IDENTIFYING, RECORDING AND MONITORING ADVERSE EFFECTS ASSOCIATED WITH ANTIRETROVIRAL TREATMENT

FLORENCE M. MULINGE

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IDENTIFYING, RECORDING AND MONITORING ADVERSE EFFECTS ASSOCIATED WITH ANTIRETROVIRAL TREATMENT

by

FLORENCE MUTHONI MULINGE

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Supervisor: Ms Susan Burton

Co-Supervisor: Mrs Beverley Gold

DECLARATION

I Florence Muthoni Mulinge (Student Number: 205032699), hereby declare that this dissertation submitted for the degree of Magister Pharmaciae at the Nelson Mandela Metropolitan University is my own work and that it has not previously been submitted for assessment to another University or for another qualification.

Signature:_____

Date:_____

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3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune-Deficiency Syndrome
ALT	Alanine aminotransferase
APV	Amprenavir
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATV	Atazanavir
AZT/ZDV	Zidovudine
bd	twice daily
CCR	Chemokine co-receptor
CNS	Central nervous system
CYP450	Cytochrome P450
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DEXA	Dual-energy x-ray absorptiometry
DLV	Delavirdine
DNA	Deoxyribonucleic acid
DRV	Darunavir
EFV	Efavirenz
ETV	Etravirine
FBC	Full blood count
FDA	Food and drug administation
FI	Fusion inhibitor
FPV/FOS	Fosamprenavir
FTC	Emtricitabine
GFR	Glomerular filtration rate

GGT	Gamma-glutamyl transpeptidase
GI(T)	Gastro-intestinal (tract)
gp	glycopretein
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HCP	Health care professional
HDL	High density lipoprotein
HepBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
HU	Hydroxyurea
IDV	Indinavir
INH	Isoniazid
IRIS	Immune reconstitution inflammatory syndrome
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LPV/r	Lopinavir/ritonavir
LPV	Lopinavir
MCC	Medicines control council
MDR	Multi-drug resistant
MVC	Maraviroc
NAD	Nicotinamide adenine dinucleotide
NADH	Reduced form of nicotinamide adenine dinucleotide
NFV	Nelfinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
od	once daily
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission
RAL	Raltegravir

RNA	Ribonucleic acid
RnRI	Ribonucleotide reductase inhibitor
RTI	Reverse transcriptase inhibitor
RTV	Ritonavir
SJS	Stevens Johnson Syndrome
SQV	Saquinavir
T-20	Enfuvirtide
TB	Tuberculosis
TDF	Tenofivir
TDM	Therapeutic drug monitoring
TPV	Tipranavir
UGT	Uridine diphosphate glucoronosyltransferase
ULN	Upper limit of normal
UNAIDS	Joint United Nations Programme on AIDS
USA	United States of America
VL	Viral load
WHO	World Health Organisation
XDR	Extreme drug resistant

Abstract

South Africa, with an estimated 5.7 million people living with HIV, continues to have one of the largest epidemics in the world. The introduction of HAART resulted in prolonged and improved quality of life of many infected patients. However, adverse effects caused by these drugs have become a major concern as they affect the adherence of patients and in some cases even result in the death of patients. Although much research has been and is still being conducted in the area of understanding, preventing and management of ARV adverse effects, there is still a need for patients to be actively involved in self-monitoring for adverse effects. This will assist health care professionals in early identification of serious or potentially serious ARV effects. This study aimed at evaluating the usefulness of strategies developed and employed in the identification, recording and monitoring of adverse effects.

The study was conducted with patients receiving HAART from a private HIV and AIDS clinic in Uitenhage, Eastern Cape, South Africa. The research project was approved by the Nelson Mandela Metropolitan University Research and Ethics Committee and the research site. This was an experimental, randomized controlled study carried out over a period of three months (August to October 2009), with a sample size of 160 patients divided into four study groups of 40 patients each. Two monitoring strategies, namely an ARV adverse effect monitoring tool and a patient self-monitoring diary were developed and used for the identification and recording of adverse effects. The four study groups included a Control group, a Tool group, a Diary group and a Tool-Diary group. Willing patients, after signing an informed consent form, were randomly assigned to one of the four groups by participating health care workers at the study site. Data was retrieved from the patient files by the researcher. Descriptive statistical analysis of the findings of the study was conducted using SPSS®.

One hundred and forty nine patients were included in the final data analysis. Of the 80 diaries handed out to patients, only 33 were returned and due to errors only 31 were suitable for analysis. Monitoring tools were completed and analysed for 36 patients. The tool was found to be more effective in identifying adverse effects of a physical nature (such as peripheral neuropathy and lipodystrophy) than the usual methods of monitoring

employed by the clinic, whilst the diary, used alone, was found to be less effective. Use of the tool and diary combined resulted in the most significant identification and recording of central nervous system related adverse effects and physical adverse effects. However due to the low return rate of the diaries and the majority of the monitoring tool not being completed in many instances the results of this study may not be generalisable.

The study results did however suggest that combining the tool and the diary methods of adverse effect identification, yielded the most favourable results when compared to each method alone. This may be attributed to the fact that the tool is useful in identifying objective symptoms and the diaries subjective symptoms, particularly in instances where the patients forget to report their symptoms to healthcare professional whilst at the clinic. The diaries were also reported to improve adherence for more than 90% (n=31) of the patients. More research would be needed in order to verify the exact significance of the tool and the diary in identifying and recording adverse effects and symptoms of adverse effects.

CHAPTER 1

INTRODUCTION

More than twenty years have gone by since the initial reports of the Human Immunodeficiency Virus (HIV) and its resultant Acquired Immune Deficiency Syndrome (AIDS) (Chao, 2006). HIV infection is characterized by slow progressive immune deficiency with a prolonged period of clinical latency, which varies between different individuals, but on average lasts approximately eight years (Regensberg and Whitelaw, 2007). If left untreated, patients eventually develop one or more serious events, known as AIDS-defining illnesses. AIDS is a collection of opportunistic infections commonly experienced by HIV immuno-compromised patients.

According to the Joint United Nations programme on HIV/AIDS (UNAIDS) global report (2008), significant positive changes are being seen in several countries most affected by the AIDS epidemic. These positive changes include increasing condom use among people especially the youth with multiple partners, and young people waiting longer to have sexual intercourse (UNAIDS Global Report, 2008). Despite tremendous advances in the understanding and management of HIV/AIDS, it remains a worldwide epidemic (Chao, 2006).

UNAIDS estimates that an average of 33.4 million adults and children are infected with HIV. Sub-Saharan Africa remains the global epicenter of the epidemic, accounting for two thirds (67%) of all people living with HIV and for three quarters (75%) of AIDS deaths in 2007. An estimated 22.4 million people in sub-Saharan Africa are living with HIV. South Africa, with an estimated 5.7 million people living with HIV, continues to be

the largest epidemic in the world. (UNAIDS Global Report, 2009) It is also estimated by the UNAIDS (2008) that for every two people who start HIV treatment, five more are infected. Therefore, despite the positive changes, much still has to be done to curb this epidemic.

Long-term reduction of HIV infection is readily achieved by combinations of antiretrovirals (ARVs) (Montessori *et al.*, 2004). These combinations are referred to as Highly Active Antiretroviral Therapy (HAART). The overall effectiveness of HAART is established by measuring the number of life-years added due to ARV therapy. Between 1996 and 2008, an estimated 11.7 million life-years were added globally and this number is expected to rise rapidly should ARV programmes continue (UNAIDS Global Report, 2009).

The range of ARV agents available for the treatment of HIV/AIDS patients has expanded to more than 20 medications since the first agent, zidovudine (AZT), was approved in 1987 (Cohen, 2006). AZT appeared to be effective, in that many patients responded to monotherapy, with a transient decrease in viral load and an increase in CD4 cell count. Eventually, in 1991 didanosine (ddI) was approved and combination therapy became the standard of care for HIV/AIDS patients since it yielded favourable results when compared to monotherapy. It was however noted that the effectiveness of nucleoside reverse transcriptase inhibitor (NRTI) therapy was often not sustained due to resistance with mono or dual NRTI therapy (Cohen, 2006).

The current standard of care for initial HAART has been defined based on the results from numerous randomized studies and consists of two NRTIs and either a non-nucleoside reverse transcriptase (NNRTI) or a ritonavir-boosted protease inhibitor (PI). The rationale for prescribing a minimum of three drugs is to reduce viral resistance,

allow for a reduction in individual ARV doses (and thus decrease risk of toxicity) and to provide for a maximal and durable suppression of viral load, to a point where viral load is undetectable (Regensberg and Whitelaw, 2007). By suppressing the viral load and thus gradually increasing CD4 cell count, ARVs allow for the restoration and preservation of the immune system. Figure 1.1 below shows the average progression of HIV disease characterized by CD4 cell drop and increase in viral load without treatment.

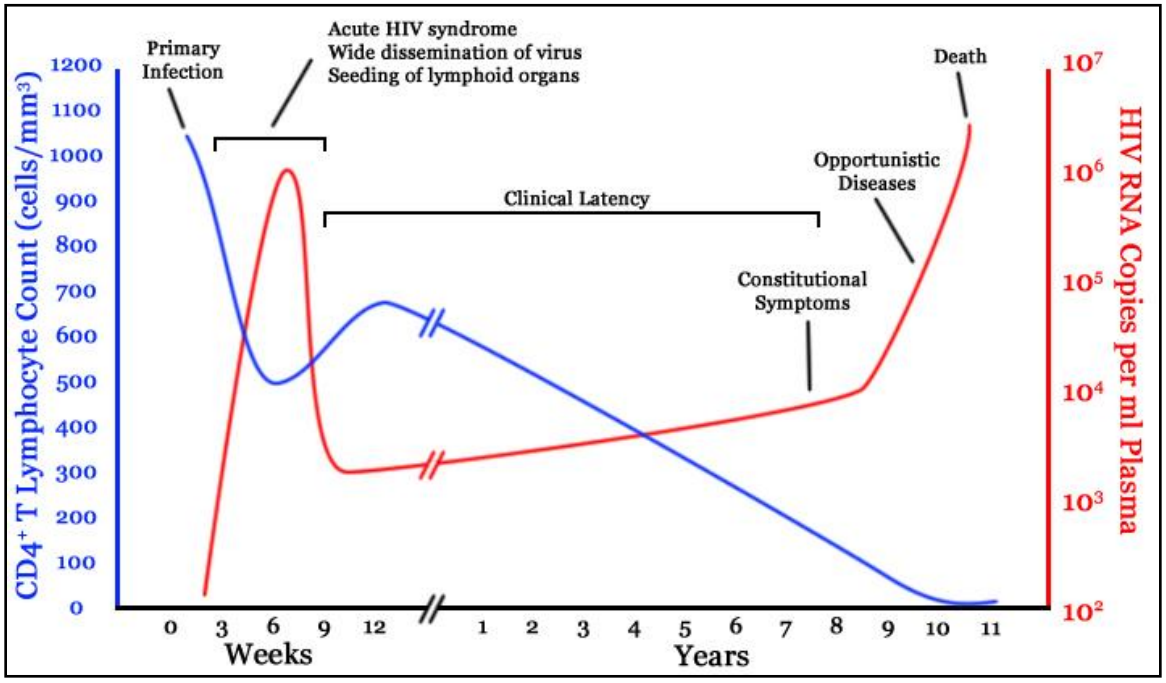


Figure 1.1 The average progression of HIV disease without treatment

(Source: Bennett and Gilroy, 2010)

Although HAART is not a cure for AIDS, it may significantly prolong the lives of patients by improving the quality of their lives. The rates of transmission of HIV as shown by a recent study are at 0.5 per 100 person-years for those receiving ARV treatment and 5.6 per person-years for those not receiving treatment (UNAIDS Global Report, 2009). Therefore the use of ARVs is not only useful to the infected patient, but also useful in

preventing infection of others. With the use of ARVs, the viral load may be reduced to undetectable concentrations. This however does not mean that the patient is cured as the virus is still found to be latent in memory T cells. It forms part of the host's genome, serving as a potential source for reactivation if treatment is stopped or fails (Fletcher and Kakuda, 2003).

The effective management of HIV infection requires complete patient adherence to HAART regimens. Adherence is defined as the engaged and accurate participation of an informed patient in a care plan. It is a broader term than compliance (the extent to which patients follow the instructions of their healthcare professionals (HCPs)), and implies understanding, consent and partnership. Adherence includes entering into and continuing in a program or care plan, attending appointments and tests as scheduled, taking medications as prescribed, modifying lifestyle as required, and avoiding risk behaviours. It includes both adherence to care and medication (Rabkin, El-Sadr and Abrams, 2004). Ideally, adherence to HAART means a patient must take more than 95% of their doses, that is, missing less than 3 doses in a month (Department of Health, 2004).

Adherence to HAART is complicated by several factors including the therapeutic complexity of the drug regimens, special food requirements, the associated drug interactions and severe side effects (Schiller, 2005). It is further complicated by the fact that HAART is a lifelong treatment, and patients are required to take at least three different ARVs twice a day, at the same time each day, for the rest of their lives (Regensberg and Whitelaw, 2007).

With the continuing development of new ARVs, efforts to maximize the effectiveness of the currently available ARV drugs include attempts to better understand and manage

adverse effects. All ARVs can have both short and long-term adverse effects (Montessori *et al.*, 2004). Adverse effects of ARVs are common and often difficult to avoid, and can range from mild to life threatening. Determining the exact causative ARV of a specific adverse effect is often difficult (Shibuyama *et al.*, 2006), even though each ARV is associated with its own specific adverse effects class adverse effects also often occur.

Approximately 50% of patients on HAART experience adverse effects. Up to 25% of patients who experience adverse effects, stop their treatment within the first year of treatment, leaving them defenseless against the virus and possibly resulting in drug resistance, a loss of drug efficacy and the loss of future treatment options (Schiller, 2005). Approximately a further 25% of patients do not take the recommended dose of their medication as a consequence of concerns regarding the side effects. Patients, who report significant side effects, are frequently non-adherent (Schieferstein and Buhk, 2006).

Common but relatively mild adverse effects that occur early in most ARV regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or persistent throughout therapy. Fatigue and headache caused by AZT and nightmares associated with efavirenz (EFV) are also common trouble-some adverse effects. Rare but severe adverse effects such as AZT-associated anaemia, stavudine (d4T) associated peripheral neuropathy, PI-associated retinoid toxicity and NNRTI-associated hypersensitivity reactions are managed according to standard treatment protocols, in the same way that these conditions would be managed in patients not receiving HAART (Montessori *et al.*, 2004). Other serious adverse effects include lactic acidosis, hepatic steatosis, hyperlactataemia, hepatotoxicity, hyperglycaemia, fat

maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash. These are discussed in more detail in Chapter 2.

Much research has been and is still being conducted in the area of understanding, preventing and managing ARV adverse effects, particularly those that threaten either the life of the patient or their adherence to treatment. However, there is still a need for patients to be actively involved in self-monitoring for adverse effects, in order to assist the HCPs in early identification of serious or potentially serious ARV effects and hence manage them appropriately.

The aim of this research was to try and develop a practical way of involving patients in their care plan, particularly with regards to reporting adverse effects or symptoms of adverse effects they may have experienced while receiving HAART. Thus two different monitoring methods including a patient journaling or diary system, which would not only monitor adverse effects but also adherence, and an adverse effect monitoring tool were developed and tested. The primary aim of the study was thus to evaluate the extent to which these monitoring strategies may contribute to the early identification and management of adverse effects associated with ARVs. This was to be achieved by modifying the adverse effect monitoring tool previously developed and piloted by Diergaardt (2005) and modified by Mulinge (2008) and developing and implementing the patient self-monitoring diary for the patients to monitor their own adverse effects. The extent to which the above strategies facilitate the identification of adverse events associated with ARV treatment as well as the perceived ease of use of the monitoring tool by HCPs and the diaries by the patients would then be determined.

CHAPTER 2

ANTIRETROVIRAL TREATMENT

2.1 Introduction to Antiretroviral Treatment

Many years of research have yielded treatment advancements able to slow the impact of HIV infection (Shibuyama *et al.*, 2006). These treatments have essentially transformed HIV and AIDS from a terminal disease to a chronic disease. As a result of the emphasis, HIV and AIDS management has moved from palliative care to "promoting adherence, minimizing treatment- and disease-related morbidities, optimizing outcome and controlling the costs of ongoing treatment" (Chao, 2006).

The range of antiretroviral (ARV) drugs approved by the United States Food and Drug Administration (FDA) for the treatment of HIV and AIDS has increased to about 27 medications since zidovudine (AZT) was first approved in 1987. Until 1991, AZT was the only approved drug for the treatment of HIV infection with many patients responding favourably to monotherapy, with a decrease in viral load and an increase in CD4+ cell count (Cohen, 2006).

Didanosine (ddI) was the second antiretroviral drug to be approved in 1991, and in combination with AZT produced favorable and superior results compared to those experienced with AZT monotherapy. However, the effectiveness of these NRTIs was often not sustained and patients eventually became viremic. This necessitated the development of other ARVs to overcome the problem of resistance to mono or dual NRTI therapy (Cohen, 2006). Eventually research resulted in the development of protease inhibitors (PIs) and combination of a PI with NRTIs in a three-drug regimen

was shown to be more potent and to achieve more durable suppression than dual NRTI therapy. Table 2.1 below shows the approval of the available ARVs.

Table 2.1 Antiretroviral drug FDA approval

Adapted from: Corbett, 2007

ARV Drug	Year approved	Available in South Africa
Zidovudine (AZT)	1987	Yes
Didanosine (ddI)	1991	Yes
Zalcitabine (ddC)	1992	No
Stavudine (d4T)	1994	Yes
Saquinavir (SQV) Lamivudine (3TC)	1995	Yes Yes
Ritonavir (RTV) Indinavir (IDV) Nevirapine (NVP)	1996	Yes Yes Yes
Nelfinavir (NFV) Delavirdine (DLV)	1997	Yes No
Efavirenz (EFV) Abacavir (ABC)	1998	Yes Yes
Amprenavir (APV)	1999	Yes
Lopinavir-ritonavir (LPV/r)	2000	Yes
Tenofovir (TDF)	2001	Yes
Fosamprenavir (FPV) Emtricitabine (FTC) Atazanavir (ATV) Enfuvirtide (T-20)	2003	Yes Yes Yes No
Tipranavir (TPV)	2004	No
Darunavir (DRV)	2006	No
Maraviroc (MVC) Raltegravir (RAL)	2007	No No
Etravirine (ETV)	2008	No

Most patients initially started treatment with AZT and other drugs were added to their regimen as they became available. This type of sequential combination therapy was

observed to have a considerably lower response when compared with simultaneously initiated combination therapy (Cohen, 2006). The current standard of care for initial HAART has been defined, based on the results from numerous randomized studies and consists of a dual NRTI backbone and either a NNRTI or a ritonavir-boosted PI. The rationale for prescribing a minimum of three drugs is to reduce viral resistance, allow for a reduction in individual ARV doses (and thus decrease risk of toxicity) and to provide for a maximal suppression of viral load, to a point where viral load is undetectable (Regensberg and Whitelaw, 2007).

Although HAART is not a cure for AIDS, it may significantly prolong the lives of patients, by decreasing the morbidity and mortality associated with HIV infection (Stanic and Grana, 2009). According to Jevtović and colleagues (2009), HIV infected patients receiving ARV therapy have their life expectancy increased by more than 10 years. Increasing numbers of patients enrolled on HAART has resulted in decreased mortality (Pitt, Myer and Wood, 2009). With the use of ARVs, the viral load may be reduced to undetectable concentrations (< 40 copies/ml) and the CD4+ cell count increased sometimes to normal levels (400-1600 cells/ml) which is a desired outcome of HAART. This however does not mean that the patient is cured as the virus is still found to be latent in memory T cells. The virus forms part of the host's genome, serving as a potential source for reactivation if treatment is stopped or fails (Fletcher and Kakuda, 2003).

2.1.1 Goals of HIV treatment

The primary goal of antiretroviral therapy (ART) is to suppress viral replication (Cohen, 2006). Suppressing or preventing HIV replication results in:

- Maximal and durable suppression of viral load
- Reducing damage to the immune system of the host
- Restoration and preservation of immunologic function. (Cohen, 2006)

Other goals of HIV treatment include:

- Prolonging life expectancy
- Improving quality of life
- Reducing HIV-related morbidity and mortality
- Preventing transmission of the virus (e.g. mother to child). (Regensberg and Whitelaw, 2007)

ART is considered effective when it consistently results in sustained suppression of HIV RNA replication and steady increases in CD4 cell count, sometimes to normal levels, even in persons with advanced HIV infection (Kojic and Carpenter, 2006).

2.1.2 Initiation of ARV treatment

The timing of when to commence ART is not a simple decision as it involves consideration of a number of factors. The benefits of initiation of ART must be carefully weighed against risks. The trend is increasingly moving toward early ART initiation, since research has shown that the risks associated with ARV therapy are less than those resulting from delayed treatment. (Thompson, Aberg and Cahn, 2010)

The patient's commitment to ARV treatment is a crucial part of the decision to initiate therapy. The patient must be willing to accept and adhere to a complex regimen of drugs before embarking on therapy (Regensberg and Whitelaw, 2007). In South Africa, the final decision to initiate treatment lies with a multi-disciplinary team consisting of

community adherence supporters, counsellors, nurses, pharmacists, doctors, nutritionists and social workers (Department of Health, 2008).

Patients on the ARV rollout program are prescribed a 28-day course of co-trimoxazole, a broad spectrum antibiotic used for prophylaxis and treatment of opportunistic bacterial infections, to assess for adherence. The patients are given a return date on which a co-trimoxazole pill count is conducted and the patients' adherence determined, based on the number of tablets remaining. Once the patient has been assessed for readiness and accepts the proposed treatment option, the clinician initiates treatment (Department of Health, 2008).

Ideally, the initial regimen should be individualized taking the following into consideration;

- Resistance patterns of the HIV strain
- Predicted virologic efficacy
- Drug toxicity profiles
- Tolerability, pill burden, dosing frequency,
- Possible drug interactions
- Other comorbidities
- Patient and provider preferences. (Thompson, Aberg and Cahn, 2010)

The criteria for ART initiation in adults and adolescents in South Africa, including pregnant women, are summarized in table 2.2 below.

Table 2.2: The South African criteria for ART initiation in adults

(Source: Department of Health, 2010, p.8)

Eligible to start ART
CD4 count <200cells/ml irrespective of clinical stage **OR** CD4 count <350cells/ml o In patients with TB/HIV o Pregnant women **OR** WHO stage IV irrespective of CD4 count **OR** MDR/XDR irrespective of CD4
Require fast track (i.e. ART initiation within 2 weeks of being eligible
Pregnant women eligible for lifelong ART **OR** Patients with very low CD4 (<100cells/ml) **OR** Stage 4, CD4 count not yet available **OR** MDR/XDR TB
Not yet eligible for ART
• Transfer to a wellness programme for regular follow up and repeat CD4 testing 6-monthly • Advice on how to avoid HIV transmission to sexual partners and children • Initiate INH prophylaxis if asymptomatic for TB • Contraceptives and annual Pap smear

ARV therapy needs to be individualized and each patient assessed for adverse effects and effectiveness. Effective ART should reduce the plasma HIV RNA by >90% (1 log10) within 2 weeks of treatment. Poor adherence, viral resistance, or inadequate exposure to the drug may result in suboptimal results. An increase in the CD4 count usually follows the decrease in viral load (Kojic and Carpenter, 2006).

2.1.2.1 Initiation of ARV treatment in patients with TB

In patients with TB who are not already on ART, the commencement of ART is guided by the CD4 count. This is because, although TB is considered an AIDS-defining illness, it can occur at any stage of HIV infection in countries where TB is endemic. The following recommendations are therefore followed in such instances;

- CD4 > 350 cells/ mm^3: ART is commenced after TB treatment is completed provided the above criteria is met (Department of Health, 2010).
- CD4 50-350 cells/ml: ART is delayed until the intensive phase of TB treatment (2 months). If however the patient has other serious HIV-related illnesses, ART should be introduced once the patient is stable on TB therapy (approximately 2 weeks) (Department of Health, 2010).
- CD4 < 50 cells/ mm^3: ART is introduced once the patient is stabilized on TB therapy (Regensberg and Makiwane, 2009).

According to the South African Department of Health (2010), the following is recommended for patients who develop TB while on ART;

- ART should be continued throughout TB treatment
- Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. These changes to Lopinavir/Ritonavir should be continued until 2 weeks after completion of TB medication
- Patients should be monitored and investigated appropriately for hepatotoxicity symptoms

Immune reconstitution inflammatory syndrome (IRIS) which may be a major concern while commencing HAART is also of importance. IRIS occurs when commencement of

ART causes a paradoxical flare up of opportunistic infections such as TB, cytomegalovirus infections, and pneumonia due to the restoration of the immune system (Garciarena, Juarbe and El-Abassi, 2009). This is common when ART is commenced within the intensive phase of TB treatment and in patients with advanced disease (indicated by low CD4 cell counts). In the case of TB, IRIS would manifest as a return of the symptoms of TB and a paradoxical enlargement of TB lesions.

2.2 ARV Classes

2.2.1 Currently approved ARVs

Several classes of ARVs have been developed but not all are currently available in South Africa. The older agents include:

- Reverse Transcriptase Inhibitors (RTIs), which are divided into three subgroups
    - Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
    - Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)
    - Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Ribonucleotide Reductase Inhibitors (RnRIs). (Regensberg and Whitelaw, 2007)

Newer ARV agents include:

- Entry inhibitors
- Fusion inhibitors
- Integrase inhibitors
- Chemokine coreceptor antagonists (Chen, Hoy and Lewin, 2007)
- The table below shows the antiretrovirals currently approved by the FDA.

Table 2.3 ARVS currently approved by the FDA

(Shibuyama *et al.*, 2006, p. 1077)

Class	Drug	Examples of Trade names
NNRTIs/ NtRTIs	AZT	Retrovir®
	ddI	Videx®/Videx EC®
	ddC**	Hivid®
	d4T	Zerit®
	3TC	Epivir®
	ABC	Ziagen®
	TDF	Viread®
	FTC	Emtriva®
NNRTIs	NVP	Viramune®
	DLV	Rescriptor®
	EFV	Sustiva, Stocrin®
	ETV	Intelence®
PIs	SQV Hard Gelatin Capsule Soft Gelatin Capsule	 Invirase® Fortovase®
	RTV	Norvir®
	IDV	Crixivan®
	NFV	Viracept®
	APV**	Agenerase®
	LPV/r	Kaletra®
	FPV	Lexiva®
	DRV	Prezista®
	ATV	Reyataz®
	TPV	Aptivus®
RnRIs	Hydroxyurea (HU)	Hydrea®
Fusion Inhibitors	T-20	Fuzeon®
CCR5 Antagonists	MVC	Selzentry®/ Celsentri®
Integrase Inhibitors	RAL	Isentress®

**Discontinued in the US

2.2.2 ARV targets in the HIV lifecycle

The figure below shows the different steps in HIV replication and the potential targets for the different classes of ARVs. The mechanism of action of the different available ARVs is discussed below.

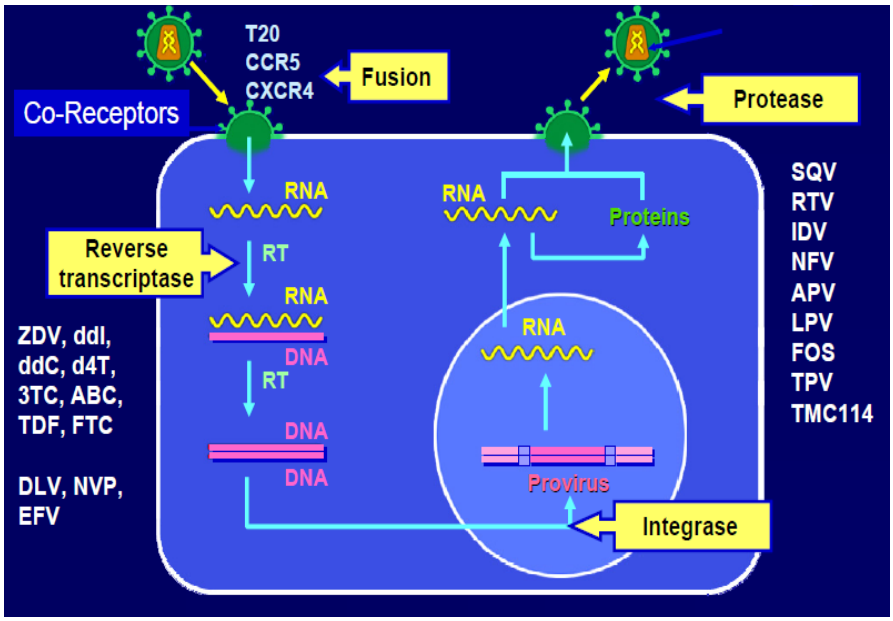


Figure 2.1 ARV targets in the HIV lifecycle

(Source: Ananworanich, 2007)

2.3 Specific ARV Classes

2.3.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

"The HIV genome is a diploid consisting of two RNA copies with identical polarity inside the HIV-1 virion" (Agrawal *et al., 2006*). The virion contains an enzyme, reverse transcriptase that catalyzes the conversion of RNA to DNA. Reverse transcriptase uses the viral genomic RNA as a template for the replication of RNA to DNA by binding to one RNA strand and copying the RNA nucleotides using corresponding DNA nucleotides. The infected host cell provides the nucleosides which are activated by the

addition of three phosphate radicals. The nucleosides are important for the formation of proviral DNA by viral reverse transcriptase.

NRTIs are prodrugs that require activation in the cell, through phosphorylation, before they are able to inhibit their target. The host cell enzymes phosphorylate the NRTIs to 5'-triphosphates, which then act as false substrates mimicking naturally occurring nucleosides (Safrin, 2004). The pseudo-analogues compete with the naturally occurring nucleosides to bind to viral reverse transcriptase, thus blocking the active site and getting incorporated into the growing viral DNA chain. The incorporation of the 5'-triphosphate into the chain results in chain termination and inhibition of viral cell production (Agrawal *et al., 2006*).

The NRTIs are subdivided into Thymidine analogues and Non-Thymidine analogues as listed in Table 2.4 below.

Table 2.4 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

(Adapted from: Gibbon, 2005)

Thymidine Analogues	Non-Thymidine Analogues
Stavudine (d4T)	Didanosine (ddI)
Zidovudine (AZT)	Zalcitabine (ddC)
	Lamivudine (3TC)

2.3.2 Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

The difference between the NtRTIs and the NRTIs is that the NtRTIs contain a phosphate group and therefore only require two phosphorylation steps to be converted to the active metabolite that serves as a false substrate in the reverse transcriptase

reaction (Fletcher and Kakuda, 2003). Reverse transcriptase fails to distinguish the phosphorylated NRTIs from the naturally occurring nucleotides, and incorporates the pseudo-analogues in the synthesis of viral DNA, which leads to inhibition of the addition of further nucleotides and hence a full-length copy of the viral DNA is not produced (Coffey and Peiperl, 2008). Tenofovir is an example of an NtRTI.

2.3.3 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The NNRTIs specifically interact with a non-substrate binding site, closely associated, but distinct from the substrate binding site of reverse transcriptase enzyme, denaturing it in a way that inhibits the enzyme's activity and therefore preventing the conversion of viral RNA to viral DNA and inhibiting replication. The use of NNRTIs is limited by emergence of resistant strains hence NNRTIs are normally used in combination with NRTIs. Examples of NNRTIs include nevirapine (NVP), efavirenz (EFV) and delavirdine (DLV). Newer NNRTIs which have been recently approved include etravirine and rilpivirine. Further NNRTIs in the developmental process include capravirine which has shown promise in early clinical trials. Capravirine and etravirine have been shown to be effective in viral strains resistant to the currently available NNRTIs. Thiocarboxanilide UC-781 is yet another NNRTI in the developmental stages for use as a topical microbicide for the prevention of sexual transmission of HIV. (Agrawal *et al., 2006*)

2.3.4 Protease Inhibitors (PIs)

Viral protease is the enzyme that catalyses the packaging, maturation and budding of new viruses, during viral cell production (Fletcher and Kakuda, 2003). This leads to the production of the mature infectious virions. PIs bind to the active site of the viral protease enzyme, preventing the processing of viral proteins into functional particles.

Viral particles are still produced when the protease is inhibited, but these particles are immature and non infectious (Coffey and Peiperl, 2008).

Since protease is not found naturally within the host, it serves as a good target associated with resistance and must therefore be used in combination treatment. High intracellular concentrations increase efficacy of PIs, hence in most cases (except for nelfinavir) a PI is boosted with a low dose of ritonavir (100-400mg/d) in order to enhance the plasma concentration of the PI through the inhibition of the PI's metabolism via the CYP3A4 system (Stanic and Grana, 2009). This mechanism is referred to as PI boosting, and in some cases it has led to the reduction of dosage frequency, pill burden and reducing food restrictions hence improving adherence (Weston, Portsmouth and Benzie, 2006). PIs are typically reserved for second line therapy (Fletcher and Kakuda, 2003).

2.3.5 Ribonucleotide Reductase Inhibitors (RnRIs)

RnRIs inhibit the enzyme ribonucleotide reductase thereby blocking the transformation of ribonucleotides into deoxynucleotides, depleting the intracellular deoxynucleotide triphosphate pool and imparing viral replication. This results in decreased production of nucleotides essential in DNA synthesis. Used in combination with NRTIs, RnRIs forces viral reverse transcriptase to use the pseudonucleotides formed by the NRTIs, thus giving rise to a synergistic effect of these agents inhibiting viral replication (Kelly, Lisziewicz and Lori, 2004). Hydroxyurea is an RnRI available for the treatment of HIV infection.

Hydroxyurea has been used for many years in hematology, particularly in the treatment of myeloproliferative disorders and recently for the treatment of sickle-cell anaemia (Kelly, Lisziewicz and Lori, 2004). Hydroxyurea provides two anti-HIV mechanisms described below:

Antiviral Mechanism

- A direct antiviral effect by blocking viral replication in macrophages which mediate neuronal damage in HIV infection
- An indirect effect by potentiating the activity of NRTIs by;
    - decreasing the relative concentration of the intracellular deoxynucleotide triphosphates, particularly the deoxyadenosine triphosphate pool hence acting synergistically with nucleotide analogues such as ddI (an adenosine analog) which mimic naturally occurring nucleotides
    - enhancing the activity of deoxycytidine and thymidine kinases which are involved in the conversion of NRTI pro-drugs to active metabolites (the triphosphorylated form) (Kelly, Lisziewicz and Lori, 2004).

Immunomodulating/Cytostatic Mechanism

- HU prevents T-cell proliferation, reducing HIV cellular targets, and therefore exhibiting an immunomodulating, cytostatic effect on HIV replication by (Kelly, Lisziewicz and Lori, 2004).

HU when prescribed alone has the following adverse effects;

- Mild toxicity- GI complaints such as nausea, vomiting, diarrhoea and anorexia
- Prolonged use- Infrequently causes alopecia, hyperpigmentation, erythema and leg ulcers

- Severe toxicity- Includes neutropenia, anaemia and thrombocytopenia which are dose related and potentiated when used in combination with other myelosuppressive drugs such as AZT (Kelly, Lisziewicz and Lori, 2004).

HU is teratogenic and is therefore not to be used in pregnancy or for lactating mothers. The HU-ddI combination is a synergistic cytostatic and virostatic one with an excellent resistance profile and potent antiviral activity that is valuable for long term treatment of HIV infection. (Kelly, Lisziewicz and Lori, 2004)

2.3.6 Entry Inhibitors

At the initial stage of its replication cycle, HIV gp120 attaches to the host CD4 receptors, which allows binding to chemokine coreceptors on CD4 cells, specifically chemokine coreceptor 5 (CCR5) expressed on dendritic cells, macrophages and T-lymphocyte cells or CXC chemokine coreceptor 4 (CXCR4) expressed only on T-lymphocytes (Stanic and Grana, 2009). This binding results in conformational changes that allow viral gp41 to form a pore in the membrane through which the virus can enter the host cell (Boyd and Pett, 2008). Entry inhibitors target this initial step in the HIV life cycle.

Entry inhibitors are mainly used in the treatment of HAART-experienced adults whose HIV infection is resistant to multiple classes of antiretrovirals or who are intolerant of other antiretrovirals (Weston, Portsmouth and Benzie, 2006).

Entry inhibitors are divided into two subclasses namely fusion inhibitors and CCR5 inhibitors (Stanic and Grana, 2009). The two classes are further discussed below.

2.3.6.1 Fusion Inhibitors (FIs)

HIV fusion inhibitors represent a novel class of antiretroviral drugs with enfuvirtide (T-20) as the first drug within this class to be approved by the FDA. T-20 acts by binding to

the first heptad repeat region of gp41, preventing conformational changes that result in interactions with the second heptad repeat region. This results in interruption of the fusion reaction and prevents the virus from penetrating and infecting the host cell. (Boyd and Pett, 2008)

Enfuvirtide is a large peptide which is broken down in the digestive tract before absorption takes place and hence cannot be orally administered (Boyd and Pett, 2008). It is administered as a subcutaneous injection twice daily. Although this route of administration is favorable due to insignificant potential for drug-drug interactions, it also presents a disadvantage as the patients require training on administration and may experience injection site reactions (Weston, Portsmouth and Benzie, 2006).

T-20 does not appear to have toxicity profiles similar to the other antiretrovirals, with its adverse effects including hypersensitivity reactions manifesting as rash, fever, chills, nausea and vomiting. The most common adverse effect is injection site reaction, characterized by local pain, erythema, pruritus, induration, ecchymosis, nodules and cysts, which occurs in about 90% of enfuvirtide users. (Boyd and Pett, 2008)

2.3.6.2 Chemokine Co-receptor (CCR5) Inhibitors

Maraviroc was the first CCR5 inhibitor to be approved by the FDA for use in combination with other antiretrovirals in patients experiencing resistance to other ARVs. Maraviroc is specifically indicated for patients infected with CCR5-tropic HIV-1 (Yost, Pasquale and Sahloff, 2009).

The HIV cell entry step involves the binding of the HIV glycoprotein complex consisting of gp41 and gp120 with the CD4 receptor on the membrane of the host cell. Subsequent conformational changes on gp120 lead to the exposure of coreceptor

binding sites as shown in the left section of Figure 2.2 below. The two major chemokine coreceptors involved in viral entry are CCR5 and CXCR4. “CCR5-tropic strains are predominant during the early stages of HIV infection while the CXCR4-tropic viruses are associated with faster disease progression and are more likely to be encountered in later stages of HIV infection” (Yost, Pasquale and Sahloff, 2009). The exposed coreceptor sites bind to CCR5 or CXCR4 on the host cell membrane as shown on the centre panel of Figure 2.2, initiating the fusion of the HIV envelope with the host cell and entry of viral contents into the host cell (see centre panel inset). Maraviroc competitively and selectively binds to CCR5 and undergoes conformational changes such that it is not recognized by gp120 coreceptor binding sites as shown on the right section of Figure 2.2. Infection of the host cell is therefore prevented (Yost, Pasquale and Sahloff, 2009).

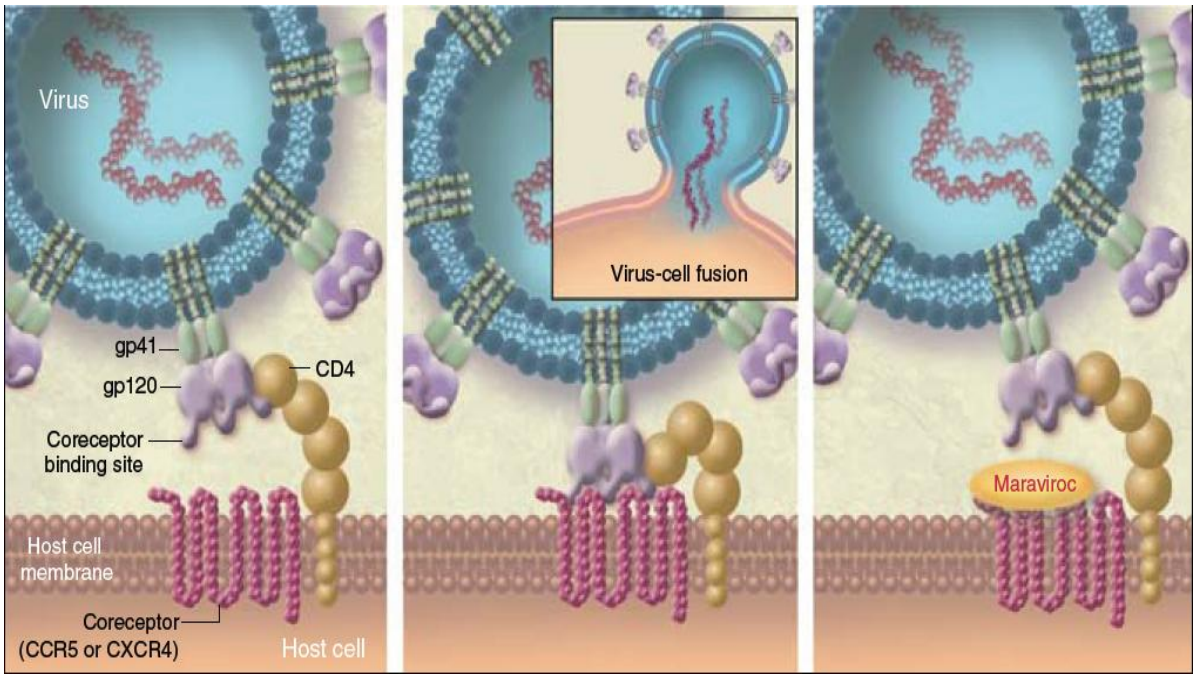


Figure 2.2 Mechanism of action of maraviroc

(Source: Yost, Pasquale and Sahloff, 2009, p. 716)

Studies have shown that maraviroc is only active against CCR5-tropic virus and it has no activity against CXCR4-tropic or dual- or mixed- tropic HIV (Yost, Pasquale and Sahloff, 2009). Tropism assays must therefore be performed to determine the coreceptor specificity of a patient's HIV strain before initiation of therapy with maraviroc. Recent studies have evaluated the use of maraviroc as a first line therapy and it has been proposed that maraviroc may be more useful in acute and early infection as CCR5 coreceptors are predominantly encountered in early HIV disease (Stanic and Grana, 2009). CXCR4 tropic viral strains are predominantly encountered in advanced HIV disease. The change in tropism from CCR5- to CXCR4-tropic viruses is often seen with disease progression and is under investigation as a cause for treatment failure with maraviroc (Yost, Pasquale and Sahloff, 2009).

Following oral administration, maximal absorption of maraviroc occurs in about 0.5 to 4 hours. Studies have shown that maraviroc may be administered without regard for food. Maraviroc is metabolized by the CYP3A system to inactive metabolites. The use of maraviroc in patients with hepatic or renal dysfunction has not been adequately studied. Therefore, maraviroc should be used with caution in patients co-infected with hepatitis B or C and in patients with hepatic dysfunction due to potential for increased maraviroc concentrations as it is mainly metabolized by the liver. (Yost, Pasquale and Sahloff, 2009)

Maraviroc has generally been well tolerated. The adverse effects of maraviroc include abdominal pains, sleep disturbances, upper respiratory tract infections, cough, pyrexia, rash, bronchitis, herpes infection, sinusitis, constipation, appetite disorders, dizziness or postural dizziness, joint signs and symptoms and musculoskeletal or connective tissue signs and symptoms (Yost, Pasquale and Sahloff, 2009). The most commonly observed

of these include upper respiratory tract infections, cough, pyrexia, rash and dizziness (Stanic and Grana, 2009). At the recommended dosage, postural hypotension is unlikely. However, if appropriate dosage adjustments are not made for concomitant interacting drugs, increased exposure to maraviroc may occur leading to an increase in the potential risk of postural hypotension (Yost, Pasquale and Sahloff, 2009).

Concern regarding the potential for CCR5 antagonists to increase the risk of infection and malignancies has been expressed. The CCR5 coreceptor has a role in human infections that is still not fully understood. So far, no definitive association between the use of CCR5 inhibitors and the onset of malignancies has been determined. In reported studies, it was found that some of the patients who developed malignancies were already predisposed to malignancies. (Yost, Pasquale and Sahloff, 2009)

In the USA, maraviroc contains a black-box warning regarding hepatotoxicity. Symptoms such as an itchy rash, increased eosinophils or liver inflammation warrant immediate medical attention. Maraviroc should be used with caution in patients with risk factors for cardiovascular disease as some patients with cardiac risk factors developed myocardial ischaemia or infarction in clinical trials. (Yost, Pasquale and Sahloff, 2009)

Maraviroc is metabolized by CYP3A4 and subsequently drug-drug interactions with inducers and inhibitors of the same system may lead to decreased or increased maraviroc plasma levels respectively. Maraviroc is formulated in 150- and 300mg tablets, and its standard dosing is 300mg orally twice daily. Studies have been conducted with regards to maraviroc interactions with other agents and a summary is provided below:

- Maraviroc dose is to be reduced to 150mg twice daily if concomitantly administered with CYP3A inhibitors, for example ketoconazole, itraconazole, clarithromycin, telithromycin and protease inhibitors- except tipranavir.
- Maraviroc dose should be increased to 600mg twice daily in the presence of CYP3A inducers for example efavirenz, rifampicin, carbamazepine, Phenobarbital and phenytoin.

Since approximately 25% of total maraviroc is cleared via the kidneys, it should be used in caution in patients with creatinine clearance of <50ml/min, particularly when co-administered with a CYP3A inhibitor as maraviroc may accumulate to toxic levels. Maraviroc should also be used with caution in patients with hepatic insufficiency as its metabolism may be impaired, leading to accumulation and potential adverse effects. (Yost, Pasquale and Sahloff, 2009)

Vicriviroc is another CCR5 inhibitor under development that is currently in phase III clinical trials.

2.3.7 Integrase Inhibitors

Integrase inhibitors are a new class of ARVs with raltegravir as the first in this class to be approved by the FDA. Raltegravir was approved in October 2007 for use in the treatment of HIV in treatment-experienced patients and patients who have ongoing viral replication while receiving ART. Studies have been conducted in treatment-naïve patients, and raltegravir was approved as initial treatment in July 2009. (Coffey, 2010)

Raltegravir inhibits the catalytic activity of HIV-1 integrase, an enzyme required for viral replication. Inhibition of integrase prevents incorporation of viral DNA into the host cell genome thus preventing the formation of the HIV-1 provirus. The provirus directs the

production of progeny virus, therefore inhibiting integration prevents propagation of the viral infection. (Stanic and Grana, 2009)

Raltegravir is formulated in 400mg tablets and administered orally (400mg) twice daily without regard for food. Raltegravir is not a substrate of the cytochrome P450 enzymes, and has no significant drug interactions via this route. However, raltegravir is metabolized by a uridine diphosphate glucoronosyltransferase (UGT) 1A1-mediated glucoronidation pathway. Thus drug-drug interactions with inducers and inhibitors of this system may occur with co-administration with raltegravir. For instance, rifampicin which induces UGT1A1 significantly reduces plasma concentrations of ralgetravir; therefore the dose of raltegravir should be increased to 800mg twice daily when co-administered with rifampicin. The impact of other inducers of drug metabolizing enzymes such as phenytoin and phenobarbital on UGT1A1 is unknown. Co-administration with inhibitors of UGT1A1 may increase plasma levels of raltegravir. (Merck & Co., 2007)

While mild to moderate hepatic impairment does not require dosage adjustment, the effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied. However, since raltegravir is primarily eliminated by glucoronidation in the liver, caution should be used in these patients. Renal clearance of raltegravir is a minor pathway and studies have shown that no dosage adjustments are needed in renal impairment. (Merck & Co., 2007)

The long term effects of raltegravir are unknown although it currently appears to be well tolerated (Graziano and Djuricich, 2009). The most common adverse effects of raltegravir include diarrhea, nausea, headache and fever. Less common adverse effects include abdominal pain, vomiting, fatigue, weakness, dizziness, genital herpes, herpes

zoster, renal failure and lipodystrophy. Other adverse effects observed included new and recurrent cancer although the relationship to raltegravir is unclear and in these cases other risk factors such as neutropenia, thrombocytopenia, and elevated liver enzymes were involved. Raltegravir may also cause an increase in creatine kinase, resulting in unexplained muscle pain, tenderness or weakness. Hypersensitivity reactions, increases in ALT, AST and total bilirubin, anaemia, neutropenia and gastritis may also occur. (Merck & Co., 2007)

Post-approval of raltegravir, psychiatric disorders like anxiety and depression- including suicidal ideation and behavior, paranoia (particularly in patients with a pre-existing history of psychiatric illness), rash and stevens-johnson syndrome have been reported (Graziano and Djuricich, 2009).

Elvitegravir is another integrase inhibitor under development, currently in phase III clinical trials (Stanic and Grana, 2009).

2.4 ARV Combinations

As stated in Chapter 1, ARVs are administered in combination in order to achieve maximal viral suppression, reduce individual ARV doses (and hence reduce toxicity) and prevent or delay development of resistance. The selection of drugs should be based on existing data on effectiveness, resistance profile and on the individual patient situation, taking into account the adverse effect profile, potential interactions, and additive toxicities in each patient. A HAART regimen usually consists of three ARV drugs from different classes.

Factors to be considered when selecting initial regimens for treatment naïve patients include:

- Comorbidity such as hepatitis B, C, TB, psychiatric disease, cardiovascular disease, renal disease, chemical dependency, liver disease, pregnancy and other significant conditions
- Patient adherence potential
- Convenience - considering pill burden, dosing frequency, dosage forms, refrigeration requirements, food and fluid considerations
- Potential adverse effects – for example, women, particularly those with body mass index > 28 are at a higher risk of developing lactic acidosis and therefore d4T is contraindicated in these patients
- Potential drug-drug interactions with concurrently administered drugs, self medicated or prescribed
- Pregnancy potential - for example, women of a child bearing age or who do not have effective and consistent contraception should not receive efavirenz due to its teratogenicity
- Genotypic resistance testing results - showing resistance patterns of the particular patient's HIV strain
- Gender – In certain cases women are more likely to develop adverse effects than men, for instance with regards to lactic acidosis, the female gender is a risk factor
- Pre-treatment cd4 cell count- low cd4 counts predispose patients to more adverse effects discussed further below. On the other hand, NVP induced acute hepatitis is usually seen in patients with higher cd4 counts

- If ABC is considered, HLA B* 5701 is tested; patients who test positive are likely to develop a hypersensitivity reaction with ABC and hence an alternative NRTI should be considered. (Department of Health and Human Services, 2008)

The following NRTIs combinations should be avoided;

- AZT and d4T – due to antagonistic effect
- d4T and ddC – due to similar toxicity profiles
- 3TC and FTC – as they are used interchangeably
- TDF and ddI combined with an NNRTI – associated with high rates of early virological failure. (WHO, 2010)

Hence selection of a HAART regimen should be individualized for each patient taking into consideration their circumstances. The ARV regimens available in South Africa are tabulated below:

Table 2.5 Currently available ARV regimens in the South African public sector
(Adapted from: Department of Health, 2010)

Regimen	Drugs	Comments
First Line	TDF+3TC/FTC+EFV/NVP	• EFV for TB co-infected patients • NVP for women of child bearing age not on reliable contraception
	d4T+3TC+EFV/NVP	• If well tolerated with no adverse effects patients to remain on treatment. Substitute with TDF in high risk patients (high BMI, older, female, receiving TB treatment)
	AZT+3TC+EFV/NVP	• In cases where TDF is contraindicated (renal insufficiency)
Second Line	TDF+3TC/FTC+ LPV/r	• For patients failing on d4T or AZT based regimens
	AZT+3TC+LPV/r	• For patients failing on TDF based first line regimens

In the USA, the ARV regimens differ from those used in South Africa, most notably d4T is not commonly used as it is considered a toxic drug. Currently preferred regimens are made of two NRTIs and an NNRTI or a ritonavir boosted PI. For the NNRTI based regimens, EFV is the preferred NNRTI, except in the first trimester of pregnancy or in sexually active women of childbearing age with ineffective or inconsistent contraception. NVP may be used as the alternative NNRTI in females with a pre-treatment CD4 cell count < 250 cells/mm^3 and males <400 cells/mm^3, due to higher risk of these patients to develop acute hepatitis (Department of Health and Human Services, 2008).

The USA has a wider variety of ARVs when compared with South Africa, due to, amongst other reasons, availability of resources. The table below shows the regimens used in the USA as preferred (first line) and alternative (second line) treatment (the appropriate regimens are obtained by selecting one component from column A and one from column B).

Table 2.6 ARV regimens used in the U.S.A as first and second line treatment
(Adapted from: Department of Health and Human Services, 2008)

	Column A		**Column B**
	NNRTI	PI	NRTI
Preferred	EFV	-ATZ+RTV (od) -FPV+RTV(bd) -DRV+RTV(od) -LPV/RTV(od or bd)	TDF+FTC
Alternative	NVP	-ATZ (unboosted, od) -FPV(unboosted, bd) -FPV+RTV(od) -SQV+RTV(bd)	-ABC+3TC -ddI+3TC -AZT+3TC

Recent studies have indicated the need for a salvage therapy for patients responding poorly to second line therapy. This salvage therapy, a third line regimen, should include drugs such as integrase inhibitors, newer generation NNRTIs and newer PIs. Randomized controlled studies have been conducted in developed countries for this suggested third line regimen and the results have been favourable. Raltegravir, etravirine and ritonavir-boosted darunavir is one such combination under review as a third line regimen. (WHO, 2010)

2.5 Adverse Effects Associated with ARVs

A drug reaction includes all adverse events linked to drug administration, despite the cause (Riedl and Casillas, 2003). It has been defined as “a noxious or undesired effect to an organism that occurs at doses of a drug used for prophylaxis, diagnosis or treatment” (Couper and Mehta, 2002). It may be indicated by change such as death, altered food or water consumption, changes in body and organ weights, enzyme levels, or visible illness. A drug effect is termed as adverse if it results in functional or anatomical damage, or if it causes change that is irreversible in the homeostasis of the organism, or increases the vulnerability of the organism to other chemical or biological stresses. When these effects are considered to be secondary to a main or therapeutic effect, they are termed side-effects (Couper and Mehta, 2002).

Drug adverse effects are classified as either Type A or Type B. Type A reactions account for about 70-80% of drug adverse reactions and are due to drug factors, including the pharmacological action of the drug or its active metabolites. Unlike Type A reactions, Type B drug reactions are due to patient factors and not drug characteristics.

Type B reactions include idiosyncratic reactions, allergic or immunologic reactions and carcinogenic or teratogenic effects. (Eisenhauer, 2002)

Adverse effects have been reported with all ARVs and are among the most common reasons for switching or discontinuation of therapy and for medication non-adherence (Department of Health and Human Services, 2008). The adverse effects experienced by HIV and AIDS patients after the initiation of HAART are often non-specific as they may be due to patient factors, disease or treatment characteristics.

HIV infection is characterized by a wide range of symptoms including pain, fatigue, dyspnoea, cough and sleep disorders, which often present significant challenges in the lives of the infected patients. Adverse effects of ARVs may at times resemble the symptoms of HIV disease and lead to impaired quality of life and level of functioning. Consequently, it is essential to establish that the symptoms experienced by the patients are in fact related to the ARV therapy, before deciding on the appropriate management of the symptoms. This requires HCPs to have optimal understanding of HAART regimens and their associated complications. (Schiller, 2005)

Ideally ARVs should be selective towards HIV, aiming to hinder different targets in its lifecycle and having minimal effect on the normal human cells. This however, is not the case and the result is that these drugs are associated with numerous adverse effects that have both short-term and long-term consequences (Johnson *et al.*, 2005).

Since ARV drugs are taken in combination, deciding what contribution individual drugs have to symptoms that are manifest, as well as deciding what symptoms are due to HIV disease, or are completely unrelated either to the drugs or to the illness, is a challenge (Department of Health, 2005). Adverse effects associated with ARVs are classified as short term (such as diarrhea, nausea, vomiting) and long term (such as fat

redistribution) (Stanic and Grana, 2009). The risk of developing specific adverse effects varies with different drugs, drug classes and patients (Montessori *et al.*, 2004).

Some adverse effects of ARVs are summarized in the figure below. In some cases, only a certain drug causes a particular adverse effect and these are shown in parentheses below.

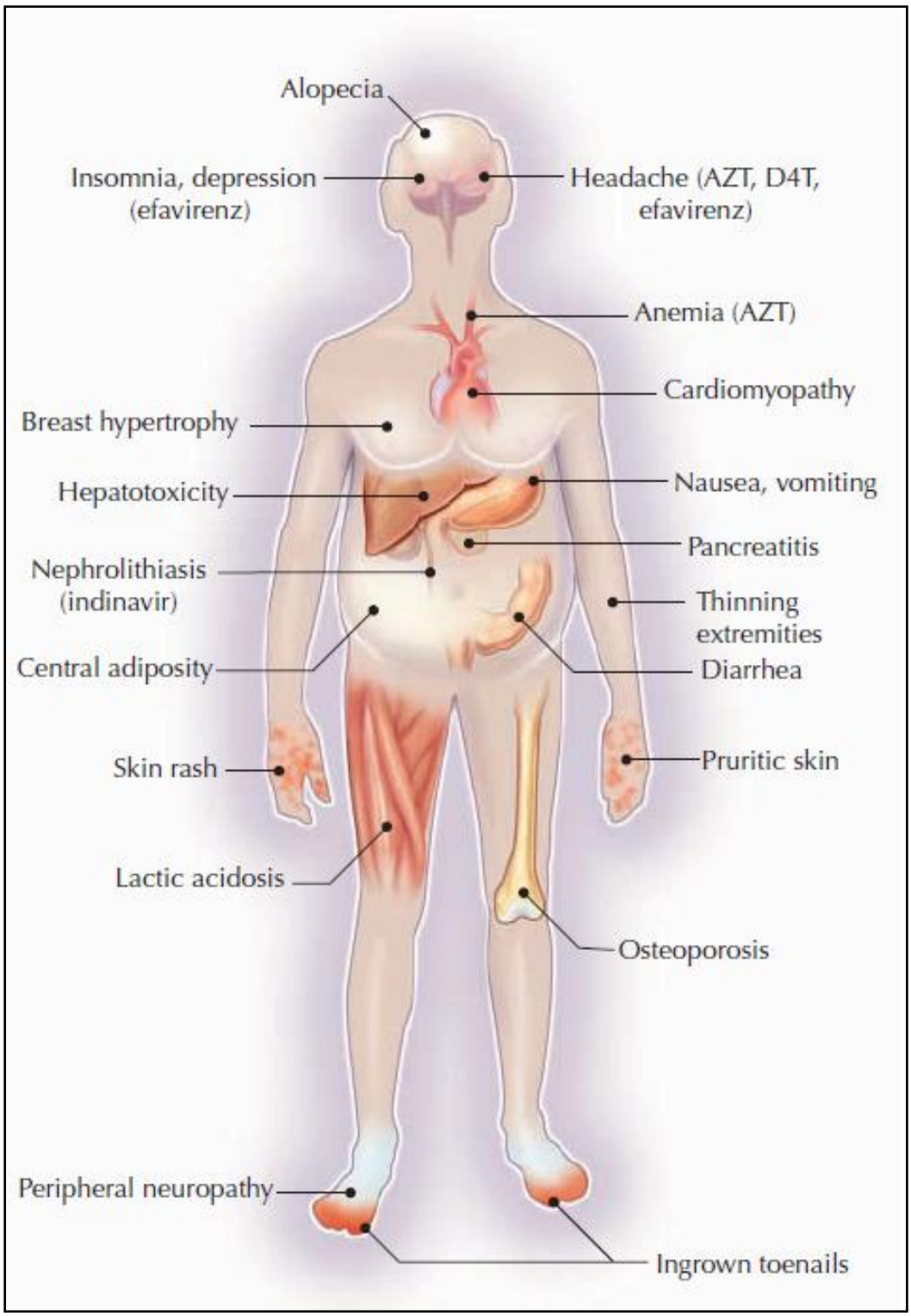


Figure 2.3 Adverse effects of ARVS

(Source: Montessori *et al.*, 2004, p.232)

2.5.1 ARV class adverse effects

Each ARV drug is associated with its own specific adverse effects that may be unique to that particular ARV or common in the ARV class in which the drug falls (Montessori *et al.*, 2004). Several adverse effects are common to many of the antiretroviral drugs, but these effects vary in severity for each individual drug. The class specific adverse effects of the different ARV classes are tabulated below.

Table 2.7 ARV class adverse effects

(Adapted from: Stanic and Grana, 2009, p.53)

ARV drug class	Associated adverse effects
NRTIs	• GI Intolerance • Peripheral neuropathy • Lactic acidosis • Pancreatitis • Bone marrow suppression • Lipoatrophy (especially d4T and AZT) • Renal toxicity (especially with TDF)
NNRTIs	• Rash • Liver toxicity • Dyslipidemias
PIs	• GI intolerance • Metabolic disorders (including fat maldistribution, insulin resistance, dyslipidemia)
FIs	• Injection site reactions • GI intolerance • Respiratory infections • Myalgias
CCR5 inhibitors	• Liver toxicity • GI intolerance
Integrase inhibitors	• Nausea • Diarrhea • Headache • Pyrexia

2.5.2 Specific ARV adverse effects

The following table indicates the adverse effects commonly associated with specific NRTIs, NNRTIs and PIs.

Table 2.8 Adverse effects associated with specific ARVs

(Department of Health and Human Services, 2008)

ARV Class	ARV drug	Common adverse effects	Comments
NRTIs	Zidovudine	• Anemia, neutropenia • Fatigue, insomnia, malaise, headache • Nausea, vomiting • Myalgia, myopathy • Hyperpigmentation of skin and nail beds	• Fatigue, nausea, headache, and myalgia usually resolve 2-4 weeks after initiation • Granulocytopenia has also been reported
	Didanosine	• Pancreatitis • Lactic acidosis • Peripheral neuropathy • Nausea, diarrhea	• Combination with d4T should be avoided
	Lamivudine	• Headache • Dry mouth • GIT effects (including mild abdominal discomfort and nausea)	• Generally well tolerated
	Emtricitabine	• Headache, nausea, insomnia • Hyperpigmentation of palms and soles (most frequently seen in dark-skinned people)	• In hepatitis B co-infection, hepatitis may flare upon discontinuation of FTC
	Stavudine	• Peripheral neuropathy • Pancreatitis • Dyslipidemia • Diarrhea • Lactic acidosis	• Increased risk of peripheral neuropathy and lactic acidosis when combined with ddI
	Abacavir	• Hypersensitivity syndrome; rash occurs in about half of cases • Rash • Headache, nausea, vomiting, diarrhea	• Counsel patients on signs of hypersensitivity syndrome • In case of hypersensitivity syndrome, ABC must be discontinued permanently
	Tenofovir	• Flatulence, nausea,	• In patients with HIV and

ARV Class	ARV drug	Common adverse effects	Comments
		diarrhea, abdominal discomfort • Asthenia • Acute renal insufficiency, Fanconi syndrome • Chronic renal insufficiency	hepatitis B co-infection, hepatitis may flare upon discontinuation of tenofovir. • Adjust dosage for renal insufficiency or failure.
NNRTIs	Nevirapine	• Rash • Elevations in liver function tests, hepatitis, liver failure	• Initial dose of 200 mg per day for first 14 days, then 200 mg twice daily, decreases frequency of rash • Should not be initiated in women with CD4 counts of >250 cells/ml or men with CD4 counts of >400 cells/ml • Monitor liver tests closely for the first 16 weeks of treatment
	Efavirenz	• Elevations in liver function tests • Abnormal/vivid dreams, somnolence, drowsiness, dizziness, confusion • Hyperlipidemia	• CNS symptoms are common; severity usually decreases within 2-4 weeks • Contraindicated during pregnancy and for use by women who may become pregnant (teratogenic)
	Delavirdine	• Fatigue • Elevations in liver function tests, hepatitis • Nausea, diarrhea	• Seldom used as it is less potent than other NNRTIs
PIs	Amprenavir	• Diarrhea, nausea, vomiting • Elevations in liver function tests • Rash	• May cause rash in patients sensitive to or intolerant of sulfonamides
	Atazanavir	• Unconjugated hyperbilirubinaemia • Dyslipidaemia (low potential)	
	Darunavir	• Diarrhea • Nausea	

ARV Class	ARV drug	Common adverse effects	Comments
		• Rash • Dyslipidemias • Insulin resistance (moderate potential)	
	Fosamprenavir	• Diarrhoea • Nausea • Vomiting • Abdominal cramps • Headache • Fatigue	• Increased thirst or urination, mood changes and peripheral neuropathy are rare but possible adverse effects
	Indinavir	• Nephrolithiasis, flank pain • Hyperbilirubinemia • Elevations in liver function tests • Alopecia, dry skin, ingrown nails • Insomnia • Taste perversion	• Patients should drink at least 1.5 liters of fluid daily to reduce risk of nephrolithias
	Lopinavir/ritonavir	• Diarrhoea, nausea, vomiting • Dyslipidemia • Elevations in liver function tests • Taste perversion	• Oral solution contains 42% alcohol; avoid combining with metronidazole or disulfiram
	Nelfinavir	• Diarrhoea • Nausea, vomiting • Elevations in liver function tests • Fatigue	• Diarrhoea is very common; usually can be managed with antidiarrheals such as loperamide and diphenoxylate/atropine.
	Ritonavir	• Nausea, vomiting, diarrhoea, abdominal pain • Elevations in liver function tests • Fatigue • Circumoral or peripheral numbness • Taste perversion • Hyperuricemia	• RTV significant interactions with many other medications.
	Saquinavir	• Nausea, vomiting, diarrhoea • Elevations in liver	• Must be used in combination with low-dose ritonavir.

