CHAPTER 1: INTRODUCTION

1.1 Background

The best practices in the monitoring of antiretroviral therapy (ART) toxicity are still unclear in industrialized countries, let alone in developing countries.[1-2] Several dilemmas exist between balancing cost and toxicity of antiretroviral therapy (ART). In resource-limited settings (RLS) most patients currently receive a first line, triple combination of lamivudine, nevirapine and stavudine or zidovudine.[3] The World Health Organization (WHO) prequalified fixed-dose combinations of stavudine/lamivudine/ nevirapine (D4T/3TC/NVP) and zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) are being widely promoted in highly active antiretroviral therapy (HAART) ‘‘scale-up’’ programmes.

ART is associated with a variety of toxicities that can limit treatment. Specifically, there is concern about the risk of peripheral neuropathy with use of stavudine, especially among patients with lower CD4 cell counts[4] and the risk of rash (including Stevens-Johnson syndrome), hypersensitivity, and life-threatening hepatotoxicity with use of nevirapine, especially among women and those with higher CD4 cell counts at initiation of therapy.[5-7] Toxicities associated with ART have been studied extensively in developed countries, but there is limited information about such toxicities from treatment programmes in sub-Saharan Africa. RLS face a major challenge with the implementation of pharmacovigilance programmes as there are usually inadequate structures to ensure the effective running of these programmes.[8] RLS are affected by problems of “brain drain,” limited infrastructure and funding for the effective implementation of these programmes.[8]

In guidelines published in the year 2009, the WHO is now discouraging the use of stavudine in treatment/naïve patients. Where there is no alternative available, the dose of stavudine has been

limited to 30 mg.[9] This recommended use of stavudine at dosages of 30 mg twice daily has become part of first line therapy in most resource limited settings. Use of stavudine at these dosages has led to various rates of toxicities that have been reported in different settings.[5-7] The rates of toxicities have a bearing on how pharmacovigilance programmes need to be implemented.

Most pharmacovigilance programmes in resource limited settings (RLS) are unable to monitor adverse drug reactions because of the inconsistent laboratory support systems. Zidovudine, which is currently being used as an alternate for stavudine especially in cases of toxicity, requires laboratory support in the initial stages of therapy. Zidovudine has the potential to cause disabling anemia and intensive laboratory support is required to detect any cases that might arise.[3]

As with monitoring the efficacy of therapy, there are tradeoffs between intense and less intense monitoring of toxicity. Patients (on nevirapine) with moderate or even severe elevations in liver enzyme levels may have no detectable symptoms or signs. For such patients, relying on clinical evaluation may result in deaths due to liver failure that might have been prevented by more intensive laboratory monitoring strategies.[3] Current WHO guidelines recommend that HAART should not be initiated unless there is the capacity to perform complete blood counts, liver function tests, and amylase measurements.[10] Pharmacovigilance is needed in every country, because there are differences between countries (and even regions within countries) in the occurrence of adverse drug reactions and other drug-related problems.

1.2 Statement of the problem

Identifying causality of ADRs in HIV positive patients who are on HAART is a challenge as these patients present with other confounding conditions which complicate a diagnosis. The

complexities of a patient compounded with the limited resources make causality assessments a complex process which requires the development of an effective strategy. There is a need to develop an effective means of implementing a pharmacovigilance programme in a RLS that can capture information effectively and utilize the structures that are available.

In Zimbabwe there are no data on the rate at which ADRs are occurring among patients who are receiving antiretroviral therapy. There is also a lack of data on the various environmental, medication and patient factors that predispose a patient on HAART to ADRs. Rates of ADRs that have been generated from clinical trials are usually not a true reflection of the rates that are found in clinical practice. No data exist on the long term toxicities of HAART and there are no studies that explicitly evaluate the impact of herbal remedies on the ADR profiles of HAART. Several factors need to be evaluated to ensure a thorough understanding of how ADRs present themselves in a population.

To date, more than 20 antiretroviral drugs from four different classes have been licensed. Establishing the indication, choosing the optimal therapy for the individual patient and monitoring of therapy requires experience with HIV-infected patients. During modern ART with compliant, initially treated patients, virologic treatment failure is rarely observed. Therefore, in choosing individual drugs for permanent ART, side effects play an important role.[11]

Despite ARVs being of much help to the health of most HIV/AIDS patients, the issues of drug induced toxicities has remained of great concern. ARVs belonging to a non-nucleoside reverse transcriptase inhibitors (NNRTIs) class have been reported to be associated with rash and hepatotoxicity.[12-13] So far, nucleoside reverse transcriptase inhibitors (NRTIs) are being implicated to be causative of lactic acidosis probably due to mitochondria damage.[14] NRTIs have also been implicated to cause hypersensitivity reactions, neuropathies, pancreatitis, anaemia and

neutropenia.[15-16] Protease inhibitors have been found to be associated with hyperlipidemia, hyperglycaemia, gastrointestinal symptoms, body-fat distribution abnormalities and insulin resistance.[16-18] Drug interactions are among the major problems in these multi-drug regimens and such interactions can lead to increased toxicities.[19] As ART programmes continue to expand, a larger population will be subjected to ARVs. Variability in drug metabolic capacity among various populations predicts variations in the gene expression of the metabolizing enzymes which could be influenced by geographical/interracial differences.[20-21] Even within the same geographical locations, variability among individuals with respect to various metabolizing isoenzymes exists.[20-22] Therefore, data derived from within the country may have greater relevance and form basis for a decision-making and for effective patient management.

Generic antiretroviral therapy has been shown to effectively work in resource-limited settings,[23] examining long-term toxicities can provide options for improving the course of antiretroviral treatment among HIV-infected individuals in resource-limited settings.

1.3 Purpose of the study

The study was conducted to implement a pharmacovigilance system and use it to determine the rate, nature & predictors of adverse drug reactions associated with the use of HAART in Zimbabwe. The study set out to ascertain the incidence of the various toxicities associated with HAART in Zimbabwe and it specifically focused on patients who were receiving first line treatment through the national government ARV rollout programme. The study was also designed to determine the severity of the ADRs due to HAART and the clinical significance in the population receiving the medicines. The study was also carried out to identify which factors (age, gender, race, duration of therapy, level of nutrition, existing OIs, concurrent drug therapies,

use of recreational drugs, use of herbs, any chronic ailments, adherence to medication, immunological characteristics and viral load) would predispose HIV positive patients on antiretrovirals to ADRs.

Pharmacovigilance is needed in every country, because there are differences between countries (and even regions within countries) in the occurrence of adverse drug reactions and other drug-related problems. To sustain such pharmacovigilance, the countries need to develop appropriate, viable, and practical approaches for collecting valid data for their own settings. WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Research is required to determine the rate and nature of toxicities associated with HAART in resource-limited settings. Data from such studies can be used to establish which monitoring strategies are best suited to particular HAART regimens in a specific setting. Identification of patients at different levels of risk may identify subgroups requiring different monitoring intensities.

1.4 Definitions

- Pharmacovigilance: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
- Adherence to medication: in HIV/AIDS care specifically refers to the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function.
- Scale up / Rollout: the process of increasing the distribution and dispensing of ARVs to the HIV positive patient population in need of the drugs.

- Bioavailability: The rate and extent of absorption of parent drugs or active metabolites from a dosage form into the systemic circulation.
- Bioequivalent products: Drug products having the same bioavailabilities.
- Therapeutically equivalent products: Drug products having the same therapeutic efficacies.
- Innovator products: Products being approved as new drugs by clinical trials or relating drug products.
- Generic products: Products whose active ingredients, strengths, dosage forms and regimen are the same as those of innovator's products.
- Fixed dose combination (FDC): a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Fixed-dose combination drug products may improve medication compliance by reducing the pill burden of patients.
- Nadir CD4 count: The lowest CD4 count that a patient has ever experienced.
- Exanthems: A widespread rash occurring all over the body.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

The use of highly active effective antiretroviral therapies (ART) has dramatically decreased the morbidity and mortality of HIV infection. Over 20 antiretroviral substances are available in four different classes.[24] Side effects of HIV therapy are common and may influence the prognosis, as the medications are required lifelong for the still incurable infection. ART-associated allergic reactions, lipodystrophy syndrome and immune reconstitution syndrome are side effects frequently seen by dermatologists.[7] Exanthems are challenging as drug reactions must be separated from immune reconstitution, syphilis and viral exanthems and then the causative agent must be identified from a long list of medications. Non-nucleoside reverse transcriptase inhibitors typically cause allergic exanthems.[7] Mitochondrial toxicity caused by nucleoside reverse transcriptase inhibitors is responsible for lipoatrophy and fatty changes in the liver.[25-26] Protease inhibitors cause diarrhea, abnormalities of glucose and fat metabolism and lipohypertrophy.[26] Before other medications or surgical measures are undertaken to address side effects of ART, the regimen should be adjusted to include alternative but equally effective agents.

2.2 Epidemiology of HIV in the World

The Human Immunodeficiency Virus or Acquired Immuno Deficiency Syndrome (AIDS) pandemic has continued since its discovery in 1981.[27-28] It was estimated in 2007 that 33.2 million people were infected with HIV worldwide, accounting for 0.8% of the world's population. This included roughly 7000 new infections each day, totaling approximately 2.5 million new infections for the entire year—a figure that was slightly higher than the 2.1 million

estimated AIDS-related deaths during the same period.[29] HIV is the fourth largest killer in the world after respiratory infections, diarrheal disorders, and tuberculosis, and the leading cause of death in Africa.[30] Although cases of HIV/AIDS have been reported from virtually every part of the world, over 90% of the people with HIV/AIDS live in the developing countries.[29] Owing to global efforts, the epidemic seems to be stabilizing.[29, 31] The incidence of new infections is believed to have peaked in the late 1990s and then declined between 2001 and 2007.[29] Although the global prevalence of HIV/AIDS rose from 29.5 million in 2001 to 33 million in 2007, the prevalence rate stayed level at 0.8%.[29] This is attributable to improved preventive education and dramatically increased availability of Highly Active Antiretroviral Therapy (HAART) throughout the world, including a 20-fold increase in HAART in sub-Saharan Africa since 2003.[29]

Despite these encouraging trends, the pandemic persists in several areas, including the ongoing epidemics in sub-Saharan Africa, the Caribbean, and Southeast Asia.[32] Sub-Saharan Africa, with 22 million people infected, accounts for roughly two-thirds of all HIV infections and 90% of all infected children. In South Africa, an astonishing 1 in 5 people are infected and AIDS remains the leading cause of death in this region. A global epidemic also continues among high-risk populations and includes intravenous drug abusers, sex workers, and men who have sex with men.[33] Unfortunately, these latter groups are marginalized in many cultures and have increased barriers to access of medical care.

Nearly 5 million people are HIV-positive in South, Southeast, and East Asia, accounting for 15% of all cases worldwide.[29] Nearly half are from India (2.4 million) and 3 quarters from the 3 most populous countries: India, China, and Thailand.[29] Many Asian countries report low HIV prevalence rates, including China, Mongolia, the Republic of Korea, and Bhutan which all report

rates less than 0.1%. Other nations, including Thailand, Myanmar, Vietnam, Indonesia, Cambodia, and Pakistan face higher prevalence rates and/or growing epidemics.[29] In 2007, there were about 380,000 new HIV infections and 380,000 deaths owing to AIDS in Asia.[29] Approximately one-third of all adults living with HIV/AIDS in Asia are women, a proportion that has remained relatively stable in recent years.[29] The mode of HIV transmission varies throughout Asia, often attributable to heterosexual intercourse, commercial sex work, and/or injection drug use.[29] In Thailand, Vietnam, Cambodia, and Indonesia, sex between men is believed to be a major factor. Over the past few years, the prevalence rates in many Asian countries have stabilized, and are often well below the global prevalence rate of 0.8%.[29] This owes, in large part to nationalized treatment and prevention efforts. In addition, the availability of antiretroviral therapy increased 6-fold between 2003 and 2007[24] although this still fell grossly short of what was needed, with only 25% of those eligible receiving treatment.[24]

In Latin America and the Caribbean, nearly 2 million people live with HIV-nearly half (43%, 730,000) live in Brazil and 70% live in Brazil, Argentina, Colombia, and Mexico.[29] The Caribbean is home to 230,000 HIV-positive patients, 75% of who live in the Dominican Republic and Haiti.[29] Although the epidemic varies from country to country, it seems to have stabilized across Latin America with an overall adult HIV prevalence of less than 0.5%in 2007.[29] More severe epidemics are present in smaller countries such as Belize, Guyana, and Suriname, with prevalence rates of 2.1%, 2.5%, and 2.4%, respectively.[29] Compared with Latin America, the prevalence rate is higher in the Caribbean, but has remained stable at 1.1% from 2001 to 2007, and varies greatly between countries from 0.1% in Cuba to 3% in the Bahamas.[29] In 2007, there were 160,000 new infections and 77,000 deaths owing to AIDS in Latin America and the Caribbean.[29] Currently women make up less than one-third of HIV-positive adults in the region,

but this seems to be increasing in Brazil, Argentina, Peru, and Uruguay.[29] Young women are especially vulnerable. The primary method of HIV transmission is through sexual intercourse—both heterosexual and between men.[29] Commercial sex work and injection drug use also play important roles.[29] There are several strong signs of progress in Latin America and the Caribbean.[29] The availability of prevention services in Latin America is increasing, particularly targeting men who have sex with men, sex workers, and injection drug users.[29] Moreover, by the end of 2007, a commendable 64% of Latin Americans in need of antiretroviral therapy were receiving it.[24] Several countries even supply ‘‘universal access’’ to their citizens, including Brazil and Costa Rica.[24] Unfortunately, this is not consistent across the region—in Bolivia, Colombia, Guatemala, Nicaragua, and Paraguay, less than 40% of those in need have access to HAART.[24] In addition, in the Caribbean HAART is available to only 43% of those in need, including a 39% increase since 2006.[24] In the Caribbean, Cuba provides universal access to its citizens, whereas less than 40% of those in need have access to HAART in the Dominican Republic.[24]

HIV/AIDS is a growing problem in Eastern Europe and Central Asia with an estimated 1.5 million HIV-positive people living in the region.[29] The prevalence more than doubled from 2001 to 2007.[29] Ninety percent of HIV-positive patients in the region live in Russia or Ukraine. Russia alone is home to 940,000 patients.[29] Estonia, the Russian Federation, and Ukraine have the highest prevalence rates in the region, between 1.1% and 1.6%.[29] The epidemic is driven primarily by the use of non sterile drug injection equipment, although heterosexual transmission also plays an increasingly important role and young women are particularly at risk. Transmission between men who have sex with men in Eastern Europe and Central Asia reportedly accounts for less than 1% of cases, likely greatly under recognized, and has been dubbed the ‘‘hidden

epidemic''[34] HAART coverage is poor in the region, particularly among injection drug abusers. Only 8% of patients who needed HAART in Ukraine were receiving it, and only 16% in the Russian Federation.[29]

Sub-Saharan Africa remains the epicenter of the HIV/AIDS epidemic. Although the region comprises only 11% of the world's population, it is home to two-thirds of the global HIV-positive population.[29] Most sub-Sahara African nations have HIV epidemics with an HIV prevalence rate greater than 1%.[29] The prevalence rate is greater than 5% in sub-Saharan Africa, with 9 countries estimated over 10%, including South Africa over 18% and Swaziland over 26%.[29] The primary route of HIV transmission in Africa is heterosexual sex, although patterns vary by region.[29] Women make up the majority (59%) of HIV-positive adults in Africa, which in turn puts children at particularly high risk.

