PRESCRIBING PATTERNS OF ANTIRETROVIRAL DRUGS IN THE PRIVATE HEALTH CARE SECTOR IN SOUTH AFRICA: A DRUG UTILISATION REVIEW

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It is not the answer that enlightens, but the question.

Eugène Ionesco (1912-1994)

This dissertations is dedicated to everyone - man, woman, and child - who suffers from HIV/AIDS.

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ABSTRACT

TITLE: Prescribing patterns of antiretroviral drugs in the private health care sector in South Africa: a drug utilisation review.

KEYWORDS: HIV/AIDS, antiviral drugs, antiretroviral (ARV) drugs, managed care, pharmacoeconomics, drug utilisation review, disease management, prevalence and medicine treatment cost, average cost, single exit price, cost savings.

HIV/AIDS is already the leading cause of death worldwide (Unicef *et al.*, 2004:10) with more than 5 million people out of a total of 46 million South Africans that were HIV positive in 2004, giving a total population prevalence rate of 11 per cent (Dorrington *et al.*, 2004:1). Many people infected do not have access to even the basic drugs needed to treat HIV-related infections and other conditions (Wikipedia, 2004:3). The relative high price of many of the antiretroviral (ARV) drugs and diagnostics on the other hand are one of the main barriers to their availability in developing countries (Unicef *et al.*, 2004:77). ARV drugs registered in South Africa include the Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs) (MCC, 2004:1).

The objective of this study was to review, analyse and interpret the prescribing patterns of antiviral drugs, with special reference to antiretroviral drugs, in the private health care sector in South Africa by using a medicine claims database. A quantitative, retrospective drug utilisation review was performed. The data ranging from 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002, and 1 January 2004 to 31 December 2004 were used, dividing each year into three four-month periods, namely January to April, May to August, and September to December.

It was found that 0.38 per cent (n=1 475 380) for 2001, 0.72 per cent (n=2 076 236) for 2002, and 1.68 per cent (n=2 595 254) for 2004 of all studied prescriptions for the research periods 2001, 2002, and 2004 respectively, contained ARV drugs. ARV drugs constituted 0.33 per cent (n=2 951 326) for 2001, 0.87 per cent (n=4 042 145) for 2002, and 1.92 per cent (n=5 305 882) for 2004 of the total number of medicine items prescribed for the study years 2001, 2002 and 2004 respectively. The total cost of ARV drugs amounted to R4 990 784.29, thus constituting 1.31 per cent of the total cost (R379 708 489) of all medicine items on the database for 2001, increased to R18 235 075.75, thus constituting 3.03 per cent of the total cost (R601 350 325) of all medicine items on the database for 2002, and increased to R34 714 483.64, thus constituting 5.25 per cent of the total cost (R661 223 146) of all medicine items on the database for 2004.

It was found that 35.31 per cent (n=5 599) for 2001, 52.68 per cent (n=15 004) for 2002, and 74.27 per cent (n=43 482) for 2004 of all studied antiviral prescriptions for the research periods 2001, 2002, and 2004 respectively, contained ARV drugs. ARV drugs constituted 46.25 per cent (n=21 183) for 2001, 70.20 per cent (n=50 246) for 2002, and 85.87 per cent (n=118 718) for 2004 of the total number of antiviral medicine items prescribed for the study years 2001, 2002 and 2004 respectively. The total cost of ARV medicine items, represented 67.33 per cent (n=R4 990 784.29) during 2001, 84.72 per cent (n=R18 235 075.75) during 2002, and 91.20 per cent (n=R34 714 483.64) during 2004 of the total cost of all antiviral medicine items claimed through the database (n=R7412577.73 for 2001, n=R21523365.56 for 2002, and n=R38 064 347.38 for 2004).

The average cost per ARV medicine items for 2004 increased from R317.93±190.80 for the period January to April to R369.20±219.50 for the period May to August, and decreased to R324.79±212.48 for the period September to December and resulted in a cost saving of R41 044.35 for the period May to August versus September to December for the ARV medicine items. The implementation of the pricing regulations could thus be a possible reason for this cost saving, due to fact that the single exit price only came into effect from May 2004.

The weighted average number of ARV medicine items per prescription was 1.75±0.31 for 2001, increased to 2.35±0.03 to 2002 and remained stable on 2.35±0.02 for 2004. It was found that majority of prescriptions contained more combination ARV medicine items than single ARV medicine items, ranging from 6 834 (69.76 per cent; n=9 796) prescriptions containing combination ARV medicine items in 2001 and 32 941 (93.39 per cent; n=35 271) prescriptions containing combination ARV medicine items in 2002 to 98 805 (96.93 per cent; n=101 938) prescriptions containing combination ARV medicine items in 2004.

Lastly, it was perceived that didanosine was the active ingredient with the largest prevalence for all three four-month periods of 2001 and also for the periods January to April and May to August of 2002, whilst efavirenz represented the active ingredient with the largest prevalence for the period September to December of 2002, and also for all three four-month periods of 2004. Didanosine represented the active ingredient with the highest total cost for the period January to April of 2001, whilst the combination of lamivudine/zidovudine represented the active ingredient with the highest total cost for the periods May to August and September to December of 2001, and also for all three-four month periods of 2002 and 2004. Nelfinavir has the highest average cost for period January to April of 2001, ritonavir for period May to August of 2001, and saquinavir mesylate for period September to December of 2001. Nelfinavir has the highest average cost for all three-four month periods of 2002, while didanosine has the highest average cost for all three four-month periods of 2004.

OPSOMMING

TITEL: Die voorskryfpatrone van antiretrovirale medisyne in die private gesondheidsorg-sektor in Suid-Afrika: 'n medisyneverbruiksbenadering.

SLEUTELWOORDE: MIV/Vigs, antivirale medisyne, antiretrovirale medisyne, bestuurde gesondheidsorg, farmako-ekonomie, geneesmiddel verbruiksoorsig, siektebestuur, voorkoms en medisyne behandelingskoste, gemiddelde koste enkel uitgangsprys, kostebesparing.

MIV/Vigs is alreeds die hoofoorsaak van sterftes wêreldwyd (Unicef *et al.*, 2004:10) met meer as 5 miljoen mense uit 'n totaal van 46 miljoen Suid-Afrikaners wat MIV positief was in 2004, wat 'n totale populasie voorkomsyfer van 11 persent gee (Dorrington *et al.*, 2004:1). Baie mense wat geinfekteerd is, het nie eens toegang tot basiese medisyne wat nodig is om MIV-verwante infeksies en ander kondisies te behandel nie (Wikipedia, 2004:3). Die relatiewe hoë pryse van baie van die antiretrovirale (ARV) medisyne en diagnostiek aan die ander kant is een van die hoof struikelblokke tot hulle beskikbaarheid in ontwikkelende lande (Unicef *et al.*, 2004:77). ARV medisynes geregistreer in Suid-Afrika sluit die nukleosied/nukleotied omgekeerde transkripsie inhibeerders (NRTIs), nie-nukleosied omgekeerde transkripsie inhibeerders (NNRTIs) en protease inhibeerders (PIs) in (MBR, 2004:1).

Die doel van hierdie studie was om die voorskryfpatrone van antivirale medisyne, met spesiale verwysing na antiretrovirale medisyne in die private gesondheidsorg-sektor in Suid-Afrika te bestudeer, analiseer, en interpreteer deur gebruik te maak van 'n medikasie-eise databasis. 'n Kwantitatiewe, retrospektiewe geneesmiddel verbruiksoorsig is gedoen. Die data wat strek vanaf 1 Januarie 2001 tot 31 Desember 2001, 1 Januarie 2002 tot 31 Desember 2002, en 1 Januarie 2004 tot 31 Desember 2004 is gebruik, en elke jaar is in drie vier-maande periodes ingedeel, naamlik Januarie tot April, Mei tot Augustus, en September tot Desember.

Daar is gevind dat 0.38 persent (n=1 475 380) vir 2001, 0.72 persent (n=2 076 236) vir 2002, en 1.68 persent (n=2 595 254) vir 2004 van alle ondersoekte voorskrifte vir die studie periodes 2001, 2002, en 2004 onderskeidelik, ARV medisyne bevat het. ARV medisyne bedra 0.33 persent (n=2 951 326) vir 2001, 0.87 persent (n=4 042 145) vir 2002, en 1.92 persent (n=5 305 882) vir 2004 van die totale aantal voorgeskrewe medisyne items geëis vir die studie periodes 2001, 2002 en 2004 onderskeidelik. Die totale koste van ARV medisyne het R4 990 784,29 bedra wat 1.31 persent van die totale koste (R379 708 489) van alle medisyne items op die databasis vir 2001 beloop, het R18 235 075.75 bedra wat 3.03 persent van die totale koste (R601 350 325) van alle medisyne items op die databasis vir 2002 beloop, en het R34 714

483.64 bedra wat 5.25 persent van die totale koste (R661 223 146) van alle medisyne items op die databasis vir 2004 beloop.

Daar is gevind dat 35.31 persent (n=5 599) vir 2001, 52.68 persent (n=15 004) vir 2002, en 74.27 persent (n=43 482) vir 2004 van alle ondersoekte voorskrifte vir die studie periodes 2001, 2002, en 2004 onderskeidelik, ARV medisyne bevat het. ARV medisyne bedra 46.25 persent (n=21 183) vir 2001, 70.20 persent (n=50 246) vir 2002, en 85.87 persent (n=118 718) vir 2004 van die totale aantal antivirale medisyne items geëis vir die studie periodes 2001, 2002 en 2004 onderskeidelik. Die totale koste van ARV medisyne verteenwoordig 67.33 persent (n=R4 990 784.29 gedurende 2001, 84.72 persent (n=R18 235 075.75) gedurende 2002, en 91.20 persent (n=R34 714 483.64) gedurende 2004 van die totale koste van alle antivirale medisyne items geëis deur die databasis (n=R7 412 577.73 vir 2001, n=R21 523 365.56 vir 2002, en n=R38 064 347.38 vir 2004).

Die gemiddelde koste per ARV medisyne items vir 2004 het toegeneem van R317.93±190.80 vir die periode Januarie tot April tot R369.20±219.50 vir die periode Mei tot Augustus, en het afgeneem na R324.79±212.48 vir die periode September tot Desember en het 'n kostebesparing van R41 044.35 vir die periode Mei tot Augustus versus September tot Desember vir die ARV medisyne items teweeggebring. Die implementering van die prys regulasies kan dus 'n moontlike oorsaak wees vir die kostebesparing, omdat die enkel uitgangsprys eers vanaf Mei 2004 in werking getree het.

Die geweegde gemiddelde aantal ARV medisyne items per voorskrif was 1.75±0.31 vir 2001, styg na 2.35±0.03 vir 2002 en bly stabiel op 2.35±0.02 vir 2004. Daar is gevind dat die meeste voorskrifte meer kombinasie ARV medisyne items as enkel ARV medisyne items bevat het, en gestrek het vanaf 6 843 (69.76 persent; n=9 796) voorskrifte wat kombinasie ARV medisyne items bevat het vir 2001 en 32 941 (93.39 persent; n=35 271) voorskrifte wat kombinasie ARV medisyne items bevat het vir 2002 tot 98 805 (96.93 persent; n=101 938) voorskrifte wat kombinasie ARV medisyne items bevat het vir 2004.

Laastens is gevind dat didanosien die aktiewe bestanddeel was met die grootste voorkoms vir al drie vier-maande periodes van 2001 en ook vir die periodes Januarie tot April en Mei tot Augustus van 2002, terwyl efavirenz die aktiewe bestanddeel met die grootste voorkoms vir die periodes September tot Desember van 2002 verteenwoordig het, asook vir al drie vier-maande periodes van 2004. Didanosien verteenwoordig die aktiewe bestanddeel met die hoogste totale koste vir die periode Januarie tot April van 2001, terwyl die kombinasie van lamivudien/zidovudien die aktiewe bestanddeel verteenwoordig met die hoogste totale koste vir die periodes Mei tot Augustus en September tot Desember van 2001, asook vir al drie vier-maande periodes van 2002 en 2004. Nelfinavir het die hoogste gemiddelde koste vir die periode Januarie tot April van 2001, ritonavir vir die periode Mei tot Augustus van 2001, en saquinavir mesylate

vir die periode September tot Desember van 2001. Nelfinavir het die hoogste gemiddelde koste vir al drie vier-maande periodes van 2002, terwyl didanosien die hoogste gemiddelde koste vir al drie vier-maande periodes van 2004 het.

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

The thesis focuses on the prescribing patterns of antiviral drugs, with special emphasis on antiretroviral (ARV) drugs, in the private health care sector in South Africa. In this chapter the problem statement, research objectives and research methodology will be discussed. The discussion on the division of chapters will mark the end of the chapter.

1.2 PROBLEM STATEMENT

When a virus infects human cells, the physician has to interfere with viral replication in order to prevent or ameliorate the disease process. This can be done by manipulating the biological system of the patient or by utilising antiviral drugs (Tritz, 2000:2).

According to Klebl (2004:162) antiviral programmes are concentrating on the development of drugs designed to inhibit the action of viral proteins. ARV drugs work by blocking human immunodeficiency virus (HIV) from replicating and functioning inside the body. While the ARV drugs are not a cure for acquired immune deficiency syndrome or acquired immunodeficiency syndrome (AIDS), they have brought extraordinary hope to people infected and have transformed AIDS into a chronic but manageable disease (Unicef *et al.*, 2004:76)

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) *(refer to section 2.7.2.1.1)* incorporate themselves into the deoxyribonucleic acid (DNA) of the virus, thereby stopping the building process in which the resulting DNA is incomplete and cannot create new viruses. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) *(refer to section 2.7.2.1.2)* stop antiviral production by binding directly onto the reverse transcriptase enzyme and preventing the conversion of ribonucleic acid (RNA) to DNA (Stein *et* al., 2000:125).

Patchen and Beal (2001:357) stated that protease inhibitors (PIs) *(refer to section 2.7.2.1.3)* inhibit viral replication by preventing pieces of new virus from being assembled into a functional copy of the virus and released from the infected cells. Fusion inhibitors (FIs) *(refer to section 2.7.2.1.4)* block virus replication by binding to glycoprotein 41 (gp41) and disrupt the conformational changes associated with virus-host-cell fusion (Matthews *et* al., 2004:215). In the hope that efficacy will be maximised and drug resistance and viral rebound minimised, there is a trend towards the development of non-nucleoside drugs with unique mechanisms of action (Hewlett *et al.*, 2004:453).

AIDS is a human disease characterised by progressive destruction of the body's immune system. It is widely accepted that AIDS results from infection with HIV. HIV/AIDS was first noticed among homosexual men and intravenous drug users in the 1980s (CDC, 2003b:1). By the 1990s the syndrome had become a global epidemic and in 2004, 58 per cent of those with HIV/AIDS were women (Wikipedia, 2004:1).

According to Unicef *et al* (2004:10) HIV/AIDS is already the leading cause of death worldwide for people aged 15 to 49 years. In 2003 alone 2.9 million people died of AIDS and 4.8 million people were newly infected with HIV/AIDS. Over 95 per cent of people currently living with HIV/AIDS are in developing countries (Bellamy, 2001:5). Many of them do not have access to even the basic drugs needed to treat HIV-related infections and other conditions. Current optimal treatment options consist of combinations of two or more types of ARV drugs such as two NRTIs, and a PI or a NNRTI (Wikipedia, 2004:3).

Unicef *et al* (2004:77) believed that the relative high price of many of the HIV-related medicines and diagnostics offered by common suppliers – especially ARV and anticancer medicines – is one of the main barriers to their availability in developing countries. A variety of barriers are more responsible for impeding access to antiretroviral treatment, including but not limited to the poverty of African countries, the high cost of antiretroviral treatment, national regulatory requirements for medicines, tariffs and sales taxes, and above all, a lack of sufficient international financial aid to fund antiretroviral treatment (Attaran & Gillespie-White, 2001:1886).

Just over 5 million people out of a total of 46 million South Africans were HIV positive in 2004, giving a total population prevalence rate of 11 per cent. This is estimated from the Actuarial Society of South Africa 2002 (ASSA2002) demographic and AIDS model which is based on a thorough analysis of a range of epidemiological and demographic data including the antenatal surveys up to the year 2002 (Dorrington *et al*., 2004:1).

Providing adequate care and support for those suffering from HIV-associated diseases, is an increasing problem, placing a heavy burden on the South African health care system. The most recent statistics according to the United Nations programme on AIDS (UNAIDS) revealed that the percentage of hospital beds occupied due to AIDS, ranges from 26 to 70 per cent for adults and from 26 to 30 per cent for children (Erasmus, 2003:2). Millions of Africans are also not receiving medication for opportunistic infections.

Persons with a positive HIV serology, who have ever had a cluster designation four (CD4) lymphocyte count below 200 cells per micro litre (cells/μL) or a CD4 lymphocyte percentage below 14 per cent are considered to have AIDS (Hollander & Katz, 2003:1272). Dramatic increases in the efficacy of ARV treatments – especially those regimens that include PIs or NNRTIs – have improved the prognosis of persons with HIV/AIDS. One consequence is that fewer persons with HIV ever develop an infection or malignancy or have a low enough CD4 count to classify them as having AIDS which means that the definition of the centres for disease control and prevention (CDC) have become a less useful measure of the impact of HIV/AIDS in the United States (Hollander & Katz, 2003:1272). Conversely, persons who had been diagnosed with AIDS, based on a serious opportunistic infection, malignancy, or immunodeficiency may now be markedly healthier, with high CD4 counts, due to the use of highly active antiretroviral therapy (HAART) (Hollander & Katz, 2003:1272).

Because HIV is a relatively new infection, many of the drugs developed specifically to treat HIV/AIDS are still under patent protection in some countries and marketed at very high prices (Bellamy, 2001:6). Most of these drugs, including ARV drugs, are also available on the international market as less expensive generic drugs. In addition, some of the major pharmaceutical manufacturers have offered donations of individual drugs – for example, ARV drugs to prevent mother-to-child transmission (MTCT) of HIV – as well as significant reductions on the price of some expensive patented items for use exclusively in developing countries (Bellamy, 2001:6).

It is thus imperative that research be conducted regarding the utilisation and cost implications associated with antiviral drugs, in particular ARV drugs in the private health care sector of South Africa.

1.3 RESEARCH QUESTIONS

The following research questions can be formulated on the basis of the preceding discussion:

- Which methods and techniques are utilised to ensure optimal health care?
- How can HIV/AIDS be conceptualised and what are the treatment characteristics of HIV/AIDS?
- How can ARV drugs be conceptualised?
- What are the prescribing patterns of antiviral drugs and what are the costs associated with these drugs in the private health care sector in South Africa?
- What are the prescribing patterns of ARV drugs and what are the costs associated with these drugs in the private health care sector in South Africa?
- What is the prevalence and cost associated with the innovator and generic forms of antiviral and ARV drugs?

- Does combination therapy of ARV drugs occur and what are the costs associated with these combinations?

1.4 RESEARCH OBJECTIVES

The research includes a general as well as various specific research objectives.

1.4.1 General objective

The general research objective of this study was to determine *the prescribing patterns of antiviral drugs, with special emphasis on antiretroviral drugs, in the private health care sector in South Africa by using a medicine claims database.*

1.4.2 Specific objective

The research project consists of two phases, namely a literature review and an empirical investigation. The research objectives of the two phases include the following:

1.4.2.1 Phase 1: Literature review

The specific research objectives of the literature review include the following:

- To conceptualise HIV/AIDS from available literature and the treatment protocols thereof.
- To describe ARV drugs according to different classification systems.
- To conceptualise from the literature what managed health care, drug utilisation, pharmacoeconomics and disease management entail.

1.4.2.2 Phase 2: Empirical investigation

The specific research objectives of the empirical investigation were:

- to investigate the possible differences in the utilisation patterns and/or costs, before and after the implementation of the pricing regulations in May 2004 for each of the specific research objectives that follows hereafter;
- to determine the prevalence and usage patterns of drugs in general, as well as the costs associated with these drugs;
- to analyse the general prescribing patterns of antiviral drugs as well as the costs associated with these drugs;

- to determine the prevalence and cost of the subdivisions of antiviral medicine items, ARV medicine items and other antiviral medicine items;
- to determine the prevalence and cost associated with innovator and generic forms of antiviral drugs;
- to determine the general prescribing patterns of ARV drugs as well as the costs associated with these drugs;
- to determine the prevalence and cost of ARV medicine items for the three study years;
- to determine the prevalence and cost of ARV medicine items for the three study years based on the different categories;
- to determine the prevalence and cost of ARV medicine items for the three study years based on the active ingredient classification;
- to determine and compare the difference in prevalence and cost of innovator ARV products versus generic ARV products before and after the implementation of the pricing regulations in May 2004 of ARV drugs;
- to determine the cost saving of ARV medicine items before and after the implementation of the pricing regulations in May 2004; and
- to identify combination therapy of ARV drugs and determine the costs associated with these combinations.

1.5 RESEARCH METHOD

The research consists of two phases in conjunction with the specific objectives *viz.* a literature review and an empirical investigation.

1.5.1 Phase 1: Literature review

The following steps will be followed in the literature study:

- **Step 1: HIV/AIDS and antiretroviral treatment.** This step of the literature study focuses on the history of HIV/AIDS, the relationship between HIV/AIDS, the transmission of HIV, the stages of HIV disease, opportunistic infections associated with HIV/AIDS and the treatment of HIV/AIDS. These aspects are described in Chapter 2.

- **Step 2: Health care concepts.** This step constitutes drug utilisation review, pharmacoeconomics and disease management, all of which are utilised to ensure optimal health care. These aspects are described in Chapter 3.

1.5.2 Phase 2: Empirical investigation

The empirical investigation compromises several steps with a complete discussion in Chapter 4. A retrospective drug utilisation study was done on the antiviral drugs claimed through Interpharm Data Systems® for the periods 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002 and 1 January 2004 to 31 December 2004.

The study population was selected according to prescriptions analysed on the medicine claims database. This study focused specifically on prescriptions prescribed for patients who received ARV drugs. The prevalence and cost associated with antiviral and in particular ARV usage as well as the innovator and generic forms of antiviral and ARV drugs were selected and utilised as measuring instruments for data analyses in order to achieve the aims of the empirical investigation. The data analysis was conducted by means of the Statistical Analysis System®, SAS 9.1® (SAS for Windows, 9.1, 2005).

The report and discussion of the results obtained from the empirical investigation, as well as the conclusion, recommendations and limitations based on the results will be discussed in Chapters 5 and 6 respectively.

1.6 DIVISION OF CHAPTERS

The division of chapters will be as follows:

Chapter 1: Introduction

Chapter 2: HIV/AIDS and antiretroviral treatment

Chapter 3: Health care concepts

Chapter 4: Empirical investigation

Chapter 5: Results and discussion

Chapter 6: Conclusion and recommendations

1.7 CHAPTER SUMMARY

In this chapter, the problem statement, research questions, research objectives, empirical research method and division of chapters have been outlined. Antiviral drugs, and in particular HIV/AIDS and ARV treatment, will be discussed in Chapter 2.

CHAPTER 2: HIV/AIDS AND ANTIRETROVIRALS

2.1 INTRODUCTION

This chapter focuses on the disease, HIV/AIDS and the treatment thereof with ARV drugs. The history of HIV/AIDS, the relationship between HIV and AIDS, transmission of HIV, the stages of HIV disease, opportunistic infections associated with HIV/AIDS and treatment of HIV/AIDS, including vaccines and ARV drugs, are discussed.

2.2 HISTORY OF HIV/AIDS

Debate around the origin of AIDS has sparked considerable interest and controversy since the beginning of the epidemic. However, in trying to identify where AIDS originated, there is a danger that people may try to use the debate to attribute blame for the disease to particular groups of individuals or certain lifestyles (Allen & Kanabus, 2005:1).

According to Kanabus and Fredriksson (2005:1) many people had AIDS in the 1970s, or indeed in the years before, but we will probably never know where the AIDS virus, HIV, originated. The earliest known case of HIV-1 in a human was from a blood sample collected in 1959 from a man in Kinshasa, Democratic Republic of Congo. (How he became infected is not known.) Genetic analysis of this blood sample suggested that HIV-1 might have stemmed from a single virus in the late 1940s or early 1950s. The virus has existed in the United States since the mid-to-late 1970s (CDC, 2003b:1).

From 1979 to 1981 rare types of pneumonia like *Pnemocystis carinii* pneumonia (PCP), cancers like Kaposi's sarcoma (KS), and other illnesses were being reported by doctors in Los Angeles and New York among a number of homosexual men. These were conditions not usually found in people with healthy immune systems. In 1982 public health officials began to use the term "acquired immunodeficiency syndrome," or AIDS, to describe to the occurrences of opportunistic infections like KS and PCP in previously healthy people. Formal tracking (surveillance) of AIDS cases began that year in the United States (CDC, 2003b:1).

In 1983, scientists discovered the virus that causes AIDS. The virus was at first named HTLV-III / LAV (human T-cell lymphotropic virus-type III / lymphadenopathy-associated virus) by an international scientific committee. This name was later changed to HIV (human immunodeficiency virus) (CDC, 2003b:1).

2.3 THE RELATIONSHIP BETWEEN HIV AND AIDS

The body's health is defended by its immune system. White blood cells called lymphocytes (B-cells and T-cells) protect the body from viruses, bacteria, parasites and fungi. B-cells and T-cells are activated to defend the body, when viruses, bacteria, parasites and fungi are detected. This process is hindered in the case of AIDS. AIDS is a disease that breaks down the body's immune system (HIVpositive.com, 2005b:1).

AIDS stands for Acquired Immune Deficiency Syndrome:

- *Acquired* means you can get infected with it and therefore the disease could not be inherited or be due to genetic mutation in the foetus.
- *Immune Deficiency* means a weakness in the body's system that fights diseases.
- *Syndrome* means a specific group of health problems which always occur together that make up a disease (Brown *et al.*, 2003:1; New Mexico AIDS education and training centre, 2005:1).

According to Weiss (1993:1273) it is increasingly evident that both the tropism and burden of HIV infection correlate closely with the manifestations of the disease. AIDS is a degenerative disease of the immune and central nervous system. The ability of ARV drugs to effectively penetrate the central nervous system and to deliver a therapeutic drug concentration constitutes important requirements for the control of HIV (Wiebe & Knaus, 1999:63).

HIV stands for Human Immunodeficiency Virus:

- *Human* means the virus can only affect humans.
- *Immunodeficiency* means the virus causes the immune system to lack the required elements for it to function properly.
- *Virus* means the microorganism responsible for the infection (Brown *et al.*, 2003:1).

A person with HIV infection may remain healthy for many years. People with HIV infection are said to have AIDS when they are sick with serious illnesses and infections that can occur with HIV. The illnesses tend to occur late in HIV infection, when few T-cells remain (HIVpositive.com, 2005b:1).

Untreated HIV disease is characterised by a gradual deterioration of immune function. Most notably, crucial immune cells called CD4 positive T-cells are disabled and killed during the typical course of

infection. These cells, sometimes called "T-helper cells," play a central role in the immune response, signalling other cells in the immune system to perform their special functions (NIAID, 2004:1).

According to the National Institute of Allergies and Infectious Diseases (NIAID, 2004:1) a healthy, uninfected person usually has 800 to 1 200 CD4 positive T-cells per cubic millimetre (mm^3) of blood. During untreated HIV infection, the number of these cells in a person's blood progressively declines. When the CD4 positive T-lymphocyte count falls below $200/mm^3$ or a CD4 positive percentage of less than 14 (Castro, 1993:4), a person becomes particularly vulnerable to the opportunistic infections and cancers that typify AIDS, the end stage of HIV disease *(refer to section 2.5)*. People with AIDS often suffer infections of the lungs, intestinal tract, brain, eyes, and other organs, as well as debilitating weight loss, diarrhoea, neurological conditions, and cancers such as Kaposi's sarcoma and certain types of lymphomas (NIAID, 2004:1).

Most scientists think that HIV causes AIDS by directly inducing the death of CD4 positive T-cells of interfering with their normal function, and by triggering other events that weaken a person's immune function. For example, the network of signalling molecules that normally regulates a person's immune response is disrupted during HIV disease, impairing a person's ability to fight other infections. The HIV-mediated destruction of the lymph nodes and related immunologic organs also plays a major role in causing the immunosuppression seen in people with AIDS. Immunosuppression by HIV is confirmed by the fact that medicines, which interfere with the HIV lifecycle, preserve CD4 positive T-cells and immune function as well as delay clinical illness (NIAID, 2004:1).

2.3.1 HIV is a retrovirus

HIV is the retrovirus, according to Schaeffer and Krylov (2000:208) that causes AIDS. HIV has genes composed of ribonucleic acid (RNA) molecules. Retroviruses can only replicate within a living host cell because they contain only RNA and they do not contain deoxyribonucleic acid (DNA) (Avert.org, 2005b:2). In order to replicate (duplicate), they must make a DNA copy of their RNA. It is the DNA genes that allow the virus to replicate (NIAID, 2004:2).

HIV belongs to a subgroup of retroviruses (Sanders, 2003:287) known as lentiviruses, or "slow" viruses. The course of infection with these viruses is characterised by a long interval between initial infection and the onset of serious symptoms (NIAID, 2004:2).

2.3.2 Structure of HIV

HIV has a diameter of 1/10 000 of a millimetre. The outer shell of the virus is known as the viral envelope. Embedded in the viral envelope is a complex protein known as *env*, which consists of an outer protruding cap *glycoprotein* (*gp*) *120*, and a stem *gp41*. Within the viral envelope is an HIV protein called *p17* (matrix), and within this is the viral core or *capsid*, which is made of another viral protein *p24* (core antigen). The major elements contained within the viral core are two single strands of HIV RNA, a protein *p7* (nucleocapsid), and three enzyme proteins, *p51* (reverse transcriptase), *p11* (protease) and *p32* (integrase) (Avert.org, 2005b:2).

The bipartite envelope glycoprotein (*env*) of HIV-1 performs two essential functions for initiating virus infection. The *gp120* surface subunit of *env* binds cell receptors to attach virus to target cells and regulate viral entry. The *gp41* transmembrane subunit fuses host-cell and viral membranes to deliver the viral core into the cell cytoplasm. The two subunits derive from a polyprotein precursor, *gp160*. Cleavage of *gp 160* in the biosynthetic pathway creates mature *env* consisting of the noncovalently-associated *gp120/gp41* that is primed for viral entry. While performing distinct operations in HIV entry, the activities of the *gp120* and *gp41* subunits must be highly coordinated in order to lead to successful infection (Weiss, 2003:214).

Figure 2.1 indicates the structure of HIV.

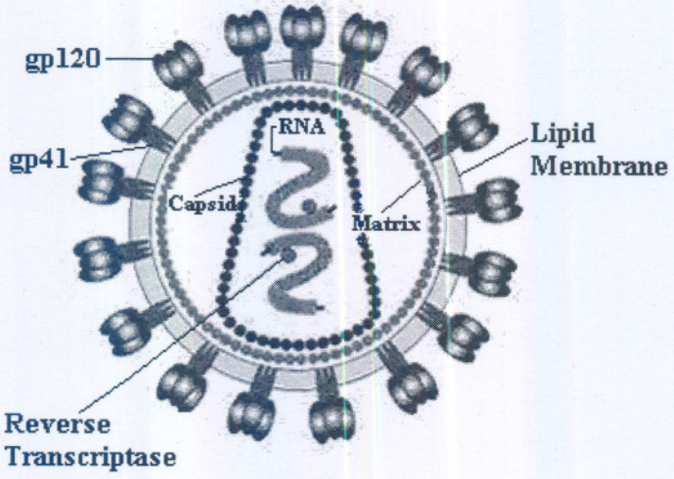


Figure 2.1 Structure of HIV (NIAID, 2004:2)

2.3.3 Replication cycle of HIV

The replication cycle of HIV consists of the following steps:

- Entry of HIV into cells
- Reverse transcription
- Integration
- Transcription
- Translation
- Assembly and budding

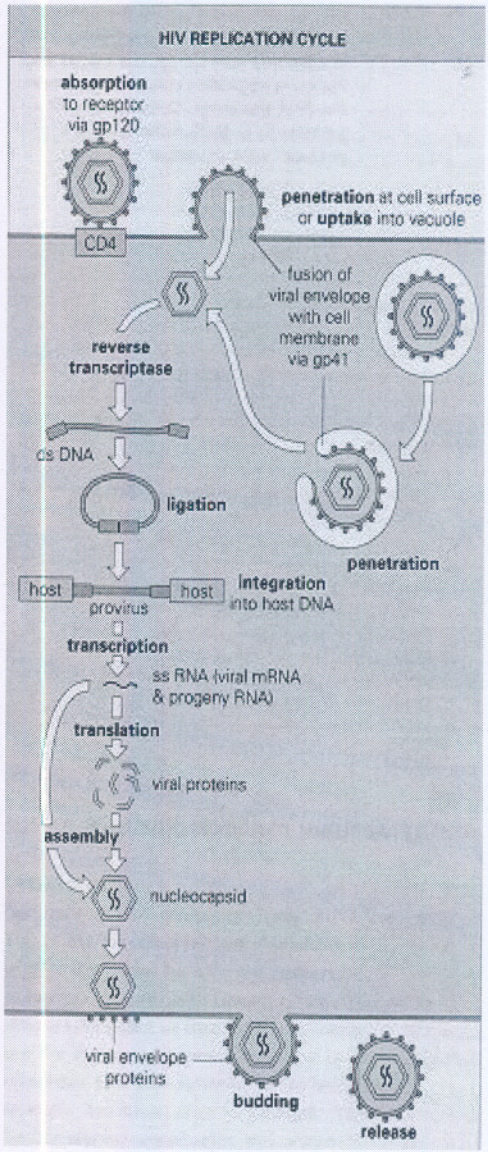


Figure 2.2 HIV replication cycle (HIVpositive.com, 2005c:1)

A description of the replication cycle of HIV as described in Figure 2.2 (above) follows:

2.3.3.1 Entry of HIV into cells

The first step in HIV infection involves virus-cell or cell-cell fusion mediated by the viral envelope glycoproteins (*env*) *gp41* (transmembrane subunit of HIV envelope) and *gp120* (surface envelope glycoprotein of HIV) (Freed & Martin, 1995:23883). *Gp120* binds the host cell receptors, whereas *gp41* is thought to be responsible for fusing the viral and target cell membranes. CD4 binding has been shown

to induce a *gp120* conformation that is able to bind the CCR5 chemokine receptor with high affinity (Sodroski, 1999:243).

According to Sodroski (1999:243) similar effects on *gp41* exposure were observed for both the CCR5 and CXCR4 chemokine receptors, even though only one of these coreceptors supported *gp120* binding and virus entry of the HIV-1 strains tested. The envelope glycoproteins of some HIV-1 strains exhibited the same *gp41* exposure after binding only CD4, whereas chemokine receptor binding is necessary for the efficient entry of all known HIV-1 isolates. CXCR4 is the coreceptor for HIV-1 strains that infect T-cells (T-tropic or X4 strains), and CCR5 is the coreceptor for HIV-1 strains that infect macrophages (M-tropic or R5 strains). CXCR4 and CCR5 have not evolved simply to act as coreceptors for HIV entry; they normally act as receptors for chemokines (De Clercq, 2001:5).

The interaction of the X4 or R5 HIV-1 envelope glycoprotein *gp120* with the coreceptor CXCR4 or CCR5, respectively, is followed by a spring-loaded action of the viral glycoprotein *gp41* (normally covered by the bulkier *gp120*), that then anchors through its amino termini (the 'fusion peptides') into the target cell membrane. This initiates the fusion of the two lipid bilayers, that of the viral envelope with that of the cellular plasma membrane (Sodroski, 1999:243).

2.3.3.2 Reverse transcription

Reverse transcriptase is a multi-functional heterodimeric enzyme that converts the genomic HIV RNA into proviral DNA by catalysing RNA-dependent and DNA-dependent DNA polymerise reactions (Ren & Stammers, 2005:4).

Inhibitors of reverse transcriptase, such as zidovudine, were the first anti-HIV medications, and are still a critical part of treating patients who have HIV. Reverse transcriptase inhibitors are divided into two classes – nucleoside analogues and non-nucleoside reverse transcriptase inhibitors – based on their structure and how they inhibit reverse transcriptase (Gandhi *et al.*, 1999:1).

2.3.3.3 Integration

An essential step in the viral life cycle is integration of the viral DNA into the host cell chromosome (Katz *et al.*, 1990:87). This step is catalysed by the viral enzyme, HIV integrase (Chen *et al.*, 2000:2385). Retroviral DNA integration involves a coordinated set of DNA cutting and joining reactions (Craigie *et al.*, 1990:829).

Inhibitors of integrase are under study as a new way to block HIV replication. Once the viral DNA is integrated into the genetic material of the host, it is possible that HIV may persist in a latent state for many years. This ability of HIV to persist in certain latently infected cells is the major barrier to eradication or cure of HIV. For this reason, based on our current knowledge, patients must remain on anti-viral therapy for life (Gandhi *et al.*, 1999:1).

2.3.3.4 Transcription

For a provirus to produce new viruses, according to NIAID (2004:5), RNA copies must be made that can be read by the host cell's protein-making machinery. Gandhi *et al.* (1999:1) described that activation of the host cells result in the transcription of viral DNA into messenger RNA (mRNA), which is then translated into viral proteins and production of mRNA that is called transcription, a process that involves the host cell's own enzymes (NIAID, 2004:5).

The new viral RNA forms the genetic material of the next generation of viruses. The viral RNA and viral proteins assemble at the cell membrane into a new virus. Amongst the viral proteins is HIV protease, which is required to process other HIV proteins into their functional forms. Protease inhibitors, one of the most potent types of anti-viral medications, act by blocking this critical maturation step (Gandhi *et al.*, 1999:1).

2.3.3.5 Translation

After HIV mRNA has been processed in the cell's nucleus, it is transported to the cytoplasm. HIV proteins are critical to this process. In the cytoplasm, the virus co-opts the cell's protein-making machinery - including structures called ribosomes – to make long chains of viral proteins and enzymes, using HIV mRNA as a template. This process is called translation (NIAID, 2004:6).

2.3.3.6 Assembly and budding

Newly made HIV core proteins, enzymes, and genomic RNA gather inside the cell and an immature viral particle forms and buds off from the cell, acquiring an envelope that includes both cellular and HIV proteins from the cell membrane. During this part of the viral life cycle, the core of the virus is immature and the virus is not yet infectious. The long chains of proteins and enzymes that make up the immature viral core are now cut into smaller pieces by a viral enzyme called protease (NIAID, 2004:6).

Drugs called protease inhibitors, like indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, and amprenavir, interfere with this step of the viral life cycle (NIAID, 2004:6).

Unless the HIV lifecycle is interrupted by treatment, the virus infection spreads throughout the body and results in the destruction of the body's immune system. With current anti-viral medications, such as reverse transcriptase inhibitors and protease inhibitors, HIV infection can be contained. However, a great deal more must be achieved before the AIDS epidemic can be brought under control. One important immediate goal is to design new, more potent medications that are easier to take and have fewer side effects. However, the ultimate challenges are to use our understanding of the HIV lifecycle to develop medications that will eradicate HIV from people who are already infected and to create a vaccine that will prevent new infections in the future (Gandhi *et al.*, 1999:1).

2.4 TRANSMISSION OF HIV

2.4.1 How is HIV transmitted?

HIV is transmitted horizontally and vertically. "Horizontal" transmission occurs during heterosexual and homosexual intercourse, with an HIV infected person, when no barrier method (e.g. condom) is used. It is also transmitted between injecting drug users from sharing infected needles. Needlestick injuries are where health care workers sustain an injury with a sharp object (like a needle) which has been contaminated with the blood of an HIV positive person. "Vertical" transmission occurs between mothers and their children during or after pregnancy (Gardiner, 2001:2).

HIV is spread by sexual contact with an infected person, by sharing needles and/or syringes (primarily for drug injection) with someone who is infected, or, less commonly (and now very rarely in countries where blood is screened for HIV antibodies), through transfusions of infected blood or blood clotting factors. Babies born to HIV-infected women may become infected before or during birth or through breast-feeding after birth (CDC, 2003c:1).

HIV can be passed from one person to another when infected blood, semen, or vaginal secretions come in contact with an uninfected person's broken skin or mucous membranes. A mucous membrane is wet, thin tissue found in certain openings to the human body. These can include the mouth, eyes, nose, vagina, rectum, and opening of the penis (CDC, 2003c:2).

Research suggests that immune system cells of the dendritic cell type, which live in the mucosa, may begin the infection process after sexual exposure by binding to and carrying the virus from the site of infection to the lymph nodes where other immune system cells become infected. A molecule on the surface of dendritic cells, DC-SIGN, may be critical for this transmission process (NIAID, 2004:6).

Some people fear that HIV might be transmitted in other ways; however, no scientific evidence to support any of these has been found. If HIV were being transmitted through other routes (such as through air, water, or insects), the pattern of reported AIDS cases would be much different from what has been observed (CDC, 2003c:1).

2.4.2 Possible methods of transmitting HIV

2.4.2.1 Venereal transmission

AIDS was first defined in homosexual men in the United States and although male-to-male sex remains the predominant mode of transmission in most industrialised countries, the predominant mode of transmission worldwide continues to be heterosexual contact. Of all reported AIDS cases, 91 per cent are estimated to have been heterosexually acquired (Gayle & Hill, 2001:327).

HIV is transmitted by certain specific behaviours involving the exchange of bodily fluids between people. Sexual activities can transmit HIV when they involve direct contact between the HIV-infected bodily fluids (such as semen, vaginal secretions, and blood) of one person and the mucous membranes (such as in the vagina, rectum, and mouth) of another (Horn & Sciolla, 1998:1).

Several risk factors have been associated with the heterosexual transmission of HIV (Gayle & Hill, 2001:331), including lack of circumcision, high virus load and decreased CD4-cell count in an infected partner, presence of a sexually transmitted disease (STD) (genital ulcer disease or nonulcerative STDs), and certain sexual practices (sex during menses, bleeding during intercourse, and receptive anal intercourse). According to several studies, uncircumcised men were eight times more likely to be HIV infected than were those who had been circumcised, and men with foreskins were more likely to transmit HIV to their sex partners during unprotected sex (Halperin & Bailey, 1999:1813).

Strong epidemiologic, clinical and laboratory data demonstrate the increased risk for HIV transmission and acquisition due to other STDs. The presence of ulcerative and inflammatory nonulcerative STDs may promote the infectiousness of HIV and susceptibility to it by (i) disrupting normal mucosal barriers, which allows HIV into the bloodstream; (ii) facilitating HIV shedding in the genital tract; and (iii) recruiting HIV inflammatory cells to the genital tract (Fleming & Wasserheit, 1999:3).

The reduction in STDs can prevent HIV transmission in a population at high or medium risk, and accessible and effective STD treatment services can lower the incidence of HIV infection (Grosskurth, 1999:83). The proper and consistent use of latex or polyurethane condoms when engaging in sexual

intercourse can greatly reduce a person's risk of acquiring or transmitting sexually transmitted diseases, including HIV infection. There are many different types and brands of condoms available, however; only latex or polyurethane condoms provide a highly effective mechanical barrier to HIV (CDC, 2003c:4).

2.4.2.2 Mother-to-child transmission (MTCT)

The South African Department of Health (DOH, 2003a:4) assumed that HIV-positive, pregnant women accurately represented all women aged 15 to 49 years. By the end of 2003, 3.1 million women (aged 15 to 49 years) and 96 228 babies were infected with HIV in South Africa. HIV prevalence among pregnant women in 2003 was observed to be 27.9 per cent, in comparison with a prevalence of 26.5 per cent for 2002 and shows that South African HIV prevalence rates increased from 2002 to 2003.

Mother-to-child transmission of the virus (also known as vertical transmission) is the main route of HIV infection in children under 10 years of age in South Africa. The virus can be transmitted during pregnancy, labour and delivery (perinatal transmission), or through breastfeeding. Among infants who are not breastfed, two-thirds are believed to have contracted HIV around the time of delivery (Muko *et al.*, 2004:133).

According to Raisler and Cohn (2005:280) MTCT via breastfeeding seems to be the highest in women who have a new HIV infection, high viral load in the milk, mastitis, nipple pathology, and variation in feeding practices (Semba *et al.*, 1999:98). Mixed feeding may lead to more HIV transmission than exclusive breastfeeding, perhaps other foods and fluids (especially if contaminated) can irritate the gut, allowing increased penetration of the virus through microbreaks in the infant's intestinal tract (Coutsoudis *et al.*, 2001:386). If exclusive breastfeeding significantly lowers transmission risk compared with mixed feeding, it would offer a way to allow breastfeeding during the first few months of life (when it is most critical for provision of the best nutrition and disease prevention to the infant), while limiting the risk of postnatal transmission (Mofenson & McIntyre, 2000:2241).

Provision of antiretroviral prophylaxis to the infant, the mother, or both, or passive immunisation of the infant during breastfeeding followed by early weaning are alternative strategies under evaluation. Active immunisation of the infant during the period of prophylaxis would allow the infant to continue breast-feeding after immunity was induced rather than weaning at an early age. The effects of replacement feeding or early weaning of infant nutrition, morbidity, and mortality, maternal fertility and birth spacing, and on community breastfeeding practices will be important to monitor (Mofenson & McIntyre, 2000:2241).

The World Health Organisation (WHO) recommends the following for mothers with HIV:

- Avoid breastfeeding entirely when replacement feeding is acceptable, feasible, affordable, sustainable and safe.
- Breast-milk should be fed exclusively during the first months in cases where the mother chooses to breastfeed.
- If mothers choose not to breastfeed from birth or stop breastfeeding later, they should be provided with specific guidance and support for at least the first 2 years of the child's life to ensure adequate replacement feeding (Muko *et al.*, 2004:133).

According to the European Mode of Delivery Collaboration (1999:1039) elective caesarean section delivery significantly reduces the risk of mother-to-child transmission of HIV-1 infection. The role of elective caesarean delivery in preventing transmission seems most evident for infected women receiving no antiretroviral treatment or only zidovudine, who have detectable HIV-1 RNA load, and reside in more developed countries (Mofenson & McIntyre, 2000:2241).

HIV-1 infected pregnant woman should be treated with ARV drugs, not only for their own HIV infection, but also to prevent vertical transmission to the infant. Sub-optimal regimens, such as monotherapy schemes, which are not able to totally suppress viral replication, may be selected for resistant strains. These may have serious implications for the woman and for the infant. The former will no longer benefit with the drug to which resistance has emerged, neither for the treatment of her own infection nor for its prophylactic use in present or future pregnancies. In addition, if the infant gets vertically infected, resistant variants may be transmitted. This will certainly impair the choice of active drugs for his/her treatment, and the situation may be even worse if the child is a rapid progressor (Kijak *et al.*, 2001:34).

Among the many antiretroviral regimens that have been proved to reduce MTCT in developing countries (Raisler & Cohn, 2005:278), the simplest, least expensive, and most widely promoted is single-dose nevirapine. One 200-mg tablet is taken by the mother in labour, and the infant is given a dose of syrup within 72 hours after birth. Because nevirapine is a key component of first-line highly active antiretroviral therapy (HAART) regimens in most developing countries, there is increasing concern that women who take single-dose nevirapine in labour may develop resistance to HAART for their own health in the future (Raisler & Cohn, 2005:280).

Refer to section 2.7.2.4.3 on treatment of a pregnant HIV positive woman in South Africa according to the national antiretroviral guidelines.

2.4.2.3 Transmission via blood products

2.4.2.3.1 Blood transfusions

Transmission of HIV through blood transfusion is rare in industrialised countries, an achievement attained through recruitment of safe donors, deferral of high-risk donors, and screening of all donations for HIV-antibody (Lackritz *et al.*, 1995:1721). In many areas of Africa, however, blood screening and banking programmes have been difficult to implement and sustain. In a study done by Moore *et al.* (2001:657) they estimated that 2 per cent of transfusions transmitted HIV infections. Although blood screening removed more than two-thirds of infected donations, they concluded that increased attention to blood safety is needed to prevent this unacceptable risk of HIV transmission by transfusion.

In 1985, a blood-screening test became available to blood testing centres. The blood test is close to perfect (reportedly 99.9 per cent accurate), but it is not perfect. In newly infected individuals, there is a "window-period" after HIV infection, before the development of antibodies, when this test is useless. This window-period could be as long as 3 to 6 months. Thus it is possible that HIV infected blood could be collected during this window-period. However, the likelihood of catching HIV from a heterologous blood transfusion will remain an extremely remote possibility (Jennings, 1996:18).

Before 1985, hospitals were not required to report transfusions to patients, thus many elderly people are unaware that they might have been transfused with infected blood. The number of AIDS cases originating from infected blood certainly has declined over recent years and will continue to decline in years to come (Williams & Donnelly, 2002:106).

2.4.2.3.2 Transmission via needlesticks

Some health care workers have become infected with HIV by being stuck with needles containing HIV-infected blood (Avert.org, 2005a:3).

Intravenous needles and hypodermic needles (needles inserted under the skin – usually into a muscle) and syringes (the plastic container attached to the needles) are all transmitters of HIV. HIV is transmitted via the small amount of blood that remains in the needle or syringe after use (Jennings, 1996:18).

Needle sharing habits according to Jennings (1996:18) are common among intravenous drug abusers. Intravenous drug abusers commonly include people who inject heroin and/or cocaine into their veins. Intravenous drug abusers also include individuals using steroids for bodybuilding who share intravenous needles with their friends. They may be using either intravenous or hypodermic needles. It is the practice

of sharing contaminated needles and syringes, not the use of any particular drug, which holds the risk of HIV infection. Infection drug use is a major cause of HIV transmission in the United States (CDC, 1997:165). When HIV-infected drug users are hospitalised, they are brought in contact with healthcare professionals who could alleviate drug use withdrawal discomfort and possibly intervene in the cycle of drug use (Umbricht *et al.*, 2003:263).

Post exposure prophylaxis is recommended as soon as possible after a person might have been exposed to HIV via a needle prick. The HIV status of the source of your exposure through the needle prick should be determined. For medical and legal purposes, it is highly recommended that an HIV test be done immediately after the needle prick. Both the source of exposure and the exposed person should be tested immediately to establish the baseline status (Brown *et al.*, 2003:20).

2.4.2.3.3 Surgical

Some health care workers have become infected by HIV-infected blood getting into their bloodstream through an open cut or splashes into a mucous membrane (e.g. eyes or the inside of the nose) (Avert.org, 2005a:3).

2.4.3 No HIV transmission found

Research indicates that HIV is not transmitted by casual contact such as touching, hugging, sharing household items such as utensils, towels and bedding, contact with sweat or tears, sharing facilities such as swimming pools, saunas, hot tubs, sharing toilets with HIV-infected people, coughs or sneezes (PositiveSingles.com, 2005:1).

2.4.3.1 Casual contact

According to Williams and Donnelly (2002:108) hugging, breathing, spitting, coughing, and using the same bathroom facilities cannot cause HIV infection. There is a great fear of contracting AIDS through casual contact, such as shaking hands, being in the same room with an HIV-infected person and touching doorknobs. The fear is far, far greater than the risk. Diseases, which are spread by casual contact invariably, are spread via saliva or sputum, and exist in saliva or sputum in very high concentrations (Jennings, 1996:20).

2.4.3.2 HIV in the environment

Scientists and medical authorities agree that HIV does not survive well in the environment, making the possibility of environmental transmission remote (CDC, 2003c:2).

2.4.3.3 Saliva, Tears, and Sweat

HIV has been found in saliva and tears (CDC, 2003c:3) in very low quantities from some AIDS patients. It is important to understand that finding a small amount of HIV in a body fluid does not necessarily mean that HIV can be transmitted by that body fluid. HIV has not been recovered from the sweat of HIV-infected persons. Contact with saliva, tears, or sweat has never been shown to result in transmission of HIV. The main protective mechanism of saliva is reported to be inactivation of HIV-transmitting leukocytes by its unique hypotonicity (Baron *et al.*, 2000:498).

2.4.3.4 Kissing

According to Centers for Disease Control and Prevention (2003c:3) casual contact through closed-mouth or "social" kissing is not a risk for transmission of HIV. The risk of acquiring HIV during open-mouth kissing is believed to be very low. Unless either partners have large open sores in their mouth, or severely bleeding gums, there is no transmission risk from mouth-to-mouth kissing (Avert.org, 2005a:4).

The first possible case of HIV transmission through kissing (Watson & Witkin, 1997:87) is when a woman became infected with the AIDS virus between June 1994 and July 1995. The woman and her HIV-positive partner told researchers that they always used condoms during sex. But they also regularly engaged in "deep kissing" after the man had brushed and flossed – which, because of his gum disease, left enough blood in his mouth to infect the woman (Strauss, 1997:89).

2.4.3.5 Biting

The Centers for Disease Control and Prevention (CDC) found only two cases in which HIV was transmitted through biting since the onset of the AIDS epidemic. In October 1995, the CDC and Florida health officials reported that a female prostitute, Naomi Morrison, transmitted HIV to a 91-year-old man by biting him during a robbery attempt in West Palm Beach. The other case was reported in the August 1987 issue of the Lancet. Two adult sisters had a violent fight in which several of the HIV-positive sister's teeth were knocked out. Bloodied, she then bit her HIV-negative sister, who contracted the virus (Anon, 1996:5).

A bite from and HIV-seropositive individual (Pretty *et al.*, 1999:232) that breaks the skin or is associated with a previous injury carries a risk of infection for the bitten individual. Biting is not a common way of transmitting HIV. In fact, there are numerous reports of bites that did not result in HIV infection (CDC, 2003c:3).

2.4.3.6 Tattooing

According to the CDC (2003c:3) there are no known instances of HIV transmission through tattooing or body piercing, although hepatitis B virus has been transmitted during some of these practices. One case of HIV transmission from acupuncture has been documented. The authors of a New England Journal of Medicine article, about the transmission of HIV via acupuncture needles, Vittecoq *et al.* (1989:250) wrote that their patient might have exposed himself through sexual intercourse or by using drugs. However, they wrote that physicians experienced in AIDS-patient care carefully questioned him.

They did not claim acupuncture was the definite cause of HIV infection, but instead reported the case to draw attention to the possible route of HIV infection in some countries where adequate sterilisation is not practiced. They wrote that they agreed that acupuncture poses no risk of infection when performed with adequately sterilised needles. However, they claimed that acupuncture as a route of HIV infection, demonstrates the need for studies aimed at providing or disproving a link between acupuncture and HIV transmission (Vittecoq *et al.*, 1989:250).

To reduce the risk of infections such as hepatitis and HIV, ensure that the razor/instruments used are new or have been properly sterilised. People who carry out body piercing or tattoos should follow procedures called "universal precautions" which are designed to prevent the transmission of hepatitis or HIV (Brown *et al.*, 2003:9).

Universal precautions are a set of guidelines designed to protect both workers and their customers from HIV and other blood-borne illnesses such as hepatitis. The guidelines state that any instrument designed to penetrate the skin such as tattoo or acupuncture needles either should be used only once and discarded, or should be thoroughly cleaned and sterilised after each use (Brown *et al.*, 2003:9).

2.4.3.7 Insects

From the very beginning of the HIV epidemic there has been concern that biting or bloodsucking insects, including mosquitoes, may spread infection. However, there is no evidence to show that transfer of HIV by mosquitoes occurs, and theoretical, epidemiological and clinical evidence highlight the lack of risk. For example, if mosquitoes could transmit HIV, the pattern of reported HIV and AIDS cases would be very different to that actually seen, and many more young children would be expected to be infected (Macnair, 2004:443).

Blood feeding insects can transmit viruses in two ways (Mohlenbrock, 1991:54), mechanically and biologically. With mechanical transmission, infected blood on the insect's mouthparts might be carried to another host while the blood is still fresh and the virus alive. Infection by this means is possible but highly unlikely, because mosquitoes seldom have fresh blood on the outside of their mouthparts. Thus, the risk of mechanical spread of HIV is neglible, for several reasons. The piercing structure, or fascicle, of the mosquito contains two channels. Saliva is injected down into the victim through one, while blood is sucked up through the other. So blood only flows in one direction, into the mosquito, and is not regurgitated out or flushed into the next person at the next feed (Macnair, 2004:443).

With biological transmission, the pathogen must complete a portion of its cycle within the carrier, or vector, species. The HIV virus does not replicate or develop in the mosquito; once in the insect's gut, the virus quickly dies (Mohlenbrock, 1991:54).

2.5 THE STAGES OF HIV DISEASE

Most doctors have adopted the term "HIV Disease" to cover the entire HIV spectrum, from initial infection to full-blown AIDS (which can also be called "Advanced HIV Disease"). The time that it takes for each individual person to go through these stages of HIV disease varies. For most people, however, the process of HIV disease is fairly slow, taking several years from infection to the development of severe immunodeficiency (San Francisco AIDS Foundation, 1998:1).

Signs of infection with HIV are

- rapid weight loss;
- dry cough;
- recurring fever or profuse night sweats;
- profound and unexplained fatigue;
- swollen lymph glands in the armpits, groin, or neck;
- diarrhoea that lasts for more than a week;
- white spots or unusual blemishes on the tongue, in the mouth, or in the throat;
- pneumonia;
- red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids; and
- memory loss, depression, and other neurological disorders (CDC, 2003a:1).

People with HIV are considered to be infectious immediately after infection with the virus. The level of infectivity varies over time depending on the stage of the disease in which the person is. A person with HIV is infectious at all times. A person does not need to have symptoms or look sick to have HIV. People may look perfectly healthy for many years despite the fact that they have HIV in their bodies (San Francisco AIDS Foundation, 1998:1).

HIV progression can generally be broken down into four distinct stages; primary infection, clinically asymptomatic stage, symptomatic HIV infection, and advanced HIV infection (full-blown AIDS) (Avert.org, 2004:1).

2.5.1 Primary HIV infection

Primary HIV infection is the period of time between a person's first infection with HIV and when antibodies against the virus are produced by the body (usually 6 to 12 weeks) (San Francisco AIDS Foundation, 1998:2). It is often characterised by flu-like signs and symptoms like fever, sore throat, swollen glands and cough (University of Ottawa, 2005:1). These symptoms may also include fevers, chills, night sweats and rashes (San Francisco AIDS Foundation, 1998:2).

This flu-like illness (Avert.org, 2004:1) is sometimes referred to as "seroconversion". In up to about 20 per cent of people the symptoms are serious enough to consult a doctor, but the diagnosis is frequently missed. Time to seroconversion is around 21 to 90 days. During this stage there is a large amount of HIV in the peripheral blood and the immune system begins to respond to the virus by producing HIV antibodies and cytotoxic lymphocytes. The tests that are used to diagnose HIV detect the presence of antibodies in the blood. HIV tests can therefore be negative if they are done before the body has had enough time to produce enough antibodies for the test to detect. This is why there is a 3-month period necessary between the time of transmission and the time the test is done, for the test to be accurate (so called "window-period") (University of Ottawa, 2005:1).

Most HIV specialists believe that early HAART is useful *(refer to section 2.7.2.2)*, and that its benefits are likely to outweigh the disadvantages of no treatment (San Francisco AIDS Foundation, 1998:2).

2.5.2 Clinically asymptomatic stage

This stage lasts for an average of ten years and as its name suggests, is free from any symptoms, although there may be swollen glands. The level of HIV in the peripheral blood drops to very low levels but people remain infectious and HIV antibodies are detectable in the blood. HIV is not dormant during this

stage, but is very active in the lymph nodes. Large amounts of T-helper cells are infected and die. A large amount of virus can be produced (Avert.org, 2004:1).

Starting treatment against HIV prolongs this stage so that people live longer and healthier (University of Ottawa, 2005:1).

2.5.3 Symptomatic HIV infection

The virus appears to slowly damage the immune system for a number of years after infection. In most people, however, a faster decline of the immune system occurs at some point, and the virus rapidly replicates (San Francisco AIDS Foundation, 1998:3).

Over time the immune system loses the struggle to contain HIV. Three of the main reasons for this are the following:

- The lymph nodes and tissues become damaged or 'burnt out' because of the years of activity.
- HIV mutates and becomes more pathogenic leading to more T-helper cell destruction.
- The body fails to keep up with replacing the T-helper cells that are lost (Avert.org, 2004:2).

As the immune system fails (Avert.org, 2004:2), symptoms develop. Initially many of the symptoms are mild, but as the immune system deteriorates the symptoms worsen. Mild symptoms include skin rashes, fatigue, slight weight loss, night sweats, thrush in the mouth, and so on. Most, though not all, will experience mild symptoms such as these before developing more serious illnesses. It is generally believed that it takes the average person five to seven years to experience the (or his/her) first mild symptom. These symptoms are not specific to AIDS. They should be of concern to people who have tested positive to HIV. Usually, the symptoms occur when the virus has already caused considerable damage to the immune system (San Francisco AIDS Foundation, 1998:4).

Symptomatic HIV infection is mainly caused by the emergence of opportunistic infections and cancers that the immune system would prevent normally. These can occur in almost all the body systems, but common examples are featured in the table below (Avert.org, 2004:2).

Symptomatic HIV infection is often characterised by multi-system disease, as table 2.1 indicates. Treatment for the specific infection or cancer is often carried out, but the underlying cause is the action of

HIV as it erodes the immune system. Unless HIV itself can be slowed down the symptoms of immune suppression will continue to worsen (Avert.org, 2004:2).

Table 2.1 Multi-system disease (Avert.org, 2004:2)

System	Examples of infection/cancer
Respiratory system	*Pneumocystis Carinii* Pneumonia (PCP) Tuberculosis (TB) Kaposi's Sarcoma (KS)
Gastro-intestinal system	Cryptosporidiosis Candida Cytomegalovirus (CMV) Isosporiasis Kaposi's Sarcoma (KS)
Central/peripheral nervous System	HIV Cytomegalovirus (CMV) Toxoplasmosis Cryptococcosis Non Hodgkin's lymphoma Varicella Zoster Herpes simplex
Skin	Herpes simplex Kaposi's Sarcoma (KS) Varicella Zoster

2.5.4 Advanced HIV infection (Full-blown AIDS)

As the immune system becomes more and more damaged the illnesses that present become more and more severe leading eventually to an AIDS diagnosis. At present in the United Kingdom an AIDS diagnosis is confirmed if a person with HIV develops one or more of a specific number of severe opportunistic infections or cancers. However, people can still be very ill with HIV but not have an AIDS diagnosis (Avert.org, 2004:2).

2.5.5 World Health Organisation staging system

In resource-poor countries and communities, sometimes medical facilities and testing is unavailable, and it is not possible to decide the appropriate time to begin treatment on the basis of test results. The World Health Organisation has developed a disease staging system for HIV infection, which is not dependent on testing (Avert.org, 2004:3).

Table 2.2 indicates the WHO staging system for HIV infection and disease in adults and adolescents.

Table 2.2 WHO staging system for HIV infection and disease in adults and adolescents (WHO, 2003a:61)

Clinical Stage I
1. Asymptomatic
2. Persistent generalized lymphadenopathy
3. Acute retroviral infection (seroconversion illness)
Performance scale 1: asymptomatic, normal activity
Clinical Stage II
4. Weight loss < 10% of body weight
5. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
6. Herpes zoster within the last five years
7. Recurrent upper respiratory tract infections (e.g. bacterial sinusitis)
And/or performance scale 2: symptomatic, normal activity
Clinical Stage III
8. Weight loss < 10% of body weight
9. Unexplained chronic diarrhoea > 1 month
10. Unexplained prolonged fever (intermittent or constant) > 1 month
11. Oral candidiasis
12. Oral hairy leucoplakia
13. Pulmonary tuberculosis
14. Severe bacterial infections (e.g. pneumonia, pyomyositis)
15. Vulvovaginal candidiasis > 1 month or poor response to therapy
And/or performance scale 3: bedridden < 50% of the day during last month
Clinical Stage IV
16. HIV wasting syndrome *
17. *Pneumocystis carinii* pneumonia (PCP)
18. CENTRAL NERVOUS SYSTEM toxoplasmosis
19. Cryptosporidiosis with diarrhoea > 1 month
20. Isosporiasis with diarrhoea
21. Cryptococcosis, extrapulmonary
22. Cytomegalovirus infection other than liver, spleen or lymph node (e.g. retinitis)
23. Herpes simplex virus infection, mucocutaneous (>1month) or visceral
24. Progressive multifocal leucoencephalopathy
25. Disseminated mycosis (e.g. histoplasmosis, coccidiomycosis)
26. Candidiasis of oesophagus, trachea, bronchi
27. Atypical mycobacteriosis, disseminated or pulmonary
28. Non-typhoid Salmonella septicaemia
29. Extrapulmonary tuberculosis
30. Lymphoma
31. Kaposi's sarcoma (KS)
32. HIV encephalopathy **
33. Invasive cervical carcinoma
And/or performance scale 4: bedridden > 50% of the day during last month

* HIV wasting syndrome: weight loss of > 10% of body weight, plus either unexplained chronic diarrhoea (> 1 month) or chronic weakness and unexplained prolonged fever (> 1 month).

** HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

Table 2.3 the modified WHO clinical staging system for paediatric HIV and AIDS classification.

Table 2.3 Modified WHO clinical staging system for paediatric HIV and AIDS classification* (DOH, 2004b:80)

Clinical Stage I
1. Symptomatic
2. Generalised lymphadenopathy
3. Hepatomegaly
4. Splenomegaly
5. Paromegaly
6. Chronic suppurative OM
7. Eczema/seborrhoeic dermatitis
Clinical Stage II
8. Unexplained chronic diarrhoea (≥2 weeks)
9. Failure to thrive - 60 to 80% expected body weight - Not responding to nutritional rehabilitation or anti-TB therapy (if clinically indicated). Other correctable causes excluded.
10. Recurrent or severe bacterial infection (≥2 episodes pneumonia or 1 episode meningitis)
11. Oral candidiasis beyond neonatal period - Severe persistent or recurrent, not responding to topical therapy
12. Haematological - Thrombocytopenia (platelet count < 40 000 X 109/1) not responding to prednisone 2mg/kg/day after 2 weeks - Neutropenia (neutrophil count < 500 X 109/1) not responding to switch from co-trimoxazole to dapsone
13. Severe lymphoid interstitial pneumonitis: - Persistent hypoxia <90% in the absence of acute infection and/or - Persistent tachypnoea in the absence of acute infection and/or - Easy fatigability on exertion and/or - Evidence of bronchiectasis and/or - Cor pulmonale
14. ≥2 episodes zoster or severe herpetic disease
Clinical Stage III
15. Sever failure to thrive - <60% expected body weight - Not responding to nutritional rehabilitation or TB therapy if clinically indicated
16. Encephalopathy
17. Recurrent septicaemia (≥2 episodes)
18. Bronchiectasis
19. Cardiomyopathy
20. Progressive nephropathy
21. Candidiasis (oesophageal or pulmonary)
22. Disseminated fungal infection (Coccidioidomycosis, Cryptococcosis, Histoplasmosis)
23. Disseminated mycobacterial infection (M. tuberculosis, BCG, avium-intracellulare, Kansasii)
24. CMV disease with onset at age > 1 month (at site other than lymph nodes, spleen, liver)
25. HSV causing mucocutaneous ulcer persisting > 1 month, or oesophagitis, pneumonitis, oesophagitis in a child older > 1 month
26. *Pneumocystis carinii* Pneumonia (PCP)
27. Progressive multifocal leukoencephalopathy
28. Cerebral toxoplasmosis with onset > 1 month of age
29. Recurrent/persistent salmonella
30. Malignancies

* The South African national paediatric HIV consensus team has modified the original WHO clinical staging guidelines for practical reasons.

2.6 OPPORTUNISTIC INFECTIONS ASSOCIATED WITH HIV/AIDS

HIV does not kill anybody directly. Instead, it weakens the body's ability to fight diseases. Infections, which are rarely seen in those with normal immune systems, are deadly to those with HIV. People with HIV can get many infections (called opportunistic infections). Although many of these illnesses are very serious, and they need to be treated, some can be prevented (AEGIS, 2001:1).

Figure 2.3 indicates the areas where the different opportunistic infections present.

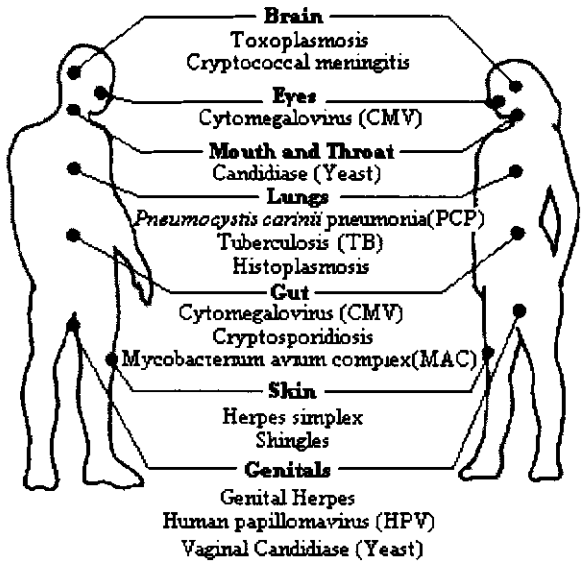


Figure 2.3 Opportunistic Infections (AEGIS, 2001:1)

2.6.1 Bacterial and mycobacterial

2.6.1.1 Mycobacterium Avium Complex (MAC)

Atypical mycobacterium species are less virulent than *mycobacterium tuberculosis*; a defect in local or systemic host defence is usually a pre-condition for disease. MAC – the closely related species of *M. avium* and *M. intracellulare* – accounts for most of these diseases. Disseminated MAC disease is emerging in importance in patients with AIDS (Beers & Berkow, 1999:1204).

It is a bacterium commonly found in human saliva (Jennings, 1996:11). The mode of transmission for MAC infection is thought to be through inhalation, ingestion, or inoculation through respiratory or gastrointestinal tract portals of entry (Benson *et al.*, 2004:22).

Most cases of MAC disease occur among persons with CD4 positive T-lymphocyte counts less than 50 cells/μL. Other factors associated with increased susceptibility to MAC disease are high plasma HIV-1 RNA levels (>100 000 copies/mL), previous opportunistic infections [particularly cytomegalovirus (CMV) disease], previous colonisation of the respiratory or gastrointestinal tract with MAC, and reduced in vitro lymphoproliferative immune response to *M. avium* antigens, possible reflecting defects in T-cell repertoire (Benson *et al.*, 2004:22).

Azithromycin 600 mg, when given in combination with ethambutol, is an effective agent for the treatment of disseminated MAC in HIV-infected patients (Dunne *et al.*, 2000:1250). Treatment for those cases of MAC-infection also includes ethambutol, rifabutin, ciprofloxacin, and levofloxacin (Benson *et al.*, 2004:23).

2.6.1.2 Salmonellosis

Salmonellae are a non-spore-forming, gram-negative rod from the family *Enterobacteriaceae*. *Salmonellae* cause diarrhoea (AEGIS, 2001:1). HIV-infected persons are more frequently infected with *Salmonellae* than are individuals not infected with HIV. *Salmonellae* are likely to be more severe, recurrent, or persistent and associated with extra-intestinal disease when they occur in HIV-infected persons (Angulo & Swerdlow, 1995:84).

As with non-HIV associated salmonellosis (Benson *et al.*, 2004:27), the probable source of *Salmonellae* infection is contaminated food or water from one person to another, and are devastating to individuals with compromised immune systems (Guerrant *et al.*, 2001:331).

The three major clinical syndromes of salmonellosis among patients with HIV-1 infection include a self-limited gastroenteritis; a more severe and prolonged diarrhoeal disease, associated with fever, bloody diarrhoea, and weight loss; and *Salmonellae* septicaemia, which might present with or without gastrointestinal symptoms (Benson *et al.*, 2004:28).

The "Danger Zone" for HIV-patients with salmonellosis is for any CD4 positive count. Individuals infected with HIV should be informed of their increased risk of acquiring these diseases and should be counselled on the recommended precautions (Angulo & Swerdlow, 1995:84). The initial treatment of choice for *Salmonellae* infection is a fluoroquinolone (Guerrant *et al.*, 2001:343). Treatment for salmonellosis in HIV-infected persons includes ciprofloxacin, ampicillin, chloramphenicol and trimethoprim/sulfamethoxazole (TMP/SMX). Maintenance therapy is with ciprofloxacin (AEGIS, 2001:1).

2.6.1.3 Syphilis and Neurosyphilis

Treponema pallidum, a spirochetal bacterium, is the etiologic agent of syphilis and is spread through contact with infectious lesions or body fluids (Golden *et al.*, 2003:1510). HIV-1 infection appears to alter the diagnosis, natural history, management, and outcome of *T. pallidum* infection (Musher *et al.*, 1990:872).

Syphilis and neurosyphilis are sexually transmitted diseases that have three stages:

1. Primary syphilis symptoms: painless lesions (chancre) at the site of infection (usually penis, vulva, or vagina). These sores heal in about a month or less.
2. Secondary syphilis symptoms: rash (condyloma lata, lymphadenopathy), fever.
3. Late syphilis: lesions on internal organs, especially the brain and heart (AEGIS, 2001:1).

Among HIV-uninfected persons, primary syphilis commonly presents as a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, among HIV-infected persons, multiple or atypical chancres occur, and primary lesions might be absent or missed (Benson *et al.*, 2004:31).

Management of HIV-1 infected patients with syphilis is similar to the management of HIV-uninfected persons with the disease (Workowski & Levine, 2002:19). All patients with syphilis, regardless of disease stage or HIV-status should be evaluated for clinical evidence of central nervous system or ocular involvement. HIV-1 infected persons with early-stage (i.e., primary, secondary, or latent) syphilis should receive a single intramuscular injection of benzathine penicillin G. Alternative therapies include oral doxycycline, ceftriaxone and azithromycin (Benson *et al.*, 2004:33).

2.6.1.4 Tuberculosis (TB)

TB is the most common opportunistic infection in people with AIDS and it is the leading killer of people with AIDS (Sriram *et al.*, 2004:5865). TB is caused by *Mycobacterium tuberculosis*, a bacterium and a non-opportunistic infection found in non-HIV-infected people. TB may reflect socio-economic status rather than being an opportunistic infection due to AIDS. Infection may occur prior to HIV infection, as a damaged immune system is not required to catch TB (Jennings, 1996:12).

TB is usually transmitted when a person with active TB coughs or sneezes or talks, releasing microscopic particles into the air. These particles contain live tubercle bacilli, and may result in infection when

inhaled by another person. Once infected by TB, most people remain healthy and develop only latent infection. People with latent infection are neither sick nor infectious. However, they do have the potential to become sick and infectious with active TB (AEGIS, 2001:1).

TB disease occurs among HIV-1 infected persons at all CD4 positive T-lymphocyte counts (Benson *et al.*, 2004:33). Active TB may be an independent marker of advanced immunosuppression in HIV-infected patients, and may also act as a cofactor to accelerate the clinical course of HIV infection (Whalen *et al.*, 1995:129). With CD4 positive T-lymphocyte counts more than 350 cells/μL, HIV-1 related TB appears like TB among HIV-uninfected persons (Benson *et al.*, 2004:16).

Of particular concern for people with AIDS is multi-drug-resistant TB (MDR-TB). MDR-TB occurs when patients fail to take their TB medicine for the prolonged periods necessary to destroy all parts of the TB organism and it becomes resistant to the drugs. These resistant organisms can be spread to other people. Even with treatment, for individuals co-infected with HIV and MDR-TB, the death rate may be as high as 80 per cent, as opposed to 40 to 60 per cent for people with MDR-TB only. The time from diagnosis to death for some patients with HIV and MDR-TB may be only months as they are sometimes left with no treatment options. Symptoms include cough, fever, night sweats, weight loss and fatigue (AEGIS, 2001:1).

Ensuring cure the first time round can prevent resistance. The effectiveness of preventive therapy in persons exposed to MDR-TB bacteria is not known. Treatment is often required for a period of two or more years. The cure rate is only between 30 to 50 per cent. All close contacts should be screened for signs and symptoms of MDR-TB and by sputum sampling to detect early disease. Side-effects of TB drugs are more pronounced in HIV/AIDS patients (DOH, 2003b:220).

Treatment of TB usually includes multiple drugs (AEGIS, 2001:1) like isoniazid, rifampin, pyrazinamide and ethambutol (or streptomycin). Treatment should be given five times per week in both the intensive and continuation phases. In special circumstances, treatment may be given three times per week in the continuation phase, provided it is properly supervised (DOH 2003b:221).

Refer to section 2.7.2.4.2 and *section 2.7.2.5.5* on treatment of concomitant TB in adults and in children in South Africa according to the national antiretroviral guidelines.

Table 2.4 indicates the different fixed dose drug combinations available in South Africa. The fixed-dose combinations reflected here represent the current international recommendations.

