baseline hemoglobin, incidence of peripheral neuropathy/baseline CD4, sex/ Baseline BMI, Sex/WHO stage, Employed/hemoglobin, CD4_baseline/WHO stage, WHO stage/ baseline hemoglobin.

Limitations of the study

There were a number of limitations to this study.The primary problem was the limitation of the secondary data. The data was primarily collected for daily care of patient and with different intentions. Firstly, the data on breaks in therapy which was available was for the first break only. Analysing the frequency of breaks was not possible because the lengths of the breaks were already aggregated in days and

months, and it was not possible to know when other breaks than the first break occurred. Secondly, the last-CD4 count was used instead of serial measures of CD4 count because the latter were not available in the data set. The data set was in wide and not longitudinal format. Thirdly, though the viral load is more sensitive and an earliest indicator of failing regimen, it was not used in this study because only a few patients had viral load. This was so because it is an expensive test and not routinely done unless drug resistance is suspected. A sub analysis would be useful in this case.

Another limitation of the study was what constituted a 'breaks' in therapy using the method of missing appointments. This may not have been true for every patient. Not missing appointments did not equate to not breaking therapy while at home. Another limitation was where the break was very long e.g. more than two years. These spread out the data and weakened analysis (very wide standard deviation).

There were a small number of patients with more than one break in ART. If these breaks were significant, this inevitably affected the last CD4 count and possibly negatively. There were also some patients who had less than less than 10 days of break, but these breaks were more than one. Thus, it is possible that cumulatively, these breaks may have been significant and may have had a negative influence on the last CD4 count. The last CD4 value is dependant of the previous series of CD4 counts. Thus, using last CD4 count as outcome measures may not be as accurate as using a series of CD4 done at different time intervals during the course of ART therapy.

Ethical Considerations

All individuals in the secondary data were identified by unique identification codes, such that researchers were not able to identify individuals in the samples by name. Permission to use the data was sought from the authorities of Helen Joseph Hospital where Themba Lethu clinic is located (see Annex A). The Protocol was submitted to,

and permission sought and approval given from the University of Witwatersrand Committee for Research on Human Subjects.

The data was not in any way shared with non-researchers or used for other purposes than for the sought permission. Results of this study would be made available to the health-care providers and appropriate authorities for the purpose of improving care of the patients.

CHAPTER 3

RESULTS

The previous chapter described methods used in the study. This chapter describes results, and is divided in two parts. The first part describes the first break in taking of antiretroviral therapy and factors (demographic, laboratory and clinical) associated with the first break in taking the antiretroviral therapy. The second part deals with the association of the first break in taking antiretroviral therapy and the last CD4 count.

PART 1

DESCRIPTION OF THE FIRST BREAK IN ART

The first section describes baseline characteristics of patients with the first break in therapy, while the second part gives detailed description of the first break in terms of *when* it occurred and *how long* the break in therapy lasted.

Baseline characteristics of patients with first break in treatment with ARVs

There were a total of 7,930 patients included in the study after applying the inclusion and exclusion criteria. Majority of these patients were females (*n*=5,162(65%)) *vs.* (*n*=2,768(34.9 %)). The median age at the initiation of antiretroviral therapy for females was 34 (26-41.8) years and 37.5 (29.1-45.2) years for males. The median baseline CD4 count for females was 94(21-166) cells/µl and 74(2.5-143) cells/µl for males.

Comparing patients who had a break in taking of ARVs to those who had no break in taking of ARVs, majority (*n* = 5,046 (63.6%)) had a break in the taking ARV's, while only (*n* =2,884 (36.4%)) did not have any breaks. Among the patients with breaks, majority were females (*n*= 3,259(64.6%)) *vs*. (*n*= 1,787(35.4%)). There were also more females (*n*=1,903(65.9%)) than males (*n*=981(34.0%)) among patients without breaks in therapy. There were no significant differences between the two

comparison groups in the ages at initiation of therapy, sex , baseline BMI, baseline CD4 count and the overall duration on Antiretroviral therapy, However, there was a statistically significant difference in employment status (p=0.04), (Table 3.1).

Table 3.0: Table showing baseline characteristics of patients with and without first breaks in taking of Anti-retroviral therapy

		BREAKS	NO BREAKS	Total	P value
		***n*=5,046 (63.63%)**	***n*= 2,884 (36.37%)**	***n*=7,930 (100%)**	
Age (median(Q1-Q3)) years		35.3 (30.3-41.4)	35.6 (31.1-41.9)	**35.4 (30.6-41.5)**	**0.10**
Sex	Female *n* (%)	3,259(64.6)	1,903 (65.9)	**5,162 (65.1)**	**0.09**
	Male *n* (%)	1,787(35.4)	981(34.0)	**2,768 (34.9)**	
Employment status (%)	Unemployed	3,036(60.1)	1,590(55.1)	**4,626 (58.3)**	**0.04**
	Employed	2,010(39.8)	1,294(44.8)	**3,304 (41.7)**	
Baseline BMI (median(Q1-Q3))kg/m^2		21.4 (18.9-24.7)	21.8 (19.3-25.1))	**21.6 (19.0-24.9)**	**0.25**
Baseline CD4 (median(Q1-Q3))cells/µl		83(29-153)	91(36-160)	**86 (32-155)**	**0.08**
Duration on Antiretroviral therapy (Median (Q1-Q3)) days		764 (406-1122)	737 (421-1106)	**756 (414-1115)**	**0.99**
Age of patients(years) at initiation of therapy	**<25**	302 (5.98)	155 (5.37)	**457(5.76)**	0.01
	25-29.9	890 (17.64)	413 (14.36)	**1304(16.44)**	
	30-34.9	1248(24.73)	774(26.84)	**2022(25.50)**	
	35-39.9	1097(21.74)	634(21.98)	**1731(21.83)**	
	40-44.9	714 (14.15)	418 (14.49)	**1132(14.27)**	
	45-49.9	399 (7.91)	243(8.43)	**642(8.1)**	
	≥50	396 (7.85)	246(8.53)	**642(8.1)**	
	Total	**5046(63.63)**	**2884 (36.37)**	**7930(100)**	
CD4 count (cells/µl)	**0-49**	1804(35.75)	928 (32.18)	**2732(34.45)**	0.011
	50-99	1020(20.21)	628 (21.78)	**1648(20.78)**	
	100-149	908(17.99)	508 (17.61)	**1416(17.86)**	
	150-199	865(17.14)	535 (18.55)	**1400(17.65)**	
	≥200	449(8.9)	285 (9.88)	**734(9.26)**	
	Total	**5046(63.63)**	**2884 (36.37)**	**7930(100)**	
	Q1-Q3 Quartile Range; BMI Body Mass Index				

The median duration on Antiretroviral therapy for patient who had the first break in therapy was 764(406-1,122) days while for patients without first break in therapy it was 737(421-1,106) days. There was no statistically significant difference in duration on therapy between the two comparison groups (p=0.99) (for details, see Table 3.1).

Age at initiation of therapy and baseline CD4 count were categorised for a more detailed description. Age was categorised into <25, 25-29, 30-34, 35-39, 40-44, 45-49 and ≥50 years. Majority of patients on ARVs were younger patients, with peak ages between 30-34 and 35-39 years irrespective of whether with or without break in therapy. The smallest proportions of patients were <25 years for both those with breaks in treatment (n=302 (5.98%)) and those without break in treatment (n=155 (5.32%)). Differences in proportions of patients in different age groups between those with and without breaks was statistically significant (p=0.01).

The baseline CD4 count was categorised into 0-49, 50-99, 100-149, 150-199 and ≥200 cells/µl. The proportions of patients decreased as the CD4 count increased for both those with breaks and those without breaks in therapy. The largest proportions of patients were in the CD4 count category of <49 cells/µl. The smallest proportions (n= 449 (8.9%) with breaks *vs*. n= 285(9.8%) without breaks) were patients in the CD4 count category of ≥200 cells/µl. The differences in proportions in the comparison groups were statistically significant (p = 0.01), (Table 3.1). There was also a statistically significant difference in proportions between females and males in all CD4 count categories in comparison groups (p=0.01).

There were some sex differences among patients with breaks and those without breaks in therapy in the baseline Basal Metabolic Rate (BMI). The median baseline BMI for the females was higher 22.50(16.9-29.2) (n=2,526) than for the males with 20.0(16.0-22.9) (n=1,386), and was statistically different (p=0.01).

Detailed description of the first break in ART

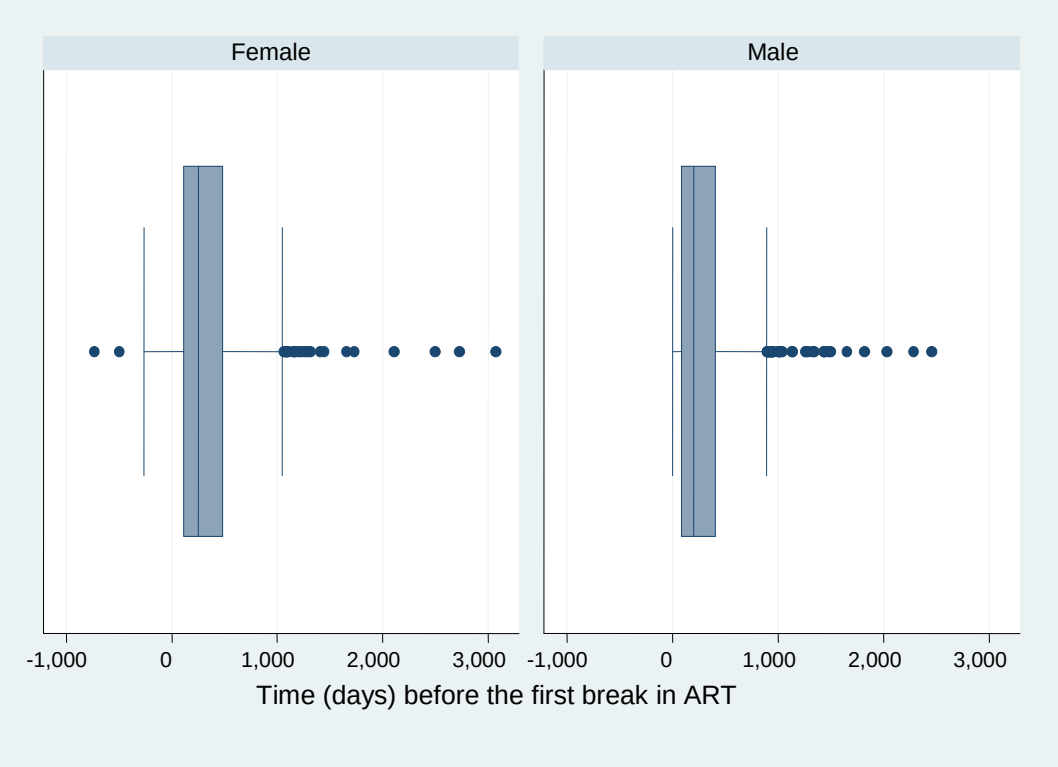
This section gives a detailed description of the break in the ART continuity. Firstly, the section describes *when* the first break in ART continuity occurred after ART initiation (Period before the first break in ART). The second part describes how *long* the first break lasted (duration of first break in therapy).

Description of *when* the first break occurred, after initiation of ART

The median time, in days, taken for a patient to have a break after starting ARVs was 234 (39-501) days. Female patients took longer to break treatment continuity than their male counterparts (254 (21-499) days *vs*. 203 (03-462) days). This difference was statistically significant (p = 0.01). With respect to when the break occurred and the total period on ART, both female and male patients had a break in therapy within the first half of the entire duration on therapy, though there were more male (skewness =2.13, kurtosis=11.8) breaking earlier than female (skewness = 1.59, kurtosis=10.7) patients. Majority of the patients with a break in therapy (n=1,219 (26.78%)) were aged between 30 and 34 years and minority (n=271, 5.95%) were those less than 25 years of age. The second largest proportion (n = 989 (21.73%) were patients aged between 35 and 39 years of age. However, these age groups were of not statistically different from one another (p=0.10).

The CD4 count was categorized into 0-49 cells/µl, 50-99 cells/µl, 100-149 cells/µl, 150-199 cells/µl and >200 cells/µl. These categorized represented strengths of the immune system. The lower the CD4 count the weaker the immune system. Out of 4,552 patients who had a first break in treatment, proportions of patients decreased as the CD4 count increased. In other words, the lower the CD4 count the larger the number of patients in that category. Majority of patients (n=1,544 (33.92%)) had CD4 count less than 49 cells/µl and minority had the CD4 count more than 200 cells/µl (n=400 (8.79%)). The difference of these categories was statistically significant (p=0.01).

Figure 3.0: Graph showing the skewed distribution of duration/Time taken by patients before the first break in ART continuity



The World Health Organization (WHO) HIV/AIDS clinical stage has four stages (I to IV) with higher score reflecting more severe immunosuppression. Stage I had the highest number of patients (2,446 (53.73%)), while stage 2 had the smallest (91 (2.00%)). Stage 3 was the second highest (1,610 (35.37%)) and stage 4 had 405 (8.90%) patients. These clinical stages were statistically significantly different (p=0.01) from each other.

Out of 4,537 observations of patients who had baseline BMI readings, a look at the relationship between baseline BMI between *when* the first break occurred showed a positive relationship . It can be concluded with 95% confidence that an increase in

the BMI by 1 kg /m^2 had a 3.02 (range 1.47 to 4.59) days' increase risk of breaking therapy. This relationship was statistically significant (p=0.01).

There were 4,552 patients whose employment status was known. There were more unemployed (n= 2,689 (59.1%)) *vs*. (n=1,863(40.9%)) employed patients. The median time taken before the first break in ART therapy for the unemployed was longer, 255 days (11-512) days compared to the median time taken to have a break among the employed, 216 days (5-445 days). This difference in time taken before the patient had the first break in their ART therapy between the employed and unemployed was statistically significant (p=0.01).

Characteristics of patients in different periods of *when* the break occurred

From the time patients start taking ARVs, a break in treatment may occur at any stage. Period in which these breaks could occur were grouped in 6 monthly intervals up to 2 years, and thereafter. The 6 monthly intervals were chosen because they are related to matters of treatment, ART side-effects, patients' clinical reviews, CD4 count measurement and monitoring of ART resistance.

Comparing the first two years of therapy and thereafter, majority of the patients (n = 2,701(53.5%)) had their first break in therapy after 2 years. Otherwise, for the remainder of patients the break occurred within the first two years. This first two years was further divided into 6 monthly intervals. The Largest group (n=1,144(22.7%)) had a break in therapy within the first 6 months of antiretrovirals therapy. The proportion of patients having breaks progressively decreased. Thus smallest proportion (n=249(4.9%)) of patients had a break between 18 and 24 months of therapy. The differences in the break periods were statistically significant for sex (p=0.01), Age at initiation of therapy (p= 0.01), CD4 count (p =0.03), baseline BMI (p=0.01) and employment status (p = 0.01), (Table 3.1).

Table 3.1 describes the characteristics of patients who had their first break in the first 6 months of therapy. In this period, there were a total of 1,144/ 5,046 (22.7%),

Table 3.1: Table showing characteristics of patients in different periods of *when* the break in ART after initiation

		Period when the break in treatment occurred (months after therapy)					
		<6	**6- <12**	**12-<18**	**18-<24**	**≥24 mo**	**Total**
Sex	**Female *n* (%)**	705(61.6)	354(65.7)	287(69.5)	181(72.7)	1,732(64.1)	**3,259(64.6)**
	Male *n*(%)	438(38.4)	185(34.3)	126(30.5)	68(27.3)	969(35.9)	**1,787(35.4)**
	Total *n* (%)	**1,144(22.7)**	**539(10.7)**	**413(8.2)**	**249(4.9)**	**2,701(53.5)**	**5,046(100)**
		***p*=0.01**					
Age at initiation of therapy (years)	**<25**	65(5.7)	47(7.9)	17(4.1)	8(20)	165(6.1)	**302(6.0)**
	25-29.9	199(17.4)	88(14.8)	86(20.8)	43(10.9)	474(17.53)	**890(17.6)**
	30-34.9	285(24.9)	138(23.2)	118(28.6)	76(30.5)	631(23.4)	**1,248(24.7)**
	35-39.9	263(23.0)	125(21.0)	60(14.5)	51(20.5)	598(22.1)	**1,097(21.7)**
	40-44.9	167(14.6)	63(10.6)	57(13.8)	36(14.5)	391(14.5)	**714(14.2)**
	45-49.9	77(6.7)	45(7.6)	34(8.2)	21(8.4)	222(8.2)	**399(7.9)**
	≥50	88(7.7)	88(14.8)	41(9.9)	14(5.6)	220(8.1)	**396(7.9)**
	Total	1,144(100)	539(100)	413(100)	249(100)	2,701(100)	**5046(100)**
		***P*=0.01**					
Baseline CD4 count (cells/ μl)	**≤49**	415(36)	192(36)	142(34)	82(33)	973(36)	**1,804(35.8)**
	50-99	230(20)	125(23)	77(19)	68(27)	520(19)	**1,020(20.2)**
	100-149	195(17)	84(16)	94(23)	50(20)	485(18)	**908(18)**
	150-199	208(18)	96(18)	65(16)	34(14)	462(17)	**865(17.1)**
	>200	96(8)	42(8)	35(8)	15(6)	261(10)	**449(8.9)**
	Total	1,144(100)	539(100)	413(100)	249(100)	2,701(100)	**5,046(100)**
		***P*=0.03**					
Average baseline BMI (kg/m^2)		914(23.4)	445(11.4)	355(9.1)	212(5.4)	1986(50.8)	**3,912(100)**
		***P*=0.01**					
Employed	**no**	680(59.4)	299(55.5)	276(66.8)	171(68.7)	1,610(59.6)	**3,036(100)**
	yes	464(40.5)	240(44.5)	137(33.2)	78(31.3)	1,091(40.6)	**2,010(100)**
	Total	1,144(100)	539(100)	413(100)	249(100)	2,701(100)	**5,046(100)**
		***p*=0.01**					

making it the largest proportion of patients on with a break in therapy. Patients on ARVs constituted the largest proportion in the first two years of therapy. Majority were females (*n*=705(61%)) *vs*. 438(38.4%) males, and the groups were statistically significantly different (*p*=0.01). The largest proportion (*n*=285 (24.9%)) of these patients were 30-34.9 years of age followed by 35-39.9 years (*n*= 263(23.0%)), and these age groups were significantly different statistically (*p*=0.004). There were

more unemployed (*n*=680/1,144, (59.4%)) than employed (464/1,144, (40.5%)) patients (*p*=0.01). As regards the CD4 count, proportions of patients decreased as CD4 count rose. The largest proportion ((*n*= 415 (36%)) of patients had a baseline CD4 count less than 49 cells/µl followed by those with 50-99 cells/µl (20%). The CD4 categories were a statistically significant difference (*p*=0.03). For further details refer to table 3.1.

There were a total of 539/5,046(10.7%) patients who had the first break in treatment between 6 and 12 months of starting therapy, constituting the second largest proportion. Majority (*n*= 354(65%) were females. The largest proportion of patients were in the age group 30-34.9 years (*n*= 138 (23.2%)) followed by those between 35-39.9 years (*n*= 125(21.0%)). As regards CD4, proportions decreased as CD4 count rose. The largest proportion (*n*= 192 (36%)) of patients had a CD4 count less than 49 cells/µl followed by (*n*= 125, (23%) patients with CD4 count of 50-99 cells/µl. There were more unemployed (*n*=299(9.9%)) than employed (240(11.9%)) patients. For further details refer to table 3.1.

There were 413 (8.2%) patients on who had a break in therapy between 12 and 18 months accounting for the third largest proportion. Majority (*n*= 287(69.5%)) were females. Majority (*n*=118 (28.6%) were in the age group 30-34.9 years followed by a younger age group of 25-29.9 years (*n* = 86(20.8 %)). There were more unemployed (*n*=279(66.8%)) than employed (n=137(33.2%)) patients. Concerning the CD4 count, majority (*n*=142(34%) of patients had a count of less than 49 cells/µl followed by those with CD4 count of 100-149 cells/µl (*n*=94(23%)). For further details refer to (Table 3.1).

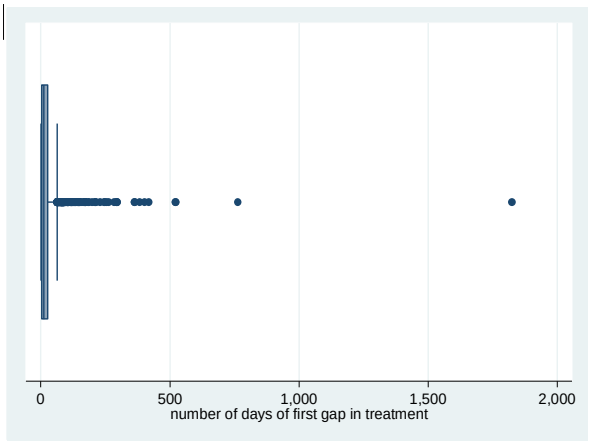
For the period in therapy between 18 and 24 months, only 249(4.9%) patient had a break of therapy. This constituted the smallest proportion of patients, with females (*n*=181 (72.7%)) still in the majority. Similarly, most were in the age group 30-34.9 years (*n*=76 (30.5%)) and between 35-39.9 years (*n* = 51(20.5%)). As regards the CD4 count, the proportions progressively decreased as CD4 count got higher. the

largest proportion (*n*= 82(33%)) of patients had a CD4 count less than 49 cells/µl followed by those with CD4 count of 50-99 cells/µl(*n*= 68(27%)). Most were unemployed (*n*=171(68.7%)) patients, (Table 3.1).

***How long,* the first break in therapy was**

The period under consideration was the period when a patient stayed away from collecting his/her ARVs for more than 10 days. The patient population for this analysis was 4,552. The median length of days on break was 11 (3-17) Days. This is above 10 days meaning that the patients was actually 21 days away. Patients who were away for more than 60 days were considered as 'suspected' loss-to-follow-up. This is so because some patients stayed away for so many days or months and suddenly reappeared in the ART clinic. So excluding those who had been on 'break' for more than 60 days (n=2,994) the 'gaps' (or absence from ART clinic to collect ARVs) look different. The median length of break was thus 19 (3-32) days.

Figure 3.1: Graph showing distribution of lengths (in days) of first break in ART



The association between length of first break and sex, Age at initiation of therapy, baseline CD4 count and employment status were studied. The longest first break (15 days) in therapy was among patient's ≥50 years of age, and the shortest break was among the age group 30-34.9 years of age. The association between length of first

break and the age group was statistically significant (p=0.05). As regards employment status 2,475/ 4,228 (58.5%) were employed while 1,753/4,228(41.5%) were not. The median length of break in treatment for the employed was 20 days (SD=4.1-35.9) while for the unemployed was 18 (2.2-33.8) days. There was a strong association (p=0.02) between length of first break and employment status. There was no strong association between length of first break and sex (p=0.20), baseline CD4 count (p=0.45), baseline BMI (p=0.18).

Factors associated with first break in ART

This section has univariate and multivariate analysis of factors associated with break in taking ARVs. They factors were patients demographic, laboratory and clinical factors.

Univariate analysis was used determine the association of break in continuity in therapy and each variable. Multiple logistic regression model was used to study the association with other factors controlled for. Results were used to construct a model to predict the occurrence of a break in ART treatment based on demographic (sex, age at initiation of therapy, employment status) and clinical (BMI, WHO HIV/AIDS staging, Tuberculosis at initiation of ART, military TB at the initiation of ART, peripheral neuropathy at the initiation of ART, Tuberculosis episodes after initiation of ART and episodes of periphery neuropathy after the initiation of ART. Table 3.4 shows the results of this analysis. Details of the methods can be found in Index 1.

There were 5,404 patients in analysis. Analysis was done at 95% confidence interval. Analysis of duration/period before the first break in therapy was analysed first. This was followed by the length of the first break in therapy.

Demographic factors studied to determine the associations with *when* the break occurred were sex, age at initiation of therapy and employment status.

Sex; The relationship between sex of patient and *when* the first break in taking of Anti-retroviral therapy would occur was compared. There was neither statistically significant association in univariate analysis (OR=1.1(95% CI: 0.95-1.24; *p*=0.20) nor after controlling for other factors (OR= 1.14(95% CI: 0.97-1.3; *p*=0.12).

*Age at initiation of therapy***:** The relationship between Age at initiation of therapy and *when* the first break in the continuity of Anti-retroviral therapy occurred was compared. There was no statistically significant association in univariate analysis between Sex and *when* the first break in the continuity of Anti-retroviral therapy occurred (OR=0.99(95% CI: 0.99-1.00; *p*=0.13)).

*Employment status***:** There was a statistically significant association between employment status and *when* the first break in taking of Antiretroviral therapy (OR=0.87(95% CI: 0.77-0.98; *p*=0.03). Controlling for other factors, this association was still statistically significant (OR= 0.87(95% CI: 0.78-0.98; *p*=0.02). Thus, the odds of breaking therapy were 1.2 times less likely if the patient was unemployed.

Clinical factors which were studied included baseline BMI, WHO HIV/AIDS clinical staging, Tuberculosis at the beginning of ART, Milliary tuberculosis at the beginning of ART, Peripheral neuropathy at the initiation of ART and Total incidence (episodes) of Peripheral neuropathy after initiation of ART.

*BMI***:** The relationship of baseline Basal Metabolic Index and *when* the first break in the continuity of Anti-retroviral of therapy occurred was neither statistically significant in univariate analysis (OR= 0.99(95% CI: 0.98-1.00; *p*= 0.11) nor after controlling for other factors (OR=0.064 (95% CI: -0.082 to 0.21; *p*= 0.39).

Table 3.2: Table showing univariate and multivariate analysis of the association between *when* the break in taking of ARVs and different demographic, laboratory and clinical factors

Variable		*Univariate Analysis*		*Multivariate Analysis*	
		OR(Confidence Interval)	***P-value***	*OR(Confidence Interval)*	***P-value***
Sex	Female				
	Male	1.1(0.95-1.24)	**0.2**		
Age at initiation of therapy (Years)		0.99(0.987-1.00)	**0.13**		
Baseline BMI (Kg/m^2		0.99(0.98-1.00)	**0.11**		
Employed	No	1	**1**	1	
	Yes	0.87(0.77-0.98)	**0.03**	0.87(0.78-0.98)	**0.02**
Baseline CD4 (cells/μl)		0.99(0.998-0.999)	**0.01**	0.94(0.94-0.99)	**0.01**
WHO HIV/AIDS Stage	I	1			
	II	0.93(0.60-1.45)	**0.76**		
	III	1.12(0.98-1.28)	**0.08**		
	IV	1.40(1.40-.1.74)	**0.01**		
Baseline hemoglobin (mg/dl)		0.99(0.96 to 0.995)	**0.02**	0.97(.94-0.99)	**0.01**
Tuberculosis at initiation of ART	None	1			
	Yes	1.07(0.90 to 1.27)	**0.46**		
	unknown	1.72(0.16 to 19.0)	**0.66**		
Total Incidence (episodes) of Tuberculosis after ART	None	1			
	Once	1.11(0.86 to 1.44)	**0.42**		
	Twice	0.38(0.12 to 1.2)	**0.11**		
Peripheral neuropathy at the initiation of ART	No(Ref)	1			
	Yes	1.04(0.69-1.5)	**0.81**		
Total Incidence (episodes) of peripheral neuropathy after ART	None (Ref.)	1	**1**		
	Once	0.83(0.7 to 0.97)	**0.02**	1.72(0.8-3.7)	**0.15**
	Twice	0.90(0.5 to 1.6)	**0.72**		
	Thrice	0.82(0.05 to 13.2)	**0.89**		
Milliary TB at initiation of ART	None (ref.)	1			
	Yes	1.44(1.1 to 1.94)	**0.02**	1.26(0.80-2.00)	**0.33**

WHO clinical staging: The relationship between WHO staging and *when* the first break in Anti-retroviral therapy occurred was compared. Univariate analysis was

done between WHO stages (with stage I as reference group) and *when* the first break of therapy occurred (OR=0.93(0.60-1.45; *p*=0.76) for stage II; 1.12(0.98-1.28; p=0.08) for Stage III. There was there was an association with stage WHO IV. However, this association was not statistically significant after controlling for other factors.

Tuberculosis at the beginning of ART: The association of *when* the break in antiretroviral therapy and patient having Tuberculosis at the beginning of ART, total episodes of Tuberculosis after starting ART and peripheral neuropathy at initiation of ART were also studied. There was no statistically significant association with *when* the first break in Anti-retroviral therapy occurred and the mentioned factors (Table 3.2).

Milliary tuberculosis: The association between having milliary tuberculosis at the beginning of ART and *when* the first break in Anti-retroviral therapy was studied. This association was statistically significant on univariate analysis (OR=1.44(95% CI: 1.1-1.94; *p*= 0.02) but not in multivariate analysis (*p*=0.33). The relationship between total incidence(episodes) of peripheral neuropathy after initiation of ART and *when* the first break in the continuity of Anti-retroviral therapy occurred showed a statistically significant association in univariate analysis (OR=0.83 (95% CI: 0.7-0.97; *p*=0.02) but not in multivariate analysis (p= 0.15).

Laboratory factors which studied included baseline CD4 count and baseline Hemoglobin.

*Baseline CD4 count***:** The relationship of baseline CD4 count and *when* the first break in Anti-retroviral therapy occurred was studied. The association was statistically significant in both univariate analysis (OR= 0.99(95% CI: 0.998-0.999; *p*= 0.01) and multivariate analysis when controlled for other factors (OR =0.94(95% CI: 94-0.99; *p*=0.01). The odds that a break would occur were 1.01 less likely as the baseline CD4 count rose by 1 cell/µl, (Table 3.2).

*Baseline haemoglobin***:** The relationship of baseline hemoglobin and *when* the first break in Anti-retroviral therapy occurred was studied. The association was statistically significant in both univariate analysis (OR= 0.99(95% CI: 0.96-0.995; *p*= 0.02) and multivariate analysis when controlled for other factors (OR =0.97(95% CI: 94-0.99; *p*=0.01). The odds that a break would occur were 1.01 less likely as the hemoglobin rose by 1 g/dl, (Table 3.2).

Association between *the length (*duration) of the first break in therapy and patients demographic, laboratory and clinical factors

The relationship of baseline hemoglobin and the duration of the first break in Anti-retroviral therapy was studied. The relationship was negative and was statistically significant on univariate analysis (coef.=-0.12 (-0.24 to -0.001) (*p*= 0.05). This relationship was positive in multivariate analysis when controlled for other factors and was statistically significant (coef. =0.95(0.93-0.99) (*p*=0.01). Thus for every unit rise in hemoglobin there was a drop in the length of break by 0.95 days. For further details, please refer to table 3.5 below.

However**,** Sex, BMI baseline CD4, WHO clinical stages , tuberculosis at the beginning of ART, total Episodes (incidences) of tuberculosis after beginning ART, milliary Tuberculosis at the beginning of ART, peripheral neuropathy at the initiation of ART had no statistically significant association with the *length of* the first break in therapy.

PART 2

THE ASSOCIATION OF FIRST BREAK IN ART AND LAST CD4 COUNT

The association between the last CD4 count and break in the ART was studied. The first section analysed the association of *period* (total number in days) before the first break in ART and the last CD4 count, while the next section looked at the association between the *length* of the first break and last CD4 count. Analysis was done at 95% Confidence interval.

Association between the *period* (total number in days) on Antiretroviral therapy before the first break and the last CD4 count

The association between the *period* (total number of days) of starting ART up to the first break and the last CD4 count was studied. In univariate analysis, the direction of influence was positive. It can be stated with 95% confidence that for every days increase in days on ART before the first break, the last CD4 count increase by 0.21(95% CI: 0.16-0.25; p=0.01). Thus, the longer it took (in days) on therapy before the first break in therapy the higher the last CD4 count. Controlling for other factors this relationship was still positive. The factors which were controlled for were Total Incidence of peripheral neuropathy after ART, Peripheral neuropathy at initiation of ART, Sex, Age at initiation of ART, Baseline BMI, Employment status, Baseline CD4 count, WHO clinical stage IV, Baseline hemoglobin, incidence of tuberculosis after ART. Details are in Table 3.4.

Of these, the factors which had a significant effect on the last CD4 count after multivariate analysis were, Total Incidence of peripheral neuropathy after ART, Sex, Age at initiation of ART, Baseline BMI, WHO clinical stage I, Baseline CD4 count and baseline hemoglobin. For a day's increase in period on therapy before the first break there was 0.005(95% CI: 0.001-0.01; p=0.02) increase in last CD4 count.

Table 3.3: Table showing univariate and multivariate analysis of the association between length/duration of first break in taking of ARVs and different demographic, laboratory and clinical factors.

Variable		Univariate Analysis		Multivariate Logistic Analysis	
		Coefficient (Confid.Interval)	***P-value***	*Coefficient (Conf.Intervl)*	***P-value***
Sex	Male	0.1(1.1-0.91)	**0.84**		
	Female	1			
Age at initiation	years	0.03(-0.03-0.08)	**0.39**		
Baseline BMI	Kg/m^2	-0.07(-0.18-0.03)	**0.18**		
Employed	yes	-0.98(-1.9 to -0.01)	**0.04**	0.59(0.38-0.92)	**0.02**
	no	1			
Baseline CD4		-0.004(-0.011 to 0.003)	**0.23**		
WHO Stage	I	1			
	II	0.68(0.47-0.97)	**0.04**	0.94(0.6-1.5)	**0.79**
	III	1.03(0.93-1.15)	**0.53**		
	IV	1.24(1.05-1.46)	**0.01**	2.1(1.1-4.1)	**0.02**
Baseline hemoglobin	mg/dl	-12 (-.24 to -.001)	**0.04**	0.95(0.93-0.99)	**0.01**
Tuberculosis at initiation of ART	None	1			
	Yes	0.08(-1.3 to 1.50)	**0.91**		
	Unknown	4.50(-13.5 to 22.4)	**0.63**		
Total Incidence (episodes) of Tuberculosis after ART	None	1			
	Once	1.2(-0.87 to 3.2)	**0.26**		
	Twice	3.2(-0.52 to 12.0)	**0.44**		
Peripheral neuropathy at the initiation of ART	No				
	Yes	0.36(-3.3 to 4.0)	**0.84**		
Total Incidence (episodes) of peripheral neuropathy after ART	None	1			
	Once	0.35(-0.92 to 1.62)	**0.59**		
	Twice	1.43(-3.2 to 6.0)	**0.54**		
	Thrice	-4.6 (-26.6 to 17.3)	**0.68**		
Miliary TB at initiation of ART	No	1			
	Yes	-0.8(-3.1 to 1.5)	**0.51**		

Peripheral neuropathy: Incidence of peripheral neuropathy after starting ART had a positive effect on the last CD4 count in univariate and multivariate analysis. For those patients who had experienced one episode of peripheral neuropathy, it can be stated with 95% confidence that with one episode of peripheral neuropathy, the last CD4 was higher by 82.9 (95% CI: 66.4 -126.2; p=0.01) cells/µl. Controlling for other factors, the last CD4 count was high by 24 (6.5-41.1; p=0.01) cells/µl. For those patients with two episodes of peripheral neuropathy the last CD4 count was high by 163.5(64.2- 262.7; p=0.01). With other factors controlled for, however, the last CD4 count rose by 41(95% CI: 6.2- 75.7; p=0.02) cells/µl. For patients with three episodes of peripheral neuropathy, there was no statistically significant effect on the last CD4 count (p=0.56).

Sex: Sex had negative effect on the last CD4 count. Compared to males, the last CD4 count for females was lower by 66 cells/µl (95% CI: -81.9 to -49.9; p=0.01). In multivariate analysis Females compared to males had a statistically significant lower last CD4 count by 75.5(95% CI: -95.9 to -55.1; p=0.01) cells/µl.

Age of patient at initiation of ART: Age of patient at initiation of ART had a negative effect on the last CD4 count. For every added year the last CD4 count decreased by 1.67(95% CI: -2.57 to -0.77; p=0.01) cells/µl. In Multivariate analysis, the association was still negative. For every increase in age of patient by one year the last CD4 count decreased by 2.9(-3.8 to -2.1; p=0.01) cells/µl.

Baseline BMI: Baseline BMI had positive effect on the CD4 count. For every increase in BMI by 1 kg/m^2 there was an increase by 2.1(95% CI: 0.73 to 3.5; p=0.01) cells/µl of the last CD4 count. In multivariate analysis, for every increase in BMI by 1 kg/ m^2 the last CD4 count decreased by 5.6(-7.6 to -3.66; p=0.01) cells/µl.

Table 3.4: Table showing analysis of the association of duration on ART before break and other factors and with the last CD4

		Univariate analysis		Multivariate analysis	
		Coefficient (95% CI)	**P-value**	**Coefficient (95% CI)**	**P-value**
Duration on ART before the break in therapy(days)		0.21 (0.16 to 0.25)	**0.01**	0.005 (0.001 to 0.01)	**0.02**
Total incidence of peripheral neuropathy after ART	0	1			
	1	82.9 (66.4-126.2)	**0.01**	24 (6.5- 41.1)	**0.01**
	2	163.5 (64.2 to 262.7)	**0.01**	41 (6.2- 75.7)	**0.02**
	3	150.5 (-354 to 655)	**0.56**		
Peripheral neuropathy at initiation of ART	**No**	1			
	Yes	24.3 (-39.6 to 88.1)	**0.46**		
Sex	M	1			
	F	-66 (-81.9--49.9)	**0.01**	-75.5 (-96 to -55.1)	**0.01**
Age at initiation of ART		-1.67 (-2.57--0.77)	**0.01**	-2.9 (-3.8 to -2.1)	**0.01**
Baseline BMI (kg/m.sq)		2.1 (0.73-3.5)	**0.01**	-5.6 (-7.6 to -3.66)	**0.01**
Employed	No	1			
	Yes	-15 (-30.7- 0.6)	**0.06**		
Baseline CD4 (cell/µl)		0.78(0.69- 0.89)	**0.01**	0.68 (0.54 -0.81)	**0.01**
WHO Stage	I	1			
	II	56.9(-8.9- 121.9)	**0.09**		
	III	7.9(-9.1- 24.9)	**0.36**		
	IV	-63.4(-89.0 to -37.7)	**0.01**	-15.3 (-37.3- 6.7)	**0.17**
Baseline hemoglobin (mg/dl)		-3.3(-1.2to - 5.4)	**0.02**	-7.2 (-11.2 to -3.1)	**0.01**
Total incidence of tuberculosis after HAART	0	1			
	1	9.6(-26.3 to 45.5)	**0.60**		
	2	-61.1(-252.9 - 130.8)	**0.53**		

Baseline CD4 count: Baseline CD4 count had a positive effect on the last CD4 count. For every increase in baseline CD4 count by 1 cell/µl the last CD4 count increased by

0.78(95% CI: 0.54-0.81; *p*=0.05) cells/µl. In multivariate analysis, for every increase in baseline CD4 count by 1 cell/µl the last CD4 count increased by 0.68(95% CI: 0.54 -0.81; *p*=0.01) cells/µl.

Baseline hemoglobin: Baseline hemoglobin had a negative effect on the last CD4 count. For every increase in baseline hemoglobin by 1 g/dl the last CD4 count increased by 3.3(95% CI: 1.2 to 5.4; *p*=0.012) cells/µl. In multivariate analysis for every increase in baseline hemoglobin by 1 g/dl the last CD4 count decreased by 7.2(95% CI: -11.2 to -3.1; *p*=0.01) cells/µl.

Peripheral neuropathy: Peripheral neuropathy at initiation of ART, Employment status of patient, WHO clinical stage (I, II and III) and Total incidence of tuberculosis after ART did not have a significant effect on the last CD4 count in multivariate analysis.

The association between the length of the first break in therapy and the last CD4 count was studied. The factors controlled for were Incidence of peripheral neuropathy after starting ART, peripheral neuropathy at initiation of ART, Sex, Age of patient at initiation of ART, Baseline BMI, Employment status, Baseline CD4 count, WHO staging at ART initiation, Baseline Hemoglobin and Incidence of tuberculosis after initiation of ART. Only sex, baseline BMI, WHO stage IV had a statistically significant association with the last CD4 count. There was statistically significant association between the length of the first break in therapy and the last CD4 count (0.05(95% CI: -0.3 - 0.4); p= 0.79) in the analyses.

CHAPTER 4

DISCUSSION

In the previous chapter, results were described detail. This chapter discusses these results. Baseline characteristics of patients with first break in ART will be discussed and factors associated with the break. This is followed by a detailed discussion of the description of the first break in therapy. And finally, the last part of this chapter discusses the association of first break in the continuity of therapy and the last CD4 count.

Majority (63.6%) of patients on had a break in ART of more than 10 days. The largest proportion of these patients (33.4%) had their first break within the first year of taking Antiretrovirals. The average length of the first break in therapy was 19 (3-32) days. Most of these patients had advanced HIV/AIDS infection with CD4 counts less than 100 cells/µl at baseline. Determinants of the first break in therapy included being female, baseline CD4 count of less than 100 cells/µl, low hemoglobin and being unemployed. Since ART demands having no break in therapy, 63.6% is a very high proportion of patients with breaks and this would have a negative effect on the overall goal of ART, as seen by the relatively lower last CD4 counts in patients who had a first break in therapy. The earlier the break (within the first 6 months of therapy) occurred, the lower the last CD4 count, regardless of how long the first break was. Incidence of peripheral neuropathy after ART, Sex, Age at initiation of ART, baseline BMI, WHO clinical stage I, baseline CD4 count and baseline hemoglobin had an influence in last CD4 count. Increasing public awareness campaigns on the availability of ART services, decentralization of ART services and possibly increasing staffing at *Themba Lethu* ART centre may be possible solutions to reducing the occurrence of first break. Though the methods of calculating first break in therapy had its shortfalls, for instance, not providing information on whether the patient was

actually taking ARVs at home or not, it may be more cost-effective and reliable in predicting the virological state of patient on ART. There is need to explore the breaks in therapy further to identify their associations with serial CD4 counts, viral load and overall goal of ART.

Majority of the 7,930 patients in the study were females (*n*=5,162(65%)). The median time these patients were on ARVs was 756 (415-1117) days. Females were relatively younger than males (34 *vs.* 37.5 years). All the patients started ARVs when the HIV/AIDS was very advanced as seen by very low baseline CD4 counts. However, men (median CD4 count 74cells/µl) had more advanced disease than females (median CD4 count 94 cells/µl) at presentation to ART clinic. Majority of patients (63%) on ART had break in taking of ARVs.. This may negatively affect the overall treatment outcome of these patients. At start of therapy there was no significant differences in Sex, Age at initiation of therapy, baseline BMI, baseline CD4 count, between those with and without breaks. However, proportion of unemployed patients were significantly higher among those who had the break in therapy suggesting that unemployment was an important cause of failure to come to clinic to collect ARVS on time.

The high number of females on ART could suggests that females are more affected with HIV/AIDS than males and more committed to appointments to collect ARVs than males as also observed in a study in Cameroon (Rougemont, M., et al., 2009). The first break in therapy could be attributed to overcrowding at clinic. Some patients may not have been able to withstand long waiting times especially if unwell (advanced disease with CD4 count less than 100 cells/ µl and severe anaemia). More men missed their appointment and had relatively more advanced disease than female as seen from lower CD4 counts at baseline. Another reason would be that patients who were unemployed were facing transport problems to come to collect ARVs either because they don't have transport money. It is also possible that they may have had other competing responsibilities like job-seeking, (Mosoko, J., et al., 2007). Females had a statistically significant higher CD4 count (94 *vs* 74 cells/µl) at

the start of ART than males, suggesting that women came earlier to seek health services than men. Females were younger (median age 34 *vs.* 37.5 years) suggesting that the epidemic HIV/AIDS epidemic affected younger women more than their male counterparts.

Patients who had the first break in therapy had a relatively lower CD4 count (83 *vs.* 91; p=0.011) cells/µl than those without the break. The largest proportions of these patients had CD4 counts <49 cells/µl followed by 50-99 cells/ µl . This could suggest that patients with a lower CD4 count may have had more morbid conditions making it difficult to keep to appointments to collect ARVs. This has been observed elsewhere. In addition morbidity and mortality was higher within the first six months of therapy (Lawn, S., et al. 2006; Brinkhof, M., et al. 2008).

The first break in Antiretroviral therapy

The first break in therapy was described by *when* the break occurred from the time a patient started antiretrovirals, and for *how long the* first break was. Regarding *when* the first break occurred, most patients took less than a year (median time 234 days) before having the first break in therapy. Males had earlier first break (median 203 *vs*. 254 days; p = 0.01) than their female counterparts. A possible explanation is that males were more ill, hence having difficulties to come for therapy. Another possible explanation was that they responded faster to antiretroviral therapy and attained a sense of wellbeing. It may also be that since men had more advanced disease, they had a bit more ARVs side-effects like nausea and weakness. Thirdly, it is usually in this period when patients are adjusting (acceptance) to a new lifestyle making it a bit harder for men than women. It may also be possible that immediately the males feel better socio-economic responsibilities become competing issues and they take up the time required to come for refills. . Age did not influence when the break would occurred (p=0.10)(Enriquez & McKinsey, 2011).

As regard the CD4 count, among the patient who had the break in therapy in the first 6 months, majority had CD4 less than 49 followed by those with CD4 between 50-99 and the proportion of patients decreased as the CD4 count rose. This pattern was similar for different periods when the breaks occurred. Very low CD4 counts were associated with more advanced HIV/AIDS and hence higher morbidity and mortality. Possible explanation of the higher chance of breaks earlier than later in therapy could have been more morbid events like opportunistic infections, anemia and also that ARVs may not have caused much positive effects yet. In the first 6 months as well the chances of immune reconstitution are higher than later in the period of therapy.

Baseline BMI was also a predictor of when the first break occurred. For an increase in the BMI by 1 kg /m^2 had a 3.02 (1.47-4.59; p=0.01) days' increase risk of breaking therapy. More wasted patients were less likely to break therapy earlier than those who were less wasted, suggesting that those patients who were more wasted at beginning of therapy were eager to take medication and with hope of recovery, while those who were less wasted may not have seen the actual benefit of ARVs as regard weight gain and hence had a chance of breaking in therapy earlier. Individualised adherence may be on use is such cases though this may be difficult in cases were there health provider: patient ratio is poor (Rueda, S.,et al., 2009).

Up to 46.6% of all the patients had their first break within the first two years of therapy. The largest proportion (n=1,144(22.7%)) had a break in therapy within the first 6 months. The proportion of patients having breaks progressively decreased. Thus smallest proportion (n=249(4.9%)) of patients had a break between 18 and 24 months of therapy. As regards *how long* the first break in therapy was, the median length of days on break was 19 (3-32) days.

Factors associated with first break in ART

Predictors of *when* the break occurred included employment status, baseline hemoglobin and baseline CD4 count. Among the demographic factors studied were

sex, age at initiation of therapy and employment status. Only employment status was a predictor of when the break in therapy would occur. With clinical, demographic and laboratory factors controlled for, the odds of breaking therapy were 1.2 times less likely if the patient was unemployed. This may suggested that those who were in employment had to seek permission or had other responsibilities while at work and maybe were failing to come on time, or that there were uncomfortable so get permission to come to hospital opting not to be identified by workmates as coming to the ART clinic.

Clinical factors which were studied included baseline BMI, WHO HIV/AIDS clinical staging, Tuberculosis at the beginning of ART, milliary tuberculosis at the beginning of ART, peripheral neuropathy at the initiation of ART and Total incidence (episodes) of peripheral neuropathy after initiation of ART and employment status. Controlling for other factors, none of the clinical factors predicted *when* the break would occur. This may be partly due to the variability and subjectivity of clinical features. Most of the information was based on the information given by the patient and information collected from them. Some of the information collected was of events prior to starting ART hence information/recall bias and some was based on information on file.

Laboratory factors studied included baseline CD4 and hemoglobin. Controlling for other factors the odds that a break would occurred were 1.01 less likely as the hemoglobin rose by 1 g/dl. Anemia is associated with weakness lassitude and malaise fatigue and breathlessness. Thus these features might have affected or reduced the chances of the patients coming for ART on time due to feeling unwell. The odds that a break would occur were 1.02 less likely as the CD4 count rose by 1 cells/ul. Thus the break in therapy was higher if the baseline CD4 count was lower. As observed elsewhere lower CD4 counts were associated with higher advanced disease and more opportunistic infections hence this may have affected their coming to collect medication.

Among the predictors studied of *how long* the break would be, only baseline hemoglobin was the predictor. After controlling for clinical laboratory and demographic factors for every unit rise in hemoglobin there was a drop in the length of break by 0.95 days. This again suggested that those who were more anaemic took were more likely to stay at home away from collecting medicine because of malaise, weakness of other anaemia related complications. Baseline CD4 was not a predictor of *how* long the first break in the continuity of antiretroviral therapy was, Muko, K.N., et al., 2004).

The association between the *duration* (total number of days) on ART before the first break and the last CD4 count.

In univariate analysis, for every days increase in days on ART before the first break, the last CD4 count increased by 0.21(95% CI: 0.16-0.25; p=0.01) cells/µl. Thus the longer it took (in days) on therapy before the first break higher the last CD4 count was. Controlling for other factors, for a day's increase in period on therapy before the first break there was 0.005(95% CI: 0.001-0.01; p=0.02) increase in last CD4 count. This is expected because one purpose of ART is suppress viral replication, which in turn leads to rise in CD4 count (no further virus induced breakdown of CD4 cells), an indication of positive effect of ARVs on the immune system. Factors which had a statistically significant influence of the last CD4 count in multivariate analysis were Peripheral neuropathy, sex, age of patient at initiation of ART, baseline BMI, Baseline CD4 count and hemoglobin. Employment status, WHO staging at ART initiation, Incidence of tuberculosis after initiation of ART and Incidence of tuberculosis after initiation of ART did not have a statistically significant influence eon the last CD4 count.

Peripheral neuropathy had a significant influence on the last CD4 count. One episode of peripheral neuropathy increased the last CD4 count by 24 (6.5-41.1; p=0.01) cells/µl. For those patients with two episodes of peripheral neuropathy the last CD4 count rose by 41(95% CI: 6.2- 75.7; p=0.02) cells/µl. This suggested that that those

who at least experienced p. neuropathy were more compliant to taking ARVs than those who did not experience the p. neuropathy. However, three episodes of P. neuropathy did not have an influence on the last CD4 count (p=0.56). Three episodes of p. neuropathy may actually have suggested that patient was having breaks in therapy each time there was p. neuropathy.

Sex had a significant influence on the last CD4 count. Females had relatively lower last CD4 count by 75.5(95% CI: -95.9 to -55.1; p=0.01) cells/µl suggesting that the overall response of the immune system, as monitored by CD4, to ART was lower/poor in females than males. Whether this is related to risk on opportunistic infections hence higher mortality due to opportunistic infection in this group, was beyond the scope of this study.

The age of patient at initiation of ART had a negative influence on the last CD4 count. For every increase in age by one year the last CD4 count decreased decreased by 2.9(-3.8 to -2.1; p=0.01) cells/µl. Thus the older the patient at initiation of therapy the lesser would be the CD4 count. This could have been due to a number of reasons. It is possible that compliance to ART was poorer in the elderly, or that the response of the immune response to ART was blunted as the patients became older.

The baseline BMI had a positive influence on the last CD4 count. For every increase in BMI by 1 kg/ m^2 the last CD4 count decreased by 5.6(-7.6 to -3.66; p=0.01) cells/µl. This suggests that those who had better weight had a sense of wellbeing and possibly were omitting taking ART more.

The baseline CD4 count had an influence on the last CD4 count. For for every increase in baseline CD4 count by 1 cell/µl the last CD4 count increased by 0.68(95% CI: 0.54 -0.81; p=0.01) cells/µl. This suggested that the nadir CD4 count is directly related to the overall outcome on ART. It may mean that if the immune system in very low, with CD4 count as a proxy measure, it may not respond as good to ARVs at the ones where the immune system is not so impaired.

Baseline hemoglobin had a negative influence on the CD4 count. For every increase in baseline hemoglobin by 1 g/dl the last CD4 count decreased by 7.2(95% CI: -11.2 to -3.1; *p*=0.01) cells/µl. As regards break it may suggest that patients who were more anaemic (probably symptomatic) took medication better than those who were not anaemic, hence there lower last CD4 count.

Employment status, WHO staging at ART initiation, Incidence of tuberculosis after initiation of ART and Incidence of tuberculosis after initiation of ART did not have an statistically significant influence on the last CD4 count.

The association between *how long* the first break was and the last CD4 count

The longer patients stayed away, more than 10 days, from coming to collect medicine the more the last CD4 count was affected negatively. This strongly suggests therefore, that not coming for appointments for more than 10 years was strongly associated with not taking ARVs. Thus missing appointment for more than 10 days did not only exhaust the remaining extra tablets patients were given but also made them stay without taking ARVS. This emphasizes the importance of continued taking of ARVs.

The factors controlled for were Incidence of peripheral neuropathy after starting ART, peripheral neuropathy at initiation of ART, Sex, Age of patient at initiation of ART, Baseline BMI, Employment status, Baseline CD4 count, WHO staging at ART initiation, Baseline Hemoglobin and Incidence of tuberculosis after initiation of ART. Only sex, baseline BMI, WHO stage IV, had a statistically significant influence on the last CD4 count level.

Females had a lower last CD4 count by 65.1(95% CI: -86 to -43.9; *p*=0.01) cells/µl, compared to their male counterparts. This suggests that though the length of the first break affected both female and male patients as regards the ART outcome, female patients were more affected. For every increase in BMI by 1 kg/m^2 the last CD4

decreased by 4.4(95% CI: -6.4 to -2.4; p=0.01) cells/µl. Among different WHO clinical stages, only WHO stage IV influenced the last CD4 count. The last CD4 count reduced by 47.8 (95% CI: -74 to -21.6; p=0.01) cells / µl for patients in Stage four compared to those in stage I.

Limitations of the study

Serial CD4 counts, which were not available, could have provided a better picture about virological suppression and immune recovery as compared to the last CD4 count. This is so because rather than looking at absolute values, they provide a trend of CD4 counts. The last CD4 count is not a standalone value. It is directly related to the previous set of serial CD4 counts, especially its predecessor. Not only that, since serial CD4 are done constantly every six months, and since it is possible to monitor it, a 30% drop of the next CD4 count is usually a indicator of possible resistance development. The last CD4 count and any single reading CD4 count is also influenced downwards if there is an ongoing opportunistic infection and variably due to laboratory associated factors. Thus a corresponding viral load may compensate for this.

The CD4 count is used extensively to monitor treatment success in most resource limited countries primarily because it is affordable than viral load, and it does provide useful information on whether therapy is successful or not. Based on WHO guidelines, therapy is not successful if a CD4 count drops to more than 50% of the highest CD4 count value or a drop to levels of baseline CD4 count after a year of treatment or if there is failure for the CD4 count to rise to 50-100cells/ul after a year of therapy. However, CD4 count has its limitations. Firstly, CD4 count decline occurs way after virological failure by which time many 2nd line ARVS may not work because of accumulated resistant mutations. Secondly, CD4 count may fall in the absence of virological failure, forcing a clinician to change ARVs prematurely, (WHO, 2007; Phillip, A.N., et al., 2008).

Due to these limitations of the CD4 counts, pharmacy refill adherence and monitoring of break in therapy could be used in combination or in place of CD4 as studies in southern Africa have shown that the former was a better predictor of viral load suppression than CD4 count. Thus an immediate follow-up of those patients as risk of breaking in ART therapy could minimize development of resistance or improve adherence, (Bisson, G.P., 2008). However, it still remains unclear whether pharmacy refill methods would be sufficiently precise or time sensitive to inform the clinicians when the viral rebound would occur, (Harrigan, R., et al., 2003; Wood, E., 2003).

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

Although *Themba Lethu* clinic has a system already put in place to check if patients are missing appointments to collect antiretrovirals, there are up to 5,046 (63.6% of patients in the study) patients who missed appointment is excess of 10 days between June 2004 and July 2008. The failure of the patient to come to collect medicine on scheduled time had a lowering effect on the last CD4 count. This number of patients is too large, and as such, there is need to strengthen existing follow-up mechanisms in order to reduce these numbers for the ART program to meet its intended goal. Since as many as 15,928 HIV positive and ART patients received services at Themba Lethu clinic, one possible action would be to decentralize the ART centre within Johannesburg. The ART clinic when visited appeared crowded and patients were in long queues. This suggested that the work load is higher for the health workers and as such counseling (before and during therapy) may not be as effective as expected. The clinics data collection and storage system at this clinic is very well developed and could be used to provide more detailed and accurate information which would be used to seek solutions to this problem and inform policy.

The mean duration on ART for the patients was 764 days. 47.5% of patients had their first break in therapy within the first 2 years of being on the ART program, with the largest proportion within the first 6 months of therapy. Though possible known reasons include for this break in therapy is antiretroviral side-effects, opportunistic infections which may still occur in the early months of therapy, other explanation ought to be sought for instance 'acceptance' of inevitable change in life-style patients. There is need for continued emphasis on pre-ART counseling, improving patient-medical staff ratios and possibly decongestion of the clinic. There is need to pay attention to individual problems and address them as quickly as possible. Since the largest proportion of patients have a break within the first six months, there is need to investigate in details why this should be so and tailor the services to solve

individual patient's problems. Though the individualized approach is the best, it may not be possible in there are high population and the public resources are limited.

As regards the actual break in therapy it was more of *when* the first break occurred than *how long* the break in therapy lasted when looking at the association with the last CD4. Those patients who took longer on ART before their first break in therapy, their immune restoration was better as seen in their significant higher last CD4 counts. Thus, it is very important to make sure that the break does not occur in the first place, worse still in the first 1 year of therapy. Though some studies show that some of these breaks are beneficial to some patients, this could be misleading because it is done in few clinics and under strict structured programs with few number of patients. So far, WHO does not recommend any break in treatment therapy. Thus, encouraging maximum adherence is the best for these patients. Further research may look at different breaks in a patient and its effects on treatment outcomes, influence of these breaks on CD4 count if different classes of ARVs are put into consideration and the effect of different breaks with different lengths of these breaks.

Low baseline hemoglobin and milliary tuberculosis at the beginning of ART were predictors of *when* the first break in therapy would occur. It may thus be important to identify patients who have low baseline hemoglobin and advanced (milliary) Tuberculosis and place intervention measures including scheduling appointment to fit patients' needs. Literature shows that anemia is a manifestation of Advanced AIDS and could also mean an underlying opportunistic infection especially advanced TB. It may be useful to investigate the actual cause of the anemia besides it being an indication of advanced AIDS and do active screening for opportunistic infection prior to ART. One possible solution would be to identify these 'at risk' patients and provide them preferential treatment, for example, not standing in queues since they tend to be ill and weak.

Baseline hemoglobin and unemployment were predictors of *length* of the first break. Further analysis of the available data would provide more useful information and inform policy for action. Further research needs to establish trends of the hemoglobin levels while patient is on ART with clinical (symptom and signs) and laboratory parameter to identify what exactly makes them have a break and why it should be prolonged. Further research would be recommended to investigate mortality rates in these patients with anaemia and the unemployed. There should be improved social network support for the unemployed patients who are on ARVs to facilitate their coming to the ART clinic.

Patients who took longer to have the first break in therapy had better last CD4 counts but ended up developing peripheral neuropathy. This was probably due to Stavudine. It may be advisable to substitute Stavudine with another ARV e.g. Zidovudine, if the patent is not anaemic. Another approach is for the clinician to be proactive in order to identify early peripheral neuropathy so that it is controlled before patients breaks the continuity of taking ARVs.

Females account for two-thirds of the ART patients. They are more affected by the first break in therapy as seen by lower CD4 counts compared to men. However, men came with more advanced disease, improved early and stopped ART earlier than women. It is possible that there are gender-specific responses (e.g. slower immunological response in women than men), social, cultural and economical reasons for this difference hence the need for further research in order to make decision at individual and institution level.

A large number of the patients started ARVs when the disease was is very advanced(very low baseline CD4 count, very low BMI, WHO clinical stage IV, low baseline hemoglobin) and this directly affected the response to ART using last CD4 count as the marker. Steps could be taken to inform community the importance of coming early ART intervention and provision of logistic and active case detection. Both public and private institutions with capacity to help with and spread

educational information on the disease ought to be strengthened since it may be possible that lack of information, stigma could be reason for the delay to seek medical services.

Further research

1. Reasons why patients miss their appointment to collect medicines in the first 2 years, especially in the first 6 months.
2. Investigate health-service related factors why patient may miss their appointment to collect ARVs.
3. Effectiveness of pre-ART and adherence counseling in a public health facility like Themba Lethu clinic.
4. Determinant of morbidity and mortality in the first six months of ART therapy at Themba Lethu clinic.
5. Sex related factors of adherence to antiretroviral therapy.
6. Associated benefits of individualized approach in patients on antiretroviral therapy.
7. Description of different types of breaks in continuity of antiretroviral therapy and determinant of the breaks.
8. Laboratory outcomes (CD4 count and viral load) in outpatient with break in the continuity of ART.
9. Different breaks in a patient on antiretroviral therapy and its effects on treatment outcomes, and influence of these breaks on CD4 count in different classes of ARVs.
10. Most preferred waiting time for a patient receiving ART services at Themba Lethu clinic.
11. Sex-related difference in immunological response (CD4 and CD8 count) to ART in first 2 years of ART .
12. Most effective method of encouraging patients to come early to start ART.
13. The effectiveness of sms (short message sending from mobile phones) in reminding patients to come for their Antiretroviral collection and its cost-effectiveness.
14. Investigate the reliability of *last* CD4 count compared to a *series* of CD4 counts measures in informing the clinician about ART success in patients on ARVs.

REFERENCES

Bangsberg, D. R., Perry, S. & Charlebois, E. D. et al. 2001. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*, vol 15(9), pp 1181-1183.

Bangsberg, D.R., Charlebois, E. D.& Grant, R. M.et al. 2003. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS*, Vol. 17(13), pp 1925-1932.

Bangsberg, D.R., Moss A.R. & Deeks, S.G. 2004. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *Journal of Antimicrobial Chemotherapy*; **53: p** 696–699

Begley, K., McLaws, M-L. & Ross, M. W., et al. 2008. Cognitive and behavioural correlates of non-adherence to HIV anti-retroviral therapy: Theoretical and practical insight for clinical psychology and health psychology. *Clinical Psychologist*, vol 12 (1), pp 9 – 17.

Bisson, G.P., Gross, R., Bellamy, S., Chittams, J., Hislop, M., et al. 2008. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS Med* vol 5: e109. doi:10.1371/journal.pmed.0050109.

Brinkhof, M.W., Dabis, F., Myer, L., Bangsberg, D.R., et al. 2008. Early loss of HIV-infected on potent antiretroviral therapy programmes in lower-income countries. *Bull World Health Organisation,* vol 86(7), pp559-67.

Chesney, M.A.,2000. Factors affecting adherence to antiretroviral therapy. *Clinical infectious Disease,* vol 30(2), pp 171-179.

Enriquez, M., McKinsey, D.S. 2011. Strategies to improve HIV treatment adherence in developed countries: clinical management at the individual level, Vol 2011(3) DOI 10.2147/HIV.S8993, pp 45 – 51.

Esch, L.D., Klem, K.,Kuhman, L., Hewitt,G., Morse, G.D., 2002. Intensive Adherence Interventions Improve Virologic Response to Antiretroviral Therapy (ART) in Treatment Naïve Patients**.** *Presented at the 14th International AIDS Conference, Barcelona, Spain, July 7-12, 2002.*

Falagas, M.E., Zarkadoulia, E.A., Pliatsika, P.A., Panos, G,. 2008. Socioeconomic status(SES) as a determinant of adherence to treatment in HIV infected patients: A systematic review of literature. *Retrovirology, Feb 1; 5, p 13.*

Garenne, M., Lydie, N. 2001. Sex and AIDS. World Health Organsiation. Downloaded from www.who.int/Sex/documents/en/SexAIDS.pdf on the 13th January , 2009.

Global HIV/AIDS Epidemic, 2007. HIV/AIDS policy fact sheet. *HIV/AIDS*. <http://www.kff.org/hivaids/upload/3030-103.pdf.> (accessed 12.07.2008).

Godin, G., Côté, J. & Naccache, H., et al. 2005. Prediction of adherence to antiretroviral therapy: A one-year longitudinal study. *AIDS Care*, vol 17(4) , pp 493 – 504.

Gulick, R.M. 2002. Structured Treatment Interruptions in patients infected with HIV: An approach to Therapy. *Drugs,* vol 62(2), pp245-253

Harrigan, R., Dong, W., Alexander, C., Yip, B., Ting, L., et al. 2003. The association between drug resistance and adherence determined by two independent methods in a large cohort of drug naive individuals starting triple therapy. Second International Conference on HIV Treatment and Pathogenesis; 13–17 July 2003, Paris, France. Abstract LB12. .

Heyer, A. & Ogunbanjo, G.A., 2006. Adherence to HIV antiretroviral therapy Part II: Which interventions are effective in improving adherence? *SA Fam Pract.,*vol 48(9), pp 6-10.

Harzke, A. J.,Williams, M.L. & Nilsson-schönnesson, L., et al. 2004. Psychosocial factors associated with adherence to antiretroviral medications in a sample of HIV-positive African American drug users. *AIDS Care*, vol 16 (4), pp 458 – 470.

Hosek, R. S., Harper, G.W. & Domanico, R. 2005. Predictors of medication adherence among HIV-infected youth Psychology. *Health & Medicine*, vol 10 (2),pp 166 – 179.

Ickovics, J. R. & Meade, C. S. 2002. Adherence to HAART among patients with HIV: breakthroughs and barriers. *AIDS Care*, vol 14(3), pp 309 —318.

Ingersoll, K. 2004. The impact of psychiatric symptoms, drug use, and medication regimen on non-adherence to HIV treatment. *AIDS Care*, vol 16 (2), pp 199 – 211.

Kerr, T., Marshall, A. & Walsh, J. et al. 2005. Determinants of HAART discontinuation among injection drug users. *AIDS Care*, vol 17(5), pp 539 – 549.

Lawn, S., Myer, L., Harling, G., Orrell, C., Bekker, L., Wood, R., et al. 2006. Determinants of motality and nondeath losses from an antiretroviral treatment service in South Africa: Implications for program evaluation. *Clinical Infectious Disease*, 43(6), pp 770-6.

Lima, V.D., Hogg, R.S. & Harrigan, R. et al. 2007. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS*, vol 21, pp 685–692.

Muko, K.N., Ngwa, V.C. & Chingan L.C. et al. 2004. Adherence to Highly Active Antiretroviral Therapy (HAART): A Self-reported Case Study from a Rural Area in Cameroon. *Sahel Medical Journal*, vol 7(4).

Murphy, D.A., Marelich, W.D. & Hoffman, D. 2004. Predictors of antiretroviral adherence. *AIDS Care*, vol 16(4), pp 471 – 484.

New Vision (Kampala), 2007. HIV/Aids - Southern Regions Worst Hit . *NEWS, vol* 20, <http://allafrica.com/stories/printable/200711210150.html> (Accessed 01.06.2008).

Nicca, D., Moody, K. & Elzi, L. et al. 2007. Comprehensive Clinical Adherence Interventions to Enable Antiretroviral Therapy: A Case Report. *JANAC,* vol 18 (6).

Olubusoye, O.E., Meshesha, A.T. 2008. Determinants of Adherence to Antiretroviral Treatment among HIV patients in Ethiopia. *African Research Review, v*ol. 2 (2), pp 1-12

Overview Medication adherence, where are we today? 2006. American Society on Aging and American Society of Consultant Pharmacists Foundation. http://www.adultmeducation.com/downloads/Adult_Med_Overview.pdf (Accessed 14th June, 2008).

Phillips, A.N., Pillay, D., Miners, A.H., Bennett, D.E., Gilks, C.F., et al. 2008. Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: A computer simulation model. *Lancet* vol 371, pp 1443–1451.

Røge, B.T., Barfod, T.S. & Kirk, O. et al. 2004. Resistance profiles and adherence at primary virological failure in three different highly active antiretroviral therapy regimens: analysis of failure rates in a randomized study . *HIV Medicine, vol* 5, pp 344–351.

Rougemont, M., Stoll, B, et al. 2009. Antiretroviral treatment adherence and its determinants in Sub-Saharan Africa: a prospective study at Yaounde Central hospital Cameroon. *AIDS and research therapy,* vol 6:21, pp 1-12.

Rueda S., Park-Wyllie L.Y., Bayoumi, A., Tynan, A.M., Antoniou, T., Rourke, S., Glazier R. Patient support and education for promoting adherence to highly active antiretroviral

therapy for HIV/AIDS. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001442. DOI: 10.1002/14651858.CD001442.pub2.

Stratified Analyses, 2007. Methods and formulae. Trustees of the University of Pennsylvania.. *EP 521,* vol I, prt 3.

Sungkanuparph, S., Groger, R.K. & Overton E.T., et al. 2006. Persistent low-level viraemia and virological failure in HIV-1-infected patients treated with highly active antiretroviral therapy. *HIV Medicine*, vol 7, pp 437–441.

Schönnesson, L.N., Diamond, P.M., & Ross, M.W., et al. 2006. Baseline predictors of three types of antiretroviral therapy (ART) adherence: A 2-year follow-up. *AIDS Care*, vol 18 (4), pp 406 – 414.

Singh, N., Squier, C. & Sivek, C., et al. 1996. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care*, vol 8 (3), pp 261 – 270.

Schroedera, K., Faheyb, T., Ebrahimc, S. & Peters,T.J., 2004. Adherence to long-term therapies: recent WHO report provides some answers but poses even more questions (COMMENTARY) Journal of Clinical Epidemiology 57 (1): p2–3

Schrooten, W., Florence, E. & Dreezen, C., et al. 2004. Five-year immunological outcome of highly active antiretroviral treatment in a clinical setting: results from a single HIV treatment centre. Belgium. *Int. Jrnl STD & AIDS,* vol 15, pp 523-528.

Sungkanuparph, S., Chakriyanuyok, T. &, Butthum, B. 2008. Antiretroviral therapy in AIDS patients with CMV disease: Impact on the survival and long-term treatment outcome. Journal of Infection;56:p40-43

Uldall, K.K., Palmer, N.B. & Whetten, K., et al. 2004. Adherence in people living with HIV/AIDS, mental illness, and chemical dependency: a review of the literature. *AIDS Care*, vol 16 (S1), pp 71 – 96.

USAID, 2005. http://www.avert.org/safricastats.htm. Downloaded 27th January, 2009

Weiser, S, Wolfe, W., Bangsberg, D., Thior,I.,et al., 2003. Barriers to Antiretroviral adherence for Patients Living with HIV Infection and AIDS in Botswana. J Acquir Immune Defic Syndr ;34, pp 281–288.

Williams, A., 1997. Antiretroviral Therapy: Factors Associated With Adherence. *Journal of the Association of Nurses in Aids Care,* vol 8, pp18-23.

Wolf, M.S., Davis, T.C. & Arozullah, A., et al. 2005. Relation between literacy and HIV treatment knowledge among patients on HAART regimens. *AIDS Care*, vol17(7), pp 863 – 873.

Wood, E., Hogg, R.S., Yip, B., Harrigan, P.R., O'Shaughnessy, M.V., et al. 2003. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 × 10(9) cells/L. Annals Internal Medicine, vol 139,pp 810–816.

World Health Organisation. 2003. Adherence to Long-Term Therapies: Evidence for Action. Site accessed 12th September, 2008 [http://www.who.int/mip2001/files/1987/Adherencetolong-termtherapies.pdf]

World Health Organization. 2007. Management of HIV Infection and Antiretroviral Therapy in Adults and Adolescents. A Clinical Manual. Site accessed 17th May, 2009. http://www.searo.who.int/LinkFiles/Publications_Management_HIV_infection_antiretroviral_therapy_adults_adolescents.pdf .

Youle, M. 2002. Structured Treatment Interruptions. Conference report from NATAP. 9th Conference on Retroviruses and Opportunistic infections. Site accessed 20th June, 2010. http://www.natap.org/2002/9retro/day23.htm

APPENDIX 1

Details of the methods used to determine the association of break in therapy and demographic, clinical and laboratory factors

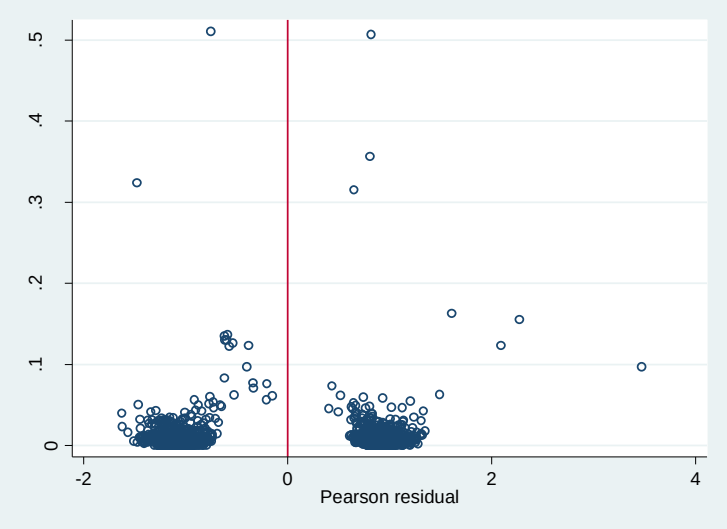
Univariate analysis was used determine the association of break in continuity in therapy and each variable. Multiple logistic regression techniques were used to study the association with other factors controlled for. Results were used to construct a model to predict the occurrence of a break in ART treatment based on demographic (sex, age at initiation of therapy, employment status) and clinical (BMI, WHO HIV/AIDS staging, Tuberculosis at initiation of ART, military TB at the initiation of ART, peripheral neuropathy at the initiation of ART, Tuberculosis episodes after initiation of ART and episodes of periphery neuropathy after the initiation of ART. Table 3.4 shows the results of this analysis.

A break was coded 1 if a break occurred and 0 if there was no break. Categorical variables were also coded with the smallest value being the reference. All assumptions of multiple logistic regression analysis were met. With predicted probabilities, there were 926 missing values generated. Predicted (pearsons residues, leverage values (none), pregobon dbeta were taken in account and the logistic model for goodness-of-fit test revealed number of observations of 3,299, with 10 groups. The Hosmer-Lemeshow chi2(8) was 3.02. The *p*-value was statistically insignificant (p= 0.93). Figure 3.3 below is the scatter plot of residue versus leverage values.

Each explanatory variable as indicated above underwent univariate analysis first. Those variables whose *p-value* was less that 0.2 (some authorities use 0.1) were included in the final model. Interactions were checked, one variable at a time sequentially and consecutively with other variables (two per time) per time. A star was used to merge two variables to create an interaction term. The interaction term was included in initial analysis. If the term was statistically significant, it was

included in the final model. Significant interactions were seen between episodes of pneumonia after ART initiation and BMI, peripheral neuropathy and baseline hemoglobin. Their interaction terms were included in the final equation. Intercooled Stata 10.0 was used in this analysis.

Figure 3.3 Scatter plot showing Pearsons residues for break in continuity of therapy



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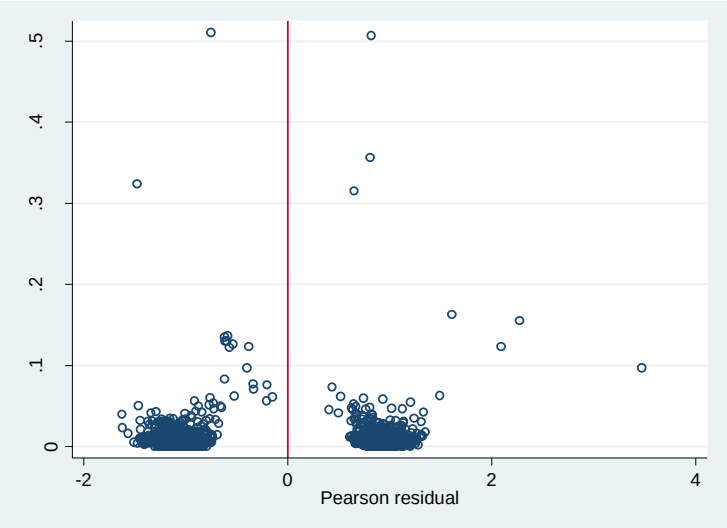
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.1
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.3
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-2
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