It has been estimated that there are 24.7 million HIV-seropositive adults and children in the Sub-Saharan Africa region. In the same region in 2006 an estimated 2.8 million people acquired HIV infection and 2.1 million adults and children died of AIDS.[35] At the end of June 2006, antiretroviral therapy coverage for sub-Saharan Africa was 23% of those deemed eligible for treatment by WHO/UNAIDS guidelines; the overall coverage for low- to middle-income countries was 24%.[35] In 2006, of the more than 4 million people who were newly infected with HIV, 8% were children, approximately 90% of whom live in sub-Saharan African countries and were infected through mother-to-child transmission.[35] Despite tremendous progress in preventing mother-to-child transmission of HIV, the high incidence of disease among children raises a number of other important issues, such as the availability of suitable pediatric drug formulations, adherence issues among pediatric populations, and the effect of nutritional status on therapeutic response.

2.3 Adverse Drug events of Nucleoside/tide Reverse Transcriptase Inhibitors

NRTIs are a necessary portion of HAART for patients receiving treatment. The use of two or more NRTIs in a regimen is based on results from randomized clinical trials which demonstrate virologic and immunologic improvement in HIV-infected patients.[36] Alternatively, three NRTIs without the aid of a second class can also be used in an HIV treatment regimen; however, studies have demonstrated lower efficacy with these regimens.[37] In order to properly discuss some of the side effects of NRTIs, a brief explanation of the mechanism of action is warranted. Each NRTI is a structural analog of a nucleoside (adenosine, cytosine, guanosine, or thymidine) which forms the building blocks of DNA in human cells.[38-39] These analogs require intracellular triphosphorylation by human cellular kinases to achieve their active triphosphate form.[38] The triphosphate form of the NRTI then competes with naturally occurring nucleosides for the HIV reverse transcriptase enzyme, to be incorporated into the viral DNA chain being developed. Reverse transcriptase is an RNA-dependent DNA polymerase enzyme that is endogenous to the virus and is required for HIV DNA translation; fortunately, human cells neither use nor possess reverse transcriptase.[38-39]

Because of their common use within HIV treatment regimens, side effects associated with NRTIs are likely to pose a significant obstacle to effective, long-term treatment. Fortunately, most NRTIs (at currently prescribed doses) are fairly well tolerated by most patients. Class-wide side effects seen with NRTIs include lactic acidosis, hepatic steatosis, and lipoatrophy.[39] Some of the more significant drug specific side effects include anemia, cardiomyopathy, gastrointestinal (GI) distress, drug-induced hypersensitivity, myopathy, nephrotoxicity, pancreatitis, ototoxicity, peripheral neuropathy, and retinal lesions.[39-40] These side effects, their causes, and possible methods of prevention are discussed in more detail in this text.

2.4 Mitochondrial Toxicity due to NRTIs

The foundation of many NRTI-induced adverse events is believed to be derived from mitochondrial toxicity. Mitochondria are organelles that are present in all cells (except red blood cells) and account for <2% of total cellular DNA.[39] They have a double membrane, a circular DNA molecule, and mitochondrion-specific transcription, translation, and protein-assembly systems. These characteristics suggest that mitochondria may have been independent entities at one time.[39] The main role of mitochondria is to provide energy to the cell in the form of adenosine triphosphate (ATP) and perform an essential respiratory function known as oxidative phosphorylation.[38-39] Energy is generated using intracellular fatty acids and glucose as fuel sources.[39] Other functions of mitochondria include synthesis of heme, bile acid, estrogen and cholesterol, ammonia detoxification, cholesterol and ethanol metabolism, and cellular calcium homeostasis.[39] Mitochondria, which are inherited from the maternal oocyte, is the only extrachromosomal DNA that is naturally found in human cells.[39]

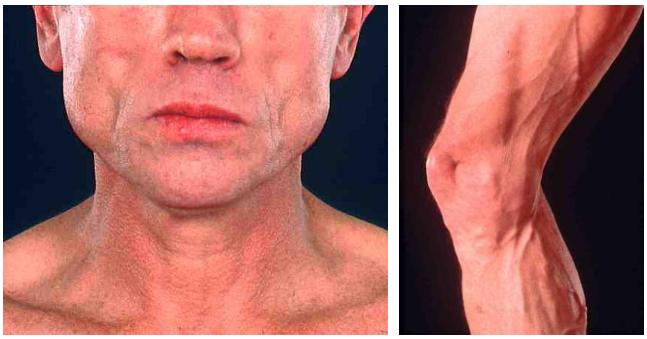
The enzyme responsible for ensuring functional mitochondrial DNA (mtDNA) is DNA polymerase-g, which closely resembles HIV reverse transcriptase (relative to the other forms of DNA polymerase found in human cells). Therefore, in addition to viral reverse transcriptase inhibition, the NRTIs may also inhibit human DNA polymerase-g leading to interference with mitochondrial DNA formation which, unfortunately, has no repair mechanisms.[40] Ultimately, this could prematurely terminate the synthesis of mitochondrial messenger and transfer RNA, and lead to faulty transcription and translation.[40] Aside from the inhibition of mtDNA polymerase-g, mitochondrial toxicity also arises from the impairment of normal oxidation of long chain fatty acids in mitochondria, leading to esterification of triglycerides and an increase in nonesterified fatty acids (NEFA).[38] Impaired energy production, and possibly direct toxic effects

of NEFAs, associated with dicarboxylic acids and free radicals are thought to contribute to the clinical manifestations of mitochondrial toxicities such as: lipoatrophy, lactic acidosis, and peripheral neuropathy.[38] *In vitro* studies to date have shown the hierarchy of mitochondrial DNA polymerase-g inhibition to be as follows: zalcitabine > didanosine > stavudine > zidovudine > lamivudine =abacavir = tenofovir.[41]

2.4.1 Lipoatrophy due to ART

Lipoatrophy is a syndrome, included under the umbrella term of lipodystrophy, that results from the loss of subcutaneous fat, most noticeably in the face, limbs, and buttocks.[38, 42-43]

Fig 2.1: Lipoatrophy of subcutaneous fat



The differential effects of lipodystrophy may be caused by the differences in the characteristics of adipocytes; generally, central adipocytes have higher lipid turnover than peripheral adipocytes.[44] Lipolysis is an energy-dependent process and the need for mitochondria is greater in central adipocytes compared with peripheral adipocytes. Impaired lipolysis can result in accumulation of lipids (visceral fat) in central and dorsocervical adipocytes- this is known as lipoaccumulation. Peripheral lipoatrophy is secondary to adipocyte apoptosis (white fat cell death).[38, 44] From many observational cohorts, risk factors for lipodystrophy have been

demonstrated in HIV-infected patients taking NRTIs; these include increased age, abnormal lipid profile prior to therapy, and a low CD4 cell nadir.[38] Of the commonly used NRTIs, stavudine has been shown to have the highest propensity for lipoatrophy.[38, 42-46] However, due to the multiple drug combinations and the variability of patient response, the prevalence for each individual NRTI has not been reported. Finally, in the absence of clear evidence of causation, the prevention and management of fat redistribution syndrome remains challenging.[38]

One strategy to prevent lipoatrophy in those with risk factors may be the use of an NRTI that has a lower affinity to DNA polymerase-g.[38] Other options for prevention include dietary methods and exercise.[38] For managing lipoatrophy, anabolic steroids may be used; these are anabolic for muscle not fat, and increased muscle mass may partly disguise fat loss in the limbs.[43] Cosmetic surgeries such as collagen or silicone injections are available, although effects may be short-lived.[38, 43] The FDA has recently approved Sculptra®, an injectable poly-Lactic acid derivative to increase the thickness of the skin. In the majority of patients, body changes due to lipoatrophy adversely affect self-esteem, social contacts, and overall daily performance.[45] Given that a lower CD4 cell nadir represents a higher risk for lipoatrophy[47], initiation of HAART earlier in the course of the disease may help decrease the risk of lipoatrophy. However, recommendations for the appropriate time to initiate therapy are typically not dependent on the risk for lipoatrophy, but on immunologic factors.[36]

2.4.2 Peripheral Neuropathy due to ART

To a varying degree, and in a dose-dependent manner, all NRTIs are neurotoxic.[48] Peripheral neuropathy is most frequently seen with zalcitabine, didanosine and stavudine.[49] The effects of NRTIs on the peripheral nervous system have not been extensively studied. In most cases, there is interference with oxidative metabolism which can lead to a reduction in acetyl-carnitine

production.[49] Low serum hydroxycobalamine levels and an inhibitory effect on nervous growth factor have also been noted.[49] Symptoms often begin in both feet with numbness and episodic shooting pains.[38] Peripheral neuropathy may gradually worsen over days to weeks to a point where some patients have difficulty walking or cannot tolerate clothes over their feet.[38] Symptoms of neuropathy, as described by patients, include burning, numbness, pins-and-needles, aching sensation, cramping, and impaired temperature sensation in the feet and legs. Pre-existing neuropathy and low CD4 cell counts (nadir CD4 count < 200cells/mm3) are predisposing factors for peripheral neuropathy with all NRTIs.[4, 48] Combination therapy may also be a risk factor: zalcitabine is more neurotoxic than didanosine, stavudine and lamivudine, but the combination of didanosine and stavudine is more toxic than either drug alone.[48] Prior peripheral neuropathy of any etiology or coadministration of other neurotoxins can also be risk factors for NRTI-induced peripheral neuropathy.[38] Other drugs commonly used in patients infected with HIV which may be associated with peripheral neuropathy include isoniazid, phenytoin, and dapsone.[38] Before concluding that one or more of the NRTIs in a regimen induced peripheral neuropathy, the clinician must first rule out two factors: first, the frequent presence of pre-existing clinical neuropathy related to AIDS; and second, clinical symptomatology due to distal sensory painful axonal neuropathy (DSPAN).[48] The way to distinguish between NRTI-induced peripheral neuropathy and DSPAN is *via* temporal association of symptom onset with the start of a NRTI, clinical or electrophysiological improvement upon cessation of therapy, and "coasting", a phenomenon of temporary (2-4 weeks) worsening of symptoms upon discontinuation of NRTI followed by clinical improvement.[48]

Overall, prevention of peripheral neuropathy is preferred. A stable CD4 cell count and careful evaluation of other existing factors, such as other neurotoxins, is important when assessing the

risk of developing peripheral neuropathy. Avoiding combinations of didanosine and stavudine is also warranted. In regards to treatment, NSAIDs and opiate analgesics can provide immediate pain relief. Tricyclic antidepressants, such as amitriptyline, can be beneficial for the neuropathic pain, whereas, valproic acid and carbamazepine may be helpful for lancinating pain.[38] Gabapentin has been studied in a randomized, placebo-controlled trial, where the results demonstrated that gabapentin significantly reduced pain scores in patients suffering with neuropathies.[50] Acetyl-L-carnitine may also be of benefit due to reported deficiencies among HIV infected patients and those with NRTI-induced peripheral neuropathy.[38] Additionally, there have been anecdotal reports of B-complex vitamins being beneficial, but these effects have not been well established.

2.4.3 ART induced lactic acidosis

The most serious NRTI-associated mitochondrial toxicity is lactic acidosis, with or without hepatic microsteatosis.[38] Among HIV-infected patients that receive NRTIs, asymptomatic elevated blood lactate levels are common, but symptomatic hyperlactatemia is rare; in addition, the risk of developing symptomatic hyperlactatemia is not well known.[51] When mitochondrial function is impaired, it yields diminished aerobic reactions.[40, 52] Oxidation of pyruvate cannot take place, and instead turns to lactate because it is the only possible reaction outside the mitochondria.[40] Lactic acidosis has been seen in patients receiving both single and dual NRTI regimens, including combinations of zidovudine or stavudine, with didanosine, zalcitabine, or lamivudine. Yet, the incidence of lactic acidosis for individual or combined agents has not been established.[38] Lactic acidosis occurs most commonly in patients on prolonged therapy (>6 months).[38, 40] The onset can be either abrupt or insidious. Initial symptoms are non-specific and include nausea, vomiting, and abdominal pain.[38, 52] Insidious cases may present with fatigue and

weight loss. Biochemical abnormalities may present as elevated lactate levels, elevated lactate pyruvate levels, and/or acidosis with a low bicarbonate concentration.[38] Prevention of lactic acidosis involves avoidance of combinations of NRTIs with a high incidence for the reaction such as didanosine, zalcitabine, and stavudine. Another recommendation may be to monitor lactate levels in patients that have non-specific initial symptoms such as unexplained nausea, vomiting, abdominal pain, hepatic steatosis or elevated transaminases.[40] Routine monitoring of serum lactate levels in non-symptomatic patients has not been shown to be cost-effective. Cessation of ARV therapy, supportive therapy, and correction of the biochemical abnormalities, including intravenous bicarbonate and glucose administration can be used for management of lactic acidosis.[38] Riboflavin (vitamin B2), thiamine, carnitine and/or coenzyme Q-10 administration have also been beneficial in some cases.[38, 53-54] Once lactic acidosis is resolved, some providers may re-initiate HAART excluding NRTIs to avoid recurrence. However, data in a small retrospective study has shown that when stavudine was part of the regimen that lead to lactic acidosis, introducing a different NRTI was safe in some patients. If this method is utilized, close monitoring is essential. Factors associated with lactic acidosis are older age, female sex, high body mass index, lipoatrophy, low $CD4^+$ T-cell count, hypertriglyceridaemia and use of stavudine and didanosine,[50, 55-56] although it has been described with all NRTIs except abacavir.

2.5 NRTI Drug Specific Adverse Events

2.5.1 Abacavir

The hypersensitivity reaction (HSR) associated with abacavir occurs in approximately 5-9% of patients receiving the drug. This reaction can have multi-system involvement that, in rare cases, has proven to be fatal.[57] Symptoms usually appear within the first six weeks of therapy, and

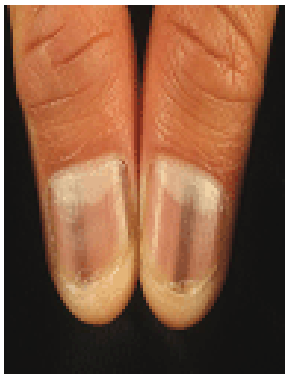
include a combination of rash, flu-like symptoms (such as fever, malaise or lethargy), and GI symptoms (such as nausea, vomiting, diarrhea, or abdominal cramping).[57-58] Upper and lower respiratory-tract infection symptoms can also suggest a possible HSR[43]; to avoid any confusion, abacavir should probably not be initiated during such an infection. With continued therapy, symptoms of HSR will worsen; therefore, it is critical to discontinue abacavir in a timely manner once diagnosed. Symptoms can improve within 72 hours after discontinuation of the drug. In abacavir clinical trials to date, having prior antiretroviral experience and being of African descent has been associated with an almost 40% reduction in the risk of HSR.[59] The exact mechanism of HSR is not known, but clinical symptoms suggest an immunological phenomenon influenced by genetic factors.[57, 60] Several HLA antigens (most notably HLA-B57) are being investigated as markers for increased risk of HSR, but no clinical tests reflecting risks are available.[57, 60] Another possible mechanism of HSR includes the reactive metabolite of abacavir accumulating in the liver which is then transported to other tissues where immune-mediated damage occurs.[59] A good diagnostic criterion for abacavir-induced HSR is an appropriate temporal relationship between symptom resolution and drug discontinuation. Supportive therapy such as intravenous hydration and cessation of abacavir therapy is very crucial.[59] Little relief has been seen with corticosteroids and antipruritics, but analgesics and antiemetics may offer short-term aid.[59] Mild rash can be treated with diphenhydramine. Once HSR is observed with abacavir, rechallenge is not recommended due to several deaths being attributed to rechallenge.[43, 59] Since abacavir HSR can be life threatening, patient education and open communication with the provider is vital.

2.5.2 Zidovudine

As noted above, anemia can be associated with zidovudine therapy.[61-63] The mechanism of zidovudine myelosuppression is unclear.[61] *In vitro* it has been suggested that zidovudine inhibits both erythroid burst-forming units and human granulocyte-macrophage colony-forming units.[61] Moreover, it has been suggested that the inhibition results from both the competitive inhibition of thymidine triphosphate and the incorporation of zidovudine triphosphate into the DNA of human bone marrow cells.[61] In addition, heme synthesis may be impaired due to the inhibition of mtDNA polymerase-g.[61] Anemia greatly impacts quality of life (QOL), mostly because of its association with nausea, fatigue and weakness.[63] Lower CD4 cell counts, increased age and African American decent have all been shown to increase the risk for anemia.[64] Careful monitoring of complete blood count (CBC) in patients on zidovudine can be an essential method to prevent clinically significant anemia. Recombinant human erythropoietin, blood transfusion and cessation of zidovudine and other myelosuppressive therapies (such as gancyclovir or sulfamethoxazole with trimethoprim) are viable treatment options for zidovudine induced anemia.[62, 65] Other causes of anemia in patients with HIV should also be considered. Potential causes include decreased erythropoietin concentrations, changes in cytokine production with subsequent effects on hematopoiesis, and opportunistic infections such as *Mycobacterium avium* complex and parvovirus B-19.[65] Nausea is another common side effect that may be present in early zidovudine use.[61] Symptoms often subside within one month of therapy.[66] However, nausea/ vomiting can be a consequence of several other aspects aside from medications, such as fluid and electrolyte imbalances, vestibular disorders, and GI disorders.[66] Knowing specific triggers for nausea (such as specific foods, the time of the day, or the surroundings) can lessen the feelings and even prevent it.[67] For treatment, there are many ant nausea options including

prochlorperazine, and dronabinol (Marinol®).[67] Ginger products (such as fresh ginger or ginger tea) have been shown to help nausea caused by various etiologies.[68-69] Other side effects of zidovudine may include: myopathy, dermatological effects, malaise, fatigue and insomnia.[61] Myopathy may occur within 6-12 months of initiating zidovudine, and has an insidious onset that involves proximal muscle weakness and exercise-induced myalgias.[61] The mechanism of myopathy is believed to be mitochondrial toxicity (as previously mentioned) within myocytes.[61] Zidovudine can also cause hyperpigmentation of the skin and nail (Figure 2) beds and occurs at a much higher incidence in African Americans than Caucasians and Hispanics.[61]

Fig 2.2: Melanonychia striata medicamentosa with zidovudine



Little information is available regarding the treatment of hyperpigmentation.

2.5.3 Stavudine

Peripheral neuropathy, lactic acidosis, and lipoatrophy are all side effects seen with stavudine.[47-49, 52, 70] These side effects are generally attributed to mitochondrial toxicity caused by mitochondrial DNA polymerase-g inhibition.[36, 39] Lactic acidosis is a severe consequence of stavudine use that can arise within several months of therapy.[40, 50, 71]

When compared to other NRTIs, lipoatrophy is most commonly seen with stavudine.[42, 45, 47, 70] The risk of adipocyte apoptosis increases with duration of stavudine therapy, concurrent protease inhibitor therapy, concurrent elevation of serum lactate levels, older age, white race, longer NRTI- experience, and lower pre-treatment body fat.[70] Other symptoms of fat depletion include: facial atrophy ("sunken cheeks") and venomegaly.[45, 47] Peripheral fat wasting can be seen in approximately 63% of patients who take stavudine for greater than one year. Switching from stavudine to zidovudine or abacavir may help to slow the progression of lipoatrophy, and to a lesser extent reverse it.[70] In general, this effect is likely to be seen when switching from an agent with high affinity for the mtDNA polymerase-g to an agent with low affinity. However, it is important to remember that all NRTIs have been shown to cause lipoatrophy to some degree.[36] Stavudine-induced lipoatrophy can adversely affect adherence secondary to decreased QOL.[45]

Finally, in the Gilead 903 study has shown stavudine to increase fasting triglycerides, total cholesterol, LDL, and lower HDL, compared to tenofovir.[72] This study was a 96 week study comparing the clinical effectiveness of stavudine and tenofovir, with both groups also receiving lamivudine and efavirenz. Other studies have not looked at the effects of stavudine on triglycerides or cholesterol.

2.5.4 Tenofovir

In the Gilead 903 study mentioned previously, data revealed that tenofovir had side effects that were generally mild and not clinically relevant. Decreases in bone mineral density at the lumbar spine were seen more often with tenofovir regimens than stavudine; however, there were no differences in bone fractures between the two groups. The occurrence of grade 3 and 4 adverse events such as rash and fever as well as elevated creatine kinase were similar, yet infrequent, among both groups.[72] In premarketing studies, the incidence of grade 3 – 4 rashes was reported

in as many as 15% of subjects on tenofovir-containing regimens.[73] Nausea, diarrhea, flatulence and vomiting are also reported side effects. The true effect of tenofovir on renal function is not fully understood. There are several case reports of renal toxicity associated with tenofovir. Peyriere *et al*.[74] reported seven cases of renal tubular dysfunction associated with tenofovir use. Patients experienced hypophosphatemia, hypokalemia, proteinurea, proximal renal tubular acidosis, and a 20 - 78% decrease in creatinine clearance. Laboratory abnormalities in these studies improved when tenofovir containing regimens were discontinued. Five patients who discontinued only tenofovir saw laboratory abnormalities improve.[74] Karras *et al*. also reported three cases of renal impairment associated with tenofovir use.[75] One patient developed diabetes insipidus, two patients had glucosuria and two had acidosis and hypokalemia.[75] Izzedine *et al*., reviewed two randomized, double blinded trials and 19 retrospective cases of TDF-associated tubular dysfunction.[76] Their report on the renal safety of tenofovir suggested that the drug was not associated with renal toxicity based on two randomized, double-blind trials; but, was a rare and reversible phenomenon. The authors also suggested that concurrent ritonavir and/or a prior history of nephrotoxicity may increase the risk of tenofovir-associated renal toxicity,[76] while others have not seen this increased risk.

2.5.5 Didanosine

Didanosine is an acid-labile drug that requires a neutral pH for absorption. The original, buffered formulation frequently caused GI disturbances and needed to be taken on an empty stomach. To improve tolerability and absorption, the manufacturer developed an enteric coated capsule. Videx EC® (ddI EC) is a delayed release capsule that is as efficacious as the buffered didanosine tablets. It does not require additional antacids to maintain stability, but is still best administered on an empty stomach.[77] When discussing didanosine side effects, it is important to keep in mind

that many studies combined didanosine with stavudine, complicating the interpretation of the rates of side effects. Additionally, earlier studies (mostly using monotherapy to treat HIV) are complicated by advanced HIV disease and may not fully represent current day drug-induced side effects.

Pancreatitis is a known complication of didanosine use occurring in approximately 1 to 7% of patients.[78] In published case reports, there were two deaths involving patients using the buffered formulation of didanosine plus stavudine, indinavir, and hydroxyurea; one death in a patient using didanosine with stavudine and nelfinavir; another lethal outcome from didanosine plus stavudine and indinavir; and one death associated with didanosine EC plus stavudine, hydroxyurea, ritonavir, indinavir and efavirenz.[78] Nelson *et al*. reported six cases of pancreatitis that were related to didanosine treatment, two of which had lethal consequences.[79] Thaddeus *et al*. suggested that didanosine dose and steady state concentration may be related to pancreatitis. Other risk factors that may be associated with pancreatitis are concomitant use of hydroxyurea, history of pancreatitis, female sex, and CD4 cell count < 200 x 10^6 cells/mm^3.[80]

Prevention is primarily limited to cautious use with agents that are known to increase didanosine plasma levels or other agents known to cause pancreatitis. Medications that are strongly associated with pancreatitis include metronidazole, tetracycline, pentamidine, and sulfonamides.[80] In particular, the didanosine dose should be reduced to 250 mg when the drug is administered with tenofovir in patients with body weight >60 kg (dosage recommendations are not available for patients weighing <60kg receiving didanosine and tenofovir). Concurrent use of two or more of the following should be avoided: didanosine, stavudine, and zalcitabine. Additionally, it may be wise to avoid didanosine in patients who consume moderate to high

amounts of alcohol regularly, or are prone to periods of alcoholic binges. The drug should be discontinued if there is clinical evidence of pancreatitis (e.g. increased lipase and amylase).[80]

Lactic acidosis has also been a noted complication of didanosine treatment. Lactic acidosis is a life-threatening reaction and is defined as lactate concentrations exceeding 5 mmol/L, with a blood pH of <7.3 and end organ failure.[56] If the lactate level is > 2 mmol/L, with clinical symptoms reflective of lactic acidosis, the medication should be discontinued and supportive therapy initiated.[80] Moyle *et al*. examined ARV combinations in both cross-sectional and longitudinal models to determine clinical and biochemical correlates of high lactate concentrations. Data revealed that a high number of patients (17.1%; n=152) who used didanosine with stavudine had lactate levels of ≥2.5 mmol/L. During a 29 month treatment period, five patients had lactate levels ≥ 5 mmol/L, and four out of the five were treated with didanosine plus stavudine regimens. Univariate analysis revealed that patients on didanosine containing treatments had significantly higher lactate levels in comparison with patients on non-didanosine regimens. The authors suggested other risk factors including female gender and concurrent illnesses.[81]

Other studies on the use of didanosine have reported an increase in uric acid concentrations,[82] a high incidence of nausea, vomiting, abdominal pain and frequent stools.[83] Nausea and diarrhea were often severe enough for patients to discontinue treatment.[83] However, these symptoms may be more related to the antacid buffer co-administered with the Videx® product used when the studies were performed. Fortunately, didanosine is not thought to be as significant an agent as stavudine in causing lipoatrophy.[84]

2.5.6 Lamivudine/Emtricitabine

Lamivudine and emtricitabine are cytosine analogues and both are similar in structure with the exception of a fluorine group on the chemical structure of emtricitabine. The only clinical difference between the two agents is that the addition of the fluorine group to lamivudine allows for a longer half ≥life. Both agents are generally well tolerated and have similar side effect profiles. Trials comparing lamivudine and emtricitabine have reported frequently occurring ADRs such as: nausea, increased appetite, headache, rash and dry skin. Most of the adverse events and laboratory abnormalities were rated as Grade 1 – 2. Emtricitabine has also been shown to cause asymptomatic hyperpigmentation of the palms and soles.[85-86] In clinical practice, both lamivudine and emtricitabine are considered well-tolerated antiretrovirals, and prevention or treatment of side effects should be considered on an individual basis.

2.6 NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Non-nucleoside reverse transcriptase inhibitors bind directly and non-competitively to HIV-1 reverse transcriptase and block RNA-dependent DNA polymerase activities. Nevirapine and efavirenz are used in clinical practice much more frequently than delavirdine (due mostly to thrice daily dosing and multiple drug interactions). Class-wide side effects include rash and hepatotoxicity.

2.6.1 Dermatologic Adverse Reactions due to NNRTIs

Rash is the most frequently reported adverse event of the NNRTIs. Carr *et al*. reported the following incidences of rash: nevirapine (17%), efavirenz (10%) and delavirdine (18%). Rash of moderate-severe or severe occurred in 6-8% patients taking nevirapine and 0.3% of the subjects experienced SJS. A small number of subjects who developed grade 3-4 rashes had been treated

with delavirdine (4%) and efavirenz (0.7%). Severe rashes led to drug discontinuation in 7% of nevirapine users, 4% of delavirdine users, and 2% of patients treated with efavirenz.[43] A separate study that compared efavirenz-based regimens, indinavir-based regimens and a combination of both showed a 34% incidence of rash in the efavirenz groups, versus 18% for those taking indinavir (p=ns). However, none of the reported rashes were considered severe and symptoms lasted an average of 14 days.[87] The trial conducted by Martinez and colleagues investigated outcomes of substitution of their PI for one of the following study medications: nevirapine, efavirenz or abacavir.[88] Patients who were stable on a PI regimen were randomized to a change in their PI drug to one of the study medications. Overall, NNRTIs had a significantly higher incidence of ADRs (54%; n=155 on nevirapine and 57%; n=156 on efavirenz) when compared to abacavir, causing more patients to withdraw from the study. More severe, cutaneous adverse events were observed in the nevirapine group when compared to the efavirenz group; as a result, more subjects discontinued nevirapine treatment than those taking efavirenz.[88] Independent risk factors for development of cutaneous reactions include female gender, CD4 cell counts < 100 cells/mm3 and age > 40 years.[43]

Prevention of nevirapine-induced rash, with the antihistamine, cetirizine, was tested in a 12 week, randomized, double-blind, placebo-controlled trial by Launay *et al*., and was found to be ineffective.[89] A study by Knobel *et al*. investigated short-term prednisone use as a means of preventing a nevirapine-associated rash, and this was also found to be ineffective.[90] Currently, only nevirapine has manufacturer's recommendations for the prevention of rash, and this involves a dose escalation at initiation of therapy (start at 200 mg daily for two weeks, then increase to 200 mg twice daily thereafter).[91] Treatment of mild to moderate rash depends upon symptomatic presentation and includes antihistamine and/or corticosteroid agents; treatment of

more severe rashes would also include discontinuation of the drug. Patients who present with rash should have liver function tests performed, because rash and hepatotoxicity may occur simultaneously.[92] Patients with severe rash or SJS should seek immediate medical attention for proper treatment.

2.6.2 Hepatotoxicity

Hepatotoxicity is also a very frequently reported side effect of the NNRTIs. The initiating mechanism for development of liver toxicity with NNRTIs is thought to be a hypersensitivity reaction. Idiosyncratic and immune-mediated hypersensitivity reactions can lead to hepatocellular necrosis, cholestasis, liver tissue eosinophilia, and hepatoparenchymal and periportal infiltration with lymphocytes and plasma cells.[93] Hepatotoxicity is usually seen during the first two to three months of therapy.[94] In addition to NNRTI treatment, other risk factors may contribute to liver damage such as concurrent PI use, preexisting liver disease[90, 93] co-infection with Hepatitis B and/or C,[90, 93, 95] and elevated baseline ALT levels (normal levels: 5 to 40 IU/dL).[94] The rate of development of hepatotoxicity is variable among NNRTIs. Kontorinis *et al*. described occurrences of liver toxicity among NNRTIs in a meta-analysis of 21 studies. A 10.8% (n= 65) incidence of grade 3 and 4 hepatotoxicity occurred with efavirenz regimens, 8.9% (n= 594) in nevirapine treatment groups, and 3.6% (n=137) among delavirdine users.[54] A prospective cohort study of 620 subjects showed that 31% of subjects on nevirapine-containing regimens had a > 3 fold increase in at least one liver function test from baseline. Commonly seen abnormalities were, a >3-fold increase in GGT (29%), ALT (10.8%), total bilirubin (2.1%) and alkaline phosphatase (1.3%). Of all the subjects in the study, 12.5% met the criteria for hepatotoxicity; 2.1% of subjects discontinued nevirapine because of liver damage; six were asymptomatic and seven developed clinical hepatitis.

Asymptomatic patients had AST and ALT enzyme levels in the range of 210-443 and 233-478 mg/dl, respectively. Subjects with clinical hepatitis had AST and values in the range of 266-1079 mg/dl and ALT values in the range of 272-996 mg/dl.[94] In a prospective observational study reviewing subjects receiving an NNRTI for at least 45 days, Sulkowski *et al*. reported higher incidences of liver toxicity with nevirapine than with efavirenz (15.6% vs. 8%, RR 1.9; 95% CI, 1.2-3.1). Median treatment duration prior to hepatotoxicity detection was 137 days with nevirapine and 100 days with efavirenz.[95]

Early identification of liver toxicity is more appropriate than preventing or treating liver failure. Liver function tests need to be evaluated at baseline. In patients with normal transaminase levels, liver tests should be performed every month for the first three months of NNRTI treatment, and then every three months if levels remain normal. In patients with liver enzyme abnormalities, transaminases should be checked every two weeks; once stable, transaminases should be monitored every month.[93] Most clinicians use nevirapine or efavirenz cautiously in patients with chronic viral hepatitis or heavy alcohol use. Treatment of hepatotoxicity includes the withdrawal of the offending agent when ALT and/or AST increases to >5-10 ULN, followed by supportive care until the enzymes normalize.[36]

2.7 NNRTI Drug Specific Adverse Events

2.7.1 Nevirapine

Recent FDA revisions have released a Public Health Advisory notice for nevirapine warning patients and providers not to initiate nevirapine in women with CD4 cell counts above 250 cells/mm3 or men with CD4 cell counts above 400cells/mm3. Nevirapine-related deaths due to hepatotoxicity have been reported to the FDA's Medwatch programme prompting these

warnings. The notice also describes symptoms that may alert one to possible liver damage.[96] The incidence of hepatotoxicity and rash, and their prevention and/or treatment, are discussed above.