Table 2.4 Fixed dose drug combination available (DOH, 2003b:221)

Adults		Children	
Rifampicin/ Isoniazid	150, 75 mg	Rifampicin/ Isoniazid	60, 30 mg
Rifampicin/ Isoniazid	150, 150 mg	Rifampicin/ Isoniazid	60, 60 mg
Rifampicin/ Isoniazid	300, 150 mg	Rifampicin/ Isoniazid/ Pyrazinamide	60, 30, 150 mg
Rifampicin/ Isoniazid/ Pyrazinamid/ Ethambutol	150, 75, 400, 275 mg		

2.6.1.5 Bacillary angiomatosis

Bartonella-associated infections occur in immunocompetent and immunocompromised patients. The spectrum of disease caused by *Bartonella* species includes cat-scratch disease, bacillary angiomatosis, bacillary peliosis, bacteremia, endocarditis, and trench fever. Bartonella-associated infections are caused by *Bartonella henselae* or *Bartonella Quintana* (Spach & Koehler, 1998:137).

Although bacillary angiomatosis is rare in people with intact immune systems, it can be fatal in people with HIV infection. They can occur anywhere on the body in numbers ranging from one to hundreds but are rarely seen on the palms, soles, or in the mouth. High fever is usually present and the infection can spread to the bone, bone marrow, spleen, lymph nodes and liver (AEGIS, 2001:1).

Antibiotics such as erythromycin and doxycycline have been used successfully to treat HIV-positive patients with bacillary angiomatosis and are considered as first-line treatment (Spach & Koehler, 1998:137).

2.6.2 Fungal infections

2.6.2.1 Aspergillosis

Aspergillosis, most frequently caused by *aspergillus fumigatus* (Benson *et al.*, 2004:42) but occasionally by other a*spergillus* species, was more common before the advent of potent antiretroviral treatment among patients with advanced HIV-1 disease. Specific risk factors for aspergillosis include neutropenia, low CD4 positive T-lymphocyte count, use of corticosteroids, exposure to broad-spectrum antibacterial therapy, and previous pneumonia or other underlying lung disease (Holding *et al.*, 2000:1253).

Two major syndromes have been described among patients with AIDS: respiratory tract disease (either semi-invasive pseudomembranous tracheitis or invasive pneumonitis) and central nervous system

infection occurring as a febrile diffuse meningoencephalitis syndrome with vascular infarction as a central feature (based on the predilection of *aspergillus* organisms to invade blood vessel walls). Semi-invasive pseudomembranous tracheitis is associated with fever, cough, dyspnoea, and stridor or wheezing. Invasive pneumonitis occurs with fever, cough, dyspnoea, chest pain, haemoptysis, and hypoxemia (Benson *et al.*, 2004:43).

Patients who have had HIV-1 associated aspergillosis diagnosed typically have extremely low CD4 positive T-lymphocyte counts (i.e., lower than 50 cells/μL), a history of other AIDS-defining opportunistic infections, and are not receiving antiretroviral treatment. The recommended treatment for invasive aspergillosis is voriconazole. Amphotericin B, either conventional or lipid formulations, is an alternative regimen (Benson *et al.*, 2004:42).

2.6.2.2 Candidiasis (thrush, yeast infection)

According to Benson *et al.* (2004:35) candidiasis is a fungus infection caused by *Candida albicans*. Candida is the most common HIV-related fungus infection. Candida is common to skin, mouth, vagina, and gastrointestinal tract of humans (Jennings, 1996:11).

In AIDS patients it usually takes the oral form: white spots or patches on lateral sides of tongue, perhaps inside mouth on mucous membranes of cheeks; commonly lodges under nailbeds and skin around armpits, groin, and rectum. It sometimes affects the lungs. Frequently, it is the first clinical sign of HIV infection (Jennings, 1996:11).

Oral candidiasis should be treated with gentian violet, 0.5 per cent (aqueous solution) applied to the inside of the mouth three times daily, continued for 48 hours after cure. In infants, oral candidiasis should be treated with nystatin suspension, oral, 100 000 IU/mL, 0.5 mL after each feed. Keep nystatin in contact with affected areas for as long as possible. In adults with oral candidiasis, antifungal lozenges (troches) should be sucked 6 hourly for 5 days. In severe cases or if the above treatment fails in adults and children, imidazole oral gel should be applied twice daily for 10 days (DOH, 2003b:12).

Oral fluconazole is as effective and, in certain studies superior to topical therapy and is more convenient and generally better tolerated (Rex *et al.*, 2000:669). Treatment for oesophageal candidiasis includes oral fluconazole, 3-6 mg/kg per day as a single daily dose for 21 days (DOH, 2003b:334) or ketoconazole or itraconazole. Treatment for vaginal candidiasis includes over-the-counter antifungal remedies, clotrimazole or miconazole (AEGIS, 2001:1).

2.6.2.3 Coccidioidomycosis

The fungus, *Coccidioides immitis*, causes coccidioidomycosis. It is an acute benign asymptomatic or self-limited respiratory infection. Increased risk is associated with extensive exposure to disturbed soil. Both localised pneumonia and disseminated infection are usually observed in those with CD4 positive T-lymphocyte counts less than 250 cells/μL. The use of antiretroviral treatment appears to have reduced the incidence in this patient population (Benson *et al.*, 2004:41).

The two most common clinical presentations of coccidioidomycosis are disseminated disease and meningitis. Disseminated disease is associated with generalised lymphadenopathy, skin nodules or ulcers, peritonitis, liver abnormalities, and bone and joint involvement. Localised meningeal disease results in symptoms or lethargy, fever, headache, nausea or vomiting, or confusion and occurs in approximately 10 per cent of patients (Benson *et al.*, 2004:41)

Symptoms include low-grade fever, anorexia, weight loss, and weakness. Extensive pulmonary involvement may cause progressive cyanosis, dyspnoea, and discharge of mucopurulent or bloody sputum. Extrapulmonary lesions are usually focal, involving one or more tissue sites in bones, joints, skin, subcutaneous tissues, viscera, brain, or meninges. Draining sinus tracts sometimes connect deeper lesions to the skin. Localised extrapulmonary lesions often become chronic and recur frequently, sometimes long after completion of seemingly successful antifungal therapy (Edwards, 2005:2).

Amphotericin B is often selected for treatment of patients with respiratory failure due to *C. immitis* or rapidly progressive coccidioidal infections (Galgiani *et al.*, 2000a:658). Therapy with amphotericin B should continue until clinical improvement is observed, which usually occurs after administration of 500 to 1 000 mg. Certain specialists would use an azole antifungal concurrently with amphotericin B. Fluconazole or itraconazole might be appropriate alternatives for patients with mild disease (Galgiani *et al.*, 2000b:676).

Coccidioidal meningitis should be treated with fluconazole (Galgiani *et al.*, 1993:33), which has been reported to be successful in approximately 79 per cent of patients with *C. immitis* meningitis. Treatment for patients with meningeal diseases requires consultation with a specialtist. Intrathecal amphotericin B is the most accepted alternative but is toxic (Benson *et al.*, 2004:42).

2.6.2.4 Cryptococcal Meningitis (Cryptococcosis)

Virtually all HIV-1 associated cryptococcal infections are caused by *Cryptococcus neoformans* (Mirza *et al.*, 2003:789); a fungus found in pigeon manure and is common among humans and other mammals, especially cats. It causes pneumonia in rare instances, but mostly causes meningitis (inflammation of the spinal cord and brain membranes) (Jennings, 1996:11). The majority of cases of infection are observed among patients who have CD4 positive T-lymphocyte counts less than 50 cells/μL (Benson *et al.*, 2004:37).

Cryptococcosis among patients with AIDS most commonly occurs as a subacute meningitis or meningoencephalitis with fever, malaise, and headache (Powerdly, 1999:400). Classic meningeal symptoms and signs (e.g., neck stiffness or photophobia) occur in approximately one fourth to one third of patients. Certain patients might present with encephalopathic symptoms (e.g., lethargy, altered mentation, personality changes, and memory loss). Disseminated disease is a common manifestation, with or without concurrent meningitis. Approximately half of patients with disseminated disease have evidence of pulmonary rather than meningeal involvement. Symptoms and signs of pulmonary infection include cough or dyspnoea and abnormal chest radiographs. Skin lesions might be observed (Benson *et al.*, 2004:38).

Untreated cryptococcal meningitis is fatal. The choice of treatment for disease caused by *C. neoformans* (Saag *et al.*, 2000:710) depends on both the anatomic sites of involvement and the host's immune status. For immunocompetent hosts with isolated pulmonary disease, indicated treatment is fluconazole. For those individuals who are unable to tolerate fluconazole, itraconazole is an acceptable alternative. For patients with more severe disease, treatment with amphotericin B may be necessary for 6 to 10 weeks. For otherwise healthy hosts with central nervous system disease, standard therapy consists of amphotericin B plus flucytosine. An alternative to this regimen is amphotericin B plus flycytosine for a 2-week duration followed by fluconazole for a minimum of 10 weeks (Van der Horst *et al.*, 1997:20).

2.6.2.5 *Histoplasmosis*

According to Kauffman (2000:487) *Histoplasma capsulatum*, a dimorphic fungus that exists as a mold in the environment and as yeast in tissues is the cause of histoplasmosis. Histoplasmosis occurs in 2 to 5 per cent of patients with AIDS who reside in areas in the United States where the disease is endemic and who are not receiving antiretroviral treatment (Karimi *et al.*, 2002:1655).

Histoplasmosis is acquired by inhalation of microconida of the mycelial phase of the organism, but reactivation of latent infection might be a mechanism for disease in certain patients. Disseminated

histoplasmosis usually occurs among persons with CD4 positive T-lymphocyte counts less than 150 cells/μL; localised pulmonary histoplasmosis might occur among persons with CD4 positive T-lymphocyte counts more than 300 cells/μL. The incidence of histoplasmosis appears to have declined with the use of potent antiretroviral treatment (Benson *et al.*, 2004:40).

The most common clinical presentation of histoplasmosis among patients with AIDS is disseminated multi-organ disease (Benson *et al.*, 2004:40). Fever and weight loss are the most common symptoms, and hepatomegaly or splenomegaly are common physical findings of disseminated histoplasmosis (Wheat *et al.*, 2000:689). Symptoms and signs might be limited to the respiratory tract for those with higher CD4 positive T lymphocyte counts and localised pulmonary histoplasmosis. Septic shock syndrome occurs in less than 10 per cent of patients. Central nervous system, gastrointestinal, and cutaneous manifestations each occur in less than 10 per cent of cases, and other sites might be less commonly involved (Benson *et al.*, 2004:40).

Patients with severe disseminated histoplasmosis should be treated with intravenous amphotericin B, either the deoxycholate formulation or liposomal amphotericin B (Wheat *et al.*, 2000:690). In a randomised clinical trial, liposomal amphotericin B was more effective than the standard deoxycholate formulation, inducing a more rapid and more complete response, lowering mortality, and reducing toxicity (Johnson *et al.*, 2002:105). Itraconazole, 200 mg daily, is effective in preventing relapse of disseminated histoplasmosis in patients with AIDS (Hecht *et al.*, 1997:100). Fluconazole, 800 mg daily, is less effective than itraconazole, but is recommended as an alternative if patients cannot tolerate itraconazole (Kauffman 2000:489). Ketoconazole is also effective for the treatment of histoplasmosis (Saag & Dismukes, 1988:848).

2.6.3 Malignancies

2.6.3.1 Human Herpesvirus-8 disease (HHV-8)

HHV-8 (Benson *et al.*, 2004:52), a transmissible DNA virus is associated with all forms of Kaposi's sarcoma (i.e., classic, endemic, transplant-related, and AIDS-related), and certain rare neoplastic disorders (e.g., primary effusion lymphoma and multicentric Castleman disease). Patients who are HHV-8 seropositive and have HHV-8 DNA in their peripheral blood have a greatly enhanced risk for experiencing Kaposi's sarcoma compared with HHV-8 seropositive men without HHV-8 DNA in their blood (Lennette *et al.*, 1996:858).

The overall incidence of Kaposi's sarcoma was as high as 20 per cent among patients with AIDS before the advent of effective antiretroviral treatment. However, even before the widespread use of antiretroviral

treatment, the incidence had declined, which certain specialists attribute to the use of ganciclovir, foscarnet, and cidofovir for the acute and maintenance treatment of CMV disease (Cannon *et al.*, 1999:4786).

Studies indicate that patients receiving ganciclovir or foscarnet (but no acyclovir) have a reduced rate for developing Kaposi's sarcoma (Glesby *et al.*, 1996:1477). Anecdotal reports exist of lesion regression among patients who have been treated with potent antiretroviral treatment, and despite the lack of precise epidemiologic studies, the incidence of Kaposi's sarcoma has declined dramatically after the introduction of protease inhibitor drugs and antiretroviral treatment. Primary effucion lymphoma and multicenter Castleman disease remain rare (Benson *et al.*, 2004:52).

Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman disease are described most frequently among HIV-1 infected persons with more advanced immunosuppression (CD4 positive T-lymphocyte counts less than 200 cells/μL), although they can occur at any CD4 positive T-lymphocyte count. Although ganciclovir, foscarnet, and cidofovir have *in vitro* activity against HHV-8, and limited studies indicate these agents might be associated with reduced disease progression or lesion regression, larger and more definite studies are needed to determine whether antiviral therapy has a useful role in managing HHV-8 associated diseases. Potent antiretroviral treatment that suppresses HIV-1 replication reduces the frequency of occurrence of Kaposi's sarcoma among HIV-1 infected persons and should be considered for all persons who qualify for such therapy (Benson *et al.*, 2004:52).

2.6.3.2 Lymphoma

Infection with HIV is associated with an increased risk of systemic and primary central nervous system Non-Hodgkin's lymphoma (Sparano, 1995:442).

2.6.3.2.1 Systemic Non-Hodgkin's Lymphoma (NHL)

NHL has been reported in patients with HIV infection, particularly in patients with a history of intravenous drug use, and it is more likely to present with advanced-stage disease and unfavourable histology (Sparano, 1995:442). NHL is frequently associated with Epstein-Barr virus (EBV), a herpesvirus that infects B-lymphocytes and stimulates their proliferation. EBV genomes can be detected in about 50 per cent of AIDS-related lymphomas. Some cytokines such as interleukin 6 (IL-6), IL-10 and tumor necrosis factor (TNF), which enhance HIV-replication and are elevated during HIV-infection, are known to induce B-cell differentiation and may also be a factor in the development of NHL (HIVpositive.com, 2005a:1).

Patients with systemic non-Hodgkin's lymphoma usually present with high- or intermediate-grade histology and extranodal dissemination (Sparano, 1995:442). Common extra-nodal sites of AIDS NHL include the central nervous system, bone marrow, gastrointestinal tract, meninges, and liver. Less common sites include the mouth, rectum, heart and pericardium, and common bile duct. NHL should be considered in patients presenting with a mass lesion at any site. Symptoms include enlarged spleen, hepatic obstruction, rectal pain, cardiac arrhythmia, unexplained gastrointestinal symptoms or gastrointestinal bleeding. Constitutional symptoms include elevated fever, unexplained weight loss, and night sweats. EBV sequences are consistently found in primary central nervous system lymphomas. This suggests that EBV might have a role as a marker in its diagnosis (HIVpositive.com, 2005a:1).

The "Danger zone" for NHL in HIV-positive patients is possible at any CD4 positive range, but it is more likely in those with CD4 positive counts less than 200 cells/μL (AEGIS, 2001:1). The incidence has not changed with the introduction of HAART for HIV despite improved data for other opportunistic infections cancers, particularly KS. Combination chemotherapy is the optimal treatment for AIDS associated NHL as patients usually have disseminated disease and extranodal involvement at presentation. Unfortunately, it was recognised early in the epidemic that most patients did not tolerate standard lymphoma chemotherapy well owing to the immunosuppression from HIV and for many patients with adverse prognostic factors the life expectancy was very short (Powles *et al.*, 2000:338).

Patients with the major adverse prognostic factors (low CD4-cell count, poor performance status, and previous AIDS defining illness) are treated with palliative intent using mild chemotherapy and/or radiotherapy (Powles *et al.*, 2000:338). Use of either myeloid growth factors or reduced-dosage chemotherapeutic regimens can reduce the morbidity associated with chemotherapy (Sandler & Kaplan, 1996:1111).

The concomitant use of ARV drugs with chemotherapy is generally acceptable practice with the exception of zidovudine, which significantly adds to the myelosuppression of combination chemotherapy, and didanosine, which may worsen the peripheral neuropathy caused by vinca alkaloids (Powles *et al.*, 2000:339). A wide range of HAART appears protective against NHL and that is probably achieved by maintaining adequate CD4 and CD8 T-lymphocyte counts (Stebbing *et al.*, 2004:2182).

2.6.3.2.2 Primary Central Nervous System (CNS) Lymphoma

Primary CNS lymphoma that has not spread to other parts of the body, is found in the brain and/or spine (Quade, 2005:1). Primary CNS lymphoma usually occurs in patients with more profound immunosuppression and is associated with a dismal prognosis (Sparano, 1995:442). Untreated, the

survival rate of patients with AIDS-related primary CNS lymphoma is less than 2 months. The increased incidence of concurrent systemic and central nervous system infections (cytomegalovirus, varicella zoster virus, progressive multifocal leukoencephalopathy) in AIDS patients with central nervous system lymphoma may indicate that viral infections are somehow linked to the pathogenesis of central nervous system lymphoma in the immunocompromised patient (HIVpositive.com, 2005a:1).

Treatment is critical for patients with primary CNS lymphoma. Treatment for primary CNS lymphoma is more successful for patients who are able to walk, are younger than 60 years old, and who do not have AIDS or other disorders of the immune system. When the tumour continues to grow, it usually does not spread beyond the central nervous system or the eye (Quade, 2005:1).

The "Danger zone" for Primary CNS Lymphoma in HIV-positive patients is possible at any CD4 positive range, but it is more likely in those with CD4 positive counts less than 200 cells/μL (AEGIS, 2001:1).

There are three types of treatments used for patients with primary CNS lymphoma:

- Surgery
- Radiation therapy
- Chemotherapy (Quade, 2005:1).

Large dose whole-brain radiation is the preferred method of treatment in patients with AIDS-related primary CNS lymphoma. Corticosteroids such as dexamethasone may be introduced to the treatment plan producing further shrinkage of oedema and tumour. Although radiation often results in complete remission (20 to 50 per cent), relapse is likely and the overall prognosis is poor. The aim of radiotherapy may not be towards greater survival time but rather an improvement of the quality of life. The role of chemotherapy (both systemic and intrathecal) prior to and following whole-brain radiation therapy is under investigation; this approach has produced improved results in patients with primary CNS lymphoma unrelated to HIV infection (HIVpositive.com, 2005:1).

2.6.4 Protozoal Infections

2.6.4.1 Cryptosporidiosis

Cryptosporidiosis is caused by *Cryptosporidium* species, a group of protozoan parasites that infect the small bowel mucosa, and in immunosuppressed persons, the large bowel and extraintestinal sites. The

three most common species infecting humans are *C. hominis*, *C. parvum*, and *C. meleagridis* (Benson *et al.*, 2004:12).

Many minor, non-life-threatening outbreaks occur in day-care centres. In AIDS patients, it may be the major cause of mortality (Jennings, 1996:11). Infection by *C. parvum* was frequent, with an incidence estimated to be approximately 1 per 100 patient-years in patients with CD4-cell counts less than 200 cells/μL (Le Moing *et al.*, 1998:1395).

Those at greatest risk for disease are patients with advanced immunosuppression (i.e., CD4 positive T-lymphocyte counts of generally less than 100 cells/μL or less than 180 cells/μL). Antiretroviral treatment with immune restoration (an increase of CD4 positive T-lymphocyte count to more than 200 cells/μL) is associated with complete resolution of cryptosporidiosis (Carr *et al.*, 1998:256), and all patients with cryptosporidiosis should be offered antiretroviral treatment as part of the initial management of their infection. Treatment of persons with cryptosporidiosis should include symptomatic treatment of diarrhoea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route is important (Benson *et al.*, 2004:13).

2.6.4.2 Isosporiasis

Isosporiasis is a disease caused by the protozoan *Isospora belli* (Grossman, 2003:1). Infection results from the ingestion of sporulated oocysts in contaminated food or water (Benson *et al.*, 2004:73). The organism infects the lining of the small intestine and can cause severe diarrhoea and malabsorption. Outbreaks of isosporiasis can be traced to water contaminated with faeces (Grossman, 2003:1).

People with compromised immune systems, usually people with a CD4 positive T-lymphoscyte count below 150, may experience prolonged and severe bouts of diarrhoea and malabsorption that can be difficult to treat. It is also important to note that not all people exposed to *I. belli*, even if their immune systems are suppressed, experience symptoms of the infection (Grossman, 2003:1).

The most common clinical manifestation of the disease is diarrhoea, which in patients with AIDS can be similar to that observed with cholera and associated with severe dehydration. Blood is not present in the faeces. Systemic symptoms of fever, headache, malaise, abdominal pain, vomiting, and weight loss are also common. Infection primarily involves the small intestine. Colitis is not generally observed (Benson *et al.*, 2004:73).

Fluid support (Benson *et al.*, 2004:73) should be offered if the diarrhoea has resulted in dehydration. Malnutrition and wasting should be treated with nutritional supplementation. The drug choice for therapy is trimethoprim (160 mg) and sulfamethoxazole (800 mg) administered four times a day for 10 days. If recurrence occurs, it can subsequently be prevented by ongoing prophylaxis with either trimethoprim-sulfamethoxazole or sulfadoxine-pyrimethamine (Pape *et al.*, 1989:1044).

2.6.4.3 Microsporidiosis

The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon (Septata) intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropopthera*, *Pleistophora* species, *P. ronneeafyi*, *Vittaforma (Nosema) corneae*, *Microsporidium* species, *Nosema ocularum*, *brachiola (Nosema) connori*, *Brachiola vesicularum*, and *Brachiola (Nosema) algerae* (Mathis, 2000:795).

The organism infects the lining of the small intestine and can cause gastrointestinal tract infection with severe diarrhoea and malabsorption (Grossman, 2002:1). There have also been reports of microsporidiosis of the lungs. Encephalitis, ocular infection, sinusitis, myositis, and disseminated infection are also described (Kotler & Orenstein, 1998:321).

In the pre-antiretroviral treatment era, reported prevalence rates of microsporidiosis varied between 2 per cent and 70 per cent among HIV-1 infected patients with diarrhoea. The incidence of microsporidiosis has declined dramatically with the widespread use of effective antiretroviral treatment. In the immunosuppressed host, microsporidiosis is most commonly observed when the CD4 positive T-lymphocyte count is less than 100 cells/μL (Benson *et al.*, 2004:14).

Not all people exposed to microsporidia, even if their immune systems are suppressed, experience symptoms of the infection (Grossman, 2002:1). A CD4-cell count greater than 100 cells/μL seems to be adequate for the complete remission of *E.intestinalis* (Lafaurie *et al.*, 2003:640). *E.intestinalis* responds well to albendazole, while no antiparasitic therapy has documented efficacy in *E.bieneusi* infections (Kotler & Orenstein, 1998:321). Itraconazole also might be useful in disseminated disease when combined with albendazole especially in infections caused by *Trachipleistophora* or *Brachiola* (Benson *et al.*, 2004:15).

2.6.4.4 Pneumocystis Jiroveci Pneumonia (PCP)

Pneumocystis jiroveci pneumonia (PCP) is caused by *Pneumocystis jiroveci*, a ubiquitous organism classified as a fungus but sharing biologic characteristics with protozoa. The taxonomy of the organism has been changed; *Pneumocystis carinii* now refers only to the pneumocystis that infects rodents, and *Pneumocystis jiroveci* refers to the distinct species that infects humans. The abbreviation PCP is still used to designate *Pneumocystis* pneumonia (Benson *et al.*, 2004:6).

PCP infects the lungs. Previous to AIDS it has been found in kidney transplant patients whose immune system had been chemically suppressed. It occurs in 60 to 80 per cent of AIDS patients. It has initially been responsible for 30 to 50 per cent of deaths among AIDS patients, now brought under better control due to chemical prophylaxis that is, chemically treating the patient before symptoms occur (Jennings, 1996:10). Symptoms of patients with PCP include subacute onset of exertional dyspnoea, fever, non-productive cough, and chest discomfort (Selwyn *et al.*, 1998:888).

Incidence of PCP has declined substantially with widespread use of prophylaxis and effective antiretroviral treatment; recent incidence rates among patients with AIDS in Western Europe and the United States are 2 to 3 cases per 100 person-years (Furrer *et al.*, 1999:1301). The majority of cases occur among patients who are unaware of their HIV-1 infection or are not receiving ongoing HIV care (Lundberg *et al.*, 2000:2563) or among those with advanced immunosuppression (CD4 positive T-lymphocyte counts of less than 100 cells/μL) (Wolff & O'Donnell, 2001:1890).

Approximately 90 per cent of cases occurred among patients with CD4 positive T-lymphocyte counts of less than 200/μL (Benson *et al.*, 2004:43). TMP/SMX is the treatment of choice (Hughes *et al.*, 1993:1521). Alternative therapeutic regimens include TMP/dapsone for mild-to-moderate disease (Medina *et al.*, 1990:776), primaquine plus clindamycin (Toma *et al.*, 1998:524; Smego *et al.*, 2001:1529), and atovaquone suspension (Hughes *et al.*, 1993:1521).

2.6.4.5 Toxoplasmosis

Toxoplasmosis is caused by the organism *Toxoplasmosa gondii* and infects blood and many tissues. It is common to humans, and many domestic and wild animals. Humans may contract it from droppings of cats and undercooked meat, especially mutton. In AIDS patients it has the tendency to infect tissues of central nervous system (brain and nerves) and also to cause pneumonia and hepatitis inflammation or dysfunction of the liver. Many minor, non-life-threatening outbreaks occur in day-care centres. In AIDS patients, it can be a major cause of mortality (Jennings, 1996:10).

Clinical disease is rare among patients with CD4 positive T-lymphocyte counts less than 200 cells/μL. The greatest risk is among patients with a CD4 positive T-lymphocyte count less than 50 cells/μL (Pueyo *et al.*, 1997:459). The initial therapy of choice consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin (Luft *et al.*, 1993:996). The preferred alternative regimen for patients unable to tolerate or who fail to respond to first-line therapy is pytimethamine plus clindamycin plus leucovorin (Katlama *et al.*, 1996:268). Pyrimethamine plus sulfadiazine with leucovorin is the preferred therapy (Benson *et al.*, 2004:10).

2.6.5 Viral infections

2.6.5.1 Cytomegalovirus (CMV)

CMV is a double-stranded DNA virus in the herpes virus family that might reactivate to cause disseminated or localised end-organ disease among patients with advanced immunosuppression who have been previously infected with CMV. The majority of infections derive from reactivation of latent infection (Benson *et al.*, 2004:43).

Before potent antiretroviral treatment, an estimated 30 per cent of patients with AIDS experienced CMV retinitis some time between the diagnosis of AIDS and death (Jabs *et al.*, 2002:49). Incidence for new cases of CMV end-organ disease reached less than 2 to 3 cases per 100 person-years; for those with established CMV retinitis, recurrences continue at a rate estimated at less than 25 per cent of the peak during the mid-1990s (Benson *et al.*, 2004:44).

CMV occurs among persons with advanced immunosuppression, typically those with CD4 positive T-lymphocyte counts less than 50 cells/μL, who are either not receiving or have failed to respond to antiretroviral treatment. Other risk factors include previous opportunistic infections, particularly mycobacterium avium complex (MAC) disease, and high plasma HIV-1 RNA levels (>100 000 copies/mL) (Jabs *et al.*, 2002:49).

Retinitis is the most common clinical manifestation of CMV end-organ disease (Benson *et al.*, 2004:44). CMV retinitis usually occurs as unilateral disease, but in the absence of therapy, viremic dissemination results in bilateral disease in the majority of patients. Peripheral retinitis might be asymptomatic or present with floaters, scotoma, or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula are associated with decreased visual acuity or central field defects. The characteristic ophthalmologic appearance of CMV lesions includes perivascular fluffy yellow-white retinal infiltrates, typically described as a focal necrotising retinitis, with or without intraretinal haemorrhage, and with little inflammation of the vitreous unless immune recovery with potent

antiretroviral treatment intervenes (Jabs *et al.*, 2002:48). Blood vessels near the lesions might appear to be sheathed. Occasionally, the lesions might have a more granular appearance (Benson *et al.*, 2004:44).

CMV neurologic disease causes dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy (Arribas *et al.*, 1996:582). CMV is suspected in promoting appearance of Kaposi's sarcoma (Jennings, 1996:11). Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, intravenous cidofovir and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis (Musch *et al.*, 1997:83; Martin *et* al., 1999:1063; Martin *et al.*, 2002:1119)

2.6.5.2 Epstein-Barr virus (EBV)

Epstein-Barr infection is caused by the EBV. EBV (McClain, 2001:351) is associated with some proliferative diseases in AIDS patients that fit in the classical connection of this virus with lymphoid tissue infections leading to lymphomas, infiltration of lung or gastrointestinal tissue. It is implicated in a number of autoimmune conditions (the body's immune system attacking itself, as sometimes occurs in advanced HIV infection). It is thought to disrupt T-cell function (Jennings, 1996:11).

In HIV-infected patients, it causes oral hairy leukoplakia, fuzzy white spots on the tongues, which do not rub off, as does "hairy tongue", caused by smoking. EBV possibly remains dormant until HIV infection occurs. Antiviral therapies are important since prophylactic use of acyclovir and other anti-EBV drugs can alter the incidence of EBV-associated neoplasms in AIDS patients (McClain, 2001:351).

2.6.5.3 Hepatitis

Hepatitis is caused by non-opportunistic hepatotrophic viruses including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and non-A, non-B, non-C hepatitis virus (HIVpositive.com, 2005a:1).

- Hepatitis A (HAV)

  Most cases of HAV are subclinical. The virus disappears following acute infection. HAV has no known carrier state and plays no role in the production of chronic active hepatitis or cirrhosis. Transmission is primarily through oral-faecal contact (HIVpositive.com, 2005a:1).

- Hepatitis B (HBV)

HBV (Bodsworth *et al.*, 1991:1138) is the leading cause of chronic liver disease worldwide (Lee, 1997:1733). HIV-1 infection is associated with an increased risk for the development of chronic hepatitis B after HBV exposure. Although certain patients are asymptomatic, symptoms of acute HBV infection include fatigue, right-upper-quadrant abdominal pain, nausea, vomiting, fever, and arthralgias followed by jaundice (Benson *et al.*, 2004:13).

- Hepatitis C (HCV)

The high rates of HCV, HBV, and HIV infections among short-term injectors emphasize the need to target both parenteral and sexual risk reduction interventions early (Garfein, 1996:655). Other potential modes of transmission of HCV include mother-to-child-transmission (MTCT), needlestick, or sexual transmission (Benson *et al.*, 2004:58). Factors that adversely influence disease progression among HCV/HIV-1 co-infected persons include older age, lower CD4 positive T-lymphocyte counts, and a history of alcoholism (Benhamou *et al.*, 1999:1054).

Acute hepatitis C is not often recognised because of a high rate of asymptomatic or mildly symptomatic presentation. A limited proportion (less than 20 per cent) of patients with acute infection have symptoms characteristic of acute hepatitis including low-grade fever, mild right-upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Liver transaminase might be elevated (Benson *et al.*, 2004:58).

Chronic hepatitis C is often asymptomatic, although complaints of fatigue are common. Serum cryoglobulins are present (60 per cent) but rarely (less than 5 per cent) cause symptomatic skin, renal, or neurologic manifestations. With progresson of liver disease, patients might experience stigmata of portal hypertension including spider angiomata, temporal wasting, splenomegaly, caput medusa, ascites, jaundice, pruritis, and encephalopathy. Small subsets of patients experience cutaneous manifestations including leukocytoclastic vasculitits and porhyria cutanea trarda (Benson *et al.*, 2004:58).

- Hepatitis D (HDV)

HDV can only replicate in the presence of HBV and occurs either as a co-infection with HBV or a superinfection in established HBV carriers. Clinically, HDV is a serious and often progressive disorder manifested by an unusually aggressive course (HIVpositive.com, 2005a:1).

Hepatitis is a threat to everyone on the planet, regardless of HIV serostatus or CD4 positive level (AEGIS, 2001:2). Alpha interferon 2b is approved for the treatment of chronic hepatitis in individuals who are not HIV-infected. Interferon 2b is typically administered by injection for either 16 weeks (HBV) or for 52 weeks (HCV). In HIV-infected individuals, studies of alpha interferon 2b and zidovudine have shown only limited response rates with high relapse rates for responders who discontinued treatment. Common side effects include flu-like symptoms that make long-term administration difficult. Lamivudine is under investigation for the treatment of chronic hepatitis B (HIVpositive.com, 2005a:1).

2.6.5.4 Herpes simplex virus (HSV)

Herpes is an infection caused by herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2). It primarily affects the mouth or genital area. HSV-1 is usually associated with infections of the lips, mouth, and face. HSV-2 is sexually transmitted and is usually associated with genital ulcers or sores (Levy, 2003:1).

In HIV-infected patients, herpes simplex infections form chronic ulcers, often affecting the face, sometimes the eyes and the anal area in homosexual males. Herpes infections are commonly found in people who are not infected with HIV; forming a cluster(s) of small, painful blisters, often, but not necessarily, on the face (Jennings, 1996:11).

Persons with AIDS who have CD4 positive T-lymphocyte counts less than 100 cells/μL may experience significant infections with HSV (Balfour *et al.*, 1994:254). Some cases are relatively mild and may not require treatment. In severe or prolonged cases, as well as in individuals who are immunosuppressed or who have frequent recurrences, antiviral medications such as acyclovir or its derivatives may be used (Levy, 2003:2). There are some strains of HSV that are resistant to acyclovir. In those cases, foscarnet is the only anti-HSV drug approved of use in the United States and should be continued for at least 10 days or until lesions are completely healed (Balfour *et al.*, 1994:254).

2.6.5.5 Varicella Zoster virus (VZV, shingles)

Up to 95 per cent of the adult population is seropositive for VZV, and recurrent disease in the form of herpes zoster occurs in 3 to 5 per cent of all adults but becomes more prevalent in the elderly and the immunocompromised host. The incidence of herpes zoster is 15 to 25 times greater in HIV-1 infected persons than in the general population and 3 to 7 times greater than among the elderly. Varicella Zoster among HIV-1 infected adults can occur at any CD4 positive T-lymphocyte count; more advanced immunosuppression might be associated with altered manifestations of VZV infection but does not appear to substantially alter the overall incidence of VZV (Benson *et al.*, 2004:50).

Clinicians have treated herpes zoster in HIV-infected patients with aciclovir, famciclovir or valaciclovir. Sorivudine is also an effective treatment for herpes zoster in HIV-infected individuals and results in accelerated cutaneous healing when compared with standard oral acyclovir therapy. Sorivudine has a simplified dosing regimen and is more convenient and may result in improved compliance among HIV-infected individuals (Gnann *et al.*, 1998:1145).

2.6.5.6 Human Papilloma Virus (HPV, genital warts, cervical cancer)

HPV infects the skin, often causing irregular cell growth or warts. There are more than 60 types of HPV. Some types of the virus are transmitted by nonsexual personal contact and cause common skin warts. Several types of HPV are spread by sex and primarily infect the genitals or anal area. Genital warts are the most common symptoms of HPV infection (King Country Public Health, 2004:1).

Frisch *et al.* (2000:1508) observed high incidences of anogenital cancers like HPV among patients with low CD4 positive counts and found no indication of a further increase in risk among patients with CD4 positive counts below 100 cells/μL compared with those having CD4 positive counts greater than or equal to 200 cells/μL. Persons who are HIV-1 infected, particularly those with lower CD4 positive T-lymphocyte counts are at even higher risk than those who are not HIV-infected. HIV positive women are 10 times more likely to have genital warts than HIV negative women. Women with CD4 positive counts less than 500 cells/μL have a high risk for developing HPV-related growths in the cervix. Treatment for HPV includes laser, freezing (cryotherapy), burning (electrocautery), cutting (excision), radiation, and chemotherapy (AEGIS, 2001:2).

2.6.5.7 Molluscum Contagiosum virus (MCV)

Molluscum contagiosum is a poxvirus (Davies *et al.*, 1999:2042), which commonly causes a self-limiting infection. MCV causes cutaneous skin growths that mainly affect children, sexually active adults, and immunocompromised individuals (Meadows *et al.*, 1997:987). In immunodeficient patients it can be severely disfiguring and intractable. Secondary bacterial infection is a common complication. About 10 to 20 per cent of people with symptomatic HIV infection develop M. *contagiosum* (AIDSMAP, 2004:2).

Standard treatment of *M. contagiosum* consists of measures to remove the lesions by spraying each lesion with liquid nitrogen spray every one to two weeks. Removing the hard core appears to be essential for effective treatment. It is important to use some anti-bacterial ointment to prevent bacterial infection of the lesions. The anti-acne drugs, tretinoin or isotretinoin can help. These drugs reduce the production of natural skin oils, encouraging the top layer to dry out and peel (AIDSMAP, 2004:2).

There is no proven specific antiviral therapy and the efficacy of immunomodulatory therapies including alpha and beta-interferons has been limited. Cidofovir is an antiviral agent with a broad range of activity against the herpes group of viruses, poxviruses, and retroviruses (De Clercq, 1997:295). It has been reported to produce resolution of *M. contagiosum* lesions in three patients with AIDS; two of whom were being treated with the drug primarily for cytomegalovirus retinitis (Meadows *et al.*, 1997:987). In the third it was found to be of benefit when used topically – the advantage of this route of administration being the avoidance of potentially serious nephrotoxicity when the drug is given systemically (Davies *et al.*, 1999:2042).

2.6.5.8 Oral Hairy Leukoplakia (OHL)

OHL has been associated with the Epstein-Barr Virus (EBV) and with the Human Papilloma Virus (HPV). The accepted consensus criteria for definitive diagnosis of OHL are demonstration of EBV in the lesion tissue in the presence of characteristic histologic features (Chattopadhyay *et al.*, 2005:44). The clinical significance of OHL in otherwise healthy, asymptomatic individuals is that it can be an early manifestation of HIV infection. While lesions usually appear on the lateral borders of the tongue, it can also appear on the buccal and labial mucosa. The lesions of OHL are corrugated or have a shaggy or "hairy" appearance (HIVpositive.com, 2005a:1).

The "Danger zone" for OHL is possible at any CD4 positive range, but it is more likely in those with CD4 positive counts less than 200 cells/mm. Treatment includes acyclovir or topical podophyllin resin (AEGIS, 2001:2).

2.6.5.9 Progressive Multifocal Leukoencephalopathy (PML)

PML is an AIDS-defining disease caused by the JC polyoma virus. The JC virus is a ubiquitous polyoma virus; the name is derived from the initials of the first patient from whom the virus was isolated. The majority of humans are infected early in life, and 70 per cent of adults have detectable serum antibodies (Benson *et al.*, 2004:53).

PML is characterised by cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, hemiparesis or quadriparesis, and eventually coma. No effective therapy for JC virus exists. Randomised clinical trials have evaluated vidarabine and cidofovir; neither is effective in producing clinical improvement and neither is recommended (Marra *et al.*, 2002:1791). When antiretroviral treatment is initiated and CD4 positive T-lymphocyte counts rise, certain patients will experience neurologic improvement and others might become neurologically stable. However, reports have documented patients experiencing worse neurologic manifestations after initiation of antiretroviral treatment. In

certain instances, an immune reconstitution syndrome *(refer to section 2.7.2.4.1)* causes this worsening; other cases represent the natural history of PML (Benson *et al.*, 2004:54).

2.6.6 Neurological conditions

2.6.6.1 AIDS Dementia Complex (ADC)

ADC may represent more than one type of disease process. A decreased concentration and rapidity of thought, loss of interest in activities, and slowness of motor movements characterise it. The link between HIV infection in the brain or in the body and this neurological condition still remains uncertain. While it its clear that patients severely affected by this disorder have HIV-infected macrophages within the brain, those with milder disease have not been shown to have active virus infection within the brain (HIVpositive.com, 2005a:1).

The "Danger zone" for ADC can happen at any CD4 positive level but is more common in those with CD4 positive counts less than 200 cells/mm. Zidovudine is effective in treating and preventing HIV activity in the brain (AEGIS, 2001:2).

2.6.6.2 Peripheral Neuropathy

Two types of neuropathy are common in HIV infection. The first type, subacute and chronic demyelinating polyneuropathies is uncommon and occurs relatively early in HIV infection, before susceptibility to major opportunistic infections. A second type, predominantly sensory axonal polyneuropathy, develops as a late complication in up to 30 per cent of people with AIDS. The first is felt to have an autoimmune pathogenesis. Like subacute (Guillain-Barré syndrome) or chronic idiopathic demyelinating polyneuropathy (CIPD), which develops in non-HIV infected persons, it responds favourably to plasma exchange, intravenous immunoglobulin (IVIG) or glucocorticoids, with the former being the currently recommended treatment (HIVpositive.com, 2005a:1).

The major morbidity of axonal predominantly sensory polyneuropathy relates to pain and to the fact that patients may have to stop neurotoxic antiretroviral drugs (i.e., didanosine, zalcitabine and stavudine). In some cases, painful burning or tingling may be so severe that the patient avoids shoes or bedclothes (HIVpositive.com, 2005a:1).

There is no "Danger zone" or CD4 positive range associated with peripheral neuropathy. Because it can be an adverse reaction to common anti-HIV drugs, peripheral neuropathy can happen to anyone taking those drugs. The drugs most commonly associated with this condition are didanosine, zalcitabine,

stavudine. Less common are lamivudine and zidovudine. Some reports indicate that HIV itself sometimes causes peripheral neuropathy. Other factors that can cause or aggravate peripheral neuropathy are diabetes and alcoholism (AEGIS, 2001:2).

Treatment for drug-induced neuropathy includes taking acetyl-carnitine (AEGIS, 2001). The mainstay is amitriptiline or other tricyclic antidepressants initiated at low doses. For patients with lancinating brief bursts of pain, phenytoin, carbamazepine, and topical capsaicin can also be tried (HIVpositive.com, 2005a:1).

2.6.7 Other conditions and complications

2.6.7.1 Apthous Ulcers

MacPhail *et al.* (1992:283) stated that oral and genital ulcers resembling recurrent aphthous ulcers (RAUs) in HIV-positive patients are being reported with increasing frequency. RAUs are commonly diagnosed in two forms. The first form of RAUs is a large, painful necrotic ulcer. The aetiology of RAUs remains unknown, however a number of factors have been cited including stress, infectious agents, and circulating growth factors (TNF). RAUs are commonly reported as adverse events of treatment with zalcitabine. Most commonly, the tongue and mucosal membranes of the oral cavity and oesophagus are the sites of infection (HIVpositive.com, 2005a:1).

The "Danger zone" is for CD4 positive rates less than 100 cells/mm. Treatment includes topical corticosteroids like fluocinonide and dexamethasone in treating minor RAUs. Prednisone is commonly prescribed for larger ulcerations (HIVpositive.com, 2005). Thalidomide has been reported recently as an effective treatment for RAUs (AEGIS, 2001:2).

2.6.7.2 Malabsorption

Malabsorption is fairly common with advanced AIDS, but is not an opportunistic infection (AEGIS, 2001:2). Malabsorption is impaired uptake of nutrients from the intestines. Nutrients are normally absorbed from food in the intestines by cells that make up the finger-like villi lining the intestinal wall. Certain disease processes, including HIV infection can cause the villi to become atrophied and shortened. This cell malfunction results in impaired absorption of nutrients (HIVpositive.com, 2005a:1).

Diarrhoea occurs at some point in the clinical course of most people with AIDS or HIV infection. It may occur early on or in end-stage infection, and may be sporadic or continuous (HIVpositive.com, 2005a:1).

The "Danger zone" for malabsorption is not associated with CD4 positive level. This condition is often associated with

- cryptosporidiosis;
- the HIV virus itself;
- a vitamin B-12 deficiency; and
- folic acid deficiency (AEGIS, 2001:2).

2.6.7.3 Lymphadenopathy

Lymphadenopathy is a mild form of HIV infection, generally characterised by unexplained fever, difficulty in swallowing, swollen glands, fatigue or lethargy, night sweats and chills, apathy, gradual loss of weight, diarrhoea, sore throat or impotence (Jennings, 1996:9).

Lymphadenopathy means "disease of the lymphatic system." The lymphatic system is a vital part of the body's immune system. One of the key signs of lymphadenopathy is swollen lymph glands. Any infection, such as flu, causes the lymph nodes to swell, but nodal swelling due to normal infections passes quickly. With HIV infection, this nodal swelling may persist for months, with no other signs of a temporary infectious disease (Jennings, 1996:9).

2.6.8 Treatment of opportunistic infections in patients with AIDS

Treatment of most major opportunistic infections in patients with AIDS consists of acute treatment, followed by suppressive therapy (or secondary prophylaxis) to prevent recurrences. Secondary prophylaxis is not routinely recommended for relatively minor infections, such as herpes simplex ulcers or oesophageal candidiasis, as resistance may occur and prophylaxis is expensive (Gibbon, 2003:320).

Primary prophylaxis with co-trimoxazole (trimethoprim 80 mg/sulfamethoxazole 400 mg or trimethoprim 160 mg/sulfamethoxazole 800 mg) daily is indicated for all patients with clinical evidence of significant immune suppression (WHO clinical stage 3 or 4) or on laboratory assessment (CD4 positive lymphocyte count less than 200 cells/μL or total lymphocyte count less than 1,25 $x10^9$/L). Alternative regimens for treatment and for secondary prophylaxis are given because patients with HIV infection are often intolerant to drugs (Gibbon, 2003:320).

2.7 TREATMENT OF HIV/AIDS

Despite the efforts of many clinical investigators, the optimal treatment for HIV-1 infection is not known (Shafer & Vuitton, 1999:73). The best long-term hope for controlling the AIDS epidemic worldwide is the development of safe, effective and affordable preventive HIV vaccines (NIAID, 2005:2). Many antiretroviral drug combinations have not yet been studied and, of those drug combinations that have been studied, most have been studied for short periods of time (usually less than one year) (Shafer & Vuitton, 1999:73).

2.7.1 Vaccines

Vaccines stimulate the body's immune system to provide protection against infection or disease. Vaccines against HIV are being developed, and they are in various stages of clinical trials, but at present none has proved to be effective (WHO, 2005:1).

Currently, over 74 HIV vaccine candidates are reported to be in research and development or preclinical testing in animals (NIAID, 2002:121). Since 1987, at least 34 different HIV candidate vaccines have begun phase I trials, and only a few have progressed to phase II trials (Gilbert *et al.*, 2003:179). Only VaxGen AIDS product, AIDSVAX, a recombinant *gp120* subunit vaccine, advanced to phase III trials, but it failed (McCarthy, 2003:755).

HIV vaccines currently being tested in humans are made from man-made materials that cannot cause HIV infection, because they do not contain HIV (NIAID, 2005:1).

The following statements illustrate the necessity and importance of conducting research to find an effective vaccine:

- The availability of a safe, highly effective and accessible preventive HIV vaccine would be a valuable complement to other preventive interventions, significantly contributing to the interruption of the chain of transmission of HIV.
- Well-conceived HIV immunisation strategies could reach populations where other interventions are not sufficiently effective.
- Research on preventive HIV vaccines is providing new information on the possible use of vaccines as therapeutic interventions, to be used in association with antiretroviral therapies, which could lead to a lowering in the cost of the treatments and to an increase on their long-term efficacy (WHO, 2005:1).

2.7.1.1 Preventive versus therapeutic HIV/AIDS vaccines

Preventive HIV/AIDS vaccines currently under development are given to HIV negative people and are designed to prevent infection and control the spread of HIV, not to cure AIDS. Multiple HIV/AIDS vaccines may be necessary to prevent infection or disease in the same way multiple drugs are needed to treat people already infected with HIV (NIAID, 2005:2).

The types of vaccines that are being studied to prevent HIV/AIDS are subunit vaccines, recombinant vector vaccines, and DNA vaccines (US DHHS, 2003:1).

Therapeutic vaccines currently under development are given to HIV positive people and are designed to improve the immune system (US DHHS, 2005:1) and to treat people with HIV infection or AIDS. While the same vaccine may be tested for both preventive and therapeutic effects, what works to prevent HIV infection may not necessarily work to treat people who are already infected with HIV (NIAID, 2005:2).

A given vaccine may be used either alone or in combination with another HIV/AIDS vaccine. One approach to HIV vaccination is called the prime-boost strategy, which combines two different types of HIV/AIDS vaccines. Administration of one type of HIV/AIDS vaccine (such as a recombinant vector vaccine) is followed by a second type of HIV/AIDS vaccine (such as a subunit vaccine). The goal of this approach is to stimulate different kinds of immune responses and enhance the body's overall immune response to HIV (US DHHS, 2003:1).

2.7.1.2 Challenges in developing HIV/AIDS vaccines

HIV continually mutates and recombines. This may mean that a vaccine would need to protect the person against many strains of the virus. Vaccines against other viruses have only had to protect the person against one or a limited number of strains. It is very difficult to design a vaccine that, to be effective, needs to activate the very cells that are infected by the virus (NIAID, 2003:1).

HIV can be transmitted as both free virus and in infected cells. This may mean that both arms of the immune system may need to be stimulated. Researchers do not know what constitutes an effective immune response to HIV. It might be antibodies, activated immune cells, perhaps a third immune response, or a combination of immune responses (NIAID, 2003:1).

Most attempts in developing HIV-1-vaccines have focused on inducing CD8 T-lymphocyte responses to viral structural proteins. New challenges in the design of novel approaches are faced, that target the generation of both CD4 and CD8 T-lymphocyte responses with broader specificities (Imami, 2004:461).

A potential obstacle to the successful development of an effective HIV vaccine is genetic variation (Huang *et al.*, 2004:198), specifically the envelope protein. The recombinant *gp120* molecule resembles the envelope protein molecule on the surface of HIV. Researchers are trying to create vaccines that more closely resemble the natural conformation of the HIV envelope on the virion surface (NIAID, 2002:122).

The long-term goal is to develop a vaccine that is 100 per cent effective and protects everyone from infection. However, even if a vaccine only protects some people, it could still have a major impact on controlling the epidemic. A partially effective vaccine could decrease the number of people who get infected with HIV; those people, in turn, would not pass the virus on to others. Even when an HIV/AIDS vaccine is developed, education and other prevention efforts will be needed so that people continue to practise safe behaviours (NIAID, 2005:1).

2.7.2 Antiretroviral treatment

Antiretroviral treatment programmes should be developed which can reach as many people as possible who are in need of therapy and require that antiretroviral treatment be standardised (WHO, 2004:11).

The goals of antiretroviral treatment for HIV infection should be to maintain immune function in as near a normal state as possible, prevent disease progression, prolong survival, preserve quality of life by effectively suppressing HIV replication (CDC, 2001:5), and suppression of viremia to less than detection limits (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:5).

Viral load reduction to below limits of detection in a treatment-naïve patient usually occurs within the first 16-24 weeks of therapy. However, maintenance of excellent treatment response is highly variable. Predictors of long-term virologic success include

- potency of the antiretroviral regimen;
- adherence to the treatment regimen;
- low baseline viremia;
- higher baseline CD4+ cell count; and

- rapid reduction of viremia in response to treatment (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:5).

For antiretroviral treatment to be effective, it is essential that the drugs in a treatment regimen be taken as scheduled to maximise oral bioavailability and intracellular drug levels. Treatment is expensive, complicated, and associated with multiple side effects. Drug side effects are more common than HIV-1 related symptoms in many HIV-1-infected individuals receiving antiretroviral treatment. Counselling is essential to maximise adherence to treatment and to decrease the risk of treatment failure and drug resistance (Shafer & Vuitton, 1999:75).

A high degree of medication adherence with all antiretroviral regimens is needed to prevent the selection of drug resistance. Short term, and even more concerning, longer-term toxicity may limit the duration of treatment needed in what can be seen as a chronic disease (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:2).

An initial regimen contains two Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI) and either a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or a ritonavir-boosted or unboosted Protease Inhibitor (PI) (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:2).

Certain drugs are similar, for example, lamivudine and emtricitabine, and they should not be combined. Others have additive or synergistic toxicity, such as stavudine with didanosine, and should generally be avoided. Others have intracellular interactions that decrease their antiviral activities, notably zidovudine with stavudine, and should thus be avoided (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:2).

Lachman (1991:195) stated that the recent advances and improvements in survival bring hope that AIDS will eventually be manageable as a chronic infection with HIV. The ideal drug for treating HIV must consider the chronicity of the infection. It must therefore be non-toxic and have a sufficiently long half-life to be taken orally. HIV/AIDS is now perceived as a manageable chronic illness rather than a plague (Palella *et al.*, 2003:620).

2.7.2.1 Antiretroviral drugs (ARV drugs)

There are 14 ARV drugs registered by the Medicines Control Council (MCC, 2004:1) of South Africa (SA) for the period 1989 to 2004. These drugs include the Nucleoside/Nucleotide Reverse Transcriptase

Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs) (see table 2.5).

Table 2.5 Registered ARV drugs in South Africa (MCC, 2004:1)

NRTI	NNRTI	PI
Abacavir	Efavirenz	Amprenavir
Didanosine	Nevirapine	Indinavir
Lamivudine		Lopinavir
Stavudine		Nelfinavir
Zalcitabine		Ritonavir
Zidovudine		Saquinavir

As of October 2003, 20 ARV drugs were approved by the United States Food and Drug Administration (US FDA, 2005:1), belonging to four classes, with which to design combination regimens containing at least three drugs. These four classes include the NRTIs, NNRTIs, PIs, and Fusion Inbibitors (FIs) (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:8).

Table 2.6 ARV drugs approved by the United States Food and Drug Administration (US FDA, 2005:1)

NRTI	NNRTI	PI	FI
Abacavir	Delavirdine	Amprenavir	Enfuvirtide
Didanosine	Efavirenz	Atazanavir	
Emtricitabine	Nevirapine	Fosamprenavir	
Lamivudine		Indinavir	
Stavudine		Lopinavir	
Tenofovir disoproxil fumarate		Nelfinavir	
Zidovudine		Ritonavir	
Zalcitabine		Saquinavir	

2.7.2.1.1 Nucleoside/NucleotideRreverse Transcriptase Inhibitors (NRTIs)

According to Stein *et al.* (2000:125) NRTIs act by incorporating themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new virus. Examples of NRTIs include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine and zalcitabine (US FDA, 2005:1).

When administered as single agents, the nucleoside analogues cause either weak or transient HIV-1 suppression. When administered in certain two-drug combinations their antiviral activity is significantly increased and prolonged. Even when used in two-drug combinations, complete HIV-1 suppression is rare and viral rebound towards baseline eventually occurs along with the development of drug resistance. There are four 2-drug nucleoside analogue combinations in widespread use: zidovudine plus lamivudine,

zidovudine plus didanosine, stavudine plus lamivudine, and stavudine plus didanosine (Shafer & Vuitton, 1999:75).

The following table (table 2.7) describes the different NRTIs approved by the U.S. FDA, their mechanism of action, and principal indication(s).

Table 2.7 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) currently available (adapted from De Clercq, 2004:115)

	Mechanism of action:	Principal indication(s):
Zidovudine (AZT)	Targeted at HIV reverse transcriptase, acts as chain terminator in the reverse transcriptase reaction, following intracellular phosphorylation to AZT 5'-triphosphate, and, after removal of the diphosphate group, incorporation of AZT 5'-monophosphate at the 3'-end of the viral DNA chain.	HIV infection, in combination with other anti-HIV agents (such as lamivudine and abacavir).
Didanosine (ddI)	Targeted at HIV reverse transcriptase, acts as chain terminator, following intracellular phosphorylation to 2',3'-dideoxyadenosine (ddA) 5'-triphosphate,and, after removal of the diphosphate group, incorporation of ddA 5'-monophosphate at the 3'-end of the viral DNA chain.	HIV infection, especially advanced HIV disease, in combination with other anti-HIV agents.
Zalcitabine (ddC)	Targeted at HIV reverse transcriptase, acts as chain terminator, following intracellular phosphorylation to ddC 5'-triphosphate, and, after removal of the diphosphate group, incorporation of ddC 5'-monophosphate at the 3'end of the viral DNA chain.	HIV infection, especially in adult patients with advanced HIV disease that are intolerant or unresponsive to zidovudine, in combination with other anti-HIV agents (not didanosine).
Stavudine (d4T)	Targeted at HIV reverse transcriptase, acts as chain terminator, following intracellular phosphorylation of d4T 5'-triphosphate, and, after removal of the diphosphate group, incorporation of d4T 5'-monophosphate at the 3'-end of the viral DNA chain.	HIV-infection, especially advanced HIV disease, in combination with other anti-HIV agents.
Lamivudine (3TC)	Targeted at HIV reverse transcriptase and HBV reverse transcriptase, acts as chain terminator, following intracellular phosphorylation to 3TC 5'-triphosphate,and, after removal of the diphosphate group, incorporation of 3TC 5'-monophosphate at the 3'-end of the viral DNA chain.	HIV and HBV infections; for HIV infection, in combination with other anti-HIV agents (such as zidovudine and abacavir).
Abacavir (ABC)	Targeted at HIV reverse transcriptase, acts as chain terminator, following intracellular phosphorylation and conversion (deamination) to the 5'-triphosphate of the corresponding guanosine analogue (carbovir), and, after removal of the diphosphate group, incorporation of carbovir 5'-monophosphate at the 3'-end of the viral DNA chain.	HIV infection, in combination with other anti-HIV agents, such as zidovudine and lamivudine.
Emtricitabine (FTC)	Similar to that of 3 TC.	HIV and HBV infections; has been recently approved for the treatment of HIV infections; is currently in Phase III clinical trials for the treatment of HBV infections; will likely be used (in the future) in combination with tenofovir disoproxil fumarate as a single tablet to be administered orally once daily.

Table 2.7 (continue) Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) currently available(adapted from De Clercq, 2004:115)

	Mechanism of action:	Principal indication(s):
Tenofovir Disoproxil Fumarate (TDF)	Serves as oral prodrug of tenofovir [PMPAP that is targeted at HIV reverse transcriptase (and HBV reverse transcriptase)], and acts as chain terminator, following intracellular phosphorylation to the diphosphate form, and after removal of the diphosphate group, incorportion at the 3'-end of the Viral DNA chain.	HIV infection(s) in combination with other anti-HIV agents such as lamivudine and efavirenz; should however, not be combined with the combination of lamivudine plus abacavir.

2.7.2.1.2 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

According to Stein *et al.* (2000:125) NNRTIs stop HIV production by binding directly onto the reverse transcriptase enzyme and preventing the conversion of RNA to DNA. Examples of NNRTIs include efavirenz, delavirdine and nevirapine (U.S. FDA, 2005:1).

The NNRTIs (CDC, 2001:11) should be used primarily in situations in which virus suppression is expected to be complete. Due to cross-resistance, there is currently no rationale for using a combination of two or more NNRTIs, and patients with HIV isolates developing drug resistance with one NNRTI are unlikely to obtain clinical benefit with other NNRTIs. In previously untreated patients, the combination of efavirenz with two nucleoside analogues has recently been shown to reduce plasma HIV levels to a degree comparable to that achieved with two nucleoside analogues in combination with a protease inhibitor (Shafer & Vuitton, 1999:78).

Nevirapine and efavirenz are administered once daily. Delavirdine must be administered three times daily. Because of autoinduction, nevirapine is started at 300mg/d and is increased to 400mg/d after two weeks (Shafer & Vuitton, 1999:77).

Nevirapine has a higher incidence of rash and a greater risk of hepatotoxicity than efavirenz. This makes the drug less suitable for treating patients who may be on other hepatotoxic medications, or that can cause rash, such as rifampicin (used for TB treatment). But efavirenz also has some major toxicity which are central nervous system related teratogenicity and rash. The central nervous system symptoms will often abate after ten to fourteen days (Kanabus, 2005:3).

Efavirenz is teratogenic (Shafer & Vuitton, 1999:77) and therefore contraindicated in pregnant women and developing children. If they decide to continue the pregnancy, efavirenz must be stopped, and nevirapine started (in their 1st trimester) *(refer to section 2.7.2.4.3)*. (DOH, 2004b:20).

The following table (table 2.8) describes the different NNRTIs approved by the U.S. FDA, their mechanism of action, and principal indication(s).

Table 2.8 Non-nucleoside reverse transcriptase inhibitors (NNRTIs) currently available (adapted from De Clercq, 2004:118)

	Mechanism of action:	Principal indication(s):
Nevirapine (NVP)	Targeted at an allosteric "pocket", nonsubstrate binding site of the HIV-1 reverse transcriptase binding.	HIV-1 infection, in combination with other anti-HIV agents, particularly NRTIs
Delavirdine (DLV)	Similar to that of nevirapine	HIV-1 infection, in combination with other anti-HIV agents (primarily NRTIs).
Efavirenz (EFV)	Similar to that of nevirapine.	HIV-1 infection, in combination with other anti-HIV agents (primarily NRTIs).

2.7.2.1.3 Protease inhibitors (PIs)

According to Stein *et al.* (2000:125) PIs work at the last stage of the viral replication cycle. PIs inhibit viral replication by preventing pieces of new virus from being assembled into a functional copy of the virus (Patchen & Beal, 2001:357) and released from the infected CD4 cells. Examples of PIs include amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (U.S. FDA, 2005:1).

Saquinavir is the most potent protease inhibitor *in vitro* but its *in vivo* activity is limited by poor intestinal absorption and extensive hepatic first-pass clearance. Because the PIs are already administered at close to their maximum tolerated dosages, it is not possible to overcome these bioavailability problems simply by increasing dosage levels. Moreover serum drug levels for most protease inhibitors are not routinely available (Shafer & Vuitton, 1999:78).

Table (table 2.9) describes the different PIs approved by the U.S. FDA, their mechanism of action, and principal indication(s).

Table 2.9 Protease Inhibitors (PIs) currently available (adapted from De Clercq, 2004:118)

	Mechanism of action:	Principal indication(s):
Saquinavir (SQV)	Transition-state, hydroxyethylene-based, peptidomimetic inhibitor of HIV protease.	HIV infection, in combination with other anti-HIV agents (NRTIs and some PIs (i.e. ritonavir)).
Ritonavir (RTV)	As for saquinavir	HIV infection, in combination with other anti-HIV agents (NRTIs and PIs) (i.e. saquinavir)).
Indinavir (IDV)	As for saquinavir	HIV infection, in combination with other anti-HIV agents (i.e. NRTIs).

Table 2.9 (continue) Protease Inhibitors (PIs) currently available (adapted from De Clercq, 2004:118)

	Mechanism of action:	Principal indication(s):
Nelfinavir (NFV)	As for saquinavir	HIV infection, in combination with other anti-HIV agents (i.e. NRTIs).
Amprenavir (APV)	As for saquinavir	HIV infection, in combination with other anti-HIV agents (i.e. NRTIs).
Lopinavir (LPV)	As for saquinavir	HIV infection, in combination with other anti-HIV agents (i.e. NRTIs).
Atazanavir (ATV)	As for saquinavir	HIV infection, in combination with other anti-HIV agents (i.e. NRTIs).

2.7.2.1.4 Fusion inhibitors (FIs)

Enfuvirtide is the first entry, or fusion inhibitor (Kempner, 2005:49) to be used in the treatment of HIV infection. Enfuvirtide blocks the virus replication cycle (Miller & Hazuda, 2004:89) by binding to gp41 and disrupts the conformational changes associated with virus-host-cell fusion (Matthews *et al.*, 2004:215). The only example of FIs thus far is enfuvirtide (U.S. FDA, 2005:2).

Enfuvirtide is prescribed as part of an antiretroviral therapy regimen (Kempner, 2005:49) and should not be used as monotherapy. Because of the complex protein structure of enfuvirtide, the drug must be injected subcutaneously in a twice-a-day regimen. The major complication is the development of injection-site reactions (ISRs), which occur in 98 per cent of patients at some time during therapy (Roberts, 2003:1). As with all antiretroviral therapy, adherence is a primary concern; and adherence rate of 95 per cent or better provides the best outcome (Kempner, 2005:49).

Table (table 2.10) describes the FIs approved by the U.S. FDA, their mechanism of action, and principal indication(s).

Table 2.10 Fusion inhibitors (FIs) currently available (adapted from De Clercq, 2004:122)

	Mechanism of action:	Principal indication(s):
Enfuvirtide (T20)	Inhibits virus-cell fusion, through a coil-coil interaction with its homologous region in *gp41*	HIV infection, in combination with other anti-HIV agents; has been recently approved for clinical use following demonstration of antiretroviral and immunologic benefit when added onto an optimised antiretroviral regimen.

2.7.2.2 Highly active antiretroviral therapy (HAART) regimens

The availability of more numerous and more potent drugs to inhibit HIV replication has made it possible to design therapeutic strategies involving combinations of antiretroviral drugs that accomplish prolonged and near complete suppression of detectable HIV replication in many HIV-infected persons (CDC, 2001:1).

HAART refers to a broad category of treatment regimens usually comprised of three or more antiretroviral drugs that, in previously untreated HIV-1 infected patients, are expected to reduce plasma virus levels below the limits of detection. In previously treated patients, the benefits of HAART are often significantly diminished. Not all HAART regimens are equally effective (Shafer & Vuitton, 1999:73).

Most HAART regimens include drugs from two of the three classes of drug therapy (NRTIs, NNRTIs and PIs). There is essentially no cross-resistance between drugs of different classes, and so the choice of drugs in one class generally does not affect the choice of drugs in another class. Clinical studies involving at least eight types of drug combinations have been reported, including combinations of (1) two nucleoside analogues and one protease inhibitor; (2) two nucleoside analogues plus one NNRTI; (3) two nucleoside analogues plus two protease inhibitors; (4) two nucleoside analogues plus one protease inhibitor plus one NNRTI; (5) one NNRTI plus one protease inhibitor; (6) two protease inhibitors; (7) three nucleoside analogues; and, (8) hydroxyurea-containing HAART regimens (Shafer & Vuitton, 1999:81).

Categories one and two contain the most commonly used HAART regimens for previously untreated persons. Categories three and four contain aggressive forms of HAART that have been used both as initial therapy for previously untreated patients and as salvage therapy for previously treated patients. It could be argued that the category three and four regimens are best suited for induction therapy, while category one and two regimens are best suited for maintenance therapy. Categories five, six, seven and eight are unorthodox forms of HAART that have so far only been studied in small groups of patients (Shafer & Vuitton, 1999:81).

Table 2.11 describes the different categories, drug classes and regimens of HAART.

Table 2.11 Categories and examples of HAART regimens (Shafer & Vuitton, 1999:81)

Categories:	Drug classes:	Regimens:
Standard		
1	2 NRTI + 1 PI	2 NRTI + Indinavir 2 NRTI + Ritonavir 2 NRTI + Nelfinavir
2	2 NRTI + NNRTI	2 NRTI + Efavirenz
Aggressive		
3	2 NRTI + dual PI	2 NRTI + Ritonavir + Saquinavir 2 NRTI + Nelfinavir + Saquinavir
4	2 NRTI + PI + NNRTI	2 NRTI + Nelfinavir + Efavirenz/Nevirapine 2 NRTI + Indinavir + Efavirenz/Nevirapine
Unorthodox		
5	3 NRTI	Zidovudine + Didanosine + Lamivudine Zidovudine + Lamivudine + Abacavir
6	2 PI	Ritonavir + Saquinavir
7	PI + NNRTI	Indinavir + Efavirenz
8	Hydroxyurea-containing HAART	Didanosine + Hydroxyurea + Indinavir

2.7.2.2.1 Adverse reactions of HAART

Treatment with HAART is not without complications. HAART is a collection of different medications, each with its own side effect profile. Some common side effects are nausea, headache, weakness, malaise, and fat accumulation on the back and abdomen ("buffalo hump," lipodystrophy). When used long-term, these medications may increase the risk of heart attack by affecting fat metabolism (Levy, 2004:4).

Any doctor prescribing HAART should carefully follow the patient for possible side effects associated with the combination of medications being taken. In addition, routine blood tests measuring CD4 counts and HIV viral load should be taken every three to four months. The goal is to get the CD4 count as close to normal as possible, and to suppress the HIV viral load to an undetectable level (Levy, 2004:4).

2.7.2.3 When to treat: indications for ARV therapy

In deciding when to initiate ARV therapy, physicians and their patients must balance the virological and immunological benefits of early treatment with the costs of drug therapy, the risk of drug side effects, and the risk of drug resistance if adherence is suboptimal (Shafer & Vuitton, 1999:80).

Initiation of therapy must be based on the fact that the types and numbers of available ARV drugs are limited. When more numerous, more effective, better tolerated, and more conveniently dosed drugs become available, it is likely that indications for initiation of therapy will change accordingly (CDC, 2001:7).

Treating patients with advanced HIV-1 infection is complicated by the need for additional drugs to prevent or treat opportunistic infections and is also associated with an increased risk of adverse reactions. Most treatment guidelines are based on the patient's stage of disease and commitment to long-term therapy. Given its theoretical benefits, antiretroviral treatment can be recommended for HIV-infected patients at all stages of the disease provided they are sufficiently motivated to adhere to therapy (Shafer & Vuitton, 1999:80).

One note of agreement by most researchers and doctors about when to start therapy is that it should be guided by looking at overall general health and measures of both CD4 positive cell counts and viral load (Project inform, 2004:4).

In patients with continued HIV-1 replication during therapy, it is essential to determine whether treatment efficacy has been compromised by decreased in vivo drug activity (non-adherence, pharmacologic factors) or by HIV-1 drug resistance. Decreased in vivo drug activity is often correctable by either improving adherence or by modifying therapy to increase drug bioavailability. Drug resistance is more difficult to manage because there is extensive cross-resistance[a] within each class of ARV drugs (Shafer & Vuitton, 1999:80).

[a] Sometimes a version is resistant to more than one drug. When this happens, the drugs are called "cross-resistant" (Kanabus, 2005:6).

Table 2.12 indicates recommendations for initiating antiretroviral treatment in adults and adolescents with documented HIV infection.

Table 2.12 Recommendations for initiating antiretroviral treatment in adults and adolescents with documented HIV infection (WHO, 2003a:10)

IF CD4 AVAILABLE: • **WHO Stage IV, irrespective of the CD4 cell count** • **WHO Stage III** (including but not restricted to HIV wasting, chronic diarrhoea of unknown aetiology, prolonged fever of unknown aetiology, pulmonary TB, recurrent invasive bacterial infections or recurrent or persistent mucosal candidiasis) **with consideration of using CD4 cell counts of less than 350/mm^3 to assist decision-making** [a] • **WHO Stage I or II with CD4 cell counts less than or equal to 200/mm^3** [b]
IF CD4 TEST UNAVAILABLE: • **WHO Stage IV, regardless of the total lymphocyte count** • **WHO Stage III** (including but not restricted to HIV wasting, chronic diarrhoea of unknown aetiology, prolonged fever of unknown aetiology, pulmonary TB, recurrent invasive bacterial infections or recurrent or persistent mucosal candidiasis) **irrespective of the total lymphocyte count** • **WHO Stage II with total lymphocyte count less than or equal to 1200/mm^3** [c]

[a] CD4 count is advisable to assist with determining need for immediate therapy. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non-HIV aetiologies (e.g. chronic diarrhoea, prolonged fever).

[b] The precise CD4 level above 200/mm^3 at which to start antiretroviral treatment has not been established.

[c] Total lymphocyte count of 1200/mm^3 can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms (Stage II or III) exist. It is not useful in the asymptomatic patient. In the absence of CD4 cell testing, asymptomatic HIV-infected patients (WHO Stage I) should not be treated because there is currently no other reliable marker available in resource-limited settings.

The DOH (2004b:3) recommends that initiation of antiretroviral treatment in adults and adolescents (including pregnant women) should start when one of the following are present (refer to table 2.13):

Table 2.13 Criteria for antiretroviral treatment initiation in adults and adolescents (DOH, 2004b:3)

- CD4 of less than 200 cells/mm^3 irrespective of stage

OR

- WHO Stage IV AIDS-defining illness, irrespective of the CD4 count

AND

- Patient expresses willingness and readiness to take antiretroviral treatment adherently *(see section 2.5)*

Treatment readiness assessment must be done for the initiation of antiretroviral treatment. This includes a first screening visit 2 to 4 weeks before starting antiretroviral treatment. Opportunistic infections must be treated, patient's information records need to be completed, treatment must be discussed with the patient and a 28-day supply of co-trimoxazole is given to the patient. The second visit includes clinical assessment, information and education session, pill count (co-trimoxazole) and adherence counselling for the patient. If the patient meets the treatment readiness criteria, commencing of antiretroviral treatment can begin (DOH, 2004b:4).

2.7.2.4 Antiretroviral treatment in adults and adolescents

The WHO (2003a:11) suggests that countries select a first-line regimen and a limited number of second-line regimens, recognising that specialist physicians will refer individuals who cannot tolerate or fail first-line regimens for individualised care. Among the factors that should be considered in the selection of antiretroviral treatment regimens at both the programme levels are

- potency;
- side-effect profile;
- laboratory monitoring requirements;
- potential for maintenance of future treatment options;
- anticipated patient adherence coexistent conditions (e.g. coinfections, metabolic abnormalities);
- pregnancy or the risk thereof;
- use of concomitant medications (i.e. potential drug interactions);

- potential for infection with a virus strain with diminished susceptibility to one or more ARV drugs, including that resulting from prior exposure to ARV drugs given for prophylaxis or treatment; and
- very importantly, availability and cost (WHO, 2003a:11).

Table 2.14 indicates the recommended antiretroviral treatment regimens in South Africa.

Table 2.14 Recommended antiretroviral treatment regimens (DOH, 2004b:6)

Regimen	Drugs
1a	Stavudine/ lamivudine/ efavirenz
1b	Stavudine/ lamivudine/ nevirapine
2	Zidovudine/ didanosine/ lopinavir/ ritonavir

The use of first-line therapy or regimen 1a in the South African public sector in antiretroviral naïve adult patients includes stavudine with lamivudine and efavirenz. It is important to ensure reliable contraception in women of childbearing age. If unable to guarantee reliable contraception, efavirenz will be substituted with nevirapine. All men, as well as women on injectable contraception and condoms should begin with regimen 1a. Women who are unable to guarantee reliable contraception while on therapy should begin with regimen 1b. Thus, regimen 1b constitutes of stavudine with lamivudine and nevirapine (DOH, 2004b:6).

In the case of treatment failure, the entire regimen should be changed to a second-line regimen (WHO, 2003a:27). Regimen 2 includes zidovudine, with didanosine, with lopinavir and ritonavir (DOH, 2004b:6).

WHO (2004:65) recommends the following ARV drugs as first-line regimens, with alternative choices depending on side effects and other co-existing conditions (refer to table 2.15):

Table 2.15 First-line regimens (WHO, 2004:65)

Choice	Drugs
a	Stavudine/ lamivudine/ nevirapine
b	Stavudine/ lamivudine/ efavirenz
c	Zidovudine/ lamivudine/ nevirapine
d	Zidovudine/ lamivudine/ efavirenz

Once antiretroviral treatment has begun, patient monitoring should cover adherence, drug toxicity, efficacy of treatment (weight, CD4 count) and detection of opportunistic infections and other conditions [occurrence/recurrence of opportunistic infections due to treatment failure and immune reconstitution syndrome (IRS)]. Laboratory monitoring (table 2.16) should cover routine testing for detection of drug toxicity [e.g. alanine aminotransferase (ALT) for stavudine, haemoglobin (Hgb) and white blood cell (WBC) for zidovudine], monitoring of treatment efficacy (e.g CD4 if available), and symptom-directed testing for detection of opportunistic infections and other conditions (e.g.sputum smears for acid-fast bacilli (AFB), chest X-rays) for drug toxicity (e.g. amylase for pancreatitis if available) (WHO, 2004:69).

Table 2.16 Laboratory monitoring for recommended first-line regimens (adapted from WHO, 2003a:26)

Regimen	At baseline (pre-therapy)	On therapy
Stavudine/ lamivudine/ nevirapine	Desirable but not required: CD4	For routine testing: ALT for toxicity For efficacy: CD4 every six to 12 months, if available
Zidovudine/ lamivudine/ nevirapine	Hgb (mandatory) Desirable but not required: FBC, CD4	For routine testing: Hgb, WBC, ALT for toxicity For efficacy: CD4 every 6-12 months, if available
Stavudine/ lamivudine/ efavirenz	Pregnancy test (mandatory) Desirable but not required: CD4	For routine testing: None routinely required for toxicity For efficacy: CD4 every 6-12 months, if available
Zidovudine/ lamivudine/ efavirenz	Pregnancy test (mandatory) Desirable but not required: FBC, CD4	For routine testing: Hgb, WBC, ALT for toxicity For efficacy: CD4 every 6-12 months, if available

FBC=Full Blood Count

Major toxic effects of first-line ARV drugs and their management including drug substitution are summarised in table 2.17 below.

