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

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RESEARCH DISSERTATION

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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.
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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

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic name</th>
<th>FDA approval date</th>
<th>MCC registration date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>Abacavir (ABC)</td>
<td>February 1999</td>
<td>June 2001</td>
</tr>
<tr>
<td></td>
<td>Abacavir/zidovudine/lamivudine</td>
<td>November 2000</td>
<td>October 2003</td>
</tr>
<tr>
<td></td>
<td>Didanosine(ddI)</td>
<td>October 1991</td>
<td>July 1992</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine(FTC)</td>
<td>July 2003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabine/tenofovir</td>
<td>August 2004</td>
<td>May 2007</td>
</tr>
<tr>
<td></td>
<td>Lamivudine(3TC)</td>
<td>November 1995</td>
<td>June 1996</td>
</tr>
</tbody>
</table>
Table 2.1. Antiretroviral agents approved by the FDA and MCC for treatment of HIV infection continued

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic name</th>
<th>FDA approval date</th>
<th>MCC registration date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>Lamivudine/zidovudine</td>
<td>November 2000</td>
<td>November 2000</td>
</tr>
<tr>
<td></td>
<td>Stavudine (d4T)</td>
<td>June 1994</td>
<td>November 1998</td>
</tr>
<tr>
<td></td>
<td>Zalcitabine(ddC)</td>
<td>June 1992</td>
<td>Not registered</td>
</tr>
<tr>
<td></td>
<td>Zidovudine(AZT,ZDV)</td>
<td>March 1987</td>
<td>May 1989</td>
</tr>
<tr>
<td>NtRTIs</td>
<td>Tenofovir (TDF)</td>
<td>October 2001</td>
<td>May 2007</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Delavirdine (DLV)</td>
<td>April 1997</td>
<td>Not registered</td>
</tr>
<tr>
<td></td>
<td>Efavirenz (EFV)</td>
<td>September 1998</td>
<td>September 1999</td>
</tr>
<tr>
<td></td>
<td>Nevirapine (NVP)</td>
<td>June 1996</td>
<td>February 1998</td>
</tr>
<tr>
<td>Fusion Inhibitors</td>
<td>Enfuvirtide (FTC)</td>
<td>March 2003</td>
<td>Not registered</td>
</tr>
<tr>
<td></td>
<td>Maraviroc</td>
<td>August 2007</td>
<td>Not registered</td>
</tr>
</tbody>
</table>
Table 2.1. Antiretroviral agents approved by the FDA and MCC for treatment of HIV infection continued

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

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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A</td>
<td>Stavudine(d4T) 40mg every 12 hours(30mg every 12 hours if body weight&lt;60 kg)</td>
<td>Lamivudine(3TC) 150mg every 12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efavirenz(EFV) 600mg at night (or 400mg if body weight&lt;40kg)</td>
</tr>
<tr>
<td>1 B</td>
<td>Stavudine(d4T) 40mg every 12 hours(30mg every 12 hours if body weight&lt;60kg)</td>
<td>Lamivuine(3TC) 150mg every 12 hours</td>
</tr>
</tbody>
</table>

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 $1.3 \pm 0.4$ 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**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood</td>
<td>0.5 – 1.6 mmol/L</td>
</tr>
<tr>
<td>Capillary blood</td>
<td>0.5 – 1.5 mmol/L</td>
</tr>
<tr>
<td>Venous blood</td>
<td>0.3 – 1.5 mmol/L</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Lactate Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactate &lt; 2.5 mmol/L</td>
<td>Mild hyperlactataemia, minimal symptoms and bicarbonate &gt; 20 mmol/L</td>
</tr>
<tr>
<td>lactate 2.5-5 mmol/L</td>
<td>Moderately severe hyperlactataemia, and or bicarbonate between 15-20 mmol/L</td>
</tr>
<tr>
<td>lactate 5-10 mmol/L</td>
<td>Severe and or bicarbonate &lt; 15 mmol/L</td>
</tr>
<tr>
<td>lactate &gt; 10 mmol/L</td>
<td>Hyperlactataemia excluded, investigate for other causes.</td>
</tr>
</tbody>
</table>


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 zidovudine 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:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 (\text{m}^2)}.$$  

Table 4.1: Body Mass index classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI in Kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>Less than 19.9</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>20-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>30-39.9</td>
</tr>
<tr>
<td>Very obese</td>
<td>More than 40</td>
</tr>
</tbody>
</table>

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/mm³ at 4 to 8 weeks after viral suppression with antiretroviral treatments and then increased an additional 50-100 cells/mm³/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

![Gender distribution chart]

Figure 5.1: Gender distribution
5.1.3. AGE

![Participants by age group (n=34)](image)

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

<table>
<thead>
<tr>
<th></th>
<th>Improved (n=48)</th>
<th>Constant (n=0)</th>
<th>Decreased (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>1.5-60.4</td>
<td>0</td>
<td>(-13.0)-(-0.2)</td>
</tr>
<tr>
<td>Mean</td>
<td>16.0</td>
<td>0</td>
<td>-4.9</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>13</td>
<td>0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>BMI classification</th>
<th>interval 1 (n= 72)</th>
<th>interval 2 (n=71)</th>
<th>interval 3 (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>29.17 %</td>
<td>9.86 %</td>
<td>12.90 %</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>40.28 %</td>
<td>43.66 %</td>
<td>43.55 %</td>
</tr>
<tr>
<td>Overweight</td>
<td>23.61 %</td>
<td>32.39 %</td>
<td>35.48 %</td>
</tr>
<tr>
<td>Obese</td>
<td>6.94 %</td>
<td>14.08 %</td>
<td>8.06 %</td>
</tr>
<tr>
<td>Very obese</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Change in CD4 count</th>
<th>Interval 2 compared with interval 1 (n=85)</th>
<th>Interval 3 compared with interval 2 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>91.76 %</td>
<td>65 %</td>
</tr>
<tr>
<td>Constant</td>
<td>1.18 %</td>
<td>0</td>
</tr>
<tr>
<td>Decreased</td>
<td>7.06 %</td>
<td>35 %</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Interval of treatment</th>
<th>Detectable</th>
<th>undetectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6 months (n=70)</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>6 to 12 months (n=84)</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>above 12 months (n=26)</td>
<td>7</td>
<td>19</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Change in viral load</th>
<th>Interval 1 (n=70)</th>
<th>Interval 2 (n=84)</th>
<th>Interval 3 (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable</td>
<td>100 %</td>
<td>7.14 %</td>
<td>26.9 %</td>
</tr>
<tr>
<td>Undetectable</td>
<td>92.86 %</td>
<td>92.86 %</td>
<td>73.1 %</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>stavudine prescribed</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMALES</td>
<td>40 mg</td>
<td>29</td>
<td>32.96%</td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td>38</td>
<td>43.18%</td>
</tr>
<tr>
<td>MALES</td>
<td>40 mg</td>
<td>7</td>
<td>7.95%</td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td>14</td>
<td>15.91%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>88</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Stavudine dose</th>
<th>Gender</th>
<th>N</th>
<th>Elevated lactate levels</th>
<th>Normal lactate levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg</td>
<td>Female</td>
<td>29</td>
<td>27.8 % (n=10)</td>
<td>52.8% (n=19)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>7</td>
<td>5.5% (n=2)</td>
<td>13.9% (n=5)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>36</td>
<td>33.3 % (n=12)</td>
<td>66.7% (n=24)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>stavudine dose</th>
<th>Gender</th>
<th>N</th>
<th>Elevated lactate levels</th>
<th>Normal lactate levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>Female</td>
<td>37</td>
<td>26 % (n=13)</td>
<td>48 % (n=24)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>13</td>
<td>4 % (n=2)</td>
<td>22 % (n=11)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>50</td>
<td>30 % (n=15)</td>
<td>70 % (n=35)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Stavudine dose</th>
<th>n</th>
<th>Elevated lactate levels</th>
<th>Normal lactate levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg→30 mg</td>
<td>19</td>
<td>n=8</td>
<td>n=11</td>
</tr>
<tr>
<td>30 mg→20 mg</td>
<td>1</td>
<td>n=0</td>
<td>n=1</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>0-6 months (n=10)</th>
<th>6-12 months (n=17)</th>
<th>Above 12 months (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>2.3-9.8 mmol/l</td>
<td>2.5-9.1 mmol/l</td>
<td>2.8-4.8 mmol/l</td>
</tr>
<tr>
<td>Mean</td>
<td>4.98 mmol/l</td>
<td>5.7 mmol/l</td>
<td>3.85 mmol/l</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>2.43</td>
<td>2.35</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Two participants had lactate levels not recorded but reportedly died of lactic acidosis complications.
Table 5.13. Classification of participants by lactate levels

<table>
<thead>
<tr>
<th></th>
<th>0-6 months (n=10)</th>
<th>6-12 months (n=17)</th>
<th>Above 12 months (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperlactataemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.1-5 mmol/l)</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperlactataemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(above 5 mmol/l)</td>
<td>4</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>stavudine 40 mg</th>
<th>stavudine 30 mg</th>
<th>Odds ratio (±95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated lactate levels</td>
<td>27.27 % (n=18)</td>
<td>19.70 % (n=13)</td>
<td>3.02 (1.10-8.29)</td>
</tr>
<tr>
<td>Normal lactate levels</td>
<td>16.66 % (n=11)</td>
<td>36.37 % (n=24)</td>
<td>3.02 (1.10-8.29)</td>
</tr>
<tr>
<td>Total</td>
<td>43.93% (n=29)</td>
<td>56.07 % (n=37)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>stavudine 40 mg</th>
<th>stavudine 30 mg</th>
<th>Odds ratio (±95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Levels</td>
<td>10 % (n=2)</td>
<td>10 % (n=2)</td>
<td>2.2 (0.24-20)</td>
</tr>
<tr>
<td>Normal levels</td>
<td>25 % (n=5)</td>
<td>55 % (n=11)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35 % (n=7)</td>
<td>65 % (n=13)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>stavudine 40 mg</th>
<th>stavudine 30 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Levels</td>
<td>20</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>Normal levels</td>
<td>16</td>
<td>35</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>50</td>
<td>86</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>stavudine 30 mg</th>
<th>stavudine 20 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated levels</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Normal levels</td>
<td>11</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>BMI classification</th>
<th>stavudine 40 mg</th>
<th>stavudine 30 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>0</td>
<td>3</td>
<td>3 (8.57%)</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>1</td>
<td>6</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>2</td>
<td>6</td>
<td>8 (22.86%)</td>
</tr>
<tr>
<td>Obese</td>
<td>5</td>
<td>2</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Missing values</td>
<td>4</td>
<td>6</td>
<td>10 (28.57%)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>23</td>
<td>35 (100%)</td>
</tr>
</tbody>
</table>

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 between 12 to 18 months.
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

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

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, 2005).
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 $\geq 3$ 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


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

<table>
<thead>
<tr>
<th>Names</th>
<th>Dose/day</th>
<th>Date started</th>
<th>ARV stop date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV re-start</td>
<td>dose/day</td>
<td>ARV stop/change date</td>
<td>Change regimen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Clinical data and laboratory findings

<table>
<thead>
<tr>
<th>Type</th>
<th>Interval 1 (0 to 6 months)</th>
<th>Interval 2 (6 to 12 months)</th>
<th>Interval3 (above 12 months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>


## Appendix 2: Datasheet

### Part 1. Demographic data

<table>
<thead>
<tr>
<th>Pt hospital file</th>
<th>Race</th>
<th>Gender</th>
<th>Age</th>
</tr>
</thead>
</table>

### Part 2. Stavudine prescribed, D4T

<table>
<thead>
<tr>
<th>D4T prescribed</th>
<th>ARV start date</th>
<th>ARV stop date</th>
<th>Regimen</th>
<th>treatment duration</th>
</tr>
</thead>
</table>

### Part 3. Clinical data I

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>6-12months</td>
</tr>
<tr>
<td>0-6 months</td>
<td>6-12months</td>
</tr>
</tbody>
</table>

### Part 4. Clinical data II

<table>
<thead>
<tr>
<th>Height</th>
<th>Weight</th>
<th>lactate levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>6-12 months</td>
<td>&gt;12 months</td>
</tr>
<tr>
<td>0-6 months</td>
<td>6-12 months</td>
<td>&gt;12 months</td>
</tr>
</tbody>
</table>

### Part 5. Clinical data III

<table>
<thead>
<tr>
<th>outcome lactate</th>
<th>side effects 1</th>
<th>interruption status</th>
<th>cause</th>
</tr>
</thead>
</table>

### Part 6. Clinical data IV

<table>
<thead>
<tr>
<th>D4T reduced dose</th>
<th>duration in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>
Part 7. Clinical data V

<table>
<thead>
<tr>
<th>Arv re-interruption</th>
<th>monitoring lactate levels</th>
<th>duration in months</th>
<th>side effects2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>month1</td>
<td>month2</td>
</tr>
</tbody>
</table>

Part 8. Clinical data VI

<table>
<thead>
<tr>
<th>regimen change</th>
<th>Date change</th>
<th>survival</th>
<th>cause death</th>
<th>comments</th>
</tr>
</thead>
</table>
APPENDIX 3: REPC APPROVAL

UNIVERSITY OF LIMPOPO
Medunsa Campus

RESEARCH, ETHICS & PUBLICATIONS COMMITTEE
FACULTY OF MEDICINE
CLEARANCE CERTIFICATE

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 Nololo

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

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.

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