HIV and the Metabolic Syndrome

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DECLARATION

This document describes original work by the author and has not been submitted in any form to any other University. Where use was made of the work of others it was duly acknowledged in the text.

The study was supervised by Prof. V. Rambiritch BSc. Pharm (Hons) MMed Sc PhD, Pharmacology Department, University of Kwazulu-Natal.

The research was conducted at the HIV clinic at KwaDabeka Primary Health Clinic, KwaDabeka and at Ithemba Clinic at St Mary's Hospital, Marianhill, Durban, Kwa Zulu Natal, South Africa.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
Ab	Abominal
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Therapy
ARV's	Anti-RetroVirals
AUC	Area Under the Curve
AZT	Zidovudine
BMI	Body Mass Index
Chol	Cholesterol
CV	CardioVascular
d4T	Stavudine
ddI	Didanosine
DoH	Department of Health
EFV	Efavirenz
fbc	Full Blood Count
GI	Gastro-Intestinal
HAART	Highly Active Anti-Retroviral Treatment
Hb	Haemoglobin
HCV	Hepatitis C Virus
HDL	High Density Lipids
HGT	HyperGlycamic Test
HIV	HI Virus
HIV +ve	HIV positive
HIV –ve	HIV negative
KDC	KwaDabeka Clinic
LDL	Low Density Lipids
lft	Liver Function Tests
MACS	Multicentred AIDS Cohort Study
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PI	Protease Inhibitor
Plt	Platelets
SMH	St Mary's Hospital
STD	Sexually Transmitted Disease
TB	TuberCulosis
TG	Triglyceride
UN	United Nations
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VL	Viral Load
WCC	White Cell Count
WHO	World Health Organisation
wt	Weight

ABSTRACT

This study investigated the relationship between HIV and the metabolic syndrome due to the immunological basis of both HIV and diabetes.

Insulin resistance is common among HIV-infected patients. Similar to other metabolic complications associated with HIV, the pathogenesis of insulin resistance is multifactorial; it is directly and indirectly affected by certain antiretroviral therapies, HIV infection itself, and patient-level risk factors, such as obesity, age, and family history. As in the general population, insulin resistance is also a major factor in the development of diabetes and cardiovascular disease among HIV-infected patients.

The aim of this retrospective study was to investigate if a relationship between HIV, anti-retroviral treatment and the development of any aspect of the metabolic syndrome exists.

Two groups of HIV-patients from 2 sites in Kwazulu-Natal namely, KwaDabeka and St Mary's Hospital comprised the study cohort.

270 patient record cards were reviewed. Laboratory results, treatment regimens, changes, side effects and other data that was recorded in these cards was captured on a data sheet and subjected to statistical analyses.

Insufficient screening is done at both institutions for glucose, and therefore it was not possible to establish if or how many patients developed hyperglycaemia or diabetes. However, 20 patients had or developed hypertension and 45 patients developed lipodystrophy. Hypertension, lipodystrophy and an elevated blood glucose comprize the three factors that define the metabolic syndrome for the WHO. Patients experiencing hypertension and/or lipodystrophy should be monitored more closely for blood glucose as they are more likely to develop the metabolic syndrome. Patients with two or more of the factors of the metabolic syndrome are at an increased risk of developing Coronary Heart Disease. Monitoring of blood glucose, will enable early detection of diabetes and early intervention could prevent the development of diabetes related complications such as reduced cardiac risk for HIV patients on HAART and subsequent cardiac complications. An outcome of this study is the need for regular screening of blood glucose and cholesterol in HIV patients on ARV treatment.

As a result of this study, we would recommend further investigations into the patients with hypertension and lipodystrophy to establish if any of those patients developed diabetes. In addition, we recommend that screening for blood glucose become part of the DoH guidelines in order to enable the early detection and prevention of the development of diabetes in patients on HAART. The patients at high risk and who need to be monitored for the development of diabetes more closely are those with hypertension, or lipodystrophy or those with traditional risk

factors for hyperglycaemia (i.e. those in the older age group categories or with high BMI). Other patient groups who should also be closely monitored for changes in blood glucose are patients with peripheral neuropathy (due to the possibility of the neuropathy worsening if patients have concurrent diabetic neuropathy) and patients on the DoH's regimen 2, which includes a protease inhibitor (which are largely documented to cause hyperglycaemia).

CHAPTER 1:

Introduction and Background

The introduction of highly active antiretroviral therapy (HAART) has dramatically improved the long term prognosis of human immunodeficiency virus (HIV)-infected patients. However, a downside is the occurrence of several abnormalities of lipid and glucose metabolism in patients receiving potent new antiretroviral combinations[41].

1.1 Prevalence of diabetes mellitus

The worldwide prevalence of diabetes mellitus may be as high as 220 million by 2010[13]. Regions with the greatest potential increases of diabetes mellitus are Africa and Asia. In South Africa, the population will continue to increase but at a slower rate because of the HIV/AIDS epidemic. The general population increase is expected to be 0.3% in 2010. Without HIV/AIDS it would be 1.5%. The burden of HIV/Aids and type 2 diabetes is likely to fall on the lower socio-economic classes[13].
The prospective Multicentre AIDS Cohort Study (MACS), examined the prevalence of hyperglycaemia in 1107 men, using data from April 1999 to September 2002[7]. Following adjustments for age and Body Mass Index (BMI, they concluded that the prevalence of diabetes among HIV positive men on HAART was 3.1 times more than that of the HIV negative group[7].

Table 1. Multicentre AIDS Cohort Study: Incidence of Diabetes[56]

Category	N	Person-years	Rate/100 Person-years	Rate Ratio
HIV-seronegative	39	1451	1.4	--
HIV positive				
- Not receiving HAART	10	709	1.7	--
- Receiving HAART	24	506	4.7	4.1

1.2 Insulin Resistance

Insulin resistance is an important component of the lipodystrophy syndrome, including body fat redistribution, hypertriglyceridemia, hypercholesterolemia, hyperinsulinaemia, and hyperglycaemia[40]. Insulin resistance occurs when the body is producing larger amounts of insulin to keep the blood glucose 'normal'[7].Impaired glucose tolerance and diabetes follow insulin resistance when the level of insulin resistance increases above the compensatory increase in pancreatic insulin output[21]. Insulin resistance can cause cardiovascular disease and can progress to diabetes[7,24].

The criteria for the diagnosis of diabetes are symptoms of diabetes plus random plasma glucose of 200mg/dL (11.0 mmol/L); classic symptoms include polyuria and polydipsia[6]. WHO definition of diabetes is a fasting glucose of >126mg/dL (6.93mmol/L) and impaired fasting glycaemia would be defined by a fasting glucose of >110mg/dL (6.05mmol/L)[21,24,43].

Diabetes, in HIV patients, is associated with the traditional risk factors of diabetes in non HIV-infected patients. These have been proven in various studies such as Yoon et. al. (2002), who showed that diabetes is associated with traditional risk factors of obesity (measured by BMI), family history and co-infection with Hepatitis C[19]. Age and ethnicity are also factors in the development of diabetes[7,35].

There is also a possibility that patients with pre-existing diabetes who are on ART may have problems controlling their diabetes[25]. Length of PI treatment and which PI is used in the treatment regimen are risk factors to the development of hyperglycaemia.

1.3 The Link between HIV and Hyperglycaemia

There are a number of theories that link HIV and hyperglycaemia.

1) *HIV effects*
   Early studies reported that clinically stable HIV +ve men had higher rates of insulin clearance and insulin sensitivity compared with the non-infected group[35,30]. Research into the prevalence and incidence of blood glucose abnormalities in men enrolled in the MACS (Multicentre AIDS Cohort Study) ongoing prospective study of HIV in men found that the prevalence of diabetes was 2.11% in the HIV positive men not on ARVs, and 5.3% in HIV positive men on ARVs compared to the HIV negative men[30]. Therefore, there is some evidence that the development of insulin resistance is associated with HIV disease component itself[21,35]. The mechanism of insulin resistance is unknown but may relate to altered nutrient metabolism or changes in body composition[24].

2) *Other medications*
   Various other medications that may be prescribed for HIV positive patients could also be the cause of hyperglycaemia in HIV positive patients[35]. Insulin resistance has been seen in patients on NRTIs (Nucleoside Reverse Transcriptase Inhibitors) but to a lesser extent than those on PIs[21]. NRTIs may affect glucose homeostasis indirectly through the chronic changes in fat distribution[24].
   Pentamidine, used for pneumonia, can cause acute hypoglycaemia followed by a later onset of diabetes[35].
   Megestrol acetate is used as an appetite stimulant in HIV patients. It has intrinsic glucocorticoid activity and therefore predisposes a number of patients to hyperglycaemia[35]. Other drugs that could also cause hyperglycaemia are prednisone, growth hormone, anabolic steroids and nicotinic acid[6,36].

3) *Traditional risk factors*
   Patients may be insulin resistant or develop diabetes as a result of traditional risk factors such as obesity (BMI), strong family history (more than 1 immediate family member with diabetes), age, inactivity, ethnicity, co-infection with HCV[21,7,38]. In a study on HIV patients co-infected with HCV and HIV patients, showed that chronic HCV is a significant factor in the development of metabolic abnormalities[22].

4) *Protease Inhibitors*

Most of the evidence available shows that HIV patients on Protease Inhibitors (PIs) are more likely to develop hyperglycaemia than those not on a PI containing regimen[7,2,17,18,21,28,24]. In order to successfully achieve the goal of HIV therapy of maximally suppressing the viral load, a combination of NRTIs and PIs are prescribed. From various studies, it is evident that HIV patients on PIs are more likely to develop hyperglycaemia than those not on a PI regimen[35]. There are various hypotheses on the pathogenesis of these metabolic effects. One is that the affinity for HIV protease could be such that they can also bind with human proteins involved in lipid metabolism especially low density lipoprotein receptor related protein which is important for post-prandial chylomicron clearance and therefore clearance of triglycerides from circulation[33]. Other suggested mechanisms behind PI induced insulin resistance are complex and multi-functional[24]. Initial studies suggest an effect on Glut-4 mediated glucose transport, islet cell dysfunction and dysregulated hepatic glucose production which may complicate glucose homeostasis[24].

5) *NRTI's*

There is accumulating evidence that NRTI exposure, particularly to thymidine analogues, is an important contributor to the development of glucose abnormalities in HIV-infected persons[107]. In both the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) and Women's Interagency HIV Study (WIHS) cohorts, incident diabetes was associated with the use of NRTIs[107]. In the MACS, each additional year of NRTI exposure was associated with an 8% increased risk of hyperinsulinemia, suggesting that the effect on incident diabetes seen in other cohorts is mediated by the worsening of insulin resistance[107].

Of the NRTIs, stavudine has the most potent effect on insulin sensitivity[107]. In a study of treatment-naive HIV-infected patients beginning PI-containing regimens, those who were randomized to stavudine and didanosine had early and sustained increases in fasting insulin concentrations compared with those who received abacavir/lamivudine, independent of changes in body composition[107].

1.4 HIV Treatment Regimens in South Africa

The primary goal of treatment is to decrease HIV-related morbidity and mortality and the secondary goal is to decrease the incidence of HIV[1].The DoH criteria for ART initiation in adults and adolescents is:

CD4<200cells/mm^3 irrespective of stage
OR
WHO Stage IV AIDS-defining illness irrespective of CD4 count
AND patient expresses willingness and readiness to take ART adherently[1].

A treatment readiness assessment is completed. This includes an analysis of the patients' social conditions and a course of co-trimoxazole for 1 month, to determine if the patient adheres to the treatment regimen. Once it is established that the patient has the capacity to adhere to the treatment, they may be enrolled on the ART programme at their local hospital. Two ART regimens are recommended for use in the South African public sector. Patients who fail both regimens will be referred for individual evaluation.

Table 2. Recommended ART *regimens*[69]

Regimen	Drugs
1a	D4T/3TC/Efavirenz
1b	D4T/3TC/NVP
2	AZT/ddI/Lopinavir/Rotinavir

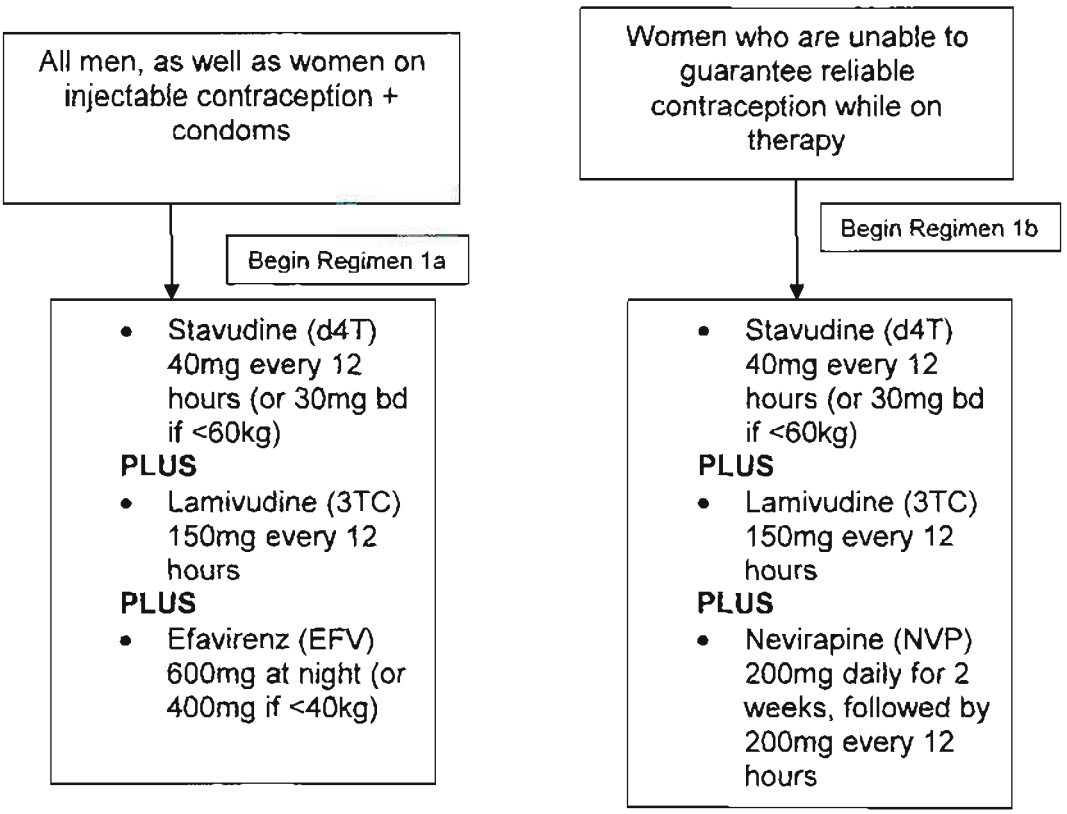


Figure 1. First-line therapy for adults (Regimen 1a and 1b)[1,39,69]

Table 3. Summary of adult ART Regimen 1 and routine monitoring[1,69]

Regimen	Drugs	Monitoring test	Frequency
1a	d4T 3TC Efavirenz	CD4	Staging, 6 monthly
		VL	Baseline, 6-monthly
		ALT	Symptomatic
1b	d4T 3TC Nevirapine	CD4	Staging, 6 monthly
		VL	Baseline, 6-monthly
		ALT	Baseline, week 2 & 4 and 8 , thereafter 6-monthly

Staging = initial testing for all patients when being referred for ART
Baseline = testing for ART eligible patients, at initiation of ART

Patients who continue to fail virologically despite demonstrated adherence may be changed to regimen 2. Before changing, the patient will need to go through patient readiness and education programmes again before commencing regimen 2 which consists of[1,69,39]:

- Zidovudine 300mg every 12 hours

WITH

- Didanosine (ddI) 400mg once daily (250mg daily if <60 kg), taken alone, dissolved in water on an empty stomach

AND

- Lopinavir/Ritonavir (LPV/r) 400/100mg every 12 hours.

Monitoring tests for Regimen 2 patients are performed as follows:

Table 4: Summary of routine monitoring tests and their frequency for patients on Regimen 2[1].

Monitoring test	Frequency
CD4	Staging, 6 monthly
FBC	Baseline, then monthly for 3 months, then 6 monthly
Fasting cholesterol and triglyceride	Baseline, 6 months and thereafter every 12 months
Fasting glucose	Baseline and 12 months

Staging = initial testing for all patients when referred for ART
Baseline = testing for ART-eligible patients at initiation of ART

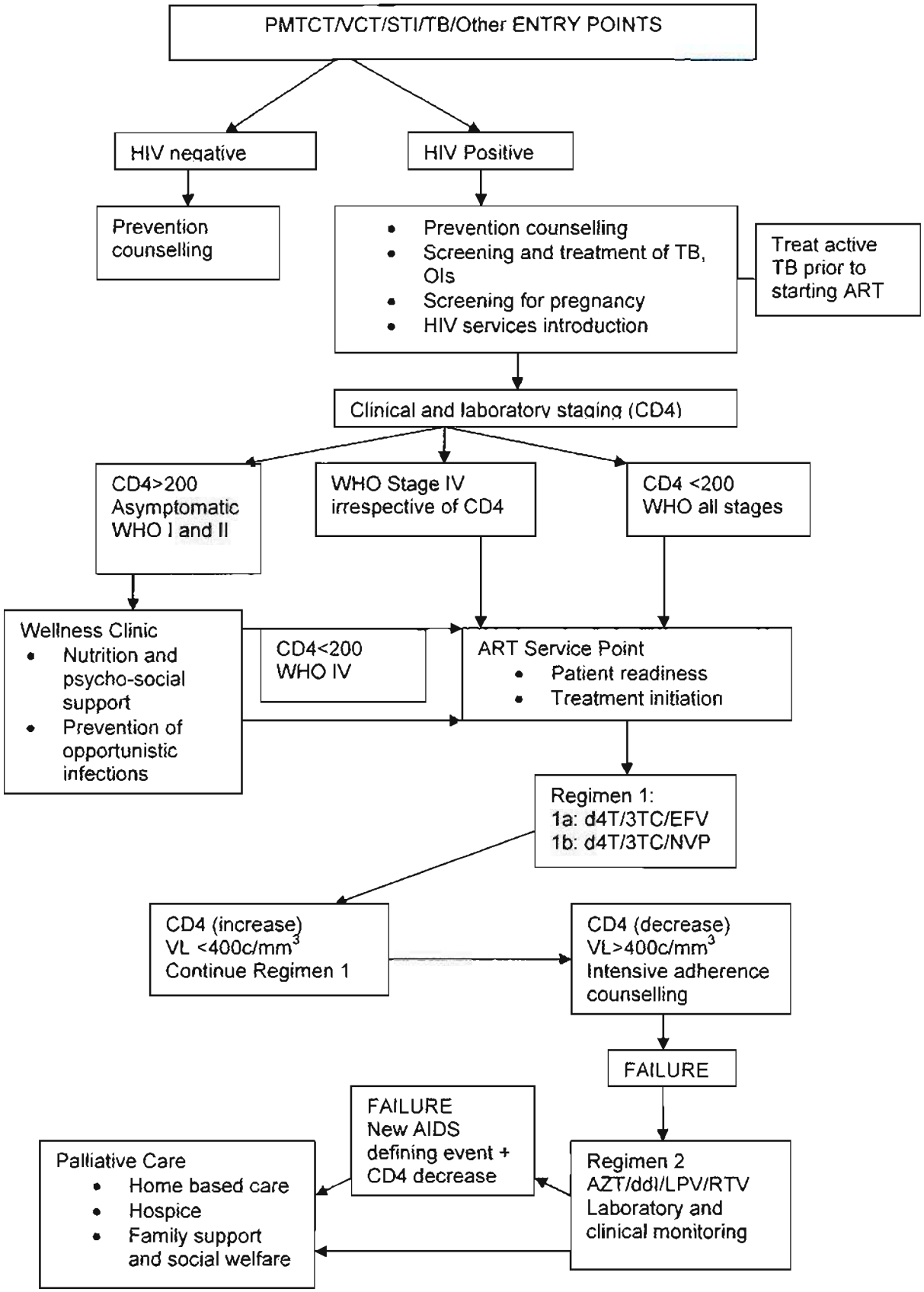


Figure 2: Adult HIV management flowchart[1]

1.5 Rationale for study

It is evident that in South Africa, HIV+ve patients are being treated with HAART regimens. The second line treatment regimen in South Africa contains a protease inhibitor, a drug associated with an increased incidence of hyperglycaemia and diabetes mellitus in patients[42]. Due to rising health care costs and lack of funds in the public sector to treat patients, it is imperative that HIV infected patients on HAART are not developing diabetes. This study will aim to investigate whether HIV infected patients at 2 clinics in the Durban area are developing hyperglycaemia. All newly diagnosed HIV+ve patients, whether the patients are on treatment or not on treatment, during the year 2006 will be evaluated. From the results, we will be able to ascertain whether hyperglycaemia is presenting as a problem to HIV positive patients. Following analysis of the results, we will be able to determine if the number of hyperglycaemic HIV+ve patients is as a result of the disease itself, the treatment regimens or co-incidental (considering whether the patients have the traditional diabetic risk factors). Depending on the outcome of the study we will be able to make certain recommendations to the Department of Health in order to decrease the cost of treating the patient for diabetes and HIV.

1.6 Aim

The aim of this study is to assess the prevalence of metabolic complications such as Metabolic Syndrome in HIV infected patients at 2 clinics in the Durban area.

1.7 Objective

1. The primary objective is to determine the prevalence of Metabolic Syndrome in HIV infected or treated patients
2. The secondary objective is to determine which possible factors are implicated in the development of Metabolic Syndrome
3. To determine whether clinics are compliant with the department of health's recommendations on recording and monitoring tests of HIV positive patients

1.8 Research Methodology

This study was a retrospective analysis of patient's clinic records (i.e. medical records). The study analysed a number of patients' medical records at 2 clinic sites in the Durban area. KwaDabeka Clinic and St Mary's Hospital were the 2 sites used for this research study. 271 HIV positive patients' clinic cards from these 2 institutions were reviewed and data extracted according to the data collection sheet (Appendix 1). Laboratory results, treatment regimens, changes to treatment regimens, side effects and other data that was recorded in the patient cards while on HIV treatment was captured on the data sheet and subjected to statistical analyses. Data was collected on site and the patient's name and address was not recorded. Confidentiality was strictly maintained and no interaction with the patient or health care provider was required. The research protocol was approved by the UKZN Ethics committee as well as by the Department of Health and the 2 clinic sites (Appendix 6).

CHAPTER 2

Literature Review

2.1 HIV Lifecycle

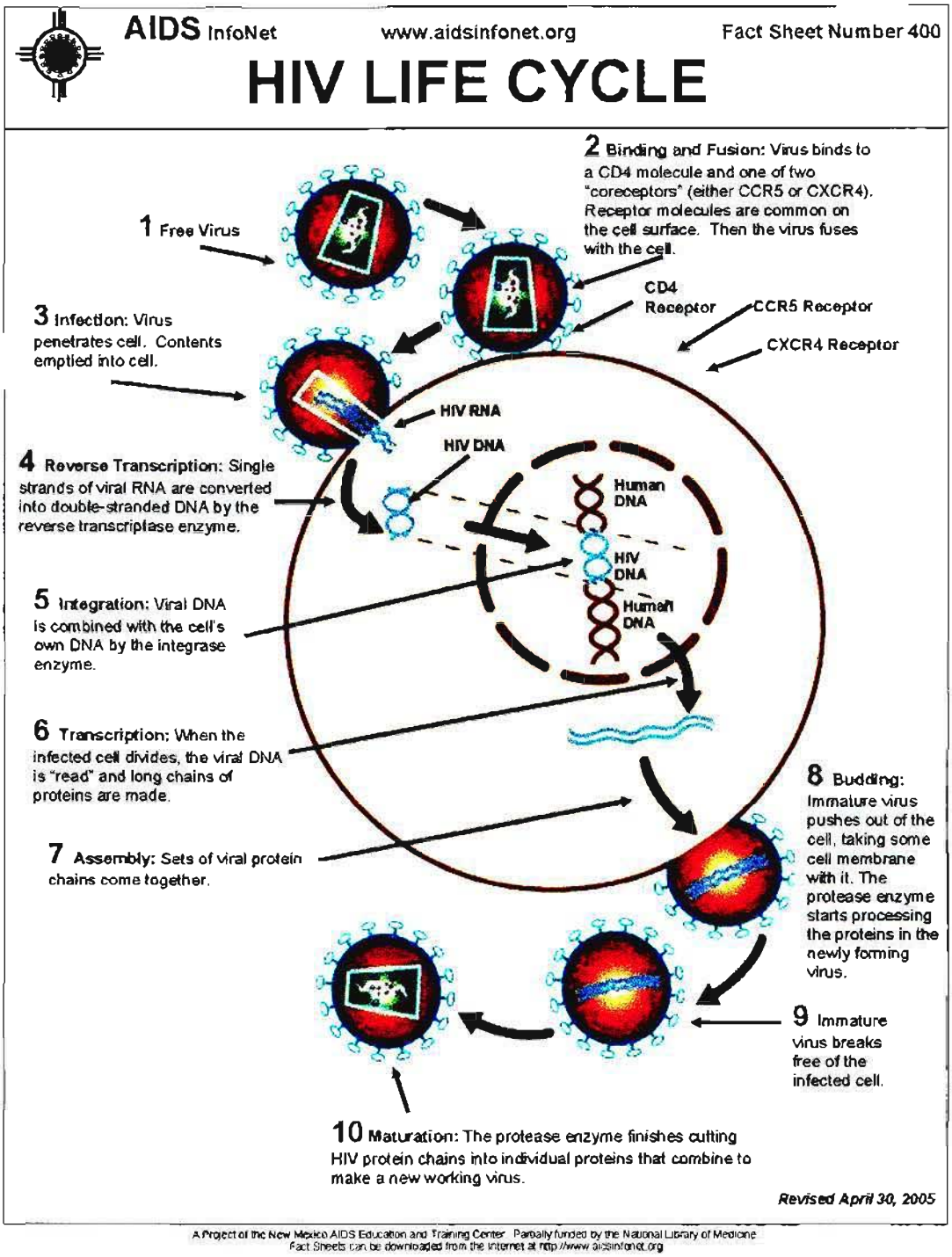


Figure 3. Diagram showing the life cycle of the HI Virus[81]

HIV enters the cell where it uncoats and undergoes reverse transcription by its own reverse transcriptase enzyme. This is an important step as the viral genome is in the RNA form and must be converted to DNA to integrate into the host genome[33]. Reverse Transcriptase Inhibitors (RTIs) act at this stage. Transcription and translation by cellular enzymes generate large polypeptide precursors especially gag- and gag-pol gene sequences[33]. Gag precursors encode for structural proteins of the viral core and the gag-pol precursors encode for the functional protein including reverse transcriptase ribonuclease integrase and protease. These polyproteins migrate to the cell membrane where they cleave into separate proteins[33]. As virus particles bud from infected cells, HIV protease becomes active and precursor proteins undergo processing by this enzyme. Gag and gag-pol precursors are cleaved at several sites to render the core protein and viral enzymes. These processed proteins assemble to form a mature infectious virion. Inhibiting this process will produce non-infectious virions. HIV targets the cells of the immune system, especially CD4 lymphocytes. As virus particles bud from infected cells, HIV protease becomes active and precursor proteins undergo processing by this enzyme[33]. The number of CD4 lymphocytes decrease modestly as the virus replicates. However the immune system responds and antibodies develop which means that the CD4 reverts to baseline. During this time, a steady-state level of virus in the body is established. This point or level differs in each patient and accounts for the variability between people and how quickly they develop AIDS[33].

2.2 HIV Treatment

New treatment strategies target HIV proteins at various levels of replication. Combinations of agents suppress viral replication, further decreasing the ability of the virus to replicate and therefore decreases disease progression.
HIV protease is a proteolytic enzyme which is related to human proteases such as pepsin, rennin etc. Inhibitors of the protease need to be specific for viral protease[33]. Protease inhibitors (PIs) are designed on peptidic, partial peptidic and non-peptidic compounds. Protease Inhibitors have some advantages over Reverse Transcriptase Inhibitors (RTI's). They are less likely to interfere with intracellular enzymes such as those involved in DNA synthesis. They don't require intracellular activation (RTI's require phosphorylation within cells to become active) and they are effective in chronically infected cells because they act post-translationally[33]. However they don't prevent new virus cells from infecting an immune cell, therefore they are necessary to be used in combination with RTI's to prevent infection of new cells[33]. HAART (Highly Active Anti-Retroviral Therapy) is the best way of reducing viral load and CD4 count. Compared with no therapy, triple therapy decreased AIDS diagnosis by 42% in the USA and deaths due to AIDS by 65%[34].

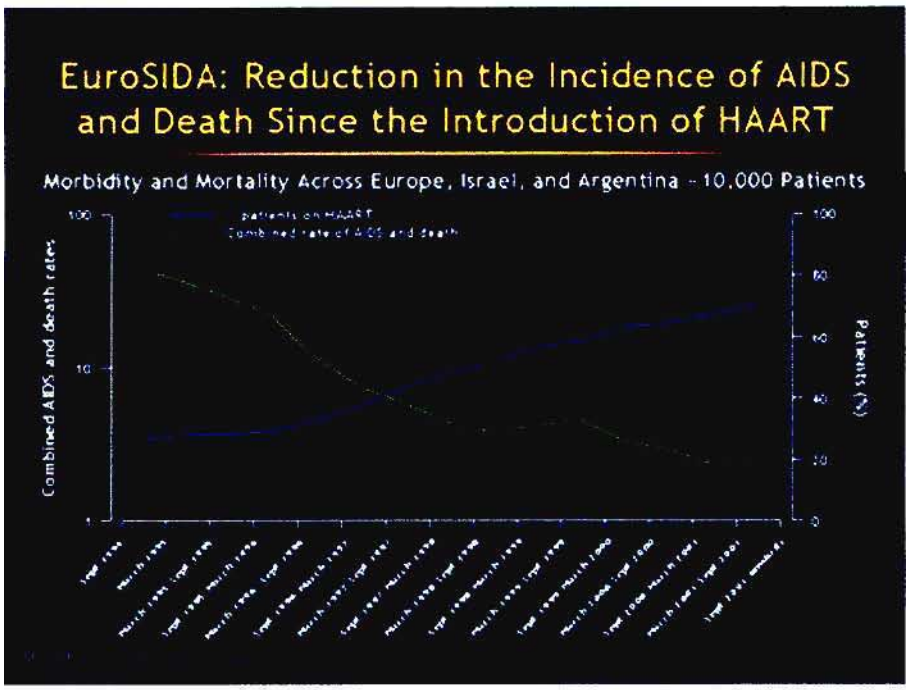


Figure 4. Graph showing the death rate with and without HAART [54]

2.3 Drugs commonly used in South Africa in Regimens 1 &2

d4T – Stavudine

d4T is one of the nucleoside reverse transcriptase inhibitors[59]. It is able to reduce HIV viral load and increase CD4 cell counts when taken in combination with at least two other ant-retroviral drugs[59]. For patients weighing over 60kg, they can take 40mg twice daily, otherwise they should be taking 30mg twice daily.