Table 2.17 Major potential toxic effects of first-line ARV regimens and recommended drug substitutions (WHO, 2004:70)

Major toxic effect	Management	Drug substitution
Nevirapine-related severe rash	Discontinue all drugs and wait until the symptoms resolve - Not life-threatening - Life-threatening (Stevens Johnsons syndrome)	Nevirapine → Efavirenz Nevirapine → Protease Inhibitor
Nevirapine-related severe hepatotoxicity	Monitor clinical symptoms and/or preferably ALT. NVP/EFV should be replaced if clinical hepatitis or elevation of ALT five times the upper normal limit.	Nevirapine → Efavirenz Efavirenz → Protease Inhibitor
Efavirenz-related persistent central nervous system toxicity	The symptoms usually improve in two to four weeks. If persist and are unacceptable or harmful, efavirenz should be replaced.	Efavirenz → Nevirapine
Stavudine-related neuropathy	The symptoms usually resolve in two to three weeks. Treat with amitriptyline 25-100 mg once a day (it takes three weeks to be effective). If severe, replace stavudine.	Stavudine → Zidovudine

Table 2.17 (continue) Major potential toxic effects of first-line ARV regimens and recommended drug substitutions (WHO, 2004:70)

Major toxic effect	Management	Drug substitution
Stavudine-related lipoatrophy (fat change)	Counsel patient. Replacement of stavudine typically does not reverse lipoatrophy but may slow its progression.	Stavudine → Tenofovir Disoproxil Fumarate or Abacavir
Stavudine-related pancreatitis	Amylase is useful for diagnosis but its role is limited. Discontinue all drugs and wait until the symptoms resolve.	Stavudine → Zidovudine
Stavudine/zidovudine-related lactic acidosis	Discontinue all drugs and wait until the symptoms resolve.	(→ NNRTI/PI regimen)
Stavudine/zidovudine-related persistent GI intolerance	Take with food. Anti-emetics (metoclopramide) and anti-diarrhoeals (loperamide). If persists, replace zidovudine.	Zidovudine → Stavudine
Zidovudine-related severe anaemia and neutropenia	Monitor clinical symptoms and/or preferalby Hgb, WBC. Anemia: Vitamin B12 and iron do not help. If severe anaemia, replace zidovudine. May require blood transfusion. Neutropenia: Replace zidovudine if severe.	Zidovudine → Stavudine

There are two main reasons why antiretroviral treatment needs to be changed:

- Firstly, the drug combinations often cause side effects. Mild side effects are easily manageable, but for severe side effects alternative drugs should be considered. If it is possible to identify the drug that is causing the side effects, it may be possible to change it to another drug that does not have the same side effects. It is important to try to use drug substitutions where possible so that early switching to a completely new regimen is minimised.
- The second reason for changing treatment is treatment failure. This is when the drugs have failed to work and are not slowing down the reproduction of the virus in the body (Kanabus, 2005:5).

Reasons for changing antiretroviral treatment because of treatment failure can be defined as virologic, immunologic and/or clinical. Treatment failure results from failure to suppress viral replication with the development of viral resistance. Secondary virologic failure is a 1-log (10 fold) increase in the lowest recorded level. Immunologic failure is defined as a 30 per cent drop in CD4 count from peak value, or a return to pre-antiretroviral treatment baseline or lower. Clinical failure is progression of disease with the development of opportunistic infections or malignancy occurring three months or more after initiation of antiretroviral treatment (DOH, 2004b:11).

In the case of treatment failure, the entire regimen should be changed to a second-line regimen. A single drug should not be added or changed to a failing regimen (WHO, 2003a:27).

Table 2.18 indicates the clinical and CD4 cell count definitions or treatment failure in adults and adolescents.

Table 2.18 Clinical and CD4 cell count definitions or treatment failure in adults and adolescents (WHO, 2003a:27)

Clinical signs of treatment failure	CD4 cell criteria for treatment failure
• **Occurrence of new opportunistic infection or malignancy signifying clinical disease progression.** This must be differentiated from immune reconstitution syndrome (IRS) which can occur in the first three months following antiretroviral treatment initiation. The latter does not signify treatment failure and the opportunistic infections should be treated as usual, without changes in the antiretroviral treatment regimen.	• **Return of CD4 cell to pre-therapy baseline of below without other concomitant infection to explain transient CD4 cell decrease** (if patient is asymptomatic and treatment failure is being determined by CD4 cell criteria alone, consideration should be given to performing a confirmatory CD4 cell count if resources permit)
• **Recurrence of prior opportunistic infections** (Recurrence of TB may not represent disease progression as re-infection may occur. Clinical evaluation is necessary) • **Onset or recurrence of WHO Stage III conditions**	• **More than 50 per cent fall from on therapy CD4 peak level without concomitant infection to explain transient CD4 decrease.** (As with the first criteria for treatment failure, do confirmatory CD4 cell count if resources permit)

Patients who continue to fail virologically despite demonstrated adherence may be changed to schedule 2. Second-line therapy or regimen 2 for adults in the South African public sector **include** zidovudine 300 mg every 12 hours **with** didanosine 400 mg once a day (250 mg daily if weighing less than 60 kg), **taken** alone, dissolved in water on an empty stomach **and** lopinavir/ritonavir (LPV/r) 400/100 mg every 12 hours (DOH, 2004b:14).

In cases of high-grade resistance to zidovudine, stavudine, or lamivudine, other NRTIs may have diminished efficacy. However, abacavir, didanosine, and tenofovir are more likely to have residual efficacy against such resistant strains. As efavirenz and nevirapine are cross-resistant, a ritonavir (r) enhanced PI component is recommended. The WHO (2003a:28) recommends second-line regimen as follows (refer to table 2.19):

Table 2.19 Recommended second-line regimens in the event of treatment failure of first-line antiretroviral regimen (WHO, 2003a:28)

Failure on:	Switch to:
Stavudine or zidovudine	Tenofovir Disoproxil Fumarate or abacavir
Lamivudine	Didanosine[a]
Nevirapine or efavirenz	Lopinavir/ ritonavir (LPV/r) or saquinavir/ ritonavir (SQR/r)[b]

[a] Dose of didanosine should be reduced from 400 mg to 250 mg when co-administered with Tenofovir Disoproxil Fumarate.

[b] LPV/r and SQV/r require cold chain. Nelfinavir can be considered as an alternative in settings without cold chain. Indinavir/ ritonavir (IDV/r) should be considered as an alternative due to its renal side effects.

Patients on second-line therapy who begin to fail virologically should receive increased adherence support, as described. If they continue to fail virologically, in spite of showing increased adherence, their antiretroviral treatment should be continued until there is no further clinical benefit from treatment. Where adherence is consistently less than 80 per cent, ongoing education and counselling is needed. If patients experience AIDS-defining (WHO Stage IV) illnesses on second-line therapy, they should be referred to an expert to discuss stopping antiretroviral treatment, and starting palliative care (DOH, 2004b:16).

2.7.2.4.1 Immune reconstitution syndrome (IRS)

Within 2 to 12 weeks after the start of antiretroviral treatment, signs and symptoms of a new or recurrent opportunistic infection or other inflammatory condition may occur as the immune system is restored because of an inflammatory response to a previously subclinical opportunistic infection. It is called IRS. IRS is more common in patients with advanced immunosuppression (CD4 counts less than 50 cells/mm^3) (WHO, 2004:72).

The patients may have signs and symptoms of sweats, loss of weight, cough, persistent fever, shortness of breath, decreasing visual acuity, to name a few. TB is a common immune reconstitution illness in South Africa. An immune reconstitution illness is not indicative of drug failure or drug side effects. It is not a reason to stop antiretroviral treatment, or to change the antiretroviral regimen. Opportunistic infections may present in atypical ways during this phase of immune reconstitution. Patients need to be referred to an experienced HIV clinician for advice regarding investigation and management (DOH, 2004b:11).

2.7.2.4.2 Concomitant TB in adults

Patients should be investigated for TB before starting with antiretroviral treatment. TB are suspected if two or more of the following are present:

- Observed weight loss of more than 1,5 kg over the past 4 weeks.
- Cough for more than 2 weeks.
- Night sweats for more than 2 weeks.
- Fever for more than 2 weeks (DOH, 2004b:17).

Recent randomised controlled trials showed that TB preventive therapy prevents TB diseases in persons coinfected with HIV and TB (Gayle & Hill, 2001:334). Evidence suggests that TB speeds the progression of HIV, altering the course of HIV in areas of high TB prevalence (Dye *et al.*, 1999:677).

If TB is diagnosed, there are two scenarios to consider:

1) The patient develops TB while on antiretroviral treatment

Antiretroviral treatment should be continued throughout TB treatment, with changes to the regimens and monitoring as follows:

- **Regimen 1:**

  A change to efavirenz is recommended for patients on nevirapine wherever possible. If this is not possible (e.g. intolerant of efavirenz or significant risk of falling pregnant), nevirapine may be continued in selected cases, with monthly ALT monitoring. These cases should be discussed with an antiretroviral treatment expert.

- **Regimen 2:**

  Lopinavir/ritonavir should change to lopinavir/ritonavir (dose: 400/400 mg every 12 hours – 3 extra caps of ritonavir). This should be continued until 2 weeks after completion of TB treatment, when the extra ritonavir can be stopped (DOH, 2004b:17).

2) The patient presents with TB before commencing antiretroviral treatment

If the patient has no history of WHO Stage IV illness, and has a CD4 count of more than 200 cells/mm^3, antiretroviral treatment is not yet needed. The need for antiretroviral treatment should be reassessed on the completion of TB treatment. If the patient has a history of WHO Stage IV illness, and/or a CD4 count of less than 200 cell/mm^3, 2 months of TB therapy must be completed before commencing with antiretroviral treatment. If the patient has a CD4 count of less than 50 cells/mm^3,

or other serious HIV-related illnesses, make sure that the patient is tolerating TB treatment before initiating antiretroviral treatment. The patient should complete at least two weeks of TB treatment before initiating antiretroviral treatment. Patients in this group should be started on first-line therapy consisting of stavudine, lamivudine and efavirenz. Nevirapine should generally be avoided because drug levels might decrease. There is also a danger that shared hepatotoxicity might increase (DOH, 2004b:18).

Figure 2.4 indicates how adult patients with concomitant TB must be treated.

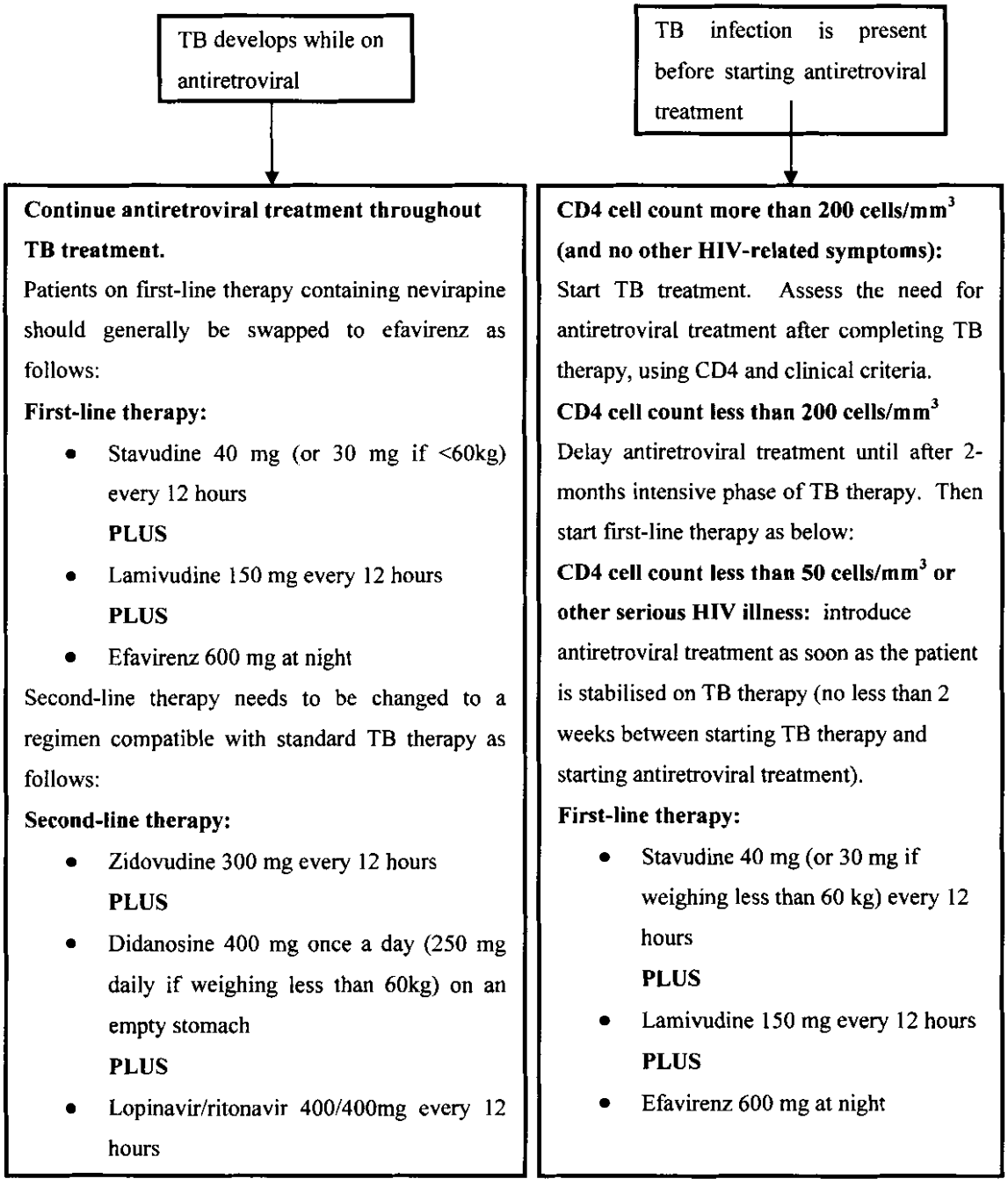


Figure 2.4 How to treat adult patients with concomitant TB (DOH, 2004b:19)

2.7.2.4.3 Pregnancy and antiretroviral treatment

2.7.2.4.3.1 Timing of initiation of antiretroviral treatment during pregnancy

Patients must be at least more than 34 weeks gestation to begin evaluation for antiretroviral treatment. Antiretroviral treatment must begin no later than 36 weeks gestation to ensure maximal viral suppression. Patients greater than 34 weeks gestation when identified with AIDS or unprepared to start antiretroviral treament by 36 weeks will receive standard primary-mother-to-child-therapy (PMTCT) treatment (DOH, 2004b:20).

2.7.2.4.3.2 Women who fall pregnant while on antiretroviral treatment

Women who fall pregnant on efavirenz must be counselled about potential teratogenicity. If they decide to continue the pregnancy, efavirenz must be stopped, and nevirapine started (in their 1st trimester). Women who fall pregnant on stavudine, lamivudine and nevirapine should continue their antiretroviral treament throughout pregnancy. Blood tests should be performed monthly. Women who fall pregnant on second-line therapy (zidovudine, didanosine and lopinavir/ritonavir) should continue their antiretroviral treatment throughout pregnancy. Full blood counts should be performed monthly (DOH, 2004b:20).

2.7.2.4.3.3 Monitoring therapy during antenatal care

If antiretroviral treatment is provided in the antenatal clinic, patients should return weekly for visits for at least 4 weeks. They can go back to twice weekly visits until 38 weeks gestation. Then weekly visits can begin again. At each follow-up visit, providers should determine patient adherence to antiretroviral treatment. At each follow-up visit, providers should determine if the patient is experiencing any adverse reactions to the antiretroviral treatment. Routine laboratory testing should follow established national maternal guidelines (DOH, 2004b:20).

2.7.2.4.3.4 Therapy during delivery

According to Raisler and Cohn (2005:276) HIV-infected women should be offered antiretroviral therapy in labour to reduce MTCT. Zidovudine is given to the mother intravenously during labour, and orally to the newborn for 6 weeks. In a treatment naïve, HIV positive pregnant woman, one simple HAART regimen is Combivir® and Viracept® (Stein *et al.*, 2000:125). Although many possible combinations of antiretroviral drugs are used in pregnancy, Combivir® and nevirapine are a frequently prescribed drug combination (Patchen & Beal, 2001:357).

For patients undergoing caesarean section, after delivery and in the postpartum ward, efforts should be made to ensure that patients receive scheduled antiretroviral treatment (DOH, 2004b:20).

Figure 2.5 indicates how pregnant women with HIV should be treated.

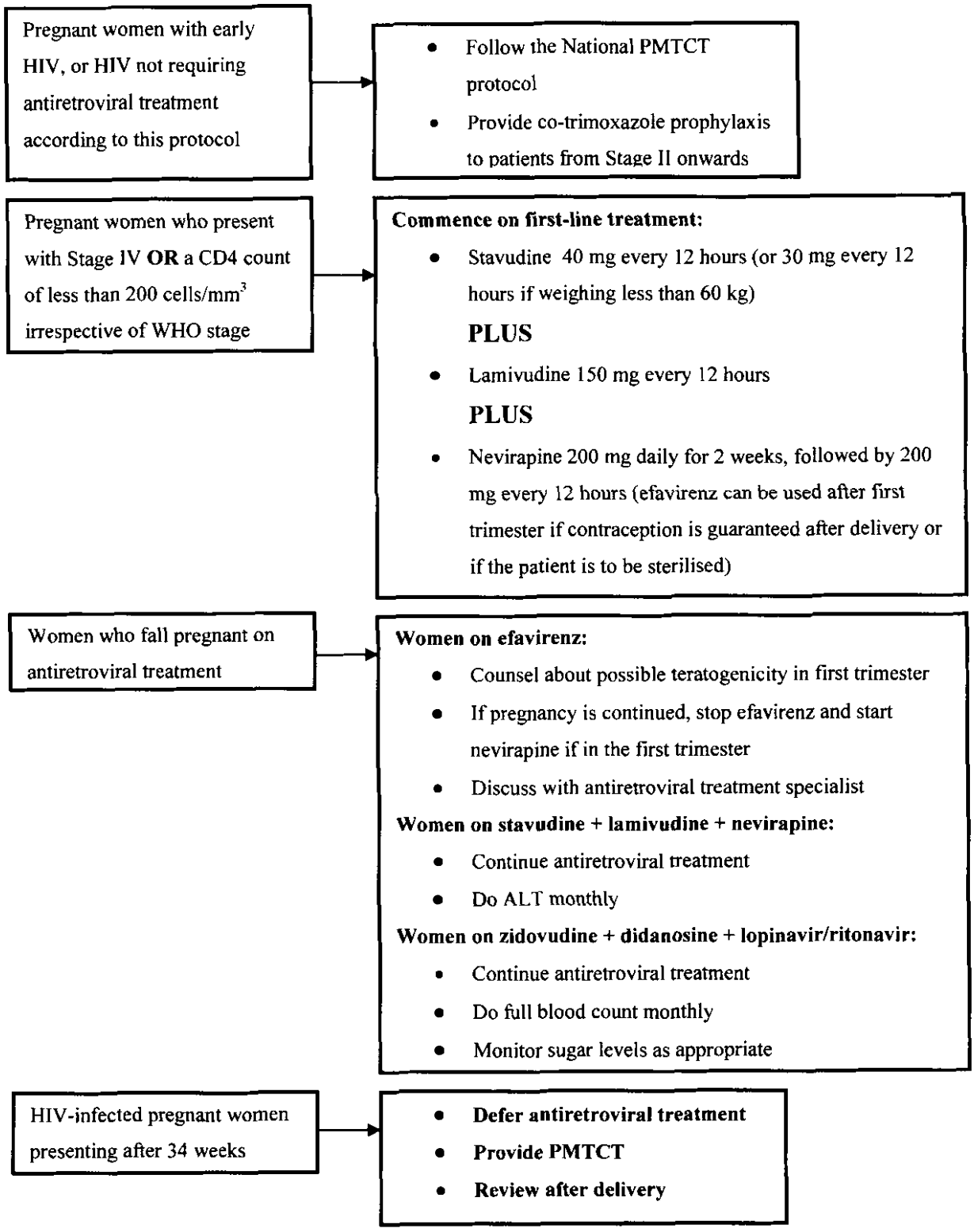


Figure 2.5 How to treat HIV pregnant women (DOH, 2004b:23)

Even though current prophylactic regimens that include zidovudine as monotherapy or in combination with lamivudine, or nevirapine may not be perfect and the risk of selection of resistant strains may exist, these schemes should be considered for the prevention of vertical transmission, as they have demonstrated to highly diminish the risk of MTCT of HIV (Kijak *et al.*, 2001:34).

2.7.2.5 Antiretroviral treatment in children

The goal of antiretroviral treatment for children is to increase survival, and to decrease HIV-related morbidity and mortality. The child's CD4 count should rise and remain above the baseline count and the child's viral load should become undetectable (less than 400 copies/mm^3) and remain undetectable on antiretroviral treatment. In some children, a suppressed though detectable viral load, with sustained elevation in CD4 count and absence of intercurrent and/or opportunistic infection, may be the best achievable goal (DOH, 2004b:27).

2.7.2.5.1 Diagnosing HIV infection in children

The majority of children are diagnosed on the basis of symptomatic HIV disease and the positive HIV antibody test of the mother of the child. The child of an HIV-infected mother acquires HIV antibodies from his/her mother during pregnancy. These may persist in his or her blood until 15 to 18 months of age, even if the child is not infected with HIV. Thus a child may test HIV positive without actually being infected (DOH, 2004b:26).

When using the HIV antibody test, it is not possible to tell whether a newborn infant has already been infected with HIV. Additional techniques exist for the detection of virus in children younger than 18 months. HIV infection can be diagnosed in most infected infants by the age of 6 weeks by using a DNA polymerase chain reaction (PCR) technique. Rapid HIV testing may be less reliable in children than in adults. Rapid HIV tests should not routinely be performed in children (DOH, 2004b:26).

A clinical examination to assess for signs and symptoms of HIV infection should be performed during all visits, and especially at 6 weeks and 3 months of age. The infant should thereafter be followed up as per recommendations for all children (see above). Postnatal transmission of HIV infection is likely to be evident by 6 weeks after termination of breastfeeding. It is recommended that the final qualitative HIV PCR test on abandoned infants be performed 3 months after breast-feeding has ceased (DOH, 2004b:27).

2.7.2.5.2 Criteria for commencing antiretroviral treatment in children

Children being considered for antiretroviral treatment will need to meet both medical and psycho-social criteria before starting therapy.

Medical criteria:

- Recurrent hospitalisations (more than 2 admissions per year) for HIV-related disease, or prolonged hospitalisation (longer than 4 weeks)

  OR

- Modified WHO Stage II or III disease

  OR

- CD4 percentage less than 20 per cent in a child under 18 months old, irrespective of disease stage

  OR

- CD4 percentage less than 15 per cent in a child over 18 months old, irrespective of disease stage (DOH, 2004b:30).

Psycho-social considerations (not exclusion criteria)

These factors are extremely important for the success of the programme, and need to be adhered to. The principle is that adherence must be at least probable.

- An identifiable adult who is able to administer medication (all efforts should be made to ensure that the social circumstances of vulnerable children, e.g. orphans, are addressed so that they too can receive treatment).
- Demonstrated reliability in the adult caregiver i.e. has attended three or more scheduled visits to the service point and the immunisation record of child is up-to-date.
- Supportive social environment as for adults (see adult section).
- Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's antiretroviral treatment (DOH, 2004b:30).

2.7.2.5.3 Treatment of mothers, caregivers and other family members

Always ask about the caregiver's health, and the health of other members of the family. Ensure that mothers and other family members have access to medical care when necessary, including antiretroviral treament if needed (DOH, 2004b:31).

2.7.2.5.4 Treatment of children

Unless contra-indicated, all children will commence therapy on the regimen indicated in table 2.20.

Table 2.20 Paediatric first-line therapy - Regimen 1 (DOH, 2004b:37)

	6 months - 3 years	>3 years old and >10 kg
First-line	Stavudine Lamuvidine Lopinavir/ ritonavir	Stavudine Lamivudine Efavienz

All infants under 6 months of age who require treatment with antiretroviral treatment should be started on treatment under specialist supervision. Nevirapine may be used in place of lopinavir/ritonavir if this has not been used to prevent PMTCT of HIV. If nevirapine was used for PMTCT, one may consider using lopinavir/ritonavir in the first-line regimen for children under 3 years of age. Switch to tablets or capsules from syrups or solutions as soon as possible. Children may occasionally need to change a drug from the first-line regimen to one from the second-line regimen, because of intolerance or a serious adverse reaction. Swapping limits the patient's second-line treatment options. Ritonavir and lopinavir/ritonavir can be substituted by nevirapine in children younger than 3 years with no prior nevirapine exposure. For children older than 3 years, efavirenz can be used as 3rd drug (DOH, 2004b:37).

Appropriate formulations for infants and children are not readily available in resource-limited settings. The WHO (2003a:36) recognises that until ARV formulations are more widely available, the splitting of adult dose solid formulations may be the only way a severely ill child can receive therapy. The preferred first-line and alternative treatment for children includes (refer to table 2.21):

Table 2.21 First-line regimens (WHO, 2003a:37)

Choice	Drugs
a	Stavudine/ lamivudine/ nevirapine
b	Stavudine/ lamivudine/ efavirenz
c	Zidovudine/ lamivudine/ nevirapine
d	Zidovudine/ lamivudine/ efavirenz

Efavirenz cannot be used in children under three years of age or weighing less than 10 kg and nevirapine should be the NNRTI of choice. There is still a great deal that is unknown about antiretroviral treatment for infants and children. Expert advice should be sought wherever possible (WHO, 2004:75).

The principles on which to base changes in therapy for children are similar to those applied to adults and management of toxicity is the same. When toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with another drug that does not have the same side effects (WHO, 2004:75).

Table 2.22 indicates the clinical and CD4 cell count definitions or treatment failure in infants and children.

Table 2.22 Clinical and CD4 cell count definitions or treatment failure in infants and children (WHO, 2003a:39)

Clinical signs of treatment failure	CD4 cell criteria for treatment failure[a]
• Lack of growth among children who show an initial response to treatment, or decline in growth among children who show an initial growth response to therapy. • Loss of neurodevelopment milestones or development of encephalopathy. • Occurrence of new opportunistic infection or malignancy signifying clinical disease progression.[b] • Recurrence of prior opportunistic infections, such as oral candidiasis that is refractory to treatment.	• Return of CD4 cell percentage (or for children older than 6 years of age, or absolute CD4 cell count) to pre-therapy baseline or below, in absence of other concurrent infection explaining transient CD4 decrease. • More than or equals to 50 per cent fall from peak level on therapy of CD4 cell percentage (or for children older than 6 years of age, of absolute CD4 cell count) in absence of other concurrent infection explaining transient CD4 decrease.

[a] If a child is asymptomatic and treatment failure is being defined by CD4 cell criteria alone, consideration should be given to performing a confirmatory CD4 count if resources permit.

[b] This must be distinguished from immune reconstitution syndrome, which can occur in the first three months following the initiation of HAART and does not signify treatment failure.

Procedure for introduction of second-line therapy:

- Do not rush into second-line therapy.
- First check adherence. If it is not possible to improve adherence, attempt directly observed therapy (DOT) with a health care worker or trusted 'other' family member or friend.
- Ensure second-line therapy does not include any drugs used in first-line therapy (DOH, 2004b:39).

Table 2.23 indicates reasons to move to second-line antiretroviral treatment in children.

Table 2.23 Reasons to change to second-line antiretroviral treatment in children (DOH, 2004b:40)

Virological	Clinical	Immunological
Rebound of viral load to baseline. A detectable viral load may be tolerated in children, providing that growth and elevated CD4 count are sustained.	Persistent oral thrush, which is refractory to treatment. New evidence of Stage III disease (not immune reconstitution disease - see below). **Note:** Short intercurrent episodes of pneumonia, lower respiratory tract infection and gastro-enteritis should not be regarded as clinical failure. Presentation with TB while on first-line therapy is **NOT** an indication to switch to second-line therapy, even though it can present as progression to Stage III disease. Immune reconstitution disease may present as a new Stage III event. This will usually be associated with a CD4 count and/or percentage which have improved over time. This is **NOT** an indication to switch to second-line therapy.	A persistent decline in the CD4 percentage over 2 months in the absence of TB. **Note:** The CD4 percentage should **NOT** be measured during an intercurrent infection - but preferably a month post resolution. If there is a modest decline in CD4 percentage (more than 5 per cent), and if no failure to thrive, do not change medication, but monitor closely.

Table 2.24 indicates paediatric second-line therapy.

Table 2.24 Paediatric second-line therapy - regimen 2 (DOH, 2004b:41)

	6 months - 3 years	>3 years old and >10 kg
First-line	Zidovudine Didanosine Nevirapine	Zidovudine Didanosine Lopinavir/ritonavir

Didanosine must be taken alone, on an empty stomach, at least an hour before (or two hours after) a meal. Tablets should be dissolved in at least 30 ml of water. For regimen 2 where there has been prior exposure to nevirapine or efavirenz, lopinavir/ritonavir can be substituted as in Regimen 1 (DOH, 2004b:41).

Second-line therapy for children in the event of failure of a first-line regimen includes a change in the nucleoside backbone, in accordance with the same principles as are applied for adults (e.g. from zidovudine + lamivudine to abacavir + didanosine), plus a PI (table 2.25). The use of PIs other than lopinavir/ritonavir and nelfinavir is more problematic in children because of a lack of suitable paediatric drug formulations for indinavir and saquinavir and a lack of appropriate dosing information for ritonavir-boosted PIs other than lopinavir/ritonavir (WHO, 2003a:40).

Saquinavir/ritonavir can be considered as an alternative for children who are able to swallow capsules and who weigh 25 kg or more, and can therefore receive the adult dose. Tenofovir Disoproxil Fumarate (TDF) cannot be recommended for paediatric treatment at present because of limited data on appropriate dosing for children, particularly those aged under 8 years, and because of questions about bone toxicity, which may be of more concern and/or more frequent in growing children than in adults (WHO, 2003a:40).

Table 2.25 indicates recommended ARV regimens for infants and children with treatment failure.

Table 2.25 Recommended ARV regimens for infants and children with treatment failure (WHO, 2003a:40)

First-line regimen	Second-line regimen
Stavudine or Zidovudine ***plus*** Lamivudine ***plus*** NNRTI: Nevirapine or Efavirenz	Abacavir ***plus*** Didanosine ***plus*** PI: Lopinevir/ ritonavir or nelfinavir, or Saquinavir/ ritonavir if weighing more or equalled to 25 kg

2.7.2.5.5 Concomitant TB in children

There are two scenarios to consider:

1) Child presents with TB before commencing antiretroviral treatment

Complete TB therapy if possible before commencing antiretroviral treatment OR delay antiretroviral treatment for at least 2 months. If the child has failed the nevirapine vertical transmission programme, or is less than 3 years old or weighs less than 10 kg, use lopinavir/ritonavir (with ritonavir at the same dosage as lopinavir) as a third drug. If the child was not on the nevirapine vertical transmission programme, and is more than 3 years old and weighs more than 10 kg, use efavirenz as the third drug. Monitor ALT monthly for the first 6 months of therapy, and then as clinically indicated (DOH, 2004b:43).

2) Child develops TB while on antiretroviral treatment

If the child is on lopinavir/ritonavir, then increase ritonavir to same dosage as lopinavir. If the child is on nevirapine, and is less than 3 years old or weighs less than 10 kg, switch to lopinavir/ritonavir (with ritonavir at the same dosage as lopinavir). If the child is on nevirapine, and is more than 3 years

old and weighs more than 10 kg, switch to efavirenz. If the child is unable to tolerate the large number of drugs, antiretroviral treatment may have to be interrupted until TB therapy has been completed. Discuss all cases with a paediatrician with antiretroviral experience, before interrupting therapy. Monitor blood tests monthly (DOH, 2004b:43).

Figure 2.6 indicates how children with concomitant TB should be treated.

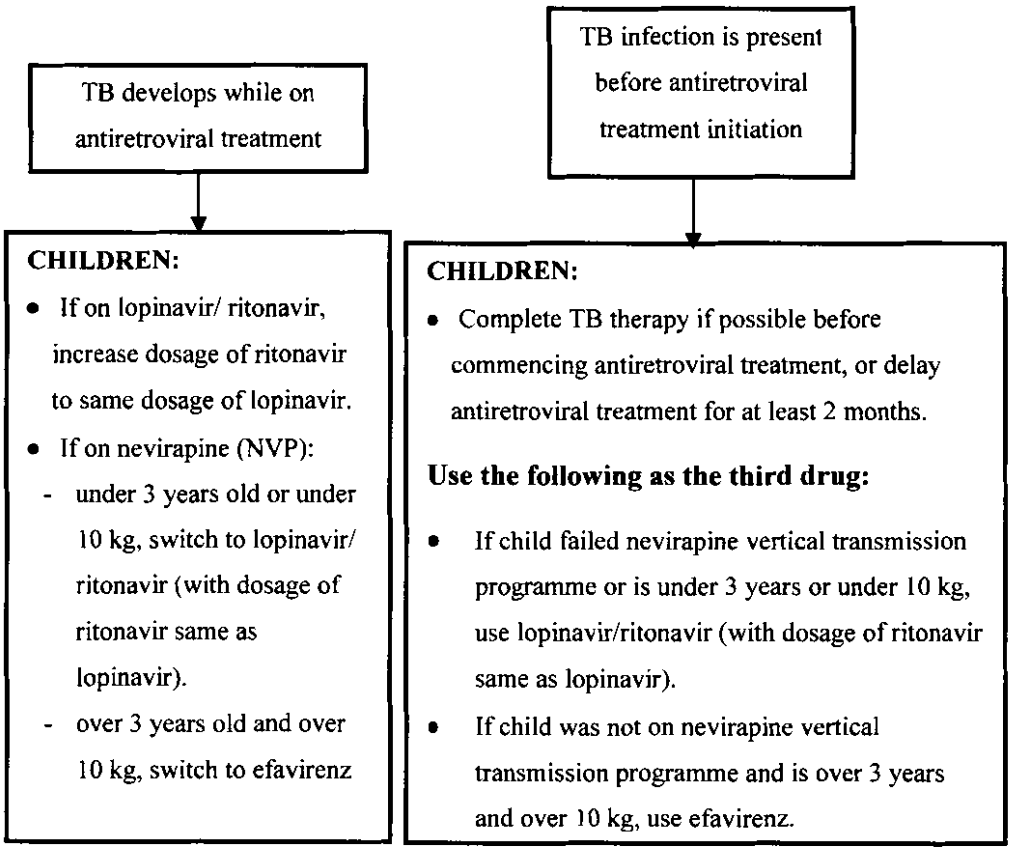


Figure 2.6 How to treat children with concomitant TB (DOH, 2004b:46)

Patients on TB medication and antiretroviral are taking a large number of doses of medications. It is important to counsel them beforehand to improve adherence. Watch liver functions (ALT) monthly while on concomitant antiretroviral and TB therapy. Recalculate doses according to weight or body surface at every 3 monthly visits (DOH, 2004b:46).

2.7.2.6 Adherence

According to Kanabus (2005:7) the term "adherence" means taking the drugs exactly as prescribed. It also means taking the drugs on time and following any dietary restrictions. Adherence to antiretroviral

treatment is essential to maintain long-term health benefit and avoid development of drug resistance (DOH, 2004b:52).

Adherence tends to be gradually neglected as time progresses. Thus, monitoring and ongoing support of adherence is essential. New diagnoses or symptoms can influence adherence. A trusting relationship between the patient and members of the health care team is essential. Optimal adherence requires full participation by the health care team: patient, family members and the community. Every patient interaction is an opportunity for reinforcement. Supportive and non-judgmental attitudes and behaviours will encourage patient honesty regarding adherence and problems (DOH, 2004b:52).

Adherence to antiretroviral treatment is an essential component of treatment success (WHO, 2004:63). Antiretroviral treatment requires 95 per cent adherence to avoid reduced viral resistance and treatment failure. This means a patient should not miss taking pills more than three times a month in the case of twice-daily regimen. If patients are taking less than 95 per cent of their doses, they are at risk of developing viral resistance and ultimately virological failure. Patients taking less than 80 per cent of their doses are unlikely to have any durable virological suppression. Patients with adherence of less than 80 per cent require increased adherence support (DOH, 2004b:53).

Table 2.26 indicates the correlation between adherence and virologic response to antiretroviral treatment.

Table 2.26 Correlation between adherence and virologic response to antiretroviral treatment (DOH, 2004b:55)

Adherence to antiretroviral treatment*	Viral load more than 400 copies/mm^3
More than 95% adherence	78%
90% to 95% adherence	45%
80% to 90% adherence	33%
70% to 80 % adherence	29%
Less than 70% adherence	18%
* (number of doses dispensed minus tablets returned) over (number prescribed) e.g. (30-5)/28=25/28=0,9 (90%)	

Strategies to improve adherence to antiretroviral therapy include the following:

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Utilise educational AIDS-programs including pictures, pillboxes, and calendars
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilise team approach with nurses, pharmacists, and peer counsellors
- Provide accessible, trusting health care team (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:66).

2.7.2.7 Diagnosis and management of adverse reactions

Principles of managing adverse reactions are to establish whether the adverse reaction is due to ARV drugs, other medication or other illness. Never stop only one antiretroviral drug (the patient should always be on 3 drugs). Individual drugs may be switched due to intolerance. If there is a need to discontinue antiretroviral treatment, all antiretroviral medications must be stopped together. Clinicians may continue antiretroviral treatment if there is a Grade I or II adverse reaction. Clinicians should consider terminating treatment in Grade III reactions. Treatment should be stopped if there is a Grade IV adverse event (DOH, 2004b:58).

Table 2.27 describes the adverse reaction of ARV drugs.

Table 2.27 Adverse reactions of ARV drugs (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:58)

NRTIs	
Abacavir	Hypersensitivity reaction which can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath.
Didanosine	Pancreatitis, pheripheral neuropathy, nausea and diarrhoea. Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs).
Lamivudine	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs).

Table 2.27 (continue) Adverse reactions of ARV drugs (US DHHS Panel on clinical practices for Treatment of HIV Infection, 2005:58)

NRTIs	
Stavudine	Peripheral neuropathy, lipodystrophy, rapidly progressive ascending neuromuscular weakness (rare), pancreatitis, lactic acidosis with hepatic steatosis (higher incidence with stavudine than with other NRTIs) and hyperlipidemia.
NRTIs	
Tenofovir Disoproxil Fumarate	Asthenia, headache, diarrhoea, nausea, vomiting, flatulence, renal insufficiency and lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs).
Zalcitabine	Peripheral neuropathy, stomatitis, lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs) and pancreatitis.
Zidovudine	Bone marrow suppression: macrocutic anemia or neutropenia, gastrointestinal intolerance, headache, insomnia, asthenia and lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with use of NRTIs).
NNRTIs	
Delavirdine	Rash, increased transaminase levels and headaches
Efavirenz	Rash, central nervous system symptoms, increased transaminase levels, false-positive cannabinoid test and teratogenic in monkeys.
Nevirapine	Rash, including Stevens-Johnson Syndrome, and symptomatic hepatitis, including fatal hepatic necrosis, have been reported.
PIs	
Amprenavir	Gastrointestinal intolerance, nausea, vomiting, diarrhoea, rash, oral paresthesias, hyperlipidemia, transaminase elevation, hyperglycemia, fat maldistribution and possible increased bleeding episodes in patients with hemophilia. Oral solution contains propylene glycol that is contraindicated in pregnant women, children under 4 years old, patients with hepatic or renal failure and patients treated with disulfiram or metronidazole.
Atazanavir	Indirect hyperbilirubinemia, prolonged PR interval - some patients experienced asymptomatic 1st degree atrioventricular block. Use with caution in patients with underlying conduction defects or concomitant medications that can cause PR prolongation. Hyperglycemia, fat maldistribution, possible increased bleeding episodes in patients with hemophilia.
Indinavir	Nephrolithiasis, gastrointestinal intolerance, nausea, indirect hyperbilirubinemia, hyperlipidemia, headache, asthenia, blurred vision, dizziness, rash, metallic taste,thrombocytopenia, alopecia, hemolytic anemia, hyperglycemia, fat maldistribtion and possible increased bleeding episodes in patients with hemophilia.
Lopinavir + Ritonavir	Gastrointestinal intolerance, nausea, vomiting, diarrhoea, asthenia, hyperlipidemia, hypertriglyceridemia, elevated serum transaminases, hyperglycemia, fat maldistribution and possible increased bleeding episodes in patients with hemophilia.
Nelfinavir	Diarrhoea, hyperlipidemia, hyperglycemia, fat maldistribution, possible increased bleeding episodes among patients with hemophilia and serum transaminase elevation.
Ritonavir	Gastrointestinal intolerance, nausea, vomiting, diarrhoea, paresthesias - circumoral and extrimities, hyperlipidemia, hypertriglyceridemia, hepatitis, asthenia, taste perversion, fat maldistribution and possible increased bleeding episodes in patients with hemophilia.
Saquinavir	Gastrointestinal intolerance, nausea, diarrhoea, abdominal pain and dyspepsia, headache, hyperlipidemia, elevated transaminase enzymes, hyperglycemia, fat maldistribution and possible increased bleeding episodes in patients with hemophilia.

2.7.2.7.1 Management of specific adverse reactions

All therapy should be stopped if severe hepatitis, pancreatitis, lactic acidosis or Stevens-Johnson syndrome are suspected (DOH, 2004b:65).

2.7.2.7.1.1 Nausea

Nausea due to antiretroviral medication must be actively managed, or adherence will suffer. Anti-emetics taken half an hour before the antiretroviral dose up to 3 times daily may be helpful. If the nausea does not settle, refer for expert advice (DOH, 2004b:65).

2.7.2.7.1.2 Rashes on first-line therapy

Do a clinical assessment to rule out any other causes of the rash. Enquire about systemic symptoms, and check the temperature in any patient presenting with a rash. Do a grading of the rash, and refer to tables for management. Both nevirapine and efavirenz may cause skin reactions. This usually occurs within the first 32 months of treatment. Concomitant TB therapy may confuse the situation as these drugs can cause similar adverse events (DOH, 2004b:65).

2.8 CHAPTER SUMMARY

In this chapter the history of HIV/AIDS, the relationship between HIV and AIDS, transmission of HIV, the stages of HIV disease, opportunistic infections associated with HIV/AIDS and treatment of HIV/AIDS, including vaccines and antiretroviral drugs, were discussed.

CHAPTER 3: HEALTH CARE CONCEPTS

3.1 INTRODUCTION

This chapter focuses on prevalence of AIDS in South Africa, the health care system in South Africa, equity in health, public/private partnerships (PPPs), methods and techniques utilised to ensure optimal and managed health care, drug utilisation review (DUR), pharmacoeconomics and disease management.

3.2 PREVALENCE OF AIDS IN SOUTH AFRICA

Slightly more than 5 million people out of a total of 46 million South Africans were HIV positive in 2004, giving a total population prevalence rate of 11 per cent. This is estimated from the Actuarial Society of South Africa's demographic and AIDS model, ASSA2002, which is based on a thorough analysis of a range of epidemiological and demographic data including the antenatal surveys up to the year 2002 (Dorrington *et al.*, 2004:iii).

One of the problems that policy and decision makers are faced with is the wide range of estimates of the extent and impact of the epidemic. Not all the uncertainty is in the estimates of the numbers infected, some of it is about the size of the population as a whole. Figure 3.1 shows a range of estimates of the total number of people infected with HIV in 2004, while the accumulated number of AIDS deaths to middle 2004 is shown in figure 3.2. Figure 3.3 shows the range of estimates of the total population. The implied prevalence rates for the population as a whole are shown in figure 3.4 (Dorrington *et al.*, 2004:14).

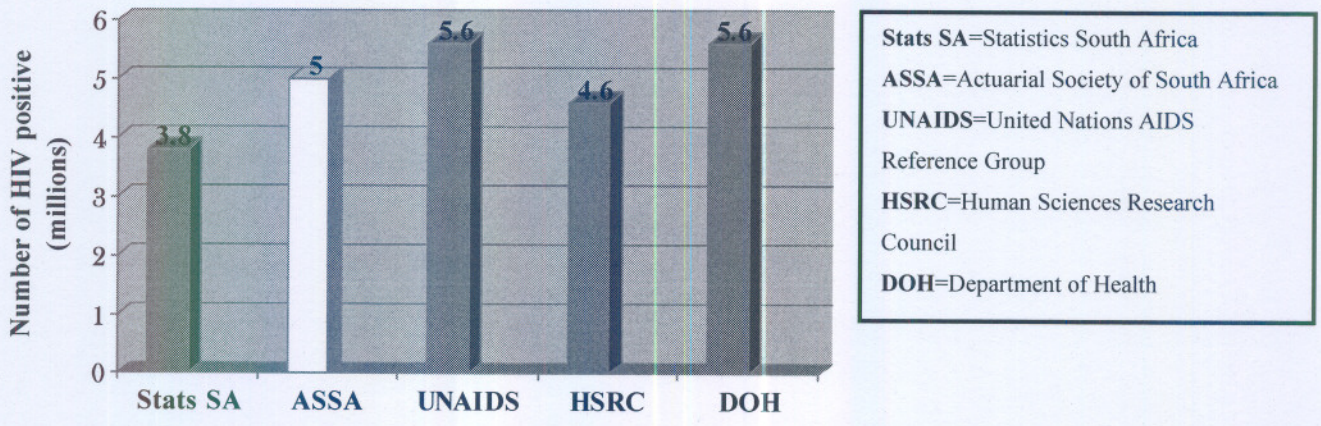


Figure 3.1 Number of people infected with HIV in 2004 (Dorrington *et al.*, 2004:14)

Notes: Stats SA published this number as the total number infected. It is actually their estimate of the number infected aged 15 to 49. The DOH estimate is for 2003.

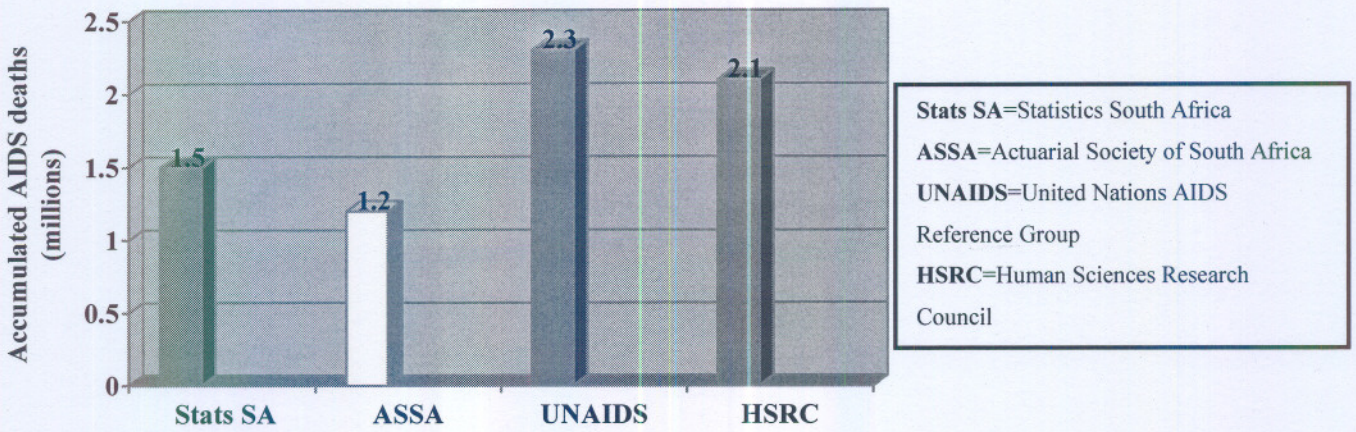


Figure 3.2 **Accumulated number of AIDS deaths to middle 2004 (Dorrington *et al.*, 2004:15)**

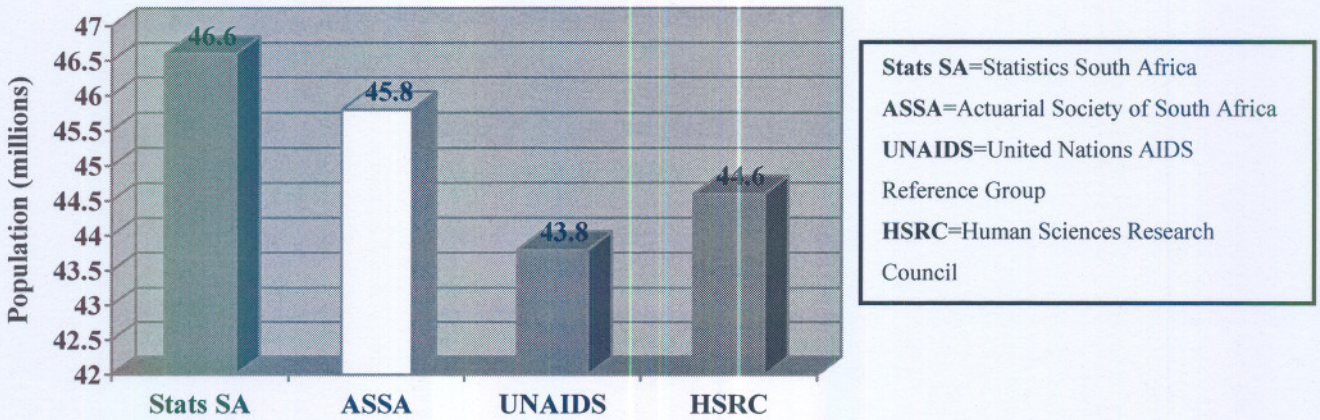


Figure 3.3 **Total population to middle 2004 (Dorrington *et al.*, 2004:15)**

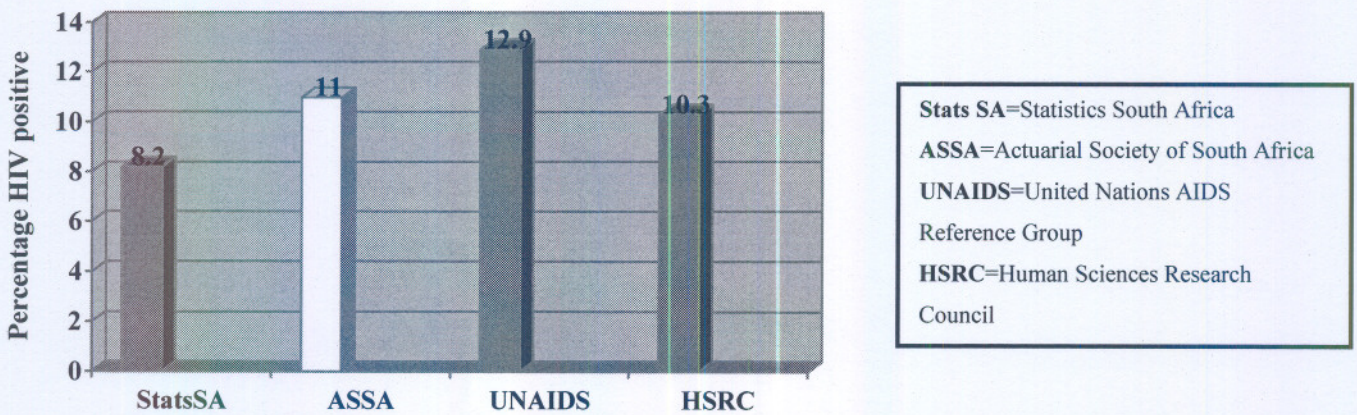


Figure 3.4 **HIV prevalence rate in the total population in 2004 (Dorrington *et al.*, 2004:16)**

It is important to note that the level of uncertainty about the estimate from the Actuarial Society of South Africa (ASSA) model is not as great as that presented to the public by the wide range of estimates. It can be demonstrated that some of these estimates are faulty. The ASSA estimates are based on the most thorough research, but it is nonetheless useful to contrast them with other estimates that have been produced recently (Dorrington *et al*., 2004:14).

The Epidemic Projection Package (EPP) recently developed by the United Nations AIDS (UNAIDS) Reference Group on Estimates, Models and Projections and the Spectrum model programme developed by the Futures Group were used by the Human Sciences Research Council (HSRC) of South Africa to model the South African HIV epidemic, project future trends in HIH/AIDS and estimate the demographic impact of AIDS. The national HIV prevalence surveys among pregnant women from 1990 to 2001 and the first national, population-based HIV survey in 2002 served as the data sets used to calibrate the input HIV prevalence values for the model (Rehle & Shisana, 2003:1).

The scenario created by the model showed the HIV prevalence in 2002 with 4.69 million infected people and it is projected that the epidemic in South Africa has now begun to level off. The annual number of deaths due to AIDS is projected to peak with 487 320 AIDS deaths in the year 2008. By 2020, the total population of South Africa is expected to be 23 per cent smaller than it would be without AIDS; however, a negative population growth rate is not expected during the projection period. Life expectancy at birth is expected to hit a low of 45.6 years in the time period 2005 to 2010, which is 22 years less than it would have been in the absence of AIDS. Ten years from now over 2.5 million AIDS orphans are projected for South Africa (Rehle & Shisana, 2003:1).

Based on results of the 2003 antenatal survey, using the Department of Health (DOH) model, it was estimated that 5.6 million South Africans were HIV positive by the end of 2003. This estimate includes 3.1 million women (15 to 49 years), and 2.4 million men (15 and 49 years) and 96 228 babies that were infected (DOH, 2003a:10).

Statistics South Africa (Stats SA, 2004:1) estimates the mid-2004 population at approximately 46.6 million. It was estimated that the HIV-positive population in 2004 would be approximately 3.83 million, which relates to an HIV-prevalence rate of 8.2 per cent of the total population. The accumulated AIDS deaths up to 2004 were estimated to be 1.49 million.

Statistics South Africa (Stats SA, 2004:2) subscribed to the specification of Special Data Dissemination Standard (SDDS) of the International Monetary Fund (IMF) and published the population estimates for

the country as a whole and the nine provinces annually. Their release uses the cohort-component methodology to estimate the mid-year population. The estimates cover all the residents of South Africa at the 2004 mid-year.

According to UNAIDS (2004:23) South Africa continues to have the highest number of people living with HIV in the world. An estimated 5.3 million (4.5 million to 6.2 million) people were living with HIV at the end of 2003 in South Africa – 2.9 million (2.5 million to 3.3 million) of them women. Unfortunately, there is no sign yet of a decline in the epidemic. Overall HIV prevalence among pregnant women was 27.9 per cent in 2003, compared to 26.5 per cent in 2002 and 25 per cent the year before that.

3.2.1 ASSA2002 AIDS and demographic model

The demographic model of ASSA uses a wide range of empirical evidence from different sources to provide estimates of the progression of the epidemic and the numbers of South Africans directly affected. The latest version of the model, ASSA2002, became available in 2004 and is calibrated to data including the antenatal clinic survey results and deaths from the population register. The most recent year for which these were available, at the time of release was 2002, hence the date in the name (Dorrington *et al.*, 2004:1).

The ASSA2002 model differs from the earlier version in that it allows for the introduction of antiretroviral treatment programmes, which will improve survival of those infected. These model-based indicators are complemented with data for selected prevention and treatment activities in the health sector at a national level. The model is used to assess the potential impact of the antiretroviral treatment rollout and the age groups in which new infections will occur (Dorrington *et al.*, 2004:1-2).

Both the public and private sectors are implementing various interventions. Assumptions about the impact of HIV on fertility and the relative levels of HIV prevalence in women using private and public antenatal services have been improved, to allow for smaller differences in HIV prevalence between the public and private sector, and bigger differences between antenatal prevalence and the prevalence of the overall population than previously assumed (Dorrington *et al.*, 2004:2-3).

Interventions have had and are having a significant impact on the course of the epidemic. The mother-to-child transmission prevention (PMTCT) programme has reduced the number of babies infected and behaviour change, in particular, has seen an increase in condom use and has reduced the number of adults infected. The national antiretroviral treatment programme can be expected to play a particularly important role in the future outcome of the epidemic (Dorrington *et al.*, 2004:5).

For example, as shown in figure 3.5, the model projects that by 2010, there are likely to be roughly 381 000 AIDS deaths per annum rather than the 495 000 that would have been expected if no antiretroviral treatment programmes were introduced. In the default scenario, it is assumed that ultimately only about half of South Africans who need antiretroviral treatment will be able to access it. If we assume that only 20 per cent manage to access antiretroviral treatment then the estimated number of AIDS deaths in 2010 increases to 450 000, but if the proportion is as high as 90 per cent the number of AIDS deaths would be reduced to 290 000 (Dorrington *et al.*, 2004:5).

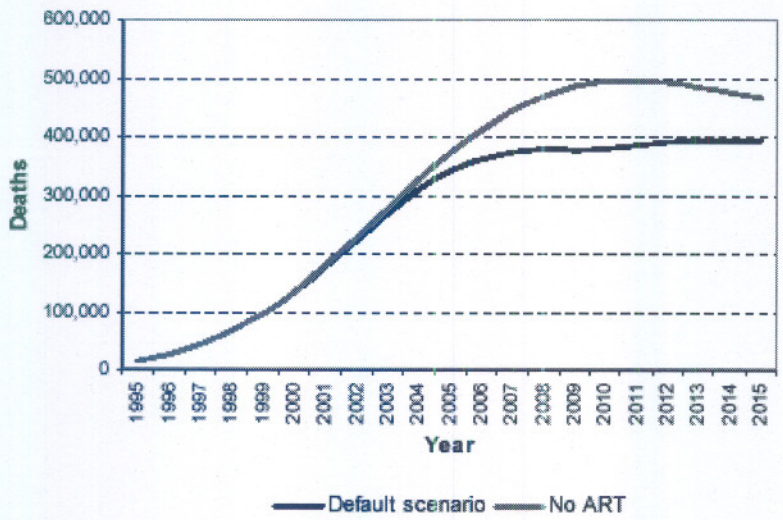


Figure 3.5 Projected number of AIDS deaths with and without national antiretroviral treatment programme, ASSA2002 (Dorrington *et al.*, 2004:5)

Figure 3.6 shows the difference that the antiretroviral treatment programme is expected to play in prolonging life expectancy. Already in 2004, the HIV/AIDS pandemic has taken about 13 years off life expectancy. Life expectancy is thus 51.0 years, rather than the 63.9 years it would have been without HIV/AIDS. Without the antiretroviral treatment programme, the decrease in life expectancy would be 18 years by 2015, with an average life expectancy of just under 48 years. With the antiretroviral treatment programme, the difference is expected to reduce to 15 years, giving a life expectancy of 50 years (Dorrington *et al.*, 2004:5).

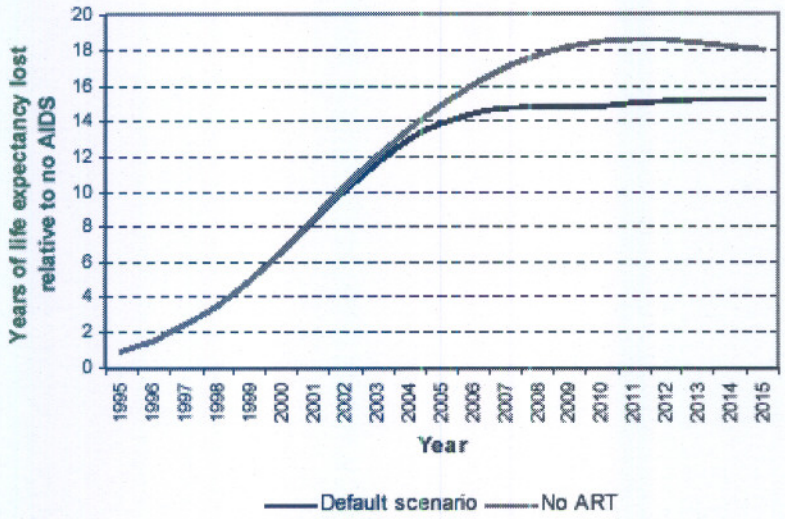


Figure 3.6 Projected impact on life expectancy with and without national antiretroviral treatment programme, ASSA2002 (Dorrington *et al.*, 2004:6)

Based on a scenario of antiretroviral treatment being made available so that half of those that need treatment would be receiving treatment by 2010, life expectancy at birth is now expected to fall to a little below 50 years by 2005 (48 years for men and 52 for women) and then plateau around this level. Previous estimates, which did not allow for interventions (some of which have been in place for a number of years) suggested that life expectancy would fall to around 43 years before climbing back up to level off at around 50 years (Dorrington *et al.*, 2004:6).

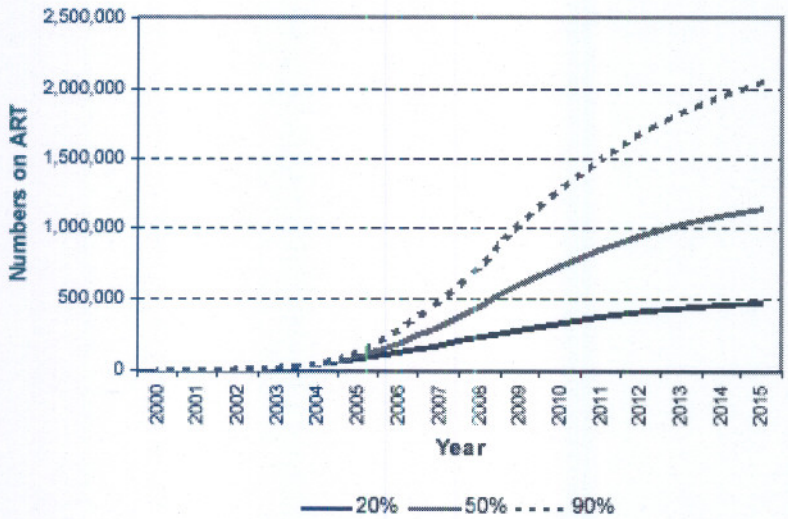


Figure 3.7 Projected numbers receiving treatment according to various coverage scenarios, ASSA2002 (Dorrington *et al.*, 2004:6)

The model suggests that in 2004 around 500 000 people would be in need of antiretroviral treatment (in terms of the definition used in terms of the rollout plan). The number of people that would be receiving treatment would be a function of how successful the role out is, and of how successful antiretroviral medicines (ARV drugs) are in extending life. Figure 3.7 shows the expected numbers on treatment under three different scenarios of ultimate coverage of the treatment programme; 20 per cent, 50 per cent (the current default) and 90 per cent (Dorrington *et al.*, 2004:7).

Without antiretroviral treatment we would have expected some 495 000 deaths due to AIDS in 2010, with antiretroviral treatment this will be reduced to approximately 380 000 – a difference of about 100 000 deaths in a year. There is uncertainty about the coverage of the antiretroviral treatment rollout and the number of deaths in 2010 could be anything between 290 000 and 450 000. With the default scenario of the interventions, life expectancy is projected to fall to just under 50 years compared with the previous estimate of 43 years (Dorrington *et al.*, 2004:iii).

3.3 THE HEALTH CARE SYSTEM IN SOUTH AFRICA

Health care issues have become increasingly globalised. Every year, for example, HIV/AIDS, malaria and tuberculosis are killing about 5 million people in developing countries. This death toll has social, political and economic consequences beyond national states and threatens sustainable development particularly in Sub-Saharan Africa. Advocates of free markets have to admit that markets are not efficiently distributing services, particularly where the health sectors in developing countries are concerned (Lehmann, 2001:2).

Health care providers worldwide are faced with the challenge of adapting to recent and anticipated future reforms in health care policy aiming to control the ever-increasing health care costs. The major difficulty encountered is how to maintain a right balance between the trio goals of adequate access, high quality and acceptable cost in health care delivery (Li, 2003:192).

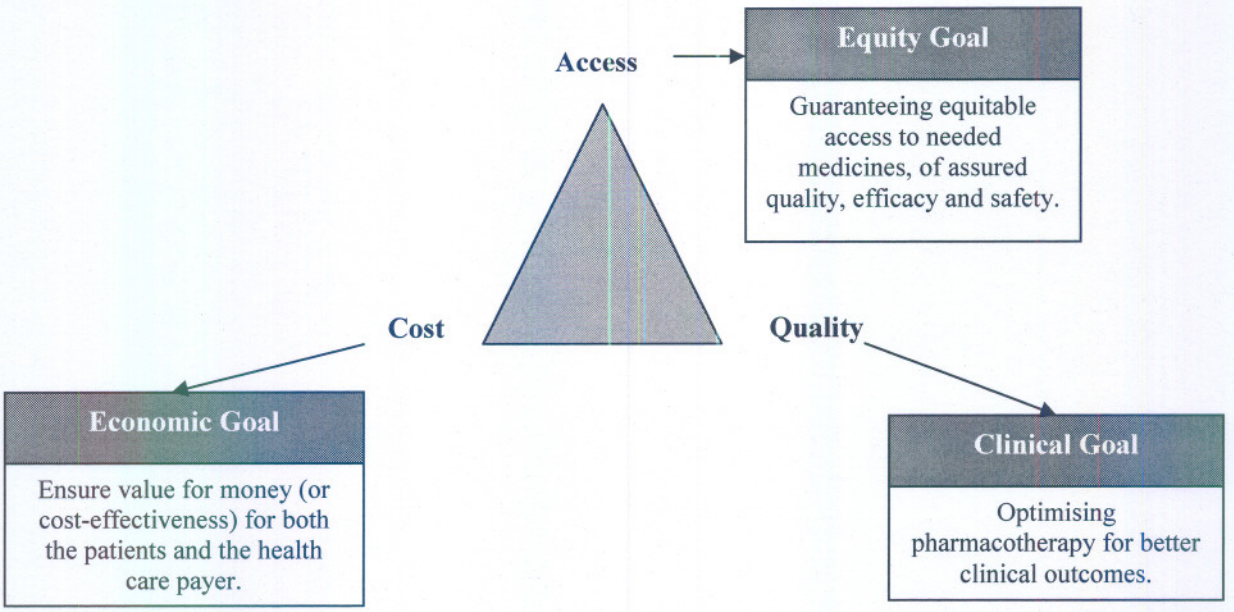


Figure 3.8 Goals of health care (Li, 2003:193)

Common to all health systems is a growing scarcity of resources necessary to meet society's health care demands, which is forcing the public and private sectors to make difficult social-economic choices. Unique to each system is an underlying framework for cultural and ethical values that drives policymaking, financing decisions, and the public's expectations. Policymakers and the private sector are eagerly leveraging global benchmarks and guidelines in an attempt to improve the health status of their respective populations and control health care expenditures (Ernst & Young, 2003:1).

Access to health care information also results in better health system performance and supports measures aimed at preventive care, which sometimes lowers the financial burden on a health system. Increased utilisation of more sophisticated treatments and procedures becomes a key driver of health care costs, as countries move forward along the path of industrialisation. Public and private sector purchasers traditionally have responded with supply-side cost containment initiatives such as

- limiting medical school enrolment;
- peer review control systems and medical audits;
- in-patient pharmaceutical formularies;
- limiting provider reimbursement; and
- introducing global budgets and capitated reimbursement systems (Ernst & Young, 2003:1).

Collaboration among the government, consumers, and the private sector is increasingly important in the successful adoption of international benchmarks and standards. Consumers are demanding that strict cost-containment strategies be replaced by those aimed at obtaining value from each health care dollar, with value being defined as a combination of quality – service quality, access, choice, and technical quality – and price. Governments and the private sector measure value along the lines of productivity, employee retention, long-term costs, and improvement of health status (Ernst & Young, 2003:1).

South Africa has a population of approximately 46.6 million people, according to Statistics South Africa (Stats SA, 2004:1), of whom 77 per cent are black, 11 per cent white, 9 per cent mixed race and 3 per cent of Asian descent. Although classified as a middle-income country, it is estimated that between 35 and 55 per cent of the population live in poverty and lack access to basic services including health care, clean water and sanitation (Ndimande, 2005:1).

It is the stated policy of the DOH to move "towards a National Health System for South Africa" (the title of its White Paper). It also sees its current reform initiatives as part of a future broad-based national social security system that will include a compulsory social health insurance system for all employed people for a defined public hospital package (Fourie, 1999:2).

Evaluating the current state of health and development in South Africa is no easy task. On the positive side, significant progress has been made in a number of health and development areas including improving literacy rates, raising life expectancy, falling infant mortality figures and greater immunisation coverage. On the other hand, there is a lack of education, low economic growth, unemployment, lack of basic services and amenities, high poverty levels, inequalities in life changes, social instability, crime and violence, and the erosion of key social institutions and values. Superimposed on these are deep inequalities and disparities in most of the health and development indices, accompanied by severe deprivation. The imminent threat of HIV/AIDS is perhaps the most important single factor in the larger health and development sector (Ndimande, 2005:5).

The South African health care system has problems like how to subject doctors and hospitals to financial discipline, how to secure adequate treatment for the poor and the elderly and how to control the apparently infinite demand for health care. In addition, it has to cope with our peculiar historical, political, demographic and economic environment (Fourie, 1999:2).

The delivery of health care services (HCS) in South Africa is managed by two systems:

- The public health care system, which is mainly government subsidised and serves the bulk of the population.
- The private health care system, which is administered by health insurance programmes and only serves a few people who can afford medical aid coverage/insurance (Ndimande, 2005:2).

The private sector is catering for approximately 22 per cent of the population covered by medical schemes and private health insurance products, and a public sector [funded primarily through taxation Wadee *et al.*, (2003:7)] that has to assume responsibility for the health needs of the remaining 78 per cent of the population. The above-mentioned 22 percent, who have access to the private sector, consume approximately 61 per cent of the country's total health care expenditure of R55 billion (Fourie, 1999:1).

The two systems are distinct and have different priorities, standards and needs. The private sector system is classified by Western-standard facilities. With the introduction of managed care in the private sector system, there is an increased need for United States expertise in the area of cost management. The public sector is undergoing tremendous changes in both its administration and facilities. The opportunities for United States companies in the public sector are in the supply of sophisticated medical equipment (Ndimande, 2005:2).

There is a direct need for cost control in the medical aid industry, with special emphasis on doctors' consulting fees and drug costs. Managed care is regarded as one of the best opportunities for United States companies interested in accessing the local health care market to joint venture with existing companies to transfer cost control information and technology. Given its capacity and relative technological advancement, broadening access to the private sector is recognised as an important step in improving the quality of health care available to all South Africans (Ndimande, 2005:6).

3.3.1 Health care expenditure

According to Lehmann (2001:2) drug expenditure mirrors the global distribution of wealth. Virtually every textbook on health economics published during the last 25 years stresses the escalating trend in health care costs whether absolute, relative or per capita, as a major cause of concern for governments, business leaders and individuals. The trend for health expenditure to demand an ever-increasing percentage of the gross national product of a country is well documented. This trend is set to continue or worsen due to factors such as the ageing of the population, expensive technological advances in

diagnostics and treatment, changes in disease patterns (e.g. AIDS) and progressively more specialised health care providers and facilities (Fourie, 1999:2).

The World Health Organisation (WHO) recommends a health care expenditure of no more than 5 per cent of its Gross Domestic Product (GDP) for developing countries. In spite of this relatively high national expenditure on health care, the health status of South Africa's people, as measured by virtually any of the standard health indicators, compares very poorly with other countries that are at a similar stage of economic development and are spending considerably less money on health services than we do (Fourie, 1999:1).

Wadee *et al.* (2003:7) stated that South Africa currently has a high total health care spending of 8.5 per cent of its GDP. The private sector expenditure exceeds that of the public sector (only 20 to 25 per cent of the population has regular access to the private sector) and is estimated at 80 per cent of the total health care expenditure (Ndimande, 2005:6). Its health status ranks poorly with respect to countries spending as much and even less on health care. One explanation for this poor performance is the inefficiency within the health system associated with its segmentation between public and private sectors (Wadee *et al.*, 2003:7).

The DOH believes that it will be possible and affordable to provide basic health care to all South Africans within the next 8 years. The Government expects significant growth in public health care expenditure (9 per cent) until it constitutes 26 per cent of the annual budget. The DOH assumes real growth of 3.6 per cent for the whole health budget (Ndimande, 2005:3).

Per capita spending at district level on Primary Health Care (PHC) ranges from R389 in richer districts to R42 in the poorest districts, meaning that many districts are simply not able to afford the PHC package estimated at approximately R220 per capita. Although spending on health in the public sector in 2005/2006 is projected to increase by R8.7 billion in real terms over a decade, much of the funding has been absorbed by HIV/AIDS, medical inflation and relatively higher salaries which have resulted in real expenditure per capita stagnating. On a positive note, 94 per cent of pregnant women receive antenatal care and there has been an improvement in the quality and quantity of health related data for planning and policy formulation purposes (Padarath, 2004:1).

There is therefore a need to understand whether, and if so, how, the public and private sectors can work together more effectively in the future in order to improve overall health system performance. An environment of constrained public sector resources and limitations on further private sector market

expansion only add to the pressure to increase the levels of interaction between the sectors (Wadee *et al.*, 2003:7).

On 18 to 20 November 2001, the Department of Health held a health summit where players in the South African health care arena had the opportunity to discuss the four key challenges currently facing the health sector, namely quality of care, public-private interactions, HIV/AIDS/STDs and TB, and human resources. Current President, Thabo Mbeki, pointed out that a major obstacle to be addressed is the gap between the private and public sectors. Partnerships between private health care providers and public health services should be utilised to eradicate this gap (SAPC, 2002b:5).

3.3.2 Private health care system in South Africa

According to Ndimande (2005:6) South Africa's private health care industry is large and highly developed. The private sector is playing an increasingly important role in the delivery of services even in countries with dominant public sectors. The South African health system compromises a strong private sector, serving less than 22 per cent of the population and financed through voluntary health insurance and out-of-pocket payments (Wadee *et al.*, 2003:7). The private sector includes for-profit corporations. There are more than 200 private hospitals, owned by consortia of private physicians or large corporations (Reich, 2000:618).

Ndimande (2005:6) stated that broadening access to the private sector is recognised as an important step in improving the quality of health care available to all South Africans, given its capacity and relative technological advancement. The quality of care of South Africa's private system is excellent. The United Nations ranked South Africa's private system 39 out of 162 nations for technological innovation and achievement. Worldwide, people fly to South Africa for operations, which are relatively cheap because of the country's weak currency (Basset, 2004:2).

Pharmaceutical research and development is time and cost intensive and is mainly carried out by the private sector. Private companies gain from access to a network of cooperations and to possibilities of technology development that might later become profitable on their main markets (Lehmann, 2001:2).

The re-regulation of the current private health sector via the recently promulgated Medical Schemes Act of 1998 (131/1998), and the proposed compulsory social health insurance system, are seen by many in organised business and the private health sector as transparent attempts by the DOH to provide central control over private health expenditure and to re-direct it progressively towards public sector providers or state hospitals (Fourie, 1999:2).

These initiatives should be seen in conjunction with the Department's other centralist-socialist policies aimed at regulating the supply-side of the private hospital industry via strict licensing and the pharmaceutical industry via price controls and parallel importation while simultaneously introducing a period of compulsory community service for medical graduates (Fourie, 1999:2).

According to Basset, (2004:2) the current concerns among private patients are that health care will become unaffordable. In the South African environment employee health benefits have similarly become a major cost of doing business with medical scheme contributions, escalating from 7.1 per cent of formal sector salaries in 1982, to 15.2 per cent in 1992, and 17.4 per cent in 1998. More than a decade of runaway medical inflation has put private health care beyond the means of its traditional customers, i.e. employers and high earning employees. For the private health care sector to survive at all, it is essential that it must contain costs far more effectively than it has in the past (Fourie, 1999:4).

Major providers of health care in South Africa are medical schemes (private health insurance companies). Medical schemes receive 7.9 per cent of all public health financing for the provision of health insurance to civil servants (Thomas & Muirhead, 2000:28). According to Cornell *et al.* (2001:1) less than 20 per cent of the population are covered by medical schemes. The inequity of health care delivery is represented in the income level of the beneficiaries. A mere 118 026 (1.5 per cent) of those covered by medical schemes have incomes in the lowest quintile, compared to 4 456 883 (58.6 per cent) of those in the highest quintile (Thomas & Muirhead, 2000:1). As with other diseases, inequity in coverage translates into an inequity of HIV/AIDS treatment. Of those in South Africa receiving HAART, the vast majority is managed through disease management schemes (Connelly, 2002:5).

According to Basset (2004:1) insurance plans are struggling because of medical inflation on the one hand and legislation to enforce 25 per cent solvency reserves on the other. There were many mergers between medical schemes. Managed health care and various innovative saving schemes have developed. More people buy limited coverage or choose to pay certain medication out of their own pockets and save their medical insurance contribution for other big expenditures (Basset, 2004:1).

3.3.2.1 Medical schemes

According to Doherty and McLeod (2002:42) medical schemes industry was de-regulated in 1989 and 1993 through legislation passed by the apartheid government. The industry's ability to deal with cost escalation was limited and between 1982 and 1992 medical scheme contributions had risen steadily from 7.1 per cent of the average salary to 15.2 per cent, while salaries had not changed much in real terms. During 1996 to 1998 cost escalations continued and the total contributions of members of medical

schemes grew faster than inflation. With risk-rating, high-risk members – typically the elderly or chronically ill – had their contributions loaded, were given life-long exclusions for pre-existing conditions or were denied membership completely (Doherty & McLeod, 2002:42).

Another practice that escalated was the 'dumping' of private patients on the public sector once their (now more limited) benefits had been exceeded. Each of these practices was a means of cost avoidance (as opposed to improvements in efficiency), and together they reduced medical scheme coverage for those private patients most in need (Doherty & McLeod, 2002:42).

In 1998, government passed a new Medical Schemes Act, No. 131. The Medical Schemes Act (Act 131 of 1998) and accompanying regulations of 1999 were implemented from January 2000, and were followed by several amendments. The Medical Schemes Act (Act 131 of 1998) made it compulsory for every scheme to accept all eligible applicants ('open enrolment') and to charge contributions that were differentiated only on the basis of income and the number of dependants, and not on age or the risk of ill-health ('community rating') (Doherty & McLeod, 2002:42-43).

The Medical Schemes Act (Act 131 of 1998) made it compulsory for every scheme to cover a comprehensive package of hospital and outpatient services, known as the Prescribed Minimum Benefits (PMBs). The Medical Schemes Act (Act 131 of 1998) was pushed through parliament successfully partly because of the commitment of the then Minister of Health to improving equity within the private sector (Doherty & McLeod, 2002:42-43).

There are two main categories of medical schemes. Registered medical schemes are those that fall fully under the regulatory control of the Medical Schemes Act (Act 131 of 1998). Bargaining Council schemes (previously called exempt schemes) are those schemes that are not able to comply fully with the Medical Schemes Act (Act 131 of 1998) and are thus granted exemptions from certain of its provisions, particularly with respect to PMBs. Historically Bargaining Council schemes included those covering the police service, correctional services and the defence force, as well as schemes that were created before the first Medical Schemes Act of 1967. In 2001 the Bargaining Council schemes that reported to the Registrar of Medical Schemes numbered only eight and serviced only four per cent of total beneficiaries (Doherty & McLeod, 2002:44).

The total number of schemes has declined steadily over the years, with smaller schemes tending to merge (Council for medical schemes, 2001:1). In contrast, the number of beneficiaries increased steadily from 3.5 million in 1974 to 7 million in 1996 and thereafter the figures remained fairly stable. This has

resulted in schemes with larger risk pools, a trend that should have made the management of risk – and associated health care costs – more effective (Doherty & McLeod, 2002:44).

South Africa always had two tariff structures, according to which tariffs for medical treatments were determined. The first tariff structure is that of the Board of Health care Funders (BHF). Most medical aids base their payments to health care providers (doctors, dentists, hospitals, etc.) on this structure. The second tariff structure is that of the South African Medical Association (SAMA), which represents doctors in private practice. This association publishes an annual rates guide of what it thinks its members should be paid for their services. These rates are generally much higher that the BHF rates. In January 2004 the DOH issued a single guideline, the National Reference Price List for Health Services (NRPL) (Health24, 2004:1).

In 2001 roughly two thirds were restricted schemes (these typically only accept members belonging to the employer or industry that set them up), while the remaining were open schemes (these are open to the general public). The membership of open schemes has grown rapidly since the early 1990s while that of restricted schemes has declined. A feature of recent years has been the shifting of beneficiaries from restricted into open schemes. Thus, in 2001, 71 per cent of registered schemes beneficiaries were located in open schemes whereas, in 1990 beneficiaries were distributed roughly evenly between the two types of registered schemes (see figure 3.9). At present, almost two-thirds of all the largest medical schemes (with 30000 or more beneficiaries) are open schemes (Doherty & McLeod, 2002:44).

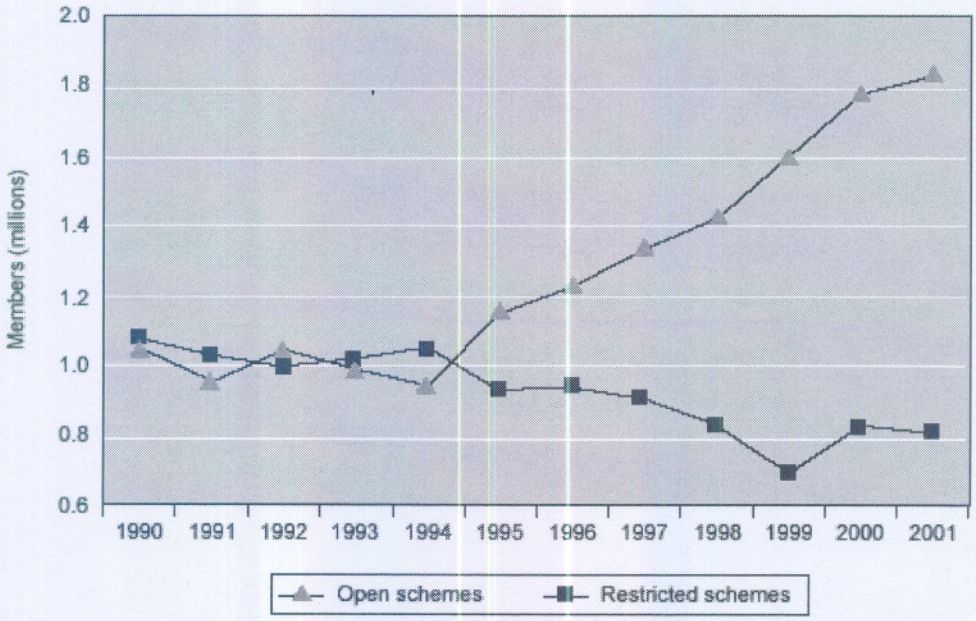


Figure 3.9 Members belonging to restricted and open schemes, 1990-2001 (Doherty & McLeod, 2002:45)

3.3.2.2 Medical scheme legislation

The Medical Schemes Act (Act 131 of 1998) is one of the most important pieces of legislation promulgated by South Africa's first democratic government according to McLeod and Stein (2002:1). The Medical Schemes Act (Act 131 of 1998) has been effective since January 2000, and regulates medical scheme coverage for certain defined health conditions in terms of PMBs (Stein *et al.*, 2002:2).

The primary objective of the Medical Schemes Act (Act 131 of 1998) is the extension of coverage in terms of both the number of members and the benefits they enjoy. The explicit tool used by the Medical Schemes Act (Act 131 of 1998) to force this extension was the combination of mandatory open enrolment, community-rating and PMBs. While community-rating and PMBs would increase the costs of cover for younger individuals, the designers of the Medical Schemes Act (Act 131 of 1998) hoped that the collective effects of opening up schemes to a large low-income market, creating larger risk pools and applying pressure to compete on the basis of efficiency, would bring down the costs of cover for the bulk of members. Many critics of the Medical Schemes Act (Act 131 of 1998) argued otherwise, however (Doherty & McLeod, 2002:43).

Unfair discrimination against people on a range of grounds including "any medical condition" is prohibited by private medical schemes. The AIDS Law Project, AIDS Consortium and current Treatment Action Campaign (TAC) members supported the passage of the legislation against powerful forces including the insurance industry, the Chamber of Mines and others (McLeod & Stein, 2002:1).

3.3.2.3 Medical scheme coverage for HIV/AIDS

According to Erasmus (2005:1) all medical schemes have to provide benefits for members who have HIV/AIDS. PMBs are benefits in respect of relevant health services prescribed by the regulations under the Medical Schemes Act (Act 131 of 1998). The Medical Schemes Act (Act 131 of 1998) makes provision for the medical and surgical management of opportunistic infections as well as localised malignancies as part of the PMB. The Amendment of Regulations on Minimum Benefits has added the following as part of the treatment of HIV infection:

- HIV voluntary counselling and testing
- Co-trimoxazole as preventive therapy
- Screening and preventive therapy for tuberculosis (TB)
- Diagnosis and treatment of sexually transmitted infections
- Pain management in palliative care

- Treatment of opportunistic infections
- Prevention of mother-to-child transmission of HIV
- Post-exposure prophylaxis following sexual assault
- Medical management and medication, including the provision of ARV therapy, and ongoing monitoring for medicine effectiveness and safety, to the extent provided for in the national guidelines applicable in the public sector (Martinson *et al.*, 2002:238; Stein *et al.*, 2002:60; Erasmus, 2005:2).

Over the last few years, most medical schemes have accepted responsibility for their members with HIV/AIDS. In addition to legislated PMB, members with HIV/AIDS are often covered through disease management programmes that provide a comprehensive response to the disease (Stein *et al.*, 2002:1).

The inclusion of antiretroviral therapy into the HIV PMB has a limited effect on medical schemes. This is the conclusion of a study done by Aid for Aids, an innovative Medscheme initiative that looked critically at the number of beneficiaries registered on HIV-programmes in relation to the estimated HIV-prevalence within medical schemes (Medscheme, 2005:1).

The study was carried out on several medical schemes covering 680 000 lives. An Aids demographic modelling technique developed by the Actuarial Society of South Africa (ASSA) was used to estimate the HIV prevalence for these schemes. This was calculated to be 10 per cent as of early 2005. Based on data from the WHO, it is estimated that 21 per cent of HIV positive patients should be on antiretroviral treatment. Using the 10 per cent prevalence indicated by the modelling exercise, this equates to 2.1 per cent of the 680 000 lives. Currently, 1.9 per cent of lives are actually on antiretroviral treatment, which is close to the estimated number who should be on treatment (Medscheme, 2005:1-2).

The data suggest therefore, that enrolment of those who stand to gain the most benefit from registering on Aid for Aids and accessing treatment is relatively high. This does not mean that management programmes should not continue to make every effort to enrol as many HIV positive beneficiaries as possible. Early enrolment provides a valuable educational opportunity and enables antiretroviral treatment to be commenced at the optimal time (Medscheme, 2005:2).

3.3.3 Pricing regulation implemented in 2004

On 30 April 2004, the current Minister of Health, doctor M.E. Tshabalala-Msimang published the finalised medicine pricing regulations in Government Gazette number 26304, with recommendations from the Pricing Committee, in terms of the Medicines and Related Substances Act, 1965 (Act No 101 of 1965) commencing on 2 May 2004 (DOH, 2004a:3).

The main objectives of the medicine pricing regulations were the following:

- To make medicines more affordable and accessible to the consumer in South Africa by capping the prices where necessary.
- To remove the incentive of using very expensive medicines to prescribers and dispensers of medicines, which add no benefit to the patients' illness if compared to a cheaper medicine.
- To remove marketing practices of volume of discounts, bonuses and rebates in the supply of medicines, that leads to huge perversities without significant gains to the consumer (DOH, 2004c:1).

According to Caelers (2004:10) the pricing regulations also enforced a Single Exit Price (SEP). SEP means the price set by the manufacturer or importer of a medicine or Scheduled substance in terms of these regulations combined with the logistics fee and Value Added Tax (VAT) and is the price of the lowest unit of the medicine or Scheduled substance within a pack multiplied by the number of units in the pack (DOH, 2004a:6).

On 2 August 2004 (Caelers, 2004:10) the practice of dispensing fees for pharmacists was officially being implemented. From May to July 2004, pharmacists and dispensing doctors could still sell medicines as they had been doing in the past. From 2 August 2004, dispensers could no longer charge a mark-up, and were entitled to charge the following dispensing fees:

- In the absence of a prescription, the dispensing fee for Schedules 1 and 2, exclusive of Value Added Tax (VAT), must not exceed
    - (a) sixteen per cent of the single exit price of a medicine or Scheduled substance where the single exit price of that medicine or Scheduled substance is less than one hundred rand;
    - (b) sixteen rand in respect of a medicine or Scheduled substance where the single exit price of that medicine or Scheduled substance is greater than or equal to one hundred rand (DOH, 2004a:14).

- Schedules 3,4,5,6,7 and 8 and the medicines and Scheduled substances falling into Schedules 1 and 2 in respect of which a prescription has been written, the dispensing fee, exclusive of VAT, must not exceed

    (a) twenty six per cent of the single exit price of a medicine or Scheduled substance where the single exit price of that medicine or Scheduled substance is less than one hundred rand;

    (b) twenty six rand in respect of a medicine or Scheduled substance where the single exit price of that medicine of Scheduled substance is greater than or equal to one hundred rand (DOH, 2004a:14).

3.3.4 Public health care system in South Africa

South Africa has well-developed high technology hospitals in the main cities, but only the basic underdeveloped health care facilities and services in rural areas. As a consequence, the poorer two thirds of the population do not have full access to essential health care services. The public sector is pursuing a major cost-cutting drive by reducing the number of secondary and tertiary health care facilities and concentrating on primary health care. The Government developed a district health system in rural areas to deliver integrated primary health care and hospital services (Ndimande, 2005:3).

The DOH has built new clinics in rural areas where health facilities were previously not accessible. The government has also imported doctors from Cuba and Germany to help alleviate the shortage of doctors in rural South Africa. Although progress has been made, more is needed to ensure that all South Africans, especially those in rural and impoverished areas, have adequate access to health care services (Ndimande, 2005:3).

According to Basset (2004:2) quality of care of South Africa's public system varies according to location. Large, urban teaching hospitals offer good, if clogged-up, service. But despite a massive building programme, many rural hospitals are run-down, with broken equipment, two patients per bed, and a shortage of basic medicine. Ambulances are worn out. There is a dire shortage of radiographers, dieticians, physiotherapists and nurses (Basset, 2004:2).

Since 88 per cent of doctors work in metropolitan areas, there is a shortage of doctors in remote areas (the ratio varies from 1:650 people in the Western Cape to 1:30000 in parts of the Eastern Cape) due to low salaries, lack of infrastructure, etc. On the plus side, more than 500 new clinics now stand in areas where formerly people used to walk seven hours for treatment (Basset, 2004:2).

The public service is funded at federal (20 per cent) and provincial (80 per cent) levels. There is serious discrepancy in health spending between the nine provinces, with some rural ones actually cutting health budgets in favour of education (Basset, 2004:2).

The Government has taken steps to rectify this imbalance and raise the standard of health care to that of the private health care system by:

- Increasing Public Private Partnerships (PPP), which is seen as one way to tap into the concentration of resources to the benefit of all citizens.
- Setting a medium term goal so that the average number of public primary health care (PHC) consultations per person is raised from 2.8 to 3.5 by 2005 (Ndimande, 2005:3).

The Government has a national HIV/AIDS and STD strategic plan for South Africa focusing on prevention, treatment, care and support, legal and human rights, and monitoring, research and evaluation. The primary goals are to reduce the number of new HIV infections (especially among youth); and to reduce the impact of HIV/AIDS on individuals, families and communities (DOH, 2000:6).

The following general strategies are followed:

- an effective and culturally appropriate information, education and communications (IEC) strategy;
- increase access and acceptability to voluntary HIV testing and counselling;
- improve STD management and promote increased condom use to reduce STD and HIV transmission; and
- improve the care and treatment of HIV positive persons and persons living with AIDS to promote a better quality of life and limit the need for hospital care (DOH, 2000:16).

3.3.5 Equity in health

Braveman and Gruskin (2002:254) defined equity in health as the absence of systematic disparities in health (or in the major social determinants of health) between groups with different levels of underlying social advantage/disadvantage – that is wealth, power, or prestige. Equity in Health is also defined as the absence of systematic and potentially remediable differences in one or more aspects of health across populations or population groups defined socially, economically, demographically, or geographically (ISEqH, 2002:1).

According to Strachan (2000:6) South Africa is one of the most inequitable countries in the world, with the wealthiest 10 per cent of the population accounting for 60 per cent of the whole country's wealth. Health equity goals were seen as an integral part of the overall political commitment to addressing poverty and redressing inequity by the first democratic government (McIntyre & Gilson, 2002:1638). Implementation of these goals has proved harder than many imagined it would be and, unfortunately, it remains the case that in South Africa at the moment it is usually those who have most who have access to the best resources (Ntuli, 2000:3).

The fact that South Africa's health service is divided into private and public sectors is a glaring manifestation of the inequity still prevalent in the society today. Although the technical care may well be of equal quality in each, the perceived quality of care is not. Factors such as waiting times, number of elective operating slates and number of available staff are very different between the two sectors. For these reasons, people who can afford it use the private sector in preference to the public sector without hesitation (Clarke, 2000:13).

Membership of a medical aid scheme is a good indication of the use of private sector health facilities. As can be seen from figure 3.10 below, the greatest percentage of any South African population group to belong to a medical scheme (and therefore to use the private sector) is white. The lowest percentage to belong to a medical aid scheme is African (Strachan, 2000:7).

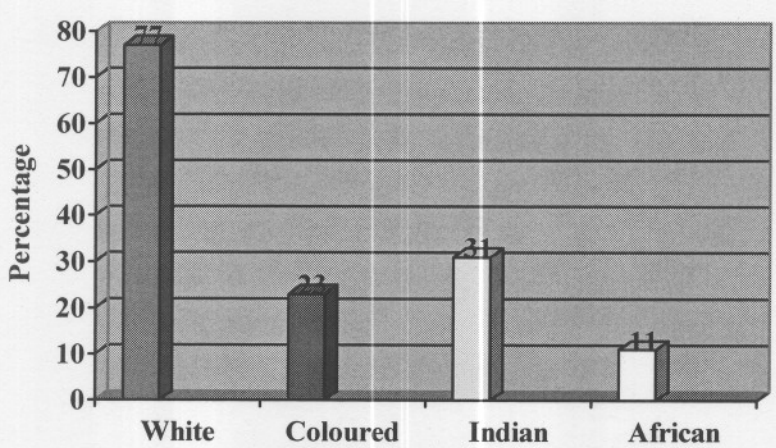


Figure 3.10 Medical Aids Coverage by Race (Strachan, 2000:8)

There are a number of ways to balance out the inequity between the private and public sectors. One of them is to improve the quality of care in public sector facilities, as well as access to these facilities. The Clinic Upgrading and Building Programme is one of the initiatives aimed at doing this. Another already

implemented is the redistribution of junior doctors and pharmacists to rural facilities for a year of compulsory community service (Strachan, 2000:8).

South Africa, unlike other countries under investigation, has some legislation that specifically addresses HIV/AIDS. Under the Employment Equity Act, an employee or job applicant may not be discriminated against in any employment policy or practice on the basis of HIV status, unless it is an inherent requirement of the job. The Employment Equity Act prohibits unauthorised employment-related HIV testing. It requires an employer to apply to the Labour Court for permission and be granted the same by the Court, before the employer can ask a job applicant or current employee to take an HIV test (HSRC, 2004:60).

3.3.6 Public/Private Partnerships (PPPs)

When the market fails to distribute health benefits to people who need them, partnerships between public and private organisations are often seen as offering an innovative method with a good chance of producing the desired outcomes (Reich, 2000:617).

According to Reich (2000:617) many organisations in public health have established partnerships with private sector organisations. Partnerships are particularly important in a global world, where traditional boundaries between what is seen as public versus private responsibilities have become increasingly blurred, and where problems such as AIDS and climate change extend beyond national boundaries (Morrison, 2003:2).

What is a public-private partnership (PPP)? A PPP is a contractual agreement in which a private party delivers a service or performs a function for the public sector with the private sector assuming the risks associated with the delivery or function. A good working definition would include three points. First, these partnerships involve at least one private-for-profit organisation and at least one not-for-profit organisation or public organisation. Second, the partners have some shared objectives for the creation of social value, often for disadvantaged populations. Finally, the core partners agree to share both efforts and benefits (Reich, 2000:619).

A true PPP begins by identifying the central problem, then asking who should help solve it. Public-private partnerships are about shared agendas and combined resources, risks, rewards, and linkages that can magnify scale. True PPPs include the following:

- Voluntary and built on the respective strengths of each partner.

- Optimising the allocation of resources.
- Achieving mutually beneficial results over a sustained period.
- Involving written agreements that specify the purpose and duration of the partnership, governance, as well as exit arrangements (Morrison, 2003:3).

True partnerships exist on a spectrum from "regulated privatisation," where governments turn certain activities largely over to private sector or community partners, all the way to altruistic arrangements in which there is no direct profit motive (Morrison, 2003:3).

PPPs for health are diverse in many respects: the number of partners involved, the kinds of organisations involved, the funding levels and funding sources, the objectives for the partnerships, and the organisational structures of the partnerships (Reich, 2000:619).

The government priority since 1994 has been to improve access to primary health care. In 1997, the White paper on the Transformation of the Health Sector stated that 'the activities of the public and private health care sectors should be integrated in a manner that makes optimal use of all available health care resources.' The public-private mix in health care should promote equity in service provision (Ndimande, 2005:2).

There are various reasons why PPPs are being explored in the health sector. One major reason is that the historical interaction between the public and private sectors has not been positive, and has resulted in a strong negative net effect on the public sector.

- Firstly, the rapid expansion of the private hospital sector in recent years has undermined public provision by draining large numbers of highly skilled staff and paying patients out of the public hospital system.
- Secondly, the private health insurance system also exploits public hospitals by dumping expensive cases once insurance benefits have been exhausted in private hospitals.
- Thirdly, insured patients frequently claim to be uninsured and do not pay for care at public hospitals (Ndimande, 2005:2-3).

These factors have translated into a fairly substantial subsidy from the public to the private sector. An inadequate regulatory environment has helped to exacerbate the situation. PPPs are therefore seen as one way to tap into the concentration of resources to the benefit of all citizens (Ndimande, 2005:3).

According to the South African Pharmacy Council (SAPC, 2002a:2) the DOH is exploring partnerships with private health care providers, as part of the ongoing effort to provide quality health care to all South Africans. South Africa has a long history of PPPs within the health system. This includes contracts with both profit and non-profit providers supporting the delivery of tuberculosis, psychiatric and secondary level hospital care for public patients (Wadee *et al.*, 2003:7).

Most PPPs involve the private sector providing large infrastructure assets through design, building, finance and operating concessions of providing services to government not core to the provision of services. In such cases, payment to the private sector is by means of a 'universal charge' paid by the public sector or user charges paid directly by the public. An alternative model is emerging in the health sector to meet the demands of the public and private sectord (Anon, 2001:1).

Leading these developments is a project undertaken by the Free State health department for the Universitas and Pelonomi hospitals in Bloemfontein. Restructuring of the manner in which public sector health services are provided has meant a greater focus on primary care in areas closer to the population and a reduced need to treat patients at large provincial hospitals. As a result, Pelonomi hospital has reduced its capacity from more than 1 500 beds to fewer than 800 beds, freeing-up a range of facilities including wards, theatres, intensive-care units and supporting services (Anon, 2001:1).

This situation creates the opportunity for a win-win partnership with the private sector. The public sector requires facilities to be upgraded and revenue for new projects. The private sector is seeking new ways to help the mid-level employed patient who cannot afford full private sector health services but requires a higher level of service than provided by the public sector. PPPs aim to achieve both aims through the co-location of privately-operated health facilities within the confines of the public hospitals (Anon, 2001:1).

Budget constraints within the public sector, as well as an inequitable distribution of resources, e.g. in urban versus rural areas and in hospitals versus primary health care facilities, have put significant constraints upon public sector services in their efforts to provide all South Africans with quality health care. One way to alleviate these pressures is the creation of partnerships between the public and private health care sectors (SAPC, 2002a:2).

The concept of partnerships between the public sector and private health care providers is wholly compatible with national health policies as set out by the DOH, via:

a. The improvement of equity within the health care system, both within and between provinces.

b. The development of primary health care delivery systems.

c. The improvement of access to primary care (SAPC, 2002a:2).

The DOH has formulated the following as its implementation strategies:

- Avoiding duplication of expensive equipment.
- Drawing more paying patients back into public hospitals to generate revenue.
- Contracting with the private sector to ensure that all hospital beds in a province are used.
- Licensing of practices on the basis of certificate of need on a geographical basis to promote the equitable distribution of limited resources (SAPC, 2002a:2).

According to the DOH the aim of public/private partnerships is ultimately to benefit the public sector. There must, however, be adherence to the core principle that government provides, or guarantees to provide clinical services to public patients. Bearing this in mind, the main goals of PPPs must be one or more of the following:

- The reduction of costs
- The improvement of access to underserved areas
- The improvement of the quality of care
- The generation of revenue for the public sector (SAPC, 2002a:2).

These goals can be reached by adhering to the following principles:

- The most cost-effective means of providing services should be used.
- Costs should be reduced or contained by maximising the use of under-utilised resources.
- Additional resources should be generated for the public sector.
- Patients should be offered more choices in health care services.
- Clinical and management skills and systems should be improved (SAPC, 2002a:2).

Although there is agreement between the public and private sectors on the ultimate goal(s) of advancing science and improving the health of the public, resolution of differences in the measures of short-term success and of incentives is likely to be achieved slowly and incrementally (Lyles, 2003:2900-2901).

3.3.7 Managed health care

3.3.7.1 Overview of managed health care

Managed care is a broad term and encompasses many different types of organisations, payment mechanisms, review mechanisms and collaborations. Managed care is sometimes used as a general term for the activity of organising doctors, hospitals, and other providers into groups in order to enhance the quality and cost-effectiveness of health care. Managed Care Organisations (MCO) include Health Maintenance Organisations (HMO), Preferred Provider Organisations (PPO), Point-of-Service Plans (POS), Exclusive Provider Organisations (EPO), Physician-Hospital Organisations (PHO), Integrated Delivery System (IDS), Accountable Health Plan (AHP), Independent Practice Associations (IPA) etc. Usually when one speaks of a managed care organisation, one is speaking of the entity that manages risk, contracts with providers, is paid by employers or patient groups, or handles claims processing. Managed care has effectively formed a "go-between", brokerage or third party arrangement by existing as the gatekeeper between payers and providers and patients (Pohly, 2005:1).

With the emphasis on containing costs within the South African private health care industry, it has become ever more important for provider networks and funders to consider managed health care as a viable alternative to reduce the cost of health care delivery (Medicross Medical Centre, 2004:1).

Managed health care plans use a variety of strategies to administer prescription drug benefits, including the use of drug formularies, generic and therapeutic interchange, use of preferred provider networks, financial incentives to promote appropriate drug use, member cost-sharing, drug utilisation review programmes, enhanced clinical and utilisation information systems, pharmaceutical care services, and disease management programmes (Sterachis *et al.*, 1996:243)

Managed care organisations do not all look alike; in fact, a broad array of health insurers, medical groups, hospitals and health systems are considered managed care organisations (IHA, 2005:1).

Health care costs in many countries are escalating at rates well in excess of their overall rates of inflation. Some of the reasons for this include the following:

- New and improved medical technology and drugs
- A demand for better services by more affluent populations
- The existence of more lifestyle illnesses such as HIV/AIDS, alcoholism and obesity (Meridian Healthcare, 2004b:1).

In addition, although HIV/AIDS will decrease the average life expectancies of populations of African countries by decimating the economically active age groups of those populations, the elderly in these populations are living longer and will thus increase the rate of health care inflation given that they consume more health care resources than the young. Supporters of managed care believe that managed care interventions reduce the costs of health care and hence the above points support the introduction of managed care plans (Meridian Healthcare, 2004b:2).

Although the introduction of managed care into the South African private health sector was (and in some cases, still is) vigorously resisted by some of the major stakeholders and vested interest groups, managed care systems are now firmly established and are likely to play an increasingly important role in a future health care dispensation in South Africa (Fourie, 1999:3).

3.3.7.2 Definition of managed health care

Managed health care may be defined as a management process that attempts to coordinate the demand for, the provision of and the financing of health care. Unlike unmanaged health care, managed health care concentrates more on keeping members healthy than merely curing illness. It attempts to achieve this by aligning the incentives of all parties in the delivery and funding of health care. These parties are the patient, the provider and the funder (Meridian Healthcare, 2004a:1).

Stated differently, managed care is an integrated system for financing and delivering health care services. It is claimed that the advantage of integrating the payer and the provider is so as to be able to maintain high awareness and control of costs (Datamonitor, 2004:7).

By definition, managed health care refers to efforts to coordinate, rationalise, and channel the use of services to achieve desired access, services, and outcomes while controlling costs. MCOs do not all look alike; in fact, they come in a broad array of insurers, medical groups, hospitals, and other health systems (Conley, 2004:1).

3.3.7.3 Objectives of managed health care

The objectives of managed health care are to ensure the following:

- Providers deliver high-quality care in an environment that manages or controls costs.
- The care delivered is medically necessary and appropriate for the patient's condition.
- The most appropriate provider renders care.

- Care is rendered in the most appropriate, least-restrictive setting (American Heart Association, 2005a:1).

Managed care plans attempt to achieve numerous goals, including improvement in the appropriate use of medications, the enhancement of favourable patient outcomes, and improvements of the cost-effectiveness and cost-efficiency of health care (Sterachis *et al.*, 1996:243)

3.3.7.4 Pharmacy Benefit Management (PBM)

PBMs are specialised entities established to develop and manage prescription drug benefits for their customers, including self-insured employers, managed care organisations (MCOs), and federal/state government-funded programmes (Mullins & Wang, 2002:10).

PBMs interact with payers (e.g., employers, insurers, managed care organisations, government), providers (e.g., pharmacists, physicians), consumers (e.g., employees) and pharmaceutical companies. PBMs attempt to control pharmaceutical costs by managing both medication cost per unit and the number of units consumed (Olson, 2003:253).

General activities of a PBM that generate cost savings to plan sponsors include:

- Efficient processing of prescription claims.
- Providing a network of retail and mail-order pharmacy services to lower ingredient and dispensing fees (e.g., formulary management, generic-use programmes, drug utilisation review, disease management, manufacturer rebates).
- Academic detailing (e.g., letters to prescribers, educational interventions, newsletters).
- Offering prescription drug insurance benefits with patient cost sharing and other incentives (Olson, 2003:253).

3.3.7.5 Managed Care Organisation (MCO)

A managed care organisation may be a physician group, health plan, and hospital or health system. It can be any organisation that is accountable for the health of an enrolled group of people. In contrast to organisations that provide services at a discount but do not attempt to coordinate care, managed care organisations actually have responsibility for the health of enrolees and, as a consequence, seek improvements in both the results and cost-effectiveness of the services provided. Most managed care

organisations still care for those with traditional indemnity insurance in addition to patients insured under managed care health insurance products (IHA, 2005:1).

Managed Care Organisation (MCO) according to Pohly (2005:1) is a health plan that seeks to manage care. Generally, this involves contracting with health care providers to deliver health care services on a capitated (per-member per-month) basis. MCOs of the future will display: risk management and accountability functions. MCOs' emphasis is on preventive medical care (Clifford, 1999:16).

Managed health care organisations use various approaches in an attempt to achieve this aligning of incentives. These approaches may be divided simplistically into two: a top down approach and a bottom up approach. The top down approach identifies certain components of health care (e.g. hospitalisation and medicines) as the most expensive or important and hence targets these costs, while at the same time attempting to ensure that the health care provided is not compromised. The bottom up approach assumes that health care outcomes and costs up a referral chain cannot be adequately controlled without intervening at the primary care level (Meridian Healthcare, 2004a:1; Meridian Healthcare, 2004b:3).

3.3.7.6 Types of managed health care plans

Health care plans can be divided into the following: Indemnity insurance, Managed fee for service, Preferred providers organisations (PPOs), Health Maintenance Organisations (HMOs), Point of service plans (POS), Physician-Hospital Organisation (PHO), Exclusive Provider Organisation (EPO), Accountable Health Plan (AHP), Integrated Delivery System (IDS), and Independent Practice Association (IPA) etc.

A discussion of the above-mentioned health care plans is as follows:

3.3.7.6.1 Indemnity insurance

According to Meridian Healthcare (2004b:3) indemnity insurance is the coverage provided by an insurer who merely pays out claims as and when they arise. Indemnity insurance is a plan that reimburses physicians for services performed, or beneficiaries for medical expenses incurred. Such plans are contrasted with group health plans, which provide service benefits through group medical practice (Pohly, 2005:1).

3.3.7.6.2 Managed fee for service

Managed fee for service is similar to indemnity insurance except that some controls are introduced. These could be anything from the use of a tariff scale (normally at a discount to providers' usual fees) to the use of a formulary from which drugs may be prescribed (Meridian Healthcare, 2004b:3).

3.3.7.6.3 Health Maintenance Organisations (HMOs)

Health Maintenance Organisations (HMOs) offer prepaid, comprehensive health coverage for both hospital and physician services. The HMO is paid monthly premiums or capitated rates by the payers, which include employers, insurance companies, government agencies, and other groups representing covered lives. The HMO must meet the specifications of the federal HMO act as well as many rules and regulations required at the state level. There are 4 basic models: group model, independent practice association, network model and staff model (Pohly, 2005:2).

An HMO enters into contractual arrangements with health care providers (e.g., physicians, hospitals and other health care professionals) who together form a "provider network." A contracted provider is one who provides services to health plan members at discounted rates in exchange for receiving health plan referrals. Members are required to see only providers within this network to have their health care paid for by the HMO. If the member receives care from a provider who is not in the network, the HMO will not pay for care unless it was pre-authorised by the HMO or deemed an emergency (American Heart Association, 2005:1).

Members select a Primary Care physician (PCP), often called "gatekeeper," who provides, arranges, coordinates and authorises all aspects of the member's health care. PCPs are usually family doctors, internal medicine doctors, general practitioners and obstetricians/gynaecologists. Members can only see a specialist (e.g. cardiologist, dermatologist, rheumatologist) if this is authorised by the PCP. If the member sees a specialist without a referral, the HMO will not pay for the care (American Heart Association, 2005:1).

HMOs may turn around and sub-capitate to other groups. For example, it may carve-out certain benefit categories, such as mental health, and sub-capitate these to a mental health HMO. Or the HMO may subcapitate to a provider, provider group or provider network. HMOs are the most restrictive form of managed care benefit plans because they restrict the procedures, providers and benefits (Pohly, 2005:2).

All HMOs bear risk, meaning they assume a contractual responsibility to deliver certain stated services for a fixed, prospective payment that is disconnected from actual services rendered. The plan thereby has an incentive to provide only medically necessary and appropriate care. The payment is capitated, that is, calculated on the basis of a defined population. Enrolment in an HMO is voluntary. HMOs deliver health care services to purchasers that are less expensive than PPO benefits (Clifford, 1999:33).

Types of HMOs:

- Staff model, in which physicians are salaried employees of the HMO.
- Group model, which contracts with multi-specialty physician group practices.
- Independent physician association (IPA) model, which contracts with Independent practice associations (IPA), which in turn, contract with independent physicians who practice in their own offices.
- Network model, which contracts with two or more independent group practices and/or IPAs (ANA, 1999:1).

3.3.7.6.4 Preferred Provider Organisations (PPOs)

According to Pohly (2005:2) Preferred provider organisations (PPOs) are combinations of hospitals and physicians that agree to render particular services to a group of people, perhaps under contract with a private insurer. It is a health care delivery system that contracts with providers of medical care to provide services at discounted fees to members. Preferred provider organisations encourage plan members to use a group of providers by providing them with incentives to do so. As providers are paid on a fee for service basis, there is still minimal transfer of risk from the insurer to the provider (Meridian Healthcare, 2004b:3).

Members may seek care from non-participating providers but generally are financially penalised for doing so by the loss of the discount and subjection to co-payments and deductibles. The services may be furnished at discounted rates and the insured population may incur out-of-pocket expenses for covered services received outside the PPO if the outside charge exceeds the PPO payment rate (Pohly, 2005:2).

A PPO can also be a legal entity or it may be a function of an already formed health plan, HMO or Physician-Hospital Organisation (PHO). The entity may have a health benefit plan that is also referred to as a PPO. PPOs are a common method of managing care while still paying for services through an indemnity plan. Most PPO plans are point of service plans, in that they will pay a higher percentage for care provided by providers in the network. Many insurers will offer PPOs as well as HMOs. Generally

PPOs will offer more choice for the patient and will provide higher reimbursement to the providers (Pohly, 2005:2).

Clifford (1999:32) stated that the principal difference between PPOs and the HMO/IPA model of managed care is in the underwriting. True PPOs do not manage risk. Unlike their peers in prepaid group practices, physicians and hospitals organised in a PPO network do not obtain prospective reimbursement via capitation for a defined population. PPOs are similar to HMOs in that they enter into contractual arrangements with health care providers (e.g., physicians, hospitals and other health care professionals) who together form a "provider network." (American Heart Association, 2005:2).

Unlike an HMO, members do not have a PCP ("gatekeeper") nor do they have to use an in-network provider for their care. However, PPOs offer members "richer" benefits as financial incentives to use network providers. The incentives may include lower deductibles, lower co-payments and higher reimbursements. For example, if you see an in-network family physician for a routine visit, you may only have a small co-payment or deductible. If you see a non-network family physician for a routine visit, you may have to pay as much as 50 percent of the total bill (American Heart Association, 2005:2).

PPO members typically do not have to get a referral to see a specialist. However, as mentioned above, there is a financial incentive to use a specialist on the PPO's provider network. PPOs are less restrictive than HMOs in the choice of health care provider. However, they tend to require greater "out-of-pocket" payments from the members (American Heart Association, 2005a:2).

3.3.7.6.5 Point Of Service plans (POS)

According to Clifford (1999) a POS plan is often called an HMO/PPO hybrid or dual-option or an "open-ended" HMO. The reason for calling it "point-of-service" is that members choose which option – HMO or PPO – they will use each time they seek health care. Like an HMO and a PPO, a POS plan has a contracted provider network (American Heart Association, 2005a:2).

In return for added choice, members pay a higher premium for the POS option. HMOs offer this "soft-lock" alternative to compete with PPOs. Unlike PPOs, however, the consumer is not lost to the HMO's data collection system whenever he or she goes outside of the network, but remains in the risk pool (Clifford, 1999:33).

Point-of-Service Plan (POS) is a health services delivery organisation that offers the option to its members to choose to receive a service from a participating or non-participating provider. Generally the level of coverage is reduced for services associated with the use of non-participating providers. It is a managed care plan that specifies that those patients who go outside of the plan for services may pay more out-of-pocket expenses. A health insurance benefits programme in which subscribers can select between different delivery systems (i.e., HMO, PPO and fee-for-service) when in need of health care services and at the time of accessing the services, rather than making the selection between delivery systems at time of open enrolment at place of employment. Typically, the costs associated with receiving care from the "in network" or approved providers are less than when care is rendered by non-contracting providers. Or the costs are less if provided by approved providers in either the HMO or PPO rather than "out of network" or "out of plan" providers. This is a method of influencing patients to use certain providers without restricting their freedom of choice too severely (Pohly, 2005:2).

3.3.7.6.6 Physician-Hospital Organisation (PHO)

A Physician-Hospital Organisation (PHO) is essentially an Independent Practice Association (IPA) with a hospital participant. A typical PHO is formed as a non-profit membership organisation controlled equally by a hospital or a medical group, and Individual Practice Association (IPA), or individual physicians who practice at or are affiliated with the hospital. The PHO provides no health care services; its primary functions are to plan and implement a coordinated, cost-effective health care delivery system that assures all needed medical treatments and resources are available and avoids duplication of services. The PHO contracts with payers on behalf of the hospital and physicians for the provision of health care services in the community. The PHO, in effect, serves as a joint marketing arrangement for the hospital and physicians (Kaiser *et al.*, 1995:2).

3.3.7.6.7 Exclusive Provider Organisation (EPO)

Exclusive Provider Organisation (EPO) is a plan that limits coverage of non-emergency care to contracted health care providers. An EPO operates similar to an HMO plan but is usually offered as an insured or self-funded product. It sometimes looks like a managed care organisation that is organised similarly to a PPO in that physicians do not receive capitated payments, but the plan only allows patients to choose medical care from network providers. If a patient elects to seek care outside of the network, then he or she will usually not be reimbursed for the cost of the treatment. An EPO uses a small network of providers and has primary care physicians serving as care coordinators (or gatekeepers). Typically, an EPO has financial incentives for physicians to practice cost-effective medicine by using either a prepaid per-capita rate or a discounted fee schedule, plus a bonus if cost targets are met. Most EPOs are forms of POS plans because they pay for some out-of-network care (Pohly, 2005:2).

3.3.7.6.8 Accountable Health Plan (AHP)

Accountable Health Plans (AHPs) can be Integrated Delivery Systems (IDS), MCOs, Health Networks, partnerships or joint ventures between practitioners, providers or payers that would assume responsibility for delivering medical care and managing the funds required to pay for the services rendered. Physicians and other providers would work for, contract with or own these health plans. When an IDS or hospital group or IPA operates one or more health insurance benefit products, or a managed care organisation acquires a large scale medical delivery component, it qualifies as an Accountable Health System or Accountable Health Plan (Pohly, 2005:2).

3.3.7.6.9 Integrated Delivery System (IDS)

Hospitals are rapidly expanding their capacity to provide outpatient services by creating alliances with individual physicians and medical groups. The forms of alliances vary, but they are generally referred to as "integrated delivery systems," because they bring together, or "integrate," the components that provide health care into one "full-service" health care delivery system (Kaiser *et al.*, 1995:1).

3.3.7.6.10 Independent Practice Association (IPA)

According to Newton (1996:1) an Independent Practice Association (IPA) is an association of physicians and other health care providers, including hospitals, who contracts with an HMO to provide services to enrolees, but usually still see non-HMO patients and patients from other HMOs. They also see regular fee-for-service patients as well. The services provided are usually in the physicians' own offices, and usually on a captitation fee basis (Rupp's Independent Practice Association, 2002:1).

3.3.7.7 The future of managed health care in Africa

As Africa becomes increasingly marginalised globally, its economies and hence public and private sectors are being forced to become more effective and competitive. This requires more attention to input costs, one of which is the cost of health care, as well as the need to retain a stable and content workforce (Meridian Healthcare, 2004a:3).

Given the above and the financial pressures on African countries' public health budgets, there is a growing need for the availability of intelligent lower cost public and private sector health care alternatives. Such alternatives will almost likely incorporate managed health care principles in order to provide and promote quality, cost effective health care and manage diseases such as HIV/AIDS that threaten our continent (Meridian Healthcare, 2004a:3).

According to the literature presented above, managed health care can be summarised as a management process that attempts to coordinate the demand for, the provision of and the financing of health care (Meridian Healthcare, 2004a:1). An overview of managed health care, definition of managed health care, objectives of managed health care, explanation of pharmacy benefit management (PBM), explanation of managed care organisation (MCO) and types of managed health care were provided.

3.4 DRUG UTILISATION REVIEW (DUR)

3.4.1 Definition of drug utilisation review

The World Health Organisation (WHO, 2003b:8) defined drug utilisation in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences."

Expressed differently, drug utilisation review (DUR) is defined as an authorised, structured, and continuing programme that reviews, analyses and interprets aggregate patterns of medication use measured against predetermined standards and criteria established for specific health care delivery systems (Edgren, 1999:119).

3.4.2 Objectives of drug utilisation review

According to WHO (2003b:6) the ultimate goal of drug utilisation research must be to assess whether drug therapy is rational or not. To reach this goal, methods for auditing drug therapy towards rationality are necessary. The goal of DUR is to increase the appropriateness of drug therapy by focusing on whether a drug is being effectively used (e.g. appropriate dose, duration of therapy, etc.) (Armstrong *et al.*, 2000:538).

According to the WHO (2003b:7) the principal aim of DUR is to facilitate the rational use of drugs in populations. For the individual patient rational use of a drug implies the prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and at an affordable price. Without knowledge on how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use and to suggest measures to change prescribing habits for the better. Information on the past performance of prescribers is the linchpin of any auditing system (Sjöqvist & Birkett, 2003:78).

Idaho State University (Idaho State University, 2005b:1) stated that the purpose of DUR is to improve patient care and reduce overall drug costs. Correct interpretation of data on drug utilisation requires investigations at the patient level. We need to know the answers to the following questions:

- Why are drugs prescribed?
- Who are the prescribers?
- To whom do the prescribers prescribe?
- Do patients take their medicines correctly?
- What are the benefits and risks of the drugs (WHO, 2003b:6)?

Many health care organisations evaluate drug utilisation to improve the quality of patient care, reduce pharmaceutical expenditures and enhance therapeutic outcomes. Pharmacists performing DURs must review past patterns of drug misuse, monitor current therapy and offer patient counselling. Drug utilisation reviews have reduced inappropriate drug use and decreased drug costs (Kubacka, 1996:257).

3.4.3 Classification of drug utilisation review

3.4.3.1 Quantitative drug utilisation review

Quantitative data may be used to describe the present situation and the trends in drug prescribing and drug use at various levels of the health care system. Quantitative data may be routinely collected data or obtained from surveys (WHO, 2003b:20).

Quantitative drug utilisation studies quantify the present state, the developmental trends, the time course of drug usage at various levels of the health care system, and whether national, regional, local, or institutional. Routinely compiled drug statistics or drug utilisation data that are the result of such studies can be used to estimate drug utilisation in populations by age, sex, social class, morbidity, and other characteristics, and to identify areas of possible over- or under-utilisation (Lee & Bergman, 1994:380).

They also can be used as denominator data for calculating rates of reported adverse drug reactions; to monitor the utilisation of specific therapeutic categories where particular problems can be anticipated (e.g. narcotic analgesics, hypnotics and sedatives, and other psychotropic drugs); to monitor the effects of informational and regulatory activities (e.g. adverse event alerts, delisting of drugs from therapeutic formularies); as markers for very crude estimates of disease prevalence (e.g. digitalis utilisation for congestive heart failure, antiparkinsonian drugs for Parkinson's disease); to plan for drug importation, production and distribution; and to estimate drug expenditures (Lee & Bergman, 1994:380).

3.4.3.2 Qualitative drug utilisation review

Qualitative studies assess the appropriateness of drug utilisation and generally link prescribing data to reasons (indications) for prescribing (WHO, 2003b:20).

The crucial difference between these studies and quantitative drug utilisation studies is that they include the concept of appropriateness. Explicit predetermined criteria are created against which aspects of the quality, medical necessity and appropriateness of drug prescribing may be compared. Drug use criteria may be based upon such parameters as indications for use, daily dose and length of therapy. Other possible criteria for poor drug prescribing include the failure to select a more effective or less hazardous drug if available, the use of a fixed combination drug when only one of its components is justified, or the use of a costly drug when a less costly equivalent drug is available (Lee & Bergman, 1994:380)

3.4.4 Types of drug utilisation studies

According to Edgren (1999:123) the application of DUR criteria can be retrospective, concurrent, or prospective. Drug use evaluation, sometimes referred to as DUR, may be based on data collected prospectively (as the drug is being dispensed or administered) or retrospectively (based on chart reviews or other data sources) (WHO, 2003b:23).

3.4.4.1 Retrospective drug utilisation studies

Retrospective DUR includes an evaluation of therapy and intervention, where necessary, after the therapy has been started. Retrospective evaluations may involve assessment of drug use in individual patients or analysis of prescribing and dispensing patterns (Armstrong *et al.*, 2000:538).

Retrospective DUR is performed after a drug has been dispensed. It warns when a potential problem has occurred, is useful for detecting patterns, is useful for designing targets for intervention and it allows for corrective action (Wisconsin Medicaid, 2001:1).

The criteria reviewed in retrospective studies include the following:

- Evaluation of indications
- Monitoring use of high-cost medicines
- Comparison of prescribing between physicians
- Cost to patient

- Adverse drug reactions
- Drug interactions (WHO, 2003b:24).

An example of a retrospective study was done by Purdum *et al.* (2004:1) where they compared the total health care costs and treatment patterns of patients in a managed care setting. The objective of the study was to investigate the total health care costs and time to occurrence of hospitalisation in HIV-infected patients treated according to the 1998 Department of Health and Human Services (DHHS) guidelines in a managed care setting. The study also investigated which patients had not received guideline treatment. They used a retrospective cross-sectional study design using medical and pharmacy claims data.

Data from 1791 HIV-infected patients using antiretroviral agents between 1 February 1998 and 31 July 1999, including demographic characteristics, medication guideline use, medication adherence and cost of care, were examined. Factors associated with total health care costs and time-to-in-patient admission (as a proxy for patient outcomes) were assessed. Patients receiving guideline (HAART) therapy (55 per cent) had higher prescription and total health care costs but lower medical costs. Patients not receiving treatment according to guidelines were more likely to be female, older, have comorbidities, lower medication adherence and no AIDS-defining illness. Treatment with HAART guidelines was associated with longer time-to-inpatient admission controlling for other factors. In a short-term cross-sectional analysis, patients treated with HAART guidelines had better outcomes based on time-to-inpatient admission but higher prescription and total health care costs (Purdum *et al.*, 2004:1).

Some patients are at risk of not receiving care according to national treatment guidelines and may be targeted for intervention programmes (Purdum *et al.*, 2004:1).

3.4.4.2 Concurrent drug utilisation studies

Concurrent DUR takes place while the drug treatment is in process, whereas prospective and retrospective DUR surveys occur before or after that process, respectively (Edgren, 1999:123).

3.4.4.3 Prospective drug utilisation studies

Prospective DUR involves a review of each prescription, and, if necessary, intervention before dispensing (Armstrong *et al.*, 2000:538).

Prospective DUR implies giving guideline information to the prescriber before the prescription process occurs; therefore, it is prospective to the filling of the prescription (Edgren, 1999:125).

Prospective DUR is performed before a drug is dispensed. A potential problem is identified before it occurs and provides real-time response to a potential problem. Prospective DUR allows for preventive or corrective action and enhances clinical quality and cost-effective drug use (Wisconsin Medicaid, 2001:1).

Typical criteria reviewed in prospective studies include the following:

- Indications
- Drug selection
- Doses prescribed
- Dosage form and route of administration
- Duration of therapy
- Costs
- Therapeutic duplication
- Quantity dispensed
- Contraindications
- Therapeutic outcome
- Adverse drug reactions
- Drug interactions (WHO, 2003b:23).

3.4.5 The unit of measurement of drug utilisation review

Different units of measurement are available. Four of the most common are the defined daily dose (DDD), the prescribed daily dose (PDD), rates of the number of prescriptions dispensed, and the number of different drugs dispensed (Bogdanovic *et al.*, 2001:5).

A discussion of the above mentioned units of measurement of drug utilisation review are as follows:

3.4.5.1 Defined Daily Dose (DDD)

According to the WHO (2003b:7) the unit was defined as the average maintenance dose of the drug when used on its major indication in adults. The rate of the number of DDDs dispensed to the population (of

residents or users) per day and per year can be calculated to measure various aspects of intensity. A clinical measure can also be calculated (Bogdanovic *et al.*, 2001:5).

The use of DDD per 1000 inhabitants per day allows aggregation of data across drug groups and comparisons between countries, regions and health facilities. However, the DDD metric may not reflect the actual PDDs, and this need to be considered when making such comparisons (WHO, 2003b:14).

3.4.5.2 Prescribed daily dose (PDD)

The prescribed daily dose (PDD) is the average daily dose prescribed, as obtained from a representative sample of prescriptions (WHO, 2003b:14).

The PDDs differ between countries and ethnic groups, and even between areas or health facilities within the same country. The PDD will also often differ for different indications of the same drug, so it will sometimes be necessary to reach this level of detail to interpret overall data (WHO, 2003b:14).

3.4.5.3 Numbers of prescriptions dispensed

Numbers of prescriptions do not accurately reflect total use, unless total quantities of drugs per prescription are also considered. However, counting of prescriptions is valuable in measuring the frequency of prescriptions and in evaluating the clinical use of drugs (e.g. diagnosis and dosages used). Although they are useful in making national comparisons it should be noted that none of these volume units is usually applicable in cross-national comparisons (WHO, 2003b:39).

The rate of the number of prescriptions dispensed per resident and per pharmaceutical user can be used as a measure of the intensity of use. This measure can be problematic because the quantity of prescription items varies from prescription to prescription (Bogdanovic *et al.*, 2001:5).

3.4.5.4 Number of different drugs dispensed

The rate of the average number of different drugs dispensed is calculated per year, per resident and per pharmaceutical user. "Different" drugs were defined as the fourth level of Anatomical Therapeutic Chemical Classification (ATC) System (the chemical/therapeutic/pharmacological subgroup). The ATC system is a drug classification system more commonly used by European countries and uses a five level step-up/step-down method (Bogdanovic *et al.*, 2001:5).

From the above given literature, drug utilisation review can be summarised as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO, 2003b:8). A definition of DUR, objectives of DUR, classification of DUR, types of DUR studies and the unit of measurement, were provided.

3.5 PHARMACOECONOMICS

3.5.1 Overview of pharmacoeconomics

Pharmacoeconomics is a relatively new health care discipline that borrows from several disciplines including health economics, decision analysis and evidence-based medicine (Li, 2003:192).

Pharmacoeconomics is likely to become an increasingly important basis for health policy decisions as a number of significant dynamics evolve in the marketplace, including

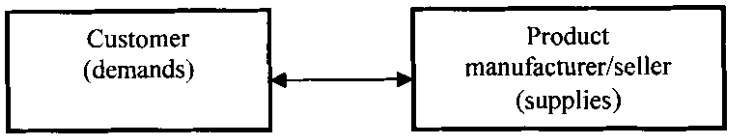
(i) consumers acting on their growing access to information and becoming more actively involved in treatment decisions;

(ii) payers, providers and patients deepening their interaction and overcoming their traditional (narrow) focus on either costs or benefits alone; and

(iii) manufacturers being challenged by other health care constituencies as sponsors of cost-based outcomes studies (Greenberg *et al.*, 1999:425).

Because demand determination in the health care sector is far more complex than that found in usual market situations, application of pharmacoeconomic tools raises special issues and concerns in a medical setting. Customers in non-health care markets typically interact directly with sellers (at times purchasing from retailers, wholesalers or even manufacturers), whereas consumers of health care products and services usually face far more complicated structures, as shown in figure 3.11 (Greenberg *et al.*, 1999:425).

Simplified non-health care case



Simplified health care case

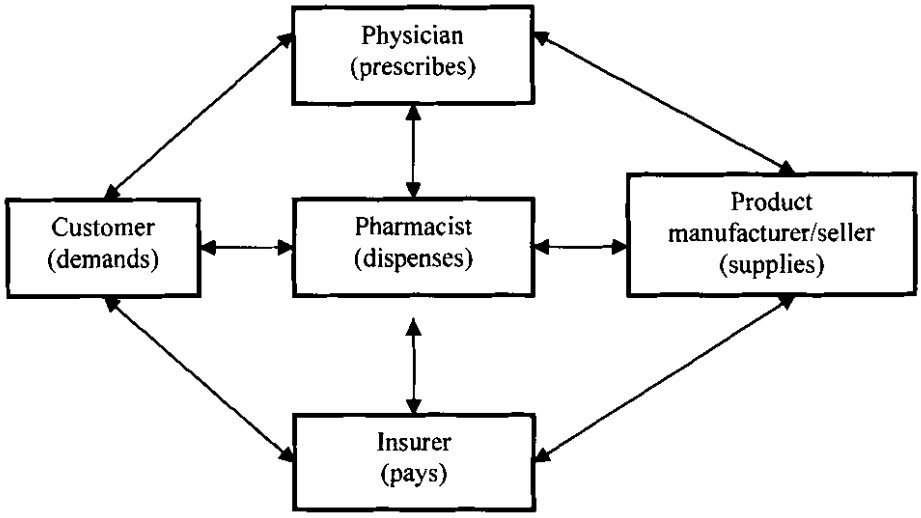


Figure 3.11 Supply and demand interactions in health care and non-health care markets (Greenberg *et al.*, 1999:426)

Pharmacoeconomic assessments have become increasingly important as a means of bridging these potentially conflicting interests in an appropriate fashion (Greenberg *et al.*, 1999:426).

The rapidly increasing health care costs and the ageing of populations in the developed countries have also contributed significantly to the need for consideration of effectiveness in the evaluation of any health care treatment, particularly in pharmaceuticals. Economics of health care includes not merely an assessment of the cost of a new therapy, but also an assessment of its overall economic and clinical impact. The discipline of pharmacoeconomics is developed to fulfil this role (Li, 2003:192).

3.5.2 Definition of pharmacoeconomics

Drummond *et al.* (according to Li, 2003:193) defined pharmacoeconomic evaluation as the comparison of the costs and consequences of two or more alternative courses of action.

Pharmacoeconomics describes and analyses the cost of drug therapy to health care systems and society. It identifies, measures, and compares the costs, and consequences of pharmaceutical products and services, with its research methods related to cost-minimisation, cost-effectiveness, cost-benefit, cost-of-illness, cost-utility, decision analysis, and quality of life assessments (Carriere & Huang, 2001:19).

Expressed differently, pharmacoeconomics represents the specific application of outcomes research to drugs, usually the more costly category of prescription agents. The relative measurements of inputs and outputs of therapeutic options are emphasised in pharmacoeconomics (Bonk, 1999:5).

3.5.3 Objectives of pharmacoeconomics

The primary goal of pharmacoeconomic analyses is to identify, measure and compare costs and consequences of pharmaceutical interventions. The objective of such an effort is to allocate health care resources, assuring that each patient receives the most suitable treatment (Venturini & Johnson, 2002:6).

The ultimate aim of pharmacoeconomics is to assist the decision makers in achieving allocation efficiency in the health care system. This is in response to the increased need for accountability during the age of cost-containment in health care. The rapidly increasing health care costs and the ageing of populations in the developed countries have contributed significantly to the need for consideration of effectiveness in the evaluation of any health care treatment, particularly in pharmaceuticals (Li, 2003:192).

The ultimate objective of all these evaluation methods is to compare the cost and outcome of alternative regimens, ideally by generating a single index or cost-outcome ratio. This ratio can be generated by using the process as shown in figure 3.12 (Li, 2003:194).

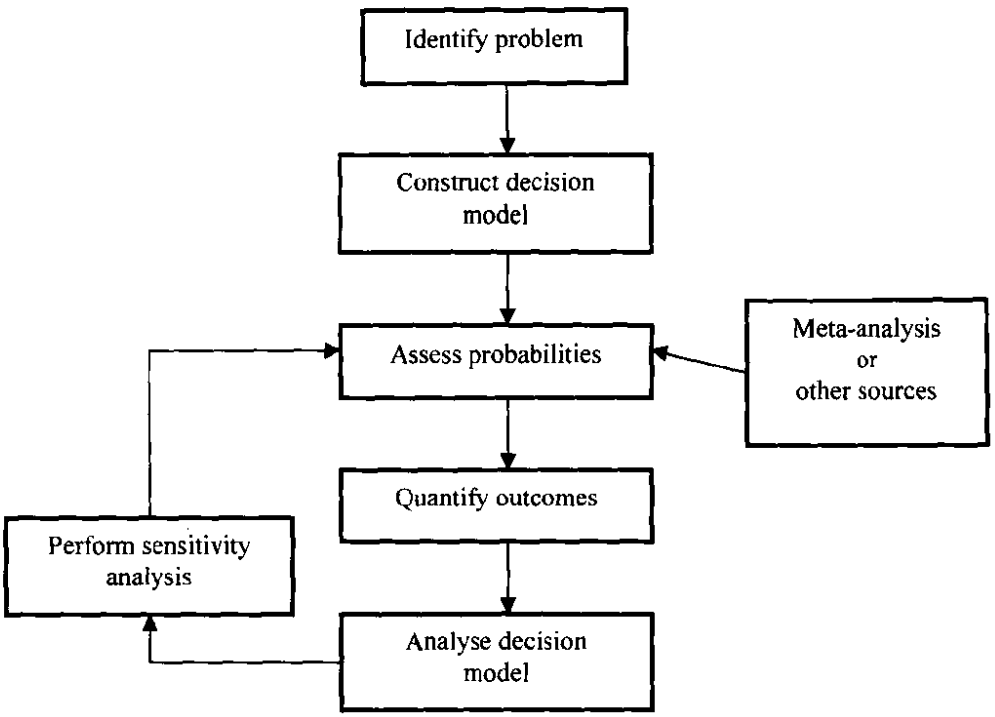


Figure 3.12 Overview of process of pharmacoeconomic evaluation (Li, 2003:194)

By relating costs to outcomes, pharmacoeconomic evaluation attempts to instil the element of cost-effectiveness into the clinical decision-making process beyond the traditional approach of considering efficacy and safety (Li, 2003:194).

A properly conducted pharmacoeconomic evaluation would provide valuable insights to allow the choosing of options representing the best value for money without compromising the quality of care delivered. In other words, a better utilisation of valuable resources can be achieved (Li, 2003:199).

Pharmacoeconomic analyses create a common ground on which to evaluate the disparate information categories for prescription drugs: efficacy or effectiveness, safety, quality of life and other preference measurements, and cost (Bonk, 1999:10).

Although not required by all regulatory agencies, pharmacoeconomic information is gaining in importance for the successful marketing of a new drug (Bonk, 1999:15).

3.5.4 Applications of pharmacoeconomics

Clinical pharmacists may find many practical applications of pharmacoeconomic methodology in their everyday pharmacy practice. The most widely utilised applications are formulary management and treatment guideline implementation (Venturini & Johnson, 2002:13).

Pharmacoeconomics has been lauded to be of great value in the following areas of health care delivery:

- To improve individual and public health through improved rational decision making.
- To determine relative values among alternative therapies.
- To improve system resource allocation.
- To assess whether care is of high quality.
- To determine whether interventions work in practice.
- To assess new diagnostic tests.
- To determine whether programmes represent good value for money (Li, 2003:194).

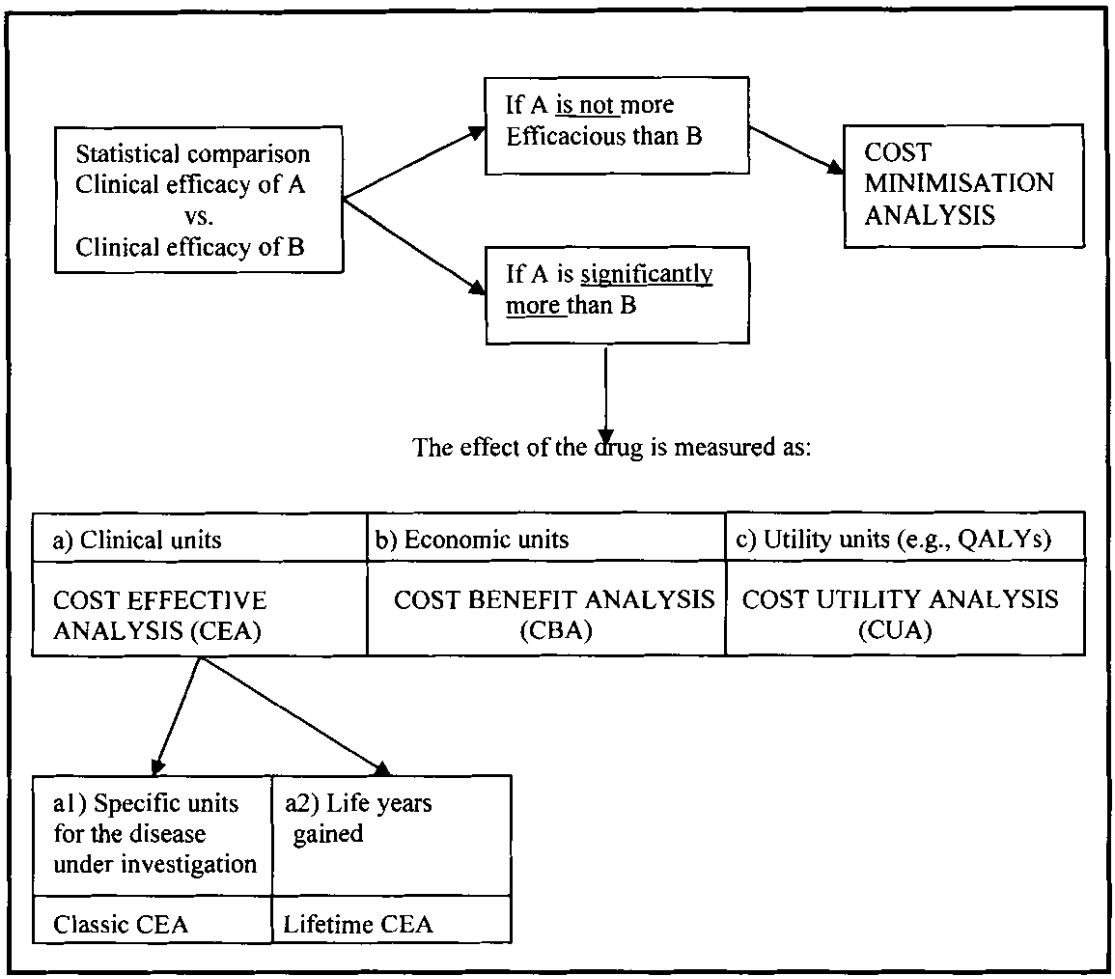
To date, the most successful application of the principles of pharmcoeconomics is in the areas of purchase decision (e.g. decision for formulary inclusion), subsidy decision (e.g. level of subsidy for pharmaceuticals), establishing practice standards (e.g. development of clinical practice guidelines) and assessment of technologies (e.g. medical procedures and technologies) (Li, 2003:192).

The proper application of pharmacoeconomic evaluation in clinical medicine would necessitate a multidisciplinary approach requiring expertise and inputs from practitioners from clinical medicine, biostatistics and psychometrics, among others. A properly conducted pharmacoeconomic evaluation would provide valuable insight for clinicians to allow the choosing of options representing the best value-for-money without compromising the quality of care delivered (Li, 2003:192).

3.5.5 Methodology of pharmacoeconomics

Pharmacoeconomic evaluations primarily consider the costs and consequences of a pharmacological intervention and are often applied among various alternatives (Venturini & Johnson, 2002:7).

Figure 3.13 describes the choice of pharmacoeconomic methodology e.g. cost minimisation analysis, cost effective analysis, cost benefit analysis and cost utility analysis.



QALYs=Quality Adjusted Life Years

Figure 3.13 Algorithm for the choice of the pharmacoeconomic methodology (Venturini & Johnson, 2002:9)

Costs are defined as the input resources utilised by the therapeutic strategy and/or intervention under study; consequences (or outcomes) are the outputs (e.g., any end result of a particular treatment and/or intervention) (Venturini & Johnson, 2002:7).

3.5.5.1 Classification of costs:

Costs are broadly classified as direct, indirect and intangible costs:

- Direct costs include the cost of goods and services that can be purchased in the marketplace. Direct costs are further classified into medical and non-medical costs.

  a) Direct medical costs:

  Examples of direct medical costs are inpatient costs (e.g., laboratory tests, drugs, hospitalisation, etc.). In the case of pharmacological treatments, these include not only

the cost of the drugs, but also the cost of their administration, clinical monitoring, costs for treatment of adverse events, etc.

b) Direct non-medical costs:

An example of a direct non-medical cost is transportation cost (Venturini & Johnson, 2002:7).

- According to Venturini and Johnson (2002:7) indirect costs are costs which result from changes in production capacity brought about by the intervention of illness. Examples of indirect costs are days lost from work, prescription charges or other treatment expenses incurred by the patient; the cost of the patients' or carers' travel to and from hospital, costs of providing social services, reduction or loss of productivity (Davey *et al.*, 1997:404).

- Venturini and Johnson (2002:7) stated that intangible costs are costs or savings associated with additional or lessened pain of suffering. These costs are very important but difficult to quantify; instruments for measuring elements of these costs are currently developed. Intangible costs, i.e. costs that are difficult to value financially (e.g. pain, anxiety and loss of energy; time given up by voluntary carers) (Davey *et al.*, 1997:404).

3.5.5.2 Classification of consequences (outcomes):

The three broad categories of consequences (outcomes) are economic, clinical and humanistic outcomes. Clinical outcomes are the clinical consequences of pharmacological treatment or strategy. Examples are death, disability, morbidity, and specific clinical indicators. Humanistic outcomes are the consequences of disease or treatment on patient functional status or quality of life along several dimensions (e.g., satisfaction, general health, physical functioning, social functioning, etc.) (Venturini & Johnson, 2002:8).

3.5.6 Types of pharmacoeconomic analyses:

By using various techniques such as cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA), pharmacoeconomic evaluation compares the economics of different pharmaceutical products or compares drug therapy to other treatments (Li, 2003:193), as illustrated in table 3.1 (Bonk, 199910).

Table 3.1 Criteria of pharmacoeconomic methods (Bonk, 1999:10)

Method	Distinguishing features
Cost-benefit analysis	Measures the costs of treating an illness, along with monetary equivalents for the treatment's outcomes.
Cost-effectiveness analysis	Measures the costs of treating an illness, but using clinical measurements for the treatment's outcomes.
Cost-of-illness analysis	Identifies and measures the costs of the illness itself, but not treatment outcomes.
Cost-minimisation analysis	Directly compares the costs of treatment options for an illness, assuming equivalence of their outcomes.
Cost-utility analysis	Measures the costs of treating an illness, but using preference equivalents for the treatment's outcomes.

3.5.6.1 Cost Benefit Analysis (CBA)

According to Carriere and Huang (2001:19) CBA is a type of clinical economic evaluation of the outcomes from a programme or intervention. CBA can be conducted for a single or for multiple interventions to provide foundations for decision making to achieve the desired objectives (Davey *et al.*, 1997:400).

CBA measures both the costs and the benefits in monetary terms by net benefits (net benefits = total benefits – total cost) or benefits-to-cost ratio (benefits-to-cost ratio = total benefits/total cost) (Carriere & Huang, 2001:19).

CBA can be used to improve the decision-making process in the allocation of funds to health care programmes (Bootman *et al.*, 1996:61).

Future costs and benefits are discounted to their current value. Although considered the best economic analysis, its application in pharmacoeconomic and health care in general is limited, due to the difficulties in assigning a monetary value to health outcomes and a patient's life (Venturini & Johnson, 2002:8).

According to Carriere and Huang (2001:19) the consequences of CBA should be measured as the willingness to pay of the individuals who bear the consequences. These consequences may include direct and indirect benefits:

- Direct benefits

  These benefits are defined as that portion of averted costs currently borne that are associated with spending for health services; they represent potential savings in the avoided use of health resources.

- Indirect benefits:

  These benefits represent potential increased earnings of productivity gains that would not have been possible without the particular health care programme (Bootman *et al.*, 1996:63).

The steps in conducting a CBA are described in figure 3.14.

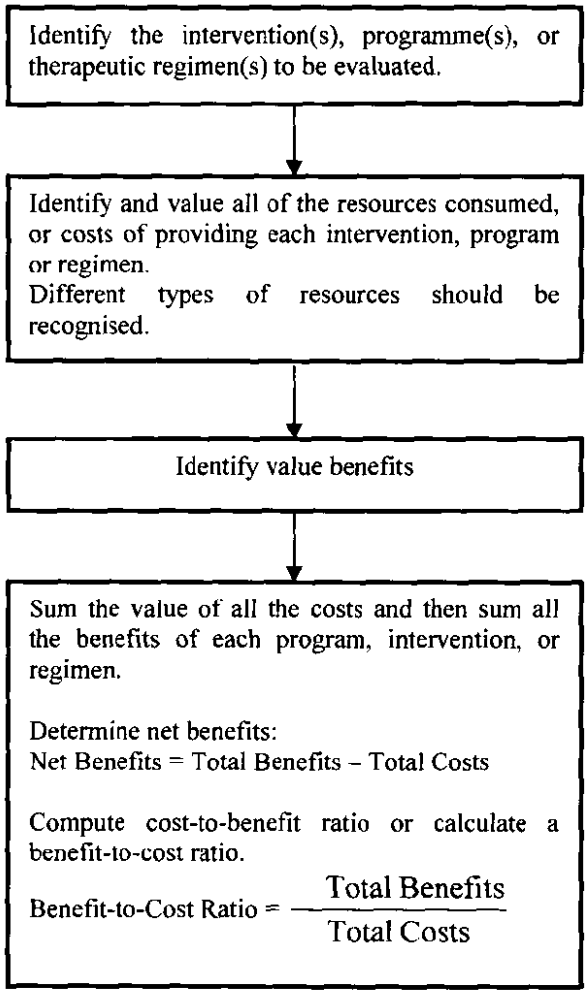


Figure 3.14 Steps in conducting a CBA (McGhan & Kitz, 1996:65-66)

An example of a cost-benefit analysis on an HIV/AIDS programme was done by Peffer *et al.* (2002:433) to prevent mother-to-child HIV transmission (PMTCT) in Mozambique. The provision and non-provision of infant feeding formula were considered, along with voluntary counselling and testing, and antiretroviral treatment with nevirapine. Costs were calculated in monetary units and benefits as deaths averted and disability-adjusted life years. The UNAIDS cost-effectiveness tool for evaluating ARV drug and substitute feeding interventions was used.

The costs of the programme were compared with the costs of treating HIV-infected children. With no infant feeding formula, there would be a total savings of United States dollar (U.S.$) 5242[c] and a negative cost per Disability Adjusted Life Years[b] (DALY) of U.S.$ 1,53[c]. With formula, net annual costs would be U.S.$ 141,268[c] and cost DALY U.S.$ 38,69[c]. Citywide, each year 132 infants deaths would be averted by use of Nevirapine and eight averted by the breast milk replacement programme. All programme options have reasonable cost-effectiveness ratios (Peffer *et al.*, 2002:433).

3.5.6.2 Cost-Effectiveness Analysis (CEA)

According to Chrischilles (1996:77) CEA is an approach used for identifying, measuring and comparing the significant costs and consequences of alternative interventions. These alternative interventions may be 2 or more different drugs or classes of drugs. The costs are calculated in monetary value, while the outcomes are valued in clinical terms (Venturini & Johnson, 2002:8).

An incremental cost effectiveness ratio (CER) is then computed, as follows:

$$CER = \frac{(\text{cost of treatment A}) - (\text{cost of treatment B})}{(\text{clinical success treatment A}) - (\text{clinical success treatment B})}$$

The results express the cost that – on average – needs to be sustained to obtain "an additional success" if treatment A is chosen instead of B (e.g., cost per avoided recurrence, cost to avoid a complication, cost to avoid an adverse event, etc.) The main objective of CEA is to evaluate the ratio between the cost surplus associated with the new treatment (e.g., the higher cost of the new pharmacological treatment) and the efficacy/effectiveness surplus derived from it. The latter (outcome) is measured in physical or clinical units, such as the number of infections, number of disease-free patients, number of remissions, etc. (Venturini & Johnson, 2002:10).

[b] Disability adjusted life years = number of years of life saved by an intervention weighted by the quality of life perceived by the person and by the social value attributed to each year of life as a function of age.

[c] One U.S.$ is equivalent to 12.47 ZAR (South African Rand) on 02 January 2002 (see **http://www.x-rates.com/calculator.html**)

Expressed differently by Carriere and Huang (2001:19) CEA is a method for comparing the health outcomes (effectiveness) and the net costs of a programme or an intervention to other alternatives with similar health outcomes. CEA measures health outcomes in real terms and not in monetary terms, such as mortality, disability, or quality of life. Cost-effectiveness should be used to imply value for money (Bootman *et al.*, 1996:79).

Two or more alternative interventions, often drugs, can be compared directly for their costs to achieve the selected outcome (Bootman *et al.*, 1996:77; Bonk, 1999:10). Because the alternative interventions may have different costs as well as different levels of effectiveness, this pharmacoeconomic approach often uses a ratio of outcomes achieved to cost expended (Bonk, 1999:36).

According to Venturini and Johnson (2002:11), in a classic CEA, the new treatment is compared with the standard treatment (usually the best available treatment in clinical practice, e.g., the gold standard) in terms of clinical and economic value. In a lifetime CEA, therapeutic problems which require long-term efficacy evaluations often correspond to the use of a methodology which measures the survival length on a long-term basis and which synthesises these data through life table curves. The main difference between a classic CEA and a lifetime CEA is in the methodology of computing the benefit (e.g. in the calculation of the denominator):

$$\text{CER} = \frac{\text{(cost for treating 100 patients with drug A)} - \text{(costs for treating 100 patients with drug B)}}{\text{Years of life gained using A instead of B}}$$

The steps in performing a cost-effectiveness analysis are described in figure 3.15.

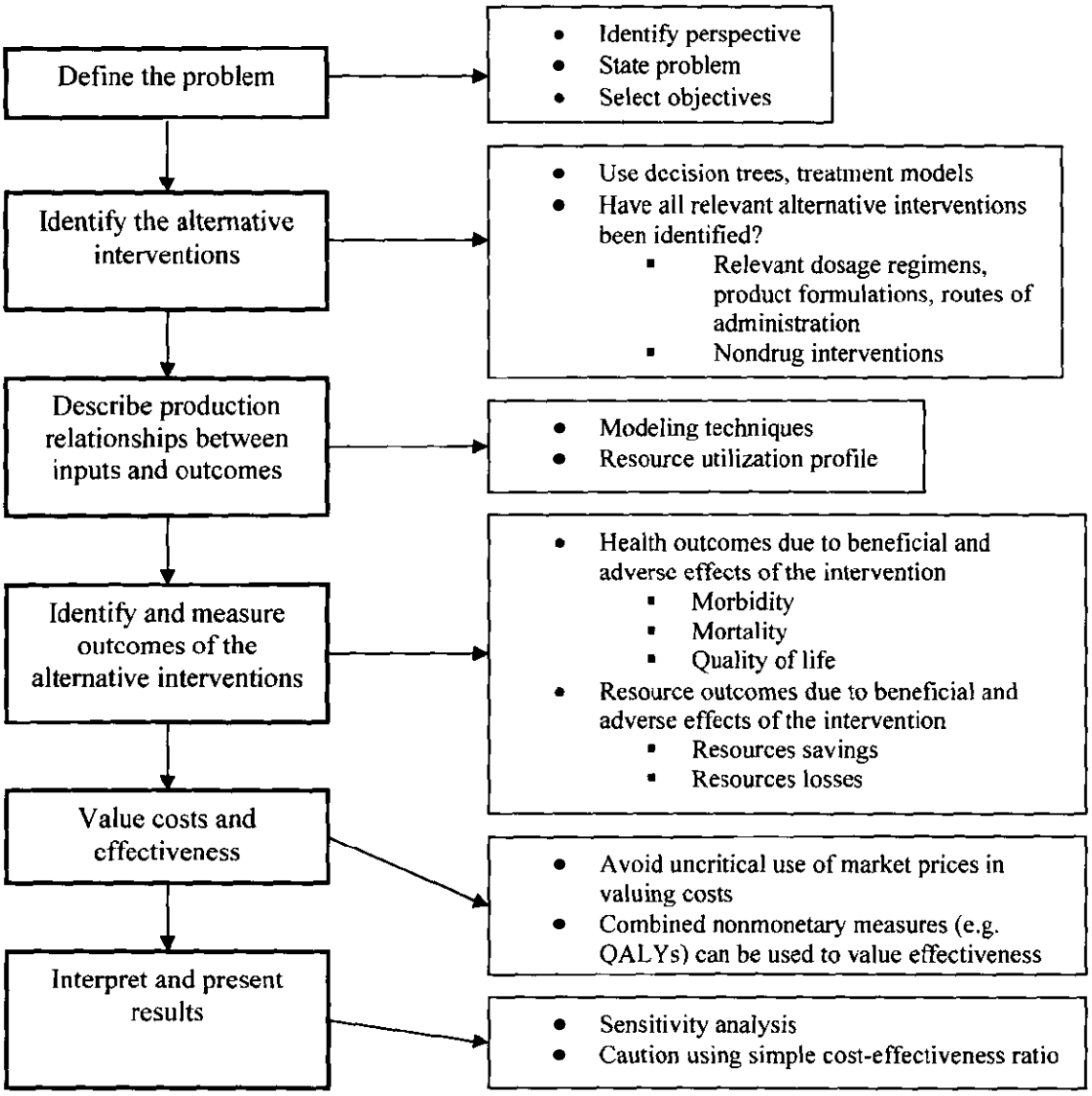


Figure 3.15 Basic steps of cost-effectiveness analysis (Bootman *et al.*, 1996:80)

A drawback of CEA is that all effects are assumed to be valued identically. This is a potential problem for two reasons:

- Firstly, some effects that may be equal in terms of effects expressed in "natural units," may differ markedly in quality associated with the effect.
- Secondly, natural units are assumed to be all equivalent in another sense (Rittenhouse, 1996:1094).

A further drawback of CEA is that health care interventions are rarely so similar so as to be measurable in terms of a single effect (Rittenhouse, 1996:1095).

An example of a cost-effective study was done by Anis *et al.* (2000:393) to determine the cost-effectiveness of antirctroviral regimens for the treatment of HIV/AIDS. The objective of the study was to estimate survival, the number of life-years gained and cost-effectiveness of antiretroviral therapy regimens, denoted as ERA-I [zidovudine + (didanosine or zalcitabinc)]; ERA-II [stavudine + (didanosine or zalciatbine) or lamivudine + (zidovudine or didanosine or zalcitabine or stavudine)]; and ERA-III [2 nucleoside reverse transcriptase inhibitors + (1 protease inhibitor or 1 non-nucleoside reverse transcriptase inhibitor)]. The design of the study was the modelling of drug costs, cost of opportunistic diseases and survival of HIV-positive men and women in the province of British Columbia who were first prescribed any antiretroviral treatment between October 1992 and June 1996. A 'reference cohort' was modelled upon individuals in a longitudinal cohort of homosexual men followed since 1982.

A third-party payer perspective in British Columbia, Canada was used. The patients were all HIV-positive men and women aged 18 years or older with a CD+ counts≤350 cells/μL who were enrolled in the province-wide drug treatment programme. Main outcome measures used were annual costs, survival and cost-effectiveness ratios of successive antiretroviral treatment regimens. The total costs [1997 Canadian dollars ($Can)] at 12 months under ERA-I, -II and –III were $Can 4897[d], $Can 6620[d] and $Can 11914[d], respectively. Survival at 12 months under ERA-I, -II and –III was 89.6 per cent, 91.0 per cent and 97.6 per cent, respectively. The annual incremental cost (estimated by the total incremental cost at 12 months) between ERA-II and ERA-I was $Can 1723[d]. The incremental cost-effectiveness ratios between ERA-III and ERA-I, and between ERA-III and ERA-II were $Can 58806[d] and $Can 46971[d] per life-year gained, respectively (Anis *et al.*, 2000:393).

They concluded that they found the cost-effectiveness of ERA-III antiretroviral treatment regimens well within the range of currently funded therapies for the treatment of other chronic diseases (Anis *et al.*, 2000:393).

3.5.6.3 Cost Minimisation Analysis (CMA)

According to Newby and Hill (2003:145) cost-minimisation is the appropriate form of economic analysis to carry out whenever two drugs have the same clinical efficacy/effectiveness. CMA is a technique designed to identify the preferred choice among possible alternatives with equivalent outcomes or consequences by examining the cost associated with each of those alternatives (Carriere & Huang, 2001:19).

[d] One $Can is equivalent to 3.42 ZAR (South African Rand) on 02 January 1997 (see **http://www.x-rates.com/calculator.html**)

Economic efficiency then dictates selection of the least costly intervention. Thus, the critical first step before conducting a CMA is determining the therapeutic equivalence of the interventions (Newby & Hill, 2003:145).

Efficacy refers generally to the outcomes obtained under ideal conditions such as in the clinical trial. Effectiveness refers to the outcomes obtained under real world conditions which incorporate patient behaviours, non-compliance, etc. (Venturini & Johnson, 2002:8).

CMA is a relatively straightforward and simple method. Very frequently, CMA is confused with cost-of-illness *(refer to section 3.5.6.5)*, but they are substantially different in scope and methodology. In reality, it is very difficult to find a situation for a true equality in efficacy/effectiveness and safety so this method is rarely applicable. The ideal situation for a CMA is the comparison of a brand and equivalent generic drug (Venturini & Johnson, 2002:8).

An example of this type of analysis may be the evaluation of two generically equivalent drugs in which the outcome has proved to be equal although the acquisition and administration costs of the two drugs may be significantly different (Bootman *et al.*, 1996:10).

An example of a cost-minimisation analysis was done by Mrus *et al.* (2001:139) by screening females in juvenile detention for *chlamydial cervicitis*. Using a decision analytic model, they compared 5 strategies: 1) do nothing; 2) treat everyone with a single 1 gm dose of azithromycin; 3) screen for current symptoms or history of a sexually transmitted disease (SH) and treat those who have a positive screen; 4) screen with urine ligase chain reaction (LCR) and treat those who have a positive test; 5) screen with cervical LCR and treat those who have a positive test. Chlamydia prevalence and SH screen test characteristics were determined from a cohort study conducted at a juvenile detention centre. Treatment and testing costs were taken from the cost accounting system at an urban teaching facility. LCR test characteristics, treatment efficacy, and complication (pelvic inflammatory disease, infertility, chronic pelvic pain, and ectopic pregnancy) rates and costs were derived from the literature. Future costs were discounted at a 3 per cent annual rate in the base case.

In this cohort (241 females, 59.8 per cent African American, 40 per cent Caucasian, mean age 14.8 years) with a prevalence of chlamydia of 16.8 per cent, empiric treatment (strategy 2) was the least expensive strategy, but screening with urine LCR (strategy 4) was only minimally more expensive (see table 3.2). Although changes in a number of variables affected the total costs, only changes in chlamydia prevalence and the pelvic inflammatory disease rate would render strategies other than 2 or 4 to be preferred. For

example, if the prevalence of chlamydia were between 0 and 3.5 per cent, then doing nothing (strategy 1) would be the least expensive strategy; between 3.5 per cent and 5.6 per cent, SH (strategy 3) would be least expensive; between 5.6 per cent and 16.4 per cent, urine LCR (strategy 4) would be least expensive; and if the prevalence of chlamydia were greater than 16.4 per cent, then empiric therapy of chlamydia were greater than 16.4 per cent, and the empiric therapy (strategy 2) would be least expensive (Mrus *et al.*, 2001:139).

Table 3.2 Different Strategies and results (Mrus *et al.*, 2001:139)

Strategy (#)	Testing ($/patient)*	Treatment ($/patient)*	Sequelae ($/patient)*	Total ($/patient)*
Treat All (2)	0	17	1,81	18,81
Urine LCR (4)	10	2,7	6,28	18,99
Symptoms &History (3)	1	3,01	28,73	32,74
Cervical LCR (5)	30	2,81	4,72	37,53
Do Nothing (1)	0	0	45,24	45,24

One U.S.$ is equivalent to 7.57 ZAR (South African Rand) on 02 January 2001 (see **http://www.x-rates.com/calculator.html**

Their conclusion was that in a detained adolescent female population, empiric treatment for chlamydia cervicitis or treatment based on urine LCR results are nearly equivalent in cost and are less costly than other strategies (Mrus *et al.*, 2001:139).

3.5.6.4 Cost Utility Analysis (CUA)

CUA is an economic tool in which the intervention consequence is measured in terms of quantity and quality of life. It is much the same as cost-effectiveness analysis with the added dimension of a particular point of view, most often that of the patient (Bootman *et al.*, 1996:11).

In CUA, cost is measured in monetary value and outcomes in clinical terms incorporating patient preferences (e.g., quality of life measures). Often the utility measure used is "quality adjusted life year" (QALY) gained. QALY incorporates both quantity and quality of life. The use of QALY as a measure of outcomes, allows a direct comparison among cost-utility ratios from different pharmacoeconomic analyses. The preferred treatment alternative is that with the lowest cost per QALY. Possible alternative measures are healthy-year equivalents or saved young life equivalents. The first measure is very difficult to compute, while the latter is not as broadly known and used as QALYs (Venturini & Johnson, 2002:8).

An example of a cost-utility analysis was done by Stein *et al.* (2003:814) on the screening for hepatitis C in genitor-urinary medicine clinics. The aim was to estimate the cost utility (cost per QALY) of

screening for hepatitis C (HCV) infection in people attending genitor-urinary medicine clinics in England. An epidemiological model of screening and diagnosis was combined with a Markov chain model of treatment with combination therapy to estimate cost utility. Parameters for the model were informed by literature review, expert opinion and a survey of current screening practice.

The base case estimate was about £85.000[e] per QALY. Selective screening is more cost-effective. If screening is restricted to only 20 per cent or 10 per cent of attenders, cost utility is estimated as £39.647[e] and £34.288[e] per QALY. If screening is restricted only to those with a history of injecting drug use, cost utility would be £27.138[e] per QALY. Estimates are particularly sensitive to acceptance rates for screening and treatment. They concluded that universal screening for HCV in Genito-Urinary Medicine (GUM) clinics is unlikely to be cost effective. There is limited evidence to support screening of people other than those with a history of injecting drug use and even this policy should be considered with some care and in the context of further research (Stein *et al.*, 2003:814).

3.5.6.5 Cost-Of-Illness analysis (COI)

COI is concerned with the identification and estimation of the overall cost of a particular disease on a defined population. This method involves the computation of direct and indirect costs attributable to a specific disease. COI does not compare competing treatment alternatives, but provides an estimation of the financial burden of a disease (Venturini & Johnson, 2002:8).

Cost-of-illness analysis provides a common framework through which to assess the potential for developing a drug to treat a particular disease (Bonk, 1999:26).

Cost-of-illness analyses are important to pharmacoeconomic evaluations of new therapies. By evaluating the humanistic impact of disease and the resources used in treating a condition prior to discovery of a new intervention, the pharmacoeconomist can effectively establish a baseline for comparison (Bootman *et al.*, 1996:12).

Quality of life (QOL) and COI studies do not explicitly consider the optimality of an intervention, but serve to measure its impact on either outcome or cost alone (Rittenhouse, 1996:1094).

[e] One £ (British Pound) is equivalent to 13.64 ZAR (South African Rand) on 02 January 2003 (see **http://www.x-rates.com/calculator.html**)

An example of a cost-of-illness analysis was done by Farquhar *et al.* (2001:143) where they estimated the economic cost of HIV/AIDS-related diseases. The study considers annual health care utilisation and costs associated with HIV infection and AIDS by applying the previously developed disease and disease combination-specific cost-of-illness methodology. Their study documents changes in age-specific mortality rates indicating the decline in age groups "20 to 39". They estimated annual economic losses resulting from 24 HIV/AIDS-related diseases among the U.S. population to be U.S. $ 18.2 billion[f]. This estimate includes direct medical cost of almost U.S. $ 9.2 billion[f], 80 per cent of which is compensated by Medicaid (a medical scheme). They demonstrated that an add-on therapy with additional mean cost of U.S. $ 7100[f] per person per year would be justifiable if it could reduce the risk of progression to AIDS by 19 per cent.

From the above given literature, pharmacoeconomics can be summarised as a method to describe and analyse the cost of drug therapy to health care systems and society (Carriere & Huang, 2001:19). A definition of pharmacoeconomics, objectives of pharmacoeconomics, applications of pharmacoeconomics, methodology of pharmacoeconomics, and types of pharmacoeconomic analyses, were provided.

3.6 DISEASE MANAGEMENT (DM)

3.6.1 Overview of disease management

According to Meridian Healthcare (2004b:4) disease management is the systematic and holistic management of a patient's chronic condition. Conditions historically managed under disease management programmes include diabetes, hypertension and asthma with HIV/AIDS joining the fold more recently. Disease management is a systematic approach to a health condition or a health care intervention that organises preventative, interventional and care approaches throughout the continuum of care and which measures outcomes in terms of populations, not individuals (Chang & Nash, 1998:11).

Disease management programmes are being used by a growing number of parties including pharmacy-benefit managers, managed care organisations, academic medical centres and other health care providers to try and improve the efficiency of health care delivery (Chang & Nash, 1998:11).

f One U.S. $ is equivalent to 7.57 ZAR (South African Rand) on 02 January 2001 (see **http://www.x-rates.com/calculator.html**)

Disease management is a method of managing care for a chronic or acute condition. One or more of the following may be encompassed in disease management:

- Patient education to help the individual become an active partner in his/her health care and to ensure compliance with a treatment plan.
- Oversight of provider practice patterns and provider education or guidance.
- Specialised management of high-cost patients.
- Tracking of patient and provider compliance.
- Data analysis to measure results (Firstpharmacy Inc., 1998:1).

The six components of DM are population identifications processes; evidence-based practice guidelines; collaborative practice models to include physician and support-service providers, self-management education; process and outcomes measurement, evaluation, and management; and a routine feedback loop. An organisation has to have all six components to be a full-service DM company. Those with some but not all are considered support services (Stone, 2001:2).

3.6.2 Definition of disease management

DM is the creation of population-based, integrated approaches to the provision of ongoing, cost-effective, and clinically efficacious care. DM has been defined in one model to contain at least four essential components: coordination of care across the health care delivery system, a comprehensive knowledge base for treatment of the disease (from primary prevention through palliation), integrated information systems, and continuous quality improvement methods (Armstrong *et al.*, 2000:543).

DM according to Stone (2001:2) is a system of coordinated care interventions and communications designed to help patients and physicians manage conditions that necessitate significant self-management. Recognised standards of care exist for these conditions, and patients who follow those standards will have better health, fewer complications and comorbidities, and lower health care costs.

3.6.3 Types of disease management

Three distinct types of programmes of disease management consist: compliance enhancement, guidelines adherence, and outcomes management (Edgren, 1999:127).

3.6.3.1 Compliance enhancement

This programme basically says that what is good for the pharmaceutical industry is clearly good for the health plan (Edgren, 1999:127).

3.6.3.2 Guidelines adherence

This programme includes two important assumptions:

- Guidelines adherence will provide more cost-effective care.
- Responsibility for guidelines adherence lies primarily with the physician (Edgren, 1999:127).

It is known that appropriate prescribing does not necessarily lead to appropriate drug use, and non-compliance with drug regimens is a major cause of guideline failure. To make this type of disease management programme work, a significant commitment must be made to identifying and correcting guideline non-compliance at the provider and patient levels (Edgren, 1999:127).

3.6.3.3 Outcomes management

Continual monitoring of physician and patient performance enhances treatment guidelines. Risk categories are defined by an outcomes research database and linked to the pharmacy database. As a patient moves into a high-risk profile, resources are committed to moving the patient out of that category. The Pharmacy Benefit Management Company (PBMC), pharmaceutical industry, and health plan work in a coordinated fashion to create better outcomes for patients (Edgren, 1999:128).

3.6.4 HIV/AIDS Disease Management Programmes (DMP)

According to Stein *et al.* (2002:10) disease management programmes (DMP) were introduced in order to provide a comprehensive management approach for beneficiaries of contracted medical schemes. In the case of HIV/AIDS, systems have been created within these programmes to ensure client confidentiality. Most medical schemes contract the burden of HIV positive beneficiaries to disease management programmes, which were created to monitor the complex treatment and manage the significant costs associated with HIV/AIDS treatment (Connelly, 2002:8).

DMPs provide some or all of the following: individual case management, confidentiality of patient's health status, clinical management of HAART, improved prices and administering fees of drugs and laboratory costs by negotiated bulk purchasers, information technology in tracking costs to monitor benefit limits and likely decreases in hospitalisation and doctor visits due to treatment and preventive

strategies. A DMP may offer various levels of these services and is paid either a capitation fee for each member eligible to access the benefit or for each actively managed patient. Accurate cost data on individual care are generally available and used to market the potential savings that managed HAART can provide in reducing hospital admissions and unscheduled doctor visits (Connelly, 2002:9).

Medical schemes tend to contract services to specialised HIV/AIDS disease management programmes (DMPs) to assist their diagnosed members and to manage defined HIV fund benefits by containing costs of HIV/AIDS treatment through PBM mechanisms. These services may be paid through capitation service contracts with medical schemes or by employer contributions. The programmes can provide accurate cost data for individual care that can be used to market potential savings that managed HAART can provide through decreased hospitalisations and fewer opportunistic infections. These DMPs have documented annual costs ranging form U.S.$ 1200[g] to U.S.$ 4810[g] per treated person year for the few who are receiving HAART under their management in South Africa. The level of treatment and care provided varies between these programmes and such per-patient data are not entirely transferable to the public sector (Connelly, 2002:1).

The Centre for Actuarial Research (CARE) at the University of Cape Town has published a review of the provision of ARVs by the health insurance industry in SA. The review included 53 per cent of all medical schemes listed in the Registrar's Statutory Returns 2000. DMPs have been retained by medical schemes to manage costs and benefits available to people accessing ARVs (Stein *et al.*, 2002:5).

DMPs potentially cover 89 per cent of all health insurance beneficiaries. Even though beneficiaries of medical schemes have access to the DMPs, very few are registered into the programme. Only 18 000 medical scheme members are registered with a DMP, representing less than 1 per cent of all beneficiaries. This is low relative to the extent of the epidemic in South Africa as it is estimated that about 5 per cent of all medical scheme members are HIV-positive (Martinson *et al.*, 2002:239).

There are seven disease management programmes in operation in South Africa, according to the authors of the monograph, "The cover provided for HIV/AIDS benefits in medical schemes in 2002":

- Accesshealth SA
- Aid-for-AIDS

[g]One U.S.$ is equivalent to 12.47 ZAR (South African Rand) on 02 January 2002 (see **http://www.x-rates.com/calculator.html**)

- Calibre Clinical Consultants
- Discovery Health
- Lifesense
- MX Health
- Newmed
- Qualsa (Stein *et al.*, 2002:10).

Disease management programmes are widely used with 78 per cent of schemes linked to either their own programme or another programme (see figures 3.16 and 3.17). These 78 per cent of schemes represent 89 per cent of the beneficiaries in open and restricted medical schemes. Aid-for-AIDS is the biggest disease management programme with 42 per cent of schemes and 36 per cent of beneficiaries linked to this programme. Eighteen per cent of schemes have their own disease management programmes, and each of the remaining programmes is linked to less than 5 per cent of the schemes (Stein *et al.*, 2002:10-11).

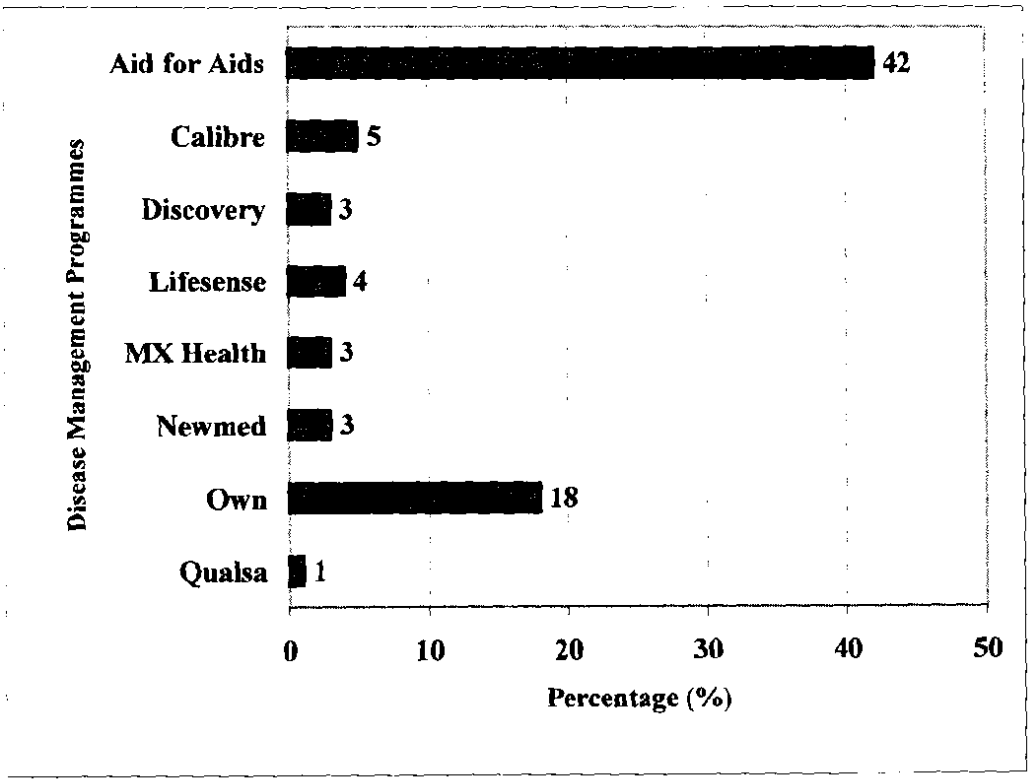


Figure 3.16 Schemes linked to each disease management programme (Stein *et al.*, 2002:11)

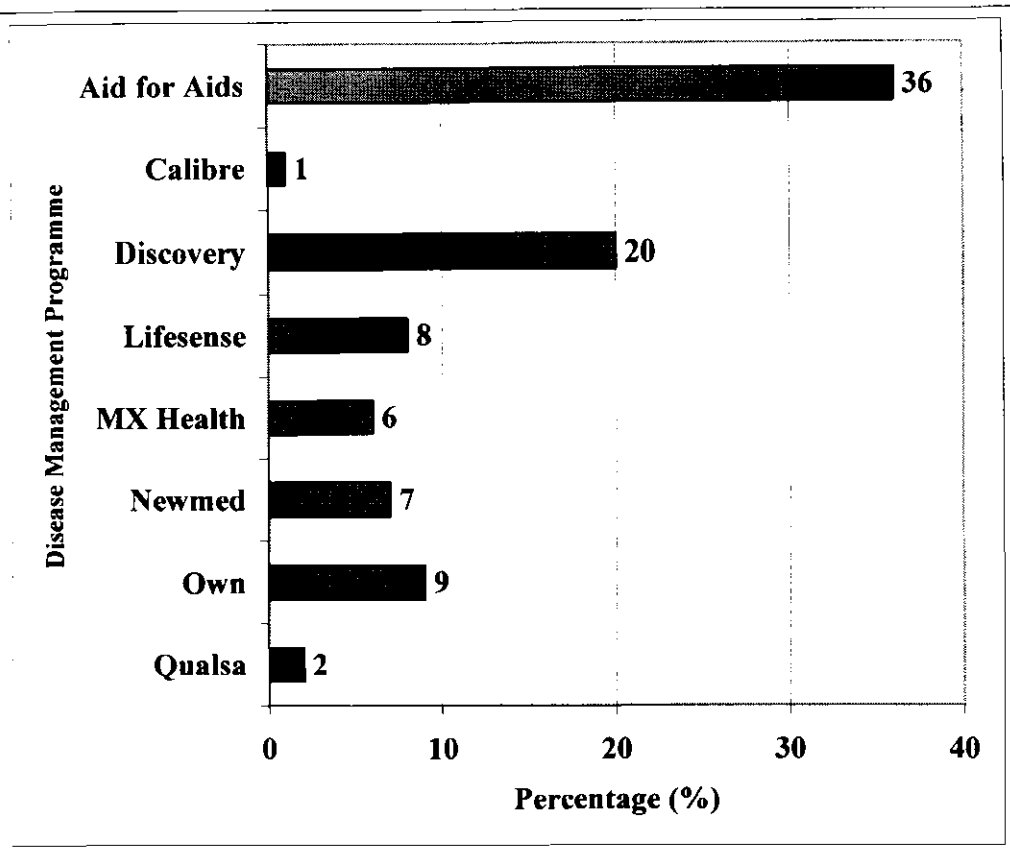


Figure 3.17 Beneficiaries linked to each disease management programme (Stein *et al.*, 2002:11)

From figure 3.17, Aid-for-AIDS is the biggest single disease management programme with 36 per cent of the beneficiaries. Discovery Health's programme represents 20 per cent of the beneficiaries, the second biggest share (Stein *et al.*, 2002:11).

Most options require benefit registration in order to manage HIV costs more effectively. However, disease management participation is very low with only 0.30 per cent of beneficiaries in the industry making use of HIV/AIDS disease management programmes. The disturbing evidence of the low participation rates in the various disease management programmes points to the inadequate marketing of these programmes and the lack of members' awareness of these services (Stein *et al.*, 2002:iii).

3.6.4.1 Example of HIV/AIDS disease management programmes

3.6.4.1.1 Aid for AIDS (AfA)

AfA is the largest disease management programme in South Africa. AfA is a division of Medscheme, South Africa's largest medical scheme administrator. AfA is contracted by 38 medical schemes and is eligible to over 1,8 million beneficiaries. Of these eligible beneficiaries, 14000 are registered with AfA and approximately two-thirds are receiving antiretroviral therapy (Connelly, 2002:9).

Their mission is to provide 'a total HIV/AIDS management solution'. HIV clinical specialists provide oversight and suggest appropriate ARV regimens for beneficiaries, both adults and children. AfA manages the initiation of therapy, adherence to treatment, laboratory monitoring, clinical response and costs. AfA ensures member confidentiality and does not allow medical schemes or the employer to know whether a patient is receiving benefits. AfA has negotiated with pharmaceutical companies to obtain ARVs at the best price and drugs can be delivered directly to the patient. Total benefits per annum are limited to R5 000 to R40 000 depending on the health insurance scheme utilising the services of AfA (Martinson *et al.*, 2002:240).

Doctors are provided with guidelines for HIV treatment including HAART and timing of laboratory monitoring. Deviation from guidelines is allowed after pre-authorisation with AfA. Patients are required to have viral load, CD4 and full blood count tests prior to starting ARV drugs and 4 to 6 monthly thereafter. A 24-hour help-line is available to both patients and their doctors (Martinson *et al.*, 2002:240).

AfA in Southern Africa currently manages 16 400 HIV-infected patients (including 36 health insurance schemes in South Africa), of whom 10 500 receive ARV drugs. Prominent companies whose health insurance is contracted to AfA are Debswana, Coca-Cola and Daimler Chrysler SA (Martinson *et al.*, 2002:240).

Table 3.3 indicates the Aid for AIDS cost per patient per month.

Table 3.3 Aid for AIDS cost per patient per month (Martinson *et al.*, 2002:240)

Scenario	Total Rand	Specialist (%)	Pathology (%)	Grose Profit (%)	Hospital (%)	All other medicine (%)	ARV (%)	Other (%)
All patients	1462	7	12	4	20	11	41	6
HAART (All)	2082	5	11	3	17	8	53	3
HAART (>70% compliance)	2579	4	10	2	12	7	62	2

3.6.4.1.2 The Discovery health enhanced HIV/AIDS disease management programme

Discovery Health's core purpose is to make people healthier and enhance and protect their lifestyles. The enhanced HIV/AIDS management programme is tailored to meet the special needs of their members who have been diagnosed with HIV/AIDS. With guidance and support of the best HIV experts in the industry, Discovery works in partnership with members and their doctors to ensure that enrolled members have

access to the most clinically sound and cost-effective treatment plans available (Discovery Heatlh, 2005:1).

This fully inclusive programme will ensure that members receive personalised service, which includes counselling and approval for antiretroviral medication. Their dedicated and experienced HIV case managers, supported by their full-time HIV specialist doctor, assist members with all aspects of their HIV treatment and lifestyle modification. They offer additional support services and access to reliable information of HIV/AIDS, and what steps members and their families can take to fight and manage the disease (Discovery Health, 2005:1).

Services offered through the enhanced HIV/AIDS management program:

- Voluntary counselling and testing with vitality incentivisation.
- Counselling (24-hour counselling is available through Smart Health Choices).
- Lifestyle and HIV/AIDS-specific education.
- HAART application and approval.
- Education on HAART and assistance in the member's choice of medication delivery.
- Compliance monitoring to ensure that HAART is effective (this includes follow-up calls to the member to assist in management of HAART).
- Management of hospitalisation for HIV/AIDS-related illnesses and ensuring that the member is treated in the most appropriate facility.
- Education and counselling for members requiring prophylactic antiretroviral therapy.
- Ensuring appropriate claims are funded by the Scheme (Discovery Health, 2005:1).

Managed by medical professionals experienced in HIV treatment, the programme also benefits from the expertise of leading HIV specialists and Discovery Health's HIV specialist and Panel. This ensures that members have access to information regarding the latest developments in HIV treatment. The treatment of HIV is an ongoing process. Once initial tests have measured the extent of the disease, they can assist with information on strengthening the body's immune system. Subsequent and regular tests monitor the response to the HIV treatment and recommended changes to treatment are made based on these results. Discovery Health believes that treating HIV requires a partnership between Discovery Health, the member and the patient's health care professional. HIV/AIDS is a sensitive matter, whether one has the condition or not. Their qualified health care consultants will always deal with any HIV/AIDS-related query or case with complete confidentiality (Discovery Health, 2005:4).

3.6.4.1.3 Qualsa health care

Qualsa health care has offered a preventive and pro-active HIV/AIDS disease management programme since early 2000. Qualsa maintains cost of care data for the patients under management and divides it into the following areas: medicines, pathology, doctor visits, counselling, and vaccines. Based on actual cases, Qualsa has made projections of the costs of treatment for one year including ARV drugs, prophylaxis, vitamins, pathology, 10 days of hospitalisation, and 30 days home care for the terminal stage. HAART treatment costs per year of life for the least expensive patient are estimated at R26 467 with ARV drugs accounting for R8 161. For the most expensive patient, the costs were estimated at R38 484 with ARV drugs accounting for R20 178 (Connelly, 2002:9).

From the above given literature, DM can be summarised as the systematic and holistic management of a patient's chronic condition (Chang & Nash, 1998:11). An overview of DM, definition of DM, types of DM and HIV/AIDS disease management programmes, were provided.

3.7 CONCLUSION

In this chapter the prevalence of AIDS in South Africa, the health care system in South Africa, equity in health, public/private partnerships (PPPs), managed health care, drug utilisation review (DUR), pharmacoeconomics, and disease management (DM), were discussed.

CHAPTER 4: EMPIRICAL INVESTIGATION

4.1 INTRODUCTION

In this chapter the research objectives, empirical research methodology, data source and database will be discussed.

4.2 GENERAL RESEARCH OBJECTIVES

The general research objective of this study was to determine *the prescribing patterns of antiviral drugs, with special emphasis on antiretroviral drugs, in the private health care sector in South Africa* by using a medicine claims database.

4.3 SPECIFIC RESEARCH OBJECTIVES

The research project consists of two phases, namely a literature review and an empirical investigation. The research objectives of the two phases include the following:

Phase 1: Literature study

The specific objectives of the literature study include the following:

- To conceptualise from available literature HIV/AIDS, and the treatment protocols thereof.
- To describe ARV drugs according to different classification systems.
- To conceptualise from the literature what managed health care, drug utilisation, pharmacoeconomics and disease management entail.

Phase 2: Empirical investigation

The specific objectives of the empirical investigation were:

- to investigate the possible differences in the utilisation patterns and/or costs, before and after the implementation of the pricing regulations in May 2004 for each of the specific research objectives that follows hereafter;
- to determine the prevalence and usage patterns of drugs in general, as well as the costs associated with these drugs;

- to analyse the general prescribing patterns of antiviral drugs as well as the costs associated with these drugs;
- to determine the prevalence and cost of the subdivisions of antiviral medicine items, ARV medicine items and other antiviral medicine items;
- to determine the prevalence and cost associated with innovator and generic forms of antiviral drugs;
- to determine the general prescribing patterns of ARV drugs as well as the costs associated with these drugs;
- to determine the prevalence and cost of ARV medicine items for the three study years;
- to determine the prevalence and cost of ARV medicine items for the three study years based on the different categories;
- to determine the prevalence and cost of ARV medicine items for the three study years based on the active ingredient classification;
- to determine and compare the difference in prevalence and cost of innovator ARV products versus generic ARV products before and after the implementation of the pricing regulations in May 2004 of ARV drugs;
- to determine the cost saving of ARV medicine items before and after the implementation of the pricing regulations in May 2004; and
- to identify combination therapy of ARV drugs and determine the costs associated with these combinations.

4.4 RESEARCH DESIGN/METHOD

The objective of the study was to review, analyse and interpret prescribing patterns as well as to analyse the costs associated with antiviral drugs, with special reference to ARV drugs. The patterns of drug utilisation were determined after the drug had been dispensed and paid for by the pharmacy benefit management company. Thus, the research design can be classified as a quantitative, retrospective drug utilisation review (Wisconsin Medicaid, 2001:1).

4.5 DATA SOURCE USED FOR THE EMPIRICAL INVESTIGATION

The data used in this study were obtained from the central database of Interpharm Data Systems®, which is a pharmacy benefit management company. The company is responsible for applying managed care concepts to claims data to ensure that the therapeutic outcomes of treatments are satisfactory to the provider, payer, and patient.

The data ranging from 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002, and 1 January 2004 to 31 December 2004 were extracted from the database of Interpharm Data Systems®. The data of 2003 have been left out of the study due to the unavailability of the data for this period.

4.6 DATA ANALYSIS

4.6.1 Data application and data analysis

This step consisted out of two parts, the first being the application of the criteria to the database. This was achieved by viewing the criteria retrospectively. Any deviations of the criteria were marked either for further review or as potential targets for intervention. The second part constituted the data analysis. The data were analysed by means of SAS 9.1® (SAS for Windows, 9.1, 2005).

4.6.2 Statistical analysis

For the purpose of the empirical investigation, various statistical methods were applied to analyse the data as follows:

4.6.2.1 Arithmetic mean (average)

The mean is an average that uses the exact value of each entry (Brase & Brase, 1999:94). To compute the mean, the sum of all values making up the set of observations, is divided by the total number of observations in the set (Banerjee, 2003:3).

$$\bar{x} = \frac{\sum x}{n}$$

Where:

- $\bar{x}$ = mean
- $\sum x$ = sum of all given x values
- n = the number of observations

4.6.2.2 Weighted arithmetic mean

The weighted average is used when the joint arithmetic mean of different sets of data is computed from the arithmetic means of the individual sets (Steyn *et al.*, 2003:102).

$$\bar{y}_w = \frac{\sum wy}{\sum w}$$

Where:

- $\bar{y}_w$ = weighted arithmetic mean
- $\sum wy$ = sum of all given y values ($y_1, y_2, \ldots, y_n$) with relative importance to all given w values ($w_1, w_2, \ldots w_n$)
- $\sum w$ = sum of all given w values ($w_1, w_2, \ldots w_n$)

4.6.2.3 Standard deviation

The standard deviation is a good descriptive measure of variability, although it can be affected strongly by outliers (Cohen & Lea, 2004:15). Brase and Brase (1999:103) defined the standard deviation as a measurement that indicates how the data entries differ from the mean.

$$s = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$

Where:

- s = standard deviation
- x = any value in the data set
- $\bar{x}$ = arithmetic mean (average)
- n = number of observations

During the analysis carried out in this study, the standard deviation was calculated with the aid of a CASIO *fx-82*SUPER FRACTION scientific pocket calculator and SAS 9.1® (SAS for Windows, 9.1, 2005).

4.6.2.4 Cost-prevalence index

Serfontein defines cost-prevalence index (1989:180) as follows:

$$Cost\text{-}prevalence\ index = \frac{Cost\ (\%)}{Prevalence\ (\%)}$$

For the purpose of this study the cost-prevalence index is an indicator of the relative expensiveness of antiviral medicine items, or in particular, ARV medicine items and will be interpreted as follows:

- If cost index < 1 then the medicine item utilised is relatively inexpensive.
- If cost index = 1 then there is an equilibrium between the cost and prevalence of the medicine item.
- If cost index > 1 then the medicine item utilised is relatively expensive.

4.6.2.5 Effect sizes (d-values)

Cohen (1988:3) defines effect sizes as "the degree to which the phenomenon is present in the population". The effect size can be calculated by the following formula (Steyn, 1999:3):

$$d = \frac{\bar{x}_a - \bar{x}_b}{s_{max}}$$

Where:

- d = effect size
- $\bar{x}_a$ = average medicine treatment value of a
- $\bar{x}_b$ = average medicine treatment value of b
- s_{max} = maximum standard deviation between a and b

The *d* value can be interpreted as follows (Steyn, 1999:3):

$d = 0.2$	small effect with no practical significant difference.
$d = 0.5$	medium effect which is observable and may be significant.
$d = 0.8$	large effect, which is significant and of practical importance.
$d > 0.8$	assumed to have practical significant value.

4.7 MEASURING INSTRUMENTS/CRITERIA FOR THE DATA ANALYSIS

In attaining the objectives set out in this study, the following measuring instruments or criteria were selected for use:

- Medicine items
- Prevalence of the different antiviral medicine items, in particular antiretroviral medicine items
- Costs

4.7.1 Medicine items

Medicine items are defined according to the Medicines and Related substances Control Act (101/1965) as "*substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man*". In this research the words "medicine items" are used interchangeably with the word "drugs". Medicine items are used in this study as a research instrument, to give an idea of the prescribing patterns by using the total number of medicine items prescribed, as well as the average number of medicine items per prescription for the total database, antiviral medicine items and ARV medicine items.

4.7.2 Prevalence

According to Waning and Montagne (2001:21) prevalence is defined as "the probability that a condition exists in a specific population or the probability of the occurrence of a condition".

In this study the prevalence of the following medicine items will be analysed as follows:

- The prevalence of all medicine items of the total database claimed during the study period.
- The prevalence of the pharmacological group, e.g. antiviral medicine items claimed during the study period.

- The prevalence of innovator and generic antiviral medicine items claimed during the study period.
- The prevalence of the sub-pharmacological group, e.g. ARV medicine items claimed during the study period.
- The prevalence of innovator and generic ARV medicine items claimed during the study period.
- The prevalence of individual ARV medicine items e.g. Ziagen 300mg®, Videx 25 mg® etc. that contain different active ingredients e.g. abacavir, didanosine etc.
- The prevalence of combination therapy of ARV medicine items claimed during the study period.

4.7.3 Costs

Costs are defined as the input resources utilised by the therapeutic strategy and/or intervention under study; consequences (or outcomes) are the outputs (e.g. any end result of a particular treatment and/or intervention) *(refer to paragraph 3.5.5)*.

The total medicine cost, the average cost per prescription, the average cost per medicine item, as well as the cost-prevalence index were analysed as follows:

- The total cost of all medicine items claimed during the three study periods were compared.
- The total cost of all antiviral medicine items claimed during the three study periods were compared for different time periods (four-month periods).
- The cost difference between innovator and generic antiviral medicine items claimed.
- The total cost of all ARV medicine items claimed during the three study periods were compared for different time periods (four-month periods).
- The cost difference between innovator and generic ARV medicine items claimed.
- The total cost of combination therapy of ARV medicine items claimed during the study period.
- The "cost saving" perceived as a result of the implementation of the new pricing regulations implemented in May 2004.

4.8 RELIABILITY AND VALIDITY OF THE RESEARCH INSTRUMENTS

The central database of Interpharm Data Systems® was utilised to obtain the data for the study. The data were obtained directly from the central database and thus no direct manipulation of the data by the researcher was possible. Data for the analysis were obtained, from the central medicine claims database, for a three year period (1 January 2001 to 31 December 2002 and 1 January 2004 to 31 December 2004)

thus, limiting external validity, implying that results can only be generalised to the specific database used, as well as to the specific study population.

Research was conducted from the viewpoint that all data obtained from the database were correct and accurate, this is a limitation of the study and will be listed in Chapter 6.

4.9 RESULTS AND DISCUSSION

The results of the empirical investigation will be discussed in Chapter 5.

4.10 CONCLUSIONS AND RECOMMENDATIONS

The conclusions and recommendations based on the results of the literature review and the empirical investigation will be discussed in Chapter 6.

4.11 CHAPTER SUMMARY

In this chapter the research methodology was discussed, which included the general and specific objectives of the study, the different phases of the research project, the research design/method, the data source, the data analysis and statistical analysis of the data. The analysis, together with the results of the empirical study will be reported in Chapter 5.

CHAPTER 5: RESULTS AND DISCUSSION

5.1 INTRODUCTION

In this chapter, the results of the empirical investigation of the prescribing patterns and cost of antiviral medicine items, in particular antiretroviral (ARV) medicine items for the study periods 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002 and 1 January 2004 to 31 December 2004 will be outlined and conferred.

For the purpose of this study, the total database was analysed and the antimicrobial medicine items have been referred to as medicine items of the main pharmacological group (pharmacological group 18 according to the MIMS® classification system). The antiviral medicine items have been referred to as medicine items of the pharmacological group (group 18.12 according to the MIMS® classification system) and have been divided into two separate categories namely the antiretroviral (ARV) medicine items (classified in this study as group 18.12.1) and the other antiviral medicine items. (Snyman, 2005:325).

Due to the nature and extent of this study, the focus of the study was on the antiviral medicine items, and in particular the ARV medicine items.

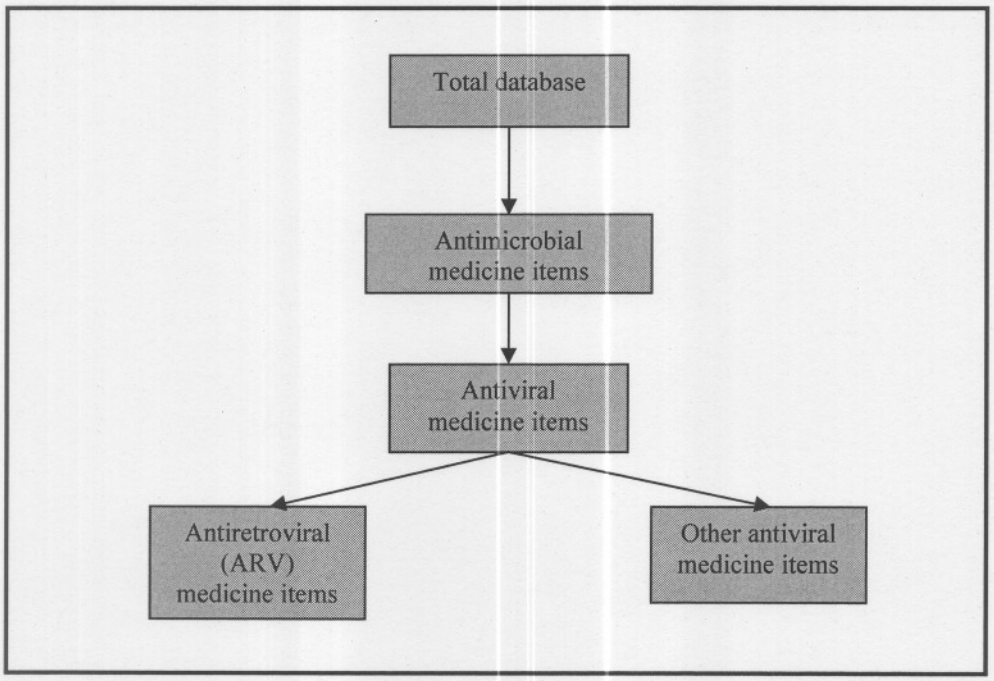


Figure 5.1 Schematic classification system of the database

The following table summarises the different antiviral medicine items divisions (adapted from Snyman, 2005:325), which can be divided into two subdivisions, namely the ARV medicine items and "other antiviral medicine items". The subdivision, ARV medicine items, constitutes different categories (MCC, 2004:1), namely the Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) (Category I), the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Category II), the Protease Inhibitors (PIs) (Category III) *(refer to section 2.7.2.1)* and the OTHER ARV medicine items (Category IV) *(refer to section 5.1.2)*. The subdivision, "other antiviral medicine items" *(refer to section 5.1.2)*, constitutes medicine items that can be used for different diseases, such as herpes simplex, herpes zoster, varicella zoster, cytomegalovirus, influenza and warts, plantar warts and skin eruptions, but are not specifically indicated for the treatment of HIV.

Table 5.1 Antiviral medicine items divisions (adapted from Snyman, 2005:325 and MCC, 2004:1)

ARV medicine items	"Other antiviral medicine items"					
	Herpes Simplex	**Herpes Zoster**	**Varicella Zoster**	**Cytomegalo-virus**	**Influenza**	**Warts, plantar warts, skin eruptions**
NRTI *(Category I)* • Abacavir • Didanosine • Lamivudine • Stavudine • Zalcitabine • Zidovudine **NNRTI** *(Category II)* • Nevirapine • Efavirenz **PI** *(Category III)* • Indinavir • Lopinavir • Nelfinavir • Ritonavir • Saquinavir **OTHER ARV medicine items** *(Category IV)* • Lamivudine/Zidovudine • Lopinavir/Ritonavir	Moroxydine Famciclovir Acyclovir	Moroxydine Famciclovir Acyclovir Valaciclovir	Acyclovir	Acyclovir Valaciclovir Ganciclovir	Zanamivir Amantadine	Moroxydine

5.1.1 Terms and definitions

For the purpose of this study, the following terms and definitions were used:

Generic medicine items:

Generic medicine items are pharmaceutical products usually intended to be interchangeable with the innovator medicine items, manufactured without a licence from the innovator manufacturer and marketed after the expiry of patent or other exclusivity rights (WHO, 2003c:116). Generic medicine items contain the same active pharmaceutical ingredients, the same quantities thereof, and are in the same pharmaceutical dosage form as the innovator medicine items (MCC, 2003:1).

Innovator medicine items:

Innovator medicine items are the original patented pharmaceutical products (Ball *et al.*, 2005:12). Innovator medicine items are generally the products that were first authorised worldwide for marketing (normally as patented products) on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorisation. The innovator product always has a brand name; this may, however, vary between countries (WHO, 2003c:116).

Medicine items:

Medicine items are defined according to the Medicines and Related substances Control Act (101/1965) as "*substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man*". In this research the words "medicine items" are used interchangeably with the word "drugs". Medicine items are used in this study, as a research instrument to give the idea of the total number of medicine items that were prescribed as well as the total number of medicine items prescribed per prescription in general (total database) as well as for antiviral medicine items. It also shows the distribution and utilisation patterns of antiviral and ARV medicine items. For the purpose of this study the term medicine items exclude "dry goods" e.g. surgical equipment, non-medical medicine items (e.g. needles, syringes, etc.) and mixtures (with unidentifiable active ingredients).

Number of prescriptions:

It refers to the total number of prescriptions claimed during a specific period.

Other antiviral medicine items:

Other antiviral medicine items constitute antiviral medicine items that are mainly used for different diseases such as herpes simplex, herpes zoster, varicella zoster, cytomegalovirus, influenza and warts, plantar warts and skin eruptions, but are not used for the treatment of HIV.

OTHER ARV medicine items:

For the purpose of this study, OTHER ARV medicine items are a category of the subdivision, ARV medicine items. It constitutes a combination of lamivudine/zidovudine, and lopinavir/ritonavir. Other subcategories of ARV medicine items include the NRTIs, the NNRTIs and the PIs (MCC, 2004:1).

Weighted arithmetic mean:

The weighted arithmetic mean is used when a joint arithmetic mean of different sets of data is computed from the arithmetic means of the individual sets *(refer to paragraph 4.6.2.3)*.

5.1.2 Comments of interest with the interpretation of the results

- For the purpose of this study, each year consists of three time periods and in total there will be 9 time periods (adapted from Bopape, 2004:108). The following time periods will be denoted in the discussion as follows: 1 January 2001 to 30 April 2001 = P1; 1 May 2001 to 31 August 2001 = P2; 1 September 2001 to 31 December 2001 = P3; 1 January 2002 to 30 April 2002 = P4; 1 May 2002 to 31 August 2002= P5; 1 September 2002 to 31 December 2002 = P6; 1 January 2004 to 30 April 2004 = P7; 1 May 2004 to 31 August 2004 = P8; 1 September 2004 to 31 December 2004 = P9. P1, P2 and P3 are denoted the first study year, P4, P5 and P6 are denoted the second study year and P7, P8 and P9 are denoted the third study year. These periods can be illustrated as follows:

Table 5.2.1 The first study year

Study year one	
1 January 2001 to 30 April 2001	P1
1 May 2001 to 31 August 2001	P2
1 September 2001 to 31 December 2001	P3

Table 5.2.2 The second study year

Study year two	
1 January 2002 to 30 April 2002	P4
1 May 2002 to 31 August 2002	P5
1 September 2002 to 31 December 2002	P6

Table 5.2.3 The third study year

Study year three	
1 January 2004 to 30 April 2004	P7
1 May 2004 to 31 August 2004	P8
1 September 2004 to 31 December 2004	P9

- The data of 2003 have been left out of the study due to the unavailability of the data for this period and thus the usage and costs of drugs associated with this period cannot be compared with the other periods.
- The new price regulations *(refer to section 3.3.3)* were implemented in May 2004 and the different time periods of 2004 (1 January 2004 to 30 April 2004, 1 May 2004 to 31 August 2004 and 1 September 2004 to 31 December 2004) will be compared to perceive and identify possible differences in the prescribing patterns and cost due to the introduction of the single exit price system (SEP).
- For the interpretation of the results of 2004, the period of 1 January 2004 to 30 April 2004 will be referred to as "before implementation", the period of 1 May 2004 to 31 August 2004 will be referred to as "transition phase", and the period of 1 September to 31 December will be referred to as "after single exit price".
- The values of the data that were used have been "rounded off" to two decimals and may not add up to 100 per cent.
- The effect sizes (d-values) were calculated *(refer to section 4.6.2.5)* and described in the text, but not indicated in any tables.
- Only $d \geq 0.8$ (practically significant difference) was used as this value indicated that the effect is large and of practical importance *(refer to section 4.6.2.5)*.
- For the purpose of this study, the effect sizes (d-values) for the weighted average costs and weighted average number of medicine items per prescription were not calculated.

5.2 GENERAL PRESCRIBING PATTERNS

5.2.1 General prescribing patterns for the years 2001, 2002 and 2004

Table 5.3 gives the prescribing patterns of the total database, of antiviral medicine items and of ARV medicine items for the three study years, 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002 and 1 January 2004 to 31 December 2004.

Table 5.3 Results of the general prescribing patterns for the years, 2001 (P1 to P3), 2002 (P4 to P6), and 2004 (P7 to P9)

Description	2001 (P1 to P3)			2002 (P4 to P6)			2004 (P7 to P9)		
	Total database	Antiviral medicine items	Antiretroviral Medicine items	Total database	Antiviral Medicine items	Antiretroviral Medicine items	Total database	Antiviral Medicine items	Antiretroviral Medicine items
Total number of prescriptions containing at least one medicine item	1475380	15857	5599	2076236	28482	15004	2595254	58549	43482
Total number of medicine items prescribed	2951326	21183	9796	4042145	50246	35271	5305882	118718	101938
Weighted average number of medicine items per prescription*	2.00±0.05 (n=1475380)	1.34±0.13 (n=15857)	1.75±0.31 (n=5599)	1.95±0.03 (n=2076236)	1.76±0.08 (n=28482)	2.35±0.03 (n=15004)	2.04±0.08 (n=2595254)	2.03±0.07 (n=58549)	2.35±0.02 (n=43482)
Total number of innovator medicine items prescribed	2161451	15473	9796	2901848	41919	35271	3529046	103350	96609
Total number of generic medicine items prescribed	789875	5710	0	1140297	8327	0	1776836	15368	5329
Total cost (R)	379708489	7412577.73	4990784.29	601350325	21523365.56	18235075.75	661223146	38064347.38	34714483.64
Weighted average cost per prescription (R)*	257.36±3.42 (n=1475380)	467.47±52.29 (n=15857)	891.37±164.71 (n=5599)	289.64±11.99 (n=2076236)	755.68±129.58 (n=28482)	1215.35±155.29 (n=15004)	254.78±18.83 (n=2595254)	650.13±44.77 (n=58549)	798.37±45.60 (n=43482)
Weighted average cost per medicine item (R)*	128.66±4.38 (n=29513216)	349.93±53.93 (n=21183)	509.48±155.66 (n=9796)	146.56±7.15 (n=4042145)	428.36±55.85 (n=50246)	517.00±64.18 (n=35271)	124.62±13.85 (n=5305882)	320.63±19.28 (n=118718)	340.55±22.44 (n=101938)
Weighted average cost of innovator medicine items per prescription (R)*	148.40±6.16 (n=2161451)	448.65±78.08 (n=15473)	509.48±155.66 (n=9796)	177.13±10.07 (n=2901848)	496.75±57.71 (n=41919)	517.00±64.18 (n=35271)	155.75±14.4 (n=3529046)	355.66±19.35 (n=103350)	352.87±21.50 (n=96609)
Weighted average cost of generic medicine items per prescription (R)*	67.39±2.22 (n=789875)	82.42±7.01 (n=5710)	0	76.61±3.08 (n=1140297)	84.06±2.48 (n=8327)	0	62.79±11.10 (n=1776836)	85.06±1.96 (n=15368)	117.06±9.23 (n=5329)

*The average number of medicine items per prescription, average cost per prescription, average cost per medicine item, average cost per innovator medicine items per prescription, and average cost per generic medicine items per prescription for each separate study year, were calculated by means of the weighted average *(refer to section 4.6.2.2).*

The ***total number of prescriptions*** containing at least one medicine item of the ***total database*** increased with 40.73 per cent (n=600 856) from 2001 to 2002, and with 25.00 per cent (n=519 018) from 2002 to 2004. There was an overall increase of 75.90 per cent (n=1 119 874) from 2001 to 2004 in the total number of prescriptions containing at least one medicine item of the total database *(refer to table 5.3)*.

Table 5.3 indicates that the ***total number of medicine items*** claimed for the ***total database*** increased with 36.96 per cent (n=1 090 819) from 2001 to 2002, and with 31.26 per cent (n=1 263 737) from 2002 to 2004. This amounted to an overall increase of 79.78 per cent (n=2 354 556) in total number of medicine items claimed from 2001 to 2004. A possible explanation for this accruement could be a rise in the number of medical schemes, medical scheme members and dependants administered by this pharmacy benefit company.

The ***total number of prescriptions*** containing at least one ***antiviral medicine item*** increased with 79.62 per cent (n=12 625) from 2001 to 2002, and with 105.57 per cent (n=30 067) from 2002 to 2004. There was an overall increase of 269.23 per cent (n=42 692) from 2001 to 2004 in the total number of prescriptions containing at least one antiviral medicine item. The ***total number of antiviral medicine items*** claimed, increased with 137.20 per cent (n=29 063) from 2001 to 2002, and with 136.27 per cent (n=68 472) from 2002 to 2004. This amounted to an overall increase of 460.44 per cent (n=97 535) from 2001 to 2004 in total number of antiviral medicine items claimed through this pharmacy benefit company *(refer to table 5.3)*.

The ***total number of ARV prescriptions*** containing at least one ARV medicine item increased with 167.98 per cent (n=9 405) from 2001 to 2002, and with 189.80 per cent (n=28 478) from 2002 to 2004. There was an overall increase of 676.60 per cent (n=37 883) from 2001 to 2004 in the total number of prescriptions containing at least one ARV medicine item. The ***total number of ARV medicine items*** claimed increased with 260.06 per cent (n=25 475) from 2001 to 2002, and with 189.01 per cent (n=66 667) from 2002 to 2004. This amounted to an overall increase of 940.61 per cent (n=92 142) in the total number of ARV medicine items claimed for the period 2001 to 2004 *(refer to table 5.3)*.

Table 5.3 shows that the ***number of prescriptions containing at least one antiviral medicine item*** represents 1.07 per cent (n=15 857) during 2001, 1.37 per cent (n=28 482) during 2002, and 2.26 per cent (n=58 549) during 2004 from the ***total number of prescriptions*** claimed through the database (n=1 475 380 for 2001, n=2 076 236 for 2002, and n=2 595 254 for 2004). The ***number of antiviral medicine items*** represents 0.72 per cent (n=21 183) during 2001, 1.25 per cent (n=50 246) during 2002, and 2.24 per cent (n=118 718) during 2004 of the ***total number of medicine items*** claimed through the database (n=2 951 326 for 2001, n=4 042 145 for 2002, and n=5 305 882 for 2004).

Of the ***total number of prescriptions*** (n=1 475 380) issued during the 2001 study year, 0.38 per cent (n=5 599) constituted ***prescriptions containing at least one ARV medicine item***, and of the total number of ***prescriptions containing at least one antiviral medicine item*** (n=15 857), 35.31 per cent (n=5 599) constituted ***prescriptions containing at least one ARV medicine item***. Of the total number of prescriptions (n=2 076 236) issued during 2002, 0.72 per cent (n=15 004) of the prescriptions constituted prescriptions containing at least one ARV medicine item, and of the total number of prescriptions containing at least one antiviral medicine item (n=28 482), 52.68 per cent (n=15 004) constituted prescriptions containing at least one ARV medicine item. Of the total number of prescriptions (n=2 595 254) issued during the 2004 study year, 1.68 per cent (n=43 482) of the prescriptions constituted prescriptions containing at least one ARV medicine item, and of the total number of prescriptions containing at least one antiviral medicine item (n=58 549), 74.27 per cent (n=43 482) constituted prescriptions containing at least one ARV medicine item *(refer to table 5.3)*.

Thus, *table 5.3* indicates that the ***number of prescriptions*** containing at least one ***ARV medicine item*** increased from 0.38 per cent (n=5 599) during 2001, to 0.72 per cent (n=15 004) during 2002, to 1.68 per cent (n=43 482) during 2004 of the number of prescriptions containing at least one medicine item of the total database. The number of prescriptions containing at least one ARV medicine item increased from 35.31 per cent (n=5 599) during 2001, to 52.68 per cent (n=15 004) during 2002, and to 74.27 per cent (n=43 482) during 2004 of the total number of prescriptions containing at least one antiviral medicine item. These accruements could be due to a rise in the number of medical schemes, medical scheme members and dependants claimed through Interpharm Data Systems® and also an increase in the prescribing of ARV medicine items for HIV positive patients.

The ***total number of ARV medicine items*** (n=9 796) was 0.33 per cent (n=9 796) of the ***total number of medicine items*** (n=2 951 326) claimed during 2001 and 46.25 per cent of the total number of antiviral medicine items claimed (n=21 183). In the year 2002, the total number of ARV medicine items (n=35 271) represented 0.87 per cent of the total number of medicine items (n=4 042 145) claimed and 70.20 per cent of the total number of antiviral medicine items (n=50 246). In 2004, ARV medicine items represented 1.92 per cent of all medicine items (n=5 305 882) claimed during that year and 85.87 per cent of all antiviral medicine items (n=118 718) claimed during that specific year *(see table 5.3)*.

Although there was a relatively small increase in the ***weighted average number of medicine items per prescription*** per study year, the increase in the average number of antiviral medicine items and ARV medicine items per prescription per study year was relatively higher with an increase of 51.49 per cent (n=0.69) for the antiviral medicine items and an increase of 34.29 per cent (n=0.6) for the ARV medicine

items *(refer to table 5.4)* from 2001 to 2004. This may indicate that treatment protocols may have changed during the 2004 study year *(refer to section 3.3.2.3)*.

Table 5.4 The weighted average number of medicine items per prescription (extraction from table 5.3)

Description	2001	2002	2004
Average number of medicine items per prescription on the total database*	2.00±0.05	1.95±0.03	2.04±0.08
Average number of antiviral medicine items per prescription	1.34±0.13	1.76±0.08	2.03±0.07
Average number of ARV medicine items per prescription	1.75±0.31	2.35±0.03	2.35±0.02

*This includes all medicine items claimed during the specific study period

As can be seen from *table 5.5*, the ***weighted average cost per medicine items*** of the total database for 2004 were relatively smaller in comparison with the weighted average cost per antiviral and ARV medicine items. It may be an indication of a wider range of price structures, whilst for the ARV medicine items, the standard deviation recorded is quite smaller in 2004 than recorded in the study years before. It may be an indication that a lower price variation was experienced during this period.

Thus, *table 5.5* indicates an increasing trend in the ***weighted average cost per prescription*** for the period 2001 to 2002, and a decreasing trend for the period 2002 to 2004. Possible reasons for the increasing trend for the period 2001 to 2002 could be the yearly cost inflation that results in higher manufacturing expenses and in its turn, higher medicine item prices. The decreasing trend for the period 2004 could be due to the implementation of the new pricing regulations in May 2004 *(refer to section 3.3.3)* or the availability of more generic products on the market during 2004. *Table 5.6* shows that generic products represented 33.49 per cent (n=1 776 836) of the total medicine database during 2004 (P7 to P9) and that generic ARV products represented 5.23 per cent (n=5 329) of the total ARV medicine items during 2004 (P7 to P9). This indicates an increase of 55.82 per cent (n=636 539) from 2002 to 2004 in generic products of the total medicine database, and an increase of 100 per cent (n=5329) from 2002 to 2004 in generic ARV medicine items.

Table 5.5 The weighted average cost (R) per prescription (extraction from table 5.3)

Description	2001 (R)	2002 (R)	2004 (R)
Weighted average cost (R) per prescription of the total medicine database	257.36±3.42	289.64±11.99	254.78±18.83
Weighted average cost (R) per prescription of antiviral medicine items	467.47±52.29	755.68±129.58	650.13±44.77
Weighted average cost (R) per prescription of ARV medicine items	891.37±164.71	1215.35±155.29	798.37±45.60

The ***total cost*** of all medicine items increased with 58.37 per cent (n=R221 641 836) from 2001 to 2002, and with 9.96 per cent (n=R59 872 821) from 2002 to 2004. The overall increase for the total database was 74.14 per cent (n=R281 514 657) for the period 2001 to 2004. The total cost of antiviral medicine items increased with 190.36 per cent (n=R14 110 787.83) from 2001 to 2002, and increased also with 76.85 per cent (n=R16 540 981.82) from 2002 to 2004. The overall increase was 413.51 per cent (n=R30 651 769.65) for the period 2001 to 2004. The total cost of ARV medicine items increased with 265.38 per cent (n=R13 244 291.46) from 2001 to 2002, and also increased with 90.37 per cent (n=R16 479 407.89) from 2002 to 2004. This resulted in an overall increase of 595.57 per cent (n=R29 723 699.35) for the period 2001 to 2004. The above increasing trends in the total costs of the total database, the antiviral medicine items and the ARV medicine items could be due to not only an increase in the prevalence of HIV/AIDS disease as such, but a change in the administration of medical schemes, compilation of medical scheme members and dependants, and increased health care expenditures *(refer to table 5.3)*.

The ***total cost of antiviral medicine items***, represents 1.95 per cent (n=R7 412 577.73) during 2001, 3.58 per cent (n=R21 523 365.56) during 2002, and 5.76 per cent (n=R38 064 347.38) during 2004 from the ***total cost of all medicine items*** claimed through the database (n=R379 708 482 for 2001, n=R601 350 325 for 2002, and n=R661 223 146 for 2004). The ***cost of ARV medicine items*** constituted 1.31 per cent (n=R4 990 784.29) of the ***total cost of all medicine items*** (n=R379 708 489) claimed for 2001, and 67.33 per cent (n=R4 990 784.29) of the ***total cost of antiviral medicine items*** (n=R7 412 577.73) claimed for 2001. Of the ***total cost of all medicine items*** (n=R601 350 325) claimed for 2002, ***ARV medicine items*** constituted 3.03 per cent (n=R18 235 075.75), and 84.72 per cent (n=R18 235 075.75) of the ***total cost of antiviral medicine items*** (n=R21 523 365.56) claimed for 2002. ***ARV medicine items*** constituted 5.25 per cent (n=R34 714 483.64) of the ***total cost of all medicine items*** (n=R661 223 146) claimed for 2004, and 91.20 per cent (n=R34 714 483.64) of the ***total cost of antiviral medicine items*** (n=R38 064 347.38) claimed for 2004 *(refer to table 5.3)*.

The ***total number of innovator medicine items*** claimed (n=2 161 451) for ***2001*** was 73.24 per cent of the total number of medicine items claimed (n=2 951 326). The generic medicine items claimed (n=789 875) represented 26.76 per cent (n=2 951 326). During the same study period the innovator antiviral medicine items represented 73.04 per cent (n=15 473) of all antiviral medicine items (n=21 183) claimed and the generic antiviral medicine items claimed (n=5 710) represented 26.96 per cent (n=21 183). For ARV medicine items, there were no generic medicine items claimed during 2001, and thus 100 per cent (n=9 796) of the ARV medicine items claimed were innovator ARV medicine items *(refer to table 5.3 and table 5.6)*.

The ***total number of innovator medicine items*** claimed (n=2 901 848) during ***2002*** was 71.79 per cent (n=4 042 145) of the total number of medicine items claimed. The generic medicine items claimed (n=1 140 297) represented 28.21 per cent (n=4 042 145) of the total number of medicine items claimed. For the antiviral medicine items, the total number of innovator medicine items claimed (n=41 919) during 2002 represented 83.43 per cent (n=50 246) of the total number of antiviral medicine items claimed and the generic antiviral medicine items represented 16.57 per cent (n=8 327). Hundred per cent of the ARV medicine items claimed during 2002 were innovator products (n=35 271) *(refer to table 5.3 and table 5.6)*.

During ***2004*** the ***innovator medicine items*** represented 66.51 per cent (n=3 529 046) of the total number of medicine items claimed (n=5 305 882) and the generic medicine items represented 33.49 per cent (n=1 776 836). The innovator antiviral medicine items claimed during the period P7 to P9 represented 87.06 per cent (n=103 350) of the total number of antiviral medicine items claimed (n=118 718) and 12.95 per cent (n=15 368) indicated generic antiviral medicine items. For the ARV medicine items, 94.77 per cent (n=96 609) innovator medicine items were claimed out of the total number of ARV medicine items (n=101 938) for 2004. A percentage of 5.23 per cent (n=5 329) generic ARV medicine items was claimed out of the total number of ARV medicine items (n=101 938) for 2004 *(refer to table 5.3 and table 5.6)*.

Table 5.6 Comparison between the percentage of innovator and generic medicine items claimed for the different study periods

Period	Innovator or Generic	Total database (%*)	Antiviral medicine items (%#)	ARV medicine items (%@)
2001 (P1 – P3)	Innovator	73.24	73.04	100
	Generic	26.76	26.96	0
2002 (P4 – P6)	Innovator	71.79	83.43	100
	Generic	28.21	16.57	0
2004 (P7 – P9)	Innovator	66.51	87.06	94.77
	Generic	33.49	12.95	5.23

%* The total number of innovator or generic medicine items claimed for the specific period divided by the total number of medicine items claimed for the corresponding period multiplied by hundred.

%# The total number of innovator or generic antiviral medicine items claimed for the specific period divided by the total number of antiviral medicine items claimed for the corresponding period multiplied by hundred.

%@ The total number of innovator or generic ARV medicine items claimed for the specific period divided by the total number of ARV medicine items claimed for the corresponding period multiplied by hundred.

There was a gradual decrease in the ***percentage innovator medicine items*** claimed, by decreasing from 73.24 per cent (n=2 161 451) for period P1 to P3, to 71.79 per cent (n=2 901 848) for the period P4 to P6,

and to 66.51 per cent (n=3 529 046) for the period P7 to P9. In turn, the generic medicine items claimed increased steadily from 26.76 per cent (n=789 875) for the period P1 to P3, to 28.21 per cent (n=1 140 297) for the period P4 to P6, and to 33.49 per cent (n=1 776 836) for the period P7 to P9. For the antiviral medicine items claimed, the innovator antiviral medicine items raised from 73.04 per cent (n=15 473) to 83.43 per cent (n=41 919) to 87.06 per cent (n=103 350) over the different time periods.

The ***generic antiviral medicine items*** claimed reduced from 26.96 per cent (n=5 710) to 16.57 per cent (n=8 327) to 12.95 per cent (n=15 368) over the different time periods. According to the database no generic ARV medicine items were claimed for the periods P1 to P3, and P4 to P6, indicating that only innovator ARV medicine items were claimed for these two periods. During the time periods P7 to P9 the data indicated that 94.77 per cent (n=96 609) innovator ARV medicine items were claimed and 5.23 per cent (n=5 329) generic ARV medicine items were claimed *(refer to table 5.6)*.

From this discussion, it can be ***concluded*** that the total volume of medicine items and the unit price (average price) influence the total cost of medicine items. The average number of medicine items per prescription makes up the total volume of medicine items. The total cost of medicine items is made up by the average cost per prescription multiplied by the number of prescriptions.

Both the ***cost*** of drug therapy and ***prevalence*** have increased from 2001 to 2002, and the prevalence increased from 2002 to 2004, but the cost of drug therapy decreased during 2004. An increase in prevalence could be due to an increase of HIV/AIDS infections in people in the private sector *(refer to section 3.2)*, or due to the availability of ARV medicine on medical aid plans *(refer to section 3.3.2.3)*, or an increase in medical scheme members *(refer to section 3.3.2.1)*. The decrease in the cost of drug therapy is probably a result of the implementation of the new pricing regulations in May 2004 *(refer to section 3.3.3)*.

5.3 ANALYSIS OF THE PHARMACOLOGICAL GROUP: ANTIVIRAL MEDICINE ITEMS

The analysis of antiviral medicine items will be outlined in this section.

5.3.1 General prescribing patterns

Table 5.7 gives the general prescribing patterns of antiviral medicine items for the study year, ***1 January 2001 to 31 December 2001***, divided into three four-month periods [1 January 2001 to 30 April 2001 (P1), 1 May 2001 to 31 August 2001 (P2), and 1 September 2001 to 31 December 2001 (P3)], ***1 January 2002 to 31 December 2002***, divided into three four-month periods [1 January 2002 to 30 April 2002 (P4), 1 May 2002 to 31 August 2002 (P5), and 1 September 2002 to 31 December 2002 (P6)], and ***1 January 2004 to 31 December 2004***, divided into three four-month periods [1 January 2004 to 30 April 2004 (P7), 1 May 2004 to 31 August 2004 (P8), and 1 September 2004 to 31 December 2004 (P9)].

Table 5.7 Results of the general prescribing patterns of antiviral items for the years 2001, 2002, and 2004, each divided into three four-month periods

Description	2001 (P1 to P3)			2002 (P4 to P6)			2004 (P7 to P9)		
	P1	P2	P3	P4	P5	P6	P7	P8	P9
Number of prescriptions containing at least one antiviral medicine item	5007	6007	4843	7963	9616	10903	9946	22224	26379
Total number of antiviral medicine items prescribed	6061	7772	7350	13156	16923	20167	18924	44744	55050
Average number of antiviral medicine items per prescription	1.21±0.48	1.29±0.62	1.52±0.83	1.65±0.87	1.76±0.89	1.85±0.88	1.90±0.86	2.01±0.81	2.09±0.81
Total number of innovator antiviral medicine items prescribed	4313	5587	5573	10638	14014	17267	16066	39414	47870
Total number of generic antiviral medicine items prescribed	1748	2185	1777	2518	2909	2900	2858	5330	7180
Total cost (R)	2636319.7	2425721.37	2350536.66	5001503	6508231.94	10013630.62	5609082.88	15425331.16	17029933.34
Average cost per prescription (R)	526.53±753.11	403.82±512.40	485.35±533.15	628.09±576.32	676.81±619.22	918.43±834.67	563.95±437.02	694.08±425.53	645.59±400.43
Average cost per antiviral item (R)	434.96±537.11	312.11±393.07	319.80±366.34	380.17±365.40	384.58±359.37	496.54±471.93	296.40±268.48	344.75±236.31	309.35±229.69
Average cost of innovator antiviral medicine items per prescription (R)	574.07±578.87	404.94±427.04	395.41±389.01	449.57±371.65	447.62±362.44	565.70±475.01	334.48±271.97	380.04±227.65	342.69±224.72
Average cost of generic antiviral medicine items per prescription (R)	91.74±89.40	74.76±70.06	82.67±79.78	86.97±87.98	80.91±84.24	84.69±85.37	82.37±86.79	83.77±90.68	87.09±104.87

The ***total number of prescriptions*** containing at least one ***antiviral medicine item*** decreased with 3.28 per cent (n=164) during 2001 (period P1 to P3), increased with 36.92 per cent (n=2 940) during 2002 (period P4 to P6), and also 123.45 per cent (n=12 278) from P7 to P8, and with 18.70 per cent (n=4 155) from P8 to P9. This resulted in an overall increase of 165.22 per cent (n=16 433) during 2004 (period P7 to P9) in the total number of prescriptions containing at least one antiviral medicine item *(refer to table 5.7)*.

The ***total number of antiviral medicine items*** claimed increased with 21.27 per cent (n=1 289) in 2001 (period P1 to P3), increased with 53.29 per cent (n=7 011) in 2002 (period P4 to P6), and also with 190.90 per cent (n=36 126) in 2004 (period P7 to P9) *(refer to table 5.7)*.

Table 5.7 indicates that the ***average number of antiviral medicine items per prescription*** increased over the three study years ranging from 1.21±0.48 antiviral medicine items per prescription in P1 to 2.09±0.81 antiviral medicine items per prescription in P9. Only the effect sizes (d-values) calculated for the differences between the average numbers of antiviral medicine items per prescription for P1 and P7, P1 and P8, P1 and P9, P2 and P8, and P2 and P9 have practical significant values (d>0.8).

The ***total number of innovator antiviral medicine items***, as well as ***total number of generic antiviral medicine items*** claimed, increased steadily over the three study years. The total number of innovator antiviral medicine items increased with 29.21 per cent (n=1 260) in 2001 (period P1 to P3), with 62.31 per cent (n=6 629) in 2002 (period P4 to P6), and with 197.96 per cent (n=31 804) in 2004 (period P7 to P9). The ***total number of generic antiviral medicine items*** inclined with 1.66 per cent (n=29) in 2001 (period P1 to P3), with 3.59 per cent (n=382) in 2002 (period P4 to P6), and with 151.23 per cent (n=4 322) in 2004 (period P7 to P9) *(refer to table 5.7)*.

The ***total cost of antiviral medicine items*** decreased with 10.84 per cent (n=R285 783.04) in 2001 (period P1 to P3), increased with 100.21 per cent (n=R5 012 127.62) in 2002 (period P4 to P6), and increased with 175.01 per cent (n=R9 816 248.28) from P7 to P8, and also with 10.40 per cent (n=R1 604 602.18) from P8 to P9. This resulted in an overall increase of 203.61 per cent (n=R11 420 850.46) in 2004 (period P7 to P9) *(refer to table 5.7)*.

Table 5.7 indicates that the ***average cost per antiviral prescription*** fluctuated during 2001 from R526±753.11 to R485.35±533.15, increased with 46.23 per cent (n=R290.34) in 2002, and increased with 23.08 per cent (n=R130.13) from P7 to P8, and decreased with 6.99 per cent (n= R48.49) from P8 to P9. There was an overall increase of 14.48 per cent (n= R81.64) for the period P7 to P9.

The ***effect sizes (d-values)*** calculated for the differences between the average costs per antiviral prescription for the three study years have no practical significant value (d<0.8).

Table 5.7 shows that the ***average cost per antiviral item*** declined with 26.48 per cent (n=R115.16) in 2001, raised with 30.61 per cent (n=R116.37) in 2002, and also raised with 16.31 per cent (n=R48.35) from P7 to P8, and decreased with 10.27 per cent (n=35.40) from P8 to P9. This resulted in an overall incline of 4.37 per cent (n=12.95) in 2004. The ***effect sizes (d-values)*** calculated for the differences between the average costs per antiviral item for the different time periods have no practical significant value (d<0.8).

