Prescribing patterns of antiretroviral (ARV) drugs at Sekgoma Memorial Hospital ARV therapy clinic in Botswana

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Dedication

This work is dedicated to my brother, Mr. John Kalokoni for his inspiration and for believing in me. To my wife Emmah, my children Mwila, Wila, Kabwe and Chile for their forbearance during the time of this study.

Above all to God be the glory.

Acknowledgement

I am highly indebted to my supervisors whose invaluable guidance has led to the completion of this work.

ABSTRACT

KEY WORDS:

Prescribing patterns, antiretroviral drugs, Sekgoma Memorial hospital ARV therapy clinic, Botswana.

TITLE:

Prescribing patterns of antiretroviral (ARV) drugs at Sekgoma Memorial Hospital ARV therapy clinic in Botswana

Acquired Immunodeficiency Syndrome (AIDS) is characterized by the progressive destruction of a person's immune system and is the latest and most serious stage of Human Immunodeficiency Virus (HIV) infection. Botswana currently has the highest estimated prevalence of HIV infection in the world. Botswana has a relatively young population structure, with about 60% of the approximately 1,8 million people aged less than 45 years.

HIV prevalence for pregnant women aged 15-45 years in Botswana did, however, decrease marginally from 36,2% in 2001 to 35,4% in 2002. It is estimated that about 258 000 Botswana are now living with HIV and AIDS, and high morbidity and mortality rates due to HIV/AIDS have seen Botswana slip down the United Nations Development Plan (UNDP) Human Development Index rankings from 71 in 1996, to 122 in 1999/2000. In 2002 Botswana initiated public antiretroviral therapy (ART) at four sites initially to provide treatment to HIV/AIDS patients before expanding the programme to the rest of the country.

The specific objective of the study was to investigate the prescribing patterns of ARV drugs at Sekgoma Memorial Hospital ARV therapy clinic (SMH-IDCC) in the central district of Botswana for a two-year period from 2005 to 2006.

Data from 1717 patients were obtained from the SMH-IDCC electronic database regarding ARV drugs prescribed during the study period, CD4-Tcell count (cells/μL) at the commencement of therapy and after six months from the commencement of therapy and side effects necessitating change of therapy for the study period 2005 until 2006.

The study showed that there were eight antiretroviral therapy (ART) regimens prescribed: zidovudine plus lamivudine plus efavirenz (AZT/3TC/EFV), zidovudine plus lamivudine plus nevirapine (AZT/3TC/NVP), Combivir® plus efavirenz (CBV/EFV), Combivir® plus nelfinavir (CBV/NFV), Combivir® plus nevirapine (CBV/NVP), stavudine plus lamivudine plus efavirenz (D4T/3TC/EFV), stavudine plus lamivudine plus nelfinavir (D4T/3TC/NFV), and stavudine plus lamivudine plus nevirapine (D4T/3TC/NVP).

The most prescribed ART regimen for adult patients was Combivir® plus efavirenz (CBV/EFV) (51,37%). This was broken down as 17,20% of females and 34,17% of males.

The second most prescribed ART regimen was Combivir® plus nevirapine (CBV/NVP)(36% of the total study population (N=1717). This represented 34,17% of females and 1,98% of males.

The most prescribed ART regimen in children was zidovudine plus lamivudine plus efavirenz (AZT/3TC/EFV) (3,73% of the total population), broken down as 1,05% of females and 2,68% of males. The second most prescribed regimen in this group was zidovudine plus lamivudine plus nevirapine (ZDV/3TC/NVP) (3,50% of total population).

The findings from this study indicated that all eight the ART regimens prescribed at the study site were in accordance with the Botswana national ART guidelines. There were thirteen different types of side effects necessitating change of therapy, including pregnancy, treatment failure and poor adherence. The average CD4-Tcell count change (155.63 cells/μL, ± 204.08 cells/μL) for the study population was more than 100% after six months from commencement of therapy, indicating success of therapy in terms of CD4-Tcell count.

OPSOMMING

SLEUTELWOORDE:

Voorskryfpatrone, antiretrovirale geneesmiddels, Sekgoma Memorial hospitaal antiretrovirale terapiekliniek, Botswana.

TITEL:

Voorskryfpatrone van antiretrovirale (ARV) geneesmiddels by Sekgoma Memorial hospitaal ARV terapiekliniek in Botswana

Verworwe immuniteitsgebreksindroom (VIGS) word gekenmerk deur die progressiewe vernietiging van ’n persoon se immuunstelsel en is die laaste en ernstigste stadium van menslike immuniteitsgebrekvirus- (MIV-) infeksie. Botswana het tans die hoogste geskatte voorkoms van MIV-infeksie ter wêreld. Botswana het ’n relatief jong bevolkingstruktuur, met sowat 60% van die ongeveer 1,8 miljoen mense wat jonger as 45 jaar is.

Die voorkoms van MIV onder swanger vroue van 15-45 jaar oud in Botswana het egter marginaal vanaf 36,2% in 2001 tot 35,4% in 2002 gedaal. Daar word geraam dat ongeveer 258 000 persone in Botswana nou met MIV en VIGS leef, en hoë morbiditeits- en sterftesyfers as gevolg van MIV/VIGS het Botswana op die Verenigde Nasies se ontwikkelingsplan (UNDP) se menslike ontwikkelingsindeks-graderings laat daal van 71 in 1996 tot 122 in 1999/2000. In 2002 het Botswana openbare antiretrovirale terapie (ART) aanvanklik op vier plekke bekend gestel om behandeling aan MIV/VIGS-pasiënte te verskaf voordat die program na die res van die land uitgebrei sou word.

Die spesifieke doelwit van die studie was om die voorskryfpatrone van ARV-geneesmiddels by die Sekgoma Memorial Hospitaal se ARV-terapiekliniek (SMH-IDCC) in die sentrale distrik van Botswana vir ’n tweejaartydperk vanaf 2005 tot 2006 te ondersoek.

Data van 1 717 pasiënte vir die studieperiode vanaf 2005 tot 2006 is verkry van die SMH-IDCC elektroniese databasis ten opsigte van ARV-geneesmiddels wat in die studietydperk voorgeskryf is, CD4-T-seltelling (selle/µL) met die aanvang van terapie en na ses maande na die aanvang van terapie, en newe-effekte wat ’n verandering in terapie genoodsaak het.

Die studie het getoon dat daar agt antiretrovirale terapie- (ART-) regimens voorgeskryf is: zidovudien plus lamivudien plus efavirenz (AZT/3TC/EFV), zidovudien plus lamivudien plus nevirapien (AZT/3TC/NVP), Combivir® plus efavirenz (CBV/EFV), Combivir® plus nelfinavir (CBV/NFV), Combivir® plus nevirapien (CBV/NVP), stavudien plus lamivudien plus efavirenz (D4T/3TC/EFV), stavudien plus lamivudien plus nelfinavir (D4T/3TC/NFV), en stavudien plus lamivudien plus nevirapien (D4T/3TC/NVP).

Die ART-regimen wat die algemeenste voorgeskryf is vir volwasse pasiënte was Combivir® plus efavirenz (CBV/EFV) (51,37%). Dit is verdeel in 17,20% vroue en 34,17% mans. Die ART-regimen wat die tweede meeste voorgeskryf is, was Combivir® plus nevirapien (CBV/NVP) (36% van die totale studiepopulasie, N = 1 717). Dit verteenwoordig 34,17% vroue en 1,98% mans.

Die ART-regimen wat die meeste vir kinders voorgeskryf is, was zidovudien plus lamivudien plus efavirenz (AZT/3TC/EFV) (3,73% van die totale populasie), opgedeel in 1,05% vroulik en 2,68% manlik. Die ART-regimen wat in hierdie groep die tweede meeste voorgeskryf is, was zidovudien plus lamivudien plus nevirapien (ZDV/3TC/NVP) (3,50% van die totale populasie).

Die bevindings van hierdie studie het aangedui dat al die ART-regimens wat by die studieterrein voorgeskryf is, met Botswana se nasionale ART-riglyne ooreengestem het. Daar was dertien verskillende soorte newe-effekte wat ’n verandering in terapie genoodsaak het, insluitend swangerskap, mislukking van behandeling en swak nakoming. Die gemiddelde CD4-T-seltellingverandering (155.63 selle/µL, ± 204.08 selle/µL) vir die studiepopulasie was meer as 100% na ses maande na die aanvang van terapie, wat die sukses van die terapie in terme van CD4-T-seltelling aandui.

LIST OF ABBREVIATIONS:

>, <	greater than, less than
3TC	lamivudine
ABC	abacavir
ACHAP	African comprehensive HIV/AIDS partnership
AIDS	acquired immune deficiency syndrome
ANC	**a**ntenatal clinic
ART	antiretroviral therapy/treatment
ARV	antiretroviral drugs
AZT	zidovudine, ZDV
BAIS	Botswana AIDS Impact Survey
BOTUSA	partnership between Botswana and the United States of America Governments
CD4	cluster of differentiation 4
CDC	Central District Council
CDC	Centers for Disease Control and Prevention, Atlanta, Georgia
d4T	stavudine
ddI	didanosine
DHT	district health team
DNA	de-oxyribonucleic acid
EFV	efavirenz
FBC	full blood count
FTC	emtricitabine
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus, type 1 (HIV-1)
LFTs	liver functioning tests
LPV/r	ritonavir-boosted lopinavir [Kaletra®, Aluvia®]
MOH	Ministry of Health
NACA	National AIDS Coordinating Agency

NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PEPFAR	president's emergency plan for AIDS relief
PCR	Polymerase Chain Reaction
PI	protease inhibitor
PMTCT	prevention of mother-to-child transmission
sd-NVP	single-dose nevirapine
SJS	Stevens-Johnson syndrome
SMH- IDCC	Sekgoma Memorial Hospital ARV therapy clinic
SQV	saquinavir
TB	tuberculosis
TDF	tenofovir
U&E	urea and electrolytes
UNAIDS	Joint United Nations Programme on AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
VCT	Voluntary Counselling and Testing
WHO	World Health Organization
WHO/AFRO	World Health Organization Regional Office for Africa

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

This thesis focuses on the prescribing patterns of antiretroviral (ARV) drugs at Sekgoma Memorial Hospital ARV therapy clinic (SMH-IDCC) in Serowe village in the central district of Botswana.

In this chapter the problem statement, research objectives and research methodology will be briefly discussed. The discussion on the division of chapters will mark the end of the chapter.

1.2 PROBLEM STATEMENT

Acquired immunodeficiency syndrome (AIDS) is characterized by the progressive destruction of a person's immune system and is the late and most serious stage of Human Immuno deficiency Virus (HIV) infection (Levy *et al.,* 2006:171). Over the past two decades, the epidemic has become a major challenge to health-care systems, with more than 20 million people dying from HIV/AIDS and a further 40.3 million people worldwide estimated to be infected with HIV in 2005 (UNAIDS/WHO, 2005).

HIV/AIDS is already the leading cause of death worldwide (United Nations Children's Fund, 2004:10). More than half of the burden of HIV/AIDS is borne by sub-Sahara, particularly the Southern African countries. In countries such as Botswana, South Africa, Zimbabwe, Swaziland and Namibia the prevalence of HIV infection among expectant mothers is consistently in excess of 20% (Sharma & Khadhiravan, 2008:162). HIV/AIDS accounts for about 20% of all deaths and disability-adjusted life-years (DALYs) lost in Africa, which makes it the biggest single component of the continent's disease burden (WHO, 2000).

Stewart *et al.* (2004:9) were of the opinion that despite the disproportionate burden of HIV epidemic in sub-Sahara Africa, to date antiretroviral therapy (ART) interventions in the region have been small scale

Yazdanpanah (2004:560). noted that it is important to remember that the great majority of HIV-infected people live in low-income countries and is of the opinion that while treatment barriers are partly social and logistic, the overwhelming barrier is cost.

Further the relative high price of many of the antiretroviral (ARV) drugs and diagnostics on the other hand forms one of the main barriers to the availability of ARV drugs in developing countries (United Nations Children's Fund, 2004:77).

Although recent advances in treatment, especially the use of potent combinations of nucleoside reverse transcriptase inhibitors, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors (referred to as highly active antiretroviral therapy, or HAART), have

resulted in dramatic reductions in the rates of HIV/AIDS disease progression, opportunistic infections, hospital admissions, and deaths (Levy *et al*., 2006:171).

According to UNAIDS/WHO (2001:7):–

- The epidemic is driving a ruthless cycle of impoverishment. People at all income levels are vulnerable to the economic impact of HIV/ AIDS, but the poor suffer most acutely.
- One quarter of households in Botswana, where the adult prevalence of the disease is over 35%, can expect to lose an income earner within the next 10 years.
- A rapid increase in the number of very poor and destitute families is anticipated in Botswana. Per capita household income for the poorest quarter of households is expected to fall by 13%, while every income earner in this category can expect to support four more dependants.

United Nations Children's Fund *(* 2004:77) believed that the relative high price of many of the HIV/AIDS-related medicines and diagnostics offered by common suppliers especially ARVs and anticancer medicines is one of the main barriers to their availability in developing countries.

A variety of barriers are futhermore responsible for impeding access to ARV treatment, including but not limited to the poverty of African countries, the high cost of ARV treatment, national regulatory requirements for medicines, tariffs and sales taxes, and above all, a lack of sufficient international financial aid to fund ARV treatment (Attaran & Gillespie-White, 2001:1886).

Allocation of new funds for HIV/AIDS requires more than ranking of cost-effectiveness. Nevertheless, value for money is important especially in African countries, where resources are particularly scarce and needs are so great. Existing cost-effectiveness data are few, and much more high quality research is needed for detailed planning and programming. Yet even the available data make it clear that a spending programme for HIV/AIDS relief in Africa that neglects to bring cost-effectiveness evidence into the consultation process risks unnecessary sacrifice of hundreds of thousands of prevention opportunities, treatment opportunities and lives (Creese *et al.,* 2002:1641).

Levy *et al.* (2006:171,176) noted that:

- Information on the direct costs of ARV drug treatment is important since it provides a basis for health planners to allocate budgets. It also enables policy makers, when faced with changes in prevention and treatment programmes, to make relevant up to date estimates of the direct cost of ARV drug treatment.

- Although economic evaluation is an important approach for establishing priorities for health interventions, in practice this type of evaluation has been of limited value in HIV/AIDS because of the paucity of accurate cost data.
- The advent of HAART has major implications on the cost of treating people infected with HIV. To date, however, only a small number of studies have been published that provide useful estimates of direct cost of ARV drug treatment, such as those conducted by Sabbatani and Cesari (2002:255) on cost assessment of ARV drugs in the treatment of patients with HIV infection.
- Creese *et al.* (2002:1638) discovered that the most cost effective interventions were for prevention of HIV/AIDS and treatment of tuberculosis, whereas HAART for adults and home-based care organized from health facilities were the least cost-effective.

More refined cost-effectiveness analyses on combination ARV therapy are needed. In low-income countries, better analyses are needed to evaluate the impact of and cost-effectiveness of available HIV/AIDS prevention, treatment and care programmes. By ensuring that such clinical economic evaluations are available, health planners and policy makers will be in a position to allocate resources better (Yazdanpanah, 2004:558). However the collection and analysis of economic data continues to be important as new drugs and new strategies will become available (Torti *et al*., 2003:266).

While Botswana has attracted much attention from international donor agencies and research institutions, surprisingly little analytical research has been published locally and much of the available research documentation is descriptive in nature. This lack of critical and analytical research indicates that critical debate about the Botswana programme has yet to take place (WHO, 2004:226).

It is therefore imperative that research be conducted regarding the utilisation and cost implications associated with ARV drugs at SMH-IDCC in Botswana.

Botswana has one of the highest HIV infection rates in the world, with approximately 38.5% of the adult population now infected (Botswana, 2006). In the year 2002 the Government of Botswana decided to start providing ARV drug therapy to qualifying citizens while prevention remained the cornerstone of the national HIV/AIDS strategy. Eligibility criteria included the following:

- presence of an HIV/AIDS-defining illness,
- a cluster of differentiation 4 (CD4)-Tcell count of less than 200 cells per micro litre (CD 4 <200 cells/μL),
- any HIV positive child younger than 12 months of age, and

- children over one year of age who are symptomatic or immunocompromised.

Botswana began Africa's first national programme for prevention of mother to child transmission (PMTCT) in 2001 and the continent's first national public antiretroviral (ARV) programme in 2002 (Creek *et al*., 2006:210)

The Ministry of Health adopted a phased approach to providing ARV therapy while growing its resource base. ARV therapy was initially available to the public in four sites before scaling to other parts of the country. These four centers were; Princess Marina hospital in Gaborone, Nyangabwe hospital in Francistown, Maun hospital in Maun and Sekgoma memorial hospital in Serowe.

According to Ministry of health (2005:10) the question of what ARV drugs should be used in Botswana is important. International recommendations for ARV therapy did not take into account questions of cost, affordability or sustainability of treatment. Other potentially important factors included climate, sophistication of the social and health infrastructure and lifestyle including food intake. Consequently, these international treatment recommendations had to be modified for use in Botswana, based on principles established before hand as follows:

- Proof of efficacy of ARV treatment (ART) regimens.
- First line ART regimens should not contain a protease inhibitor (PI) for cost and toxicity reasons.
- Because of concerns about adherence, first line regimen should :
    - have a low pill load or burden; (few pills per day);
    - have simple dosing frequency- twice a day at most; and
    - be independent of food intake.(no food restrictions)
- Should include agents with proven efficacy and safety in PMTCT;
- As the first line regimen offers the best chance for control of the virus, the best ART regimen should be preserved for first line and not second or third line.
- Reserve PIs for second or third line (salvage) regimen. In this regard, lopinavir/retonavir (Kaletra®) is the favoured PI because of its potency, durability and threshold for development of resistant mutations (Ministry of health, 2005:10).

About a decade ago Moore (2000:325-330) made the following comments about combination therapy:

- Since 1997, expert panel guidelines for HIV/AIDS care have recommended the use of combination ART with at least three ARV drugs.
- Analyses comparing a three-drug PI-containing regimen with a 1- or 2-drug non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen have consistently yielded incremental direct costs ranging from $US 10 000 to just over $US 13 000 per year of life saved.
- In western societies such an incremental cost per year of life saved compares favourably with chronic therapy for other diseases and Moore urged for the adoption of these drugs by payers and policymakers. The reason for this favourable cost-effectiveness ratio appears to be the decrease in opportunistic complications and hospitalization associated with the effective use of combination ART regimens.

From this short overview it was important that research regarding the utilisation and cost implications associated with ARV drugs at SMH-IDCC in Botswana be performed. This was done during a two year study period.

1.3 RESEARCH QUESTIONS

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

- How can HIV/AIDS be conceptualised in Botswana?
- What is the health care system in Botswana?
- What programmes are in place regarding HIV/AIDS in Botswana?
- What are the prescribing patterns of ARV drugs and what are the costs associated with these drugs in SMH-IDCC in Botswana?
- What are the prescribing patterns in other parts of the world, South Africa and sub-Saharan Africa?
- Does combination therapy of ARV drugs occur and what are the costs associated with these combinations?
- When can treatment be defined as successful?

1.4 RESEARCH OBJECTIVES

The research project included a general as well as various specific research objectives.

1.4.1 General research objective

The general research objective of this study was to determine the prescribing patterns of ARV drugs at SMH-IDCC in the central district of Botswana .

1.4.2 Specific research objective

The research project consisted 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 included the following:

- To describe the healthcare system in Botswana.
- To conceptualise HIV/AIDS prevalence in Botswana, South Africa and other countries from available literature.
- To conceptualise the HIV/AIDS treatment programmes in Botswana.
- To compare ARV treatment guidelines of Botswana with those of WHO and South Africa.

1.4.2.2 Phase 2: Empirical investigation

The specific research objectives of the empirical investigation were:

- To identify the prescribing patterns of ART regimens at the SMH-IDCC in the central district of Botswana.
- To determine the costs associated with the above ART regimens.
- To determine the prevalence of side-effects with certain ART regimens.
- To illustrate treatment outcomes with the different ART regimens by using CD4-Tcell counts.

1.5 RESEARCH METHOD

The research project consisted 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 aspects were studied in the literature study:

- Nature of HIV/AIDS
- HIV/AIDS treatment regimens and ARV drugs

- healthcare system in Botswana
- HIV/AIDS prevalence in Botswana, South African and other countries from available literature
- The conceptualisation of the HIV/AIDS treatment programmes in Botswana
- a comparison of ARV treatment guidelines of Botswana with those of WHO and South Africa

1.5.2 Phase 2: Empirical investigation

This phase of the investigation contains the results. The data utilised during this stage were obtained from the electronic database of SMH-IDCC. The study period ranged from 1 January 2005 to 31 December 2006.

1.5.2.1 Research design

A non-experimental, quantitative, retrospective drug utilization review (Wisconsin Medicaid, 2001:1) method was used in order to obtain the essential data and achieve the specific objectives for this research project. The study design is descriptive in nature and covered a period of two years (1 January 2005 to 31 December 2006).

1.5.2.2 Study site

SMH-IDCC is located about 153 kilometres from the Martin's drift border with South Africa. The hospital had four satellite clinics. These clinics initroduced patients to medication and later reviewed the patients. However, all ARV medication was dispensed from SMH-IDCC.

Patients came from all parts of the country. Some patients came to their home villages after having been ill for a long time, as home-based care patients being taken care of by their relatives. The process of patient assessment and registration for the initiation of therapy took place in the hospital as well as in the clinics, but medication was only dispensed from the SMH-IDCC during the study period. Proximity to the health facility was a major contributing factor to patient's ability to access the services offered and also affected the patient adherence to the prescribed regimen beside the medicines side effects, financial constraints, poor transport, social support, and experience of illness.

Patients commenced therapy after a thorough assessment and preparation in readiness for medication. They went through a process of check-up and laboratory investigation to establish the baseline data necessary to allow them to commence therapy. Baseline investigations included the CD4-Tcell count, (CD4-Tcell count was used as criteria for commencing therapy at SMH-IDCC), urea and electrolytes (U&E), full blood count (FBC), liver functioning tests (LFTs), presence of tuberculosis (TB) and other diseases present. Patients with renal or hepatic insufficiency are at increased risk of toxic concentrations for

ARV medication (Rakhmanina *et al.,* 2004:10). Only CD4-Tcell count for all patients in the study was fully documented. Complete data on viral load was not readily available during the time of this study and could not be analysed.

Patients went through a general HIV/AIDS counseling on the patient's knowledge and understanding of the HIV/AIDS and medication adherence counseling. This counselling helped the patient understand important issues pertaining to the relevance of adherence to the treatment process.

Patients registered with the hospital or the four satellite clinics where they were prepared for commencement of therapy. When a patient commenced therapy they collected the medications in person from the SMH-IDCC pharmacy for an initial two weeks' supply. This allowed the patient to come back to the SMH-IDCC for review early and allowed the doctor to assess the patient's reaction, tolerance and side effects and also to make necessary adjustments. This also allowed the pharmacy to augment the medication adherence counseling. The patient then collected two weeks supply and returned for review after that period. The patient then received a month's prescription and collected medication for a month. When the patient had stabilized on medication he or she then received a review period of three months but continued to collect medication supply monthly. This helped the pharmacy to collate and assess the patient's adherence to therapy. Merito *et al.* (2005:305) noted that various health conditions and stages of the HIV/AIDS infection in patients at the start of treatment made the prescribed course of treatment notably different.

The initial CD4-Tcell count is done at the start of therapy, at three months after starting therapy and then every three months as a set standard (Ministry of health, 2002:20). Similarly plasma HIV Ribonucleic acid (RNA) (viral load) is done at the same intervals. For this research project the researcher managed to collect the initial CD4-Tcell count and after six months. This data were readily available from the data base at the time of study.

According to the Botswana guidelines on ARV Treatment (Ministry of health, 2002:20, 2005:19) clinical monitoring for toxicity, opportunistic infections and adherence should be done as follows; plasma HIV Ribonucleic acid RNA (viral load) at start of therapy, at three months and every six months. CD4-Tcell count every three to four months. Liver functioning tests (LFTs), urea and electrolytes (U&Es), and full blood count (FBC) at the start of therapy, at two weeks and every three months thereafter. Clinical monitoring for toxicity, opportunistic infections and adherence is done at base line investigations stage, at two weeks, at one month, three months after commencement of therapy and then three monthly by the doctor. Adherence and toxicity should be monitored every month by the pharmacist.

1.5.2.3 Study population

Data of all ARV medicine items dispensed at SMH-IDCC were obtained from the electronic data base for two years from 01 January 2005 to 31 December , 2006. The study population included all patients that commenced therapy during the study period. The study population consisted of 1717 patients.

Data on all ARV medications dispensed to patients were obtained from the computerized hospital information system, the electronic pharmacy record and supplemented by manual records. Data on side effects, CD4-Tcell counts, and adherence recordings were collected electronically; some of this information was obtained manually from data that were recorded before the whole information system at the center was computerized. CD4-Tcell count data were collected at base line investigation stage before commencement of therapy and then at six months from commencement of therapy. Information on the cost of medication was obtained from the Government's central medical stores (CMS) purchasing unit.

The individual drugs and different drug regimens were identified and costs associated with them calculated. Side effects associated with these drugs and drug regimens were identified with CD4-Tcell response considerations at six months after commencement of therapy.

1.5.2.4 Data analysis

The data were analyzed using Statistical Analysis System, SAS® 9.1 (SAS® for Windows, 9.1, 2005). The results, the discussion of the results from the study, conclusion, recommendations and limitations based on the results will be discussed in chapters 4 and5.

1.5.2.5 Ethical permission

The researcher obtained permission for conducting this study from the Botswana Ministry of Health, research unit and from Sekgoma Memorial Hospital before the study was undertaken. It was also accepted by the ethics committee of the fulculty of healthsciences at North-West University's Potchefstroom campus (NWU-00076-10-55). In this way the researcher ensured that the research was scientifically and ethically justified according to the standards of the North-West University. No names of patients or health workers were mentioned to ensure confidentiality and all data were used for study purposes only.

1.6 DIVISION OF CHAPTERS

The division of chapters will be as follows:;

Chapter 1: Introduction

Chapter 2: Literature review

Chapter 3: Research methodology

Chapter 4: Results and discussion

Chapter 5: Conclusions and recommendations

Chapter 6: Reference

1.7 CHAPTER SUMMARY

In this chapter, the problem statement, research questions, research objectives, empirical research method and division of chapters have been outlined. The problem statement focused mainly on the prevalence, on treatment and cost aspects related to HIV/AIDS with reference to Botswana and especially the SMH-IDCC. The latter institution is the “heart” of this study. The literature review will be discussed in Chapter 2.

CHAPTER 2

LITERATURE REVIEW: HIV/AIDS IN BOTSWANA

2.1 INTRODUCTION

In this chapter an overview of the nature of HIV/AIDS, the healthcare system of Botswana, statistics of HIV/AIDS and HIV/AIDS programmes in Botswana will be discussed on the basis of the available literature. A comparison of the ART guidelines for Botswana, South Africa and the World Health Organization (WHO) will mark the end of the chapter.

2.2 NATURE OF HIV/AIDS

According to Turkoski (2006:51) viruses are the smallest of the currently known pathogens. They are incapable of reproducing outside of a living cell because they contain either DNA or RNA, never both, and use the nucleic acid of the living cell to reproduce. HIV is a retrovirus consisting of two RNA molecules.

Turkoski (2006:51) further points out that the virus relies on the enzyme reverse transcriptase to cause the transcription of one RNA strand to DNA (reverse transcription). This viral DNA is then incorporated into the host cell's nucleus with the enzyme integrates. The enzyme protease is vital for the assembly and release of the new HIV virions (complete virus material) that continue to infect other cells. There are two known species of HIV that infect humans: HIV-1 and HIV-2. HIV-1 is easily transmitted, more virulent, and responsible for HIV infections throughout the world. HIV-2 is primarily confined to West Africa.

Sharma and Kadhiravan (2008:163) explain that HIV is an enveloped single-stranded RNA virus. Embedded in its envelope are glycoprotein spikes that are crucial for binding with the host cell surface receptors, such as CD4-Tcell, CCR5 and CXC4, and subsequent entry into the host cell. HIV is a retrovirus that elaborates the enzyme reverse transcriptase. It enables transcription of genomic RNA to proviral DNA for integration into host cell DNA. Host cells that bear CD4-Tcells (helper T cells, macrophages, etc.) are the main targets of HIV infection.

2.2.1 Pathogenesis

According to Sharma and Kadhiravan (2008:165) following infection, HIV localizes to the lymphoid organs of the body, where it predominantly infects the CD4+ helper T lymphocytes in the milieu provided by the dendritic cells and subsequently spills over into the circulation. In the absence of an immune response, this results in intense viremia in the early weeks following primary infection. During this phase, extensive dissemination of the virus occurs throughout the body.

2.2.2 Stages of HIV infection

Jackson (2002:44) describes four stages of HIV infection:;

- Initial acute infection stage (primary infection): normal CD4-Tcell count of 500 - 1200 cell/μL undergoes a temporal drop and usually recovers to near normal levels within two to six weeks.
- Baseline level of HIV infection: CD4-Tcell count above 500 cell/μL; viral load 1000 up to 10,000 copies of HIV per ml of plasma. The higher the viral load the earlier the likely progression to AIDS.
- Beginnings of HIV-related disease: CD4-Tcell count 200-500 cell/μL; about one in 1000 CD4-Tcells is infected, and the viral load below 100,000 per ml.
- Definition of AIDS: CD4-Tcell count below 200 cell/μL ; up to 10 % of CD4-Tcells in the blood are infected; viral load; 100,000 to 1 million viral particles per ml.

2.2.3 Link between HIV and AIDS

Sharma and Kadhiravan (2008:166) wrote that during the phase of clinical latency, continuous viral replication leads to progressive depletion of CD4-Tcells, resulting from direct cytopathicity as well as by diverse indirect mechanisms. When the CD4-Tcell count falls below 200 cell/μL, the risk of opportunistic infections (OIs) increases greatly, culminating in AIDS. The CD4-Tcell count, as an index of immune suppression because of HIV infection, strongly predicts the risk of OIs and there by the risk of progression to AIDS and subsequent death. However when the CD4-Tcell counts are above 350 cell/μL, their usefulness in predicting the risk of disease progression is limited.

2.2.4 Rate of development of HIV into HIV/AID related disease

Jackson (2002:45) noted that over time, when the relentless replication of HIV has caused too much damage, the immune system can no longer fight infections and signs and symptoms of disease begin to appear. He further stated that reasons why some people develop AIDS faster than others are not yet fully understood but noted the following reasons as contributory:

- infection with different types of viruses.
- natural genetic differences in individual immune responses.
- stress on the immune system through a general lack of fitness and exposure to repeated or severe infection with different organisms.

- repeated sexually transmitted infections (STIs) that keep the immune system highly active and so appear to speed up HIV replication.
- state of mind – anxiety, depression and general feeling low may increase susceptibility to other infections and so stress the immune system.
- other health stressors such as overtiredness, poor diet and under-nutrition and the heavy use of alcohol.

2.3 HIV/AIDS TREATMENT REGIMENS

The following section is a review of ARV drugs, their classification, mode of action, indication for HAART, adherence and side effects.

2.3.1 Classification of ARV drugs

HIV/AIDS treatment has been achieved through development of ARV drugs used in combination as ART regimens. The rapid development of successful ARTs has dramatically changed the treatment of HIV infection (Holodniy *et al*., 2007:20).

Hofman and Nelson (2006:3121) categorize drugs against the human immunodeficiency virus (HIV) according to their mode of action as follows into four main groups:

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Fusion inhibitors (FI)

Turkoski (2006:52) further defines the ART drug classes as follows with a brief description of their mode of as action:

Nucleoside reverse transcriptase inhibitors (NRTI)

NRTI provides a "false" version of the building blocks that HIV uses to replicate itself. Using an NRTI halts reproduction of the virus.

The following are representative of this class:

Abacavir (Ziagen®), Didanosine (Videx, ® Videx®, Videx EC®), Emtricitabine (Emtriva®, FTC®, Coviracil®), Lamivudine (Epivir®, 3TC) Stavudine (Serit®, d4T), Tenofovir DF (Viread®, TDF), Zaicitabine (Hivid®, ddc), Zidovudine (Retrovir®, AZT, ZDV).

Combinations:

Abacavir/Lamivudine/Zidovudine(Trizivir®),
Emtricitabine/Tenofovir®DF(Truvada®)
Lamivudine/ Zidovudine (Combivir®)

Nonnucleoside reverse transcriptase inhibitors (NNRTI)

NNRTI binds to and disable reverse transcriptase, an enzyme HIV uses to replicate itself. The following drugs fall into this class:

Delavirdine (Rescriptor®, DLV), Efavirenz (Sustiva®, EFV), Nevirapine (Viramune®, NVP).

Protease inhibitors (PI)

PI inhibits the enzyme protease that HIV needs to replicate itself.

The following drugs belong to this class:

Amprenavir (Agenerase®, APV), Atazanavir (Reyataz®, (ATV), Fosamprenavir (Lexiva®, FPV) Indinavir (Crixivan®, IDV), Nelfinavir (Viracept®, NFV, Ritonavir (Norvir®, RTV), Saquinavir (Invirase®, SQV), Tipranavir (Aptivus®, TPV) I

Combination:

Lopinavir / Ritonavir (Kaletra®, LPV/r)

Fusion inhibitors (FI)

FI blocks entry of HIV into cells. Enfuvirtide (Fuzeon®, T-20) belongs to this group

2.3.2 ART regimens

Sharma and Khadiravan (2008:170) described Highly Active Antiretroviral Therapy (HAART) as a combination of at least three potent antiretroviral drugs, typically a combination of two NRTIs as the back bone along with either a PI or an NNRTI.

Shebu-Xhilaga *et al.* (2005:1705) mentioned that the use HAART, has dramatically improved the quality of life for HIV-1 infected individuals. According to these authors antiretroviral drugs were initially introduced as mono or dual therapy, but due to clinical failure resulting from the frequent acquisition of resistant mutations, combination regimens of HAART were initiated

Over the past four years the standard of care and outcomes of care for HIV/AIDS have changed dramatically. Potent 3- or 4- drug combination ARV regimens have resulted in substantial increases in CD4-Tcell counts and the suppression of the HIV plasma viral load in treated individuals. There is also growing evidence from randomised clinical trials that use of these combination ARV regimens results in improved clinical outcomes for those living with

HIV/AIDS (Stone *et al.* 2001). The use of these regimens also appears to have been the major factor contributing to recent reductions in morbidity and mortality due to HIV/AIDS in the United States. (Stone *et al.,* 2001).

The international treatment recommendations have been modified for use in Botswana on the basis of efficacy (Ministry of health, 2005:10).

- For cost and toxicity reasons, the first-line regimen should not contain a PI.
- The first-line regimen should have a low pill load, a simple dosing frequency and should be independent of food intake.
- The regimen should include agents with proven efficacy and safety in prevention of mother to child (PMTCT) transmission of HIV.
- The first-line regimen should be preserved for first line and not second or third line.
- PIs should be reserved for second and third-line regimen.

Holodniy *et al.(*2007:26) noted that the correlation between prescribing patterns and guidelines was greatest for recommendations that inform physicians what not to do so as to avoid harm rather than recommendations that inform physicians what to do so as to improve efficiency. Although there are specific guidelines on recommended regimens the actual prescribing remains in the hands of the individual prescriber. The prescriber is faced with commencing the patient on medication on the basis of the initial base line investigations and other factors presented by the patient such as age, gender or infection.

The Department of Health and Human Services (DHHS) panel on ARV guidelines for adults and adolescents continues to select several regimens as preferred, while appreciating that patient or provider preferences, or underlying co-morbidities, may make an alternative regimen better in such instances. The panel recommends that an initial regimen contain two nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted or un-boosted protease inhibitor (PI) (OARAC, 2006:2).

The panel notes the high degree of medication adherence with all ARV regimens needed to prevent the selection of drug resistance. It also appreciates that short term and, even more concerning, longer-term toxicity may limit the duration of treatment needed in what can be seen as chronic disease. Finally, drug interactions among the ARV drugs and with other necessary drugs are challenging and require special attention in prescribing and monitoring (OARAC, 2006:2).

Merito *et al*. (2005:305) say that combinations of at least three different ARV molecules, belonging to the class of nucleoside reverse transcriptase inhibitors (NRTI), protease

inhibitors (PI), or non-nucleoside reverse transcriptase inhibitors (NNRTI) (called HAART) have radically changed the natural course of the HIV infection. They further say that various conditions and stages of the infection in patients at the start of treatment make the prescribed course of treatment notably different. They further suggest that in analyses such as economic evaluation of HIV treatments it is important to concentrate on evaluation of the costs of the drug combinations prescribed.

2.3.3 Indications for HAART

ARV drug combinations such as HAART have been used to treat HIV/AIDS and their use has become wide spread in Western countries (Merito *et al.,* 2005:305).

Sharma and Kadhiravan (2008:168) noted the following:

- HAART has dramatically changed the long-term outcome of patients with HIV/AIDS, which once was a rapidly fatal illness. It not only improves the CD4-Tcell counts but also reduces the risk of opportunistic infections and reduces the mortality substantially. The benefit of HAART is evident even in those patients with advanced immune suppression.
- From the public-health perspective, HAART is a cost-effective intervention, in the developed world and the developing nations alike. In fact, HAART is comparatively more cost-effective than some of the widely accepted therapies for certain non-HIV diseases.
- Since the introduction of HAART in 1995, HIV/AIDS-related mortality has declined considerably in the United States.
- Recently enfuvirtide, a peptide that inhibits fusion of HIV-1 with the host cell membrane has also been approved for use in the treatment of HIV-1 infected individuals.

2.3.4 Goal of therapy

OARAC (2007:10) indicate that the goals of ARV drug therapy are to

- reduce HIV related morbidity and to improve survival,
- improve quality of life,
- restore and improve immunologic functions,
- maximally and durably suppress viral load, and
- prevent vertical HIV transmission.

2.3.5 Adherence

According to Goldie *et al*. (2003:639) the clinical effectiveness of ART for HIV/AIDS depends heavily on the patients' ability to adhere closely to complicated drug regimens and suggest that interventions that improve adherence to combination ART, such that failure rates are

reduced by about 10% to 20%, will provide quality-adjusted life expectancy gains of a similar magnitude to opportunistic infection prophylaxis.

Sharma and Khadiravan (2008:178,179) commented that adherence to prescribed treatment is a complex issue but of the utmost importance. Antiretroviral treatment is very exacting in terms of adherence when compared with other chronic diseases; missing as little as 5% to 10% of doses is known to affect virologic outcome adversely. They further noted that the natural tendency is to miss a few doses, and physician's estimates of adherence are known to be unreliable. It is therefore important to suspect non-compliance in every patient.

They stated the following causes for non-compliance with treatment:

- Patient-related factors such as substance abuse, depression, lack of social support and age
- Medication-related factors such as dosing frequency, pill burden, food/fasting requirements, and adverse effects; and
- Health-care system-related factors such as attitude of staff, communication and accessibility, all operating in tandem to influence the adherence of the patient.

The WHO (2003:5) indicated that medications that are prescribed following consultation with a medical professional are usually dispensed with an expectation of close to perfect adherence. Such expectations pertain to the dosage, timing, ingestion with specific foods, contra-indications regarding ingestion with other medications and consistent adherence to the regimen over time. Zgibor *et al.* (2004:15) concluded that these details of adherence were of crucial in maximizing the health benefits from medical treatment. Patients' non-adherence may have severe implications for the control of symptoms, recovery time, quality of life and mortality.

Kagee *et al.* (2007:445,446,447) mentioned three themes that appear in literature associated with non-adherence to therapy namely ;

- factors associated with non-adherence to treatment,
- successful prediction of potential non adherent patients
- and methods of intervention by health providers to enhance adherence to treatment.

They further stated that various studies had shown the association between demographic characteristics such as gender, age, ethnic groupings, level of education and income with non-adherence to therapy and concluded that these variables were not inherently causal but tend to act as proxies for other factors such as health literacy, poor financial resources to access health-care and cultural mistrust of the formal health sector. They discussed the factors associated with non-adherence under the following headings:

- Social and economic factors:

  Poverty in itself is likely to affect adherence, as financial resources may need to be directed elsewhere, funds for travelling to the doctor's office may not be available and child care may not be readily accessible

- Health literacy:

  Health literacy is often related to educational level. In poor communities in South Africa characterized by poor educational opportunities, health literacy is likely to be low, accounting in part for low levels of adherence.

- Social support:

  The expression of concern and encouragement from others to engage in health-promoting behaviours, including medication adherence, combine with social desirability needs on the part of the patient to yield higher rates of medical co-operation and the relationship between the doctor and the patient has shown to be strongly associated with adherence.

- Other psychological factors:

  Attitudes and beliefs about normative behaviour have also been shown to play a role in adherence. Attitudes towards treatment adherence are a person's evaluative opinions, both positive and negative, of the outcome of a health behaviour

Nachega *et al.* (2006:130) found that social support and material needs, if unattended to, could be barriers to HAART adherence. The material needs included food, transport, pill boxes, and monetary support. Other support needs included treatment for depression and alcohol abuse and assistance with resolving family conflicts.

Weiser *et al.* (2003:285) discussed from their findings that adherence rates among patients in Botswana are comparable with adherence rates in most developed countries. They found that measuring adherence by patient self-report, 54% patients were adherent with 95% of the prescribed doses.

Weiser *et al*. (2003:285,286,287) further reported the following from their findings:

- They noted the following as causes of non-adherence in Botswana: travel, malnutrition, large quantities of drugs, disappearance of symptoms, long duration of treatment.
- They further discovered that patients had to overcome great odds to adhere to treatment such as: lack of adequate funds to travel to ART centres, travelling long distances of up

to 1000 kilometres to get to clinics providing ART, patients not having access to alternative therapeutic regimens when side effects became prohibitive.

- They also noted that the following factors were not predictive of adherence to ART:
- age, education, status, sex, marital status, dosing schedules, symptoms improvement, use of traditional medicines.
- They concluded that adherence rates in Botswana were comparable with those in many developed countries despite the fact that patients in Botswana face large structural and economic barriers to treatment

Similarly, in Thailand, strategies that have helped to promote adherence include training people with HIV/AIDS as peer educators, and integrating peer support through PLHA (People Living with HIV/AIDS) groups and day centres with clinical services. (Srithanaviboonchai, 2002). Johnson *et al.* (2005:201) noted that, an association with particular adverse effects and non-adherence could not be established. They also discovered that it was possible that people have ways of managing certain adverse effects such as diarrhoea, nausea and sleep disturbances more effectively than others so that their presence does not interfere with medication taking and that it was possible that some adverse effects do not impact on daily activities and / or are not immediately relieved by skipping doses, such as lipodystrophy.

Johnson *et al.* (2005:197) noted that in their study over 85% of respondents reported at least one problem that they attributed to their ARV medications. The most frequent problems attributed to medications were diarrhoea, fatigue, nausea, skin problems, and neuropathy, bloating/pain/gas in the stomach, skin problems, and fat gain/redistribution. They also noted the following:

- Overall there were no differences in total adverse effect count or severity by gender.
- Despite being more likely to be taking a PI, older respondents had fewer adverse effects than younger (under 41) respondents.
- Those on PI containing regimens reported a greater number of adverse effects and greater adverse effects relating to severity.
- Men reported diarrhoeal adverse effects more often than women, whereas women reported greater rates of changes in hair appearance and/ or hair loss as a result of medication.

Bisson *et al*. (2008:108) confirmed that a strong relationship exist between adherence, when measured by pharmacy refill data, and virological response among HIV-1- infected individuals initiating NNRTI-based HAART in sub-Sahara Africa.

2.3.6 Toxicities to ART

Hofman and Nelson (2006:3121) noted that HAART has important side effects including a new spectrum of clinical symptoms and tissue lesions in HIV/AIDS patients. According to Justesen (2005:26) HIV-infected patients experience a variety of symptoms, some of which could be related to HIV and others to drug toxicity.

Rodriguez-Novoa *et al. (*2006:234) noted that the administration of standard doses of most antiretroviral drugs results in significant variations in plasma concentrations among different individuals, influencing antiviral activity as well as the incidence of drug-related toxicities.

The reasons for this large inter-individual variability in drug levels are multi-factorial, and involve differences in metabolism relating to gender, concomitant medications, drug compliance, underlying diseases and genetic factors. Although the combination of these drugs in triple regimens allows the complete suppression of viral replication in many instances, not all patients respond equally well. Incomplete adherence to the medication and /or drug-related toxicities frequently leads to virological failure. Each ARV drug may interact with numerous targets, such as carrier proteins, transporter or metabolizing enzymes.

AZT has long been associated with bone marrow suppression with anaemia and neutropenia. Indinavir(IDV) is significantly associated with ingrown toenail. Other epithelial changes associated with indinavir are alopecia and xerosis. Indinavir is also associated with kidney stones and rheumatologic pathology. Hearing loss has been reported with different drugs such as didanosine and stavudine. Finally, NRTI are known to increase the risk of pancreatitis (Hofman & Nelson, 2006:3129).

Peripheral neuropathy is a common toxicity in patients treated with didanosine(ddI) and /or stavudine(d4T), which seems to result from mitochondrial injury(Rodriguez-Novoa *et al.,* 2005:235).

Short and long-term toxicities of ART have emerged in high-income countries as a further complicating factor in the delivery of ART. While short-term side effects, such as diarrhoea, nausea, fatigue and rash can be managed with relatively close monitoring of patient response to treatment, long-term toxicities may require complex monitoring technologies and other treatment interventions. Central among these potential long-term complications of ART are imbalances in blood lipids, liver and kidney damage, and diabetes. The potential toxicities of ART further underscore the need for a well-developed healthcare infrastructure (International HIV/AIDS Alliance, 2002).

However, while cognizant of the possibility of toxicity, research conducted in Botswana concluded that HAART is extremely well tolerated among HIV1C-infected individuals (Wester *et al*., 2009:502).

2.3.7 Costs of ART

Levy *et al.,* (2006:171) stated that economic evaluations is an important approach for establishing priorities for health interventions and that in practice this type of evaluation has been of limited value in HIV/AIDS because of the paucity of accurate cost data. They further concludes that the advent of HAART has major implications for the cost of treating people infected with HIV/AIDS and that to date only a small number of studies have been published that provide useful estimates of the direct costs.

Yazdanpanah (2004:560) concluded that in low income countries better analyses are needed to evaluate the impact and cost-effectiveness of available HIV/AIDS prevention, treatment and care. Cost-effectiveness is only one consideration in the allocation of scarce resources. (Farmer *et al*., 2001:404-409).

There may be differences in the availability of strategies, and the selection of a strategy may be based on considerations of infrastructure, equity, qualitative attributes, monetary constraints, or synergy with other high-priority initiatives (Evans *et al.*, 2005:1137-1140).

Strategies identified as cost-effective may be unaffordable without assistance in the poorest countries. The results of this analysis may be used, however, to motivate the global community to direct resources toward investments that have the greatest promise of providing gains in health. Better data from treatment-rollout programmes, data on efficacy, toxicity, direct medical and programmatic costs (including costs of reducing wastage and scaling up) - should be incorporated when available. (Johns & Torres, 2005:1-13).

This is particularly important because non-medical costs have been found to account for a substantial proportion of the total costs of interventions in other diseases (Goldie *et al.,* 2005:2158-2168)

Limitations to the implementation of ART in developing countries

Stewart (2004:23, 25, 56, and 57) identifies aspects that limit the implementation of ARV treatment in developing countries:

- For most African countries, with the possible exceptions of South Africa and Botswana, the provision of ART through the public sector with government revenue alone is not a possibility and alternative methods of financing need to be investigated.

- Prohibitive costs of ARVs have been a major factor in limiting implementation of ART programmes in developing country settings. Wealthy nations and multinational pharmaceutical companies seeking to maximize profits and preserve their intellectual property rights have, until recently, set ARV prices at levels that are unaffordable to most people in developing countries. Literature on ART provision in developing county context remains limited. While there are examples of pilot sites and experiences of initial roll out, they have not always been comprehensively documented.
- More robust indicators and data on the full costs of HIV/AIDS and the benefits of provision of ART need to be developed in order to better measure the true impact of the epidemic at various levels, as well as the benefits of providing ART on a wide scale.
- Scaling up of ART programmes in countries such as Botswana and South Africa should allow for more reliable estimates of the costs associated with these programmes. Both the availability and effect of donor funding for HIV/AIDS prevention and treatment should be monitored. Alternative mechanisms for the funding of ART provision in resource-poor settings also need to be investigated

2.4 OVERVIEW OF THE HEALTH CARE SYSTEM OF BOTSWANA

The nation of Botswana has a vision, Vision 2016. This vision stipulates a number of goals to be achieved by the year 2016 (Ministry of health, 2008:14). The Primary Healthcare Strategy is to attain health for all, in pursuit of the national objectives in the context of vision 2016. Hence the National Health-Care policy stipulates as priority activities geared towards health for all: health promotion, provision of both preventive and geared curative care, as well as the need for initiation of special measures in respect of the high-risk groups such as children under five, pregnant women and the elderly. This vision requires *inter alia* an institutional framework of different healthcare facilities and providers, education, employment, housing, water provision, sanitation and other public services. (Ministry of health, 2008:14)

However in this section the discussion will be limited to a brief summary of the existing healthcare system in Botswana.

2.4.1 Healthcare delivery system

The Government of Botswana under the Ministry of Health (MOH) provides for most of the health needs of the population of Botswana (Ministry of health, 2008:14). The health budget comprises 8% of the total budget. However, the provision of health care is a joint venture between the MOH and Ministry of Local Government. As a result of the decentralization process the Ministry of Local Government provides the bulk of primary health care services

that are coordinated or administered on a day-to-day basis by District Health Team (DHT). The DHT has a network of 257 clinics, 336 health posts and 761 mobile stops (Ministry of health, 2003:10). The MOH administers two referral hospitals, six district hospitals, 17 primary hospitals and one mental hospital (Ministry of health, 2008:14),

2.4.2 Institutional frame work

The provision of health-care services in Botswana remains a shared responsibility of the MOH, Ministry of Local Government, private practitioners and traditional doctors. The MOH retains the portfolio responsibility for health policy development, professional/technical guidance and the supervision of healthcare irrespective of the provider or institution (Ministry of health, 2008:14).

The healthcare delivery system is based on the principle of primary health care (PHC) and national health policy whose basic objectives are to ensure that citizens of Botswana do have access to essential healthcare services as well as to ensure an equitable distribution of healthcare and optimal utilization of health services(Ministry of health 2009:185).

The MOH provides PHC through district hospitals and primary hospitals located in different parts of the districts throughout the country. The MOH has a responsibility to ensure that all health delivery institutions are provided with information on recognized standards of care not the least those being those recommended highly by the World Health Organization (WHO) and the National Standing Committee on Drugs (NASCOD). The NASCOD was established for the purpose of developing standards of healthcare system in Botswana. The ministry remains committed to the PHC strategy for attainment of health for all (Ministry of health, 2009:186),

The Ministry of Local Government mainly provides PHC services through a network of clinics, health posts (basic health facility manned by a nurse and an auxiliary or general duty attendant) and mobile stops (a clinic travels to the settlement to provide health-care) found in almost all villages throughout the country. The average distance that the residents have to walk to the nearest health facility is fifteen kilometres (Ministry of health, 2009:187),

2.4.3 Hospital services

The MOH provides primary health care (PHC) services through district hospitals and primary hospitals. These hospitals serve as referral centres for health facilities in their respective areas of jurisdictions. Complicated cases are however referred to the two national referral hospitals, Nyangabwe and Princess Marina in Francistown and Gaborone respectively (Ministry of health, 2003:189).

2.4.4 District health system

The districts and sub districts are divided according to the health regions in which they are situated in. A Public Health Specialist (PHS) who coordinates all the health service activities rendered by local government, the central government, the private sectors and parastatals leads each region. The MOH provides professional advice and policies to the districts while local government through local authorities is responsible for the provision of manpower, infrastructure such as health facilities and other material resources (Ministry of health, 2003:185).

2.4.5 Primary healthcare (PHC)

The district healthcare delivery system is based on the principle of the Alma Ata declaration of 1978, stating that preventive, promotional, curative and rehabilitative services are rendered to the community. The infrastructure development within the guiding principle aims at providing health posts within 15 kilometres and clinics within 30 kilometres of 85 % of the population (Ministry of health, 2002:45).

Botswana's health system consists of different kinds of health facilities:

- 24 district health teams,
- three referral hospitals,
- 12 district hospitals,
- 17 primary hospitals,
- 222 clinics,
- 330 health posts, and
- 740 mobile posts.

District as well as primary hospitals refer their patients to the three hospitals Princes Marina in Gaborone, Nyangabwe in Francistown and Lobatse Mental Hospital in Lobatse (Botswana, 2008:2)

2.4.6 Organisation of health services in Botswana

The MOH provides leadership on health policies and ensures their correct interpretation and implementation through the healthcare delivery system. There are six departments in the MOH (Ministry of health, 2007:14):

- Department of Policy, Planning, Monitoring and Evaluation,
- Department of Health Sector Relations and Partnership,

- Department of Ministry Management,
- Department of HIV/AIDS Prevention and Care,
- Department of Clinical Services.
- Department of Public Health.

All government hospitals fall under the Department of Clinical Services. There are 24 health districts in Botswana that are responsible for delivery of PHC services such as preventive services, curative services and programmes for controlling major public health diseases. The Ministry of Local Government provides policy direction and guidance at the local level, while the day-to-day management of local authorities (e.g. city councils, town councils and district councils). An inter-ministerial PHC Co-coordinating committee ensures adequate coordination of PHC activities conducted by both ministries (Ministry of health, 2007:14).

2.4.7 Health facilities

The figure below show the distribution of health districts in Botswana (NACA, 2003:5).

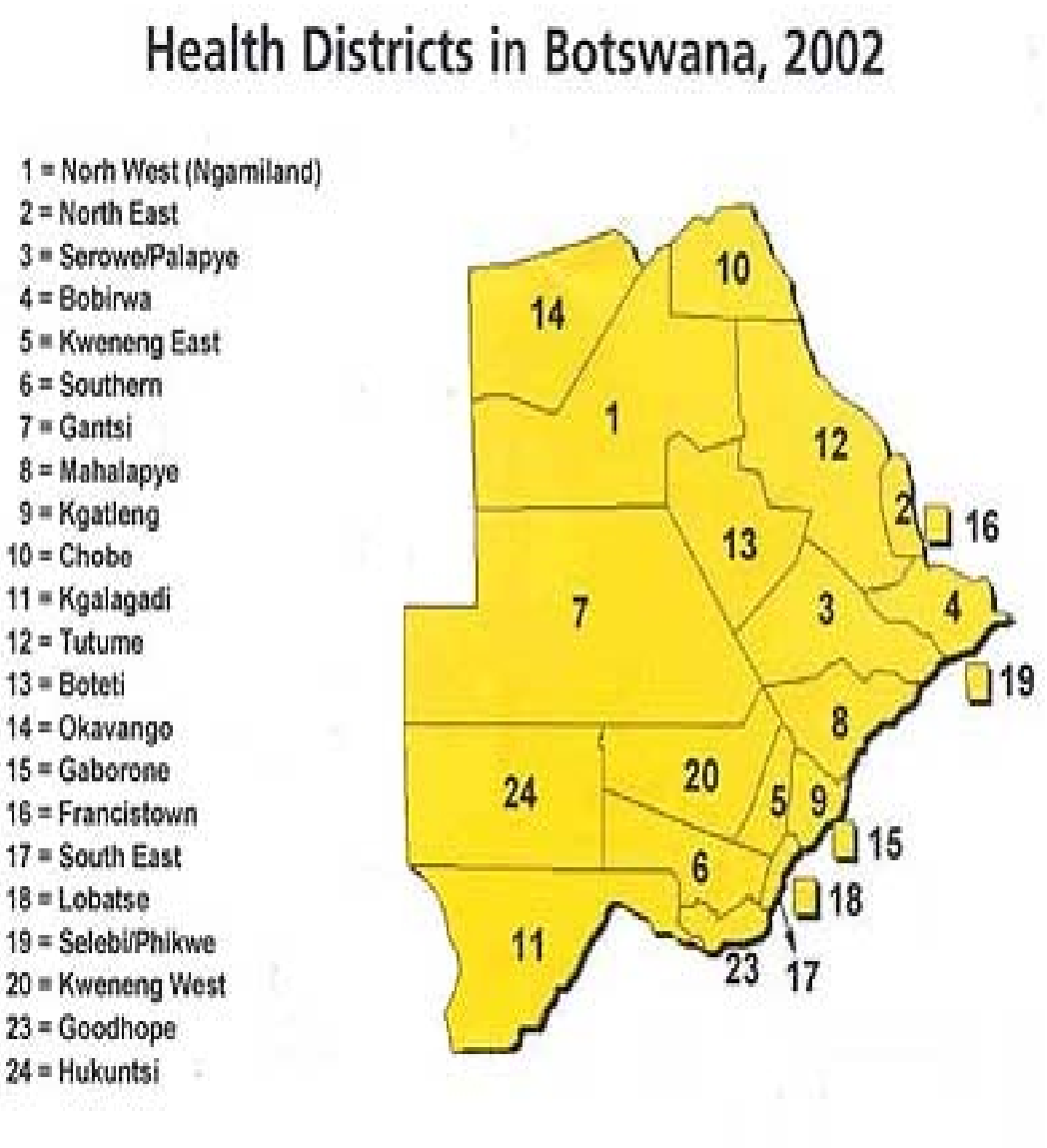

Figure 2.1. Health districts in Botswana

PHC (integrated, preventive, curative and promotive) is available at health posts, clinics and primary hospitals. The health post is the smallest unit and serves an area containing fewer than 500 people while clinics, likewise an outpatient facility, serve 500 to 10 000 people. Primary hospitals, with a bed capacity numbering from 30 to 70, play a dual role in that they not only serve as agents of primary healthcare but also perform a range of activities that include outpatient and general inpatient care. Finally, there are the district hospitals as well as two referral hospitals. The clinics refer to primary hospitals; the primary hospitals refer to the district hospitals which in turn refer to the referral hospitals (Ministry of health, 2008:14).

Over the period 1986 - 1991 the number of clinics increased from 150 to 180 and the number of health posts from 277 to 308. In 1988 the government extended its coverage of the more remote parts of the country, with the biggest increase in this period being seen in the number of mobile stops made. The availability of beds at hospitals and clinics also increased, while total attendance was higher due to easier access to health facilities. An increasing number of people are joining the family planning programme each year (Ministry of health, 2008:8).

2.4.8 The private healthcare sector

The private sector complements the government efforts to provide healthcare. The following are some of the private hospitals in different districts:

- Orapa Mine Hospital in Orapa Boteti district,
- Gaborone Private Hospital and Bokamotso Private Hospital in Gaborone district,
- Jwaneng Mine Hospital in Jwaneng district.
- Bamalete Lutheren Hospital in South-East district,
- BCL Mine Hospital in Selebi Phikwe district,
- Scottish Livingstone hospital in Kweneng district,
- Seventh Day Adventist Hospital in Southern district, and
- Deborah Retief Memorial Hospital in Kgatleng district.

These hospitals, the mission hospitals and other smaller private surgeries and pharmacies complement the government health services (Ministry of health, 2005:166,167)

2.4.9 Medicine supply system

The Central Medical Stores (CMS) under the MOH is the national source of medicines, vaccines and non-medical supplies. It distributes the medical supplies to all the health facilities throughout the country. It is responsible for sourcing medicines from local and foreign sources of supply. Health facilities particularly the private health facilities can source their medical supplies from private suppliers locally or from outside the country. Health facilities under the local authorities can source some medication not in stock in CMS from sources other than CMS.

2.4.10 Health workforce in Botswana

Health human resources are in limited supply with approximately 30 physicians and 262 nurses per 100,000 of the population (vs. 56 / 471 for South Africa and 229 / 897 for Canada). Significant proportions (approximately 70%) of the physicians are expatriates, many of whom are in the country for only two to three years. Other health professions, such as pharmacists, reportedly have similar issues (Ministry of health, 2005:2).

Table 2.1 below lists the densities of health workforce in the year 2004 (WHO, 2006:5), and Table 2.2 presents the total numbers and densities of the health workforce in Botswana in 2002 (WHO: 2006:6).

Table 2.1 Total numbers and densities of the health workforce in Botswana (2004)

Category	Number	Density per 1000	Year
Physicians	715	0.40	2004
Nurses	4753	2.65	2004
Midwives			2004
Dentists	38	0.02	2004
Pharmacists	333	0.19	2004
Public and environmental health workers	172	0.10	2004
Community health workers			2004
Laboratory technicians	277	0.15	2004
Other health workers			2004
Health management and support workers.	829	0.46	2004

Table 2.2 Total numbers and densities of the health workforce in Botswana (2002)

Category	Number	Density per 1000 Botswana	Density per 1000 Africa region
Physicians	35368	0.398	0.217
Nurses and Midwives	69749	2.648	1.172
Dentists and technicians	9553	0.021	0.035
Pharmacist and technicians	6333	0.186	0.063
Environmental and public health workers	2534	0.096	0.049
Laboratory technicians	8838	0.154	0.057
Other health workers	5088	Na	0.173
Community health workers	1062	Na	0.449
Health management and support workers	60882	0.462	0.411
Sum total	199407	3.965	2.626

2.5 HIV/AIDS IN BOTSWANA

2.5.1 History of HIV/AIDS in Botswana

Botswana's first HIV/ AIDS case was reported in 1985 (Macdonald, 1996:1325). At that time AIDS was seen as a disease that affected male homosexuals in the Western culture and people from other African countries.

HIV/AIDS is a key issue with approximately 37% of the population aged 15 to 49 year reported to be HIV positive. Life expectancy at birth is estimated to be reduced by 35 years due to HIV/AIDS and this projected to increase to 43 years by the year 2015. The Government is committed to making ARV therapy available to eligible people living with HIV/AIDS through its public health facilities (Ministry of health, 2005:2).

Botswana's response to the HIV/AIDS epidemic can be divided into three stages:

- The early stage (1987-1989) focused mainly on the screening of blood to eliminate the risk of HIV transmission through blood transfusion.
- The second stage (1989-1997), and the first Medium-Term Plan (MTP) saw the introduction of information, education and communication programmes, but the response was still quite narrowly focused. During this stage, in 1993, the government adopted the Botswana National Policy on AIDS (Ministry of health, 1993:12).
- During the third stage (1997 onwards), the response to HIV/AIDS was expanded in many different directions to include education, prevention and comprehensive care including the provision of ARV treatment. The second Medium-Term Plan (MTP II) was aimed at involving many stakeholders who had previously been excluded, with the overall goal of not only reducing HIV infection and transmission rates, but also reducing the impact of HIV/AIDS at all levels of society (UNDP, 2001:41-42).

The National AIDS Co-ordinating Agency (NACA) was formed in 1999 and given responsibility of mobilizing and coordinating a multi-sectoral national response to HIV/AIDS. NACA works under the National AIDS Council, which is chaired by the President and has representatives from 17 sectors including civil society, the public sector and the private sector (UNDP, 2001:41-42).

In 2001 the government initiated a rapid assessment of the feasibility of providing ARV drugs through the public sector. The treatment programme began at a single site in January 2002 and after a slow start expanded rapidly. By the end of 2006, almost all of those in need were receiving medication. In 2003 Botswana completed a National Strategic Framework which would guide its response to HIV/AIDS until 2009 (NACA, 2003:15).

In 2002, Botswana became the first country in sub-Saharan Africa to launch a free national ARV therapy (ART) programmed in the public health sector (Ministry of health, 2002:3).

2.5.2 Statistics on HIV/AIDS in Botswana

According to Weiser *et al.* (2003:281) HIV/AIDS is the leading cause of death in sub-Sahara Africa. According to 2001 estimates, there are 28.5 million people living with HIV/AIDS in Africa, comprising > 70% of the world's HIV-infected population. Botswana currently has the highest estimated prevalence of HIV/AIDS in the world. According to the 2002 UNAIDS update, more than 330,000 people of a population of 1.5 million in Botswana have been infected with HIV and there were 26,000 estimated deaths due to AIDS in 2001 alone.

UNAIDS/WHO (2003:5) reports that southern African countries are the worst affected countries in the world. In 1999 the top eight countries with the highest prevalence rate of HIV infection in the adult population (15- 45 years) were located in southern Africa namely Zimbabwe, Botswana, Namibia, Zambia, Swaziland, Malawi, Mozambique and South Africa. In four of South Africa's neighbouring countries, Botswana, Lesotho, Namibia and Swaziland the HIV prevalence has reached high levels without signs of leveling off. Between 1992 and 2002, the national HIV prevalence in Swaziland increased from 4% to 30% among pregnant women aged 15 to 24 years (Stewart *et al.,* 2004:1).

The table below compares the estimated numbers of people living with HIV/AIDS aged 0 to 49 years of age, the estimated number of AIDS deaths in adults and children, the estimated needs of ART in 2005 and also the ART coverage and reported people receiving ART aged 15 to 49 years by June 2004 in Southern African countries (WHO, 2004:19, 212).

Table 2.3 Estimated numbers of people living with HIV, ART needs, ART coverage and deaths from AIDS in southern Africa at the end of 2003.

Country	Population (Millions)	Estimated number of AIDS deaths in adults and children in 2003	Estimated number of people living with AIDS (0-49 years)	Estimated ART need in 2005	Reported receiving ART June 2004 (15-49 years)	ART coverage percent
Angola	14.1	21 000	240 000	3 200	700	2.2
Botswana	1.8	33 000	330 000-380 000	60 000	18000	30.0
DRC	51.2	100 000	1,100 000	160 000	2500	1.6
Lesotho	1.8	29 000	290 000 360 000	54 000	1000	1.9
Malawi	12.8	84 000	900 000	130 000	3760	2.9
Mauritius	1.2					
Mozambique	19.2	110 000	980 000 – 1,700 000	190 000	2840	1.5
Namibia	1.8	10 000	210 000	29 000	400	1.4
South Africa	44.4	370 000	5 300 000	750 000	59000	2.7
Swaziland	1.1	17 000	210 000 – 230 000	32 000	3200	10.0
Tanzania	37.7	160 000	1 200 000 - 2 300 000	260 000	1650	0.6
Zambia	10.9	89 000	730,000 – 1,100 000	140 000	8500	6.1
Zimbabwe	12.9	170 000	1 500 000 – 2 000 000	290 000	6000	2.1

From Table 2.3 above it can be seen that Botswana had the highest ART coverage by the end of 2003 in southern Africa. According to Nelson *et al*. (2005:488), in 2003, HIV prevalence in pregnant women aged 15 -45 years in Botswana was 37%. According to UNAIDS (2009:19) women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa. Women's vulnerability to HIV in sub-Saharan Africa stems not only from their greater physiological susceptibility to heterosexual transmission, but also to the severe social, legal and economic disadvantages they are often confronted with.

Botswana is one of the two worst affected countries in the world: HIV-1 prevalence has ranged from 34 % to 42.9 % in adults around the country (Novitsky *et al*., 2001:142). In 2003, HIV prevalence in pregnant women aged 15 – 49 years in Botswana was 37% (Nelson *et al.,* 2002:488)

HIV prevalence among pregnant women in Botswana rose from 18.1% in 1992 to reach a plateau of 38.5% in 2000 and it is estimated that 9000 infants become HIV infected in Botswana annually through vertical transmission in the absence of any intervention programme (Thior *et al*., 2007:297).

2.5.3 Country statistics of HIV/AIDS:

Estimated number of people requiring ART

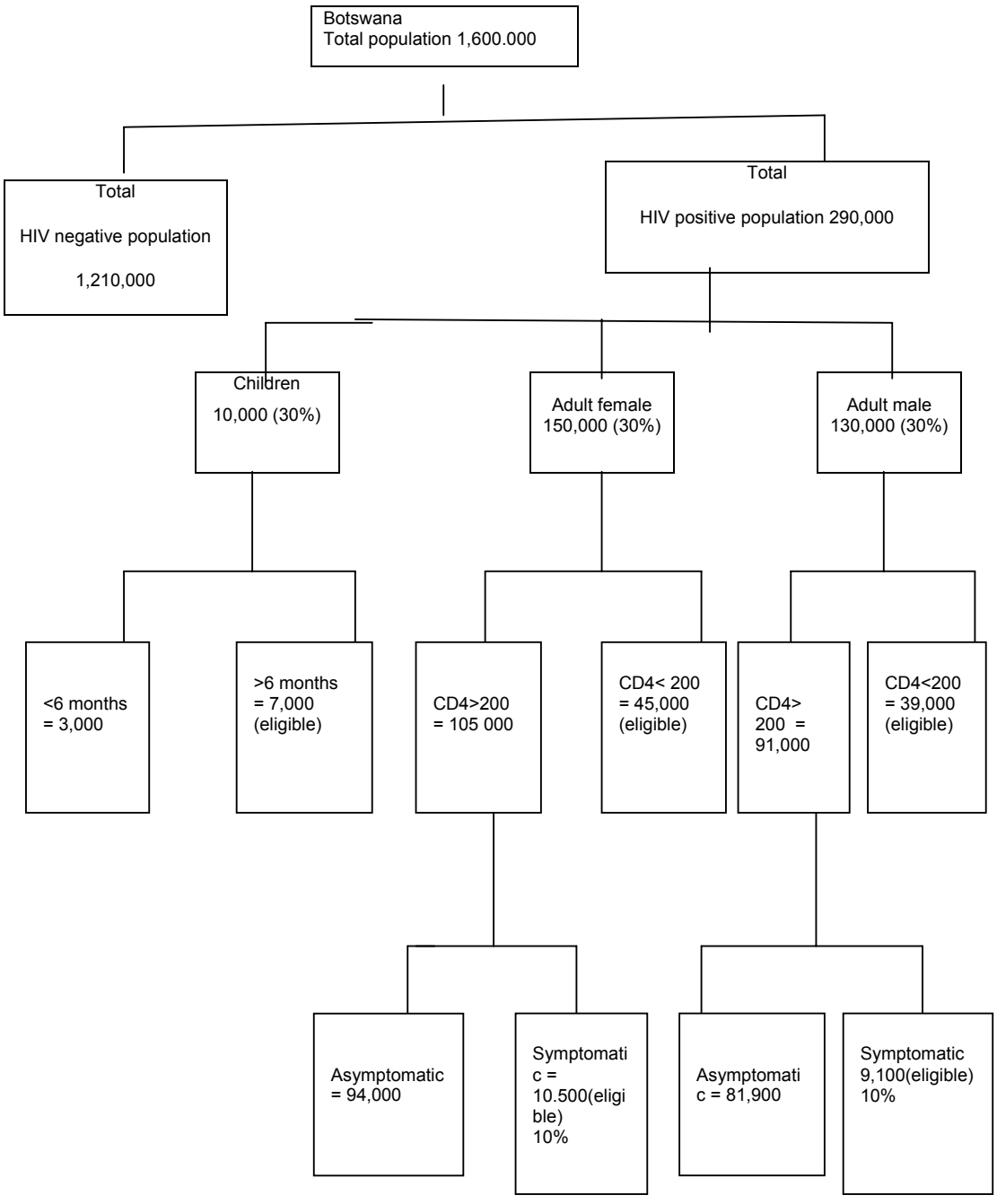

Figure 2.2. Statistics of HIV prevalence in Botswana (WHO 2004:3)

By January 2002, the aim was to provide medication during the coming year to 19,000 of the 110,000 infected people whom it was considered could benefit. As a result of poor resources, laboratory capacity, staff and infrastructure it was decided to initially target four population

groups namely: pregnant women with HIV/AIDS, HIV-positive child inpatients, HIV-positive people with TB, and adult in-patients with HIV/AIDS. (Ministry of health, 2003:14)

The following table explains the basis of the 19,000 estimates of patients requiring treatment in the first year of implementing the programme. (NACA, 2002:18)

Table 2.4: Target group needing treatment in first year of ART programme

	Gaborone	Francistown	Maun	Serowe
Pregnant women	1 600	1 000	700	900
TB patients	2 000	1 200	900	1 100
Paediatric inpatients	300	200	150	200
Adult inpatients	2 600	3 700	1 700	1 000
Total	6 500	6 100	3 400	3 200

Table 2.4 also shows the choice of the centres (Francistown, Gaborone, Maun and Serowe) as central points of need being central and convenient for the initial ART sites.

The national ARV therapy programme was given the name MASA, the Tswana word for "dawn", and the first ARV drugs were provided at the Princess Marina Hospital in Gaborone in January 2002. African comprehensive HIV/AIDS partnerships (ACHAP) is a key partner in the programme providing extensive financial and technical assistance.

By the time MASA commenced, there were already warnings about the financial sustainability of the programme. It was estimated that it would cost US$24.5 million to include 19,000 people in 2002 (around $1,300 per patient), and then an additional 20,000 people would be admitted each year (Botswana, 2003)

2.5.4 Uptake of ART

Expanding the supply of ARV drugs alone will not achieve increased access to ART. Even where ART is available and there are many people with HIV/AIDS, demand is sometimes lower than expected and many patients start treatment when they are in an advanced stage of the disease.

UNAIDS/WHO/Alliance (2002) note the following barriers to uptake of ART:

- Organizational – for example, attitudes of health workers, lack of staff, drugs and supplies, confusing procedures, corruption.
- Physical – for example, lack of transport, distance to health facilities, lack of access to voluntary counseling and testing (VCT).

- Social – for example, stigma and discrimination, lack of knowledge, denial and misinformation.
- Financial – for example, poverty, cost of drugs, user fees and other charges, cost of transport, lack of medical insurance schemes.

Programmes aiming to scale up access to ART will need to address these barriers, and to encourage people to come forward earlier for diagnosis so that treatment can be started sooner. (UNAIDS/WHO, 2002)

The table 2.5 below shows reported cases of HIV/AIDS in Botswana by district from 2000 to 2003 (NACA, 2003:42).

Table 2.5 Number of reported cases of HIV/AIDS cases in Botswana by district from, 2000 – 2003

	DISTRICT	NUMBER OF CASES	RANKING
1	Gaborone	476	Highest 21
2	Mahalapye	386	20
3	Serowe-Palapye	344	19
4	Francistown	257	18
5	Ngami	245	17
6	Lobatse	236	16
7	Selebi-Phikwe	184	15
8	SouthEast	149	14
9	Chobe	148	13
10	Boteti	125	12
11	Gantsi	111	11
12	Bobirwa	95	10
13	NorthEast	94	9
14	Kgalagadi	81	8
15	Southern	55	7
16	Goodhope	44	6
17	Tutume	43	5
18	Katleng	42	4
19	Okavango	34	3
20	KwenengEast	21	2
21	Hukuntsi	1	Lowest 1

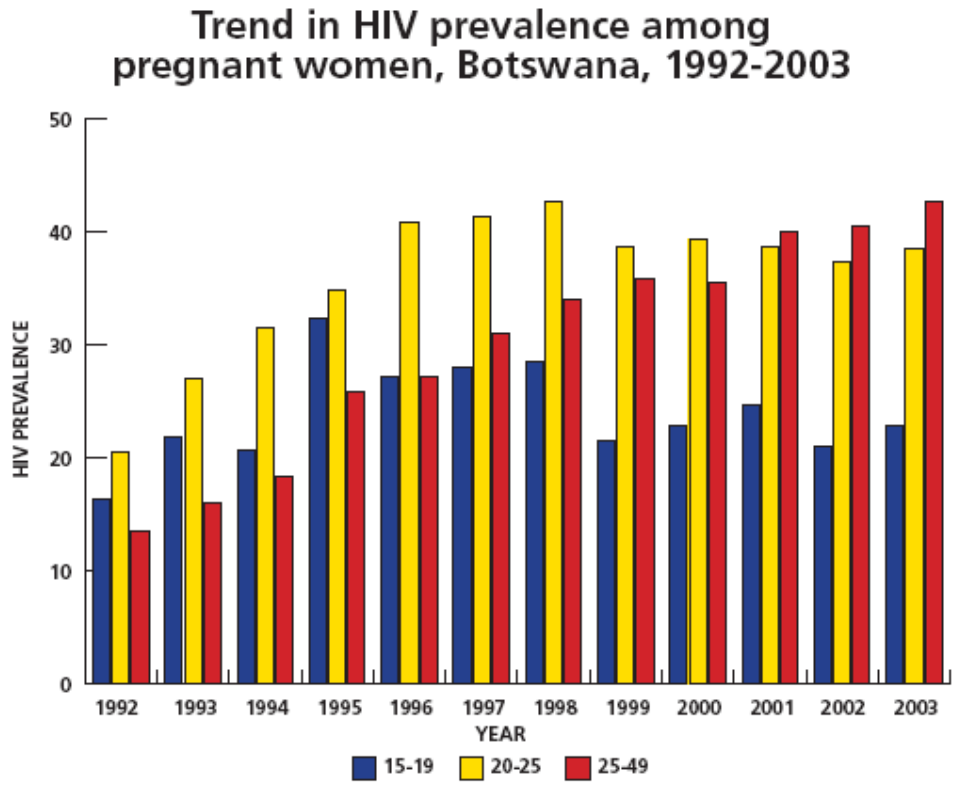

Figure 2.3 Trends in HIV/AIDS prevalence among pregnant women in Botswana, 1992 – 2003

Figure 2.3 above indicates the trends in HIV/AIDS prevalence among pregnant women in Botswana from 1992 to 2003 (NACA, 2003:42).

Table 2.6 below compares HIV/AIDS prevalence by sex and age in South Africa in 2004(Dorrington *et al.,* 2004**)**

Table 2.6 Estimated prevalence of HIV/AIDS by sex and age in South Africa 2004

Age group (Years)	**Male**	**Female**
0-4	3.6%	3.6%
5-9	1.2%	1.2%
10-14	0.0%	0.0%
15-19	0.5%	7.6%
20-24	9.5%	24.7%
25-29	23.3%	29.7%
30-34	26.4%	26.8%
35-39	24.9%	22.75%
40-44	22.2%	16.8%
45-49	19.0%	9.6%
50-54	15.3%	3.8%
55-59	11.1%	1.0%
60-64	5.8%	0.2%
65-69	1.0%	0.0%
70-74	0.0%	0.0%
75-79	0.0%	0.0%
80-84	0.0%	0.0%
85+	0.0%	0.0%

On comparison to South Africa, the HIV/AIDS prevalence in Botswana was highest in the age group 25- 29 years among pregnant women where it was 49.7% as shown in table 2.5 below. In the same age group in South Africa the prevalence was 29.7% which was also the highest in the country.

The table below compares the prevalence of HIV/AIDS in the two countries (Dorrington *et al*., 2004:15); Botswana: 2003:17)

Table 2.7 A comparison of age groups with high HIV/AIDS prevalence in females between Botswana and South Africa

Age group (Years)	% Prevalence	
	Botswana (2003)	South Africa (2004)
15-19	22.8	7.6
20-24	38.6	24.7
25-29	49.7	29.7
30-34	45.9	26.8
35-39	41.5	22.75
40-44		16.8
45-49		9.6
40-49	34.4	

The table on the next page shows the statistics of the world population aged 15 to 49 years living with HIV/AIDS (UNAIDS/WHO, 2007)

Table 2.8 Proportion of adults aged 15-49 years who were living with HIV/AIDS

Region	Adults & children living with HIV/AIDS	Adults & children newly infected	Adult prevalence*	Deaths of adults & children
Sub-Saharan Africa	22.5 million	1.7 million	5.0%	1.6 million
North Africa & Middle East	380,000	35,000	0.3%	25,000
South and South-East Asia	4 million	340,000	0.3%	270,000
East Asia	800,000	92,000	0.1%	32,000
Oceania	75,000	14,000	0.4%	1,200
Latin America	1.6 million	100,000	0.5%	58,000
Caribbean	230,000	17,000	1.0%	11,000
Eastern Europe & Central Asia	1.6 million	150,000	0.9%	55,000
Western & Central Europe	760,000	31,000	0.3%	12,000
North America	1.3 million	46,000	0.6%	21,000
Global Total	33.2 million	2.5 million	0.8%	2.1 million

During 2007 around two and a half million adults and children became infected with HIV. By the end of the year, an estimated 33.2 million people worldwide were living with HIV/AIDS. The year 2007 also saw more than two million deaths from HIV/AIDS, despite recent improvements in access to ARV treatment (UNAIDS/WHO, 2007)

2.6 HIV/AIDS PROGRAMMES IN BOTSWANA

Botswana's government is committed to HIV/AIDS-related health programmes. In recent years, the availability of healthcare for HIV/AIDS has improved substantially (Creek *et al.,* 2006:2010).

The HIV/AIDS programmes Botswana has put in place include the following preventive programmes:

2.6.1 Public education and awareness

HIV/AIDS education has also been taken to people's doorsteps by the Total Community Mobilization programme. (UN, 2005:5)

Education of young people

Prevalence rates among young people are particularly high, especially among young women, who out-number young men living with HIV/AIDS by more than two to one. It is therefore crucial that young people are provided with HIV/AIDS education and prevention messages to help protect them from infection. (AVERT, 2010:4)

2.6.2 Condom distribution

Botswana's condom access progamme is currently implemented through three initiatives: i. free government distribution, ii. Social marketing undertaken by the Population Services International(PSI), and iii. Private sector commercial sale. These programmes make male condoms widely available countrywide(NACA, 2008:41).

2.6.3 Blood safety

The MOH, the Safe Blood for Africa Foundation and other partners, with funding from ACHAP and PEPFAR, have helped to improve the safety of blood transfusions in Botswana (Botswana, 2003) To improve the safety of blood, blood transfusion has been strengthened through rapid testing and deferring high risk donors, improved blood transfusion safety, improved blood collection and transfusion safety. (Creese *et al.,* 2002:1641)

2.6.4 Prevention of mother to child transmission

Botswana began Africa's first national programmed for PMTCT in 2002 and the continent's first national public ARV programmed in 2002 (Creek *et al.,* 2006:2010).

Around 390,000 children in sub-Saharan Africa became infected with HIV in 2008. The vast majority of these children have been infected with HIV during pregnancy, childbirth or breast feeding, as a result of their mother being infected with the virus (UNAIDS, 2009:1).

The percentage of HIV-positive pregnant women attending antenatal clinics in Botswana has remained steady since 2005, at around 33%. In the absence of any interventions, around a third of babies born to HIV-positive mothers will become infected with HIV during pregnancy and delivery or through breastfeeding. This rate can be cut substantially through the use of ARV treatment and safer feeding practices (NACA, 2003:10)

Anabwani and Navario (2005:97) noted that Botswana has been a pioneer in the struggle against HIV/AIDS in many ways. In 1998, it became the first developing country to institute a national programmed to prevent mother to child transmission (MTCT) of HIV; in 2001, the

government launched the first national ARV programme in Africa (Anabwani & Navario 2005:96, 97).

2.6.5 Voluntary counseling and testing (VCT)

In 2000, the government of Botswana and Centres for Disease Control and Prevention(CDC) determined that providing voluntary counseling and testing (VCT) outside the healthcare system was a high priority. The first free-standing VCT facilities, termed *Tebelopele*, or "look into the future," opened in April 2000. Since 2003, 16 *Tebelopele* centres have provided free anonymous HIV rapid testing with same-day results for the public (Creek *et al.,* 2006:2011).

Thior *et al.* (2007:301) indicated that in Botswana prior to the initiation of the government PMTCT programme, routine HIV testing and ARV treatment, younger unmarried, and less educated post-partum women were more likely to undergo VTC and that HIV prevalence was high among women of child-bearing age.

Since 2000, the government of Botswana and the Centre for Disease Control (CDC) (through Botswana –United States of America) BOTUSA have supported the Tebelopele network of voluntary counseling and testing (VCT centres), which provide immediate, confidential VCT services for sexually active Batswana aged 18-49 years. By the end of 2009, the network had provided free VCT services to 650,000 visitors (Eduard *et al*., 2008:135).

2.6.6 Isoniazid preventive therapy programme (IPT)

Isoniazid preventive prophylaxis (IPT) against tuberculosis (TB) for HIV-infected persons became widely available in Botswana in 2003 (Creek *et a*l., 2006:2010).

IPT is an intervention that has been recommended by the WHO and the joint UN programme on AIDS (UNAIDS) since 1998 for people living with HIV/AIDS. Isoniazid is administered for six months to eligible HIV-infected individuals to prevent the development of active TB. Isoniazid decreased the incidence of TB among HIV-infected persons by about 40% and the protection period ranged from less than one year to three years (Ministry of health, 2007:21).

2.6.7 Routine HIV testing

Anabwani and Navario (2005:96, 97) noted that:

- With an estimated 25 million people living with the human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) by the end of 2003, sub-Saharan Africa, home to just 10% of the world's population, had the highest prevalence of HIV/AIDS of any region in the world.
- During 2001, an estimated 3.4 million and more Africans became infected with HIV, 700,000 of whom were children younger than 15 years. In the same year there was an

estimated 2.3 million HIV/AIDS-associated deaths in the region and sub-Saharan Africans accounted for some 75% of the 20 million deaths since the epidemic began. HIV/AIDS had become the leading cause of death in Africa, where the disease was responsible for one in five deaths, which is twice as many as deaths from respiratory infections, the second leading cause of death on the continent.

- Despite relative wealth (gross domestic product per capita of $ 8800 in 2003 ranked 61ST in the world), good governance, political stability, and commitment to reversing the HIV/AIDS epidemic, Botswana retains the dubious distinction of having one of the highest, if not the highest, prevalence of HIV/AIDS in the world. HIV/AIDS was unknown in Botswana until the mid-1980s, but within 15 years HIV/AIDS has been reported to have a prevalence of one in three pregnant women aged 15 to 45 years.
- From the beginning of 2004, Botswana became the first country to institute a national programme of routine “opt out” HIV testing to empower the 90% of the adult population who do not know their HIV status and identify those in need of immediate care and treatment. With continued leadership and aggressive efforts in prevention, care, and treatment, prospects for the future in Botswana look bright, with great aspirations for continued success in mitigating the impact of the epidemic.

2.7 COMPARISON OF ART GUIDELINES FOR BOTSWANA, SOUTH AFRICA AND WHO

The table below compares ART guidelines for Botswana, South Africa and the World Health Organization (WHO) (Botswana, 2005, South Africa, 2006, WHO, 2006)

Table 2.9 Comparison of ART guidelines for Botswana, South Africa and WHO

	Botswana		South Africa	WHO
Eligibility Criteria for ART	**Adults** Symptomatic, TB, any CD4-Tcell count/ µL Asymptomatic CD4-Tcell count/ml, less than or equal to 200		-CD4-Tcell < 350 cells/µL irrespective of stage WHO stage iv AIDS-defining, irrespective of CD4-Tcell count Patient expresses willingness and readiness to take ART adherently	CD4-Tcell < 200 cells/ µL irrespective of clinical status CD4-Tcell between 200-350 cells/µL initiate therapy before CD4-Tcell falls below 200 cell/ µL -WHO clinical stage III irrespective of CD4-Tcell count (see appendix A)
	Paediatrics HIV positive less than 12 months. All children with HIV symptoms (CDC AIDS category C, B or C).(see appendix A) All children with depressed immunity(CDC category 2 or 3) Asymptomatic aged 1-5CD4-Tcell % less than 24% and Viral load less greater than 50,000. Asymptomatic aged 5 or more CD4 less than or equal to 24%		-Recurrent hospitalization (>2 admissions per year) for HIV-related disease, or prolonged hospitalization >4weeks) -Modified WHO stage II or III disease -CD4-Tcell percentage < 20% in children under 18 months old, irrespective of disease stage -CD4-Tcell percentage < 15% in children over 18 months old irrespective of disease stage	-Infants<12 months-all -12 months to 35 months <20% CD4-Tcell or <750cells/µL absolute CD4-Tcell count -36months to 59 months <20% CD4-Tcell or <350cells/µL absolute CD4-Tcell count -Over 5 years <15% CD4-Tcell count or as in adults with <200 cells/µL CD4-Tcell count
Available drugs				
First line	**Adults** Men and women in whom there is no risk of pregnancy	zidovudine or stavudine plus lamivudineplus efavirenz	stavudine with lamivudine plus efavirenz or nevirapine	-zidovudine or stavudine plus lamivudine or emtricitabineplus nevirapine or efavirenz
	Pregnant women and women	zidovudine plus		

	in whom pregnancy is likely	lamivudine plus nevirapine		
	Paediatrics zidovudine or stavudine plus lamivudine plus nevirapine		- 6 months- 3 years: stavudine plus lamivudine lopinavir/ritonavir	-Infants not exposed to ARV-nevirapine plus 2NRTI -Infant with unknown ARV exposure- N
	Three years or older: zidovudine or stavudine plus lamivudine plus efavirenz		>3 years old and >10 kg: stavudine plus lamivudine plus efavirenz	nevirapine + 2NRTI -Infant exposed to nevirapine – lopinavir/ritonavir plus 2NRTI -Children 3 years or older NNRTI +2NRTI
Second line	**Adults** didanosine + stavudine +kaletra® if the first used Zidovudine/lamivudine as a nucleoside analogue backbone • didanosine + zidovudine + kaletra® if the first-line nucleoside analogue backbone was stavudine/Lamivudine • Those on didanosine plus dtavudine who develop peripheral neuropathy change to abacavir plus didanosine		- zidovudine with didanosine and lopinavir/ritonavir	-didanosine or tenofovir + PI/r -abacavir or lamivudine +_ zidovudine+ PI/r -PI/r + efavirenz or nevirapine
	Paediatrics Same as for adults		-6 months- 3 years; zidovudineplus didanosine plus nevirapine	
			>3 years old and >10 kg: zidovudine + didanosine + lopinavir/ritonavir	
Third line	Adults ritonavir + saquinavir + another nucleoside not yet used if possible.		.	
	Paediatrics			

	Same as for adults		
Monitoring of people on treatment	**Adults** .Viral load at start of therapy After 3 months and every 3 months thereafter. . CD4-Tcell count at the start, after 3 months and every 3 months there after .FBC at baseline, 4 weeks after starting, 3 months after starting and as indicated there after. .Urea and electrolytes at baseline and as indicated thereafter. .Liver functioning Tests (LFTs): if on nevirapine at baseline, 2 weeks after starting, at 4, at 3 months weeks after starting and as indicated thereafter. If not on nevirapine: at baseline and as indicated there after. Fasting lipid profile at baseline and every 6 months for patients on protease inhibitors. . Clinical monitoring for toxicity, opportunistic infections and adherence; -Baseline physical exam and clinical staging; chest X-ray as indicated -2 weeks (doctor/health worker) for adherence and clinical exam. -Seen by doctor at 1 month, 3 months from start of therapy and 3 monthly thereafter. Adherence and toxicity monitoring every month by pharmacist.	-Patient attend clinic monthly to collect medication -Patients on nevirapine are seen at 2 weeks to check for adverse effects, to do more blood tested, ensure correct dosing. -Patients seen by doctor at 4, at 8 and 12 weeks and 3 monthly thereafter if they are well -CD4-Tcell count and viral load done 6 monthly while patients are on regimen first line	-Clinical monitoring depends on the response to ART. - Minimum, monitoring should take place 2, 4, 8, 12 and 24 weeks after ART begins and should -Subsequently every six months once the patient has stabilized on therapy -Laboratory monitoring CD4-Tcell count every six months (recommended)

	Paediatrics -Viral load at start, 3 months and 3 months there after -CD4-Tcell count at start of therapy and every month. -Blood chemistry (LFTs, U&Es) and Haematology (FBC) at start of therapy at 2 weeks to assess toxicity from Nevirapine, and then every 3 months thereafter. -Clinical monitoring: at 2 weeks for chemistry and dosage change, at 1 month, at 3 months and then 3 monthly thereafter with the doctor. -Adherence and toxicity monitoring every month by pharmacist.	-CD4 Initial testing (staging), 6 monthly. - Viral load at base line, then 6 monthly. - Full blood count at baseline, then monthly for 3 months, then 6 monthly (with CD4-Tcell count and viral load thereafter.	
Measures of ART success	**Adults** • Viral load should fall at least by 1 log by 3 months after starting therapy. • Viral load goes below the level of detection (< 400/ml) by six months after starting therapy. • A steady rise in the CD4-Tcell count. • A steady recovery from wasting • No new opportunistic infections of HIV-related tumours or conditions. • Absence of adverse drug events	- Patient should experience fewer HIV-related illnesses. - The patient's CD4-Tcell count should rise and remain above the baseline count. -The patient's viral load should become undetectable (<400 copies/ml) and remain undetectable on treatment	
	Paediatrics Same as adults and child is growing normally	-Increased survival -Decrease in HIV-related morbidity and mortality -CD4-Tcell count should rise and remain above the baseline count	

		-viral load should become undetectable(<400 copies/ml) and remain undetectable on treatment	
Measure of failure of ART	**Adults** Viral load rebounds by greater than or equal to 0.5 log. Viral load consistently rises above the level of detection. Viral load has not fallen below the level of detection by 6 months. CD4-Tcell count fall steadily or fail to reach 200/µL by 6 months. Clinical failure(occurrence or recurrence of AIDS-defining illness)	**Adults** Patient should experience fewer side effects. Patient's CD4-Tcell count should rise and remain above the base line count. Patient's viral load should become undetected (<400 copies/mm cubed), and remain undetectable on ART.	**Adults on first line regimen** Clinical failure- new or recurrent WHO stage 4 conditions (see appendix A) CD4-Tcell failure. Fall of CD4-Tcell count to pre-therapy baseline or below /50% fall from the on-treatment peak value or persistent CD4-Tcell levels below 100 cells/µL . Virological failure- Plasma viral load above 10,000 copies /mL
	Paediatrics Virology failure; less than 1.0 log fall in HIV RNA level after 8-12 weeks of therapy; viral load is not suppressed to undetectable levels after 4-6 months of therapy; viral rebound greater than 0.7 in infants aged 2 years or greater than 5 log in children older than 2 years Immune failure: change in immune classification from one category to a worse category; a persistent decline of 5% or more in CD4-Tcell percentage for those in immune category 3; a rapid fall in CD4-T cell percentage of > 30% in less than 6 months Clinical criteria for failure: progressive neurodevelopmental deterioration; failure to gain normal neuron developmental milestones; growth failures; disease progression from one clinical		**Paediatrics** -Incomplete virologic response to therapy -Viral rebound -Incomplete immunologic response to therapy. -Immunologic decline. -Progressive neurodeterioration. -Growth failure

	category to a worse category. - Toxicity tolerance: development of significant drug toxicity (grade 3 or higher); development of severe drug intolerance(e.g. severe diarrhea or vomiting)		
Measure of success	• Adults • Viral load fall at least by 1 log by 3 months after starting therapy • Viral load goes below the level of detection (<400ml) by 6 months after starting therapy. • A steady rise in the CD4-T cell count • Steady recovery from wasting. • No new opportunistic infections or HIV-related tumors or conditions • Absence of adverse drug events.		Severe or recurrent infection or illness(see definitions below)

	Paediatrics • Viral load falls by 1 log by 3 months after starting therapy • Undetectable viral load by 6 months after starting therapy • CD4-T cell percentage rises steadily towards normal level. • The child is growing and developing normally • No new opportunity or HIV-related conditions. • Absence • of adverse drug events.	**Paediatrics** -In addition to the criteria for adults, In some children, a suppressed though detectable viral load, with sustained elevation in CD4-Tcell count and absence of intercurrent and or opportunistic infection.	

Comparisons

From table 2.9 above a number of comparisons stand out:

Eligibility criteria for initiation of ART:

Botswana, South Africa and the WHO all accept as eligibility for initiation of ART CD4-Tcell count of 350cells/μL or less in adults and in paediatrics. Botswana and the WHO both accept all HIV-positive patients less than 12 months irrespective of other criteria and South Africa has different criteria.

First-line recommended drugs:

The first-line drugs recommended by Botswana, South Africa and the WHO differ as follows:

In men and women with no risk of pregnancy Botswana recommends zidovudine or stavudine plus lamivudine plus efavirenz, South Africa recommends stavudine with lamivudine plus efavirenz or nevirapine while the WHO recommends zidovudine or stavudine plus lamivudine or emtricitabine plus nevirapine or efavirenz. All three recommend stavudine with lamivudine plus efavirenz or nevirapine

Second-line recommended drugs:

(Botswana, South Africa and WHO) recommend didanosine, stavudine and lopinavir/ritonavir as second-line therapy.

Third-line recommended drugs:

Except for Botswana which mentions ritonavir plus saquinavir plus another nucleoside not used South Africa and WHO were silent.

Monitoring of patients on therapy:

South Africa and the WHO recommend CD4-Tcell count monitoring every six months. They differ on frequency of monitoring other parameters.

Measure of treatment success:

Botswana, South Africa and the WHO all recommend the viral load below detectable levels as a measurement of treatment success.

Measures of treatment failure: Botswana, South Africa and the WHO all recommend viral rebound and fall of CD4-Tcell count to pre-therapy levels or below.

WHO definition of failure for paediatrics on therapy:

Incomplete virologic response to therapy is defined for all children as a <1.0 log10 decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400

copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection using the most sensitive assay after 12 months of therapy.

Viral rebound:

For children who have previously achieved an undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive polymerase chain reaction(PCR) assays, whereas repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound

Incomplete immunologic response to therapy:

Failure by a child <5 years old with severe immune suppression (CD4-Tcell percentage <15%) to improve CD4-Tcell values by ≥5 percentage points, or a failure by a child age 5 years old or older with severe immune suppression (CD4-Tcell <200 cells/μL) to improve CD4-Tcell values by ≥50 cells/μL above baseline within the first year of therapy.

Immunologic decline:

Sustained decline of 5 percentage points in CD4-Tcell percentage below pre-therapy baseline at any age, or decline to below pre-therapy baseline in absolute CD4-Tcell count in children who are age 5 years and older.

Clinical considerations of failure

- **Progressive neurodevelopment deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction.
- **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- **Severe or recurrent infection or illness:** Recurrence or persistence of HIV/AIDS-defining conditions or other serious infections (WHO, 2009:79)

Table 2.10 summarizes WHO-preferred ART recommendations for infants, children and adults (WHO, 2009:49)

Table 2.10 Summary of WHO-preferred ARV treatment recommendations for infants, children and adults

Patient group	Preferred first-line regimen	Preferred second-line regimen
Infants	NVP / 2NRTI	
Infants not exposed to ARV	NVP / 2NRTI	Boosted PI/2NRTI
Infants with unknown ARV exposure	NVP / 2NRTI	Boosted PI/2NRTI
Infants exposed to NVP	LPV/r / 2NRTI	NNRTI /2NRTI
Children		
Children 3 years or over	NNRTI / 2NRTI	Boosted PI/2NRTI
Adults and adolescents		
Adult or adolescent	NNRTI / 2NRTI	Boosted PI/2NRTI
Women starting ART in pregnancy	NVP / AZT / 3TC	
Women starting ART within 6 months of single dose NVP	NNRTI / 2NRTI or 3NRTI	
Concomitant conditions		
Child, adolescent or adult with severe anaemia	NVP / 2NRTI (avoid AZT)	Boosted PI+2NRTI(avoid AZT)
Child, adolescent or adult with TB	EFV / 2NRTI or 3NRTI	Boosted PI/2NRTI
Adult or adolescent with Hepatitis B	TDF / 3TC / NNRTI	Boosted PI/2NRTI
Adult or adolescent with Hepatitis C	EFV / 2NRTI	Boosted PI/2NRTI
IDU	NNRTI / NRTI	Boosted PI/2NRTI
HIV-2 or dual infection	3NRTI	Boosted PI/2NRTI

Most of these recommendations from WHO have been incorporated in the latest edition of Botswana treatment guidelines of 2008 as can be seen in the summary of changes between the 2005 and 2008 versions below (Ministry of health, 2005, Botswana, 2008).

Table 2.11 lists some of the changes that have been made to the Botswana ART guidelines from 2005 to 2008 (Ministry of health, 2008:41-44).

Table 2.11 Changes to the Botswana ART guidelines 2008

Regimen		Prior to 2005	2008
First-line	Adults	D4T plus 3TC plus NVP/EFV change to TDF plus FTC/3TC plus NVP/EFV	TDF plus FTC(or 3TC) plus NVP or EFV
	Pregnant mothers	AZT plus 3TC plus NVP or EFV	
	Paediatrics	AZT plus 3TC plus NVP or EFV	
	Paediatrics exposed to sd/NVP		AZT plus 3TC plus LPV/r
Second-line	Adults	D4T plus ddI plus LPV/r change to TDF plus FTC/3TC plus LPV/r	AZT plus 3TC plus LPV/r
	Paediatric	ABC (or ddI) plus d4T plus LPV/r	

2.8 CHAPTER SUMMARY

In this chapter the nature of HIV/AIDS, health-care system in Botswana, statistics on HIV/AIDS, HIV/AIDS programmes in Botswana and a comparison of ART guidelines for Botswana, South Africa and the WHO have been reviewed. A review of changes made to the 2008 Botswana ART guidelines marks the end of the literature review. The research methodology will be discussed in chapter 3.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 INTRODUCTION

In this chapter the research objectives of the empirical investigation and the research methodology will be discussed.

3.2 RESEARCH OBJECTIVES

The research objectives of the empirical investigation will be discussed under general objectives and specific objectives.

3.2.1 General research objective

The general research objective of this study was to determine the prescribing patterns of ARV drugs at SMH-IDCC in the central district of Botswana.

3.2.2 Specific research objectives of the empirical investigation

The specific research objectives of the empirical investigation were:

- To identify the prescribing patterns of ART regimens at the SMH-IDCC in the central district of Botswana.
- To determine the costs associated with the above ART regimens.
- To determine the prevalence of side-effects with certain ART regimens.
- To illustrate treatment outcomes with the different ART regimens by using CD4-Tcell counts.

3.3 RESEARCH DESIGN

A non-experimental, quantitative, retrospective drug utilization review method was used in order to obtain the essential outcomes and achieve the specific objectives for this research project. The study design was descriptive in nature and the study covered a period of two years (1 January 2005 to 31 December 2006).

The World Health Organization defined drug utilisation research (DUR) 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*" (WHO, 2003:2). Drug utilisation may also be regarded as a strategy that evaluates, examines and clarifies rates or costs and reviews the suitability of drug usage to determine improper use, avert adverse drug interactions and boost proper use (Wolters Kluwer Health, 2005:1) (Refer to Chapter 1).

3.4 STUDY SITE(S)

The SMH-IDCC is located about 153 kilometres from the Martin's drift border with South Africa. SMH-IDCC has four satellite clinics that initiated patients on ART and later did reviews and check-ups with follow-up reviews. The satellite clinics were the clinics closest to the main SMH-IDCC at the time centre was opened. However all ART medication was dispensed from the SMH-IDCC pharmacy.

Patients were drawn from all parts of the country. Some patients came to their home villages after long illness, as home-based care patients taken care of by their relatives. Proximity to the healthcare facility was also a major contributing factor to patient's ability to access the services offered and besides the medicines' side effects, financial constraints, transport, social support and experience of illness also affected the patients' adherence to the prescribed regimen.

3.5 DATA SOURCE

Data on all ART medicine items dispensed at SMH-IDCC for two years, from 01 January 2005 to 31 December 2006 were obtained from the electronic database of the SMH-IDCC. The study population included all patients that commenced therapy during the study period.

The population size was 1717 patients. The electronic database captured patient information on all medication dispensed at the pharmacy, CD4-Tcell counts and adverse side effects. Costs of ART medicines were obtained from the procurement unit of the central medical stores (CMS. Information initial CD4-Tcell count prior to commencement of treatment was collected from electronic patient records.

The data analysis was conducted by means of the Statistical Analysis System®, SAS 9.1® (SAS® for Windows, 9.1, 2005). The available data from the electronic database was imported into the Statistical Analysis System®, SAS 9.l in order to come up with meaningful data that were interpreted in terms of prescribing patterns of ART. The costs were obtained from the central medical stores procurement unit. These were then assigned to the different drug regimens and comparisons made between the different regimens. The regimens with the most adherence problems and changes in therapy as well as side effects encountered most often were identified from the study notes in the patients' electronic files.

3.6 RESEARCH PROCESS OF CAPTURING DATA

The retrospective study included 1717 patients who commenced ART at the study site during 01 January 2005 to 31 December 2006. Only patients who had commenced therapy at the study site were included in the study i.e. the SMH-IDCC and its surrounding satellite clinics Kadimo, Newtown, Nutrition and Serowe.

- The patients were divided into male, female, adults and children.
- All eligible patients were screened and base line investigations were done in terms of CD4-Tcell count at the time of commencement of therapy.
- All patients collected ART medication in person from the SMH-IDCC pharmacy after initiation of therapy. Patients underwent medication counseling which took into account information relevant for maximizing benefit from therapy, side effects, food interactions and contraindications.
- The patients collected a two weeks' initial supply which allowed them to return early for review.
- After the review the patients received a further two weeks supply and were allowed to return after two weeks for review on how they coped with the ART.
- After four weeks patients were sent for chemistry tests and after that the patient received a month's supply of medication. Patients continued to return to the hospital for review with the doctors. During those reviews the patients were monitored for any drug side effects, progress and compliance. Further blood tests were also ordered. After six months patients who had stabilised on ART received appointments for review after a further six months with an allowance to return earlier with any other problem, condition or comorbidity that arose before the date of appointment.
- According to the Botswana ART guidelines (Ministry of health, 2005:19) the recommended schedule for clinical monitoring of adult patients included HIV RNA (viral load) at the start of therapy, at three months after start of therapy to assess initial efficacy and every three months thereafter. CD4-Tcell count was measured at start of therapy, at three months after starting therapy and every three months thereafter.

The Botswana ART guidelines (Ministry of health, 2005:18) used the following criteria as surrogate measure of efficacy:

- Viral load fell by 1 log by three months after starting therapy.
- Undetectable viral load by six months after starting therapy.
- A steady rise in the CD4-Tcell count.

Medication failure was defined as; one or more of the following (Ministry of health, 2005:20):

- Viral load rebounds by $\geq$0.5 log,
- Viral load becomes detectable again after being undetectable,

- CD4-Tcell count falls again.

For monitoring children on treatment the following schedule was considered (Ministry of health, 2005:26):

- CD4-Tcell count every three months.
- Measurement of height, weight and head circumference every three months.
- Neurodevelopmental assessment every three to six months.
- Viral load every three to six months.

Criteria for success in paediatrics according to Botswana ART guidelines (Ministry of health 2005:28) were defined as:

- Viral load falls by 1 log by three months after starting therapy.
- Undetectable viral load by six months after starting therapy.
- The child is growing and developing normally. The weight and other growth parameters such as height and head circumference falls within the standard growth curves without opportunistic infections and other psycho-motor developments.

The central hospital (SMH-IDCC) and four satellite clinics (Nutrition, Newtown, Kadimo and Serowe) provided ART to Serowe village, its catchment area and surrounding villages. The satellite clinics prepared the patients for commencement of ART while all medication was collected only from the SMH-IDCC pharmacy in person by the patient.

The village with its health infrastructure is typical of other villages and towns in Botswana. It functions at a second tier of the national health system. The health posts refer to the clinics and clinics refer to the hospital which refers to referral hospitals with specialist facilities.

3.7 STUDY POPULATION

The study population was all patients who commenced therapy from 1 January 2005 to 31 December 2006. Both genders and all age groups were included.

Table 3.1 divides the population of the study into different age groups. For the purpose of this study the different age groups are classified as children, adolescents and adults.

Table 3.1 Age group distribution of study population

Age group	Age From year	Age To year	Classification for the purpose of this study
1	0≥	≤4	Children
2	4>	≤9	Children
3	9>	≤14	Children
4	14>	≤19	Adults
5	19>	≤24	Adults
6	24>	≤29	Adults
7	29>	≤34	Adults
8	34>	≤39	Adults
9	39>	≤44	Adults
10	44>	≤49	Adults
11	49>	≤54	Adults
12	54>	≤59	Adults
13	59>	≤64	Adults
14	64>	≤69	Adults
15	69>	≤74	Adults
16	74>	≤79	Adults
17	79>	≤84	Adults
18	84>	< 84	Adults

3.8 DATA COLLECTION METHOD

Data for this research were collected from the electronic database. It was possible to collect data on all medications collected by the patient from the SMH-IDCC pharmacy. Medications were collected by the patients themselves.

3.8.1 CD4-Tcell count

CD4-Tcell count and HIV RNA (ribonucleic acid) may be a more accurate surrogate marker for clinical outcome and is increasingly used to assess prognosis before starting treatment and to monitor progress of disease during treatment (Saag,1997:984). Information on CD4-Tcell count for 1717 patients was collected from electronic data base and manual records from the SMH-IDCC laboratory and the four satellite clinics where patients first registered for ART. The records were not centrally available and had to be collected from the different places. Only information on CD4-Tcell count could be documented as information on HIV-RNA was not always available and therefore not included in the study.

3.8.2 ARV-related side effects

Information on medication side effects for all patients who reported side effects during the study period was collected from SMH-IDCC pharmacy electronic records. Information on change of therapy and reasons for change was also collected from electronic records. Other side effects that did not lead to change of therapy were not recorded. Hofman and Nelson (2006:3121) noted that HAART has important side effects including a new spectrum of clinical symptoms and tissue lesions in HIV/AIDS patients.

3.8.3 Costs

Data on the prices of medication were collected from the Ministry of Health, Central Medical Stores which is responsible for sourcing these medications. Donations were assigned the current prevailing market price at the time of calculations. The medications were quoted in different currencies depending on the source of the medications. All currencies were converted to one currency, the US Dollar to facilitate calculations.

3.9 DATA ANALYSIS

3.9.1 Data application and data analysis

The criteria applicable to the selection of the data was consistent with the original objective which included only data for patients who had commenced therapy at the study site in the study period from January 2005 to December 20006. The data for analysis included all age groups and both gender. Different age groups had differences in some of the drug dosage forms used such as syrups for children and tablets for certain age groups of children and adults. Gender was important in considering drugs most relevant to women as opposed to men and different age groups within the same gender. The data were analysed by means of the Statistical Analysis System, SAS 9.1® (SAS for Windows, 9.1, 2005).

3.9.2 Statistical analysis

For the purposes of this study, the following descriptive statistical methods and statistical calculations were applied to analyse the data:

3.9.2.1 Percentage

A percentage is a proportion *(the number of observations or responses with a given characteristic divided by the total number of observations)* multiplied by 100%.

3.9.2.2 Arithmetic mean (average value)

Medhi (1992:53) explains that when a number of observations (denoted by *n*) are obtained from a population, the value of each sample observation is denoted by x. "*The sum of the observation values divided by the number of the values in the set"* is known as the arithmetic mean of a set of data (Agarwal, 2003:37) and is calculated by the following equation:

$$\overline{x} = \frac{\sum i}{n}$$

Where:

- $\overline{x}$ = mean
- i = values of the variables
- n = the number of observations

The mean represents the centre of the set of observations (Medhi, 1992:53).

3.9.2.3 Standard deviation

Snedecor and Cochran (1989:29) describe the standard deviation as *"a measure of the amount of variation among the values of the variables in a population"*. According to Banerjee (2003:5), standard deviation measures the spread of data around the mean. The value of the standard deviation is therefore the average distance of an observation point from the mean (Cohen & Lea, 2004:13; Salkind, 2007:68) and is calculated with the equation:

$$s = \sqrt{\frac{\sum \left(x - \bar{x}\right)^2}{n-1}}$$

Where:

- s = standard deviation
- $\sum$ = sum
- x = value of any variable in the dataset
- $\bar{x}$ = mean
- n = the number of observations

3.9.2.4 Median

The median divides the sample so that half the observations are below it and half of them are above it (Knapp, 1978:36).

3.10. ETHICAL CONSIDERATIONS

Permission for this research was obtained from the Botswana Ministry of Health and from the Ethical committee of the North-West University (NWU-00076-10-S5). In so doing the researcher ensured that the research was ethically justified according to the standards of the North-West University. The researchers ensured that permission was given by the SMH-IDCC before the study was undertaken. No names of patients or health workers were identified and mentioned by the researcher in the research project.

3.11. LIMITATIONS

Data was retrieved from the database at the end of each year.. Research was conducted from the viewpoint that all data obtained from the database were correct and accurate. All data collected were used only for research purpose.

Data for the analysis were obtained only from SMH-IDCC and the four satellite clinics Serowe, Kadimo, Newtown and Nutrition, thus, limiting external validity, implying that results could only be generalised to the specific database used, as well as to the specific study population. No specific patient or medical practitioner was identified. Thus confidentiality of information was maintained throughout the study.

All side effects that did not lead to change of therapy were not documented and could not be analysed. Another limitation of the study was that only CD4-Tcell counts data were available for the whole study population and not the data on HIV-RNA or viral load.

3.12 CHAPTER SUMMARY

In this chapter the research methodology was discussed, which included the research objectives, the process followed and the statistical analysis of the data. The result of the empirical study will be reported in Chapter 4.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 INTRODUCTION

In this chapter, the results of the empirical investigation of the prescribing patterns and cost of ART regimens for the study period 1 January 2005 to 31 December 2006 will be presented and discussed.

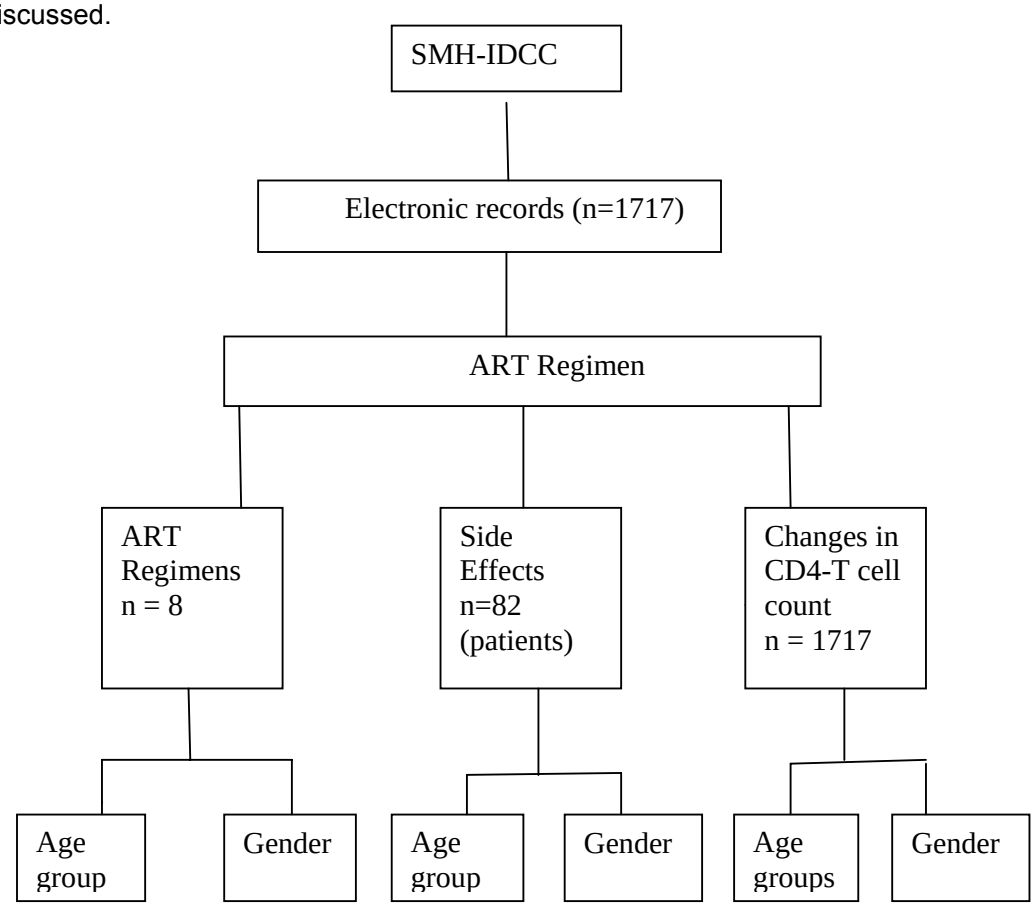

Figure 4.1 Schematic classification of the data as extracted from the database

The figure above show the classification of data as extracted from the electronic records.

Terms and definitions

For the purpose of this study, the following terms and definitions were used:

Combination medicine items

Combination medicine items refer to the ARV drugs (trade names) that are formulated with more than one ARV active ingredient.

Regimen

A regiment include more than one ARV medicines items prescribed together for a patient.

Prescriber

According to the Medicines and Related Substances Control Act (101/1965) 'authorised prescriber' means "*a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974*" (South Africa, 1997:12).

ARV and ART regimen

ARV refers to ARV medication while ART will refer to the ARV therapy or combination of individual ARV medicines combined or taken together as a regimen

Provider

For the purpose of this study, a provider is defined as the entity that dispensed the prescribed medication to the patient.

Side effects

According to Thomas (1989:1797) side-effect of a medication is an action or effect of a drug other than the effects that is desired.

CD4-Tcell change

Change in the cluster of differentiation measured in cell/µL

4.2 EMPIRICAL STUDY

4.2.1 Demographic information

A total number of HIV/AIDS patients (n = 1717), including 1010 (58.89%) females and 705 (41.11%) males treated with ART within a period of two years, 1 January 2005 to 31 December 2006 were included in this study. For two patients the gender could not be

identified. These results of the empirical study for ratio of females to males are comparable with the results of the Botswana 2003 second generation HIV/AIDS sentinel surveillance (NACA, 2003:30, 31). The results of the study were compared with figures of HIV positive females and males to those of the Botswana Sentinel Surveillance (NACA, 2003: 30, 31) as shown in the Tables 4.1

Table 4.1 below shows the estimated number of infected adult females per health district (NACA, 2003:30).

Table 4.1 Estimated numbers of infected adult females per health district and age group in Botswana, based on prevalence in pregnant women in 2003

Sentinel site	15-19yrs	20-24yrs	25-29yrs	30-34yrs	35-39yrs	40-49yrs	TOTAL
Ngami	1,302	1,606	1,646	1,046	931	1,266	7,796
North East	897	1,037	897	568	470	969	4,838
Serowe/Palapye	3,496	3,193	3,130	2,648	2,757	2,106	17,331
Bobirwa	1,642	1,809	1,819	1,200	704	1,068	8,242
Kweneng East	2,119	4,177	3,966	2,031	1,835	3,553	17,681
Southern	1,085	1,742	2,061	1,913	1,012	1,742	9,555
Gantsi	272	578	360	373	87	125	1,793
Mahalapye	1,968	1,693	2,201	1,569	1,458	1,397	10,286
Kgatleng	854	1,104	1,396	1,080	1,016	598	6,047
Chobe	220	525	546	621	274	345	2,521
Kgalagadi	354	350	527	365	195	227	2,018
Tutume	2,091	2,062	2,148	1,451	1,273	2,221	11,246
Boteti	549	1,342	1,372	910	311	739	5,222
Okavango	827	1,018	1,097	562	517	466	4,486
Gaborone	2,145	6,586	7,515	5,983	4,441	4,064	30,735
Francistown	1,465	3,231	2,934	2,005	1,433	1,885	12,952
SouthEast	852	800	1,017	1,032	773	917	5,391
Lobatse	344	672	815	622	450	423	3,325
Selebi/Phikwe	1,322	1,892	2,413	1,511	734	1,198	9,069
Kweneng West	254	437	669	274	521	483	2,638
Goohope	846	630	744	415	726	1,157	4,518
Hukuntsi	65	241	321	167	171	209	1,174
Total of HIV infected women	24,967	36,724	39,594	28,342	22,157	27,157	178,873
% of N=178,873	14.0	20.5	22.1	15.8	15.2	15.2	100
Total of women in 2003 (denominated)	109,373	95,046	79,731	61,733	78,843	78,843	477,984

In 2003 the prevalence of HIV infection in adult women was highest in the age group 25 to 29 years where the prevalence was 22.1% followed by a prevalence of 20.1% in the age group 20 to 24 years. Table 4.2 below shows the estimated number of HIV-infected males aged 15 to 49 years per health district and age group (NACA, 2003:31). In males the HIV infection was highest in the age group 35 to 39 years (43.9%) followed by the age group 40 to 49 years (43.5%).

Table 4.2 Estimated number of HIV-infected males (15-49 years) per health district and age group.

Sentinel site	15-19yrs	20-24yrs	25-29yrs	30-34yrs	35-39yrs	40-49yrs	Total
Ngami	97	448	925	812	894	1,456	4,632
North East	76	268	415	373	342	745	2,219
Serowe/Palapye	282	847	1,573	1,811	2,252	1,954	8,719
Bobirwa	144	472	823	796	531	878	3,644
Kweneng East	158	1,092	2,144	1,548	1,613	3,695	10,249
Southern	89	433	979	1,369	829	1,725	5,423
Gantsi	21	176	221	353	102	174	1,047
Mahalapye	164	469	1,237	1,173	1,250	1,364	5,658
Kgatleng	69	308	718	766	954	630	3,445
Chobe	16	194	340	584	297	494	1,925
Kgalagadi	27	101	309	317	211	272	1,237
Tutume	176	482	967	923	947	1,738	5,234
Boteti	43	367	795	704	320	992	3,220
Okavango	62	239	488	338	398	397	1,922
Gaborone	138	1,834	4,281	5,060	4,974	5,344	21,630
Francistown	91	821	1,550	1,742	1,579	2,370	8,152
South East	65	206	534	781	694	1,014	3,294
Lobatse	22	168	431	486	456	526	2,088
Selebi Phikwe	77	445	1,247	1,283	781	1,918	5,753
Kweneng West	23	137	435	244	438	529	1,807
Goodhope	78	179	386	319	583	1,188	2,732
Hukuntsi	6	80	196	146	169	265	862
Total of HIV infected men	1,923	9,765	20,993	21,929	20,614	29,668	104,892
% of total n =104892	1.8%	11.6%	27.7%	37.9%	43.9%	43.5%	25.2%
Total men denominator	104,850	84,370	75,663	57,894	47,003	68,223	438,003

4.2.2 Results of the analysis of prescribing patterns of ART regimens

Data regarding the ARV regimens prescribed during 2005 and 2006 were analyzed and the results showed eight ART regimens as shown in -Figure 4.2 below.

CBV = Combivir® is a combination of zidovudine and lamivudine

Results of Figure 4.2 belowshow that eight ART regimens were identified. Of these ART regimens Combivir® plus efavirenz (51.31%, n = 881) was the most prescribed regimen followed by Combivir® plus nevirapine (36.17%,n=621), zidovudine plus lamivudine plus efavirenz (3.73%,n=64) zidovudine plus lamivudine plus nevirapine (3.49%, n=60), stavudine plus lamivudine plus nevirapine (2.91%,n=50), stavudine, plus lamivudine plus efavirenz, 2.27% (n=39), Combivir® plus nelfinavir (0.06%,n=1), stavudine plus lamivudine plus nelfinavir (0.06%, n=1) being the least prescribed. Figure 4.2 below shows the percentage prevalence of prescribed ART regimens for the study period.

The commonly prescribed ART regimens identified at SMH-IDCC are similar to those recommended in the ART guidelines of South Africa. The following regimens from the literature were common to both SMH-IDCC and South Africa (South Africa, 2004:6,14, 48; Ministry of health, 2005:5).

Paediatric regimens

- Didanosine plus zidovudine plus efavirenz (DDI /AZT /EFV)
- Didanosine plus abacavir plus efavirenz (DDI /ABC /EFV)
- Zidovudine plus didanosine plus lopinavir/ritonavir (AZT /DDI /LPV/r)

Adult regimens

- Stavudine plus lamivudine plus nevirapine (D4T/3TC/NVP)
- Stavudine plus lamivudine plus efavirenz (D4T/3TC/EFV)
- Zidovudine plus didanosine plus lopinavir/ritonavir (AZT/DDI/LPV/r)

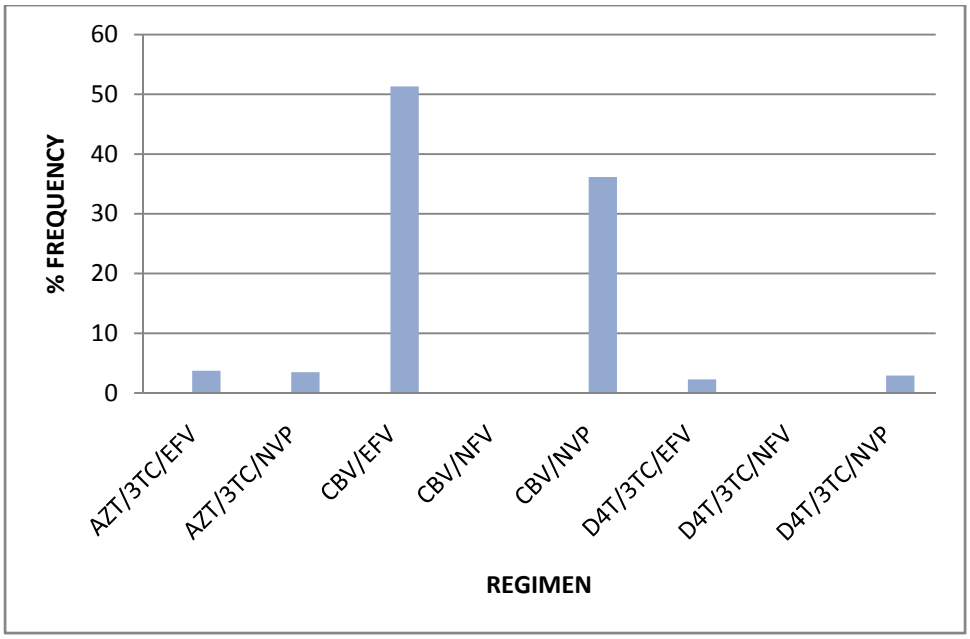

Figure 4.2 Prevalence percentage of the different ART regimens prescribed from 2005 to 2006

Figure 4.2 shows that the most prescibed ART regimen was Combivir® plus efavirenz (51.31%) followed by Combivir® plus nevirapine (36.17%). The least prescribed ART regimens being Combivir® plus nelfinavir and stavudine plus lamivudine plus nelfinavir.

4.2.2.1 Prescribing patterns of ART regimens according to gender

Table 4.3 represents the results of the analysis of the prescribing patterns of ART regimens according to gender.

Table 4.3 Commonly prescribed ART regimens according to gender

Regimen	Female patients	Male patients	Total
AZT/3TC/EFV	18 1.78%	46 6.52%	64 3.73%
AZT/3TC/NVP	44 2.57%	16 0.93%	60 3.50%
CBV/EFV	295 17.20%	586 34.17%	881 51.37%
CBV/NFV	1 0.06%	0 0.00%	1 0.06%
CBV/NVP	586 34.17%	34 1.98%	620 36.15%
D4T/3TC/EFV	22 1.28%	17 0.99%	39 2.27%
D4T/3TC/NFV	0 0.00%	1 0.06%	1 0.06%
D4T/3TC/NVP	44 2.57%	5 0.29%	49 2.86%
Total	1010	705	1715
%	58.89	41.11	100.00

(% calculated according to total number of patients n = 1717)

From table 4.3 above it can be seen that the most prescribed regimen in males was Combivir® plus efavirenz (34.17%) and in females it was Combivir® plus nevirapine (36.15%).

Table 4.4 Prevalence percentage of ART regimens in males and females calculated according to the total number of males or females

Regimen	Female patients	Male patients
AZT/3TC/EFV	18 1.78%	46 6.52%
AZT/3TC/NVP	44 4.36%	16 2.27%
CBV/EFV	295 29.21%	586 83.12%
CBV/NFV	1 0.00%	0 0.00
CBV/NVP	34.17 33.83%	34 4.82%
D4T/3TC/EFV	22 2.18%	17 2.41
D4T/3TC/NFV	0 0.00%	1 0.14
D4T/3TC/NVP	44 4.36%	5 0.71
Total	1010	705
%	100	100

Table 4.4 above compares the prevalence percentage of regimens prescribed for males and females calculated according to the total number of males or females included in the study.

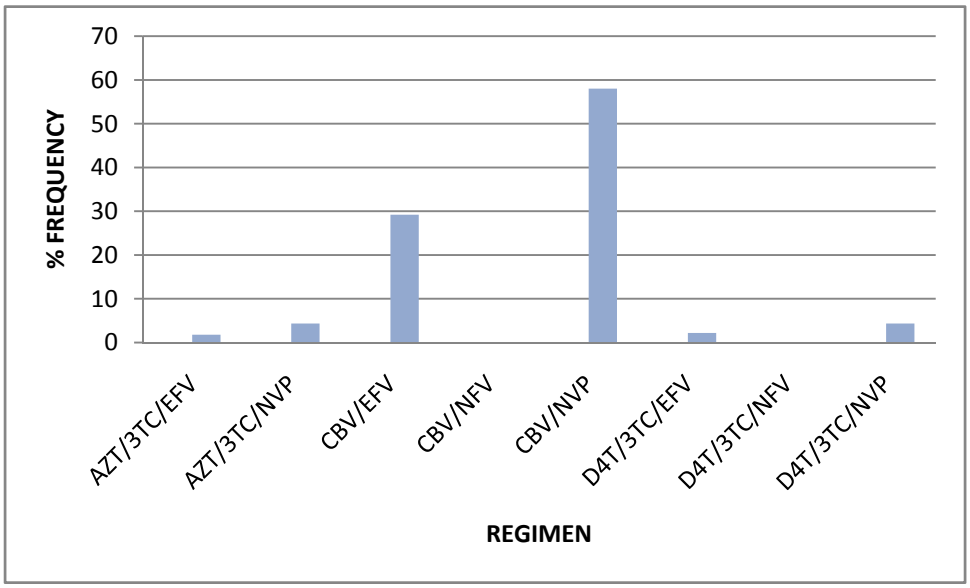

Figure 4.3 Prevalence percentage of the different ART regimens prescribed in females

Figure 4.3 above shows that in females the most prescribed regimen was Combivir® plus nevirapine (58.02%), followed by Combivir® plus efavirenz (29.20%).

Figure 4.4 shows the prevalence percentage of the different ART regimens prescribed for males. Calculations were done according to the total number of males included in the study.

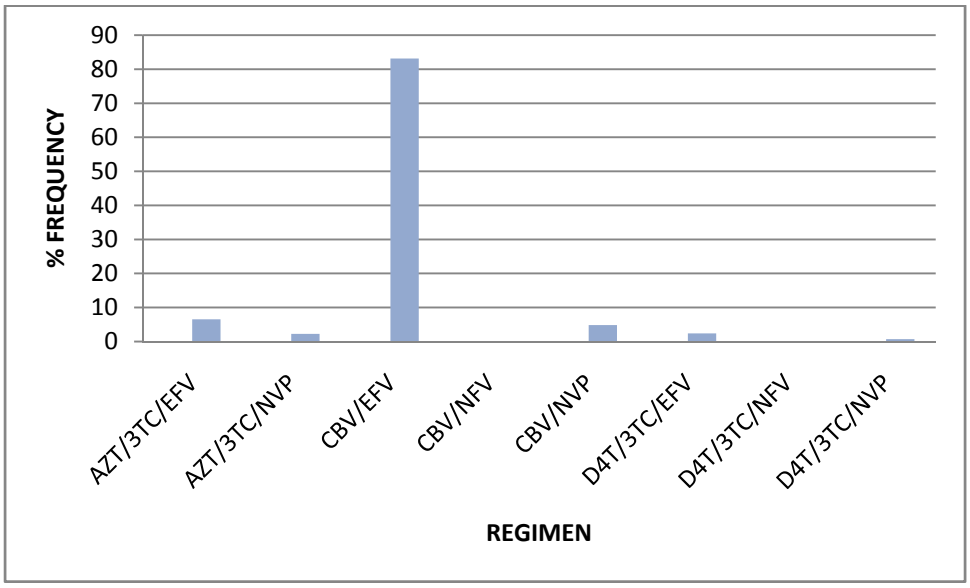

Figure 4.4 Prevalence percentage of the different ART regimens prescribed for males

From Figure 4.4 above it is clear that Combivir® plus efavirenz was the most prescribed regimen for males (83.12%) followed by zidovudine plus lamivudine plus efavirenz (6.52%).

4.2.2.2 Prescribing patterns of ART regimens according to age group

Table 4.5 shows the prescribing patterns of ART regimens according to the different age groups as indicated in Table 3.1. For the purpose of the discussion the age groups were divided into three categories namely age groups one and two are children, three and four adolescents and five to eighteen adults.

Table 4.5 Prevalence percentage of ART regimens according to the different age groups (refer to table 3.1)

	AGE GROUP																		Total	%
	NUMBER OF PATIENTS																			
REGIMEN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
AZT/3TC/EFV	9	45	9	0	0	0	0	0	1	0	0	0	0	0	0	0			64	3.73
AZT/3TC/NVP	24	24	12	0	0	0	0	0	0	0	0	0	0	0	0	0			60	3.49
CBV/EFV	0	0	3	1	16	78	157	151	154	116	80	61	27	22	10	3			879	51.25
CBV/NFV	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0			1	0.06
CBV/NVP	1	0	3	14	69	178	168	95	55	20	7	3	2	2	2	0			619	36.1
D4T/3TC/EFV	0	1	1	0	3	4	7	5	6	7	3	1	0	0	0	1			39	22.7
D4T/3TC/NFV	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0			1	0.06
D4T/3TC/NVP	9	2	2	1	7	12	5	6	4	2	0	0	0	0	0	0			50	2.91

Figure 4.5 shows Prevalence percentage of ART regimen zidovudine plus lamivudine and efavirenz according to different age groups. The regimen AZT plus 3TC plus EFV was mostly prescribed to patients in the agegroup 2 followed by age groups 1 and 3.

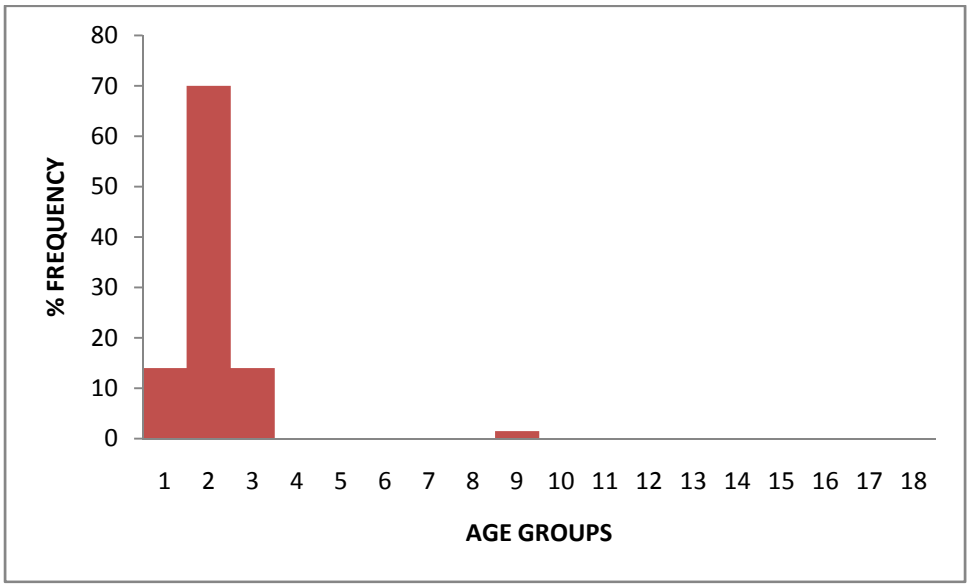

Figure 4.5 Prevalence percentage of ART regimen containing zidovudine plus lamivudine plus efavirenz according to the different age groups

Figure 4.6 shows the p**revalence percentage**y distribution of the ARV regiment AZT plus 3TC plus NVP according to different age groups. It can be seen from the figure that the frequency of usage of this regimen was the highest in the three age groups 1, 2 and 3 with its highest frequency in age group 1 and 2, both at 40%.

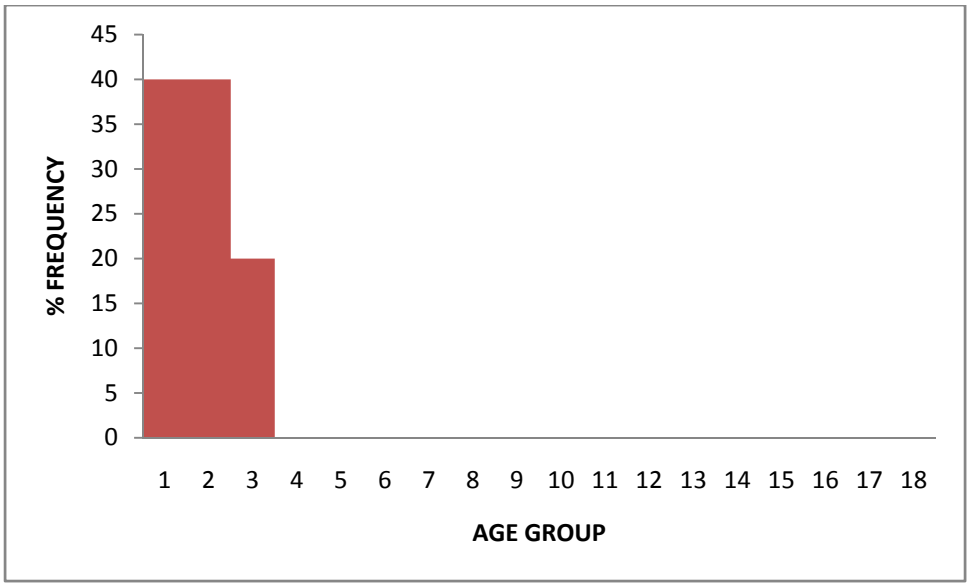

Figure 4.6 Prevalence percentage of ART regimen containing zidovudine plus lamivudine plus nevirapine in the different age groups.

Figure 4.7 below shows the percentage prevalence of regimens containing Combivir® plus EFV according to the different age groups. Figure 4.7 shows that the regimen Combivir® plus EFV was frequently prescribed in the age groups 6 to 15 with the highest frequency in the age groups 6 to12.

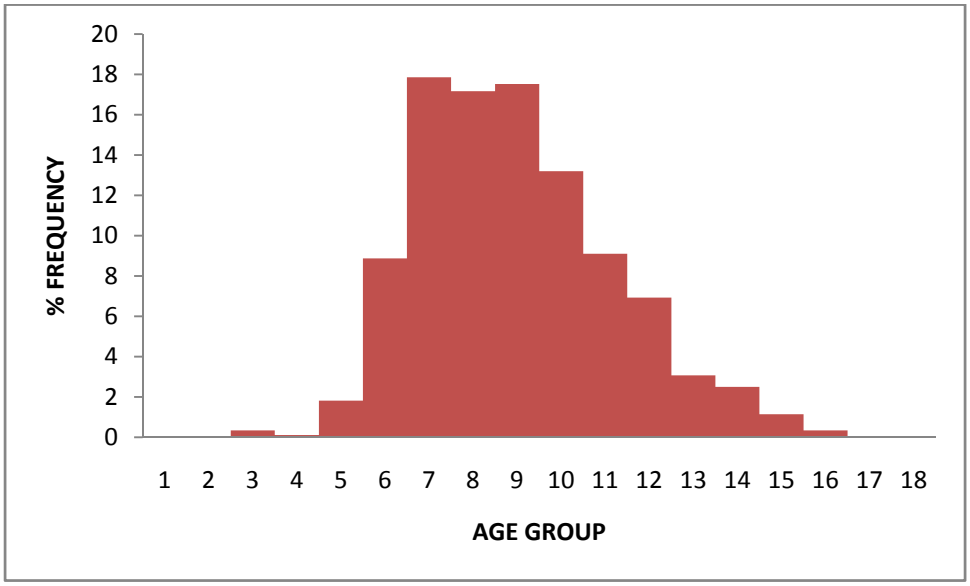

Figure 4.7 Prevalence percentage of ART regimen containing Combivir® (CBV) plus efavirenz according to the different age groups

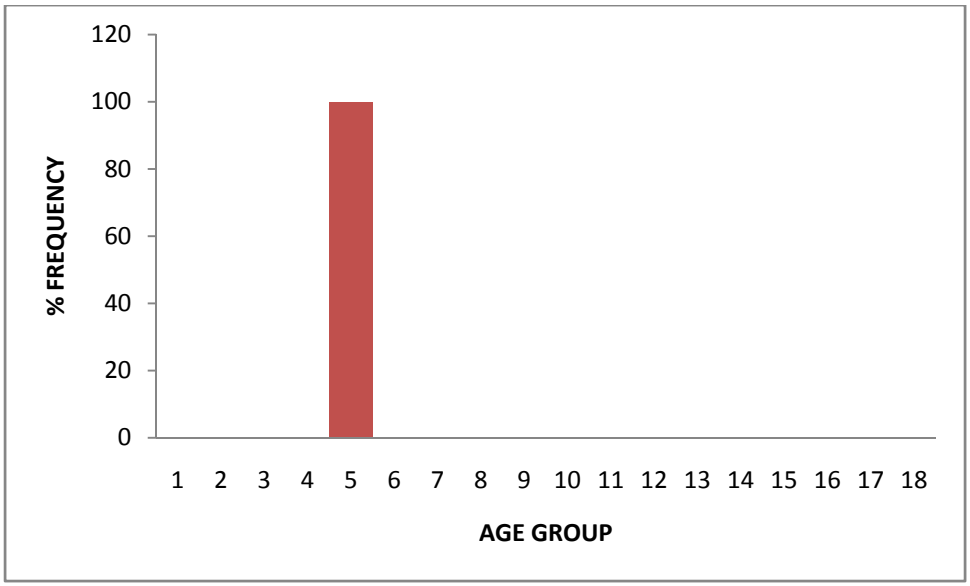

Figure 4.8 Prevalence percentage of ART regimen containing Combivir® (CBV) plus nelfinavir according to different age groups

From figure 4.8 above it is clear that the Combivir® (CBV) plus NFV was only seen in group 5, and its frequency was minimal as only one case is indicated.

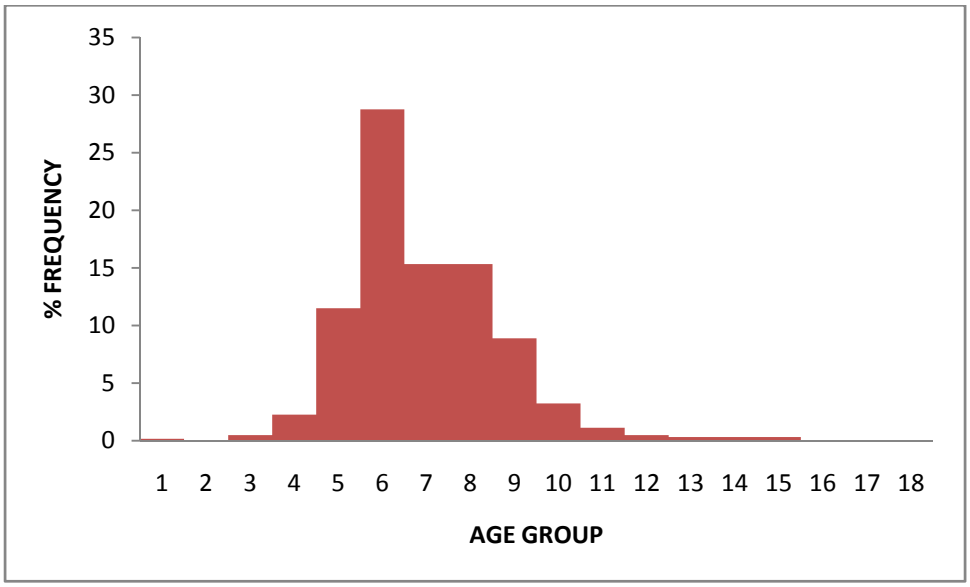

Figure 4.9 Prevalence percentage of ART regimen containing Combivir® plus nevirapine according to the different age groups

Figure 4.9 above shows that the frequency of Combivir® plus nevirapine was distributed to age groups 3 to 12 with its highest frequency being in the age group 6 followed by 7,8 and then 5,9 and then 10,4,11,12,and 3 in that sequence.

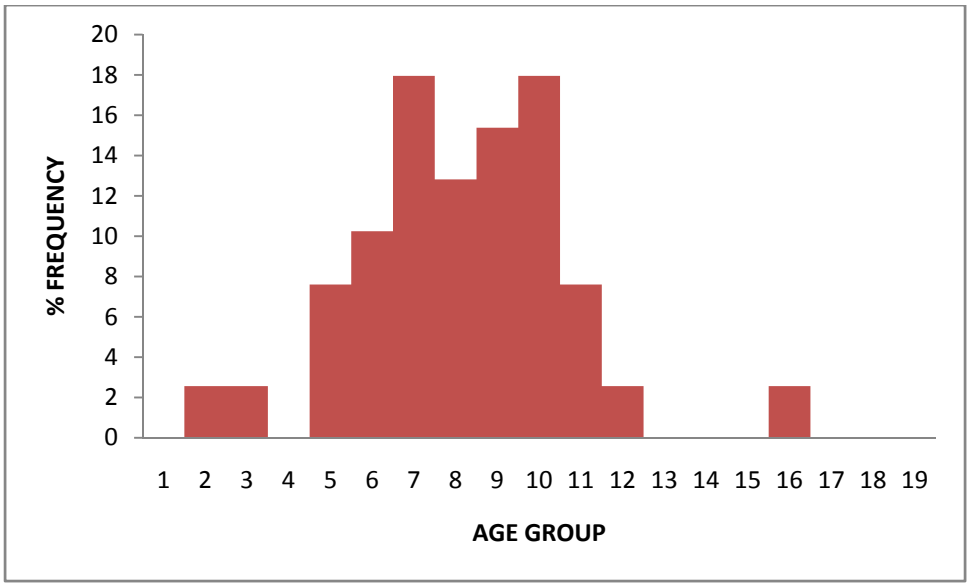

Figure 4.10 Prevalence percentage of ART regimens containing stavudine plus lamivudine plus nevirapine according to different age groups

Figure 4.10 shows the prevalence percentage of ART regimen containing stavudine plus lamivudine plus efavirenz being the highest in the age groups 7 and 10 followed by age groups 9, 8, 6, 5 and low frequencies in age groups 2, 3, 12, and 16.

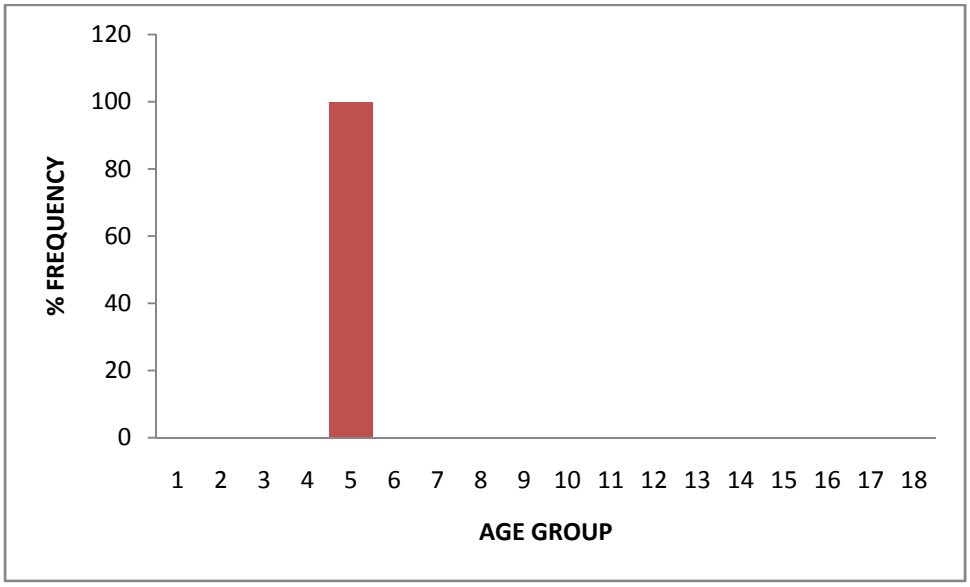

Figure 4.11 Prevalence percentage of ART regimen containing stavudine plus lamivudine plus nelfinavir according to different age groups

Figure 4.11 above shows the prevalence percentage of ART regimen containg zidovudine plus lamivudine plus nelfinavir accordint different age groups. This regimen only appears in one age group and its frequency is only indicated in single patient.

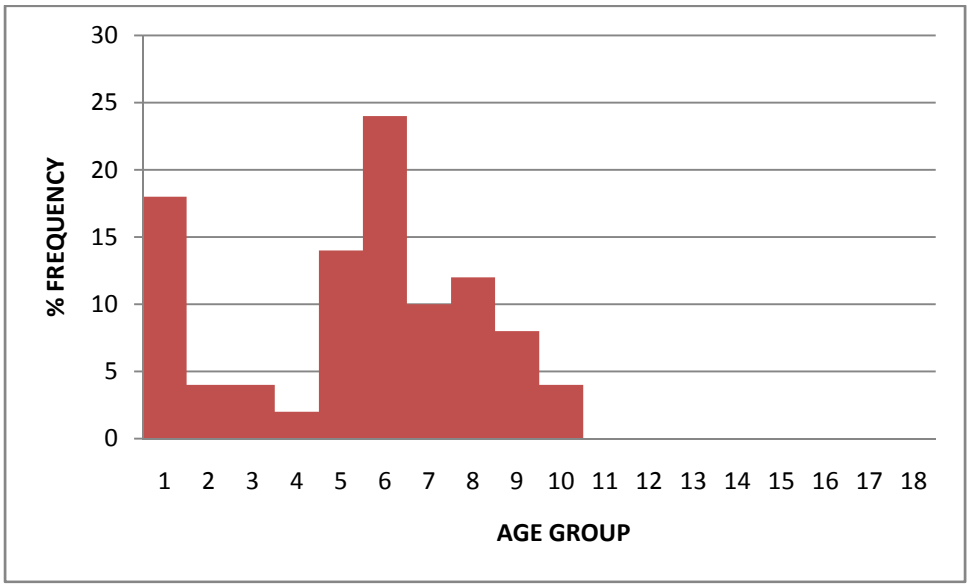

Figure 4.12 Prevalence percentage of ART regimen containing stavudine plus lamivudine plus nevirapine according to different age groups.

From figure 4.12 above it is clear that the regimen stavudine plus lamivudine plus nevirapine was frequently prescibed in age groups 1 to 10. It was highest in age group 6 followed by age groups 1, 5, 8, 7, 9, 10, 2, 3, and 4 in that sequence.

The results of the analysis of prescribing patterns of the different ART regimens at SMH-IDCC showed the following three patterns:

a General prescribing patterns of ART regimens

The results reveal that during the study period both male and female patients at SMH-IDCC were started on eight main regimens. These included the following: AZT/3TC/EFV, AZT/3TC/NVP, CBV/EFV, CBV/NFV, CBV/EFV, D4T/3TC/EFV, D4T/3TC/NFV, D4T/3TC/NVP. As was previously mentioned the prescribing patterns fall within the WHO recommendations (WHO, 2009:49) and compares with the South African ART treatment guidelines for first and second-line regimens (South Africa, 2004:6).

b Prescribing patterns of ART regimens according to gender

The pattern of prescription in the SMH-IDCC for the different genders showed that most of the efavirenz-containing regimens were prescribed in male patients while most nevirapine-containig regimens were prescribed for female patients (refer to Table 4.4). This can be explained in part by the fact that females in the reproductive age groups who indicated their intensions to have children, did not receive efavirenz-containing regimens but nevirapine containing regimens.

c Prescribing patterns according to the different age groups

In addition to the above trends it was further found that AZT/3TC/EFV and AZT/3TC/NVP regimens were mostly prescribed to patients in the age groups 1, 2 and 3 therefore the ages from 0 to 14 years. These were mainly liquid medications as syrups or powder for reconstitution. The rest of the ART regimens were distributed across the rest of the age groups. It should be noted that the age groups 17 and 18 did not have any patients although they were included in the groupings and age group, 16 had only four patients.

4.2.3 Results of the cost analysis of ART drugs and ART regimens

Notes applicable to the cost calculations:

- Approximate costs associated with different ART regimens in US dollars
- Prices of individual ARVs as obtained from Ccentral Medical Stores (all prices converted to USD and cost calculations were based on the 2005/2006 prices as obtained from Central Medical Stores)
- For the purpose of calculating the costs of ART regimens the price of efavirenz which was a donation at the time of the study was assigned the price of efavirenz in South Africa at the time of study.

Table 4.6 shows the prices of ARVs as obtained from Central Medical Stores.

Table 4.6 Prices of ARV drugs from Ccentral Medical Stores at the time of study.

Drug	Class	Strength	Unit	Trade name	Dose/day adult	Unit cost (USD)	Cost/day	Cost /year
Zidovudine	NRTI	100 mg capsule	84	Retrovir®		1.27		
Zidovudine	NTRI	10 mg/ml syrup	200 ml	Retrovir®		9.59		
Efavirenz	NNRTI	50 mg capsule	30	Stocrin®		Donation		
Efavirenz	NNRTI	200 mg capsule	90	Stocrin®	3	Donation		
Efavirenz	NNRTI	600 mg capsule	30	Stocrin®	1	Donation		
Zidovudine plus lamivudine	NRTI	300+150 mg Tab	60	Combivir®	2	15.45	0.52	187.75
Nevirapine	NNRTI	200 mg tab	60	Viramune®	2	32.70	1.09	397.85
Nevirapine	NNTRI	10 mg/ml syrup	240ml	Viramune®		29.44		
Lamivudine	NRTI	150 mg tab	60	Epivir®	2	5.70	0.19	69.35
Lamivudine	NRTI	10 mg/ml syrup	240ml	Epivir®		4.14		
Lopinavir /ritonavir	PI	133+33 mg capsule	180	Kaletra®	6	46.35	1.55	563.93
Didanosine	NRTI	25 mg tablet	60	Videx®	8	16.08		
Stavudine	NRTI	30 mg capsule	60	Zerit®	2	2.98	0.09	36.26
Stavudine	NRTI	40 mg capsule	60	Zerit®	2	3.10	0.10	37.71
Stavudine	NRTI	1 mg/ml powder	200ml	Zerit®		11.25		
Stavudine	NRTI	20 mg capsule	60	Zerit®	2	2.84	0.09	34.55
Tenofovir	NRTI	300 mg capsule	30		1	25.00	0.83	304.17
Zidovudine	NRTI	300 mg tablet	60	Retrovir®	2	53.49		
Abacavir	NRTI	20 mg/ml syrup	200ml	Ziagen®		31.32		
Saquinavir	PI	200 mg capsule	270	invirase®		95.99		
Nelfinavir	PI	250 mg tab		Viracept®	10			

Notes applicable on Table 4.6

Average cost of efavirenz in South Africa during the study period (2005) in USD:

The exchange rate of a dollar to a Rand was 6 rand to a dollar as obtained from the bank

Efavirenz 50 mg (4.29 USD)/30 capsules, Efavirenz 200 mg (51.57 USD) /90 capsules, Efavirenz 600 mg (35.77 USD) /30 tablets (these costs have been used to estimate the cost of efavirenz which was a donation for the ART programme in Botswana during the study period).

Table 4.7 shows the approximate costs of different ART regimens used at SMH-IDCC from 2005 to 2006 as calculated from prices obtained from Botswana Central Medical Stores.

Table 4.7 Approximate cost of different ART regimens (USD)

Regimen	Approximate unit cost/month (USD)	Total number of patients commenced on regimen for two years	Percentage of patients on regimen	Approximate cost of daily dose (USD)	Approximate monthly cost (USD)	Approximate cost per year/patient (USD)
AZT+3TC+EFV	9.58	64	3.73	0.32	9.58	114.96
AZT+3TC+NVP	43.18	60	3.50	1.44	43.18	518.16
CBV+EFV	49.92	881	51.37	1.66	49.92	599.04
CBV+NFV		1	0.05			
CBV+NVP	48.15	619	36.15	1.61	48.15	577.80
D4T+3TC+EFV	43.28	39	2.27	1.44	43.28	519.36
D4T+3TC+NFV		1	0.06			
D4T+3TC+NVP	41.38	49	2.86	1.37	41.3	496.56

Figure 4.13 compares the approximate costs of the different ART regimens in USD($) for 2005- 2006

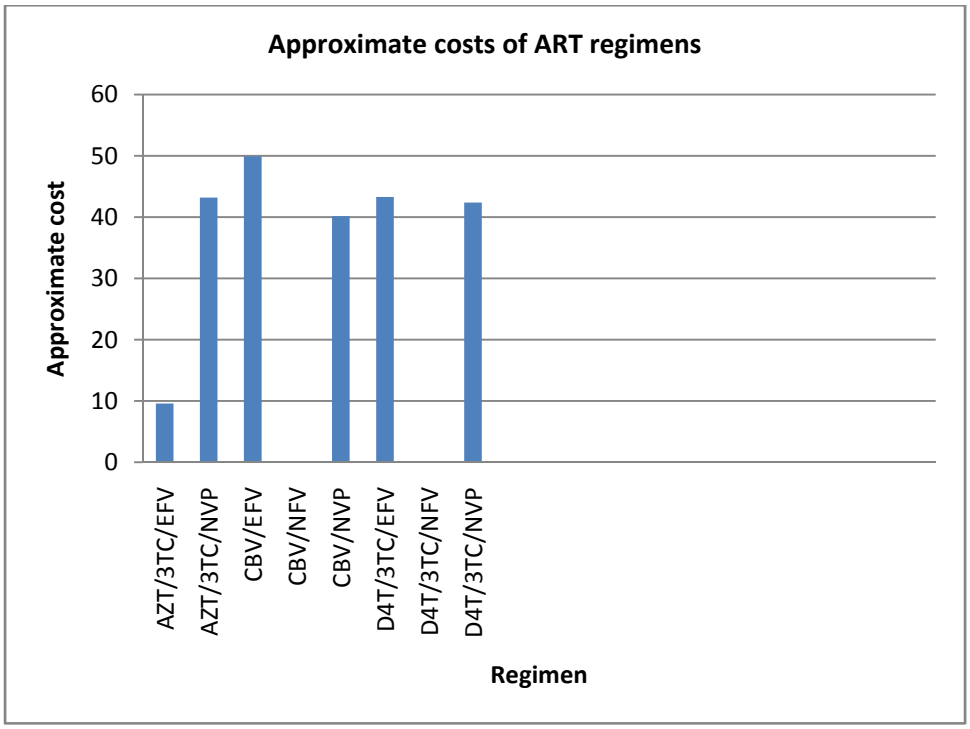

Figure 4.13. Comparison of approximate costs of ARV regimens

A comparison of the approximate costs of ART regimens used at SMH-IDCC indicated that Combivir® plus efavirenz (49.92 USD per patient per month) was the most expensive and the paediatric regimen zidovudine plus lamivudine plus efavirenz (9.58 USD per patient per month) the least expensive. It should be noted that efavirenz was a donation drug during the study period and it was assigned a value based on the market price of efavirenz in South Africa during the study period.

The approximate cost of the different ART regimens prescribed at SMH-IDCC range from 100 USD per patient per year (AZT/ 3TC /EFV) the cheapest to 600 USD per patient per year for the most expensive (CBV/EFV). All the ARV medications were innovator drugs.

Parez-Casas (2001) notes that the cost of treatment with branded drugs is often dramatically more expensive than treatment with generics. He cites an example in which Combivir® with nevirapine all branded medicines in the dosages; Combivir® 300/150 and Nevirapine as Viramune® 200mg twice a day for both taken daily cost 122 USD per month in Brazil where drugs are produced locally. The cost in Thailand where they are

not produced locally was 348 USD giving a price 22.9 times as much Parez-Casas (2001), further suggests the following mechanisms for reducing the cost of HIV/AIDS treatment namelythe use of generics, price studies, international procurement, technology transfer and safeguards on patents. It should be noted here that ART is free in Botswana and that patients do not pay for these drugs.

4.3 Results of the analysis of side-effects of ART regimens

Among all the 1717 patients that initiated treatment from January 2005 to December 2006, 82 (4.78%) patients reported drug side effects or adverse drug reactions and other effects such as pregnancy which lead to a change in therapy. From the analysis of side effects thirteen major effects were reported . Only side effects and other reasons that led to change in therapy were recorded.

Table 4.8 shows ART regimen side effects and other reasons leading to change of therapy reported during the study period

Table 4.8 Side-effects experienced with ART regimens and other reasons that led to a change in therapy

Reason for change of therapy	SE/OR		Number of patients	%
Allergic reaction	SE	AR	1	1.22
Anaemia (AN)	SE	AN	46	56.10
Central nervous system effects	SE	CN	1	1.22
Confusion	SE	CO	1	1.22
Gynacomastia	SE	GN	9	10.98
Lypodystrophy	SE	LY	I	1.22
Neuropathy	SE	NE	3	3.66
Poor adherence	SE	PA	1	1.22
Pregnancy	OR	PR	12	14.63
Rash	SE	RS	1	1.22
Reaction to medication	SE	RX	1	1.22
Steven Johnson's syndrome	SE	SJ	2	2.44
Treatment failure	OR	TF	3	3.66

SE- side effect / OR- other reason

Table 4.8 shows the prevalence of side effects experienced by patients on ART regimens and necessitated change in therapy. Those which did not lead to change of therapy were not recorded. Anaemia was the most frequent side effect followed by gynecomastia and neuropathy. Pregnancy was responsible for change of therapy in child bearing females that had been commenced on efavirenz.

The following figure below shows the frequency of side effects associated with the different ART regimens.

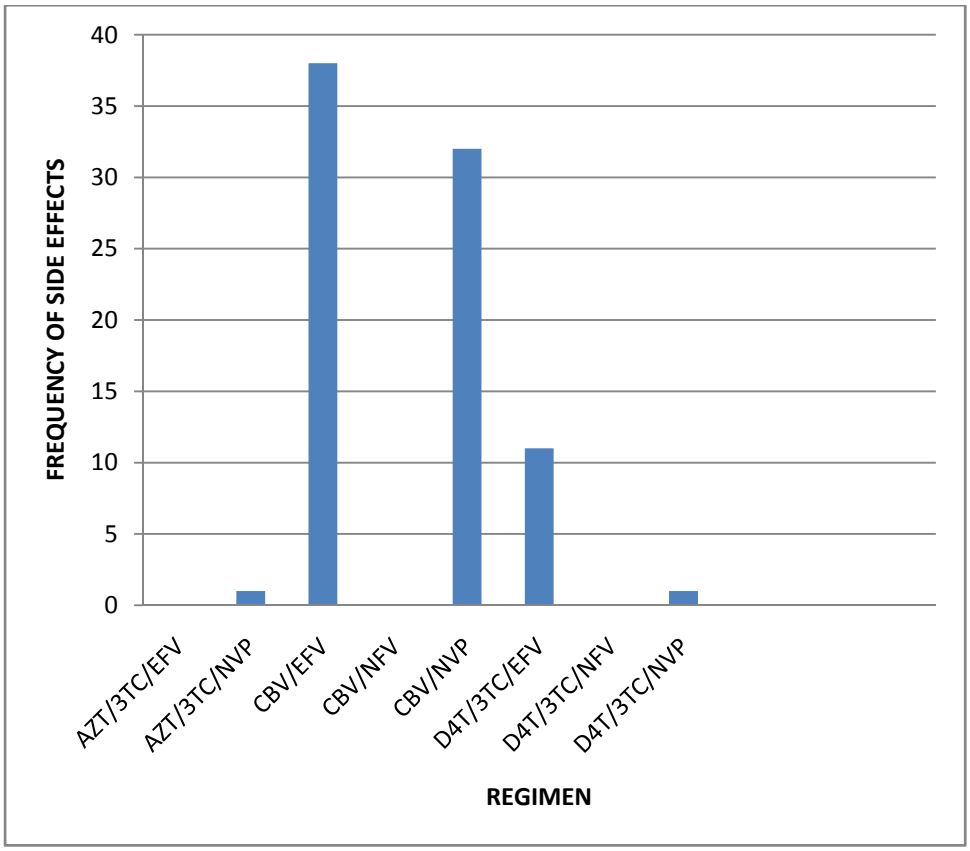

Figure 4.14 Frequency of side-effects associated with the different ART regimens

Figure 4.14 shows that the highest frequency of side effects was associated with the ART combination Combivir® plus efavirenz followed by Combivir® plus nevirapine, then the regimen stavudine plus lamivudine plus efavirenz, then zidovudine plus lamivudine plus nevirapine and least frequent was associated with stavudine plus lamivudine plus nevirapine.

Table 4.9 shows the frequency of side effects with different ART regimens

Table 4.9 Analysis of the percentage frequency of side effects with the different ART regimens

Causative drug(s)	n	% Frequency
CBV/EFV	34	41.46
CBV/NVP	28	34.15
AZT/3TC/EFV	1	1.22
CBV	8	9.76
D4T/3TC/EFV	1	1.22
D4T/3TC/NVP	1	1.22
EFV	5	6.10
NFV	1	1.22
NVP	3	3.66

The figure 4.15 below shows the frequency of change in therapy caused by different ART drugs.

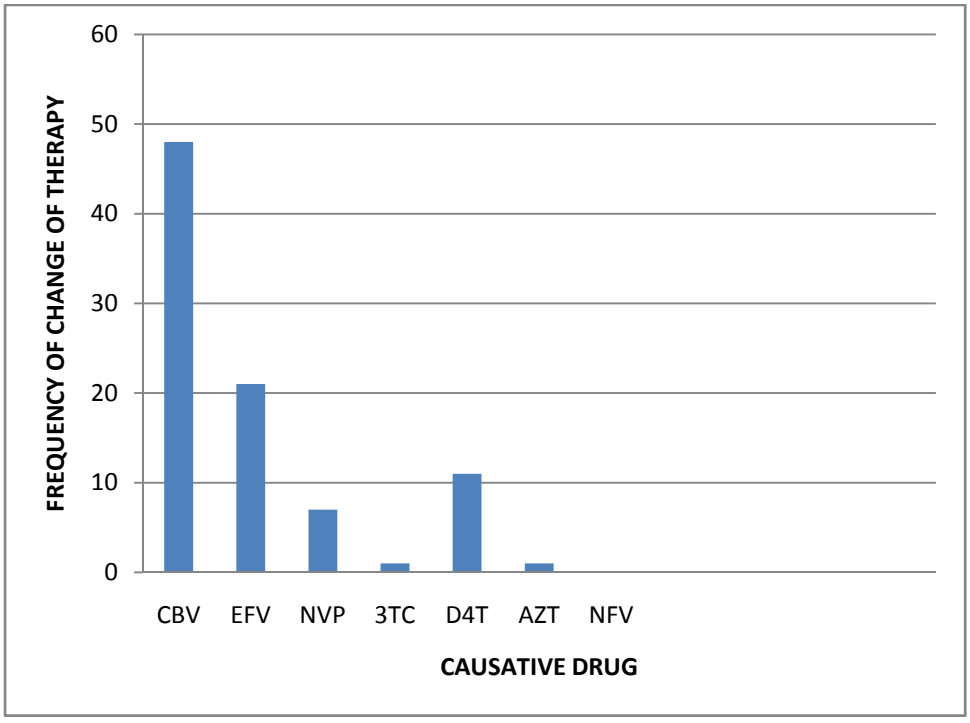

Figure 4.15 Frequency of change in therapy with causative drug(s)

From Figure 4.15 it is clear that a change in therapy as a results of side-effects or other reasons (such as pregnancy) was the highest with Combivir®-containing regimens

followed by efavirenz-containing regimens. This was followed by stavudine-containing regimens and then nevirapine-containing regimens**.**

Results of the empirical investigations on the side effects

The most frequent medication side effect (n = 82) was anaemia (56.1%). Gynecomastia (10.98%) the second most frequently side-effect in males was the reason for changing an efavirenz-containing regimen. Pregnancy (14.63%) was a major reason for changing therapy in patients who began therapy with efavirenz-containing regimens because of the risk of teratogenicity in sexually active women who had become pregnant.

HAART has important side effects including a new spectrum of clinical symptoms and tissue lesions in AIDS patients. Thus, HAART can cause several adverse reactions. The most frequent ones include immune reactions, dermatological conditions, gastrointestinal complaints, headache, disorders of lipid and glucose metabolism (Hofman & Nelson, 2006: 3121)

Hawkins (2006: 7) notes that appearance-related side effects have a negative impact on quality of life and can lead to a decreased adherence to therapy, suboptimal drug levels and the development of drug resistance which may compromise future ART.

Sharma and Kadhiraman (2009:180) note that side effects or adverse drug reactions (ADRs) are common with ART and an important cause of non-adherence. They also contribute to a significant proportion of clinic visits and mortality. ADRs can be idiosyncratic, dose-related, time-related (delayed), or dose- and time related (cumulative). A particular ADR may be common to all drugs of the same class (e.g., lactic acidosis and fatty liver because of NRTIs, lipodystrophy because of PIs), or it might be drug specific (e.g., hypersensitivity to abacavir [Ziagen®], nephrolithiasis because of indinavir [Crixivan®]).

The patient is often on other drugs as well, with overlapping ADR profiles, apart from those of the ARVs. Serious ADRs necessitate withdrawal of the offending drug, and re-challenge of the drug should not be attempted in these situations.

4.4 Results of emperical investigation of the analysis of CD4-T cell count response

Table 4.10 shows the age groupings for the purposes of CD4-Tcell count analysis (refer to Table 3.1)

Table 4.10 Age groups classification for CD4-Tcell count (in cells/μL) analysis

Age group	From	To	Grouping
1	0 year	Including 9 years	Children
2	> 9 years	Including 19 years	Adults
3	> 19 years	Including 44 years	Adults
4	> 44 years	Including 64 years	Adults
5	> 64 years	Including 74 years	Adults

Table 4.11 shows the results of the empirical investigation of the analysis of CD4 Tcell count response.

Note: CD4-Tcell count (1) is taken before commencement of ART, CD4 Tcell(2) is taken six months after commencement of ART.

Table 4.11 CD4-Tcell count analysis for the total population (N = 1717)

Variable	n	Mean	Std Dev	Median
CD4 (1) (cells/μL)	1717	139.31	116.84	126.00
CD4 (2) (cells/μL)	1713	266.11	149.16	260.00
Change in CD4 (%)	1713	126.71	68.23	122.25
CD 4 change (cells/μL)	1713	155.63	204.08	104.12

In 1717 patients initiated on ARV therapy from 1 January 2005 to 31 December 2006, 1713 patients had an average CD4-Tcell count percentage change after six months of 126.71% ± 68.22% and a median of 122.25%.

4.4.1 Analysis of CD4-Tcell count according to gender

Table 4.12 below indicates the changes in CD4-Tcell count after six month of therapy according to gender.

Table 4.12 Change in CD4-Tcell count in both male and females after six months on therapy

Gender	N	Variables	n	Mean	Std.Dev	Median
F	1010	CD4 (1) (cells/µL)	1010	138.16	115.82	127.00
		CD4 (2) (cells/µL)	1008	264.36	147.79	260.00
		% CD4 CHANGE	1008	126.18	67.17	124.28
		CD4 CHANGE (cells/µL)	1008	155.88	207.12	103.46
M	705	CD4 (1)	705	140.48	118.03	121.83
		CD4 (2)	703	267.90	150.70	260.00
		% CD4 CHANGE	703	127.22	69.69	120.00
		CD4 CHANGE (cells/µL)	703	155.46	200.04	105.26

4.4.2 Analysis of change in CD4-Tcell count according to gender and ART regimen

Table 4.13 shows CD4-Tcell count changes in both males and females on different ART regimens. From the results it appears that the average CD4-Tcell count change in both males and females was more than 100 cells/μL in 1714 patients representing 99.94% compared to 1 representing 0.058% of the total population (n=1715) with an average CD4-Tcell count change of less than 100 cells/μL.

Table 4.13. CD4-Tcell count change in males and females on different regimens

Regimen	Gender	n	Mean (cells/ μL)	Standard deviation
AZT/3TC/EFV	F	18	102.13	223.657
	M	46	144.53	57.85
AZT/3TC/NVP	F	44	175.85	91.44
	M	16	146.37	124.72
CBV+EFV	F	295	124.74	64.43
	M	586	124.33	69.35
CBV/NFV	F	1	114.68	
CBV/NVP	F	586	123.28	54.75
	M	34	145.34	62.22
D4T/3TC/EFV	F	22	142.16	60.36
	M	17	118.89	53.95
D4T/3TC/NFV	M	1	68.69	
D4T/3TC/NVP	F	44	126.74	51.37
	M	5	160.64	18.44
Total		1715		

4.4.3 Analysis of mean percentage change in CD4-Tcell count in both males and females on different regimens

Table 4.14 below shows the mean percentage change in CD4-Tcell counts in both males and females for different regimens. In 1605 patients (males and females) the mean percentage change in CD4-Tcell count after six months was more than 100%. In 110 patients representing 6.41% of patients the average percentage change was less than 100%.

Table 4.14 Mean percentage change in CD4-Tcell count in males and females for different regimens

Regimen	Gender	n	Mean percentage change(cells/ µL)	Standard deviation
AZT/3TC/EFV	F	18	33.19	40.24
	M	46	64.37	60.01
AZT/3TC/NVP	F	44	82.13	119.95
	M	16	114.73	253.14
CBV/EFV	F	295	172.40	240.53
	M	586	160.90	194.84
CBV/NFV	F	1	76.29	
CBV/NVP	F	586	155.78	196.63
	M	34	169.07	300.26
D4T/3TC/EFV	F	22	164.39	133.26
	M	17	247.03	257.168
D4T/3TC/NFV	F	0	0	0
	M	1	77.78	
D4T/3TC/NVP	F	44	168.56	217.99
	M	5	100.26	115.35
Total		1715		

4.4.4 Analysis of change in CD4-Tcell count in males and females on different ART regimens in the different age groups

Table 4.15 below shows changes in CD4-Tcell count in different age groups and with different ART regimens.

Table 4.15 Change in CD4-Tcell count in different age groups and different ART regimens

Regimen	Age group	n	Mean (cells/μL)	Standard deviation
AZT/3TC/EFV	1	54	131.47	141.11
	2	9	136.92	42.48
	3	1	155.00	
AZT/3TC/NVP	1	48	173.37	106.17
	2	12	146.47	77.65
CBV/EFV	2	4	141.45	39.19
	3	556	123.55	72.89
	4	284	124.08	56.80
	5	35	136.17	66.61
CBV/NFV	3	1	114.68	
CBV/NVP	1	1	115.32	
	2	17	123.34	49.64
	3	565	125.07	55.94
	4	32	120.77	54.07
	5	4	92.89	46.75
D4T/3TC/EFV	1	1	198.45	
	2	1	95.00	
	3	25	130.04	68.29
	4	11	136.11	47.30
	5	1	107.00	
D4T/3TC/NFV	3	1	68.69	
D4T/3TC/NVP	1	11	153.21	48.02
	2	3	114.91	33.80
	3	34	128.3	51.23
	4	2	92.20	58.27
	Total	1713		

An average change of over 100 cells/μL in the CD4-Tcell count with all the eight different regimens showed in 99.53% of patients (i.e. 1705 patients out of a total of 1713) and in 0.47% of patients the change in the CD4-Tcell was less than 100 cells/μL (i.e. 8 patients out of 1713). For the following regimens the average CD4-Tcell count change was more than 100 cells/μL; AZT/3TC/EFV, AZT/3TC/NVP, D4T/3TC/NVP, CBV/EFV, CBV/NFV, CBV/NVP. The CD4-Tcell count with and had less than 100 cells/μl CD4-

Tcell count change with D4T/3TC/NVP, D4T/3TC/NFV and D4T/3TC/EFV was less than . 100 cells/µl

4.4.5 Analysis of percentage change in CD4-Tcell count in different regimens and different age groups

Table 4.16 shows percentage change in CD4-Tcell count in different age groups and different ART regimens

Table 4.16 Percentage change in CD4-Tcell count for different age groups and different regimens

Regimen	Age group	n	Mean (%)	SD (%)
AZT/3TC/EFV	1	54	48.68	52.10
	2	9	87.4	69.90
	3	1	142.20	
AZT/3TC/NVP	1	48	95.78	182.51
	2	12	71.03	43.62
CBV/EFV	2	4	74.08	25.83
	3	556	168.54	195.95
	4	284	168.53	245.19
	5	35	144.93	131.36
CBV/NFV	3	1	76.29	
CBV/NVP	1	1	79.47	
	2	17	197.92	297.49
	3	565	151.25	186.99
	4	32	230.38	368.06
	5	4	121.69	78.67
D4T/3TC/EFV	1	1	171.74	
	2	1	339.29	
	3	25	205.24	254.32
	4	11	162.91	116.71
	5	1	382.14	
D4T/3TC/NFV	3	1	77.78	
D4T/3TC/NVP	1	11	92.76	95.27
	2	3	203.15	79.52
	3	34	182.03	242.46
	4	2	73.48	0.60
Total		1713		

The results in Table 4.16 indicated that

- in age group 3 one patient on CBV/NFV,
- in age group 1, one patient on CBV/NVP,

- in age group 3, one patient on D4T/3TC/NFV,
- in age group 1, eleven patients on D4T/3TC/NVP;
- and in age group 4, two patients on D4T/3TC/NVP

had an average percentage CD4-Tcell count change of less than 100% representing 0.93% compared to 99.07% of patients who had % CD4-Tcell count change of over 100%.

4.4.6 Analysis of change in CD4-Tcell count in both males and females for different age groups and different regimens

Table 4.17 on page 102 shows change in CD4-Tcell count in different age groups and different ART regimens

Table 4.17 Change in CD4-Tcell count in different age groups and different ART regimens

Regimen	Gender	Age group	n	Mean (cells/ml)	SD
AZT/3TC/EFV	F	1	17	100.80	236.65
		2	1	124.80	
	M	1	37	145.57	61.44
		2	8	138.44	45.18
		3	1	155.00	
AZT/3TC/EFV	F	1	33	181.69	98.00
		2	11	158.35	69.06
	M	1	15	155.08	123.97
		2	1	15.77	
CBV/EFV	F	3	147	116.11	61.36
		4	132	130.54	63.75
		5	16	156.61	84.36
	M	2	4	141.46	39.19
		3	409	126.25	76.53
		4	152	118.51	49.59
		5	19	118.95	42.00
CBV/NFV	F	3	1	114.68	
CBV/NVP	F	2	17	123.35	49.64
		3	541	123.57	55.24
		4	23	119.85	49.61
		5	3	78.85	45.79
	M	1	1	115.32	
		3	23	155.78	61.56
		4	9	123.14	67.47
		5	1	135.00	
D4T/3TC/EFV	F	3	15	164.44	140.34
		4	7	131.60	35.06
	M	1	1	198.45	
		2	1	95.00	
		3	10	104.47	47.52
		4	4	144.01	69.78
		5	1	107.00	
D4T/3TC/NFV	F	3	1	68.69	
D4T/3TC/NVP	F	1	6	143.35	62.06
		2	3	114.91	33.72
		3	33	126.89	51.26
		4	2	92.20	58.27
	M	1	4	156.32	18.15
		3	1	177.91	
Total			1711		

A CD4-Tcell count change of more than 100 cells/μL was experienced in 99.70% (n = 1706) of the patients. Four patients (0.30%) had less than 100 cells/μL CD4-Tcell count change.

One male from age group 2 had a mean CD4-T cell count change of 15.77 cells/ μL on AZT/3TC/EFV, three females from group 5 had an average CD4-Tcell count change of 78.85 ± 49.61 cells/μL on CBV/NVP, and one male patient from group 2 had a CD4-Tcell count change of 95.00 cells/ μL .

The table below shows the percentage change in CD4-Tcell count in different age groups and different ART regimens

Table 4.18 Percentage change in CD4 -Tcell count for different age groups and different regimens

Regimen	Gender	Age group	n	Mean	SD	
AZT/3TC/EFV	F	1	17	29.67	38.52	
		2	1	92.99		
	M	1	37	57.42	55.56	
		2	8	86.79	74.70	
		3	1	142.20		
AZT/3TC/EFV	F	1	33	83.75	137.22	
		2	11	77.28	39.70	
	M	1	15	122.23	260.18	
		2	1	2.20		
CBV/EFV	F	3	147	155.87	165.98	
		4	132	193.85	311.78	
		5	16	110.26	110.26	
	M	2	4	74.08	25.83	
		3	409	166.46	205.82	
		4	152	146.73	165.99	
		5	19	141.87	149.80	
CBV/NFV	F	3	1	76.29		
CBV/NVP	F	2	17	197.92	297.48	
		3	541	153.06	190.75	
		4	23	189.71	257.30	
		5	3	119.80	96.24	
	M	1	1	79.47		
		3	23	110.12	38.16	
		4	9	334.31	570.94	
		5	1	127.36		
D4T/3TC/EFV	F	3	15	165.44	140.34	
		4	7	164.31	127.26	
	M	1	1	171.74		
		2	1	339.29		
		3	10	266.46	350.60	
		4	4	160.44	114.02	
		5	1	382.14		
D4T/3TC/NFV	F	3	1	77.78		
D4T/3TC/NVP	F	1	6	92.66	84.03	
		2	3	203.15	79.52	
		3	33	184.98	245.60	
		4	2	73.48	0.60	
	M	1	4	104.11	132.82	
		3	1	84.86		
Total			1711			

The table 4.18 above shows average percentage CD4-Tcell changes according to genders and different ART treatment regimens. It was found that 89.13% (n = 1525) of patients in both genders had an average percentage CD4-Tcell change of over 100% and 10.80% of patients (n = 186) had less than 100% change. A total number of 1693 patients (98.95%) in all age groups had more than 50% CD4-Tcell count change with all regimens. Only 1.05% (n = 18) of patients had less than 50% change in CD4-Tcell counts. This group that recorded less than 50% increase in the average percentage change in CD4-Tcell count was broken down into 17 females from age group 1 and one male from age group 2. All of them were on the AZT/3TC/EFV regimen.

CD4-Tcell count response

In 1713 patients, the median increase in the CD4-Tcell count after six months was 122 cells/µl. This result compares with a similar results obtained in a research in Haiti (Severe *et al,* 2005:2330) in which, in adults and adolescents, the median increase in the CD4-Tcell count after six months was 128 cells/µL. The CD4-Tcell count at six months was greater than the baseline value in 459 of 504 patients (91%) and remained the same or decreased from baseline in 45 patients (9%). The median increase in the CD4-Tcell count at 12 months (Severe *et al.,* 2005:2330)

According to Sharma and Kadhiravan (2008:176) a reproducible change in absolute CD4-Tcell count of at least 30% and/or 3 percentage point change in the CD4-Tcell percentage is considered significant. Following the initiation of effective ARV therapy, CD4-Tcell counts rapidly improve within a few weeks, largely as a result of the redistribution of cells, and they subsequently improve at the rate of approximately 100 cells/µL per year over the subsequent years until a plateau is reached (Sharma & Kadhiravan, 2008:176)

4.5 CHAPTER SUMMARY

In this chapter a discussion of the results was made and in the next chapter a conclusion is drawn on the basis of the literature review and empirical investigations.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

In this chapter, the conclusions are discussed and where applicable recommendations made. These aspects will be discussed according to the specific objectives as stated in chapters 1 and 3. Specific limitations of this study will also be described.

5.1 CONCLUSIONS AND RECOMMENDATIONS DEDUCED FROM THE LITERATURE REVIEW

Section 5.1.1 to 5.1.4 presents the conclusions formulated regarding the theoretical objectives of the literature study.

The specific objectives of the literature review were as follows:

- To describe the healthcare system in Botswana
- To conceptualise the prevalence of HIV/AIDS in Botswana, South Africa and other countries from available literature
- To conceptualise the HIV/AIDS treatment programmes in Botswana
- To compare ARV treatment guidelines of Botswana with those of WHO and South Africa

5.1.1 Overview of the healthcare system in Botswana

The first objective of the literature study was to obtain an overview of the Botswana healthcare system (refer to 2.4).

From the study of the overview of the healthcare system in Botswana it was evident that a country with a population of 1.8 million people in an area of 600,370 km² with the following: 24 district health teams, three referral hospitals,12 district hospitals , 17 primary hospitals, 222 clinics, 330 health posts and 740 mobile stops would be considered adequate. With an infrastructure aiming at providing health posts within 15 kilometres and clinics within 30 kilometres of 85% of the population (and the following densities of health workforce: 0.40 physicians, 2.65 nurses, 0.19 pharmacists per 1000 patients by 2004) Botswana should have adequate health facilities to cover its population and therefore a reliable health care system. The Ministry of Health provides

leadership on heath policies and ensures the correct interpretation and implementation through the healthcare delivery system.

5.1.2 HIV/AIDS in Botswana

The second objective was to conceptualize the HIV/AIDS situation in Botswana (refer to section 2.5).

From the literature study on the impact of HIV/AIDS in Botswana it was concluded that the impact as shown from the statistics, was high in a country with a population of 1.8 million people. The prevalence rate was 35% (UNAIDS.2004). The total number of HIV infections was estimated at 350,000 in 2003 (UNAIDS, 2004). The epidemic pattern was generalised, sparing no district (Seloilwe, 2005:3)

5.1.3 HIV/AIDS programmes in Botswana

The third objective was to conceptualize the HIV/AIDS programmes in Botswana (refer section to 2.6).

Botswana become the first country in sub-Saharan Africa to launch a free national ARV therapy programme in the public health sector in 2002 (Ministry of health, 2002:3). The government initiated a rapid assessment of the feasibility of providing drugs through the public healthcare sector. The treatment programme that began at a single site in 2002 and after a slow start expanded rapidly so that by the end of 2006 almost all patients in need were receiving medication. The programme now covers the entire country providing ART to all eligible citizens in Botswana with supporting programmes that augment the provision of antiretroviral therapy such as Prevention of mother to child transmission , blood safety, condom promotion, isoniazid prevention therapy, voluntary counseling and testing and public education.

5.1.4 Comparison of ARV guidelines for Botswana, South Africa and the WHO

The fourth objective was to compare the ARV treatment guidelines of Botswana, South Africa and the WHO, (refer to section 2.7).

On comparison the three ART guidelines had similarities. It could be said that the guidelines for South Africa and Botswana were in accordance with the WHO treatment guide lines that served as standard guidelines. However these WHO guidelines had been adapted to suit the different settings in the two countries. It can be concluded that the guidelines for Botswana did not deviate from the international recommendations. The international recommendations have been modified for use in Botswana (Ministry of health, 2002:8).

5.2 CONCLUSIONS AND RECOMMENDATIONS DEDUCED FROM THE EMPIRICAL INVESTIGATION

5.2.1 Prescribing patterns of ART regimens

The first research objective of the empirical study was to identify the prescribing patterns of ART regimens at the SMH-IDCC in the Central District, Botswana. (refer to section 4.2.2)

The results from the study showed that the following 8 ART regimens were prescribed at the SMH-IDCC:

- Zidovudine plus Lamivudine plus Efavirenz (AZT/3TC/EFV),
- Zidovudine plus Lamivudine plus Nevirapine (AZT/3TC/NVP),
- Combivir plus Efavirenz (CBV/EFV),
- Combivir plus Nelfinavir (CBV/NFV),
- Combivir plus Nevirapine (CBV/NVP),
- Stavudine plus Lamivudine plus Efavirenz (D4T/3TC/EFV),
- Stavudine plus Lamivudine plus Nelfinavir (D4T/3TC/NFV) ; and
- Stavudine plus lamivudine plus Nevirapine (D4T/3TC/NVP).

The most prescribed regimen in adults was CBV/EFV (51.37%) which was prescribed to 17.20% of females and 34.17% of males. The second most prescribed regimen in adults was CBV/NVP (36.15%). This ART regimen was prescribed to 34.17% females and 1.98% males.

The most prescribed regimen in children was AZT/3TC/EFV (3.73%) which was prescribed to 1.05% of females and 2.68% of males. The second most prescribed regimen in children was AZT/3TC/NVP (3.50%).

NNRTI regimens were more commonly prescribed. According to the Botswana guidelines all the regimens fall within the national recommended guidelines for regimen selection such as proven clinical efficacy, low toxicity, low pill count and simple to administer first-ine regimens (Ministry of health, 2002:12). Evaluation of clinical practice patterns against contemporary treatment guidelines can inform guideline developers (Holodniy *et al*., 2007:20).

5.2.2 Costs associated with different ART regimens at SMH-IDCC

The second research objective of the empirical investigation was to determine the costs associated with ART regimens (refer to section 4.2.3.).

It was found that, of the eight predominant ART regimens that were prescribed during the study period, the most expensive ART regimen was Combivir® plus efavirenz (CBV/EFV) at approximately USD 49.92 followed by Combivir® plus nevirapine (CBV/NVP) at approximately USD 48.15. The least expensive was the paediatric ART regimen zidovidine plus lamivudine plus efavirenz AZT/3TC/EFV) at approximately USD 9.58.

5.2.3 Side effects experienced with certain ART regimens

The third research objective of the empirical study was to determine the prevalence of side-effects with certain ART regimens (refer to section 4.2.4)

It was found that the most common side effect was zidovudine-induced anaemia 56.10% of 82 observations followed by gynecomastia in males (10.98% of 82 observations). The least frequent side effects were allergic reactions (with several ART regimens) and lipodystrophy (associated with stavudine-containing ART regimens) both at 1.22% of 82 observations. Pregnancy was responsible for change of therapy in 14.63% of 82 observations and this involved females with reproductive potential who had commenced therapy with efavirenz but got pregnant whilst on therapy and had to be switched to a non-efavirenz-containing regimen. Stephen Johnson's syndrome, central nervous

systems symptoms and rash accounted for 2.44%, 1.22% and 1.22% of 82 observations respectively.

It was found that the regimens with the most side effects that would contribute to adherence challenges and necessitate a change in ART regimen were CBV/EFV followed by CBV/NVP with 41.46% and 34.15% of 82 observations respectively.

5.2.4 CD4-Tcell count analysis

The fourth research objective of the empirical study was to illustrate treatment outcomes with the different ART regimens by using CD4-Tcell counts (refer to sections 4.4).

The average CD4-Tcell count change in both males and females was more than 100 cells/μL in 99.94% of the patients. This was a positive change indicating a great improvement in the change in CD4-Tcell count from the start of therapy to six months. This indicated that the initial CD4-Tcell count had doubled in 99.94% of the patients after six months from commencement of therapy.

In the following regimens the average CD4-Tcell count change was more than 100 cells/μL: AZT/3TC/EFV, AZT/3TC/NVP, D4T/3TC/NVP ,CBV/EFV, CBV/NFV,CBV/NVP and the following ART regimens had less than 100 cells/μL CD4-Tcell count change in D4T/3TC/NVP, D4T/3TC/NFV and D4T/3TC/EFV.

The measure of success of the treatment as regards CD4-Tcell count is described according to the Botswana treatment guidelines as a steady rise in the CD4-Tcell count (Ministry of health, 2005:18). This study showed a positive results, with a steady increase in CD4-Tcell count as described in the guidelines indicating a measure of success in terms of CD4-Tcell count change.

5.3 RECOMMENDATIONS

The results of the study showed a strong adherence of the prescribing patterns to the national guidelines. An valuation of prescribing patterns against ART standard guidelines can be a great source of information for the development and improvement of current guidelines. With more new ARV drugs being developed it is recommended that the evaluation of prescribing patterns be done periodically to assess adherence and any deviation from the standard guidelines. The feedback that would serve as information for the development of future guidelines and a feed back to the prescribers would serve as a valuable tool in future planning process.It would be recommended in future that a system be put in place for following up transferred patients and the use of viral load be made use of in future.

5.4 LIMITATIONS

Success is not measured by CD4-Tcell count change alone. It is a number of factors taken into consideration. These include a measure of viral load, absence of side effects, patients improving their lives, recovery from wasting, absence of opportunistic infections and related HIV related tumours or conditions (Ministry of health, 2005:18). It was not possible to collect data on viral load. This information was not available during the study period as most of the laboratory procedures were not done at the study site.

After 2006 there was rapid scale-up of ART services throughout the country. A number of ART centres were opened in addition to the initial four centres. This led to many patients transferring to facilities closer to their homes. Most of these facilities did not have the electronic database and were not linked to the SMH-IDCC. This meant it became difficult to follow up these patients who had transferred out to the new sites.

Another limitation was that the side effects that did not lead to change in ART regimen were not recorded as only data on side effects that necessitated change in ART regimen were recorded and was available for this study.

5.5 CHAPTER SUMMARY

In conclusion the study on prescribing patterns at SMH-IDCC showed strong adherence to the national guidelines. Thirteen side effects necessitating change of therapy were identified. The change in CD4-Tcell count for six months from commencement of therapy was a positive change. Average cost of ART per person per year, although ART is free for citizens in Botswana, was 49.92 USD per person per month for combivir plus

efavirenz and 9.58 USD per person per month for zidovudine plus lamivudine plus efavirenz children's dosages.

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APPENDIX A

WHO CLINICAL STAGING OF HIV FOR INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION (WHO, 2006:68,69)

CLINICAL STAGE 1

Asymptomatic

Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained persistent hepatosplenomegaly

Papular pruritic eruptions

Fungal nail infections

Angular cheilitis

Lineal gingival erythema

Extensive wart virus infection

Extensive molluscum contagiosum

Recurrent oral ulceration

Unexplained persistent parotid enlargement

Herpes zoster

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis)

CLINICAL STAGE 3

Unexplained moderate malnutrition or wasting not adequately responding to standard therapy

Unexplained persistent diarrhoea (14 days or more)

Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month)

Persistent oral candidiasis (after first 6-8 weeks of life)

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis or periodontitis

Lymph node tuberculosis

Pulmonary tuberculosis

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis

Chronic HIV-associated lung disease including bronchiectasis

Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x 109/µL) and or chronic thrombocytopenia

(<50 x 109/ µL)

CLINICAL STAGE 4

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)

Extrapulmonary tuberculosis

Kaposi sarcoma

Oesophageal candidiasis (or Candida of trachea, bronchi or lungs)

Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with

onset at age over 1 month

Central nervous system toxoplasmosis (after the neonatal period)

Extrapulmonary cryptococcosis (including meningitis)

HIV encephalopathy

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

Chronic cryptosporidiosis (with diarrhoea)

Chronic isosporiasis

Disseminated non-tuberculous mycobacteria infection

Cerebral or B cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy

HIV-associated cardiomyopathy or nephropathy

(WHO, 2006:68, 69)

WHO CLINICAL STAGING OF HIV DISEASE IN ADULTS AND ADOLESCENTS

CLINICAL STAGE 1

Asymptomatic

Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained moderate weight loss (under 10% of presumed or measured body weight)

Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)

Herpes zoster

Angular cheilitis

Recurrent oral ulceration

Popular pruritic eruptions

Seborrhoeic dermatitis

Fungal nail infection

CLINICAL STAGE 3

Unexplained severe weight loss (over 10% of presumed or measured body weight)

Unexplained chronic diarrhoea for longer than one month

Unexplained persistent fever (intermittent or constant for longer than one month)

Persistent oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis (current)

Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection,

Meningitis, bacteraemia, severe pelvic inflammatory disease)

Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Unexplained anemia (below 8 g/dl), neutropenia (below 0.5 x 109/µL) and/or chronic

Thrombocytopenia (below 50 x 109 /µL)

CLINICAL STAGE 4

HIV wasting syndrome

Pneumocystis pneumonia

Recurrent bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extra pulmonary tuberculosis

Kaposi sarcoma

Cytomegalovirus infection (retinitis or infection of other organs)

Central nervous system toxoplasmosis

HIV encephalopathy

Extra pulmonary cryptococcosis including meningitis

Disseminated non-tuberculosis mycobacterium infection

Progressive multifocal leukoencephalopathy

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated mycosis (coccidiomycosis or histoplasmosis)

Recurrent septicemia (including non-typhoid *Salmonella*)

Lymphoma (cerebral or B cell non-Hodgkin)

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy