Effect of stavudine dosage reduction on the incidence of symptomatic hyperlactataemia/lactic acidosis in adults female HIV/AIDS infected patients treated at Dr George Mukhari Hospital

by

Mr. MANIMBULU NLOOTO

Student Number: 210589881

RESEARCH DISSERTATION

Submitted in the fulfillment of the requirements for the degree of

MASTER OF SCIENCE (MEDICAL)

in

PHARMACOLOGY

in the

FACULTY OF HEALTH SCIENCES
(School of Medicine)

at the

UNIVERSITY OF LIMPOPO

SUPERVISOR: Prof. W.J. Du Plooy

2010

DECLARATION

I declare that the dissertation hereby submitted to the University of Limpopo, for the degree of Master of Science (Medical) in Pharmacology has not previously been submitted by me for a degree at this or any other university; that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

__________________________ 8 May 2010

M. Nlooto (Mr.)

Student Number: 210589881

ABSTRACT

With the availability of Highly Active Antiretroviral Therapy (HAART), one of the limitations of treatment safety is the occurrence of adverse events associated with antiretroviral agents.

The aim of this study was to establish whether stavudine dosage reduction prevents toxicity from developing and minimizes the incidence of symptomatic hyperlactataemia/lactic acidosis (LA) in adults female HIV/AIDS infected patients.

This retrospective study covered adult patients treated at the adult ARV clinic, Dr George Mukhari Hospital. The records of 88 patients aged between 27 and 59 years, initiated and treated from August 2004 to January 2006, were analyzed (67 females and 21 males). Twenty nine females started their treatment on a regimen containing 40 mg stavudine while 38 females were started on 30 mg stavudine. A group of male patients (n=21) were included for comparison. Seven males started on 40 mg stavudine and 14 were on 30 mg stavudine. Ten out of twenty nine females who started treatment on 40 mg stavudine developed elevated lactate levels while nineteen received 30 mg stavudine as reduced dose. Eight out of nineteen further developed elevated lactate levels when on 30 mg stavudine but eleven out of nineteen remained stable on treatment with 30 mg stavudine as reduced dose. In the group started on 30 mg stavudine, thirteen females out of thirty seven developed elevated lactate levels while twenty four were stable on their treatment.

Key words: stavudine, dosage reduction, lactate levels, hyperlactataemia, lactic acidosis.

DEDICATION

To my wife, M.C. Kiaku Mafuta ; my children Tonda Patrick Nlooto, Gracia Nlooto, Heroique Nlooto, Prosper Nlooto, Elizabeth Nlooto for their patience and support.

ACKNOWLEDGEMENTS

A special note of gratitude to Prof W J Du Plooy, Head of the Department of Pharmacology and Therapeutics, and supervisor, for his support and sense of constructive criticism.

I am grateful to Dr George Muntingh who was my supervisor before he had left the Department of Pharmacology and Therapeutics for his guidance.

I wish to express my gratitude to Dr Gustave Ntambwe Malangu at the National School of Public Health, for his invaluable suggestion, comments and continual encouragements.

Special thanks to Ms Marlize Schoeman for her assistance with statistics.

Thanks to Mr. Prosper Nlooto for his assistance with computer skills.

Thanks to Dr E.M Kangawaza at Tshepang ARV clinic, Dr George Mukhari Hospital, for her encouragements to undertake this study.

I would like to thank the management of Dr George Mukhari Hospital for allowing me to conduct this study at the site.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

WHO……………………………………………World health Organization

HAART…………………………………………Highly active antiretroviral therapy

LA………………………………………………Lactic acidosis

HIV……………………………………………..Human immunodeficiency virus

ARV……………………………………………Antiretroviral

FDA……………………………………………Food and Drug Administration

NRTI……………………………………………Nucleoside reverse transcriptase inhibitors

AIDS……………………………………………Acquired immune deficiency syndrome

NtRTIs…………………………………………Nucleotide reverse transcriptase inhibitor

TDM……………………………………………Therapeutic drug monitoring

BMI…………………………………………….Body mass index

NNRTIs…………………………………………Non nucleoside reverse transcriptase inhibitors

CHAPTER 1: INTRODUCTION

HIV and AIDS is one of the main challenges in health care facing South Africa today. In 2007 the UNAIDS report indicated that there were an estimated 33 million people living with HIV worldwide. The Sub-Saharan Africa remains the most heavily affected by HIV, accounting for 67 % of all the people living with HIV and for 72 % of AIDS deaths. In South Africa about 5.70 million people were estimated to be living with HIV, with 26.1 % of the adult population (15-49 years) and about 350000 AIDS deaths in 2007 (UNAIDS, 2008).

The Acquired Immunodeficiency Syndrome (AIDS) was first recognized in 1981, in the United States of America in young homosexual men who had Kaposi sarcoma and serious infections (Piot et al, 1992). Treatment options for HIV infected people were very limited and therapies which had been demonstrated to affect the behavior of the virus itself were not available (Floyd & Gilks, 1997).

With the availability of Highly Active Antiretroviral Therapy (HAART), the use of a combination of three or more antiretroviral (ARV) agents is aimed at reducing the plasma viral load as much as possible and for as long as possible. The need for drug treatment should, however, be balanced against the development of toxicity (WHO Model Formulary, 2004).

Although the recent treatments are not a cure and present new challenges with respect to side-effects and drug resistance, they have dramatically reduced rates of mortality and morbidity, have improved the quality of life of people with HIV/AIDS, and have revitalized communities. Moreover, HIV/AIDS is now perceived as a manageable chronic illness rather than as a plague".

The benefits of HAART have been well established; however, one of the limitations to treatment safety and efficacy is the occurrence of adverse events associated with antiretroviral agents. Adverse effects have been reported with virtually all antiretroviral drugs and are among the most common reasons for switching or discontinuation of therapy and for medication non adherence (O'Brien et al, 2003).

Availability and cost were very importantly to be considered among other factors in the selection of antiretroviral therapy regimens at both the programme level and the level of the individual patient when the WHO treatment guidelines for commencing antiretroviral therapy in resource-limited settings were revised in 2003. For least developed countries, stavudine is used in preference to zidovudine as it is cheaper. In June 2003 the price for stavudine, lamivudine and nevirapine containing combinations was 281-385 $ vs. 611-986$ for those containing zidovudine, lamivudine and nevirapine (UNICEF/UNAIDS, 2003).

In South Africa the National Antiretroviral Treatment guidelines were first implemented in 2004. This guideline served to assist clinics in the management of patients on antiretroviral drugs as outlined in the Comprehensive Plan for HIV and AIDS Care, Management and Treatment (National Department of Health of South Africa, 2004).

Since 1991, cases of severe lactic acidosis have been reported in association with nucleoside reverse transcriptase inhibitors therapy and severe adverse events have been attributed to mitochondrial dysfunction. A typical complication of mitochondrial toxicity is manifested as an elevated serum lactate (Cornejo et al, 2003). Longitudinal cohort and retrospective studies suggest that symptomatic hyperlactataemia and lactic acidosis may be more associated with antiretroviral combinations containing stavudine (Moore et al, 2001, Lonergan et al, 2000).

A large HIV treatment programme in Khayelitsha, Cape Town, which began using stavudine as a first line therapy in 2003, had reported approximately 10 % of patients switching from both zidovudine and stavudine after 12 months (Wood, 2006).

During 2005, clinicians at the adult ARV clinic at Dr George Mukhari Hospital had been concerned by the side-effects experienced by adults female HIV/AIDS patients above 60 kg body weight who were on stavudine containing regimens , relatively stable on their treatment for months but who developed symptomatic hyperlactataemia/lactic acidosis. The package dose recommendation for stavudine was 30 mg stavudine twice daily for patients < 60 kg of body weight and 40 mg stavudine twice daily for patients > 60 kg of body weight.

One of the strategies adopted by clinicians was to reduce stavudine dosage from 40 mg to 30 mg in the group of female patients with a weight of 60 kg or above and in a few cases from 30 mg to 20 mg in the group of females less than 60 kg.

Therefore new female patients and those already on treatment received 30 mg stavudine regardless of their weight.

At that time the strategy of stavudine dosage reduction fell outside not only the package insert dose recommendation but also it was totally outside the standard guidelines implemented by the National Department of Health of South Africa in 2004.

Recommendations for care and treatment change rapidly, and opinion can be controversial; this is the reason that the study was conducted in order to establish whether the development of toxicity could be prevented or minimized by reducing the stavudine dosage.

We report here the results pertaining to the effect of stavudine dosage reduction on the incidence of symptomatic hyperlactataemia/lactic acidosis in adult female HIV/AIDS patients treated at Dr George Mukhari Hospital.