ARV Class	ARV drug	Common adverse effects	Comments
		function tests • Headache • Oral ulcerations	

2.5.2.1 ARV metabolic disorders

Metabolic disorders refer to a group of adverse effects that have been linked to long term use of ARVs. They include dyslipidaemias, lipodystrophy, diabetes mellitus, insulin resistance and decreased bone mineral density. Individual metabolic disorders are further discussed below. (Montessori *et al.*, 2004)

Table 2.9 Features of ARV-mediated metabolic syndrome

(Adapted from: Montessori *et al.*, 2004, p.234)

Condition	Observation/ test
Clinical	
Central fat accumulation	Intra-abdominal, dorsocervical spine, breast hypertrophy, lipomas
Peripheral lipoatrophy	Face, legs, arms, buttocks
Laboratory	
Dyslipidaemia	Hypertriglyceridaemia, low HDL cholesterol, high LDL cholesterol
Diabetes	High fasting blood glucose and HbA_{1c} levels
Insulin resistance	Increased insulin and c-peptide levels
Osteoporosis	Bone densitometry
Note: HDL = high density lipoprotein, LDL = low density lipoprotein, HbA_{1c} = haemoglobin A_{1c} (glycosylated haemoglobin)	

2.5.2.1.1 Lipodystrophy

Lipodystrophy, first described in 1998, is also known as fat redistribution and it refers to a disorder that the body uses and stores fat (Montessori *et al.*, 2004). The main clinical features of lipodystrophy are fat wasting/ peripheral fat loss, also known as lipoatrophy and central fat accumulation, also known as hyperadiposity or lipohypertrophy.

Lipodystrophy is primarily caused by PIs although d4T and AZT may also cause lipodystrophy (Department of Health and Human Services, 2008). Montessori and colleagues (2004) report that the overall prevalence of at least one physical abnormality associated with lipodystrophy is estimated to be about 50% after more than a year of ARV therapy, while Shibuyama and co-workers (2006) suggest that lipodystrophy is reported in 20% to 80% of patients receiving HAART.

Lipoatrophy usually occurs in the face (resulting in sunken cheeks, temples and eyes), arms and legs (where it may result in veins becoming more visible) and the buttocks. Lipohypertrophy is usually observed in the dorso-cervical region (buffalo hump), the abdominal region (crixivan potbelly) and in the breasts of both men and women (gynaecomastia). Lipodystrophy generally develops steadily, months after initiation of therapy. Some clinical features of lipodystrophy are illustrated in the figure below.

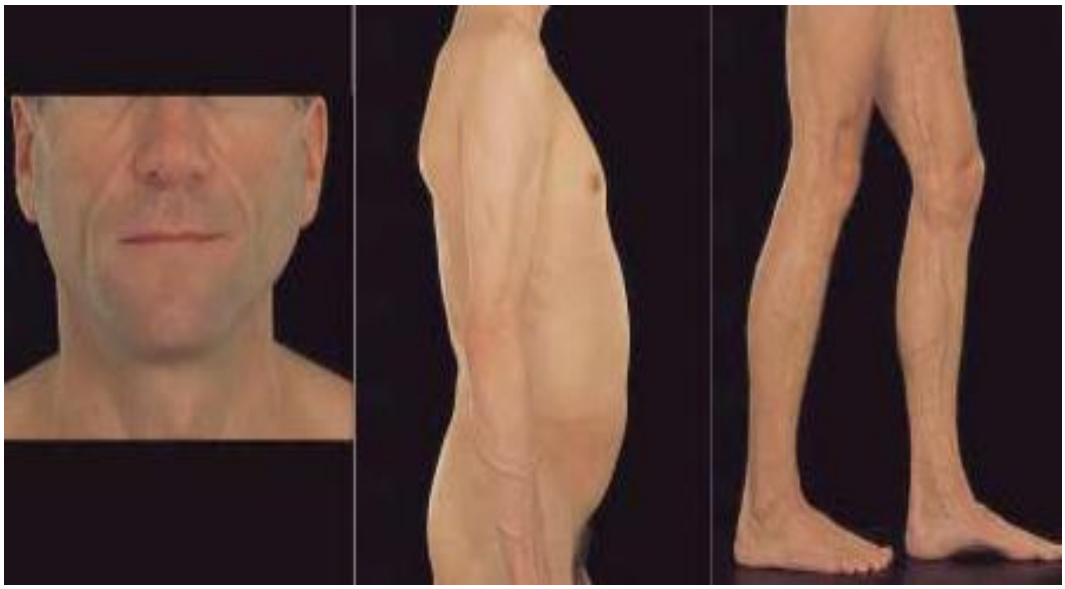


Figure 2.4 Clinical features of lipodystrophy

(Source: Carr and Cooper, 2000, p.1426)

The pathogenesis of lipodystrophy is poorly understood, but the cause is most likely to be due to several factors, with combined endocrine and metabolic abnormalities having effects on fat distribution (Montessori *et al.*, 2004). Risk factors for developing lipodystrophy include;

- increasing age
- white ethnicity
- obesity
- advanced HIV and AIDS disease
- low baseline body mass index. (Department of Health and Human Services, 2008)

Lipodystrophy diagnosis is based on physical examination of fat changes to the body, including measurements of changes in circumference of the arms, thighs, waist, hips and neck. Lipodystrophy causes significant cosmetic concerns to patients and ultimately

threatens the privacy of their HIV positive status. Inability to effectively manage lipodystrophy threatens the effectiveness of ART as patients may discontinue treatment. Patients ought to be counselled extensively regarding these disfiguring effects so that they are aware of their possible development and to avoid poor adherence because of the associated abnormality.

Non-pharmacological methods of managing lipodystrophy include exercise, low fat diets and smoking cessation (Regensberg and Makiwane, 2009). In severe cases patients may consider surgery or growth hormone therapy (Department of Health and Human Services, 2008). The disadvantage of using growth hormone therapy is that it decreases fat accumulation, but this effect is reversed on discontinuation and this method of treatment is expensive. The FDA approved the injectable drug Sculptra® (poly-L-lactic acid) to treat facial wasting in August 2004. Sculptra® is made from similar material to that used in dissolvable sutures and is used to fill sunken cheeks, eyes and other areas affected by lipoatrophy. The long term safety of Sculptra® needs to be monitored, as recommended by the FDA. (Gold, 2010)

Lipoatrophy may be reversed to some extent, by switching to TDF or ABC, which are not associated with lipodystrophy. However, although switching to other agents may slow or stop progression, it may not fully reverse effects (Department of Health and Human Services, 2008). In patients with risk factors for lipodystrophy (stated above), avoidance of thymidine nucleosides such as AZT and d4T may help prevent lipoatrophy.

Montessori and co-workers (2004) suggest that an increase in visceral and abdominal fat as seen with lipodystrophy has been linked to an increased risk for glucose intolerance. It is therefore recommended that patients with fat redistribution be screened

for glucose (diabetes mellitus and glucose intolerance) and lipid metabolism (high levels of triglycerides, total cholesterol, LDL cholesterol, low HDL cholesterol) disorders. Clinicians should monitor patients closely and recommend regular exercise, proper nutrition and provide psychological support where necessary (Department of Health, 2008).

2.5.2.1.2 Dyslipidaemia

Serum lipid changes that occur with HAART may be of concern due to the potential for complications of premature atherosclerosis and coronary artery disease. Both NNRTIs and PIs have been shown to increase triglyceride and total cholesterol levels (Shibuyama *et al.*, 2006). However, NNRTIs cause dyslipidaemias to a lesser extent than PIs (Capili and Anastasi, 2006). Dyslipidaemias, associated with increased risk of cardiovascular disease, occur in approximately 70% of HIV infected patients receiving ARV treatment (Montessori *et al.*, 2004). Severe triglyceridemia, low high density lipoprotein (HDL) cholesterol and high low density lipoprotein (LDL) cholesterol are the clinical features of dyslipidaemia.

According to Shibuyama and co-workers (2006), HAART regimens containing PIs often increase triglycerides, total cholesterol and LDL cholesterol but their effects on HDL cholesterol is unclear. The proposed mechanism by which PI-induced dyslipidaemias occurs is that they “bind to or interfere with LDL receptor-related protein and cytoplasmic retinoic acid binding protein type 1, both of which are lipid regulatory proteins involved in fat storage and lipid release” (Montessori *et al.*, 2004).

Regimens containing PIs have been found to increase total cholesterol and LDL cholesterol by about of 30mg/dL. Ritonavir has the highest rate of dyslipidaemias while

fosamprenavir and saquinavir have lower rates and atazanavir typically does not result into significant dyslipidaemias. (Shibuyama *et al.*, 2006)

Patients should be assessed for risk factors such as familial hyperlipidaemia, diabetes mellitus, Cushing's disease, obesity, hypothyroidism, hypogonadism, and hepatic and renal disease which may contribute in dyslipidaemias. Drugs such as beta blockers, thiazide diuretics, corticosteroids, thyroid hormones, androgens and estrogens may also affect serum lipid levels and as such, use of these medications by patients, should be established. (Capili and Anastasi, 2006)

Although currently proposed treatments for dyslipidaemias in HIV are not always effective in lowering serum lipids to acceptable levels and may cause a concern of drug interactions with ARVs, the following are suggested for management;

- Diet and Exercise: Diet has been shown to be useful in lowering total cholesterol, LDL cholesterol and triglycerides and is the first line approach to managing dyslipidaemias. In a randomized study examining the effects of diet and exercise versus the use of atorvastatin in 44 HIV infected patients with hypertriglyceridaemia, it was revealed that diet and exercise lowered total cholesterol by 11% and triglycerides by 21% while atorvastatin lowered total cholesterol by 19% and triglycerides by 21% (Capili and Anastasi, 2006).
- Medication: 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) such as pravastatin, fluvastatin and lovastatin are recommended for the management of elevated LDL cholesterol while fibrates such as gemfibrozil and fenofibrate are recommended for management of hypertriglyceridaemia (Capili and Anastasi, 2006). Pravastatin is preferred due to its low potential for drug interactions with PIs as it is not extensively metabolized by the CYP450 system. Statins and fibrates may be

combined if the serum lipid level is not sufficiently lowered by either agent alone (Shibuyama *et al.*, 2006).

- Switching therapies: PIs may be substituted with either an NRTI or NNRTI or even with “less metabolically active” PIs in order to lower elevated lipids. This option however may expose the patients to the possibility of new adverse effects as well as limit their future treatment options (Capili and Anastasi, 2006).
- Omega 3: Omega 3 fatty acids, for example in fish and fish oil, have been shown to lower triglycerides. These fatty acids act by inhibiting the synthesis of very low-density lipoproteins (VLDL) and triglycerides (Capili and Anastasi, 2006).

2.5.2.1.3 Hyperglycaemia

According to Shibuyama and co-workers (2006), the development of insulin resistance is common with PI containing HAART regimens but, not all PIs are equally implicated. Insulin resistance has been reported in 30% to 90% of patients receiving PI-based HAART, with true diabetes occurring in only 1% to 11% patients. Insulin resistance may also be a symptom associated with HIV infection, due to the effects of the virus on the pancreatic beta cells and hence insulin secretion (Montessori *et al.*, 2004).

Blood glucose changes are usually measurable about two to three months after initiation of ART. Clinical monitoring of patients’ fasting blood glucose levels at baseline and at 3 to 6 months intervals, when receiving PI-based HAART is recommended. Random glucose, fasting blood glucose and haemoglobin A1c measurements may not be reliable methods to measure insulin resistance because of compensatory increases in insulin. Other methods of testing include measuring fasting insulin, C-peptide and oral glucose tolerance for patients with borderline fasting glucose. (Shibuyama *et al.,* 2006)

Management of most cases of hyperglycaemia is through diet and exercise. Shibuyama and colleagues (2006) suggest that diet should contain 50-60% carbohydrates, 10-20% proteins, <30% fat, <100mg cholesterol daily and <10% total calories from saturated fat. For cases which fail to respond to diet and exercise and triglyceride levels remain greater than 10mmol/L or total cholesterol greater than 7,5 mmol/L, drug therapy is warranted (Regensberg and Makiwane, 2009). In these cases, agents used to improve insulin resistance include;

- Sulfonylureas
- Insulin sensitizing drugs such as metformin and thiazolidinediones

The insulin sensitizing agents may also reduce visceral fat accumulation and possibly result in a reduction of cardiovascular risk.

2.5.2.1.4 Osteonecrosis, osteopenia and osteoporosis

Osteonecrosis has been reported in both adults and children receiving HAART and it results in apoptosis of several components of the bone such as fat marrow and mineralized tissue (Montessori *et al.*, 2004). Osteonecrosis usually results from poor circulation and mostly affects the femoral and humeral heads (Regensberg and Makiwane, 2009). In children, avascular necrosis of the hips is referred to as “Legg-Calvé-Perthes disease” (Dybul *et al.*, 2002). Osteopenia refers to a moderate decrease in bone mineral density while osteoporosis is a severe decrease in bone mineral density.

Before the introduction of HAART, osteoporosis was thought to be as result of either poor nutrition or increased cytokines due to infection. Although the exact pathophysiology is unclear, the following possibilities have been proposed;

- Osteoporosis occurring in conjunction with ARV-associated lactic acidosis, where the phosphate may act as a buffer
- PIs inhibition of osteoblast activity while stimulating osteoclast activity thereby inhibiting new bone formation
- Inhibition of CYP450 enzymes that mediate vitamin D activation. (Montessori *et al.*, 2004)

The risk factors for osteoporosis include HIV infection, alcohol abuse, haemoglobinopathies, corticosteroid therapy, hyperlipidemia and certain hypercoagulability states (Dybul *et al.*, 2002). Patients on HAART, with additional risk factors for osteoporosis, need to be considered for evaluation. The diagnosis of osteoporosis is achieved by measuring bone mineral density usually using dual-energy x-ray absorptiometry (DEXA) (Montessori *et al.*, 2004).

Osteonecrosis is a rare condition but it can lead to joint replacement, therefore patients who present with constant knee, hip or shoulder pain, particularly when there is no trauma should be evaluated for osteonecrosis (Dybul *et al.*, 2002).

Patients suspected to have osteoporosis need to be referred to a specialist for further investigation. Treatment of osteoporosis includes the following;

- Vitamin D and calcium supplementation
- Weight bearing exercise
- Hormone replacement therapy including estrogen, particularly for postmenopausal women on HAART
- Biphosphonates, raloxifene and calcitonin therapy in severe cases such as fractures. (Montessori *et al.*, 2004)

2.5.2.2 ARV mitochondrial toxicity

The main role of mitochondria is the production of energy as adenosine triphosphate (ATP) via oxidative phosphorylation. Mitochondria also play a regulatory function in cellular survival (White, 2001) and glucose and fat metabolism (Montaner *et al.*, 2004). NRTIs and NtRTIs are phosphorylated intracellularly before they are incorporated into the viral DNA chain by viral reverse transciptase enzyme, preventing DNA elongation and viral replication. DNA polymerase γ (an enzyme involved in the replication of mitochondrial DNA) resembles HIV reverse transcriptase and therefore NRTIs may also inhibit it, leading to interference with mitochondrial DNA formation. (Montaner *et al., 2004*)

Mitochondrial toxicity is initially characterized by a reduction in energy production with an accompanying increase in lactate production (Montaner *et al.*, 2004). The NRTIs are associated with mitochondrial toxicities ranging from myopathy, neuropathy, heptic steatosis, pancreatitis and lactic acidosis. Lactic acidosis and pancreatitis are the most serious (Carr and Cooper, 2000). Individual mitochondrial toxicities are discussed below.

2.5.2.2.1 Lactic acidosis

Hyperlactataemia and lactic acidosis are conditions characterised by an increase in venous lactate levels. Due to the life threatening nature of lactic acidosis it is important for patients and HCPs to be aware of the symptoms and the management thereof (Montessori *et al.*, 2004). Lactic acidosis may present alone or with hepatic steatosis (accumulation of triglycerides resulting from the inhibition of fatty acid oxidation) (White, 2001).

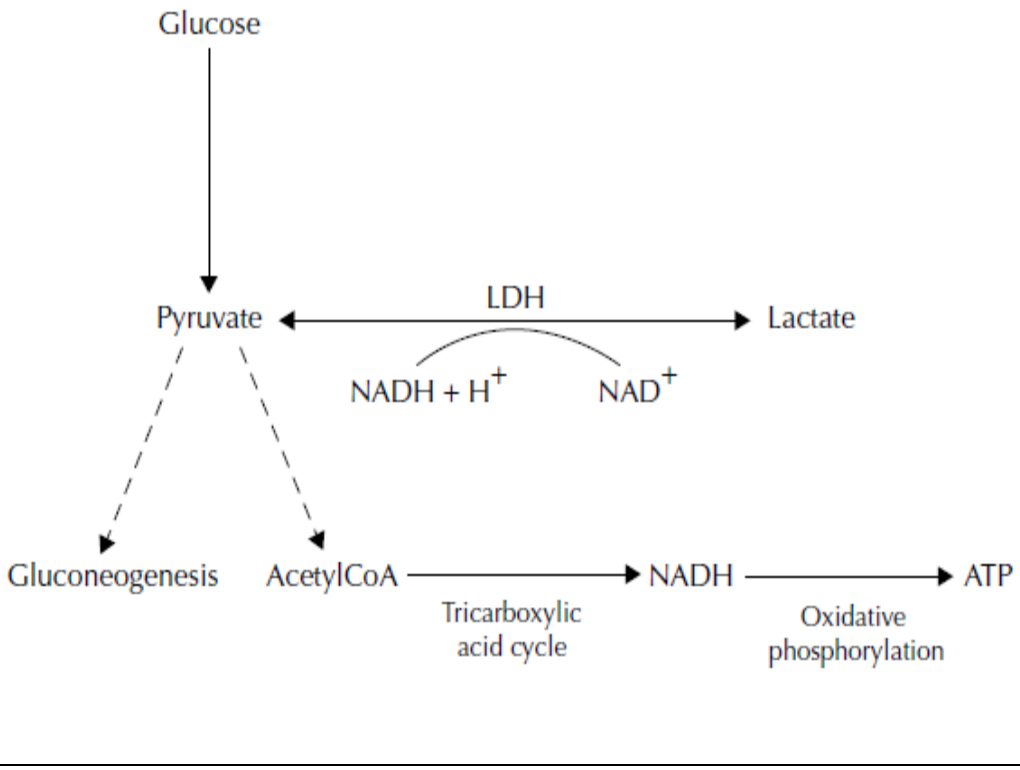
Lactic acidosis onset may be abrupt or gradual with initial non-specific symptoms such as;

- Gastrointestinal disorders such as nausea, vomiting and abdominal pain
- Muscular abnormality
- Weight loss
- Unexplained fatigue
- Enlarged and tender liver
- Cold or blue hands
- Cardiac dysrhythmias. (Department of Health and Human Services, 2008)

Other severe symptoms may include;

- Hypotension
- Kussmaul's breathing
- Loss of consciousness. (Regensberg and Makiwane, 2009)

Lactic acidosis has been reported with AZT, ddI and d4T especially in patients on therapy for more than 6 months. These NRTIs interfere with the functionality of mitochondria. The mechanism of lactic acidosis is shown in Figure 2.9 below. The dashed lines in the figure represent the processes occurring in the mitochondria that require normal mitochondrial function. These steps are impaired by NRTIs resulting in accumulation of pyruvate and NADH (the reduced form of nicotinamide adenine dinucleotide- NAD) which further enhances the conversion of pyruvate into lactate, leading to lactic acidosis.



AcetylCoA= acetylcoenzyme A

ATP= adenosine triphosphate,

LDH= lactate dehydrogenase

Figure 2.5 The mechanism of NRTI-associated lactic acidosis

(Source: Montessori *et al.*, 2004, p.233)

Confirmatory lactic acidosis laboratory tests indicate elevated random serum lactate levels (> 5mmol/L), elevated lactate-pyruvate levels, increased creatine phosphokinase, decreased serum pH and/or low bicarbonate concentration (<20mmol/L) (Shibuyama *et al.,* 2006). The anion gap (which represents the concentration of all unmeasured anions in the plasma) may also be elevated in the case of lactic acidosis, that is, [Na] – ([Cl] + [HCO_3]) >10 mmol/l (Montessori *et al.*, 2004). Measuring peripheral venous lactate levels may not be useful in distinguishing patients at risk for severe lactic acidosis and those suffering from chronic hyperlactatemia (elevated venous lactate). Therefore,

measuring the ratio of mitochondrial DNA to nuclear DNA may be a more sensitive and reliable method of evaluating patients at risk of severe lactic acidosis (Montessori *et al.*, 2004).

The risk factors for lactic acidosis are not fully understood but may include the following;

- HIV infection, as it usually results in mitochondrial necrosis even in the absence of ARV therapy
- Combination of ddI and hydroxyurea or ribavirin
- d4T, AZT, ddI use (especially d4T and combination of d4T and ddI)
- Long duration of NRTI use (> 6 months)
- Excellent adherence to therapy
- Gender (females more susceptible)
- Obesity and nutritional deficiency of cofactors and vitamins essential for mitochondrial function, such as thiamine and riboflavin (Montessori *et al.*, 2004)
- Pregnancy (especially with use of d4T and ddI)
- Chronic renal failure
- High body mass index (Department of Health and Human Service, 2008).

Management of lactic acidosis is largely supportive. According to the Department of Health and Human Service (2008), lactic acidosis should be managed as follows;

- Lactate 2-5 mmol/L: monitor patients monthly and look out for clinical symptoms
- Lactate 5-10 mmol/L (symptomatic): Stop all ART and refer the patient immediately. Exclude other causes of raised lactate such as;
    - sepsis
    - renal failure

    - diabetic ketoacidosis
- Lactate >10 mmol/L: Stop all antiretroviral drugs immediately and seek urgent expert help (30% mortality reported)
- Metabolic acidosis with raised lactate: Stop all ART and seek urgent expert help
- Supportive care including,
    - respiratory support
    - monitoring cardiac function
    - intravenous fluid therapy
    - administering agents such as riboflavin (vitamin B2), thiamine (vitamin B1), co-enzyme Q, -10 carnitine, or vitamins C, E and K
- Other measures attempted include plasmapheresis, high-dose corticosteroid and intravenous immunoglobulin.

Patient recovery usually takes months and may range from complete recovery to substantial residual deficits. The symptoms may be irreversible in various patients while lactic acidosis may be fatal in others. The patient should generally not be re-challenged with the offending agent even after recovery. If the patients bicarbonate level is less than 15 mmol/L, NRTIs may not be restarted, instead PIs should be introduced. Instead, NRTIs with fewer propensities of mitochondrial toxicities such as ABC, TDF, 3TC, FTC, should be used. However, these may not be introduced until the patient's lactate level returns to normal. Close monitoring of the patient's serum bicarbonate or lactate after restarting NRTIs is recommended (Department of Health and Human Services, 2008).

2.5.2.2.2 Hepatotoxicity

Hepatotoxicity generally refers to liver damage which encompasses several conditions namely;

- Hepatitis (inflammation of the liver)
- Hepatic necrosis (death of the liver cells)
- Hepatic steatosis (accumulation of fat in the liver). (Department of Health and Human Services, 2008)

Hepatotoxicity may also lead to “hepatic tissue eosinophilia, hepatoparenchymal and periportal infiltration with lymphocytes and plasma cells” (Shibuyama *et al.,* 2006).

Most ARV agents are associated with hepatotoxicity and transaminitis. NRTIs, particularly d4T and ddI may cause hepatic steatosis, generally after 6 months of therapy. NNRTIs, particularly NVP and EFV may cause hepatitis after 2-3 months of therapy which is sometimes related to hypersensitivity reactions, for example NVP associated rash and fever. The mechanism by which PIs cause hepatitis is unknown although the rate of hepatotoxicity is about twice as high in patients with hepatitis B or C co-infection (Montessori *et al.*, 2004). Conversely, it has been suggested that long term use of PIs may have a beneficial effect on the progression of liver fibrosis in patients co-infected with hepatitis C. Certain case of hepatitis are idiosyncratic while others arise from immune reconstitution where by the restored immune system recognizes previous infection in chronic carriers of hepatitis B or C (Carr and Cooper, 2000).

Symptoms of hepatotoxicity include;

- abrupt onset of flu-like symptoms including nausea, vomiting, myalgia, fatigue
- abdominal pain
- jaundice

- fever with or without skin rash
- sometimes progresses to hepatic failure with encephalopathy (Department of Health and Human Services, 2008).

According to the Department of Health and Human Services (2008) the risk factors for the development of hepatotoxicity include;

- underlying liver disease prior to starting ARVs
- treatment-naive patients with higher CD4 count at initiation (>250 cells/mm^3 in women and >400 cells/mm^3 in men)
- female gender (including pregnant women)
- HIV negative individuals when NVP is used for post-exposure prophylaxis
- high NVP concentration (which may be as a result of drug interactions with drugs that may inhibit CYP450 enzyme metabolism of NVP)
- co-infection with hepatitis B or C virus
- elevated liver enzymes at baseline
- alcoholism
- concomitant use of other hepatotoxic drugs.

Early identification of hepatotoxicity is critical. For NVP associated hepatotoxicity, some guidelines may be followed in order to prevent and/or monitor patients. Firstly, initiation of NVP in women with CD4 >250 cells/mm^3 or men with CD4 >400 cells/mm^3 unless the benefit clearly outweighs the risk should be avoided. Patients should be counselled regarding signs and symptoms of hepatitis and advised to stop NVP and seek medical attention immediately if signs and symptoms of hepatitis, severe skin rash, or hypersensitivity reactions develop (Department of Health and Human Services, 2008).

Baseline ALT and AST should be performed and liver function tests (LFTs) monitored regularly. In patients with normal transaminase levels, LFTs should be performed every month for the first 3 months of NNRTI therapy and then every 3 months if levels remain normal. Patients with raised transaminases need to be monitored every two weeks and then monthly after they stabilize (Shibuyama *et al.,* 2006). It is recommended that hepatitis B surface antigen tests be performed for all patients at baseline (Regensberg and Makiwane, 2009).

The management of hepatotoxicity involves the following;

- The offending ARVs should be immediately discontinued when ALT and/or AST is greater than 5-10 ULN. Caution should be taken in discontinuation of 3TC, FTC, or TDF in hepatitis B co-infected patients as they may experience a flare up
- All other hepatotoxic agents should also be discontinued if possible
- Other causes of hepatitis such as alcoholism, viral hepatitis, chronic hepatitis B with 3TC, FTC, or TDF withdrawal, or hepatitis B resistance should be ruled out
- Aggressive supportive care should be given (Department of Health and Human Services, 2008)
- If GGT, alkaline phosphatase or conjugate bilirubin are elevated, a liver ultra sound should be performed to rule out biliary obstruction which may be due to hepatic steatosis or TB permeation of the liver (Regensberg and Makiwane, 2009).

Hepatic injury may still progress even with treatment discontinuation. Therefore, careful monitoring of hepatic function should continue until symptom resolution occurs. The patient may not be re-challenged with NVP if it was the offending ARV. The safety of other NNRTIs (such as EFV and DLV) in patients who experienced significant hepatic

event from NVP is unknown, therefore they should be used with caution. (Department of Health and Human Services, 2008)

2.5.2.2.3 Pancreatitis

Pancreatitis refers to inflammation of the pancreas and is marked by increased serum amylase and lipase concentrations. HIV infected people are at risk of developing pancreatitis due to immunodeficiency as well as exposure to pancreatotoxic drugs, such as pentamidine, for treatment of opportunistic infections (White, 2001). The most common causative ARV agent is ddI used alone or with d4T, HU or TDF. Didanosine alone has been reported to cause pancreatitis in about 1-7% of patients. When ddI is given in combination with HU, pancreatitis incidence increases by 4-5 fold (Department of Health and Human Services, 2008).

The onset of pancreatitis is usually within weeks to months after initiation of therapy. The main symptoms are;

- post-prandial abdominal pain
- nausea and vomiting
- shock
- respiratory distress
- decreased bowel sounds
- fever, and
- tachycardia. (Department of Health and Human Services, 2008)

The risk factors for developing pancreatitis include;

- high intracellular and/or serum ddI concentrations
- previous history of pancreatitis

- alcoholism
- hypertriglyceridemia
- concomitant use of ddI with d4T, HU, or ribavirin
- use of ddI in combination with TDF without ddI dose reduction. (Department of Health and Human Services, 2008)

Shibuyama and colleagues (2006) suggest that females and patients with CD4 cell counts of less than 200 cells/mm^3 are at risk of developing pancreatitis. Prevention of the occurrence of pancreatitis involves caution when using ddI in patients with a history of pancreatitis and avoiding the concomitant use of ddI with d4T, TDF, HU, ddC or ribavirin. Cotrimoxazole and pentamidine may also cause pancreatitis, increasing the risk of pancreatitis. When used in combination with TDF, the dose of ddI should be reduced as TDF increases plasma concentrations of ddI (Department of Health and Human Services, 2008). In patients who consume moderate to high amounts of alcohol regularly, ddI should be avoided as the risk of pancreatitis increases (Shibuyama *et al.,* 2006).

The management of pancreatitis involves;

- discontinuation of the offending ARV agent(s) if there are laboratory results that indicate raised lipase and amylase (Shibuyama *et al.,* 2006)
- symptomatic management involving;
    - intravenous hydration
    - pain management
    - gradual resumption of oral intake of foods

- parenteral nutrition may be necessary in patients with persistent symptoms upon recommencement of oral intake. (Department of Health and Human Services, 2008)

2.5.2.2.4 Neuropathy

Peripheral neuropathy is an abnormality commonly caused by d4T, ddI and ddC. The onset of symptoms may occur within several weeks to months after initiation of therapy but it may manifest earlier in patients with pre-existing neuropathy. Peripheral neuropathy begins with numbness and paresthesia of toes and feet, which may progress to painful neuropathy of feet and calf. The upper extremities are seldom involved. Other symptoms include a burning sensation, aching sensation, cramps and altered temperature sensation in the affected areas (Shibuyama *et al.,* 2006). It can be debilitating for some patients to the point of difficulty in walking or even intolerance for clothing on their feet, depending on the severity and the individual response of the patient. Peripheral neuropathy is normally reversible with the termination of therapy, and treatment may be cautiously resumed if the associated problems resolve adequately. However, it may be irreversible despite discontinuation of the offending agent (Department of Health and Human Services, 2008).

Increased immunosuppression increases the incidence of peripheral neuropathy. It is difficult however to distinguish between HIV related and ARV related peripheral neuropathy although ARV related neuropathy is thought to be more painful and progress more rapidly. NRTIs are thought to cause peripheral neuropathy by interfering with oxidative metabolism leading to lower acetyl-carnitine production, low serum hydroxycobalamine and inhibition of nervous growth factor. (White, 2001)

Risk factors for developing peripheral neuropathy include;

- pre-existing peripheral neuropathy either related to HIV infection or due to distal sensory painful axonal neuropathy (Shibuyama *et al.,* 2006)
- combination therapy; ddC is more neurotoxic that ddI, d4T and 3TC but ddI combined with d4T is more toxic than either drug administered alone (Shibuyama *et al.,* 2006)
- concomitant use of neurotoxic drugs such as isoniazid
- nutritional deficiency
- advanced HIV disease indicated by low CD4 cell counts (<200 cells/mm^3)
- high dose or concomitant use of drugs that may interact with and increase the plasma concentration of these drugs. (Department of Health and Human Services, 2008)

In order to prevent the development of peripheral neuropathy HCPs should avoid using implicated agents in patients at risk and if possible, avoid the use of these agents in combination. This however may not always be possible due to the increased incidence of opportunistic infections, associated with HIV, which need to be treated. For instance a patient with a CD4 count of 50 cells/mm^3 or less, with other HIV-related illnesses, diagnosed with TB would need to be initiated on both HAART and TB medication. However, in order to try and minimize the additive adverse effects of these drugs, the patient should be initiated on TB medication at least two weeks before starting HAART. It is essential that the patient is able to tolerate TB medication before initiation of HAART (Department of Health, 2004). It is also necessary to monitor patients at each encounter to assess whether they are experiencing symptoms indicative of peripheral neuropathy such as a tingling or numb sensation in their hands and feet.

The management of peripheral neuropathy may involve discontinuing the offending agent before the pain becomes disabling. This may stop further progression, but in some cases the symptoms may be irreversible (Department of Health and Human Services, 2008). Pharmacological management may include treatment of the neuralgic pain associated with peripheral neuropathy with agents such as pyridoxine, opiates (e.g. tramadol), non-steroidal anti-inflammatory drugs, amitriptyline, neurontin, topical capsaicin and topical lidocaine. Gabapentin, lamotrigine, oxycarbamazepine and topiramate may also be used. These agents have variable successes in managing peripheral neuropathy (Department of Health and Human Services, 2008). Valproic acid and carbamazepine are beneficial for lancinating pain. Anecdotal reports have shown that vitamin B complex may also be useful although these effects are yet to be well established (Shibuyama *et al.,* 2006).

2.5.2.3 Haematological toxicity

HIV infection has been associated with haematological toxicities such as anaemia, neutropenia and thrombocytopenia. About 15% to 61% of adults with HIV infection experience haematological toxicity. HIV related thrombocytopenia has been shown to improve with AZT therapy. AZT therapy causes anaemia or neutropenia in about 1.1% and 9.7%. White (2001) suggests that AZT associated haematological toxicity is as a result of its effect on haem metabolism or gene expression while Shibuyama and colleagues (2006) further elaborate that AZT inhibits erythroid burst-forming units and human granulocyte-macrophage colony-forming units by competitively inhibiting thymidine triphosphate.

Patients with pre-existing anaemia, lower CD4 cell counts, increased age and of black ethnicity are reported to be at a higher risk of developing anaemia. Decreased erythropoietin, alterations in cytokine production and certain opportunistic infections may also increase the risk of anaemia. A high dose of AZT as well as concomitant use of bone marrow suppressants such as cotrimoxazole, ribavirin, hydroxyurea, pyrimethamine, interferon-alfa and ganciclovir may also increase the risk of bone marrow suppression (Department of Health and Human Services, 2008). The concomitant use of AZT with other bone marrow suppressants should be avoided although it may not always be possible since these agents are commonly used in treating opportunistic infections associated with HIV progression.

Patients treated with AZT-containing regimens require close monitoring of full and differential blood counts on initiation of therapy, followed by monthly monitoring for three months, and then once every six months (Safrin, 2004). The quality of life of anaemic patients is affected due to nausea, fatigue and weakness that result from low haemoglobin levels.

AZT should be avoided in patients with haemoglobin <10 mmol/L and neutrophils less than 1.5 mmol/L. The management of bone marrow suppression with haemoglobin less than 8 mmol/L and neutrophils less than 1 mmol/L may involve switching AZT to another NRTI and discontinuing concomitant bone marrow suppressant if there is an alternative option (Regensberg and Makiwane, 2009). In the case of neutropenia, the exact cause should be identified and treatment with filgrastim, which regulates the production and release of functional neutrophils from the bone marrow initiated (Gibbon, 2005). Similarly, for anemia, other possible causes should be identified and managed

appropriately. Erythropoietin therapy and blood transfusion may be indicated in some cases.

2.5.2.4 Renal toxicity

There have been reported cases of renal toxicity, including, renal tubular dysfunction, acute renal failure and Fanconi syndrome reported among patients taking TDF. TDF renal toxicity initially presents as “hypophosphatemia resulting from both reduced phosphate reabsorbtion and excessive loss of phosphates into urine”. (Buchacz *et al.*, 2006, p. 451-452)

Other markers of renal toxicity associated with TDF are serum cystatin C (a protein produced by nucleated cells) and β_2-microglobulin (more sensitive marker of TDF associated renal toxicity) (Ndegwa and Nkansah, 2008).

Studies have however documented a positive renal safety profile of TDF in patients with normal baseline renal function, with no reported cases of renal failure. Risk factors for electrolyte disorders include;

- previous hypophosphatemia
- HIV infection
- use of acyclic nucleotide analogues such as cidofovir and tenefovir
- some ARVs such as lopinavir/ritonavir
- renal disease
- Comorbidities such as diabetes and hypertension. (Ndegwa and Nkansah, 2008)

It is recommended that patients be assessed for any existing renal disease before TDF is initiated. This may include glucosuria, proteinuria and estimated glomerular filtration rate (GFR). If there is no proteinuria at this stage then patients,particularly those at risk

of developing proteinuria (such as black race, advanced HIV disease, hepatitis C and the above mentioned risk factors) should be monitored annually. (Ndegwa and Nkansah, 2008)

The table below shows the recommended dosing for TDF for different GFR values.

Table 2.10 Dosing recommendations for TDF

(Adapted from: Ndegwa and Nkansah, 2008, p.6)

Creatine clearance (ml/min)	**TDF dose**
≥ 50	300mg od
30-49	300mg every 48 hours
10-29	300mg twice weekly
< 10 (patients with end stage renal disease requiring hemodialysis)	300mg every 7 days or after a total of 12 hours of dialysis (estimated at 4hours per dialysis). TDF is administered after dialysis

TDF is generally well tolerated but further studies are required to assist in properly understanding and managing TDF-associated nephrotoxicity.

2.5.2.5 Central nervous system (CNS) effects

EFV is the ARV drug most commonly associated with CNS effects. EFV related CNS effects range from 1-116 days and last for a median of 13 days (Shibuyama *et al.,* 2006). More than 50% of patients taking EFV may experience CNS symptoms (Department of Health and Human Services, 2008). These CNS effects include drowsiness, nervousness, irritability, somnolence, insomnia, abnormal/vivid dreams or nighmares, dizziness, impaired concentration and attention span, depression, hallucination, exacerbation of psychiatric disorders, psychosis, paranoia, aggression,

manic reactions and suicidal ideation. Symptoms usually subside within 2-4 weeks of therapy.

Risk factors for the development of CNS effects include the following;

- pre-existing psychiatric illnesses
- injectable drug use
- concomitant use of psychoactive drugs or alcohol
- genetic predisposition to slower clearance related to black ethnicity. (Department of Health and Human Services, 2008)

In order to minimize or prevent the occurrence of CNS effects, patients should be advised to take EFV at bedtime or 2–3 hours before bedtime because adverse effects may be more tolerable. Patients should be warned that EFV may impair their ability to perform activities requiring alertness or physical co-ordination during the first 2–4 weeks of therapy (Gibbon, 2005).

If the symptoms persist and cause significant impairment in the patient's normal functioning or worsens psychiatric illness, then EFV should be discontinued (Department of Health and Human Services, 2008). Insomnia may be managed with zolpidem, a benzodiazepine-related drug, which has minimal interaction with EFV (Gibbon, 2005).

Due to the possible CNS effects of efavirenz, the recommended protocol for initiating treatment with efavirenz is;

- Screen patients for and stabilize pre-existing neuropsychiatric symptoms.
- Reassure the patients that EFV is effective in managing HIV, CNS adverse effects are usually mild to moderate and time limited (2-4 weeks) and they rarely result in discontinuations of therapy.

- New and persistent CNS symptoms should be addressed. Early and effective management of CNS side effects in the patient taking EFV is imperative to improve patient outcomes (Department of Health, 2008).

2.5.2.6 Gastrointestinal (GIT) effects

Gastrointestinal problems are the most common side effects of almost all ARV drugs including NRTIs, NNRTIs and particularly PIs and occur especially during the early stages of therapy (Schieferstein and Buhk, 2006). GIT effects reported include abdominal discomfort, nausea and vomiting, loss of appetite, diarrhoea, abdominal pain, pancreatitis, constipation, meteorism and heartburn. Nausea is a common symptom with AZT-containing regimens, diarrhea occurs frequently with AZT, ddI and all PIs, particularly with ritonavir and nelfinavir. Treatment with AZT, may in rare cases, lead to a severe form of gastritic pain, nausea and vomiting in the early phase of therapy, in which case it should be discontinued (Schieferstein and Buhk, 2006).

Patients should be informed that most GIT symptoms are self-limiting but some can persist for some time or reappear and could be a sign of a serious condition. GIT effects can be troublesome and greatly impact drug therapy outcome and the patient's quality of life. GI side effects can cause dehydration, electrolyte imbalance, weight loss and malabsorption leading to low plasma drug levels with the risk of emergence of resistant viral strains (Schieferstein and Buhk, 2006).

If the administration of drugs on an empty stomach leads to nausea and vomiting, most drugs can also be taken together with meals. However, when drugs such as ddI, indinavir, rifampin have to be administered on an empty stomach, small quantities of low-fat salty crackers may reduce the nausea. Ginger, peppermint or chamomile teas or

sweets may also be helpful. Care should be taken with fatty foods and dairy products. Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided if possible (Schieferstein and Buhk, 2006).

For symptomatic treatment of nausea, metoclopramide has been demonstrated to be useful. Dimenhydrinate, cimetidine, ranitidine or ondansetron may also be administered. Anti-emetic drugs should not only be administered if the patient is already nauseated, but should rather be taken regularly for prophylaxis, ideally 30 to 45 minutes before HAART. If taken on a regular basis, attention should be paid to side effects such as dyskinesia. After a few weeks, anti-emetic doses can be slowly tapered down. If nausea persists for more than two months, a change of treatment should be considered, or else adherence problems may occur (Schieferstein and Buhk, 2006).

It is important that the underlying cause or complication of GI problems be identified in order to take proper corrective measures. For instance if diarrhoea occurs, infection and lactose intolerance should first be excluded (Department of Health and Human Services, 2008). In patients with severe diarrhoea, the priority is to treat dehydration and loss of electrolytes. Difficult to digest foodstuffs (particularly those rich in fats or glucose) should be avoided and those that are easy to digest such as potatoes, rice, noodles, eaten instead (Schieferstein and Buhk, 2006).

The cornerstone of symptomatic treatment of diarrhoea is loperamide which inhibits bowel movement. If loperamide is ineffective, opiates may be used as an alternative, with caution due to the risk of intestinal obstruction, especially if overdosed. PI-associated diarrhoea may be alleviated by calcium, taken as calcium carbonate 500 mg twice a day. However, as calcium binds to many other substances, it should be taken two hours before or after taking ARVs. The probiotics, *Saccharomyces boulardii* and

Lactobacillus acidophilus are used in infectious diarrhea and for the prevention of antibiotic-associated diarrhoea. They can sometimes ameliorate medication-associated diarrhoea. Psyllium which may also be effective should not be taken together with loperamide or opium tincture, or at the same time as HIV medication. (Schieferstein and Buhk, 2006)

2.5.2.7 Hypersensitivity reactions

Hypersensitivity reactions are a common occurrence with drug therapy although their exact pathogenesis is unknown. They occur about 100 times more frequently in the HIV positive population than in HIV negative patients (Carr and Cooper, 2000). All NNRTIs, the NRTI ABC, and the PI amprenavir usually cause hypersensitivity. Amprenavir is a sulfonamide and should therefore be administered with great caution in patients with sulfonamide allergies. Hypersensitivity reactions with NVP and EFV usually occur within the second or third week of treatment (Schieferstein and Buhk, 2006). The risk factors for hypersensitivity reactions are;

- advanced disease
- immune reconstitution
- long exposure and high doses of treatment
- glutathione deficiency which may alter drug metabolism
- slow acetylators
- co-existing infections for instance with cytomegalovirus or Epstein Barr virus. (Carr and Cooper, 2000)

The hypersensitivity reaction is usually an erythematous, maculopapular, pruritic, and confluent rash distributed over the trunk and arm as shown in Figure 2.6 below. Fever,

myalgias, rigors and arthralgias may precede the rash (Carr and Cooper, 2000). Further symptoms include fatigue and mucosal ulceration. Severe but rare reactions such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis and hepatitis have been reported and require immediate intervention by an expert should they occur (Schieferstein and Buhk, 2006).

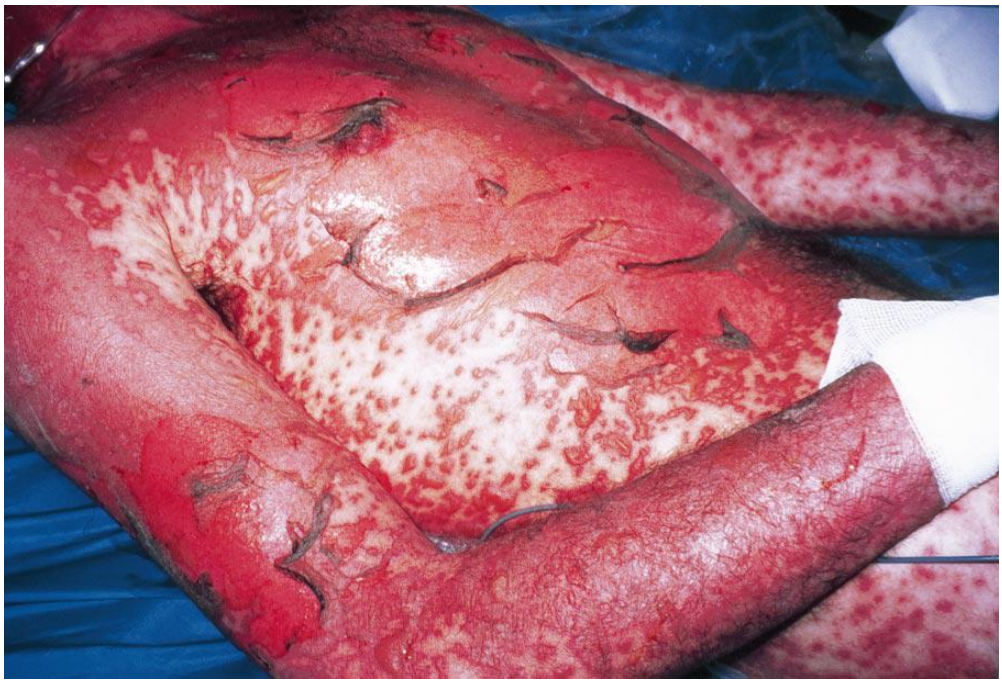


Figure 2.6 Stevens Johnson Syndrome

(Source: Fagot *et al.*, 2001)

ABC causes a hypersensitivity reaction in 5-10% of patients which can be fatal. The hypersensitivity reaction is not dose dependent and usually involves multi-organ systems. ABC hypersensitivity reaction is characterized by fever and usually accompanied by general malaise, nausea, vomiting, diarrhoea and abdominal. Rash may occur but is often mild. ABC must be discontinued and never rechallenged as several deaths and life threatening hypotension have been reported with rechallenge (Department of Health and Human Services, 2008). The symptoms usually occur within

6 weeks after initiation of therapy, but can occur anytime during treatment with ABC (Schieferstein and Buhk, 2006).

Approximately half the cases of ARV hypersensitivity resolve spontaneously during therapy. However, in the cases of mucosal involvement, exfoliation, blistering, severe hepatic dysfunction with transaminases more than 5 times the ULN, fever (>39°C) and severe pruritus, offending drugs should be discontinued (Carr and Cooper, 2000). Antipyretics and antipruritics are commonly used. In the case of mild to moderate NNRTI hypersensitivity, re-challenge is not contraindicated but should be preferably done under observation, in a hospital setting.

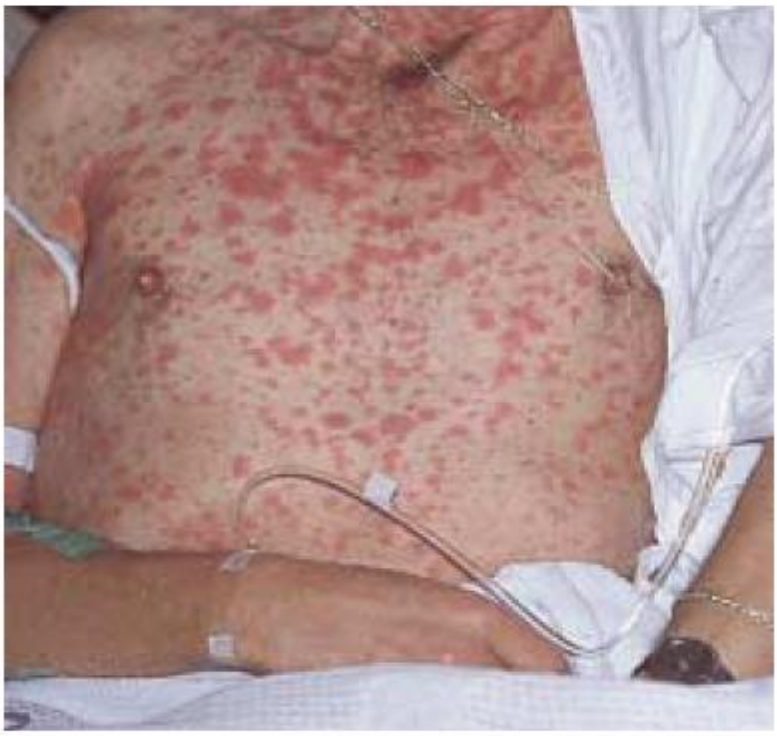


Figure 2.7 A drug hypersensitivity reaction

(Source: Carr and Cooper, 2000, p.1424)

2.6 Future Developments

In the past few years the release of novel ARVs has provided new treatment options particularly for treatment experienced patients. Several drugs that provide an expansion of already existing ARV classes and additional new classes are under development. These drugs will take several years before they are available.

Below is a summary of the drugs further along in the developmental process (those in pre-clinical and early development are excluded).

Table 2.11 HIV drugs in development

(Adapted from Graziano and Djuricich, 2009)

Agent	ARV Class	Status
AMD11070	CXCR4 antagonist	Suspended/Phase 2
Amdoxovir	NRTI	Phase 2
Apricitabine	NRTI	Phase 2/3
Bevirimat (PA-457)	Maturation inhibitor	Phase 2
Eltegravir	Integrase inhibitor	Phase 3
IDX899	NNRTI	Phase 2
KP-1461	Viral decay accelerator	Suspended/Phase 2
PRO 140	Entry inhibitor/ monoclonal antibody	Phase 2
RDEA806	NNRTI	Phase 2
Rilpivirine	NNRTI	Phase 3
TNX-355	CD4 blocker/ monoclonal antibody	Phase 2
Vicriviroc	CCR5 antagonist	Phase 3

2.7 Monitoring Patients Receiving HAART

Montessori and colleagues (2004) suggest that patients receiving HAART should have routine monitoring every three months in order to determine whether the treatment is

working or not and what the effects of the treatment are on the normal bodily function. The tests to be performed include;

- **CD4 cell count and viral load** in order to determine patients' adherence to treatment or detect treatment failure early. CD4 monitoring is recommended to be performed every 4-6 months while viral load is initially to be done 6-8 weeks after initiating therapy and then routinely, every 4-6 months. A log reduction of 1, in viral load, is expected within about 8 weeks of commencing ARV therapy and after 16-24 weeks it is expected to be undetectable, that is, <50 copies/ml. Treatment failure is defined as a "sustained increase to >1000 copies/ml" (Regensberg and Makiwane, 2009). CD4 cell count rises rapidly within the first few weeks and then steadily thereafter with an average rise of 150 cells/mm^3 in the first year and approximately 80 cells/mm^3 yearly thereafter.
- **Other tests** include complete and differential blood counts, electrolytes, creatinine, liver function tests, bilirubin, amylase, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides,blood glucose. Patients also need to be monitored for dyslipidemias, diabetes, lipodystrophy.

According to the National Department of Health (2008), the following routine monitoring of ART regimens should be performed.

Table 2.12 Routine monitoring for first line regimens (at the time of the study)

(Adapted from: Department of Health, 2008)

Regimen	Drugs	Monitoring Tests	Frequency
1a	d4T / 3TC / EFV	▪ CD4 ▪ VL ▪ ALT ▪ FBC ▪ Hep BsAg	▪ Staging, 6 monthly ▪ At 3 months, then 6 monthly ▪ Baseline ▪ Baseline ▪ Baseline
1b	d4T / 3TC / NVP	▪ CD4 ▪ VL ▪ ALT ▪ FBC ▪ Hep BsAg	▪ Staging, 6 monthly ▪ At 3 months then 6 monthly ▪ Baseline, week 2, 4, 8, 12 thereafter 6 monthly ▪ Baseline ▪ Baseline
1c	AZT / 3TC / EFV or NVP	▪ CD4 ▪ VL ▪ ALT (if NVP use) ▪ FBC ▪ Hep BsAg	▪ Staging, 6 monthly ▪ At 3 months then 6 monthly ▪ Baseline, week 2, 4, 8, 12 thereafter 6 monthly ▪ Baseline then monthly for 3 months then at 6 months then 6-monthly ▪ Baseline
1d	TDF / 3TC / EFV or NVP	▪ CD4 ▪ VL ▪ ALT (if NVP use) ▪ Creatinine clearance ▪ FBC • Hep BsAg	▪ Staging, 6 monthly ▪ At 3 months then 6 monthly ▪ Baseline, week 2, 4, 8, 12 thereafter 6 monthly ▪ Baseline, monthly x3, 6 months, then 6 monthly ▪ Baseline ▪ Baseline

- VL- Viral load
- ALT- Alanine aminotransferase
- FBC- Full blood count
- Hep BsAg- Hepatitis B surface antigen

Therapeutic drug monitoring (TDM) has also been suggested as a method of monitoring ARV treatment although studies are still being conducted to determine the usefulness of TDM. TDM has been defined as “the adjustment of drug doses based on plasma concentrations in order to attain values within a therapeutic range associated with maximal virological suppression and /or minimal adverse effects”. (Paul, 2010)

TDM may be useful for NNRTIs and PIs which have high inter-patient variability in serum concentrations but not NRTIs because there has been no evidence of a correlation between plasma concentration and intracellular triphosphate active drugs. Concerns with the accuracy of drug assays and lack of agreed parameters to predict drug therapeutic response have presented challenges with TDM as a method of monitoring ART. (Paul, 2010)

Patient self-monitoring diaries are yet another way of monitoring patients on ARVs. A patient self-monitoring system ensures that patients are actively involved in their monitoring. It mainly aims to identify subjective data such as the patient experience of pain, fatigue and other symptoms. Self-monitoring, for HIV positive patients, provides a way for the patients to follow up their own progress. (Gómez *et al.,* 2002)

A type of self-monitoring diary, commonly referred to as a pill diary, has been used in HIV positive patients to monitor adherence to ARVs. Web-based patient self-monitoring has also been used, although it may not be feasible for majority of patients in resource limited countries. The information contained in patient self-monitoring diaries includes;

- Personal data - such as their date of birth, gender, date they were diagnosed with HIV.

- Clinical data – including their baseline CD4 cell count and subsequent CD4 counts and baseline viral loads as well as subsequent viral loads. Opportunistic infections and other co-morbidities are also included here.
- Life style data – including substance use, such as smoking, alcohol consumption and recreational drugs. It also includes patient's subjective symptoms and moods such as sadness, pain, fatigue, appetite and others. The patients use visual analogue scales to visualize and enter subjective data.
- Treatment data – this includes, ARVs and other drugs taken for any reason, including complementary and alternative treatments. Adherence to treatment may also be assessed by the patients. (Gómez, Cáceres, López and Del Pozo, 2002)

The goal of these diaries is get patients to record therapy, including doses and any changes to treatment, adherence, perceived adverse effects and perceived benefits of treatment. (Gómez, Cáceres, López and Del Pozo, 2002)

The patient diary developed for this study was mainly aimed at identifying adverse effects or symptoms of adverse effects experienced and reported by patients. The other information regarding patients' treatment (including current ARV regimen, treatment change and concomitant medications) and clinical progress (including comments on general well-being, virological suppression and co-morbid disease states) was obtained from patient records.

2.7.1 Treatment change

Numerous treatment naïve patients receiving their first ART usually achieve undetectable viral loads after 24 weeks. The most commonly cited reason for treatment

change within the first 3 months of ART is drug toxicity, with lipodystrophy and metabolic disorders being the major concern. (Hart, Curtis, Wilkins and Johnson, 2007)

Treatment failure, including clinical failure, immunological failure and virological failure, has also been cited as an important reason for treatment change. Clinical failure is characterized by new or recurrent opportunistic infections or the onset of or recurrent WHO clinical stage 3. Immunological failure is characterized by a drop in CD4 cell count by more than 50% or a drop in CD4 count to baseline or less. Virological failure has been defined as failure to suppress viral load to undetectable levels, detecting the virus after a long period of un-detectability, that is, loss of virological control and less than ten-fold decrease in viral load from baseline after 8-12 weeks of ART. (Smith, 2010)

Treatment failure may occur as a result of;

- Inadequate drug delivery – due to malabsorption, poor adherence or vomiting
- Sub-optimal plasma concentration of HAART – resulting from drug interactions, incorrect dosing
- Patient genetic variations – such as rapid drug clearance, excessive drug metabolism, poor drug activation, pre-existing resistance
- Interruption of therapy. (Smith, 2010)

Other reasons for treatment change include adherence difficulties, patient choice due to compromised quality of life, patients planning pregnancy or pregnant, comorbidity and potential for drug interactions and poor CD4 response. (Hart, Curtis, Wilkins and Johnson, 2007)

Clinicians need to carefully weigh the risks with the benefits of changing patients' treatment. The risk of increased drug resistance with a resultant loss of future treatment options needs to be considered. Therapeutic failure is often associated with poor

adherence and therefore in such cases changing treatment may not change the non-adherence issue. Intensive counseling is recommended in such instances before proceeding to change therapy. When therapy is changed for non-adherence patients, they should receive easier to adhere to treatments with lower pill burden and less dosing frequency.

Advantages of an early switch are that the immune system may be preserved and viremia controlled, hence preventing clinical progression of the infection and avoiding further development of resistance. (Smith, 2010)

ARV toxicities such as severe GIT effects, physical changes or life threatening effects such as organ damage may necessitate treatment change. Smith (2010) states that it is estimated that about 50% of patients receiving HAART for 3 years will require a treatment change due to ARV adverse effects. Due to the high incidence of treatment change due to ARV drug toxicity, a section on recommended drug substitutions was included in the adverse effect monitoring tool to act as a quick reference for the HCPs when considering treatment change of ARVs due to specific adverse effects.

2.8 Adherence to ARV Treatment

Much research has been conducted in the area of adherence to ARV treatment. According to the National Department of Health (2008), ideal adherence means that patients must take more than 95% of their doses that is, missing less than 3 doses per month. Patients taking less than 95% of their doses are at risk of developing resistance and eventually may have limited future treatment options.

Certain behaviors such as missing clinic sessions, taking incorrect doses, taking medication at the wrong times, lack of understanding of instructions, adjusting doses

due to adverse effects or stopping medication have been attributed to non-adherence patterns (Chesney, 2003).

Some of the barriers to adherence are listed below;

- Drug factors
    - Regimen complexity
    - Adverse effects
- Patient factors
    - Belief system
    - Patient-HCP relationship
    - Psychosocial issues

2.8.1 Drug factors

These are the factors that involve the actual drugs as discussed below.

2.8.1.1 Regimen complexity

HAART is complicated by multiple daily doses to be taken at specific times of the day, everyday for life. It is further complicated by food restrictions, and the possible adverse effects. In addition to these factors, HIV positive patients usually take multiple drugs for prophylaxis or treatment of different conditions such as opportunistic infections; therefore there is a propensity for drug interactions. Regimens that fit into the patient's lifestyle or schedule as well as the patient's attitude to their treatment rather than the dosing schedule of the drugs have been reported to be better predictors of adherence (Chesney, 2003).

2.8.1.2 Adverse effects

The adverse effects discussed above, pose a great threat to adherence. The limitations to adherence that arise from adverse effects are sometimes dependent on patient factors, discussed below. Approximately 50% of patients receiving HAART experience adverse effects and up to 25% of these patients stop their treatment within the first year of treatment leaving them defenseless against the virus and possibly resulting in drug resistance, a loss of drug efficacy and the loss of future treatment options (Schiller, 2005). Approximately 25% of patients do not take the recommended dosages of their medication due to concerns regarding the side effects. Patients, who report significant side effects, are often non-adherent (Schieferstein and Buhk, 2006).

2.8.2 Patient factors

According to Chesney (2003), patients who are less adherent have reported more significant confusion over their dosing schedule.

2.8.2.1 Belief system

Some patients do not understand their disease progression or how HAART works and therefore the utmost importance of adherence. These patients are therefore at higher risk of non-adherence. Patients with positive belief systems, such as believing that HAART works have been reported to be more adherent to their treatment regimen. Recreational drug users have a belief that ARVs reduce the “high” they get from their drugs and thus are likely to not be adherent. (Chesney, 2003)

2.8.2.2 Patient-HCP relationship

Patient-HCP relationships, where the HCPs routinely offer counseling to the patients, may aid in improving patient adherence to their treatment. Concordance rather than

compliance would help patients as it would mean individualizing treatment to suit patients'own lifestyles. The patient-HCP relationship would also address patient perceptions of HCP competence, clarity of communication, patient involvement in their treatment as well as any regimen inconvenience. HCPs need to address any adverse effects or any treatment problems with patients at each clinic visit in order to ensure the relationship is maintained and patients adhere correctly to their treatment (Chesney, 2003).

2.8.2.3 Psychosocial issues

Intravenous drug use may affect the ability of patients to adhere to their treatment. Depression, stress, negative feelings and hopelessness are also significant predictors of non-adherence. Patients need support from both their health care providers and family in order to cope with life's stresses and continue adhering to their medication. (Chesney, 2003)

2.8.3 Methods for improving adherence

The following have been suggested as ways of improving patient adherence;

- Involving patients in decisions affecting their treatment
- Instructing and educating patients in behavioral skills that augment adherence
- Patients need to understand the consequences of non-adherence such as treatment failure, disease progression and even death
- Patients and HCPs need to have a relationship that involves routine monitoring and counseling

- Making treatment practical, for example morning doses may be associated with brushing teeth and evening doses with programs like the evening news. Cell phone reminders may also be of assistance
- HCPs should discuss the possible adverse effects of ARVs and some practical ways to manage them may be a pro-active way of improving adherence
- A “treatment-buddy” system may ensure patients remain accountable and consistent in taking their treatment. (Chesney, 2003)

2.9 Drug Interactions Involving ARVs

2.9.1 Drug-drug interactions

Drug interactions have become an increasingly complex challenge for HCPs treating HIV-infected patients. Generally, drug interactions can be classified into two broad categories:

- interactions altering pharmacokinetics
- interactions affecting pharmacodynamics (Meemken and Dickinson, 2006).

Although both are likely to be problematic in patients receiving HAART, pharmacokinetic interactions are more frequent and more difficult to predict due to the complex nature of drug metabolism. Most interactions are minor and may not be obvious or of any clinical significance; however there are a number of interactions that may cause a decrease in patient or clinical outcomes, therapeutic failures, mild to moderate toxicity and severe to life threatening toxicities. Clinically significant drug interactions are those that produce at least a 30% change in pharmacokinetic parameters.

Drug interactions arise in almost all HIV positive patients who receiving treatment due to the average number of drugs (for HIV and opportunistic infections), food interactions,

vitamins, complementary and herbal or traditional medicines that the patient may be taking (Meemken and Dickinson, 2006).

2.9.1.1 Pharmacokinetic interactions

Pharmacokinetic drug interactions are classified according to the pharmacokinetic parameters they affect; absorption, distribution, metabolism, or elimination of other drugs. Most common drug interactions encountered in HIV infection involve those that affect metabolism or absorption. Drug interactions involving metabolism are the most common and difficult to predict. Drugs used in HAART, especially NNRTIs and PIs, are metabolized via the CYP450 enzyme system. CYP3A4 is the enzyme responsible for the majority of drug metabolism, although CYP2C19 and CYP2D6 are also common and, to a lesser extent, CYP1A2 (Department of Health, 2005). The abundance of CYP450 enzymes are illustrated below.

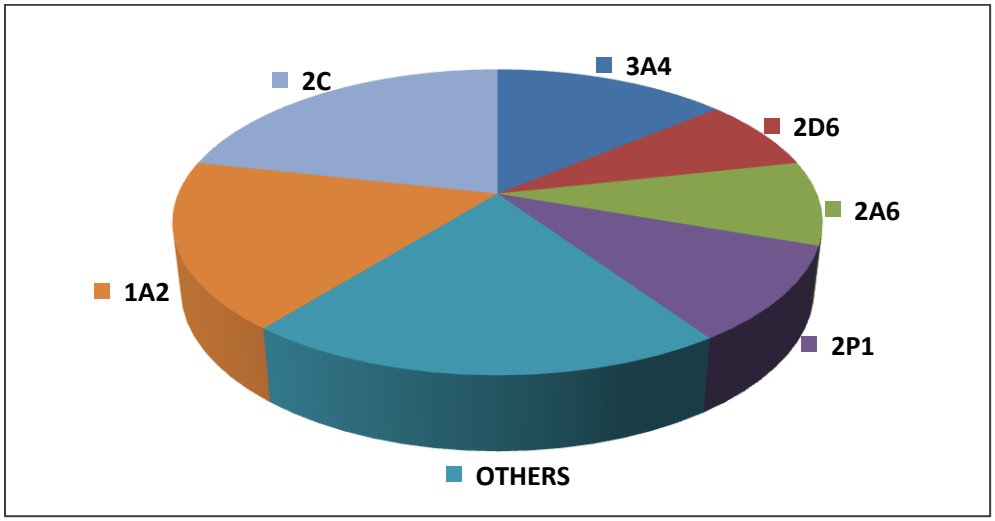


Figure 2.8 Abundance of CYP450 enzymes in the human liver

(Adapted from: Banoo, 2008)

Drugs may interact with the CYP450 enzymes in one of three ways:

- through inhibition (resulting in potentially toxic levels due to decreased drug metabolism),
- through induction (resulting in sub-therapeutic levels due to increased drug metabolism)
- by acting as a substrate. (Department of Health, 2005)

2.9.1.2 Pharmacodynamic interactions

Pharmacodynamic interactions occur when one drug causes an alteration in the pharmacologic response (including efficacy and toxicity) of a second without a consequent change in drug concentrations or pharmacokinetic parameters. In this type of interaction, the pharmacologic response from the drug may be antagonistic, additive, or synergistic as discussed below;

- Antagonistic effects result in the drug's pharmacologic effect being reduced due to concurrent therapy, for instance co-administration of AZT and d4T, where by AZT may interfere with the phosphorylation of d4T thus antagonizing its effects
- Additive effects occur when the use of two drugs leads to enhanced pharmacologic activity, such as
- Synergy occurs when the use of two or more drugs concurrently results in an effect that is greater than the addition of all of the drugs together, that is, the effect is exponential, not additive (Department of Health, 2005).

Drug interactions may take place when ARVs are co-administered with other drugs which are substrates of, or induce or inhibit certain CYP enzymes. Therefore, practitioners need to possess an in depth knowledge of potential drug-drug interactions

and always check before co-administering other drugs with ARVs. This will prevent the potential problem of toxicity which may be fatal or sub-therapeutic ARV levels, which predisposes patients to resistance.

In order to prevent potential drug interactions, the following should be considered;

- Patients should be counselled with regarding self medication with over the counter products or herbal products and urged to consult with their HCP before taking any other medicines
- HCPs need to enquire at each visit whether the patients are receiving any other medications
- Drugs with potential interactions should be avoided unless benefits outweigh risks

(Mohammed *et al.*, 2005).

2.9.2 Drug-food Interactions

Food may enhance or inhibit the absorption, metabolism, distribution and excretion of drugs. Dietary management to improve the efficacy of a drug includes taking it with food, on an empty stomach, taking it with particular foods or avoiding particular foods as shown in the following table.

Table 2.13 ARV drugs and food restrictions

(Adapted from: Department of Health, 2005)

Drug	Food restriction	Other restrictions
Efavirenz	Take on an empty stomach, food seems to increase absorption	Avoid alcohol
Nevirapine	Not affected by food	None
Stavudine	Give without regard to meals	None
Lamivudine	Take without regard to meals (though may delay absorption)	None
Didanosine	Take on an empty stomach, 1hr before a meal or 2hrs after	Buffered tablets can be dispersed in clear apple juice
Zidovudine	Take with low fat meal	None
Lopinavir/ritonavir	Food significantly increases plasma concentration; Take with meals	None

2.9.3 Herb/traditional/complementary-drug Interactions

It is estimated that about 90% of HIV positive patients take some complementary or herbal medicine (Deparment of Health, 2005). This implies that a majority of patients on ARTs will also be taking some form of herbal, traditional or complementary medicine. Research on herbal or traditional medicines is still very limited. There is inadequate HCP experience combining herbal, traditional or complementary medicines with ARVs. HCPs should document as much as possible the name, source and quantity of any other medicines that their patients take. They should counsel patients on the possibility of drug interactions that may result in therapeutic failure or toxicities (Department of Health, 2005). The following complementary medicines have however been documented to have an effect on the CYP450 enzyme system:

- St. John's wort (Induction of CYP3A4)
- Garlic (Induction of intestinal CYP450)
- Sutherlandia and "African potato" (Inhibits cytochrome P450). (Banoo, 2008)

Ginseng, melatonin, milk thistle, geniposide and skullcap have also been reported to have an effect on the CYP450 system (Department of Health, 2005). Because of possible drug interactions with ARVs patients should be advised to refrain from concurrently using the herbal remedies with ARVs. They should be encouraged to report any and all symptoms they may experience which may cause them to seek alternative remedies. Phytovigilance which involves the safety of complementary and traditional medicines is also necessary in the South African context because of the large population that takes traditional medicines (Department of Health, 2005).

2.10 Pharmacovigilance Relating to ARV Therapy

When the HIV epidemic begun, there was an urgent need to develop drugs to arrest the disease progression but the need and importance of safety monitoring of the drugs appears to have been neglected. More recently, it is evident that regardless of the success of HAART, drug toxicity remains a weighty issue. (Bisson, 2003)

Pharmacovigilance has been defined in the WHO handbook of pharmacovigilance of ARVs (2009, p.1) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".

Pharmacovigilance involves the following:

- monitoring medicines used in everyday practice to identify current and/or previous unidentified adverse effects
- assessing the risks and benefits of medicines

- providing information to users to optimize safe and effective use of medicines
- monitoring the impact of any action taken. (WHO, 2009)

Pharmacovigilance is aimed at detecting previously unknown adverse effects of drugs (Bisson, 2003). The primary goal of pharmacovigilance is to ensure the safe and effective use of medicines in order to improve patient well-being and public health (Department of Health, 2005).

Drug safety is monitored pre- and post approval, with pre-approval monitoring providing information on efficacy, adverse events and immediate drug safety and post approval monitoring establishing sustained safety of the drugs (Bisson, 2003).

The WHO (2009) has described two types of pharmacovigilance that can be used to monitor for drug safety, namely;

- Passive pharmacovigilance - Also referred to as spontaneous or voluntary pharmacovigilance. It implies that there are no active measures taken to detect adverse effects and that reporting is entirely dependent on the initiative and motivation of the reporter. Passive pharmacovigilance is the most commonly used all over the world as it is easy to establish and inexpensive to run.
- Active pharmacovigilance - Also referred to as proactive reporting. Here, active measures are taken in order to detect adverse effects for instance by directly asking patients or screening their medical records. This method is more elaborate, but delivers more accurate and reliable results compared to passive pharmacovigilance.

Different countries have different methods set up for pharmacovigilance but the WHO describes the requirement for reporting and recording adverse events. An ARV adverse effect reporting form (Appendix 7) is a sample of an ARV adverse effect recording tool in use. This recording tool provides for identification of adverse effects patients

experience and interventions taken. The monitoring tool developed for this study is aimed at identifying symptoms indicative of adverse effects as well as actual adverse effects whilst also rating the severity of these effects. This is because of the need to identify adverse effects early in order to prevent fatalities and avoid patients stopping their treatment. Any necessary tests and interventions can therefore be made and recorded in attempts to identify and prevent adverse effects, particularly the life threatening effects. The tool was not only an adverse effect monitoring tool but also provided the HCP with a reference for managing specific adverse effects (including the possible causative ARV agents) as well as recommended ARV drug substitutions for specific adverse effects (see Appendix 1b).

In 1987 a regulatory infrastructure to monitor pharmacovigilance activities was established in South Africa. This program is conducted by the pharmacovigilance center based at the University of Cape Town - called the National Adverse Drug Event Monitoring Center. This institution functions as a WHO collaborating center and provides support to the Medicine Control Council's (MCC) safety monitoring program. The pharmacovigilance program involves a national adverse drug reaction-reporting database, which is compatible with the WHO pharmacovigilance database (Department of Health, 2005). All ARV centres should have the adverse event reporting forms which may then be sent to the pharmacovigilance centre for record keeping.

In her speech during the opening of the pharmacogivilance centre, Dr Tshabalala-Msimang (2004) stated that the risk and toxicity profile of ARVs needs to be understood in South African settings and the complexities associated with various regimens continually assessed and suitably and responsibly managed.

CHAPTER 3

METHODOLOGY AND DATA COLLECTION

Introduction

This chapter describes the strategy and methodology used to meet the primary aim of this study which was to evaluate the extent to which monitoring strategies, including an adverse effect monitoring tool to be used by HCPs to monitor patients, and a self-monitoring patient diary can contribute to the early identification and management of adverse effects associated with ARVs.

3.1 Study Aim and Objectives

The primary aim of the study is to evaluate the extent to which monitoring strategies, including a tool to be used by HCPs, and a self-monitoring patient diary can contribute to the early identification and management of adverse effects associated with ARVs.

The objectives of this study are to:

i. Implement the tool previously developed and piloted by Diergaardt (2005) and modified by Mulinge (2008)
ii. Develop and implement a patient diary for the patients to monitor their adverse effects
iii. Determine the extent to which the above strategies facilitate the identification of adverse events associated with ARV treatment
iv. Determine the perceived ease of use of the monitoring tool by HCPs and the diaries by the patients.

3.2 Literature Review

An in depth literature review was conducted on ARVs including their mechanism of action, adverse effects, the pharmacological and non-pharmacological management of these adverse effects, contraindications, drug interactions as well as pharmacovigilance practices relating to ARVs. New ARVs available in the United States and those under development were included in the review. The currently available methods of monitoring patients for adverse effects were also included in the discussion.

3.3 Study Setting

The study was conducted at a private HIV and AIDS clinic, hereafter referred to as the Centre, in Uitenhage, in the Eastern Cape Province of South Africa. The Centre was chosen following a pilot study, conducted there by Mulinge (2008), which led to the realization that it would be appropriate to expand the study, including changes to the pilot study and a new strategy of monitoring (self-diary). There are over two hundred patients receiving HAART at the Centre.

3.4 Study Population and Sample

The target study population was all the patients at the Centre who were receiving HAART. The study sample was made up of one hundred and sixty patients from the study population who were chosen using convenience sampling. The sample population was grouped into four categories each consisting of 40 patients:

- Control Group (neither the monitoring tool nor the diary were used)
- Tool Group (only the monitoring tool was used)
- Diary Group (only the patient diary was used)
- Tool-Diary Group (both the tool and patient diary were used).

Patients were allocated to each group by HCPs at the clinic, by means of convenience sampling. The inclusion criteria to participate in the study included that the patients be HIV positive and receiving HAART, and after the nature and purpose of the study was fully explained to them, that they be willing to participate and be able to sign informed consent.

The patients were allocated study numbers and the four groups were represented by four different coloured stickers (placed on the patients' files) as shown in Figure 3.1 below. This was done by the researcher in order to minimize the work the HCPs were to do and to ensure uniformity and accuracy.

Figure 3.1: The study sample

Clearly labelled research packages were prepared for each study group containing the following;

- Control group
    - Informed consent forms
    - Green stickers with study numbers
- Tool group
    - Informed consent forms
    - Pink stickers with study numbers
    - Pink ring-bound monitoring tools each with a pink sticker containing the patient study number.
- Diary group
    - Informed consent forms
    - Blue stickers with study numbers
    - Patient self-monitoring diaries each with a blue sticker containing the patient study number.
- Tool-Diary group
    - Informed consent forms
    - Yellow stickers with study numbers
    - Yellow ring-bound monitoring tools, each with a yellow sticker containing the patient study number
    - Patient self-monitoring diaries each with a yellow sticker containing the patient study number.

3.5 Research Design

This study was experimental in nature, seeking to describe the extent to which the use of an adverse effect monitoring tool and/or the use of a patient self-monitoring diary impacted on the early identification and management of adverse effects associated with ARV use (Peter, 2007). It was a randomized controlled study with participants being assigned to one of four groups, as described in Section 3.3 above.

3.6 Data Collection Tools

3.6.1 Antiretroviral recording and monitoring chart (adverse effect monitoring tool)

In the pilot study (Mulinge, 2008), unstructured and informal meetings were held with the HCPs at the Centre, in order to determine the manner in which they monitor ARV adverse effects and to determine their requirements for a specific tool to monitor these adverse effects. After taking into consideration the recommendations of Diergaardt's study (2005), Mulinge's study (2008) and the requirements of the HCPs at the study site, the adverse effects monitoring tool was modified and adapted for the study site (Appendix 1a and Appendix 1b). Feedback from the HCPs involved in the previous study (Mulinge 2008) indicated that the previous tool (Appendix 1c) was too extensive and time consuming. Therefore, one of the modifications included splitting the previous tool into two separate forms: a Researcher's Data collection Form (Appendix 2) and the Antiretroviral Recording and Monitoring chart (the Tool - Appendix 1b).

The researcher's data collection form, a history taking tool, was used by the researcher towards the end of the study to collect relevant data (for the three months study period) from patient files while the tool was used by the HCPs to record aspects involving adverse effects of ARVs. The tool also included the South African Department of Health

(2008) recommendations for further management of specific adverse effects and ARV substitutions in cases of specific toxicities.

A chart with the human body indicating the different ARV adverse effects included in the monitoring tool was colour printed and laminated and a copy was provided to each HCP participating in the study (Appendix 1a). The HCPs used this chart as a reference point to direct them to the relevant place in the tool where they were to record adverse effects experienced by the patients (Appendix 1b). The chart was therefore a prompt, assisting with ease of identification of the symptoms of the different adverse effects and the tool was used to record these in details; including severity, any interventions made and the outcomes of these interventions. The chart was included to make it easier to record the symptoms the patients were experiencing hence it reduced the time it would have taken to locate those symptoms on the tool.

3.6.2 Self-monitoring patient diary

A patient diary provides for the patient to assess their own health status without clinician bias and to evaluate the impact of their treatment (Zanni, 2007). HIV infection is often accompanied by other co-morbid disease states. Patients taking ARVs may experience adverse effects which may be similar to disease states or conditions that they have previously experienced. The patients may therefore overlook these adverse effects and fail to mention them to the HCP during their regular follow up sessions. Patients may also feel rushed while in consultation with the HCPs due to the allocated consultation time, judged or uncomfortable talking about their symptoms or may even forget to mention certain symptoms they have experienced or are currently experiencing. It is

because of this possibility that a patient diary was developed. The diary aimed to identify such symptoms or adverse effects if they existed.

The patients used the diary to self-monitor for any symptoms they experienced during the study period. An initial pilot study of the diary (Appendix 3a) was conducted on four patients (not included in the final study), for a period of two weeks to assess the usability, validity and reliability of the diary. The researcher then collected the four diaries and made necessary modifications suggested by the patients and the HCPs before compiling the final diary to be implemented (Appendix 3b).

Instructions on how to use the diaries were communicated to the HCPs by the researcher; both verbally in an informal meeting and in writing, in the form of colour printed and laminated copies.

Patients in the two categories involving the diary (Diary Group and Tool-Diary Group) were given their diaries by the HCPs to take home. The diaries included a figure of the human body which patients used to identify symptoms they are experiencing. The intention was for patients to indicate against the symptoms indicated on the figure they experienced, or add any symptoms that were not included on the figure, and include the date they experienced those symptoms. They would then complete weekly journals indicating the severity of their symptoms, any interventions made and the result of the intervention(s). Illiterate patients or patients who cannot communicate in English were asked to merely draw a line/arrow pointing to the affected body part and the HCP would then follow up and intervene as required.

The HCPs explained the use of the diary to the patients and instructed them to return their diaries at their next scheduled clinic visit. The diaries were to be presented at each clinic visit. The HCPs were required to sign the diaries on receiving them and any

necessary investigations and interventions could then be made based on the patients recorded symptoms.

At the end of the study period, the HCPs conducted an evaluation of the diaries, including the patients' perspectives and the HCPs perspectives of the different aspects of the diary, using the diary evaluation form provided (Appendix 4). This feedback was obtained from the patients when they handed in their diaries at the end of the study period and stored with the diaries.

3.7 Data Collection

Before commencing, the researcher explained the nature and purpose of the study to the HCPs and the team that would be involved in the data collection. The HCPs and data collection team were asked to sign informed consent forms (Appendix 5) stating willingness to participate in the study. In turn, the HCPs explained the study to the patients and obtained signed informed consent forms (Appendix 5) provided by the researcher, from them.

At the beginning of the study the researcher met with the HCPs at the Centre and explained the study to them. The researcher also demonstrated how the project was to be conducted, including randomly assigning patients to groups, and collecting the data. Due to set backs in the printing of the tools and diaries, the control group began the study earlier than the other groups. The other groups then began three weeks later, when the control group already had the required number of patients (forty).

The modified monitoring tool was used by the HCPs at the Centre in the course of their work for a period of three months, August to October, 2009. The researcher, after requesting for (Appendix 6a) and obtaining written permission (Appendix 6b) from the

Director of the Centre and informed consent from the participating HCPs and patients, documented relevant patient details, from the patient files, using the data collection form, at the end of the study period. This data was safely stored in a separate box and locked away to maintain patient confidentiality.

The researcher assigned each participating patient a unique study number on the relevant colour sticker, which were placed on each document in an envelope, such that all the HCPs had to do was randomly select a research package and proceed appropriately for the patient in that particular group. These research packages, in the form of envelopes, containing all relevant documentation for each patient in each group, were stored in separate clearly labeled boxes. The boxes had a checklist, prepared by the researcher, that was ticked off by the receptionist each time a patient was assigned to a particular group, to ensure uniformity in the number of patients per group. The checklist was for use by the HCPs and other clinical staff participating in the study, for easy retrieval of information.

During the three month study period, the researcher met regularly with the HCPs to provide ongoing support and follow up. At the end of the study period, the researcher collected the completed diaries and monitoring tools from the HCPs for analysis.

Data relating to the adverse effect monitoring and management of the Control Group was obtained from patient files, by the researcher, using the researcher's data collection form, since there was no monitoring tool provided to the HCPs for use in this group.

In a post-intervention briefing, the researcher met with the HCPs responsible for the collection of the data at the Centre and in an unstructured interview, obtained their views regarding the usefulness of the tool and diary. The debriefing was also used to

assess any short comings in the tool and hence make recommendations for future modifications or adjustments.

A summary of the processes involved in the collection of data are described in Figure 3.2 below:

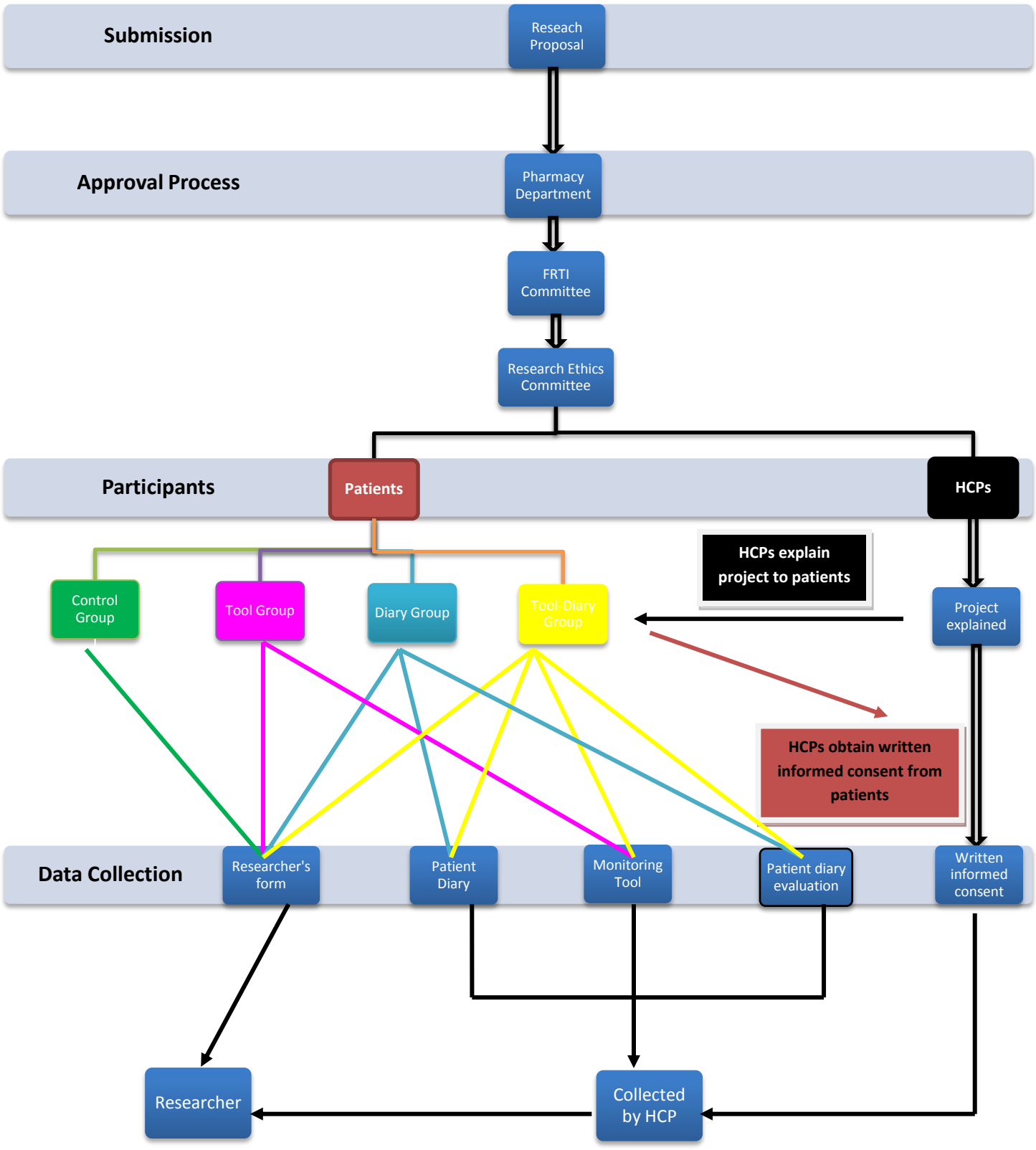


Figure 3.2: An overview of the research methodology

3.8 Data Analysis

Data from all the research tools were captured using Microsoft Excel® software. All the data was entered by the researcher in order to maintain accuracy and consistency. A statistician was consulted for assistance with the analysis and SPSS® was used for the purposes of statistical analysis. In order to evaluate the effectiveness of the monitoring strategies, the identified adverse effects were analyzed using descriptive statistics.

3.9 Ethical Considerations

HIV and AIDS is a highly stigmatized condition and infected individuals are considered to be a vulnerable group. Because of its sensitive nature and the vulnerability of this group of people, patient confidentiality and ethical consideration were of utmost importance.

In order to give careful attention to the ethical considerations involved in the study, the following steps were undertaken:

- The researcher requested permission to conduct the study at the Centre
- A letter of approval for the study was obtained from the Chairman of the Centre (Appendix 6b).
- The HCPs participating in the study were provided with a detailed explanation of the proposed study after which they signed informed consent forms.
- The HCPs participating in the study explained the study to the patients where after they obtained written informed consent from patients willing to participate. The researcher did not have any direct contact with the patients.

- Patient confidentiality was maintained by making use of unique patient study numbers and no patient names and/or personal details were linked to the data. All individual patient information was treated with utmost confidentiality.
- The statistician who was consulted for guidance with the data analysis had access to the Microsoft Excel® spreadsheet, which only had patient study numbers. Therefore, patient confidentiality was not breached at any point in time.
- Any interventions made to the treatment of patients experiencing adverse effects were done by the HCPs, according to their professional judgment and in the normal course of their work and were not at any time individually suggested or carried out by the researcher.
- Ethical approval was sought and obtained from the NMMU Research Ethics Committee (Human).

The tool under investigation was used by HCPs at the Centre in the normal course of their work. It was also the HCPs who gave the diaries to the patients ensuring that the researcher did not have direct contact with the patients at the Centre. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2002).

CHAPTER 4

RESULTS AND DISCUSSION

In order to establish the effectiveness of the methods used for identification and monitoring of adverse effects, the findings of this study and the statistical analysis thereof will be presented and discussed in this chapter.

4.1 Study sample

4.1.1 Number of participants

The total number of patients recruited for participation in the research was 160, 40 patients per study group. However due to human error, 10 patients were assigned to 2 different groups. Another patient's file was missing at the clinic and therefore a total of 11 participants have been omitted from the analysis of the results. With these factors taken into account, the total number of participants was 149.

4.1.2 Participants gender and age

The study sample consisted of 43 males (28.9%) and 106 females (71.1%). This gender distribution might have been expected since a UNAIDS report (2008) indicates that in sub-Saharan Africa women account for about 60% new HIV infections and that 14 women are infected for every 10 males.

Table 4.1 below shows the random gender and age distribution among the participants in the four different study groups.

Table 4.1 Gender and age distribution of the respondents

Characteristic	Control(n=35)	Tool (n=38)	Diary (n=38)	Tool-Diary (n=38)
Gender				
Male	28.6% (10)	60.5% (23)	21.1% (8)	5.3% (2)
Female	71.4% (25)	39.5% (15)	78.9% (30)	94.7% (36)
Age Group				
05 - 17	0	2.6% (1)	0	0
18 - 25	8.6% (3)	0	0	7.9% (3)
26 - 35	37.1% (13)	39.5% (15)	36.8% (14)	44.7% (17)
36 - 45	31.4% (11)	31.6% (12)	47.4% (18)	42.1% (16)
46 - 55	22.9% (8)	23.7% (9)	13.2% (5)	5.3% (2)
56 - 65	0	2.6% (1)	2.6% (1)	0

From the table it is evident that that there is a difference in the number of males and females that participated in the study. The number of females that participated was 106 and the number of males was 43, a difference of 63 persons.

The highest numbers of the respondents in the study were in the age group of 26 – 35 (39.6% of participants) and 36 – 45 (38.3% of participants). This observation was expected as the majority of HIV infections are in persons between 15 and 44 years of age (UNAIDS global report, 2010). Figure 4.1 below, shows the distribution of the participants' ages.

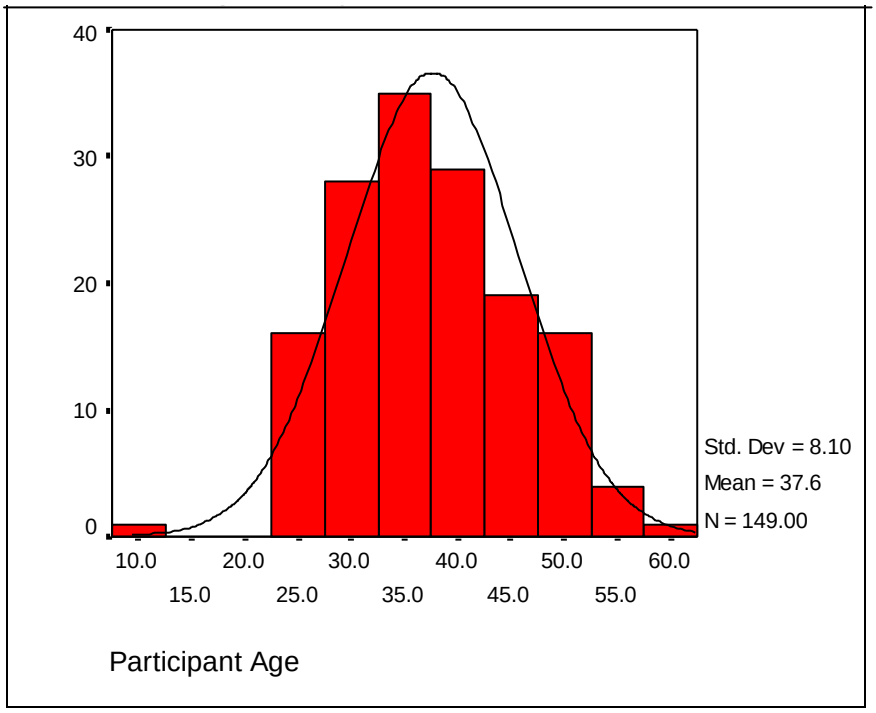


Figure 4.1 Participants mean age curve (n=149)

As shown in the graph above, there was a normal distribution of the ages of the study participants although the graph was skewed to the left (0.188) with a standard error of 0.199 which implies that there was bias towards the younger ages throughout the study groups.

4.1.3 Substance use

Of the 149 participants, one admitted to smoking whilst 15 admitted to alcohol consumption. Although there is no further evidence from this study, substance abuse, including smoking, alcohol consumption and other recreational drugs may lead abusers to risky behaviours such as feeling uninhibited, impulsive and seeking stimulus (Bryant, 2006). This may lead to sex without condoms hence risking infecting others, or missing treatment doses due to altered consciousness or possible interactions with ARVs.

According to Dybul and co-workers (2002), alcohol consumption in HIV patients has also been associated with the following:

- non-adherence to treatment
- increased risk of hepatotoxicity in patients receiving HAART
- osteonecrosis in patients receiving HAART
- increased potential for drug interactions, for example increasing plasma concentrations of ABC to toxic levels.

Considering the data collected for the research participants who admitted to alcohol consumption (n=15), the following was noted;

- Two patients were not taking their medication regularly
- Two admitted to missing treatment on weekends whilst drinking.
- Two were found to have raised gamma-glutamyl transpeptidase (GGT)
- One patient was late in collecting their medication,
- Another patient defaulted for a 2 week period.

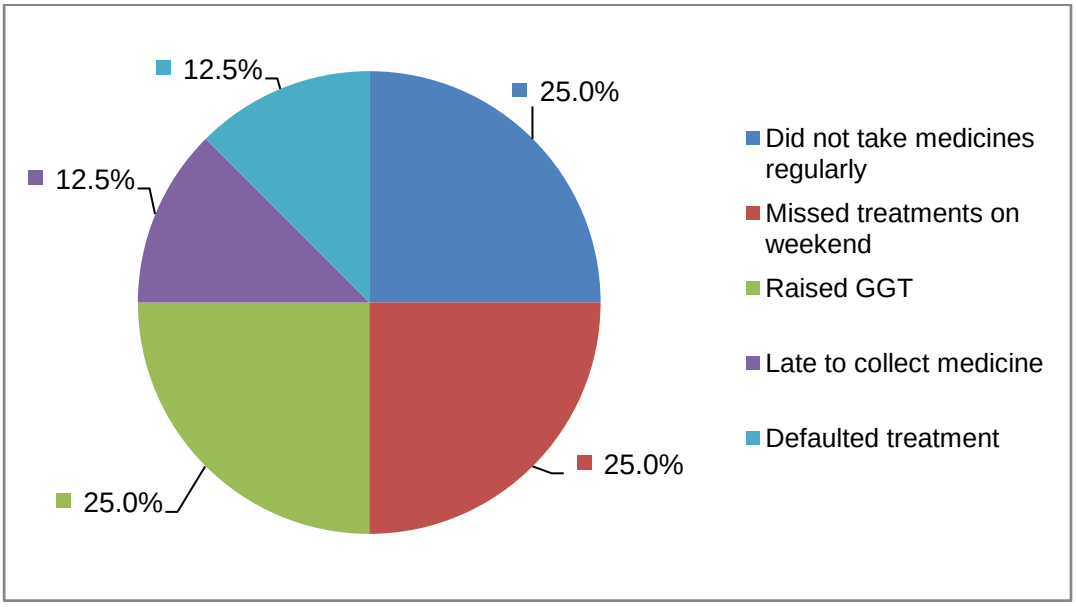


Figure 4.2 Effects of alcohol consumption on the study participants (n=15)

In 46.7% (n=15) of the patients who admitted to alcohol consumption, there was no recorded effect of the alcohol on their health or treatment. In more than half of the patients who admitted to taking alcohol (53.3%), there was a negative effect either to their health (such as raised GGT) or an effect on their treatment (such as poor adherence, defaulting), recorded. These effects were to be expected as alcohol may alter the consciousness of an individual and cause behavioral changes as suggested by Bryant (2006). Bryant (2006) further suggests that no safe level of alcohol consumption has been identified, particularly for patients receiving HAART. The records of three of these patients reflected that they had been counselled regarding their alcohol consumption. A total of 15 patients (n=149) were reported to be defaulters, or not taking their medication regularly. 33.3% of these were alcohol consumers while 66.7% were not reported to be alcohol consumers.

4.2 Co-morbidities

Many patients who develop severe opportunistic infections are usually unaware of their HIV positive status (Hoffmann, 2006). CD4 cell count is directly related to development of infections, with low CD4 counts being associated with higher risk of developing opportunistic infections. Immune reconstitution inflammatory syndrome (IRIS) may also present as an opportunistic infection. All opportunistic infections in HIV positive patients need to be treated quickly and adequately in order to prevent further damage to the immune system.

The co-morbidities observed in this study will be discussed with respect to their WHO staging and whether they are related to HIV and AIDS or not. According to the WHO (2005), clinical staging of HIV and AIDS is as follows.

Table 4.2 WHO clinical staging of HIV and AIDS

(Adapted from WHO, 2005, pp.5-6)

WHO Staging	Characteristics/Comorbidities
Stage 1	• Asymptomatic • Persistent general lymphadenopathy
Stage 2	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulcerations • Papular pruritic eruptions • Seborrhoeic dermatitis • Fungal nail infections
Stage 3	• Severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than one month • Unexplained persistent fever (intermittent or constant for longer than one month) • Oral candidiasis • Oral hairy leukoplakia • Pulmonary tuberculosis (TB) diagnosed in last two years • Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Stage 4	• HIV wasting syndrome • Pneumocystis pneumonia • Recurrent severe or radiological bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration) • Oesophageal candidiasis • Extrapulmonary TB • Kaposi's sarcoma • CNS toxoplasmosis • HIV encephalopathy

The above WHO clinical staging was used to classify the participants in the study as shown in Table 4.3 below.

Table 4.3 WHO clinical staging of the study respondents

WHO Staging	Control (n= 35)	Tool (n= 38)	Diary (n= 38)	Tool-Diary (n= 38)
Stage 1	74.3% (26)	47.4% (18)	42.1% (16)	42.1% (16)
Stage 2	2.9% (1)	2.6% (1)	5.3% (2)	5.3% (2)
Stage 3	22.9% (8)	28.9% (11)	42.1% (16)	47.4% (18)
Stage 4	0	21.1% (8)	10.5% (4)	5.3% (2)

The above WHO clinical staging is illustrated in Figure 4.3 below.

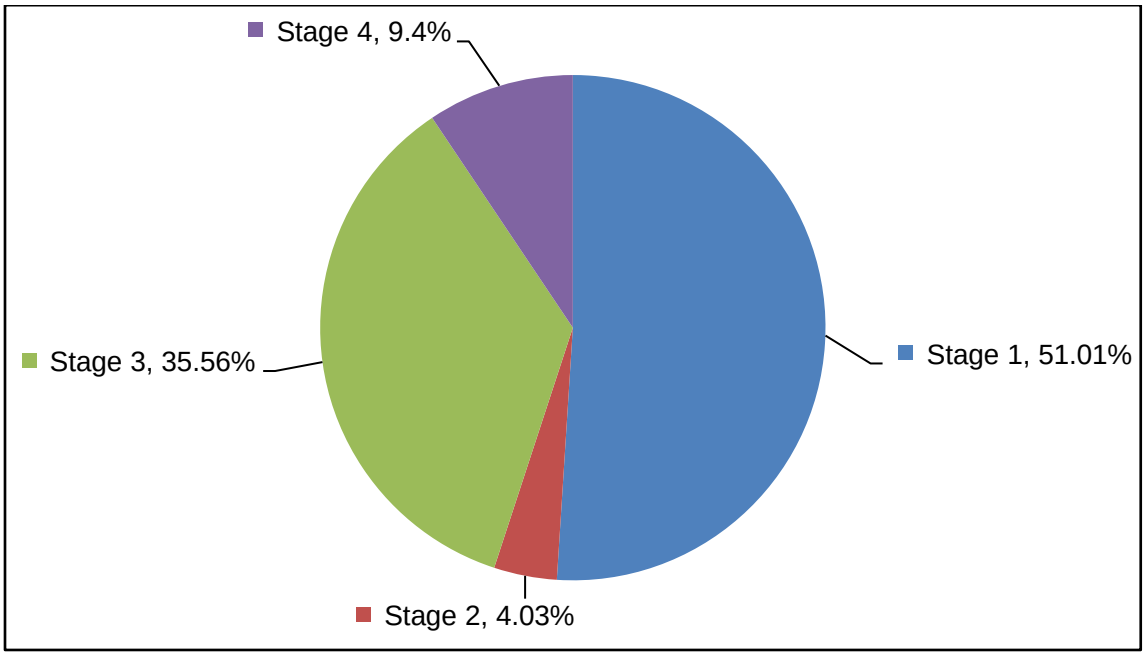


Figure 4.3 Respondents WHO clinical staging (n=149)

The above suggests that about half of the patients (51.0%) could be classified as stage 1 of HIV and AIDS, whilst only 4.0% were classified stage 2. AIDS-related co-

morbidities were identified in 74 of the 149 patients in the study. Several patients often presented with more than one of the following co-morbidities.

- TB
- Oral candidiasis
- Lymphadenopathy
- PCP
- Vaginal candidiasis
- Oral hairy leukoplakia
- Shingles
- Cryptococcal meningitis
- Genital warts (HPV infection)
- CMV eye infection
- Herpes zoster infection
- Kaposi's Sarcoma

AIDS defining illnesses may be categorized as opportunistic infections, wasting syndrome, malignancies and diseases affecting the CNS and peripheral nervous systems. Patients with advanced HIV infection may respond poorly to HAART with resulting IRIS or treatment failure due to the extent of damage to their immune system. They are also more susceptible to adverse effects than patients whose infection is not advanced. (WHO, 2010) Special attention ought to be given to the monitoring of patients with advanced HIV disease and these conditions treated aggressively.

The most common co-morbidity identified in the study was TB, with 30.2% (n=149) of the patients having TB during the study period. Oral candidiasis was also commonly

reported among the patients with 14.1% (n=149) of participants presenting with it, whilst lymphadenopathy followed with 8.05% of the patients presenting with swollen lymph nodes. The least reported conditions were CMV eye infection (0.7%; n=149) and Kaposi's Sarcoma (0.7%; n=149).

The non-AIDS related illnesses identified in the study (n=149) are shown below. The majority of patients often presented with more than one co-morbidity. The identified co-morbidities were grouped as follows as there were numerous individual conditions;

- Infection (84 patients) - Upper respiratory tract infections (URTIs) were the most common with 49 patients presenting with URTIs.
- GIT disorders (66 patients) - Majority of patients in this group (28 patients) presented with abdominal cramps.
- Skin disorders (19 patients) - Hyperpigmentation was the most reported skin disorder with 4 patients presenting with skin hyperpigmentation.
- Blood and urine abnormalities (12 patients) - Anaemia and proteinuria, each with 4 patients presenting, were the most common abnormalities recorded for this category.
- Chronic conditions (17 patients) - 11 of the 17 patients were known hypertensives.
- Respiratory (41 patients) - 35 patients presented with cough within the 3 months study period.
- Psychosocial (24 patients) - 19 patients reported some kind of stress in their lives for various reasons, including loss in the family and work related stress among others.
- Pain (53 patients) - In this category the most reported form of pain was headache, reported by 39 patients.

- Miscellaneous (44 patients) - This category was made up of different conditions the most common of which was fatigue, reported by 12 patients.

Although the above conditions are non-AIDS related, they may be more frequent and serious in immuno-compromised patients. Immediate treatment needs to be administered in order to prevent advancement of these conditions which may further compromise the immunity of the patients. With respect to chronic conditions requiring long term treatment, special considerations in order to ensure that drug-drug interactions are avoided in order to avoid sub-therapeutic plasma concentrations of ARV or accumulation to toxic levels.

4.3 Concomitant Medication

It is important to note any and all medication the patients take concurrently with their ARVs particularly because of the potential for drug interactions that may result in sub-therapeutic or toxic levels of ARVs (see Section 2.9.1 above). Some patients in the study received more than one other medication, besides their ARVs, in the 3 months of the study. The following medications were used with ARVs in the study sample.

- Anti-infective agents - this group included co-trimoxazole, dapsone, amoxicillin, fluconazole and TB medication.
- Supplements- including iron, folic acid, brewer's yeast, vitamin C and vitamin B complex.
- Chronic disease medication- including antihypertensives, simvastatin, gliclazide, metformin, colchicine and barbiturates.
- Contraceptives- included Nur-isterate® (norethisterone enantate), Depo-Provera® (medroxyprogesterone acetate) and Triphasil® (ethinyl oestradiol and

levonorgesterol). It was recorded that patients were counselled to use condoms although some reported that their partners did not want to use them whilst others were trying to conceive.

- Pain medication- Including paracetamol and codeine or paracetamol alone.
- Topical preparations- such as aqueous cream, zinc ointment and betamethasone cream were prescribed to patients with different skin problems.
- Other medications- These included anti-tussives, flu medication, amitriptyline, prednisone and sutherlandia.

The above reported medicines do not seem to match the number and nature of the reported co-morbidities in Section 4.2. This may be due to several possible reasons including;

- patients self medicating and not reporting to the HCPs
- patients visiting their general practitioners in other clinics or hospitals and receiving medication for their co-morbidities
- patients admitted to hospital and hence the medication they received is not recorded at the Centre
- inadequate recording of concomitantly used medications by HCPs at the Centre.

In order to avoid the potential problem of drug interactions, it is essential for the HCPs to ensure that they ask patients whether they are receiving any other treatment besides ARVs. This needs to be done in a manner that does not intimidate the patients but rather makes them feel comfortable enough to report any self medication. The result would be that there would be better documentation of all medications used by the

patients and hence patients can be advised appropriately about any potential interactions.

4.4 ARV Regimens

At the time of the study the recommended ARV regimens according to the South African Department of Health guidelines (2008) were as follows;

- First Line
    - 1a- d4T/3TC/EFV
    - 1b- d4T/3TC/NVP
    - 1c- AZT/3T/EFV or NVP
- Second Line
    - 2a- AZT/ddI/Lopinavir-ritonavir
    - 2b- TDF/3TC/Lopinavir-ritonavir
    - 2c- AZT/ddI/Double dose Lopinavir-ritonavir

Due to the variations in patients' response to treatment, these standard regimens are not always adhered to. The following are some of the possible reasons for regimens other than the standard recommended ones;

- In certain cases clinicians change treatment for various reasons such as replacing agents which have caused intolerable adverse effects with agents from the same group or a different group with a better profile.
- In other cases, regimens are changed due to treatment failure, discussed in Section 2.7.1 above, resulting in individualized regimens that may be different from the standard recommended regimens.

- For some patients, their economic status may determine the treatment that they may be able to receive. People who can afford to buy ARVs may be started on newer regimens not available to everyone in the country.

The ARV regimens identified in this study are shown in the table below.

Table 4.4 ARV regimens in the study

First Line	Second Line
d4T/ddI/EFV	ddI/AZT/Lopinavir
d4T/3TC/EFV	ddI/3TC/ Lopinavir
d4T/3TC/NVP	TDF/3TC/ Lopinavir
AZT/3TC/NVP	AZT/3TC/ Lopinavir
TDF/FTC/EFV	TDF/FTC/ Lopinavir
TDF/FTC/NVP	d4T/ddI/ Lopinavir
TDF/3TC/EFV	d4T/3TC/ Lopinavir
ddI/3TC/EFV	SQV/ Lopinavir
TDF/FTC/3TC/EFV	

Figure 4.4 below illustrates the ARV regimens observed across the four study groups.

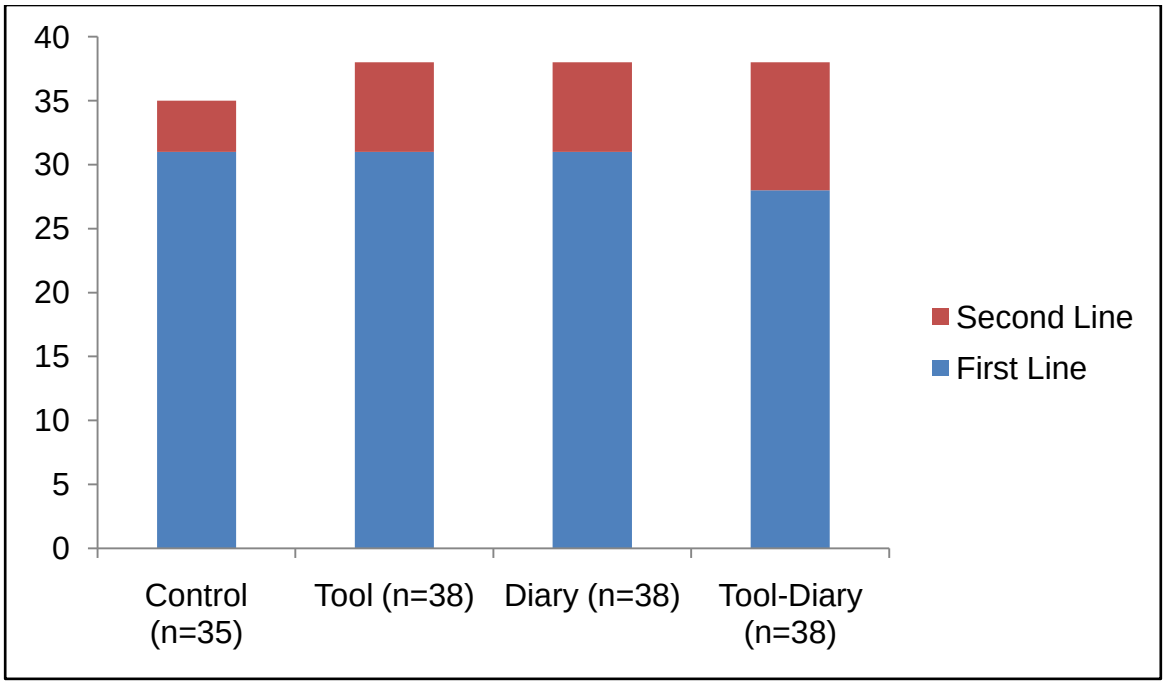


Figure 4.4 ARV regimens in the different study groups

Of the 149 patients in the study, 81.2% were receiving first line regimens whilst 18.8% were receiving second line regimens. Second line regimens are usually reserved and used as salvage therapy in patients not responding to first line regimens due to treatment failure (see Section 4.6), resistance or adverse effects to first line regimens.

4.5 Adverse Effects Identified

The reporting of adverse effects by participants in the different study groups is summarised in Table 4.5 below.

Table 4.5 Adverse effects recorded for the different study groups

Study Groups	Reported Adverse Effects	
	Yes	No
Control (n=35)	51.4% (18)	48.6% (17)
Tool (n=38)	50.0% (19)	50.0% (19)
Diary (n=38)	60.5% (23)	39.5% (15)
Tool-Diary (n=38)	50.0% (19)	50.0% (19)

The above data was collected from the Centre's patient records by the researcher and recorded in the data collection form and not the individual adverse effects monitoring tools, that is, the tool and the diary. From the table above, it is observed that 53.0% of the patients in the study (n=149) reported adverse effects or symptoms of adverse effects that were identified and recorded using the Centre's monitoring method. This was expected as it is estimated that about 50% of patients receiving HAART experience adverse effects (Schiller, 2005).

The specific adverse effects identified in this study have been grouped for reasons of statistical analysis and are listed below.

- **Biological** - including raised liver enzymes, anaemia, hyperlactatemia, lactic acidosis, anaemia, pancreatitis, pancytopenia, tachypnoea, tachycardia,
- **CNS** - including dizziness, drowsiness, moody, nightmares, insomnia, hallucinations, memory problems
- **GIT** - including abdominal cramps, nausea, vomiting, diarrhoea, loss of appetite, post prandial abdominal pain, heart burn,

- **Physical** - including weight gain, weight loss, gynaecomastia, lipodystrophy (Crixivan potbelly and buffalo hump), fat wasting, rash, muscle pain, loss of hair, hyperpigmentation, increased hunger and thirst, fatigue, headaches, peripheral neuropathy

Some patients presented with more than one category of adverse effects. The following table breaks down the adverse effects identified in the Centre for the four study groups according to the above stated categories.

Table 4.6 Adverse effects identified using the Centre's method of monitoring

Study Groups	Adverse Effects			
	Biological	**CNS**	**GIT**	**Physical**
Control (n=35)	5	6	3	8
Tool (n=38)	6	9	1	10
Diary (n=38)	7	6	2	19
Tool-Diary (n=38)	4	1	1	17

The above table indicates adverse effects recorded for the four study groups in the patients' files, that is, the Centre's monitoring method. This excludes information obtained from the monitoring strategies.

The monitoring strategies used in this study were useful in identifying some adverse effects or symptoms that were not identified using the Centre's normal method of monitoring. These "extra" effects were included in the analysis of the effectiveness of the monitoring strategies and included muscle pains, memory problems, night sweats, difficulty walking, hallucinations, dizziness, headaches and constipation. The following

table illustrates the frequency of identification of these “extra” adverse effects categories for the Tool, Diary and Tool-Diary group.

Table 4.7 Adverse effects identified using the research monitoring strategies only (“Extra adverse effects”)

Adverse effects	Tool	Diary	Tool-Diary
Biological	3	0	3
CNS	3	10	13
GIT	5	6	6
Physical	3	6	7

In order to determine the effectiveness of the interventions, a comparison can be made between the adverse effects identified using the Centre’s usual method of monitoring patients and the tool, diary and tool-diary methods used in the study. This will be done per study group in order to establish the effectiveness of each monitoring strategy. Since the monitoring strategies were not incorporated into patients’ clinical records, but were treated as a separate means of monitoring, the comparisons made will be between the adverse effects identified by the Centre versus the monitoring strategies, for each study group as shown below.

4.5.1 Adverse effects identified using the adverse effects monitoring tool alone

A comparison will be made for the tool group between the adverse effects identified for the patients in this group using the Centre’s monitoring method and those identified using the adverse effect monitoring tool for the 38 patients in the Tool group.

Table 4.8 Comparison of the Tool and Centre's adverse effects monitoring methods for the Tool Group

	Centre Biological		Total	Significance
Tool Biological	**No**	**Yes**		
No	16	0	16	-
Yes	3	0	3	
			19	
	Centre CNS		**Total**	**Significance**
Tool CNS	No	Yes		
No	9	5	14	0.516
Yes	4	1	5	
			19	
	Centre GIT		**Total**	**Significance**
Tool GIT	No	Yes		
No	10	0	10	-
Yes	9	0	9	
			19	
	Centre Physical		**Total**	**Significance**
Tool Physical	No	Yes		
No	9	2	11	0.141*
Yes	4	4	8	
			19	

Note:

- *** significant at 99 percent confidence level ** significant at 95 percent confidence level * significant at 90 percent confidence level using two tailed t-test.
- Yes represents the frequency at which the adverse effect was detected while No indicates that the adverse effect was not detected.

The above data applies to only 19 (50.0%; n=38) of the filled monitoring tools. Therefore, the other 19 tools have been excluded from the above comparison with the Centre's method of monitoring for adverse effects in order to yield a more accurate result of how the two methods compare with regards to identification and recording of adverse effects.

The above table shows that the tool had a statistically significant effect on the reporting of physical adverse effects only at 90% confidence level. This means that the tool as compared to the Centre's monitoring method was better in reporting of the physical adverse effects at the 90% confidence level. There was no significance change in reporting biological and GIT adverse effects as there were no reported cases of these effects.

4.5.2 Adverse effects identified using the patient self-monitoring diary alone

From the diary group 15 diaries were returned although one was not included in the analysis as it was written in Afrikaans which the researcher does not understand. Therefore, only 14 (36.8%; n=32) diaries were analysed and used to establish the effectiveness of the diary as compared to the Centre's method of adverse effect monitoring in the identification and recording of adverse effects for the patients in the diary group. The comparison below is therefore of the adverse effects identified using the Centre's method of monitoring for adverse effects versus those identified using the diary, for the 14 Diary group patients.

Table 4.9 Comparison of the Diary and Centre's adverse effects monitoring methods for the Diary Group

	Centre Biological		Total	Significance
Diary Biological	No	Yes		
No	11	3	14	-
Yes	0	0	0	
			14	
	Centre CNS		**Total**	**Significance**
Diary CNS	No	Yes		
No	4	1	5	0.649
Yes	8	1	9	
			14	
	Centre GIT		**Total**	**Significance**
Diary GIT	No	Yes		
No	7	7	14	-
Yes	0	0	0	
			14	
	Centre Physical		**Total**	**Significance**
Diary Physical	No	Yes		
No	5	3	8	0.640
Yes	3	3	6	
			14	

Note:

- *** significant at 99 percent confidence level ** significant at 95 percent confidence level * significant at 90 percent confidence level using two tailed t-test.
- Yes represents the frequency at which the adverse effect was detected while No indicates that the adverse effect was not detected.

The table above indicates that the diary alone did not have any significant impact on adverse effect monitoring, that is, there was no substantial change when compared with the Center's method of monitoring in all the categories of adverse effects. The significance of the diary in monitoring for the biological and GIT adverse effects could not be established since there were no reported effects.

With regards to the biological adverse effects, the diary group was insufficient in reporting as these are mainly derived from blood tests and other tests. The diary would therefore only be useful in identifying symptoms of the biological adverse effects and not the actual biological adverse effects because it identified subjective symptoms.

4.5.3 Adverse effects identified using the patient self-monitoring diary and the monitoring tool in combination

Of the 38 patients in the Tool-Diary group only 17 (44.7%; n=38) will be analysed in terms of comparison with the clinic's normal monitoring method as the rest of the diaries and tools were not returned or completed respectively. A comparison will be made between the adverse effects identified by the Centre's adverse effect monitoring method and those identified using the Tool-Diary method for the 17 patients in the Tool-Diary group.

Table 4.10 Comparison of the Tool-Diary and the Centre's adverse effects monitoring methods for the Tool-Diary Group

	Centre Biological		Total	Significance
Tool-Diary Biological	No	Yes		
No	13	3	16	0.633
Yes	1	0	1	
			17	
	Centre CNS		**Total**	**Significance**
Tool-Diary CNS	No	Yes		
No	7	0	7	0.388*
Yes	9	1	10	
			17	
	Centre GIT		**Total**	**Significance**
Tool-Diary GIT	No	Yes		
No	11	1	12	0.506
Yes	5	0	5	
			17	
	Centre Physical		**Total**	**Significance**
Tool-Diary Physical	No	Yes		
No	5	2	7	0.201*
Yes	4	6	10	
			17	

Note:

- *** significant at 99 percent confidence level ** significant at 95 percent confidence level * significant at 90 percent confidence level using two tailed t-test.
- Yes represents the frequency at which the adverse effect was detected while No indicates that the adverse effect was not detected.

It is evident from the above table that the tool and diary had a statistical significant effect on the reporting of CNS and physical adverse effect at 90% confidence level. This implies that using the tool and diary together was more effective in identification and reporting of these adverse effects as compared to the Centre's method of monitoring.

The Tool-Diary method of monitoring did not have a notable significant effect on the identification of biological and GIT categories of adverse effects.

4.6 Evaluation of the Monitoring Tools

4.6.1 The adverse effect monitoring tool

The evaluation for the perceived effectiveness of the tool was done through an informal feedback session with the HCPs involved in the study. The HCPs indicated that they were sometimes very busy and hence they did not fully utilize the monitoring tool. This was reflected by the number of monitoring tools that were utilized for the study (47.4%; n=76, that is, 38 Tool group and 38 Tool-Diary group). They also indicated that the whole study was very time consuming considering the already existing work load. This may be the reason that 52.6% (n=76) of the monitoring tools were not completed at all. Therefore, the results obtained from the comparison of the tool and the Centre's monitoring method may not be a true representation of the adverse effects encountered by patients in this study or the usefulness of the tools.

4.6.2 The patient self-monitoring diary

The diary was made up of different sections which were to be completed by the patients. The analysis of these different sections of the diaries is combined for the diaries used in the Diary and Tool-Diary group as shown in the table below.

Table 4.11 Analysis of the completion of the different sections of the patient self-monitoring diary

(n=32)	Human Figure	Weekly Journals	Adherence Self - Rating	Physical Changes
Filled	5	28	29	5
Not Filled	27	4	3	27

From the table above it is observed that only 15.6% (n=32) of the patients made use of the human figure provided in the diaries to pin-point adverse effects or symptoms that they were experiencing. 87.5% (n=32) of the weekly journals were filled and 90.6% (n=32) adherence self-ratings completed. The final section of the diary required the patients to state whether they have had any physical changes in their bodies since initiation of HAART and this was only completed by 15.6% (n=32) of the patients. It can therefore be concluded that the diary instructions were followed by majority of patients for two sections only (weekly journals and adherence rating) and not followed for the human figure and the physical changes part of the diary.

A diary evaluation form was provided to the HCPs by the researcher in order to further evaluate the perceived usability and usefulness of the diary. This form was to be used at the end of the study, when the patients returned their diaries. The HCPs were to familiarize themselves with the evaluation forms and then ask the patients the questions in the different sections. The diary evaluation form had the following patient sections:

- User-friendliness of the different sections of the diary
- Clarity of instructions
- Overall perception of the diary
- Effect on their lives

A final evaluation question directed to the HCP was included to establish the HCP's perception of whether the diaries were useful in identification of adverse effects in their patients. For the Tool-Diary group, the HCPs were also asked to state whether they perceived the diary to be useful in identifying adverse effects not identified or recorded in the tool or the patient file.

The evaluation forms were not fully completed. The following figures illustrate the evaluation of the diary (n=33).

- User-friendliness of the different sections of the diary - 30 responses

The patients were asked to rate the diary as very user-friendly, fairly user-friendly or not user-friendly. 9.1 % (n=33) of the patients did not respond to this question. The figure below illustrates how user-friendly the patients found the diary (n=30).

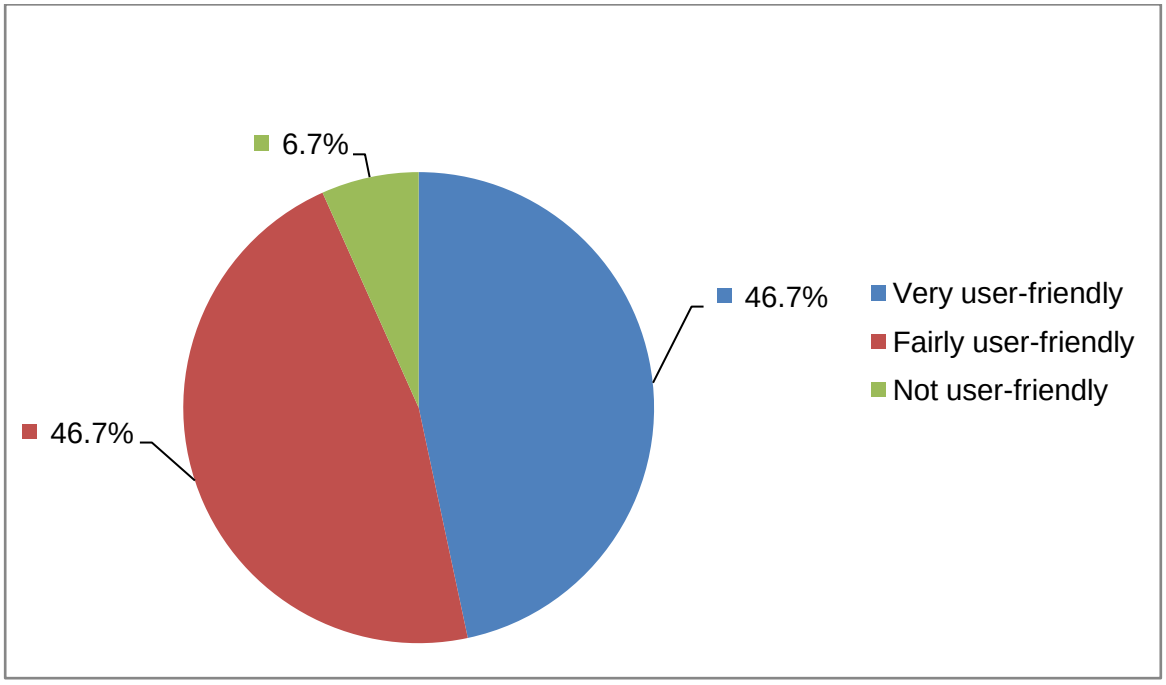


Figure 4.5 Perceived user-friendliness of the diary (n=30)

- Clarity of instructions - 31 responses

The patients were to rate the diary instructions as very clear, clear or not clear. The figure below shows how the patients rated the clarity of the instructions. 6.1% (n=31) of the evaluation forms did not have a response to this question.

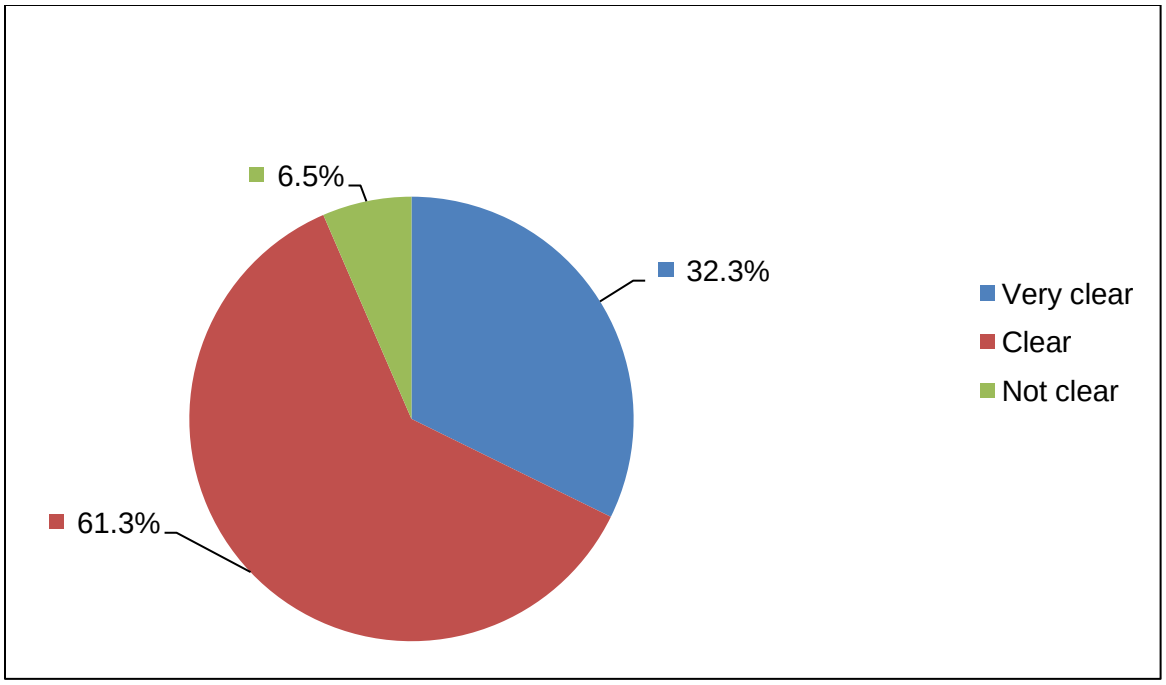


Figure 4.6 Perceived clarity of instructions (n=31)

Although more than half the patients (n=33) indicated that the diary instructions were clear, they did not always follow them. For instance, several patients did not fill in their weekly diaries, rate their adherence or tick any symptoms on the human diagram on the first page of the diary. Others still did not use the provided scale of one to ten to rate their adherence but rather used words such as “very well” or “very good” or just “good”, among others. When they missed any of their doses, some patients wrote the reasons as to why they missed.

- Overall perception of the diary - 27 responses

The perceived usability and usefulness of the diary was rated as shown in the figure below. In 18.2% of the evaluation forms, this question had no response.

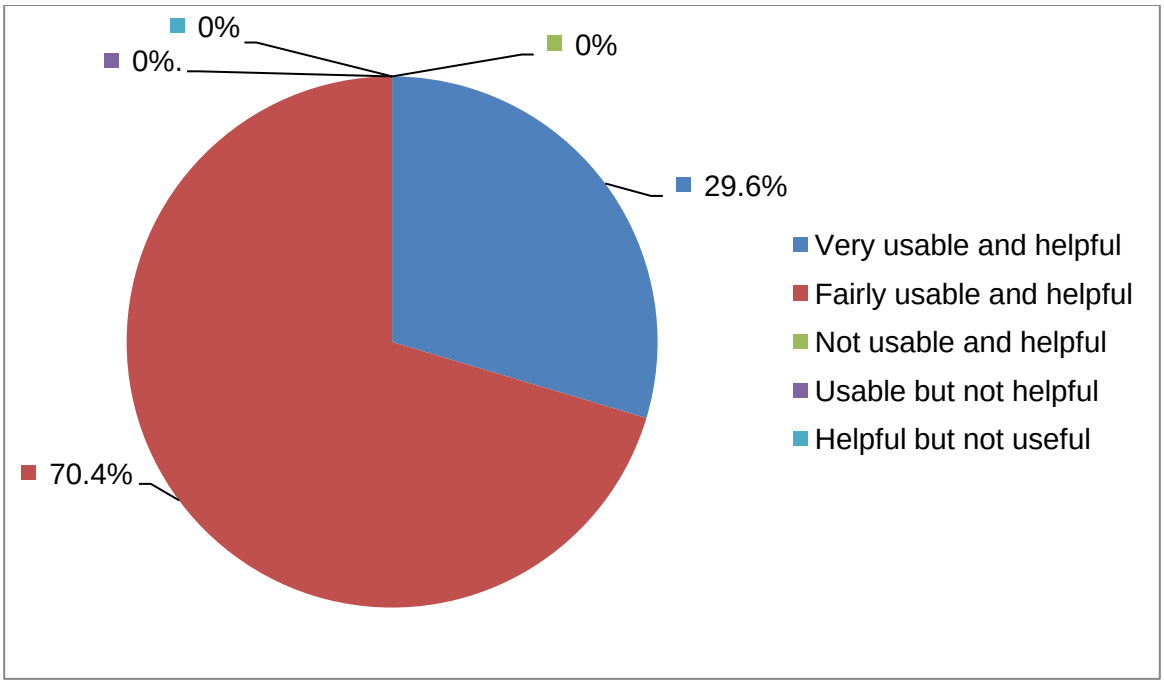


Figure 4.7 Perceived usability and usefulness of the diary (n=27)

70.4% (n=27) of the patients thought the diary was fairly usable and helpful while 29.6% (n=27) rated the diary as very usable and helpful. The term “helpful” was used to refer to perceived usefulness or effectiveness.

- Effect on their lives
    - Adherence - 28 responses (n=33)
    - Daily activities -27 responses (n=33)

The patients who used the diary were asked to indicate whether the diaries had an effect on their adherence and their daily activities as illustrated in the figures below.

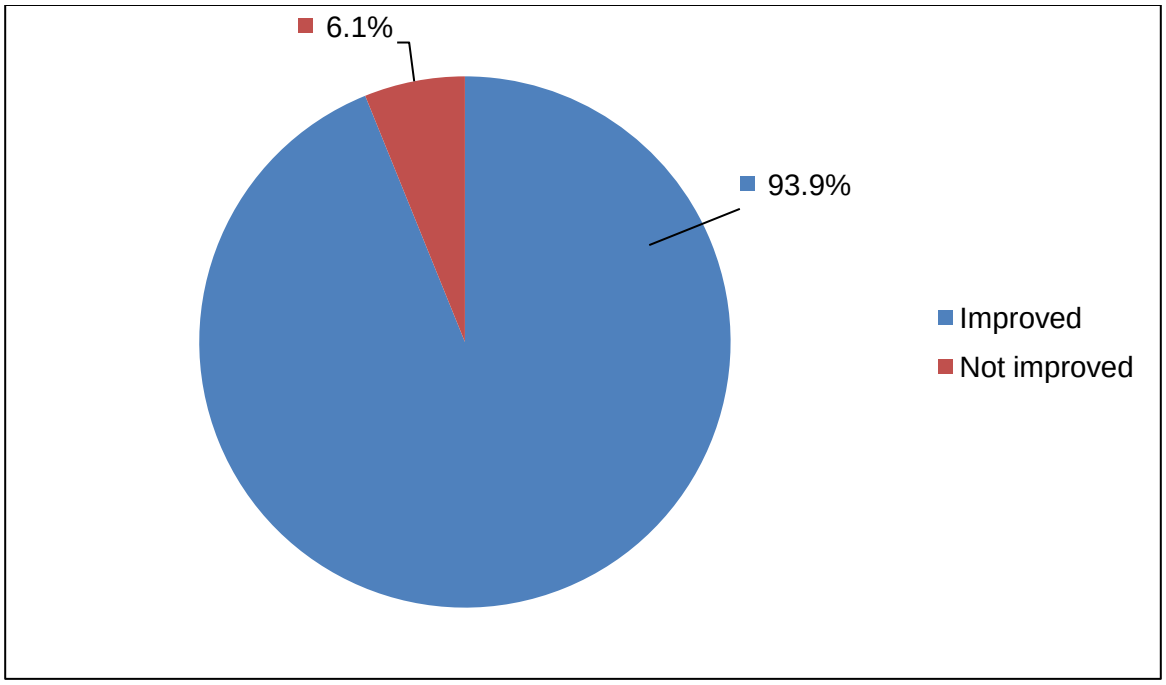


Figure 4.8 Perceived effect on adherence (n=33)

15.2% (n=28) of the evaluation forms did not have a response to this question. However, it is observed that the majority of the patients indicated that the diary aided in improving their adherence.

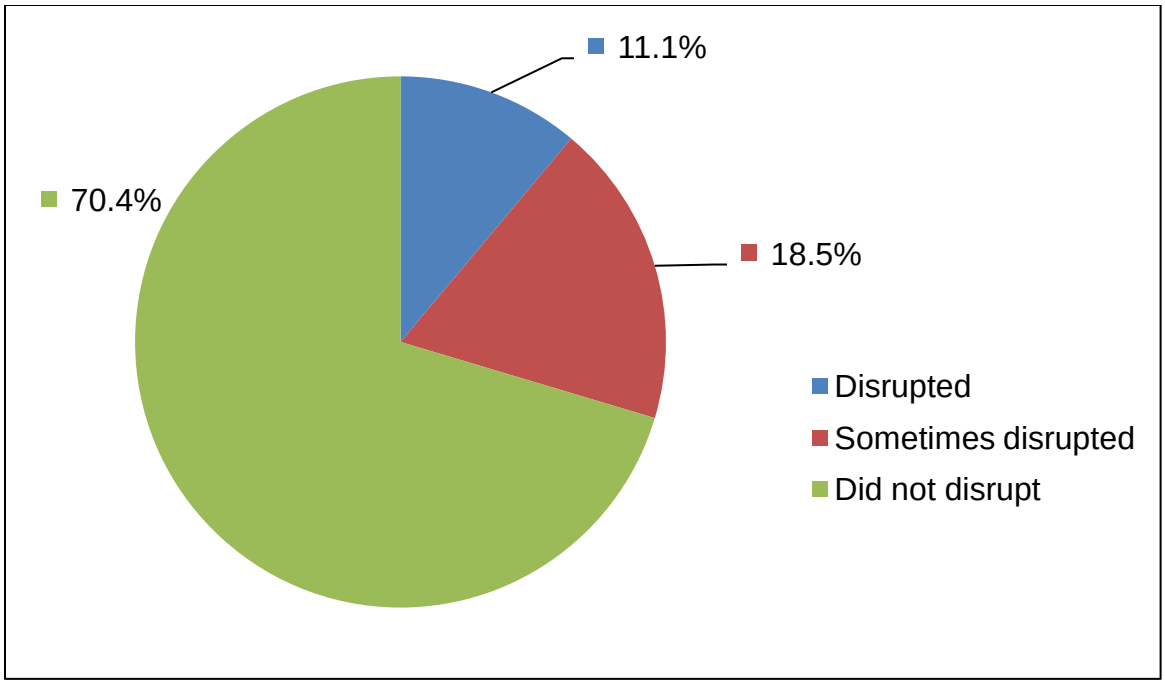


Figure 4.9 Perceived effect of the diaries on the patients daily lives (n=33)

No response was given to the question of effect on daily activities by 18.2% (n=27) of the patients. About 30% of patients felt that the diaries disrupted their daily lives either always or sometimes. They felt that the diary required a lot of work and was cumbersome and time consuming. Others felt it disrupted their daily lives because they did not understand the instructions properly, as reflected by the manner in which they completed or did not complete their diaries. However, 70.4% (n=27) of the patients reported that the diaries did not disrupt their lives.

- Adverse effect identification - 23 responses

This section was for the HCPs to indicate whether the diaries were useful in identifying adverse effects. They were further asked to indicate, in the case of the Tool-Diary group, whether the diaries were useful in identifying adverse effects not identified using the tool. The results of this evaluation are shown in the Figure 4.10 below.

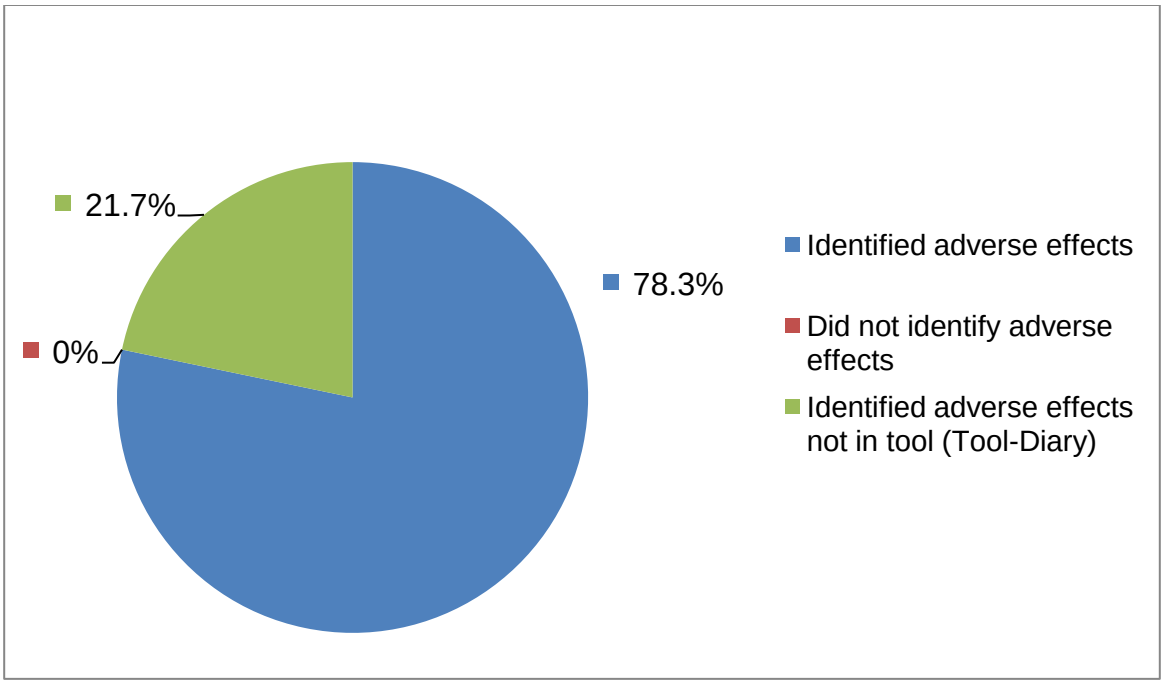


Figure 4.10 HCP perceived effectiveness of diaries in adverse effect identification (n=23)

There was no response to this question for 30.3% (n=23) of the patients who returned their diaries. From the remaining patients, the HCPs indicated that the diaries were useful in adverse effect identification in 78.3% (n=23) of the patients. In the evaluation of the Tool-Diary group, the HCPs indicated that the diaries were useful in identifying adverse effects not indicated in the tool in 21.7% of the patients.

In conclusion, the diary was reported to have been user-friendly, usable and helpful, the instructions pertaining to it were clear, and generally it improved adherence without disrupting patients' daily activities. The diaries were also reported by the HCPs to be effective in aiding adverse effect identification. There were however a small number of patients who reported that the diary was cumbersome to use and time consuming.

Only 31 of the 76 diaries distributed for the study were returned. Some reasons cited for this low return rate included patients forgetting to bring their diaries to the clinic and patients being transferred to different healthcare facilities.

4.7 Treatment Change

Of the 149 patients, 56.0% had their treatment changed for various reasons, indicated in Table 4.12below.

Table 4.12 Reasons for treatment change

Reason for change	Control Group (n=35)	Tool Group (n=38)	Diary Group (n=38)	Tool-Diary Group (n=38)
Adverse effects	15	11	15	13
Prevention of mother to child transmission (PMTCT)	2	2	4	5
Resistance (treatment failure)	3	4	5	10
Treatment changed but reason not stated in file	7	7	4	6

From the above table, it is evident that adverse effects were the main reason for treatment change, with 36.2% (n=149) of patients presenting with adverse effects necessitating treatment change. 14.8% (n=149) of patients had their treatment changed due to resistance, either as a result of treatment failure or defaulting. This observation was expected as adverse effects and treatment failure account for majority of treatment change as discussed in Section 2.7.1. The figure below illustrates the above findings.

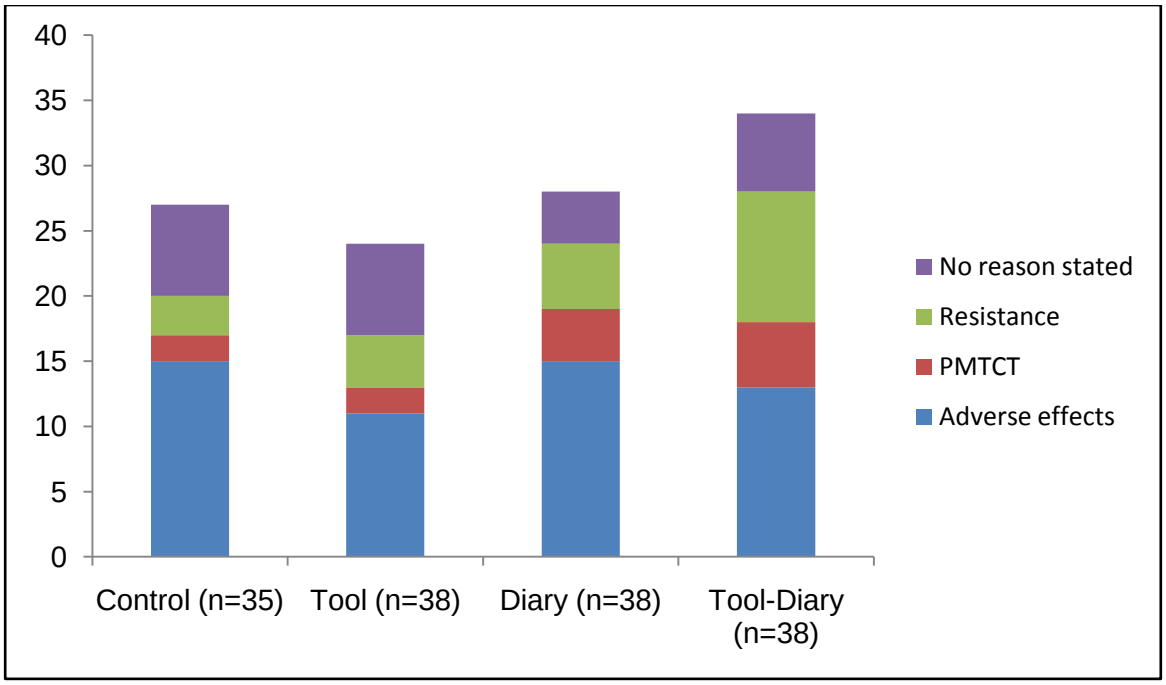


Figure 4.11 Reasons for treatment change across study groups

ARV toxicities that resulted in treatment change were severe peripheral neuropathy, lipodystrophy including Crixivan potbelly, gynaecomastia, lipoatrophy of arms and legs, severe CNS adverse effects including drowsiness, dizziness and hallucinations and severe GIT effects including diarrhoea, nausea and vomiting. 12.3% of the female patients (n=106) had their treatment changed as a result of PMTCT. A number of female patients whose CD4 cell count was above that required for HAART initiation discontinued ART after delivery out of choice, but were sometimes resistant to the same treatment when they commenced HAART, necessitated by low CD4 cell counts. 14.8% of the patients (n=149) were noted to have developed resistance to treatment characterized by treatment failure for reasons such as defaulting, for various reasons.

CHAPTER 5

CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

5.1 Conclusion

Monitoring patients receiving HAART for adverse effects, with the aim of identifying potentially life threatening adverse effects, such as lactic acidosis, is of high importance. Once an adverse effect is suspected further tests may be conducted to verify any abnormalities in the normal body function. Physical adverse effects may also be problematic, particularly those that have the potential to be of cosmetic concern to patients and those that reduce patient's quality of life by causing pain or disruption.

Early identification of such adverse effects means that timely interventions are able to be made which may avoid loss of quality of life for patients and in some cases even prevent fatal outcomes. This also may mean that patients are less likely to default or discontinue treatment, for fear of adverse effects.

The study was conducted with 149 participants, all receiving HAART and was aimed at evaluating three strategies employed for early adverse effect identification. The effectiveness of the three strategies, a patient self-recording diary, a HCP initiated adverse effect monitoring tool or a combination of both, were compared with the method usually used by HCPs at the study site.

The table below shows the category of adverse effects each method was most effective in identifying when compared to the Centre's method of monitoring for adverse effects at 90% confidence level.

Table 5.1 Overall effectiveness of the monitoring strategies

Adverse Effects	Tool	Diary	Tool-Diary
Biological	**-**	**-**	**-**
CNS	**-**	**-**	**0.388**
GIT	**-**	**-**	**-**
Physical	**0.141**	**-**	**0.201**

The above table indicates that the tool was statistically significant when used alone in the identification and recording of physical adverse effects, while the diary was not statistically significant at identification and recording of adverse effects at a 90% confidence level. Overall, combining the tool and diary methods of adverse effect monitoring appears to have been the most effective method of identifying and recording of CNS and physical adverse effects at 90% confidence level. This is to be expected because the HCPs use the tool at each clinic visit to record any symptoms or adverse effects experienced by the patients, whilst the patients take the diaries home and record any symptoms or adverse effects they experience in their daily lives. The Tool-Diary method of monitoring may also be more effective than simply recording experienced symptoms because the tool groups together symptoms of a particular adverse effect, thereby making it easier to speculate which adverse effect may be occurring before and makes deciding which tests to conduct easier. The diary is mainly useful in identifying subjective signs and symptoms experienced by the patients. Combining the two appears to yield the most favourable results. The tool when used alone may not be useful in detecting subjective symptoms while the diary on its own may not be useful in identifying any chemical blood or urine abnormalities. Another unintended but significant

effect of the diaries was the perceived improvement of adherence in 93.9% (n=33) of the patients. This may in turn aid in reducing adverse effects which tend to be common in non-adherent patients.

Patients in the study who presented with adverse effects or symptoms of adverse effects that were then confirmed using the appropriate tests either had pharmacological or non-pharmacological interventions implemented or their treatment changed to more appropriate ARV regimens with a lower propensity for these effects. This was noted in all four study groups.

Since the monitoring tool method was compared to the Centre's method of monitoring for adverse effects for only 19 patients (50%; n=38) in the Tool group, the results obtained may not be generalisable. The same applies for the diary group, where only 14 patients (36.8%, n=38) were analyzed and the Tool-Diary group where only 17 patients (44.7%; n=38) were included. In total, this only amounted to 50 patients (43.9%, n=114-Tool, Diary and Tool-Diary groups). The results of this study therefore need to be further investigated in larger sample groups in order to verify the true effectiveness of the monitoring strategies used.

The results analyzed indicate that none of the comparisons between the monitoring strategies and the Centre's monitoring method met the 95% confidence interval which is the most commonly used and accurate estimate in statistics. This inadequacy may be attributed to the poor return rate and or completion of the monitoring diaries and tools respectively. Out of 80 monitoring tools handed out, only 32 (15 Tool Group and 17 Tool-Diary Group) were completed. The reason given for this by the HCPs was that they were often very busy and therefore just wrote in the patient files which are the Centre's

records whilst forgetting to complete the monitoring tool. Of the 80 dairies handed out, only 33 were returned for analysis. The majority of the patients forgot to return their diaries to the clinic at each clinic visit whilst some of the patients were transferred to other wellness centres, during the study period.

Therefore, the above results may not be a true representation of the overall effectiveness of the monitoring strategies in identification and recording of ARV adverse effects. However, despite these challenges, the monitoring strategies appear to have been helpful in adverse effect identification and recording.

5.2 Limitations

The limitations of this study are discussed below:

- Firstly, the study period may have been too short to collect substantial data. The study period was further shortened by the time taken to assign patients to the different study groups.
- Some patients, who had been on ARVs for a longer period, were given 2 or 3 months supply of ARVs at a time. This was a problem as the study period was only 3 months and therefore a proper follow up was not always possible for these patients.
- It may have been difficult and rather cumbersome for the health care team participating in the study to record adverse effects in both the patient files and the monitoring tools. This therefore resulted in inconsistencies between the adverse effects recorded in the files and the tools. It is envisaged that in practice the monitoring tool would be incorporated into the patient file, removing the need for duplication.

- Because the adverse effects of ARVs are sometimes non-specific, for example headaches and GIT symptoms such as nausea, it is difficult to distinguish between co-morbidities and symptoms indicating adverse effects.
- Another limitation of this study involves handing out diaries for patients to take home. This may cause problems when they do not return them for various reasons, accounting for the poor number of returned diaries.
- The study was reported to be time consuming and hence may have been negatively perceived by the HCPs and seemed to have required too much effort, which was a hindrance due to their already busy schedules. This may be the reason why the tools were not fully utilized in the study. Again the incorporation of the tool into a patient record would assist in overcoming this problem.
- The diaries were designed to be completed daily but only a minority of patients did that. This may be because they forgot, they were too tired to attend to it or it disrupted their daily activities.

5.3 Recommendations for future research

Early identification of ARV adverse effects may mean that potentially fatal adverse effects are managed on time and that bothersome adverse effects such as nausea, vomiting and diarrhoea are dealt with appropriately in order to ensure patients remain adherent to their treatment. Due to the non-specific nature of certain adverse effects, it may be necessary to incorporate a separate monitoring strategy, as was done in this study, in order to record adverse effects and distinguish them from co-morbidities.

The results obtained in this study are indicate that these strategies have potential in symptom and adverse effect identification and recording. However, additional research

is required in order to verify the generalisability of the results and clarify the usability and effectiveness of these methods in pharmacovigilance of ARVs.

The following are some recommendations for further studies;

- Increasing the study period
- In order to distinguish between early, mid-term versus late adverse effects, it is recommended that the duration of HAART treatment of the patients be incorporated into the data collection form, used by the researcher
- Providing reminders to patients due for a clinic visit to bring back their diaries to the clinic via sms
- Incorporating the monitoring tool into the patient record, in order to reduce the amount of writing for busy HCPs
- Special attention ought to be given to those symptoms which are non-specific such as headaches in order to ensure they are not neglected without establishing their exact seriousness and implications for the patients.
- The reasons for the poor return rate of the diaries and the poor filling of the monitoring tools may need to be further investigated in order to establish the exact cause of this poor response. This may be done through interviews with the HCPs involved as well as the available patients who did not return their diaries.

Much research still needs to be conducted in order to establish the most effective method of monitoring patients for ARV adverse effects, including subjective and objective symptoms of adverse effects experienced. Other convenient means of adverse effect reporting by the patients need to be explored in order to ensure early identification of adverse effects which would in turn ensure that necessary interventions

are undertaken made in order to ensure that patients remain adherent to their treatment, improve their quality of life, prevent fatal adverse events and preserve their confidentiality.

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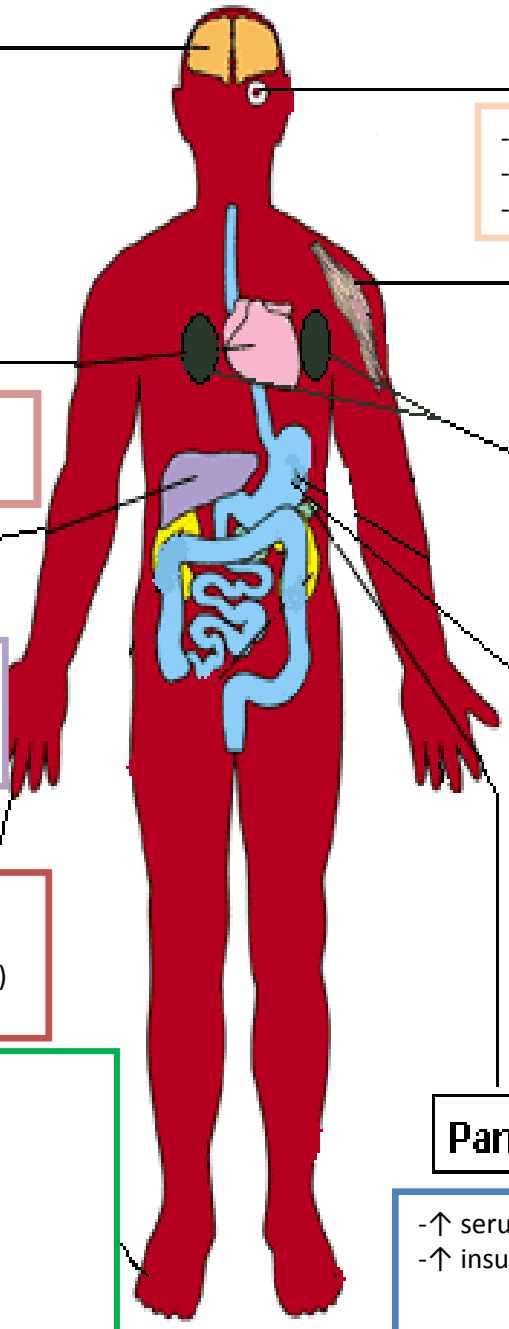
APPENDICES

Appendix 1a

ADVERSE EFFECT INDICATOR CHART



Nervous System
-Headaches (6e)
-Sleep disorders (10c)
-Hallucinations (10d)

Eyes
-Yellow (3a)
-Blisters (6b)
-Sunken eyes (9.1a)

Skeletal Muscle
-Muscle spasms (10a)

Heart
-Abnormal heart beat (2h)
-Tachycardia (5e, 10e)

Lungs
-Dyspnoea (2a, 7c)
-Tachypnoea (2b)
-Respiratory distress (5b)

Liver
-Enlarged/tender (2g)
-Hepatomegaly (3b)
-↑ serum ALT concentration (3d)

Digestive Tract
-Abdominal pain (2c, 5a)
-Nausea (3c, 4a, 5c)
-Vomiting (3c, 4b, 5d)
-Diarrhoea (3c, 4c)
-Constipation (4e)

Hands & Feet
-Tingling or numbness (1a)
-Pain (1b)
-Difficulty standing or walking (1c, 10b)
-Cold blue hands (2f)

Pancreas
-↑ serum amylase and lipase (5f)
-↑ insulin levels (8d)

Others
-Weight loss (2d, 8c)
-Fatigue (2e, 7a)
-Loss of appetite (4d)
-Heart burn (4f)
-Skin rash (6a)
-Blisters in the mouth or genitals (6b)
-Peeling skin (6c)
-Fever (6d)
-Chest pain (7b)
-Anaemia (7d)
-Neutropenia (7e)
-↑ urination with glucose in the urine (8a)
-↑ thirst and hunger (8b)
-Change in calcium and phosphate levels (10f)
-↓ haemoglobin (10g)
-↓ MCV (mean corpuscular volume) (10h)

Lipodystrophy
-Sunken face and cheeks (9.1a)
-Veins on arms and legs more visible (9.1b)
-Fat wasting in buttocks (9.1c)
-Buffalo hump (9.2a)
-Crixivan potbelly (9.2b)
-Breast enlargement (9.2c)

Appendix 1b

ANTIRETROVIRAL RECORDING AND MONITORING CHART

Patient study no:	

Please note the following:

1. If one of the following adverse effects is experienced (Refer to Figure 1 for code for adverse effect) , indicate the **severity** using the severity scale below:
   1=Mild; 2=Moderate; 3=Severe; 4=Excessive/Disabling

2. Indicate in the **intervention** column any interventions made in relation to the adverse effect experienced and in the **result/comment** column the result of the intervention. The management of specific adverse effects is listed in **Table 1**; indicate the number of any intervention in the intervention column below (e.g. 9a – for discontinuing offending drugs in peripheral neuropathy). Indicate in full in the block provided **any other** intervention initiated (including any ARV substitutions made: Refer to **Table 2**).
3. The three blocks provided for each symptom are for the three months study period.
4. Table 2 indicates recommended ARV substitutions for specific adverse effects.

Patient's Current Regimen: …….

Symptoms	Date	Severity	Intervention	Result/Comment	HCP Initials and Signature
1. Peripheral neuropathy: (d4T, ddC, ddI)					
a. Tingling or numb sensation in hands and/or feet					

b. Pain in hands and/or feet					
c. Difficulty walking or standing					
2. Lactic acidosis: (NRTIs esp d4T, ddI, AZT)					
a. Dyspnoea (shortness of breath)					
b. Tachypnoea (hyperventilation)					
c. Abdominal pain					
d. Weigh loss					

e. Fatigue (tired)					
f. Cold blue hands					
g. Enlarged/tender liver					
h. Abnormal heartbeat					
3. Hepatotoxicity: (All NNRTIs, all PIs, most NRTIs)					
a. Jaundice (skin yellow tinge as well as white of eyes)					
b. Hepatomegaly					

c. Nausea/vomiting/diarrhoea					
d. Increased serum ALT concentration					
4. GIT distress: (All PIs, AZT, ddI)					
a. Nausea					
b. Vomiting					
c. Diarrhoea					
d. Loss of appetite					

e. Constipation					
f. Heartburn					
5. Pancreatitis: (ddI alone, ddI + d4T, hydroxyurea, TDF)					
a. Poststprandial abdominal pain					
b. Respiratory distress					
c. Nausea					
d. Vomiting					

e. Tachycardia					
f. Increased serum amylase and lipase					
6. Hypersensitivity Reaction: (ABC, All NNRTIs and Amprenavir)					
a. Flat or raised spots with blisters in centre (skin rash)					
b. Blisters in the mouth, eyes and /or genitals					
c. Peeling of the skin resulting in sore					
d. Fever					

e. Headaches					
7. Bone marrow suppression: (AZT)					
a. Fatigue					
b. Chest pain					
c. Dyspnoea					
d. Decrease in RBCs/MCV (anaemia)					
e. Decrease in white blood cells (neutropenia)					

8. Hyperglycaemia: (All PIs)					
a. Increased urination with glucose in urine					
b. Increased thirst and hunger					
c. Weight loss					
d. Increased insulin levels					
9.Lipodystrophy/Fat redistribution					
9.1 Fat wasting: (NRTIs (d4T > AZT > TDF, ABC, 3TC, FTC), esp when combined with EFV)					
a. In face (sunken cheeks, temples and eyes)					
b. Arms and legs (veins are more					

visible-condition called “roping”					
c. Buttocks					
9.2 Fat accumulation: (PI- or NNRTI-based regimens & with thymidine analogs (e.g. d4T, AZT))					
a. Dorsocervical region (forming buffalo hump)					
b. Abdomen (eg “Crixivan potbelly”)					
c. Breast development/ enlagement in both men and women					
10. Other					
a. Muscle spasms					

b. Impaired mobility					
c. Sleep disorders					
d. Hallucinations					
e. Tachycardia					
f. Change in serum calcium and phosphate ion levels					
g. Decreased haemoglobin					
h. Decreased MCV					

Table 1: MANAGEMENT OF SPECIFIC ARV ADVERSE EFFECTS

	ADVERSE EFFECT	ASSOCIATED ARVs	MANAGEMENT
1.	Anaemia and Neutropenia	AZT	a. AZT dose can be reduced to 200 mg 12 hourly b. If no improvement, AZT may be replaced with d4T (refer)
2.	Diarrhoea	All PIs, AZT, ddI	a. Bulk-forming agents, such as psyllium products b. Antimotility agents, such as loperamide or diphenoxylate/ atropine c. Rehydration and electrolyte replacement
3.	Hepatotoxicity	All NNRTIs, all PIs, most NRTIs	a. Rule out other causes of hepatotoxicity (e.g alcoholism, viral hepatitis, chronic HBV, 3TC, FTC, or TDF withdrawal, HBV resistance) b. For asymptomatic patients, if ALT>5-10xULN, consider discontinuing ARVS (or monitor closely unless bilirubin is also elevated) c. For symptomatic patients STOP all ARVs and other potential hepatotoxic agents d. After symptoms subside and serum transaminases normalize, start new ARV regimen without the offending agent
4.	Hyperlipidaemia	All PIs, EFV, NVP	a. Lifestyle modification: diet, exercise, reducing cholesterol and saturated fat intake, and/or smoking cessation b. If triglyceride >5.6 mmol/L after dietary changes or LDL >4.9 mmol/L or LDL >3.4 mmol/L with 2 or more other ischaemic heart disease risk factors, commence fibrates (or atorvastatin 5-10mg or pravastatin).
5.	Lactic acidosis	NRTIs esp d4T, ddI, AZT	a. Lactate 2-5 mmol/L**:** monitor monthly b. Lactate 5-10 mmol/L with symptoms:STOP all ART and seek urgent expert help

6.	Lipodystrophy	<u>Lipoatrophy</u> NRTIs (d4T > AZT > TDF, ABC, 3TC, FTC), esp when combined with EFV <u>Lipohypertrophy</u> PI- or NNRTI-based regimens & with thymidine analogs (e.g. d4T, AZT)	a. Encourage exercise to reduce fat accumulation b. Switch protease inhibitor to an NNRTI c. Fibrates for lowering cholesterol and triglyceride levels d. Insulin resistance can be improved with anti-diabetic agents
7.	Nausea & Vomiting	All PIs, AZT, ddI	a. Antiemetic half an hour before the ARV dose up to 3 times daily b. Switch to less emetogenic ARV if very problematic
8.	Pancreatitis	ddI alone, ddI + d4T, hydroxyurea, TDF	a. Reduce ddI dose when used with TDF b. Discontinue offending agent(s) c. Symptomatic management; pain control, bowel rest, IV hydration, then gradual resumption of oral intake
9.	Peripheral Neuropathy	d4T, ddC, ddI	a. Discontinue offending agent before the pain becomes disabling b. Pharmacological management; treatment of the neuralgic pain with pyridoxine, opiates (e.g. tramadol), NSAIDs, amitriptyline, neurontin, topical capsaicin and topical lidocaine. c. Gabapentin, lamotrigine, oxycarbamazepine and topiramate may also be used

(Adapted from Department of Health, 2004)

Table 2: RECOMMENDED ARV SUBSTITUTIONS FOR SPECIFIC ADVERSE EFFECTS

Regimen	Toxicity	Drug substitution
d4T/3TC/EFZ (1a)	• d4T-related neuropathy or pancreatitis	• Switch d4T to AZT
	• EFV-related persistent CNS toxicity	• Switch EFV to NVP
d4T/3TC/NVP (1b)	• d4T-related neuropathy or pancreatitis	• Switch d4T to AZT
	• NVP-related severe hepatotoxicity	• Switch NVP to EFV (except early pregnancy)
	• NVP-related severe rash (but not life threatening)	• Switch NVP to EFV
	• NVP-related life-threatening rash	• Switch NVP to EFV or lopinavir/ ritonavir
	• Stevens-Johnson syndrome	• Switch to lopinavir/ritonavir
AZT/ ddI / lopinavir / ritonavir (2)	• AZT related anaemia or neutropenia	Switch AZT to d4T (monitor closely for peripheral neuropathy and lactic acidosis)
	• ddI related GIT side effects	• Switch ddI for enteric coated ddI

(Source: Department of Health, 2004)

Appendix 1c

PREVIOUS ANTIRETROVIRAL ADVERSE EFFECTS MONITORING TOOL (2008)

DATE: …… **Patient Study no: ……**

PATIENT DEMOGRAPHICS

Gender:	
Weight:	
Height:	
BMI:	
Smoke Yes/No: **How many per day?**	
Alcohol Yes/No: **How much in a day?**	
Substance Use (eg marijuana; mandrax etc) **Yes/No**	
If so which substances:	

MEDICAL HISTORY:

List all medication presently being taken:

List any previous medication taken (in the past month):

List all medical conditions past and present:

ARV Medical History:

Date diagnosed:	
Place at which diagnosed:	

	Doctor	**Nurse**	**Other**
By whom diagnosed			
HCP who initiated initial regimen			

Current Antiretroviral Regimen:

Medication name	**Dose**	**Times to be taken**

Changes in Antiretroviral treatment:

Previous drug	Dose of previous drug	New drug	Dose of new drug	Date changed	Reason for change

Comments by HCP:

Antiretroviral Monitoring Chart

If one of the following adverse effects is experienced, indicate the **severity** using the guide below:

1=mild; 2=moderate; 3=severe; 4=excessive/disabling

Also indicate in the **intervention** column any interventions made in relation to the adverse effect experienced.

Date observed: ……..

Current regimen: ……

Patient Study no: ……

Symptoms	**Severity**	**Intervention**	**Date**
1. Peripheral neuropathy			
• Tingling or numb sensation in hands and/or feet			
• Pain in hands and/or feet			
2. Lactic acidosis			
• Dyspnoea (shortness of breath)			
• Tachypnoea (rapid breathing)			
• Weigh loss			
• Fatigue (tired)			
• Cold blue hands			
• Enlarged/tender liver			
• Abnormal heartbeat			
3. Hepatotoxicity			
• Jaundice (skin yellow tinge as well as white of eyes)			
• Hepatomegaly			
• Nausea/vomiting/diarrhoea			
• Increased serum ALT concentration			

4. GIT distress			
• Nausea			
• Vomiting			
• Diarrhoea			
• Loss of appetite			
• Constipation			
• Heartburn			
5. Pancreatitis			
• Moderate to severe abdominal pain			
• Shock			
• Respiratory distress			
• Nausea • Vomiting			
• Tachycardia			
• Increased serum amylase and lipase			
6. Skin rash			
• Flat or raised spots with blisters in centre			
• Blisters in the mouth, eyes and /or genitals			
• Peeling of the skin resulting in sore			
• Fever			
• Headaches			
7. Bone marrow suppression			
• Fatigue			
• Chest pain			

• Dyspnoea			
• Decrease in RBCs/MCV (anaemia)			
• Decrease in white blood cells (neutropenia)			
8. Hyperglycaemia			
• Increased urination with glucose in urine			
• Increased thirst and hunger			
• Weight loss			
• Increased insulin levels			
9.Lipodystrophy/Fat redistribution			
9.1 Fat wasting			
• In face (sunken cheeks, temples and eyes)			
• Arms and legs (veins are more visible-condition called “roping”			
• Buttocks			
9.2 Fat accumulation			
• Dorsocervical region (forming buffalo hump)			
• Abdomen (eg “Crixivan potbelly”)			
• Breast development/enlagement in both men and women			
10. Other			
• Muscle spasms			
• Impaired mobility			
• Sleep disorders			
• Hallucinations			
• Tachycardia			
• Change in serum calcium and phosphate ion levels			
• Decreased haemoglobin			

• Decreased MCV			

Name of HCP who made the intervention:……

Signature of HCP……

Indicate whether or not the patient was counselled on the adverse effect prior to experiencing it (Y/N):

……

Appendix 2

RESEARCHER'S DATA COLLECTION FORM

Patient Study no: ……

PATIENT DEMOGRAPHICS

Gender:	
Age	
Weight:	
Height:	
BMI:	
Smoke Yes/No: **How many per day?**	
Alcohol Yes/No: **How much in a day?**	
Substance Use (eg marijuana; mandrax etc) **Yes/No**	
If so which substances:	

MEDICAL HISTORY:

List all medication presently being taken:

AUGUST	SEPTEMBER	OCTOBER

Any previous medication taken (in the past month):

All medical conditions past and present:

Past	Present		
	August	September	October

Current Antiretroviral Regimen:

Medication name	Dose	Times to be taken

Changes in Antiretroviral treatment:

Previous drug	Dose of previous drug	New drug	Dose of new drug	Date changed	Reason for change

HCPs General comments (including patient adherence):

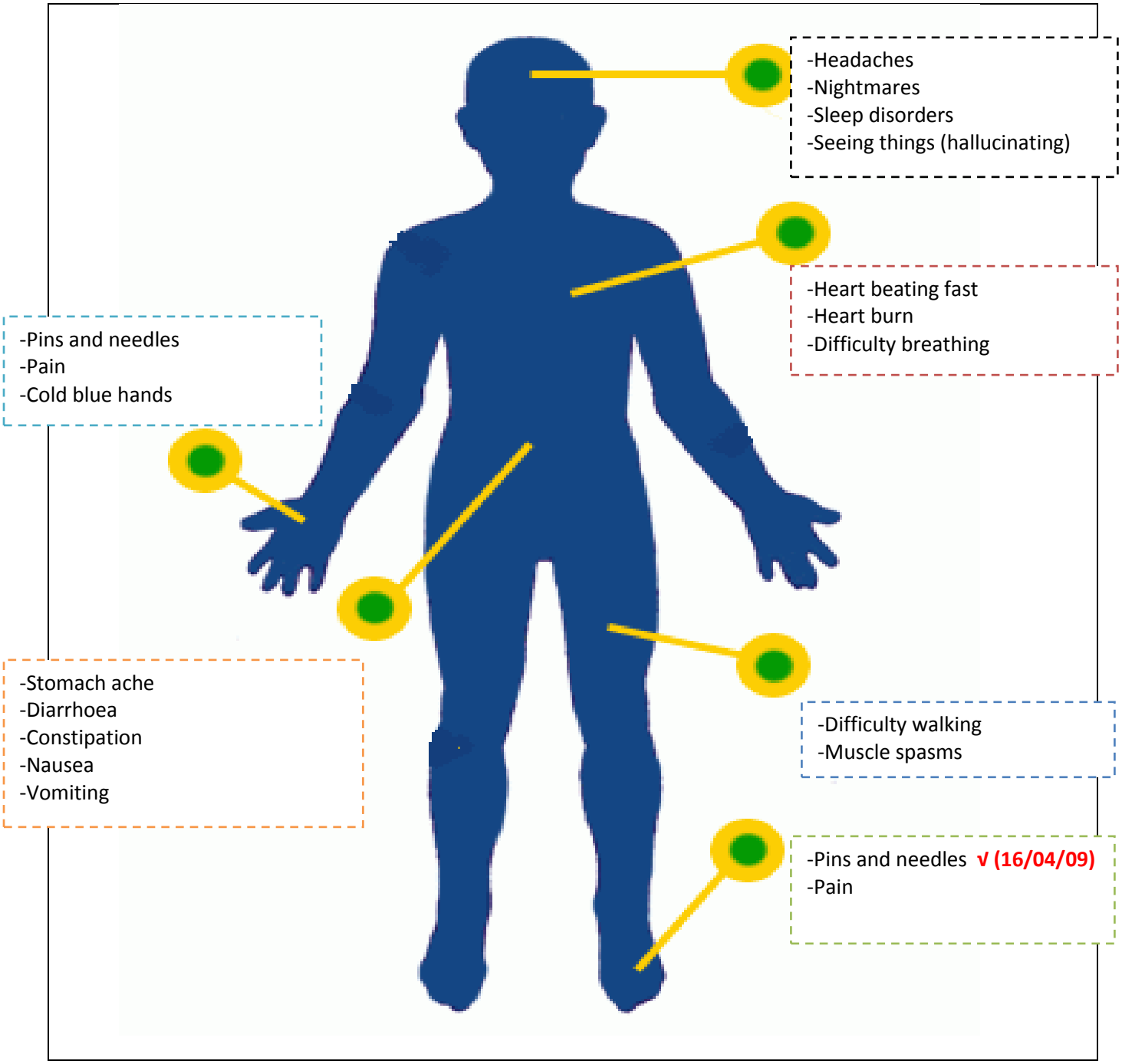
AUGUST	SEPTEMBER	OCTOBER

Appendix 3a

PATIENT SELF-MONITORING DIARY (Pilot Diary)

Please note the following:

1. If you experience the symptoms indicated in the figure below, indicate with a tick (√) and write the date next as shown in the example.
2. Indicate any other symptoms you feel that are not in the figure.
3. Complete the weekly tables below following the example shown in week 1 table.
4. **Take your diary to the clinic at each visit.**



Use the following severity scale to indicate how painful or uncomfortable the symptom you experience is.

Severity scale (1 to 4):
1 - Able to carry out daily activities normally 2 – Symptoms mildly affect my day 3 – Severe symptoms but gained relief after you did something about it 4 – Severe symptoms and no relief after you did something about it

Use the following adherence scale to rate how you took your ARVs each week.

Adherence scale (0 to 10)
0 – Did not take my tablets this week 5 - I took half my doses this week 10 – I took all my tablets this week

Week 1

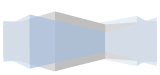
					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**
1/05/09	Headache	2	Took 2 Panado tablets	Headache reduced			

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

List any changes that you have experienced physically since you started taking ARVs.

-
-
-
-
-
-
-
-
-
-
-
-

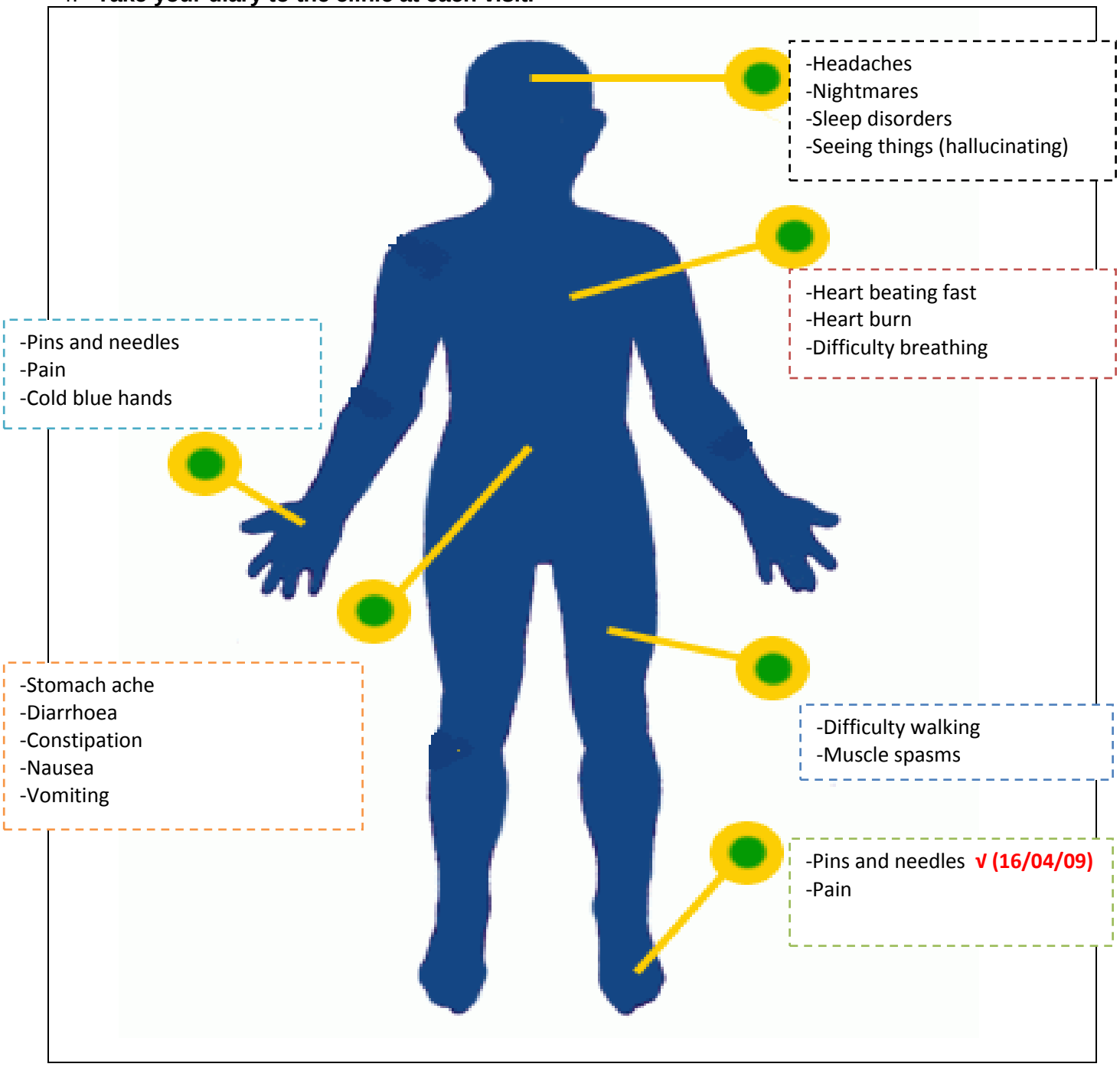


Appendix 3b

PATIENT SELF-MONITORING DIARY (Modified Diary)

Please note the following:

1. If you experience the symptoms indicated in the figure below, indicate with a tick (√) and write the date next as shown in the example.
2. Indicate any other symptoms you feel that are not in the figure.
3. Complete the weekly tables below following the example shown in week 1 table.
4. **Take your diary to the clinic at each visit.**



Use the following severity scale to indicate how painful or uncomfortable the symptom you experience is.

Severity scale (1 to 4):
1 - Able to carry out daily activities normally 2 – Symptoms mildly affect my day 3 – Severe symptoms but gained relief after you did something about it 4 – Severe symptoms and no relief after you did something about it

Use the following adherence scale to rate how you took your ARVs each week.

Adherence scale (0 to 10)
0 – Did not take my tablets this week 5 - I took half my doses this week 10 – I took all my tablets this week

Week 1

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**
1/05/09	Headache	2	Took 2 Panado tablets	Headache reduced			

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 2

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 3

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 4

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 5

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 6

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 7

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 8

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 9

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 10

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 11

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

Week 12

					To be filled in by Nurse		
Date	**What did you feel?**	**Severity**	**What did you do about it?****	**Result/ Comment**	**When reported**	**Intervention**	**Nurse's Signature**

How good were you at taking your medication this week?

**Including whether you stopped or skipped your ARVs

List any changes that you have experienced physically since you started taking ARVs.

-
-
-
-
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-

Appendix 4

PATIENT SELF-MONITORING DIARY EVALUATION FORM

PATIENT STUDY NUMBER ☐

Please note the following:

This form is only to be used on patients who used the diary, i.e. patients in the **Diary Group (Blue)** and **Tool-Diary Group (Yellow)**

- ***Circle the appropriate patient's perception in the following aspects of the patient diary***

- **User-friendliness of the different sections of the diary**

1= Very user-friendly (It was easy to use without too much effort)
2= Fairly user-friendly (It was fairy easy to use with some effort)
3= Not user-friendly (It was difficult/cumbersome to use)

- **Clarity of instructions**

V.C= Very clear (They easily understood the instructions and followed them correctly)
C= Clear (They understood the instructions on careful reading and followed them correctly)
N.C= Not clear (They struggled to understand the instructions and may not have followed them correctly)

- **Overall perception of the diary**
  - Very usable and helpful
  - Fairly usable and helpful
  - Not usable and helpful
  - Usable but not helpful
  - Helpful but not usable

- **Effect on their lives**

a) **Adherence**

Did the diary help improve their adherence
Y= Yes
N= No

b) **Daily activities**

Did the diary affect or disrupt their normal daily activities
Y= Yes, it was too time consuming it disrupted their daily activities
S= Sometimes
N= No, it did not disrupt their lives

- ***Circle your appropriate personal perception of the patient diary (to be filled in by the HCP)***

- **Adverse effect identification of the patient diary**

Y= It was useful in adverse effect identification
N= It was not useful in adverse effect identification
Z= It was useful in identification of adverse effects **not** identified by the tool (**this section is for patients in the Tool-Diary Group-Yellow ONLY**)

Appendix 5

WRITTEN CONSENT FORM TEMPLATE (HCP and Patients)

NELSON MANDELA METROPOLITAN UNIVERSITY

INFORMATION AND INFORMED CONSENT FORM

RESEARCHER'S DETAILS	
Title of the research project	
Reference number	
Principal investigator	
Address	
Postal Code	
Contact telephone number (private numbers not advisable)	

A. DECLARATION BY OR ON BEHALF OF PARTICIPANT		Initial
I, the participant and the undersigned	(full names)	
ID number		

A.1 HEREBY CONFIRM AS FOLLOWS:		Initial
I, the participant, was invited to participate in the above-mentioned research project		
that is being undertaken by		
From		
of the Nelson Mandela Metropolitan University.		

THE FOLLOWING ASPECTS HAVE BEEN EXPLAINED TO ME, THE PARTICIPANT:					Initial
2.1	**Aim:**				
2.2	**Procedures:**				
2.3	**Risks:**				
2.4	**Possible benefits:**				
2.5	**Confidentiality:**				
2.6	**Access to findings:**				
2.7	**Voluntary participation / refusal / discontinuation:**	My participation is voluntary	YES	NO	
		My decision whether or not to participate will in no way affect my present or future care / employment / lifestyle	TRUE	FALSE	

3. THE INFORMATION ABOVE WAS EXPLAINED TO ME/THE PARTICIPANT BY:									Initial
(name of relevant person)									
In	**Afrikaans**		**English**		**Xhosa**		**Other**		
and I am in command of this language, **or** it was satisfactorily translated to me by									
(name of translator)									
I was given the opportunity to ask questions and all these questions were answered satisfactorily.									

4.	No pressure was exerted on me to consent to participation and I understand that I may withdraw at any stage without penalisation.	

5.	Participation in this study will not result in any additional cost to myself.	

A.2 I HEREBY VOLUNTARILY CONSENT TO PARTICIPATE IN THE ABOVE-MENTIONED PROJECT:		
Signed/confirmed at	on	20
Signature or right thumb print of participant	Signature of witness: Full name of witness:	

B. STATEMENT BY OR ON BEHALF OF INVESTIGATOR(S)									
I,								**declare that:**	
1.	**I have explained the information given in this document to**							**(name of patient/participant)**	
	and / or his / her representative							**(name of representative)**	
2.	**He / she was encouraged and given ample time to ask me any questions;**								
3.	**This conversation was conducted in**	**Afrikaans**		**English**		**Xhosa**		**Other**	
	And no translator was used OR this conversation was translated into								
	(language)		**by**	**(name of translator)**					
4.	**I have detached Section D and handed it to the participant**			**YES**		**NO**			
Signed/confirmed at			on					20	
Signature of interviewer	Signature of witness: Full name of witness:								

C. IMPORTANT MESSAGE TO PATIENT/REPRESENTATIVE OF PARTICIPANT

Dear participant/representative of the participant

Thank you for your/the participant's participation in this study. Should, at any time during the study:

- **an emergency arise as a result of the research, or**
- **you require any further information with regard to the study, or**
- **the following occur**

(indicate any circumstances which should be reported to the investigator)

Kindly contact	
at telephone number	

Appendix 6a

REQUEST LETTER TO CONDUCT STUDY

• PO Box 77000 • Nelson Mandela Metropolitan University
• Port Elizabeth • 6031 • South Africa • www.nmmu.ac.za

Nelson Mandela Metropolitan University
for tomorrow

Summerstrand South Campus
Faculty of Health Sciences
Department of Pharmacy
Tel . +27 (0)41 504-2128 Fax. +27 (0)41 504-2744
pharmacy@nmmu.ac.za

28th April 2009

ATTENTION: The Chairman: Uitenhage and Despatch Independent Practitioners Association

SUBJECT: Request for permission to conduct a study at UDIPA

Dear Dr Naidoo,
I am hereby requesting permission to conduct a research project at the UDIPA Life and Wellness Centre, in collaboration with my supervisors Ms S Burton and Mrs. B Gold. The aim of the research project is to evaluate the extent to which monitoring strategies, including a tool to be used by healthcare professionals (HCPs), and a self-monitoring patient diary can contribute to the early identification and management of adverse effects associated with ARVs.

The health care professionals and the patients involved in the study will be provided with informed consent forms which they will be required to complete, should they choose to participate in the study. The researcher will meet with the HCPs, explain the project to them and obtain their written informed consent. Since I will at no time have direct contact with the patients, the HCPs will describe the project to the patients and obtain their written informed consent. I will then collect these.

The target sample population will be grouped into four categories of a minimum of 40 patients each: a Control Group (no monitoring tool will be used- normal clinic procedures will continue), a Tool Group (only the monitoring tool will be used), a Diary Group (only the patient diary will be

used) and a Tool-Diary Group (both the tool and diary will be used). The different groups will be identified by different coloured stickers. Patients will be selected by means of convenience sampling and the data will be collected by the HCPs and then given to the researcher. The patient diary is attached.

A previous study to determine the usefulness and usability of a revised monitoring tool was conducted at UDIPA. One of the findings and the recommendations of the HCP involved in that study was that the previous tool was too long and hence time consuming and cumbersome. Modifications were thus made to the tool, including separating the history taking part and the adverse effect monitoring part into two separate sections. The history taking section is to be used by the researcher and the monitoring tool by the HCP. I would like to request permission to collect relevant data from patient files as a part of the history taking. The patients will be made aware of this by the HCPs and their written consent is required. The patients will be assigned study numbers and their personal details will be kept confidential at all times. The HCPs will use the monitoring tool and at the end of the study period, get feedback from the patients who will have used the diary regarding the usability of the diary.

Data collection is estimated to run over a period of three months, starting in June 2009. A research report summarizing the findings will be written and submitted to UDIPA and the Pharmacy Department in the Faculty of Health Sciences at the Nelson Mandela Metropolitan University (NMMU). A paper will be prepared for publication in an accredited journal and the results will be presented at a local, national or international conference. This will form part of my fulfilment criteria for completion of my Masters degree in Pharmacy at this institution. More information on the study can be found on the attached research proposal as submitted to the Pharmacy Department, the Faculty of Health Sciences Research Innovation and Technology Committee, and the Research Ethics Committee (Human) at the NMMU. Please feel free to contact myself or my supervisors should you have any queries in this regard.

Thank you for your consideration.

Yours faithfully

Florence Mulinge
Mobile: 084 854 0118
E-mail: flomulinge@gmail.com
(Researcher)

Beverley Gold (Mrs)
Lecturer: Department of Pharmacy
W: 041 504 4290; Cell 082 572 7332
(Supervisor)

Sue Burton (Ms)
Lecturer: Department of Pharmacy
W: 041 504 4212
(Supervisor)

Appendix 6b

STUDY APPROVAL LETTER

UDIPA LIFE & WELLNESS CENTRE

38 A Cuyler Street

Cuyler Hospital Grounds

P. O. Box 832

Uitenhage

Tel / Fax 041- 9911892

"Defending your health"

Date: 28th April 2009

Re: NMMU Pharmacology Research Project

We hereby grant permission for the research project at Udipa Life Centre for 2009.

Thank you for your interest.

Yours faithfully

Dr L. M. Naidoo

Udipa Chairperson

Appendix 7

A SAMPLE OF AN ARV ADVERSE EFFECTS MONITORING TOOL

IN STRICT CONFIDENCE

Adverse Event Form for Anti-Retroviral Medicines

IN STRICT CONFIDENCE

Please complete as much as possible, regardless of any missing details

PATIENT DETAILS

Folder Number: Patient initials: Sex: [M] [F]

Residential Address: Town/City:

District: Region:

Date of birth: .../.../... Age: ..... years ..... months Weight (kg): .....

Type of Treatment ☐ HAART ☐ PMTCT ☐ PEP

DRUG DETAILS

	Drug I	Drug 2	Drug 3	Drug 4
1st Line Drugs	Combivir/Nevirapine	Combivir/Efavirenz	Stavudine/Lamivudine/ Nevirapine	Stavudine/Lamivudine/ Efavirenz
	Dose:	Dose:	Dose:	Dose:
	Date started: .../.../...	Date started: .../.../...	Date started: .../.../...	Date started: .../.../...
2nd Line Drugs	Abacavir/ Didanosine/ Nelfinavir	Abacavir/ Didanosine/ Kaletra		
	Dose:	Dose:		
	Date started: .../.../...	Date started: .../.../...		
CONCOMITANT DRUG	Co-trimoxazole prophylaxis Dose:	Drug: Dose:	Drug: Dose:	Drug: Dose:
	Date started: .../.../...	Date started: .../.../...	Date started: .../.../...	Date started: .../.../...

DETAILS OF ADVERSE EVENT

Date event started:: .../.../... Date event stopped: .../.../...

Adverse reaction observed (please tick all that apply)

☐ Mouth sores ☐ Abdominal pains ☐ Vomiting ☐ Nausea ☐ Itching ☐ Skin rashes ☐ Diarrhoea

☐ Headache ☐ Dizziness ☐ Insomnia ☐ Dark-coloured urine ☐ Other (please specify): .....

Description of event (*continue on back page if necessary*):

Treatment or action taken (*continue on back page if necessary*):

Outcome (*please tick all that apply*)

☐ Change of therapy ☐ Recovered without change of therapy ☐ Death

☐ Required / prolonged hospitalization ☐ Ongoing ☐ Other outcome (please specify)

REPORTER DETAILS

Profession: ☐ Doctor ☐ Pharmacist ☐ Nurse ☐ Other

Last Name: ..... Other Name(s): ..... Title: .....

Address: ..... Tel No. ..... Email: .....

Signature: ..... Date:.....