2.7.2 Efavirenz

Certain central nervous system (CNS) side effects are unique to efavirenz. Several studies have observed some or all of the following CNS side effects more commonly with efavirenz than with comparator arms: insomnia, dizziness, light-headedness, nervousness, irritability, impaired concentration, abnormal/vivid dreaming, and hallucinations.[87, 97-99] Efavirenz-related CNS side effects have been shown by different groups to last for a median of 13 days, with a range of 1-116 days.[87, 97] CNS symptoms usually decrease within two to four weeks. Administration of efavirenz at bedtime may help reduce the impact of some side effects on patient's daily lives. Elimination of alcohol and close attention to psychoactive medications may also decrease CNS abnormalities.[36] Other psychiatric symptoms (including severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behavior, paranoid reactions, and manic reactions) have been reported among patients using efavirenz. Injectable drug use, a history of psychiatric disorders, and receipt of a psychiatric medication have been shown to be correlated with these symptoms. Therefore, the association between these severe psychiatric symptoms and efavirenz use is unclear; and is it not known if initial CNS events are precursors to other psychiatric symptoms.[100]

2.8 PROTEASE INHIBITORS

The class of antiretroviral agents that first had a large impact on treatment outcomes of people with HIV infection was the protease inhibitors. While the effects of the PIs on wild-type virus are quite dramatic and can last for long periods (when combined with 2 NRTIs), side effects

often limit the long-term tolerability of these agents. Thus, management of these side effects is essential for optimal outcomes in patients. All PIs appear to be associated with some risk of lipodystrophy, hepatotoxicity, hyperglycemia, increased bleeding episodes among patients with hemophilia, GI disturbances (e.g. nausea, vomiting, and diarrhea) and lipid abnormalities.[36] The four most common class-wide side effects are GI complaints, lipid abnormalities, hyperglycemia, and lipoaccumulation. It is important to note, however, that atazanavir is less likely to cause GI disturbances and metabolic side effects compared to the other PIs.

2.8.1 Gastrointestinal Effects

Diarrhea is a common and often inadequately treated complication in patients with HIV infection. The Centers for Disease Control and Prevention (CDC) defines chronic diarrhea as an average of > 2 loose or watery stools per day for > 1 month. Acute diarrhea can be defined as > 3 loose or watery stools for three to ten days. Since PIs were first marketed, chronic diarrhea has been a common complaint. The incidence of diarrhea associated with specific PIs is: amprenavir 33%-56%, nelfinavir 14%-32%, ritonavir 12.8%-21.6%, saquinavir 12.3%-19.9%, and indinavir 0-4.6%.[100]

Atazanavir has an incidence of 1-3%,[101] and fosamprenavir has an incidence of 5-13%.[102] In a retrospective cohort study, lopinavir/ritonavir actually had significantly less diarrhea when compared to nelfinavir[103]; yet, for both drugs diarrhea is listed in the package insert as the most common side effect.[104-105] Clinically, it is common for a given patient to have varying degrees of diarrhea with different PIs. The incidence of diarrhea is typically greatest during the early stages of treatment. In general, the following caveats should be considered when patients are initiating protease inhibitor therapy.

Full dose ritonavir is poorly tolerated due to diarrhea (as well as flatulence, bloating and nausea). When first released, dose escalation of ritonavir was recommended to minimize the impact of diarrhea. However, currently, most patients receiving ritonavir are on low doses (as when being used to boost the levels of other PIs). Even so, some patients are remarkably sensitive to ritonavir and cannot even tolerate doses as low as 100-200 mg per day. Diarrhea from amprenavir is likely augmented by the vitamin E component in the capsules; however, the prodrug of amprenavir (fosamprenavir) does not contain vitamin E. The incidence of diarrhea with fosamprenavir (with and without low dose ritonavir) appears to be less than nelfinavir and less than amprenavir without ritonavir; yet, similar to lopinavir/ritonavir.[106-108] The manufacturer's package inserts for both the hard and soft gel formulations of saquinavir (Invirase® and Fortovase®, respectively) list the incidence of diarrhea based on the Fortovase® formulation.[109-110]

Diarrhea associated with the use of PIs can be managed in several ways, including with over-the-counter (OTC) remedies and prescription medications (i.e. atropine with diphenoxylate, contained in Lomotil® or Lonox®). OTC management for diarrhea includes loperamide 4 mg, then 2 mg with every loose stool, up to 16 mg per day. Other treatment options less studied include calcium 500 mg twice daily,[111] psyllium 1 teaspoonful or 2 bars daily, or oat bran 1500 mg twice daily. Pancreatic enzymes, 1-2 tablets or capsules with meals, may also be used.[100]

2.8.2 Metabolic Changes

Most protease inhibitors are well know to increase triglycerides and cholesterol,[112] as well as insulin resistance (with resulting hyperglycemia),[113] and lipoaccumulation.[114] The proposed mechanism of PI-induced peripheral lipodystrophy, hyperlipidemia, central obesity, breast hypertrophy, and insulin resistance is multifaceted. One mechanism may involve altered binding of retinoic acid within the cytochrome enzyme system, resulting in a redistribution of lipids from

peripheral adipocytes. These lipids either remains within the circulatory system causing hyperlipidemia, or is deposited into visceral adipocytes.[115] Another possible cause is drug effects on lipoprotein-receptor related protein (LRP). LRP is important for post-prandial chylomicron clearance, as it permits free fatty acids to be stored as fat. Inhibition of this protein may increase circulating lipids contributing to abnormal lipid levels and insulin resistance.[116]

2.8.3 Alteration of lipid profiles due to PIs

An increased risk of cardiovascular disease associated with HAART was initially assumed based on serum lipid changes. The most comprehensive study of serum lipid changes is an observational study of 11 HIV cohorts with data including over 20, 000 HIV-infected patients in 188 clinics. The initial results based on analysis of 17, 852 patients showed both NNRTIs and PIs caused increases in triglyceride and total cholesterol levels.[112] Grinspoon and Carr, in their review of ARVs and cardiovascular disease, concluded that there is an increased risk of heart disease among patients on HAART.[117] A change in blood lipids is an important concern with HAART, due to the potential for premature atherosclerosis and coronary artery disease.[112] With PI-based HAART, there are often increases in triglycerides, total cholesterol, and LDL cholesterol.

The effect of PIs on HDL is not fully understood; some trials have demonstrated no changes from baseline while others have reported an increase.[118-120] To complicate matters further, a review by Penzak and Chuck concluded there was a decrease in HDL levels as a result of PI use.[121] Triglyceride levels may increase to more than 1000 mg/dL. These levels are associated with an increased risk of both pancreatitis and atherosclerosis. Total cholesterol and LDL cholesterol levels may increase an average of 30 mg/dL, however, there is substantial individual variation.[122-123]

All PIs have this effect; with the exception of atazanavir, which typically results in little or no increase in lipids from baseline. Rates of hyperlipidemia with fosamprenavir and saquinavir are lower compared to the other PIs. The most profound effects are seen with ritonavir, and this is dose dependent. These changes are usually apparent within two to three months of initiating therapy.[112] Hypertriglyceridemia appears more frequently with the use of full dose ritonavir-based regimens compared to indinavir and nelfinavir-based regimens.[123] Conversely, mild to moderate hypercholesterolemia is more common among subjects who receive ritonavir and nelfinavir than indinavir. Slight to no anomalies of serum lipid levels are usually observed during treatment with saquinavir compared with indinavir, ritonavir, and nelfinavir.[124] Increased cholesterol and triglyceride levels have been reported in healthy, HIV negative volunteers receiving ritonavir for two weeks, confirming a direct effect of ritonavir on lipid levels.[125]

A baseline assessment should consist of fasting lipid profile, including total cholesterol, LDL, HDL, and triglycerides. Fasting is necessary for accurate measurement of triglycerides and the calculation of LDL cholesterol; however, LDL cholesterol measurements are unreliable when triglyceride levels exceed 400 mg/dL regardless of the fasting state. The lipid profile should be repeated at 3 to 4 months, and then as needed (at least once per year). Therapeutic lifestyle modifications (such as diet, exercise, and smoking cessation), treatment of hypertension and/or diabetes, and weight loss (for obese patients) should be recommended when triglycerides exceed 400 mg/dL, cholesterol is great than 240 mg/dL, and HDL is less than 35 mg/dL.[126-127]

Therapy for hyperlipidemia includes 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (often referred to as “statins”), fibrates, nicotinic acid derivatives, bile acid sequestrants, and cholesterol absorption inhibitors. Treatment with HMG-CoA reductase inhibitors appears to be more effective at reducing cholesterol while fibrates appear more

effective at lowering triglycerides. Due to potential drug interactions and combined toxicities, clinicians should be cautious regarding the use of HMG-CoA reductase inhibitors with PIs.

Pravastatin is not extensively metabolized by the cytochrome P450 system; therefore, it is less affected by PI-induced enzyme inhibition. Atorvastatin is partially metabolized by the cytochrome P450 system, but is still relatively safe in combination with PIs. Although no specific dosing recommendations are available, the manufacturer recommended initial dose of atorvastatin at 10 mg daily, with dose escalation until desired lipid effects, should be used, with the understanding that a lower final dose will most likely be required because of the drug interaction.[128] Treatment with fibrates alone may be effective in lowering triglycerides, and the drugs can be combined with HMGCoA reductase inhibitors if lipids are not adequately lowered with either agent alone.[126] The use of cholesterol absorption inhibitors has not been reported in HIV positive patients sufficiently enough to recommend its use in this population. Finally, there are no published studies that have examined the use of newer HMG-CoA reductase inhibitors including rosuvastatin.

2.8.4 Hyperglycemia

The development of insulin resistance is common with PI-based HAART. Insulin resistance has been noted in 30% to 90% of patients treated with PIs, and overt diabetes occurs in 1% to 11%, with a mean of approximately 7% at five years.[113] Changes in blood glucose are usually apparent within 2 to 3 months and can be detected with a fasting blood glucose level. With indinavir, insulin resistance has been detected following a single dose.[129] Comparative data with other PIs are not available. The role of PIs in causing glucose intolerance has been clearly established; however, it is not clear if all PIs are equally implicated.[36] Random blood glucose, fasting blood glucose, and Hemoglobin A1c measurements are insensitive methods to measure insulin

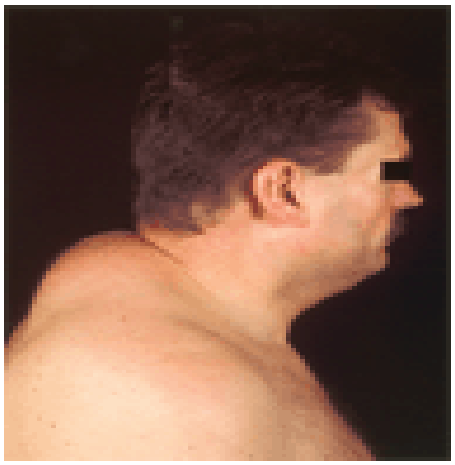
resistance, due to compensatory increases in insulin. PI-treated patients with normal fasting blood glucose levels may have severe insulin resistance as demonstrated by glucose clamp techniques.[130] The 2004 DHHS and IASUSA guidelines recommend fasting blood glucose levels at baseline and at 3 to 6 month intervals in PI-treated patients. Additional measurements may be needed based on initial results and diabetes risk.[36, 131] Aggressive testing may include fasting insulin levels, C-peptide levels, and oral glucose tolerance testing for those with borderline fasting glucose levels (110-126 mg/dL).[36] American Diabetes Association guidelines are recommended for the management of diabetes.[54] Most cases involve type II diabetes and can be managed with diet and exercise. One's daily diet should consist of 50% to 60% carbohydrates, 10% to 20% protein, and <30% fat, with <100 mg cholesterol per day and <10% of total calories from saturated fat. When drug therapy for hyperlipidemia is necessary, the two major classes of agents that are beneficial include sulfonylureas and insulin sensitizing agents such as metformin and thiazolidinediones. Metformin and thiazolidinediones have the potential advantage of improving insulin resistance and decreasing visceral fat accumulation with a possible reduction in cardiovascular risk.[132] However, caution must be taken when combining metformin with NRTIs that have a propensity for lactic acidosis. Hadigan *et al.* did not report any incidence of lactic acidosis when metformin was used to treat insulin resistance[133]; but, one case report described a fatality as a result of this drug interaction in a 52 year old male with advanced HIV disease who was being treating with didanosine, stavudine and tenofovir and was started on metformin for new onset diabetes.[134]

2.8.5 Lipoaccumulation

Lipodystrophy has been reported in 20% to 80% of patients receiving antiretroviral therapy. A meta-analysis of 5 studies with 435 HAART recipients reported fat accumulation in 17% to 67%

of subjects. Fat accumulation (lipoaccumulation) can be seen within the abdominal cavity ("Crixybelly" or "protease paunch"), the upper back (dorso-cervical fat pad or "buffalo hump" Figure 3), the breasts (gynecomastia), and irregularly in subcutaneous tissue (peripheral lipomatosis).

Fig 2.3: Buffalo hump: due to hypertrophy of subcutaneous fat in the nape of the neck in lipodystrophy syndrome in an HIV patient during treatment with the boosted protease inhibitor lopinavir.