CHAPTER 2: LITERATURE STUDY

2.1. BACKGROUND

Since 1987 more than twenty antiretroviral agents have been approved for use in HIV-infected adults and adolescents in the United States of America (Department of Health and Human Services, 2005). The Medicines Control Council (MCC) has registered some of these drugs; however, some of the approved antiretroviral drugs are not easily available in the public sector in South Africa (Bartlett et al, 2008).

The antiretroviral drugs fall into several major classes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors.

Table 2.1.Antiretroviral agents approved by the FDA and MCC for treatment of HIV infection

Drug class	Generic name	FDA approval date	MCC registration date
NRTIs	Abacavir (ABC)	February 1999	June 2001
	Abacavir/zidovudine/lamivudine	November 2000	October 2003
	Didanosine(ddI)	October 1991	July 1992
	Emtricitabine(FTC)	July 2003	
	Emtricitabine/tenofovir	August 2004	May 2007
	Lamivudine(3TC)	November 1995	June 1996

Table 2.1.Antiretroviral agents approved by the FDA and MCC for treatment of HIV infection *continued*

Drug class	Generic name	FDA approval date	MCC registration date
NRTIs	Lamivudine/zidovudine	November 2000	November 2000
	Stavudine (d4T)	June 1994	November 1998
	Zalcitabine(ddC)	June 1992	Not registered
	Zidovudine(AZT,ZDV)	March 1987	May 1989
NtRTIs	Tenofovir (TDF)	October 2001	May 2007
NNRTIs	Delavirdine (DLV)	April 1997	Not registered
	Efavirenz (EFV)	September 1998	September 1999
	Nevirapine (NVP)	June 1996	February 1998
Fusion Inhibitors	Enfuvirtide (FTC)	March 2003	Not registered
	Maraviroc	August 2007	Not registered

Table 2.1.Antiretroviral agents approved by the FDA and MCC for treatment of HIV infection *continued*

Drug class	Generic name	FDA approval date	MCC registration date
PIs	Amprenavir (APV)	April 1999	September 2001
	Atazanavir (ATV)	June 2003	*
	Fosamprenavir (FPV)	November 2003	Not registered
	Indinavir (IDV)	March 1996	October 1996
	Lopinavi/ritonavir (LPV/r)	September 2000	August 2002
	Nelfinavir (NFV)	March 1997	October 1999
	Ritonavir (RTV)	March 1996	July 1997
	Saquinavir (SQV) hard gel capsules	December 1995	January 1997
	Tripanavir (TPV)	June 2005	Not registered
	Darunavir (DRV)	June 2006	Not registered

Source: Adapted from Bartlett et al, 2008.

In 2002 the World Health Organization (WHO) treatment guidelines recommended that developing countries should select a first-line treatment regimen and identified regimens composed of two nucleosides plus either a non-nucleoside, or abacavir, or a protease inhibitor as possible choices. Triple nucleoside regimens including abacavir were almost never selected because of their cost and concerns over hypersensitivity reactions, and regimens containing a protease inhibitor became secondary options, mainly because of their cost notwithstanding price decreases (WHO, 2004).

In line with the WHO recommendations, the South African National Antiretroviral treatment guidelines, first edition 2004, indicated the following regimens for therapy in adults and adolescents.

Table 2.2: South African HAART first line regimens

Regimen	Drugs		
1 A	Stavudine(d4T) 40mg every 12 hours(30mg every 12 hours if body weight<60 kg)	Lamivudine(3TC) 150mg every 12 hours	Efavirenz(EFV) 600mg at night (or 400mg if body weight<40kg)
1 B	Stavudine(d4T) 40mg every 12 hours(30mg every 12 hours if body weights<60kg)	Lamivuine(3TC)150mg every 12 hours	Nevirapine (NVP) 200mg daily for the first two weeks, increasing to 200mg every 12 hours after this.

Source: National Department of Health, South Africa, 2004.

Limitations to treatment safety and efficacy of antiretroviral therapy are influenced by a certain number of factors in individual patients. Patients on HAART commonly suffer side effects. As quoted by Schieferstein (2005) “As a result, treatment of HIV infection has become a complicated balancing act between benefits of durable HIV suppression and the risks of drug effects. About 25% of patients stop therapy within the first year of treatment because of side effects “.

2.2. NEW APPROACHES OF STAVUDINE THERAPY

Stavudine was first approved in 1994 by the Federal Drug Agency in the United States but stavudine based therapy had been discouraged due to toxicity for several years in the united Kingdom and the United States. In August 2006, during the World AIDS Conference in Toronto, the WHO advised low-income countries to drop stavudine from the first line therapy if they could afford to but because of the current wide availability of fixed dose combinations and considerably lower prices, stavudine containing regimens may still remain the most accessible option for people in urgent need of treatment in the short to medium term (Alcorn, 2006). Following a meta-analysis showing lower doses were safer and as effective, WHO issued a statement that that only low dose stavudine (30 mg) should be used (Hill A. et al, 2007).

The use of stavudine in clinical practice was being reconsidered in the light of recent trial results which indicated that alternative NRTI drugs had comparable efficacy and a lower risk of adverse events. The data had prompted new approaches to the use of this drug, with an increased emphasis on altered dosing to improve tolerability and targeted selection of patients who had a lower risk of stavudine associated toxicity (Mallal et al, 2006).

Regardless of etiology clinicians need effective strategies for managing side effects. One of the strategies they suggest may involve dosing or treatment strategies outside the approved utilization of the drugs or diagnostic tests that do not reflect the actual indication of the drug manufacturer or any regulatory agency (Lichtenstein et al, 2004).

Another view was expressed that although there might be only a single licensed dosage of a drug, in reality decision making regarding dosing can be complex when faced with the range of possible drug combinations to be used in patients of varying weight, hepatic and renal status , baseline genotype, race and gender (Back, 2005).

British treatment guidelines recommend therapeutic drug monitoring (TDM) in circumstances where providers are using doses other than recommended by the manufacturer. TDM should also be used in cases of severe liver impairment and to manage toxicity. In patients with high peak levels, but no evidence of toxicity, dosage reduction may be a strategy to prevent toxicity from developing while the treatment remains still clinically effective (Family Health International, 2004).

2.3. SYMPTOMATIC HYPERLACTATAEMIA/LACTIC ACIDOSIS

Clausen first identified in 1925 the accumulation of lactic acid in blood as a cause of acid-base disorder and in their classic 1976 monograph; Cohen and Woods classified the causes of lactic acidosis according to the presence or absence of adequate tissue oxygenation and divided lactic acidosis into 2 categories, type A and type B.

Type A is lactic acidosis occurring in association with clinical evidence of poor tissue perfusion or oxygenation of blood (e.g. hypotension, cyanosis, cool and clammy extremities) while in type B such clinical evidence does not exist (Cohen & Woods, 1976).

Lactate is a by-product of the breakdown of glucose in the body and accumulates under anaerobic conditions due to mitochondrial toxicity. Although lactic acidosis is very rare, people who develop it can become dangerously ill, or even die. Lactic acidosis has been linked to body fat and metabolic changes seen among people on highly active antiretroviral therapy (Carr, 2000). Wilson (2002) describes lactic acidosis as follows:"This serious and potentially fatal side-effect of the NRTIs is most frequently associated with stavudine (d4T). The mechanism of action is thought to be related to mitochondrial toxicity". The molecular target of NRTI-induced mitochondrial toxicity is DNA gamma polymerase which is responsible for the replication of mitochondrial DNA. As quoted by Moyle (2001) "Initial symptoms often include nausea, vomiting, and abdominal pain although in more insidious cases fatigue and weight loss may predominate. Subsequently, shortness of breath, tachypnea and hyperventilation, liver and/or renal failure, clotting abnormalities, seizures, cardiac arrhythmia, and death ensue. Biochemical abnormalities include elevated lactate and lactate: pyruvate ratio, acidosis with pH <7.35, low bicarbonate, widened anion gap, elevated lactate dehydrogenase and often (but not invariably) elevated hepatic transaminases, and creatinine kinase ".

Normal blood lactate levels in healthy adults are 1.3 ± 0.4 with a normal range from 0.5 to 1.6 mmol/L. Arterial blood lactate levels above 2 are considered clinically important (Kost, 2002).

Table 2.3. Reference ranges of blood lactate using different sample sites in healthy volunteers

Sample	Reference range
Arterial blood	0.5 – 1.6 mmol/L
Capillary blood	0.5 – 1.5 mmol/L
Venous blood	0.3 – 1.5 mmol/L

Source: adapted from Kost, 2002.

Serum lactate levels of 2 to 5 mmol/liter are considered as elevated and need to be correlated with symptoms. A lactate level above 5 mmol/liter is severe. Acidosis may or may not be present. It is important to know either the bicarbonate or the pH in order to diagnose acidosis. The Department of Health and Human Services (2005) indicated that a confirmed lactate level above 10 mmol/liter established the diagnosis of NRTI-associated lactic acidosis in a patient receiving such a therapy and measurement of arterial pH to confirm the presence of acidosis was not necessary in most cases.

Vrouenraets et al, 2001 classified hyperlactataemia as mild if between 2.0 - 5 mmol/liter, serious if > 5 mmol/liter.

Table 2.4 Lactate levels as defined by the Southern African HIV Clinicians Society

lactate< 2.5 mmol/L	lactate 2.5-5mmol/L	lactate 5-10 mmol/L	lactate>10 mmol/L
Hyperlactataemia excluded, investigate for other causes.	Mild hyperlactataemia, minimal symptoms and bicarbonate>20 mmol/L	Moderately severe and or bicarbonate between 15-20 mmol/L	Severe and or bicarbonate< 15 mmol/L

Source: adapted from Southern African Journal of HIV Medicine, March 2006.

For this study, we applied the standard outlined by the National Department of Health, South Africa, 2005 and will consider hyperlactataemia as lactate levels above 2.0 mmol/L and lactic acidosis as elevated lactate levels with the clinical signs and or biochemical abnormalities as described above.

Elevated blood lactate level had also been observed in HIV – negative infants with HIV–positive mothers who were exposed to antiretroviral drugs during gestation, birth and postnatally. The risks of this was greatest in children exposed to didanosine, but the majority of the infants showed regression to normal lactate levels within the first year of life. Symptoms were very rare but included slow psychomotor development (Noguera, 2004). However, the effect of didanosine in infants was not investigated in this thesis.

2.4. EPIDEMIOLOGY

A French study reported that 0.8 % of patients taking antiretroviral drugs developed symptoms of high lactate each year (Gerard, 2000). A case series from Spain showed that ten of twelve individuals receiving treatment with stavudine developed symptoms of high lactate levels (Falco, 2002). All NRTIs have been implicated in lactic acidosis, but several reports linked stavudine and didanosine most closely with lactic acidosis (Mokrzycki, 2000; Moore, 2000; Lonergan, 2000). Lactic acidosis with hepatic steatosis was more frequent in patients taking stavudine than with other NRTIs, such as zidovudfine and didanosine. Its estimated frequency is rare, about 0.85 cases per 1000 patients per year (Department of Health and Human Services Guidelines, 2005).
Chronic and asymptomatic mild hyperlactataemia (2.1-5.0 mmol/L) was relatively frequent among HIV-infected patients receiving NRTI therapy usually longer than six months, with an occurrence of approximately 15 to 35 % in those patients (Dagan et al, 2002).

Approximately 1 % of individuals starting antiretroviral therapy in Botswana developed the potentially fatal side-effect; lactic acidosis (Wester et al, 2007).This incidence of 1 % of lactic acidosis was significantly higher than that seen in industrialized countries.

2.5. CAUSES AND RISK FACTORS

The following have been identified as risk factors: high body mass index (BMI), female gender, pregnancy, underlying liver disease, age, use of stavudine (Bartlett et al, 2008).
A reported average duration of exposure to nucleoside analogs usually longer than six months may be a factor in the development of lactic acidosis (Dagan et al, 2002).

However, some cases have been reported in people within 20 months of starting antiretroviral therapy, suggesting that lactic acidosis is not always the result of long-term accumulative toxicity (Falco, 2002).

2.6. SURVIVAL

Despite the occurrence of side effects and challenges to people living with HIV and AIDS; the antiretroviral therapy with stavudine containing regimens remains the most accessible option for people in urgent need of treatment in the short to medium term. Therapy for HIV presented new challenges but it has dramatically improved rates of mortality and morbidity, prolonged lives, improved quality of life, revitalized communities and transformed perceptions of HIV/AIDS from a plague to a manageable disease (WHO, 2004).

CHAPTER 3: AIM AND OBJECTIVES

3.1. AIM

The aim of this study was to establish whether stavudine dosage reduction prevent toxicity from developing and minimize the incidence of symptomatic hyperlactataemia/lactic acidosis (LA).

3.2. OBJECTIVES

The objectives of the study were to:

-Determine the proportion of female adult HIV/AIDS infected patients on HAART with symptomatic hyperlactataemia/lactic acidosis.

-Compare the incidence of symptomatic hyperlactataemia/lactic acidosis with regard to gender, weight and body mass index.

-Compare the incidence of LA in the group receiving a reduced dose of stavudine and those taking the standard dose with regard to gender, body mass index, CD4 count and viral load.

CHAPTER 4: METHODOLOGY

4.1. STUDY DESIGN

A retrospective study using patient files was done. This is a pilot study to lay a foundation for a bigger study in order to obtain conclusive data on the incidence of symptomatic hyperlactataemia/lactic acidosis.

4.2. STUDY SITE

This study was conducted at the Adult ARV clinic of Dr George Mukhari Hospital, Tshepang Clinic. Dr George Mukhari is a tertiary or academic hospital located in Ga-Rankuwa, North of Pretoria. It is one of the biggest hospitals in Gauteng and patients are referred to this institution from Mpumalanga, Limpopo and North West provinces. The ARV roll out began in August 2004. At the time of data collection, between February and March 2006, more than a thousand adult patients were on antiretroviral treatment and many more on co-trimoxazole and vitamin B Complex as part of routine care (Personal communication, Dr Kangawaza).

4.3. MATERIALS

Patient cards (prescription sheets), clinical and laboratory sheets in patients files were accessed and data transferred to data collection forms (See appendix1).

4.4. STUDY POPULATION

Only patients on stavudine containing regimens and treated at the Adult ARV clinic, Tshepang Clinic, Dr George Mukhari Hospital from August 2004 to January 2006 were included.

4.4.1. STUDY SAMPLE

With alpha 0.05 and beta 0.5, a response rate of 50%, a sample size of 86 is required to compare the incidence of lactic acidosis in dichotomous groups with ± 10 % precision levels (Israel, 1992). Records of treated patients were scrutinized for the purpose of this study. A total of 88 patients were included in the analysis as part of this study.

4.4.2. INCLUSION CRITERIA

Subjects used included only adult patients (≥14 years); male and female HIV/AIDS patients on stavudine based regimens that were on treatment during the period from August 2004 to January 2006 (18 months). Patients who died or stopped their treatment within the 18 months were also included. Inclusion criteria focused on stavudine dose prescribed when the patients started first their treatment.

4.4.3. EXCLUSION CRITERIA

Treatment issued after 31 January 2006 and all combinations without stavudine.

4.5. DATA COLLECTION

Between February and March 2006, a data capturer collected the data from patient files and the researcher reviewed the same medical record to avoid bias and mistakes that were likely to occur. The following information was recorded (see also appendix 2):

- patient file number
- gender
- age

- race
- names of prescribed drugs and dosages
- ARV start date
- ARV stop date
- duration of treatment
- height
- weight between 0-6 months of treatment
- weight between 6-12 months of treatment
- weight above 12 months of treatment
- BMI between 0-6 months of treatment
- BMI between 6-12 months of treatment
- BMI above 12 months of treatment
- CD4 count between 0-6 months of treatment
- CD4 count between 6-12 months of treatment
- CD4 count above 12 months of treatment
- viral load between 0-6 months of treatment
- viral load between 6-12 months of treatment
- viral load above 12 months of treatment
- lactate levels between 0-6 months of treatment
- lactate levels between 6-12 months of treatment
- lactate levels above 12 months of treatment
- ARV interruption first time
- ARV interruption second time

- side effects before first interruption
- side effects after first interruption
- ARV re-start date after first interruption
- cause of interruption
- stavudine reduced dose received
- outcome lactate levels before and after interruption
- change of regimen
- survival
- death and cause death

4.6. BRIEF DESCRIPTION OF CERTAIN VARIABLES

4.6.1. BODY MASS INDEX

The body mass index was calculated using the formula:

BMI=weight (kg)/height² (m²).

Table 4.1: Body Mass index classification

Classification	BMI in Kg/m²
Underweight	Less than 19.9
Healthy weight	20-24.9
Overweight	25-29.9
Obese	30-39.9
Very obese	More than 40

Source: Standard Treatment Guidelines and Essential Drug list, edition 2003.

4.6.2. CD4 COUNT

As quoted by Bartlett (2008) “This is a standard test to assess prognosis for progression to AIDS or death, to formulate the differential diagnosis in a symptomatic patient, and to make therapeutic decisions regarding antiviral treatment and prophylaxis for opportunistic pathogens”. Furthermore Bartlett (2008) also indicated that in response to highly active antiretroviral treatment, the CD4 count typically increased ≥50 cells/mm^3 at 4 to 8 weeks after viral suppression with antiretroviral treatments and then increased an additional 50- 100 cells/mm^3/year thereafter.