According to *table 5.7* the ***average cost of innovator antiviral medicine items per prescription*** decreased with 31.12 per cent (n=R178.66) in 2001(period P1 to P3), increased with 25.83 per cent (n=R116.13) in 2002 (period P4 to P6), and inclined with 13.62 per cent (n=R45.56) from P7 to P8, and declined with 9.83 per cent (n=R37.35) from P8 to P9. This resulted in an overall increase of 2.45 per cent (n=R8.21) in 2004 (period P7 to P9). The ***effect sizes (d-values)*** calculated for the differences between the average costs of innovator antiviral medicine items for the different time periods have no practical significant value (d<0.8).

Table 5.7 indicates that the ***average cost of generic antiviral medicine items per prescription*** declined with 9.89 per cent (n=R9.07) in 2001 (period P1 to P3), declined with 2.62 per cent (n=R2.28) in 2002 (period P4 to P6), and inclined with 1.70 per cent (n=R1.40) from P7 to P8 and with 3.96 per cent (n=R3.32) from P8 to P9. This resulted in an overall incline of 5.73 per cent (n=R4.72) in 2004 (period P7 to P9). The ***effect sizes (d-values)*** calculated for the differences between the average costs of innovator antiviral medicine items for the different time periods have no practical significant value (d<0.8).

The ***effect sizes (d-values)*** calculated for the differences between the ***average cost of innovator antiviral medicine items*** and ***generic antiviral medicine items*** for each period separately (period P1 to P9 separately), have practical significant values (d>0.8).

5.3.2 Prevalence and cost of the subdivisions of antiviral medicine items, ARV medicine items and Other antiviral medicine items, for the periods 1 January 2001 to 31 December 2001 (P1 to P3), 1 January 2002 to 31 December 2002 (P4 to P6), and 1 January 2004 to 31 December 2004 (P7 to P9)

Table 5.8 provides information about the prevalence and cost of the subdivisions of antiviral medicine items, ARV medicine items and Other antiviral medicine items, for the three study years: 2001, 2002, and 2004, each divided into three four-month periods.

The average cost trends of ***ARV medicine items*** do not experience the same trends as the ***other antiviral medicine items***. In P1, the average cost of ARV medicine items was R802.10±681.03 versus R317.93±190.80 in P7. The other ARV medicine items seem to be more stable over the three study years ranging from R239.66±342.74 in P4 to R194.28±276.88 in P8 *(refer to table 5.8).*

Table 5.8 Prevalence, cost, and cost-prevalence index of antiviral medicine items according to periods P1 to P3, P4 to P6, and P7 to P9

Period	Different categories	Prevalence	Prevalence (%*)	Cost (R)	Cost (%#)	Cost-Prevalence index	Average Cost (R)	Standard deviation (R)
P1	ARV medicine items	2143	10.12	1718891.1	23.19	2.29	802.1	681.03
	Other antiviral medicine items	3918	18.5	917428.60	12.38	0.67	234.16	280.39
P2	ARV medicine items	3614	17.06	1613176.09	21.76	1.28	446.37	488.92
	Other antiviral medicine items	4158	19.63	812545.28	10.96	0.56	195.42	227.53
P3	ARV medicine items	4039	19.07	1658717.1	22.38	1.17	410.68	422.78
	Other antiviral medicine items	3311	15.63	691819.56	9.33	0.6	208.95	239.90
Total	-	21183	100.01	7412577.73	100	-	349.93*	182.34
P4	ARV medicine items	8253	16.43	3826432.21	17.78	1.08	463.64	352.65
	Other antiviral medicine items	4903	9.76	1175070.79	5.46	0.56	239.66	342.74
P5	ARV medicine items	11811	23.51	5425893.98	25.21	1.07	459.39	373.17
	Other antiviral medicine items	5112	10.17	1082337.96	5.03	0.5	211.72	250.99
P6	ARV medicine items	15207	30.27	8982749.56	41.74	1.38	590.7	488.42
	Other antiviral medicine items	4960	9.87	1030881.06	4.79	0.49	207.84	252.32
Total	-	50246	100.01	21523365.6	100	-	428.36*	146.48

Table 5.8 (continue) Prevalence, cost, and cost-prevalence index of antiviral medicine items according to periods P1 to P3, P4 to P6, and P7 to P9

Period	Different categories	Prevalence	Prevalence (%*)	Cost (R)	Cost (%#)	Cost-Prevalence index	Average Cost (R)	Standard deviation (R)
P7	ARV medicine items	15030	12.66	4778518.69	12.55	0.99	317.93	190.8
	Other antiviral medicine items	3894	3.28	830564.19	2.18	0.67	213.29	448.47
P8	ARV medicine items	38488	32.42	14209891.7	37.33	1.15	369.2	219.5
	Other antiviral medicine items	6256	5.27	1215439.48	3.19	0.61	194.28	276.88
P9	ARV medicine items	48420	40.79	15726073.3	41.31	1.01	324.79	212.48
	Other antiviral medicine items	6630	5.59	1303860.07	3.43	0.61	196.66	306.40
Total	-	118718	100.01	38064347.4	99.99	-	320.63*	53.39

%* Prevalence of the antiviral medicine items for a specific period divided by the total prevalence of the antiviral medicine items for corresponding periods multiplied by hundred.

%# Cost of the antiviral medicine items for a specific period divided by the total cost of the antiviral medicine items for corresponding periods multiplied by hundred.

* Weighted average cost (R)

Other antiviral medicine items of period 2, *table 5.8* represents the largest proportion of antiviral medicine items claimed for the 2001 (P1 to P3), amounting to a prevalence of 4 158 (19.63 per cent; n=21 183) with the fourth largest cost of R812 545.28 (10.96 per cent; n=R7 412 577.73). ***Other antiviral medicine items*** of period 1 represent the third largest prevalence being 3 918 (18.50 per cent; n=21 183) and the largest cost being R917 428.60 (33.25 per cent; n=R7 412 577.73). ***ARV medicine items*** of period 6, table 5.8 represent the largest proportion of antiviral medicine items claimed for the 2002 (P4 to P6), amounting to a prevalence of 15 207 (30.27 per cent; n=50 246) with the largest cost of R8 982 749.56 (41.74 per cent; n=21 523 365.6). ***ARV medicine items*** of period 7, table 5.8, represent the largest proportion of antiviral medicine items claimed for the 2004 (P7 to P9), amounting to a prevalence of 48 420 (40.79 per cent; n=118 718) with the largest cost of R15 726 073.30 (41.31 per cent; n=R38 064 347.40).

The ***cost percentage of ARV medicine items*** increased from 23.19 per cent (n=R7 412 577.73) in P1 to 41.31 per cent (n=R38 064 347.40) in P9. The prevalence percentage of ARV medicine items increased from 10.12 per cent (n=21 183) in P1 to 40.79 per cent (n=118718) in P9. Thus, the ***cost-prevalence index*** of ARV medicine items is more than one for the three study years, indicating that ARV medicine items utilised are relatively expensive *(refer to table 5.8)*.

The ***cost percentage of other ARV medicine items*** decreased from 33.25 per cent (n=R7 412 577.73) in P1 to 3.43 per cent (n=R1 303 860.07) in P9. The prevalence percentage of ARV medicine items also decreased from 18.5 per cent (n=21 183) in P1 to 5.59 per cent (n=118 718) in P9. Thus, the ***cost-prevalence index*** of the other antiviral medicine items is lower than one for the three study years *(refer to table 5.8).*

The ***effect-sizes (d-values)*** calculated for the differences between the average costs of ARV medicine items for the denoted periods, P1 to P3, P4 to P6, and P7 to P9, and the effect sizes (d-values) calculated for the differences between the average costs of the other antiviral medicine items for the denoted periods, P1 to P3, P4 to P6, and P7 to P9 have no practical significant values (d<0.8).

5.3.3 Prescribing patterns of generic and innovator antiviral medicine items

Table 5.9 provides an overview of the prescribing patterns of innovator and generic antiviral medicine items for the study years 2001, 2002, and 2004, each divided into three four-month periods.

Table 5.9 Summary of the prescribing patterns of innovator and generic antiviral medicine items for 2001 (P1 to P3), 2002 (P4 to P6), and 2004 (P7 to P9)

	Period	Innovator or Generic	Number of antiviral medicine items	Prevalence of antiviral medicine items (%*)	Average cost per Antiviral item (R)	Standard Deviation (R)	Total cost of antiviral medicine Items (R)	Cost of antiviral medicine items (%#)	Cost-Prevalence index	d-values
2001	P1	Innovator	4313	71.16	574.07	578.87	2475956.64	93.92	1.32	0.83
		Generic	1748	28.84	91.74	89.40	160363.06	6.08	0.21	
	P2	Innovator	5587	71.89	404.93	427.04	2262369.19	93.27	1.30	0.77
		Generic	2185	28.11	74.76	70.06	163352.18	6.73	0.24	
	P3	Innovator	5573	75.82	395.41	389.01	2203632.91	93.75	1.24	0.80
		Generic	1777	24.18	82.67	79.78	146903.75	6.25	0.26	
2002	P4	Innovator	10638	80.86	449.57	371.65	4782508.34	95.62	1.18	0.98
		Generic	2518	19.14	86.97	87.98	218994.66	4.38	0.23	
	P5	Innovator	14014	82.81	447.62	362.44	6272878.72	96.38	1.16	1.01
		Generic	2909	17.19	80.91	84.24	235353.22	3.62	0.21	
	P6	Innovator	17267	85.62	565.70	475.01	9768018.04	97.55	1.14	1.01
		Generic	2900	14.38	84.69	85.37	245612.58	2.45	0.17	
2004	P7	Innovator	16066	84.90	334.48	271.96	5373676.74	95.80	1.13	0.93
		Generic	2858	15.10	82.37	86.79	235406.14	4.20	0.28	
	P8	Innovator	39414	88.09	380.04	227.65	14978851.78	97.11	1.10	1.30
		Generic	5330	11.91	83.77	90.68	446479.38	2.89	0.24	
	P9	Innovator	47870	86.96	342.69	224.72	16404601.18	96.33	1.11	1.13
		Generic	7180	13.04	87.09	104.87	625332.16	3.67	0.28	

%* Number of the innovator or generic antiviral medicine items divided by the corresponding total number of innovator or generic antiviral medicine items claimed during that specific period multiplied by hundred.

%# Cost of the innovator or generic antiviral medicine items divided by the total cost of the corresponding innovator or generic antiviral medicine items claimed during that specific period multiplied by hundred.

The ***innovator antiviral medicine items*** increased with 29.21 per cent (n=1 260) in 2001(period P1 to P3), with 62.31 per cent (n=6 629) in 2002 (period P4 to P6), and with 197.96 per cent (n=31 804) in 2004 (period P7 to P9). The ***generic antiviral medicine items*** increased with 1.66 per cent (n=29) in 2001 (period P1 to P3), with 15.17 per cent (n=382) in 2002 (period P4 to P6), and with 151.22 per cent (n=4 322) in 2004 (period P7 to P9) *(refer to table 5.9).*

In all the study periods, the ***innovator antiviral medicine items*** prescribed entailed more than 70 per cent of the prescribed antiviral medicine items ranging from 71.16 per cent (P1) to 75.82 per cent (P3), to 85.62 per cent (P6), and to 86.96 per cent (P9). The ***cost of innovator antiviral medicine items*** prescribed, in all the study periods, entailed more than 90 per cent of the prescribed antiviral medicine items ranging from 93.92 per cent (P1) to 93.75 per cent (P3), 95.62 per cent (P4) to 97.55 per cent (P6), and 95.80 per cent (P7) to 96.33 per cent (P9) *(refer to table 5.9).*

The ***average cost per innovator antiviral medicine item*** was R547.07±578.87 in P1 versus R395.41±389.01 in P3 and declined with 31.12 per cent (n=R178.66) in 2001 (period P1 to P3). The average cost per innovator antiviral medicine item was R449.57±371.65 in P4 versus R565.70±475.01 in P6 and inclined with 25.83 per cent (n=R116.13) in 2002 (period P4 to P6). In 2004, the average cost per innovator antiviral medicine item was R334.48±271.96 in P7, versus R380.04±227.65 in P8, versus R342.69±224.72 in P9 and increased with 13.62 per cent (n=R45.56) from P7 to P8, and declined with 9.83 per cent (n=R37.35) from P8 to P9. The effect-sizes (d-values) calculated between the average cost per innovator antiviral medicine item for all the study periods (2001, 2002, and 2004) were not practical significant ($d < 0.8$) *(refer to table 5.9).*

The ***average cost per generic antiviral item*** seemed to be more stable over the whole study period ranging from R91.74±89.40 in P1 to R82.67±79.78 in P3, from R86.97±87.98 in P4 to R84.69±85.37 in P6, and from R82.37±86.79 in P7 to R87.09±104.87 in P9. The effect-sizes (d-values) calculated between the average cost per generic antiviral item for all the study periods (2001, 2002, and 2004) were not practical significant ($d < 0.8$) *(refer to table 5.9).*

The ***effect sizes (d-values)*** between the ***average cost per innovator antiviral item*** and the ***average cost per generic antiviral item*** for the whole study period (2001, 2002 and 2004) were all greater than 0.8, and of practical significance ($d > 0.8$) *(refer to table 5.9).*

The ***total cost of innovator antiviral medicine items*** lowered with 11.00 per cent (n=R272 323.73) in 2001 (period P1 to P3), increased with 104.24 per cent (n=R4 985 509.70) in 2002 (period P4 to P6), and also with 205.28 per cent (n=R11 030 924.44) in 2004 (period P7 to P9). The ***total cost of generic antiviral medicine items*** declined with 8.39 per cent (n=R13 459.31) in 2001 (period P1 to P3), inclined with 12.15 per cent (n=R26 617.92) in 2002 (period, P4 to P6), and also with 165.64 per cent (n=R389 926.02) in 2004 (period P7 to P9) *(refer to table 5.9)*.

The ***cost-prevalence index*** of the ***innovator antiviral medicine items*** was higher than one for the whole study period (2001, 2002, and 2004), indicating that the treatment is relatively expensive *(refer to section 4.6.2.4)*. The ***cost-prevalence index*** of the ***generic antiviral medicine items*** was lower than one for the whole study period (2001, 2002, and 2004), indicating that the treatment is relatively inexpensive *(refer to section 4.6.2.4)*.

5.4 ANALYSIS OF THE SUBPHARMACOLOGICAL GROUP: ANTIRETROVIRAL (ARV) MEDICINE ITEMS

The analysis of the ARV medicine items will be outlined in this section.

5.4.1 General prescribing patterns

Table 5.10 gives the general prescribing patterns of the ARV medicine items for the study year, ***1 January 2001 to 31 December 2001***, divided into three four-month periods [1 January 2001 to 30 April 2001 (P1), 1 May 2001 to 31 August 2001 (P2), and 1 September 2001 to 31 December 2001 (P3)], ***1 January 2002 to 31 December 2002***, divided into three four-month periods [1 January 2002 to 30 April 2002 (P4), 1 May 2002 to 31 August 2002 (P5), and 1 September 2002 to 31 December 2002 (P6)], and ***1 January 2004 to 31 December 2004***, divided into three four-month periods [1 January 2004 to 30 April 2004 (P7), 1 May 2004 to 31 August 2004 (P8), and 1 September 2004 to 31 December 2004 (P9)].

Table 5.10 Results of the general prescribing patterns of ARV medicine items from 1 January 2001 to 30 April 2001 (period P1), 1 May 2001 to 31 August 2001 (period P2), and 1 September 2001 to 31 December 2001 (period P3)

Description	2001 (P1 to P3)			2002 (P4 to P6)			2004 (P7 to P9)		
	P1	P2	P3	P4	P5	P6	P7	P8	P9
Total number of prescriptions containing at least one ARV medicine item	1512	2222	1865	3590	4970	6444	6350	16598	20534
Total number of ARV medicine items prescribed	2143	3614	4039	8253	11811	15207	15030	38488	48420
Average number of ARV medicine items per prescription	1.42±0.68	1.63±0.84	2.17±0.96	2.30±0.88	2.38±0.82	2.36±0.76	2.37±0.72	2.32±0.68	2.36±0.68
Total number of innovator ARV medicine items prescribed	2143	3614	4039	8253	11811	15207	14570	37048	44991
Total number of generic ARV medicine items prescribed	0	0	0	0	0	0	460	1440	3429
Total Cost (R)	1718891.10	1613176.09	1658717.10	3826432.21	5425893.98	8982749.56	4778518.69	14209891.68	15726073.27
Average cost per ARV prescription (R)	1136.83±1067.51	726.00±668.61	889.39±606.11	1065.86±474.97	1091.73±563.77	1393.97±756.93	752.52±276.68	856.12±326.81	765.86±329.73
Average cost per ARV item (R)	802.10±681.03	446.37±488.92	410.68±422.77	463.64±352.65	459.39±373.17	590.70±488.42	317.93±190.80	369.20±219.50	324.79±212.48
Average cost of innovator ARV medicine items per prescription (R)	802.10±681.03	446.37±488.92	410.68±422.77	463.64±352.65	459.39±373.17	590.70±488.42	324.93±189.90	379.34±216.81	340.12±209.80
Average cost of generic ARV medicine items per prescription (R)	0	0	0	0	0	0	96.15±85.74	108.35±87.80	123.52±128.13

The ***total number of prescriptions*** containing at least one ***ARV medicine items*** increased with 23.35 per cent (n=353) during 2001 (period P1 to P3), increased with 79.50 per cent (n=2 854) during 2002 (period P4 to P6), and with 161.39 per cent (n=10 248) from P7 to P8, and also with 23.71 per cent (n=3 936) from P8 to P9. This resulted in an overall increase of 223.37 per cent (n=14 184) during 2004 (period P7 to P9) *(refer to table 5.10).*

The ***total number of prescriptions*** containing at least one ARV ***medicine item*** represented 0.31 per cent (n=1 512) of the ***total number of prescriptions of the total database*** (n=481 029) for P1, 0.41 per cent (n=2 222) of the total number of prescriptions of the total database (n=548 598) for P2, 1.09 per cent (n=1 865) of the total number of prescriptions of the total database (n=445 753) for P3, 0.57 per cent (n=3 590) of the total number of prescriptions of the total database (n=626 496) for P4, 0.71 per cent (n=4 970) of the total number of prescriptions of the total database (n=701 234) for P5, 0.86 per cent (n=6 444) of the total number of prescriptions of the total database (n=748 506) for P6, 0.89 per cent (n=6 350) of the total number of prescriptions of the total database (n=713 475) for P7, 1.77 per cent (n=16 598) of the total number of prescriptions of the total database (n=935 644) for P8, and 2.17 per cent (n=20 534) of the total number of prescriptions of the total database (n=946 135) for P9 *(refer to table 5.10 and table 5.3).*

The ***total number of ARV prescriptions*** represented 30.20 per cent (n=1 512) of the ***total number of prescriptions containing at least one antiviral medicine item*** (n=5 007) for P1, 36.99 per cent (n=2 222) of the total number of prescriptions containing at least one antiviral medicine item (n=6 007) for P2, 38.51 per cent (n=1 865) of the total number of prescriptions containing at least one antiviral medicine item (n=4 843) for P3, 45.08 per cent (n=3 590) of the total number of prescriptions containing at least one antiviral medicine item (n=7 963) for P4, 51.68 per cent (n=4 970) of the total number of prescriptions containing at least one antiviral medicine item (n=9 616) for P5, 59.10 per cent (n=6 444) of the total number of prescriptions containing at least one antiviral medicine item (n=10 903) for P6, 63.84 per cent (n=6 350) of the total number of prescriptions containing at least one antiviral medicine item (n=9 946) for P7, 74.69 (n=16 598) of the total number of prescriptions containing at least one antiviral medicine item (n=22 224) for P8, and 77.84 per cent (n=20 534) of the total number of prescriptions containing at least one antiviral medicine item (n=26 379) for P9 *(refer to table 5.10 and table 5.7).*

Table 5.10 indicates that the ***total number of ARV medicine items*** claimed rose with 88.47 per cent (n=1 896) in 2001 (period P1 to P3), increased with 84.26 per cent (n=6 954) in 2002 (period P4 to P6), and rose with 156.07 per cent (n=23 458) from P7 to P8, and also with 25.81 per cent (n=9 932) from P8 to P9. This resulted in an overall increase of 222.16 per cent (n=33 390) in 2004 (period P7 to P9).

The ***total number of ARV medicine items*** claimed represented 0.22 per cent (n=2 143) of the ***total number of medicine items claimed*** (n=966 161) for P1, 0.32 per cent (n=3 614) of the total number of medicine items claimed (n=1 125 367) for P2, 0.85 per cent (n=4 039) of the total number of medicine items claimed (n=859 798) for P3, 0.68 per cent (n=8 253) of the total number of medicine items claimed (n=1 216 939) for P4, 0.85 per cent (n=11 811) of the total number of medicine items claimed (n=1 392 115) for P5, 1.06 per cent (n=15 207) of the total number of medicine items claimed (n=1 433 091) for P6, 1.10 per cent (n=15 030) of the total number of medicine items claimed (n=1 363 585) for P7, 1.97 per cent (n=38 488) of the total number of medicine items claimed (n=1 953 845) for P8, and 2.44 per cent (n=48 420) of the total number of medicine items claimed (n=1 988 452) for P9 *(refer to table 5.10 and table 5.3).*

The ***total number of ARV medicine items*** claimed represented 35.36 per cent (n=2 143) of the ***total number of antiviral medicine items*** claimed (n=6 061) for P1, 46.50 per cent (n=3 614) of the total number of antiviral medicine items claimed (n=7 772) for P2, 54.95 per cent (n=4 039) of the total number of antiviral medicine items claimed (n=7 350) for P3, 62.73 per cent (n=8 253) of the total number of antiviral medicine items claimed (n=13 156) for P4, 69.79 per cent (n=11 811) of the total number of antiviral medicine items claimed (n=16 923) for P5, 75.41 per cent (n=15 207) of the total number of antiviral medicine items claimed (n=20 167) for P6, 79.42 per cent (n=15 030) of the total number of antiviral medicine items claimed (n=18 924) for P7, 86.02 per cent (n=38 488) of the total number of antiviral medicine items claimed (n=44 744) for P8, and 87.96 per cent (n=48 420) of the total number of antiviral medicine items claimed (n=55 050) for P9 *(refer to table 5.10 and table 5.7).*

According to *table 5.10*, the ***average number of ARV medicine items per prescription*** increased over the three study years ranging from 1.42±0.68 ARV medicine items per prescription in P1 to 2.36±0.68 ARV medicine items per prescription in P9, stabilising on 2.36 ARV medicine items per prescription. The ***effect sizes (d-values)*** calculated between the average number of ARV medicine items per prescription for P1 an P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P5, P2 and P6, P2 and P7, P2 and P8, and P2 and P9 are of practical significant value (d>0.8).

The ***total number of innovator ARV medicine items*** claimed rose steadily over the first two years, with a relatively high increase during the last study year. The total number of innovator ARV medicine items claimed increased with 88.47 per cent (n=1 896) in 2001 (period P1 to P3), with 84.26 per cent (n=6 954) in 2002 (period P4 to P6), and with 208.79 per cent (n=30 421) in 2004 (period P7 to P9) *(refer to table 5.10).*

There were no ***generic ARV medicine items*** claimed during the period P1 to P3, and period P4 to P6. The total number of generic ARV medicine items claimed through Interpharm Data Systems® increased with 213.04 per cent (n=980) from P7 to P8, and with 138.13 per cent (n=1 989) from P8 to P9. This resulted in an overall rise of 532.39 per cent (n=2 449) for the period, P7 to P9 *(refer to table 5.10).*

The ***total cost of ARV medicine items*** decreased with 3.50 per cent (n=R60 174.00) in 2001 (period P1 to P3), increased with 134.76 per cent (n=R5 156 317.35) in 2002 (period P4 to P6), and increased with 197.37 per cent (n=R9 431 372.99) from P7 to P8, and also with 10.67 per cent (n=R1 516 181.59) from P8 to P9. This resulted in an overall increase of 229.10 per cent (n=R10 947 554.58) in 2004 (period P7 to P9) *(refer to table 5.10).*

The ***total cost of ARV medicine items*** claimed represented 1.37 per cent (n=R1 718 891.10) of the ***total cost of medicine items claimed*** (n=R125 667 469.00) for P1, 1.16 per cent (n=R1 613 176.09) of the total cost of medicine items claimed (n=R138 897 443.00) for P2, 1.44 per cent (n=R1 658 717.10) of the total cost of medicine items claimed (n=R115 143 577.00) for P3, 2.17 per cent (n=R3 826 432.21) of the total cost of medicine items claimed (n=R175 986 674.00) for P4, 2.76 per cent (n=R5 425 893.98) of the total cost of medicine items claimed (n=R196 621 130.00) for P5, 3.93 per cent (n=R8 982 749.56) of the total cost of medicine items claimed (n=R228 742 521.00) for P6, 2.40 per cent (n=R4 778 518.69) of the total cost of medicine items claimed (n=R198 934 122.00) for P7, 5.85 per cent (n=R14 209 891.68) of the total cost of medicine items claimed (n=R242 721 616.00) for P8, and 7.16 per cent (n=R15 726 073.27) of the total cost of medicine items claimed (n=R219 567 408.00) for P9 *(refer to table 5.10 and table 5.3).*

The ***total cost of ARV medicine items*** claimed represented 65.20 per cent (n=R1 718 891.10) of the ***total cost of antiviral medicine items*** claimed (n=R2 636 319.70) for P1, 66.50 per cent (n=R1 613 176.09) of the total cost of antiviral medicine items claimed (n=R2 425 721.37) for P2, 70.57 per cent (n=R1 658 717.10) of the total cost of antiviral medicine items claimed (n=R2 350 536.66) for P3, 76.51 per cent (n=R3 826 432.21) of the total cost of antiviral medicine items claimed (n=R5 001 503.00) for P4, 83.37 per cent (n=R5 425 893.98) of the total cost of antiviral medicine items claimed (n=R6 508 231.94) for P5, 89.71 per cent (n=R8 982 749.56) of the total cost of antiviral medicine items claimed (n=R10 013 630.62) for P6, 85.19 per cent (n=R4 778 518.69) of the total cost of antiviral medicine items claimed (n=R5 609 082.88) for P7, 92.12 per cent (n=R14 209 891.68) of the total cost of antiviral medicine items claimed (n=R15 425 331.16) for P8, and 92.34 per cent (n=R15 726 073.27) of the total cost of antiviral medicine items claimed (n=R17 029 933.34) for P9 *(refer to table 5.10 and table 5.7).*

Table 5.10 shows that the ***average cost per ARV prescription*** and the ***average cost per ARV medicine item*** followed the same changing trends during the three study years. These average costs decreased in the first study year, increased in the second study year, and increased from P7 to P8, and decreased from P8 to P9 during 2004. The average cost per ARV prescription increased with 13.77 per cent (n=R103.60) from P7 to P8, and decreased with 10.54 per cent (n=R90.26) from P8 to P9. The average cost per ARV medicine item inclined with 16.13 per cent (n=R51.27) from P7 to P8, and declined with 12.03 per cent (n=R44.41) from P8 to P9. The decreasing trend in the average costs for the period P8 to P9 could be due to the implementation of the pricing regulations in May 2004.

The ***effect sizes (d-values)*** calculated for the differences between the ***average cost per ARV prescription*** for the three study years have no practical significant value ($d<0.8$), except for the effect size (d-value) for the period P6 to P7, which has a practical significant value ($d>0.8$). The ***effect sizes (d-values)*** calculated for the differences between the ***average cost per ARV medicine items*** for the three study years have no practical significant values ($d<0.8$).

There were no ***generic ARV medicine items*** claimed during the first two study years (period P1 to P6), and thus the average cost of ***innovator ARV medicine item per prescription*** is the same as for the ***average cost per ARV item*** (as described above) *(refer to table 5.10)*.

Table 5.10 indicates that the ***average cost of innovator ARV medicine*** items per prescription increased with 16.75 per cent (n=R54.41) from P7 to P8, and with 10.34 per cent (n=R39.22) from P8 to P9. The overall increase was with 4.67 per cent (n=R15.19) for the period P7 to P9. The ***effect sizes (d-values)*** calculated for the differences between the average costs of innovator ARV items per prescription for the three study years have no practical significant values ($d<0.8$). The ***average cost of generic ARV medicine items per prescription*** increased with 12.69 per cent (n=R12.20) from P7 to P8, and with 14.00 per cent (n=R15.17) from P8 to P9. This resulted in an overall increase of 28.47 per cent (n=R27.37) in the average cost of generic ARV medicine items per prescription for the period, P7 to P9. The ***effect sizes (d-values)*** calculated for the difference between the average cost of generic ARV items per prescription have no practical significant value for the period, P7 to P9.

5.4.2 Prevalence and cost of ARV medicine items for the periods 1 January 2001 to 31 December 2001 (P1 to P3), 1 January 2002 to 31 December 2002 (P4 to P6), and 1 January 2004 to 31 December 2004 (P7 to P9)

The prevalence and cost of ARV medicine items for the periods 1 January 2001 to 31 December 2001 (P1 to P3), 1 January 2002 to 31 December 2002 (P4 to P6), and 1 January 2004 to 31 December 2004 (P7 to P9) will be compared and discussed, as indicated in *table 5.11*.

Table 5.11 Prevalence, cost, and cost-prevalence index of ARV medicine items according to periods P1 to P3 (2001), P4 to P6 (2002), and P7 to P9 (2004)

Period	Prevalence	Prevalence (%*)	Cost (R)	Cost (%#)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P1	2143	21.88	1718891.10	34.44	1.57	802.10	681.03
P2	3614	36.89	1613176.09	32.32	0.88	446.37	488.92
P3	4039	41.23	1658717.10	33.24	0.81	410.68	422.77
Total	9796	100.00	4990784.29	100.00	-	509.48	155.66
P4	8253	23.40	3826432.21	20.98	0.90	463.64	352.65
P5	11811	33.49	5425893.98	29.76	0.89	459.39	373.17
P6	15207	43.11	8982749.56	49.26	1.14	590.70	488.42
Total	35271	100.00	18235075.75	100.00	-	517.00	64.18
P7	15030	14.74	4778518.69	13.77	0.93	317.93	190.80
P8	38488	37.76	14209891.68	40.93	1.08	369.20	219.50
P9	48420	47.50	15726073.27	45.30	0.95	324.79	212.48
Total	101938	100.00	34714483.64	100.00	-	340.55	22.44

%* Prevalence of the ARV medicine items for a specific period divided by the total prevalence of the ARV medicine items for corresponding periods multiplied by hundred.

%# Cost of the ARV medicine items for a specific period divided by the total cost of the ARV medicine items for corresponding periods multiplied by hundred.

* Weighted average cost

The ***prevalence percentage of ARV medicine items*** for each individual period (period P1 to P9 individually) increased from 21.88 per cent (n=2 143) in P1 to 41.23 per cent (n=4 039) in P3, from 23.40 per cent (n=8 253) in P4 to 43.11 per cent (n=15 207) in P6, and from 14.74 per cent (n=15 030) in P7 to 47.50 per cent (n=48 420) in P9 *(refer to table 5.11)*.

The ***cost percentage of ARV medicine items*** for each individual period (period P1 to P9 individually) decreased from 34.44 per cent (n=R1 718 891.10) in P1 to 33.24 per cent (n=R1 658 717.10) in P3, increased from 20.98 per cent (n=R3 826 432.21) in P4 to 49.26 per cent (n=R8 982 749.56) in P6, and also increased from 13.77 per cent (n=R4 778 518.69) in P7 to 45.30 per cent (n=R15 726 073.27) in P9 *(refer to table 5.11)*.

Table 5.11 indicates that the ***cost-prevalence index*** is higher than one for periods P1, P6 and P8 and indicates that treatment is relatively expensive for these periods. The cost-prevalence indices for periods P2, P3, P4, P5, P7, and P9 are all lower than one and indicate that treatment is relatively inexpensive for all these periods *(refer to section 4.6.2.4)*. The ***effect sizes (d-values)*** calculated for the differences between the average costs per ARV medicine item for the different time periods have no practical significant values (d<0.8).

The ***average cost per ARV medicine items*** decreased by almost 50 per cent (n=R391.42) during 2001 from R802.10±681.03 to R410.68±422.77, increased with 27.40 per cent (R=127.06) during 2002, and remained stable during 2004, increasing with 16.13 per cent (n=R51.27) from P7 (before implementation) to P8 (transition phase), and decreasing with 12.03 per cent (n=R44.41) from P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen clearly *(refer to table 5.11)*.

5.4.3 Prevalence and cost of ARV medicine items based on the different categories

Table 5.28, *table 5.29* and *table 5.30* are summaries of the prevalence and cost of ARV medicine items, the prevalence percentage and cost percentage of ARV medicine items, as well as the cost-prevalence index calculated for the different periods, P1 to P3, P4 to P6, and P7 to P9.

The different categories are described as follows (MCC, 2004:1):

- Category I consists out of NRTI medicine items, namely abacavir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine.
- Category II consists out of NNRTI medicine items, namely efavirenz and nevirapine
- Category III consists out of PI medicine items, namely indinavir, lopinavir, nelfinavir, ritonavir and saquinavir.
- Category IV consists out of OTHER ARV medicine items, namely the combination of lamivudine/zidovudine and the combination of lopinavir/ritonavir *(refer to section 5.1.1)*.

To obtain a clearer picture of the prevalence and cost of ARV medicine items, the prevalence and cost percentages are illustrated in *figure 5.1*, *figure 5.2* and *figure 5.3*. The effect sizes (d-values) calculated for the differences between the weighted average costs of ARV medicine items were not calculated *(refer to section 5.1.2)*.

Table 5.12 Prevalence, cost and cost-prevalence index values of ARV medicine items based on the different categories for the period P1 to P9

Period	Different categories	Number of ARV medicine items	Prevalence of ARV medicine items (%*)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%#)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P1	Category I	1434	66.92	1052142.37	61.21	0.92	733.71*	221.26
	Category II	106	4.95	84079.54	4.89	1.00	793.20*	276.31
	Category III	115	5.37	239112.48	13.91	2.59	2079.24*	456.23
	Category IV	488	22.77	343556.71	19.99	0.88	704.01*	823.15
P2	Category I	1998	55.29	644824.04	39.97	0.72	322.74*	155.11
	Category II	533	14.75	295887.45	18.34	1.24	555.13*	18.14
	Category III	133	3.68	87201.15	5.41	1.47	655.65*	132.93
	Category IV	950	26.29	585263.45	36.28	1.38	616.07	804.30
P3	Category I	2448	60.61	614653.55	37.06	0.61	251.08*	148.17
	Category II	896	22.18	497651.59	30.00	1.35	555.42*	15.46
	Category III	107	2.65	62730.95	3.78	1.43	589.56*	64.89
	Category IV	588	14.56	483681.01	29.16	2.00	822.59*	831.99
2001 (P1–P3)	Total	9796	100.00	4990784.29	100.00	-	509.48	155.66
P4	Category I	4411	53.45	1264042.23	33.03	0.62	286.56*	163.25
	Category II	2296	27.82	1197648.34	31.30	1.13	521.63*	14.20
	Category III	279	3.38	128208.24	3.36	1.00	459.53*	126.82
	Category IV	1267	15.35	1236533.40	32.32	2.11	975.95*	465.99
P5	Category I	6014	50.92	1594623.59	29.39	0.58	265.16*	181.54
	Category II	3499	29.62	1897457.76	34.97	1.18	542.28*	27.28
	Category III	445	3.77	254647.72	4.69	1.24	572.24*	469.40
	Category IV	1853	15.69	1679164.91	30.95	1.97	906.19*	512.28
P6	Category I	6385	41.99	1907190.23	21.23	0.51	298.70*	289.62
	Category II	4607	30.30	2744212.90	30.55	1.01	595.66*	39.56
	Category III	1107	7.28	833390.30	9.28	1.27	752.84*	716.40
	Category IV	3108	20.44	3497956.13	38.94	1.91	1125.47*	36.17
2002 (P4–P6)	Total	35271	100.00	18235075.75	100.00	-	517.00	64.18
P7	Category I	5549	36.92	920247.43	19.26	0.52	165.84*	114.11
	Category II	5218	34.72	2008329.30	42.03	1.21	384.89*	43.77
	Category III	550	3.66	216943.12	4.54	1.24	394.44*	253.88
	Category IV	3713	24.70	1632998.84	34.17	1.38	439.81*	24.99
P8	Category I	13265	34.47	2383176.86	16.77	0.49	179.66*	157.10
	Category II	13425	34.88	5997631.90	42.21	1.21	446.75*	50.99
	Category III	1831	4.76	926494.82	6.52	1.37	506.00*	361.61
	Category IV	9967	25.90	4902588.10	34.50	1.33	491.87*	27.52
P9	Category I	17982	37.14	2838646.99	18.05	0.49	157.86*	137.84
	Category II	16901	34.91	6577607.91	41.83	1.22	389.19*	67.89
	Category III	1901	3.93	945319.76	6.01	1.53	497.27*	377.69
	Category IV	11636	24.03	5364498.61	34.11	1.42	461.03*	31.59
2004 (P7–P9)	Total	101938	100.00	34714483.64	100.00	-	340.55	22.44

%* Prevalence of the ARV medicine items for a specific category divided by the prevalence of the total number of ARV medicine items for the same specific category, multiplied by hundred.

%# Cost of the ARV medicine items for a specific category divided by the total cost of the ARV medicine items for the same specific category, multiplied by hundred.

* Weighted average *(refer to section 4.6.2.2 and section 5.1.2).*

To obtain a clearer picture of the prevalence and cost of ARV medicine items for periods P1, P2, and P3, the prevalence and cost percentages are illustrated in figure 5.1 *(refer to table 5.12).*

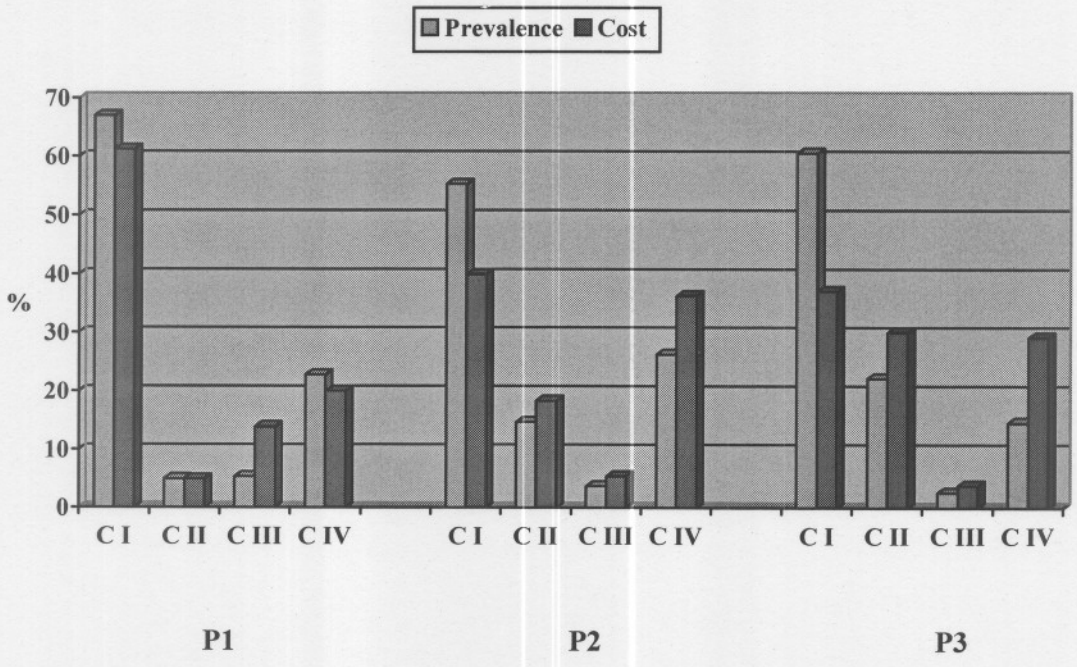


Figure 5.2 Prevalence and cost percentages of ARV medicine items based on different categories for the periods P1, P2 and P3 (2001)

Periods P1, P2 and P3 of *figure 5.1* and *table 5.12* indicate that category I represents the ***largest proportion*** of ARV medicine items and ***largest cost***, amounting to a prevalence of 1 434 (66.92 per cent; n=2143) with the cost thereof representing R1 052 142.37 (61.21 per cent; n=R1718891.10) in period P1, amounting to a prevalence of 1998 (55.29 per cent; n=3614) and to a cost of R644 824.04 (39.97 per cent; n=R1 613 176.09) in period P2, and amounting to a prevalence of 2 448 (60.61 per cent; n=4 039) and to a cost of R614 653.55 (37.06 pr cent; n=R1 658 717.10) in Period P3.

Figure 5.1 and *table 5.12*, periods P1, P2 and P3 show that category II is the group with the ***lowest prevalence*** representing 106 (4.95 per cent; n=2143) as well as the ***lowest cost*** of R84 079.54 (4.89 per

cent; n=R1 718 891.10) in period P1, and category III in periods P2 and P3 is the group with the lowest prevalence and cost, representing a prevalence of 133 (3.69 per cent; n=3 614) as well as the lowest cost of R87 201.15 (5.41 per cent; n=R1 613 176.09) in P2 and a prevalence of 107 (2.65 per cent; n=4 039) as well as the lowest cost of R62 730.95 (3.78 per cent; n=R1 658 717.10) in P3.

Categories I and IV of period P1 and category I of periods P2 and P3 respectively, have a ***cost-prevalence index*** of lower than one, indicating that the prevalence is higher than the cost associated with this group, and is thus relatively inexpensive. Remaining categories of periods P1 to P3 all have cost-prevalence indices of higher than one, indicating that these medicine items are very expensive *(refer to section 4.6.2.4)*.

Category III of periods P1 and P2 has the ***highest weighted average cost*** per ARV medicine item, being R2079.24±456.23 and R655.65±132.93 respectively, whilst category IV of period P3 has the highest weighted average cost per ARV medicine item, being R822.59±831.99.

Figure 5.2 provides a clearer picture of the prevalence and cost of ARV medicine items for periods P4, P5, and P6 (2002) *(refer to table 5.12)*.

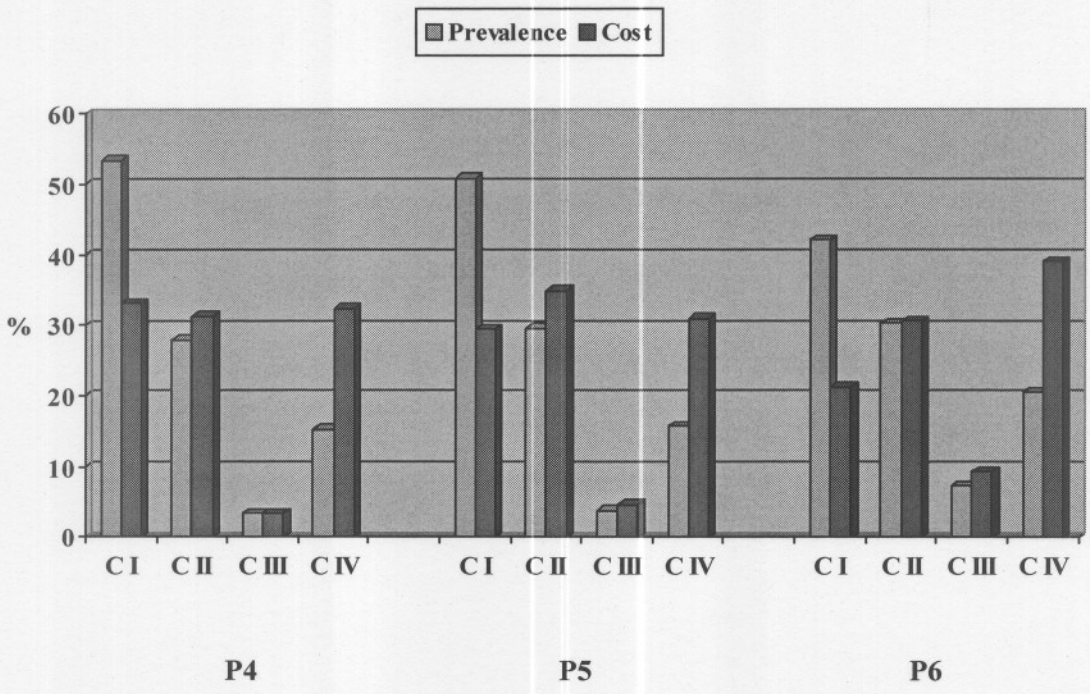


Figure 5.3 **Prevalence and cost percentages of ARV medicine items based on different categories for the periods P4, P5 and P6 (2002)**

Periods P4, P5 and P6 indicate that category I of period P4 represents the ***largest proportion*** of ARV medicine items used and cost, amounting to a prevalence of 4 411 (53.45 per cent; n=8253) with the cost thereof representing R1 264 042.23 (33.03 per cent; n=R3 826 432.21). Category I of period 5 represents the largest proportion of ARV medicine items used, amounting to a prevalence of 6 014 (50.92 per cent; n=11 811), whilst category II of period 5 have the largest cost of R1 897 457.76 (34.97 per cent; n=R5 425 893.98). Category I of period P6 represent the largest proportion of ARV medicine items used, amounting to a prevalence of 6 385 (41.99 per cent; n=15 207), with Category IV of period P6 indicating the largest cost of R3 497 956.13 (38.94 per cent; n=R8 982 749.56) *(refer to figure 5.2 and table 5.12).*

Periods P4, P5 and P6 of *figure 5.2* and *table 5.12* show that category III is the group with the ***lowest prevalence and cost*** percentage, representing a prevalence of 279 (3.38 per cent; n=8 253) and a cost of R1 28 208.24 (3.36 per cent; n=R3 826 432.21) in P4, representing a prevalence of 445 (3.77 per cent; n=11 811) and a cost of R254 647.72 (4.69 per cent; n=R5 425 893.98) in P5, as well as a prevalence of 1 107 (7.28 per cent; n=15 207) and a cost of R833 390.30 (9.28 per cent; n=R8 982 749.56) in P6.

Category I of periods P4, P5 and P6 all have a ***cost-prevalence indices*** of lower than one, indicating that their prevalence is slightly higher than the costs, and thus relatively inexpensive. The remaining categories of periods P4 to P6 all have cost-prevalence indices of higher than one, indicating that these medicine items utilised are very expensive *(refer to section 4.6.2.4)*.

Category IV of periods P4, P5 and P6 has the ***highest weighted average cost*** per ARV medicine item, being R975.95±465.99 for P4, R906.19±512.28 for P5, and R1125.47±36.17 for P6.

In *figure 5.3*, the prevalence and cost of ARV medicine items for periods P7, P8, and P9 are expressed as percentages *(refer to table 5.12)*.

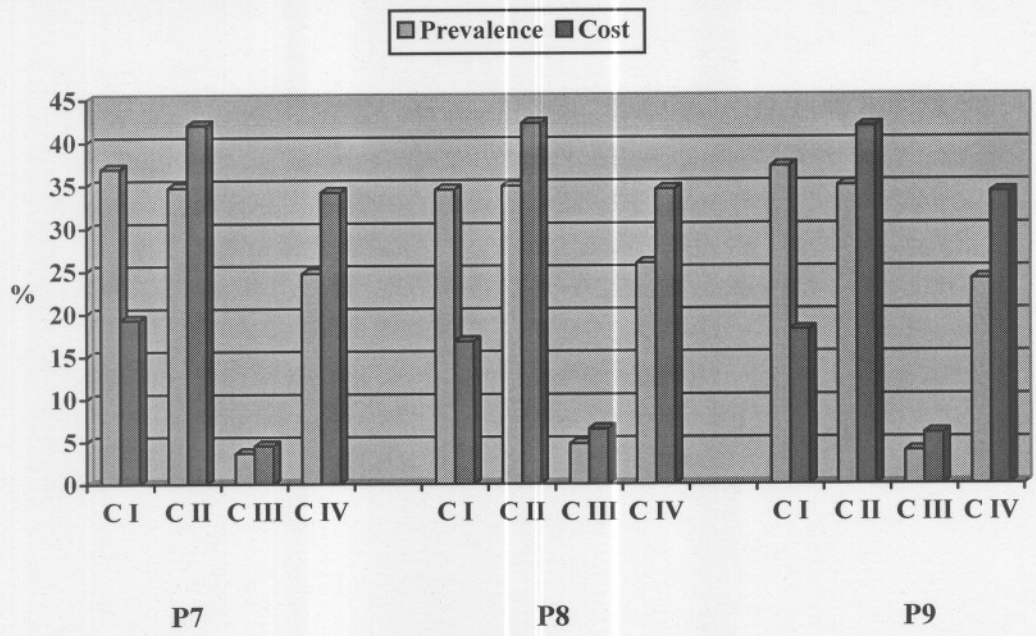


Figure 5.4 Prevalence and cost percentages of ARV medicine items based on different categories for the periods P7, P8 and P9 (2004)

Figure 5.3 and *table 5.12* indicate that categories I, II, and IV of periods P7, P8, and P9 all have ***high prevalence and cost*** percentages. Category I of period P7 represents the largest proportion of ARV medicine items amounting to a prevalence of 5 549 (36.92 per cent; n=15 030), whilst category II of period P7 represents the largest cost of R2 008 329.30 (42.03 per cent; n=R4 778 518.69). Category II of period P8 has a slightly higher prevalence than Category I of period P8, amounting to a prevalence of 13 425 (34.88 per cent; n=38 488), whilst category II of period P8 represents the largest cost of R59 97 631.90 (42.21 per cent; n=R14 209 891.68). Category I of period P9 represents the largest proportion of ARV medicine items used, amounting to a prevalence of 17 982 (37.14 per cent; n=48 420), and category II has the largest cost of R6 577 607.91 (41.83 per cent; n=R15 726 073.27).

Periods P7, P8 and P9 of *figure 5.3* and *table 5.12* show that category III is the group with the ***lowest prevalence and cost*** percentage, representing a prevalence of 550 (3.66 per cent; n=15 030) and a cost of R216 943.12 (4.54 per cent; n=R4 778 518.69) in P7, indicating a prevalence of 1 831 (4.76 per cent; n=38 488) and a cost of R926 494.82 (6.52 per cent; n=R14 209 891.68) in P8, as well as a prevalence of 1 901 (3.93 per cent; n=48 420) and a cost of R945 319.76 (6.01 per cent; n=R15 726 073.27) in P9.

Category I of periods P7, P8 and P9 all have a ***cost-prevalence indices*** of lower than one, indicating that their prevalence is slightly higher than the costs, and thus relatively inexpensive. The remaining categories of periods P7 to P9 all have cost-prevalence indices of higher than one, indicating that these medicine items utilised are very expensive *(refer to section 4.6.2.4)*.

Category IV of period P7 has the ***highest weighted average cost*** per ARV medicine item, being R439.81±24.99, whilst category III of periods P8 and P9 has the highest weighted average cost per ARV medicine item, being R506.00±361.61 and R497.27±377.69 respectively.

5.4.4 Prevalence and cost of ARV medicine items based on the active ingredient classification

Table 5.13, *table 5.14* and *table 5.15* summarise the prevalence and cost of ARV medicine items based on the active ingredient classification, the prevalence percentage and cost percentage for the different active ingredients, the cost-prevalence index calculated for the different active ingredients, the average cost per active ingredient, as well as the standard deviation per active ingredient.

Table 5.13 Prevalence, cost and cost-prevalence index values of ARV medicine items based on the active ingredient classification for the period P1 to P3 (2001)

Period	Category	Active ingredient classification	Number of ARV medicine items	Prevalence of ARV medicine items (%)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P1	I	Didanosine	794	37.05	595318.69	34.63	0.93	749.77	234.89
		Lamivudine	209	9.75	110149.12	6.41	0.66	527.03	587.31
		Stavudine	90	4.20	137138.13	7.98	1.9	1523.76	193.97
		Zidovudine	341	15.91	209536.43	12.19	0.77	614.48	373.36
	II	Efavirenz	41	1.91	46718.29	2.72	1.42	1139.47	786.74
		Nevirapine	65	3.03	37361.25	2.17	0.72	574.79	109.95
	III	Indinavir	89	4.15	191141.08	11.12	2.68	2147.65	1306.61
		Nelfinavir	5	0.23	16929.00	0.98	4.26	3385.80	0
		Ritonavir	16	0.75	18417.47	1.07	1.43	1151.09	926.48
		Saquinavir mesylate	5	0.23	12624.93	0.73	3.17	2524.99	1389.52
	IV	Lamivudine/ Zidovudine	488	22.77	343556.71	19.99	0.88	704.01	823.15
		Total	2143	99.98	1718891.10	99.99	-	802.10	681.03
P2	I	Didanosine	1134	31.38	405898.39	25.16	0.80	357.94	198.34
		Lamivudine	95	2.63	54891.31	3.40	1.29	577.80	500.57
		Stavudine	514	14.22	46079.33	2.86	0.20	89.65	171.35
		Zalcitabine	3	0.08	2693.10	0.17	2.13	897.70	0
		Zidovudine	252	6.97	135261.91	8.38	1.20	536.75	344.81
	II	Efavirenz	402	11.12	219006.48	13.58	1.22	544.79	43.42
		Nevirapine	131	3.62	76880.97	4.77	1.32	586.88	115.57
	III	Indinavir	80	2.21	45246.35	2.80	1.27	565.58	122.91
		Nelfinavir	1	0.03	25.08	0.00	0.00	25.09	0
		Ritonavir	49	1.36	40056.00	2.48	1.82	817.47	505.93
		Saquinavir mesylate	3	0.08	1873.72	0.12	1.50	624.57	299.57

Table 5.13 (continue) Prevalence, cost and cost-prevalence index values of ARV medicine items based on the active ingredient classification for the period P1 to P3 (2001)

Period	Category	Active ingredient classification	Number of ARV medicine items	Prevalence of ARV medicine items (%)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P2	IV	Lamivudine/ Zidovudine	950	26.29	585263.45	36.28	1.38	616.07	804.30
		Total	3614	99.99	1613176.09	100.00	-	446.37	488.92
P3	I	Didanosine	1224	30.30	406870.70	24.53	0.81	332.41	124.97
		Lamivudine	66	1.63	46363.81	2.80	1.72	702.48	503.50
		Stavudine	947	23.45	77897.89	4.70	0.20	82.26	55.33
		Zalcitabine	3	0.07	2694.63	0.16	2.29	898.21	0.88
		Zidovudine	208	5.15	80826.52	4.87	0.95	388.59	328.22
	II	Nevirapine	167	4.14	98145.44	5.92	1.43	587.70	192.08
		Efavirenz	729	18.05	399506.15	24.09	1.33	548.02	43.14
	III	Indinavir	63	1.56	34476.93	2.08	1.33	547.25	147.59
		Ritonavir	43	1.06	27312.04	1.65	1.56	635.16	419.00
		Saquinavir mesylate	1	0.02	941.98	0.06	3.00	941.98	0
	IV	Lamivudine/ Zidovudine	588	14.56	483681.01	29.16	2.00	822.59	831.99
		Total	4039	99.99	1658717.10	100.02	-	410.68	422.78

%* Prevalence of the ARV medicine items for a specific active ingredient divided by the prevalence of the total number of ARV medicine items for the same specific active ingredient, multiplied by hundred.

%# Cost of the ARV medicine items for a specific active ingredient divided by the total cost of the ARV medicine items for the same specific active ingredient, multiplied by hundred.

Table 5.14 Prevalence, cost and cost-prevalence index values of ARV medicine items based on the active ingredient classification for the period P4 to P6 (2002)

Period	Category	Active ingredient classification	Number of ARV medicine items	Prevalence of ARV medicine items (%)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P4	I	Didanosine	2130	25.81	850599.38	22.23	0.86	399.34	152.21
		Lamivudine	166	2.01	102165.62	2.67	1.33	615.46	298.30
		Stavudine	1824	22.10	180709.60	4.72	0.21	99.07	65.49
		Zalcitabine	3	0.04	2793.66	0.07	1.75	931.22	27.75
		Zidovudine	288	3.49	127773.97	3.34	0.96	443.66	330.21
	II	Efavirenz	1655	20.05	877904.68	22.94	1.14	530.46	114.99
		Nevirapine	641	7.77	319743.66	8.36	1.08	498.82	127.12
	III	Indinavir	153	1.85	76823.08	2.01	1.09	502.11	181.74
		Nelfinavir	3	0.04	4447.11	0.12	3.00	1482.37	20.78
		Ritonavir	121	1.47	45395.95	1.19	0.81	375.17	288.09
		Saquinavir mesylate	2	0.02	1542.10	0.04	2.00	771.05	0

Table 5.14 (continue) Prevalence, cost and cost-prevalence index values of ARV medicine items based on the active ingredient classification for the period P4 to P6 (2002)

Period	Category	Active ingredient classification	Number of ARV medicine items	Prevalence of ARV medicine items (%)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P4	IV	Lamivudine/ Zidovudine	1267	15.35	1236533.40	32.32	2.11	975.95	465.99
		Total	8253	100.00	3826432.21	100.01	-	463.64	352.65
P5	I	Abacavir	12	0.10	23223.05	0.43	4.30	1935.25	279.33
		Didanosine	2884	24.42	977835.51	18.02	0.74	339.06	113.81
		Lamivudine	266	2.25	176853.65	3.26	1.45	664.86	321.34
		Stavudine	2546	21.56	237763.52	4.38	0.20	93.39	52.06
		Zalcitabine	4	0.03	2870.10	0.05	1.67	717.53	366.33
		Zidovudine	302	2.56	176077.76	3.25	1.27	583.04	346.05
	II	Efavirenz	2413	20.43	1352684.49	24.93	1.22	560.58	104.91
		Nevirapine	1086	9.19	544773.27	10.04	1.09	501.63	157.33
	III	Indinavir	243	2.06	147618.21	2.72	1.32	607.48	202.69
		Nelfinavir	20	0.17	48578.91	0.90	5.29	2428.95	1441.87
		Ritonavir	161	1.36	33879.09	0.62	0.46	210.43	226.13
		Saquinavir mesylate	21	0.18	24571.51	0.45	2.50	1170.07	821.34
	IV	Lamivudine/ Zidovudine	1853	15.69	1679164.91	30.95	1.97	906.19	512.28
		Total	11811	100.00	5425893.98	100.00	-	459.39	373.17
P6	I	Abacavir	70	0.46	159991.43	1.78	3.87	2285.59	430.80
		Didanosine	2867	18.85	909294.62	10.12	0.54	317.16	153.42
		Lamivudine	424	2.79	312541.82	3.48	1.25	737.13	324.23
		Stavudine	2595	17.06	232553.59	2.59	0.15	89.62	45.83
		Zalcitabine	11	0.07	7100.80	0.08	1.14	645.53	459.23
		Zidovudine	418	2.75	285707.97	3.18	1.16	683.51	467.39
	II	Efavirenz	3108	20.44	1936686.14	21.56	1.06	623.13	127.13
		Nevirapine	1499	9.86	807526.76	8.99	0.91	538.71	144.26
	III	Indinavir	430	2.83	306136.65	3.41	1.21	711.95	193.58
		Nelfinavir	69	0.45	215758.95	2.40	5.33	3126.94	1559.91
		Ritonavir	418	2.75	77562.93	0.86	0.31	185.56	142.38
		Saquinavir mesylate	190	1.25	233931.77	2.60	2.08	1231.22	260.16
	IV	Lamivudine/ Zidovudine	3089	20.31	3485334.48	38.80	1.91	1128.31	419.30
		Lopinavir/ Ritonavir	19	0.13	12621.65	0.14	1.08	664.30	90.15
		Total	15207	100.00	8982749.56	99.99	-	590.70	488.42

%* Prevalence of the ARV medicine items for a specific active ingredient divided by the prevalence of the total number of ARV medicine items for the same specific active ingredient, multiplied by hundred.

%# Cost of the ARV medicine items for a specific active ingredient divided by the total cost of the ARV medicine items for the same specific active ingredient, multiplied by hundred.

Table 5.15 Prevalence, cost and cost-prevalence index values of ARV medicine items based on the active ingredient classification for the period P7 to P9 (2004)

Period	Category	Active ingredient classification	Number of ARV medicine items	Prevalence of ARV medicine items (%)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P7	I	Didanosine	39	0.26	42839.06	0.90	3.46	1098.44	405.28
		Lamivudine	1986	13.21	461202.63	9.66	0.73	232.23	116.55
		Stavudine	936	6.23	156321.52	3.27	0.53	167.01*	6.77
		Zalcitabine	2280	15.17	158123.48	3.31	0.22	69.35*	3.63
		Zidovudine	308	2.05	101760.74	2.13	1.04	330.39	155.92
	II	Efavirenz	3505	23.32	1241786.37	25.99	1.11	354.29	143.86
		Nevirapine	1713	11.40	766542.93	16.04	1.41	447.49	167.53
	III	Indinavir	191	1.27	77351.33	1.62	1.28	404.98	150.78
		Nelfinavir	31	0.21	21604.28	0.45	2.14	696.91	259.63
		Ritonavir	219	1.46	30420.11	0.64	0.44	138.91	102.82
		Saquinavir mesylate	109	0.73	87567.40	1.83	2.51	803.37	388.76
	IV	Lamivudine/ Zidovudine	3363	22.38	1506171.51	31.52	1.41	447.87*	6.70
		Lopinavir/ Ritonavir	350	2.33	126827.33	2.65	1.14	362.36	76.99
		Total	15030	100.02	4778518.69	100.01	-	317.93	190.80
P8	I	Abacavir	168	0.44	217906.90	1.53	3.48	1297.06	284.22
		Didanosine	3247	8.44	845039.60	5.95	0.71	260.25	114.49
		Lamivudine	3673	9.54	630347.50	4.44	0.47	171.62*	10.04
		Stavudine	5404	14.04	389485.04	2.74	0.20	72.08*	7.50
		Zidovudine	773	2.01	300397.82	2.11	1.05	388.61	210.47
	II	Efavirenz	9315	24.20	3845990.17	27.07	1.12	412.88	89.78
		Nevirapine	4110	10.68	2151641.73	15.14	1.42	523.52*	7.16
	III	Indinavir	742	1.93	369658.31	2.60	1.35	498.19	109.78
		Nelfinavir	103	0.27	91623.68	0.65	2.41	889.55	467.78
		Ritonavir	604	1.57	56570.67	0.40	0.26	93.66	98.09
		Saquinavir mesylate	382	0.99	408642.16	2.88	2.90	1069.74	455.18
	IV	Lamivudine/ Zidovudine	9258	24.05	4624352.51	32.54	1.35	499.49*	10.27
		Lopinavir/ Ritonavir	709	1.84	278235.59	1.96	1.07	392.43	84.33
		Total	38488	100.00	14209891.68	100.01	-	369.20	219.50
P9	I	Abacavir	177	0.37	221873.23	1.41	3.81	1253.52	310.22
		Didanosine	3685	7.61	908219.23	5.78	0.76	246.46*	4.04
		Lamivudine	5639	11.65	891866.49	5.67	0.49	158.16*	4.12
		Stavudine	7520	15.53	483323.88	3.07	0.20	64.27*	9.76
		Zidovudine	961	1.98	333364.16	2.12	1.07	346.89	178.41
	II	Efavirenz	12241	25.28	4251289.88	27.03	1.07	347.30	104.63
		Nevirapine	4660	9.62	2326318.03	14.79	1.54	499.21*	9.50

Table 5.15 (continue) Prevalence, cost and cost-prevalence index values of ARV medicine items based on the active ingredient classification for the period P7 to P9 (2004)

Period	Category	Active ingredient classification	Number of ARV medicine items	Prevalence of ARV medicine items (%)	Cost of ARV medicine items (R)	Cost of ARV medicine items (%)	Cost-Prevalence index	Average cost (R)	Standard deviation (R)
P9	III	Indinavir	710	1.47	334818.33	2.13	1.45	471.58	130.16
		Nelfinavir	97	0.20	93805.92	0.60	3.00	967.07	548.18
		Ritonavir	655	1.35	53804.15	0.34	0.25	82.14	91.47
		Saquinavir mesylate	439	0.91	462891.36	2.94	3.23	1054.42	492.73
	IV	Lamivudine/ Zidovudine	10586	21.86	4985733.28	31.70	1.45	470.98*	12.72
		Lopinavir/ Ritonavir	1050	2.17	378765.33	2.41	1.11	360.73	65.90
		Total	48420	100.00	15726073.27	99.99	-	324.78	212.48

%* Prevalence of the ARV medicine items for a specific active ingredient divided by the prevalence of the total number of ARV medicine items for the same specific active ingredient, multiplied by hundred.

%# Cost of the ARV medicine items for a specific active ingredient divided by the total cost of the ARV medicine items for the same specific active ingredient, multiplied by hundred.

* Weighted average cost (refer to section 5.1.1).

As shown in *table 5.13*, didanosine represents the active ingredient with the ***highest prevalence*** for periods P1, P2 and P3, being 794 (37.05 per cent; n=2143) for period P1, 1134 (31.38 per cent; n=3614) for period P2, and 1224 (30.30 per cent; n=4039) for period P3. Didanosine represents the active ingredient with the ***largest total cost*** for period P1, being R595318.69 (34.63 per cent; n=R1718891.10). The combination of lamivudine/zidovudine represents the active ingredient with the highest total cost of R585263.45 (36.28 per cent; n=R1613176.09) for period P2 and being R483681.01 (29.16 per cent; n=R1658717.10) for period P3.

The active ingredient, nelfinavir, as well as saquinavir mesylate represents the ***lowest prevalence*** of respectively 5 for both (0.23 per cent; n=2143) and the ***lowest total cost*** of respectively R16929.00 (0.98 per cent; n=R1718891.10) and R12624.93 (0.73 per cent; n= R1718891.10) for period P1. Nelfinavir represents the ***lowest prevalence and total cost*** during period P2 with a prevalence of 1 (0.03 per cent; n=3614) and a total cost of R25.08 (0.00 per cent; n=R1613176.09) (refer to table 5.13). Saquinavir has the ***lowest prevalence*** of 1 (0.02 per cent; n=4039) and the ***lowest total cost*** of R941.98 (0.06 per cent; n=R1658717.10) for period P3 *(refer to table 5.13)*.

Nelfinavir has the ***highest average cost*** of R3385.80±R0.00 for period P1, because it is only prescribed five times. Ritonavir has the highest average cost of R817.47±505.93 for period P2, and saquinavir

mesylate has the largest average cost being R941.98±0.00 for period P3. Lamivudine has the ***lowest average cost*** for period P1 of R527.03±587.31, nelfinavir the lowest for period P2 being R25.09±0.00, and stavudine the lowest for period P3 being R82.26±55.33 *(refer to table 5.13).*

The ***cost-prevalence index*** of didanosine, for periods P1, P2, and P3, zidovudine for periods P1 and P3, stavudine for periods P2 and P3, as well as nevirapine, lamivudine and the combination of lamivudine/zidovudine for period P1 are all lower than one indicating that these active ingredients are all relatively inexpensive. The cost-prevalence indices of the remaining active ingredients for the period P1 to P3 are all higher than one, indicating that they are relatively expensive *(refer to table 5.13).*

As shown in *table 5.14*, didanosine represents the active ingredient with the ***highest prevalence*** for both periods P4 and P5, of 2130 (25.81 per cent; n=8 253) and 2884 (24.42 per cent; n=11 811) respectively. Efavirenz represents the active ingredient with the highest prevalence for period P6, being 3 108 (20.44 per cent; n=15 207). The combination of lamivudine/zidovudine represents the active ingredient with the ***highest total cost*** for periods P4, P5, and P6, with total costs of respectively R1 236 533.40 (32.32 per cent; n=R3 826 432.21) for P4, R1 679 164.91 (30.95 per cent; n=R5 425 893.98) for P5, and R3 485 334.48 (38.80; n=R8 982 749.56) for P6.

Saquinavir mesylate represents the active ingredient with the ***lowest prevalence*** and cost, being 2 (0.02 per cent; n=8 253) and R1 542.10 (0.04 per cent; n=R3 826 432.21) for period P4. Zalcitabine represents the active ingredient with the ***lowest total cost*** and prevalence for both periods P5 and P6, being 4 (0.03; n=11 811) and R2 870.10 (0.05 per cent; n=R1 679 164.91) for P5 and being 11 (0.07 per cent' n=15 207) and R7 100.80 (0.08 per cent; n=R8 982 749.56) for P6 *(refer to table 5.14).*

The ***cost-prevalence indices*** of didanosine, stavudine and ritonavir for periods P4, P5, and P6, as well as stavudine for periods P4 and P5 and nevirapine for period P6 are all lower than one indicating that these active ingredients are all relatively inexpensive. The cost-prevalence indices of the remaining active ingredients for the period P4 to P6 are all higher than one, indicating that they are relatively expensive *(see table 5.14).*

The ***average costs*** of nelfinavir are the highest for each period from P4 to P6, being R1482.37±20.78 for P4, R2428.95±1441.87 for P5, and R3126.94±1559.91 for P6. Stavudine has the lowest average costs for periods P4 to P6, ranging from R99.07±65.49 in P4 to R93.39±52.06 in P5 to R89.62±45.83 in P6 *(refer to table 5.14).*

Efavirenz represents the active ingredient with the ***highest prevalence*** for periods P7, P8 and P9, with the prevalence being 3 505 (23.32 per cent; n=15 030) for P7, being 9 315 (24.20 per cent; n=38 488) for P8 and being 12 241 (25.28 per cent; n=48 420) for P9. The combination of lamivudine/zidovudine represents the active ingredient with the ***largest total cost*** for periods P7, P8 and P9, with total costs of respectively R1 506 171.51 (31.52 per cent; n=R4 778 518.69) for P7, R4 624 352.51 (32.54 per cent; n=R14 209 891.68) for P8, and R4 985 733.28 (31.70 per cent; n=R15 726 073.27) for P9 *(refer to table 5.15).*

Table 5.15 indicates that nelfinavir represents the active ingredient with the ***lowest prevalence*** for periods P7, P8 and P9, with a prevalence of respectively 31 (0.21 per cent; n=15 030) for P7, 103 (0.27 per cent; n=38 488) for P8, and 97 (0.20 per cent; n=48 420) for P9. Nelfinavir also represents the active ingredient with the ***lowest total cost*** for period P7 being R21 604.28 (0.45 per cent; n=R4 778 518.69), whilst ritonavir represents the active ingredient with the lowest cost for periods P8 and P9, with respectively R56 570.67 (0.40 per cent; n=R14 209 891.68) and R93 805.92 (0.60 per cent; n=R15 726 073.27).

The ***cost-prevalence indices*** of lamivudine, stavudine and ritonavir for periods P7, P8, and P9, as well as zidovudine and didanosine for periods P8 and P9 are all lower than one indicating that these active ingredients are all relatively inexpensive. The cost-prevalence indices of the remaining active ingredients for the period P7 to P9 are all higher than one, indicating that they are relatively expensive *(see table 5.15).*

The ***average costs*** of didanosine are the highest for each period from P7 to P9, being R1 098.44±405.28 for P7, R1 297.06±284.22 for P8, and R1 253.52±310.22 for P9. Zalcitabine has the lowest average cost for period P7 being R69.35±3.63. Stavudine has the lowest average costs for periods P8 and P9, ranging from R72.08±7.50 in P8 to R64.27±9.76 in P9 *(see table 5.15).*

The ***effect sizes (d-values)*** of all the active ingredients of the ARV medicine items for ***2001*** (study period P1 to P3), ***2002*** (study period P4 to P6), and ***2004*** (study period P7 to P9) can be interpreted as follow:

The ***effect sizes (d-values)*** calculated between the average costs for didanosine for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P2 and P7, P3 and P7, P4 and P7, P4 and P8, P5 and P7 and P6 and P7 are of practical significant value (d>0.8). The effect sizes (d-values) calculated between the average costs for lamivudine for P3 and P7, P4 and P7, P5 and P7, and P6 and P7 are of practical significant value (d>0.8). For stavudine, the effect sizes calculated between the average costs

for P1 and P2, P1 and P3, P1 and P4, P1 and P5, and P1 and P6, as well as for zidovudine for P2 and P8 are of practical significant value (d>0.8).

The ***effect sizes (d-values)*** calculated between the average cost for zalcitabine for P2 and P4, and P3 and P4, as well as for efavirenz for P1 and P7, P1 and P8, P1 and P9, P2 and P7, P2 and P8, P2 and P9, P3 and P7, P3 and P8, P3 and P9, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9, and for nevirapine for P2 and P7 are of practical significant value (d>0.8).

The ***effect sizes (d-values)*** calculated between the average costs for indinavir for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P3 and P6, P3 and P7, P4 and P6, P6 and P7, P6 and P8, and P6 and P9, as well as for nelfinavir for P1 and P4, P1 and P7, P1 and P8, P1 and P9, P2 and P4, P2 and P5, P2 and P6, P2 and P7, P2 and P8, P2 and P9, P4 and P6, P4 and P7, P4 and p8, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value (d>0.8).

For ritonavir, the ***effect sizes (d-values)*** calculated between the average costs for ritonavir for P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P4, P2 and P5, P2 and P6, P2 and P7, P2 and P8, P2 and P9, P3 and P5, P3 and P6, P3 and P7, P3 and P8, P3 and P9, P4 and P7, P4 and P8, and P4 and P9, as well as for saquinavir mesylate for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P3, P2 and P6, P2 and P8, P2 and P9, P3 and P6, P4 and P6, and P6 and P7, and for the combination of lopinavir/ritonavir for P6 and P7, P6 and P8, and P6 and P9 are of practical significant value (d>0.8).

Thus, the above ***d-values*** are all greater than 0.8 (d>0.8), indicating that the difference in price is of statistical and practical significance *(refer to section 4.6.2.5)*.

5.4.5 Prescribing patterns of innovator and generic ARV medicine items

Table 5.16 provides an overview of the prescribing patterns of innovator and generic ARV medicine items for the study years 2001, 2002, and 2004, each divided into three four-month periods.

Table 5.16 Summary of the prescribing patterns of innovator and generic ARV medicine items for 2001 (P1 to P3), 2002 (P4 to P6), and 2004 (P7 to P9)

	Period	Innovator or Generic	Number of ARV medicine items	Prevalence of ARV medicine items (%*)	Average cost per ARV medicine item (R)	Standard deviation (R)	Total cost of ARV medicine items (R)	Cost of ARV medicine items (%#)	Cost-Prevalence Index	d-values
2001	P1	Innovator	2143	100	802.10	681.03	1718891.10	100	1	1.18
		Generic	0	0	0.00	0.00	0.00	0	-	
	P2	Innovator	3614	100	446.37	488.92	1613176.09	100	1	0.91
		Generic	0	0	0.00	0.00	0.00	0	-	
	P3	Innovator	4039	100	410.68	422.78	1658717.10	100	1	0.97
		Generic	0	0	0.00	0.00	0.00	0	-	
2002	P4	Innovator	8253	100	463.64	352.65	3826432.21	100	1	1.32
		Generic	0	0	0.00	0.00	0.00	0	-	
	P5	Innovator	11811	100	459.39	373.17	5425893.98	100	1	1.23
		Generic	0	0	0.00	0.00	0.00	0.00	-	
	P6	Innovator	15207	100	590.70	488.42	8982749.56	100	1	1.21
		Generic	0	0	0.00	0.00	0.00	0.00	-	
2004	P7	Innovator	14570	96.94	324.93	189.00	4734291.25	99.07	1.02	1.21
		Generic	460	3.06	96.15	85.74	44227.44	0.93	0.30	
	P8	Innovator	37048	96.26	379.34	216.81	14053872.10	98.90	1.03	1.25
		Generic	1440	3.74	108.35	87.79	156019.58	1.10	0.29	
	P9	Innovator	44991	92.92	340.12	209.80	15302512.55	97.31	1.05	1.03
		Generic	3429	7.08	123.52	128.13	423560.72	2.69	0.38	

%* Total number of the innovator or generic ARV-medicine items claimed divided by the total number of ARV-medicine items claimed during a specific period multiplied by hundred.

%# Cost of the innovator or generic ARV-medicine items claimed divided by the total cost of the ARV-medicine items claimed during a specific period multiplied by hundred.

The ***innovator ARV medicine items*** increased with 88.47 per cent (n=1 896) in 2001 (period P1 to P3), with 84.26 per cent (n=6 954) in 2002 (period P4 to P6), and with 208.79 per cent (n=30 421) in 2004 (period P7 to P9). There were no generic products claimed during 2001 (study period P1 to P3), and 2002 (study period P4 to P6) *(refer to table 5.16)*.

From *table 5.16* can be seen that ***generic ARV medicine items*** had been claimed through the database in 2004 (study period P7 to P9). The generic ARV medicine items increased with 213.04 per cent (n=980) from P7 to P8, and with 138.13 per cent (n=1 989) from P8 to P9. This resulted in an overall incline of 645.43 per cent (n=2 969) for the generic ARV medicine items in 2004 (period P7 to P9).

The ***innovator ARV medicine items*** prescribed, for 2004 (study period P7 to P9), entail more than 92 per cent of the prescribed ARV medicine items, ranging from 96.94 per cent (P7) to 96.26 per cent (P8) to 92.92 per cent (P9). The ***cost of innovator ARV medicine items*** prescribed for 2004 (study period P7 to P9), entails more than 97 per cent of the prescribed ARV medicine items ranging from 99.07 per cent (P7) to 98.90 per cent (P8) to 97.31 per cent (P9) *(refer to table 5.16)*.

The ***average cost per innovator ARV medicine item*** was R802.10±681.03 in P1 versus R410.68±422.78 in P3 and declined with 48.80 per cent (n=R391.42) in 2001 (period P1 to P3). The average cost per innovator ARV medicine item was R463.64±352.65 in P4 versus R590.70±488.42 in P6 and inclined with 27.40 per cent (n=R127.06) in 2002 (period P4 to P6). In 2004, the average cot per innovator ARV medicine item was R324.93±189.00 in P7, versus R379.34±216.81 in P8, versus R340.12±209.80 in P9 and increased with 16.75 per cent (n=R54.41) from P7 to P8, and declined with 10.34 per cent (n=R39.22) from P8 to P9. The effect-sizes (d-values) between the average cost per innovator ARV medicine item for all the study periods (2001, 2002, and 2004) are of no practical significance ($d < 0.8$) *(refer to table 5.16)*.

The ***average cost per generic ARV medicine item*** was R96.15±85.74 in P7 versus R108.35±87.79 in P8 versus R123.52±128.13 in P9, and increased with 12.72 per cent (n=R12.23) from P7 to P8, and increased with 14.00 per cent (n=R15.17) from P8 to P9. There was an overall increase of 28.47 per cent (n=R27.37) in the average cost per generic ARV medicine item for the period P7 to P9. The effect-sizes (d-values) calculated between the average cost per generic ARV medicine item for the period P7, P8 and P9 are of no practical significance ($d < 0.8$) *(refer to table 5.16)*.

The ***effect sizes (d-values)*** calculated between the ***average cost per innovator ARV medicine item*** and the ***average cost per generic ARV medicine item*** for the whole study period (2001, 2002 and 2004) are all greater than 0.8, and of practical significance *(refer to table 5.16)*.

The ***total cost of innovator ARV medicine items*** decreased with 3.50 per cent (n=R60 174) in 2001 (period P1 to P3), increased with 134.76 per cent (n=R5 156 317.35) in 2002 (period P4 to P6), and also with 223.23 per cent (n=R10 568 221.30) in 2004 (period P7 to P9). The ***total cost of generic ARV medicine items*** rose with 252.77 per cent (n=R111 792.14) from P7 to P8, and also with 171.48 per cent (n=R267 541.14) from P8 to P9. There was an overall increase of 857.69 per cent (n=R379 333.28) in the total cost of generic ARV medicine items for the period P7 to P9.

According to *table 5.16*, the ***cost-prevalence index*** of the ***innovator ARV medicine items*** was exactly one for 2001 (study period P1 to P3) and 2002 (study period P4 to P6), indicating that there is equilibrium between the cost and prevalence of these medicine items utilised *(refer to section 4.6.2.4)*. The cost-prevalence index of the innovator ARV medicine items was slightly higher than one for 2004 (study period P7 to P9), indicating that treatment is relatively expensive *(refer to table 5.16)*. The ***cost-prevalence index*** of the ***generic ARV medicine items*** was lower than one for 2004 (study period P7 to P9), indicating that the treatment is relatively inexpensive *(refer to section 4.6.2.4)*.

5.4.6 Individual ARV medicine items

The utilisation patterns and the costs of individual ARV medicine items will be discussed in this section. NRTIs will be discussed first, followed by the NNRTIs, the PIs and followed lastly by the other ARV medicine items.

5.4.6.1 NRTIs

The utilisation patterns and cost of medicine items containing abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine as active ingredient will be discussed in this section.

5.4.6.1.1 Abacavir

The usage patterns and cost of medicine items containing abacavir as an active ingredient will be discussed under this paragraph.

5.4.6.1.1.1 Prevalence and cost of medicine items containing abacavir as an active ingredient

There were ***no medicine items***, containing abacavir as an active ingredient, claimed for the period P1 to P3. There were also no individual medicine items, containing abacavir as an active ingredient, claimed for the period P4. The ***total number of medicine items*** containing abacavir as an active ingredient increased from 82 to 384 during the second and third study years respectively. Though there was an increase in the actual number of drugs containing abacavir as an active ingredient, the prevalence percentages decreased and abacavir accounted for 2.28 per cent (n=16 810) and 0.22 per cent (n=36 796) of the total number of NRTIs and hence 0.23 per cent (n=35 271) and 0.38 per cent (n=101 938) of the total number of ARV medicine items claimed during the second and third study years respectively *(refer to table 5.17 and table 5.18).*

As shown in *tables 5.17* and *5.18,* the ***total cost*** of Ziagen® 300mg accounted for 3.80 per cent (n=R4 765 856.05) and 7.36 per cent (n=R6 139 071.28) of the total cost of all NRTIs, and 0.01 per cent (n=R18 235 075.75) and 1.30 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the second and third study years respectively. The total cost of Ziagen® 100mg/5ml represented a very small proportion of the total cost of all NRTIs for the second study year. During the third study year, the total cost of Ziagen® 100mg/5ml accounted for 0.50 per cent (n=R6 139 071.28) of the total cost of all NRTIs, and 0.09 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the second study year.

The ***cost-prevalence index*** of Ziagen® 300mg and Ziagen® 100mg/5ml fluctuated higher than one during the second and third study years, indicating that the therapy was relatively expensive. The ***average cost*** of Ziagen® 300mg increased from P5 to P6 and decreased from P6 to P7 where it fluctuated on R1 356.53±191.86 and R1 326.03±249.44 for P8 and P9. The average cost of Ziagen® 100mg/5ml decreased from P6 to P7, and increased steadily from P7 to P9. This could be due to an increase in the dosage and/or a change in the treatment period, with a possible effect on the cost *(refer to table 5.17 and table 5.18).*

The ***effect sizes (d-values)*** calculated between the average cost per medicine item for Ziagen® 300mg for P5 and P6, and P6 and P7, as well as for Ziagen® 100mg/5ml between P6 and P7 are of practical significance ($d > 0.8$).

Table 5.17 Prevalence and cost of individual medicine items containing abacavir as an active ingredient for the period P4 to P6 (2002)

Period	Abacavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	-	-	-	-	-	-	-	-
P5	Ziagen® 300mg	12	0.10	23223.05	0.43	4.3	1935.25	279.33
P6	Ziagen® 300mg	69	0.45	157895.88	1.76	3.91	2288.35	433.34
	Ziagen® 100mg/5ml	1	0.01	2095.55	0.02	2	2095.55	0

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.18 Prevalence and cost of individual medicine items containing abacavir as an active ingredient for the period P7 to P9 (2004)

Period	Abacavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Ziagen® 300mg	29	0.19	37402.42	0.78	4.10	1289.74	221.82
	Ziagen® 100mg/5ml	10	0.07	5436.64	0.11	1.57	543.66	283.76
P8	Ziagen® 300mg	153	0.40	207549.13	1.46	3.65	1356.53	191.86
	Ziagen® 100mg/5ml	15	0.04	10357.77	0.07	1.75	690.52	362.08
P9	Ziagen® 300mg	156	0.32	206860.13	1.32	4.13	1326.03	249.44
	Ziagen® 100mg/5ml	21	0.04	15013.10	0.10	2.50	714.91	137.99

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.1.2 Didanosine

The usage patterns and cost of medicine items containing didanosine as an active ingredient will be discussed under this paragraph.

5.4.6.1.2.1 Prevalence and cost of medicine items containing didanosine as an active ingredient

It is evident from *table 5.19*, *table 5.20* and *table 5.21* that the ***total number of medicine items*** containing didanosine as an active ingredient increased from 3 152 to 8 154 to 8 918 during the first, second and third study years respectively. This accounted for 53.61 per cent (n=5 880), 48.51 per cent (n=16 810) and 24.24 per cent (n=36 796) of the total number of NRTIs and 32.18 per cent (n=9 796), 23.12 (n=35 271) and 8.75 per cent (n=101 938) of the total number of all ARV medicine items claimed through the database during the first, second and third study years respectively.

As shown in *table 5.19*, Videx® 25mg, Videx® 50mg, Videx® 100mg, Videx® 150mg, Videx® 4g powder for injection and Videx® paediatric 2g suspension constituted 7.65 per cent, 2.06 per cent, 78.59 per cent, 11.29 per cent, 0.25 per cent and 0.16 per cent of the ***total number of medicine items*** containing didanosine as an active ingredient during the first study year (n=3 152) respectively.

The ***prevalence*** of Videx® 25mg, Videx® 50mg, Videx® 100mg, and Videx® paediatric 2g suspension increased during the second study year, on the other hand that of Videx® 150mg and Videx® 4g powder for injection decreased. The five medicine items accounted for 9.38 per cent, 4.00 per cent, 80.11 per cent, 0.11 per cent, 6.07 per cent and 0.00 per cent of the total number of drugs containing didanosine as an active ingredient (n=8 154) respectively for the second study year *(refer to table 5.20).*

During the third study year, the ***prevalence*** of Videx® 25mg decreased and accounted for 9.05 per cent, the prevalence of Videx® 50mg increased and accounted for 4.25 per cent, the prevalence of Videx® 100mg decreased and accounted for 63.99 per cent, the prevalence of Videx® 150mg increased and accounted for 21.35 per cent, the prevalence of Videx® paediatric 2g suspension increased and accounted for 0.54 per cent, and Aspen didanosine was claimed for the first time and accounted for 0.82 per cent of the total number of drugs containing didanosine as an active ingredient (n=8 918) respectively *(refer to table 5.21).*

It is apparent from *table 5.19*, *table 5.20* and *table 5.21* that the ***total cost of all medicine items*** containing didanosine as an active ingredient augmented from R1 408 087.78 to R2 737 729.51 to R2 214 461.46 during the first, second and third study years respectively. This accounted for 60.91 per cent (n=R2 311 619.96), 57.44 per cent (n=R4 765 856.05) and 36.05 per cent (n=R6 142 071.28) of the total cost of all NRTIs, and 28.21 per cent (n=R4 990 784.29), 15.01 per cent (n=R18 235 075.75) and 6.38 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively.

Videx® 25mg, Videx® 50mg, Videx® 100mg, Videx® 150mg, Videx® 4g powder for injection and Videx® paediatric 2g suspension accounted for 3.08 per cent, 0.96 per cent, 86.40 per cent, 9.39 per cent, 0.10 per cent and 0.07 per cent respectively of the ***total cost of medicine items*** (n=R1 408 087.78) containing didanosine as an active ingredient during the first study year. The trend of the total cost of only Videx® 100mg was similar to that of the prevalence, as can be seen from the cost-prevalence index of Videx® 100mg for the first study year *(refer to table 5.19).*

Videx® 25mg, Videx® 50mg, Videx® 100mg, Videx® 150mg and Videx® paediatric 2g suspension accounted for 6.23 per cent, 2.63 per cent, 87.03 per cent, 3.74 per cent and 0.37 per cent respectively of the ***total cost*** (n=R2 737 729.51) of medicine items containing didanosine as an active ingredient during the second study year *(refer to table 5.20).*

Videx® 25mg, Videx® 50mg, Videx® 100mg, Videx® 150mg, Videx® paediatric 2g suspension, and Aspen didanosine accounted for 6.87 per cent, 4.07 per cent, 67.25 per cent, 20.24 per cent, 0.66 per cent and 0.91 per cent respectively of the ***total cost of medicine items*** (n=R2 737 729.51) containing didanosine as an active ingredient during the third study year *(refer to table 5.21).*

The ***cost-prevalence index*** of Videx® 100mg was more than one for the three study years. The cost-prevalence index of Videx® 150mg was higher than one for P1, as well as for Videx® paediatric 2g suspension for P7, P8 and P9. The cost-prevalence index of Aspen dianosine® was also higher than one for P9, indicating that all these medicine items utilised were relatively expensive.

The ***average cost of all medicine items*** containing didanosine as active ingredient fluctuated during the three study years and the trend of the average cost was unpredictable. The possible effect of the new pricing regulations cannot be seen clearly, as the average cost per item of Videx® 25mg, Videx® 50mg and Videx® 100mg decreased from P8 (transition phase) to P9 (after single exit price), and the average cost per item of Videx® 150mg and Videx® paediatric 2g suspension increased from P8 (transition phase) to P9 (after single exit price) *(refer to table 5.19, table 5.20 and table 5.21).*

The ***effect sizes (d-values)*** calculated between the average cost of Videx® 25mg for P1and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P4, P2 and P5, and P4 and P9 are of practical significant value ($d > 0.8$). The effect sizes (d-value) calculated between the average cost of Videx® 50mg for P1 and P2 is of practical significant value. The effect sizes (d-values) calculated between the average cost of Videx® 100mg for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P3 and P7, P3 and P9, P4 and P7, P4 and P8, P4 and P9, P5 and P7, and P5 and P9 are of practical significant value. The effect sizes (d-values) calculated between the average cost of Videx® 150mg for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9 are of practical significant value. The effect sizes (d-values) calculated between the average cost of Videx® paediatric 2g suspension for P3 and P7, P3 and P8, and P3 and P9 are of practical significant value.

Table 5.19 Prevalence and cost of individual medicine items containing didanosine as an active ingredient for the period P1 to P3 (2001)

Period	Didanosine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Videx® 25mg	50	2.33	5777.16	0.34	0.15	115.54	34.06
	Videx® 50mg	6	0.28	1308.02	0.08	0.29	218.00	0.76
	Videx® 100mg	631	29.44	513696.19	29.89	1.02	814.10	153.76
	Videx® 150mg	107	4.99	74537.32	4.34	0.87	696.61	196.14
P2	Videx® 25mg	84	2.32	14467.58	0.90	0.39	172.23	46.02
	Videx® 50mg	13	0.36	2369.24	0.15	0.42	182.25	30.10
	Videx® 100mg	895	24.77	353106.74	21.89	0.88	394.53	193.52
	Videx® 150mg	142	3.93	35954.83	2.23	0.57	253.20	185.51
P3	Videx® 25mg	107	2.65	23129.41	1.39	0.53	216.16	57.12
	Videx® 50mg	46	1.14	9908.97	0.60	0.53	215.41	55.30
	Videx® 100mg	951	23.55	349779.54	21.09	0.90	367.80	114.19
	Videx® 150mg	107	2.65	21687.76	1.31	0.49	202.69	76.87
	Videx® 4g powder for injection	8	0.20	1436.63	0.09	0.45	179.58	167.13
	Videx® paediatric 2g suspension	5	0.12	928.39	0.06	0.50	185.68	106.29

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.20 Prevalence and cost of individual medicine items containing didanosine as an active ingredient for the period P4 to P6 (2002)

Period	Didanosine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Videx® 25mg	185	2.24	47207.64	1.23	0.55	255.18	84.64
	Videx® 50mg	90	1.09	23301.52	0.61	0.56	258.91	67.30
	Videx® 100mg	1969	23.86	742371.17	19.40	0.81	437.72	139.72
	Videx® 150mg	149	1.81	34930.93	0.91	0.50	234.44	95.62
	Videx® paediatric 2g suspension	10	0.12	2788.12	0.07	0.58	278.81	306.86
P5	Videx® 25mg	289	2.45	63553.17	1.17	0.48	219.91	52.27
	Videx® 50mg	125	1.06	26571.54	0.49	0.46	212.57	47.16
	Videx® 100mg	2302	19.49	851450.81	15.69	0.81	369.87	101.71
	Videx® 150mg	151	1.28	30951.39	0.57	0.45	204.98	76.46
	Videx® paediatric 2g suspension	17	0.14	5308.60	0.10	0.71	312.27	191.00
P6	Videx® 25mg	291	1.91	59795.53	0.67	0.35	205.48	80.21
	Videx® 50mg	111	0.73	22046.68	0.25	0.34	198.61	89.78
	Videx® 100mg	2261	14.87	788713.25	8.78	0.59	348.83	152.15
	Videx® 150mg	195	1.28	36586.42	0.41	0.32	187.62	87.81
	Videx® paediatric 2g suspension	9	0.06	2152.74	0.02	0.33	239.19	115.40

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.21 Prevalence and cost of individual medicine items containing didanosine as an active ingredient for the period P7 to P9 (2004)

Period	Didanosine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Videx® 25mg	199	1.32	38519.32	0.81	0.61	193.56	69.99
	Videx® 50mg	58	0.39	13544.60	0.28	0.72	233.53	97.97
	Videx® 100mg	1192	7.93	288430.60	6.04	0.76	241.97	134.48
	Videx® 150mg	523	3.48	116499.18	2.44	0.70	222.75	78.57
	Videx® paediatric 2g suspension	14	0.09	4208.93	0.09	1.00	300.64	112.22
P8	Videx® 25mg	291	0.76	55646.84	0.39	0.51	191.23	62.63
	Videx® 50mg	156	0.41	39516.56	0.28	0.68	253.31	106.96
	Videx® 100mg	2096	5.45	580845.56	4.09	0.75	277.12	121.72
	Videx® 150mg	683	1.78	162627.59	1.14	0.64	238.11	94.69
	Videx® paediatric 2g suspension	21	0.06	6403.05	0.05	0.83	304.91	77.41
P9	Videx® 25mg	317	0.66	57960.02	0.37	0.56	182.84	62.65
	Videx® 50mg	165	0.34	37032.94	0.24	0.71	224.44	98.36
	Videx® 100mg	2419	5.00	619930.57	3.94	0.79	256.28	92.53
	Videx® 150mg	698	1.44	169176.53	1.08	0.75	242.37	78.79
	Videx® paediatric 2g suspension	13	0.03	4051.92	0.03	1.00	311.69	49.18
	Aspen didanosine®	73	0.15	20067.25	0.13	0.87	274.89	72.92

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.1.3 Lamivudine

The usage patterns and cost of medicine items containing lamivudine as an active ingredient will be discussed under this paragraph.

5.4.6.1.3.1 Prevalence and cost of medicine items containing lamivudine as an active ingredient

The ***total number of medicine items*** containing lamivudine as an active ingredient increased from 370 to 856 to 10 248 during the first, second and third study years respectively. Though there was an increase in the actual number of drugs containing lamivudine as an active ingredient, the prevalence percentage decreased from the first to the second study years and accounted for 6.29 per cent (n=5 880) and 5.09 per cent (n=16 810) of the total number of NRTIs, and 3.78 per cent (n=9 796) and 2.43 per cent (n=35 271) of the total number of ARV medicine items. The third study year showed an increase and accounted for

27.85 per cent (n=36 796) of the total number of NRTIs, and 10.05 per cent (n=101 938) of the total number of ARV medicine items claimed *(refer to table 5.22, table 5.23 and table 5.24)*.

As witnessed in table 5.24 below, the ***prevalence percentage*** of 3TC® 150mg inclined from P7 to P8 to P9. 3TC® 150mg constituted 6.42 per cent (n = 10 248), 25.77 per cent (n = 10 248), and 40.52 per cent (n=10 248) of the total number of individual medicine items containing lamivudine as an active ingredient for P7, P8, and P9 respectively.

3TC® 150mg accounted for 6.40 per cent (n=R2 311 619.96), 7.42 per cent (n=R4 65 856.05) and 19.11 per cent (n=R6 142 071.28) of the ***total cost*** of all NRTIs and 2.96 per cent (n=R4 990 784.29), 1.94 per cent (n=R18 235 075.75), and 3.38 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively. The ***cost prevalence index*** for 3TC® 150mg was higher than one for the period P2 to P6, indicating that 3TC® 150mg was relatively expensive compared to 3TC 240ml® for the same period (P2 to P6) *(refer to table 5.22, table 5.23 and table 5.24)*.

The ***average cost*** of 3TC® 150mg increased from P1 to P3, and also from P4 to P6, but in the third study year, it increased slightly from P7 (before implementation) to P8 (transition phase), and decreased from P8 (transition phase) to P9 (after single exit price). The same trend can be observed for 3TC® 240ml. The average cost of Cipla-lamivudine® slightly increased from P7 (before implementation) to P8 (transition phase), but decreased with 22.04 per cent (n=44.00) from P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the medicine pricing regulations applied in 2004 can be seen clearly by the increasing and decreasing trends of the average cost per medicine item *(refer to table 5.24)*.

The ***effect sizes (d-values)*** calculated between the average cost of 3TC® 150mg for P1 and P3, P2 and P3, P3 and P7, P3 and P8, P3 and P9, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value ($d > 0.8$). The effect sizes (d-values) calculated between the average cost of 3TC® 240ml for P1 and P7, P1 and P8, and P1 and P9, P2 and P7, P2 and P8, P2 and P9, P3 and P7, P3 and P8, P3 and P9, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value ($d > 0.8$).

Table 5.22 Prevalence and cost of individual medicine items containing lamivudine as an active ingredient for the period P1 to P3 (2001)

Period	Lamivudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	3TC® 150mg	163	7.61	89692.00	5.22	0.69	550.26	658.85
	3TC® 240ml	46	2.15	20457.12	1.19	0.55	444.72	151.01
P2	3TC® 150mg	49	1.36	33442.68	2.07	1.52	628.50	669.13
	3TC® 240ml	46	1.27	21448.63	1.33	1.05	466.28	145.52
P3	3TC® 150mg	21	0.52	24704.53	1.49	2.87	1176.41	649.72
	3TC® 240ml	45	1.11	21659.28	1.31	1.18	481.32	159.38

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.23 Prevalence and cost of individual medicine items containing lamivudine as an active ingredient for the period P4 to P6 (2002)

Period	Lamivudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	3TC® 150mg	69	0.84	61977.29	1.62	1.93	898.22	197.14
	3TC® 240ml	97	1.18	40188.33	1.05	0.89	414.32	164.50
P5	3TC® 150mg	122	1.03	113154.05	2.09	2.03	927.49	240.51
	3TC® 240ml	144	1.22	63699.60	1.17	0.96	442.36	183.60
P6	3TC® 150mg	181	1.19	178566.40	1.99	1.67	986.55	201.09
	3TC® 240ml	243	1.60	133975.42	1.49	0.93	551.34	269.22

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.24 Prevalence and cost of individual medicine items containing lamivudine as an active ingredient for the period P7 to P9 (2004)

Period	Lamivudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	3TC® 150mg	658	4.38	105030.65	2.20	0.50	159.62	27.69
	3TC® 240ml	217	1.44	39540.88	0.83	0.58	182.22	63.70
	Cipla-lamivudine®	61	0.41	11749.99	0.25	0.61	192.62	24.72
P8	3TC® 150mg	2641	6.86	428456.29	3.02	0.44	162.23	21.46
	3TC® 240ml	627	1.63	121278.09	0.85	0.52	193.43	83.47
	Cipla-lamivudine®	403	1.05	80449.38	0.57	0.54	199.63	26.63
	Lamaid®	2	0.01	163.74	0.00	0.00	81.87	32.68

Table 5.24 (continue) Prevalence and cost of individual medicine items containing lamivudine as an active ingredient for the period P7 to P9 (2004)

Period	Lamivudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P9	3TC® 150mg	4153	8.58	640295.99	4.07	0.47	154.18	22.77
	3TC® 240ml	742	1.53	138642.57	0.88	0.58	186.85	86.11
	Cipla-lamivudine®	622	1.29	96799.47	0.62	0.48	155.63	20.69
	Lamaid®	9	0.02	921.13	0.01	0.50	102.35	18.03
	Lamivudine® 150mg	9	0.02	1186.72	0.01	0.50	131.86	94.21
	Aspen lamivudine®	104	0.22	14020.61	0.09	0.41	134.81	52.79

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.1.4 Stavudine

The usage patterns and cost of medicine items containing stavudine as an active ingredient will be discussed under this paragraph.

5.4.6.1.4.1 Prevalence and cost of medicine items containing stavudine as an active ingredient

It is evident from *table 5.25*, *table 5.26* and *table 5.27* that the ***total number of medicine items*** containing stavudine as an active ingredient increased from 1 551 to 6 965 to 15 204 during the first, second and third study years respectively. This accounted for 26.38 per cent (n=5 880), 41.43 per cent (n=16 810) and 41.32 per cent (n=36 796) of the total number of NRTIs and 15.83 per cent (n=9 796), 19.75 per cent (n=35 271) and 14.91 per cent (n=101 938) of the total number of all ARV medicine items claimed through the database during the first, second and third years respectively.

The ***prevalence percentage*** of Zerit® 40mg was the highest for each period, from P1 to P9. As shown in *table 5.25*, *table 5.26* and *table 5.27*, Zerit® 40mg constituted 76.53 per cent (n=1 551), 78.26 per cent (n=6 965) and 54.48 per cent (n=15 204) of the total number of medicine items containing stavudine as an active ingredient during the first, second and third study years respectively. The prevalence percentage of Zerit® 30mg was the second highest for each period, constituting 19.73 per cent (n=1 551), 18.31 per cent (n=6 965) and 17.70 per cent (n=15 204) of the total number of medicine items containing stavudine as an active ingredient during the first, second and third study years respectively.

It is apparent from *table 5.25*, *table 5.26* and *table 5.27* that the ***total cost*** of medicine items containing stavudine augmented from R261 115.35 to R651 026.71 to R1 030 932.40 during the first, second and third study years respectively. This accounted for 11.30 per cent (n=R2 311 619.96), 13.66 per cent (n=R4 765 856.05) and 16.78 per cent (n=R6 142 071.28) of the total cost of all NRTIs, and 5.23 per cent (n=R49 90 784.29), 3.57 per cent (n=R18 235 075.75) and 2.97 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively.

Zerit® 40mg accounted for 76.58 per cent (n=R261 115.35), 73.54 per cent (n=R651 026.71) and 52.97 per cent (n=R1 030 932.40) respectively of the ***total cost*** of medicine items containing stavudine as an active ingredient during the first, second and third study years. Zerit® 30mg constituted 17.23 per cent (n=R261 115.35), 17.22 per cent (n=R651 026.71) and 16.82 per cent (n=R1 030 932.40) respectively of the total cost of medicine items containing stavudine as an active ingredient during the first, second and third study years *(refer to able 5.25, table 5.26 and table 5.27)*.

The ***cost-prevalence index*** was higher than one for Zerit® 40mg and Zerit® 30mg only for P1, and also for Zerit® suspension for P2, P3, P4, P7 and P9. A cost-prevalence index of higher than one indicates that therapy is relatively expensive *(refer to table 5.25, table 5.26 and table 5.27)*.

It is perceptible from *table 5.25*, *table 5.26* and *table 5.27* that the ***average cost*** of Zerit® 40mg decreased from P1 to P3, and from P4 to P6, but increased from P7 (before implementation) to P8 (transition phase), and decreased from P8 (transition phase) to P9 (after single exit price). The same pattern can be seen for Zerit® 30mg and Zerit® suspension. Aspen stavudine® 20mg, Aspen stavudine® 30mg and Aspen stavudine® 40mg all declined from P7 to P9, a possible cause of the implementation of the pricing regulation in 2004.

The ***effect sizes (d-values)*** calculated between the average cost of Zerit® 30mg for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P3 and P4, P3 and P5, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value ($d > 0.8$). The effect sizes (d-values) calculated between the average cost of Zerit® 40mg for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P3 and P4, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, and P6 and P9 are of practical significant value ($d > 0.8$). The effect sizes (d-values) calculated between the average cost of Zerit® suspension for P1 and P2, P1 and P3, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, and P2 and P7 are of practical significant value ($d > 0.8$). The effect sizes (d-values) calculated between the average cost of Zerit® 20mg for P2 and P4, P2 and P5, P2 and P6, P3 and P4, P3 and P5, P3 and P6, P4 and P9, P6 and P7, P6 and P9, and P8 and P9 are of practical significant value.

The effect sizes (d-values) calculated between the average cost of Aspen stavudine® 20mg for P7 and P8, and P7 and P9, as well as the average cost of Aspen stavudine® 40mg for P7 and P9 are of practical significant value.

Table 5.25 Prevalence and cost of individual medicine items containing stavudine as an active ingredient for the period P1 to P3 (2001)

Period	Stavudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Zerit® 30mg	14	0.65	21489.11	1.25	1.92	1534.94	1.67
	Zerit® 40mg	75	3.50	115026.26	6.69	1.91	1533.68	184.82
	Zerit® suspension	1	0.05	622.76	0.04	0.80	622.76	0
P2	Zerit® 15mg	3	0.08	136.39	0.01	0.13	45.46	16.57
	Zerit® 20mg	1	0.03	63.11	0.00	0.00	63.11	0
	Zerit® 30mg	107	2.96	9677.74	0.60	0.20	90.45	200.29
	Zerit® 40mg	392	10.85	30888.47	1.92	0.18	78.80	151.26
	Zerit® suspension	11	0.30	5313.62	0.33	1.10	483.06	104.35
P3	Zerit® 20mg	21	0.52	1316.12	0.08	0.15	62.67	14.88
	Zerit® 30mg	185	4.58	13831.12	0.83	0.18	74.76	8.63
	Zerit® 40mg	720	17.83	54043.53	3.26	0.18	75.06	7.79
	Zerit® suspension	21	0.52	8707.12	0.53	1.02	414.63	151.41

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.26 Prevalence and cost of individual medicine items containing stavudine as an active ingredient for the period P4 to P6 (2002)

Period	Stavudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Zerit® 20mg	29	0.35	2434.76	0.06	0.17	83.96	22.91
	Zerit® 30mg	344	4.17	31118.99	0.81	0.19	90.46	16.50
	Zerit® 40mg	1416	17.16	129940.22	3.40	0.20	91.77	16.70
	Zerit® suspension	35	0.42	17215.63	0.45	1.07	491.88	230.57
P5	Zerit® 20mg	38	0.32	3028.86	0.06	0.19	79.71	16.05
	Zerit® 30mg	453	3.84	39692.49	0.73	0.19	87.62	13.79
	Zerit® 40mg	2006	16.98	175449.53	3.23	0.19	87.46	15.82
	Zerit® suspension	49	0.42	19592.64	0.36	0.86	399.85	182.87
P6	Zerit® 20mg	50	0.33	4138.65	0.05	0.15	82.77	19.06
	Zerit® 30mg	478	3.14	41265.65	0.46	0.15	86.33	21.18
	Zerit® 40mg	2029	13.34	173393.13	1.93	0.15	85.46	23.85
	Zerit® suspension	38	0.25	13756.16	0.15	0.60	362.00	180.09

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.27 Prevalence and cost of individual medicine items containing stavudine as an active ingredient for the period P7 to P9 (2004)

Period	Stavudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Zerit® 20mg	63	0.42	3815.52	0.08	0.19	60.56	24.76
	Zerit® 30mg	521	3.47	31743.91	0.66	0.19	60.93	21.54
	Zerit® 40mg	1275	8.48	83450.74	1.75	0.21	65.45	20.00
	Zerit® suspension	48	0.32	16307.78	0.34	1.06	339.75	148.22
	Stavir 30®	34	0.23	1426.60	0.03	0.13	41.96	3.51
	Stavir 40®	74	0.49	3387.98	0.07	0.14	45.78	8.81
	Aspen stavudine® 20mg	5	0.03	323.28	0.01	0.33	64.66	12.93
	Aspen stavudine® 30mg	71	0.47	3795.86	0.08	0.17	53.46	10.03
	Aspen stavudine® 40mg	189	1.26	13871.81	0.29	0.23	73.40	17.52
P8	Zerit®20mg	138	0.36	9436.17	0.07	0.19	68.38	18.86
	Zerit® 30mg	1044	2.71	71434.72	0.50	0.19	68.42	19.66
	Zerit® 40mg	3145	8.17	218083.27	1.54	0.19	69.34	18.84
	Zerit® suspension	99	0.26	35631.87	0.25	0.96	359.92	186.58
	Stavir 30®	86	0.22	3889.26	0.03	0.14	45.22	13.05
	Stavir 40®	248	0.64	12279.17	0.09	0.14	49.51	16.13
	Aspen stavudine® 20mg	21	0.06	890.54	0.01	0.17	42.41	20.13
	Aspen stavudine® 30mg	140	0.36	7420.88	0.05	0.14	53.01	14.09
	Aspen stavudine® 40mg	483	1.26	30419.16	0.21	0.17	62.98	20.82
P9	Zerit® 20mg	151	0.31	9590.40	0.06	0.19	63.51	21.04
	Zerit® 30mg	1126	2.33	70188.12	0.45	0.19	62.33	23.06
	Zerit® 40mg	3863	7.98	244587.11	1.56	0.20	63.32	19.24
	Zerit® suspension	138	0.29	48445.70	0.31	1.07	351.06	190.86
	Stavir 30®	125	0.26	5056.18	0.03	0.12	40.45	7.12
	Stavir 40®	511	1.06	22085.63	0.14	0.13	43.22	8.60
	Aspen stavudine® 20mg	40	0.08	1430.86	0.01	0.13	35.77	13.21
	Aspen stavudine® 30mg	347	0.72	16923.56	0.11	0.15	48.77	18.40
	Aspen stavudine® 40mg	1219	2.52	65016.32	0.41	0.16	53.34	13.06

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.1.5 Zalcitabine

The usage patterns and cost of medicine items containing zalcitabine as an active ingredient will be discussed under this paragraph.

5.4.6.1.5.1 Prevalence and cost of medicine items containing zalcitabine as an active ingredient

The ***total number of individual medicine items*** containing zalcitabine as an active ingredient augmented from 6 to 18 during the first and second study years respectively. There were no individual medicine items claimed, containing zalcitabine, for the third study year (P7 to P9). Only Hivid® combo pack was claimed through the database in the first study year, and in the second study year, Hivid® combo pack constituted 72.22 per cent of the total number (n=18) of individual medicine items claimed, containing zalcitabine as an active ingredient. Hivid® 0.75mg was first claimed in P5, and for the second study year, it constituted 27.78 per cent of the total number (n=18) of individual medicine items claimed, containing zalcitabine as an active ingredient *(refer to table 5.28 and table 5.29)*.

The ***total number of medicine items*** containing zalcitabine as an active ingredient accounted for 0.1 per cent (n=5 880) and also 0.1 per cent (n=16 810) of the total number of NRTIs, and 0.06 per cent (n=9 796) and 0.05 per cent (n=35 271) of the total number of ARV medicine items claimed during the first and second study years respectively *(refer to table 5.28 and table 5.29)*.

The ***total cost*** of all individual medicine items containing zalcitabine as an active ingredient accounted for 0.23 per cent (n=R2 311 619.96) and 0.27 per cent (n=R4 765 856.05) of the total cost of all NRTIs claimed, and 0.11 per cent (n=R4 990 784.29) and 0.07 per cent (n=R18 235 075.75) of the total cost of all ARV medicine items claimed during the first and second study years respectively. The ***cost-prevalence index*** for the second study year is higher than one for the most medicine items, except for Hivid® combo pack which are 0.60 for P6, which means that its cost was relatively inexpensive for that period *(refer to table 5.28 and table 5.29)*.

It is apparent from *table 5.28* and *table 5.29* that the ***average cost*** of Hivid® combo pack was more or less the same for the first study year, and it decreased substantially in the second study year. The average cost of Hivid® 0.75mg stayed the same on R1 224.70±0.00 for P5 and P6.

The ***effect sizes (d-values)*** calculated between the average cost of Hivid® combo pack for P2 and P4, P2 and P5, P2 and P6, P3 and P4, P3 and P5, P3 and P6, P4 and P5, P4 and P6, and P5 and P6 are of practical significant value.

Table 5.28 Prevalence and cost of individual medicine items containing zalcitabine as an active ingredient for the period P1 to P3 (2001)

Period	Zalcitabine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	-	-	-	-	-	-	-	
P2	Hivid® combo pack	3	0.08	2693.10	0.00	0.00	897.70	0
P3	Hivid® combo pack	3	0.00	2694.63	0.00	-	898.21	0.88

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.29 Prevalence and cost of individual medicine items containing zalcitabine as an active ingredient for the period P4 to P6 (2002)

Period	Zalcitabine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Hivid® combo pack	3	0.04	2793.66	0.07	1.75	931.22	27.75
P5	Hivid® combo pack	3	0.03	1645.40	0.03	1.00	548.47	172.67
	Hivid® 0.75mg	1	0.01	1224.70	0.02	2.00	1224.70	0
P6	Hivid® combo pack	7	0.05	2202.00	0.03	0.60	314.57	8.45
	Hivid® 0.75mg	4	0.03	4898.80	0.06	2.00	1224.70	0

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.1.6 Zidovudine

The usage patterns and cost of medicine items containing zidovudine as an active ingredient will be discussed under this paragraph.

5.4.6.1.6.1 Prevalence and cost of medicine items containing zidovudine as an active ingredient

It is evident from *tables 5.30, 5.31* and *5.32* that the ***total number of individual medicine items*** containing zidovudine as an active ingredient increased from 801 to 1 008 to 2 042 during the first, second and third study years respectively. This accounted for 13.62 per cent (n=5 880), 6.00 per cent (n=16 810) and 5.55 per cent (n=36 796) of the total number of NRTIs and 8.18 per cent (n=9 796), 2.86 per cent (n=35 271) and 2.00 per cent (n=101 938) of the total number of all ARV medicine items claimed through the database during the first, second and third years respectively.

The ***prevalence percentage*** of Retrovir® 250mg was the highest for periods P1 and P2. Thereafter, the prevalence percentage of Retrovir S® syrup was the highest for period P3 to P9. As shown in table 5.30 Retrovir® 250mg constituted 37.82 per cent of the total number (n=801) of medicine items containing zidovudine as an active ingredient during the first study year. Retrovir S® syrup constituted 32.33 per cent (n=801), 60.52 per cent (n=1 008), and 57.74 per cent (n=2 042) of the total number of medicine items containing zidovudine as an active ingredient during the first, second and third study years respectively *(refer to table 5.30, table 5.31 and table 5.32).*

It is apparent from *tables 5.30, 5.31* and *5.32* that the ***total cost of all individual medicine items*** containing zidovudine as an active ingredient augmented from R216 088.43 to R589 559.70 to R735 522.72 during the first, second and third study years respectively. This accounted for 9.35 per cent (n=R2 311 619.96), 12.37 per cent (n=R4 765 856.05) and 11.98 per cent (n=R6 142 071.28) of the total cost of all NRTIs, and 4.33 per cent (n=R4 990 784.29), 3.23 per cent (n=R18 235 075.75) and 2.12 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively.

Retrovir S® syrup constituted 21.48 per cent (n=R425 624.86), 63.16 per cent (n=R589 559.70) and 56.43 per cent (n=R735 522.72) respectively of the ***total cost of medicine items*** containing stavudine as an active ingredient during the first, second and third study years *(refer to table 5.30, table 5.31 and table 5.32).*

The ***cost-prevalence index*** for Retrovir® 100mg was higher than one for the first, second and third study years. The cost-prevalence index for Retrovir® 300mg was higher than one for P3 to P6. The cost-prevalence index for Retrovir S® syrup was higher than one for P5 to P9, and the cost-prevalence index for Retrovir® 250mg was higher than one for P7 to P9. A cost-prevalence index of higher than one indicates that therapy is relatively expensive *(refer to table 5.30, table 5.31 and table 5.32).*

It is perceptible from *table 5.32* that the ***average cost*** of Retrovir S® syrup increased from P7 (before implementation) to P8 (transition phase), and decreased from P8 (transition phase) to P9 (after single exit price). The same pattern can be seen for Retrovir® 100mg, Retrovir® 300mg and Retrovir® 20ml IV solution. The average cost of Retrovir® 250mg declined from P7 to P8 to P9.

The ***effect sizes (d-values)*** calculated between the average cost of Retrovir® 100mg for P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P7, P2 and P8, P2 and P9, P3 and P7, P3 and P8, P3 and P9, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8,

and P6 and P9 are of practical significant value. The effect sizes (d-values) calculated between the average cost of Retrovir® 20ml IV solution for P1 and P7, P2 and P7, P3 and P7, P4 and P7, P5 and P7, P5 and P8, and P6 and P7 are of practical significant value. The effect sizes (d-values) for Retrovir® 300mg between P2 and P4, P2 and P6, P2 and P7, P2 and P8, P2 and P9, P3 and P7, P3 and P8, P3 and P9, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value.

Table 5.30 Prevalence and cost of individual medicine items containing zidovudine as an active ingredient for the period P1 to P3 (2001)

Period	Zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Retrovir® 100mg	97	4.53	91131.10	5.30	1.17	939.50	217.71
	Retrovir® 250mg	145	6.77	84716.97	4.93	0.73	584.26	373.36
	Retrovir® S syrup	82	3.83	27656.75	1.61	0.42	337.28	240.83
	Retrovir® 20ml IV solution	17	0.79	6031.61	0.35	0.44	354.80	124.51
P2	Retrovir® 100mg	45	1.25	36487.53	2.26	1.81	810.83	281.74
	Retrovir® 250mg	94	2.60	56112.78	3.48	0.34	596.94	353.29
	Retrovir® 300mg	1	0.03	830.95	0.05	1.67	830.95	0
	Retrovir S® syrup	89	2.46	33650.24	2.09	0.85	378.09	294.45
	Retrovir® 20ml IV solution	23	0.64	8180.41	0.51	0.80	355.67	118.70
P3	Retrovir® 100mg	19	0.47	15517.26	0.94	2.00	816.70	239.57
	Retrovir® 250mg	64	1.59	19576.18	1.18	0.74	305.88	390.80
	Retrovir® 300mg	3	0.07	2990.72	0.18	2.25	996.91	0.01
	Retrovir S® syrup	88	2.18	30138.22	1.82	0.83	342.48	260.70
	Retrovir® 20ml IV solution	34	0.84	12604.14	0.76	0.91	370.71	123.50

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.31 Prevalence and cost of individual medicine items containing zidovudine as an active ingredient for the period P4 to P6 (2002)

Period	Zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Retrovir® 100mg	14	0.17	9370.68	0.25	1.47	669.33	337.86
	Retrovir® 250mg	87	1.05	28163.49	0.74	0.71	323.72	337.06
	Retrovir® 300mg	17	0.21	16111.78	0.42	2.00	947.75	125.11
	Retrovir S® syrup	146	1.77	64218.55	1.68	0.95	439.85	299.85
	Retrovir® 20ml IV solution	24	0.29	9909.47	0.26	0.90	412.90	138.70

Table 5.31 (continue) Prevalence and cost of individual medicine items containing zidovudine as an active ingredient for the period P4 to P6 (2002)

Period	Zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P5	Retrovir® 100mg	35	0.30	25072.60	0.46	1.53	716.36	253.14
	Retrovir® 250mg	53	0.45	28848.26	0.53	0.18	544.31	440.51
	Retrovir® 300mg	14	0.12	12902.40	0.24	2.00	921.60	154.98
	Retrovir S® syrup	179	1.52	99681.90	1.84	1.21	556.88	337.63
	Retrovir® 20ml IV solution	21	0.18	9572.60	0.18	1.00	455.84	142.12
P6	Retrovir® 100mg	42	0.28	27203.50	0.30	1.07	647.70	205.13
	Retrovir® 250mg	62	0.41	32351.20	0.36	0.88	521.79	306.24
	Retrovir® 300mg	10	0.07	9682.84	0.11	1.57	968.28	89.48
	Retrovir S® syrup	285	1.87	208441.63	2.32	1.24	731.37	525.68
	Retrovir® 20ml IV solution	19	0.13	8028.80	0.09	0.69	422.57	191.53

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.32 Prevalence and cost of individual medicine items containing zidovudine as an active ingredient for the period P7 to P9 (2004)

Period	Zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Retrovir® 100mg	50	0.33	16686.09	0.35	1.06	333.72	150.41
	Retrovir® 250mg	26	0.17	10905.52	0.23	1.35	419.44	44.52
	Retrovir® 300mg	25	0.17	9183.94	0.19	1.12	367.36	107.81
	Retrovir S® syrup	186	1.24	59868.60	1.25	1.01	321.87	169.76
	Retrovir® 20ml IV solution	21	0.14	5116.59	0.11	0.79	243.65	118.81
P8	Retrovir® 100mg	123	0.32	45606.57	0.32	1.00	370.79	166.81
	Retrovir® 250mg	54	0.14	21525.12	0.15	1.07	398.61	91.30
	Retrovir® 300mg	95	0.25	42279.74	0.30	1.20	445.05	93.19
	Retrovir S® syrup	472	1.23	181695.80	1.28	1.04	384.95	247.04
	Retrovir® 20ml IV solution	29	0.08	9290.59	0.07	0.88	320.37	105.40
P9	Retrovir® 100mg	155	0.32	52718.29	0.34	1.06	340.12	147.79
	Retrovir® 250mg	53	0.11	20417.83	0.13	1.18	385.24	74.49
	Retrovir® 300mg	161	0.33	66126.11	0.42	1.27	410.72	102.74
	Retrovir S® syrup	521	1.08	173513.29	1.10	1.02	333.04	206.85
	Retrovir® 20ml IV solution	49	0.10	13875.06	0.09	0.90	283.16	117.40
	Aspen zidovudine®	22	0.05	6713.58	0.04	0.80	305.16	241.72

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.2 NNRTIs

The utilisation patterns and cost of medicine items containing efavirenz and nevirapine as active ingredient will be discussed in this section.

5.4.6.2.1 Efavirenz

The usage patterns and cost of medicine items containing efavirenz as an active ingredient will be discussed under this paragraph.

5.4.6.2.1.1 Prevalence and cost of medicine items containing efavirenz as an active ingredient

The ***total number of individual medicine items*** containing efavirenz as an active ingredient increased from 1 172 to 7 176 to 25 061 during the first, second and third study years respectively. This class of drugs accounted for 76.35 per cent (n=1 535), 68.99 per cent (n=10 402) and 70.51 per cent (n=35 544) of the total number of all NRTIs as well as 11.96 per cent (n=9 796), 20.35 per cent (n=35 271) and 24.58 per cent (n=101 938) of the total number of all ARV medicine items claimed during the first, second and third study years respectively *(refer to table 5.33, table 5.34 and table 5.35)*. As can be seen, there was an increase in the number of medicine items containing efavirenz as an active ingredient from the first to the second study year, and from the second to the third study year, as well as an increase towards other NRTIs and ARV medicine items.

Stocrin® 200mg constituted 100 per cent (n=1 172) of the ***total number of medicine items*** containing efavirenz as an active ingredient during the first and second study years, Stocrin® 200mg constituted 99.32 per cent (n=7 176) of the total number of medicine items containing efavirenz as an active ingredient during the second study year. During the third study year, Stocrin® 200mg constituted 79.21 per cent (n=25 061). The prevalence percentages of Stocrin® 200mg declined over the three years, because different products of efavirenz became available on the market during the second year, but especially during the third study year *(refer to table 5.33, table 5.34 and table 5.35).*

The ***total cost of medicine items*** containing efavirenz as an active ingredient inclined from R665 230.92 to R4 167 275.31 to R9 339 066.42. This accounted for 75.80 per cent (n=R877 618.58), 71.4 per cent (n=R5 839 319.00), and 64.04 per cent (n=R14 583 569.11) of the total cost of all NNRTIs, and 13.33 per cent (n=R4 990 784.29), 22.85 per cent (n=R18 235 075.75), and 26.90 per cent (n=R34 714 483.64) of

the total cost of all ARV medicine items claimed during the first, second and third study years respectively *(refer to table 5.33, table 5.34 and table 5.35).*

The ***cost-prevalence index*** of Stocrin® 200mg fluctuated for the three study years at higher than one, indicating that the therapy was relatively expensive. On the other hand, Stocrin® 50mg and Stocrin® 600 had a cost-prevalence index of lower than one for the three study years, indicating that therapy was relatively inexpensive *(refer to table 5.33, table 5.34 and table 5.35).*

It is perceptible from *table 5.33*, *table 5.34* and *table 5.35* that the ***average cost*** of Stocrin® 200mg decreased in the first study year and slightly increased in the second study year. In the third study year, the average cost of Stocrin® 200mg increased for P7 (before implementation) to P8 (transition phase), and decreased for P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the pricing regulations implemented in 2004, can be seen.

The ***effect sizes (d-values)*** calculated between the average cost of Stocrin® 200mg forP1 and P7, P1 and P8, P1 and P9, P2 and P7, P2 and P8, P2 and P9, P3 and P7, P3 and P8, P3 and P9, P4 and P6, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value. The effect size (d-value) calculated between the average cost of Stocrin® 50mg for P4 and P6 is of practical significant value ($d > 0.8$).

Table 5.33 Prevalence and cost of individual medicine items containing efavirenz as an active ingredient for the period P1 to P3 (2001)

Period	Efavirenz	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Stocrin® 200mg	41	1.91	46718.29	2.72	1.42	1139.47	786.74
P2	Stocrin® 200mg	402	11.12	219006.48	13.58	1.22	544.79	43.42
P3	Stocrin® 200mg	729	18.05	399506.15	24.77	1.37	548.02	43.14

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.34 Prevalence and cost of individual medicine items containing efavirenz as an active ingredient for the period P4 to P6 (2002)

Period	Efavirenz	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Stocrin® 50mg	5	0.06	256.34	0.01	0.17	51.27	5.05
	Stocrin® 200mg	1650	19.99	877648.34	22.94	1.15	531.91	112.09
P5	Stocrin® 50mg	19	0.16	1475.76	0.03	0.19	77.67	33.97
	Stocrin® 200mg	2394	20.27	1351208.73	24.90	1.23	564.42	96.01
P6	Stocrin® 50mg	25	0.16	2156.07	0.02	0.13	86.24	40.39
	Stocrin® 200mg	3083	13.70	1934530.07	21.54	1.57	627.48	117.99

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.35 Prevalence and cost of individual medicine items containing efavirenz as an active ingredient for the period P7 to P9 (2004)

Period	Efavirenz	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Stocrin® 50mg	32	0.21	1997.71	0.04	0.19	62.43	40.67
	Stocrin® 200mg	3473	23.11	1239788.66	25.95	1.12	356.98	141.70
P8	Stocrin® 50mg	94	0.24	7171.18	0.05	0.21	76.29	53.25
	Stocrin® 200mg	8808	22.89	3732190.91	26.27	1.15	423.73	76.94
	Stocrin® 600	413	1.07	106628.08	0.75	0.70	258.18	51.60
P9	Stocrin® 50mg	154	0.32	12101.38	0.08	0.25	78.58	62.15
	Stocrin® 200mg	7570	15.63	3018777.01	19.20	1.23	398.78	85.11
	Stocrin® 600	4517	9.33	1220411.49	7.76	0.83	270.18	67.44

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.2.2 Nevirapine

The usage patterns and cost of medicine items containing nevirapine as an active ingredient will be discussed under this paragraph.

5.4.6.2.2.1 Prevalence and cost of medicine items containing nevirapine as an active ingredient

The ***total number of medicine items*** containing nevirapine as an active ingredient increased from 363 to 3 226 to 10 483 during the first, second and third study years respectively. This accounted for 23.65 per cent (n=1 535), 31.01 per cent (n=10 402) and 29.49 per cent (n=35 544) of the total number of NNRTIs

and 3.71 per cent (n=9 796), 9.15 per cent (n=35 271) and 10.28 per cent (n=101 938) of the total number of all ARV medicine items claimed from the database during the first, second and third study years respectively *(refer to table 5.36, table 5.37 and table 5.38).*

The ***prevalence percentage*** of Viramune® 200mg was the highest for each period, from P1 to P9. As shown in table 5.36, table 5.37 and table 5.38 Viramune® 200mg constituted 90.91 per cent (n=363), 88.28 per cent (n=3 226) and 89.44 per cent (n=10 483) of the total number of medicine items containing nevirapine as an active ingredient during the first, second and third study years respectively. The prevalence percentages of Viramune® 200mg remained stable over the three study years *(refer to table 5.36, table 5.37 and table 5.38).*

It is apparent from *tables 5.36*, *5.37* and *5.38* that the ***total cost of all medicine items*** containing nevirapine as an active ingredient augmented from R212 387.66 to R1 672 043.69 to R5 244 502.69 during the first, second and third study years respectively. This accounted for 24.20 per cent (n=R877 618.58), 28.63 per cent (n=R5 839 319.00) and 35.96 per cent (n=R14 583 569.11) of the total cost of all NNRTIs, and 4.26 per cent (n=R4 990 784.29), 9.17 per cent (n=R18 235 075.75) and 15.11 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively.

It is perceptible from *table 5.36*, *table 5.37* and *table 5.38* that Viramune® 200mg accounted for 93.21 per cent (n=R212 387.66), 88.28 per cent (n=R1 672 043.69) and 89.81 per cent (n=R5 244 502.69) of the total cost of medicine items containing nevirapine as an active ingredient during the first, second and third study years respectively. The ***cost-prevalence index*** was higher than one for Viramune® 200mg for P2, P3, P4, P5, P7, and P8. The cost-prevalence index was higher than one for Viramune® suspension for P3, P4, P5 and P8, and also for Nevran® for P8. A cost-prevalence higher than one indicates that therapy is relatively expensive *(refer to section 4.6.2.4)*.

From *table 5.36*, *table 5.37* and *table 5.38* can be seen that the ***average cost*** of Viramune® 200mg remained stable for the first study year, increased very marginally in the second study year, and in the third study year, it rose from P7 (before implementation) to P8 (transition phase), and decreased from P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen. The average cost of Viramune® suspension was unpredictable for the first study year, remained fairly stable for the second study year, and rose in the third study year.

The ***effect sizes (d-values)*** calculated between the average cost of Viramune® 200mg for P1 and P4, P1 and P5, P1 and P7, P2 and P4, P2 and P5, P2 and P7, P3 and P4, and P3 and P7 are of practical significant value. The effect sizes (d-values) calculated between the average cost of Viramune® suspension for P1 and P2, P1 and P4, P1 and P9, P2 and P3, P2 and P4, P2 and P5, P2 and P6, P2 and P8, P2 and P9, P4 and P7, and P7 and P9 are of practical significant value.

Table 5.36 Prevalence and cost of individual medicine items containing nevirapine as an active ingredient for the period P1 to P3 (2001)

Period	Nevirapine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Viramune® 200mg	60	2.80	35983.91	2.09	0.75	599.73	57.62
	Viramune® suspension	5	0.23	1377.34	0.08	0.35	275.47	152.08
P2	Viramune® 200mg	128	3.54	76523.82	4.74	1.34	597.84	88.24
	Viramune® suspension	3	0.08	357.15	0.02	0.25	119.05	194.35
P3	Viramune® 200mg	142	3.52	85467.51	5.15	1.46	601.88	79.66
	Viramune® suspension	25	0.62	12677.93	0.76	1.23	507.12	458.19

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.37 Prevalence and cost of individual medicine items containing nevirapine as an active ingredient for the period P4 to P6 (2002)

Period	Nevirapine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Viramun®e 200mg	562	6.81	276482.01	7.23	1.06	491.96	81.28
	Viramune® suspension	79	0.96	43261.65	1.13	1.18	547.62	286.95
P5	Viramune® 200mg	958	8.11	480220.13	8.85	1.09	501.27	109.10
	Viramune® suspension	128	1.08	64553.14	1.19	1.10	504.32	348.94
P6	Viramune® 200mg	1328	8.73	719451.05	8.01	0.92	541.76	95.35
	Viramune® suspension	171	1.12	88075.71	0.98	0.88	515.06	334.33

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.38 Prevalence and cost of individual medicine items containing nevirapine as an active ingredient for the period P7 to P9 (2004)

Period	Nevirapine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Viramune® 200mg	1566	10.42	728846.57	15.25	1.46	465.42	125.40
	Viramune® suspension	147	0.98	37696.36	0.79	0.81	256.44	346.91
P8	Viramune® 200mg	3754	9.75	1978424.93	13.92	1.43	527.02	134.38
	Viramune® suspension	353	0.92	172440.88	1.21	1.32	488.50	416.22
	Nevran®	3	0.01	775.92	0.01	1.00	258.64	0
P9	Viramune® 200mg	4056	8.38	2002635.12	5.77	0.69	493.75	148.98
	Viramune® suspension	454	0.94	283391.75	0.82	0.87	624.21	324.89
	Nevran®	7	0.02	1779.97	0.01	0.50	254.28	27.02
	Aspen nevirapine®	143	0.30	38511.19	0.11	0.37	269.31	39.19

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.3 PIs

The utilisation patterns and cost of medicine items containing indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir as active ingredient will be discussed in this section.

5.4.6.3.1 Indinavir

The usage patterns and cost of medicine items containing indinavir as an active ingredient will be discussed under this paragraph.

5.4.6.3.1.1 Prevalence and cost of medicine items containing indinavir as an active ingredient

The ***total number of medicine items*** containing indinavir as an active ingredient increased from 232 to 826 to 1 643 during the first, second and third study years respectively. Though there was an increase in the actual number of drugs containing indinavir as an active ingredient, the prevalence percentage decreased from the first to the second to the third study years and accounted for 65.35 per cent (n=355), 45.11 per cent (n=1 831) and 38.37 per cent (n=4 282) of the total number of PIs, and 2.37 per cent (n=9 796), 2.34 per cent (n=35 271) and 1.61 per cent (n=101 938) of the total number of ARV medicine items respectively *(refer to table 5.39, table 5.40 and table 5.41).*

As can be seen from *table 5.39*, *table 5.40* and *table 5.41*, Crixivan® 400mg constituted 97.84 per cent (n=232), 99.88 per cent (n=826) and 99.33 per cent (n=1 643) of the ***total number of medicine items*** containing indinavir as an active ingredient during the first, second and third study years respectively. Crixivan® 200mg was also claimed during P1, P6, P7, P8, and P9.

The ***total cost*** of all individual medicine items containing indinavir as an active ingredient accounted for 69.62 per cent (n=R389 044.58), 43.62 per cent (n=R1 216 246.26) and 37.43 per cent (n=R2 088 757.70) of the total cost of all PIs claimed, and 5.43 per cent (n=R4 990 784.29), 2.91 per cent (n=R18 235 075.75) and 2.25 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively. The cost-prevalence index for both Crixivan® 400mg and Crixivan® 200mg was higher than one for the three study years, except for Crixivan® 200mg in P9 *(refer to table 5.39, table 5.40 and table 5.41).*

It is apparent from *table 5.39*, *table 5.40* and *table 5.41* that the ***average cost*** of Crixivan® 400mg decreased in the first study year, increased in the second study year, and in the third study year, the average cost inclined from P7 (before implementation) to P8 (transition phase), and declined to P9 (after single exit price). The average cost of Crixivan® 200mg decreased from P6 to P7 and decreased from P7 (before implementation) to P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen in the lower average costs of Crixivan® 400mg and Crixivan® 200mg in the period P9.

The ***effect sizes (d-values)*** calculated between the average cost of Crixivan® 400mg for P1 and P2, P1 and P3, P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P7, P3 and P6, P3 and P7, P4 and P6, P5 and P7, P6 and P7, P6 and P8, P6 and P9, and P8 and P9, as well as for Crixiva®n 200mg for P1 and P7, P1 and P8, P1 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value.

Table 5.39 Prevalence and cost of individual medicine items containing indinavir as an active ingredient for the period P1 to P3 (2001)

Period	Indinavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Crixivan® 200mg	5	0.23	7440.71	0.43	1.87	1488.14	1176.56
	Crixivan® 400mg	84	3.92	183700.37	10.69	2.73	2186.91	1309.81
P2	Crixivan® 400mg	80	2.21	45246.35	2.81	1.27	565.58	122.91
P3	Crixivan® 400mg	63	1.56	34476.93	2.01	1.29	547.25	147.59

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.40 Prevalence and cost of individual medicine items containing indinavir as an active ingredient for the period P4 to P6 (2002)

Period	Indinavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Crixivan® 400mg	153	1.85	76823.08	2.01	1.09	502.11	181.74
P5	Crixivan® 400mg	243	2.06	147618.21	2.72	1.32	607.48	202.69
P6	Crixivan® 200mg	1	0.01	803.40	0.01	1.00	803.40	0
	Crixivan® 400mg	429	2.82	305333.25	3.40	1.21	711.73	193.76

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.41 Prevalence and cost of individual medicine items containing indinavir as an active ingredient for the period P7 to P9 (2004)

Period	Indinavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Crixivan® 200mg	5	0.03	1276.19	0.03	1.00	255.24	194.76
	Crixivan® 400mg	186	1.24	76075.14	1.59	1.28	409.01	148.01
P8	Crixivan® 200mg	3	0.01	739.73	0.01	1.00	246.58	9.67
	Crixivan® 400mg	739	1.92	368918.58	2.60	1.35	499.21	108.82
P9	Crixivan® 200mg	3	0.01	484.06	0.00	0.00	161.35	93.01
	Crixivan® 400mg	707	1.46	334334.27	2.13	1.46	472.89	128.75

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.3.2 Nelfinavir

The usage patterns and cost of medicine items containing nelfinavir as an active ingredient will be discussed under this paragraph.

5.4.6.3.2.1 Prevalence and cost of medicine items containing nelfinavir as an active ingredient

The ***total number of medicine items*** containing nelfinavir as an active ingredient increased from 6 to 92 to 231 during the first, second and third study years respectively. Though there was an increase in the

actual number of drugs containing nelfinavir as an active ingredient, the prevalence percentage decreased from the first to the second to the third study years and accounted for 1.69 per cent (n=355), 5.02 per cent (n=1 831) and 5.39 per cent (n=4 282) of the total number of PIs, and 0.06 per cent (n=9 796), 0.26 per cent (n=3 5271) and 0.23 per cent (n=101 938) of the total number of ARV medicine items respectively *(refer to table 5.42, table 5.43 and table 5.44).*

As can be seen from *tables 5.42*, *5.43* and *5.44* Vira-cept® constituted 100 per cent (n=6), 95.65 per cent (n=92) and 81.39 per cent (n=231) of the ***total number of medicine items*** containing nelfinavir as an active ingredient during the first, second and third study years respectively. Vira-cept® suspension was also claimed during P6, P7, P8, and P9.

The ***total cost of all individual medicine items*** containing nelfinavir as an active ingredient accounted for 4.36 per cent (n=R389 044.58), 22.10 per cent (n=R1 216 246.26) and 9.91 per cent (n=R2 088 757.70) of the total cost of all PIs claimed, and 0.34 per cent (n=R4 990 784.29), 1.47 per cent (n=R18 235 075.75) and 0.60 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively. The ***cost-prevalence index*** for both Vira-cept® and Vira-cept® suspension was higher than one for the three study years, thus both are relatively expensive *(refer to table 5.42, table 5.43 and table 5.44).*

It is apparent from *tables 5.42*, *5.43* and *5.44* that the ***average cost*** of Vira-cept® decreased in the first study year, increased in the second study year, and in the third study year, the average cost inclined from P7 (before implementation) to P8 (transition phase), and declined to P9 (after single exit price). The average cost of Vira-cept® suspension increased from P6 to P9. Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen in the lower average costs of Vira-cept in the period P9, but not for Vira-cept® suspension.

The ***effect sizes (d-values)*** calculated between the average cost of Vira-cept® for P1 and P4, P1 and P7, P1 and P8, P1 and P9, P2 and P4, P2 and P5, P2 and P6, P2 and P7, P2 and P8, P2 and P9, P4 and P6, P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value. The effect sizes (d-values) calculated between the average cost of Vira-cept® suspension for P6 and P9, and P7 and P9 are of practical significant value ($d > 0.8$).

Table 5.42 Prevalence and cost of individual medicine items containing nelfinavir as an active ingredient for the period P1 to P3 (2001)

Period	Nelfinavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Vira-cept®	5	0.23	16929.00	0.99	4.30	3385.80	0
P2	Vira-cept®	1	0.03	25.08	0.00	0.00	25.08	0
P3	Vira-cept®	-	-	-	-	-	-	

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.43 Prevalence and cost of individual medicine items containing nelfinavir as an active ingredient for the period P4 to P6 (2002)

Period	Nelfinavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Vira-cept®	3	0.04	4447.11	0.12	3.00	1482.37	20.79
P5	Vira-cept®	20	0.17	48578.91	0.90	5.29	2428.95	1441.87
P6	Vira-cept®	65	0.43	212351.15	2.36	5.49	3266.94	1495.52
	Vira-cept® suspension	4	0.03	3407.80	0.04	1.33	851.95	340.58

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.44 Prevalence and cost of individual medicine items containing nelfinavir as an active ingredient for the period P7 to P9 (2004)

Period	Nelfinavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Vira-cept®	30	0.20	20778.89	0.44	2.20	692.63	262.95
	Vira-cept® suspension	1	0.01	825.39	0.02	2.00	825.39	0
P8	Vira-cept®	86	0.22	67083.14	0.47	2.14	780.04	255.51
	Vira-cept® suspension	17	0.04	24540.54	0.17	4.25	1443.56	810.91
P9	Vira-cept®	72	0.15	54875.33	0.35	2.33	762.16	271.26
	Vira-cept® suspension	25	0.05	38930.59	0.25	5.00	1557.22	703.97

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.3.3 Ritonavir

The usage patterns and cost of medicine items containing ritonavir as an active ingredient will be discussed under this paragraph.

5.4.6.3.3.1 Prevalence and cost of medicine items containing ritonavir as an active ingredient

The ***total number of medicine items*** containing ritonavir as an active ingredient increased from 108 to 1 831 to 4 282 during the first, second and third study years respectively. This accounted for 30.42 per cent (n=355), 38.23 per cent (n=1 831), and 34.52 per cent (n=4 282) of the total number of PIs and 1.10 per cent (n=9 796), 1.98 per cent (n=35 271), and 1.45 per cent (n=101 938) of the total number of all ARV medicine items claimed from the database during the first, second and third study years respectively *(refer to table 5.45, table 5.46 and table 5.47).*

As shown in *table 5.45*, *table 5.46* and *table 5.47*, Norvir® 100mg constituted 75.93 per cent (n=108), 79.71 per cent (n=700) and 84.37 per cent (n=1 478) of the ***total number of medicine items*** containing ritonavir as an active ingredient during the first, second and third study years respectively. Norvir® solution constituted 24.07 per cent (n=108), 20.29 per cent (n=700) and 15.63 per cent (n=1 478) of the total number of medicine items containing ritonavir as an active ingredient during the first, second and third study years respectively.

It is apparent from *table 5.45*, *table 5.46* and *table 5.47* that the ***total cost*** of all medicine items containing ritonavir as an active ingredient augmented from R85 785.51 to R156 837.97 to R140 794.93 during the first, second and third study years respectively. This accounted for 22.05 per cent (n=R389 044.58), 12.90 per cent (n=R1 216 246.26) and 6.74 per cent (n=R2 088 757.70) of the total cost of all PIs, and 1.72 per cent (n=R4 990 784.29), 0.86 per cent (n=R18 235 075.75) and 0.41 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively.

Norvir® 100mg accounted for 66.45 per cent (n=R85 785.51), 71.53 per cent (n=R156 837.97) and 71.25 per cent (n=R140 794.93) respectively of the ***total cost*** of medicine item containing ritonavir as an active ingredient during the first, second and third study years. Norvir® solution constituted 33.55 per cent (n=R85 785.51), 28.47 per cent (n=R156 837.97) and 28.75 per cent (n=R140 794.93) respectively of the

total cost of medicine items containing ritonavir as an active ingredient during the first, second and third study years *(refer to table 5.45, table 5.46 and table 5.47).*

The ***cost-prevalence indices*** were higher than one for Norvir® 100mg for P2 and P3, and for Norvir® solution for P1, P2, P3, and P4. A cost-prevalence index of higher than one indicates that therapy is relatively expensive *(refer to section 4.6.2.4) (refer to table 5.45, table 5.46 and table 5.47).*

It is perceptible from *table 5.45*, *table 5.46* and *table 5.47* that the ***average cost*** of Norvir® 100mg and Norvir® solution decreased gradually over the three study years.

The ***effect sizes (d-values)*** calculated between the average cost of Norvir® 100mg for P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P4, P2 and P5, P2 and P6, P2 and P7, P2 and P8, P2 and P9, P3 and P4, P3 and P5, P3 and P6, P3 and P7, P3 and P8, P3 and P9, P4 and P8, P4 and P9, P6 and P8, and P6 and P9 are of practical significant value ($d > 0.8$). The effect sizes (d-values) calculated between the average cost of Norvir® solution for P1 and P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P4, P2 and P5, P2 and P6, P2 and P7, P2 and P8, P2 and P9, P4 and P6, P4 and P7, P4 and P8, and P4 and P9 are also of practical significant value ($d > 0.8$).

Table 5.45 Prevalence and cost of individual medicine items containing ritonavir as an active ingredient for the period P1 to P3 (2001)

Period	Ritonavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Norvir® 100mg	7	0.33	4324.17	0.25	0.76	617.74	91.27
	Norvir® solution	9	0.42	14093.30	0.82	1.95	1565.92	1077.34
P2	Norvir® 100mg	43	1.19	33187.85	2.06	1.73	771.81	415.63
	Norvir® solution	6	0.17	6868.15	0.43	2.53	1144.69	927.26
P3	Norvir® 100mg	32	0.79	19492.17	1.18	1.49	609.13	210.98
	Norvir® solution	11	0.27	7819.87	0.47	1.74	710.90	768.70

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.46 Prevalence and cost of individual medicine items containing ritonavir as an active ingredient for the period P4 to P6 (2002)

Period	Ritonavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Norvir® 100mg	105	1.27	37701.70	0.99	0.78	359.06	297.98
	Norvir® solution	16	0.19	7694.25	0.20	1.05	480.89	186.06
P5	Norvir® 100mg	118	1.00	19441.35	0.36	0.36	164.76	138.06
	Norvir® solution	43	0.36	14437.74	0.27	0.75	335.76	346.07
P6	Norvir® 100mg	335	2.20	55046.93	0.61	0.28	164.32	102.14
	Norvir® solution	83	0.55	22516.00	0.25	0.46	271.28	226.55

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.47 Prevalence and cost of individual medicine items containing ritonavir as an active ingredient for the period P7 to P9 (2004)

Period	Ritonavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Norvir® 100mg	164	1.09	20514.67	0.43	0.40	125.09	110.80
	Norvir® solution	55	0.37	9905.44	0.21	0.57	180.10	57.58
P8	Norvir® 100mg	511	1.33	39788.02	0.28	0.21	77.86	95.66
	Norvir® solution	93	0.24	16782.65	0.12	0.50	180.46	57.75
P9	Norvir® 100mg	572	1.18	40017.31	0.26	0.22	69.96	87.33
	Norvir® solution	83	0.17	13786.84	0.09	0.53	166.11	73.85

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.3.4 Saquinavir mesylate

The usage patterns and cost of medicine items containing saquinavir mesylate as an active ingredient will be discussed under this paragraph.

5.4.6.3.4.1 Prevalence and cost of medicine items containing saquinavir mesylate as an active ingredient

The ***total number of medicine items*** containing saquinavir mesylate as an active ingredient increased from 9 to 213 to 930 during the first, second and third study years respectively. This class of drugs

accounted for 2.54 per cent (n=355), 11.63 per cent (n=1 831) and 21.72 per cent (n=4 282) of the total number of PIs, and 0.09 per cent (n=9 796), 0.60 per cent (n=35 271) and 0.91 per cent (n=101 938) of the total number of ARV medicine items respectively *(refer to table 5.48, table 5.49 and table 5.50).*

As can be seen from *table 5.48*, *table 5.49* and *table 5.50*, Forto-vase® 400mg constituted 44.44 per cent (n=9), 96.71 per cent (n=213) and 60.65 per cent (n=930) of the ***total number of medicine items*** containing saquinavir mesylate as an active ingredient during the first, second and third study years respectively.

The ***total cost*** of all individual medicine items containing saquinavir mesylate as an active ingredient accounted for 3.97 per cent (n=R389 044.58), 21.38 per cent (n=R1 216 246.26) and 45.92 per cent (n=R2 088 757.70) of the total cost of all PIs claimed, and 0.31 per cent (n=R4 990 784.29), 1.43 per cent (n=R18 235 075.75) and 2.76 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively. The ***cost-prevalence indices*** for both Forto-vase® and Invi-rase® 200mg were higher than one for the three study years, indicating that these medicine items utilised are relatively expensive *(refer to table 5.48, table 5.49 and table 5.50).*

It is apparent from *table 5.48*, *table 5.49* and *table 5.50* that the ***average cost*** of Forto-vase® increased during the three study periods. The average cost of Invi-rase® 200mg decreased during the second study year and increased from P7 (before implementation) to P8 (transition phase) and decreased from P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen in the lower average cost of Invi-rase® 200mg in the period P9.

The ***effect sizes (d-values)*** calculated between the average cost of Forto-vase® for P2 and P3, P2 and P6, P2 and P8, P2 and P9, P3 and P6, P4 and P6, P4 and P8, P4 and P9, and P6 and P7, as well as for Invi-rase® 200mg for P1 and P7, P1 and P8, P1 and P9, P5 and P6, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9 are of practical significant value.

Table 5.48 Prevalence and cost of individual medicine items containing saquinavir mesylate as an active ingredient for the period P1 to P3 (2001)

Period	Saquinavir mesylate	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Invi-rase® 200mg	5	0.23	12624.93	0.74	3.22	2524.99	1389.52
P2	Forto-vase®	3	0.08	1873.72	0.12	1.50	624.57	299.57
P3	Forto-vase®	1	0.03	941.98	0.06	2.00	941.98	0

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.49 Prevalence and cost of individual medicine items containing saquinavir mesylate as an active ingredient for the period P4 to P6 (2002)

Period	Saquinavir mesylate	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Forto-vase®	2	0.02	1542.10	0.04	2.00	771.05	0
P5	Invi-rase® 200mg	3	0.03	8204.31	0.15	5.00	2734.77	0
	Forto-vase®	18	0.15	16367.20	0.30	2.00	909.29	538.13
P6	Invi-rase® 200mg	4	0.03	6444.93	0.07	2.33	1611.23	21.14
	Forto-vase®	186	1.22	227486.84	2.53	2.07	1223.05	256.80

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.50 Prevalence and cost of individual medicine items containing saquinavir mesylate as an active ingredient for the period P7 to P9 (2004)

Period	Saquinavir mesylate	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Invi-rase® 200mg	46	0.31	36492.81	0.76	2.45	793.32	283.77
	Forto-vase®	63	0.42	51074.59	1.07	2.55	810.71	452.42
P8	Invi-rase® 200mg	130	0.34	106974.31	0.75	2.21	822.88	249.79
	Forto-vase®	252	0.66	301667.85	2.12	3.21	1197.09	484.33
P9	Invi-rase® 200mg	190	0.39	136054.03	0.87	2.23	716.07	243.42
	Forto-vase®	249	0.51	326837.33	2.08	4.08	1312.60	478.54

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.4 Others

The usage patterns and cost of medicine items containing the combination of lamivudine/zidovudine and the combination of lopinavir/ritonavir as an active ingredient will be discussed in this section.

5.4.6.4.1 Lamivudine/zidovudine

The usage patterns and cost of medicine items containing the combination of lamivudine/zidovudine as an active ingredient will be discussed under this paragraph.

5.4.6.4.1.1 Prevalence and cost of medicine items containing lamivudine/zidovudine as an active ingredient

The ***total number of individual medicine items*** containing lamivudine/zidovudine as an active ingredient augmented from 2 026 to 6 209 to 23 207. This accounted for 100 per cent (n=2 026), 99.69 per cent (n=6 228) and 91.67 (n=25 316) of the total number of OTHER ARV medicine items (category IV) *(refer to section 5.1.1)*, and 20.68 per cent (n=9 796), 17.60 per cent (n=35 271) and 22.77 per cent (n=101 938) of the total number of ARV medicine items respectively *(refer to table 5.51, table 5.52 and table 5.53)*.

As can be seen from *table 5.51*, *table 5.52* and *table 5.53*, Combivir® constituted 99.31 per cent (n=2 026), 99.81 per cent (n=6 209) and 97.55 per cent (n=23 207) of the ***total number of medicine items*** containing lamivudine/zidovudine as an active ingredient during the first, second and third study years respectively. Retrovir/3TC® was also claimed during the three study years, Duovir® during P7, P8, and P9, and Aspen lamzid® was only claimed during P9.

The ***total cost*** of all individual medicine items containing lamivudine/zidovudine as an active ingredient accounted for 100 per cent (n=R1 412 501.17), 99.80 per cent (n=R6 401 032.79) and 93.41 per cent (n=R11 116 257.30) of the total cost of OTHER ARV medicine items (category IV) *(refer to section 5.1.1)*, and 28.30 per cent (n=R4 990 784.29), 35.10 per cent (n=R18 235 075.75) and 32.02 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the first, second and third study years respectively. The ***cost-prevalence index*** of Combivir® is higher than one for the three study years, except for P1. The cost-prevalence indices of Duovir® and Aspen lamzid® are also higher than one, indicating that these medicine items utilised are very expensive *(refer to table 5.51, table 5.52 and table 5.53)*.

It is apparent from *table 5.51*, *table 5.52* and *table 5.53* that the ***average cost*** of Combivir® fluctuated from R705.70±824.42 to R617.44±805.72 to R829.90±835.36 during the first study year, fluctuated from

R979.43±464.31 to R907.48±511.66 to R1 129.21±418.48 during the second study year, and in the third study year, increased from P7 (before implementation) to P8 (transition phase), and decreased from P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen in the lower average costs of Combivir® in the period P9.

The ***effect sizes (d-values)*** calculated between the average cost of Combivir® for P4 and P7, P4 and P8, P4 and P9, P5 and P7, P5 and P8, P5 and P9, P6 and P7, P6 and P8, and P6 and P9, as well as for Retrovir/3TC® for P1 and P5, P1 and P8, P1 and P9, P2 and P5, P2 and P8, P2 and P9, P3 and P5, P3 and P8, P3 and P9, P4 and P5, P4 and P7, P4 and P8, P4 and P8, and P6 and P8 are of practical significant value.

Table 5.51 Prevalence and cost of individual medicine items containing lamivudine/zidovudine as an active ingredient for the period P1 to P3 (2001)

Period	Lamivudine/ zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P1	Combivir®	486	22.68	342972.35	19.95	0.88	705.70	824.42
	Retrovir/3TC®	2	0.09	584.36	0.03	0.33	292.18	0
P2	Combivir®	946	26.18	584094.73	36.21	1.38	617.44	805.72
	Retrovir/3TC®	4	0.11	1168.72	0.07	0.64	292.18	0
P3	Combivir®	580	14.36	481343.57	29.02	2.02	829.90	835.36
	Retrovir/3TC®	8	0.20	2337.44	0.14	0.70	292.18	0

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.52 Prevalence and cost of individual medicine items containing lamivudine/zidovudine as an active ingredient for the period P4 to P6 (2002)

Period	Lamivudine/ zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	Combivir®	1261	15.28	1235057.18	32.28	2.11	979.43	464.31
	Retrovir/3TC®	6	0.07	1476.22	0.04	0.57	246.04	113.02
P5	Combivir®	1850	15.66	1678842.07	30.94	1.98	907.48	511.66
	Retrovir/3TC®	3	0.03	322.84	0.01	0.33	107.61	159.84
P6	Combivir®	3086	20.29	3484734.79	38.79	1.91	1129.21	418.48
	Retrovir/3TC®	3	0.02	599.69	0.01	0.50	199.90	159.84

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.53 Prevalence and cost of individual medicine items containing lamivudine/zidovudine as an active ingredient for the period P7 to P9 (2004)

Period	Lamivudine/ zidovudine	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Combivir®	3334	22.18	1496281.04	31.31	1.41	448.80	79.26
	Retrovir/3TC®	3	0.02	218.55	0.01	0.50	72.85	0
	Duovir®	26	0.17	9671.92	0.20	1.18	372.00	89.50
P8	Combivir®	9195	23.89	4603974.17	32.40	1.36	500.70	83.31
	Retrovir/3TC®	9	0.02	646.81	0.01	0.50	71.87	26.48
	Duovir®	54	0.14	19731.53	0.14	1.00	365.40	120.64
P9	Combivir®	10110	20.88	4792274.17	30.47	1.46	474.01	91.85
	Retrovir/3TC®	9	0.02	1165.48	0.01	0.50	129.50	189.14
	Duovir®	38	0.08	14031.37	0.09	1.13	369.25	34.77
	Aspen lamzid®	429	0.89	178262.26	1.13	1.27	415.53	57.37

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.6.4.2 Lopinavir/ritonavir

The usage patterns and cost of medicine items containing the combination of lopinavir/ritonavir as an active ingredient will be discussed under this paragraph.

5.4.6.4.2.1 Prevalence and cost of medicine items containing lopinavir/ritonavir as an active ingredient

There were ***no individual medicine items*** containing lopinavir/ritonavir for the period P1 to P3 and periods P4 and P5. The ***total number of individual medicine items*** containing lopinavir/ritonavir as an active ingredient augmented from 19 to 2 109 during the second and third study years respectively. Kaletra® capsules and Kaletra® syrup were claimed through the database in the second and third study years (from P6 to P9). Kaletra® capsules was first claimed in P6, and for the second study year, it constituted 94.44 per cent of the total number (n=18) of individual medicine items claimed, containing lopinavir/ritonavir as an active ingredient. During the third study year, Kaletra® capsules constituted 94.83 per cent (n=2 109) of individual medicine items claimed containing lopinavir/ritonavir as an active ingredient *(refer to table 5.54 and table 5.55)*.

The ***total number of medicine items*** containing lopinavir/ritonavir as an active ingredient accounted for 0.29 per cent (n=6 228) and 8.33 per cent (n=25 316) of the total number of OTHER ARV medicine items (category IV) *(refer to section 5.1.1)*, and 0.05 per cent (n=35 271) and 2.07 per cent (n=101938) of

the total number of ARV medicine items claimed during the second and third study years respectively *(refer to table 5.54 and table 5.55).*

The ***total cost*** of all individual medicine items containing lopinavir/ritonavir as an active ingredient accounted for 0.20 per cent (n=R6 401 032.79) and 7.05 per cent (n=R11 116 257.30) of the total cost of all OTHER ARV medicine items (category IV) *(refer to section 5.1.1)* claimed, and 0.07 per cent (n=R18 235 075.75) and 2.26 per cent (n=R34 714 483.64) of the total cost of all ARV medicine items claimed during the second and third study years respectively. The ***cost-prevalence indices*** for Kaletra® capsules were higher than one for the second and third study years, as well as for Kaletra® syrup for the second study year (P6), indicating that these medicine items utilised were relatively expensive *(refer to table 5.54 and table 5.55).*

It is apparent from *table 5.54* and *table 5.55* that the ***average cost*** of Kaletra®capsules and Kaletra® syrup increased from P7 (before implementation) to P8 (transition phase), and decreased from P8 (transition phase) to P9 (after single exit price). Thus, the possible effect of the implementation of the pricing regulations in 2004 can be seen in the lower average costs of Kaletra® capsules and Kaletra® syrup in the period P9. The ***effect sizes (d-values)*** calculated between the average cost of Kaletra® capsules and Kaletra® syrup for P6 and P7, P6 and P8, and P6 and P9, are of practical significant value.

Table 5.54 Prevalence and cost of individual medicine items containing lopinavir/ritonavir as an active ingredient for the period P4 to P6 (2002)

Period	Lopinavir/ ritonavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P4	-	-	-	-	-	-	-	
P5	-	-	-	-	-	-	-	
P6	Kaletra® capsules	18	0.12	11904.07	0.13	1.08	661.34	91.81
	Kaletra® syrup	1	0.01	717.58	0.01	1.00	717.58	0

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

Table 5.55 Prevalence and cost of individual medicine items containing lopinavir/ritonavir as an active ingredient for the period P7 to P9 (2004)

Period	Lopinavir/ ritonavir	Prevalence	Prevalence percentage %*	Cost (R)	Cost %#	Cost-prevalence index	Average cost per item (R)	Standard deviation (R)
P7	Kaletra® capsules	327	2.18	120046.99	2.51	1.15	367.12	74.36
	Kaletra® syrup	23	0.15	6780.34	0.14	0.93	294.80	83.58
P8	Kaletra® capsules	678	1.76	267837.67	1.89	1.07	395.04	84.44
	Kaletra® syrup	31	0.08	10397.92	0.07	0.88	335.42	58.46
P9	Kaletra® capsules	995	2.06	362559.81	2.31	1.12	364.38	62.70
	Kaletra® syrup	55	0.11	16205.52	0.10	0.91	294.65	85.72

%* Is the prevalence of individual ARV medicine items divided by the prevalence of the total number of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

%# Is the total cost of individual ARV medicine items divided by the total cost of all ARV medicine items for the corresponding period (calculated from table 5.12) multiplied by hundred.

5.4.7 Prevalence and cost of combinations of ARV medicine items

The availability of more numerous and more potent drugs to inhibit HIV replication has made it possible to design therapeutic strategies involving combinations of antiretroviral drugs that accomplish prolonged and near complete suppression of detectable HIV replication in many HIV-infected persons (CDC, 2001:1). Recommended antiretroviral treatment regimens in South Africa consist of stavudine with lamivudine and nevirapine, or stavudine with lamivudine and efavirenz, or if treatment fails, of zidovudine, with didanosine, with lopinavir and ritonavir *(refer to paragraph 2.7.2.4. table 2.14).*

The ***average cost, standard deviation and prevalence of ARV medicine items prescribed as monotherapy*** were analysed for the different study periods of 2004, namely January to April, May to August, and September to December *(see table 5.56).* The ***"average cost saving per unit price"*** in Rand and as percentage, as well as the ***"cost savings"*** in Rand (adapted from Steyn, 2005:162) for the different study periods can be calculated from *table 5.56. Table 5.57* summarises these "cost savings" of each ARV medicine item.

Table 5.56 Summary of average cost, standard deviation and prevalence of ARV medicine items prescribed as monotherapy for the different study periods for 2004

2004		January - April			May - August			September - December		
Active ingredient	Trade name®	n	Average cost (R)	Standard deviation (R)	n	Average cost (R)	Standard deviation (R)	n	Average cost (R)	Standard deviation (R)
Abacavir	Ziagen 300mg	1	1473.09	0	6	1427.87	97.78	8	1269.12	216.71
	Ziagen 100mg/5ml	-	-	-	1	707.90	0	2	538.34	239.80
Didanosine	Aspen didanosine	-	-	-	-	-	-	2	174.06	18.22
	Videx 25mg	2	309.88	125.77	10	245.71	101.14	3	164.00	5.92
	Videx 50mg	-	-	-	11	236.31	92.29	5	234.41	107.98
	Videx 100mg	20	244.66	132.43	41	280.00	93.03	52	265.58	93.75
	Videx 150 mg	3	268.47	26.62	6	260.02	66.95	8	196.85	65.30
Efavirenz	Stocrin 50mg	1	35.61	0	5	97.92	76.14	12	131.37	99.39
	Stocrin 200mg	73	302.18	200.80	182	423.91	78.78	172	386.99	75.93
	Stocrin 600	-	-	-	24	271.70	18.40	161	254.90	45.14
Indinavir	Crixivan 200mg	2	370.45	281.78	-	-	-	-	-	-
	Crixivan 400mg	2	349.14	106.65	13	486.71	116.23	11	473.37	127.23
Lamivudine	3TC 150mg	12	141.10	37.95	51	141.35	38.19	52	138.67	30.95
	3TC 240ml	11	164.52	78.57	49	164.80	91.03	39	184.98	103.95
	Aspen lamivudine	-	-	-	-	-	-	3	123.63	27.53
	Cipla-lamivudine	-	-	-	3	178.80	38.04	7	134.34	43.50
	Lamivudine 150mg	-	-	-	-	-	-	1	0.02	0
Lamivudine/Zidovudine	Aspen lamzid	-	-	-	-	-	-	12	353.23	47.94
	Combivir	175	469.56	80.56	442	499.51	81.19	468	459.78	91.03
	Retrovir/3TC	3	72.85	0	8	67.29	24.21	6	67.73	7.11
	Duovir	9	360.32	137.52	8	212.10	173.00	2	314.47	26.63
Lopinavir/Ritonavir	Kaletra	14	402.10	94.45	29	417.18	107.33	44	374.27	74.19
	Kaletra syrup	1	402.95	0	9	370.33	76.05	12	276.04	89.96
Nelfinavir	Vira-cept	1	819.08	0	8	838.23	203.17	7	813.79	268.84
	Vira-cept suspension	-	-	-	2	620.33	291.87	-	-	-
Nevirapine	Viramune 200mg	31	492.58	55.02	75	525.41	148.14	94	520.01	138.02
	Viramune suspension	10	307.47	350.76	23	603.20	480.19	27	512.21	407.47

Table 5.56 (continue) Summary of average cost, standard deviation and prevalence of ARV medicine items prescribed as monotherapy for the different study periods for 2004

2004		January - April			May - August			September - December		
Active ingredient	Trade name*	n	Average cost (R)	Standard deviation (R)	n	Average cost (R)	Standard deviation (R)	n	Average cost (R)	Standard deviation (R)
Ritonavir	Norvir 100mg	9	184.65	141.28	19	248.44	91.96	29	153.48	92.74
	Norvir solution	3	117.51	98.45	8	232.51	78.38	14	149.89	28.54
Saquinavir mesylate	Forto-vase	5	503.45	470.82	5	755.31	678.80	4	933.23	643.84
	Invi-rase 200mg	1	668.77	0	6	895.95	104.33	8	865.45	176.60
Stavudine	Aspen stavudine 20mg	2	51.07	0	-	-	-	1	0.26	0
	Aspen stavudine 30mg	-	-	-	2	46.27	0.24	4	41.30	0.42
	Aspen stavudine 40mg	-	-	-	5	64.71	10.38	6	81.61	29.13
	Stavir 30	2	45.80	0	2	45.20	4.98	-	-	-
	Stavir 40	4	46.92	3.22	13	68.79	34.81	15	49.32	20.78
	Zerit 20mg	2	52.30	28.47	9	70.83	16.02	9	67.47	6.84
	Zerit 30mg	6	77.91	32.88	15	70.24	28.01	20	46.07	21.09
	Zerit 40mg	15	69.72	17.63	46	70.84	19.14	55	56.34	12.18
	Zerit suspension	2	181.15	88.98	9	423.37	384.70	8	318.29	93.84
Zidovudine	Aspen Zidovudine	-	-	-	-	-	-	1	296.76	0
	Retrovir 100mg	4	349.98	176.47	6	421.32	190.53	13	317.22	194.75
	Retrovir 250mg	3	352.97	7.66	3	423.38	41.86	1	323.76	0
	Retrovir 300mg	2	317.94	67.20	8	406.38	59.46	9	425.75	71.79
	Retrovir S syrup	19	212.94	156.74	65	241.39	194.82	39	202.11	157.35
	Retrovir 20ml IV solution	1	337.09	0	4	385.00	63.60	5	270.28	118.50

From *table 5.56* can be seen that the ***average cost per ARV medicine items*** fluctuated during the three four-month periods, with the average cost of some ARV medicine items that decreased over the three study periods (a possible effect of the influence of the pricing regulations implemented in May 2004). Ziagen® 300mg, Ziagen® 100mg/5ml, Videx® 25mg, Videx® 50mg, Videx® 150 mg, Stocrin® 600, Cipla-lamivudine®, Retrovir/3TC®, Kaletra® syrup, Norvir® 100mg, Aspen stavudine® 20mg, Aspen stavudine® 30mg, Stavir® 30, and Zerit® 30mg all showed a decreasing trend over the three four-month periods.

The ***average cost of some ARV medicine items*** increased from the first to the second period, and decreased from the second to the third study period [the rise could be due to the fact that pharmacists increased their medicine prices during the implementation phase (May to August of 2004) to make up for the expected losses during the post single exit price period, and the decrease could then be due to the effect of the influence of the pricing regulations]. Videx® 100mg, Stocrin® 200mg, Crixivan® 400mg, 3TC® 150mg, Combivir®, Duovir®, Kaletra®, Viracept®, Viramune® 200mg, Viramune® suspension, Norvir® solution, Invi-rase®, Aspen stavudine® 40mg, Stavir® 40, Zerit® 20mg, Zerit® 40mg, Zerit® suspension, Retrovir® 100mg, Retrovir® 250 mg, Retrovir S® syrup, and Retrovir® 20ml IV solution all showed an increasing trend from the first to the second period, and a decreasing trend from the second to the third period *(refer to table 5.56)*.

The ***average cost of some ARV medicine items*** increased over the three four-month periods, and the implementation of the pricing regulations did not have an effect on these items, namely Stocrin® 50mg, 3TC® 240 ml, Forto-vase®, and Retrovir® 300mg *(refer to table 5.56)*.

Only seven ARV medicine items had ***d-values*** greater than 0.8 for the period January to April versus May to August, namely Stocrin® 50mg (0.82), Crixivan® 400 mg (1.18), Duovir® (0.86), Norvir® solution (1.17), Invi-rase® 200mg (2.18), Retrovir® 250mg (1.68), and Retrovir® 300mg (1.32). For the period January to April versus September to December Ziagen® 300mg (0.94), Videx® 25mg (1.16), Videx® 150mg (1.10), Stocrin® 50mg (0.96), Crixivan® 400mg (0.98), Kaletra® syrup (1.41), Invi-rase® 200mg (1.11), Zerit® 30mg (0.97), Zerit® suspension (1.46), Retrovir® 250mg (3.81), and Retrovir® 300mg (1.50) had d-values of greater than 0.8. Videx® 25mg (0.81), Videx® 150mg (0.94), Cipla-lamivudine® (1.02), Kaletra® syrup (1.05), Norvir® 100mg (1.02), Norvir® solution (1.05), Aspen stavudine® 30mg (11.83), Zerit® 30mg (0.86), Retrovir® 250mg (2.38), and Retrovir® 20ml IV solution (0.97) had d-values of greater than 0.8 for the period May to August versus September to December. Effect sizes (d-values) of 0.8 and greater have practical significant value *(refer to section 4.6.2.5)*.

From *table 5.57* the "average cost saving per unit price" in Rand and as percentage, as well as the "cost savings" in Rand for the different study periods can be calculated.

Table 5.57 Average cost saving per unit price and cost savings of ARV medicine items for the different study periods for 2004

2004		Average cost saving per unit price* Jan-Apr vs. May -Aug		Cost savings Jan-Apr vs. May -Aug	Average cost saving per unit price* Jan-Apr vs. Sept-Dec		Cost savings Jan-Apr vs. Sept-Dec	Average cost saving per unit price* May-Aug vs. Sept-Dec		Cost savings May-Aug vs. Sept-Dec
Active ingredient	Trade name#	(R)[a]	(%)[b]	(R)[c]	(R)[c]	(%)[b]	(R)[c]	(R)[a]	(%)[b]	(R)[c]
Abacavir	Ziagen 300mg	45.22	3.07	45.22	203.97	13.85	203.97	158.75	11.12	952.50
	Ziagen 100mg/5ml	-	-	-	-	-	-	169.56	23.95	169.56
	Videx 25mg	64.17	20.71	128.34	145.88	47.08	291.76	81.71	33.25	817.10
	Videx 50mg	-	-	-	-	-	-	1.90	0.80	20.90
	Videx 100mg	+35.34	+14.44	+706.80	+20.92	+8.55	+418.40	14.42	5.15	591.22
	Videx 150 mg	8.45	3.15	25.35	71.62	26.68	214.86	63.17	24.29	379.02
Efavirenz	Stocrin 50mg	+62.31	-174.98	+62.31	+95.76	268.91	+95.76	133.45	+34.16	+167.25
	Stocrin 200mg	+121.73	+28.72	+8886.29	+84.81	+28.07	+6191.13	36.92	8.71	6719.44
	Stocrin 600	-	-	-	-	-	-	16.80	6.18	403.20
	Crixivan 400mg	+137.57	+39.40	+275.14	+124.23	+35.58	+248.46	13.34	2.74	173.42
Lamivudine	3TC 150mg	+0.25	+0.18	+3.00	2.43	1.72	29.16	2.71	1.92	136.68
	3TC 240ml	+0.28	+0.18	+3.08	+20.46	+12.44	+225.06	+20.18	+12.25	988.82
	Cipla-lamivudine	-	-	-	-	-	-	44.46	24.87	133.38
Lamivudine/Zidovudine	Combivir	+29.95	+6.38	-5241.25	9.78	2.08	1711.50	39.73	7.96	17560.66
	Retrovir/3TC	5.56	7.63	16.68	5.12	7.03	15.36	+0.44	+0.65	+3.52
	Duovir	148.22	41.14	412.65	45.85	12.72	412.65	+102.37	+48.26	+818.96
Lopinavir	-	-	-	-	-	-	-	-	-	-
Lopinavir/Ritonavir	Kaletra	+15.08	+3.75	+211.12	27.83	6.92	389.62	42.91	10.29	1244.39
	Kaletra syrup	32.62	8.10	32.62	126.91	31.50	126.91	94.29	25.46	848.61
Nelfinavir	Vira-cept	+19.15	+2.34	+19.15	5.29	0.65	5.29	24.44	2.92	195.52
Nevirapine	Viramune 200mg	+32.83	+6.66	+1017.73	+27.43	+5.57	+850.33	5.40	1.03	405.00
	Viramune suspension	+295.73	+96.18	+2957.30	+204.74	+66.59	+2047.40	90.99	15.08	2092.77
Ritonavir	Norvir 100mg	+63.79	+34.55	+574.11	31.17	16.88	280.53	94.96	38.22	1804.24
	Norvir solution	+115.00	+97.86	+345.00	+32.38	+27.56	+97.14	82.62	35.53	660.96

Table 5.57 (continue) Average cost saving per unit price and cost savings of ARV medicine items for the different study periods for 2004

2004		Average cost saving per unit price* Jan-Apr vs. May -Aug		Cost savings Jan-Apr vs. May -Aug	Average cost saving per unit price* Jan-Apr vs. Sept-Dec		Cost savings Jan-Apr vs. Sept-Dec	Average cost saving per unit price* May-Aug vs. Sept-Dec		Cost savings May-Aug vs. Sept-Dec
Active ingredient	**Trade name**	**(R)[a]**	**(%)[b]**	**(R)[c]**	**(R)[a]**	**(%)[b]**	**(R)[c]**	**(R)[a]**	**(%)[b]**	**(R)[c]**
Saquinavir mesylate	Forto-vase	+251.86	+50.03	+1259.30	+429.78	+85.37	+2148.90	+177.92	+23.56	+889.60
	Invi-rase 200mg	+227.18	+33.97	+227.18	+196.68	+29.41	+196.68	30.50	3.40	183.00
Stavudine	Aspen stavudine 20mg	-	-	-	50.81	99.49	101.62	-	-	-
	Aspen stavudine 30mg	-	-	-	-	-	-	4.97	10.74	9.94
	Aspen stavudine 40mg	-	-	-	-	-	-	+16.90	+26.12	84.50
	Stavir 30	0.60	1.31	1.20	-	-	-	-	-	-
	Stavir 40	+21.87	+46.61	+87.48	+2.40	+5.12	+9.60	19.47	28.30	253.11
	Zerit 20mg	+18.53	+35.43	+37.06	+15.17	+29.01	+30.34	3.36	4.74	30.24
	Zerit 30mg	7.67	9.84	46.02	31.84	40.87	191.04	24.17	34.41	362.55
	Zerit 40mg	+1.12	+1.61	+16.8	13.38	19.19	200.70	14.50	20.47	667.00
	Zerit suspension	+242.22	+133.71	+484.44	+137.14	+75.71	+274.28	105.08	24.82	945.45
Zalcitabine	-	-	-	-	-	-	-	-	-	-
	Retrovir 100mg	+71.34	+20.38	+285.36	32.76	9.36	131.04	104.10	24.71	624.60
	Retrovir 250mg	+70.41	+19.95	+211.23	29.21	8.28	87.63	99.62	23.53	298.86
	Retrovir 300mg	+88.44	+27.82	+176.88	+107.81	+33.91	+215.62	+19.37	4.77	154.96
	Retrovir S syrup	+28.45	+13.36	+540.55	10.83	5.09	205.77	39.28	16.27	2553.20
	Retrovir 20ml IV solution	+47.91	+14.21	+47.91	66.81	19.82	66.81	114.72	29.80	458.88
Total	-	-	-	+22968.93	-	-	+8382.88	-	-	41044.35

* "Unit price" can be defined as the number of tablets or capsules or suspensions in millilitre or injections in millilitre prescribed per month.

R[a] is calculated by subtracting the average cost of the second study period from the first, or the third study period from the first, or the third study period from the second.

%[b] is calculated by dividing the average cost of the initial study period through R[a] for the corresponding study period under investigation.

R[c] is calculated as follows: [the first study period's average cost multiplied by its prevalence (n)] minus [the second study period's average cost multiplied by the first study period's prevalence (n)].

Table 5.57 indicates that there was ***no cost saving for ARV medicine items*** for the period January to April versus May to August with a total increase of R22 968.93. For the period January to April versus September to December there was also ***no cost saving for ARV medicine items*** with a total increase of R8 382,88, but for the period May to August versus September to December there was a ***cost saving*** of R41 044.35 ***for the ARV medicine items***. The implementation of the pricing regulations could be a possible reason for this cost saving, due to the fact that the single exit price came only into effect from May 2004.

The ARV medicine item with the ***highest average cost saving per unit price*** for the period January to April versus May to August was Duovir® (R148.22), which also had the ***highest lowering in the average cost saving per unit price percentage*** (41.14 per cent), while Stavir 30® (R0.60, 1.31 per cent) represented the lowest average cost saving per unit price. The ***highest cost savings*** was represented by Duovir® (R412.65) and Videx® (R128.34), while the ***lowest cost savings*** was indicated by Stavir 30® (R1.20). Viramune® suspension (+R295.73), Forto-vase® (+R251.86) and Zerit® suspension (+R242.22) showed the ***highest increase in the average total cost*** for the period, while Stocrin® 200mg (+R8 886.29) and Combivir® (+R5 241.25) indicated the ***highest increase in the total cost savings*** for the period January to April versus May to August *(refer to table 5.57)*.

From *table 5.57* can be concluded that the ARV medicine item with the ***highest average cost saving per unit price*** for the period January to April versus September to December was Ziagen® 300mg (R203.97, 13.85 per cent), while Videx® 25mg (47.08 per cent) had the ***highest lowering in the average cost saving per unit price percentage.*** The ***lowest cost saving per unit price*** was 3TC® 150mg (R2.43, 1.72 per cent), and the ***highest cost savings*** were represented by Combivir® (R1 711.50), followed by Duovir® (R412.65) and Kaletra® (R389.62). The ***highest increase in the average total cost*** for the period was represented by Forto-vase® (+R429.78), while Stocrin® 200mg (+R6 191.13) and Forto-vase® (+R2 148.90) indicated the ***highest increase in the total cost savings*** for the period January to April versus September to December.

Ziagen 100mg/5ml® (R169.56, 23.95 per cent) was the ARV medicine item with the ***highest average cost saving per unit price*** for the period May to August versus September to December, while Norvir® 100mg had the ***highest lowering in the average cost saving per unit price percentage.*** The ***lowest cost saving per unit price*** was represented by Videx® 50mg (R1.90, 0.80per cent). The ***highest cost saving*** was indicated by Combivir® (R17 560.66), followed by Stocrin® 200mg (R6 719.44) and by Retrovir S® syrup (R2 553.20), while Aspen stavudine® 30mg (R9.94) represented the lowest cost saving. Only Stocrin® 50mg (+R167.25), Retrovir/3TC® (+R3.52), Duovir® (+R818.96) and Forto-vase® (+R889.60) showed an

increase in the total cost savings for the period May to August versus September to December *(refer to table 5.57)*.

The ***total ARV prescriptions*** on the database, as well as the prescriptions containing ***one ARV medicine items*** was identified from the database and tabled in *table 5.58* to *table 5.63*, representing the data of 2001, 2002, January to April 2004, May to August 2004, September to December 2004, as well as for the whole 2004. Thus, the ***prevalence (n)*** and the ***average cost (R)*** of the prescriptions only containing ***combination ARV medicine items*** can be calculated.

Table 5.58 Summary of the total, single and combination ARV medicine items for 2001

2001		Total medicine items		Single medicine item		Combination medicine items	
Active ingredient	Trade name®	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	"Average cost" (R)
Didanosine	Videx 25mg	241	179.98±62.29	1	217.50±0	240	179.82
	Videx 50mg	65	209.02±50.03	2	179.52±1.05	63	209.96
	Videx 100mg	2477	491.15±245.64	996	650.20±266.87	1481	384.19
	Videx 150 mg	356	371.29±270.12	153	496.56±292.36	203	276.87
	Videx 4g powder for injection	8	179.58±167.13	-	-	8	179.58
	Videx paediatric 2g suspension	5	185.68±106.29	1	276.08±0	4	163.08
Efavirenz	Stocrin 200mg	1172	567.60±186.58	18	615.67±401.69	1154	566.85
Indinavir	Crixivan 200mg	5	1488.14±1176.56	2	727.12±682.11	3	1995.49
	Crixivan 400mg	227	1160.46±1123.84	7	876.73±1099.17	220	1169.49
Lamivudine	3TC 150mg	233	634.50±681.31	8	1123.11±497.28	225	617.13
	3TC 240ml	137	463.98±151.65	13	433.47±121.32	124	467.18
Lamivudine/Zidovudine	Combivir	2012	700.01±823.39	1629	642.91±810.94	383	942.87
	Retrovir/3TC	14	292.18±0	13	292.18±0	1	292.18
Nelfinavir	Vira-cept	6	2825.68±1372.01	-	-	6	2825.68
Nevirapine	Viramune 200mg	330	599.92±79.52	13	535.51±190.70	317	602.56
	Viramune suspension	33	436.74±424.38	2	173.45±240.46	31	453.73
Ritonavir	Norvir 100mg	82	695.17±337.32	1	639.99±0	81	695.85
	Norvir solution	26	1106.97±961.73	2	1156.20±206.62	24	1102.87
Saquinavir mesylate	Forto-vase	4	703.93±291.57	1	584.95±0	3	743.59
	Invi-rase 200mg	5	2524.99±1389.52	-	-	5	2524.99
Stavudine	Zerit 15mg	3	45.46±16.57	-	-	3	45.46
	Zerit 20mg	22	62.69±14.52	4	66.95±5.43	18	61.74
	Zerit 30mg	306	147.05±326.65	21	356.90±601.25	285	131.59
	Zerit 40mg	1187	168.46±368.14	1	350.55±0	1186	168.31
	Zerit suspension	33	443.74±140.79	-	-	33	443.74
Zalcitabine	Hivid combo pack	6	897.96±0.62	-	-	6	897.96

Table 5.59 Summary of the total, single and combination ARV medicine items for 2002

2002		Total medicine items		Single medicine item		Combination medicine items*	
Active ingredient	Trade name*	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	"Average cost" (R)
Zidovudine	Retrovir 100mg	161	889.04±246.19	13	863.48±298.19	148	891.29
	Retrovir 250mg	303	529.39±387.58	34	300.25±369.65	269	558.35
	Retrovir 300mg	4	955.42±82.98	1	996.91±0	3	941.59
	Retrovir S syrup	259	353.07±266.52	23	270.27±175.70	236	361.14
	Retrovir 20ml IV solution	74	362.38±120.82	3	345.91±136.11	71	363.08
Abacavir	Ziagen 300mg	81	2236.04±431.59	7	2360.35±510.46	74	2224.28
	Ziagen 100mg/5ml	1	2095.55±0	-	-	1	2095.55
Didanosine	Videx 25mg	765	222.95±74.62	14	297.42±135.79	751	221.56
	Videx 50mg	326	220.61±73.57	4	285.36±115.81	322	219.81
	Videx 100mg	6259	380.66±136.90	157	401.69±145.31	6102	380.12
	Videx 150 mg	495	207.08±88.99	13	255.85±134.47	482	205.76
	Videx paediatric 2g suspension	36	284.71±211.77	12	349.75±314.05	24	252.19
Efavirenz	Stocrin 50mg	49	79.35±36.86	1	162.32±0	48	77.62
	Stocrin 200mg	7127	584.17±116.62	145	602.95±104.34	6982	583.78
Indinavir	Crixivan 200mg	1	803.40±0	-	-	1	803.40
	Crixivan 400mg	825	642.15±210.18	15	721.03±241.81	810	640.69
Lamivudine	3TC 150mg	372	950.80±216.62	19	1023.30±284.39	353	946.90
	3TC 240ml	484	491.45±235.35	27	388.05±127.93	457	497.56
Lamivudine/Zidovudine	Combivir	6197	1032.54±468.04	1546	873.14±629.27	4651	1085.52
	Retrovir/3TC	12	199.90±136.31	10	236.81±116.73	2	15.35
Lopinavir/Ritonavir	Kaletra	18	661.34±91.81	3	651.94±116.60	15	663.22
	Kaletra syrup	1	717.58±0	-	-	1	717.58
Nelfinavir	Vira-cept	88	3015.65±1518.79	13	1836.12±1356.41	75	3220.10
	Vira-cept suspension	4	851.95±340.58	-	-	4	851.95
Nevirapine	Viramune 200mg	2848	518.31±100.16	59	569.97±79.75	2789	517.22
	Viramune suspension	378	518.23±329.71	25	267.70±248.75	353	535.97
Ritonavir	Norvir 100mg	558	201.06±180.65	13	172.98±77.64	545	201.73
	Norvir solution	142	314.42±271.26	19	298.79±203.85	123	316.83
Saquinavir mesylate	Forto-vase	206	1191.24±305.20	3	1591.46±570.74	203	1185.33
	Invi-rase 200mg	7	2092.75±600.74	-	-	7	2092.75

Table 5.59 (continue) Summary of the total, single and combination ARV medicine items for 2002

2002	Trade name®	Total medicine items		Single medicine item		Combination medicine items*	
Active ingredient		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	"Average cost" (R)
Stavudine	Zerit 20mg	117	82.07±19.11	4	75.90±15.45	113	82.29
	Zerit 30mg	1275	87.90±17.65	13	84.87±11.24	1262	87.93
	Zerit 40mg	5451	87.83±19.55	50	88.10±13.69	5401	87.83
	Zerit suspension	122	414.46±202.00	10	453.42±170.50	112	410.98
Zalcitabine	Hivid 0.75mg	5	1224.70±0	-	-	5	1224.70
	Hivid combo pack	13	510.85±268.59	-	-	13	510.85
Zidovudine	Retrovir 100mg	91	677.44±246.73	19	675.44±335.36	72	677.97
	Retrovir 250mg	202	442.39±371.55	27	258.33±365.99	175	470.79
	Retrovir 300mg	41	943.83±127.27	29	978.09±84.74	12	861.04
	Retrovir S syrup	610	610.40±445.26	70	520.05±400.25	540	622.11
	Retrovir 20ml IV solution	64	429.86±155.78	3	385.39±229.76	61	432.05

* Combination medicine items is calculated by subtracting the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the one combination from the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the total medicine items.

Table 5.60 Summary of the total, single and combination ARV *medicine* items for the different study periods for 2004

January - April	Trade name®	Total medicine items		Single medicine item		Combination medicine items	
Active ingredient		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	"Average cost" (R)
Abacavir	Ziagen 300mg	29	1289.74±221.82	1	1473.09±0	28	1283.19
	Ziagen 100mg/5ml	10	543.66±283.75	-	-	10	543.66
Didanosine	Videx 25mg	199	193.56±69.99	2	309.88±125.77	197	192.38
	Videx 50mg	58	233.53±97.97	-	-	58	233.53
	Videx 100mg	1192	241.97±134.48	20	244.66±132.43	1172	241.92
	Videx 150 mg	523	222.75±78.57	3	268.47±26.62	520	222.49
	Videx paediatric 2g suspension	14	300.64±112.22	-	-	14	300.64
Efavirenz	Stocrin 50mg	32	62.43±40.67	1	35.61±0	31	63.30
	Stocrin 200mg	3473	356.98±141.70	73	302.18±200.80	3400	358.16
Indinavir	Crixivan 200mg	5	255.24±194.76	2	370.45±281.78	3	178.43
	Crixivan 400mg	186	409.01±148.01	2	349.14±106.65	184	409.66
Lamivudine	3TC 150mg	658	159.62±27.69	12	141.10±37.95	646	159.96
	3TC 240ml	217	182.22±63.69	11	164.52±78.57	206	183.17
	Cipla-lamivudine	61	192.62±24.72	-	-	61	192.62
Lamivudine/Zidovudine	Combivir	3334	448.79±79.25	175	469.56±80.56	3159	447.64
	Retrovir/3TC	3	72.85±0	3	72.85±0	0	0
	Duovir	26	372.00±89.50	9	360.32±137.52	17	378.18
Lopinavir/Ritonavir	Kaletra	327	367.12±74.36	14	402.10±94.45	313	365.56
	Kaletra syrup	23	294.80±83.57	1	402.95±0	22	289.88
Nelfinavir	Vira-cept	30	692.63±262.95	1	819.08±0	29	688.27
	Vira-cept suspension	1	825.39±0	-	-	1	825.39
Nevirapine	Viramune 200mg	1566	465.42±125.40	31	492.58±55.02	1535	464.87
	Viramune suspension	147	256.44±346.91	10	307.47±350.76	137	252.72
Ritonavir	Norvir 100mg	164	125.09±110.80	9	184.65±141.28	155	121.63
	Norvir solution	55	180.10±57.58	3	117.51±98.45	52	183.71
Saquinavir mesylate	Forto-vase	63	810.71±452.42	5	503.45±470.82	58	837.20
	Invi-rase 200mg	46	793.32±283.77	1	668.77±0	45	796.09

Table 5.60 (continue) Summary of the total, single and combination ARV medicine items for the different study periods for 2004

January - April		Total medicine items		Single medicine item		Combination medicine items*	
Active ingredient	Trade name®	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	"Average cost" (R)
Stavudine	Aspen stavudine 20mg	5	64.66±12.93	-	-	5	64.66
	Aspen stavudine 30mg	71	53.46±10.03	2	51.07±0	69	53.53
	Aspen stavudine 40mg	189	73.40±17.52	-	-	189	73.40
	Stavir 30	34	41.96±3.51	2	45.80±0	32	41.72
	Stavir 40	74	45.78±8.81	4	46.92±3.22	70	45.71
	Zerit 20mg	63	60.56±24.76	2	52.30±28.47	61	60.83
	Zerit 30mg	521	60.93±21.54	6	77.91±32.88	515	60.73
	Zerit 40mg	1275	65.45±20.00	15	69.72±17.63	1260	65.40
	Zerit suspension	48	339.75±148.22	2	181.15±88.98	46	346.65
Zidovudine	Retrovir 100mg	50	333.72±150.41	4	349.98±176.47	46	332.31
	Retrovir 250mg	26	419.44±44.51	3	352.97±7.66	23	428.11
	Retrovir 300mg	25	367.36±107.81	2	317.94±67.20	23	371.66
	Retrovir S syrup	186	321.87±169.76	19	212.94±156.74	167	334.26
	Retrovir 20ml IV solution	21	243.65±118.81	1	337.09±0	20	238.98

* Combination medicine items is calculated by subtracting the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the one combination from the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the total medicine items.

Table 5.61 Summary of the total, single and combination ARV medicine items for the different study periods for 2004

May - Augustus	Trade name	Total medicine items		Single medicine item		Combination medicine items	
Active ingredient		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	"Average cost" (R)
Abacavir	Ziagen 300mg	15	690.52±362.08	6	1427.87±97.78	9	198.95
	Ziagen 100mg/5ml	153	1356.53±191.86	1	707.90±0	152	1360.80
Didanosine	Videx 25mg	291	191.23±62.63	10	245.71±101.14	281	189.29
	Videx 50mg	156	253.31±106.96	11	236.31±92.29	145	254.60
	Videx 100mg	2096	277.12±121.72	41	280.00±93.03	2055	277.06
	Videx 150 mg	683	238.11±94.69	6	260.02±66.95	677	237.92
	Videx paediatric 2g suspension	21	304.91±77.41	-	-	21	304.91
Efavirenz	Stocrin 50mg	94	76.29±53.25	5	97.92±76.14	89	75.07
	Stocrin 200mg	8808	423.73±76.94	182	423.91±78.78	8626	423.73
	Stocrin 600	413	258.18±51.60	24	271.70±18.40	389	257.35
Indinavir	Crixivan 200mg	3	246.58±9.67	-	-	3	246.58
	Crixivan 400mg	739	499.21±108.82	13	486.71±116.23	726	499.43
Lamivudine	3TC 150mg	2641	162.23±21.46	51	141.35±38.19	2590	162.64
	3TC 240ml	627	193.43±83.46	49	164.80±91.03	578	195.86
	Cipla-lamivudine	403	199.63±26.63	3	178.80±38.04	400	199.79
	Lamaid	2	81.87±32.68	-	-	2	81.87
Lamivudine/Zidovudine	Combivir	9195	500.70±83.31	442	499.51±81.19	8753	500.76
	Retrovir/3TC	9	71.87±26.48	8	67.29±24.21	1	108.51
	Duovir	54	365.39±120.64	8	212.10±173.00	46	392.05
Lopinavir/Ritonavir	Kaletra	678	395.04±84.44	29	417.18±107.33	649	394.05
	Kaletra syrup	31	335.42±58.46	9	370.33±76.05	22	321.14
Nelfinavir	Vira-cept	86	780.04±255.51	8	838.23±203.17	78	774.07
	Vira-cept suspension	17	1443.56±810.91	2	620.33±291.87	15	1553.32
Nevirapine	Nevran	3	258.64±0	-	-	3	258.64
	Viramune 200mg	3754	527.02±134.38	75	525.41±148.14	3679	527.05
	Viramune suspension	353	488.50±416.22	23	603.20±480.19	330	749.92
Ritonavir	Norvir 100mg	511	77.86±95.66	19	248.44±91.96	492	71.27
	Norvir solution	93	180.46±57.75	8	232.51±78.38	85	175.56

Table 5.61 (continue) Summary of the total, single and combination ARV medicine items for the different study periods for 2004

May - Augustus		Total medicine items		Single medicine item		Combination medicine items*	
Active ingredient	Trade name®	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)
Saquinavir mesylate	Forto-vase	252	1197.09±484.33	5	755.31±678.80	247	1206.03
	Invi-rase 200mg	130	822.88±249.79	6	895.95±104.33	124	819.34
Stavudine	Aspen stavudine 20mg	21	42.41±20.13	-	-	21	42.41
	Aspen stavudine 30mg	140	53.01±14.09	2	46.27±0.24	138	53.11
	Aspen stavudine 40mg	483	62.98±20.82	5	64.71±10.38	478	62.96
	Stavir 30	86	45.22±13.05	2	45.20±4.98	84	45.22
	Stavir 40	248	49.51±16.13	13	68.79±34.81	235	48.44
	Zerit 20mg	138	68.38±18.86	9	70.83±16.02	129	73.15
	Zerit 30mg	1044	68.42±19.66	15	70.24±28.01	1029	68.39
	Zerit 40mg	3145	69.34±18.84	46	70.84±19.14	3099	69.32
	Zerit suspension	99	359.92±186.58	9	423.37±384.70	90	353.58
Zidovudine	Retrovir 100mg	123	370.79±166.81	6	421.32±190.53	117	368.20
	Retrovir 250mg	54	398.61±91.30	3	423.38±41.86	51	397.15
	Retrovir 300mg	95	445.05±93.19	8	406.38±59.46	87	448.61
	Retrovir S syrup	472	384.95±247.04	65	241.39±194.82	407	407.88
	Retrovir 20ml IV solution	29	320.37±105.40	4	385.00±63.60	25	310.03

* Combination medicine items is calculated by subtracting the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the one combination from the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the total medicine items.

Table 5.62 Summary of the total, single and combination ARV medicine items for the different study periods for 2004

September - December	Trade name®	Total medicine items		Single medicine item		Combination medicine items	
Active ingredient		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)
Abacavir	Ziagen 300mg	156	1326.03±249.44	8	1269.12±216.71	148	1329.11
	Ziagen 100mg/5ml	21	714.91±137.99	2	538.34±239.80	19	733.50
Didanosine	Aspen didanosine	73	274.89±72.92	2	174.06±18.22	71	277.73
	Videx 25mg	317	182.84±62.65	3	164.00±5.92	314	183.02
	Videx 50mg	165	224.44±98.36	5	234.41±107.98	160	224.13
	Videx 100mg	2419	256.28±92.52	52	265.58±93.75	2367	256.08
	Videx 150 mg	698	242.37±78.79	8	196.85±65.30	690	242.90
	Videx paediatric 2g suspension	13	311.69±49.18	-	-	13	311.69
Efavirenz	Stocrin 50mg	154	78.58±62.15	12	131.37±99.39	142	74.12
	Stocrin 200mg	7570	398.78±85.11	172	386.99±75.93	7398	399.29
	Stocrin 600	4517	270.18±67.44	161	254.90±45.14	4356	270.74
Indinavir	Crixivan 200mg	3	161.35±93.01	-	-	3	161.35
	Crixivan 400mg	707	472.89±128.75	11	473.37±127.23	696	472.88
Lamivudine	3TC 150mg	4153	154.18±22.77	52	138.67±30.95	4101	154.38
	3TC 240ml	742	186.85±86.11	39	184.98±103.95	703	186.95
	Aspen lamivudine	104	134.81±52.79	3	123.63±27.53	101	135.14
	Cipla-lamivudine	622	155.63±20.69	7	134.34±43.50	615	155.87
	Lamaid	9	102.35±18.03	-	-	9	102.35
	Lamivudine 150mg	9	131.86±94.21	1	0.02±0	8	148.34
Lamivudine/Zidovudine	Aspen lamzid	429	415.53±57.37	12	353.23±47.94	417	417.32
	Combivir	10110	474.01±91.85	468	459.78±91.03	9642	474.70
	Retrovir/3TC	9	129.50±189.14	6	67.73±7.11	3	253.04
	Duovir	38	369.25±34.77	2	314.47±26.63	36	372.29
Lopinavir/Ritonavir	Kaletra	995	364.38±62.68	44	374.27±74.19	951	363.92
	Kaletra syrup	55	294.65±85.72	12	276.04±89.96	43	299.84
Nelfinavir	Vira-cept	72	762.16±271.26	7	813.79±268.84	65	756.60
	Vira-cept suspension	25	1557.22±703.97	-	-	25	1557.22
Nevirapine	Aspen nevirapine	143	269.31±39.19	-	-	143	269.31
	Nevran	7	254.28±27.02	-	-	7	254.28
	Viramune 200mg	4056	493.75±148.97	94	520.01±138.02	3962	493.13
	Viramune suspension	454	624.21±324.89	27	512.21±407.47	427	663.68

Table 5.62 (continue) Summary of the total, single and combination ARV medicine items for the different study periods for 2004

September - December	Trade name[@]	Total medicine items		Single medicine item		Combination medicine items[*]	
Active ingredient		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)
Ritonavir	Norvir 100mg	572	69.96±87.33	29	153.48±92.74	543	65.50
	Norvir solution	83	166.11±73.85	14	149.89±28.54	69	169.40
Saquinavir mesylate	Forto-vase	249	1312.60±478.54	4	933.23±643.84	245	1318.79
	Invi-rase 200mg	190	716.07±243.42	8	865.45±176.60	182	709.50
Stavudine	Aspen stavudine 20mg	40	35.77±13.21	1	0.26±0	39	36.68
	Aspen stavudine 30mg	347	48.77±18.40	4	41.30±0.42	343	48.86
	Aspen stavudine 40mg	1219	53.34+13.06	6	81.61±29.13	1213	53.20
	Stavir 30	125	40.45±7.12	-	-	125	40.45
	Stavir 40	511	43.22±8.60	15	49.32±20.78	496	43.04
	Zerit 20mg	151	63.51±21.04	9	67.47±6.84	142	63.26
	Zerit 30mg	1126	62.33±23.06	20	46.07±21.09	1106	62.62
	Zerit 40mg	3863	63.32±19.24	55	56.34±12.18	3808	63.42
	Zerit suspension	138	351.06±190.86	8	318.29±93.84	130	353.08
Zidovudine	Aspen Zidovudine	22	305.16±241.72	1	296.76±0	21	305.56
	Retrovir 100mg	155	340.12±147.79	13	317.22±194.74	142	342.22
	Retrovir 250mg	53	385.24±74.49	1	323.76±0	52	386.42
	Retrovir 300mg	161	410.72±102.74	9	425.75±71.79	152	409.83
	Retrovir S syrup	521	333.04±206.85	39	202.11±157.35	482	343.63
	Retrovir 20ml IV solution	49	283.16±117.40	5	270.28+118.50	44	278.30

[*] Combination medicine items is calculated by subtracting the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the one combination from the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the total medicine items.

Table 5.63 Summary of the total, single and combination ARV medicine items for 2004

2004 Active ingredient	Trade name®	Total medicine items		Single medicine item		Combination medicine items*	
		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)
Abacavir	Ziagen 300mg	338	1336.72±223.00	15	1346.22±185.21	323	1336.28
	Ziagen 100mg/5ml	46	669.73±264.54	3	594.86±195.80	43	674.95
Didanosine	Aspen didanosine	73	274.89±72.92	2	174.06±18.22	71	277.73
	Videx 25mg	807	188.51±64.62	15	237.92±98.31	792	187.57
	Videx 50mg	379	237.72±102.55	16	235.71±93.74	363	237.81
	Videx 100mg	5707	260.94±114.12	113	267.11±101.10	5594	260.82
	Videx 150 mg	1904	235.45±85.11	17	231.78±67.20	1887	235.48
	Videx paediatric 2g suspension	48	305.50±81.66	-	-	48	305.50
Efavirenz	Stocrin 50mg	280	75.97±57.20	18	116.76±91.64	262	73.17
	Stocrin 200mg	19851	402.54±97.31	427	388.23±116.53	19424	402.85
	Stocrin 600	4930	269.18±66.33	185	257.08±42.97	4745	269.65
Indinavir	Crixivan 200mg	11	227.27±136.85	2	370.45±281.78	9	195.45
	Crixivan 400mg	1632	477.53±125.60	26	470.49±121.38	1606	477.64
Lamivudine	3TC 150mg	7452	157.51±23.11	115	140.11±34.77	7337	157.78
	3TC 240ml	1586	188.82±82.38	99	172.72±94.75	1487	189.89
	Aspen lamivudine	104	134.81±52.79	3	123.63±27.53	101	135.14
	Cipla-lamivudine	1086	174.03±31.60	10	147.68±45.22	1076	174.27
	Lamaid	11	98.62±20.87	-	-	11	98.62
	Lamivudine 150mg	9	131.86±94.21	1	0.02±0	8	148.34
Lamivudine/Zidovudine	Aspen lamzid	429	415.53±57.37	12	353.23±47.94	417	417.32
	Combivir	22639	481.14±88.56	1085	477.54±87.39	21554	481.32
	Retrovir/3TC	21	96.71±124.24	17	68.43±16.64	4	216.90
	Duovir	118	368.09±93.24	19	293.09±159.09	99	382.48
Lopinavir/Ritonavir	Kaletra	2000	375.22±73.98	87	393.05±90.78	1913	374.41
	Kaletra syrup	109	306.27±79.92	22	320.38±94.65	87	302.70
Nelfinavir	Vira-cept	188	759.24±263.15	16	826.34±219.83	172	753.00
	Vira-cept suspension	43	1495.27±740.09	2	620.33±291.87	41	1537.95
Nevirapine	Aspen nevirapine	143	269.31±39.19	-	-	143	269.31
	Nevran	10	255.59±22.16	-	-	10	255.59
	Viramune 200mg	9376	502.34±141.27	200	517.78±132.82	9176	502.00
	Viramune suspension	954	517.33±385.81	60	512.97±433.88	894	517.62

Table 5.63 (continue) Summary of the total, single and combination ARV medicine items for 2004

2004 Active ingredient	Trade name®	Total medicine items		Single medicine item		Combination medicine items*	
		Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)	Prevalence (n)	Average cost (R)
Ritonavir	Norvir 100mg	1247	80.45±95.72	57	190.05±108.28	1190	75.20
	Norvir solution	231	175.22±64.06	25	172.44±70.12	206	175.56
Saquinavir mesylate	Forto-vase	564	1204.93±500.54	14	716.20±581.49	550	1217.37
	Invi-rase 200mg	366	763.72±255.34	15	864.54±150.47	351	759.41
Stavudine	Aspen stavudine 20mg	66	40.07±17.30	1	0.26±0	65	40.68
	Aspen stavudine 30mg	558	50.43±16.65	8	44.99±4.35	550	50.51
	Aspen stavudine 40mg	1891	57.80±17.18	11	73.93±23.35	1880	57.71
	Stavir 30	245	42.33±9.57	4	45.50±2.89	241	42.28
	Stavir 40	833	45.32±11.72	32	56.93±27.66	801	44.86
	Zerit 20mg	352	64.89±21.10	20	67.47±14.14	332	64.73
	Zerit 30mg	2691	64.42±21.73	41	59.57±28.38	2650	64.50
	Zerit 40mg	8283	65.93±19.40	116	63.82±17.37	8167	65.96
	Zerit suspension	285	352.23±182.39	19	353.63±275.56	266	352.13
Zidovudine	Aspen Zidovudine	22	305.16±241.72	1	296.76±0	21	305.56
	Retrovir 100mg	328	350.64±155.90	23	350.07±187.63	305	350.68
	Retrovir 250mg	133	397.36±77.87	7	378.97±49.36	126	398.38
	Retrovir 300mg	281	418.47±102.23	19	406.25±70.52	262	419.36
	Retrovir S syrup	1179	352.06±220.34	123	224.54±177.71	1056	366.91
	Retrovir 20ml IV solution	99	285.68±116.38	10	322.85±104.23	89	281.50

* Combination medicine items is calculated by subtracting the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the one combination from the result of the prevalence (n) multiplied by the average cost (R) (thus total cost) of the total medicine items.

From *table 5.58* can be calculated that a total of 6 834 (69.76 per cent; n=9 796) prescriptions containing ***combination ARV medicine items*** were issued during 2001, and a total of 2 962 (30.24 per cent; n=9 796) prescriptions containing ***one ARV medicine item*** were issued during 2001. From table 5.59 can be calculated that a total of 32 941 (93.39 per cent; n=35 271) prescriptions containing combination ARV medicine items were issued during 2002, and a total of 2 330 (6.61 per cent; n=35 271) prescriptions containing one ARV medicine item were issued during 2002.

A total of 14 579 (97.00 per cent; n=15 030) prescriptions containing ***combination ARV medicine items*** were issued during the period January to April 2004, as calculated from table 5.60. From table 5.61 can be calculated that a total of 37 257 (96.80 per cent; n=38 488) prescriptions containing combination ARV medicine items were issued during the period May to August 2004. A total of 46 969 (97.00 per cent; n=48 420) prescriptions containing combination ARV medicine items were issued during the period September to December 2004, as calculated from *table 5.62.*

Thus, as summarised in *table 5.63*, it can be calculated that a total of 98 805 (96.93 per cent; n=101 938) prescriptions containing ***combination ARV medicine items*** were issued during 2004, and a total of 3 133 (3.07 per cent; n=101 938) prescriptions containing ***one ARV medicine item*** were issued during 2004.

The above trends indicate that the most ***ARV medicine items*** are prescribed as ***combination therapy***, however the nature and detailed analysis of ARV prescribing patterns fall outside the scope of this study, and were not further investigated.

5.5 CHAPTER SUMMARY

In this chapter the results of the empirical investigation were outlined. The focus mainly fell on the prescribing patterns and cost of ARV medicine items for the study periods 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002 and 1 January 2004 to 31 December 2004, as well as the influence of the pricing regulations implemented in May 2004 on the cost of ARV medicine items. In chapter six, the conclusion, limitations and recommendations of the study will be discussed.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

The conclusions of the study, based on the results of the literature review and the empirical investigation, as well as recommendations derived from this study regarding the utilisation patterns of ARV medicine items will be discussed. Limitations encountered during the study are also discussed in this chapter.

6.2 CONCLUSIONS

The following conclusions can be formulated with regard to the literature review:

*The **first research objective** was to examine HIV/AIDS from available literature and describe the treatment protocols thereof.*

This was done through a thorough review of the literature *(refer to chapter 2)*. The history of HIV/AIDS, the relationship between HIV and AIDS, the transmission of HIV, the stages of HIV disease, opportunistic infections associated with HIV/AIDS and treatment of HIV/AIDS, including vaccines and ARV drugs, were discussed. According to Shafer and Vuitton (1999:73) the optimal treatment for HIV-1 infection is not known *(refer to section 2.7)*. HIV/AIDS vaccines are under development, but even a partially effective vaccine could decrease the number of people who get infected with HIV (NIAID, 2005:1) *(refer to paragraph 2.7.1.2)*.

*The **second research objective** was to describe ARV drugs according to different classification systems.*

Table 2.12 indicates recommendations for initiating antiretroviral treatment in adults and adolescents with documented HIV infection according to the World Health Organisation (WHO, 2003a:10) *(refer to section 2.7.2.3)*. Recommended antiretroviral treatment regimens in South Africa consist of stavudine with lamivudine and nevirapine, or stavudine with lamivudine and efavirenz, or if treatment fails, antiretroviral treatment consists of zidovudine, with didanosine, with lopinavir and ritonavir *(refer to paragraph 2.7.2.4, table 2.14)*. *Table 2.15* indicates first-line regimens recommended by the World Health Organisation (WHO, 2004:65). *Figure 2.4* indicates how adult patients with concomitant TB and HIV/AIDS must be treated in South Africa (DOH, 2004b:19). The treatment protocols of HIV/AIDS in pregnant women *(refer to paragraph 2.7.2.4.3)* and in children *(refer to paragraph 2.7.2.5)* are also discussed.

According to the Medical Control Council (MCC, 2004:1) of South Africa, fourteen ARV drugs have been registered during the period 1989 to 2004. These drugs include the Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs) *(see table 2.5)*. Twenty ARV drugs were approved, as of October 2003, by the United States Food and Drug Administration (US FDA, 2005:1), which contain an extra drug class, namely the Fusion Inhibitor (FIs) *(see table 2.6)*. De Clercq (2004:115) also described these four drug classes *(refer to paragraph 2.7.2.1.1)*. *Table 2.11* describes the different categories, drug classes and regimens of Highly Active Antiretroviral Therapy (HAART) *(refer to section 2.7.2.2)*.

*The **third research objective** was to describe what managed health care, drug utilisation, pharmacoeconomics, and disease management entail.*

This was done through an extensive literature review *(refer to chapter 3)*. Managed heath care, drug utilisation review (DUR), pharmacoeconomics and disease management (DM) were defined, classified and discussed, with examples, to conceptualise the implementation of these tools as an aid for decision making in health care management.

The following conclusions can be formulated with regard to the empirical investigation:

*The **fourth research objective** was to investigate the possible differences in the utilisation patterns and/or costs, before and after the implementation of the pricing regulations in May 2004.*

The *fourth research objective* was investigated in the following research objectives: *research objectives five, six, seven, eight, nine, ten, and eleven.*

*The **fifth research objective** was to determine the prevalence and usage patterns of drugs in general, as well as the costs associated with these drugs.*

It can be perceived from *section 5.2* that the total number of all medicine items claimed during 2001 was 2 951 326 increasing with 36.96 per cent (n=1 090 819) to 4 042 145 in 2002, and increasing with 31.26 per cent (n=1 263 737) to 5 305 882 in 2004. On the other hand, the total number of prescriptions increased from 1 475 380 in 2001 to 2 076 236 in 2002 to 2 595 254 in 2004. The weighted average number of medicine items per prescription on the total database rose from 2.00±0.05 in 2001 to 1.95±0.03 in 2002 to 2.04±0.08 in 2004. Although there was an increase in the total number of medicine items claimed for the three study years, the effect sizes (d-values) for the total number of prescriptions on the total database were not calculated, because the calculation of the d-values of the weighted average results in a smaller standard deviation and in its turn, if calculated, results in greater d-values than normal *(refer to paragraph 5.1.2)*. The weighted average cost (R) per prescription of the total medicine database increased from R257.36±3.42 in 2001 to R289.64±11.99 in 2002, and decreased to R254.78±18.83 in

2004. A similar trend was observed for the average cost per medicine item. The effect sizes (d-values) were also not calculated for the same reasons as above *(refer to paragraph 5.1.2)*. Results revealed that the utilisation of innovator medicine items claimed, gradually decreased from 73.24 per cent (n=2 951 326) for 2001 to 71.79 per cent (n=2 901 848) for 2002 to 66.51 per cent (n=3 529 046) for 2004 of the total number of medicine items claimed during these study periods. On the other hand, generic prescribing increased steadily over the three study years from 26.76 per cent (n=2 951 326) for 2001, to 28.21 per cent (n=4 042 145) for 2002, to 33.42 per cent (n=1 776 836) for 2004 of the total number of medicine items claimed during the three study years. Thus, as can be seen from above and from *section 5.2*, it can be concluded that the cost of drug therapy and prevalence increased from 2001 to 2002, and the prevalence increased from 2002 to 2004, but the cost of drug therapy decreased from 2002 to 2004 and could be a possible result of the implementation of the pricing regulations implemented in May 2004 *(refer to section 3.3.3)*.

*The **sixth research objective** was to analyse the general prescribing patterns of antiviral drugs as well as the costs associated with these drugs.*

Through the analyses of the general prescribing patterns *(section 5.2)*, it was evident that antiviral drugs contributed considerably to the prevalence and cost of all prescriptions claimed through the medicine claims database, constituting a total prevalence of 1.07 per cent (n=1475380) for 2001, 1.37 per cent (n=2076236) for 2002, and 2.26 per cent (n=2595254) for 2004 of all the prescriptions. A similar trend was observed with the prevalence of antiviral medicine items claimed through the database, constituting a prevalence of 0.72 per cent (n=2951326) for 2001, 1.25 per cent (n=4042145) for 2002,and 2.24 per cent (n=5305882) for 2004, and a total cost of 1.95 per cent (n=R379708482) for 2001, 3.58 per cent (n=R601350325) for 2002, and 5.76 per cent (n=R661223146) for 2004 of all the medicine items. The average number of antiviral medicine items per prescription increased over the three study years, from 2.21±0.48 in P1 to 1.65±0.87 in P4 to 1.90±0.86 in P7 to 2.09±0.81 in P9. Only the effect sizes (d-values) calculated for the differences between the average numbers of antiviral medicine items per prescription for P1 and P7, P1 and P8, P1 and P9, P2 and P8, and P2 and P9 have practical significant value (d>0.8). The average cost per antiviral prescription fluctuated during 2001, rose with 46.23 per cent (n=R290.34) in 2002 and increased with 23.08 per cent (n=R130.13) from P7 to P8, and decreased with 6.99 per cent (n= R48.49) from P8 to P9. The same trend was observed for the average cost per antiviral medicine items, and the effect sizes (d-values) calculated for both the differences between the average costs per antiviral medicine item and the average cost per medicine item separately, for the different time periods have no practical significant value (d<0.8). The decreasing trend in the average costs for the period P8 to P9 could be due to the implementation of the pricing regulations in May 2004. Results indicated that innovator antiviral medicine items largely increased from 29.21 per cent (n=1260) for 2001, to 62.31 per cent (n=6629) for 2002, to 197.96 per cent (n=131804) for 2004. Generic antiviral medicine items increased gradually from 1.66 per cent (n=29) for 2001 to 3.59 per cent (n=382) for 2002.

and rose sharply to 151.23 per cent (n=4322) for 2004. The effect sizes (d-values) calculated for the differences between the average cost of innovator antiviral medicine items and generic antiviral medicine items for each period separately (period P1 to P9 separately), have practical significant values (d>0.8) *(refer to section 5.3.1)*.

*The **seventh research objective** was to determine the prevalence and cost of the subdivisions of antiviral medicine items, ARV medicine items and "other antiviral medicine items".*

The average cost of ARV medicine items fluctuated over the nine study periods, ranging from R802.10±681.03 in P1 to R410.68±422.78 in P3 to R590.70±488.42 in P6 to R324.79±212.48 in P9. The "other ARV medicine items" seemed to be more stable over the three study years ranging from R234.16±280.39 in P1 to R208.95±239.90 in P3 to R207.84±252.32 in P6 to R196.66±306.40 in P9. Results revealed that there were no practical significant differences between the average cost of ARV medicine items, and also not for the "other antiviral medicine items". The cost-prevalence index of ARV medicine items is more than one for the three study years, indicating that ARV medicine items utilised are relatively expensive. In turn, the cost-prevalence index of the "other antiviral medicine items" is lower than one for the three study years, indicating that the "other antiviral medicine items" utilised are relatively inexpensive *(refer to section 5.3.2)*.

*The **eighth research objective** was to determine the prevalence and cost associated with innovator and generic forms of antiviral drugs.*

For the antiviral drugs, it was found that the prevalence of generic drugs increased with 1.06 per cent (n=29) in 2001, with 15.17 per cent (n=382) in 2002, and with 151.22 per cent (n=4322) in 2004. On the other hand, innovator drugs also increased with 29.21 per cent (n=1260) in 2001, with 62.31 per cent (n=6629) in 2002, and with 197.96 per cent (n=31804) in 2004. It was found that the total number of innovator antiviral medicine items prescribed entailed more than 70 per cent of the prescribed antiviral products ranging from 71.16 per cent (P1) to 75.82 per cent (P3), to 85.62 per cent (P6), and to 86.96 per cent (P9). The total cost of innovator antiviral medicine items lowered in 2001, and increased in 2002 and 2004. The total cost of generic antiviral medicine items experienced the same trend. The cost-prevalence index of the innovator antiviral medicine items was higher than one for the three study years, indicating that the treatment was relatively expensive. In turn the cost-prevalence index of the generic antiviral medicine items was lower than one for the whole study period, indicating that the treatment was relatively inexpensive. The average cost per innovator antiviral medicine item declined during 2001, inclined during 2002, and in 2004, it increased with 13.62 per cent (n=R45.56) from P7 to P8, and declined with 9.83 per cent (n=R37.35) from P8 to P9. Thus, the decline in cost from P8 to P9 could be due to the implementation of the pricing regulations in May 2004. The average cost per generic antiviral medicine item fluctuated during the three study years, from R91.74±89.40 in P1 to R87.09±104.87 in P9.

The effect sizes (d-values) between the average cost per innovator antiviral item, and also the average cost per generic antiviral medicine item respectively, are of no practical significant value. The effect sizes (d-values) between the average cost per innovator antiviral item and the average cost per generic antiviral item for the three study periods are all greater than 0.8, and of practical significance (d > 0.8) *(refer to section 5.3.3)*.

*The **ninth research objective** was to determine the general prescribing patterns of ARV drugs as well as the costs associated with these drugs.*

Section 5.2 indicates that ARV drugs also contributed to the prevalence and cost of all the medicine items available on the database, constituting a total prevalence of 0.38 per cent (n=1475380) for 2001, 0.72 per cent (n=2076236) for 2002, and 1.68 per cent (n=2595254) for 2004 of all the prescriptions. A similar trend was observed for the prevalence per ARV medicine items, constituting a total prevalence of 0.33 per cent (n=2951326) for 2001, 0.87 per cent (n=4042145) for 2002, and 1.92 per cent (n=5305882) for 2004 of all the medicine items, with a total cost of 1.31 per cent (n=R379 708 489) for 2001, 3.03 per cent (n=R601350325) for 2002, and 5.25 per cent (n=R661223146) for 2004 of all the medicine items. ARV drugs contributed considerably to the prevalence and cost of antiviral drugs, constituting a total prevalence of 35.31 per cent (n=15857) for 2001, 52.68 per cent (n=28482) for 2002, and 74.27 per cent (n=58549) for 2004 of all the antiviral prescriptions. A similar trend was also observed for the prevalence per ARV medicine items, constituting a total prevalence of 46.25 per cent (n=21183) for 2001, 70.20 per cent (n=50246) for 2002, and 85.87 per cent (n=118718) for 2004 of all the antiviral medicine items, with a total cost of 67.33 per cent (n=R7412577.73) for 2001, 84.72 per cent (n=R21523365.56) for 2002, and 91.20 per cent (n=R38064347.38) of all the antiviral medicine items. The effect sizes (d-values) calculated between the average number of ARV medicine items per prescription for P1 an P4, P1 and P5, P1 and P6, P1 and P7, P1 and P8, P1 and P9, P2 and P5, P2 and P6, P2 and P7, P2 and P8, and P2 and P9 are of practical significant value (d>0.8). The average cost per ARV prescription and the average cost per ARV medicine item followed the same changing trends during the three study years with an increase from P7 to P8, and a decrease from P8 to P9. The effect sizes (d-values) calculated for the differences between the average cost per ARV prescription for the three study years have no practical significant value (d<0.8), except for the effect size (d-value) for the period P6 to P7, which has practical significant value (d>0.8). The effect sizes (d-values) calculated for the differences between the average cost per ARV medicine items for the three study years have no practical significant value (d<0.8). The decreasing trend in the average costs for the period P8 to P9 could be due to the implementation of the pricing regulations in May 2004. From the results it is evident that there were no generic ARV medicine items claimed during the first and second study years. Thus, there were only innovator ARV medicine items available during the first and second study years, and rose with 88.47 per cent (n=1896) during 2001, with 84.26 per cent (n=6954) during 2002, and with 208.79 per cent (n=30421) during 2004. Generic ARV medicine items claimed during 2004 rose with 532.39 per cent (n=2449) *(refer to section 5.4.1)*.

*The **tenth research objective** was to determine the prevalence and cost of ARV medicine items for the three study years.*

The prevalence percentages increased during the three study years, while the cost percentages fluctuated during 2001 from 34.44 per cent (n=R1718891.10) in P1 to 33.24 per cent (n=R1658717.10) in P3, and increased during 2002 and 2004. A cost-prevalence index of higher than one for period P1, P6, and P8 indicate that treatment was relatively expensive for these periods, while cost-prevalence indices of lower than one were calculated for the other periods, indicating that treatment was relatively inexpensive for those periods. The average cost per ARV medicine items decreased by almost 50 per cent (n=R391.42) during 2001, increased with 27.40 per cent (R=127.06) during 2002, and remained stable during 2004, increasing with 16.13 per cent (n=R51.27) from P7 (before implementation) to P8 (transition phase), and decreasing with 12.03 per cent (n=R44.41) from P8 (transition phase) to P9 (after single exit price). Thus, the decreasing trend from P8 to P9 could be a possible effect of the implementation of the pricing regulations in May 2004 *(refer to section 5.4.2)*.

*The **eleventh research objective** was to determine the prevalence and cost of ARV medicine items for the three study years based on the different categories.*

From *section 5.4.3* can be seen that the PIs (category III) is the group representing the lowest prevalence and cost for all the study periods from period P2 to P9, except for the NNRTIs (category II) in period P1 with a prevalence of 106 (4.95 per cent; n=2143) and a cost of R84079.54 (4.89 per cent; n=R1718891.10). On the other hand, the NRTIs (category I) represent the group with the highest prevalence for all the study years, except for period P8 where the NNRTIs (category II) represent the group with the highest prevalence of 13 425 (34.88 per cent; n=38488). The NRTIs (category I) represent the group with the highest cost for all the study periods during 2001 (P1 to P3). The NRTIs (category I) also represent the group with the highest cost during P4, the NNRTIs (category II) during P5, the OTHER ARV medicine items (category IV) during P6, whilst the NNRTIs (category II) represent the group with the highest cost for all the study periods during 2004 (P7 to P9). The NRTIs (category I) and the OTHER ARV medicine items (category IV) of period P1 and the NRTIs (category I) of period P2 and P3 respectively, and the NRTIs (category I) of period P4, P5 and P6, and the NRTIs (category I) of period P7, P8 and P9 all have a cost-prevalence index of lower than one, indicating that their prevalence is slightly higher than the costs, and thus relatively inexpensive. The rest have a cost-prevalence index of higher than one, indicating that these medicine items utilised are very expensive. The PIs (category III) of period P1, P2, P8, and P9 and the OTHER ARV medicine items (category IV) of period P3, P4, P5, P6, and P7 have the highest weighted average cost per ARV medicine item. Each highest weighted average cost per ARV medicine item for 2004 are significantly lower than the study years before, whilst the effect of the pricing regulations implemented in May 2004 cannot be seen clearly *(see table 5.12)*.

*The **twelfth research objective** was to determine the prevalence and cost of ARV medicine items for the three study years based on the active ingredient classification.*

It can be perceived from *section 5.4.4* that didanosine represents the active ingredient with the largest prevalence for periods P1 to P5, and efavirenz represents the active ingredient with the largest prevalence for period P6 to P9. Didanosine also represents the active ingredient with the highest total cost for period P1, whilst the combination of lamivudine/zidovudine represents the active ingredient with the highest total cost for period P2 to P9. On the other hand, the following active ingredients represent the lowest prevalence: saquinavir mesylate for P1, P3, and P4, zalcitabine for P5 and P6, and nelfinavir for P2, P7, P7 and P9. The following active ingredients represent the lowest total cost: saquinavir mesylate for P1, P3, and P4 nelfinavir for P2 and P7, zalcitabine for P5 and P6, and ritonavir for P8 and P9. The cost-prevalence indices of didanosine, for period P1, P2, and P3, zidovudine for period P1 and P3, stavudine for period P2 and P3, nevirapine, lamivudine and the combination of lamivudine/zidovudine for period P1, didanosine, stavudine and ritonavir for period P4, P5, and P6, stavudine for period P4 and P5, nevirapine for period P6, and lamivudine, stavudine and ritonavir for period P7, P8, and P9, as well as zidovudine and didanosine for period P8 and P9 are all lower than one indicating that these active ingredients are all relatively inexpensive. Nelfinavir has the highest average cost for period P1, ritonavir for period P2, and saquinavir mesylate for period P3. The average costs of nelfinavir are the highest for each period from P4 to P6, while the average costs of didanosine are the highest for each period from P7 to P9. The high average costs, mostly of drugs prescribed only a few times, resulted in effect sizes (d-values) calculated between the average costs of individual active ingredients with practical significant values *(see section 5.4.4)*.

*The **thirteenth research objective** was to determine and compare the difference in prevalence and cost of innovator products versus generic products before and after the implementation of the pricing regulations in May 2004 of ARV drugs.*

As can be perceived from *section 5.4.5*, no generic ARV medicine items were claimed during 2001 and 2002. Innovator ARV medicine items increased with 88.47 per cent (n=1 896) in 2001, with 84.26 per cent (n=6 954) in 2002, and with 208.79 per cent (n=30 421) in 2004. Generic ARV medicine items increased with 213.04 per cent (n=980) from P7 to P8, and with 138.13 per cent (n=1 989) from P8 to P9, resulting in an overall incline of 645.43 per cent (n=2 969) in 2004. The prevalence percentage for 2004 entailed more than 92 per cent, while the cost percentage entailed more than 97 per cent. The total cost of innovator ARV medicine items decreased in 2001, and rose in 2002 and 2004, while the total cost of generic ARV medicine items inclined during 2004. The average cost per innovator ARV medicine item decreased during 2001, increased during 2002, and during 2004, it increased from R324.93±189.00 in P7 to R379.34±216.81 in P8, and decreased to R340.12±209.80. Thus, a 10.34 per cent (n=R39.22) can be seen from P8 to P9, a possible effect of the implementation of the pricing regulations in May 2004. The average cost per generic ARV medicine item steadily increased during the three study years. The effect

sizes (d-values) calculated between the average cost per innovator ARV medicine item and the average cost per generic ARV medicine item for the entire study period are all greater than 0.8, and of practical significance. The cost-prevalence index of the innovator ARV medicine items was exactly one for 2001 and 2002, indicating that there was equilibrium between the cost and prevalence of these medicine items utilised. The cost-prevalence index of the innovator ARV medicine items was slightly higher than one for 2004, indicating that treatment was relatively expensive, while the cost-prevalence index of the generic ARV medicine items was lower than one, indicating that treatment was relatively inexpensive.

*The **fourteenth research objective** was to determine the cost saving of ARV medicine items before and after the implementation of the pricing regulations in May 2004.*

It can be concluded that there were no cost savings for ARV medicine items for the period January to April versus May to August with a total increase of R22 968.93. For the period January to April versus September to December there was also no cost saving with a total increase of R8 382,88, but for the period May to August versus September to December there was a cost saving of R41 044.35 for the ARV medicine items. The implementation of the pricing regulations could thus be a possible reason for this cost saving, due to fact that the single exit price came into effect only from May 2004 *(refer to table 5.57, section 5.4.7).*

***The fifteenth research objective** was to identify combination therapy of ARV drugs and to determine the costs associated with these combinations.*

It was found that a total of 6 834 (69.76 per cent; n=9 796) prescriptions containing combination ARV medicine items were issued during 2001, a total of 32 941 (93.39 per cent; n=35 271) prescriptions containing combination ARV medicine items were issued during 2002, a total of 98 805 (96.93 per cent; n=101 938) prescriptions containing combination ARV medicine items were issued during 2004. For 2004, which was divided into the three four-month periods, a total of 14 579 (97.00 per cent; n=15 030) prescriptions containing combination ARV medicine items were issued during the period January to April 2004, a total of 37 257 (96.80 per cent; n=38 488) prescriptions containing combination ARV medicine items were issued during the period May to August 2004, and a total of 46 969 (97.00 per cent; n=48 420) prescriptions containing combination ARV medicine items were issued during the period September to December 2004 *(refer to section 5.4.7).*

6.3 LIMITATIONS AND SHORTCOMINGS OF THIS STUDY

The following limitations and shortcomings should be taken into account when evaluating the results and conclusions of this study:

- All the data concerning medicine usage and the cost of medicine usage obtained from the database after data refinement, were considered accurate and correct *(refer to section 4.8)*.
- Due to the unavailability of the data of 2003, usage and costs associated with this period cannot be compared with the other periods.
- No demographic data, such as age, gender and race were available on the database.
- Compliance could not be determined.
- Only single combinations of ARV medicine items were analysed.

6.4 RECOMMENDATIONS

The following recommendations can be made after the completion of this study:

- The nature and detailed analysis of ARV prescribing patterns fall outside the scope of this study, and were not further investigated.
- A data system must be developed to monitor (in general) the usage of ARV medicine on a continuing base.
- Outcomes strategies to determine the "success" of ARV treatment must be part of the monitoring system.
- A more in-depth study of the combinations of ARV medicine items needs to be compiled.
- The cost-savings due to generic substitution should be investigated.
- Possible drug-drug interactions should be analysed.

6.5 CHAPTER SUMMARY

In this chapter, the conclusions of this study were drawn and discussed. The recommendations that were derived in completion of the study, as well as the limitations and shortcomings that were encountered during the course of the study have been discussed.

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