Lipoaccumulation is primarily associated with PI use, with an odds ratio in case-controlled studies of 2.6 to 3.4.[114] Various treatment options are available. Low fat diet and aerobic exercise are more effective in preventing than treating fat accumulation. Testosterone replacement therapy (in hypogonadal men) or anabolic steroids (in eugonadal men) may be beneficial in cases of fat accumulation. In combination with resistance exercise, these steroids may increase muscle mass, which may help to compensate for lipoatrophy involving the limbs. Growth hormone (6

mg/kg/day injected subcutaneously) may reduce fat accumulation but the benefits fade after treatment is discontinued.[135] Disadvantages include high costs and side effects (such as hyperglycemia, further loss of subcutaneous fat, and the need for maintenance treatment). Metformin (500 mg twice daily) improves insulin sensitivity and results in weight loss and decreased intra-abdominal fat in patients with insulin resistance.[54] Restorative surgery for fat accumulation includes removal of lipomas, breast/fat tissue or dorso-cervical fat pad by either surgery or liposuction and is limited by recurrence.[36]

2.8.6 Ritonavir

In a prospective study by Bonfanti *et al*. comparing the adverse effects of ritonavir, indinavir, nelfinavir, saquinavir and saquinavir/ritonavir, ritonavir clearly emerged as the least tolerated drug with 27.5% of patients stopping treatment after six months and 36% after one year.[136] Included among the side effects that can occur are allergic reactions consisting of urticaria, mild skin eruptions, bronchospasms and angioedema; or, in rare cases, anaphylaxis and SJS.[136-137] Pancreatitis can also develop, particularly in patients with severe hypertriglyceridemia. GI and neurological problems including diarrhea, nausea, vomiting, anorexia, abdominal pain, taste perversion, and paresthesias have also been reported.[137]

Ritonavir has been shown to increase transaminase levels. Clinical hepatitis and jaundice have occurred when transaminase levels are > 5x the upper limit of normal (ULN). In a study by Danner *et al*., 6 out of 86 subjects withdrew from therapy due to elevated AST or ALT levels.[138] In another study, by Gisolf *et al*., 18 subjects developed increased transaminase levels; however, the majority of these subjects had their AST and ALT concentrations decline by over 50% while still on treatment. The authors concluded that while co-infection with Hepatitis B is an important risk factor for transaminitis, it is possible to continue treatment in these patients without

worsening hepatotoxicity.[139] Coinfection with Hepatitis B or C increases the likelihood of developing elevated transaminase levels. As such, it is recommended to obtain baseline liver function tests and closely monitor for signs and symptoms of hepatic impairment.[137]

Even at low doses, ritonavir has been shown to elevate total cholesterol and triglycerides.[138] In an open-labeled study comparing amprenavir versus amprenavir plus ritonavir, hypertriglyceridemia occurred in 11% of the patients in the amprenavir + ritonavir arm versus none in the amprenavir only arm. However, the increase in serum triglyceride levels rarely required adding an antihyperlipidemic agent or cessation of PI therapy.[140] Studies have shown that cholesterol can increase by 30-40% and triglycerides by 200-300% above baseline while on ritonavir treatment.[138] Preventive measures include obtaining a baseline fasting lipid panel before starting treatment, and periodically while on ritonavir.[137] Paresthesia is another reported side effect of ritonavir, with a possible dose-effect relationship. In an open-labeled study comparing amprenavir (1200 mg) verses amprenavir (600 mg) boosted with ritonavir (100 mg), oral and perioral paresthesias occurred more commonly in subjects receiving low dose ritonavir. Higher proportions of paresthesias have been seen in previous studies that used full dose ritonavir (600 mg twice daily).[137, 140]

2.8.7 Lopinavir/ritonavir

The most frequently reported adverse events are gastrointestinal, particularly diarrhoea. The most commonly noted laboratory abnormalities are elevations in lipid profiles and, less commonly, hepatic transaminases. Overall, lopinavir/ritonavir is relatively well tolerated, with low reported rates of drug discontinuation due to side effects in clinical trials. In antiretroviral-naive patients, the most common adverse effects associated with lopinavir/ritonavir are diarrhoea, nausea and abnormal stools.[141-143] Discontinuation rates as a result of adverse events

were 2% or less in these two trials. In the longest study of lopinavir/ritonavir to date, 28% of patients reported diarrhea of at least moderate severity at some time through week 312.[144] In the study comparing once- and twice-daily dosing of lopinavir/ritonavir, the incidence of diarrhoea was increased among patients receiving once-daily dosing.[145] Similar adverse event profiles have been seen in antiretroviral-experienced patients, with diarrhoea being the most frequently reported adverse event of moderate or greater severity.[146-147]

Lipid elevations are the most common laboratory abnormalities associated with lopinavir/ritonavir treatment. In registrational trials, grade III/IV elevations in total cholesterol and triglycerides were reported in ≈10% of antiretroviral-naive patients during the first 48 weeks of therapy.[141, 143] Mean increases in total cholesterol were 49–53 mg/dL and in triglycerides 111–125 mg/dL. In antiretroviral-naive patients receiving lopinavir/ritonavir for over 6 years, 23% developed grade III/IV elevations in total cholesterol, and 26% in triglycerides.[144] Similar results were seen in protease inhibitor-experienced patients.[147] In both patient populations, subjects with elevations at baseline were more likely to experience grade III/IV elevations during the course of the study. While the trials mentioned above involved samples that may not have been obtained in the fasting state, some studies have been specifically designed to assess lipids measured under fasting conditions. Martinez et al.[148] examined the impact of 6 months of lopinavir/ritonavir therapy on metabolic parameters in 353 HIV-infected patients, the majority of whom had received therapy with other protease inhibitors previously. During the follow-up period, significant increases in triglyceride levels and total cholesterol were observed. Elevated total cholesterol and triglycerides before study entry as well as the use of lipid-lowering medications at baseline were independently associated with the results. Similar results were seen in a cohort of antiretroviral-naive patients.[149] All available data indicate that increases in lipid profiles tend

to occur within the initial months of therapy, and reach a plateau thereafter. In one study of antiretroviral-naive patients, lipodystrophy was reported in 13% of patients through week 312.[144] This side effect (which remains relatively poorly characterized) has not been rigorously studied in other clinical trials, mainly because this complication was not widely recognized at the time the studies were designed.

Although protease inhibitors have been associated with the development of insulin resistance, significant increases in fasting glucose levels have not been reported in patients treated with lopinavir/ritonavir.[148] Asymptomatic elevations in hepatic transaminases have also been noted in persons treated with lopinavir/ritonavir. Grade III/ IV elevations have been reported in 5–8% of antiretroviral-naïve patients receiving lopinavir/ritonavir in the first year of therapy, and in 11% of patients over 6 years of therapy[141, 143-144] Similar results were observed in antiretroviral-experienced patients.[146] Over time, these elevations tended to normalize, and few patients discontinued therapy due to hepatic inflammation. Patients with transaminase elevations at baseline are more likely to experience elevations while receiving therapy with lopinavir/ritonavir. Concomitant infection with hepatitis B or C also appears to increase the risk of transaminase elevation, but does not increase the risk of hepatotoxicity.[141, 150-152]

2.9 Methods of Monitoring for ADRs

Broadly speaking there are three major methods of monitoring:

- Cohort event monitoring
- Spontaneous reporting
- Special phase IV studies.

If cohort event monitoring is selected as the principal means of monitoring, there are distinct advantages to encouraging spontaneous reporting as well. It should be seen as an option for reporting in the programme and reporting cards should be made widely available whether or not a spontaneous reporting programme is in existence. If a pharmacovigilance system is already operational, the same reporting card should be used and these cards should be processed in the established way, the information being channeled to the HIV/AIDS programme by the pharmacovigilance centre.

2.9.1 Cohort event monitoring

Cohort event monitoring is often referred to as prescription event monitoring (PEM), but this terminology is inappropriate where individual prescriptions with subsequent dispensing are not part of the process. Examples of users of this methodology are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and PEM run by the Drug Safety Research Unit in England. A similar method is being used successfully in China to monitor contraceptives and includes monitoring in rural areas. Cohort event monitoring is an adaptable and powerful method of getting good comprehensive data. It is essentially a phase IV study. There are two basic requirements for the collection of data for cohort event monitoring:

- establishing a cohort of patients for each medicine and/or medicine combination;
- Recording adverse events for patients in the cohort(s) for a defined period.

2.9.2 Spontaneous reporting

Methodology

A spontaneous report is an unsolicited communication by health care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Spontaneous reports play a major role in the identification of safety signals once a medicine is marketed. Spontaneous reports can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs.

Spontaneous reporting is dependent on encouraging clinicians and other health professionals to report details of suspected adverse reactions in patients on ARV treatment. Under-reporting is a serious problem with this method, but reporting can be intensified in selected units e.g. hospitals.

There is no standard global reporting form for spontaneous reports as the needs of countries differ and it is important that they are involved in developing their own form. The Medicines Control Authority of Zimbabwe form is shown in Appendix 2. The completed reports can be mailed individually or in bulk, faxed, sent electronically (if forms are available on the Internet or by email) or reports can be made by telephone. If a national pharmacovigilance system is in place, then consideration should be given to using the reporting form already in use or adapting it as necessary.

Health professionals will need advice on what types of suspected adverse reactions to report. Most pharmacovigilance programmes request reports of all serious events (which include death) and fetal abnormalities and in addition, all suspected reactions to new medicines. In general, deaths are very poorly reported. The special requirements for ARV monitoring would need to be

specified e.g. those reactions that affect adherence; reactions of special interest; all suspected reactions in children.

All spontaneous reports should first be sent to the pharmacovigilance centre in the country for evaluation (MCAZ). The processing of data will be the same as for cohort event monitoring. Spontaneous reporting for ARVs should be integrated with the national pharmacovigilance programme and regarded as an ongoing monitoring method continuing after any special studies are completed.

The reports should then be forwarded to the WHO Collaborating Centre for International Drug Monitoring for entry into a global database that uses systematic methods for the detection of safety signals from spontaneous reports. These methods include the use of Bayesian Confidence Propagating Neural Networks (BCPNN) and other techniques for signal detection. Data-mining techniques should always be used in conjunction with, and not in place of, analyses of single case-reports. Data-mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. Confounding factors that influence reporting of spontaneous adverse events are not removed by data-mining. The results of data-mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate for different medicines and countries and the many potential biases inherent in spontaneous reporting. All signals should be evaluated while recognizing the possibility of false-positives. In addition, the absence of a signal does not mean that a problem does not exist.

2.9.3 Comparative advantages and disadvantages of the monitoring methods

Cohort event monitoring

Advantages

- It has the ability to produce rates.
- It enables the production of a complete adverse event and/or adverse reaction profile for the medicines of interest.
- It is very effective in identifying signals at an early stage.
- Reactions can be characterized in relation to age, sex and duration to onset and thus produce risk factors. Other relevant data may be collected, such as weight, or co-morbidity, to enable other risk factors to be determined.
- It enables accurate comparisons to be made between medicines.
- It allows a pregnancy register to be established; this can be used to define and calculate rates of any abnormalities.
- The routine follow-up enables confident detection of reduced or failed therapeutic effect and thus raises suspicion of inaccurate diagnosis of disease, programme failure, or poor quality or counterfeit medicines.
- It enables details of all deaths to be recorded and examined and provides rates of death.
- It has the ability to produce rapid results in a defined population.
- It enables the collection of comprehensive and near-complete data that will provide for the special needs of the programme including effects in pregnancy, specific toxicities and safety in children.

- Because the method looks intensively at new medicines of great interest in a specific area of need, and provides clinically significant results rapidly, it stimulates interest in medicine safety in general.
- The method provides sound evidence with which to deal with any medicine scares.

Disadvantages

- This method is more labour intensive and more costly than spontaneous reporting.
- It will be new to most health professionals and pharmacovigilance centres.

Spontaneous reporting

Advantages

- It is administratively simpler and less labour intensive than cohort event monitoring.
- It is less costly.
- It is the method most commonly used in pharmacovigilance.
- National pharmacovigilance centres and health professionals (to a certain extent) will be familiar with the method.

Disadvantages

- The data are incomplete. In developed countries less than 5% of reactions are reported. A report from the WHO filariasis programme suggests that reporting compliance in resource-poor countries is much less than this, leaving many unanswered questions.
- Reliable rates cannot be calculated and therefore risks cannot be measured and risk factors cannot be established with confidence.

- There are strong biases in reporting.
- Deaths are poorly reported.
- Special studies will need to be set up to collect accurate information on areas of particular interest e.g. pregnancy, children and the elderly. These special studies add to the overall cost and reduce the cost advantage of spontaneous reporting.

2.10 The Zimbabwe ARV roll-out programme

In May 2002, the government of Zimbabwe declared the lack of access to ART, an emergency. The country also adopted the global 3 by 5 initiative (providing ART services to 3 million people globally by end of 2005). Initially the national 3 by 5 target which was calculated using the disease burden was to provide at least 171 000 patients with ARVs by year 2005. This however was revised to a new target of reaching 60 000 patients based on resource availability. However by the end of 2005, only 25 000 PLWHA were on ART, leaving as many as 319 000 in need. The government has made considerable efforts towards preparation for scaling up access to treatment. By end of 2005, over 50 sites in all provinces had been assessed for the provision of ART services, with 48 sites already providing them.

The Ministry of Health and Child Welfare (MOHCW) introduced the OI/ART programme in April 2004 and 'Plan for the Nationwide Provision of ART' was finalized in December 2004 covering the period (2005-2007).[153-154] As part of its strategy to scale-up OI/ART services towards universal access in 2010, the MOHCW commissioned a review of the OI/ART programme.[155] According to the 'Review of the National HIV and AIDS Treatment and Care Programme (OI/ART) 2004-2007, ART coverage increased from about 5,000 to over 100,000 (29%) by December 2007. Findings of this review contributed immensely to the development of the 'Plan for the Nationwide Provision of Antiretroviral Therapy 2008-2012.[156] A number of key

players support the implementation of the policy and strategies espoused by the national pharmaceutical body, NatPharm. In particular UNICEF, United States Government (USG), Clinton Foundation, and NAC procure the ARV drugs. Once the drugs are procured and arrive in the country, NatPharm delegates the distribution of the drugs to MoHCW AIDS and TB Logistics Sub-Unit (LSU), which was set up by the JSI/DELIVER project. The numbers of adults and children accessing ART were 148 144 (39.7%) in December 2008 and 215 109 (56.8%) in November 2009.[157] Guiding the scale up of paediatric ART is the detailed plan for Pediatric HIV and AIDS care that was finalized in the last quarter of 2006. Meanwhile, the number of children accessing ART was 8 627 (24.8%) in 2007, 13 287 (38.7%) in 2008 and 20 003 (57.1%) in 2009.[158] The trend observed above was mainly attributed to the scale up and decentralization of the OI/ART programme associated with an increase in OI/ART initiation and follow up as well as training of healthcare workers. Generally, funding gaps have been a hindrance in terms of Zimbabwe achieving universal access to OI/ART.

The Government made efforts to subsidize local manufacture of ARVs through provision of foreign currency for purchase of raw materials and waiver of duty on raw materials for local production of ARVs and imported ARVs in 2008. Consequently, the supply of ARVs has improved in 2009 with minimal number of sites experiencing drug stock outs.

2.11 Summary

ART remains the cornerstone of managing HIV. Strategies need to continue to be developed for ensuring that patients receive optimum benefit from their therapy. While adverse drug reaction profiles of a vast number of antiretroviral drugs have been characterized significantly in developed country settings, the developing country systems need to increase and sustain their

own vigilance programmes for monitoring and detecting ADRs in patients who are on ART. Since ART is life-long therapy and ADRs are a barrier to good adherence to therapy, there is need for increased generation of appropriate knowledge on these ADRs.

CHAPTER 3: AIMS AND OBJECTIVES

3.1 Aim

To determine the rate, nature & predictors of adverse drug reactions associated with the use of HAART in a resource limited setting.

3.2 Specific objectives

1. To implement a 3-step approach for the qualitative assessment and confirmation of adverse drug events in a resource limited setting.
2. To determine the rate (incidence) of the toxicities associated with HAART in the Zimbabwe government ARV rollout programme.
3. To determine the nature (severity) of the Adverse Drug Reactions due to HAART in the ARV rollout programme.
4. To identify and determine which factors may influence (Age, gender, race, duration of therapy, level of nutrition, existing OIs, concurrent drug therapies, use of recreational drugs, use of herbs, any chronic ailments and adherence to medication) the rate and severity of adverse drug reactions.

3.3 Justification for the study

There is considerable experience in the developed world with the use of antiretroviral medicines (ARVs). They are associated with significant safety concerns including serious adverse reactions to medicines (ADRs), with both short- and long-term effects. The outcome of these long-term adverse effects is unknown. The reactions include altered body fat distribution (lipodystrophy), hypersensitivity reactions, hepatic disorders, acute pancreatitis, muscle damage (myopathy) of

the newborn and lactic acidosis. These and other reactions may damage confidence in any national ARV programme and affect patient adherence. With the erosion of confidence in the safety of medicines and of the programme, patients may stop taking these life-prolonging medicines leading to problems for themselves and for society as a whole. Poor adherence is known to lead to failure of therapy in the patient (he or she will not get well and may die) and development of resistance by the virus leading to reduced efficacy of these life-prolonging medicines.

Little is known about the toxicity profile of ARVs in developing countries. These countries have special factors and conditions that are very different from those of the developed world and medicine use and safety may therefore vary considerably. The relevant factors and conditions include the existence of comorbid conditions such as tuberculosis (TB), malaria and other infections; malnutrition; heavy reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; abuse of prescription-only medicines; and likelihood of medicine interactions. In addition, the local systems for the delivery of health care will rely on people who may not have the necessary training, knowledge or expertise, and medicine regulatory systems are either nonexistent or are not adequately equipped to deal with medicine safety issues.

The monitoring of ARVs in these populations is therefore of paramount importance, and methods of monitoring are the subject of this study.

CHAPTER 4: METHODOLOGY

4.1 Research Design

This was a cross sectional descriptive study carried out in HIV positive patients as part of implementation science within the pharmacovigilance programme at the Family Care Centre (Outpatient opportunistic infections clinic at Parirenyatwa Hospital, Harare, Zimbabwe). The study was designed to achieve two goals:

1) Test a 3-step approach for the qualitative assessment and confirmation of adverse drug reactions in this population.