4.6.3. VIRAL LOAD

Viral load is another laboratory marker used to monitor treatment progression. One key goal of therapy is a viral load below the limits of detection at < 50 copies/mL for the Amplicor assay, < 75 copies/ml for the Versant assay and < 80 copies/mL for the Nuclisens assay. This goal should be achieved by 16-24 weeks (Department of Health and Human Services Guidelines, 2005).

4.7. STATISTICAL ANALYSIS

For the purpose of this study, descriptive statistics were used. Results were expressed as mean values with standard deviation or as percentage/proportion. The odds ratios were calculated using the formula 2 by 2 table with a confidence interval of 95 % (Barber et al, 1999).

4.8. ETHICAL CONSIDERATIONS

The study was approved by the Medunsa Research Ethics Committee; reference number MP 156/2005(See Annex 3).

No personal contact was made with the patients during this study.

CHAPTER 5: RESULTS

The results are divided into demographic and clinical data.

5.1. DEMOGRAPHIC DATA

5.1.1. NUMBER OF PARTICIPANTS

We report the findings of 88 patients who had been enrolled in this study. In some of the calculations the number was reduced due to insufficient data in respect of that particular variable e.g. in calculating the number of patients who had a change in weight and body mass index, 15 participants had their height not recorded in the file thus making it impossible for the body mass index to be calculated and 7 participants had their weight not recorded between 6 to 12 months. All participants were black Africans.

5.1.2. GENDER DISTRIBUTION

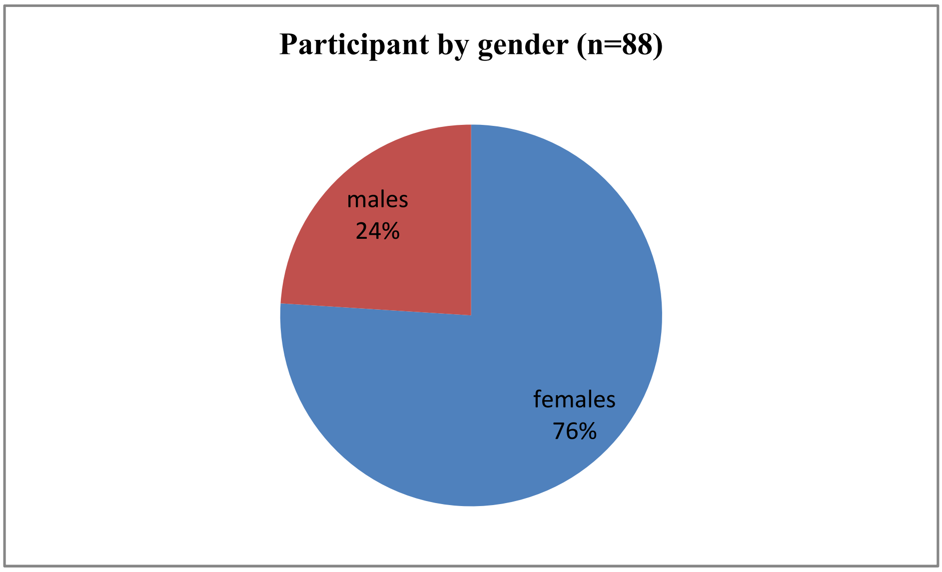

Figure 5.1: Gender distribution

5.1.3. AGE

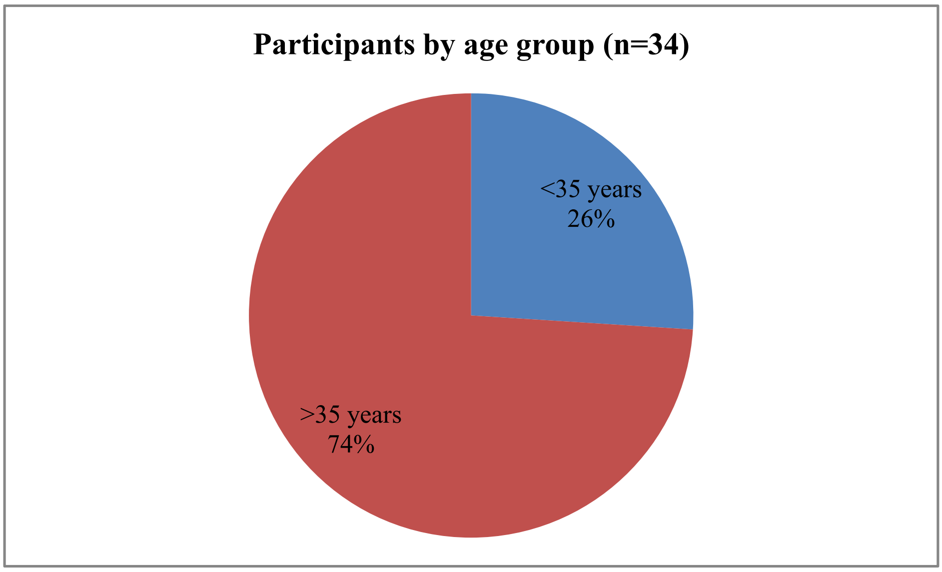

Figure 5.2: Age distribution

5.2. CLINICAL DATA

5.2.1. RATIONALE FOR RECORDING DATA INTO 3 INTERVALS

The Standard Treatment Guidelines and Essential Drug List, South Africa 2006, recommend monitoring CD4 Count and viral load 6 monthly. CD4 counts were expressed as cells/milliliter and values of viral load as copies/milliliter. Lactate levels were expressed as millimoles/liter (mmol/l) at the interval that they were checked. Lactate levels were not measured routinely, only when lactic acidosis was suspected. All the variables were grouped into intervals of six months each. Therefore, in this study interval 1 refers to treatment duration between 0 to 6 months, interval 2 refers to treatment duration between 6 to 12 months and interval 3 refers to above 12 months of treatment.

5.2.2. HEIGHT

We recorded the height of participants (n=73) in meter (m). However, 16 participants had their height not recorded. The height was used to calculate the body mass index (BMI) values.

5.2.3. WEIGHT DISTRIBUTION

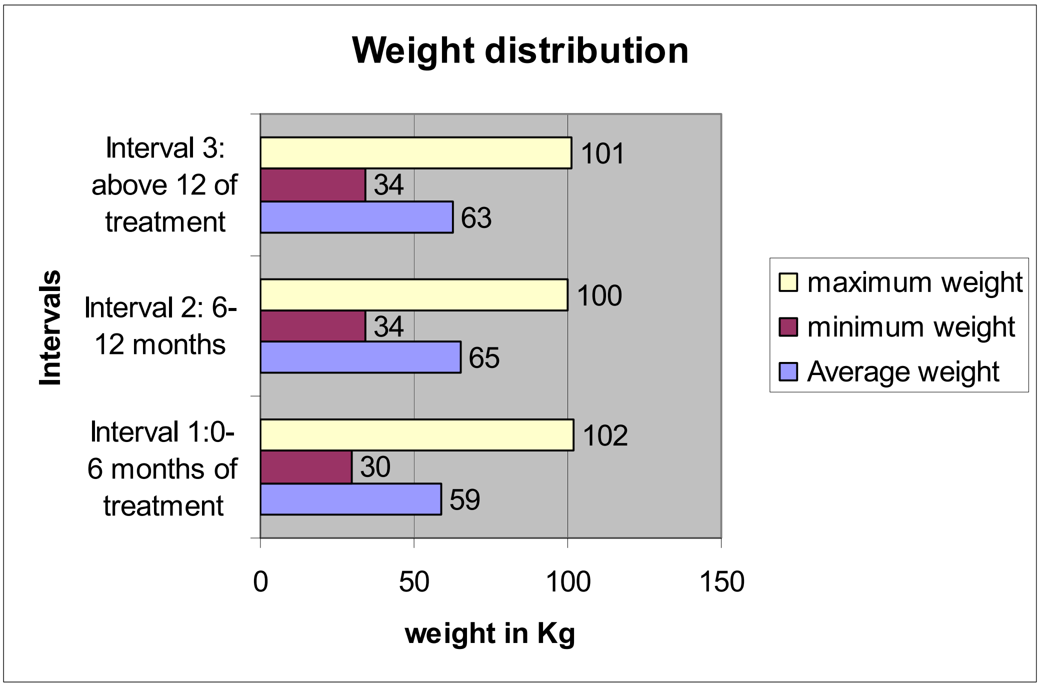

Figure 5.3: Weight distribution

5.2. 4. CHANGE IN WEIGHT

The weight changes were expressed as the percentage of weight difference between intervals of treatment in individual participants.

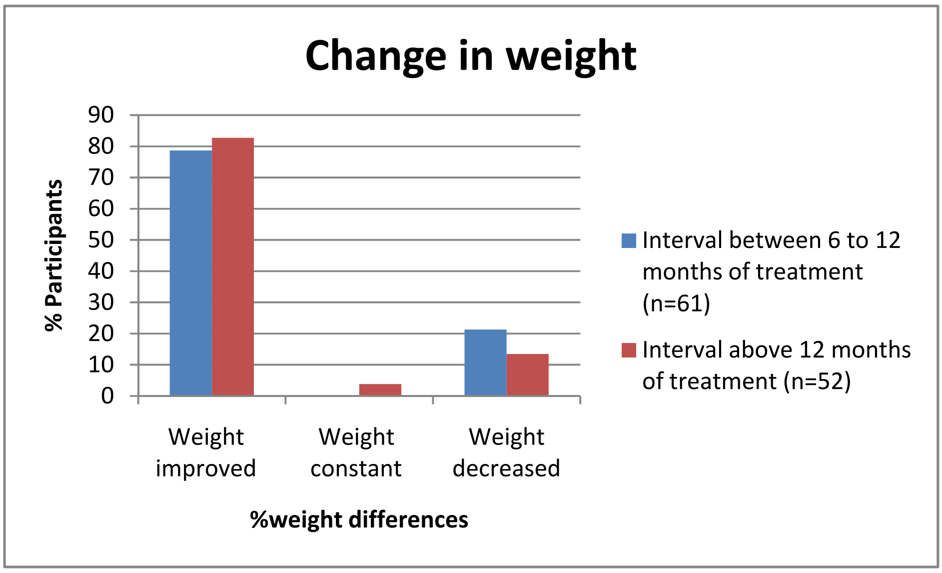

Figure 5.4: Comparison of weight change between intervals of treatment in females.

There was a body weight improvement in 78.7 % of female participants and a body weight decrease in 21.3 % of female participants between 6 to 12 months of treatment vs. 82.7 % of body weight improvement, 3.8 % constant body weight and 13.5 % of body weight decrease above 12 months of treatment. Twenty male participants' weights were recorded between 0 to 6 months of treatment and between 6 to 12 months of treatment, 87.7 % had gained body weight at 6-12 months of treatment.

Table 5.1.weight differences in percentage at 6-12 months of treatment

	Improved (n= 48)	Constant (n= 0)	Decreased (n= 13)
Range	1.5-60.4	0	(-13.0)-(-0.2)
Mean	16.0	0	-4.9
Standard deviation	13	0	3.5

Sixty-one female patients weight were recorded for 0 to 6 months and 6 to 12 months of treatment, when compared using a paired t-test, there was a highly significant difference, $p<0.05$. The range of weight differences between 6 to 12 months is shown in table 5.1.

Table 5.2.weight differences in percentage above 12 months of treatment

	Improved (n= 23)	Constant (n= 7)	Decreased (n= 22)
Range	0.3-12.6	0	(--26.5)-(-0.1)
Mean	4.6	0	-6.6
Standard deviation	3.2	0	6.59

Above 12 months of treatment, 52 female participants had their weight recorded, when compared with the precedent interval of treatment (6 to 12 months) using a paired t- test, there was a significant difference, $p < 0.05$. The range of weight differences above 12 months of treatment is shown in table 5.2.

5.2.5. CHANGE IN BODY MASS INDEX

Table 5.3. Comparison of body mass index of patients

BMI classification	interval 1(n= 72)	interval 2 (n=71)	interval 3 (n=62)
Underweight	29.17 %	9.86 %	12.90 %
Healthy weight	40.28 %	43.66 %	43.55 %
Overweight	23.61 %	32.39 %	35.48 %
Obese	6.94 %	14.08 %	8.06 %
Very obese	0	0	0

The comparison of body mass index (BMI) in individual participants during the 3 intervals of treatment was used to estimate the percentage of the participants whose BMI classification changed in the course of treatment.

After the first six months of treatment the BMI showed an improvement in underweight participants; 29.17 % of participants were underweight between 0-6 months of treatment vs. 9.86 % of participants between 6 to 12 months of treatment. Overweight and obese participants increased after six months of treatment, with a cumulative percentage of 30.55% between 0-6 months vs. 46.47% between 6 to 12 months of treatment.

5.2.6. CD4 COUNT DISTRIBUTION

Table 5.4. CD4 count distribution

Interval of treatment	Range	Median
0 to 6 months (n=86)	3-621 cells/mm³	75.5 cells/mm³
6 to 12 months (n=84)	95-456 cells/mm³	221.5 cells/mm³
above 12 months (n=21)	93-864 cell/mm³	306 cells/mm³

In the first six months of treatment (n=86), the baseline CD4 cell count ranged from 3 to 621 cells/mm³, median = 75.5 cells/mm³. In the interval between 6 to 12 months (n=84) the CD4 count ranged from 95 to 456 cells/mm³, median=221.5 cells/mm³. Above 12 months of treatment (n=21), the CD4 count ranged from 93 to 864 cells/mm³, median =306 cells/ mm³. The median CD4 count for the first six months was 75.5 vs. 221.5 cells/ mm³ for the period between 6 to 12 months vs. 306 cells/mm³ for the period above 12 months.

5.2.7. CHANGE IN CD4 COUNT

Table 5.5. Change in CD4 count

Change in CD4 count	Interval 2 compared with interval 1 (n=85)	Interval 3 compared with interval 2 (n=20)
Improved	91.76 %	65 %
Constant	1.18 %	0
Decreased	7.06 %	35 %

The change in CD4 count in individual participants was expressed as the difference of CD4 count values between interval 2 (6 to 12 months of treatment) and the baseline CD4 count at 0 to 6 months of treatment, (n=85) and the difference between interval 3 (above 12 months of treatment) and interval 2 (6 to 12 months), (n=20). Sixty-six female patients' CD4 counts were recorded for 0-6months and 6-12months, when compared using a paired t-test, there was a highly significant difference p value <0.05. 19 male patients CD4 counts were recorded for 0-6months and 6-12months, when compared with a paired test, there was a highly significant difference, p value<0.05.

Between 6 to 12 months of treatment, 91.76 % of participants had improved their CD4 cell counts vs. 65 % above 12 months of treatment.

All the 19 female participants who received stavudine reduced dose from 40 mg to 30 mg had an improvement on their CD4 counts even in those 8 who developed further elevated lactate levels.

5.2.8. VIRAL LOAD DISTRIBUTION

Table 5.6. Viral load

Interval of treatment	Detectable	undetectable
0 to 6 months (n=70)	68	2
6 to 12 months (n=84)	6	78
above 12 months (n=26)	7	19

In the first 6 months of treatment the baseline viral load was done in 70 patients and ranged from 50 to 750000 copies/mL. Between 6 to 12 months of treatment (n=84) the viral load ranged from undetectable values to 74784 copies/ mL. Above 12 months of treatment (n=26) the range was from undetectable to 230000 copies/ mL.

5.2.9. CHANGE IN VIRAL LOAD

Table 5.7. Change in viral load

Change in viral load	Interval 1(n=70)	Interval 2 (n=84)	Interval 3 (n=26)
Detectable	100 %	7.14 %	26.9 %
Undetectable		92.86 %	73.1 %

Between 6 to 12 months of treatment only 7.14 % of participants had detectable viral load (> 50 copies/mL) values vs.100 % of participants that had detectable values of viral load in the first six months of treatment; this is a highly significant difference.

Above 12 months the data was relatively little with 26 participants that may justify the increased percentage of detectable values; 26.9 % of detectable values of viral load vs. 7.14 % of detectable values at 6 to 12 months of treatment.

5.3. STAVUDINE PRESCRIBED

Table 5.8: Participants by gender and stavudine prescribed

Gender	stavudine prescribed	N	Percent
FEMALES	40 mg	29	32.96
	30 mg	38	43.18
MALES	40 mg	7	7.95
	30 mg	14	15.91
	Total	88	100.0

The stavudine containing regimen had either 40 mg or 30 mg. 32.96% (n=29) were female adults who started treatment on 40 mg stavudine while 43.18% (n=38) were females on 30 mg stavudine. 7.95 % (n=7) were males who started on 40 mg stavudine while 15.91% (n=14) started on 30 mg stavudine.

5.4. LACTATE LEVELS

5.4.1. LACTATE LEVELS OF PATIENTS BEFORE STAVUDINE DOSE REDUCTION

Table 5.9: Participants on 40 mg stavudine

Stavudine dose	Gender	N	Elevated lactate levels	Normal lactate levels
40 mg	Female	29	27.8 % (n=10)	52.8% (n=19)
	Male	7	5.5% (n=2)	13.9 % (n=5)
	Total	36	33.3 % (n=12)	66.7 % (n=24)

Out of 29 female participants on 40 mg stavudine 10 developed elevated lactate levels while 19 further changed from 40 mg to 30 mg stavudine but 8 further developed elevated lactate levels on 30 mg stavudine. Only 2 out of 7 male participants developed elevated lactate levels on 40 mg stavudine.

Table 5.10: Participants on 30 mg stavudine

stavudine dose	Gender	N	Elevated lactate levels	Normal lactate levels
30 mg	Female	37	26 % (n=13)	48 % (n=24)
	Male	13	4 % (n=2)	22% (n=11)
	Total	50	30 % (n=15)	70 % (n=35)

Out of 37 female participants on 30 mg stavudine 13 developed elevated lactate levels. In the group of males 2 out of 13 developed elevated lactate levels on 30 mg stavudine.

Treatment duration on onset of the first symptoms of elevated lactate levels ranged from 2 to 18 months, mean=7.89 and standard deviation=3.47.

5.4.2. LACTATE LEVELS AFTER STAVUDINE DOSE REDUCTION

Table 5.11: Female participants by stavudine reduced dose (n=20)

Stavudine dose	n	Elevated lactate levels	Normal lactate levels
40 mg→30 mg	19	n=8	n=11
30 mg→ 20 mg	1	n=0	n=1

In the group of female participants started on 40 mg stavudine 19 out of 29 further received stavudine reduced dose from 40 mg to 30 mg while only one received reduced dose from 30 mg to 20 mg stavudine. Eight (42.1 %) out of nineteen female participants further developed elevated lactate levels vs. 52.38 % (n=11) who remained stable on treatment. There were only 11 females participants started on 40 mg stavudine who did not develop elevated lactate levels after they changed their stavudine dosage. No cases of elevated lactate levels were recorded in the group from 30 mg to 20 mg.

Female participants who received reduced dose had a cumulative exposure to 40 mg stavudine and 30 mg stavudine as reduced dose for a period ranged from 7 to 14 months of treatment, mean=10 and standard deviation=2.3

5.4.3. LACTATE LEVELS DISTRIBUTION

In the 18 months of this study, there were 40.70 % (n=35) cases of elevated lactate levels and 59.30% (n=51) cases of participants not having elevated lactate levels. Two participants were lost to follow up.

Table 5.12: Elevated lactate levels by treatment duration

	0-6 months (n=10)	6-12 months (n=17)	Above 12 months (n=6)
Range	2.3-9.8 mmol/l	2.5-9.1 mmol/l	2.8-4.8 mmol/l
Mean	4.98 mmol/l	5.7 mmol/l	3.85 mmol/l
Standard deviation	2.43	2.35	0.90

Two participants had lactate levels not recorded but reportedly died of lactic acidosis complications.

Table 5.13. Classification of participants by lactate levels

	0-6 months (n=10)	6-12 months (n=17)	Above 12 months (n=6)
Mild or moderate hyperlactataemia (2.1-5 mmol/l)	6	8	6
Severe hyperlactataemia (above 5 mmol/l)	4	11	0
Total	10	19	6

Out of 35 cases identified, two female participants had their lactate levels not recorded but reportedly died of complications of lactic acidosis, thirteen participants had recorded lactate levels above 5 mmol/l and twenty had lactate levels between 2.1-5.0 mmol/l. Thirty-one participants were females while 4 were males. Twenty-seven cases of elevated lactate levels occurred before stavudine dose reduction and 8 after stavudine dose reduction. This may suggest that the stavudine dose reduction may increase the chances of patients being stable on their treatment but does not prevent toxicity from developing.

5.4.4. COMPARISON OF LACTATE LEVELS BY STAVUDINE DOSE

Table 5.14: Female participants by stavudine dose

	stavudine 40 mg	stavudine 30 mg	Odds ratio (±95% CI)
Elevated lactate levels	27.27 % (n=18)	19.70 % (n=13)	3.02 (1.10-8.29)
Normal lactate levels	16.66 % (n=11)	36.37 % (n=24)	
Total	43.93% (n=29)	56.07 % (n=37)	

The odds ratio of developing elevated lactate levels when commencing treatment on 40 mg stavudine were 3.02 times higher than on 30 mg stavudine, 95% CI (1.10-8.29).

Table 5.15: Male participants by stavudine dose

	stavudine 40 mg	stavudine 30 mg	Odds ratio (±95% CI)
Elevated Levels	10 % (n=2)	10 % (n=2)	2.2 (0.24-20)
Normal levels	25 % (n=5)	55 % (n=11)	
Total	35 % (n=7)	65 % (n=13)	

The odds for developing elevated lactate levels on stavudine 40 mg were 2.2 times higher than on stavudine 30 mg, 95% CI (0.24-20).

Table 5.16: Comparison of participants on 40 mg stavudine and 30 mg stavudine

	stavudine 40 mg	stavudine 30 mg	Total
Elevated Levels	20	15	35
Normal levels	16	35	51
Total	36	50	86

Odds for developing elevated lactate levels in participants when commencing treatment were 2.92 times higher in the group on stavudine 40 mg than in the group on stavudine 30 mg, 95% CI (1.10-2.51).

Table 5.17: Female participants by stavudine reduced dose (n=20)

Outcomes	stavudine 30 mg	stavudine 20 mg	Total
Elevated levels	8	0	8
Normal levels	11	1	12
Total	19	1	20

The sample being really small with no participants with elevated lactate levels in the group received 20 mg stavudine as reduced dose, objectively no statistical analysis could be attempted.

5.4.5. LACTATE LEVELS BY BODY MASS INDEX VALUES

Table 5.18: BMI values by stavudine dose

BMI classification	stavudine 40 mg	stavudine 30 mg	Total
Underweight	0	3	3 (8.57%)
Healthy weight	1	6	7 (20%)
Overweight	2	6	8 (22.86%)
Obese	5	2	7 (20%)
Missing values	4	6	10 (28.57%)
	12	23	35 (100%)

Out of 35 cases of elevated lactate levels, 42.86 % (n=15) were overweight and obese, 20 % (n=7) had a healthy weight and 8.57% (n= 3) were underweight.

The BMI values ranged from 15.9 to 39.1 kg/m²; mean=27.2 kg/m² ± 6.57.

.

5.5. TREATMENT DURATION

5.5.1. TREATMENT DURATION ON ONSET OF ELEVATED LACTATE LEVELS

A total follow up duration of 18 months was recorded with all the patients initiated by the study site with an exception of 1 female participant who started treatment in the private sector but transferred to the site who had a total duration of 23 months of treatment.

28.57 % (n=10) developed elevated lactate between 0 to 6 months, 54.29 % (n=19) had elevated lactate levels in the period from 6 to 12 months and 17.14 %(n=6) of elevated lactate levels occurred above 12 months of treatment. This may suggest that the length of treatment may impact on the incidence of elevated lactate levels.

Patients started on 40 mg and 30 mg stavudine had a treatment duration ranged from 3 to 18 months, mean=8.5 months ± 3.85 while those received reduced dose had a cumulative exposure to 40mg stavudine and 30 mg stavudine as reduced dose for a period ranged from 7 to 14 months, mean= 10 months ± 2.3.

5.5.2. TREATMENT INTERRUPTION DURATION

All the 35 participants with elevated lactate levels interrupted their treatment until lactate levels returned to normal. The interruption ranged from 1 to 3 months in order to allow lactate levels to come back to normal before rechallenging the patient with antiretroviral agents.

5.5.3. TREATMENT RE-START AND CHANGE IN REGIMEN

Out of 35 cases of elevated lactate levels, 31 participants re-started after normalization of lactate levels and were all switched to zidovudine containing regimen for the rest of their treatment while 4 died due to complications of lactic acidosis related symptoms.

5.6. CONSEQUENCES OF HYPERCLACTATATEMIA AND CLINICAL FEATURES

Table 5.19: Symptoms/clinical features reported

Type	Before interruption (n=34)	After interruption (n=27)
Hospitalization	14.71%(n=5)	3.70%(n=1)
Death	11.76%(n=4)	0
Dyspnoea	2.94%(n=1)	0
Fatigue	5.88%(n=2)	0
Lipodistrophy	2.94%(n=1)	7.40%(n=2)
Peripheral neuropathy	8.82%(n=3)	7.40%(n=2)
Severe headache	0	3.70%(n=1)
Skin rash	5.88%(n=2)	0
No side effects	47.05%(n=16)	77.77%(n=21)

The symptoms/clinical features reported refer to 35 participants who had elevated lactate levels in this study. There was an improvement in symptoms/clinical features reported after the stavudine dose reduction. 47 % of participants (n=16) were reported not having symptoms/clinical features before the first interruption of treatment vs. 78 % (n=21) after the interruption and stavudine dose reduction.

CHAPTER 6: DISCUSSION

6.1. STAVUDINE CONTAINING REGIMEN AND STUDY POPULATION

All the 88 participants followed in this study were started on an appropriate stavudine combination with other antiretroviral drugs as required by the guideline for the South African public sector, except for one female participant who commenced her treatment in the private sector with a combination containing stavudine and didanosine. She was the only participant exposed to didanosine and had also elevated lactate levels after 18 months of treatment. Several reports have linked stavudine and didanosine closely with lactic acidosis (Moore, 2000).

Incidence as such could not be calculated in this study due to a small sample size to allow such calculations therefore we could not discuss incidence but the study showed that the treatment duration on onset of elevated lactate levels (mean=8.5 months ± 3.85) was consistent with the findings of another study conducted in South Africa which reported that most patients (85%) presented with severe hyperlactataemia after having been on ART for between 6 and 14 months (Osler et al, 2006).

This study showed that 40.70 % of participants (n=35) had elevated lactate levels with signs or symptoms that obliged clinicians to stop treatment in those patients. Four out of thirty-five (11.42 %) reportedly died due to complications of symptoms of lactic acidosis. Vrouenraets (2002) found that between 30 and 60 % of people on NRTI therapy had elevated levels of lactate in their blood, although levels were rarely high enough to induce symptoms of lactic acidosis. A Spanish study concluded that symptomatic hyperlactataemia was reported in 0.2 to 2.5% of infected adults and the syndrome of lactic acidosis /hepatic steatosis was rare (Falco et al 2002).

Another study conducted in Botswana reported that approximately 1% of individuals starting antiretroviral therapy developed lactic acidosis (Wester et al, 2007). Michael Carter (2007) commented that the incidence of lactic acidosis found in Botswana was significantly higher than that seen in industrialized countries. The findings in this study are contradictory with the following findings in studies conducted in Europe (Vrouenraets, 2002; Gerard, 2000; Falco, 2002).

The US Department of Health and Human Services (2005) reported that lactic acidosis with hepatic steatosis had a rare estimated frequency, about 0.85 cases per 1000 patients per year. A French study reported 0.8% of patients taking antiretroviral agents develop symptoms of high lactate each year (Gerard 2000).

6.2. WEIGHT AND BODY MASS INDEX

Obesity, severe infection and malnutrition are indicated as risk factors for developing lactic acidosis (Brinkman 1999). High body mass index, female gender and African-American ethnicity were among other factors for developing lactic acidosis in Americans (Department of Health and Human Services, 2005).

In this study 15 out of 35 cases (43 %) with elevated lactate levels were overweight and obese. An increase of body weight is an indication of a successful therapy but obesity should be avoided. Once an adult has achieved his/her normal body weight, discourage further weight gain in those on antiretroviral drugs (Spencer et al, 2007).

One of the goals of antiretroviral treatment is to increase the weight of the patient. Evidence –based research confirms that weight loss predicts death (Wheeler et al, 1998). The weight improvement was shown in a decrease of underweight participants and an increase in overweight and obese participants. During the first six months of treatment, 29.17% of participants were underweight, 40.28% had a healthy weight while 30.55% were overweight and obese. In the period between 6 to 12 months, there was a decrease in the underweight category with a 9.86% of participants and an increase in the category of overweight and obese with 46.47% of the participants while 43.66% maintained a healthy weight. During the 1980s and early 1990s,"Slim Disease" was a term used throughout Central Africa to characterize a patient with end-stage HIV infection or AIDS (Serwadda et al, 1985)

6.3. CHANGE IN CD4 COUNT AND VIRAL LOAD

Another study reported that after six months of highly active antiretroviral therapy, median CD4 cell count had increased to 343 cells/mm³ and 72 % of patients had a viral load below 500 copies/ml (Arch Intern Med, 2005). In this study 91.76 % of participants had improved their CD4 cell count and 93 % of participants had a viral load below 50 copies/ml between 6 to 12 months of treatment. Participants who received stavudine reduced dose showed an increase in their CD4 count and a reduction in viral load as well as those patients started on stavudine 30 mg.

6.4. TREATMENT DURATION AND LACTATE LEVELS

Most patients presented with severe symptomatic hyperlactataemia after being on antiretroviral therapy for between 6 and 14 months and that period was thus the critical time to monitor symptoms of symptomatic hyperlactataemia and weight loss (Osler et al , 2007). In this study participants presented with elevated lactate levels from 3 to 18 months of treatment with the majority of cases between 6 to 12 months of treatment. Some other authors hold the view that duration of exposure to NRTI may be a factor in the development of lactic acidosis. However, some cases had been reported in people within 20 months of starting antiretroviral therapy, suggesting that lactic acidosis is not always the result of long- term cumulative toxicity (Falco, 2002). Lactic acidosis most commonly occurs in persons on prolonged (> 6 months) therapy; although there may be additional risk factors (Moyle, 2001).

6.5. STAVUDINE REDUCED DOSE

Of 29 female participants started on 40 mg stavudine, 19 received a reduced stavudine dose (30 mg) between 2 and 6 months after a previous exposure to 40 mg stavudine but 8 participants (42 %) further developed elevated lactate levels and 11 were stable on treatment. Regarding the use of lower dose stavudine, a randomized study in Thailand (ACTT002/ARV 065) found that half dose stavudine (20 mg) was as effective as full dose stavudine (40 mg), lactic acidosis occurred in 3 subjects (2.7 %) in the full dose arm and none in the half-dose arm (Mallal et al, 2005). In this study only one participant received 20 mg stavudine in the group started on 30 mg stavudine and no toxicity was reported in this case.

6.6. CONSEQUENCES OF HYPERLACTATAEMIA

Patients with elevated lactate levels also reported side effects such as fatigue, abdominal pain, peripheral neuropathy, severe headache, dyspnoea and lipodistrophy. Those side effects were consistent with the presentation of symptomatic hyperlactataemia/lactic acidosis in persons on antiretroviral therapy. Overweight women are at higher risk and should be monitored most closely. Symptoms such as abdominal pain, diarrhea, nausea and vomiting, and weight loss ≥ 3 kg as well as symptoms of neuropathy are important heralds of symptomatic hyperlactataemia (Osler et al, 2007).

CHAPTER 7: CONCLUSIONS AND RECOMMENDATIONS

7.1. CONCLUSIONS

The aim of this study was to establish whether stavudine dose reduction prevent or minimize toxicity from developing.

Odds ratio for developing elevated lactate levels in participants when commencing treatment on 40 mg stavudine were 2.92 times higher than on 30 mg stavudine, 95% CI (1.10-2.51).

The stavudine dose reduction increased the odds of patients being more stable on their treatment with less side effects reported. Cases of elevated lactate levels identified in the reduced stavudine -arm (30 mg) may suggest that the toxicity is dose and or molecule related. Halving the stavudine dose to 20 mg may even increase the probability of patients being more stable to treatment, thus reducing the limitations to treatment safety. It is of interesting note that the majority of participants in this study survived despite the side effects. Four out of 35 cases of elevated lactate levels died due to complications of lactic acidosis.

7.2. RECOMMENDATIONS

Although the sample size used in this study was relatively little, it was recommended that a tool for reporting adverse events especially in the first six months during antiretroviral therapy should be developed.

Stavudine should be completely taken out of antiretroviral combinations despite its cost and be replaced by other molecules with fewer side effects.

REFERENCES

A joint UNICEF-UNAIDS-WHO-MSF Project.2003. Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS. Available at http:// www.who.int/HIV_AIDS. Accessed on 20/06/2005.

Alcorn K. 2006. Drop stavudine from first line therapy, WHO advises low-income countries-if you can afford to. [Online].Available at http://www.aidsmap.com. Accessed: 11/08/2006.

Back D.J. 2005. Intervariability in antiretroviral therapy: a role for Therapeutic Drug Monitoring.39th Congress of South African Pharmacology Society. Cape Town. 2005.

Barber N. & Willson A. Clinical pharmacy survival guide. Churchill Livingstone. 1999.

Bartlett J.G., Gallant J.E. & Conradie F.M. 2008. Medical management of HIV infection. South African edition. Durham 2008.

Brinkmann K. et al, 1999. Mitochondrial toxicity induced by nucleoside –analogue reverse transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral therapy related lipodistrophy. Lancet 354(9184): 1112-1115, 1999.

Carr A. & Cooper D.A. Adverse effects of antiretroviral therapy. Lancet, 2000. 356(9239):1423- 1430.

Carter M. 2007. Avoid d4T say investigators after finding high incidence of lactic acidosis in Botswana. [Online] Available at http;//www.aidsmap.com. Accessed: 16/11/2007.

Cohen R. & Woods H.F. 1976. Clinical and biochemical aspects of lactic acidosis. Blackwell Scientific. Oxford 1976.

Cornejo et al, 2003. Metabolic acidosis and hepatic steatosis in two HIV-infected patients on stavudine treatment. Arch Med Res. 2003. Jan-Feb; 34(1): 64- 69.

Dagan T., Sable C., Bray J., Gershenson M. 2002. Mitochondrial dysfunction and antiretroviral nucleoside analogue toxicities: what is the evidence? Mitochondrion, 2002.1(5):397-414.

Essential Drugs Programme, South Africa, 2006. Standard treatment guidelines and essential drug list. Edition 2006.

Essential Drugs Programmme, South Africa, 2003. Primary health care. Standard treatment guidelines and essential drugs list. Edition 2003.

Falco V., Rodriguez D., Ribera E., et al, 2002. Severe nucleoside associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. Clinical infectious Diseases.2002.34 (6):838-846.

Family Health International. 2004. Clinical course for people caring for persons living with HIV/AIDS. Arlington.

Floyd K. & Gilks C. 1997. In: Van Praag, E., Fernyaks S. & Katz A.M. The implications of antiretroviral treatments; Informal consultation, in collaboration with UNAIDS/ WHO.

Gerard Y., et al, 2000. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. AIDS 14(17): 2723-2730, 2000.

Hill A., Ruxrungtham K., Hanvanich M. et al, 2007. Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. Expert Opin Pharmacoter.2007; 8(5):679-88.

Israel G. Determining sample size. University of Florida. Nov 1992.

Journal of American medical Association, 2002; 288:222.

Kost J. Principle and practice of point care testing. Lippincott & Wilkins. 2002.

Lichtenstein A.K. & Corales B.R., 2004. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors in the treatment of HIV: focus on safety. [Online] Available at http: //www.hivatis.org. Accessed: 12/09/2005.

Lonergan J.T., Hlavir D., Barber E. & Matthews W.C. 2000. Incidence and outcome of hyperlactataemia associated with clinical manifestations in HIV-infected adults receiving NRTI containing regimens. Eighth conference on retroviruses and opportunistic infections. Chicago, abstract 624, 2001.

Mallal A.S. & Nolan A.D. 2005. Adverse events associated with nucleoside reverse transcriptase inhibitors. Available at http://www.medscape.com/view_article/487729. Accessed : 01/04/2005.

Moore et al, 2000. Difference in anion gap with different nucleoside reverse transcriptase inhibitors combinations. Seventh conference on retroviruses and opportunistic infections, San Francisco, abstract 55, 2000.

Moore R. et al, 2000. Difference in anion gap with different nucleoside RTI combinations. Seventh Conference on Retroviruses and Opportunistic infections, San Francisco, abstract55, 2000.

Moyle G.2001. Hyperlactataemia and lactic acidosis during antiretroviral therapy: causes, management and possible etiologies. AIDS REV.2001. 3. Pages 150-156.

National Department of Health, South Africa, 2004. National antiretroviral treatment guidelines. Pretoria 2004.

National Department of Health, South Africa, 2005. Guidelines for the management of HIV-infected children. 1st edition. Pretoria. 2005.

Noguera A. et al, 2004. Hyperlactataemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. Pediatrics 114.598-603.

O'Brien M.E., Clark R.A., Besch C.L. et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. J Acquired Immune Defic Syndr. 2003.34(4):407- 414.

Osler M. et al, 2007. Severe hyperlactataemia complicating antiretroviral therapy with stavudine first-line therapy in South Africa: incidence, risk factors and outcomes. Southern African Journal of HIV Medicine. June 2007.Pages34-36.

Palella F.J., Jr., Deloria-Knoll M., Choniel J.S., et al, 2003. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4 cell strata. Ann Intern Med 2003; 138(8): 620-626.

Piot et al, 1992. AIDS in Africa, a manual for physicians. World Health Organization. Geneva. 1992.

Schieferstein C. & Bunk T. 2005. Side effects 2005. [Online]. Available at http://www.hivmedecine.com/textbook/nw.htm. Accessed: 18/05/2005.

Serwadda D., Mugerwa R., Sewankambo N. 1985. Slim disease: anew disease in Uganda and its associations with HLTV-III infection. Lancet 1985; 2: 849-852.

Southern African HIV clinicians Society. 2006. Guidelines for the prevention, diagnosis and management of NRTI-associated symptomatic hyperlactataemia and lactic acidosis. Southern African Journal of HIV Medicine. March 2006.Pages 8-15.

Spencer D.C., Harman C., Naicker T., Gohre S. 2007. Nutritional guidelines for HIV-infected adults and children in Southern Africa: Meeting the needs. Southern African Journal of HIV Medicine. June 2007. Pages 22-30.

UNAIDS/WHO. Report on the global AIDS epidemic. Geneva, 2008.

US Department of Health and Human Services. 2005. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http:// www.aidsinfo.nih.gov. Accessed on: 12/30/2005.

Vrouenraets S.M., Treskes M., Regez R.M., Troost N., Smulders Y.M., Weigel H.M., Frissen P.H., Brinkmann K. 2001 .Hyperlactataemia in HIV-infected patients: the role of NRTI-treatment. [online]. Available at http://www.pubmed.gov. Accessed: 15/10/2006.

Wester C.W. et al, 2007. Higher than expected rates of lactic acidosis among highly active antiretroviral therapy treated women in Botswana. Preliminary results from a large randomized clinical trial. Journal of Acquired Immune Deficiency Syndrome 46:318-322.2007.

Wheeler D.A., Gilbert C.L., Launer C.A. et al, 1998. Weight loss as a predictor of survival and disease progression in HIV infection. Journal of Acquired Immune Deficiency Syndrome 1998; 18:80-85.

Wilson D. et al, 2002. Handbook of HIV medicine. Oxford University Press Southern Africa. Cape Town. 2002.

Wood Robin. 2006. The role of stavudine in the South African public sector antiretroviral programme: should the perfect be the enemy of the good? Southern African journal of HIV medicine, Issue twenty-three, June 2006.

World Health Organization, Model Formulary 2004. Geneva 2004.

World Health Organization. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach.2003 revision. Geneva 2004.

APPENDICES

Appendix 1: Data Collection Form

1. Demographic information

Patient name……………….Patient file number……………………………..
Age…………………………Gender…………………………………………
Race…………………………

2. Medication history

Dosage and stavudine containing regimen prescribed

Names	Dose/day	Date started	ARV stop date	Comments
ARV re-start names	dose/day	ARV stop/change date	Change regimen	

3. Clinical data and laboratory findings

Type	Interval 1(0 to 6 months)	Interval 2(6 to 12 months)	Interval3(above 12 months)	Comments
CD4 count				
Viral load				
Lactate levels				
Weight				
Height				
BMI				

Appendix 2: Datasheet

Part1. Demographic data

Pt hospital file	Race	Gender	Age

Part 2. Stavudine prescribed,

D4T prescribed	ARVstart date	ARV stop date	Regimen	treatment duration

Part 3. Clinical data I

CD4 Count			viral load		
0-6 months	6-12months	>12 months	0-6months	6-12months	>12months

Part 4. Clinical data II

Height	Weight			lactate levels		
	0-6months	6-12months	>12months	0-6months	6-12months	>12months

Part 5. Clinical data III

outcome lactate	side effects 1	interruption status	cause

Part 6. Clinical data IV

D4T reduced dose		D4T reduced dose	
30 mg	duration in months	20 mg	duration in months

Part 7. Clinical data V

Arv re-interruption	monitoring lactate levels			side effects2
duration in months	month1	month2	month3	

Part 8. Clinical data VI

regimen change	Date change	survival	cause death	comments

APPENDIX 3: REPC APPROVAL

APPENDIX 3: REPC APPROVAL

UNIVERSITY OF LIMPOPO
Medunsa Campus

UNIVERSITY OF LIMPOPO

RESEARCH, ETHICS & PUBLICATIONS COMMITTEE

FACULTY OF MEDICINE

CLEARANCE CERTIFICATE

P O Medunsa
Medunsa
0204
SOUTH AFRICA

Tel: 012 - 521 4000
Fax: 012 - 560 0086

MEETING: 09/2005 **PROJECT NUMBER:** MP 156/2005

PROJECT	**Title:**	Effect of stavudine dosage reduction on the incidence of symptomatic hyperlactataemia/ lactic acidosis in adults female HIV/AIDS infected patients treated at Dr George Mukhari Hospital
	Researcher:	Mr M Nlooto
	Supervisor:	Dr G Muntingh
	Co-supervisor:	Prof SWP du Plooy
	Department:	Pharmacology & Therapeutics
	Degree:	MSc (Med) (Pharmacology)

DATE CONSIDERED: November 23, 2003

DECISION OF COMMITTEE:

REPC approved the project.

DATE: December 08, 2005

UNIVERSITY OF LIMPOPO
DEPUTY DEAN
2005 -12- 08
RESEARCH
Medunsa Campus

PROF GA OGUNBANJO
CHAIRMAN (RESEARCH) REPC OF FBM

Note:	**i)**	**Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.**
	ii)	**The budget for the research will be considered separately from the protocol. PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.**

African Excellence - Global Leadership