The most common side effect of d4T is peripheral neuropathy[59]. This is nerve damage in the feet, legs and hands, which can cause numbness, tingling, or pain in the extremities[59]. Peripheral neuropathy occurs in 15-20% of patients on d4T, particularly in those on higher doses, with more advanced HIV disease, or who are also taking ddI. Studies have shown that halving or reducing the dose by 10mg, has no effect on its efficacy but can reduce the symptoms of peripheral neuropathy[59]. As it can make peripheral neuropathy worse, it is not recommended to people with pre-existing peripheral neuropathy[59].

A number of studies have found an association between lipodystrophy and the nucleoside reverse transcriptase inhibitors, with the strongest association observed with d4T. Consequently the British HIV Association recommends that d4T should not be used in first line therapy[59]. However in South Africa, it forms part of regimen 1a and 1b which is first line therapy (see table above). Risk factors for d4T-related fat loss include:

- being over 40 years old
- having high baseline triglyceride levels (over 200 mg/dL)

- using standard immediate-release d4T (the new once-daily extended release version of the drug produces a slightly lower incidence of lipoatrophy over 48 weeks.

Elevated lactate and other metabolic abnormalities have also been linked to d4T treatment. Lactic acidosis is a rare but serious side effect of d4T, causing symptoms of nausea, malaise and liver pain, which can lead to death if NRTI treatment is not stopped[59]. Of all the NRTIs, d4T has been particularly associated with increased lactate levels[59].

Around 2% of patients taking d4T develop pancreatitis, although the risk of this occurring is greater in patients who have had pancreatitis in the past [59]. Elevated amylase levels are common and can be a warning sign for increased risk of pancreatitis[59].

Other side effects of d4T are most likely to occur during the early weeks of treatment and include nausea, diarrhoea, headaches, constipation, abdominal pain and dehydration[59]. Other less common toxicities of d4T include elevated liver enzymes and fatty liver, especially in people with Hepatitis B or C co-infection[59].

3TC (Lamivudine)
3TC is also a Nucleoside analogue reverse transcriptase inhibitor and is able to reduce viral load and increase CD4 cell counts in the majority of people when taken in combination with at least two other anti-retroviral agents[60]. It is also approved as treatment for hepatitis B virus [60]. 3TC can be taken once daily as a 300mg dose or twice daily as a 150mg dose. 3TC is generally a safer drug, with fewer side effects than other nucleoside reverse transcriptase inhibitors[60]. The most common side effects are nausea, vomiting, diarrhoea, headache, tiredness, abdominal pain, peripheral neuropathy and insomnia[60]. The side effects of 3TC are more likely to occur during the early weeks of treatment[60]. Less common side effects of 3TC are neutropenia (low white blood cell counts) and rash[60]. There have also been reports of hair loss, severe anaemia, and lactic acidosis among people receiving 3TC[60].

There is considerable cross-resistance amongst the nucleoside reverse transcriptase inhibitors (NRTIs), meaning that once a patient has developed resistance to one NRTI, the effectiveness of the other NRTIs will be diminished[60].

3TC is licensed as a treatment for hepatitis B in an increasing number of countries[60]. It may be prescribed to patients with chronic hepatitis B virus infection with liver damage, liver inflammation or fibrosis. The standard dose for hepatitis B infection is 100mg daily[60].

AZT (Zidovudine)
AZT is a nucleoside reverse transcriptase inhibitor (NRTI) which forms a common component of anti-HIV regimens[61].
The commonest side effects of AZT are nausea, vomiting, headache, dizziness, fatigue, weakness and muscle pain[61]. These often occur in the early weeks of treatment[61]. Other side effects include rashes, severe muscle pain and inflammation, insomnia, nail discoloration, and kidney disorders[61]. AZT may damage the bone marrow and for people with more advanced HIV infection, blood deficiencies such as anaemia or neutropenia are more likely[61]. There is a small risk of muscle damage (myopathy) after prolonged treatment with AZT, with some pain, wasting and weakness usually in muscles around the hips, thighs and buttock. Blood tests for muscle enzymes can detect this wasting early if suspected[61]. Rare adverse reactions to AZT include developing an enlarged fatty liver and raised levels of lactic acid.

These complications appear to be more common in obese women and people with risk factors for liver disease[61]. There is some evidence that AZT may trigger body fat loss and metabolic changes, although it is not as likely to occur as it is with d4T[61]. AZT should not be taken with d4T as these two drugs reduce each others anti-retroviral effects[61].

Efavirenz (Stocrin)
Efavirenz is a non-nucleoside reverse transcriptase inhibitor that is active in combination with other anti-retrovirals against HIV-1[62]. A large scale, comparative study, ACTG 384, 2002, found that efavirenz, AZT and 3TC were the preferred first line therapy in terms of anti-viral efficacy and toxicity after 144 weeks of follow-up[62]. In addition, two observational studies have suggested that people taking efavirenz are more likely to achieve and sustain undetectable viral loads than those taking a protease inhibitor[62]. Similarly, a retrospective study based in San Francisco has shown that first-line anti-HIV drug regimens containing efavirenz give better survival outcomes than any other combinations available prior to 2002[62]. Efavirenz is dosed as 600mg at night[62].

Trials have shown that between 14 and 50% of people who take efavirenz develop side effects in the first few months of treatment including drowsiness, insomnia, dizziness, vivid dreams and nightmares, confusion, abnormal thinking, impaired concentration, loss of memory, agitation, hallucinations, delusions, euphoria, and depression[62]. These side effects are more common in people with existing psychotic disorders. After two to four weeks, these side effects diminish markedly[62]. Rash is common in people taking efavirenz, affecting around a quarter of the people on trials. It can usually be controlled using antihistamines, and tends to resolve within a month of starting efavirenz-based therapy[62]. Elevated liver enzymes were reported in 2% of patients taking efavirenz in a study called 006, but were more common in patients co-infected with Hepatitis B or C [62]. Less common side effects include headache, alcohol intolerance, aches, pains, fatigue, fluid retention in hands and feet, dry mouth, elevated lipid levels, pancreatitis, skin problems, asthma, changes to vision and taste[62]. Gynecomastia has been observed in a small number of patients on efavirenz[62].

Animal studies of efavirenz show high rates of birth defects, therefore it is not recommended in pregnancy[62].

Nevirapine
Nevirapine, like efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI), that is active in combination against the HIV1 virus [63]. The 2NN study found no significant difference between efavirenz and nevirapine when taken with d4T and 3TC in terms of the percentage of patients with undetectable viral loads at week 48, CD4 cell increases and quality of life, although nevirapine treated individuals were more likely to develop liver toxicity in this study[63]. The standard dose of nevirapine is 400mg daily either as a once or twice daily dose.

The most common side effects are rash, nausea, headache, vomiting, diarrhoea, abdominal pain, and muscle pain[63]. Approximately 16% of patients on nevirapine develop a rash in the form of red blotches, itchy lumps or speckles on the skin. It usually appears after one to four weeks on treatment and goes away after two to four weeks on treatment[63]. Liver toxicity is another problem experienced by patients on nevirapine[63]. The greatest risk of liver toxicity occurs in the first 6 weeks of treatment and patients should have liver enzymes monitored every 2 weeks during the first month of treatment and monthly thereafter for the first 18 weeks of treatment[63]. Symptoms of liver toxicity include nausea, loss of appetite, fatigue, liver tenderness

or swelling, malaise, yellowing of the whites of the eyes, dark green/brown urine, yellowing of the skin and greyish or white stools[63]. HDL cholesterol may rise in patients on nevirapine and therefore it seems to have a better lipid profile than efavirenz[63].

Drug interactions are numerous but patients taking fluconazole should do so with caution as fluconazole can double the concentration of nevirapine, increasing the risk of side effects[63].
Nevirapine is safe in pregnancy although the possibility of liver toxicity is higher[63]. Although single dose nevirapine during labour with or without a dose for the infant after birth can reduce the risk of transmission of HIV, subsequent triple therapy with nevirapine or any NNRTI is compromised[63].

ddI (Didanosine)
DDI is a NRTI, used in combination with other anti HIV medication to reduce the HIV levels in the blood[108]. It commonly causes diarrhoea and peripheral neuropathy as a side effect[108]. It can also cause pancreatitis, and severe liver damage in some rare cases[108].

Kaletra® (fixed dose combination of ritonavir and lopinavir)

Ritonavir and lopinavir are protease inhibitors used in regimen in 2 in South Africa. Ritonavir is used to boost lopinavir levels in the blood. It has a long half life and has a high genetic barrier to resistance which makes it useful as salvage therapy even in people who have previously been exposed to other protease inhibitors[64]. The standard adult dose is 400mg lopinavir and 100mg ritonavir twice daily with food.

The most common side effects of Kaletra® are diarrhoea and nausea[64]. Diarrhoea and loose stools were experienced usually in the first two months of treatment[64]. Fatigue, muscle weakness, headache, stomach pain and vomiting are less common side effects associated with Kaletra in clinical trials[64]. Body fat changes and metabolic disorders are associated with protease inhibitors as a class[63]. Elevated lipids, including triglycerides and cholesterol levels occur among 10 to 25 % of patients on Kaletra®, particularly amongst those with high cholesterol or triglycerides before starting to take the drug[64]. Kaletra® is also associated with insulin resistance and the development of type 2 diabetes[64]. The other key side effect is elevated liver enzymes which occur most commonly in patients co-infected with hepatitis B or C[64]. Kaletra® should not be used in pregnancy as preliminary animal studies show some toxicity[64].

Nelfinavir
Nelfinavir is a protease inhibitor used in some babies as part of a clinical trial in South Africa. The most commonly experienced side effects are most likely to occur during the early weeks of treatment and include diarrhoea, nausea and headache[65]. As a protease inhibitor, nelfinavir is also associated with fat and metabolic irregularities[65]. Following nelfinavir failure, Kaletra® or dual protease inhibitor therapy will still be beneficial[65].

Combivir®
Combivir® is a fixed dose combination of 150mg 3TC and 300mg AZT. It is usually given twice daily[66]. It was available at state hospitals for a while but now 3TC and AZT are administered separately.

2.4 Cardiovascular Risk factors in HIV

- Metabolism refers to a range of physical and chemical processes which maintain the human body, including the process of turning fat and sugar into energy[68]. Metabolic complications have been associated with HIV infection and treatment[8]. Use of Highly Active Anti-Retroviral Therpay (HAART) is associated with the development of traditional cardiovascular risk factors, including dyslipidaemia and insulin resistance[24]. HIV physicians are increasingly concerned with metabolic disturbances in individuals receiving HAART, and the likely increase in cardiovascular and cerebrovascular disease prevalence that will emerge over time[18].

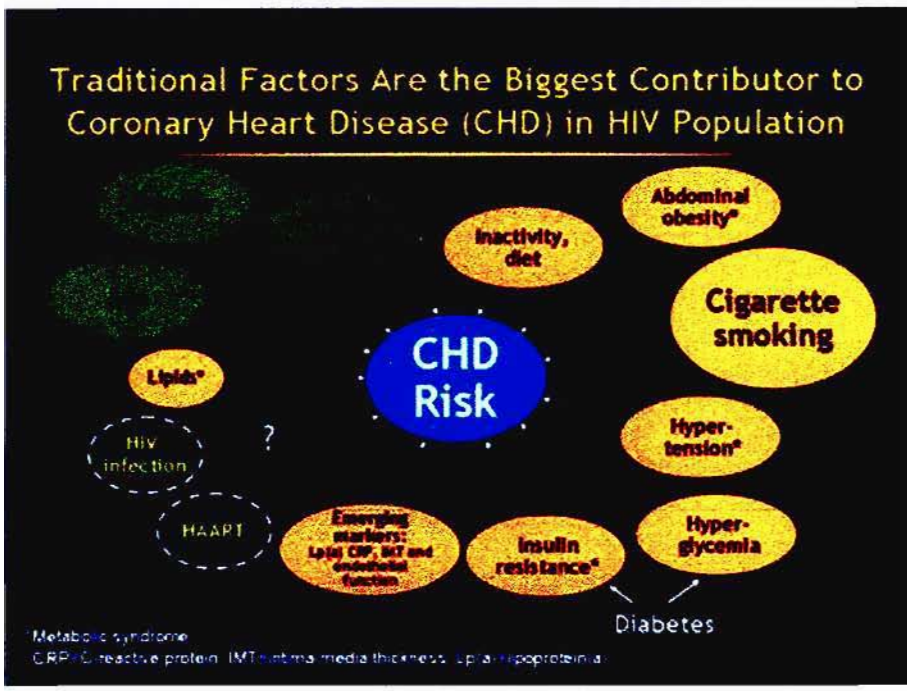


Figure 5. Diagram showing the traditional factors contributing to Coronary Heart Disease in HIV population [54]

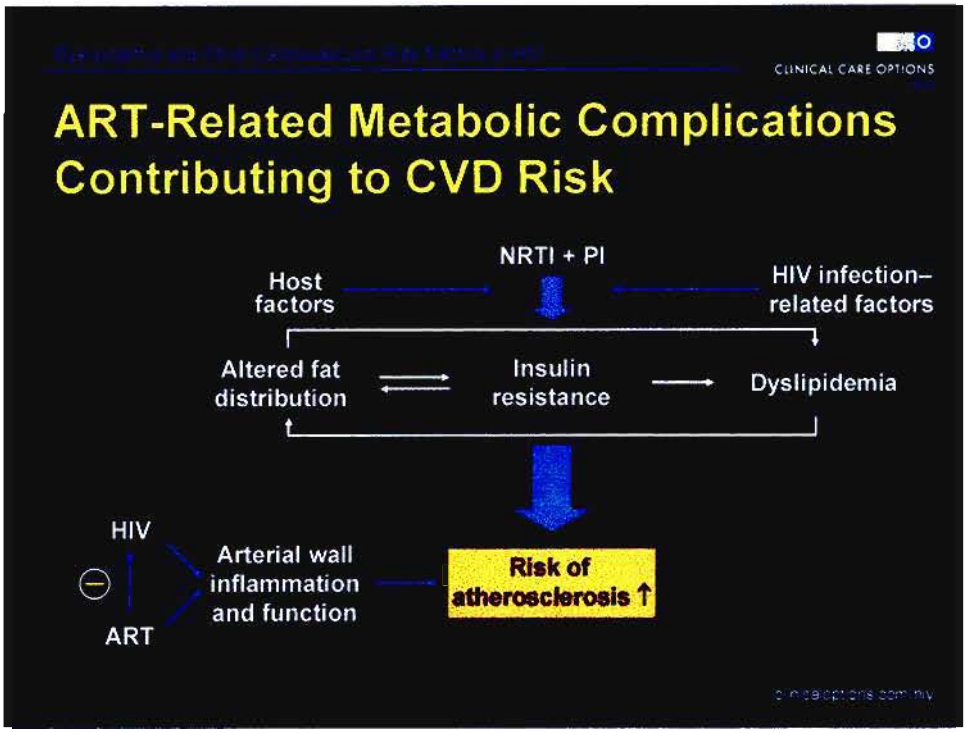


Figure 6. Slide of ART-Related Metabolic Complications contributing to CVD Risk[54]

The metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include[57]:

- abdominal obesity
- artherogenic dyslipidaemia (blood fat disorders – high triglycerides, low HDL cholesterol and high LDL cholesterol)
- Elevated blood pressure
- Insulin resistance or glucose intolerance
- Prothrombotic state (e.g. high fibrinogen or plasminogen activator inhibitor-1 in the blood
- Proinflammatory state (e.g. elevated C-reactive protein in the blood)
- High levels of lactate [68]
- Elevated ALT [68]

The WHO definition of the metabolic syndrome in HIV-negative people is fasting plasma glucose >6.1mmol (110mg/dL) plus at least two of the following[68]:

- Serum triglycerides above 1.9mM (150mg/dL) or serum HDL cholesterol below 0.9mM (35mg/dL)
- Blood pressure above 140/90 mmHg
- Abdominal obesity defined as waist to hip ratio above 0.9, waist girth above 94cm or BMI above 30kg/m^2 in men [68].

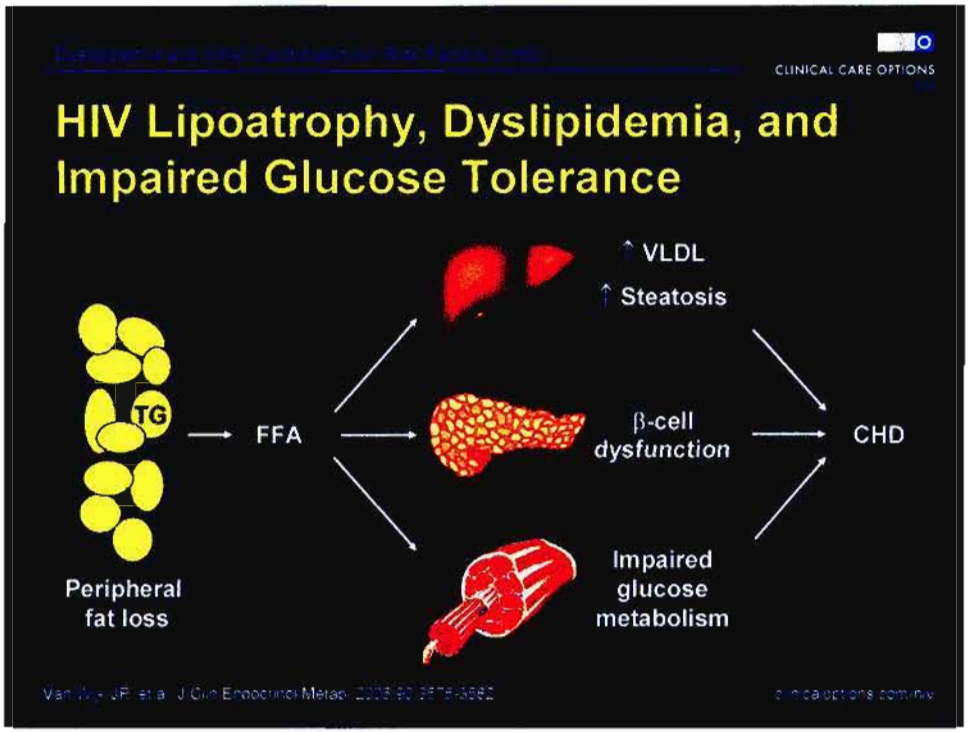


Figure 7. Slide showing HIV lipoatrophy, dyslipidaemia and impaired glucose tolerance[54]

2.4.1 Dyslipidaemia

Altered lipid metabolism is known to occur in association with HIV disease itself[24,54]. HDL, LDL and Total Cholesterol levels are decreased while triglyceride levels are increased in HIV positive patients. Various HIV-related factors such as viral load, CD4 count, proximity/severity of opportunistic infections, and mechanism of HIV acquisition appear to have modest or minimal effect on artherosclerotic lesions[24].

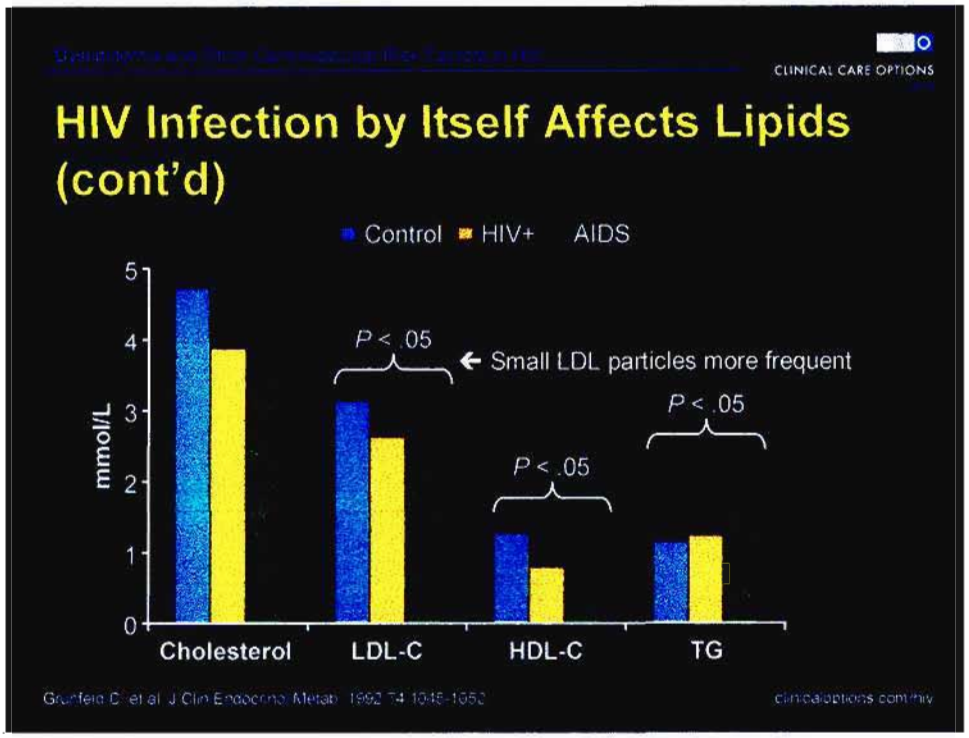


Figure 8. Graph showing how HIV Infection by itself affects lipids[54]

Protease Inhibitor (PI) use has been linked to further abnormalities in the serum lipid profile in HIV positive patients. Increased total cholesterol, increased triglycerides and LDL levels are seen in PI-treated patient[24]. These abnormalities have also been reported with the nucleoside reverse transcriptase inhibitor, efavirenz[32]. Comparison between the NNRTIs suggests the difference between the lipid levels is slight, although patients receiving nevirapine in the 2NN study (a randomised comparison of nevirapine or efavirenz) had significantly greater increases in HDL cholesterol, significantly larger decrease in the total cholesterol: HDL cholesterol ratio and significantly greater triglyceride reduction after commencing therapy[68]. The proposed mechanism by which PIs cause hyperlipidaemia is that a PI binds reversibly to proteins that regulate lipid metabolism, thereby inhibiting their activity[32]. These metabolic abnormalities can occur as early as the first few weeks of therapy and require aggressive treatment.

2.4.2 Lipodystrophy

Lipodystrophy is a spectrum of abnormalities involving fat redistribution and can be broadly divided into fat accumulation and fat atrophy. The central, visceral fat accumulation that occurs in HIV-infected patients is considered a CAD risk factor[32]. HIV-positive individuals receiving HAART commonly manifest evidence of fat redistribution, characterized by loss of subcutaneous extremity fat, relative preservation of fat in the trunk and an increased waist-to-hip ratio[24]. The following signs have been described as part of the syndrome in reports since 1997[67]:

- increased waist size
- increased breast size
- 'buffalo hump' (fat accumulation around neck and upper back)
- Fat accumulation around neck and jaw ('moon face')
- Fat deposits in other locations
- Facial wasting, especially of the cheeks

- Loss of subcutaneous fat in all parts of the body, most visibly in the limbs
- Wasting of the buttocks
- Prominent leg veins[67]

Although lipodystrophy is more frequently associated with patients taking PIs for longer than 18 months, some studies have reported the development of enlarged dorsocervical fat pads in patients whom had never been treated with a PI[32]. Although there is an association between PIs and body fat changes, this does not mean that they are the sole cause[67]. Nucleoside reverse transcriptase inhibitors (NRTIs) are increasingly shown to cause body fat changes in patients who are PI-naïve[67]. Despite the substantial evidence linking NRTIs to lipodytrophy, there is little evidence linking NNRTIs to it although efavirenz is associated with increased lipid levels[67].
d4T is more strongly associated with body fat changes than other NRTIs[67]. The mechanism by which nucleoside analogues might cause fat loss is unclear. One suggestion is that they may damage the DNA of mitochondria in fat cells that store fat in the limbs[67]. Other studies have found that there are increased risk factors for lipodystrophy that could include:

- CD4 cell count below 100cells/mm3 after 2 years follow up associated with fat loss
- CD4 cell count increase of less than 50cellls/mm3 after nearly two years of observation on treatment, regardless of drugs taken or total duration of treatment
- Low to average body mass (below 24kg/m2)at start of treatment is associated with fat depletion
- Overweight or high body mass index before starting therapy are more likely to experience fat accumulation
- White race (a possible marker of better access to healthcare) experienced lipodystrophy rather than atrophy
- Two studies found that African Americans are less likely to experience body fat changes than other races
- Later initiation of therapy
- HCV co-infection
- Australian Lipodystrophy Prevalence study found that the risk of body fat changes increased with age.
- Several studies show that women are more likely than men to experience fat accumulation while men are more likely to experience fat depletion[67]

A study presented to the 2001 International AIDS Society meeting Buenos Aires showed that the risk of developing lipodystrophy is vastly increased when nucleoside analogues are combined with protease inhibitors[67].

Patients with lipodystrophy frequently have elevated lipids in their blood and insulin resistance[67]. However the connection between high lipids and other metabolic disorders is not fully understood[67].

2.4.3 Hypertension

Data on the prevelance of hypertension in HIV patients is lacking, but earlier reports suggested no age-adjusted increase in hypertension[32].Newer data in the HAART era, suggest an increasing prevalence of hypertension, especially in patients with other metabolic abnormalities, such as diabetes mellitus, hyperlipidaemia and lipodystrophy.

2.4.4 Insulin resistance, Impaired glucose tolerance and diabetes mellitus

Impaired glucose tolerance and diabetes mellitus can occur in HIV patients, especially those on HAART regimens. Data from the MACS cohort using the WHO criteria found diabetes in 14% of men with an odds ratio of 4.4 after adjustment for age and BMI[24]. Use of WHO definitions (fasting glucose >26mg/dL defines diabetes and fasting glucose>110mg/dL defines impaired fasting glycaemia.[24]. Insulin resistance means the body is not able to use insulin properly to regulate sugar[68]. High levels of insulin resistance have been noted in individuals with fat accumulation and lipoatrophy and these are closely related to high levels of soluble tumour necrosis factor receptors[68]. Tumour necrosis factor is implicated in the development of diabetes and high levels of TNF receptors are an indication that an inflammatory condition is present[68]. Insulin resistance is associated with an increased risk of cardiovascular disease, it affects endothelial function, inhibits fibrinolysis and contributes to the development of diabetes. PI therapy is associated with higher rates of diabetes mellitus, impaired glucose tolerance and hyperinsulinaemia among HIV positive individuals[24].

2.5 Metabolic effects of HIV infection and ARV drugs

Hyperglycemia means higher than normal (hyper) levels of glucose in the blood[55]. Hyperglycaemia can be a sign of undiagnosed or uncontrolled diabetes. The signs of hyperglycaemia include increased urination, thirst, hunger, dry-itchy skin and fatigue[55]. Diabetes is a medical condition associated with increased levels of sugar in the blood[25]. Type 1 diabetics can't metabolise sugar. The pancreas can't produce insulin and therefore there is no control over the levels of glucose[25]. Type 2 diabetics show a resistance to insulin therefore there is an increase in blood glucose levels. This can lead to kidney failure, eye problems and cardiovascular disease[25].The signs of diabetes are increased urination, thirst, hunger and unexplained weight loss.[55].
An estimated 16 million people in the USA are living with diabetes[28]. Most of these are type 2 diabetics. The usual risk factors are age, obesity and family history of diabetes.

2.5.1 Protease Inhibitors effect on metabolic syndrome

The main disadvantage of PI therapy is the metabolic effects of the PIs. Various factors constitute metabolic syndrome, which is a collection of physical and metabolic problems prevalent in persons with cardiovascular disease[16]. Lipodystrophy, is the mobilisation of fats around the body. It usually presents with fat wasting in the face and extremeties with or without central obesity[34]. Lipid disorders, present with increased total cholesterol and increased plasma triglycerides. Insulin resistance usually presents in patients with lipodystrophy. Hyperglycaemia has been reported with the first 4 marketed Protease Inhibitors. There is no proven biochemical explanation for these metabolic effects[34].

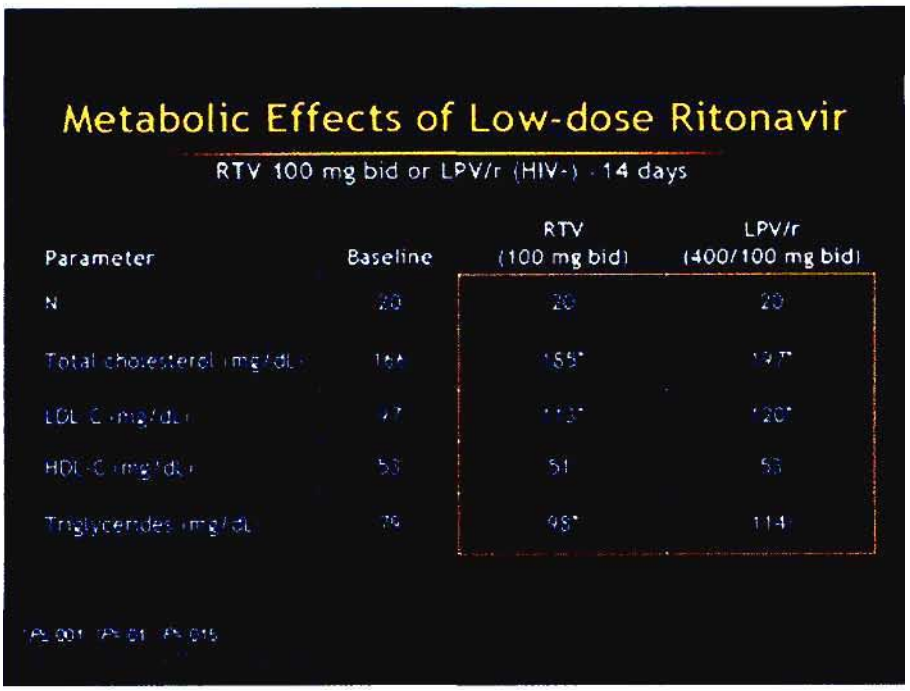


Figure 9. Table showing the metabolic effects of low dose Ritonavir on the lipid profile [54]

Protease Inhibitor's effect on metabolic abnormalities is not a class effect and some PIs don't cause insulin resistance at all (e.g. atanavir)[21,38]. This may be due to different pathways through which the various PIs induce insulin resistance. The metabolic effects are as follows: Indinavir>> Nelfinavir, ritonavir, lopinavir/ritonavir>saquinavir, amprenavir>>atanavir[36]. In order to successfully achieve the goal of HIV therapy of maximally suppressing the viral load, a combination of NRTIs and PIs are prescribed. From various studies, it is evident that HIV patients on PIs are more likely to develop hyperglycaemia than those not on a PI regimen[35]. There are various hypotheses on the pathogenesis of these metabolic effects. One is that the affinity for HIV protease could be such that they can also bind with human proteins involved in lipid metabolism especially low density lipoprotein receptor related protein which is important for post-prandial chylomicron clearance and therefore clearance of triglycerides from circulation[33]. However as the metabolic effects caused by various PI's differ between each one, the hypothesis can't be a class effect as this implies[33]. Other suggested mechanisms behind PI induced insulin resistance are complex and multi-functional[24]. Initial studies suggest an effect on Glut-4 mediated glucose transport, islet cell dysfunction and dysregulated hepatic glucose production which may complicate glucose homeostasis[24]. Preliminary data suggest PIs may inhibit the processing of insulin from pro-insulin[24]. Site specific evidence is available at various sites. Adipose tissue[21], here indinavir, amprenavir and ritonavir inhibit insulin stimulated glut-4 mediated glucose uptake by adipocytes. It has a rapid onset and is reversible[21,16]. Ritonavir, nelfinavir and saquinavir induce peripheral insulin resistance and impair glucose stimulated insulin secretion from B-cells. Adipocytes exposed to nelfinavir showed decrease in insulin mediated recruitment of protein kinase B and C to plasma membrane which indirectly interferes with glut-4 mediated glucose metabolism in adipocytes[21]. At the site of skeletal muscle, indinavir inhibits glucose transport[21]. In the liver, indinavir decreases insulin stimulated glycogen synthesis[21]. It is also found that HIV patients treated with PIs show an increase in alanine transaminase (ALT)[21,38]. This elevated level indicates insulin resistance in lipodystrophy patients[21,38]. At the pancreas, intravenous indinavir impairs glucose sensitivity by B-cells therefore inhibiting glucose stimulated insulin

release[21]. Nelfinavir impairs compensatory increase in insulin production in insulin resistant HIV infected patients[21]. Indinavir increases insulin concentration and insulin:glucose ratio[21].

2.5.2 HIV effects on hyperglycaemia and CV disease

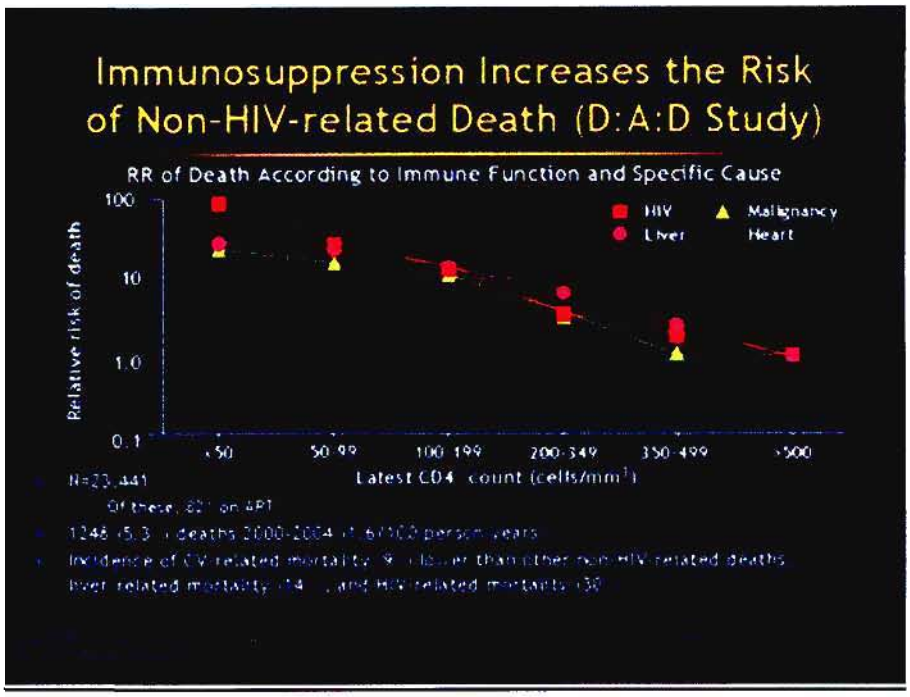


Figure 10. Graph showing the various causes of death for patients with HIV [54]

In the MACS (Multi-centred AIDS Cohort Study), researchers investigated 3 groups. HIV positive men on ARVs, HIV positive men without ARV therapy, and HIV negative men. Increase in non-insulin mediated glucose uptake is seen in those with HIV and has been accounted for by the increase in non-oxidative glucose disposal[35]. Glucose production from the liver tends to increase but glucose cycling doesn't change[35].Another suggested mechanism is that HIV associated DM is a combination of pancreatic B-cell dysfunction and peripheral insulin resistance[32].

2.5.3 Other medications – how they affect hyperglycaemia

Data from the Multicentre AIDS Cohort Study (MACS) shows that PIs, d4T and efavirenz are all associated with the development of diabetes and hyperglycaemia[68]. Insulin resistance has been seen in patients on NRTIs (Nucleoside Reverse Transcriptase Inhibitors) but to a lesser extent than those on PIs[21]. The production of adiponectin is decreased by lipodystrophy (a side effect of NRTIs). Adiponectin improves insulin sensitivity by increasing transportation or oxidation of free fatty acids and inhibition of hepatic glucose output[21]. NRTIs may also affect glucose homeostasis indirectly through the chronic changes in fat distibution[24]. Mitochondrial toxicity could contribute to the detrimental effects of NRTIs on tissue insulin sensitivity through impaired oxidative phosphorylation and excess lipid accumulation in liver or muscle or via a reduction in absolute or relative amounts of subcutaneous fat[24].

Megestrol acetate is used as an appetite stimulant in HIV patients. It has intrinsic glucocorticoid activity and therefore predisposes a number of patients to hyperglycaemia. It increases caloric intake and weight gain associated with the drug. This also has a role in the development of diabetes[35]. Other drugs that could also

cause hyperglycaemia include prednisone, growth hormone, anabolic steroids and nicotinic acid[6,36].

2.5.4 Traditional risk factors and their effect on hyperglycaemia

Patients may be insulin resistant or develop diabetes as a result of traditional risk factors such as obesity (BMI), strong family history (more than 1 immediate family member with diabetes), age, inactivity, ethnicity, co-infection with HCV[21,7,38]. In a study on HIV patients co-infected with HCV and HIV patients, showed that chronic HCV is a significant factor in the development of metabolic abnormalities[22].

2.5.5 Hepatitis C Co-infection

Jain and colleagues (2003) retrospectively reviewed 1547 charts from patients attending an HIV outpatient clinic and found that 8.8% had glucose intolerance or diabetes and 24% and HCV infection[50]. In the univariate analysis, older age, black race, family history and BMI>25kg/m^2 were significantly associated with the presence of diabetes or glucose intolerance. In a multivariate analysis adjusted for age and race, the odds ratio for diabetes or glucose intolerance was 1.6 for patients with HCV-co-infection compared with HIV infection alone[50].

In a study[38], of HIV patients with type 2 diabetes, they found that liver damage as measured by ALT levels appears to be unique in HIV associated diabetics[38]. This suggests that a liver pathway may be a marker for, or a pre-disposing factor of diabetes. This study found that steps can be taken to decrease the risk of diabetes in HIV patients. If the patient is overweight, has a strong family history (2/> family members with diabetes), and/or has lipodystrophy, dyslipidaemia, fatty liver and HCV – PI based therapy should be avoided[38].

2.6 Biochemical markers of Cardiovascular risk and altered metabolism

Impaired fibrinolysis is evident because the anti-fibrinolytic factor PA1-1 is increased in association with insulin resistance and correlates with the risk of myocardial infarction[24]. An increase in tPA is associated with myocardial infarction and stroke in HIV negative individuals[24]. Increased homocysteine levels correlate with excessive cardiovascular risk[24]. Among HIV positive patients on HAART, homocysteine, tPA and PA1-1 are increased[24]. Metformin decreases serum tPA and PA1-1 in patients with lipodystrophy and results in an associated improvement in insulin sensitivity[24]. Adiponectin is a gene produced in adipose tissue and has anti-diabetic properties such as

a) It can affect insulin signalling protein insulin receptor substrate.
b) Upregulation of muscle B-oxidation
c) Supression of hepatic glucose production
d) Suppression of inflammatory cell infiltration of the vascular intimal space in animal and cell culture models[24].

Preliminary data suggests a decrease in the concentration of adiponectin increases the risk of myocardial infarction but this hasn't been studied in HIV patients[24].

2.7 Treatment of metabolic disorders

Prevention and treatment of insulin resistance and other metabolic syndrome symptoms can be achieved through lifestyle modifications[15,21,31]. Diet and exercise are the two main lifestyle modifications that need to take place. Exercise improves insulin resistance by decreasing trunk adiposity and lipid parameters[21,24]. In addition, the patients should be alerted to watch for symptoms, and monitor fasting blood glucose every 3 months[15]. Smoking cessation is important to decrease CV risks, lipid control is important and aspirin treatment may be a necessary pre-caution[36].

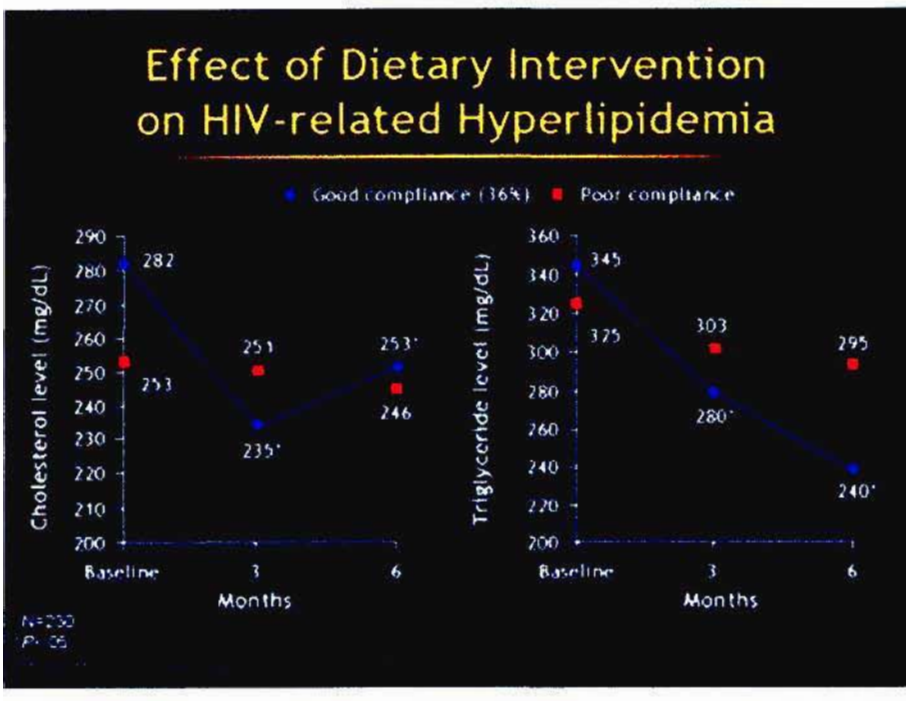


Figure 11. Graph showing how dietary interventions can improve lipid profiles[54]

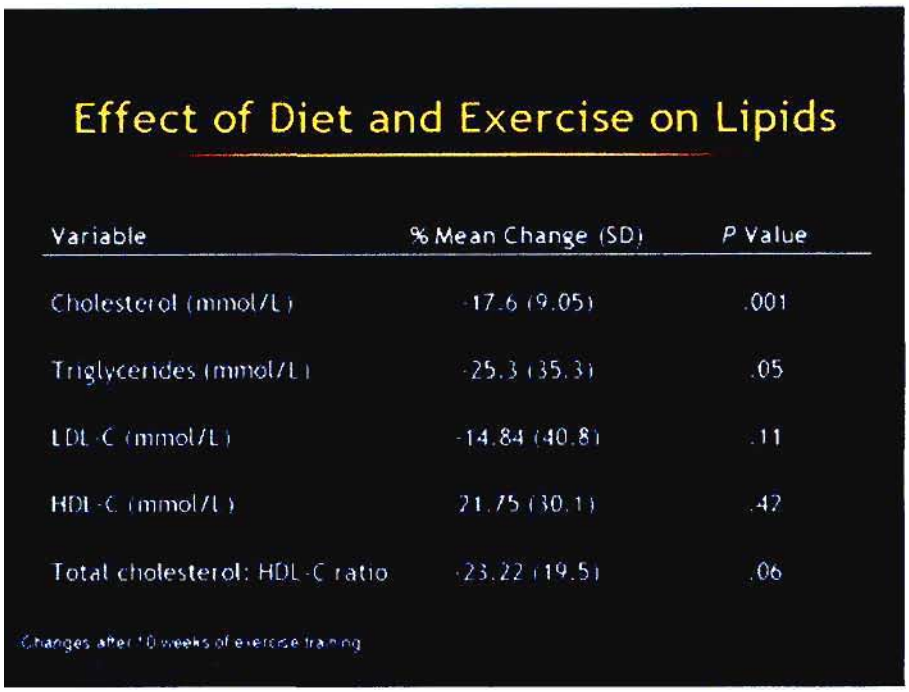


Figure 12. Table showing the how dietary interventions can change the lipid profile[54]

If the hyperglycaemia cannot be controlled through diet and exercise, it is recommended to switch patients to a NNRTI if possible or change to a PI that doesn't cause insulin resistance e.g. atazanivir[21]. In some cases switching to efavirenz from a PI, can improve total cholesterol, insulin resistance and lipid ratios[7].

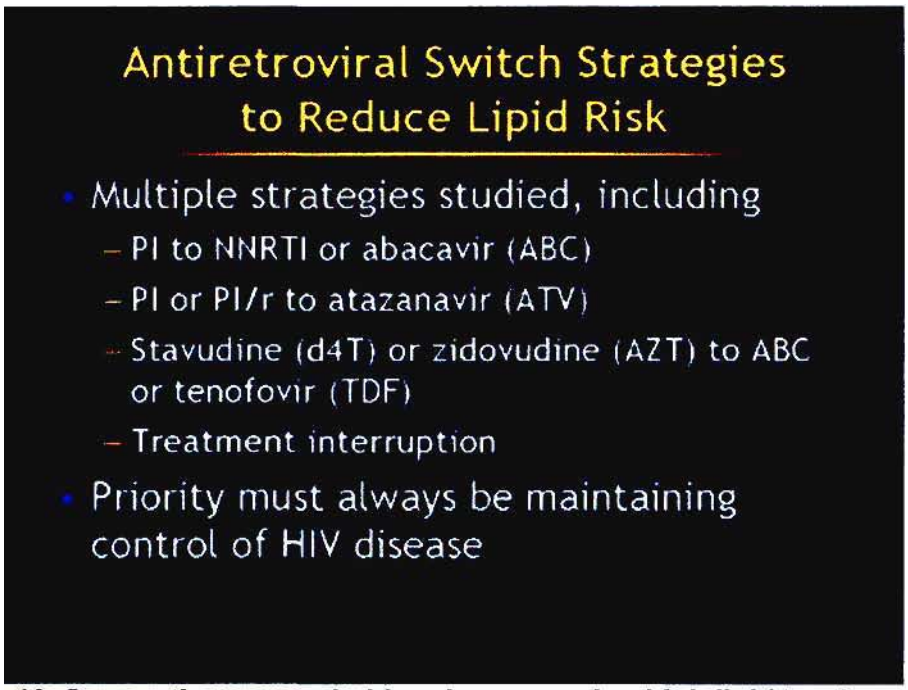


Figure 13. Suggestions on switching drugs causing high lipid levels to drugs that have less effect or a positive effect on lipid levels[57]

If there is a treatment failure risk, rather treat the insulin resistance separately[21]. If treatment is working and virological and immunological suppression is good, switch to nevirapine ART[21]. Patients with pre-existing diabetes may find glucose control

changes with PI treatment and therefore self-monitoring of blood glucose is important and medications may be necessary[35]. First line treatment of insulin resistance in HIV patients who are resistant to lifestyle modifications and can't be switched to a different treatment, involves the use of oral hypoglycaemic agents. Sulphonylureas or insulin sensitizers like thiazolidediones or biguanides like metformin can be administered[21]. Each class has advantages and disadvantages to their use. Sulphonylureas stimulate the pancreas to produce more insulin but can cause weight gain[31] Ritonavir can increase the AUC of sulphonylureas and potentiate their effect therefore should be started at low doses[14].

Metformin decreases hepatic glucose toxicity, it improves insulin resistance or glucose intolerance and decreases insulin and LDL and TG levels and decreases weight[35]. It improves hepatic insulin sensitivity[24]. It has quite severe GI side effects and can cause lactic acidosis which is a problem if already taking NRTIs[31]. But lactic acidosis risk increases because NRTIs also can cause lactic acidosis especially stavudine, zidovudine, and didanosine. Symptoms of lactic acidosis include fatigue, nausea, abdominal pain, nausea, weight loss, and dyspnoea[35]. There is no evidence that co-administration of metformin and NRTIs can increase the risk of lactic acidosis[21].

Thiazolidiones have become an important agent in the treatment of type 2 diabetes as they cause the stimulation of adipocyte differentiation and function. They improve insulin sensiivity[24]. Rosglitazone and pioglitazone increase insulin sensitivity in peripheral tissues and therefore improve insulin resistance. Liver function tests are required and if there is pre-existing liver disease, these drugs are contra-indicated[35]. These drugs have an effect on fat changes. Rosglitazone is preferred because it is not metabolized by the CYP34AA path[36]. Low dose insulin may be necessary if failing oral agents[36].

2.8 Basis for Research

From the above literature review, there is evidence that diabetes and cardiovascular disease are more common in HIV-infected populations compared with HIV-uninfected control populations[107].
The etiology of insulin resistance in HIV-infected patients is multifactorial, with contributions from various components of antiretroviral therapy, patient factors (such as age, BMI, and family history), and HIV infection itself[107]. Although literature suggests that insulin resistance and consequently hyperglycaemia are concerns for patients on ARV therapy, DoH guidelines do not include random or fasting blood glucose testing.

CHAPTER 3

Results and discussion

St Mary's Hospital (SMH) is a 200-bed, level one district hospital, situated on the outskirts of Durban, in the Marianhill Mission Complex. More than 750 000 people, living in the Inner and Outer West Operational Areas of the Durban Metropolitan area are serviced at St Mary's Hospital.[95] It is estimated that more than 250 000 people, living in the St Mary's Hospital catchment area are HIV-positive [95].

Kwa Dabeka Community Health Centre (KDC) is a provincial clinic which refers patients to district hospitals, one of which is St Marys. KDC currently serves a population of approximately 130 000[96].

This study was conducted on 271 patients (137 at SMH and 134 at KDC) at these 2 facilities. The results have been reported collectively on the joint populations from both clinics

3.1 Demographics

3.1.1 Gender

The gender distribution of the study population for KDC and SMH is presented below in table 1:

Table 5. Table showing gender distribution at the two clinics

Clinics	Female (n)	Male (n)	Total (n)
St Marys	78	57	137
KDC	104	28	134
Total	182	85	271
Percentage %	67.2%	31.4%	100.0%

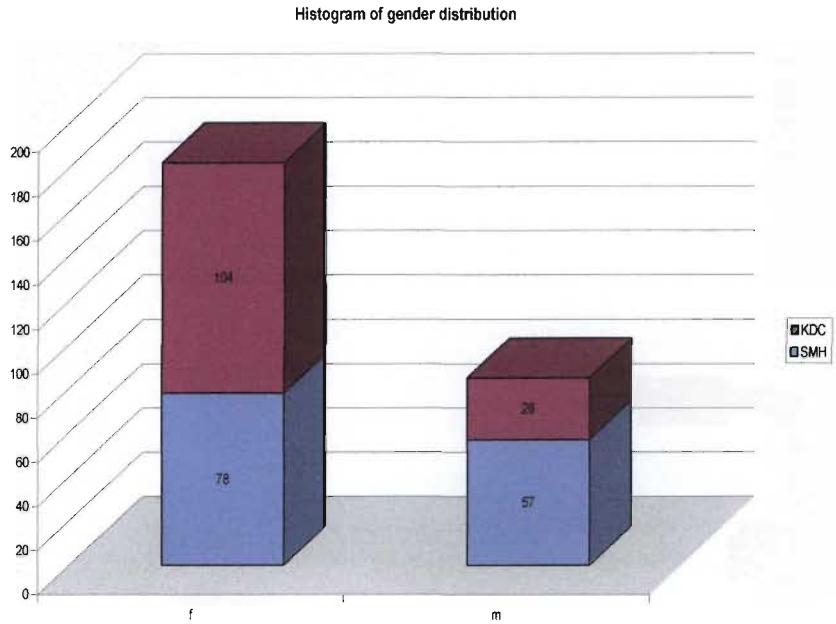


Figure 14: Histogram showing the gender distribution at the two health facilities investigated.

Figure 14 shows that the majority of HIV infected patients at both facilities were female (77.6%, n=104) at KDC and 56.9%, n=78) at SMH).
This is in congruence with other Southern African studies (as reported in the UNAIDS HIV report for 2006[83] which found that 59% of HIV-infected adults across all age groups (15 years and older) in sub-Saharan Africa are female [83]. For every 10 adult men living with HIV, there are 14 women [83]. This report states that globally, of a total 39.5 million people infected with HIV, 17.7 million (48%) were women [83]. In the Caribbean, Middle East and North Africa one in every two adults is female and in North America and Europe the number of infected women is increasing [83].

South African women are at an increased risk of HIV infection as heterosexual intercourse has an increased risk of transmission for women over men. This is enhanced in South Africa by certain cultural sexual practices such as dry sex and anal sex[84]. In addition, unequal power relations between men and women, a lack of economic power, physical and sexual violence, a lack of access to information and migratory labour practices increase the risk of HIV transmission to women[84].

3.1.2 Age

Table 6. Age distribution of patients investigated at KwaDabeka and St Marys' hospitals

Clinic	Number of patients in each age group							Total
	0-9	10-19	20-29	30-39	40-49	50-59	>=60	0-9
St Marys	32	19	16	33	23	11	1	135
KDC	5	3	25	51	32	9	2	127
Total	37	22	41	84	55	20	3	262
Percentage	14.1%	8.4%	15.6%	32.1%	21.0%	7.6%	1.1%	100.0%

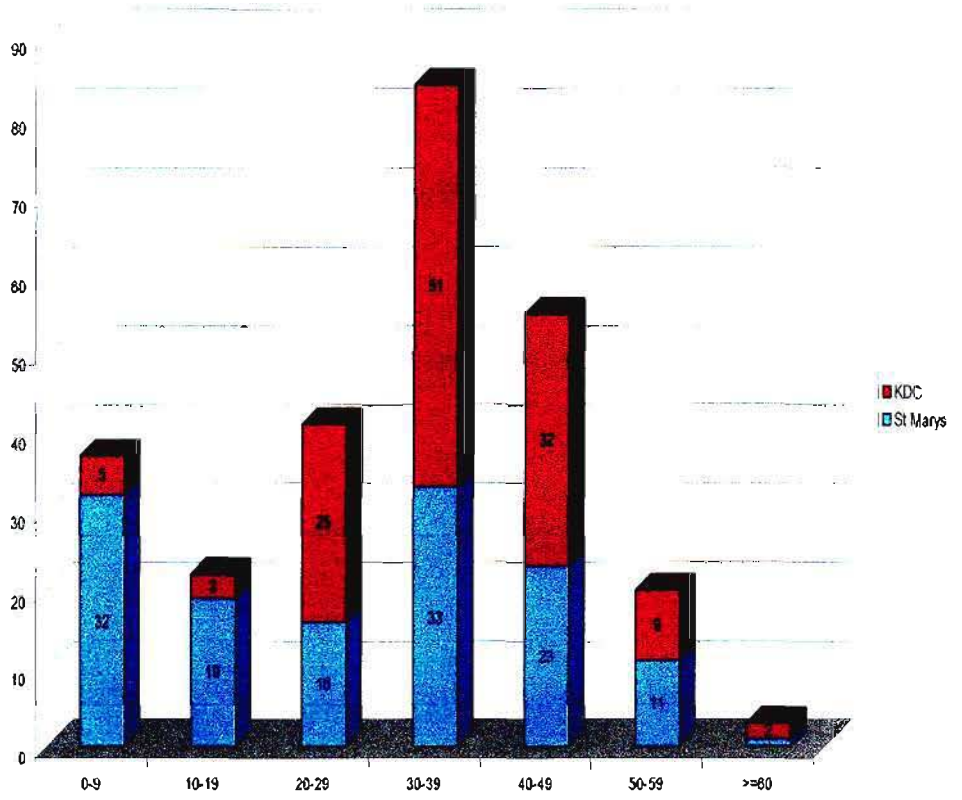


Figure 15. Graph showing age distribution of patients investigated

These results show that most of the patients investigated (32.1%, n=84) were in the 30 to 39 year old age group category, followed by the 40-49 age group (21%, n=55)).
At SMH, 23.7% (n=32) of the patients were under the age of 10 years. This is because SMH has an extensive anti-retroviral programme and it encourages the enrollment of children and babies, starting from birth. It is also involved in a clinical trial on newborns involving the use of nelfinavir[94]. See explanation under *Starting regimen (Section 3.2.4)*

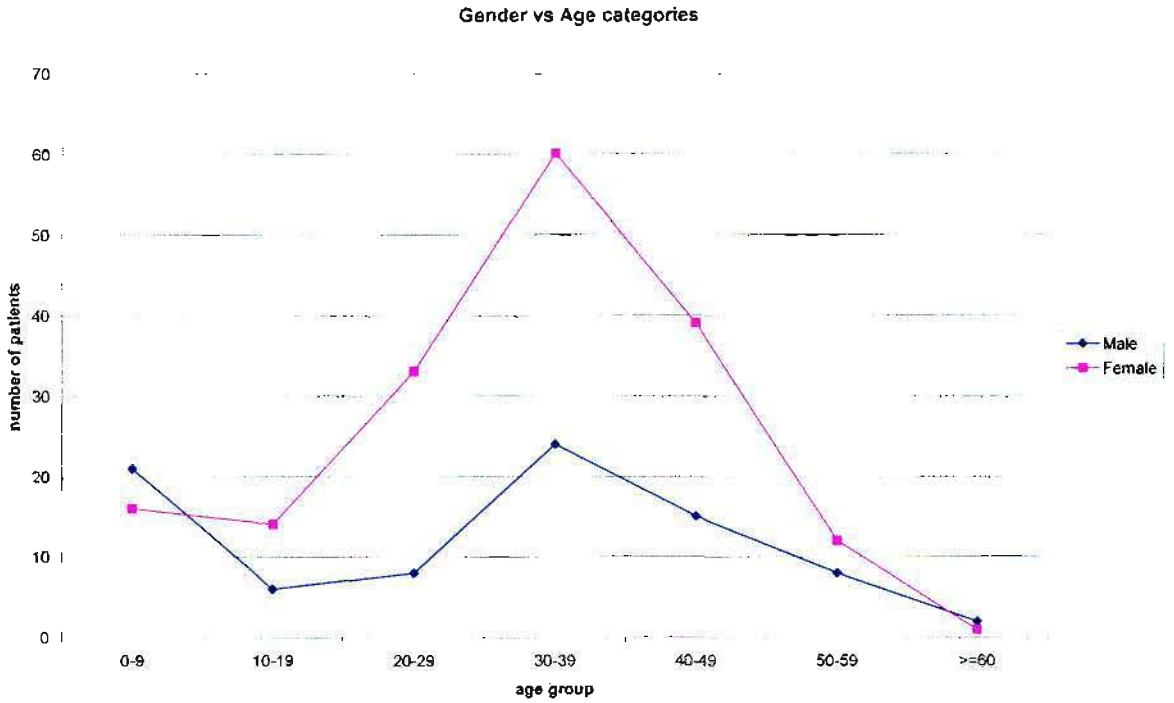
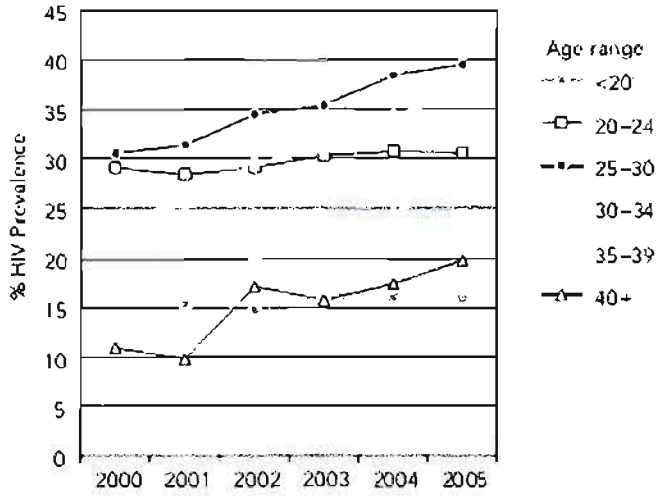


Figure 16: Sex and Age distribution of study cohort

According to the UNAIDS report (2006), the majority of HIV patients in South Africa are between the ages of 20 -24, followed by the 30-34 age group, which has increased significantly in the last 5 years [83]. Figure 16 shows that more women than men in all age groups (apart from those under 10) were HIV-infected. However, in the older age groups the difference between men and women appears to be smaller and in the over 60 age group, more men presented with HIV than women. HIV is often present in older males in Southern Africa due to various cultural practices, such as the practice of having more than one wife, the belief that raping a virgin will cure HIV, and child abuse[84]. Due to these practices, often the younger age groups have more women than men with HIV and the reverse is then seen in the older age groups.

HIV prevalence by age group among antenatal clinic attendees in South Africa, 2000–2005



Source: Department of Health (2006, National HIV and Syphilis Prevalence Survey South Africa; 2005. National HIV and Syphilis Antenatal Sero-Prevalence Survey in South Africa)

Figure 17. HIV prevalence by age group among antenatal clinic attendees in South Africa, 2000-2005[83]

Antenatal surveys (figure 17) show that the age group with the highest prevalence of HIV was age 25-29[83]. As this data is extrapolated from a study of HIV in antenatal attendees, the assumption is that this is the prevalent age group of HIV in women. Accordingly, this finding would be in congruence with our study, where HIV is prevalent in a much younger age group amongst women in comparison with men.

UNAIDS (2006) reports that in South Africa, 240000 children under 15 years are living with HIV in 2005 [83] and internationally of 39.5 million infected people with HIV, 2.3 million were children under 15 years. This accounts for some of the patients in our study population being children. However, in this study, the percentage of children was even higher due to recruitment for the nelfinavir (Viracept®) trial being conducted at St Mary's (see *Starting regimen*).

The majority of patients in this study were over 30 years old in comparison to the data from UNAIDS (2006) with the majority of patients in the 25-29 age group. This is because some of these patients have been on anti-retroviral treatment for some time (19.71 months) and are therefore surviving for longer on ARV treatment.

3.1.3 Socio-economic status

From the socio-economic data collected, it was found that 73% of patients have electricity in their homes, 11.7% use paraffin, 62.8% have access to tap water in their homes, 19.7% use a shared tap, 2.2% access water from the river. 47.4% of the patients use a pit latrine as

opposed to a flush toilet. This shows that the majority of patients in the study were poor and did not all have access to healthy and sterile facilities.

Nelson Mandela/HSRC study (2002) showed that there was no significant difference between people employed (14.2%) or unemployed (12.1%) [86], in terms of contracting HIV. The same study also showed that all strata of African society were at risk of contracting HIV, not only the poor[86].

3.2 Medical History

3.2.1 Body Mass Index

Body Mass Index is a measure of obesity and a high body mass index is a determinant for diabetes mellitus (type 2). Patients with a higher body mass index are more likely to develop metabolic abnormalities including high blood glucose.

SMH did not record heights of patients and therefore body mass index could not be calculated. The body mass index (BMI) of 54 patients at KDC were recorded. The mean BMI for these 54 patients was 28.4 units.(kg/m2)

A BMI of 28.4 for the patients at KDC is indicative of the South African population. Le Roux et al (2005) showed that of younger physically inactive women with HIV (N=151) 49.0 percent had a BMI > 25 kg/m² indicating that they were overweight or obese[99].

3.2.2 Concomitant Diseases

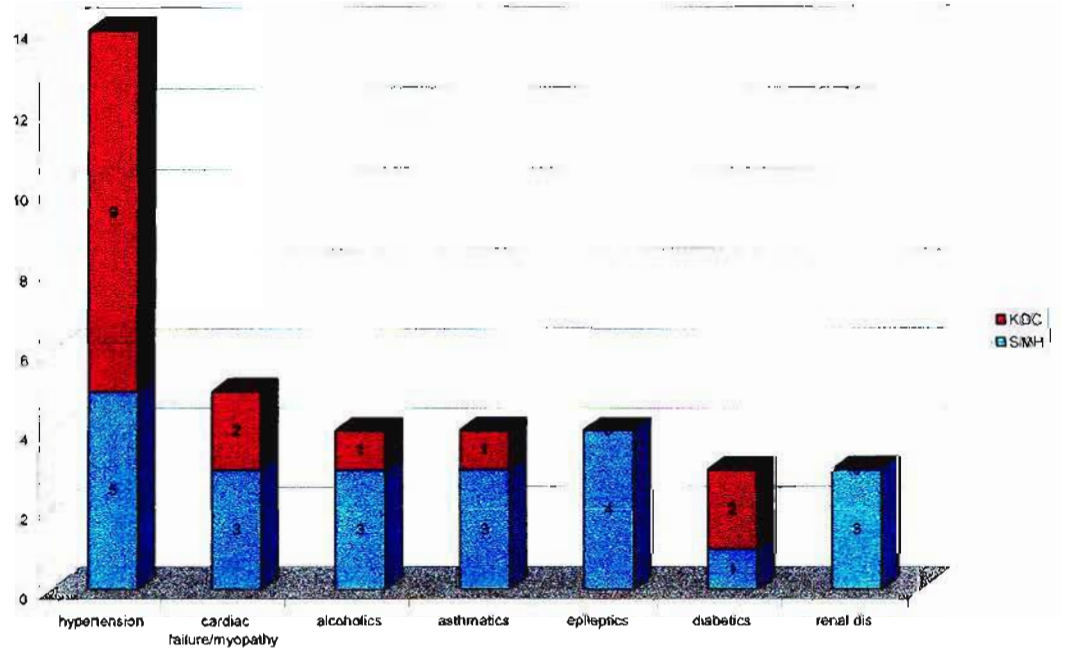


Figure 18. Concomitant diseases of patients at each clinic at the start of their HIV treatment

Hypertension (5.2%, n=14)) was the most common concomitant condition with HIV at the initiation of ARVs in the patient population (figure 18). 6.7% (n=9) of patients at KDC and

3.65% (n=5) of patients at SMH had concomitant hypertension. 1.1% (n=3) of the patients had diabetes (1.5% (n=2) of patients at KwaDabeka and 0.73% (n=1) at St Mary's). There were 1.8% (n=5) of patients with cardiac failure or cardiomyopathy (1.5% (n= 2) at KwaDabeka and 2.2% (n=3) at St Marys). 1.5% (n=4) of patients were alcoholics (2.2%, n=3) at St Marys and 0.8% (n=1) at KwaDabeka), which presents extra strain on the liver with the initiation of ARVs. 2.9% (n=4) of patients at St Mary's were epileptic which presents challenges with drug interactions when initiating ARV treatment. 1.5% (n=4) of the patients were asthmatic, (2.2% (n=3) at St Mary's and 0.8% (n=1) at KwaDabeka).

These data were obtained from the medical history of the patients, a review of their current drug therapy and by clinical measures such as a blood pressure. The only screening that was performed before initiation of ARV treatment was BP measurement, liver enzymes and full blood counts. Cholesterol and glucose screening was not performed at initiation of treatment. As Currier et al (2002) report, metabolic complications have been associated with HIV treatment as well as with the disease itself[8]. Kamin et al (2005) states that the use of HAART is associated with traditional cardiovascular risk factors including dyslipidaemia and insulin resistance[24]. Considering the growing concern surrounding metabolic complications for patients on HAART, it may be useful for increased metabolic screening to occur at baseline including a total cholesterol and glucose measurement. DoH only requires screening for CD4, VL, liver function and blood counts for patients on Regimen 1 at 6 monthly intervals. For Regimen 2 patients, DoH guidelines state that cholesterol and blood glucose should be monitored in addition to the above at baseline and annually[1].

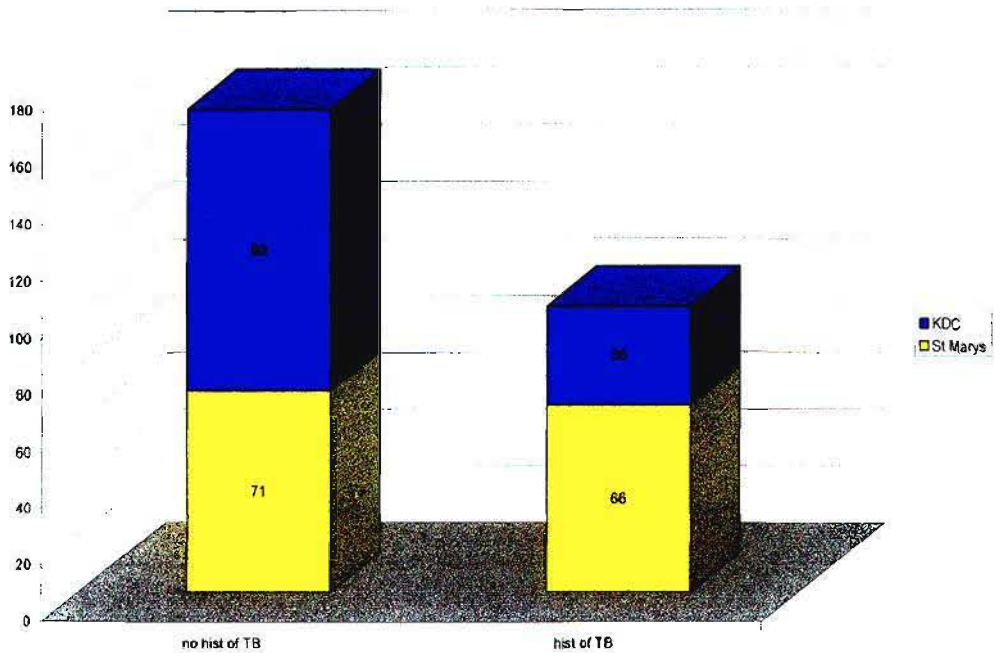


Figure 19. Patients with a history of TB at start of treatment

The most common co-infection that patients at both clinics presented was TB either prior to, or at the start of ARV treatment (n=101, %=37.3%). 26.1% (n=35) at KDC and 48.2% (n=66) at SMH had a history of TB at the point of initiation of treatment of ARVs.

At the beginning of 2005, the detection of multi-drug resistant TB in KwaZulu-Natal highlighted the lethal combination of TB and HIV in South Africa[83]. UNAIDS reports that in South Africa, 60% of TB patients are also co-infected with HIV. [83]. At the Tugela Ferry clinic in rural KZN, where the XDR-TB was first diagnosed, 53 patients were initially diagnosed with XDR-TB and of the 44 who were tested for HIV, all were HIV positive[83].
This highlights the significant number of patients who are HIV positive and co-infected with TB. The importance of this, is that without treatment, 90% of patients living with HIV, die within months of contracting TB[100]. *Health 24.com*[100], states that the rapid spread of concomitant HIV and TB is due to the geography and biology of co-infection. This means that as people live in close proximity to one another and due to the air-borne nature of TB, it is very easily spread from one person to another. One third of the global population is infected with TB, but in the vast majority of those infected, the disease is latent[100]. Only one in ten people develop active TB disease in their lifetime. Of those whose immune systems have been weakened by HIV, 10% will develop active TB each year[100].

3.2.3 *Opportunistic infections*

Table 7. Table showing different opportunistic infections experienced by patients at each clinic.

OI	SMH	KDC	Total
URTI	68	21	89
TB	34	26	60
STD	23	27	50
Diarrhoea	30	12	42
Oral thrush	19	11	30
Shingles	6	6	12
Kaposi's sarcoma	2	2	4
Cryptococcal meningitis	0	3	3
Anaemia	2	1	3
Swollen cervical gland	2	0	2
Oral leukoplakia	1	1	2
Aids dementia	2	0	2
UTI	1	0	1
HIV encephalitis	1	0	1

The most common opportunistic infection noted was upper respiratory tract infections, (68 patients at St Mary's and 21 at KDC).TB was the second most common concomitant disease seen at both clinics (n=60) and is discussed in more detail below. STDs were common (n=50) especially at KDC (n=27). This highlights the fact that the patients are not practicing safe sex which increases the risks of re-infection. It is recommended that there be increased awareness and education to promote the use of condoms in order to ensure that re-infection and resistant viruses are not introduced.

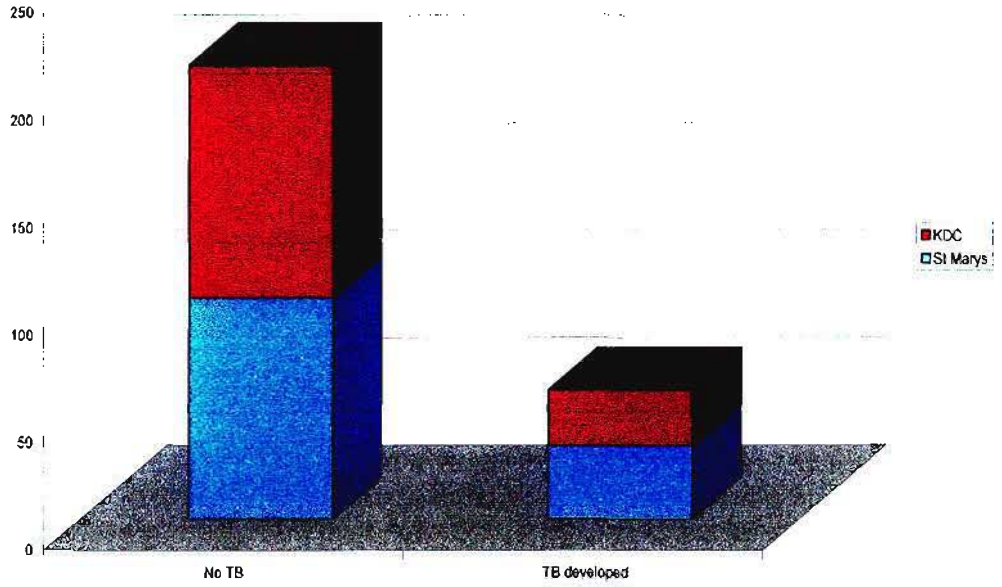


Figure 20. Number of patients who developed TB while on ARV treatment at each clinic.

Figure 20 shows that 34 patients at SMH and 26 patients at KDC developed TB while on ARV treatment. This increases the pill load for patients, with consequent adverse effect on compliance. Concomitant treatments can also increase the potential for side effects, especially peripheral neuropathy, as both ARV and TB treatment have the potential to cause peripheral neuropathy. This, together with the increased pill burden may compromise patient adherence. See section below on *Peripheral Neuropathy.*

3.2.4 Starting Regimen

Table 8. Table showing number of patients (by clinic) on each starting regimen (refer to key below)

Clinic	Regimen						Total
	1	2	3	4	5	6	1
St Marys	102	12	7	11	0	4	136
KDC	111	11	1	0	1	0	124
Total	213	23	8	11	1	4	260
Percentage	81.9%	8.8%	3.1%	4.2%	.4%	1.5%	100.0%

Key:
Regimen 1: 3tc, d4t, efv
Regimen 2: 3tc, d4t, nvp
Regimen 3:3TC, AZT, EFV
Regimen 4:3TC, AZT, NVP
Regimen 5:AZT, Kaletra, ddI
Regimen 6:3TC, AZT, Nelfin

Table 8 shows that at both clinics, the majority of patients, 75% (n=102) at St Mary's and 89.5% (n=101) at KDC, started on regimen 1 (3TC, d4T and efavirenz which is equivalent to the DoH regimen 1a). This would be in accordance with the DoH guidelines[1].
Regimen 2 (as labeled in the key above), is the DoH's regimen1b and would be used for women who were not able to guarantee birth control (8.9%, n= 23) of patients at both clinics. A small percentage started on different regimens (8.1%, n=11 at SMH) started on regimen 4 (As per key above, 3TC, AZT, NVP). This is due to the fact that some of the patients were initiated on treatment before the guidelines were in place and AZT was the drug of choice at that stage. 2.9% (n=4) of patients were on regimen 6, (according to the above key includes 3TC, AZT and Nelfinavir)[94]. This was part of a trial that was initiated at SMH where a cocktail of nelfinavir, nevirapine, AZT and 3TC were given to three sets of babies: those infected in the womb (HIV positive at birth), those infected during birth (HIV negative at birth but HIV positive at six weeks) and those infected by breastfeeding (HIV negative at birth and at six weeks, but HIV positive at 13 weeks)[94].

3.2.5 *Duration of treatment (measured in months)*

Table 9. Table showing the average length of time on treatment (in months)

Clinic	Mean (months)	Number	Std. Deviation
St Marys	25.02	135	7.800
KDC	13.89	123	6.677
MEAN(TOTAL)	19.71	258	9.162

Table 9 shows the average length of treatment time for the study population was 19.7 months (St Mary's was 25.0 months while at KwaDabeka it was 13.9 months).
St Marys initiated their ARV clinic from 2001[95]. To date, more that 1 100 people have had access to ART, as a result of additional funding obtained through the "U.S. President's Emergency Plan for AIDS Relief[95]. The ARV clinic at KwaDabeka was started in 2005. Some of the patients at KwaDabeka have been on treatment for a longer length of time, this is because some of the patients had been initiated on treatment at other district hospitals (e.g. St Marys) and transferred to KwaDabeka at a later stage to collect their monthly prescriptions. The success of the treatment is demonstrated below by an increase in CD 4 counts for the patients on ARV treatment.

3.2.6 Drug Regimen Changes

Table 10. Table showing the regimen changes at each clinic

Clinic	regimen change		Total
	no	yes	no
St Marys	114	23	137
KDC	129	5	134
Total	243	28	271
Percentage	89.7%	10.3%	100.0%

Table 10 shows that 10.3 % (n=28) of all patients at both clinics had drug regimen changes during the time they were on treatment (23 at St Mary's and 5 people at KwaDabeka). Drug changes usually occur if the patients are experiencing side effects or if resistance develops. As the patients at St Mary's have been on ARV treatment for a longer time (25 months vs. 13 months at KDC), they are more likely to have experienced drug changes as they are more likely to have developed side effects or drug resistance.

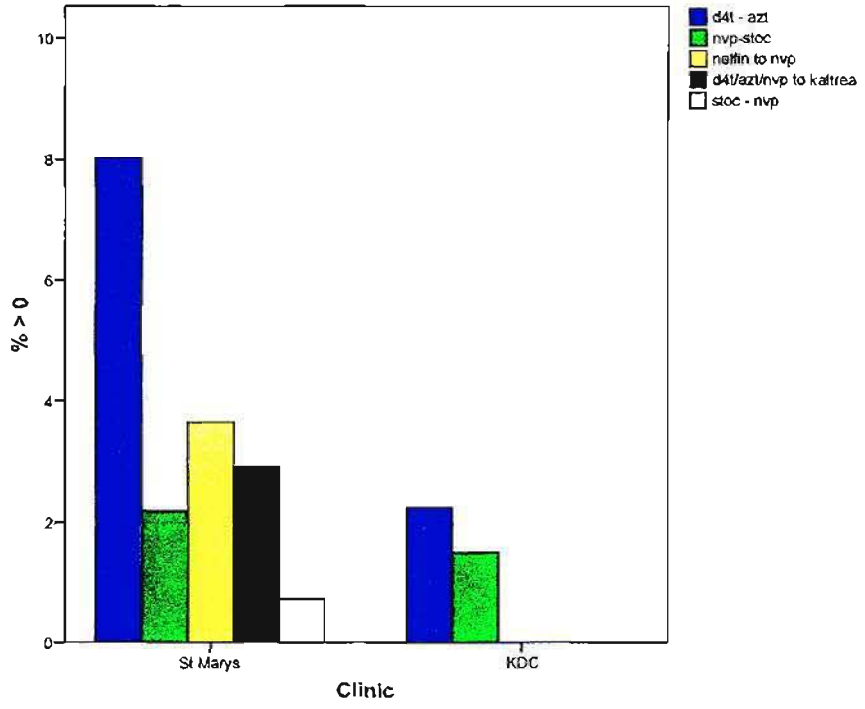


Figure 21. Different regimen changes for patients at KDC and SMH

Figure 21 shows that the most likely drug change was from d4T to AZT (11 at St Mary's and 3 at KwaDabeka). This could be due to side effects mainly peripheral neuropathy (see section on peripheral neuropathy section 3.7).

3 patients at St Marys and 2 at KwaDabeka were changed from nevirapine to efavirenz. Side effects of nevirapine include liver toxicity and facial or body rash[63]. Therefore efavirenz is preferred. Once the patient can guarantee birth control, efavirenz becomes a feasible option.

One patient at St Mary's was changed from efavirenz to nevirapine because she became pregnant. Animal studies showed high rates of birth defects in pregnant women on efavirenz, therefore it is not recommended in pregnancy[62]. 4 patients at St Mary's and none at KwaDabeka were switched to DoH's Regimen 2 which includes Kaletra® (a protease inhibitor). These patients were demonstrating immunological or virological failure (See section on *Regimen 2 patients* below). This would arise in patients who had good adherence but whose CD4 counts were still not increasing or the viral loads were not decreasing. 5 patients at St Marys and none at KwaDabeka were switched from nelfinavir to nevirapine. This is due to the trial that was conducted at SMH (see section on drug regimens). Once the babies completed the trial, they are maintained on ARV medication that is available to the state (which does not include nelfinavir).

3.3 Biochemical Data

3.3.1 Frequency of test results

DoH guidelines state that the biochemical data should be monitored at regular (6 monthly) intervals at baseline (start of ARV therapy) and then every 6 months thereafter.[1]. Patients on Regimen 1 should be monitored for CD4, VL, full blood counts and liver enzymes[1].

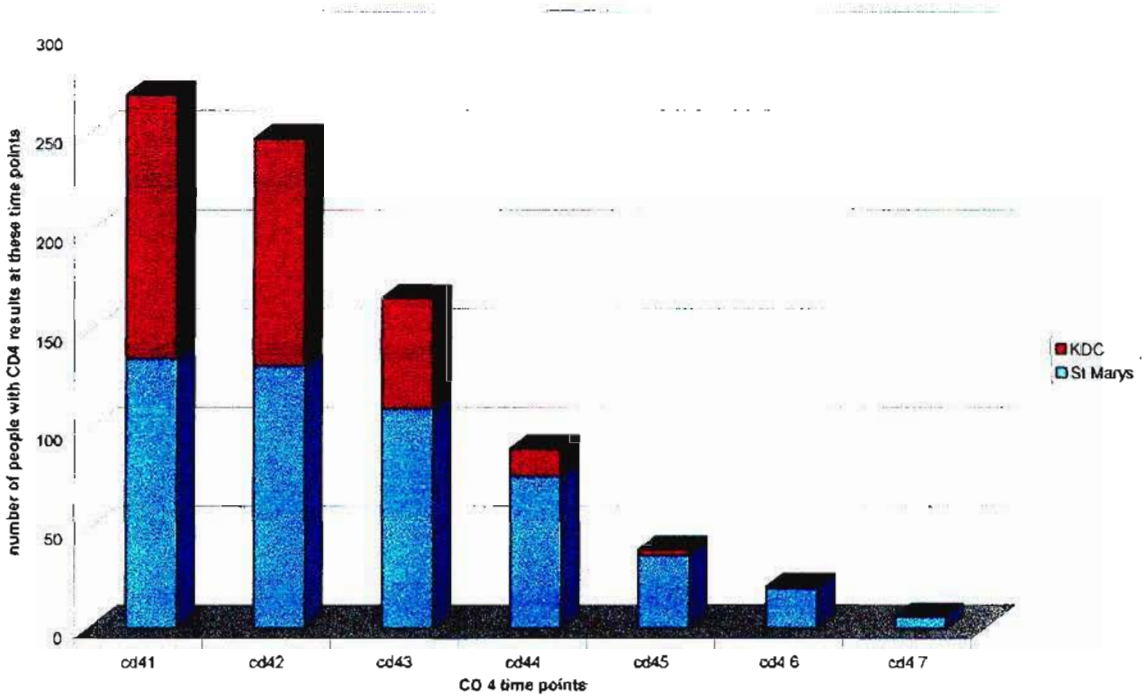


Figure 22. Number of tests done at each clinic for CD4 during study period at different time points

Key:
CD41 – CD4 at time point 1 – i.e. at initiation
CD42 – CD4 at time point 2 – i.e. 6 months after initiation
CD43 – CD4 at time point 3 – i.e. 12 months after initiation

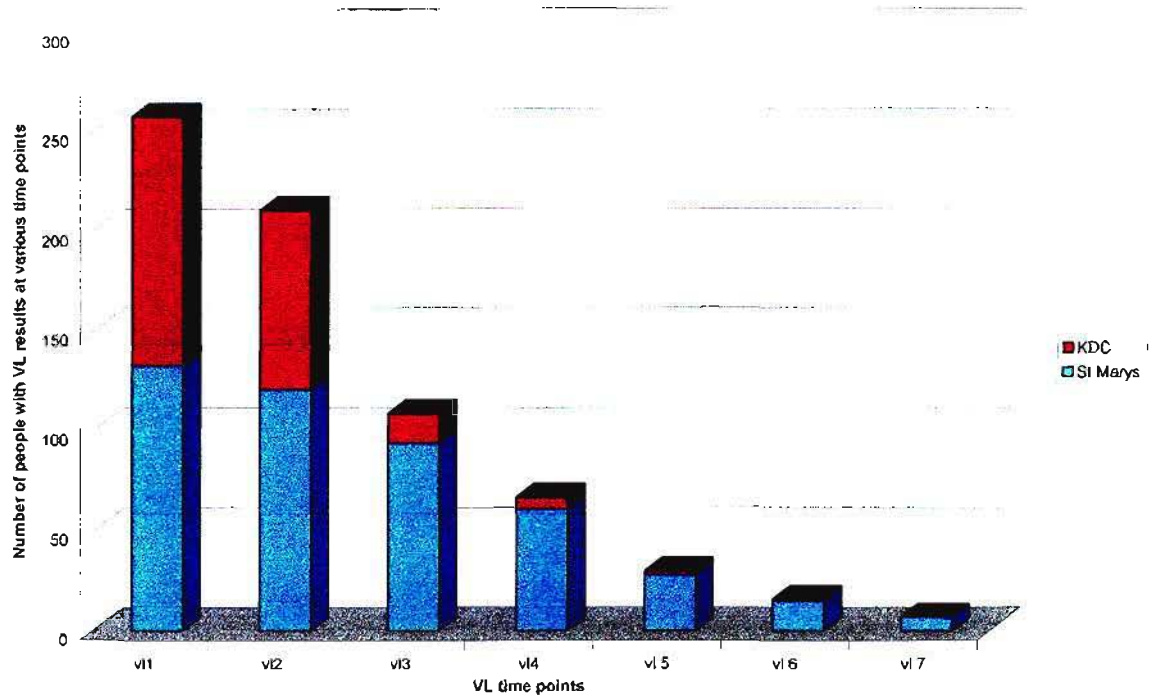


Figure 23. Number of tests for VL at each clinic

Key:
VL1 – VL at time point 1 – i.e. at initiation
VL2 – VL at time point 2 – i.e. 6 months after initiation
VL3 – VL at time point 3 – i.e. 12 months after initiation

DoH recommends that the CD4 and VL is evaluated and recorded every 6 months[1]. These results show that the frequency of CD4 and VL testing decreases with time. At KDC the average length of time on treatment is 13 months, therefore on average patients at KDC would have between 2 to 3 CD4 and VL results recorded. At St Marys the patients have on average been on treatment for longer (25 months) and therefore they should have an average of 4 CD4 and 4 VL results recorded. As the average time on treatment is 19 months, the number of tests performed will decrease with time. From the above it appears that CD4 results are recorded more regularly than the VL results. A factor to be considered may be that the cost of CD4 test is significantly lower than that for a VL test (a private laboratory pricelist quotes CD4 at R180.40 and HIV VL at R719.40).

Liver function tests were performed on a regular basis but with decreasing frequency as time increased. See Appendix 2. Frequency of Liver Function Tests

Liver enzymes should be recorded regularly as d4T and efavirenz can cause elevated liver enzymes and a fatty liver as a less common side effect[59,62]. Nevirapine is associated with liver toxicity and those patients should be monitored more frequently[63].
With the passage of time, the number of liver enzyme tests performed decreases (Appendix 2). At KDC, ALT, GGT, and ALP were measured while at SMH, ALT and AST were measured. This is clear in the graph in Appendix 2 where KDC displays no results under AST and SMH commonly has results for ALT and AST but not for GGT and ALP. This means that there is no uniformity between the clinics on liver enzyme testing.

ALT is an enzyme present in hepatocytes and will rise dramatically in acute liver damage. AST is similar but is also present in other cells of the body and therefore not specific to the liver[103]. The ratio of ALT to AST is useful in differentiating the cause of liver damage[103]. GGT is usually raised in alcohol toxicity and can be useful in identifying the cause of isolated elevated ALT levels[103]. ALP levels will rise with bile duct obstruction[103].

From Appendix 2, it is evident that the liver function tests are not performed as frequently as CD4 counts. This is significant because as time on treatment increases, the likelihood of liver toxicities also increases. As the guidelines are not being closely followed, side effects affecting the liver from the medications would not be diagnosed at an early stage.

Blood counts were performed on a regular basis but the number of tests performed decreased with time. (Appendix 3: Frequency of Blood Count tests).

3TC can cause neutropenia (low white cell count) and there have been reports of severe anemia with 3TC[60]. AZT can damage bone marrow and result in severe anaemias or neutropenia[61].
Appendix 3 shows that the number of blood results collected decreases with increasing time points. DoH guidelines state that full blood counts should be recorded every 6 months. From the graphs in appendix 3, it can be seen that this is not the case, unlike for CD4 tests. As the patients at SMH have been on treatment for a longer time than those at KDC, there are more results for the SMH patients. However, again the blood count results (Hb, wcc and platelets) are not recorded as regularly as CD4 results (SMH: 137 patients had CD results at timepoint 1 but only 135 had an Hb measurement at the same time point; KDC: 133 had a CD4 result at timepoint 1 but only 126 had a HB result at the same timepoint.)

Table 11. Number of Patients with metabolic tests at the two clinics

	St Marys	KDC	total	Mean result
chol	2	3	5	4.4
tdl	2	1	3	1.87
hdl	2	1	3	1.49
tg	2	1	3	1.28
hgt1	4	11	15	6.2
hgt2	1	5	6	6.2
hgt3	1	3	4	7.45
hgt4	1	3	4	16.35
hgt5	1	1	2	22.65
hgt6	1	1	2	25.4
hgt7	0	1	1	14.1
hgt8	0	1	1	16.4
hgt9	0	1	1	16.4

Only 5 patients were tested for total cholesterol and 15 patients for a random blood glucose. Only patients with raised blood glucose were monitored. This is evident from the increase in the median result for random blood glucose from 6.2 to 16.4 from time point 1 to time point 4 (hgt1 to hgt4). 3 of the 5 patients who were monitored for cholesterol had a total blood lipid profile (lipogram) completed. The mean results of the lipogram were, LDL = 1.87 and HDL = 1.49 and TGs = 1.28. These were within the normal range. KDC screened more regularly for blood glucose (11 of 15 results) compared with 4 of 15 at SMH.

3.3.2 Liver enzyme results

Liver function test results are tabulated and graphically represented in Appendix 4.
Appendix 4, shows that there were no significant changes in liver enzymes over an 18 month period. However, there is evidence that the ARV treatment can cause liver toxicity, which necessitates that clinics continue testing liver function regularly (6-monthly) as per DoH guidelines.

3.3.3 Haematology

Haemoglobin, white cell count and platelet counts are tabulated and graphically represented in Appendix 5.

Appendix 5 shows that there were no significant changes in the blood counts over the first three time points (18 months) for patients on anti-retroviral therapy. Although 3TC and efavirenz are known to cause neutropenia or anemias[60,61], these did not appear in the patients in this study. It is however, important for the clinics to continue monitoring for any changes in the haematology of these patients. To detect and react to adverse changes timeously, these blood counts should continue to be monitored on a 6 monthly basis as per DoH guidelines.

3.3.4 CD4 and VL results

Table 12. Number of patients who had CD4 results recorded at various time intervals

CD 4 measurements	cd41	cd42	cd43	cd44	cd45
Number of patients tested	270	248	167	91	40
Mean	186.99	288.67	361.42	487.21	840.10

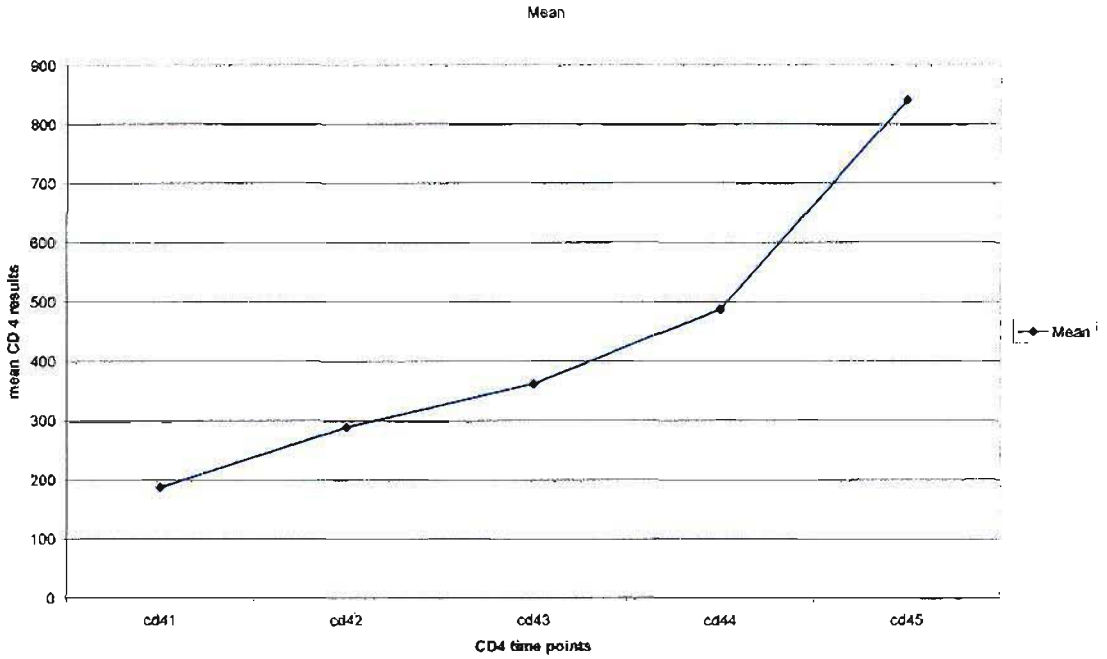


Figure 24 Mean CD4 results over time

Figure 24 shows that for patients tested over five time points, the CD4 counts on average, increase over time. ***The CD4 results at time points 6, 7, 8 have been omitted due to the low number of patients who had results at those time points.***

Table 13. Table showing the number of patients who had VL results recorded at various time intervals.

VL MEASUREMENTS	vl1	vl2	vl3	vl4	vl 5
Number of patients tested	258	211	109	67	30
Median	64432.00	50.00	50.00	50.00	50.00

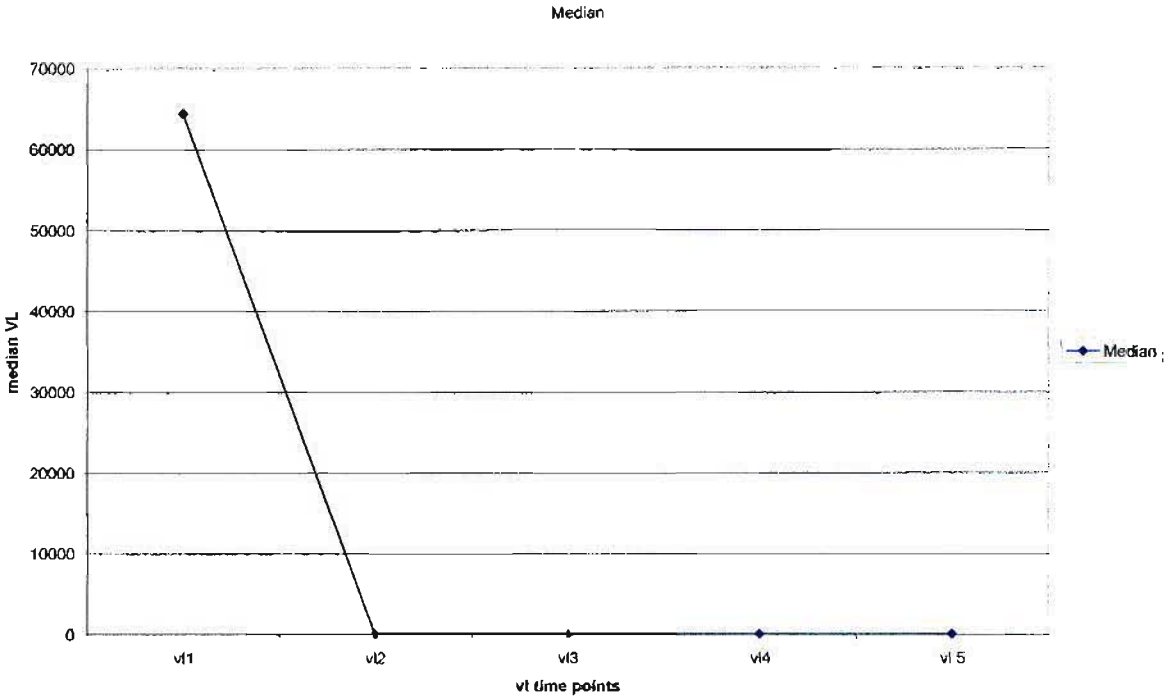


Figure 25: Median viral load results over time

Figure 25 shows that the viral load decreases within six months of initiation of ARV treatment. From the first to the second time point measurement, the viral load dropped to below 50 for the population under study. On average, this low viral load (<50) was maintained over time on treatment. ***The VL results at time points 6, 7, 8 have been omitted due to the low number of patients who had results at those time points.***

The number of patients' results for CD4 and viral load decreased with time because as time increased, less patients were remaining on treatment (average patient was on treatment for 19 months).

3.4 Immunological failure

For the purposes of this study, immunological failure was defined as a decreasing CD4 count for the patient over time.

Table 14. Percentage of patients at each clinic with immunological failure.

Clinic	Immunological failure	Total
St Marys	14	137
KDC	26	133
Total	40	270
Percentage	14.8%	100.0%

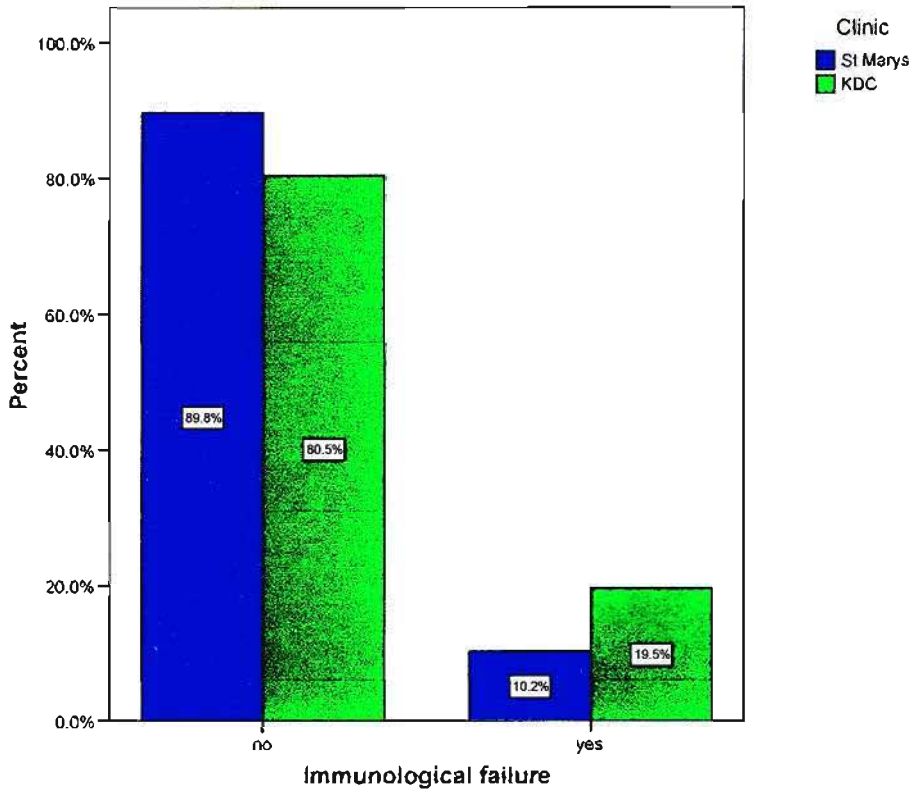


Figure 26. Number of patients at each clinic who experienced immunological failure.

Table 14 shows that 40 patients experienced immunological failure (10.2%, n= of patients at SMH and 19.5% n= of patients at KDC). Of these 40 patients, 32 were female. This is in accordance with the study population demographics. 8 of the patients were in the 0-9 year age group and were therefore dependent on a caregiver to give them their medicine which could contribute to poor adherence and therefore immunological failure. The majority of patients (13 of the 40) with immunological failure are in the 30 – 39 age group.
The possible explanations for immunological failure could be related to patient adherence or to length of time on treatment. *Aidsmap.com*, states that the short and long term success of antiretroviral therapy is directly related to levels of adherence to medication regimes[104].

Table 15. Table showing mean length of time on treatment (in months) for patients with immunological failure.

Clinic	Mean (in months)	Std. Deviation	N
St Mary's	22.77	5.615	13
KDC	12.05	3.184	22
Total	16.03	6.710	35

Table 15 shows that 13 patients with immunological failure had been on treatment for an average of 22.8months. At KDC, the 22 patients with immunological failure had been on treatment for an average of 12.1 months. 5 of 40 patients with immunological failure did not have their length of time on treatment recorded. This shows that at St Mary's the length of treatment may be associated with the immunological failure but this does not hold true for patients at KDC. This highlights the fact that length of time on treatment is not causing immunological failure but rather adherence to the treatment regimen.

Adherence is measured at each clinic by pill counts.

Table 16. Table showing adherence of patients with immunological failure at the two clinics.

Clinic	Adherence (n=)					Total
	excellent	good	satisfactory	poor	very poor	
SMH	2	2	1	7	2	14
KDC	5	5	0	4	5	19

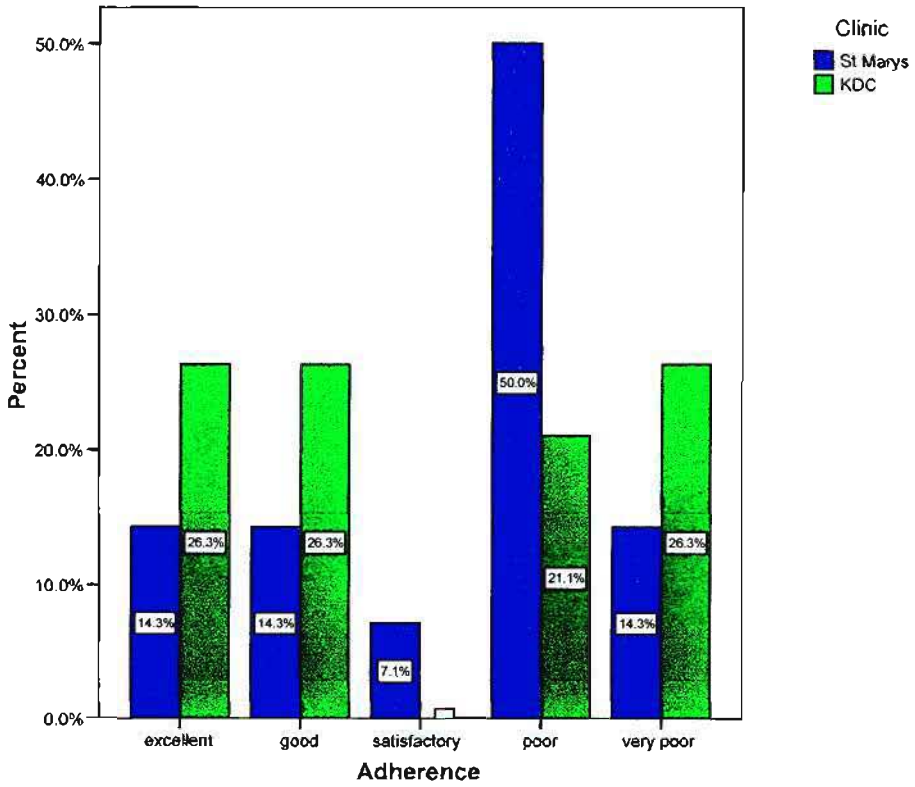


Figure 27. Patient adherence and immunological failure at the two clinics

Definitions of adherence
Excellent adherence = patient collected medicines monthly and returned with the correct pill count
Good adherence = patient collected medicines monthly and only had less than 2 returns with incorrect pill count
Satisfactory = patient collected medicines monthly with more than 2 returns with incorrect pill count
Poor – patient defaulted on collecting medicines on correct date less than twice
Very poor – patient defaulted on collecting medicines on correct date more than twice.

Figure 27 shows that 9 of the 14 patients at SMH and 9 of the 19 patients at KDC with immunological failure had poor or very poor adherence. This means that they consistently did not take their medication as directed or failed to collect their medication timeously. The assumption would be that poor or very poor adherence can contribute to immunological failure as the patient is not taking their medication as directed.

Although the trend is that poor adherence equates to immunological failure, the Fischer's exact test states that the p-value is 0.104 which means that there is no statistical significance between adherence and immunological failure.

3.5 Virological Failure

Virological failure in this study was defined as an increase in viral load over time.

Table 17. Table showing virological failure in patients at both clinics

Clinic	Virological failure
St Marys	6
KDC	0
Total	6
Percentage	2.3%

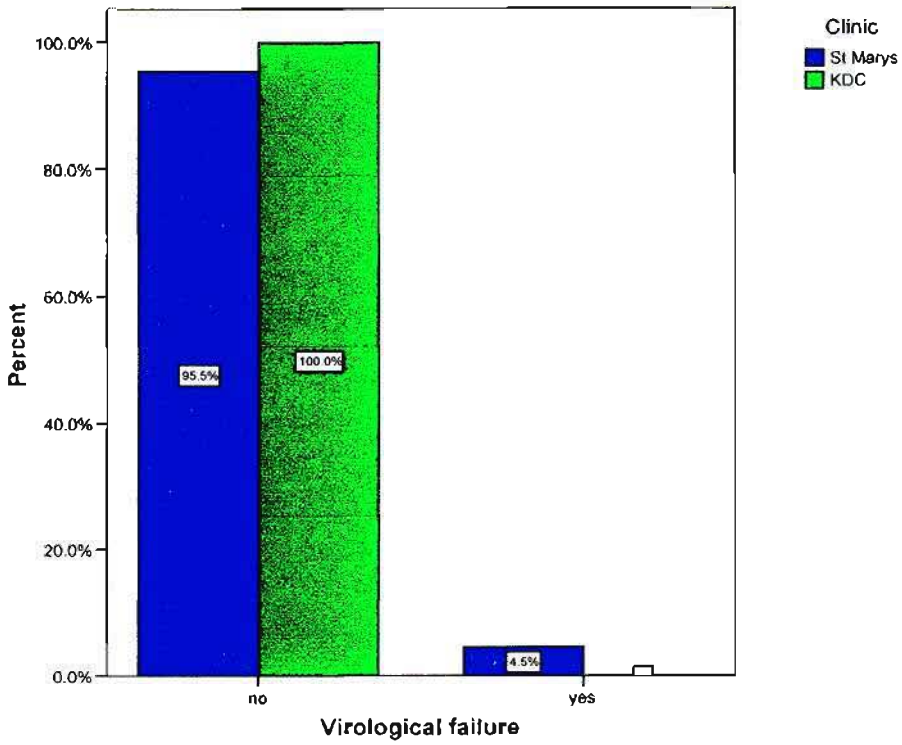


Figure 28. Graph showing number of patients at each clinic with virological failure.

Figure 28 shows that only 6 patients at St Mary's and none at KDC experienced virological failure. As with immunological failure, this could be a function of their adherence or length of time on treatment. It is evident that immunological failure was more common than virological failure in this study population. This means that although 40 patients experienced a decrease in CD4 over time, their viral load remained suppressed over time.

Data shows that the 6 patients who experienced virological failure had been on treatment for an average of 21.5 months. However, patients at SMH who did not experience virological failure had been on treatment for an average of 25.46 months, therefore it is not likely that the length of time on treatment in these cases was the reason for the virological failure. Therefore adherence to the treatment regimen could be the reason for causing virological failure. This is investigated more fully below.

Table 18. Adherence with respect to virological failure

Adherence (n =)					
excellent	good	satisfactory	poor	very poor	Total
0	0	1	2	3	6
.0%	.0%	16.7%	33.3%	50.0%	100.0%

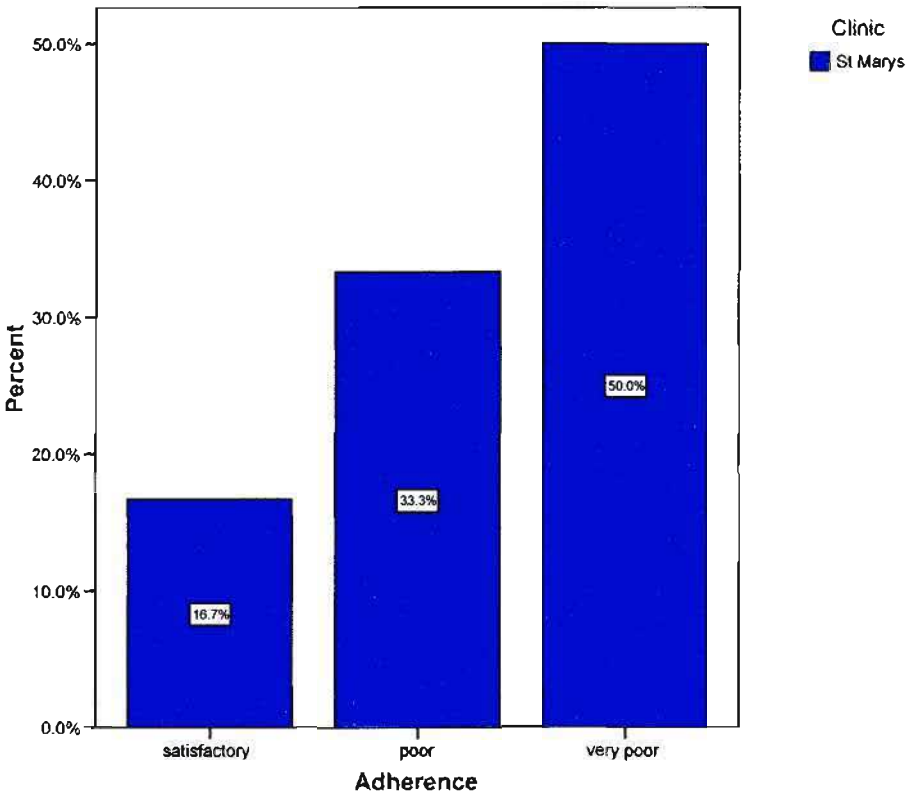


Figure 29. Adherence and virological failure at St Mary's

Figure 29 shows that 5 of 6 patients who experienced virological failure had poor or very poor adherence. This implies an association between adherence and virological failure, however, there is no statistical significance between virological failure and adherence ($p = 0.057$; Fischer's exact test).

The ability of HAART to improve survival in HIV-positive patients is contingent on its ability to reduce HIV RNA levels and to improve CD4 cell counts[106]. Reducing viral load to undetectable levels is necessary to achieve maximal and sustained CD4 cell count and anti-viral responses[106]. Immunological responses to HAART have significant prognostic value even among patients with viral load measurements <500 copies/ml. Moore et al (2006) report that virological suppression has been validated as a therapeutic goal for patients receiving HAART, but CD4 cell responses appear to be important predictors of risk for disease progression[106]. Clinicians should monitor patients to ensure immunological and virological responses remain positive to maximize benefits of treatment.

3.6 Side effects

Table 19. Table showing the side effects experienced by patients during ARV treatment at both clinics.

Side effect	SMH (N=)	KDC (N=)	Total (N=)
Peripheral neuropathy	43	25	68
Rash on face/body	36	29	65
Ab pains	24	16	40
Excess wt gain	4	15	19
Nausea and vomiting	12	7	19
Change in body shape	11	4	15
Deranged lft	1	13	14
Lipodystrophy	7	4	11
Hypertension	4	7	11
Diarrhoea	5	1	6
Diabetes (loss of glycaemic control	1	2	3
Lactic acidosis	0	1	1
Abnormal fbc	0	0	0

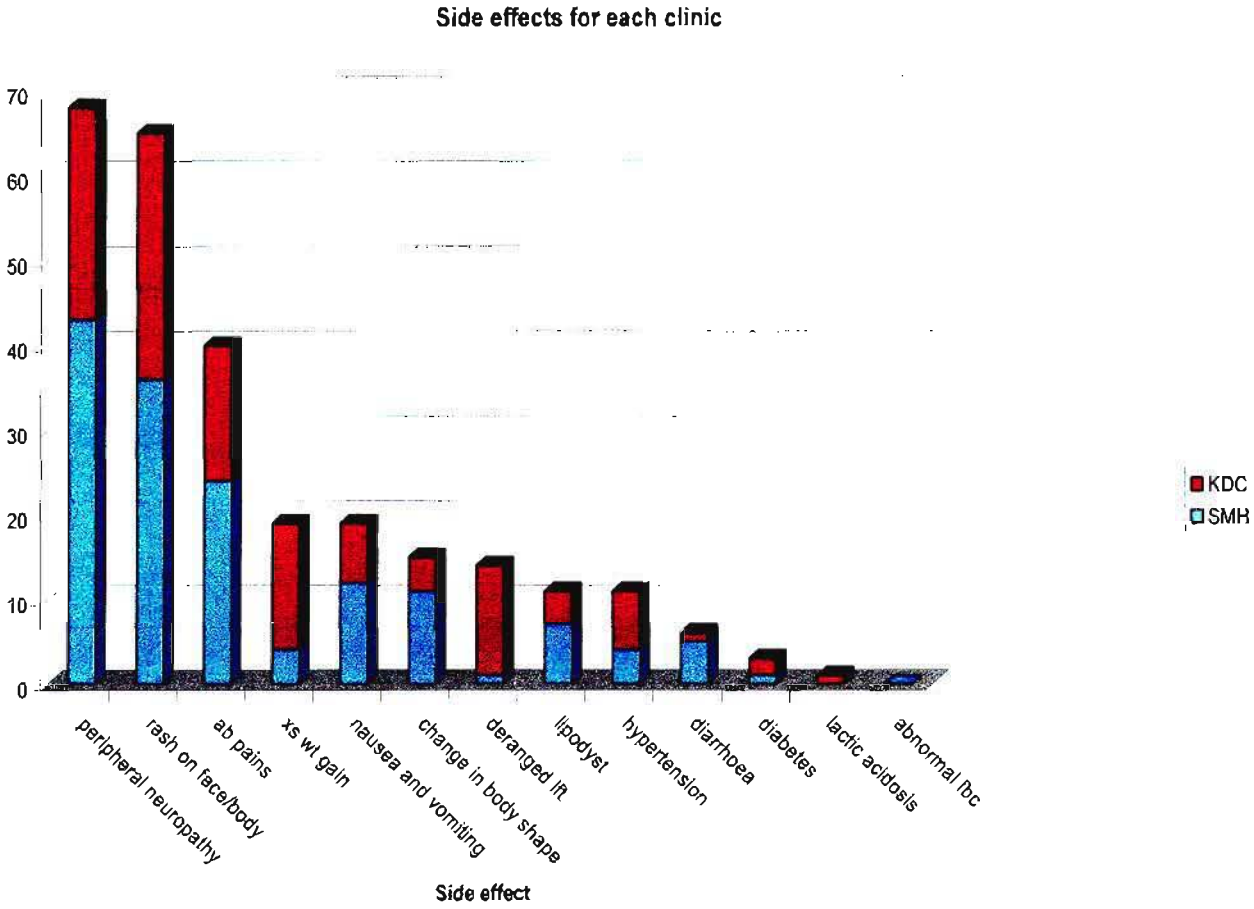


Figure 30. Side effects experienced by patients on ARV treatment at both clinics

Figure 30 shows that the most common side effect (n=68) is peripheral neuropathy (43 patients at St Mary's and 25 at KDC). This is a documented side effect of d4T. A rash on the face or body is the next major side effect (n=65; 36 patients at SMH and 29 at KDC). This is a common side effect of the NNRTIs, efavirenz and nevirapine[62,63].Abdominal pains (n=40) were also a significant side effect experienced at both clinics, with 24 patients at SMH and 16 at KDC presenting with this side effect.
Biochemical data showed that no patients experienced abnormal full blood counts, 1 patient at SMH and 13 patients at KDC presented with abnormal liver enzymes and only 1 patient at KDC experienced lactic acidosis.
15 patients (11 at SMH and 4 at KDC) reported changes in body shape and 19 patients (4 at SMH and 15 at KDC) reported excess weight gain.
11 patients (7 at SMH and 4 at KDC) were recorded by the doctor as having lipodystrophy. 11 patients (4 at SMH and 7 at KDC) developed or experienced worsening symptoms of hypertension.

Insulin resistance and hyperinsulinaemia are important components of the metabolic syndrome[107]. The course of development of type 2 diabetes mellitus is generally thought of as a progression from a state of euglycaemia and normal glucose tolerance, where some degree of insulin resistance and decreased pancreatic reserve of beta-cells is detectable, to a

state of IGT (the inappropriate postprandial hyperglycaemia in the presence of normal fasting glycaemia[107] and then ultimately, sustained fasting hyperglycaemia[107].

The WHO definition of the metabolic syndrome in HIV-negative people is fasting plasma glucose >6.1mmol (110mg/dL) plus at least two of the following[68]:

- Serum triglycerides above 1.9mM (150mg/dL) or serum HDL cholesterol below 0.9mM (35mg/dL)
- Blood pressure above 140/90 mmHg
- Abdominal obesity defined as waist to hip ratio above 0.9, waist girth above 94cm or BMI above 30kg/m2 in men [68].

From the above WHO definition, it means that these patients have at least one of the factors associated with the metabolic syndrome. This highlights the importance of monitoring for elevated lipids and glucose in these patients as they are at a high risk for developing the metabolic syndrome.
There were 2 diabetic patients at KDC and 1 at SMH, with reported uncontrolled blood glucose, which highlights that ARV medication can cause loss of glycaemic control

A number of studies have found an association between lipodystrophy and the nucleoside reverse transcriptase inhibitors, with the strongest association observed with d4T[59]. This is confirmed in this study, in which the majority of patients are on d4T and a number (n=11) experienced lipodystrophic symptoms. This also shows the importance of screening for other metabolic conditions such as HGT and lipids. Therefore, this study highlights the need for baseline screening of cholesterol and glucose and constant monitoring of these metabolic indicators throughout the treatment regimens.

As stated in *Aidsmap.com*, the most common side effect of d4T is peripheral neuropathy[59], which occurs in 15-20% of patients on d4T, particularly in those on higher doses, with more advanced HIV disease, or who are also taking ddI[59]. In this study population, 68 (25%) patients experienced peripheral neuropathy while on d4T treatment. (See discussion on peripheral neuropathy below).

3.7 Peripheral Neuropathy

Peripheral neuropathy was the most common side effect experienced (n=68) by patients in the study population. Diabetics are prone to suffer from diabetic neuropathy and therefore the side effect of peripheral neuropathy in diabetics has the potential to be more debilitating than in non-diabetic patients. In addition, TB medication can also cause peripheral neuropathy. TB was the most common concomitant condition experienced in this study group and peripheral neuropathy was the most common side effect reported by patients in this study, therefore patients experiencing peripheral neuropathy were investigated more fully.

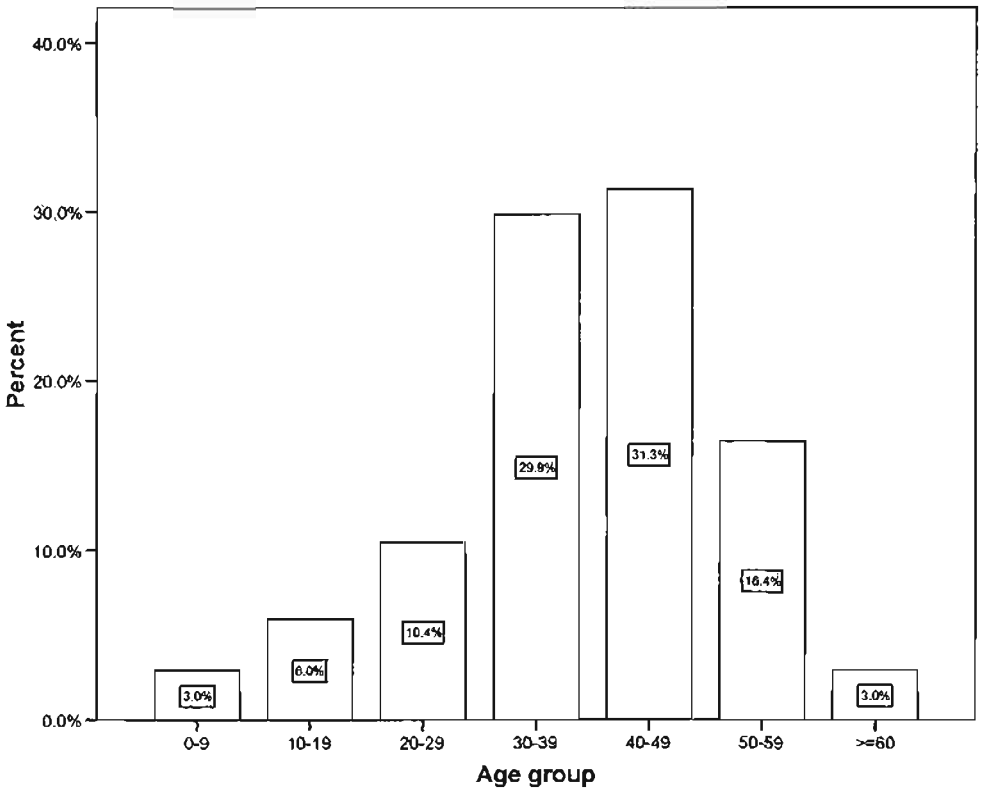
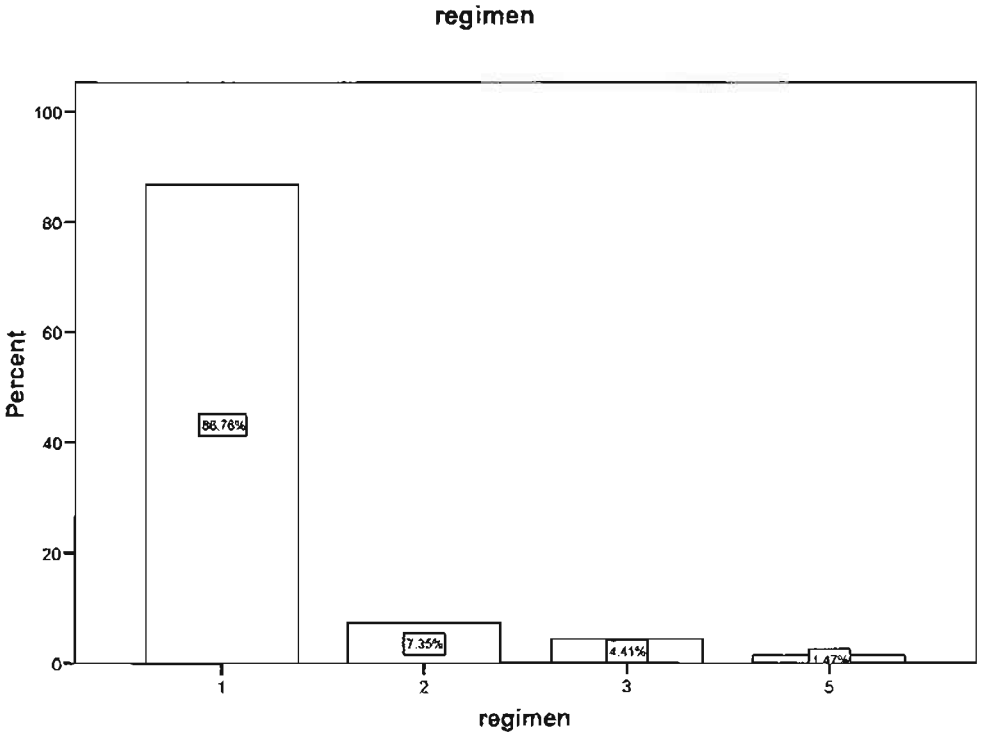


Figure 31. Age distribution of patients experiencing peripheral neuropathy.

Figure 31 shows that although the majority of patients screened were in the 30 to 39 age category, most of the patients experiencing peripheral neuropathy were in the 40-49 year old age category. This means that the likelihood of peripheral neuropathy occurring increases with age. *Living well with HIV.com*, states that an increase in age increases the incidence of peripheral neuropathy[93]. Diabetic patients are more likely to be in the older age categories (diabetics were in age categories 30-39; 40-49 and 50-59), which would increase the likelihood of them suffering from neuropathy.



Key:
Regimen 1: 3tc, d4t, efv
Regimen 2: 3tc, d4t, nvp
Regimen 3:3TC, AZT, EFV
Regimen 4:3TC, AZT, NVP
Regimen 5:AZT, Kaletra, ddI
Regimen 6:3TC, AZT, Nelfin

Figure 32. The number of patients on each regimen experiencing peripheral neuropathy

The majority of patients are on DoH's regimen 1a and this figure shows that the majority of patients experiencing peripheral neuropathy (86.7%) are also on regimen 1a. This is largely due to the fact that d4T is the major cause of peripheral neuropathy[59].

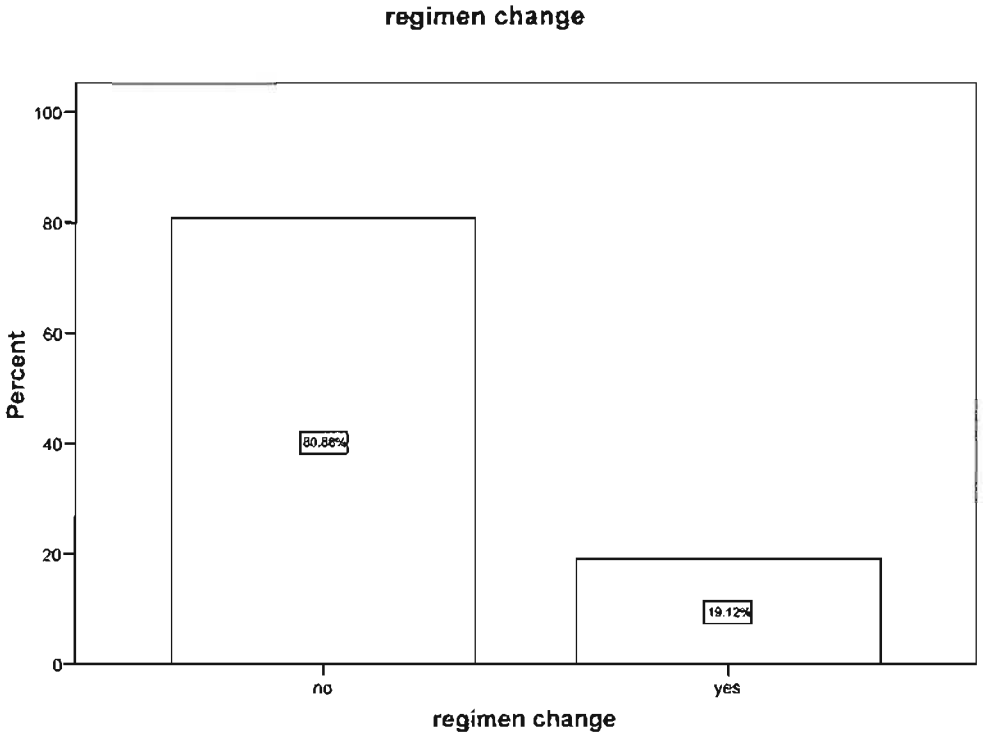


Figure 33. Percentage of patients with peripheral neuropathy who were changed to a different regimen

Figure 33 shows that 19.12% (n=13) of patients presenting with peripheral neuropathy were changed to a different drug regimen. This would be in an effort to decrease the peripheral neuropathy side effects.

Of the patients presenting with peripheral neuropathy who were changed to a different drug regimen, 11 were switched from d4T to AZT. 1 patient changed from NVP to EFV and 2 were changed from D4T/AZT/NVP to Kaletra®.

As peripheral neuropathy is also a side effect of TB medication, the following concomitant conditions were recorded at the start of ARV treatment in patients with peripheral neuropathy[93].

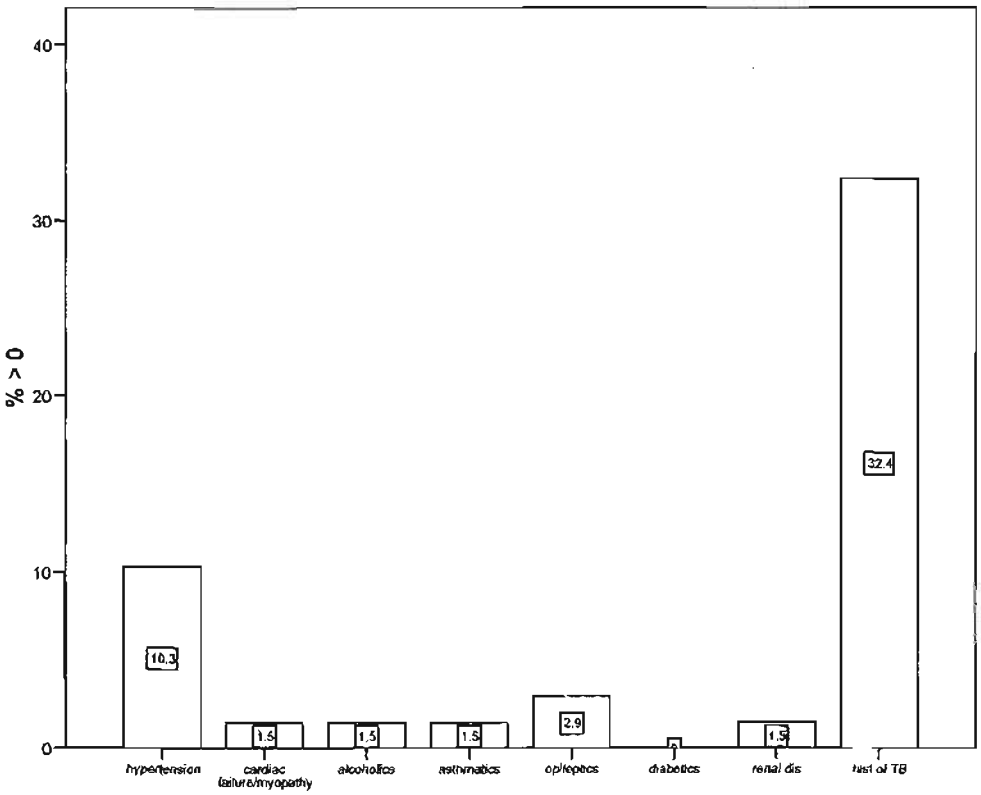


Figure 34. Concomitant diseases in patients with peripheral neuropathy at the start of ARV treatment

Figure 34 shows that 32.4% (n=22) of 68 patients of patients with peripheral neuropathy had a history of TB at the start of their ARV treatment. In addition, 14 patients with peripheral neuropathy developed TB during their ARV treatment. This means that there is likelihood that the TB medication could be potentiating the side effect of the ARV medication in terms of causing peripheral neuropathy [93]. However, there is no statistical significance between peripheral neuropathy and a history of TB (p=0.386).

Peripheral neuropathy is often a side effect of the medications used to treat HIV, but low CD4 cell counts are also associated with an increased incidence of peripheral neuropathy[93].

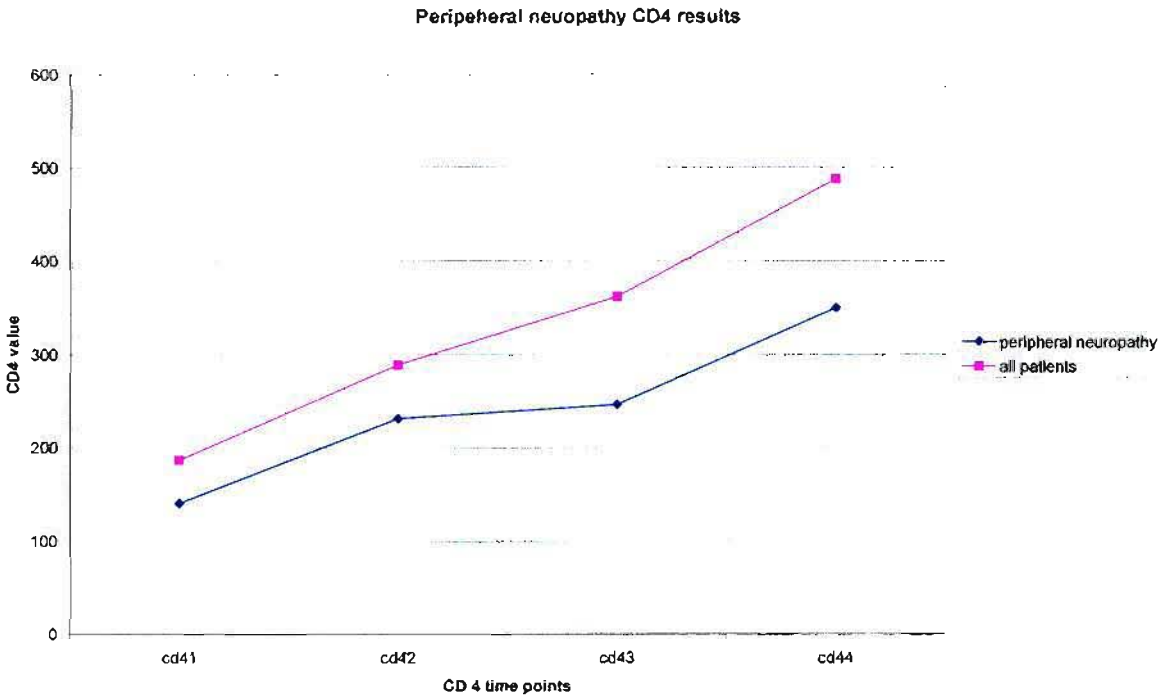


Figure 35. Mean CD4 results of patients with peripheral neuropathy and the average patient population.

Figure 35 shows that patients with peripheral neuropathy had lower average CD4 counts over different time points than the average patient population. This could be a factor that results in so many of the patients experiencing peripheral neuropathy.

3.8 Metabolic results

3.8.1 Diabetic data

There were 2 diabetic patients at KDC and 1 at SMH.

Table 20. Table showing gender distribution of diabetic patients on ARVs

Gender	Frequency	Percent
F	1	33.3
M	2	66.7
Total	3	100.0

Table 20 shows there were two male and 1 female diabetic patients on ARV treatment at the two clinics. Each was in a different age category, 1 30-39; 1 in the 40-49 and one was 50-59.

Only two of the three diabetic patients had a recorded BMI. The one patient was underweight with a BMI of 18.4 while the other patient was overweight with a BMI of 28. High BMI is a traditional risk factor for diabetes and for the metabolic syndrome.

All 3 diabetic patients on ARV treatment were also hypertensive. This would increase their risk for the metabolic syndrome[68].

1 diabetic patient had a history of TB. A diabetic patient on TB treatment and ARV treatment has an increased likelihood of suffering from neuropathy. TB treatment as well as ARV treatment can cause peripheral neuropathy and a diabetic is more susceptible to diabetic neuropathy.

None of the diabetic patients had concomitant cardiac failure or myopathy, alcoholism, asthma, epilepsy or renal disease.

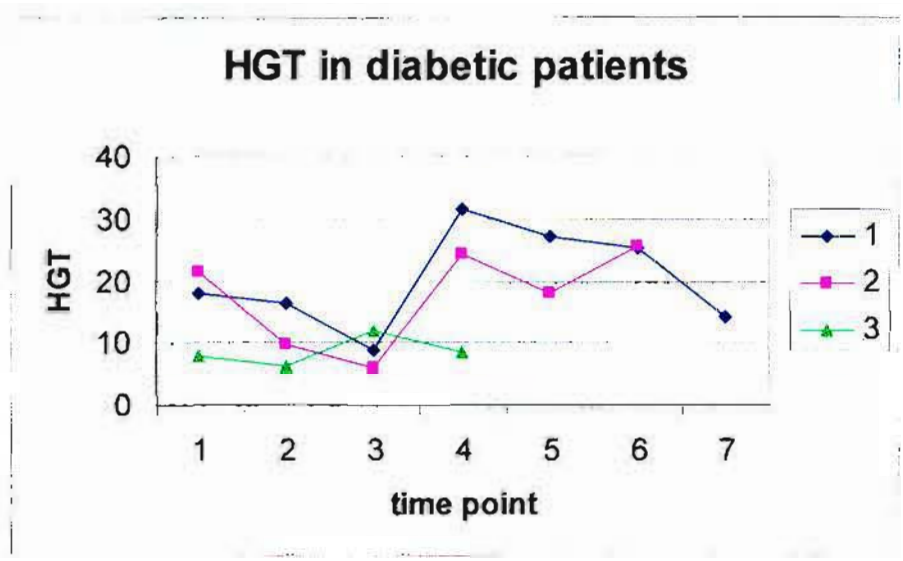


Figure 36 . Changes in blood glucose in diabetic patients on ARV treatment

Figure 36 shows that all three patients experienced changes in their blood sugar readings at different time points recorded, while on ARV treatment. Patient 3 was the most controlled diabetic with random blood glucose readings around 10mmol/L, while patient 1 and 2 had very high and erratic readings. This highlights the fact that diabetic patients with concomitant HIV on treatment can have worsening glycaemic control due either to HIV itself or the medication[7].

Research into the prevalence and incidence of blood glucose abnormalities in men enrolled in the MACS (Multicentre AIDS Cohort Study) ongoing prospective study of HIV in men found that the prevalence of diabetes was 2.11% in the HIV positive men not on ARVs, and 5.3% in HIV positive men on ARVs compared to the HIV negative men[30]. Therefore there is some evidence that insulin resistance may be associated with the HIV disease itself or the loss of glycaemic control may be related to the HAART.

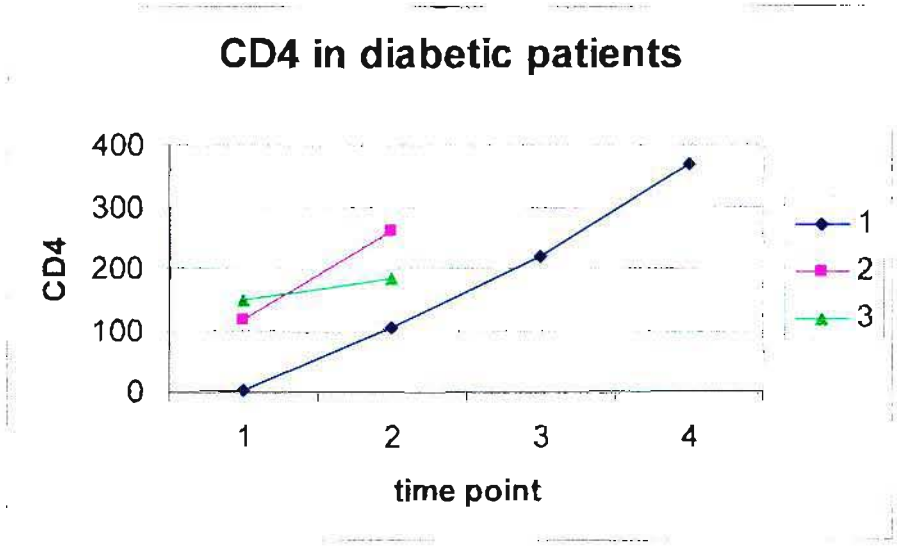


Figure 37. CD4 results for the 3 diabetic patients

Figure 37 shows that in all 3 diabetic patients, the ARV treatment succeeded in increasing the CD4 counts. All three diabetic patients were on Regimen 1a – d4T, 3TC and efavirenz.

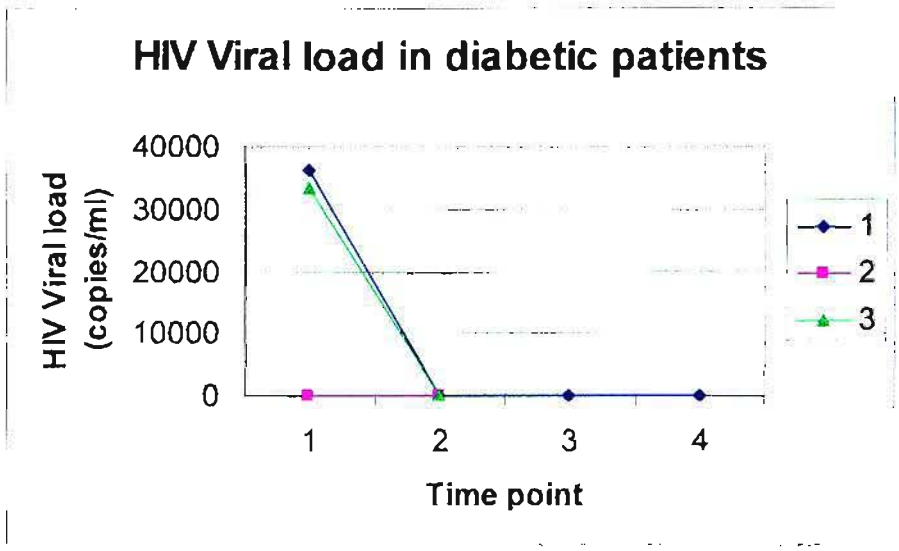


Figure 38. VL for the 3 diabetic patients

Figure 38 shows that in all 3 diabetic patients, the ARV treatment is successfully decreasing the VL and keeping it at less than 50.

This highlights the success of anti-retroviral medicines in HIV positive patients, even in diabetic patients as is evident from the decrease in VL and concurrent increase in the CD4 count.

As all three diabetic patients are hypertensive, they already have two of the conditions for the metabolic syndrome, namely high blood sugar and elevated blood pressure. In addition, these patients are in the older age groups which also increases their risk for cardiovascular

complications. This highlights the importance of monitoring for lipids, blood sugar and blood pressure in these patients.

Another concern in diabetic patients on ARV therapy is peripheral neuropathy. Diabetics are likely to suffer from diabetic neuropathy; the potential for this is further increased in patients on ARV therapy as peripheral neuropathy is a well-documented side effect of d4T. If TB medication is added to this combination, there would be a higher possibility of peripheral neuropathy occurring.

The clinics are not focusing on the possibility of diabetes as a side effect of HIV or its treatment. Therefore insufficient blood glucose monitoring occurs at the clinics. Hence only these 3 patients were identified as diabetics.

In spite of the lack of blood glucose monitoring, a number of patients showed characteristics of the metabolic syndrome. These include an increase in cholesterol, a blood pressure above 140/90mmHg, and abdominal obesity. As patients in this population have access to ARV therapy, their lives will be prolonged. This will mean that the population is more likely to succumb to diabetes mellitus in the future as the metabolic syndrome or insulin resistance precede beta cell dysfunction in diabetes mellitus. The patients with increased blood pressure, BMI, lipodystrophy or raised cholesterol would be at an increased risk of developing diabetes mellitus and therefore these patients should be more closely monitored for changes in blood glucose. This highlights the importance of random blood glucose testing in patients on ARVs. Patients' records for hypertension and lipodystrophy were analyzed and presented below.

3.8.2 Hypertension

There are 14 (7 female and 7 male) hypertensive patients in the population under study who were on ARV treatment at both clinics.

6 of the 14 patients were between 40 and 49 years and 5 were between 50 and 59 years of age. This shows that as age increases, the likelihood of hypertension increased accordingly. Patients on therapy are likely to live a longer to an older age. In these older age groups, the likelihood of chronic diseases such as hypertension and diabetes increases and therefore the likelihood of cardiovascular complications increases too. This again highlights the importance of consistent simple screening tests such as blood pressure, blood glucose and cholesterol in patients on ARV therapy.

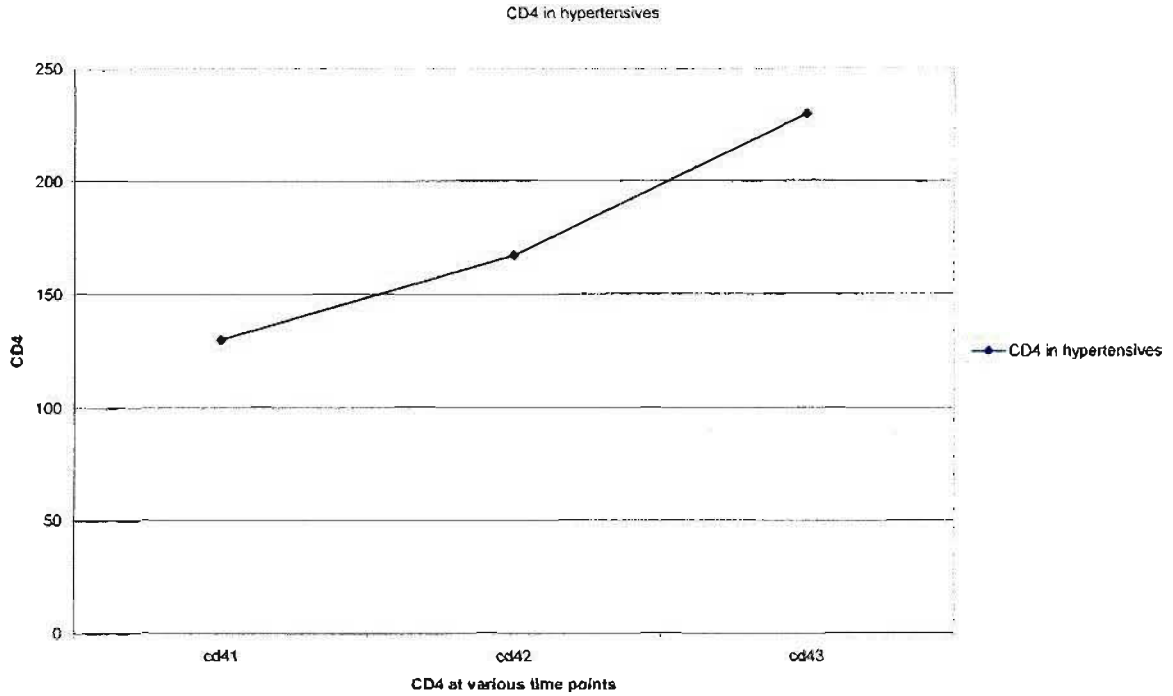


Figure 39. Average CD4 counts over time for the hypertensive patients on ARV treatment.

The above figure shows that for all the hypertensive patients on ARV treatment, their average CD4 count is increasing with time.

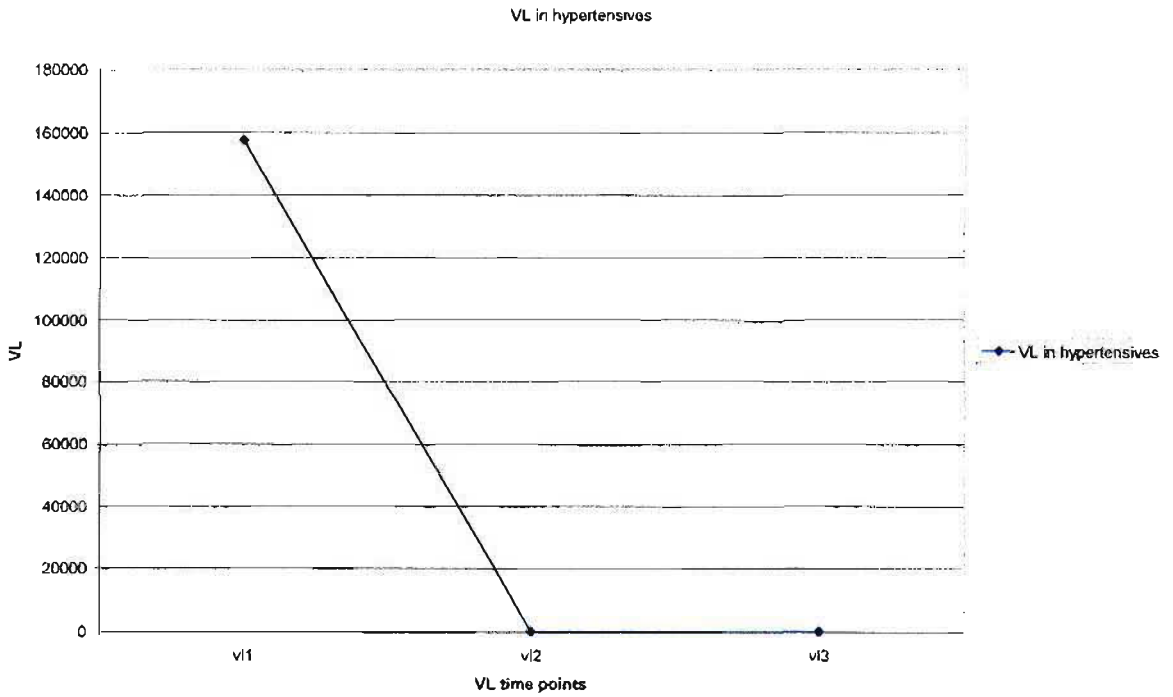


Figure 40. Average VL recorded for hypertensive patients on ARV treatment.

Figure 40 shows that on average the VL results have decreased dramatically with the initiation of ARV treatment.

6 patients developed hypertension or an increase in blood pressure while on ARV treatment. This means that 20 people (either prior to or after initiation of ARV treatment) developed hypertension.
A blood pressure greater than 140/90 is a determinant for insulin resistance[68]. Consequently, these 20 patients were investigated for any other metabolic conditions (lipodystrophy, changes in body shape and excess weight gain) that may have occurred and therefore increased their likelihood of developing insulin resistance.

An investigation of any other concomitant metabolic problems (as defined above) that developed for patients with hypertension (either prior to or during ARV treatment) showed that no hypertensive patients had recorded lipodystrophy, but 2 had reported changes in body shape and 1 had reported excess weight gain. These patients should be screened for glucose regularly as they fulfill two of the three criteria of the metabolic syndrome and early detection of insulin resistance could prevent the development of diabetes.

According to Fischer's exact test, ($p=0.423$) there is no statistical significance between lipodystrophy and hypertension.
Although 2 patients reported a change in body shape and had concomitant hypertension, the Fischer's exact test, $p=0.305$, indicated no statistical significance between change in body shape and hypertension.
A comparison of excess weight gain and hypertension, ($p=0.580$) shows no statistical significance between excess weight gain and hypertension.

Although there is no statistical significance, the concern is that patients with 2 of the conditions for metabolic syndrome, will be more likely to become insulin resistant and potentially diabetic. Therefore in these patients with lipodystrophy, changes in body shape or excess weight gain as well as hypertension should be monitored and undergo more intensive metabolic screening during ARV therapy to prevent the development of cardiovascular complications such as diabetes.

3.8.3 Lipodystrophy

There were 37 patients who presented with lipodystrophy. This was collectively defined for the purposes of this study as a report by the doctor of lipodystrophy, a record of excess weight gain or a report by the patient of a change in body shape. Patients with lipodystrophy need to be monitored for other metabolic disorders, as this can lead to an increased chance of developing the metabolic syndrome, or contributing to an increased risk for a cardiac event. This highlights the importance of regular screening and monitoring for other metabolic disorders.

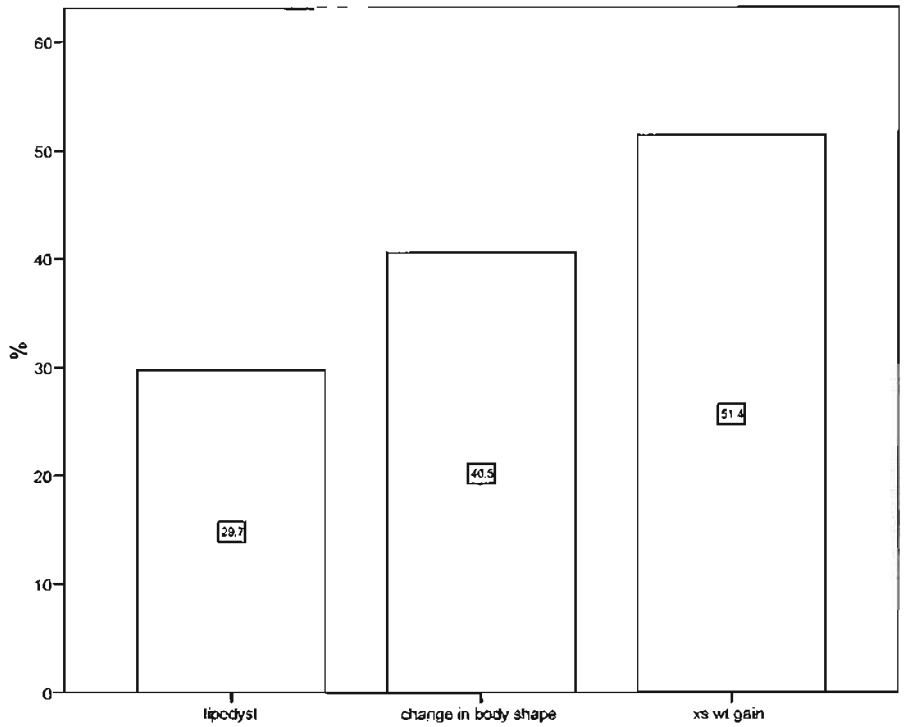


Figure 41. Percentage of patients with various forms of lipodystrophy.

Of the 37 patients reporting either lipodystrophy, excess weight gain or change in body shape, 11 had lipodystrophy (as reported by the doctor), 15 had a change in body shape (as reported by the patient) and 19 had excess weight gain (as recorded by the clinic sister)

Table 21. Table showing drug regimens of patients with 'lipodystrophy'

Regimen	Frequency	Percent
1	32	86.5
2	3	8.1
5	1	2.7
Total	36	97.3

Key:
Regimen 1: 3tc, d4t, efv
Regimen 2: 3tc, d4t, nvp
Regimen 3:3TC, AZT, EFV
Regimen 4:3TC, AZT, NVP
Regimen 5:AZT, Kaletra, ddI
Regimen 6:3TC, AZT, Nelfin

Table 21 shows that only one of these patients was on DoH Regimen 2 (regimen 5 according to key above) which includes Kaletra® (the PI) and that 32 of the patients were on DoH's Regimen 1a (Regimen 1 on key above. The patient on the protease inhibitor (Kaletra®) would be at an increased risk for developing insulin resistance as glucose abnormalities are most commonly recorded in patients on PIs. In addition, this patient is presenting with lipodystrophy which would also increase the likelihood of the patient developing insulin resistance.

The NRTI's, especially d4T are known to cause lipodystrophy or changes in body shape and excess weight gain[24]. With a change in body shape or increase in weight, the likelihood of developing an raised blood sugar is increased[54]. This once again highlights the importance of screening and monitoring for glucose and cholesterol in order to prevent cardiovascular complications.

Only 3 of 37 patients experiencing lipodystrophy had random blood glucose measurements performed.

Serum cholesterol especially in patients with lipodystrophy should be monitored in order to enable early detection and prevention of cardiovascular complications.

Only 3 of 37 patients with lipodystrophy had blood cholesterol measurements recorded. One of these patients had a high total cholesterol of 6.47mmol/L. Therefore a full lipogram should have been performed. Since the results could not be found in the patient records, it is assumed that it was not performed.

Of the patients with lipodystrophy, two developed immunological failure. Falutz J. (2006), states that body-shape changes can have a negative impact on quality of life and consequently on adherence to treatment[107], which could therefore lead to immunological failure[104]. Patients are very aware of the changes in body shape and therefore the experience of this side effect, could contribute to non-compliance in taking medication and this would therefore lead to immunological failure. However, there is no statistical significance between lipodystrophy and immunological failure (p=0.131).

None of the patients with lipodystrophy had virological failure.

9 patients with lipodystrophy were changed to a different drug regimen. Of those 9 patients, 8 were changed from d4T to AZT and 1 was changed from Nevirapine to efavirenz. As d4T is the drug most likely to cause lipodystrophy, if patients are experiencing this side effect, it seems that the trend is to switch the patients to another drug in an effort to decrease the side effect, however, there is no statistical significance between lipodystrophy and regimen changes (p=0.006).

3.9 Regimen 2 patients

Regimen 2 (DoH regimen 2) implies that the patient treatment regimen includes a protease inhibitor. Protease Inhibitors are the drugs most documented to cause metabolic disorders, especially glycaemic changes.
In this study, 5 patients were on regimen 2 or a protease inhibitor.

Table 22. Table showing the age distribution of patients on regimen 2.

Age Group	Frequency	Percent	Valid Percent	Cumulative Percent
0-9	1	20.0	20.0	20.0
30-39	3	60.0	60.0	80.0
40-49	1	20.0	20.0	100.0
Total	5	100.0	100.0	

Table 22 shows that 3 out of the 5 patients are in the 30-39 age group category.
Of the patients on regimen 2, only 3 had recorded the length of time on treatment. Of these 3 patients, the average length of time on treatment was 35.7 months.

According to the DoH guidelines[1], before initiating treatment on a protease inhibitor, a baseline blood glucose and cholesterol should be performed. This should also be monitored on an annual basis according to the DoH guidelines. None of the patients were screened for blood glucose, before or during treatment on the protease inhibitors, even though it is in the DoH guidelines that these patients are screened for a baseline glucose and annually after initiation of treatment[1]. This implies that the guidelines are not being followed correctly for patients on regimen 2. This could perhaps be due to the small number of patients that are currently on regimen 2 and therefore the staff at the clinic facilities are not as familiar with the guidelines for regimen 2 as they are for regimen 1. This highlights the need for continuing education of staff.

Table 23. Table showing cholesterol statistics recorded for patients on regimen 2.

		chol	ldl	Hdl	Tg
N=	Valid	2	2	2	2
	Missing	3	3	3	3
Mean result		3.4750	1.5550	2.0050	2.890
Median result		3.4750	1.5550	2.0050	2.890
Std. Deviation of result		1.30815	1.09602	.72832	2.2769

Table 23 shows that only 2 patients were screened for cholesterol and a full lipogram was performed in each case. Both these patients had a total cholesterol below 5 mmol/L which means they are at a lower metabolic risk.

Of the patients on Regimen 2, none reported lipodystrophy or a change in body shape but one reported excess weight gain. This could be considered a risk for metabolic syndrome and should be monitored more closely for the development of diabetes.

3.10 RELATIONSHIP BETWEEN FINDINGS OF STUDY AND THE METABOLIC SYNDROME

In this study, there is no strong correlation between diabetes and HIV. Only 3 people in the study were diabetic. All three diabetic patients showed loss of glycaemic control. This highlights that HIV and/or HAART can lead to hyperglycaemia. Unfortunately, neither of the institutions in this study, performed routine blood glucose tests. Mention the relatively small cost.
It is therefore recommended that routine random blood glucose testing should be included in the DoH guidelines.

The prospective Multicentre AIDS Cohort Study (MACS), examined the prevalence of hyperglycaemia in 1107 men, using data from April 1999 to September 2002[7]. Following adjustments for age and Body Mass Index (BMI), they concluded that the prevalence of diabetes among HIV positive men on HAART was 3.1 times more than that of the HIV negative group[7].

Diabetes, in HIV patients and non-HIV infected patients, is associated with the same traditional risk factors. These have been shown by Yoon et al (2002), that diabetes is associated with traditional risk factors of obesity (measured by BMI), family history and co-infection with Hepatitis C[19]. Age and ethnicity are also factors in the development of diabetes[7,35].

In reviewing the age groups of the patients in this study, 55 were in the age 40-49 age group, 20 were in the 50-59 age group and 3 were over 60. This would mean that these 78 patients would be in a higher risk group for developing diabetes.
As most South Africans with HIV are already largely overweight, (BMI average of 28 at KDC), these patients are likely to be susceptible to developing metabolic abnormalities on HAART and also would require closer monitoring of blood glucose.

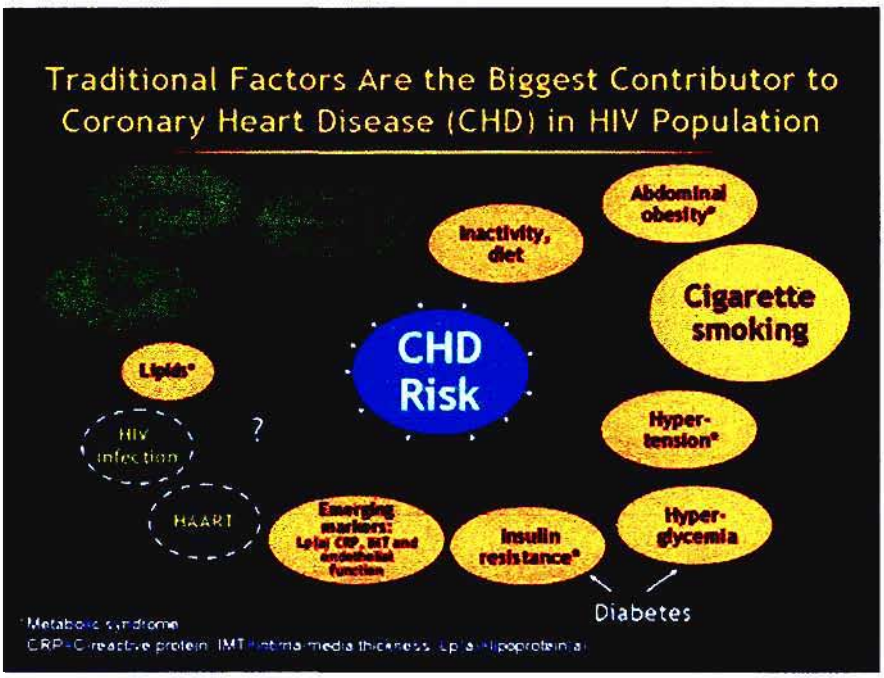


Figure 42. Diagram showing the traditional factors contributing to Coronary Heart Disease in HIV population [64]

As can be seen in the above diagram, the metabolic syndrome increases the risk for CHD. It is therefore important to monitor simple markers, such as blood glucose and cholesterol to enable early detection of diabetes and therefore prevent the development of CV risks.

As there was insufficient data on blood glucose at each of the clinics investigated, hypertension and lipodystrophy were investigated as these are two of the factors that can lead to metabolic syndrome.

3.11 SIGNIFICANT FINDINGS: METABOLIC SYNDROME

- A large number of patients presented with hypertension at the start of ARV treatment (n=14) and 6 more patients developed hypertension during treatment. Of these patients, 2 reported a change in body shape and 1 reported excess weight gain. This means that they already have two of the risk factors for metabolic syndrome. These three patients should have been more closely monitored for development of hyperglycaemia.
- 11 of the patients with hypertension were over the age of 40 and therefore also had a traditional risk factor of age, which could contribute to the development of diabetes in these patients. These patients should also have undergone closer monitoring of their blood glucose for the development of hyperglycaemia.
- The 3 diabetic patients were all hypertensive and two of the three were obese. These 3 diabetics should have been more closely monitored for other cardiovascular complications. However no lipograms were performed on these patients.
- 45 patients experienced lipodystrophy, either as reported by the doctor, or as recorded by a change of body shape or by excess weight gain. Therefore these 45 patients had one of the factors that could contribute to the metabolic syndrome. These patients should also have undergone glucose monitoring as they are at a higher risk of developing hyperglycaemia and/or diabetes.
- Patients on DoH's regimen 2 are on a regimen which includes Kaletra®, a protease inhibitor. Protease inhibitors are the drugs most likely to cause the development of insulin resistance and diabetes. Therefore monitoring of patients on PI containing regimens is recommended for the early detection of hyperglycaemia or diabetes. DoH guidelines also recommend regular screening for blood glucose and cholesterol due to the known risks associated with the use of these drugs. However, in the study population, no monitoring of glucose and cholesterol was performed. Therefore for patients on regimens containing a PI monitoring of these parameters is recommended.
- Peripheral neuropathy is the most common side effect of ARVs. In diabetic patients there is an increased likelihood that they will experience peripheral neuropathy as they are prone to diabetic neuropathy. Older patients and patients with lower CD4 results are more likely to experience peripheral neuropathy which held true in our study population. Patients experiencing peripheral neuropathy should also be monitored for blood glucose as the complications and severity of neuropathy are likely to be worse in diabetic patients, therefore early detection of loss of glycaemic control in these patients will prevent severe complications.

The screening for hyperglycaemia/diabetes is increasingly important in view of the high prevalence of hyperglycaemia among the African population. As an increasing number of HIV positive patients are exposed to ARV medication, the prevalence of hyperglycaemia will increase. In addition, as patients are on treatment for longer periods of time, there will be an increase in the number of patients with virological or immunological failure. This will result in more patients being switched to regimen 2 which includes a protease inhibitor. As there is an increased likelihood of patients on a protease inhibitor developing hyperglycaemia, the need for screening blood glucose and cholesterol will increase. It will be beneficial to include screening for blood glucose so that it becomes routine and therefore early detection can be achieved. If it is in the monitoring guidelines as routinely as the full blood counts and liver enzymes, a large proportion of blood glucose abnormalities will be detected at an early stage and action can be taken to prevent these two severe chronic immunological diseases occurring simultaneously.

3.12 STUDY LIMITATIONS

- The study was limited by the amount of information recorded in the patient records therefore the quality of the information was dependent on how well the health care workers at the facility had recorded the patient's history
- Patient records of concomitant diseases are stored in separate files in different locations in the clinic. For example a TB patient with HIV will have a record card in the TB clinic which will have all the history related to TB and the TB medications while the HIV medication and history will be stored and recorded on a different record card. The same is true for other concomitant conditions such as hypertension. Therefore it makes correlation of medical information difficult.
- Only three patients in this study were diabetic. A larger study population may have included more diabetics.
- Hyperglycaemic data was not recorded routinely and therefore not available for analysis
- Diabetes is not monitored as a potential adverse outcome of the disease HIV or the treatment with ARV's.
- There were no insulin measurements to confirm insulin resistance

3.13 RECOMMENDATIONS

- Inclusion of random blood glucose monitoring for all patients (on regimen 1 & 2) in the DoH guidelines at baseline and every 6 months together with the CD4 and VL counts
- Inclusion of markers of the metabolic syndrome such as serum cholesterol testing in the DoH guidelines for all patients at baseline and every 6 months.
- Education of health care workers on the prevalence of hyperglycaemia and the increased risk of hyperglycaemia for patients on ARV therapy.
- Awareness of health care workers on the contribution of ARV therapy to cardiovascular risk.
- Monitoring of patients for cardiovascular complications, especially those with traditional risk factors such as increased age and obesity.
- A follow-up study on patients identified in this study as 'high-risk' for the development of diabetes or hyperglycaemia.
- All patient information for any disease e.g. TB and HIV should be recorded on the same patient data file. This would allow for easier access to information for health care professionals, earlier detection of adherence problems and drug interactions or concomitant conditions.

Appendix 1. Patient Information DATA COLLECTION SHEET

Hospital card / ID Number: _____

Demographic Data:

Gender: _____ Date of Birth: _____

Ethnicity: _____ Hospital entry: _____

BMI: _____ Weight: _____

Height: _____ Abdominal Circumference: _____

Family history:

_____

_____

_____

Medical history: _____

_____

_____

_____

Current treatment: _____

(Drugs and dosages)

_____

_____

_____

_____

_____

HIV data

Date of HIV diagnosis: _____

Which tests were performed and when (include test results):

CD4: _____

_____

Viral load: _____

_____

_____

Other tests:

Test	Result	Date
Blood Glucose		
Fasting Cholesterol		
Full Blood Count		
Liver function		

Date of Initiation of treatment:

_____

Treatment regimen:

_____

_____

_____

_____

Is patient collecting medications monthly?

Always: ___ Missed 1 month: ____ Missed 2 months: ____

Missed > 2 months: ___

If missed more than 2 months, Reason? _____

Monitoring

Follow up monitoring performed?

At start of Rx___; 1st month: ___; 2nd month ___; 3rd Month ____;

at 6 months: ____; at 12 months: ___

Which screening tests were done and when? Record results of all tests performed during the year.

1st month:

Test	Result	Date

2 months after Tx:

Test	Result	Date

3 months after Tx:

Test	Result	Date

6 months after Tx:

Test	Result	Date

12 months after diagnosis:

Test	Result	Date

Record any additional test results following Tx:

_____

_____

_____

HIV Treatment changes

Was HIV Treatment changed? Yes _____ No _____

If yes, what was it changed to and when:

_____

_____

_____

_____

_____

On what basis was the treatment changed?

_____

_____

_____

_____

Diabetes data

Did the patient have diabetes at the start of HIV treatment? Yes _____

No _____

If yes, how many years have they had diabetes? _____

_____

If No, did any hypoglycaemic agents get introduced during the year of analysis? Yes _____ No _____

If Yes,

Which medications were prescribed and when:

Medications	Date

On which results were these medications prescribed?

Fasting Blood Glucose? Yes _____ No _____ Other:

_____

Results and dates:

Results	Date

Was blood glucose measured regularly? Yes _____ No _____

If yes, how often: _____

Results	Date

Lipid data

_____

Was there pre-existing elevated cholesterol condition? Yes _____ No _____

If No, did any cholesterol lowering agents get introduced during the year of analysis? Yes _____ No _____

Which medications were prescribed and when were they introduced?

Medications	Date

On which results were these medications prescribed?

Fasting cholesterol? Yes _____ No _____

Triglycerides? Yes _____ No _____

Were these tests performed according to monitoring guidelines?

Yes _____ No _____

What were the results?

Results	Date

Opportunistic infection data:

Did other opportunistic infections present? Yes _____ No _____

If yes, which ones and when? _____

_____

_____

_____

_____

_____

What were these infections treated with and when were the treatments initiated and state the duration of therapy?

Other comments (including overall adherence to guidelines):

Appendix 2. Frequency of Liver function tests

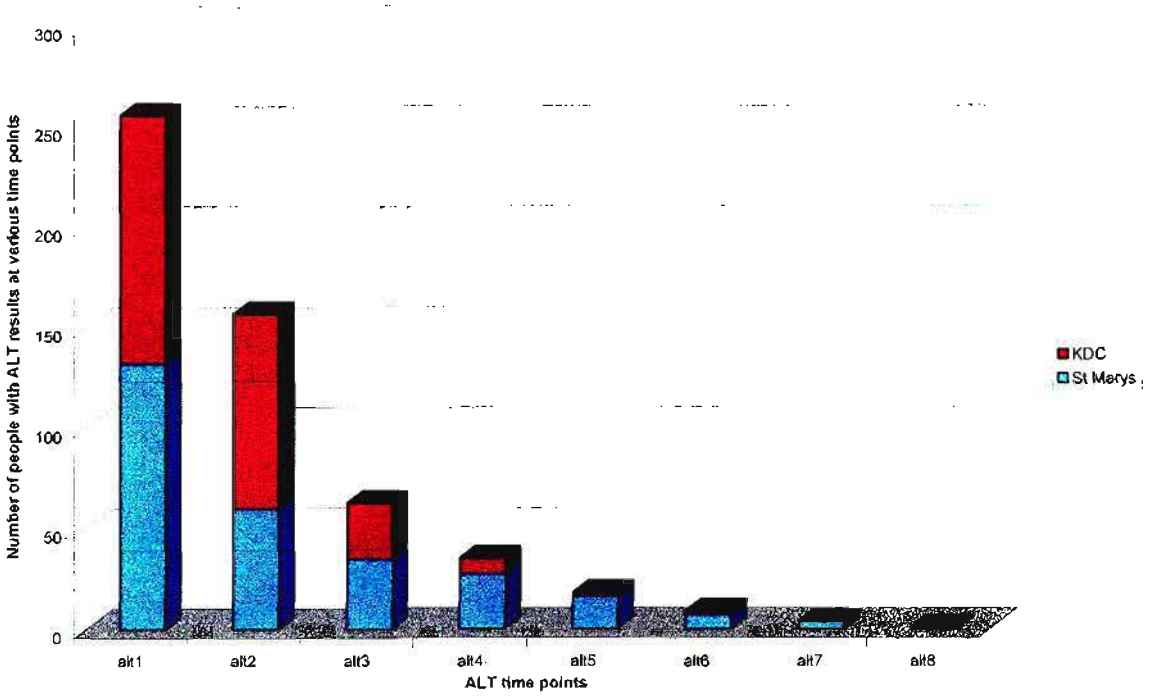


Figure 43. Frequency of ALT testing

Key:
ALT1 – ALT at time point 1 – i.e. at initiation
ALT2 – ALT at time point 2 – i.e. 6 months after initiation
ALT3 – ALT at time point 3 – i.e. 12 months after initiation

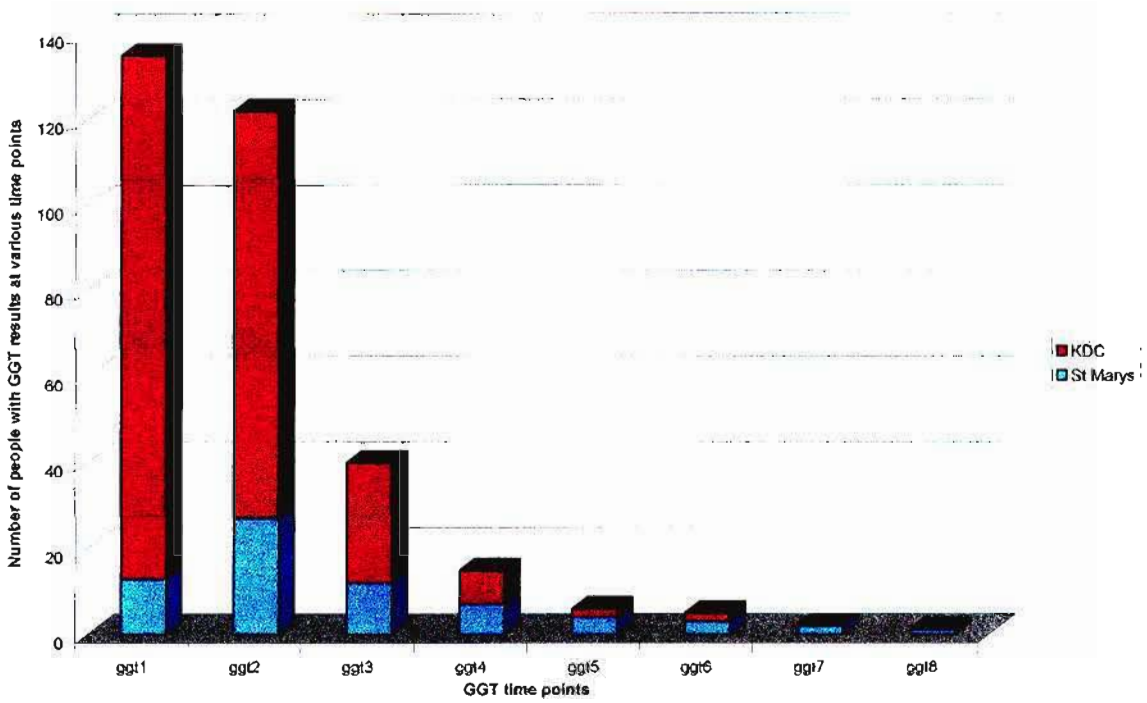
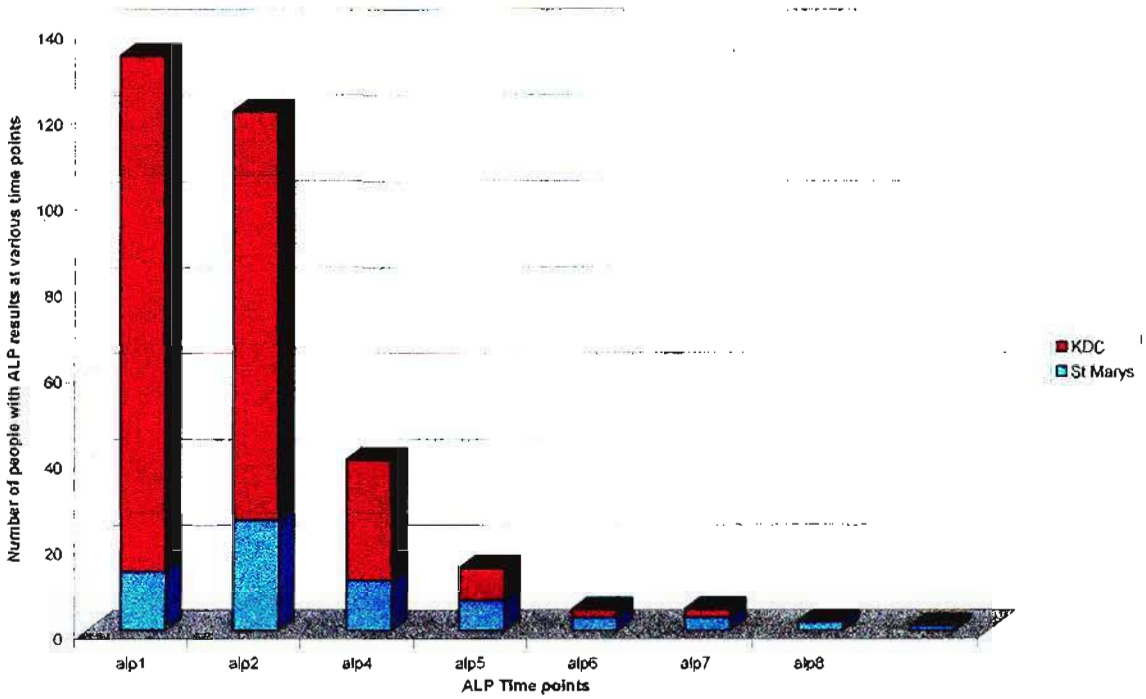


Figure 44. Frequency of GGT testing

Key:
GGT1 – GGT at time point 1 – i.e. at initiation
GGT2 – GGT at time point 2 – i.e. 6 months after initiation
GGT3 – GGT at time point 3 – i.e. 12 months after initiation



Frequency 45. Frequency of ALP testing

Key:
ALP1 – ALP at time point 1 – i.e. at initiation
ALP2 – ALP at time point 2 – i.e. 6 months after initiation
ALP3 – ALP at time point 3 – i.e. 12 months after initiation

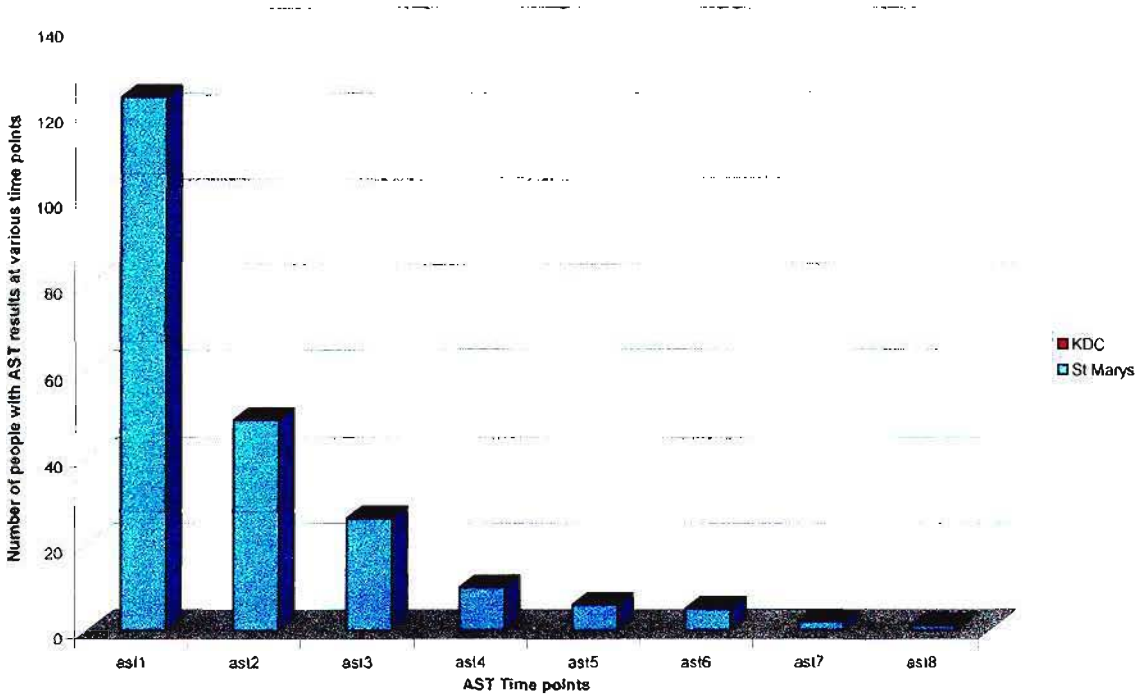


Figure 46. Frequency of AST testing

Key:
AST1 – AST at time point 1 – i.e. at initiation
AST2 – AST at time point 2 – i.e. 6 months after initiation
AST3 – AST at time point 3 – i.e. 12 months after initiation

Appendix 3. Frequency of Blood Count Testing

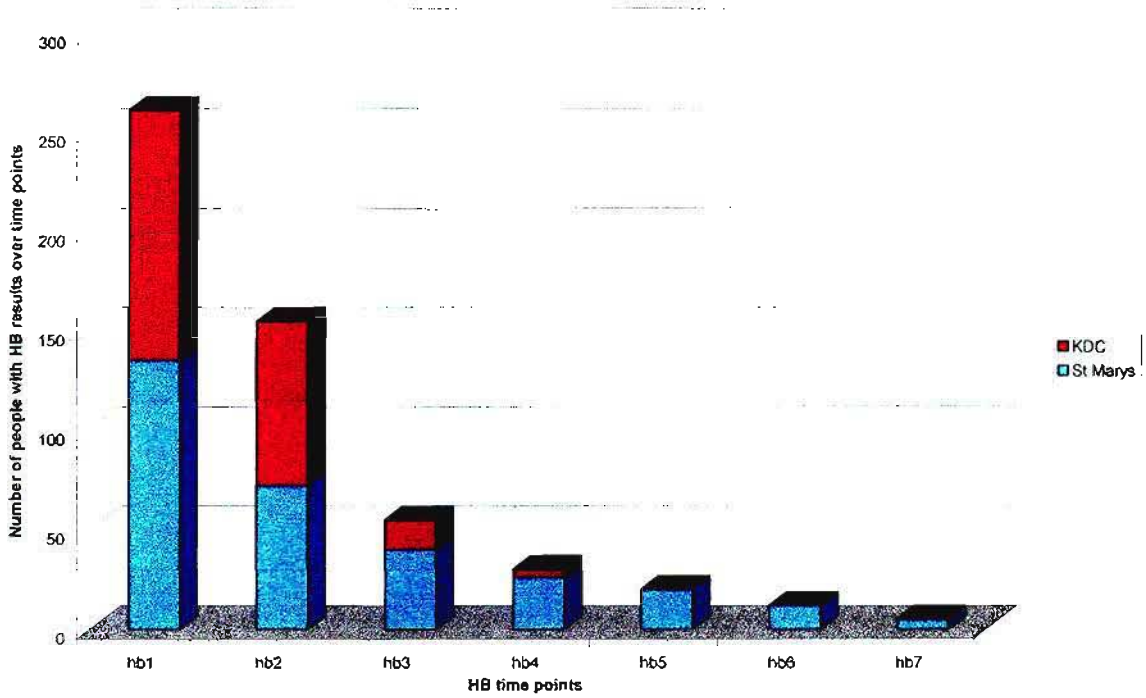


Figure 47. Frequency of haemoglobin testing

Key:
Hb1 – Hb at time point 1 – i.e. at initiation
Hb2 – Hb at time point 2 – i.e. 6 months after initiation
Hb3 – Hb at time point 3 – i.e. 12 months after initiation

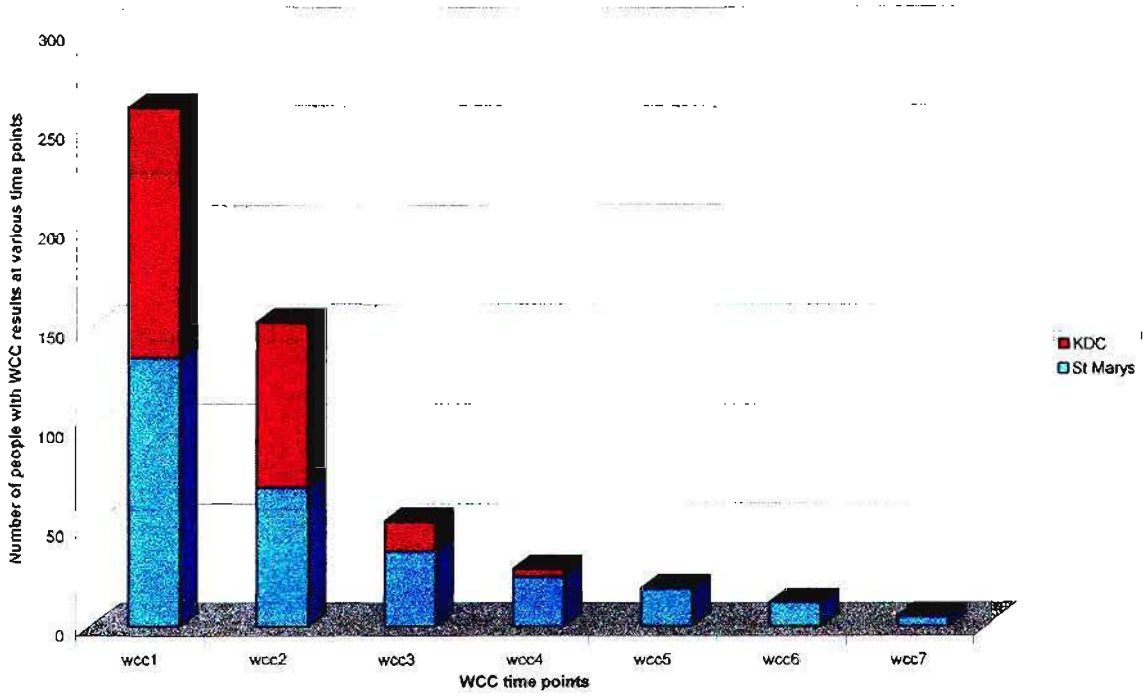


Figure 48. Frequency of white blood cell count

Key:
WCC1 – WCC at time point 1 – i.e. at initiation
WCC2 – WCC at time point 2 – i.e. 6 months after initiation
WCC 3 – WCC at time point 3 – i.e. 12 months after initiation

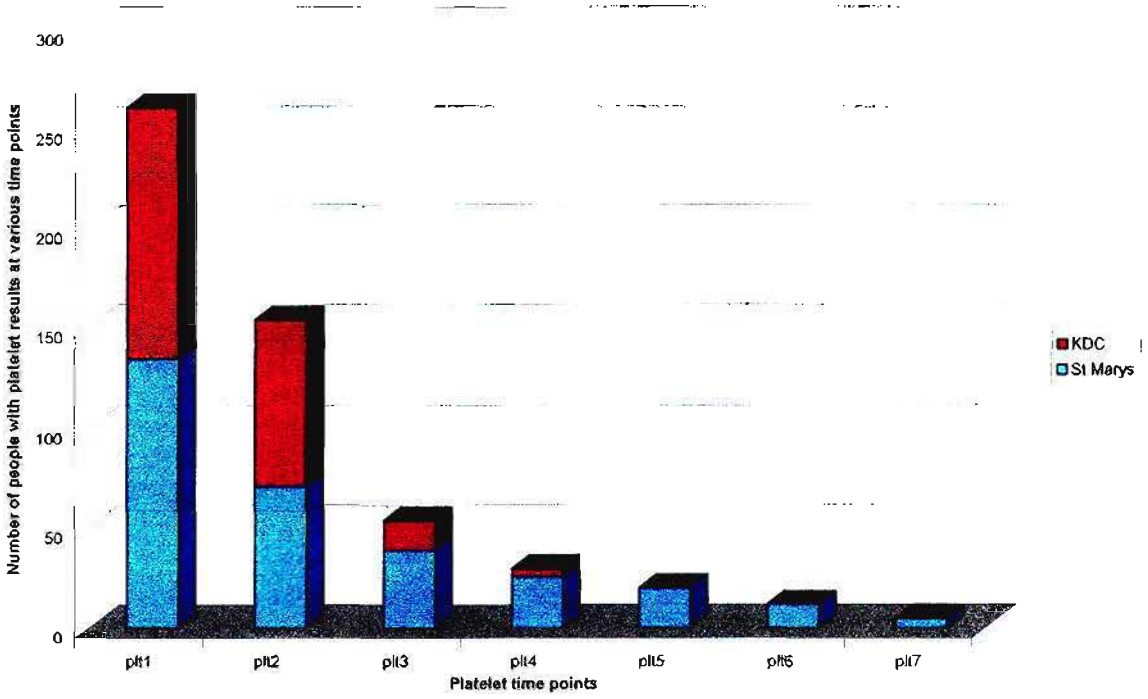


Figure 49. Frequency of platelet testing

Key:
Plt1 – Plt at time point 1 – i.e. at initiation
Plt2 – Plt at time point 2 – i.e. 6 months after initiation
Plt3 – Plt at time point 3 – i.e. 12 months after initiation

Appendix 4. Liver Function Results

Liver enzyme measurements at time point 4 to 8 have not been included in the tables as the results reported are only for a few patients (less than 40 patients) and are therefore not representative of the population.

ALT

Table 24. Statistics for the ALT results recorded at both clinics

ALT measurements	alt1	alt2	alt3
NUMBER of patients tested	256	157	63
Mean	42.80	51.81	52.32
Median	33.00	34.00	38.00
Std. Deviation	51.696	66.560	53.672

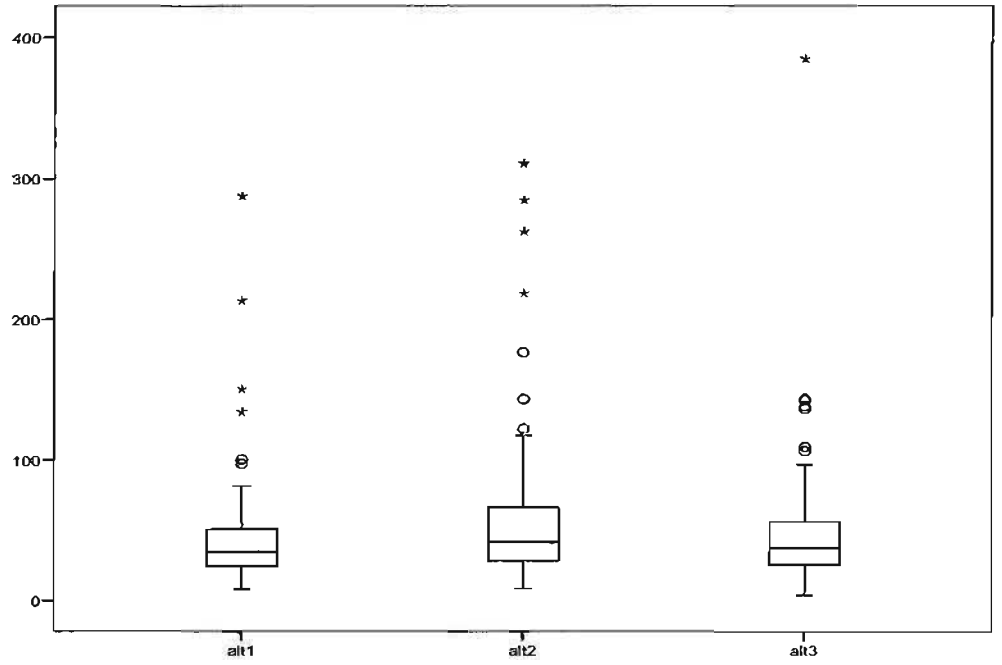


Figure 50. Box Plot graph showing the median ALT values recorded at both clinics.

Key:
ALT1 – ALT at time point 1 – i.e. at initiation
ALT2 – ALT at time point 2 – i.e. 6 months after initiation
ALT3 – ALT at time point 3 – i.e. 12 months after initiation

Apart from some outliers, figure 50 shows no significant changes in the ALT results for patients during the first 18 months of treatment (i.e. over the first 3 time points measured).

GGT

Table 25. GGT results for patients at both clinics

GGT measurements	ggt1	ggt2	ggt3
Number of patients tested	135	122	40
Mean	57.68	121.64	334871 448.08
Median	31.00	59.00	69.00
Std. Deviation	88.865	226.62 2	211791 1908.2 96

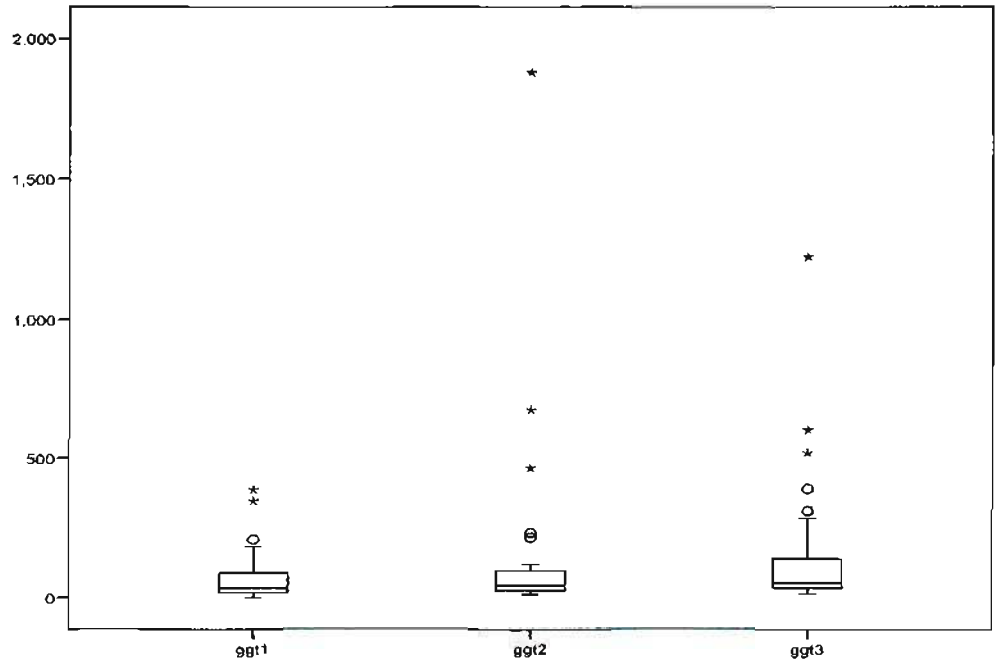


Figure 51. Box plot graph showing the median GGT results for both clinics

Key:
GGT1 – GGT at time point 1 – i.e. at initiation
GGT2 – GGT at time point 2 – i.e. 6 months after initiation
GGT3 – GGT at time point 3 – i.e. 12 months after initiation

Figure 51 shows that there is no significant change in the GGT results over 18 months on treatment.

ALP

Table 26. ALP results over time at both clinics

ALP measurements	alp1	alp2	alp3
Number of patients tested	134	121	40
Mean	110.31	159.22	203.18
Median	77.50	104.00	121.50
Std. Deviation	141.146	149.783	222.306

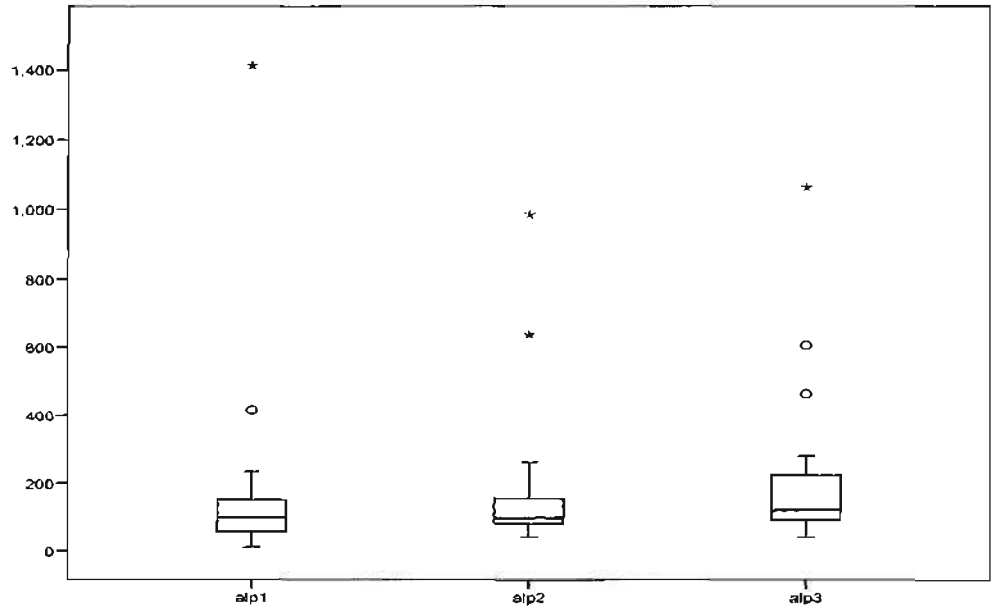


Figure 52. Box plot graph showing the median ALP results over time at the two clinics.

Key:
ALP1 – ALP at time point 1 – i.e. at initiation
ALP2 – ALP at time point 2 – i.e. 6 months after initiation
ALP3 – ALP at time point 3 – i.e. 12 months after initiation

Figure 52 shows that there is no significant change in the ALP results over 18 months on treatment.

AST

Table 27: AST results over time for both clinics

AST measurements	ast1	ast2	ast3
Number of patients tested	124	49	26
Mean	55.46	85.96	75.73
Median	43.50	46.00	41.00
Std. Deviation	43.403	94.587	83.208

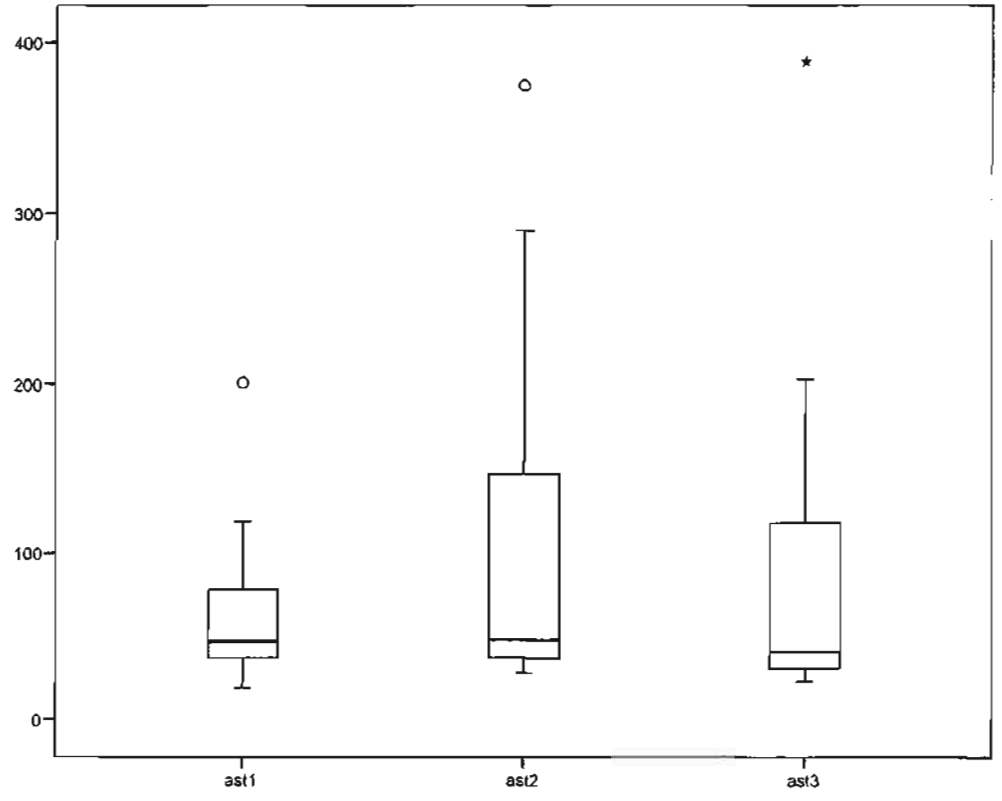


Figure 53. Box plot graph showing the median AST results at both clinics over time

Key:
AST1 – AST at time point 1 – i.e. at initiation
AST2 – AST at time point 2 – i.e. 6 months after initiation
AST3 – AST at time point 3 – i.e. 12 months after initiation

Figure 53 shows that there were no significant changes in the AST results over an 18 month time period.

Appendix 5. Blood Count results

Blood measurements at time point 4 to 8 have not been included in the tables as the results reported are only for a few patients (less than 40) and are therefore not representative of the population.

Haemoglobin

Table 28. Table of haemoglobin recorded for the two clinics

Haemoglobin measurements	hb1	hb2	hb3
Number tested	261	155	55
Mean	10.979	11.889	12.080
Median	11.100	11.900	11.600
Std. Deviation	1.8964	2.0681	4.6483

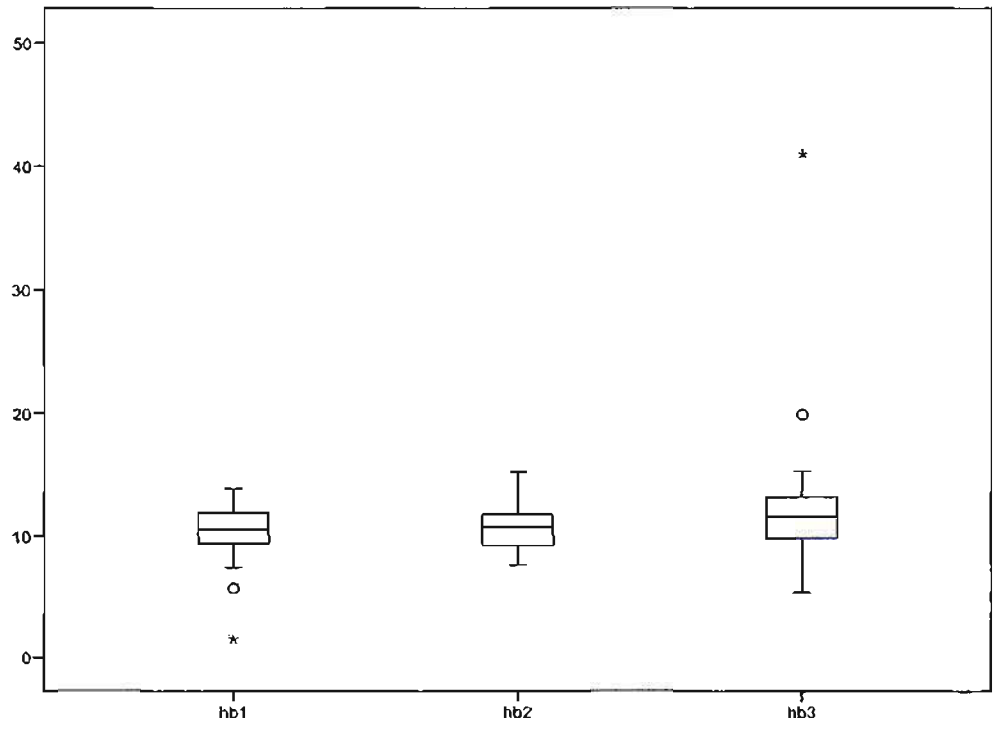


Figure 54. Box plot graph of the haemoglobin changes over the first 3 time points measured at the two clinics

Key:
Hb1 – Hb at time point 1 – i.e. at initiation
Hb2 – Hb at time point 2 – i.e. 6 months after initiation
Hb3 – Hb at time point 3 – i.e. 12 months after initiation

Figure 54 shows that there is no significant change in the haemoglobin levels over time on HAART.

White cell count

Table 29. Table showing white cell count over time on treatment for two clinics

White cell measurements	wcc1	wcc2	wcc3
Number of patients tested	261	153	53
Mean units	7.095	6.235	5.992
Median	5.010	5.310	5.300
Std. Deviation	23.2105	3.5603	2.6386

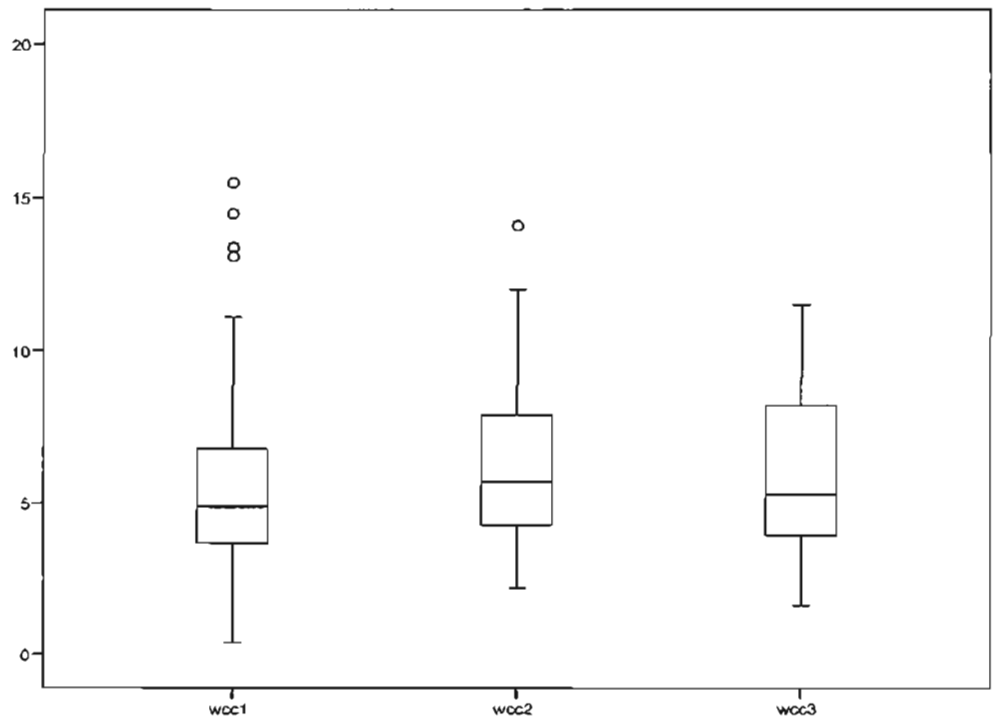


Figure 55. Box-plot graph showing white cell count over the first three time points recorded for patients at both clinics on ARVs

Key:
WCC1 – WCC at time point 1 – i.e. at initiation
WCC2 – WCC at time point 2 – i.e. 6 months after initiation
WCC 3 – WCC at time point 3 – i.e. 12 months after initiation

Figure 55 shows that, there is no significant change in white cell count over the first three time points on HAART treatment.

Platelets

Table 30. Table showing platelet number over time at both clinics

Platelet measurements	plt1	plt2	plt3
Number of patients tested	261	154	54
Mean	291.464	315.130	335.259
Median	275.000	293.500	316.000
Std. Deviation	118.0630	123.8764	121.5120

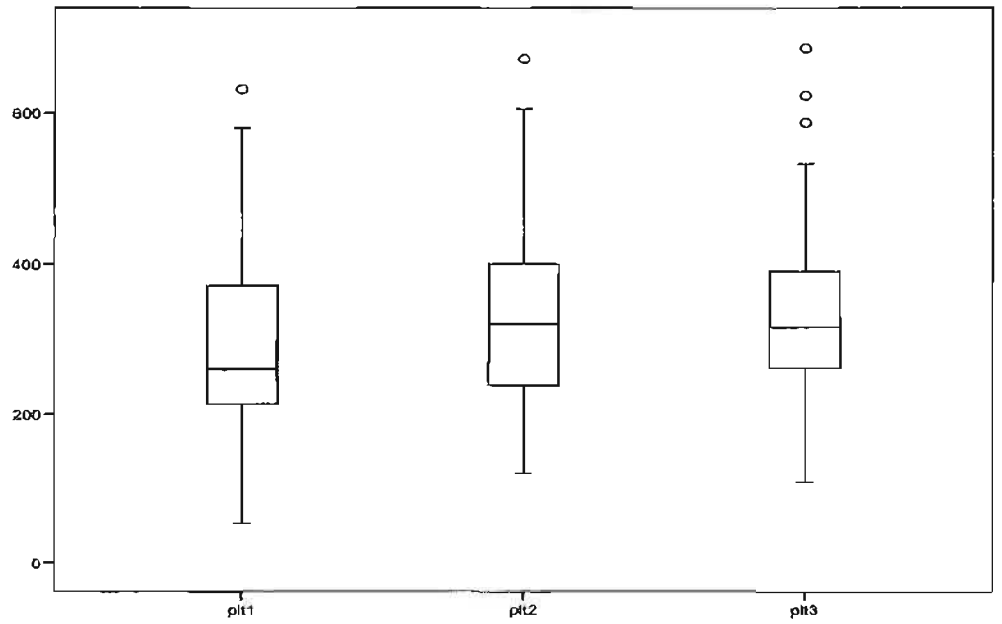


Figure 56. Box-plot graph showing changes in platelet count over the first three time points for patients on ARVs at both clinics

Key:
Plt1 – Plt at time point 1 – i.e. at initiation
Plt2 – Plt at time point 2 – i.e. 6 months after initiation
Plt3 – Plt at time point 3 – i.e. 12 months after initiation

Figure 56 shows that there is no significant change in the platelet count over the first 18 months on treatment.

Appendix 6: Letters for Research approval

UNIVERSITY OF
KWAZULU-NATAL

2 July 2007

Ms LB Bryant
School of Pharmacy and Pharmacology

Dear Ms Bryant

ETHICAL CLEARANCE APPROVAL NUMBER : FEC/SC 008/07

I wish to confirm that ethical clearance has been granted for the following project:

"HIV and Diabetes"

Yours faithfully

SUGEN REDDY
PRINCIPAL FACULTY OFFICER
HEALTH SCIENCES

PS: The following general condition is applicable to all projects that have been granted ethical clearance:

THE RELEVANT AUTHORITIES SHOULD BE CONTACTED IN ORDER TO OBTAIN THE NECESSARY APPROVAL SHOULD THE RESEARCH INVOLVE UTILIZATION OF SPACE AND/OR FACILITIES AT OTHER INSTITUTIONS/ORGANISATIONS. WHERE QUESTIONNAIRES ARE USED IN THE PROJECT, THE RESEARCHER SHOULD ENSURE THAT THE QUESTIONNAIRE INCLUDES A SECTION AT THE END WHICH SHOULD BE COMPLETED BY THE PARTICIPANT (PRIOR TO THE COMPLETION OF THE QUESTIONNAIRE) INDICATING THAT HE/SHE WAS INFORMED OF THE NATURE AND PURPOSE OF THE PROJECT AND THAT THE INFORMATION GIVEN WILL BE KEPT CONFIDENTIAL.

cc. Head of School
cc. Supervisor

HEALTH
KwaZulu-Natal

KWADABEKA COMMUNITY HEALTH CENTRE
PHARMACY DEPARTMENT
P O Box 371, Clermaville, 3602
4 Spine Road, KwaDabeka
Tel.:031-714 3763, Fax.:031-714 3752
Email.:zakiya.essa@kznhealth.gov.za
www.kznhealth.gov.za

Reference research
Enquiries : Ms Z I Essa

29 October 2007

ATT: Lynda Bryant
V Ramburitch

Re : Request for permission to conduct research at KwaDabeka Community Health Centre

Your request dated the 22nd October 2007 to conduct research at KwaDabeka Community Health Centre has been approved.

Please can you forward details regarding the time period of your research at KwaDabeka CHC to Ms Z I Essa (Pharmacy Manager).

Thanking you

B S Malaise
CHC Manager

UNIVERSITY OF
KWAZULU-NATAL

Professor Viren Rambiritch
BSc(Pharm) (Hons) MMed Sc(Pharmacol) PhD, SAPS
Department of Pharmacology
Westville Campus
Durban
Tel: 031 260 7356
Fax: 031 260 7907
Email: rambiritchv@ukzn.ac.za

20 September 2007

Ms Rizwana Desai
Department of Health KZN
Secretary of Department of Health

Request for permission to conduct research

I am a masters student in Clinical Pharmacology at the University of Kwa-Zulu Natal, Westville Campus. In order to complete my degree, I need to complete a dissertation. My topic is HIV and Diabetes and I will be investigating any connections between HIV infection, treatment and the development of hyperglycaemia.

I would like to request permission to study the patient history cards of the patients attending the ARV Clinic at KwaDabeka Clinic and St Mary's Hospital. I would like to look at all the history pertaining to those patients over a one year period. Please find a copy of my protocol attached. The questionnaire in appendix 1 will highlight the information that I will be collecting from the cards.

I can assure you that patient confidentiality will not be compromised. The only means of identification will be the patient card number which will be recorded for my investigative purposes only and will not be published in any of the results or data.

Please feel free to contact me at any time on 0823380991, if you require any further information.

Looking forward to your positive response.

Yours sincerely

Lynda Bryant (Researcher)
V Rambiritch (Supervisor)

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