2) To determine the rate, nature & predictors of adverse drug reactions associated with the use of HAART in a resource limited setting.

4.2 Study site and population

The study was carried out at the Family Care Centre (FCC), ART clinic in Harare, Zimbabwe. The Family Care Centre is part of Parirenyatwa Hospital which is a public and teaching medical facility. The FCC had approximately 6000 HIV positive patients registered to receive care through its facilities. The FCC is integrated into the outpatient department for patients to receive antiretrovirals free of charge and for the treatment of opportunistic infections. The FCC was chosen as it houses 1 of the biggest ART populations and it caters for patients from different sectors in the society. Due to the fact that the FCC is both an initiating and follow-up site it is representative of the population receiving ART services within the national roll out programme in Zimbabwe.

The study was carried out as part of operational research within the pharmacovigilance programme at the FCC. The results reported are for patients who had been on first line or

alternate first line ART for at least 24 weeks. Inclusion criteria were a documented HIV infection in patients ≥ 18 years old on first line or alternate first line HAART for at least 24 weeks. The study was carried out from February 2009 to June 2009. Patients coming to the ART clinic for their scheduled visits during this time were recruited for the study.

4.3 Inclusion criteria

- Documented HIV infection in the patient
- Aged between 18 and 65 years
- Patients taking Stavudine (30 or 40 mg twice daily), Lamivudine 150 mg twice daily and Nevirapine 200 mg twice daily
- Patients who were taking alternate first line therapy:
  - Zidovudine 300 mg + Lamivudine 150 mg + Nevirapine 200 mg
  - Stavudine (30 or 40 mg twice daily) + Lamivudine 150 mg + Efavirenz 600 mg
  - Zidovudine 300 mg + Lamivudine 150 mg + Efavirenz 600 mg
- Patients who have been on HAART for at least 6 months

4.4 Exclusion criteria

- Patients with missing information from their medical records
- Patients with documented adherence less than 95% as sub-optimal adherence could lead to decreased incidence of concentration dependent ADRs.
- HIV negative patients

4.5 Medication and ethical approvals

The first line antiretroviral treatment available through the government roll out programme consisted of a triple fixed dose combination of nevirapine 200 mg, stavudine 30 mg and lamivudine 150 mg twice daily. Alternate first line therapy was available for patients who did not tolerate stavudine and consisted of nevirapine 200 mg, zidovudine 300 mg and lamivudine 150 mg twice daily. For patients concomitantly taking anti-tuberculosis therapy, efavirenz (EFV) 600 mg once daily at night was prescribed instead of nevirapine as per the national guidelines. The ADRs reported were based on evidence-based knowledge of ADRs for specific ARVs allowing a differential approach to identifying the most likely causative drug. Being an operational study, there were no medications given to patients solely for the purpose of this research. Ethical approval of the study was granted by the Joint Research Ethics Committee (JREC) and by the Medical Research Council of Zimbabwe. All participants gave voluntary, written informed consent for inclusion in the study.

4.6 Pilot study

A pilot study was carried out to test whether the questionnaire would be able to identify predictors of ADRs. The questionnaire assessed whether the formulation used by the patient was a predisposing factor to ADRs due to HAART. In the pilot study, every third patient at the FCC pharmacy was selected to receive information about the study and those who consented were interviewed. One hundred and thirty patients were interviewed who were taking stavudine 30 mg or 40 mg, lamivudine 150 mg and nevirapine 200 mg. The patients were required to identify the exact brand name of the generic FDC they were taking and to identify the ADRs that they were experiencing. After conducting this pilot study a preliminary analysis of results was performed to

determine feasibility. The preliminary results were analyzed using the pearson chi-square test to test for any statistical significance in the incidence of ADRs due to the respective generic brands. The data collection procedure was amended so that interviewing was done on every eighth patient instead of every third patient to allow ample time to answer the questionnaire. There was also a need to develop a method to qualitatively assess and ascertain the causality of ADRs. To ascertain causality of ADRs a 3-step approach was developed which would ensure that a qualitative assessment and confirmation of causality can be made.

4.7 3 Step approach and causality assessment

A 3-step approach was used for assessing causality of ADRs caused by HAART. This approach utilized the available tools to collect data on ADRs and have it analyzed by an independent body of professionals that are experienced in ADR assessment. The approach was developed as a hybrid of the current spontaneous reporting system that is used in detecting ADRs. This novel approach for detecting ADRs was being tested for the first time.

Fig 4.1: Flow of information in the 3-step approach and causality assessment

The approach utilized patient charts that were available through the FCC's medical records room. The pharmacist in the pharmacovigilance programme extracted information from the patient charts onto a standardized data extraction form. The data from the medical records was recorded on the Medicines Control Authority of Zimbabwe (MCAZ) adverse drug reaction case

report forms (Appendix 2). These were subsequently sent to the MCAZ for assessment and causality classification. The MCAZ has a panel of experts (Adverse Drug Reaction Committee) that meet to evaluate the case report forms and ascertain causality of ADRs. The ADR committee consented to categorizing the ADRs according to the following causality classification:

i. CERTAIN
    - The event or laboratory test abnormality has plausible time relationship to drug intake.
    - Cannot be explained by disease or other drugs.
    - Response to withdrawal clinically plausible.
    - Event definitive pharmacologically or phenomenologically.
    - Rechallenge if necessary.

ii. PROBABLE/LIKELY
    - The event or laboratory test abnormality has plausible time relationship to drug intake.
    - Unlikely to be attributed to disease or other drugs
    - Response to withdrawal clinically reasonable

iii. POSSIBLE
    - The event or laboratory test abnormality has plausible time relationship to drug intake.
    - Could also be explained by disease or other drugs.
    - Information on drug withdrawal lacking or unclear.

iv. UNLIKELY

- The event or laboratory test abnormality, with a time to drug intake which makes relationship improbable.
- Disease or other drugs provide plausible explanations

v. CONDITIONAL/UNCLASSIFIED

- Event or laboratory test abnormality needs more data for proper assessment.

vi. UNASSESSIBLE/UNCLASSIFIED

- The report suggesting an adverse reaction cannot be judged because of insufficient or contradictory information.
- Report cannot be verified.

This approach was used to determine whether an effective process can be developed to ascertain the incidence of ADRs in a resource limited setting. The results obtained from using this 3-step approach were then compared to incidences obtained from other settings that used various pharmacovigilance techniques. The 3-step approach was developed for resource limited settings as it uses structures that are already in existence.

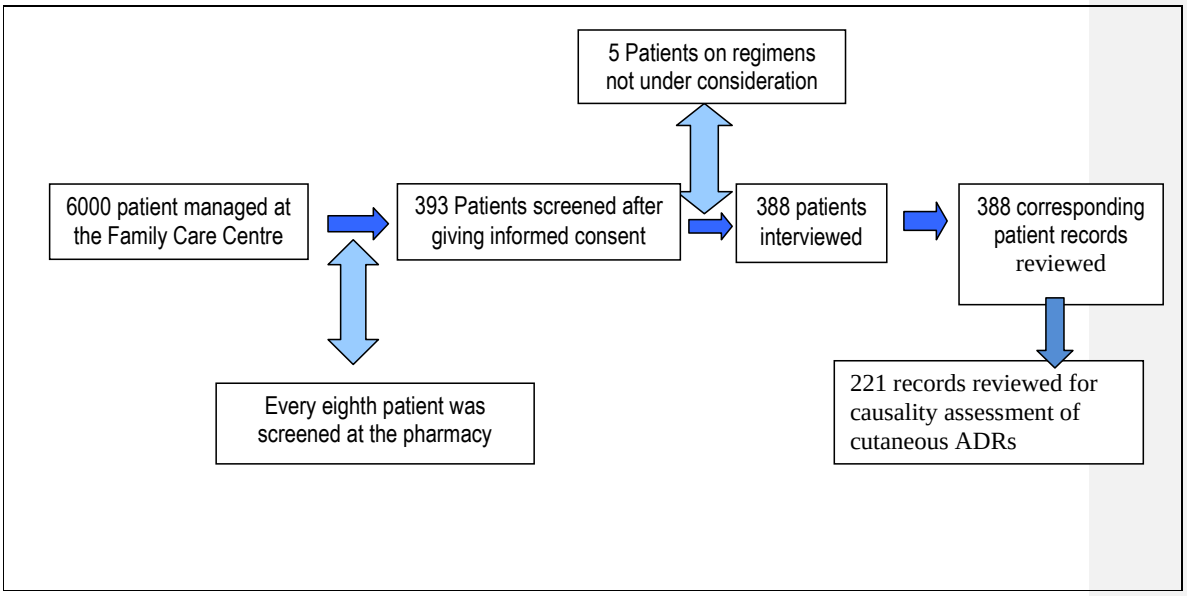
4.8 Data collection

Every eighth patient presenting at the FCC pharmacy was selected to receive information about the study. Eligible patients provided a written consent before being enrolled for study. Structured interviews using a questionnaire (Appendix1) were carried out on patients in whom HAART was initiated after January 2006 (inclusive).The FCC pharmacist and peer counselor, who were not members of the regular ART clinic staff, conducted interviews concerning ADRs. The patient data collected included age, gender, tribe, ART, co-morbidities and herbal medicine use. The co-morbidities that were considered were those that were prevalent in the patient before they started

treatment. Just as well herbal medicine use was considered to be the ingestion of a herbal formulation at least 3 times a week. The patients who were on herbal formulations were those who had started using these formulations before and during the time they were taking HAART.

Patients were assured that the information obtained during the interview would remain confidential and would not affect their treatment. The data collection form included three sections all with closed ended questions. Interviews took place in either the local language or English, depending on the patient's preference. No additional laboratory tests were carried out on the patients. Data on the ADRs was extracted from the ART patient files. The interviews were only conducted once for each of the enrolled patients. Prevalence of any ADRs experienced by the patients were documented on the MCAZ form for reporting ADRs (Appendix 2) and submitted to the Medicines Control Authority of Zimbabwe (MCAZ).

Fig 4.2: Data collection procedure



4.9 Data analysis

The data from the questionnaires and the data extraction form were encoded in an excel spreadsheet. Co-morbidities were tabulated as binary variables with a value of "1" representing the occurrence of a comorbidity and a "0" representing absence. Frequencies were reported from the excel spreadsheet and these were expressed as percentages of the total sample. The nature of the adverse drug reactions were reported from the data collected using the WHO classification of ADRs. The ADRs were classified from grades 1 to 4, with grade 4 being the most severe.

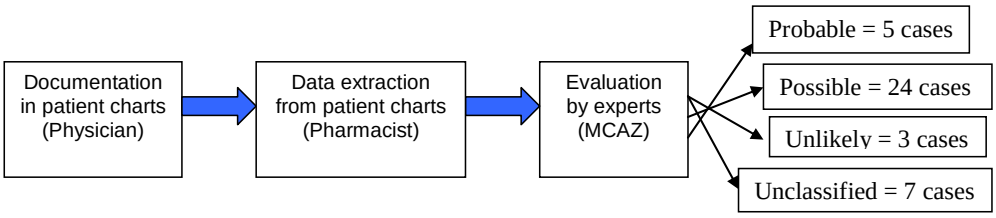
Data analysis was carried out using the Statistical Analysis System (SAS version 9.2, Cary, North Carolina, USA). Three regression models, one multiple linear regression model and two logistic regression models were run to identify predictors of ADRs. Multiple regression analysis was used to test the demographic characteristics that were associated with the ADRs that occurred in the patient population and whether they had any influence on the severity of the ADR. A logistic regression model was used to test whether the herbal therapy use affected incidence and severity of ADRs.

CHAPTER 5: RESULTS

5.1 Causality Assessment

In the 3 step approach, a total of 221 patient case report forms [appendix 2] were reviewed for causality assessment by the MCAZ. The mean age of the patients that were assessed by the MCAZ was 40.6 years (SD 11.16, range 19-76 years). Of the 221 case report forms analyzed, thirty-nine patients had cutaneous drug eruptions. The causality assessment revealed 5 (10.9%) cases to be probable, 24 (52.2%) to be possible, 4 (8.7%) to be unlikely and 13 cases were unclassified due to unavailability of patient's clinical data relating to the assumed adverse drug reaction.

Fig 5.1: Results of causality assessment



5.2 Frequency of adverse drug reactions

393 patients were interviewed in the study – five of the participants were however on regimens that were not under consideration for the study. These participants were excluded in the analysis of the results. There were 388 participants whose data was considered for this study. The group of participants was mostly (92%) of the shona tribe (the predominant tribe in Zimbabwe) and comprised mainly of females [Table 5.1]. Approximately 84% of the patients received D4T, 3TC and NVP which was being taken as twice daily doses of 30 mg, 150 mg and 200 mg, respectively.

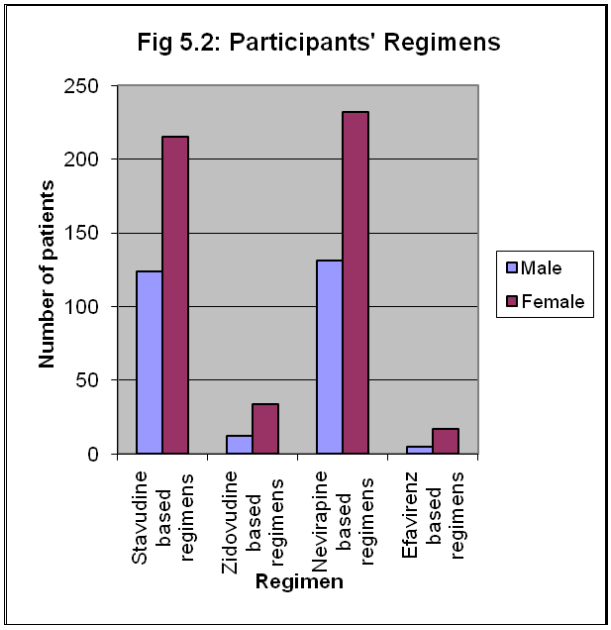


Table 5.1: Distribution of participants on regimens

	D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV
Male	122	3	10	2
Female	208	9	26	8

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Of the 388 patients who were considered in the study, 279 (72%) participants reported at least one adverse event. The most common ADRs were Peripheral neuropathy (42%) and skin rash (26%): [Table 5.2]. These results from this site are in close synchrony with what is observed in most ART programmes in Zimbabwe (i.e. there are more women on the programme than men).

Table 5.2: Frequencies and percentages of adverse drug reactions and total number of ADRs per patient (N=388).

	N	%
Adverse drug reactions	272	70.2
ADR severity (N=272)		
Grade 1	161	41.5
Grade 2	96	24.7
Grade 3	15	3.9
Grade 4	1	0.3
Type of ADRs		
Peripheral neuropathy	162	41.8
Skin rash	101	26.0
Lipodystrophy	13	3.4
GI symptoms	28	7.2
Abdominal pain	30	7.7
Headache	10	2.6
Fatigue	53	13.7

Peripheral neuropathy was mainly observed with the stavudine (93%) based regimens [Table 5.3] and skin rash was mainly observed with the nevirapine (88%) based regimens. The other ADRs that were observed in the population were lipodystrophy, abdominal pain, gastro-intestinal

symptoms (nausea, vomiting, or heartburn) and headache. The 3-step approach yielded an incidence of cADRs of 17.6%.

Table 5.3: Drug regimens and the number of patients who experienced adverse events

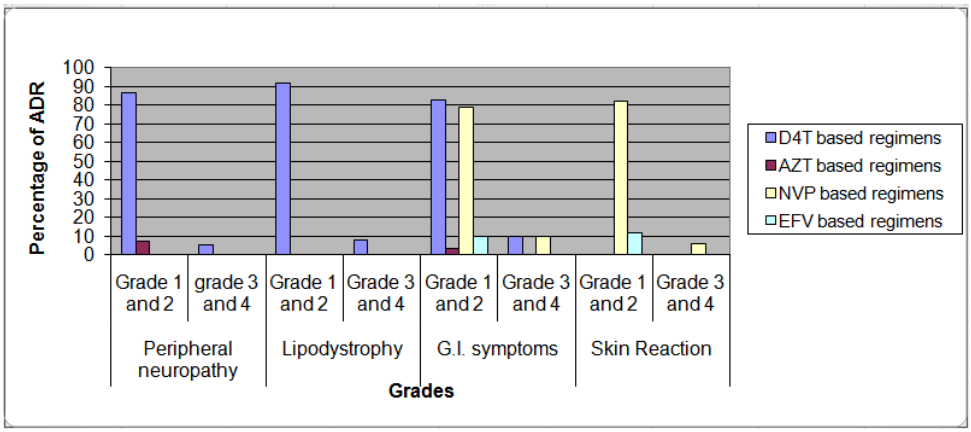
	Adverse Event					
Regimen	Peripheral neuropathy	Skin rash	Lipodystrophy	G.I symptoms	Abdominal pain	Headache
d4t/3tc/nvp (n=330)	148(45%)	79(24%)	11(3%)	25(8%)	27(8%)	5(2%)
d4t/3tc/efv (n=12)	2(17%)	8(68%)	2(17%)	2(17%)	1(8%)	2(17%)
azt/3tc/nvp (n=36)	10(28%)	10(28%)	0	0	1(3%)	0
azt/3tc/efv (n=10)	2(20%)	4(40%)	0	1(10%)	1(10%)	1(10%)

5.3 Severity of adverse drug reactions

Of the adverse drug reactions reported in the study, 161(58%) of them were grade 1 adverse drug events as graded by the WHO ADR grading system, 96(34%) were grade 2, 15(7%) were grade 3 and 1(0.3%) was grade 4. Only one patient had a grade 4 adverse event which was Stevens Johnson Syndrome which occurred in a patient who had received a nevirapine containing regimen. 8 (2.9%) patients developed grade 3 peripheral neuropathies which warranted switching therapy from a d4t containing regimen to an azt containing regimen. 5 (1.8%) patients also developed grade 3 rashes whilst on nevirapine containing regimens which required a switch in

therapy. Patients who were on stavudine based regimens experienced more toxicity compared to those participants who were on zidovudine based therapy [Figure 5.3]. Patients on Nevirapine regimens also experienced more toxicity when compared with patients that were on Efavirenz based therapy [Figure 5.3].

Fig 5.3: Severities of Adverse drug reaction



5.4 Predictors of Toxicity

The participants were also investigated for co-morbidities which were present at the initiation of ART as possible factors in influencing the ADR profiles [Table 5.4].

Table 5.4: Frequencies, means, and medians of demographics, co-morbidities, ARV regimens, number of herbs per patient (N=388). Unless specified, figures represent frequencies and percentages

	N	**%**
Age (Mean, SD) years	40.8	9.2
Gender		
Male	137	35.3
Female	251	64.7
Tribe		
Shona	357	92.3
Other	31	7.7
Co-morbidities		
Diabetes Mellitus	5	1.3
Hypertension	67	17.3
Aneamia	34	8.8
Asthma	21	5.4
Epilepsy	4	1.0
Malaria	155	40.0
Tuberculosis	131	33.8
Shingles	125	32.2
Total number of co-morbidities per patient (Median, Range)	1.0	5
ARV regimen		
AZT/3TC/EFV	10	2.6
AZT/3TC/NVP	36	9.3
D4T/3TC/EFV	12	3.1
D4T/3TC/NVP	330	85.1
Total number of herbs per patient (Mean, SD)	7.9	4.4

Significant associations were determined between the nature of ADR that a patient experienced and the HAART regimen. The severity of the adverse drug event that occurred in the patient was associated with the antiretroviral regimen that was received (p=0.032). This reveals that the type of regimen is a predictor of how severe an adverse drug reaction will present.

5.4.1 Co-morbidities as a predictor of toxicity

In a multiple regression model controlling for age and gender, anemia was associated with the total number of ADRs (p=0.0119). Another significant co-morbidity associated with adverse drug reactions in patients was malaria (p=0.0173). Malaria and anemia proved to be significantly associated with the toxicity profiles of the drugs in the patients even after the multiple regression model controlled for the total number of herbs taken by patients. Just as important, when the model was controlled for herbal use, age became a predictor of adverse drug reactions in the patient population. However, the statistical significance was marginal (p=0.0488). This brings out the importance of considering all predictors of adverse drug reactions together. There is the possibility that when these predictors present in a patient they might interact resulting in a reduced severity of an ADR or amplify its effects.

The results from the logistic regression showed that there was no association between the co-morbidities and the severity of the adverse drug reactions in the patients. The overall multiple regression model for analyzing the data and interpreting the results was significant for this data analysis (Wald's p-value = 0.0055).

5.4.2 Age as a predictor of Adverse Drug Reactions

The mean age of the group was 41 (SD 11.16, range 20-77). The adverse drug reactions were comparable across all ages. In a multiple regression model whereby a summation of the co-morbidities and a summation of the total herbs was analyzed to determine other predictors of

ADRs, age proved to have a statistically significant association with ADRs (p=0.049). The analysis determined that the older a patient is the more likely they will have an increase in the total number of ADRs that they will experience (p=0.049, Standardized estimate = 0.000916).

5.4.3 Herbal drug use

381(98%) of the patients were taking herbal remedies. The distribution of how the patients were taking these herbals is shown in Table 5.5. 370 patients were on ≥ 3 herbal remedies. The herbals that had the higher rates of use (mutsine, garlic and nyevhe) were ingested as part of the diet.

Table 5.5: Frequencies of herbal use in study population (N=388)

	N	%
African potato *(Hypoxis hemerocallidea)*	41	10.6
Chifumuro *(Dicoma anomala)*	103	26.6
Gavakava *(Aloe vera)*	108	27.8
Moringa (*Moringa oleifera*)	171	44.1
Murunguyane	62	16.0
Musakavakadzi	13	3.4
Musosote (*Flueggea virosa)*	15	3.9
Mutsine (*Bidens pilosa*)	256	66.0
Mzumbani (*Lippia javanica*)	141	36.3
Ndorane (*Elephantorrhiza species*)	133	34.3
Ngoka 11	30	7.7
Comfrey *(Symphytum officinale*)	41	10.6
Eucalyptus (*Eucalyptus globulus)*	203	52.3
Garlic *(Allium Sativum)*	282	72.7

A one-way ANOVA test revealed a statistically significant difference in the average number of herbs and the type of ARV regimen (F=6.40; df = 3, 384; p = 0.0003). A post hoc analysis using Duncan's test revealed that patients on AZT/3TC/EFV were using fewer herbs (mean= 4.0) compared to those using other regimens.

A logistic regression procedure was used to analyze the likelihood of any of the herbal therapies influencing the ADR profiles of the ARVs. There was no statistically significant association between the majority of the herbals and the occurrence of ADRs. However, the indigenous herb, *Musakavakadzi* was seen to reduce the occurrence of adverse drug events (OR = 0.25; 95% CI 0.076-0.828; p=0.023) and another indigenous herb, *Ndorane* also reduced the occurrence of adverse drug events (OR = 0.495; 95% CI 0.292-0.839; p=0.0091). These associations identified these 2 herbs as probable interventions in reducing the incidence of ADRs if co-administered with HAART. Abdominal pain (odds ratio = 3.0, p-value=0.004) and rash (odds ratio=2.5, p-value=0.02) were the only adverse events significantly associated with herbal drug use during antiretroviral therapy. Other adverse events assessed in the study did not have a significant association with use of herbal remedies during antiretroviral therapy.

5.4.4 Formulation as a predictor of ADRs

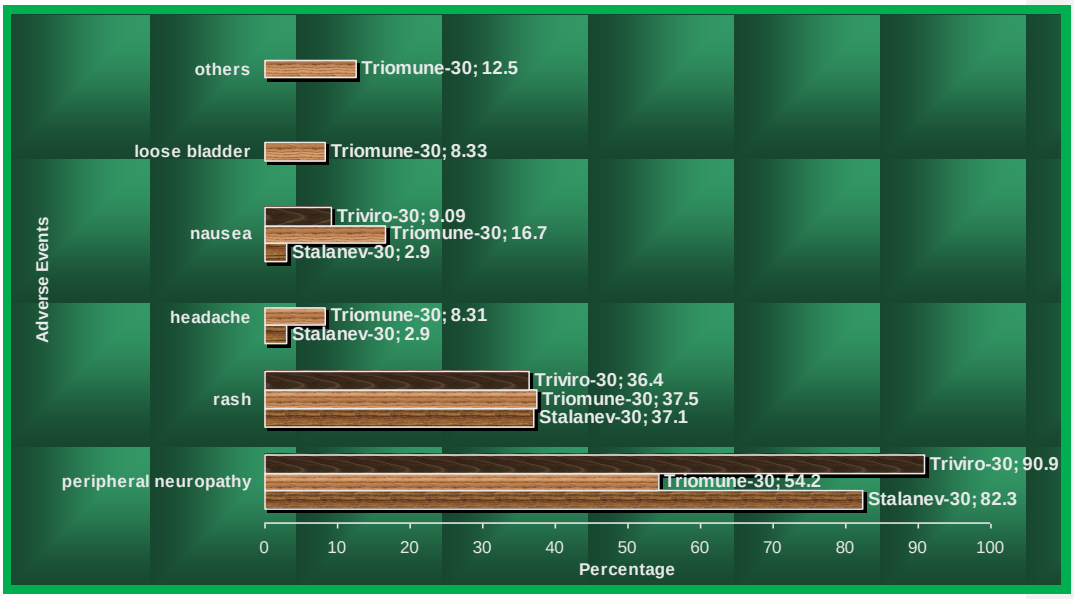
In the pilot study a sub analysis of the data showed that some medication factors played a role in the ADR profile that can be caused by HAART. One hundred and thirty patients who were receiving equivalent formulations of stavudine, lamivudine and nevirapine were reviewed. The distributions of the patients on the formulations were as shown in table 5.6.

Table 5.6: Distribution of patients on FDCs

FDC	Frequency %(n)
Stalanev 30	26.92 (35)
Stalanev 40	26.15 (34)
Triomune 30	18.46 (24)
Triomune 40	8.46 (11)
Triviro 30	8.46 (11)
Triviro 40	2.31 (3)
Coviro 30 + Nevirapine	1.54 (2)
Coviro 30 + efavirenz	5.38 (7)
Combivir + Nevirapine	2.31 (3)

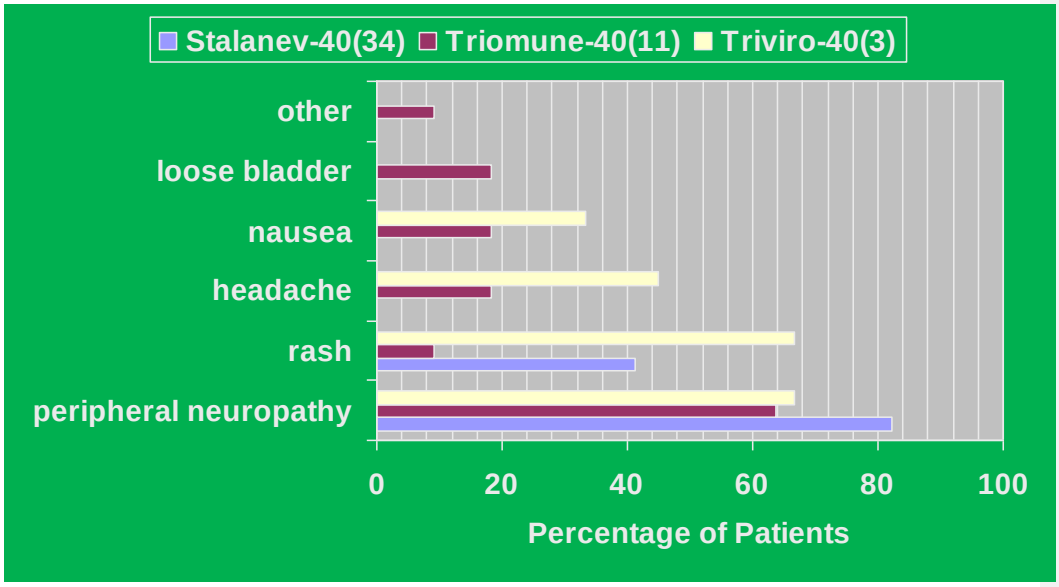
Data from 17 of the participants who were interviewed was not considered as they were on formulations that were not under consideration in this sub analysis. A comparison of adverse effects caused by generic FDCs with 30 mg of stavudine revealed the following rates:

Fig 5.4: Comparison of adverse effects of FDCs with 30 mg of Stavudine



A comparison was also made of the ADR profiles that were being caused by the FDCs with 40 mg of stavudine. The following rates were identified:

Fig 5.5: Adverse effects of FDCs with 40 mg of Stavudine



Using Pearson Chi-square test, a significant difference in the incidence of peripheral neuropathy ($p=0.039$) between the FDCs was observed. Stalanev-40 had the greatest incidence of peripheral neuropathy. The FDC, Triomune® also caused headache, dizziness and urinary incontinence, not caused by other FDCs. No statistically significant differences were noted for incidence of other adverse drug reactions ($p>0.05$).

CHAPTER 6: DISCUSSION

6.1 Causality assessment

The incidence of cutaneous ADRs identified through assessment by the MCAZ was 13.1% compared to an incidence of 17.6% which was identified by health practitioners in the clinic. The results obtained through the 3-step approach are comparable to results obtained in other resource limited settings.[159-161] In these 3 settings, the rates of cutaneous adverse drug reactions were determined by spontaneous reporting and in clinical studies of ART. Whilst these methods are accurate in identifying rates of ADRs these are more costly to implement when compared with the 3-step approach. Thus the 3 – step approach would prove to be a useful tool in identifying ADRs in areas where resources are scarce. This approach provides a method that can be implemented successfully in resource limited settings that have drug regulating bodies.

6.2 Rates of ADRs

This study provides the ADR profiles in participants that have been exposed to ART on a long term basis. Significant ADRs were documented and different risk factors have been identified with the use of stavudine or nevirapine. Different ADR rates have been identified in different settings which imply that there are individual factors that need to be investigated further. The rates of peripheral neuropathy in ART studies that have been done previously have reported incidence rates in the range of 1% to 56%.[159-160, 162-166] The incidence rate of peripheral neuropathy identified in this study also fall within this range (41%). Our findings show that the rates of skin rash (26%) were similar to those found in Blantyre, Malawi.[165] Skin rash occurrences due to ART have also been studied in several studies and have yielded incidence rates that are comparable to those that were observed in our study.[159-161] Lipodystrophy rates

were lower when compared to studies that were conducted elsewhere.[159, 167-168] However India had rates that were similar to those found in the Zimbabwean setting.[160] Similarly GI symptoms, headache and abdominal pain rates were comparable to those found in other studies conducted elsewhere.[159, 165]

Varying toxicities in different settings can be attributed to patient factors (i.e. difference in genetic build up) but through this study it has shown that it is important to consider medication factors (differences in medication properties) as well. Such differences in the rates of toxicity can be explained by the use of differing generic fixed dose formulations (FDCs) in the respective locations. The use of equivalent fixed dose formulations from different manufacturers could result in different toxicity profiles.[169] One possible explanation for the difference in ADR characteristics could be as a result of the different excipients that are used when formulating the tablet. These could also have the potential to cause adverse effects.

6.3 Nature of ADRs

Among the 279 patients who experienced ADRs, 257 (92%) ADRs were either moderate or 'mild' in severity. Most of the mild ADRs were noted in patients on an AZT in combination with EFV combination. Sixteen (5.7%) of the patients had severe (grade 3 or grade 4) ADRs that warranted discontinuation of treatment and switching of therapy. In a study done in India[170], 301 ADRs were reported and 139 (46%) of these ADRs each were 'moderate' and 'mild' in severity. Almost all the ADRs that were 'moderate' in severity [92.2% (131/139)] required discontinuation of suspected drug(s). ADRs that required hospitalization or increased the hospital stay [20.6% (62/301)] included anaemia, hyperlactatemia, Stevens Johnson syndrome and hepatitis. Reactions were 'severe' in 23 (7.6%) cases with one fatal reaction (immune

reconstitution syndrome - paradoxical type following the initiation of zidovudine/lamivudine/efavirenz treatment). However Modayil et al.,[170] included analysis of ADRs that were identified using laboratory support while in this study; only clinically observed ADRs were considered.

In this study only 1 patient developed Stevens Johnson Syndrome (SJS). ADRs due to stavudine and nevirapine were more prevalent and more toxic when compared to zidovudine and efavirenz respectively. In contrast to the 52.8%[170] who developed ADRs whilst on HAART in India, there was a 72% incidence of ADRs in this study. This difference is probably due to the high number of patients on stavudine based regimens that were included in this study (84%) compared to those in the Indian study (31.8%).

6.4 Predictors of ADRs

The results demonstrate associations between co-morbidities, herbal medicines use and age with the occurrence of ADRs in the study population. These factors included the regimen, the total number of herbal remedies taken, aneamia, malaria, age, *Musakavakadzi* and *Ndorane*. The study revealed that there were higher incidences of ADRs due to D4T and NVP.

Littera et al. and Hiroyuki et al. have identified gender as a risk factor in causing hypersensitivity reactions due to nevirapine.[171-172] In these studies, women were shown to be more likely to develop rash/liver toxicity when initiated on a nevirapine containing regimen when compared to men. However, in the Zimbabwean population even though there were a greater proportion of women, a regression analysis revealed that gender was not associated with the occurrence of ADRs. The results in this study with respect to gender have also been shown by de Maat et al. and Tansuphaswadikul et al.[173-174]

The study also investigated the impact that herbal use has on the ADR profiles of the first-line regimens. Development of rash (odds ratio=2.5, p-value=0.02) and abdominal pain (odds ratio = 3.0, p-value=0.004) were the most common adverse events experienced by patients taking herbal remedies together with antiretroviral drugs. This is consistent with other studies which have shown that some herbal remedies cause certain types of skin rashes when used alone.[175-176]

Moringa oleifera has been identified as an offending agent responsible for abdominal pains ($p<0.05$). Monera et al.,[177] found moringa to have significant inhibitory effects on CYP3A4. This results in the elevation of plasma levels of drugs metabolized by this pathway. Nevirapine and Efavirenz are both metabolized via the cytochrome P450 enzyme pathway. Thus a potential interaction exists between the NNRTIs with moringa. Nevirapine and Efavirenz are both documented as causing abdominal pains (BNF, 2007). There is therefore a potential that the abdominal pains may be due to elevated NVP/EFV levels while a patient is on moringa.

It is important to note that herbs contain a mixture of naturally occurring phytochemicals which may be substrates for enzymes or transporters that act on drugs, potentially inhibiting the drugs' metabolism or transportation. These processes can result in altered drug absorption, distribution, metabolism and/or elimination. This results in altered drug plasma levels hence a different ADR profile due to altered drug/herb concentrations. Toxicity or sub-therapeutic drug concentrations, pathogen resistance and treatment failure are also possible outcomes.

One of the reasons that patients use herbals is to try and alleviate the discomforts caused by antiretroviral ADRs. As such an association was identified between the antiretroviral received and the total herbal use in the population. Those patients who were on the regimen containing AZT/3TC/EFV used less herbal therapies when compared to the other regimens. One possible

reason for this could be the decreased rates of ADRs that are associated with this therapy decrease the need for herbal use for alleviating side effects.

Another important finding was the relationship that *Musakavakadzi* and *Ndorane* had with the rates of ADRs that were observed in this population. These herbal remedies were associated with decreased incidences of ADRs, indicating that these herbals might offer some protection to the patients. It is important to note that 381(98%) of the patients were taking herbal remedies and with such a high rate of herbal use there is a need to increase research in herbal remedies that have the potential to influence treatment outcomes. Antiretroviral therapy seeks to improve the quality of life of patients. Thus there is the need to introduce therapies that have milder ADR profiles. ADRs reduce patient confidence in medicines thereby impacting on adherence.

The study investigated associations between factors and ADR outcomes. Identification of these factors forms a key step in developing further studies that will aim to explore the mechanisms of action through which they elicit their action. The study also identifies groups of patients that will need more intense monitoring such as those patients who are aneamic and those who develop malaria whilst on ART. Unfortunately, because of the limited laboratory support the study could only record ADRs that were clinically apparent. Although the study attempted to verify all data collected from the patient with the patient charts there is a possibility that those patients who experienced grade 4 adverse events and died whilst they were at home might have not had their data recorded in the patient file and thus resulting in underreporting of grade 4 adverse drug events. The results show that associations do exist between various co-morbidities, herbal medicines use and age with the occurrence of ADRs in the Zimbabwean population. The study revealed that there were higher incidences of ADRs due to D4T and NVP. Where most developing countries would argue that AZT based regimens would be more expensive, a cost

benefit analysis might be warranted to weigh the costs versus the benefits of shifting to AZT based combinations.

Three in every four patients placed on ART in the public roll out programme reported at least one adverse event. Strategies now need to be put in place that will alleviate the burden of adverse events on the patient whilst ensuring that the limited resources that are available are put to optimum use.

One limitation of the study was that the data collected relied heavily on documentation in patient charts by the clinician. This data was then extracted by the pharmacist from the patient charts. HAART with stavudine/lamivudine/nevirapine was shown to be a strong predictor of ADR when compared with the other regimens. Attention needs to be drawn to the monitoring of ADRs to antiretrovirals whilst simultaneously improving access to ART for the Zimbabwean population.

CHAPTER 7: CONCLUSION

With the challenges that exist in resource constrained settings, chief among them insufficient professional personnel, it is important to introduce systems that utilize the available resources in running pharmacovigilance programmes. Pharmacovigilance programmes can be based on a 3-step approach which will allow data from even the remote areas to be assessed by professionals.

The results of this study showed that 3 in every 4 patients initiated on first-line HAART in the government roll-out programme experienced a clinical adverse drug event. Only 5.7% of the ADRs were severe and warranted discontinuation of therapy. It was also revealed in this study that patients on HAART used a vast number of herbal remedies for a number of reasons.

7.1 Recommendations

As a means of improving the detection and assessment of ADRs in Zimbabwe, the 3-step approach provides an efficient system to implement in pharmacovigilance. This approach can be introduced to healthcare personnel at primary health care level in rural areas. In this approach, a patient receiving ART from a rural setting can have a record kept at the respective facility where the health professional documents the patient's progress. A roving pharmacist can be used to travel to these health centres to extract information of suspected ADRs from these charts and this extracted data submitted to MCAZ for causality assessment. The advantage of such a system is the ability to detect ADRs that occur away from the urban medical centres while utilizing the available manpower.

There is need to develop a scientific method for predicting the probability of developing some ADRs. There is a need to develop a biomarker for determining the likelihood of a patient developing a hypersensitivity rash due to nevirapine which may be life threatening. Just like the

pharmacogenetic screening for the HLA-B 5701 allele which is associated with abacavir hypersensitivity, a biomarker needs to be identified for determining the nevirapine hypersensitivity reaction. Since nevirapine is widely used in resource limited settings, such an intervention has the potential to drastically reduce the morbidity and mortality due to nevirapine associated hypersensitivity.

There is also a need to further screen the herbal therapies and identify those with the potential to reduce the occurrence of ADRs in patients on HAART. In this study 2 herbal therapies were associated with a reduced incidence of ADRs (*Musakavakadzi* and *Ndorane*). There is now a need to further evaluate these 2 herbal formulations to identify the active ingredient and carry out in vitro studies which will investigate on the interaction between these herbal products and ARV drug products.

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APPENDIX 1: QUESTIONNARE

Informed Consent Obtained?	**Yes**	**Date Obtained:** MM/DD/YYYY		**No – Do not proceed**
Gender			**Male**	**Female**	**Other**
Subject's Age		**Between 18 and 75**	**YES**	**NO – do not proceed**
Does the subject have documented HIV-1 infection?			**YES** _____	**NO – do not proceed**
Is patient currently receiving ART or beginning ART as described in the schema of this protocol?			**YES**	**NO – do not proceed**

Tribe	☐ **Ndebele**	☐ **Shona**	☐ **Other** _____
Race	☐ **Native African**	☐ **Caucasian**	☐ **African-American**
	☐ **Asian**	☐ **Hispanic**	☐ **Other** _____

Antiretrovirals		
Antiretroviral / Product Name		**Dose (mg)** **Regimen (QD, BID, TID)**
Antiretroviral Product Name		Dose (mg)
Start Date	Stop Date	Regimen (QD, BID, TID)
Antiretroviral Product Name		Dose (mg)
Start Date	Stop Date	Regimen (QD, BID, TID)

Medications taken by patient after initiating HAART		
List all medications the subject received after initiating HAART.		
Drug Name		**Dose (mg) Regimen (QD, BID, TID)**
		Dose
Start date	Stop date	Regimen (QD, BID, TID)
		Dose
Start date	Stop date	Regimen (QD, BID, TID)

Has the subject ever been diagnosed with any of the following(Y/N)?		**Currently Active (Y/N)?**
Diabetes Mellitus		
Hypertension		
Anemia		
Asthma		
Epilepsy		
Malaria		
Tuberculosis		
Shingles		
OTHER_____		

Has the subject experienced any of the following after initiating HAART?			**Date of diagnosis**	**Duration**	Suspected FDC
Skin Rash	**YES**	**NO**			
Peripheral Neuropathy	**YES**	**NO**			
Abd Pain	**YES**	**NO**			
Lipodystrophy	**YES**	**NO**			
Fever	**YES**	**NO**			
Fatigue	**YES**	**NO**			
GI, Emesis, Diarrhea	**YES**	**NO**			
Other_____ _____	**YES**	**NO**			

Substance Use Form

1	**Did you smoke cigarettes after you were initiated on ART?** If NO, skip to question 2				No	Yes
	If YES, for how long did you smoke the cigarettes?	Start date	Stop date	**If YES,** what is the average number of cigarettes per day that you smoked in that period?		None ☐

2	**Did you at any time have a drink containing alcohol* after being initiated on ART?** *A drink containing alcohol means a can or glass of beer, a glass of wine, "spirits," a shot of liquor, a mixed drink with a shot of liquor or any other kind of alcoholic beverage. **If NO, skip to question 3**					No	Yes
	If YES, how often did you have a drink containing alcohol after being initiated on ART?	Daily ☐	5 or 6 times a week ☐	3 or 4 times a week ☐	Once or twice a week ☐	2 or 3 times a month ☐	Once a month ☐
	If YES, how many drinks containing alcohol did you usually drink in one day?	12 or more drinks ☐	9 to 11 drinks ☐	7 or 8 drinks ☐	5 or 6 drinks ☐	3 or 4 drinks ☐	1 or 2 drinks ☐
	If YES, for how long did you take alcohol?	Start date	Stop date				

3	**Did you use cannabis* at any time after being initiated on ART?** *Cannabis means mbanje, marijuana or any other name for cannabis.					No	Yes
	If YES, how often did you use this drug after being initiated on ART?	Daily ☐	5 or 6 times a week ☐	3 or 4 times a week ☐	Once or twice a week ☐	2 or 3 times a month ☐	Once a month ☐
	If YES, how many times did you usually take this drug in one day?	12 or more times a day ☐	9 to 11 times a day ☐	7 or 8 times a day ☐	5 or 6 times a day ☐	3 or 4 times a day ☐	1 or 2 times a day ☐
	If YES, for how long did you use cannabis?	Start date	Stop date				

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Mild discomfort ☐	Assistance may be reqd ☐	Assistance reqd ☐	Significant assistance reqd ☐
No limitation in activity ☐	Moderate limitation ☐	Marked limitation in activity ☐	Extreme limitation in activity ☐
No medical intervention ☐	No/minimal medical Intervention ☐	Medical intervention reqd ☐	Significant medical intervention reqd ☐
		Possible hospitalization ☐	Hospitalization ☐
			Change in regimen ☐

Liver Function Tests				Lipid Profile			
Test	**Result**	**Units**	**Date**	**Test**	**Result**	**Units**	**Date**
ALT				**Albumin**			
AST				**Trig**			
ALKP				**HDL**			
TBIL				**Cholesterol**			
GGT				**LDL**			

Herbal / Traditional Medicines Use								
Indigenous Herbs	**Ever Used? Yes/No**	**Prescribed by? traditional healer, self-prescribed, doctor/nurse**	**Used in last 3 months Yes/No**	**How many times in last month?**	**How many times in last week?**	**How many times in last 48 hours?**	**Amount used each time in last 48 hours?**	**Reason for using herb / medicine?**
African Potato								
Chifumuro								
Gavakava								
Moringa								
Murunguyane								
Musakavakadzi								
Musosote								
Mutsine								
Mzumbani								
Ndorane								
Ngoka 11								
Exotic Herbs								
Comfrey								
Eucalyptus								
Garlic								
Ginger								
Grapefruit								
Guava Tree								
Lavender								
Lemon Grass								
Lemon Tree								
Menthol								
Pennyroyal								
Rosemary								
Thyme								
Wormwood								
Specify: _____								

APPENDIX 2: MCAZ CASE REPORT FORM

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Report of a Suspected Adverse Drug Reaction			
Identities of Reporter, Patient and Institute will remain confidential			
Patient Details (to allow linkage with other reports)			
Family Name:			
Forenames:			
Date of Birth:		Weight	Sex:
Age:		Kg	M/F
Adverse Reaction			
Date of Onset:			
Duration:	Less than one hour	Hours	Weeks
		Days	Months
Description			
Outcome	Recovered	Fatal	Unknown
	Not yet recovered		
Suspected Drug(s)			
Drug:	Generic Name:		
	Brand Name:		
Condition/indication Drug given for:			
Daily dose/route:			
Date begun:		Date stopped	
All other drugs used by patients:			
Laboratory tests results			
Reported by			
Family Name:			
Forename(s):			
Status:	Doctor	Pharmacist	Nurse
Address:			
Signature:		Date:	
Send to: The Director-General, Medicines Control Authority of Zimbabwe, 106 Baines Avenue, P O Box 10559, Harare, FAX: +263-4-736980, Tel: +263-4-736981/5, E-mail: mcaz@africaonline.co.zw			

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

REPORT ON MEDICINAL (PHARMACEUTICAL) PRODUCT DEFECT OR PROBLEM

To be completed by Pharmacists, Pharmacy Technicians, Medical Practitioners, Nurses, Veterinary Surgeons and other Distributors of Medicines.

1. Product Name (Brand and Generic)			
2. Description of the Device	3. Intended Use	4. Size/Type of Container	5. Registration No.
6. Batch Number		7. Expiry Date	
8. Name and Address of Manufacturer			
9. Name and Title of Reporter			
10. Your Practice Location and Address of Hospital, Clinic, Retail Surgery etc.			
11. Phone Number		12. Date Problem Occurred or Observed	
13. If requested will the actual product involved be available for examination by MCAZ. **YES** **NO**			
14. Signature of Reporter		15. Date	
16. Defects/Problem Noted or Suspected (see a-j below)			

NATURE OF DEFECT OR PROBLEM

a) Presence of foreign material
b) Unusual odour
c) Colour changes
d) Fungal growth
e) Suspected contamination
f) Parenteral solution - leaks, particulate matter, discoloration etc.
g) Wrong label, wrong packaging, wrong strength
h) Lack of therapeutic response
i) Leakages
J) Other (specify)

Return To: The Director-General
Medicines Control Authority of Zimbabwe
106 Baines Avenue
P O Box 10559
Harare
Fax: 736980 Tel: 736981-5
E-mail: mcaz@africaonline.co.zw

For Office Use Only
Report Number:
Date Received: