DEVELOPMENT AND ASSESSMENT OF MEDICINES INFORMATION FOR ANTIRETROVIRAL THERAPY IN SUB-SAHARAN AFRICA

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ABSTRACT

Sub-Saharan Africa is home to the majority of people living with HIV/AIDS worldwide. Highly active antiretroviral therapy (HAART) slows the progression to AIDS and significantly improves quality of life but demands adherence rates in excess of 95%. One of the factors contributing to inadequate adherence to complex, chronic treatment such as HAART is the lack of proper patient education, resulting in a poorly informed patient. Much of the available written patient education material has proven to be of an unacceptably high reading level and only a limited number of studies on the design, development and evaluation of such materials have been conducted in sub-Saharan Africa.

The aim of this research project was to design, develop and evaluate a simple, easily readable patient information leaflet (PIL) for a typical HAART regimen. An English 2-page A4-size PIL for the antiretroviral regimen of Stavudine, Lamivudine and Efavirenz was developed in collaboration with members of the target population. Six pictograms were modified, tested and incorporated into this PIL, which was evaluated both objectively by using readability formulae and by consumer testing. Results from a pilot study were used to modify the PIL and to refine and validate the questionnaire. The PIL was then translated into isiXhosa and Kiswahili via a comprehensive three-step approach of initial translation, professional proofreading and back-translation. In the main study, 60 South African and 60 Tanzanian participants of varying educational levels were interviewed. Participants had a choice of reading either the English, isiXhosa or Kiswahili PIL. Demographic data were collected, and the understanding and acceptability of the PIL were assessed. Data collected were statistically analysed.

The PIL was well comprehended and was accepted by almost all the participants. Education and the self-reported ease of reading the PIL had a significant association with the understanding of the PIL, thus emphasizing the importance of matching the reading level of patient educational materials with the reading skills of the target population.

This PIL, designed for a population with widely varied reading skills, included simple text and well designed pictograms, and was relatively easy to read and understand. The appropriateness of the format and content, and its equally good acceptance by participants from both southern and eastern Africa, can be attributed to knowledge of the target population as well as the comprehensive design and assessment processes employed in this study. This approach should be used in designing medicines information for diverse populations in developing countries.

This work is dedicated to my Beloved Mum

Catherine Mbwambo

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AIDS:	Acquired Immunodeficiency Syndrome
ART:	Antiretroviral therapy
ARVs:	Antiretroviral drugs
AZT:	Zidovudine
CMI:	Consumer Medicines Information
DRP:	Drug Related Problem
DHHS:	U.S. Department of Health and Human Services
EC:	European Commission
EFV:	Efavirenz
FDA:	Food and Drug Administration (agency of the DHHS)
FDC:	Fixed Dose Combination
FHL:	Functional Health Literacy
HAART:	Highly Active Antiretroviral Therapy
HBM:	Health Belief Model
HCP:	Health Care Professional
HIV:	Human Immunodeficiency Virus
HL:	Health Literacy
HLC:	Health Locus Control
ILO:	International Labour Organisation
MCC:	Medicines Control council (South Africa)
MIDAS:	Medication Information Design Assessment Scale
MI:	Medicines Information
NNRTIs:	Non-nucleoside Reverse Transcriptase Inhibitors
NRTIs:	Nucleoside Reverse Transcriptase Inhibitors
NtARTIS:	Nucleotide Analogue Reverse Transcriptase Inhibitors
NVP:	Nevaripine
d4T:	Stavudine
OTC:	Over the counter
OIs:	Opportunistic Infections
PHATAM:	Pan-African HIV/AIDS Treatment Access Movement
PIs:	Package Inserts
PI:	Protease Inhibitors
PIL:	Patient Information Leaflet
PLWHAs:	People living with HIV and AIDS
PMTCT:	Prevention of Mother to Child Transmission
PPIs:	Patient Package Inserts
RAIN:	Readability Assessment Instrument
REALM:	Rapid Estimate of Adult Literacy in Medicine
RTI:	Reverse Transcriptase Inhibitors
SAM:	Suitability Assessment of Materials
SORT-R:	Slosson Oral Reading Test-Revised
SPC:	Summary of Product Characteristics
STIs:	Sexually Transmitted Infections
TAC:	Treatment Action Campaign (South Africa)
TADATIS:	Tanzania Drug and Toxicology Information Services
TB:	Tuberculosis
UFI:	User Friendly Index
UIS:	UNESCO Institute of Statistics
UNAIDS:	Joint United Nations Programme on HIV/AIDS
UNESCO:	United Nations Educational, Scientific and Cultural Organisation
USP:	United States of America Pharmacopeia
VCT:	Voluntary Counselling and Testing

WDI:	Written Drug Information
WMI:	Written Medicines Information
WHO:	World Health Organisation
WRAT:	Wide Range Achievement Test
3TC:	Lamivudine

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CHAPTER ONE
INTRODUCTION

1.1 Background to Research

In order to achieve the optimal therapeutic benefit from medicines, they must be used safely and appropriately. A major reason for therapy failure is patient non-adherence to drug regimens, which has been identified globally as a major public health problem [1]. A poorly informed patient is at a higher risk of practising non-adherent behaviour as a result of the lack of effective patient education [2]. The use of written patient education materials has increased over the years, along with the awareness that they play a valuable role in improving patient knowledge and recall of health-related and medicine instructions [2,3,4]. These materials may improve patient adherence to drug regimens [4,5,6]. The use of written educational materials in the form of patient information leaflets (PILs) designed specifically to provide patients with information about their drug regimens has been advocated [7,8].

Regulation 10 of the new South African medicines legislation, the Medicines and Related Substances Control Act, Act 101 as amended, published in April 2003, made the provision of PILs mandatory with certain groups of medicines [9]. Studies conducted on PILs in the United States, Europe and Australia have shown that, for PILs to be effective, they must be designed in collaboration with the target population [4,10,11]. A study conducted locally in 1993 to investigate the value and use of PILs, demonstrated that they improved patient knowledge and recall of information, were well accepted by patients and increased their satisfaction [12]. This study recommended that PIL design be population specific, particularly in a multicultural society such as South Africa. This was the approach adopted in a recent study by Mansoor *et al* [13], who also took cognisance of the limited reading skills of a large proportion of the local population. She designed simple, easily readable PILs that incorporated pictograms and showed that this format was preferred over a text-only format and was significantly better understood by a low-literate population.

The 2004 UNAIDS report on the AIDS epidemic stated that an estimated 25 million people were infected with HIV/AIDS in sub-Saharan Africa, with Southern Africa having an HIV prevalence rate above 17% [14]. Many people in this region will, at some stage, need to take Highly Active Antiretroviral Therapy (HAART), which consists of a minimum of three

drugs, for the remainder of their lives. More than 95% adherence to HAART has been advocated, with poor adherence being associated with the development of resistance and ultimate therapy failure [1,15]. The need for multiple interventions that may assist patients on HAART to remain adherent is evident.

Multiple therapies like HAART would normally require a number of individual PILs. However, given the socio-demographic characteristics of the average patient in sub-Saharan Africa, the approach adopted was to design one PIL for the triple therapy that would be more practical and appropriate for patients with limited reading skills.

1.2 Field of Research

This project has focused on the design, development and assessment of a PIL for a typical ART regimen consisting of three drugs. It covers a diverse range of issues such as selection of a drug regimen, pharmacological information on the drugs and instructions for safe and effective use, the use of pharmaceutical pictograms, and the design and evaluation of written medicines information.

1.3 Overview of Chapters

The chapters to follow begin with a literature review that gives an overview of the global HIV/AIDS epidemic, its impact on social and economic issues, and its management. The chapter then reviews adherence to chronic therapies, the factors that lead to non-adherence, and interventions that have been used to promote adherence. Patient education using written materials, and the history and use of PILs is then reviewed. Literacy and health literacy is reviewed with a special focus on the developing world. The next chapter outlines the modification and evaluation of pictograms using a comprehensive iterative process.

The methodology chapter commences with the selection of a drug regimen and a step-by-step procedure that was used to search for information of the drugs selected. An in-depth process of designing the PIL is then presented along with justification for using the combination of various guidelines. The design of the research tool is then outlined, followed by the objective assessments of the PIL. The pilot study is then presented and the modifications to the PIL

based on the feedback obtained are highlighted. Finally, the main study consisting both of a South African and a Tanzanian arm is described.

The results chapter begins with the findings of the pilot study, following which the results from the main study are presented. The quantitative and qualitative results from both the pilot and main studies are presented. Lastly, statistical tests conducted to investigate associations between understanding of the PIL and a number of variables are presented.

The discussion chapter aims to make sense of the both the quantitative and qualitative results obtained through a critical analysis of these results substantiated by findings from the literature. It also highlights the limitations of the study and interesting issues that were observed in the two diverse populations.

The conclusion chapter presents the practical applications of the findings of the project and discusses opportunities for future research. Recommendations on the future of PILs in developing countries are presented.

CHAPTER TWO
HIV and AIDS

2.1 History of HIV and AIDS

In early 1980, doctors in the United States of America (USA) reported male patients with poorly functional immune systems dying of a rare disease [16,17,18]. An investigation conducted by the US Centre for Disease Control (CDC) to find a connection between these men, found that they were all young gay men, in a gay community, who suffered from this incurable illness that made them weak and thin with an ultimate painful death; thus this rare disease was associated with homosexual sexual relations [16]. It was then named Gay Related Immune Deficiency (GRID) [16,17,18]. However, in 1982 it was discovered that even women and children could get infected and suffer from this incurable disease [17] and in the same year, patients in Uganda, East Africa, were also reported to have suffered from and died of a new disease after losing a lot of weight; hence, it was named the "slim disease"[19]. Patients presented with incurable skin disease, chronic diarrhoea and, in some cases, a terrible cough [19,20]. Cases in the US were closely investigated and a virus that caused a deficiency in the immune system was noted; this explained why patients were prone to infections that the normal body was able to fight. The virus was named Human Immunodeficiency Virus (HIV) and the condition it caused was named Acquired Immune Deficiency Syndrome (AIDS) [16,17,18].

2.2 Estimated HIV and AIDS Statistics

2.2.1 Worldwide

According to the Joint United Nations programme on HIV/AIDS (UNAIDS) 2004 report of the global AIDS epidemic an estimated 40 million people worldwide are infected with HIV [14]. Globally in 2003, an estimated 5 million people were newly infected and 3 million people died of AIDS [14]. Since the first cases of AIDS were identified in 1981, over 20 million people have died of AIDS [14].

Of the estimated 40 million infected with HIV worldwide, more than 95% live in low- and middle-income countries with approximately 70% of these people (28.1 million) living in sub-Saharan Africa. In contrast the high-income countries, such as the USA and Western

European countries, have a much lower HIV burden with an estimated 1.6 million people living with HIV [14].

2.2.2 Sub-Saharan Africa

Even though Africa is home to only 10% of the world's population, it hosts 70% of the global HIV-positive population [14]. Sub-Saharan Africa is the most severely affected region with an estimated 25 million HIV-positive people [14]. In 2003 alone, an estimated 3 million people were newly infected and 2.2 million people died of AIDS, accounting for 75% of the worldwide deaths due to AIDS [14]. In this region, the estimated number of people living with HIV grew very rapidly from the mid-1980s through the mid-1990s, with continued, but slower growth since then [14,21].

The predominant mode of HIV transmission is heterosexual transmission. The infection gap in this region continues to grow as women are infected at an earlier age than men [14]. On average it is estimated that there are 13 infected women for every 10 infected men [14].

There is no single clarification as to why the epidemic is so out of control in Southern Africa. Instead, an amalgamation of factors, working together, seems to be accountable. According to the UNAIDS 2004 report, these factors include [14]:

- poverty and social instability that result in family disruption
- sexual violence
- high levels of other sexually transmitted infections (STIs)
- the low status of women
- ineffective leadership during critical periods in the spread of HIV
- migratory labour systems.

Another important factor to note is high mobility, which is linked to migratory labour systems. A study conducted in the Eastern Cape, South Africa, to investigate the relationship between labour migration and HIV, found that areas with higher migrant populations had higher HIV prevalence as measured by mortality [14,22].

The first reported cases of AIDS in South Africa were of two homosexual men in Johannesburg who died in 1982 [23]. By 1990, more than 600 cases of AIDS had been

reported [23] and by 1994, the number of HIV-positive people was estimated to be between 300 000 and 750 000. This disastrous trend continued and by the year 2000, AIDS had become the biggest single cause of death in South Africa. Currently, it is estimated that 4.8 million South Africans are infected with HIV/AIDS [14] and 18 000 people die of AIDS every month while 600 people die every day. The adult infection rate of HIV in South Africa is estimated at 19.94% [24]. This implies that nearly one in every five adult South Africans is living with HIV/AIDS, the majority being unemployed and living below the poverty line.

According to South Africa's first systematically sampled community-based survey of HIV prevalence conducted by the Human Sciences Research Council (HSRC) in 2002, 11.4% of the population of two years and older is living with HIV/AIDS [24]. An AIDS and demographic model developed by the Actuarial Society of South Africa [23] that can be used to project the impact of AIDS nationally and provincially has considered the HIV/AIDS epidemic as a series of "waves"[23]:

- new HIV infections - peaked in about 1998 at around 930 000 new infections
- total HIV infections - projected to peak in about 2006 at about 7.5 million infections
- number of AIDS deaths - to peak soon after in 2010 at about 800 000 deaths a year
- number of AIDS orphans - expected to peak at about 1.85 million in 2025.

With these projections, the importance for antiretroviral therapy (ART) to manage AIDS is paramount and constitutes an emergency.

The first cases of HIV/AIDS in Tanzania were reported in 1983. The epidemic has evolved from being a rare and new disease to a common household problem that has affected most Tanzanian families [25]. In order for Tanzanians to understand the disease, an acronym in Kiswahili was formulated. AIDS is known was UKIMWI - Uharibifru Wa Kinga Mwilini. This literally translates to 'damage of the immune system'. According to a recent report, a total of 1.9 million people aged 15 years and above were living with HIV during 2002 [26]. These estimates are based on prevalence among blood donors and the 2002 census data. At the end of 2001, the prevalence rate for adults aged between 15 - 49 years was 7.8% [26]. These estimates are not exact figures since it has been observed that many people living with HIV/AIDS (PLWHAs) in Tanzania do not to get tested, die in their home villages unrecorded or have HIV-related illnesses that are not recognised by health care professionals (HCPs), resulting in many unknown and unrecorded AIDS deaths [27].

2.3 Impact of HIV and AIDS and associated problems

The impact of HIV and AIDS is widespread, with virtually no country in the world remaining unaffected [14]. In most developing countries, this epidemic has been shown to reduce the capacity of households, communities and nations to cope with the complex social, political and economic consequences [14,28]. The Director-General of the International Labour Organisation (ILO) stated that *"HIV and AIDS is a human crisis but it is also a threat to sustainable social and economic development"* [28].

HIV/AIDS is not only a public health issue, but also a developmental one [14,28] as it is eroding the growth of economies through its direct effect on labour supply, productivity, savings rates, economic growth and the delivery of public services [28]. Estimates show that more than 26 million labour force participants between the ages of 15 and 64 years are HIV-positive or are already living with AIDS, a vast majority (over 70%) of whom live in Africa [28].

In South Africa, there are nearly 3.7 million economically active people who are HIV-positive; in Tanzania the figure is around 1.4 million [28]. The ILO reports that, in the absence of increased access to Antiretroviral (ARV) treatment, the cumulative loss of labour force participants worldwide is projected to reach 28 million in 2005, 48 million in 2010 and 74 million in 2015 [28]. By causing the illness and death of workers, the HIV/AIDS epidemic reduces the labour force's stock of skills and experience, this loss in human capital being a direct threat to goals for poverty eradication and sustainable development [28]. The ILO estimates propose that South Africa, with the largest economy in the African region, but not the highest HIV prevalence, has lost over US$7 billion of its economy annually from 1992 to 2002 because of the loss of its labour force [28].

According to ING Barings Bank, the overall economic growth rate over the next decade in this country is likely to be 0.3 to 0.4 percentage points lower every year than it would have been without AIDS [29]. A further study found that by 2010, taking account of the cumulative effect of this slower economic growth over time, the real gross domestic product will be 17% lower than it would have been in the absence of AIDS, which would eliminate US$22 billion from the South African economy [29].

The United Nations Food and Agriculture Organisation (FAO) estimates that 7 million agricultural workers globally died of AIDS between 1985 and 2000 and further projects that by 2020, a further 16 million are likely to die; this represents between 10.7% and 26% of the agricultural labour force in the worst affected countries [28]. The countries said to be the worst affected in Africa include Botswana, Central African Republic, Cameroon, Cote d'Ivoire, Kenya, Malawi, Mozambique, Namibia, South Africa, Tanzania, Uganda and Zimbabwe [28].

A number of strategies that include both prevention and treatment programmes, need to be implemented in the workplace to reduce the projected loss of the labour force and to, maintain profitability and ensure growth [28]. Treatment programmes that have already been established by a number of enterprises have been shown to be the least costly option for maintaining profitability and ensuring growth. In South Africa, for example, some large companies now provide ART to their workers, after a cost-benefit analysis showed it was more profitable to provide treatment than to lose skilled, trained and experienced infected workers [30].

The HIV/AIDS epidemic has been accompanied by social responses of denial, fear, stigma and discrimination [14,31]. Stigma is a potent societal control tool that can be used to marginalize, reject and exercise power over individuals who show certain characteristics [31]. Discrimination has spread speedily, fuelling anxiety and prejudice against the most affected groups and PLWHAs [31]. As the main method of transmission of HIV infection is unsafe sexual intercourse, this has resulted in AIDS being labelled a 'shame disease', one that associates the infected person with 'sexual promiscuity' and irresponsibility [31]. HIV infection has also been associated with minority groups or behaviours like homosexuality in some societies or, in some cases, 'perversion'; thus some believe that those infected are being punished [31]. These have been the leading factors in discriminating against PLWHAs. The fear of discrimination often prevents infected people from admitting their HIV status publicly or from seeking treatment for AIDS related illnesses, which in turn forces many infected people to die silently in their home villages, 'in shame' [31].

A recent Ugandan study found that the AIDS illness and death syndrome are strongly associated with witchcraft and superstitions [32]. The spread of HIV in some rural areas is thought to be by witchcraft, in other areas, it has been attributed mainly to traditional beliefs

or practices such as wife inheritance (whereby the brother or uncle of a deceased husband inherits the widow) and also to polygamy practices [32]. Misleading claims of AIDS cures by religious sects and traditional healers as well as a denial of the reality of the true threats posed by AIDS also contribute to the spread of HIV in these areas [32].

There is thus a need to narrow the gap in HIV/AIDS knowledge between rural and urban areas in most developing countries. Increased awareness of social, cultural and traditional aspects of rural life and preventive education on issues associated with HIV/AIDS are required in order to empower communities to act positively [32]. This may in turn reduce discrimination against PLWHAs and encourage more PLWHAs, especially those in rural areas, to talk about their status and be accepted back into those communities who tend to isolate or abandon them.

In 2003, the estimated number of children under 18 years who were orphans as a result of AIDS was 15 million, with more than 12 million of them living in Africa [33]. For countries currently most affected by HIV/AIDS, it has been projected that the proportion of all children likely to be orphans will range from 15% to 25% [33]. In South Africa alone, it is estimated that by 2010, there will be 1.5 million orphaned children [33]. The HIV/AIDS epidemic makes children susceptible in two ways: firstly, by robbing them of parental care and guidance; secondly, by requiring them to move away from school and into work [28,33]. Orphans and vulnerable children are also at risk of the loss of the provision of basic needs like nutrition, health services and shelter [33] and are at greater risk of illness, abuse and sexual exploitation. These have lifelong effects on the individual child and long-term effects on the skills level and well-being of the next generation [28,33].

2.4 HIV and AIDS

2.4.1 Transmission of HIV

The most common type is known as HIV-1 and is the infectious agent that has led to the worldwide AIDS epidemic [18,34]. The HIV-1 type itself has a number of subtypes (A through H and O), which have differing geographic distributions, but all produce AIDS similarly [18,34].

The HI virus is harboured in most of the body fluids of an infected person who becomes an asymptomatic carrier, and it may be transmitted from an infected person to an unaffected one in a number of ways [18,35]:

- by engaging in unsafe sexual practices, as HIV is a sexually transmitted virus. In the genital region, the Langerhans cells in mucosal epithelial surfaces, which can become infected, actually aid infection during unprotected sexual intercourse. Infection is also aided by the presence of other sexually transmitted diseases that can produce mucosal ulceration and inflammation, resulting in penetration of HIV.
- by the transfusion of contaminated blood or blood products, and by sharing contaminated needles used by persons engaging in intravenous drug use.
- from mother to child. Mothers who are HIV-infected can pass the virus on to their foetuses in utero or to infants via breast milk.

2.4.2 HIV testing

Testing for HIV and the communication of the test result are conducted using a three-step process called Voluntary Counselling and Testing (VCT), [36,37] which constitutes a cornerstone for early access to prevention as well as to care and support services. The first step is pre-test counselling, whereby the person has the opportunity of asking questions about HIV/AIDS and discussing the test with a trained counsellor. In the second step, the person must sign a consent form, after which some blood is taken by a health care provider (HCP) and tested. This accurate scientific test will show whether or not the person has indeed been infected with HIV. It does not indicate the presence of AIDS or assess the severity of the infection. Most clinics use a rapid test that gives results after about 20 minutes. The test is followed by post-test counselling - the third step. If the patient is found to be HIV-positive, he is referred to a hospital for more tests. High public awareness of HIV, the increasing numbers of persons becoming sick and dying of AIDS, and a knowledge of personal risk behaviours is resulting in an increased desire to learn one's serostatus [18,37].

2.4.3 HIV infection

HIV is a retrovirus that contains only RNA [38,39] which mainly infects the CD4+ cells, as well as CD8+ and B-cells, gradually destroying them and causing the immune cell populations to decrease [18,38-40]. The CD4+ T-lymphocytes have surface receptors to

which HIV can affix to promote entry into the cell (Figure 2.1). The infection then extends to lymphoid tissues, which contain follicular dendritic cells that can become infected and provide a reservoir for continuing infection of CD4+ T-lymphocytes [18,38-40,42].

When HIV infects a cell, it uses its reverse transcriptase enzyme to transcribe its RNA to host cell pro-viral DNA. It is this pro-viral DNA that directs the cell to produce additional HIV virions, which are then released (Figure 2.1) [40]. HIV damages the body's ability to protect itself from disease organisms by decreasing the number of CD4 cells, making the infected person prone to opportunistic infections (OIs) [18,38-41].

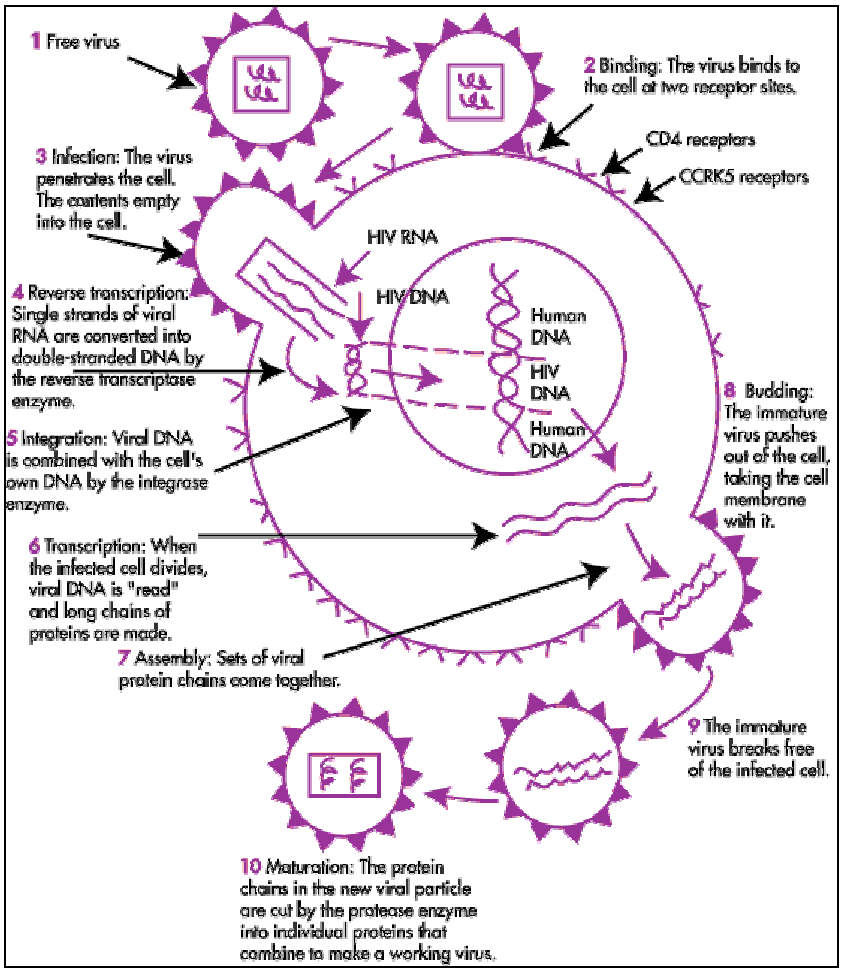


Figure 2.1 Diagram of HIV and infection into cell [40]

2.4.4 Opportunistic infections

Opportunistic infections (OIs), which can be bacterial, fungal or viral, occur when the immune system is compromised in HIV-infected persons (Table 2.1) [18,41-43,45].

Table 2.1 Common opportunistic infections in PLWHAs

The OI and causative agent	Site of infection and presentation	Treatment/prophylaxis
Tuberculosis (TB), most common OI caused by *Mycobacterium tuberculosis*	the lungs loss of weight, cough, night sweats and loss of appetite	combination of rifampicin, isoniazid, pyrazinamide and ethambutol for periods of up to 18 months
Cryptococcal infection, a life threatening fungal infection caused by *Cryptococcus neoformans*	enters through the lungs and may spread to the central nervous system Cryptococcal meningitis is also common and it presents with headaches and fever	with amphotericin B and supportive measures maintained on fluconazole for life to suppress recurrence
Cytomegalovirus (CMV), one of the herpes virus group	causes retinitis leading to blindness and disseminated disease which kills prolonged fever, malaise, lack of appetite, fatigue, night sweats and muscle and joint pain	oral gancyclovir along with the implantation of tiny pellets of the same drug into the eyes which delays/prevents CMV complications
Pneumocystis carinii Pneumonia (PCP) caused by *Pneumocystis carinii*, an opportunistic pathogen which lives naturally in the lungs	the lungs fever, shortness of breath and a non-productive cough	regular prophylaxis with cotrimoxazole (trimethoprim-sulphamethaxazole).
Kaposi's sarcoma was one of the first illnesses noticed among the San Francisco homosexual population in the early 1980s	purple vascular nodules on the skin may remain as skin patches or may spread to the lymph nodes, gastrointestinal tract and the lungs	radio- and chemotherapy for severe infection
Oral candidiasis or thrush mainly caused by *Candida albicans*, is an AIDS-defining condition	a rough feeling and pain in the soft palate and pain on swallowing may develop into disseminated candidiasis in which the fungus spreads through the body, the symptoms are non-specific with fever, shock and renal failure endocarditis and candida meningitis may occur	antifungal agents like itraconazole or fluconazole are effective severe infection requires intensive care and supportive treatment with amphotericin B
Certain lymphomas are more common	high-grade non-Hodgkin's lymphoma and lymphoma of the brain Hodgkin's disease is atypically aggressive and involves multiple sites	chemotherapy
Toxoplasma gondii is a protozoan parasite with a wide distribution and is associated with cat faeces and eating uncooked meat which may contain its cysts	variety of manifestations such as toxoplasma encephalitis, retinitis and pneumonitis Toxoplasma encephalitis is the most common, presents with single or multiple brain abscesses	use of combinations of sulphadiazine-pyrimethamine and pyrimethamine-clindamycin. for prophylaxis - cotrimoxazole, dapsone-pyrimethamine or dapsone-trimethoprim
Mycobacterium avium complex (MAC) includes *M.avium* and *M.intracellulare*	presents with persistent fever, night sweats and massive weight loss	treatment as for TB

Apart from ART, prophylactic treatment of OIs is also essential to prevent their onset in individuals who have never suffered from them, and those who have been treated for OIs successfully require secondary prophylaxis to prevent a second infection [18,41-43].

The routes of transmission of HIV are shared with hepatitis B and hepatitis C, resulting in some HIV-infected people becoming concurrently infected with one of these viruses [18]. This co-infection is significant when choosing ARV drugs as patients with active hepatitis need to avoid certain ARV combinations.

2.4.5 WHO disease staging system

The WHO staging system for HIV infection and disease is a method of describing people with HIV as being at different stages of HIV infection, according to their clinical symptoms [44,45]. When the CD4 lymphocyte count drops below 200 per micro litre, the characteristic OIs and neoplasms of AIDS tend to appear, signifying the clinical AIDS stage [41-45]. The WHO staging system will be used to describe AIDS (Table 2.2) [44].

Table 2.2 WHO staging system for HIV infection and disease

WHO Clinical Stage and Clinical symptoms	**Performance scale[1]**
Stage I ・ Asymptomatic ・ Generalized lymphadenopathy	1: asymptomatic, normal activity
Stage II ・ Weight loss, < 10% of body weight ・ Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) ・ Herpes zoster within the last five years ・ Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)	2: symptomatic, normal activity
Stage III ・ Weight loss of more than 10% of body weight ・ Unexplained chronic diarrhoea for more than 1 month ・ Unexplained prolonged fever (intermittent or constant), > 1 month ・ Oral candidiasis (thrush) ・ Oral hairy leucoplakia ・ Pulmonary tuberculosis ・ Severe bacterial infections (i.e. pneumonia, pyomyositis)	3: bedridden < 50% of the day during last month
Stage IV ・ HIV wasting syndrome which presents with: weight loss of > 10% of body weight, plus either unexplained chronic diarrhoea (> 1 month) or chronic weakness and unexplained prolonged fever (> 1 month) ・ Most of the OIs in combination and with increased severity ・ Cryptosporidiosis with diarrhoea > 1 month ・ HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings	At this stage a patient has full blown AIDS and requires ART

[1]The performance scale shows how the patient presents and rates how they cope with normal daily activities

2.5 HIV and AIDS Care, Management and Treatment

AIDS is a chronic condition that requires lifelong therapy. The strategies employed in caring for AIDS patients consist of preserving immune function as long as possible with ART, using prophylactic pharmacologic therapies to prevent OIs, and diagnosing and treating acute infections as soon as possible [45].

In the mid-1980s, the first class of anti-HIV drugs was formulated. These agents prolonged lives, but, in the early 1990s, they became unable to inhibit HIV replication. The lives of PLWHAs followed an often fixed course of slow annihilation of the immune system, commencement of prophylaxis to prevent OIs, premature retirement, wasting, periods of wellness and illness punctuating an inevitable decline towards complete immune exhaustion and, finally, death [45]. Because HIV mutated readily, the virus developed resistance to single drug therapy.

Appropriate treatment with drug combinations appears to slow the progression of HIV infection and reduce the frequency of OIs. Since 1996, the way that people in the richest countries think about HIV and AIDS has changed because of the advent of new classes of Antiretroviral drugs (ARVs) and their use in combination [45]. These treatments do not cure AIDS, but significantly improve both mortality and morbidity rates, improve the quality of life and change perceptions of AIDS to being a manageable chronic illness, rather than a plague [45]. The triple combination of ARVs was termed Highly Active Antiretroviral Therapy (HAART), and is an ARV regimen that can reasonably be expected to reduce the viral load to <50 cells/mL in treatment-naïve patients [46]. It usually includes a combination of protease inhibitors with reverse transcriptase inhibitors [46]. The combination of ARVs is also commonly known as a ‘drug cocktail’.

In contrast, the accessibility of ARVs in resource-poor settings was still very limited and various stakeholders had to take a further step. In August 2002, at the World Summit on Sustainable Development in Johannesburg, South Africa, the Pan-African HIV/AIDS Treatment Access Movement (PHATAM) was launched by AIDS activists from 21 African countries [47]. At its inaugural meeting, AIDS activists assessed the gaps in their countries’ HIV/AIDS policies and programmes, noting in particular the scarcity of ARV treatment programmes. PHATAM called for African countries to implement the World Trade

Organisation's (WTO) Declaration and insisted that the US and other wealthy countries allow countries with limited pharmaceutical manufacturing capacity to purchase low-cost, generic versions of patented medicines from exporting countries once WTO rules on patents had been fully implemented [47,48].

The Director-General of WHO stated that *"Lack of access to antiretroviral therapy (ART) is a global health emergency. To deliver ART to the millions who need it, we must change the way we think and change the way we act"* [49]. On World AIDS Day, 1st December 2003, WHO and UNAIDS released a detailed and concrete plan to reach the '3 by 5' target of providing ARV treatment to '3 million' people living with AIDS in developing countries and those in transition by the end of '2005', with the ultimate goal of universal access to HIV/AIDS treatment for everyone who needs it [49]. As of June 2004, 440 000 people with AIDS were receiving ART in developing and transitional countries. Although this is 60 000 less than the target for the initial six months of the '3 by 5' initiative, it has shown some progress in both national and international efforts to scale up ARV treatment [49].

2.5.1 Antiretroviral drugs

Only regimens with at least three ARV drugs used in combination have been found to be potent enough to drastically reduce viral replication, prevent the emergence of resistance and, ultimately, prevent treatment failure [18,50]. Triple therapy, HAART, has also been associated with immunological restoration, a slowing of disease progression, durable therapeutic responses, improvements in quality of life and prevention of the emergence of drug resistance, resulting in a reduced morbidity and mortality in all settings (i.e. both resource-rich and poor settings) [45].

According to the WHO the following are the established goals of HAART [50]:

- clinical goals: prolongation of life and improved quality of life
- virologic goals: stop disease progression and prevent or reduce resistant variants
- immunological goals: quantitative and qualitative immune reconstitution
- therapeutic goals: rational drug sequencing to achieve virologic goals, maintain therapeutic options, have relatively few side effects and have a realistic adherence probability
- epidemiologic goals: a reduction of HIV transmission.

2.5.1.1 When to initiate HAART

As recommended by the WHO, HIV-infected adolescents and adults should commence therapy when they have the following [45]:

- WHO stage IV of HIV disease (clinical AIDS) and advanced stage III, regardless of CD4 count
- WHO stages I, II or III of HIV disease, when CD4 count is near or falls below 200/mm3 or when the CD4 percentage is below 15%
- WHO stages II or III of HIV disease with total lymphocyte count (TLC) below 1200/mm3 (when CD4 cell monitoring is not available).

2.5.1.2 Choice of ART in resource-limited settings

A public health approach where ART is standardised has been proposed by WHO to be used in countries with limited resources [45]. The key element of this public health approach is to provide potent and effective ARV therapies that maximize benefits for individual participants in programmes and preserve the treatment prospects of future participants, taking into account the social circumstances in the developing world [45]. WHO suggests that these countries select a single first-line and a limited number of second-line regimens for large scale use whilst identifying patients who do not tolerate or who fail the first and second-line regimens and referring them for individualised care by specialist physicians [45].

The WHO document states that the choice of therapy in resource-limited settings depends on a number of factors such as [45]:

- drug potency
- the side effects profile
- the potential for maintaining future treatment options
- the anticipated adherence of the patient population to the regimen
- co-existent conditions like co-infections, pregnancy or the risk thereof
- the use of concomitant medications; their cost and access
- access to a limited number of ARV drugs
- a limited health service infrastructure
- the need to deliver drugs to rural areas

- a high incidence of TB and hepatitis B and/or C and
- the presence of various HIV groups and subtypes.

2.5.1.3 Antiretroviral Therapy

ARVs are a group of drugs that are used in the management of HIV infection [18]. They inhibit the reproduction of retroviruses, which are viruses composed of RNA rather than DNA. The HI virus is the best-known retrovirus. ARV agents are virustatic agents that block steps in the replication of the virus. The drugs are not curative; however continued use of drugs, particularly in multi-drug regimens, significantly slows disease progression [18,45,50].

The first ARV effective against the HI virus was marketed in the US in 1987 [51,52]. To date, more than 20 ARVs have been registered worldwide; research on ARVs is still expanding, owing to the growing emergence of mutations of HIV, resulting in resistance to the available ARVs [45]. The three main groups of ARVs that have different modes of action are the reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors. In South Africa, the Medicines Control Council (MCC) has registered a total of 13 different types of ARVs [53].

As a retrovirus is composed of RNA only; it must make a DNA strand in order to replicate itself. Reverse transcriptase is an enzyme that is essential to make the DNA copy [18,38]. The reverse transcriptase inhibitors (RTIs) are incorporated into the DNA strand, forming faulty DNA molecules that are incapable of reproducing, thus inhibiting HIV reproduction in the body [18]. RTIs are sub-divided into three groups shown in Table 2.3.

The protease inhibitors (PI) work by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new HIV virons, and so they prevent viral replication [18]. This was the second class of ARVs developed. Fusion inhibitors inhibit the fusion (entry) of HIV into the cell membrane thus preventing infection of uninfected cells. This is the newest class of ARV drugs and only Enfuvirtide has been registered by the US Food and Drug Administration (FDA) so far [52]. Details of these drugs are presented in Table 2.3.

Table 2.3 A list of the currently available ARV drugs

Drug Class	Groups	Drug names	Year of FDA approval	Year of MCC registration
Reverse Transcriptase Inhibitors (RTIs)	NRTIs [1]	Zidovudine (AZT)	1987	1989
		Didanosine (ddI)	1991	1992
		Zalcitabine (ddC)	1992 for monotherapy 1996 for use in combination with AZT	1994
		Stavudine (d4T)	1994	1998
		Lamivudine (3TC)	1995 for use in combination with AZT	1996
		Abacavir (ABC)	1998	2001
		Emtricitabine (FTC)	2003	Not yet registered
	NNRTIs [2]	Nevirapine (NVP).	1996 for adult use	1998
		Efavirenz (EFV)	1998	1999
	NtARTIs[3]	Delavirdine	1997	Not yet registered
		Tenofovir	2001	Not yet registered
Protease inhibitors (PI)	none	Saquinavir	1995	1997
		Ritonavir	1996	1997
		Indinavir [4]	1996	1996
		Nelfinavir	1997	1999
		Amprenavir	1999	2001
		Atazanavir	2003	Not yet registered
		Fosamprenavir [5]	2003	Not yet registered
		Tipranavir	Not yet approved	Not yet registered
Fusion inhibitors	none	Enfuvirtide [6] (T-20)	2003	Not yet registered

[1] Nucleoside Reverse Transcriptase Inhibitors (NRTIs).
[2] Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).
[3] Nucleotide Analog Reverse Transcriptase Inhibitors (NtARTIs) or (NtreatmentIs) - general nucleoside analogs are converted into nucleotide analogs by the body
[4] Indinavir is much more powerful than any prior antiretroviral drug
[5] Fosamprenavir is a pro-drug of amprenavir in a slow-release formulation
[6] Enfuvirtide is available in injectable form only.

From 1996, after the introduction of HAART, a combination of ARVs had to be taken together. This meant a very high pill count for the patient, which was thought to severely affect adherence to ART [54]. Fixed dose combinations (FDCs) were formulated to help reduce the pill burden (Table 2.4).

Table 2.4 Fixed dose combinations

Drug name	Components	FDA approval	MCC registration
Combivir®	AZT and 3TC, a dual combination with 2 NRTIs	1997	2000
Trizivir®	ABC, AZT and 3TC a triple combination with 3 NRTIs	2000	2003
Kaletra®	lopinavir and ritonavir, 2 PIs	2000	2002

There is also a group of synergistic enhancers that do not possess any ARV properties, but when taken concurrently with ARV drugs they enhance the effect of ARVs. These include

hydroxyurea, resveratrol, mycophenolic acid (CellCept®), grapefruit juice, ritonavir (Norvir®) and leflunomide (Arava®).

ARVs have been associated with a number of adverse effects, some of which are class specific and may be intolerable and serious, requiring medical intervention [18,45,50]. The most common side effects associated with ART are listed in Table 2.5, together with the ARVs commonly associated with them.

Table 2.5 Most common ARV side effects and the causative ARVs [45,50]

Adverse clinical events	**Drug Class**		
	NRTI	**NNRTI**	**PI**
Lactic acidosis may be severe, with or without pancreatitis; mostly associated with risk factors of pregnancy, obesity, being female and prolonged use of NRTIs. ART should be suspended if clinical and laboratory manifestations of lactic acidosis syndrome occur	Common-d4T, ddI	Rare	Rare
Hepatotoxicity, with or without hepatitis, may be mild or severe, requires liver function monitoring	Rare	Common	Common
Hyperglycaemia, new onset of diabetes mellitus, diabetic ketoacidosis, and exacerbation of pre-existing diabetes	Rare	Rare	Common
Lipodystrophy syndrome presents with fat malabsorption with metabolic abnormalities such as insulin resistance and hyperlipidemia	Common	Common	Common-
Bone disorders like osteonecrosis, osteopenia, and osteoporosis, avascular necrosis and a decrease in bone density are emerging metabolic complications of HIV infection that might be linked to ART	Rare	Rare	Common
Skin rash or severe cutaneous manifestations such as Stevens-Johnson syndrome and toxic epidermal necrosis, which requires immediate discontinuation of therapy	Common-ABC	Very common	Common-Amprenavir

Note: the side effects of the newest class of ARVs, the FI, are yet to be documented.

The choice of ARVs is dependent on many factors. One of the most notable advances in recent years has been the success of HAART. The most commonly used combination is triple therapy, with a dual NRTI ‘backbone’, upon which an additional third or fourth agent confers sufficient potency for long-term efficacy [45,50]. The choice of the two NRTIs is made on the basis of potency and durability, short- and long-term toxicities, drug-drug interactions, the propensity to select for resistance mutations and dosing convenience [45,50]. The most commonly used combinations are of one thymidine base NRTI (AZT or d4T) alongside 3TC as the ‘backbone’, and a third ARV, either a NNRTI or a PI, which is added to this dual NRTI backbone [50].

2.6 ART in the South African context

The use of ARVs is the only hope for countries severely affected by HIV and AIDS and their access is also a fundamental to realising the right to health for all [48,55]. In 1998, the provision of ARVs for the prevention of mother to child transmission (PMTCT) became a controversial issue in South Africa, as the Government had opposed their use owing to toxicity and safety issues. The Treatment Action Campaign (TAC) was established and began a movement to demand the provision of ART for PMTCT to save newborn babies from contracting HIV. Only when TAC threatened with legal action, did the Government commit to a pilot programme for the provision of ARVs to expecting mothers [48]. Since its existence, TAC has also fought for the reduction of the prices of ARVs and other drugs required for the prophylaxis and treatment of OIs and for the registration of generic drugs [48]. TAC activists also launched the PHATAM in 2002 as described in Section 2.4, which aimed at pressurising the governments of some African countries to provide ARVs to all who need them [48].

The main campaigning effort of TAC thus far has been to make the South African government commit to the development and implementation of a national treatment plan that will include national provision of ARVs [48]. The plan was set up, but its implementation was delayed, which again caused controversy and TAC threatened legal action.

The South African government detailed three main objectives in dealing with the AIDS pandemic [56]:

- to ensure that non-infected South Africans remain HIV-negative; by sending the messages of prevention and lifestyle change
- to ensure that the disease in HIV-positive South Africans progresses very slowly; by enhanced efforts in prophylaxis and treatment of OIs, as well as healthier nutrition and lifestyle
- to manage AIDS patients by providing ART to those with “AIDS defining illness” in order to improve functionality and postpone death.

2.6.1 The release and implementation of the operational plan

In November 2003, the National Department of Health (DOH) released the Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa and implemented a national ARV roll-out program [57]. This plan aims to accomplish two inter-related goals: to provide comprehensive care and treatment for PLWHAs and to facilitate the strengthening of the national health system in South Africa [57]. The primary goals of ART stated in this plan, are similar to the WHO goals stated in Section 2.5.1.

The interventions in this plan aim to also strengthen the existing public health infrastructure, which includes pharmacies, laboratories, transportation, information technology, referral systems, facilities and staff capacity, surveillance systems, communication systems, monitoring and evaluation capacity and research [57]. The main objective of this operational plan is to ensure that all individuals requiring ART are able to access comprehensive care and treatment by 2009 [57].

According to this plan, AIDS patients who are prepared, trained and willing to adhere will be given free ART in the public sector. This will be done in phases after potential roll-out sites have been inspected, the proper requirements met and the HCPs trained to give ARVs to identified patients. The patients will have undergone a few weeks of training and assessment to ensure that they will be as adherent as possible to ART [57].

The two rural pilot ART provision sites in Lusikisiki and Khayelitsha have proven that ART can be implemented in rural areas despite the many acclaimed socio-economic barriers to implementation such as stigma, lack of knowledge, poverty, lack of food and traditional attitudes opposed to safer sex practices [58]. Lessons learnt include the need for implementation programs that include medical training for nurses and political mobilization of the community [58].

2.6.1.1 Eligibility Criteria to receive ART

Criteria for ART eligibility for adults, adolescents and pregnant women include [57]:

- CD4 count of less than 200 cells/mm3, symptomatic, irrespective of stage or
- WHO Stage IV AIDS-defining illness, irrespective of CD4 count and
- prepared and ready to take ARVs in an adherent manner.

2.6.1.2 ARV regimens to be provided

The choice of regimens is limited owing to availability of approved drugs and resource constraints and considers factors such as safety profiles, monitoring requirements, cold storage and potential for development of resistance. The first-line regimen (1a/1b) is for men and for women of childbearing age and the second-line regimen is available in the event of treatment failure of the first line treatment (Table 2.6) [57,59].

Table 2.6 Adult ARV regimen and routine monitoring during treatment [57,59]

Regimen	Drugs	Test	Frequency
1a [1]	d4T + 3TC + EFV	· CD4 cell count to show prognosis · Viral load to show the amount of HIV in the body · Alanine Transferase to test for liver function	· Staging [4], 6-monthly · Baseline [5], 6-monthly · Baseline [5]
1b [2]	d4T + 3TC + NVP	· CD4 cell count to show prognosis · Viral load to show the amount of HIV in the body	· Staging [4], 6-monthly · Baseline [5], 6-monthly
2 [3]	AZT + ddI + lopinavir/ritonavir	· CD4 cell count to show prognosis · Full blood cells count to check how the immune system is functioning · Fasting cholesterol	· Staging [4], 6-monthly · Baseline [5], 1-, 3- 6-monthly, continue 6-monthly · Baseline [5] only

[1] Regimen 1a: first-line regimen for all men and for women on injectable contraception and use condoms
[2] Regimen 1b: alternate first-line regimen for women unable to guarantee reliable contraception while on therapy
[3] Regimen 2: to be used as a second-line regimen for patients who fail regimens 1a or 1b, or first-line regimen in patients who have evidence of NVP resistance prior to ART initiation
[4] Staging is initial testing for all patients after testing HIV-positive
[5] Baseline is testing for ARV eligible patients, at initiation of ART

Together with treatment with HAART, regular monitoring and evaluation are critical for management and may maximise treatment success [57]. Clinical and laboratory monitoring to detect drug intolerance, drug reactions, drug toxicity, drug-drug interactions and treatment failure is needed so as to either reinforce adherence or switch regimens [57]. TB is the leading cause of death in HIV-infected persons and it is estimated that it accounted for 30%

of all the AIDS-related deaths in 1999 [57]. HIV and TB co-infection rates are high in South Africa; therefore, many patients who meet the criteria to receive HAART may have pulmonary TB [57]. WHO recommends that ART should only be initiated in patients on TB treatment when the risk of AIDS progression and mortality is deemed high [45]. Careful drug selection and combination are essential to avoid toxicity and drug interactions.

2.6.1.3 The continuum of care approach

The continuum of care is based on one seeking healthcare at different levels of the health system and is followed through diagnosis and duration of HIV infection [57]. The continuum of care model has multiple entry points into the health care delivery system that include VCT, PMTCT, delivery of reproductive health and STI services, primary health care, TB clinics, inpatient hospital settings and prisons [57].

Components of the continuum of care also include prevention strategies, medical care and treatment by a dedicated, trained medical team, psychological support, nutritional assistance, social support and home- and community-based care services [57].

After diagnosis and staging of HIV infection, individuals with advanced disease are then referred for either ART and/or prophylaxis of OIs, and those with less advanced disease for routine follow up and monitoring [57]. However, patients will have the right to choose the treatment of their choice [57]. As of October 2004, close to 8 000 people were on ARV treatment at public facilities throughout South Africa.

2.6.2 Issues pertaining to adherence to HAART

Adherence to HAART is recognised as one of the key determinants of its success. Poor adherence may lead to virologic failure, the evolution of drug resistance and subsequent immunological and clinical failure [1,15,45,48]. ART necessitates an extremely high level of adherence in order to attain sustained suppression of viral replication and to prevent the onset of resistance. Adherence of more than 95% has been advocated, and in a twice-daily regimen this equates to not missing more than 3 doses a month [1,15].

No single tool can be applicable in all regions and cultures. Each country or centre needs to develop a culturally appropriate tool to assess and monitor adherence [45]. Ongoing attention to and reinforcement of adherence throughout the entire course of ART is an essential part of a successful treatment programme [45,57], as evidence indicates that adherence may decline as time progresses [57]. It has been established that well-informed and engaged patients are the most successful with adherence to therapy [57].

The South African operational plan outlines strategies to promote adherence to ART and its assessment and monitoring by the health care team, which include [57]:

- multiple encounters with patients to explain goals of therapy and the need for very high adherence levels
- monitoring the use of and adherence to medications like cotrimoxazole or other surrogates, prior to ART initiation
- negotiating an understandable treatment plan with the patients, to which they can commit
- encouraging patients to disclose their status to family and friends who can support the treatment plan
- informing the patients of the potential side-effects, their severity, duration and coping mechanisms
- establishment of 'readiness' to take medication before ARV initiation
- provision of adherence tools such as written medication calendars and pill boxes where available
- encouraging the use of mechanical aids for adherence such as alarms or pagers
- anticipation, monitoring and treatment of side-effects
- inclusion of adherence discussions in support groups
- development of links with community-based organizations to support adherence
- encouragement of links with support groups and a creation of links with patient advocates
- avoidance of adverse drug interactions by encouraging patients to fully disclose the use of over-the-counter medicines, complementary medicines and traditional medicines.

When suboptimal adherence is identified, intensive adherence support will be provided. Members of the health care team will be offered specific training regarding ARV treatment

and adherence with regular updates [59]. Studies have recommended the use of more than one tool or method to measure and assess adherence to HAART [47].

2.7 Adherence to drug treatment

For medicines to be effective, prescribers must prescribe properly, dispensers must dispense correctly and patients must use them as instructed [2]; however, the decision to take any medicines ultimately lies with the patient. A drug related problem (DRP) is said to exist when a patient experiences or is likely to experience either a disease or a symptom having an actual or suspected relationship with drug therapy [60]. Eight diverse categories of DRPs have been described and they include the failure to receive prescribed drugs, untreated indications, improper drug selection, sub-therapeutic dosage, over dosage, adverse drug reactions, drug interactions and drug use without indication [60,61]. Studies have shown that between 1% and 4% of new prescriptions in pharmacy will have at least one DRP. Non-adherence is known to contribute significantly to DRPs [61].

There has been a shift from the use of the term "compliance" to the use of "adherence" when referring to patient requirements to follow instructions. Compliance can be simply defined as the need for a patient to follow medical instructions exactly as directed by an HCP [62,63]. It does not take into consideration priorities and beliefs about medicine taking, and it regards patients as passive recipients of instructions to which they 'must comply' [64]. The use of the word "adherence" is advocated as it implies greater involvement of the patient in decision-making about their health and is not as despotic [65]. Adherence to prescribed medicines may be regarded as the extent to which a person's medication-taking behaviour, following a diet, and/or executing lifestyle changes, corresponds with the agreed recommendations of the HCP. This is an adaptation of the definition of adherence to long-term therapy adopted by the 2003 WHO adherence project [1].

In the UK there is now a move to 'concordance', which is defined as a process of prescribing and medicine taking based on partnership between the patient and the HCP [65]. Concordance is said to be "*a refreshing and innovative approach to achieving the best possible use of medicines and promoting better understanding between patients and HCPs*" [66].

Concordance recognises the importance of involving patients in their health decisions whereby the patients are empowered and given the opportunity to share their health beliefs, opinions and values [66]. Concordance is a process of collaboration between patients and HCPs and is one in which pharmacists have been identified as having a potentially vital role to play in promoting appropriate medicine-taking behaviour [65,66].

Poor adherence has been identified as the primary reason patients do not achieve the full health benefits that medicines can provide [1]. The phenomenon of adherence is a complex, multidimensional one that is influenced by a number of factors that may be grouped into five broad dimensions [1,67] as will be discussed in Section 2.7.4.

Poor adherence is said to cause both medical and psychological complications of disease, decrease patient quality of life, enhance the likelihood of development of drug resistance and squander health care resources [1,67,70]. The economic impact of non-adherence is highlighted in a US study, which showed that 10% of hospital admissions, which cost $15.2 billion and affect 3.5 million people, are due to non-adherence [68]. In the UK, it is estimated that around £230 million worth of medicines are returned to pharmacies for disposal each year; it is estimated that many more medicines are disposed of by the patients themselves [66].

A review on patient adherence showed that non-adherence is so widespread that there is no combination of socio-demographic variables that can reliably predict its occurrence [1,69-77]. It seems there is not a single theory that adequately explains, let alone predicts, patient adherence to prescribed regimens [69,73].

The Health Belief Model (HBM), a social psychological model that was developed to explain preventative health behaviour, has been used in conjunction with other models to try to explain and predict non-adherence [72,73]. One adaptation describes the psychology of non-adherent behaviours according to the three factors of susceptibility, severity and benefit [72,73]. It suggests that patients are more likely to adhere to instructions from the HCP when they feel susceptible to illness, believe the illness to have potentially serious consequences to health or daily functioning and do not anticipate major obstacles like side effects [69,73].

Other researchers have also used the HBM in conjunction with other models to explore the association between certain psychosocial variables and adherence in an attempt to predict non-adherent behaviour. Variables investigated include patient preference [74], health values [75,76], social support, the influence of powerful others [76] and the health locus of control [76,77]. So far not one theory can be used to successfully predict patient adherence to therapies.

2.7.1 Adherence to chronic therapy

Poor adherence to long-term treatment of chronic or asymptomatic conditions is a well-documented worldwide problem [1], which has been called an “invisible epidemic” and is regarded as a major public health problem [1,78]. The consequences of non-adherence to long-term therapies are poor health outcomes and increased health care costs [1,67]. In 2001, chronic diseases represented 54% of the burden of all illnesses worldwide [1,67] and are projected to exceed 65% of the global burden of disease in 2020 [1,67]. Failure to take prescribed medicines undermines efforts to control and manage chronic conditions as the access to drugs alone is not sufficient to control them [67].

Reviews on adherence in patients with chronic illnesses conducted in developed countries show that adherence averages around 50% [1,67,79]. In the US, for example, only 51% of hypertensive patients adhere to their medicines [1] and in Australia, only 43% of asthmatic patients take their medicines as prescribed [1]. It is assumed that the magnitude and impact of poor adherence in developing countries is even higher. Adherence to anti-hypertensive medication regimens in China, the Gambia and Seychelles for example, is 43%, 27% and 26% respectively [1].

Low-cost interventions that improve adherence may be the best investment for effectively managing chronic conditions as they have been shown to result in substantial cost-savings and increased effectiveness of health interventions [1]. Acute care models of health service delivery present barriers to adherence to chronic care and thus a chronic care model is required to effectively deal with chronic therapies [67].

2.7.2 Methods used to assess adherence

HCPs tend to underestimate patient adherence problems as they are difficult to identify and assess accurately [1,70], whereas patients tend to misreport their adherence levels [1]. Many HCPs assume that good predictors of non-adherence are factors associated with socio-economic status such as lack of education and poverty. However, most studies have shown that predictors of adherence significantly differ across populations and settings, and no single factor has been consistently linked with adherence [1,70,82].

Direct and indirect methods have been used to assess patient adherence [73,81]. Direct measurements involve the detection of a chemical in the body fluid while the indirect measurements are either by patient self-reports, pill counts, patient interviews, therapeutic or preventative outcomes and by the use of recording devices [61,70,73,80,81]. All these methods have flaws and are inaccurate, whereas those that could generate more reliable results are tedious, laborious and expensive. The use of more than one method has been advocated [1,73,80], for example pill counts used with other measures such as patient interviews have been more successful in predicting adherence results [81].

2.7.2.1 Direct methods used to assess adherence

The concentration of the drug, a metabolite or a marker is detected in either blood or urine. This gives accurate results although variations may occur due to pharmacokinetic differences rather than to adherence. This method is, however, tedious and expensive for routine use and is restricted to research studies on adherence [78,80].

2.7.2.2 Indirect methods used to assess adherence

Adherence using a pill count is commonly used in adherence studies and is easy and inexpensive, providing an objective measure of the number of dosage units taken over the given period [78,80,81]. However, it is time consuming and it is acknowledged that some patients dispose of their medicines before a scheduled check on their adherence in order to appear to have adhered [80,81]. Thus it is best done randomly, with no prior warning, to

minimise patient manipulation. This method is not very accurate especially for chronic medicines where patients tend to combine monthly leftover medicines [73].

Patient interviews are conducted using a standard questionnaire containing questions for determining the degree of adherence. The interviewer can also pick up non-verbal cues that may also assist in determining adherence. Although it may be tedious and time consuming, it is inexpensive and allows the HCP to interact with the patient and provide immediate feedback [73,78]. This method is mostly used to identify non-adherent patients as it helps identify the causes and guides the HCP in determining the appropriate intervention to use [78]. It is a useful research tool as ongoing records can be maintained [78].

Two types of adherence devices have been described: the medication monitor which contains a uranium source and photographic film that records the regularity with which the drug is removed [80] and the silicon chip recorder that is incorporated into the bottle cap and is activated whenever the cap is removed [80]. These allow for easy data collection and have been primarily used in research. They both presuppose that the removal of the drug implies that the drug has been taken, thus they are susceptible to recording errors if this does not happen. Electronic monitoring provides an unobtrusive and objective measure when compared with pill counts or serum levels and has resulted in a better measure of adherence [73,80].

Self-assessment is a method whereby a patient is given a chart to tick each time medicines are taken [73,78]. This is an easy, less laborious and non-invasive measurement. These self-reports tend to be exaggerated perhaps due to both recall bias and a desire on the part of the patient to please the HCP and avoid criticism [1]. The literature indicates that most self-reported measures tend to overestimate adherence, sometimes by as much as 100% [81,83]. It has been suggested that self-reports might be better used to identify potential low adherers rather than to quantify adherence [86]. This method has been advocated for use in chronic therapies like ART [87].

2.7.3 The importance of adherence to antiretroviral therapy

The rapid replication and mutation of the HI virus necessitates extremely high levels of adherence of more than 95% in order to achieve durable viral load suppression [15]. Sub optimal adherence may rapidly lead to resistance, which is a serious public health issue as the resistant virus can in turn be transmitted to other people [1]. Adherence to ART has been shown to vary between 37% and 83% depending on the drug under study and the patient population demographic characteristics [1].

Studies have found that adherence to ART is associated with improved clinical outcomes [1,15,88,90]. The results of a multivariate analysis from a large clinical cohort study conducted in British Columbia, clearly showed that the development of HIV drug resistance had strong associations with an adherence of between 60% and 90%, drug interactions and/or malabsorption issues as well as a high baseline viral load [89]. Ninety percent adherence is the equivalent of missing no more than 5 doses of a twice-daily regimen in a four week period or 3 doses of a once daily dose regimen in a month [92].

Paterson *et al* [15] measured adherence using plasma viral load as an effectiveness indicator. This study was conducted on 81 HIV-infected patients on a protease inhibitor regimen and adherence was monitored, over a period of 6 months, by the use of electronic monitors attached on the medicines bottles. During the duration of the study, 81% of patients with an adherence of more than 95% maintained undetectable viral load, whereas only 64% of those with 90 - 95%, 50 % of those with 80 - 90%, and 30% of those with less than 80% adherence maintained this. It was shown that for every 10% decrease in adherence, mortality increased by 16%. Adherence at levels less than 95% independently predicted viral resistance, hospital admissions and the occurrence of OIs [15]. This study recommended an adherence of more than 95%.

In a study by Bangsberg and colleagues [91], none of the patients with an adherence of more than 90% progressed to AIDS, whereas in those with adherence rates of less than 50% and between 51 - 89%, 38% and 8% respectively progressed to AIDS. This study also emphasises that there is a direct link between adherence and therapy failure resulting in the progression to AIDS [91].

The large number of medicines involved in HAART, the complicated dosing requirements and the sub-optimal tolerability result in variable adherence [1,45,92]. It is essential to accompany the provision of ART with intervention strategies intended to improve adherence [45,57,90,93]. A cross-sectional study on 109 HIV-infected ambulatory patients on HAART that assessed beliefs about therapy and their association with adherence, showed that adherence was related to the necessity-concerns differential (NCD); this implies that low adherence may be a result of an implicit 'risk-benefit' analysis in which beliefs about the necessity of HAART for maintaining health now and in the future are balanced against the concerns about the perceived adverse effects [94].

A personalized approach that includes careful drug selection, routine follow-up, the provision of information, and feedback and reminder systems, may optimise patient adherence to HAART [95]. Ongoing patient education and adherence monitoring has been shown to play a significant role in the success of HAART [96-97]. Throughout the literature, a number of studies aimed at assessing the effectiveness of adherence interventions lack evidence of their success [99]; a Cochrane review of interventions done between 1996-1999 [100] showed that the only intervention which improved ART adherence was a pharmacist-led educational program and supportive counselling.

2.7.4 Factors affecting adherence to HAART

Non-adherence takes many different forms that include patients simply failing to fill a prescription and patients taking the incorrect dose of medicines and/or at the incorrect time because they misunderstood or forgot the instructions. Patients may also completely or prematurely terminate their therapy and they may self-adjust their regimens due to side effects and toxicity or personal beliefs [1,101]. Some patients tend to totally forget to take their medicines [1,85].

Both intentional and unintentional non-adherence have been explored in the literature [102]. It has been suggested that intentional non-adherence is another significant health problem occurring mostly in patients with chronic conditions requiring long-term therapy [73,85]. Patient responses have included *'felt good and decided not to take'* or *'feared the side effects'* and believed that *'treatment was not necessary'* [85]. Unintentional non-adherence occurs

when the patient wishes to take his medicines as prescribed but cannot do so because of one or more barriers [102]. The five interacting dimensions affecting adherence to ART include therapy-related, patient-related and condition-related factors as well as the health care system and social and economic factors [1,67,73,92,102,104]. These factors will be briefly discussed.

2.7.4.1 Therapy-related factors

Research has shown that for chronic therapies, adherence decreases as the complexity of the medicines regimen increases [1,88,92]. These complexities include the number of units per dose, the number of doses per day and the prerequisite to comply with strict and special requirements related to food and fluid intake [1,88].

Adherence to ARV drugs is a tremendously complex process that does not only include the drugs themselves but involves major lifestyle modifications in order to support the conditions necessary for effective drug therapy [1]. Some regimens consist of several doses of medicines per day alongside various requirements or limitations on food intake and other activities that have resulted in poor adherence [1,103]. In addition to these complexities are the problems of toxicity and side effects that may greatly influence an individual's readiness and willingness to adhere to the therapy [1]. Studies have shown that regimens with a lower pill burden [92,103,105], a maximum dosing of twice a day [1], fewer alterations in lifestyle patterns (eg dietary restrictions) [1] and with minimal side effects [1] are likely to be better adhered to [1]. For HAART, the use of fixed dose combination (FDC) medicines has reduced the number of units a patient has to take and has shown to improve adherence [54,106]. However, FDCs are associated with problems such as the need for a lead-in dose required for Nevirapine for example, and the occurrence of adverse effects from one of the components [106].

The literature on side effects clearly outlines that optimal adherence occurs with medicines that alleviate symptoms and it is reduced by those that produce intolerable side effects [87,107,108]. ART regimens usually have temporary side effects including transient reactions (diarrhoea and nausea) as well as longer lasting effects (like lipodystrophy and neuropathy). Although HAART significantly increases the quality of life in patients with symptoms, it may have negative effects on the quality of life in asymptomatic patients [109]. Studies conducted

in Europe have shown that patients tend to discontinue ART due to toxicity and side effects [1,10,111]. The duration of treatment, previous treatment failures and availability of HCPs have also been shown to affect adherence [1,67].

Interventions that have been proposed to minimise these therapy-related factors that result in poor adherence include education on the use of medicines and on the importance of adherence [1,45,67], regimen simplification [1,45,54,71,99] and tailoring of the prescription to fit into the patient's lifestyle with the goal of establishing a realistic routine [1,71], continuous monitoring and assessment of treatment [112], as well as the management of side effects [107,108]. The use of reminder devices has also been advocated where affordable [1,99].

2.7.4.2 Patient-related factors

Among the most important factors influencing adherence to medicines are the patient-related factors that include psychological issues, the patient belief system, confusion, forgetfulness and patient-provider relationship [1,71,108,113]. Co-morbidities such as depression, alcohol and drug abuse, risk perception, motivation and self-efficacy, and information and skills for self-management, have also been identified as contributing factors [1,105].

2.7.4.2.1 Psychological issues

It has been shown that life stress can greatly interfere with the proper use of some ARVs [114,115] and it has been inconclusively linked with low economic status. Optimal adherence is also thought to be difficult to attain in low-literate patients [1,78,102,116-120]. Active substance abuse has been identified as one of the stronger predictors of non-adherence, although this is not supported by all studies [1,92,95,122]. Psychological distress including depression [1,92], stress and the manner in which individuals manage stress, are thought to be some of the most significant predictors of adherence [1,88,114]. Social support is also an important determinant of adherence [1,122]. Patients with supportive family and friends tend to adhere better to ART than those lacking this type of support [1,123]. It is therefore important to encourage patients to involve family and friends in their care and to attend follow-up referrals to support groups, peer-counselling and community-based organisations.

A behavioural and motivational intervention that includes counselling or psychotherapy has also been shown to be beneficial [1,88,100,123].

Adherence may also be influenced by patients' knowledge and beliefs about medicines [1,92,128]. Patient understanding of the relationship between adherence, viral load and disease progression is vital to better adherence [1,121,124]. A study conducted on HIV-infected New Yorkers taking HAART showed that patients who believed that taking their medicines is worthwhile tended to be more adherent than those who doubted the efficacy, with no demographic variables predicting non-adherence [125].

Confusion and forgetfulness constitute major obstacles to adherence to HAART as confusion may arise from requirements and/or restrictions on food or water intake and misunderstandings of complex regimens and/or poor instructions from the HCP [1,124]. One study showed that less adherent patients reported greater confusion than adherent ones over how many units to take and how to take them [127]. Forgetfulness has been cited as the most common reason for non-adherence, with the middle dose in a three times daily regimen being the most commonly forgotten one [1].

A pilot project dealing with forgetfulness in taking anti-TB medicines at a TB clinic is being conducted in Cape Town, South Africa. A reminder technique using cell phones is used whereby patients on anti-TB medicines receive reminders on their cell phones using the short messaging service (SMS) technology [68]. Reports to date indicate good success in improving adherence.

2.7.4.3 The quality of patient-HCP relationship

Significant barriers to adherence may be overcome in the presence of a meaningful and supportive relationship between the patient and their HCP [1,67,95,99,128]. Factors that may establish and strengthen such a relationship include the quality and clarity of communication, patient perception of HCP competence, compassion, patient-active participation in treatment decisions, and regimen convenience [1,128].

In order to address these issues, patient-oriented interventions to improve adherence have been proposed which include providing accessible education and information, e.g. leaflets in

the appropriate language, and actively involving a patient in his or her treatment through encouraging the patient to talk about the symptoms, how they respond to them and how their medicines are taken [1,90,98,99,125]. To supplement this, a number of aids like pill organizers and cap alarms may be recommended to help establish a daily routine [88,115].

2.7.4.4 The health care team and health system factors

The reliability of medicines distribution systems and the cost of treatment may impact on adherence, as may the level of training and workload of HCPs and their capacity to educate and follow up patients [1]. Adherence may also be affected by the monitoring of performance systems and the ability of the health care system to establish community support and self-management capacity [1,99].

Poor implementation of educational interventions by the health care system and lack of clear instructions from the HCPs who are not trained on adherence issues have resulted in poor adherence [128]. Interventions proposed to improve adherence include the proper training of HCPs and care givers on adherence education, which should proceed hand in hand with the identification of treatment goals and the development of treatment strategies to meet them. Readily available information with unlimited access by the patient is also important [1,71,93].

There is a range of evidence suggesting that education of both HCPs and patients about the disease, the taking of medicines and the management of side effects improves adherence [1,99] and that "*the use of clear written instructions is synergistic with the use of FDC or unit-of-use packing*" [106]. Enhanced patient understanding of the relationship between adherence, viral load and disease progression resulted in improved adherence [124]. The interventions proposed to improve adherence included education on the use of medicines [1,98,99,124], supportive medical consultation and screening for co-morbidities [1].

2.7.4.5 Condition-related factors

Factors related to the disease or condition of the patient such as the rate of progression of the disease, the level of disability, the severity of symptoms and the availability of effective treatment may influence adherence [1,67]. A study conducted to investigate the relationship between disease severity, health beliefs and medicines adherence among HIV patients showed that asymptomatic patients tended to be less adherent compared to symptomatic patients [129].

2.7.4.6 Social and economic factors

Factors such as poverty, illiteracy, lack of social support, poor access to services, high cost of transport, unstable living conditions, family dysfunction, cultural beliefs, war-adverse material and psychological effects have been associated with poor adherence [1].

A study conducted in Rwanda to analyse the impact of socio-economic factors on adherence to HAART found no significant differences between adherent and non-adherent patients when considering criteria like profession, level of education and distance from the hospital [130]. These findings are similar to others obtained in South African studies [58]. The main reasons given by patients were ‘forgetfulness’ and ‘lack of understanding of the instructions’ [130]. Counselling and the provision of appropriate, understandable information on the disease and treatment seemed to be the key elements to enhance adherence [130].

Although it is often thought that poor adherence is more prevalent in developing countries, some studies have shown otherwise. In a study conducted in Botswana, pill counts conducted showed that 85% were taking their medicines faultlessly, and this improved to 90% when the criteria were relaxed slightly [131]. A similarly impressive adherence level was found in a South African ART pilot programme where, after six months of treatment, 96% of patients were taking 95% of their medicines, as determined by pill count [132]. A further finding was that older patients, those patients on twice daily instead of three times a day dosing regimens, and patients who spoke the same language as the clinic staff had better adherence rates. In conjunction with the pill counts, adherence was also measured by blood tests to check the viral load and this showed that 91% were adherent [132].

It should be noted, however, that in order to qualify for treatment in this pilot programme, patients had to comply with certain criteria including stopping alcohol and drug use, satisfactorily completing a three month course of a simple antibiotic, being on time for four consecutive clinic appointments, revealing to their families that they are HIV-positive and choosing a friend who will also attend counselling, make sure the medicines are taken and report any problems to the nurse [132]. These were demanding, tough criteria but were necessary to ensure that patients had a high likelihood of adhering to ART [132]. The high adherence rates obtained may be attributed to these entrance criteria, as the patients were well prepared. This approach has been recommended for ART scale-up in resource-limited settings [45].

2.7.5 Interventions to improve adherence to HAART

Interventions to improve adherence need to be [67,88,99,125,133]:

- multidimensional, in that several methods are used simultaneously all with the primary goal of assisting the HCP and patient to reach a treatment consensus
- integrated, in the sense that all measures to promote adherence become a standard part of the therapeutic service offered and
- personalised, whereby adherence strategies are negotiated with each patient as part of the treatment process, tailored to meet their specific needs along with the treatment.

It is proposed that all stakeholders who may be involved in devising ART treatment plans should build on established interventions. The following four interventions have been suggested [1,67,90,99,125]:

1. Patients should have access to
- culturally appropriate educational materials like pamphlets that describe clearly how the pills should be taken and the possible side effects
- HCPs who can help them identify necessary physical, psychological and social supports
- technologies like printed medication charts, beepers and pill boxes that may assist reliable medicines ingestion.

2. Patients should receive help in
- identifying lifestyle characteristics like irregular work schedules, that may interfere with the treatment plan and may need to be changed before treatment is initiated

- designing a draft plan that links regimens to established daily routines like brushing teeth

3. Patients should be offered

- an experimental ‘dry run’ with dummy pills to test the viability of proposed treatment plans
- regular feedback on viral load and T-cell counts after therapy begins
- tools with which to assess the treatment plan such as medication diaries

4. Patients should be assured of continued access to these types of support as long as treatment is medically indicated.

Emerging evidence highlights the importance of the involvement of HCPs, social support network, family as well as friends in interventions to promote adherence; this may, however, require a substantial investment in terms of time and effort [1,101,127,133]. However, the rewards associated with optimal ARV treatment adherence are worth the effort.

2.7.6 Adherence and patient education

The most common healthcare intervention is the correct use of medicines. The literature consistently shows that most patients would like to know more about their treatment [5,6,8,134-139] as there is a global trend towards greater self-involvement in healthcare. The most commonly used method of patient education has been the use of written materials to improve patient knowledge of their medicines, reduce medication errors and to a certain extent, increase patient adherence to medicines, thus improving therapy outcomes [5,6,8,136-145].

CHAPTER THREE
PATIENT EDUCATION

3.1 Patient education in healthcare

Patient education has become a fundamental part of healthcare in most countries, especially in preventative issues [146-148]. The 1994 WHO assembly declaration stated that [149] "*patients have the right to be given factual, supportable, understandable and appropriate information, to be provided in such a way as to allow them to decide whether they wish to receive therapy*".

Communication is the keystone of any patient-physician relationship with the critical component of this relationship being the education of the patient about his or her condition and treatment options [150]. Patient education is an integral part of both good medical and pharmaceutical practice [138,151,152,153] and has been shown to have a significant effect on the appropriate use of medicines [137]. When patients meet with HCPs, be it for consultation or treatment, the main mode of communication is verbal and, in many cases, patients leave the premises with only the information they have heard [136,137]. In one study it was found that patients forget half the information they obtain from the practitioner within five minutes of leaving the consulting room [6]. It is known that people can only retain and remember about 20% of what they hear [154-156]; however, this may increase to 50% with the provision of an additional visual or written input [155]. Over the years, much focus has been accorded to the need to empower patients by further educating them, the WHO being in the forefront with its 1994 declaration as stated above.

A number of methods other than one-to-one verbal communication have been used to educate patients. These include audio materials, audio-visual materials and written materials [5, 6, 8,137-145], which have been used more extensively in developed countries than in the developing countries [5, 8,137,158]. Thus far, the most effective method of patient education in the management of various chronic illnesses and in the appropriate use of pharmaceuticals has been the use of written materials [4,5,8,138,158,168]. However, it should augment and not replace oral instructions [158,159,160], in that verbal information should be the core and written information its complement [2,159,160]. Studies have shown that patients prefer to receive a combination of verbal and written information to assist them with both management

and treatment of their illnesses [8,136,137]. This combination is considered superior to a single intervention as it provides multiple reinforcements to the patient [136,137,161].

The inadequacy of relying on verbal communication alone is evidenced by reviewing the five processes through which any information, be it verbal or written, must pass [151].

- First is the exposure stage in which the patient is exposed to the information by the HCP [138]. Studies have shown that a majority of patients receive insufficient information from their HCPs, even when required by law, mainly because of lack of time [151,162,163].
- Secondly, the patient must pay attention to the information when it is provided. It has been pointed out that people tend to recall only 20% of what they hear [154-156] and it has been observed that some patients tend to remember only what they consider to be the most important information [2,162].
- Thirdly, patients must understand the information provided. Some HCPs tend to use medical jargon and terms that are not familiar to the patients, resulting in misunderstanding [2,141,166,168]. Despite this, some patients, in order to avoid looking 'stupid', do not ask for clarification [165], or they may be reluctant to disturb the busy HCP [167].
- Fourthly, the patient must accept the information. This may be influenced by the health, emotional, attitudinal and educational state of the patient when receiving the information. Acceptance also relies on the patient's perception of the importance of both the therapy and the information provided [151,168].
- Last but not least, the patient must remember the information. The ability to recall information can be influenced by how well the information is structured and presented [151]. Instead of delivering information to patients in a series of disjointed remarks, it is best to present the information in a simple form, one point at a time, in a well-organised manner [4,10,169].

3.2 Medicines information

3.2.1 History of medicines information

As early as the 1960s, HCPs identified the need to provide patients with additional information about their condition, health status and nutrition, as well as about pharmaceutical products [163,168]. Written materials such as leaflets, brochures and booklets were widely used to educate patients [151,163]. Medicines information provided with pharmaceuticals has

significantly evolved over the past three decades. Initially, in the 1960's, pharmaceutical companies aimed at providing extra information about their products for the HCPs to refer to, when prescribing or dispensing a product [141,151,163]. This information tended to be scientific and technical and was contained in package inserts (PIs) that accompanied most pharmaceutical products, even those for self-medication [135,141].

In the 1970's patient package inserts (PPIs) were formulated with the focus being on patient use [151,163]. Some medicines were distributed with both PIs for the HCP and PPIs for the patient [163,168]. The rationale behind the provision of PPIs was simply stated as [151] "*in order to properly use prescription drugs, people need, and have the right to receive information about their drugs"*. However, most PPIs were too technical and contained medical jargon that was not easily understood by patients [141,151,162]. They were also not presented in a user-friendly manner, as the information was written in small font size and the leaflet was folded to fit into the packaging [8,162].

Not being accessible and understandable by most patients, the PPIs needed further improvement [141]. Thus, in the 1980s, the PPIs evolved into patient information leaflets (PILs) specifically designed for patient use, with patient oriented language and less medical jargon [8,172]. PIs were then accompanied with PILs in some medicine packs, i.e. PILs were also supplied as PIs. In different countries, PILs are known variously as package leaflets, medicines information (MI), prescription medicine information, written drug information (WDI), written medication information (WMI) and consumer medicines information (CMI). In this review, these terms will be used interchangeably.

The name change has proceeded hand in hand with an evolution in the way the information was presented, since it was identified that the readability and design of most written health materials was very poor [8,145]. In 1984, for example, the Belgian health authorities transformed the traditional, technical PIs into PPIs, which were written in lay language, a transition which took about two years for a total of 6 000 medicines [141].

It has been observed that most health education materials presented to patients in medical settings are often either written at a high reading level [4,10,145,161,163] or contain a lot of medical jargon and terminology unfamiliar to the average patient [10,163]. By the mid-1990s, studies in developed countries showed that patients who received PILs reacted negatively, as

they were not satisfied with their content and their quality [134,162]. More needed to be done to improve their quality and, ultimately, their understandability and acceptability by their consumers, the patients [152,168]. To date, a vast number of studies have been conducted in developed countries to investigate the design, development and distribution of PILs [4,7,10,11,168,172-174].

3.2.2 A worldwide perspective of medicines information

Table 3.1 shows a brief summary of the presence of PILs worldwide as reported in the literature [9,11,163,168,176,177,181,183].

Table 3.1 Availability of formal patient-oriented medicines information leaflets

Feature	USA	Europe	Australia	South Africa	Tanzania
Content guidelines: an outline on the kind of information to be included in a PIL	Have (1995)	Have (1987)	Have (1993)	Have (2003/04)	None
Format guidelines: a requirement for the structure, presentation and /or readability of the information	Have (1995)	Have (1996)	Have (1993)	Have (2004)	None
Regulations /Legislation : legal requirements mandating PIL provision, the year and the legal document	Have (1996), Section 601, Public law 104 - 180	Have (1992), Council Directive 92/27/EEC	Have (1993), Therapeutic Goods Regulations Amendment No 208	Have (2003), Regulation 10, Act 101 as amended	None [1]
Accessibility to consumer: the commencement of MI provision with medicines	Yes (1968)	Yes (1989)	Yes (1993)	Yes (2004)	Yes [2] (2004)
Time frame target set: a time framework for the extent of provision	Provide 95% of patients by 2006	PILs for all medicines by 1999, 5-year phase-in	For all medicines by 2002, 7-year phase-in	PILs for all medicines by 2007, 4-year phase in	None

[1] The only legislation for the provision of PIs is with all products requiring registration

[2] Very few PILs have been developed and distributed to a limited number of patients, mostly for general information on a class of drugs, they are not similar to the PILs developed and distributed elsewhere.

- **Europe**

Since 1977, WMI has been available to patients in most European countries [168]. The available information was found to be variable, both in content and format, and thus required interventions to improve the quality and utility to patients [168,179].

In 1992, the European Economic Community (EEC) published Council Directive 92/27/EEC that required all medicines to be accompanied by a comprehensive information leaflet in language suitable for the patients. This Directive established that "*the package leaflet is a document that must be included in the packaging of all medicinal products for human use in the EU countries*" [176]. This document was intended to provide extensive, comprehensive and understandable information to patients [10,176,178], in accordance with the contents of Summary of Product Characteristics (SPC) documents. The SPC includes all the essential information on medicines necessary for HCPs to ensure that medicines are used correctly, effectively and safely [176].

This mandate to design and provide PILs represented the most important change in the provision of information to patients [162]. The law ordered the inclusion of information, obligatory instructions and warnings in clear, understandable and easy legible terms [176,181]. It also suggested the inclusion of symbols and pictograms as tools to elucidate the information [176].

PILs were developed and distributed, but most were not user-friendly and failed to educate most patients [179]. Thus, in 1996, the EC produced a draft Guideline to improve the readability of PILs and it included a 'model' leaflet that gave particulars on the structure and phrasing of the information to be included [180]. A subsequent draft also included a process to be used to test readability [183]. The 92/27/EEC Directive had a 5-year phasing-in period and came into full effect across the EU in January 1999 [181]. Medicines information is also available online and is accessible to patients across the EU [182].

- **United Kingdom**

The only form of printed information supplied with medicines prior to the mid-1980s in the United Kingdom (UK) was that on medicine labels [181]. In 1987, it was proposed by a pharmaceutical working group that pharmaceutical manufacturers develop leaflets, and this group developed guidelines for the design of patient oriented medicines information [183]. These guidelines were based on the concept that leaflets should be "*succinct, intelligible and of uniform design*" [181] and they were also influenced by work from Gibbs *et al* [183] that had shown in 1987 that the provision of A5-size leaflets to patients resulted in a small but

noteworthy increase in both patient knowledge and satisfaction with their treatment. In 1989, these new styled PILs were distributed as PIs [181].

In the past decade, the acceptability of PILs has significantly improved. In a recent British study, 83% of patients reported receiving PILs [184] that are much more accessible and understandable, as the information was written simply, was legible and was better presented compared to the older PILs they had received in the past years [184]. In 1999, the provision of PILs in the UK came under the control of the EU Directive 92/27 EEC [181]. Medicines information is also available online to UK residents via a number of sites [185-188].

The electronic Medicines Compendium (eMC) provides information about most prescribed medicines available in the UK. The information is supplied by researchers and developers of medicines, is approved by the Department of Health in collaboration with the Association of the British Pharmaceutical Industry (ABPI) and is a reliable source of information [188]. The eMC has two types of information documents about most medicines available in the UK: the SPC and PILs. The manufacturers develop both types of documents when a medicine is first produced and they are frequently updated. Currently, 140 pharmaceutical companies support the eMC, which is available online [188].

- **USA**

In 1968, in the USA, the first prescription medicine to require consumer-oriented written information was isoproterenol inhalation [189]. This resulted from a request made by consumers to receive more information on their prescription medicines [163], and the FDA proposed that PPIs should be provided with some prescription drugs [163,190]. In 1979, the FDA then tried to make the provision of PPIs mandatory for all prescription drugs [163,190] and this proposal was opened to public discussion. Generally, consumers were in favour of the idea, but HCPs and the pharmaceutical industry opposed it as they felt it would impose ‘unnecessary burdens on manufacturers and pharmacists’ and also ‘encourage self-diagnosis’ [163]. Having considered all the comments, the FDA published a final rule in 1980 requiring manufacturers and distributors of prescription drugs to prepare PPIs [163,190]. A review conducted in 1982 highlighted the fact that the use of voluntary systems would enable consumers not only to receive an adequate supply of information from a variety of sources, but also a wider variety than they would from the mandatory system [163]. The FDA revoked

its mandatory program in 1982, based, in part, on assurances by the private sector that the goals of the final rule would be met; thus, a private sector initiative was promoted [163,190].

Over a decade later, in 1991, the FDA revisited the provision of patient information and found that only 32% of patients received information and that the information was of variable quality with respect to content and design [163,190]. The content and quality of the PPIs were not regulated and these PPIs were not well understood, thus failing in their objective to educate a majority of the patients [163]. In 1995, a government-led initiative mandated the provision of PPIs for ten drug classes that were selected as having particular risks [163,190]; the FDA published a rule entitled 'Prescription Drug Product Labelling: Medication Guide Requirements' also known as 'MedGuide' that required manufactures to prepare and distribute 'Medication Guides' [163,190]. These 'medication guides' to be supplied as PIs were to be comprehensive, written by the manufacturer and had to be approved by the FDA [63,190]. For voluntary efforts, the FDA proposed a target goal that by 2000 and 2006, 75% and 95% of patients respectively, should receive a PPI with a new prescription [190].

In August 1996, the Public Law 104-180 was Congress-approved and enacted [191]. Section 601 of this law established 'medication guides' for the improvement and assessment of medication information given to patients. This section mandated the Department of Health and Human Services (DHHS) to formulate a long-range comprehensive action plan through collaboration with various stakeholders. A steering committee formed by HCPs and lay members met in December 1996 and drafted recommendations for the content of written drug information in an action plan that was accepted in January 1997 [189,190,193]. They established eight criteria related to content and utility of useful medication information [189,192,193]. The plan recommended that all information should be scientifically accurate, unbiased, easily understood and comprehensive enough to be useful to patients [192,193]. The FDA distribution and quality goals of 75% by 2000 and 95% by 2006 were emphasised [191].

An FDA-commissioned interim study conducted in 1998 showed deficiencies in the distribution and usefulness of the information and identified the need to develop information assessment instruments [189,190]. In 2001, a follow up FDA-commissioned evaluation study of written information reported that, on average, 89% of patients received some form of

written medication information and the average ‘usefulness’ of this information was only 50% [194,198].

Currently, in all states, the private sector voluntarily develops and distributes leaflets with medicines [168,194]. Leaflets are computer-generated in pharmacies at the time a prescription is dispensed [163,194]. A recent study conducted in ten states reported that patients are receiving written medicines information with a new prescription at least 87% of the time [194]. Consumer drug information applicable to the US is also available on a number of websites [195-197].

- **Australia**

Prior to the 1990s, Australian patients had limited knowledge of and exposure to written medicines information [199]. In 1991, a report on the future of drug evaluation in Australia made two recommendations that resulted in the formulation of a standardized format of WMI and consequently in the incorporation of the need for WMI in the Australian legislation [200]. This legislation mandated all new medicines to be accompanied by a patient oriented leaflet [177]. The leaflets were named Consumer Product Information (CPI). The regulations were evidence-based and were a result of collaboration between professionals, government, industry and patients [199]. In 1993, the name Consumer Medicines Information (CMI) was introduced, replacing CPI [201].

Guidelines for writing and testing CMI were produced [11]. CMI is brand specific, written information about prescription and pharmacist-only medicines whose contents are defined by the Therapeutic Goods Regulations for Schedules 12 and 13 [177]. Thus CMI is produced by the manufacturers according to the set regulations and distributed either electronically printed from the dispensary computer, as package inserts in the medicine packs, or as loose leaflets sent directly to pharmacies by manufacturers [199]. The format of the CMI is not standardised and can vary from a one-page package insert (in six point type) to a seven-page computer generated printout. The usability guidelines for CMI clearly state all the requirements relating to the content and format expected in a standard CMI [11]. CMIs for a number of medicines are freely available online [202].

A study conducted in 2002 by Koo *et al* [199] revealed a number of issues pertaining to the use of CMIs and their impact on patient medicine-taking behaviour. Most participants were aware of WMI about prescription medicines, but were unfamiliar with the term 'CMI', this being almost a decade after their introduction [199]. According to this study, the likelihood of a CMI being used appeared to depend on factors such as appropriate timing of information provision, information-oriented coping mechanism, severe disease, internal locus of control and care giver role [199].

- **South Africa**

Regulation 10 of the Medicines and Related Substances Control Act, Act 101 of 1965, as amended, mandated the pharmaceutical industry as from May 2003 to develop PILs and distribute them with all medicines. This Regulation reads that [9]: "*Each package of a medicine shall have a PIL that must contain the following information* (as described) *with regard to the medicine in at least English and one other official language*". This Regulation includes guidelines on the content of the PILs, and some compulsory warning phrases that must be included. The format and design of the PIL are not regulated. A PIL Task Team, which is a sub-committee of the Medicines Control Council (MCC), has since reviewed these content guidelines.

In May 2004, the MCC published a preliminary guideline on the requirements for PIL design in South Africa [203]. All PILs will need to be approved by the MCC prior to distribution. The primary objective of this guideline is to ensure that PILs are readable [203]. The purposes of this guideline are stated to be the provision of information and guidance to PIL designers on the format and data requirements for the preparation and submission of PILs for evaluation, and also the requirements regarding the readability, format and content of PILs for consumer use [203].

According to this guideline, the approval of PILs for existing registered products will follow a phase-in implementation process commencing with medicine categories of the Essential Drugs List (EDL) that have the most urgent need for patient distribution [203]. The priority sequence is as follows [203]:

i. antiretroviral agents, including those with existing PILs not formally approved
ii. antimicrobial agents including antimalarial, anti-TB and antifungal agents

iii. chronic medication products including antihypertensive agents, antidiabetic agents, anti-asthmatic agents, anti-epileptic agents and hormonal contraceptive agents
iv. antidepressant agents
v. antianxiety, sedative and hypnotic agents
vi. over-the-counter (OTC) products with high volume use and/or high abuse potential
vii. other products, including those with existing PILs not formally approved.

The MCC intends for this process to be completed by May 2007.

- **Tanzania**

There are currently no regulations regarding the provision of PILs in Tanzania. The only written information most patients receive is that appearing on the labels or on the original medicine package. Most of the medicines are imported and contain English PIs. Instructions on how to take the medicines also appear in English. Most dispensers tend to throw out the PI as it is of no use to the average Tanzanian, who mainly speaks Kiswahili and is unable to read English. Most of the locally manufactured medicines have instructions in Kiswahili that are not user-friendly and have very little information about the medicines. The guidelines regarding the registration of medicinal products simply state that if a PI is present, it should be in English and/or Kiswahili and contain accurate information [204]. The Tanzania Food, Drugs and Cosmetics Act, 2003 only has provision for medicines packaging and labelling, with no mention of PILs [205].

In 1989, the first drug information centre, the Tanzania Drug and Toxicology Information Services (TADATIS) was established [206]. TADATIS is not only the national centre for drug information but also the national pharmacovigilance centre [206]. It mainly promotes rational drug use, produces a drug information bulletin and monitors drug advertisements; this centre also provides continuing education to pharmacists, doctors, dentists and the public in general on rational use of drugs [206]. Unfortunately, TADATIS has produced very few patient-oriented medicines information leaflets with limited distribution to the public.

3.2.3 The value and acceptability of medicines information

A study done in the US in 1986 to investigate the impact of drug information sheets revealed that their provision yielded a small, but significant, improvement in patient understanding of

therapy instructions [207]. Written information materials for patients have to be user-friendly and appropriate for the target population [10,168,181]. Studies show that 75% of patients would like to receive written information and of these, 80% would actually read the information [184]. A 1993 South African study indicated patient acceptance of and satisfaction with appropriately designed PILs for their prescription medicines [12]. It also found that PILs improved knowledge and recall of medicine instructions [12].

PILs have proven to be beneficial in enhancing understanding and memory of instructions [12,208-210], reducing patient anxiety about treatment and bridging the information gap between patients and HCPs [4,138,143,216]; they also communicate more information than can be achieved by counselling alone [5,6,143,144,210]. PILs also improve patient knowledge about their medicines [5,6,210], reduce medication errors, and, to a certain extent, increase patient adherence to medicines [6,142,143,145,207,209,210], thus improving the therapy outcome and patient satisfaction with their medicines. PILs are available for continued reference by the patient and are a useful source of information should problems or questions arise in the future [136,140]. PILs are also accessible to family members and other carers that provide care and support to patients [137,138].

Studies have shown that well written medicines information is readily received and gladly accepted by patients [8,142,143,199,211]. People tend to learn and retain more information if it is culturally and educationally appropriate [10,12,168,171,199]. The effectiveness of PILs is determined by a number of factors:

- PILs must be readily available on request [4,10,168,199]. This can be achieved if they are handed to the patient, as opposed to being put in a pack as a PI [8,162,168]. Investigators found that some patients do not regard PIs as containing patient-relevant information. Some patients never bother to look inside the box or may throw the box away after removing their medicines [8,162]
- PILs must be population specific [10,168]. They should appear in the first language of the target population [10,12,214] with terms and illustrations that can be identified by this population. This approach has resulted in a significant improvement in information utility [10,12,214] and patient perception of PILs
- the content of PILs must be useful to the patient, be easy to read and understandable [3,9,137,143,160]. There must be evidence of comprehensiveness, appropriateness and

accuracy of information [175,219]. Knowledge of the average reading level of the target population is, therefore, essential [160,168,175,219]

- PILs must be well presented [9,168,175,202]. This includes the font size, layout, paper quality and mode of delivery [162,168,220,221]. PILs reported to be unattractive, difficult to read owing to small print size and printed on poor quality paper have been poorly accepted and utilised [141,149,168,199].

Three issues must, therefore, be addressed in ensuring the optimal provision of written information: the information must be readily accessible to patients, the content must be comprehensive, accurate and specific enough to be helpful to patients, and the information must be presented in a way that makes it effortless to read and understand [168,217].

3.2.4 The distribution of medicines information

The mode of distribution of PILs either in the medicine pack as PIs or at the point of dispensing as a printout has been shown to have an influence on patients' perception and acceptance [162,168,218]. The information to be printed at the point of dispensing is available from software provided by the manufacturer or can be printed from the manufacturer's website or other accredited drug information agencies.

3.2.4.1 PILs as package inserts

Most pharmaceutical companies have designed and attached PILs with the PIs [141,171]. This mode of distribution of PILs has been shown to be ineffective, since most patients still do not bother to read them as they are too small, and intricately folded, while many are still too technical [157,168]. Studies conducted in the UK show that the major problem is the perception of a lack of importance and relevance associated with this delivery method [3,157,162]. Most of these PILs, once published, tend to remain the same for a number of years and they cannot be updated, even if changes occur before the expiry date of the pack [8,162].

In developing countries, the majority of patients do not even get to see a PI since most medicines are bought in bulk and are pre-packed prior to distribution, in packaging containing no information from the manufacturer [219]. These pre-packs contain only a label with

instructions on how to use the medicines. The method of distribution of PILs as PIs may, therefore, present problems in developing countries [219].

3.2.4.2 Computer generated PILs

North America, Australia and Japan have moved towards the production of PILs at the point of use [162]. Software has been developed that enables HCPs to print out PILs on request at the distribution point [8]. Some of the advantages computer-generated PILs have shown over those sealed in packs include:

- personal handing of the PIL to patients thus showing importance and relevance [8,134,162]
- sharing of information between the pharmacist and patient, whereby the pharmacist points out the important issues as consultation progresses [8,162]
- personalization of the PIL by including the patient's name, which may significantly influence patient perception of PIL [8,162]
- individualization of the information by omitting irrelevant information, such as that for a different age group or condition [8,162]
- the possibility of regular updates of the information in the PIL, particularly for patients taking chronic medicine [8,162].

In summary, computer-generated PILs can be stored, edited, updated, retrieved and printed on demand. This availability in electronic form also allows for conversion into other media that provide access to blind and partially sighted people [220]. Although this is a very good method of distribution, it requires the respective software and hardware for PILs to be generated. This translates into significant expense, which poses challenges and potential problems in resource-poor settings.

3.2.4.3 PILs on-line

A number of websites have medical and drug information, much of which is neither regulated nor validated by regulatory bodies [223]. Patients should be encouraged to access information from accredited websites or official websites of health-related organisations [223]. They should be cautioned about the quality of information from other sites, and be encouraged to

always countercheck the information they access with their HCPs before making any final decisions concerning their health [223].

Currently, Internet use is more prevalent in developed countries as most developing countries are struggling to provide basic needs to their poor communities with computers still constituting a luxury. Accessing patient information on-line is, therefore, not an appropriate approach in resource-poor settings where even reliable electricity supply is still a problem.

3.2.5 The design of written medicines information

PILs need to be written at an appropriate reading level for the target population since the main commonly cited problem limiting their utility is the use of language of an unacceptably high reading level [4,8,10,168,173,174]. Knowledge of the reading skill of the target population and their perception of medicines information may help to overcome this obstacle [10,168,237]. Written educational materials need not be complex, elaborate or highly technical to affect the foregoing desirable outcomes [10,168]. However, they should not be oversimplified as they may then lack 'authority' and result in skilled readers feeling undermined [10,226].

A number of guidelines have been proposed for use in PIL design [4,10,11,168,174,180]. Most of them have emphasised the importance of customising the information with respect to content, quantity and quality, to suit the target population [10,168]. It has been shown that this is best achieved by incorporating the end-users or consumers of the PIL throughout the entire PIL design and development process [10,181].

3.2.5.1 The information content

In 1978 Hermann and Herxheimer [135] proposed a guide on the minimum information patients need in order to take their prescription medicines as effectively and safely as possible. Previously established minimum information for OTC drugs provided the basis for prescription medicine information [135]. He proposed that each country produce its own set of guidelines and then adopt the model set to local practice circumstances. To date, guidelines on the content to be included in PILs have been published in most countries where PILs are distributed (Section 3.2.2). A summary of the minimum information for prescription medicine

as proposed by Hermann *et al* [135] and others [2,3,6,10,118,119,173,226] is presented in Table 3.2.

Table 3.2 A guide on the minimum information for patients

Know how to take the drug
- take the specific dose: amount of drug per dosage form
- take a dose in a specific manner, as directed
- take a dose at specific times: clock time; time since last dose; time since or until food intake and the duration of treatment

Know how to store the drug:
- how to store it properly and safely
- how to recognise the time the medicine becomes sub-potent and its expiry date

To know how the drug is expected to help and recall the basic facts about the complaint:
- note disease symptoms affected, potential consequences of adherence/non-adherence
- recognise the desired effect and act upon its absence, if relevant

Know how to recognise problems caused by the drug and take action
- to verify components of medicine
- to recall circumstances indicating need for change of treatment, and act if they occur
- to recognise unwanted effects and act if they occur
- to act if over dosage occurs

3.2.5.2 Format of the information

The format of PILs includes size, shape, appearance and general visual aspect. A number of varying formats has been proposed [7,11,13]. An appealing format serves to increase PIL acceptability by consumers.

- **PIL size**

Most PILs distributed as PIs are of varying sizes and there is no set standard. Patient-specific PILs have been distributed as A4, A5 and Z-fold with three folds. The A5 and Z-fold have proven to be the popular sizes as they are small and portable [7,11,13,181]. The South African MCC guidelines propose A4-and A5-sized PILs [203].

In the UK and the EU, the first PILs to be distributed were A5 size [7,181], but this size limits the amount of information that can be included [181]. The Australian CMI guidelines propose A4 size leaflets with 3 columns on each page but do not specify the text size or the final leaflet size [11]. Size is not specified by either the EC or the US guidelines.

- **Font style and size**

Font style and size used in PILs also vary significantly. Font size is mostly dependant on the paper size and the amount of information to be included. Some PILs with a font size as small as 6 points are barely visible to patients with impaired vision and such PILs have been deemed user-unfriendly. The font size is of particular importance when PILs are distributed as PIs as they cannot be modified to cater for the different needs of patients. Generally, font size 10 - 12 is considered to be the acceptable size [10,168,226].

Graphic experts have proposed a number of different font styles to be readable. Typefaces are either 'serif' (with a small decorative line added as embellishment to the basic form) or 'sans serif' (without) [227]. Some researchers prefer the 'serif' font style because it allows more variation among letters, hence easier recognizability [10,227]. The most commonly used serif font style, the Times New Roman, is still the most popular. Sans serif fonts like Arial and Helvetica are recommended by some graphics experts [11], but others have argued that they are difficult to read [10]. They all look similar to the layman's eye, thus, the PIL designer needs to determine the most popular font in accordance with feedback from the target population. The final choice of the font size and style lies with the PIL designer. The following is an illustration of the serif and sans serif font styles at size 12:

- serif: abcdefghijklmnopqrstuvwxyz
- sans serif: abcdefghijklmnopqrstuvwxyz

The use of italics, bold letters, capital letters to highlight information, and different forms of text layout has been variously regarded over the years [4,10,168,226]. While some recommend the use of capital letters for headings, others have commented that bold letters provide more emphasis [4,10,168,226]. All capitals tend to slow down reading, thus many researchers have discouraged their use [10]. The use of italics is also a source of disagreement [10,168,226].

- **PIL format**

A wide variety of opinions exists with respect to the format of the PIL such as the use of bullets, justification, headings, line length, paragraphs and white space [4,10,168,226]. In a study conducted to provide an overview of the use and impact of written drug information on

consumers, Koo *et al* [168] recommended some essential features of well-presented WMI (Table 3.3). These features are a combination of those in the Australian usability guidelines for CMI and those developed by individual groups of researchers.

Table 3.3 Features of well-presented written medicine information

Characteristic	**Desirable feature**
Font	Typeface: serif Style: no italics; bold for emphasis; mix of upper and lower case Size: at least 10 point and 12 point for elderly consumers
Numerals	Arabic rather than Roman
Colour	To increase appeal and enhance text, not distract from it
Illustrations	Pictograms/pictographs, to be used with caution; must be tested in the target population
Paper	Colour: there should be a good contrast between text and paper. Black ink on white paper is the most widely used
Format	Bullets: their use is encouraged to organise information Headings: should be clear and outstanding with a mix of upper and lower case Justification: should be justified to the left but not right Line length: with between 30-50 characters and spaces Paragraph: first line should be indented White space: should be sufficient to ensure the leaflet does not appear overcrowded with text

- **Language of PILs**

A number of studies has shown that PILs should be written in succinct, simple language that is appropriate for the intended audience [10,168,226,230]. This may be achieved by using the following guidelines [4,10,226]:

- use simple short words
- use the active voice in conversational style rather than the passive voice
- avoid the use of medical terms and jargon
- personalise the material by using ‘you’ instead of ‘he’, ‘she’ or ‘they’
- keep sentences simple and short
- follow the rules of grammar and syntax
- use concepts readers can understand
- present the most important information first.

It has been shown that the provision of written materials in a patient’s native or first language increases their acceptability [10,214]. Researchers have, however, warned that a simple direct translation from English is often inadequate and may result in unnatural phrasing in the other

language [10]. Careful translation is vital to ensure that the same message is communicated. Ideally, PILs should be designed in the language in which they are to be used.

3.2.6 Evaluation of PIL design

A number of methods have been developed and used to evaluate PILs from a consumer's perspective; these include both direct and indirect methods as well as objective and subjective methods that assess their utility before distribution [10,217]. The indirect methods include design assessment tools and readability tests that are objective, while the direct methods include focus group discussions, individual interviews and self-administered questionnaires [217]. All these methods have both strengths and limitations and it is often recommended that more than one method be used for evaluation so as to attain reliable results [10,217].

The design assessment tools all score PILs in terms of design characteristics that may enhance comprehension. They are useful in determining the acceptability of PIL layout for the target population. Several instruments have been developed to assess the design characteristics of PILs. These include the User Friendliness Index (UFI) [174], the Readability Assessment Instrument (RAIN) [229], the Baker Able Leaflet Design (BALD) [173], Suitability Assessment of Materials (SAM) [10] and the Medication Information Design Assessment Scale (MIDAS) [217].

- User Friendliness Index [174]

  This method makes use of an index based on subjective characteristics such as print size, graphics, colour printing, amount of white space and paper quality. Its major strength is the fact that it considers limitations for the elderly and sight-impaired consumers. It may be useful to assess specific aspects of a PIL, but is limited to only one aspect of the material.

- The Readability Assessment Instrument (RAIN) [229]

  This method consists of an 8-item tool based on characteristics such as global and local coherence, unity, audience appropriateness, adjunct questions, writing style, illustrations and typography. Its major strength is the fact it takes into account a vast number of factors. It was developed and validated for assessing the readability of patient information

brochures. One study found it to be an easy-to-use, appropriate instrument for assessing and optimising the readability of medication information leaflets [230].

- The Baker Able Leaflet Design (BALD) [173]

  This method consists of a more objective scoring system, which considers 16 characteristics of a PIL. It takes into account a large number of factors and the scale discriminates between the worst and best examples, between zero and a maximum of 32. As it has only been used to assess a few CMIs [217], it is considered to be an unreliable method.

- The Medication Information Design Assessment Scale (MIDAS) [217]

  This method makes use of a scale that quantifies the extent to which a PIL meets various recommended design characteristics [217]. It is a straightforward and reproducible method, but has only been applied in a limited way, with no evidence of large-scale reliability [217]. The developers of MIDAS also developed another tool, the Consumer Information Rating Form (CIRF) [217]. The CIRF is a direct method of quantifying consumers' perceptions of the comprehensibility, utility, and overall quality of a PIL [217]. The CIRF also served to validate MIDAS. MIDAS and CIRF are two easy to use tools for the assessment of design quality and consumer perceptions of the quality and usefulness of written information [217].

- Suitability Assessment of Material (SAM) [10]

  This instrument consists of a scoring sheet that has a list of a number of design factors to be rated. The percentage score obtained is then used to determine the suitability of the material for the intended audience. The material is rated to be either superior, adequate or not suitable for the target population. It is easy to use and gives reliable results [10]. Validation of SAM was conducted with 172 HCPs and university students from several cultures in the US [10].

Of the five design assessment tools described above, only three have been validated; these are RAIN, SAM and MIDAS [10,217,229].

3.2.7 Readability of PILs

Readability can be subdivided into three distinct concepts [145]:

- legibility, which refers to the ease and speed with which each letter or word can be recognized and is dependent on font size and style, ink and paper colour, and paper texture
- ease of reading
- ease of comprehension of the material, which is related to prior knowledge of the reader, vocabulary and structure of the text.

The three different reading levels that have been established are [232]:

- Independent - a person is literate and can read comfortably
- Instructional - a person can read, but requires some guidance
- Frustrational - a person can read minimally and struggles to do so.

Studies have shown that the health-related information routinely given to patients is often written at a level higher than their reading level [4,10,168,232,233,236]. Many adults with limited reading ability are deeply ashamed and unwilling to reveal this lack to others [116,232,234]. It is necessary for HCPs to estimate the reading ability of a patient so as to communicate with him accordingly.

In the US, most written patient information materials have been found to have an average reading level higher than the 8^{th} grade level, which is higher than the reading level of the average American [161,208,233,236,238,240]. One study showed that comprehension of WMI is dependent on reading skills and concluded that WMI should be written in the [237] "*simplest manner possible in order to be understood and judged as understandable by patients"* and "*that materials written at higher level serve to depress understanding and clarity"*. PIL designers must, therefore, have an idea of the reading skills of the intended recipients in order to ensure that the materials developed are written at an appropriate reading level and will be useful to them [4,10,168]. The assessment of both the reading skills of the target population and the readability of the information is essential.

3.2.7.1 Assessment of health literacy of patients

Two studies conducted in the US noted that patients most likely to need extra information to manage complex therapies for chronic diseases are often those patients with restricted reading skills [10,117]. It has been observed that relying on patients to tell HCPs of their limited reading skills is likely to result in missed opportunities to provide useful medicines information resources [10,271].

The assumption that educational level correlates with adequate reading skills has been found to be flawed [236,240]. In 1994, a study conducted by Davis *et al* [236] to evaluate the reading skills of some parents prior to testing the utility of paediatric written materials, found that self-reported education level did not accurately indicate their reading ability. Another study by Davis *et al* [240] confirmed the discrepancy between tested reading level and actual comprehension. A patient's ability to read is not only determined by his or her reading skills, but also by elements found in the text such as technical accuracy, format, learnability, motivational messages or legibility [2,168,199,233]. Experiential and cultural factors also need to be considered [10,168].

Several formal methods that can provide a quick estimation of reading skills and health literacy have been developed for use in healthcare settings [119,168]. They are divided into word recognition and comprehension tests [119,168]. The word recognition tests include the Rapid Estimate of Adult Literacy in Medicine (REALM) test, the Word Recognition Achievement Test-Revised (WRAT) test and the Slosson Oral Reading Test-Revised (SORT-R). Comprehension tests used in health care settings include the Test of Functional Health Literacy in Adults (TOFHLA) and the Cloze Technique; these tests measure both reading and comprehension skills. Most of these tests were developed and validated in the US for an English speaking audience.

The REALM test was developed in 1993. It is a word recognition test that measures a patient's ability to pronounce medical-related words of increasing difficulty [243]. It takes 1 to 2 minutes to administer and is designed to estimate reading level below Grade 9, as it was assumed that above this level, one is functionally literate. The grade level estimate is based on the number of words pronounced correctly. This grade estimate is useful in determining health-related information that may be read and understood by a particular audience. This test

has been shown to work only in English as its Spanish version yielded unreliable results [243,244].

In 2000, a study conducted by Lecoko to assess the applicability of the REALM test in South Africa found it to be neither reliable nor acceptable as an instrument to assess the reading skills or health literacy of an English second language population [245]. As per recommendations given by Lecoko to develop a locally appropriate health literacy test, La Rose [246] modified the REALM test to produce the REALM-M test that included words more appropriate for use in this population. This 2003 study found that the relexicalisation conducted on the REALM test increased the number of acceptable words from eight to 38 out of a total of 66 words. This showed an improvement of content validity, but lacked construct validity, and thus failed to produce reliable health literacy results. La Rose highlighted the need for a locally validated tool to measure health literacy [246].

The WRAT test consists of two equivalent forms that allow for pre- and post-testing. Each form contains three sub-tests: reading recognition, spelling and arithmetic. The reading subtest entails letter reading i.e. naming 15 letters of the alphabet, and word reading i.e. pronouncing 42 words. The more words pronounced correctly, the higher the reading skills. It takes 3 to 5 minutes to administer [10,168].

The SORT-R is a word recognition test that entails reading a list of words of increasing difficulty. The results obtained are converted to age and grade equivalents. It is a rapid test taking between 5 to 10 minutes to administer. It is not recommended for poor readers, as it has small print and contains many intimidating items. It does not test comprehension [168].

The TOFHLA is a functional health literacy test. It tests both prose reading and numeracy skills that are essential components of functional health literacy [247]. It tests the ability of patients to read prose as well as phrases containing numbers, using real materials from a healthcare setting. The assessment of numeracy skills makes it very useful for evaluating the ability of patients to comply with complex medication regimens [247]. The results are interpreted as inadequate, marginal or functionally health literate [247]. It takes approximately 22 minutes to administer, thus it is a more useful as a research tool than a clinical tool [247].

The Cloze technique is designed so that every fifth word is deleted from a passage, and the reader's task is to fill in the blanks with the appropriate replacements [10,168]. The ability of the reader to fill in the missing words correctly is a valid indicator of how well they understand the passage [168,175]. It takes between 10 to 20 minutes to administer.

The above-mentioned tests may prove difficult to use in a typical public healthcare setting in developing countries. The simplest test suggested is one in which HCPs hand patients written materials upside down; whereas literate patients will quickly turn them the right way up, a non-literate patient may not recognise the need to do so [241].

3.2.7.2 Assessing readability of written health-related information

The readability of written information for disease states [10,243,247] and medicines [168,216,231] has been widely studied. Readability tests are objective tests and mostly involve computation of scores using formulae based on word and sentence length to predict the comprehension level necessary to understanding the written information [4,10,168].

These tests are simple to administer and are widely used. They only employ syntactic (arrangement of words) and semantic (choice of words) measures [10,216]. However, they do not account for difficult words and medical jargon that may artificially inflate scores and they also have various validity and reliability problems [4,10,216]. Researchers have cautioned that even materials written backwards will score the same reading levels when a formula is employed, thus stressing the need to use them with vigilance [216].

Despite their limitations, their use in the evaluation of written patient information is vital as they enable one to obtain the reading level of existing materials, which in turn provides a valuable marker in the design process as the reading level of the material should be matched to that of the target population. A number of researchers who have examined existing written patient materials using formulae have concluded that most of them are written at a level beyond the comprehension of potential users [4,10,168].

The following are the most commonly used readability formulae that have been reviewed for use in healthcare settings [4,168,248]:

- The Flesch reading ease formula

- The Simplified Measure of Gobbledygook (SMOG) grading
- The Fry's readability graph
- The Gunning's Fog Index and
- The Flesch-Kincaid formula.

The Flesch method [249,250] is complex, but universally used. It entails selecting samples of text and determining the average sentence length (SL). The word length (WL) is calculated by counting the syllables in the sample, dividing the syllables by the number of words and multiplying by 100.
The reading ease (RE) score is the product of the following equation:
RE = 206.835 – [1.015 (SL) – 0.0846 (WL)]. Scores range from 0 (very difficult to read) to 100 (very easy to read). This method assumes 70% comprehension [250]. Similar to the Flesch method is the Flesch-Kincaid grade level method, which uses the same methodology as described above, but translates the reading ease score into the typical grade level needed to read a document [250]. These two are useful tests for medicines information as they place less emphasis on word length [249,250].

The McLaughlin SMOG formula [4,168,216] uses 10 sentences selected from the beginning, the middle and the end of a document. From this sample, words with three or more syllables are then counted. The square root of the nearest perfect square to the number counted is then determined. The grade level is the result of adding three to the square root. This method assumes 100% comprehension or that the reader is able to read each word of the document; it is a rigorous test that is preferred above the others in evaluating medicines information [4].

The Gunning Fog Index [4] is one of the simplest tests. A sample of 100 consecutive words is taken from the document and the number of complete sentences (S) contained in this sample is counted. Additional words are included if the last sentence is not complete. The total number of words (W) and the number of words having three or more syllables (A), that are not combination words, capitalized or verbs ending in 'ed' or 'es' are then determined. The grade level needed to read the document is calculated by the following equation: (W/S + A) X 0.4. This method is also used for the Fry's test, but the values obtained (S and A values) are instead plotted on the Fry readability graph to determine the grade level [4]. Both FOG and Fry methods assume 50 - 75% comprehension [10].

Readability formulae for text are also available in other languages, including Chinese, Danish, Dutch, French, German, Hebrew, Hindi, Korean, Russian, Spanish, Swedish and Vietnamese [10].

The readability of written materials can also be assessed by a number of computer programs [4,10]. The Word program by Microsoft has incorporated the Flesch reading ease score, the Flesch-Kincaid, Coleman-Liau and Bormuth grade level assessments [4]. Other software programs include the Grammatix IV, Corporate Voice and Right Writer [4]. These programs can be used to evaluate material created on a variety of word processing systems. The major advantages of using computer programs include a reduction of work requirement and an elimination of human error that is inherent in manual calculation [4,10]. They also have limitations in that they tend to produce significantly different results, thus their use in combination with other methods is advised [4].

3.2.8 Evaluation of the usability and acceptability of PILs

Consumer testing of PILs has been shown to be superior to other methods as it provides the developers with invaluable feedback that enables them to refine the material [181]. All aspects of a PIL need to be evaluated to ensure that they are excellently presented to suit the target population [10,11,174,181]. This is best achieved by collaborating with the target population throughout the design and evaluation processes [10,11,181]. One-to-one interviews conducted by the developer of the PIL have been shown to be the best way to evaluate patient educational materials on the end-users, the consumers [11,181].

The understanding of a PIL may be assessed using the methodology proposed by the European Commission's (EC) guidelines on PIL testing [181]. This method, pioneered by the Communication Research Institute of Australia, is known as 'diagnostic testing' and involves interviewing consumers and aims to evaluate the following two aspects of the document under test:

- can consumers find the information in the PIL quickly and easily?
- having found it, can consumers understand and act upon it appropriately?

Therefore, the participant is asked questions concerning the information in the PIL, which they first have to find and then explain in their own words; each question asked consists of

two parts. To deem a material suitable for use, at least 80% of the participants tested must be able to both locate and understand the information [181].

In order to assess acceptability of a PIL, 'diagnostic testing' can also be employed [11]. Diagnostic testing recommends that the designer/writer of the material conduct its testing so as to observe how participants struggle with a document they created; this may help the writer to begin to understand why some find it difficult and then be able to modify and improve the document accordingly [11]. The method entails asking participants open-ended questions about the PIL and recording all the responses given [11]. Participants are also encouraged to give their opinions and comments regarding the PIL while reminding them that the aim of the interview is to improve the PIL and not to test their intelligence [11]. Assessing acceptability of a PIL is an essential part of the consumer testing process as it provides a convenient and potent tool for identifying problem areas and improving consumer ability to use the information effectively [11,181].

3.2.9 PILs and chronic illness

In a typical primary health care setting, patients would receive information in the following manner: doctors would provide information about the disease and the initial use of medicines, nurses would inform the patient of any techniques they might need to master, for example the use of asthma inhalers, and pharmacists would dispense the medicines and counsel the patient [252]. Pharmacists play a primary role in patient education as they are the last HCP to make contact with the patient, before the initiation of therapy and they provide crucial information on the safe and effective use of medicines [253-255].

People taking medicine for chronic illnesses have shown a desire to know more about both their conditions and their treatment and have acknowledged that user-friendly medicines information is vital and essential in order to empower them to manage their conditions [144,255]. Contrary to a commonly held perception that patients on chronic medicines may 'master' their therapy instructions, studies have consistently shown otherwise [144,255]. Some patients require a constant reminder each time they receive a refill of their medicines [255]. Written information may have an impact on their medicine-taking behaviour since they will have 'a take home document' for regular referral [199,255].

The use of PILs has been shown to result in better management of most of the chronic illnesses [5,6,139-146]. Jones *et al* [144] conducted a study to evaluate the value of PILs in improving the knowledge of HIV-positive patients about their medicines. This study found a significant improvement in patients' knowledge and understanding of their treatment after using a PIL. These patients also indicated that they used PILs as a reference source. These findings are similar to those from previous studies [144,155,199], which found increased awareness of medicines and improved knowledge of therapy pertaining to the correct dosage, what to do when a dose was missed and side effects.

3.2.10 PILs and patient adherence

Some of the factors that contribute to appropriate medicine taking are health and cultural beliefs, perception of the severity of the illness, past experiences with the use of medicines and the social support system surrounding the patient [1,168]. Although having the proper information is no assurance of adherence to a medication regimen or to lifestyle guidelines, it is an essential minimum requirement [2,135]. Lack of patient knowledge about prescribed medicines may lead to unintentional non-adherence [2,102]. In order for information to be understood and potentially impact on adherence, it must be presented in a language the patient understands, with familiar words and simple sentences [5,10,168,226].

3.2.11 PILs and Pharmacists

In their expanding role as patient counsellors, pharmacists require targeted, absolute and useful tools to ensure that patients receive the medicine information they need and desire [120,253,254,304]. Pharmacists should be familiar with design considerations and content readability that may affect the value and use of PILs. This will in turn help the pharmacist to compare, choose and develop patient counselling materials.

Pharmacists are one of the HCPs responsible for educating patients and for ensuring appropriate medicines use [120,226,254,258]. In the past, most patients received this critical information verbally, after which much was likely to be forgotten [6,138]. It was thus important to further empower patients with written information, which is retained as a hard copy, allowing for constant referral if queries or problems arise.

3.3 Use and acceptability of written medicines information

In addition to the factors of design, content and distribution that contribute to the use of PILs, a number of patient- and 'environment'–related factors tend also to influence their use [168,199]. The patient-related factors have been divided into psychological and non-psychological factors [168]. The psychological factors depend on the individual's psyche and disposition, while the non-psychological factors are relatively independent of the individual's personality and include health literacy, role of the caregiver and demographics [168]. The 'environmental' factors are related to the atmosphere and the time the PIL is given to a patient or is used, and the patient's experience with PILs [168].

3.3.1 Patient related factors

- Health literacy

Readability tests tend to assume that patients have adequate health literacy skills enabling them to read and understand the presented health information yet this is often an incorrect assumption [168]. Health literacy is explored further in Section 3.4.6.

- Demographics

The association between the use of WMI and demographic characteristics such as gender, age, educational level and employment status has been investigated. The strongest association with readership of written patient materials was found to be education [10,119]. Generally, no significant association has been found between gender, age and readership [168]. However, one study found that women and younger patients were appreciably more interested in receiving WMI, compared with men and older patients [168]. Despite the inconclusiveness of these associations, health behaviour has shown reliable associations with demographics [168].

Younger, better-educated, wealthier, persons with low stress levels and excellent social support networks are more likely to engage in health-enhancing behaviour [168]. If one considers the use of written medicines information to constitute a health-enhancing behaviour, then it can be postulated that these socio-demographic factors may also influence the use of WMI [168].

- Health Locus of Control

Although inconclusive, the Health Locus of Control (HLC) has mainly been used to predict preventive behaviours where it is postulated that individuals with an internal HLC are more likely to engage in health-promoting activities [257]. The HLC concept relates to the degree to which individuals attribute personal health outcomes to their own action (internal HLC), the actions of others (powerful other HLC) or to chance, fate or luck (chance HLC) [168,199].

A qualitative study of consumers found some to believe that they should personally control their own well-being, which may be said to be internal HLC whereas, in contrast, others were happy to trust their HCPs and expressed no desire to read WMI. These findings suggest a link between HLC and the use of WMI [199].

- Coping style

In Leventhal's self-regulatory model of illness behaviour one of the stages, 'coping', occurs when a patient decides on a coping process based on his or her perception of the problem. It has been shown that, while some patients cope by becoming more involved, others tend to cope by avoidance. In this regard, the former would welcome WMI while the latter would not. Therefore, it is important to cater for both consumer types by providing information at a level and depth appropriate for each patient so as to ensure that their information needs are met [168,199].

3.3.2 Environmental factors

Although no studies have investigated the effect of the time a PIL is given to a patient as an independent variable, it has been suggested as playing a vital role in PIL use. Some studies have shown that, depending on the disease state, patients either tend to want to know more just after diagnosis or nothing until treatment has been decided upon [168,199,202]. Some consumers have highlighted that the provision of PILs when they are unwell or upset is not a good idea [168,199]. The provision of information to patients when they are preoccupied with other issues may be counterproductive, even reflecting lack of consideration on the part of the HCP. It is, therefore, important for HCPs to determine the appropriate time to provide their patients with WMI.

Patients have complex belief sets obtained from their own experiences or those of families and friends that may influence their use of WMI. A patient who has had a good experience with using WMI in the past may respond positively in the future; this may be directly related to the usefulness of previous WMI or a meaningful interaction with an HCP while receiving the information [168,199].

3.4 Literacy

Education has long been shown to have an association with health [10,116,234-243]. Generally, educational level is not a good predictor of patients reading level or reading skills [238,240,242,243] as, over the years, it has become evident that the knowledge and skills acquired in school are more significant than the number of years spent in school [10,238], i.e. skills and knowledge attained as opposed to merely exposure to an educational environment. Educational level has been related to various health factors that range from smoking prevalence and cessation, to relative body weight [238,239,265]. Lower education has been shown to correlate with poorer health status; therefore, literacy should be a more reliable predictor of health than the number of years spent in school [10,238,265].

Literacy can be defined simply as ‘the ability for one to be able to read and write’ [245]. This definition is extremely limited as it only concentrates on reading and writing. The definitions of literacy are not fixed and are said to remain fluid across disciplines and time [246]. Literacy has thus been described in a number of ways, as varying literacy skills are required to conduct different activities, this being related to competency [268]. Literacy definitions are phrased in terms of what a person should do to be considered ‘literate’, and include an ability to sign one’s name, to read and write a simple sentence, to describe one’s daily activities, to pass a written test for reading comprehension at the same level as a US Grade 4 learner, and to participate in community activities that require literacy for effective functioning [268]. Thus, literacy is not a simple concept with a single accepted meaning [245]. It does not purely engage straightforward reading or decoding of words but also includes skill at comprehension and verbal reasoning capability [245].

According to UNESCO, three general literacy categories have been identified [268]:

- *Illiterates*: people who cannot read or write in any language
- *Semi-literates:* people with a minimal ability to read and write, whose skills have not been enduringly acquired and who may easily regress to being illiterate
- *Literates*: people who have permanently acquired reading and writing skills

The different broad levels of proficiency of literate people include [268]:

- *Pre-literacy:* this is the first level of progress on the path to literacy where a person starts to acquire the knowledge of basic language and arithmetical skills that are needed to master literacy. A person at this level is not permanently literate and may easily relapse into illiteracy
- *Basic literacy:* this is a level where one can permanently read and write short simple communications that relate to everyday life
- *Functional literacy:* this may be linked to either a specific work environment or a service or a community. The ability to read, understand and interpret what has been read and to then use it accordingly is essential to cope adequately in a complex demanding society.

3.4.1 Statistics and dynamics of literacy

In 1991, UNESCO stated that illiteracy is a worldwide problem with major socio-economic, political and health implications [269]. According to the UNESCO Institute for Statistics' (UIS) 2004 report, an estimated 862 million people are illiterate worldwide, with the global illiteracy rate estimated at 20.3%. In Africa it is estimated that 183 million people are illiterate, with an estimated illiteracy rate of 40%, and 136 million of these live in sub-Saharan Africa. It is not only in the developing countries that illiteracy is prevalent, as in the US, an estimated 40 to 44 million people are functionally illiterate (indicating they cannot, with understanding, both read and write a short simple statement on their everyday life) while around 50 million have only marginal reading skills. Worldwide there is a disproportionate distribution of illiteracy between males and females with the number of illiterate females higher than that of males [269].

According to the 2002/03 South African Institute of Race Relations' survey of literacy [270], the estimated proportion of functionally literate people aged 20 and over in 2001 was 71.6% which implies that an estimated 28.4% of the South African population is functionally

illiterate. These estimates are based on the notion that to achieve functional literacy, a minimum of a Grade 7 education is required [270]. These statistics show that almost a third of the South African population may have a reading problem.

According to the UIS 2004 report, the estimated proportion of adult literacy in Tanzania is 77.1%, with an estimated 4.5 million illiterate adults [269]. Literacy here is also disproportionately distributed between males and females with over a third of the rural women having no education at all, and 41% being unable either to read or write [269].

3.4.2 Literacy and its influence on health

Numerous studies conducted in the US have shown that health status is directly linked to literacy levels, although a significant association has yet to be established [272-279]. This association has been noted in developing countries as well [271]. Across the world, the education and empowerment of patients with self-management skills that will promote their involvement with their own health issues has been shown to be advantageous [118,271,277].

Patients need to participate fully in the management of their own healthcare [271,277]. Patients with chronic diseases such as diabetes or hypertension require basic, foundation information on their diseases such as the symptoms of hypoglycaemia for the diabetics, or dietary requirements for the hypertensives [271,277]. Studies have shown that low-literate patients with chronic conditions have less knowledge of their disease and its treatment, as well as fewer correct self-management skills than literate patients [10,154,276]. Most information on self-management is available in a written format, but the majority of these materials has proven to be inaccessible to patients with low literacy [10,154,276]. Insufficient literacy is particularly prevalent among the elderly, the population with the largest burden of chronic diseases [67]. It is thus imperative to develop accessible, appropriate and comprehensible health information for patients with chronic conditions.

3.4.3 Health Literacy

Health literacy (HL) has been defined as [168] "*the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to*

make appropriate health decisions". HL may also be described as both a goal and an outcome, becoming the currency and capital needed to develop and sustain health [265,278].

The health promotion model aims at a multidisciplinary approach to HL [279]. This model and the WHO both define HL as "*the personal cognitive and social skills which determine the ability of individuals to gain access to, understand and use information to promote and maintain good health"*. HL has been identified as being at the core of improving health [279].

Nutbeam [279] identified three types or levels of HL: level one - functional HL, level two - interactive HL and level three - critical HL. Functional HL reflects the product of customary health education based on the communication of factual information on health risks and on how to use the health system, but is limited to improved knowledge of health risks, health services and adherence to prescribed actions. It also entails the ability to read and comprehend prescription bottles, appointment slips and other essential health-related materials. Interactive HL focuses on the development of personal skills in an accommodating environment and is directed towards improving personal capability to act independently on knowledge and to improve motivation and self-confidence to act on advice received. Critical HL entails superior cognitive skills that may be applied in scrutinizing information critically and using this information to exert greater control over life events and situations [279]. Only functional HL will be reviewed in this thesis as it is the basic level required to read, understand and act on medicines information.

Inadequate HL has been associated with increased hospital admissions [275] and higher prevalence of adverse health behaviours like smoking, alcohol, drug use and inadequate diet [266,267]. Poor HL has also been associated with poor health in PLWHAs [267]. A community-based study demonstrated that low-literate PLWHAs had poorer health status and their HL had an association with an unfavourable viral load and CD4 cell count [267].

3.4.3.1 Functional health literacy

Functional health literacy (FHL) is defined as [168] "*the ability to read, understand, and act upon health information.* Patients with inadequate FHL are less likely to read, understand and take action on written health information [168,275] and, therefore, present with a higher probability of misreading and misinterpreting instructions on medicine labels [280-2834].

This could lead to over- or under-dosing of their medicines [282], missed doses due to confusion, depression and conflicting health beliefs [280]. A study that examined the association between FHL and adherence to ART regimens found that, after controlling for other demographic factors, FHL was an independent predictor of medication adherence [267]. FHL can be assessed by using instruments like the REALM, TOFHLA, WRAT-R tests and the Cloze Technique described previously.

3.4.4 The low literate patient and written information

In many cases, the only written information patients receive about their prescription medicine appears on the label [226,280]. The problem of insufficient information is exacerbated in those who cannot read or who experience visual problems [226,280-283], as most labels are written in small print owing to space limitations on the packaging [281-283]. Labels for prescription medicines need to be simplified and include readable size fonts to improve their readability and comprehension. It has been shown that the incorporation of pictograms on labels significantly increases and improves recall of instructions in a low-literate population [13,256,284-286].

It is difficult to identify patients who cannot read as there is an overwhelming reluctance to admit to a lack of reading skills, which is accompanied by feelings of shame [10,232,234], thus illiteracy has been termed a ‘quiet disability’ [10,232,261,264]. Illiteracy carries a stigma and creates feelings of insufficiency, fear and low self-esteem. These patients will hide their status from HCPs [10,235] by the use of cover-up mechanisms such as ‘I’ve forgotten my glasses’, when told to read, or ‘I do not have time right now, I will read it at home’ [10].

Low literacy has been associated with a number of factors that may lead to poor health including [10,175,238,261-267]:

- poor understanding of chronic conditions
- poor participation in preventive care
- inadequate assessment by HCPs
- receipt of ineffective care because of lack of understanding of directions from the HCPs
- lack of awareness of educational materials posted such as posters for flu vaccine
- unintentional non-adherence due to their inability to read or comprehend their written medical instructions resulting in errors in drug use

- failure to obtain or understand information regarding their personal medical care.

The health care system is a complex system that is challenging for most patients, but is even more so for the low-literate patient who encounters many difficulties in negotiating a system that requires some degree of health literacy. Low-literates may not understand how to use the health care system, potentially resulting in inappropriate over- or under-use of these services [271,273].

HCPs need to have some idea of the literacy skills of their patients in order to tailor their advice accordingly [10,116-120,271-279]. The appropriate terminology should be used when discussing health matters with patients to ensure that these are understood [10,116,118,154]. This category of patient also requires extra consultation and counselling time to ensure that an acceptable degree of understanding of medicines information is attained [263,265]. For patients who cannot read, verbal communication is the main method of conveying a message, therefore, it should be done systematically. This entails the HCP spending more time [10,232] by first explaining the directions and precautions to the patient and then asking him or her to repeat the information repeatedly, until it is evident that he has understood the information and is likely to recall it [10,265]. Such patients are also encouraged to make use of family members or friends who can assist them with any written information provided [265].

Pharmaceutical care is a philosophy of practice that has been adopted worldwide by pharmacists and is a practice in which the pharmacist takes responsibility for a patient's drug-related needs and is held accountable for this commitment [61]. This entails accepting responsibility for patients' pharmacotherapeutic outcomes and empowering the patient to practise responsible medicine-taking behaviour by educating and counselling. For pharmacists to deliver pharmaceutical care to low-literate patients, they need to identify such patients then use the appropriate method of communication [10,120,232,271] in order to ensure that they understand their medicine instructions [10,258,262-265] and, consequently, avoid errors in medicine use.

People of all literacy levels prefer simple written materials to complex materials. Generally, these materials should be written in simple, straightforward language with uncomplicated layouts, incorporating illustrations such as diagrams, symbols, pictographs or pictograms to clarify instructions and warnings [10,13,233,276,293].

3.5 The use of visual aids in patient education

Since ancient times, drawings and symbols have been used to convey messages. Generally, a symbol is said to be ‘any graphical character or other presentation that is intended either to stand for something else, communicate a use for an object or a structure or communicate what should or should not be done at a given time or location’ [291]. Worldwide, the use of pictures on prescription labels has been shown to be useful to persons with limited education or vision [10,13,283-290].

There is evidence that memory for pictures may be superior to memory for words in people of all ages since pictures are dual-coded, both as pictures and as words [10,291]. The use of illustrations to improve understanding of patient educational materials is an important component of the literature on cancer prevention and its early detection [148], hospital discharge instructions [293], the management of rheumatologic disorders [294], the proper use of medical devices [293] and medicine instructions and warnings [292,295,296]. It has been shown that carefully designed illustrations are extremely useful for presentation of simple messages and for clarification of more complex messages [10]; however, even the best illustrations cannot be a substitute for verbal communication and well-organised simply written text [10,13,297,298,301].

3.5.1 Cultural considerations in the use of visual aids

When readers view written materials containing illustrations and graphics that they recognize and symbols with which they are familiar, they tend to understand and accept them more readily than materials with text only [10,13]. Cultural appropriateness of patient education materials is enhanced when the graphics are designed and developed in collaboration with members from the target population [10,215,300-303].

The history of misinterpretations and misunderstandings of visual messages has suggested that visual messages that successfully communicate a message to one population may prove meaningless or even offensive to another. To be useful, visuals must be simple, practical and relate to what the users know and understand. They must also be meaningful, learnable, unforgettable and consistently used [10,215,298].

3.5.2 USP Pictograms

In 1987, the US Pharmacopoeia (USP) Drug Information division commenced the process of designing a standard set of signs or symbols, known as pictograms, for use in pharmaceutical labelling. Over 10 months, the first set of pictograms underwent an iterative design-testing-modify procedure with the aid of focus group sessions, to produce the first set of pictograms that was published in the 1989 issue of the USP-DI [299]. To date, over 81 pictograms have been developed and published in the USP-DI.

The USP defines pictograms as [299]*"images representing proper ways to take or store medications, precautions, or other important information about a medication that a health care provider should provide to his or her patient"*. They are available for use by HCPs and others to reinforce printed or oral instructions. The USP also states that "*pictograms are particularly helpful in passing on important information to patients with a lower level reading ability and patients for whom English is a second language"*". These pictograms are copyrighted by the USP, but a free licence may be issued to a user, provided the user meets a set number of conditions as stated on their web page.

3.5.3 South African pictograms

Dowse and Ehlers [289] tested the USP pictograms in a low-literate South African population and found them inappropriate for use in this population. The USP pictograms were highly misunderstood and misinterpreted by a majority of the participants on whom they were tested. This was partly attributed to the fact that the USP pictograms were 'Westernised', containing symbols and concepts that are presumably familiar to the average American. For the instruction to 'take with meals', for example, the USP pictogram had a picture of a table set for a meal, consisting of an empty plate and cutlery. Most of the South African participants interpreted it as 'take with no food', a result of the plate being empty of food. To the average American, such a concept is obvious, but to this non-westernised population, this is not familiar, as plates on a table would always contain food and the table is rarely 'set'.

Dowse and Ehlers [300] also developed a set of local pictograms for use in the local South African population by modifying the USP pictograms. A follow-up phase comparing 23 USP

pictograms with their local versions found a significant improvement in understanding of the local pictograms compared to the USP pictograms [289]. Twenty of the local pictograms met the 85% ANSI criterion as compared with 11 of the USP. All the participants of this study preferred the local pictograms to the USP pictograms in 21 out of 23 cases, with a significant difference in 17 cases. These local pictograms have been extensively tested and their shortfalls recorded. Some have subsequently been re-modified and re-tested [Dowse R, personal communication].

3.5.4 The use of pictograms in pharmacy

Pharmacists have shown the ability to intervene in different ways in order to improve the understanding of instructions by the various groups [256,293-298] that include those people who do not understand written information such as the elderly, those with vision problems, users with different languages and those who cannot read [10,286,290]. One such way is to use charts and appropriate illustrations such as pictograms and pictographs [10,256,292-298,301].

The use of pictograms in pharmacy in conjunction with verbal reinforcement may help to convey health and medicine information to patients with low-literacy skills [10,290,301]. They also have a major positive effect on those with visual impairment because they tend to be much larger than typewritten words [10,290]. Pictogram use may also be critical for persons who are not proficient with the language used in the medicines information [167]. In the US, two studies by Houts *et al* [296,297] showed that pictographs tend to increase the amount of medical information low-literate patients recall over a significant period of time.

Mansoor and Dowse [13], in a South African study, concluded that the incorporation of pictograms on medicine labels and PILs significantly improved patient recall and understanding of instructions. They also found that, in agreement with previous studies [290,301] patients preferred information with pictograms over text-only information [13].

3.5.5 The design of pictograms

Pictograms for conveying medicines information should communicate one instruction at a time [10,301,302], contain appropriate symbols and appear as realistic as possible [10,301]. Guidelines for designing pictograms have been proposed by a number of researchers in the field [10,301-303]. Consultation with and feedback from the target population is essential [10,301,303]. Pictogram design is an iterative process, involving multiple cycles of design, testing, re-design, modification and further testing until they are deemed acceptable according to the established guidelines [301,303]. The criteria used for pictogram evaluation will be discussed in Section 4.1.

3.6 Barriers to effective communication in South Africa

In South Africa, cross-cultural communication occurs approximately 80% of the time in health-care consultations [304]. Language represents the most common communication barrier in this country, as there are 11 different official languages [305]. The number of people using each of the 11 different languages is shown in Table 3.4.

Table 3.4 The South African population by language (Census 2001)

Language	**Population (number)**	**Per cent (%)**
isiNdebele	711 821	1.6
Tshivenda	1 021 757	2.3
SiSwati	1 194 430	2.6
Xitsonga	1 992 207	4.4
Sesotho	3 555 186	7.9
English	3 673 203	8.2
Setswana	3 677 016	8.2
Sesotho sa Leboa	4 208 980	9.4
Afrikaans	5 983 426	13.3
isiXhosa	7 907 153	17.6
isiZulu	10 677 305	23.8
Other	217 293	0.5
Total	44 819 777	

IsiZulu is the most prevalent first language, with isiXhosa being the second most spoken language in South Africa. These languages are mainly geographically distributed. As pharmacists and other HCPs often need to use interpreters, they should, ideally, be trained in using these interpreters [304]. Written patient education materials may be used to overcome this barrier if the information is available in the patient's first language and if the patient is able to read it.

Health beliefs of a population must be acknowledged as they have been shown to directly influence patient health and medicine-taking behaviour. HCPs need to understand patient cultures and beliefs in order to provide relevant healthcare services in an appropriate manner. In South Africa, approximately 80% of the total population is dependant on and utilises public sector health services [305] and a large proportion of these are African language speakers. It is thus important for HCPs who work in the public sector to appreciate the different approaches to health and the diverse health beliefs prevalent in the various cultures.

As has been described in previous sections, each patient needs to be treated as an individual as there is no universal model that can predict how to handle a specific type of patient group, especially in a country like South Africa with its wide range of different cultural groups.

CHAPTER FOUR
MODIFICATION AND EVALUATION OF PICTOGRAMS

4.1 Introduction

The inclusion of pictograms in written medicines information has been proven to enhance the usability of the information by increasing the understanding and recall of instructions [13,283-287]. Pictograms have been defined as *"simple, clear, graphic symbols able to convey their intended meaning to all patients, including those who are illiterate, elderly or visually impaired"*[301].

The design of pictograms is a complex, multistage iterative process [300-303] and a number of publications have proposed guidelines for this process [297-300]. A major strategy recommended to reduce problems with interpretation is to involve the target population throughout all the stages of the design process to ensure cultural appropriateness of any pictorial materials used to convey a message [10,174,215,300,301].

The evaluation of pictograms is generally based on a measure of success at conveying the intended meaning [10,301]. Evaluation methods that have been used include open-ended tests, multiple-choice tests and a ranking method. In the open-ended test, a participant is shown a pictogram and asked to offer their interpretation in their own words [301]. In the multiple choice test, participants are provided with a restricted set of options and are required to opt for the correct one; this method is useful for assisting in the development of pictograms rather than in their evaluation [301]. With the ranking method, participants are asked to sort different symbols into an order from the easiest to the hardest to understand; the problem is that the highest-ranked symbol of a set of poor symbols will remain a poor symbol [301]. Subjective tests produce invaluable data as it has been shown that culturally recognizable symbols are preferred and they improve understanding and recall of the message conveyed [301]. In general, it has been proposed that more than one method be used to evaluate pictograms.

Acceptability of pictograms is guided by international standards that have been established for evaluating the comprehensibility of pictorial symbols. In a pictorial comprehension test, the American National Standard's Institute (ANSI Z535.3) [306] advises that a pictorial

symbol must reach at least a criterion of 85% correct for it to be acceptable, while the International Standards Organisation's (ISO 3864) [307] suggests 67% correct in a comprehension test. These standards have been said to be capricious, but owing to the significance of understanding the correct medication instructions in order to use medicines safely, the comprehension should be above the 85% level, if possible. The ANSI 85% criterion will be used in this study to deem pictograms acceptable for the target population.

This chapter aims to describe the comprehensive iterative process that was used to modify and evaluate pictograms that were subsequently included in written medicines information.

The objectives of this part of the study were:

1. To identify the most important instructions that can be augmented by pictograms
2. To locate existing pictograms that illustrate the instructions and to modify and evaluate them for understanding and acceptability in the target population
3. To identify the need for any new pictograms and to design and evaluate such pictograms.

4.2 Methodology

The patient information leaflet for ART was examined to identify those instructions that could be represented using pictograms. These included when and how to take the medicines, storage of the medicines and concomitant use with alcohol.

A search for pictograms to convey these instructions was conducted. Our research group has extensively researched 23 of the USP-DI pictograms, which were modified for use in a low-literate African population and were evaluated [289]. Problems with interpretation of both the USP pictograms and the locally developed pictograms (to be referred to as SA pictograms) have been documented [289, Dowse R, personal communication]. Five of the six pictograms required for this project were adapted from the SA pictograms and were modified. One entirely new pictogram was designed.

4.2.1 Design and modification of pictograms

A workshop was held with undergraduate university students who were in their second year of study towards a Pharmacy degree; students representative of the target population were present in this group. Background information on the design, use and problems associated with pharmaceutical pictograms was presented. Examples of both USP and SA pictograms were discussed and their misinterpretations were highlighted. The students were then split into two groups and, without prior exposure to the USP or SA versions of these pictograms, were asked to draw pictures that illustrated the following instructions:

- 'Keep all medicines out of reach of children'; no previous work had been done in South Africa on the design of this pictogram
- 'Keep all medicines in a cool, safe, dry place away from heat and direct sunlight'; although this pictogram had been previously modified and evaluated locally, results were unsatisfactory and did not comply with the ANSI criterion [306].

The ideas and rough sketches generated from this workshop were examined and discussed with a graphics designer who produced initial versions suitable for testing. A focus group discussion (FGD) with five Xhosa participants identified the need for further minor changes to these pictograms. Similarly, FGDs were conducted for each of the three SA pictograms to be incorporated in the ART PIL. Details of the design and modification of individual pictograms to be included in the PIL are illustrated and discussed below.

- **Take medicines with a glass of water**

The original SA pictogram without any modification (Figure 4.1) was used in the testing process.

SA pictogram

Figure 4.1 Take medicines with a glass of water

- **Do not take alcohol while taking these medicines**

Frequent social alcohol intake is common in the target population, so this was a particularly important pictogram to consider. The SA pictogram was considered 'outdated' by the members of the focus group as it contained alcohol containers that are no longer available. These images were updated according to current, popularly used alcohol containers. A glass of beer was also added to the pictogram.

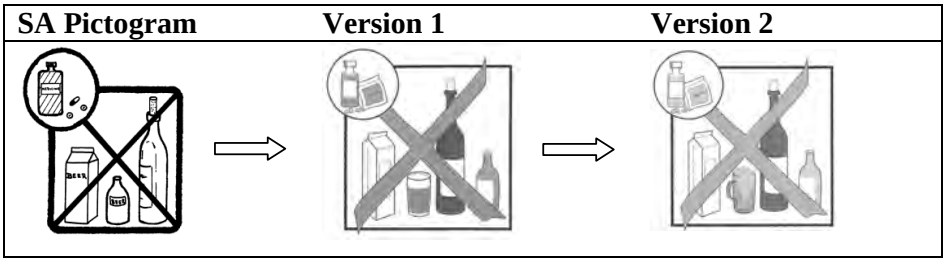


Figure 4.2 Do not take alcohol while taking these medicines

Version 1 was obtained from the graphics designer as a result of the ideas discussed and images from the SA pictogram (Figure 4.2). After a FGD, the following modifications were made:

- The glass in Version 1 was changed into a mug with overflowing foam (Version 2)
- The width of the cross was slightly reduced, it was made transparent and was moved slightly to increase visibility of the bottles (Version 2)

- **Store all medicines in a cool dry place, away from heat and direct sunlight**

In previous studies, the SA pictogram for the instruction 'Keep medicines in a cool place, away from heat and direct sunlight' did not comply with the ANSI 85% criterion, as only 47.8% interpreted it correctly [289]. It therefore required further modification before incorporation into the written information used for this study (Figure 4.3)

We introduced the concept of keeping the medicine in a dark, cool place by showing the shaded interior of the cupboard, and maintained the images of the sun and fire to represent sources of heat. The image of the sun in Version 1 was felt to be too stylised. An informal mini survey was conducted with five Xhosas who were asked for their opinion of representing an image of the sun. This resulted in the modification to Version 2. The image representing the fire was also modified via a similar process. The image of the fire was increased in size to avoid it being obscured by the cross as was the case in Version 1. An

extra shelf was added to the cupboard and the medicines placed on the top shelf after decreasing their size.

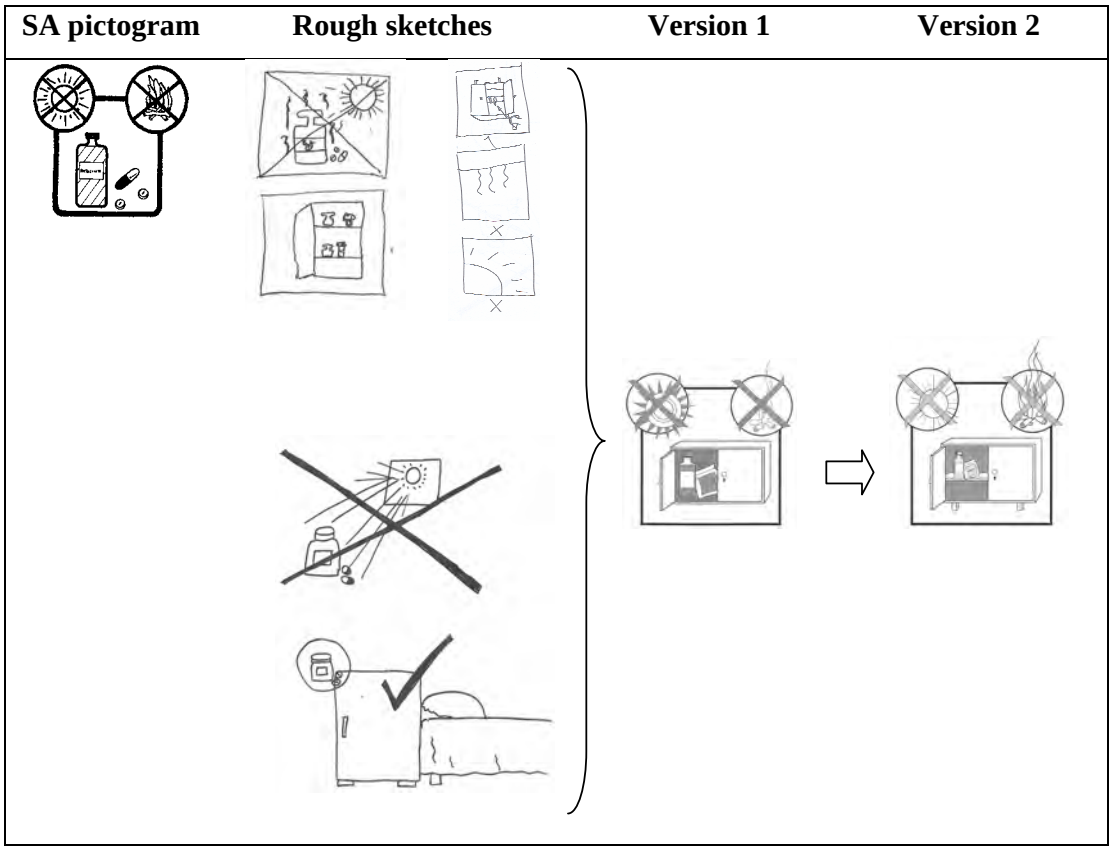


Figure 4.3 Store all medicines in a cool dry place, away from heat and direct sunlight

A further concern was the double cross signifying negation. Previous findings indicated that some people with limited visual literacy totally ignored it. For this study, the conventional refined cross was thickened, shaded and slightly skewed in an attempt to enhance its noticeability (Version 2).

- **Keep all medicines out of reach of children**

Using the USP version as a starting point, the ideas and rough sketches produced by the pharmacy students were discussed with the graphics designer who generated Version 1 (Figure 4.4). As a result of a FGD, this was modified to the final image (Version 2). The following changes were made:

- The baby was moved to the other side
- The other child was replaced by a woman

- The shelf was changed into a cupboard that resembled the one in the above pictogram and was placed within easy reach of an adult, but well above the height of the child.

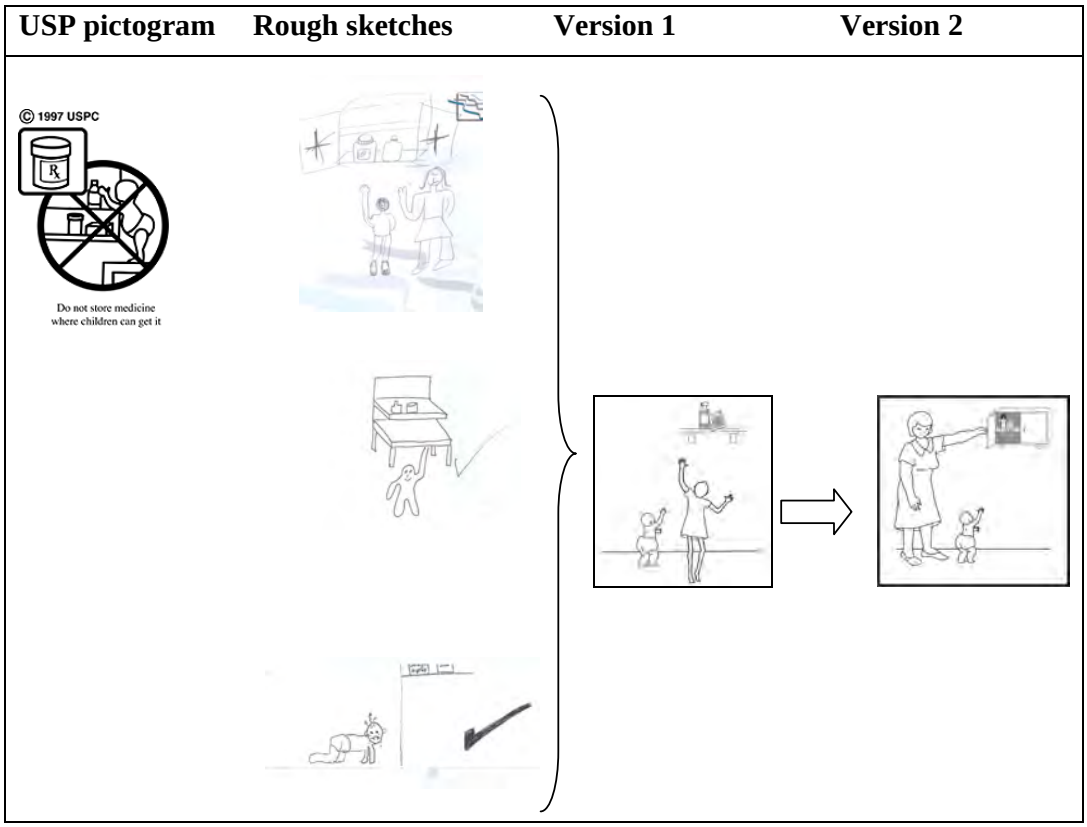


Figure 4.4 Keep all medicines out of reach of children

4.2.2 Evaluation of pictograms

4.2.2.1 Pictograms included for evaluation

An interpreter was used for all the interviews. She was given background information about the study and was specially trained. A questionnaire designed and validated by Dowse and Ehlers [289] for use in pictogram testing was used to capture data. A total of 10 pictograms were tested, five of which were to be incorporated into the PIL. This was done firstly to allow for randomization that would not be possible with only three pictograms and, secondly, to cross check results with those obtained for the same pictograms tested in a similar population in previous studies. Seven of the 10 SA pictograms had been previously tested; the remaining three were the newly modified pictograms.

4.2.2.2 Study site and study population

Testing of the pictograms was conducted at the Grahamstown Day Hospital, which is a public sector health centre where most patients with chronic illnesses and on chronic medicines see an HCP and collect their monthly supplies of medicine. A total of 30 Xhosa participants were individually interviewed. They were recruited by the interpreter who introduced herself and asked the patients waiting to be attended to if they had time to spare after they had seen an HCP. Those who agreed to participate were recruited and interviewed.

4.2.2.3 Interview process and collection of data

With the aid of the interpreter, the researcher introduced herself, gave a brief explanation about pictograms and used two pictograms as examples to orientate the participant. The participants were reassured that it was the pictograms that were being tested, not the participants themselves.

Demographic data were collected (sex, race, age, education). The participants were then shown the pictograms in a random order, one at a time and asked to give their interpretation. Their responses were recorded for each of the 10 pictograms. The interviews lasted between 15 - 30 minutes, depending on the ability of the participant to interpret and to explain the pictograms. At the completion of the interview, the participants were thanked for their time and given an honorarium (R10). The ANSI 85% correct criterion was used to accept or reject the pictograms.

4.3 Results

4.3.1 Demographic results

The demographic results are presented in Table 4.1. Of the 30 participants interviewed, 20 (66.7%) were female and 10 (33.3%) were male. This can be attributed to the fact that the majority of public health attendants are female as they are also the caregivers responsible for taking children to hospital. All the participants (100%) were black Xhosas and had isiXhosa as their home language.

A majority of the participants (53.3%) were between 40 and 65 years of age. Six (20%) of the participants had not received any formal education and 16 participants (53.3%) had more than 5 years of formal education Twenty eight of the 30 participants could tell the time from a clock face.

Table 4.1 Demographic results (N = 30)

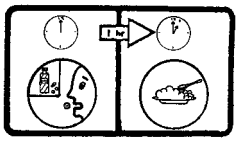
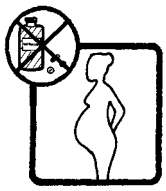
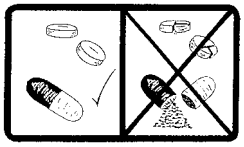
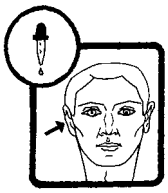
Demographic parameter	**Participants, N (%) N = 30**
Sex	
Male	10 (33.3)
Female	20 (66.7)
Age	
< 21	0 (0.0)
21 - 40	11 (36.7)
40 - 65	16 (53.3)
> 65	3 (10.0)
Highest Qualification	
None	6 (20.0)
Grade 1- 4	8 (26.7)
> Grade 5	16 (53.3)
Tell time from a clock face	
Yes	28 (93.3)
No	2 (6.67)
Digital time only	0 (0.0)

4.3.2 Interpretation and discussion of pictograms not included in final ARV PIL

The results for interpretation of pictograms not included in the final ARV PIL are presented in Table 4.2. These pictograms have been previously tested in this population by Dowse and Ehlers [289, Dowse R. personal communication]; the results obtained in this study will be compared to these findings.

The pictogram for the instruction ‘Take one hour before meals’ was poorly understood by this group, with only 13 (43.3%) of the 30 participants giving the correct interpretation. This is lower than previous results obtained by Dowse and Ehlers [289]. This score was noted and the pictogram will need to be further modified and tested.

Table 4.2 Interpretation of pictograms not included in final ARV PIL

Instruction	Pictogram	% Correct	
		This study	Dowse et al
1. Take one hour before meals		13 (43.3)	36 (78.3)
2. This medicine may make you drowsy		4 (13.3)	28 (48.6)
3. Do not take this medicine if pregnant		22 (73.3)	37 (80.4)
4. Do not break or crush capsules or tablets		15 (50.0)	28 (75.7)
5. Place drops in the ear		28 (93.3)	44 (95.7)

shading indicates pictograms that did not meet the ANSI 85% correct criterion

A particularly poorly interpreted pictogram was the one pertaining to drowsiness, which was correctly interpreted by only 4 (13.3%) of the 30. This was the lowest score obtained and it may be partly attributed to the fact that it is made up of three different pictures, with no evidence of medicines hence making it very confusing. Participants had difficulty in integrating the messages of all the images, as frequently they merely offered a description of these images, and gave no general interpretation of the entire pictogram. This pictogram was previously poorly understood as well as it scored 48.6% [Dowse R. personal communication].

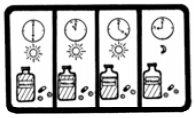
Twenty-two of the 30 (73.3%) participants understood the pictogram illustrating the information on avoiding the use of medicines when pregnant, a result almost similar to that obtained previously (80.4%). The pictogram for the instruction ‘Do not break or crush capsules or tablets’, was understood by half of the participants (50%). This may be attributed to the fact that it is quite a busy picture that led to some participants interpreting each segment independently. The previously obtained results were much better as it was understood by 75.7% of the participants it was tested on [289].

The most successful pictogram illustrated the instruction ‘Place drops in the ear’ that was understood by 93.3% of the participants. This exceeded the 85% ANSI criterion and is in agreement with previous findings of 95.7% correct interpretation [289]. If it were to be incorporated into the PIL, no further modifications would have been necessary.

4.3.3 Interpretation, discussion and modification of pictograms included in final ARV PIL

All the pictograms to be incorporated in the ART PIL were modified based on feedback from the evaluation conducted and focus groups.

Table 4.3 Interpretation of pictograms included in final ARV PIL

Instruction	Pictogram	% Correct	Misinterpretations
6: Take with a glass of water		C: 26 (86.7) O: 35 (76.1)	▪ Shows someone coughing/a spoon and glass/ patient coughing out body parts ▪ Take medicines with food ▪ Take medicines with a little water as may cough out pill
7: Take four times a day		C: 25 (83.3) O: 43 (93.5)	▪ Take 3 tablets 3 times a day ▪ Time on the clock was misread
8: Store all medicines in a cool dry place, away from heat and direct sunlight		20 (66.7)	▪ Stop smoking and use the medicines ▪ Keep safely and use medicines properly ▪ Keep medicine in cupboard that should be closed at all times/away from children ▪ Keep medicines in cupboard and the tree with leaves is to provide shade ▪ Give medicines through a window
9: Do not take alcohol while taking these medicines		12 (40.0)	▪ Do not take with food/milk/ paraffin/traditional medicines ▪ Do not drink these drinks at the same time with medicines only later ▪ These are drinks to drink while taking the medicines ▪ Take medicines with milk/ice cream/water in a jug ▪ Bottles containing paraffin/medicines - do not keep together
10: Keep all medicines out of reach of children		27 (90.0)	▪ Keep medicines in a cupboard, the nurse will then take them to give the child ▪ Always keep medicine cupboard locked so that children do not reach, the open cupboard shows a sign of carelessness ▪ The medicines displayed are for the baby

C = results from this study
O = results from a previous study
shading indicates pictograms that did not meet the ANSI 85% correct criteria
[2] Pictogram score from previous study

Pictogram 6. Take medicines with a glass of water

The pictogram 'Take with a glass of water' satisfied the 85% ANSI criterion, whereas in the previous study it scored 76.1%. This pictogram was minimally modified as per feedback from some of the participants and a FGD (Figure 4.5). A slight modification of the SA pictogram was deemed necessary after a feedback from the study and a FGD.

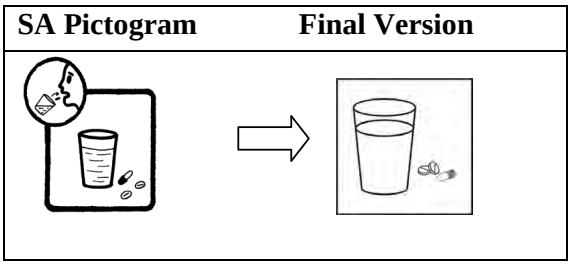


Figure 4.5 Take medicines with a glass of water

The following modifications were made:

- The insert with the profile was not well understood and was confusing, thus it was removed.
- A clear glass of water was depicted as the lines representing the liquid evoked negative comments
- The capsule and tablets were modified to more closely represent those used in practice.

Pictogram 7. Take four times a day

This pictogram just missed meeting the 85% ANSI criterion, but scored very high in the previous study (93.5%). The comments were noted and used to modify the twice daily pictogram for use in the PIL (Figure 4.6).

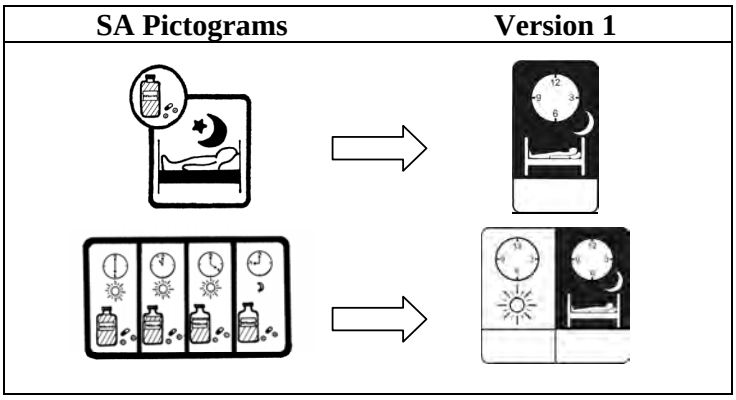


Figure 4.6 Take medicines at night/twice a day

Ideas from the two SA pictograms were combined to produce new versions (Figure 4.6). To convey the idea of night time, a 'negative' version of the white image was used to give a dark background. The image with the moon and the star in the SA pictogram was modified to include just the moon, as the original symbol was too similar to the Muslim symbol of a moon and a star.

Pictogram 8. Store all medicines in a cool dry place, away from heat and direct sunlight

This pictogram was correctly interpreted by 20 (66.7%) of the 30 participants and required further modification. In some cases, the individual elements of the picture were not integrated but were regarded independently.

The image of the sun elicited negative comments and was said to look like a clock face, the moon, a broken tablet; some did not recognise it at all. Comments on the fire included "looks like a tree with leaves" and "a lit cigarette ready to be smoked".

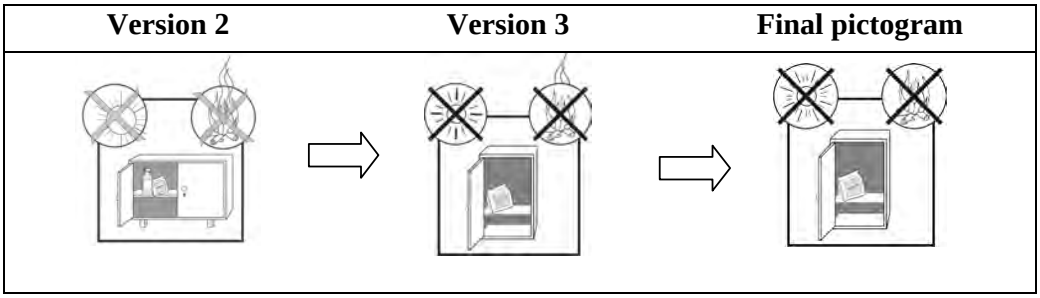


Figure 4.7 Store all medicines in a cool dry place, away from heat and direct sunlight

For this pictogram, the following modifications were made:

- The sun was placed at the centre on the circle (Version 3)
- The smoke was removed from the fire (Final version)
- Both the crosses were placed symmetrically over the sun and the fire (Version 3)
- The shape of the cupboard was changed and only one door included (Version 3)
- The medicine packet was increased in size and the medicine bottle was removed (Version 3).

Pictogram 9. Do not take alcohol while taking these medicines

Only 40% of the participant understood this pictogram. It was noted that the alcohol containers used were outdated thus a change was necessary.

Some of the comments given by the participants included the following:

- The box and shorter bottle resembled milk containers that confused most of the participants
- The bottles had no labels thus they could be bottles containing any liquid other than alcohol.

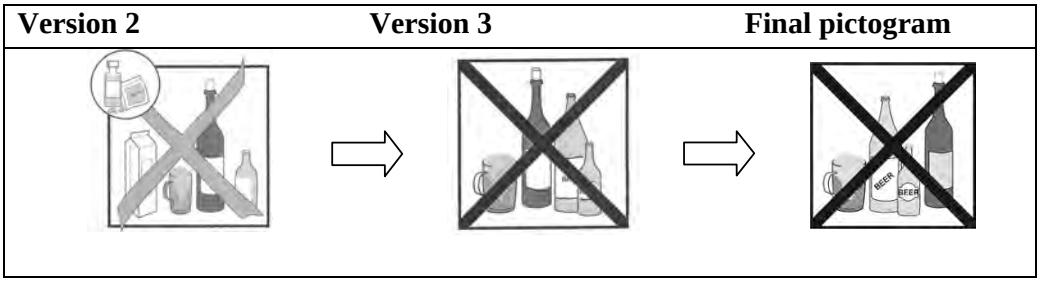


Figure 4.8 Do not take alcohol while taking these medicines

The following modification were made to this pictogram (Figure 4.8)

- The majority saw the carton/box as a carton of milk. The local brew was originally packed in this type of carton but is now sold in 20 litre containers and is poured into bottles by the vendors, thus the carton was removed. A larger popular beer bottle replaced it (Version 3).
- The short bottle looked like a milk bottle that is popular in this population and therefore needed modifying more closely to depict a slender, longer beer bottle (Version 3). Two of the bottles were labelled as 'beer' (Version 3)
- The bottles were repositioned to increase their visibility below the cross (Final Version).

Pictogram 10: Keep all medicines out of reach of children

The new pictogram was well interpreted and exceeded the 85% ANSI criterion. This pictogram did not need any further modifications, but the cupboard was modified to look similar to the one used for the instruction 'Store all medicines in a cool dry place, away from heat and direct sunlight' (Figure 4.9).

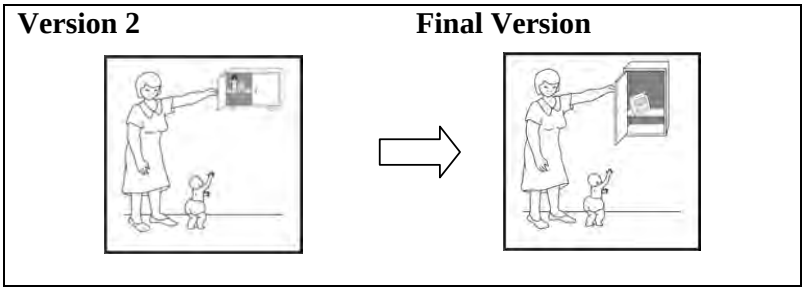


Figure 4.9 Keep all medicines out of reach of children

4.4 Conclusion

It was evident that a comprehensive iterative process was necessary in designing these pictograms. The comments and suggestions obtained from the Xhosa participants were invaluable in modifying and refining the pictograms and in ensuring their acceptability in the target population. The importance and need to use pictograms in conjunction with verbal and/or textual instructions is also evident in order to overcome any misinterpretations that may lead to improper medicine use.

CHAPTER FIVE
METHODOLOGY

5.1 Introduction

The previous chapters established the background, context and significance of this research project. The literature has shown that patients need to receive both verbal and written information about their medicines to improve their medicine-taking behaviour [5,6,136-145]. Adherence to complex therapies with multiple dosage units such as HAART has been shown to improve as a result of patient education and counselling [1,100]. Ideally, HAART requires a patient to be 100% adherent; only minimal mistakes can be tolerated since adherence has been directly correlated to therapy failure [1,15].

PILs are an effective, convenient way of conveying written information to patients about their medicines [6,8,13,138,142-144]. Consumer testing of these materials has been shown to be the best method of evaluation [11,181]. This chapter presents the aims and objectives of this research project and the methodology employed to address them.

5.2 Aims and objectives

The main aim of this study was to design, develop and evaluate a patient information leaflet (PIL) for an antiretroviral regimen. The objectives were:

1. to identify an ARV regimen likely to be used in resource-limited settings
2. to design and develop a PIL for the identified ARV regimen
3. to objectively assess readability of the PIL
4. to evaluate the format, content and general design of the PIL
5. to investigate the relationship between various demographic variables and understanding of the PIL
6. to determine whether previous medicine-taking behaviour has an influence on current perception and understanding of medicine instructions
7. to compare participant opinion of the PIL and a standard Australian CMI document containing similar ARV information.

5.3 Selection of a drug regimen

5.3.1 Phase 1

A comprehensive search of available ARV drug combinations used worldwide was conducted and this was then restricted to identifying the most popular combinations that have proven their effectiveness in resource-limited settings. The most popular regimen used in developing countries was identified as including

- two nucleoside reverse transcriptase inhibitors (NRTIs) and
- one non-nucleoside reverse transcriptase inhibitor (NNRTI).

This regimen has been popular because of having less restrictive storage restrictions, a better dosage profile and a low pill burden.

A mini, informal survey was then conducted at the March 2003 conference of the South African Association of Hospital and Institutional Pharmacists (SAAHIP) to identify the most commonly used ARVs in South African hospitals. Although ARVs were not, at that time, available in the public sector, pharmacists in the public sector were asked for their opinion on the most likely ARV regimen to be used should they become available. Results revealed that a dual NRTI backbone with an additional NNRTI were being extensively used in private hospitals.

The initial regimen chosen for this study was of Zidovudine (AZT), Lamivudine (3TC) and Nevirapine (NVP). The guidelines on finding and identifying reliable HIV and AIDS information from the Internet [308] were consulted to ensure that all the information obtained was reliable. Information on these drugs was sourced mainly from the Internet. Individual drug names were entered as the search terms using the Google search engine. Information was obtained from the manufacturers' websites as well as from accredited websites that contained patient-oriented information. The following websites were consulted:

- http://www.gsk.com – the manufacturer site for AZT and 3TC (innovator products)
- http://www.boehringer-ingelheim.com – the manufacturer of NVP (innovator)
- http://www.cipla.com - manufacturer of generic ARVs
- http://www.usp.org - patient-oriented information
- http://www.nlm.nih.gov/medlineplus.druginfo/ - patient-oriented information

- http://www.aidsmap.com - patient-oriented information
- http://www.hivinsite.usf.edu – patient-oriented information
- http://www.aidsmeds.com - patient-oriented information

The United States Pharmacopoeia-Drug Information Vol II (USP - DI) was used as the major source of information as it contains drug information intended for use by laypersons.

Relevant and appropriate information to include in the PIL was identified. This process was informed by the guidelines published in Regulation 10 of the Medicines and Related Substances Control Act, Act 101, as amended, published in April 2003 [9]. Individual profiles for each of the three drugs were composed and information common to all three drugs was extracted. Important information applying to a single drug was considered separately.

5.3.2 Phase 2

The major initiative that influenced the change of the ARV regimen during Phase 2 was a case study report published by the WHO in May 2003, on the feasibility of provision of large scale ART in resource-poor settings [132]. This case study was on the Médecins Sans Frontières (MSF) Khayelitsha township primary health care ART program, which was the first large scale pilot project that provided ART in resource-poor settings in South Africa. The regimen consisting of AZT, 3TC and Efavirenz (EFV) was being used successfully by 60% of the patients in this pilot project. Only 40% of the patients were using NVP as it was generally not very well tolerated. Though teratogenic, EFV is the NNRTI recommended for patients on concurrent TB treatment. Given that the majority of AIDS patients in South Africa also have TB co-infection, the change from NVP to EFV was necessary. Information on EFV was sourced and extracted as described previously. Table 5.1 highlights the advantages and disadvantages of the two NNRTIs.

Table 5.1 Advantages and disadvantages of NVP and EFV

Drug	Nevirapine (NVP)	Efavirenz (EFV)
Advantages	・ Can be used in pregnancy ・ Has been used for PMTCT at a large scale thus HCPs have had some experience with its use	・ May be used concurrently with TB therapy ・ Does not requires a lead - in phase ・ Fairly well tolerated ・ May be used in patients with abnormal liver function
Disadvantages	・ Cannot be used with TB treatment ・ Poorly tolerated ・ May cause severe adverse reactions thus requires a two week lead - in phase	・ Teratogenic, therefore cannot be used in pregnancy

5.3.3 Phase 3

In November 2003, the South African National Department of Health released the Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa [57]. This document contained a list of the ARV regimens to be used in the public health sector. We therefore decided to align our research closely with the guidelines in this plan, which recommended three regimen options depending on patient profile and co-infections. We altered our initially selected regimen to the first-line regimen in this plan, replacing AZT with Stavudine (d4T). The advantages and disadvantages of AZT and d4T are presented in Table 5.2.

Table 5.2 Advantages and disadvantages of AZT and d4T

Drug	Zidovudine (AZT)	Stavudine (d4T)
Advantages	・ First ARV in the market, has been extensively researched ・ Recommended for therapy initiation in treatment naïve patients ・ Can be used in pregnancy	・ May be a useful substitute for AZT for people who cannot tolerate AZT or who wish to avoid using it. ・ Crosses the blood - brain barrier. ・ Has no food restrictions, may be taken with or without food.
Disadvantages	・ Causes anaemia ・ Causes headaches and nausea; ・ To be taken with or after food in order to minimise GIT effects	・ Causes peripheral neuropathy ・ Higher incidences of lipodystrophy occurrence have been reported compared to other NRTIs ・ Need to be used with caution with other ARVs to avoid adverse effects like lactic acidosis. Other potential drug interactions still unknown.

The final regimen selected consisted of d4T, 3TC and EFV.

- Stavudine (d4T) - 40mg 1 capsule twice daily
- Lamivudine (3TC) - 150mg 1 tablet twice daily
- Efavirenz (EFV) - 200mg 3 capsules once daily

5.4 Design of the patient information leaflet

5.4.1 Content

Guidelines on the content of PILs for South Africa published in Regulation 10 of the 2003 South African Medicines and Related Substances Act, Act 101 as amended, were consulted and all the stated information requirements were included. These guidelines included no mention of the design or format of PILs. Table 5.3 presents an outline of this required information and the headings under which the relevant information was located in the PIL.

Table 5.3 PIL information and compliance with Regulation 10 guidelines

Regulation 10 requirements	**Location in PIL**
a) Scheduling status -	With the generic name (at the top)
b) Proprietary name and dosage form -	What are your medicines?
c) The composition of the medicine -	Product description
d) The approved indications and use -	What are your medicines for?
e) Instructions before taking the medicine	
Contraindications -	Before you take your medicines
Precautions -	Before you take your medicines
Warnings -	Before you take your medicines
Interactions -	Before you take your medicines
General statements -	Before you take your medicines
f) Instructions on how to take the medicine -	How should your take your medicines
Do not share your medicines -	While taking these medicines
Overdose -	While taking these medicines
g) Side effects and statement -	What are the possible side effects?
h) Storage and disposal information -	After taking your medicines
i) Presentation -	Product description
j) Identification of medicine -	What are your medicines? and Product description
k) Registration number of medicine -	Product description
l) The name, business address and telephone number of the holder of the certificate of registration	Product description
m) The date of publication of the PIL -	At the end

5.4.1.1 Format

Guidelines for the design of WMI published in the EEC [180], Australia [11], US [190] and locally [12,13] were consulted as well as research reports and reviews conducted by various researchers [4,10,168,174,211,226].

The Australian Usability Guidelines for Consumer Medicines Information (CMI) [11] provided valuable guidance as they give specific details for the format of the entire PIL. According to these guidelines, over 90% of literate consumers should be able to find the information on the CMI quickly and easily; over 90% of those who find the information should be able to understand and act on it appropriately; thus, over 81% of literate consumers should be able to use the CMI appropriately.

These guidelines assume a reasonable literacy level, which is not the case in our target African population, which has varying reading skills. The CMI format could therefore not be rigidly applied to the design of this PIL, but it was invaluable in informing the general layout of the information. The final product was a result of careful and critical shredding of these guidelines and the incorporation of ideas from other validated guidelines.

5.4.1.2 Language

Guidelines on language usage in patient information advocate the necessity to simplify all medical jargon and to avoid complex words and phrases [4,10,168,226]. Special attention was paid to ensuring the inclusion of simple words, translating medical terminology to commonly used plain language as well as using short sentences to suit people with limited reading skills. The active voice was used and most of the information was aimed at directly informing the reader about their therapy. The principles of writing in 'Plain English' were closely observed [249,280].

5.4.2 The design process of the patient information leaflet

The information on the three ARV drugs was compiled in accordance with the requirements of Regulation 10. A number of different font styles recommended by various researchers were examined and the font style and size finally used was Arial size 10. With the aid of focus groups, consisting of five Xhosa participants from the target population, the PIL was modified by changing the words, reconstructing the phrases and repositioning the information, during discussion sessions. This multistage process included eight different drafts before the final draft deemed to be satisfactory was obtained. Pictograms (Appendix A) were incorporated into the final draft that was then ready for initial testing.

The pilot PIL (Appendix B1) consisted of 2 pages. It was A-4 size and each page had 3 columns. This PIL was evaluated in a pilot study and modified accordingly to produce the final PIL (Appendix B3). The layout format of the final PIL is illustrated in Figure 5.1.

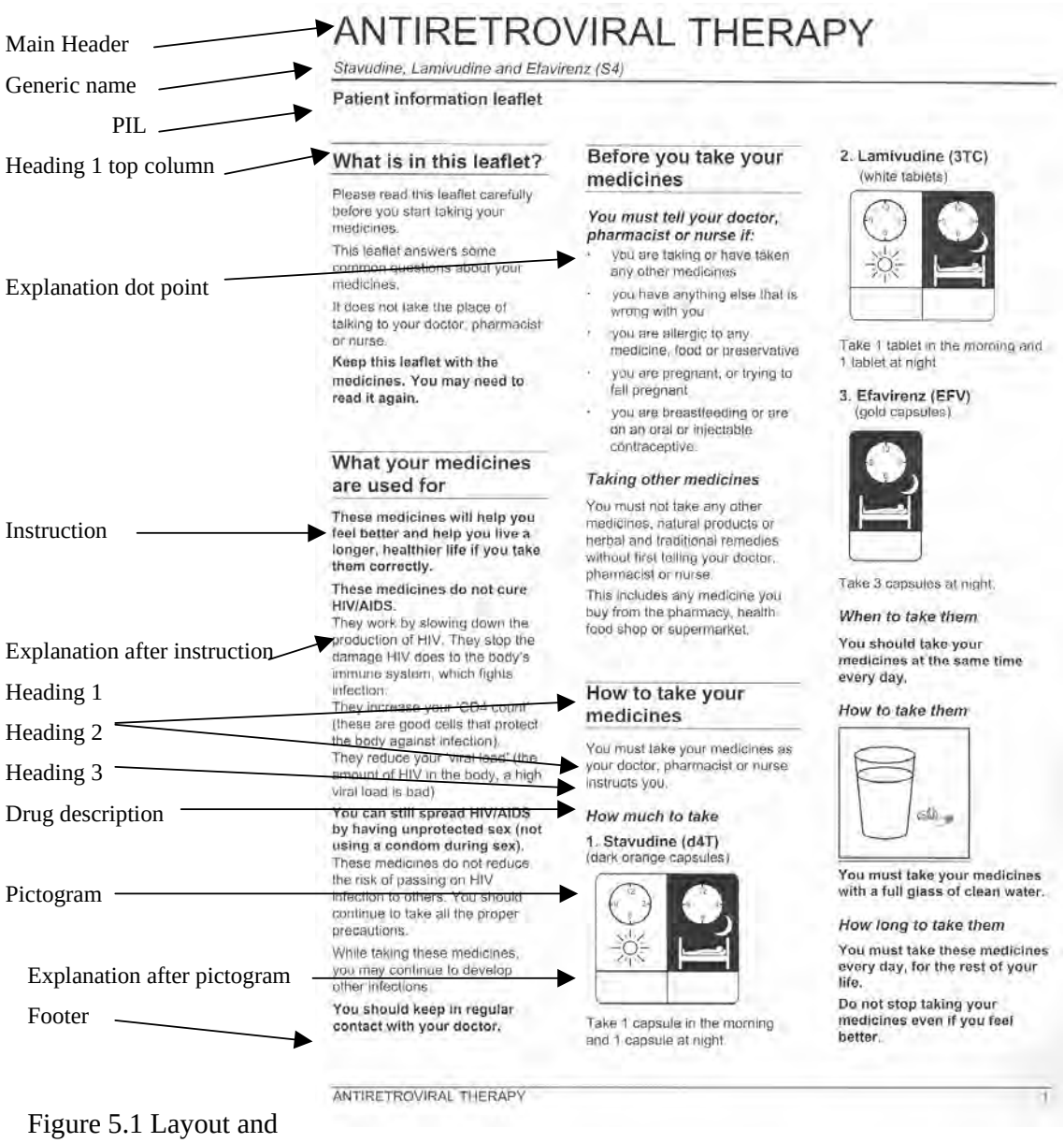


Figure 5.1 Layout and format of sections in the final PIL

Table 5.4 The layout specifications used for the PIL

- The type styles used: Arial for text and Helvetica for headings
  - The text style bold and italic
  - The text size a minimum of 10 points
- Page specifications
  - A4 tall: 210 X 297 mm tall
  - Left margin: 1.5 cm
  - Right margin: 1.5 cm
  - Top margin: 1.5 cm
  - Bottom margin: 2 cm
  - 3 columns in text section with 1 cm gap between columns
  - Column width 5.33 cm each
  - Footer at 0.78 mm away from the bottom of the page
- Type specifications
  - Main header:
  - Helvetica 28 pt on 28 pt lead, bold, flush left, space after 3 pt
  - Generic name:
  - Arial 11 pt on 11 pt lead, italic, flush left, rule before with 6 pt space after
  - PIL:
  - Helvetica 12 pt on 12 pt lead, bold, flush left, space after 9 pt
  - Heading 1 top column:
  - Helvetica 14 pt on 14 pt lead, bold, flush left, spacing: before 15 pt, after 8 pt, single line spacing
  - Explanation dot point:
  - Arial 10 pt on 10 pt lead, flush left, regular, flush left, special hanging at 0.6 cm, spacing: before 1 pt, after 4 pt, line space: exactly at 12 pt
  - Instruction:
  - Arial 10 pt on 10 pt lead, flush left, bold, flush left, spacing: before 4 pt, after 4 pt, single line spacing
  - Explanation after instruction:
  - Arial 10 pt on 10 pt lead, flush left, regular, flush left, spacing: before 0 pt, after 0 pt, line space: exactly at 12 pt
  - Heading 1:
  - Helvetica 14 pt on 14 pt lead, bold, flush left, spacing: before 32 pt, after 8 pt, single line spacing, outline level: body text
  - Heading 2:
  - Helvetica 11 pt on 11 pt lead, bold, italic, flush left, spacing: before 12 pt, after 6 pt, single line spacing
  - Heading 3:
  - Helvetica 11 pt on 11 pt lead, bold, flush left, body text, spacing: before 3 pt, after 0 pt, line space: exactly at 12 pt
  - Drug description:
  - Arial 10 pt on 10 pt lead, flush left, regular, flush left, spacing: before 0 pt, after 0 pt, single line spacing
  - Pictogram:
  - Size: height: 3.3 cm, Size range width: 3.3 – 3.7 cm, rotation 0 degrees, scale: height/weight: 90%, brightness/contrast: 50%/50%
  - Explanation after pictogram:
  - Arial 10 pt on 10 pt lead, flush left, regular, flush left, body text, spacing: before 3 pt, after 3 pt, line space: exactly at 12 pt
  - Footer
  - Arial 10 pt on 10 pt lead, flush left, regular, capital letters, spacing: before 0 pt, after 0 pt, single line spacing.

5.4.3 Design of a CMI document for ART

One of the objectives was to assess consumer opinion and acceptability of a different, more comprehensive version of ARV medicines information. The PIL designed in this study aimed at optimising readability in a population of varying reading skills. To this end, the minimum amount of information necessary to convey the required information was included. In order to compare the general opinion of this 2-page PIL with a much more comprehensive medicines information document, a document based on the Australian Usability guidelines for CMI was developed [11] for the same ARV regimen. This CMI document was A-4 size, with a total of four pages, each page consisting of three columns. The format, font size and style used were those specified in the usability guidelines [11]. This CMI document was used for comparison with our newly designed PIL (Appendix B2).

5.5 Assessment of the PIL using objective tests

Prior to consumer testing, the PIL was objectively assessed for readability and suitability. The tools used were readability formulae as well as validated readability and suitability assessment tools.

The Fry's and Flesch readability formulae and the RAIN were chosen to evaluate the readability of the PIL, and the SAM tool was applied to assess its suitability for the target population.

Fry's readability test is widely accepted in the reading literature and amongst reading professionals [10]. It is not copyrighted and correlates well with the Flesch and Dale - Chall formulae. It is not necessary to test the readability of every word and sentence in the material. A 5-step manual procedure [10] was used to determine reading level of the PIL.

Both the Flesch Ease Score scale and the Flesch-Kincaid Grade Level Index were employed to assess the readability of the PIL. For the Flesch Ease Score, the average number of words per sentence and number of syllables per word is calculated. This was done by selecting sections of the PIL and then applying a six-step process [250]. The output of this formula is a number from 0 to 100, with a higher score indicating easier

reading. The Flesch-Kincaid Grade Level formula converts the Reading Ease Score to a U.S. grade-school level.

Readability statistics can be computer-generated from Microsoft Word, which computes readability based on the average number of syllables per words and the average number of words per sentence, by assessing the entire document. The score obtained indicates the US grade school level. After the grammar check is completed in a Word document, the readability statistics are automatically displayed. The PIL was also subjected to this automatic test. The results obtained will be presented in the next chapter. In addition to the grade level, this method also checks for the number of sentences written in the passive voice that have been used in the document. This is usually under 5% for popular fiction, and can be as high as 30% in technical writing, even good technical writing.

The relevance of the applicability and reliability of the use of the US grade level measurement in an African context is uncertain. The number of years spent in school was used as an interpretation of the grade levels as there is no formula that relates directly to any of the African grade levels.

The Readability Assessment Instrument (RAIN) was also used to assess the readability of the PIL. This instrument was developed and validated for assessing the readability of patient information leaflets based on the findings of various researchers [229] and has been found suitable for use to assess the readability of medication information leaflets by Kirkpatrick *et al* [230].

A number of researchers have recommended the validated tool, the Suitability Assessment of Materials (SAM) developed by Doak *et al* [10] as an instrument to evaluate patient education materials. This tool was used to assess the suitability of the PIL in the target population. The six main factors assessed by the SAM instrument are the content, literacy demand, graphics, layout and typography, learning stimulation and motivation, and cultural appropriateness [10].

5.6 Evaluation of the PIL using consumer testing

The understanding of the PIL was assessed using the EC's guideline for PIL testing as highlighted in Section 3.2.8. [180,181]. This adopted method is termed 'consumer testing' and the aim is for 80% of participants tested to be able to both find and understand the information [180,181]. To collect this data, a research instrument was developed as described in the following section.

5.6.1 Development of the research instrument

A questionnaire consisting of 5 sections was developed (Appendix C1). The first section was aimed at obtaining demographic data such as gender, race, age, home language, educational level and employment status. Language proficiency was evaluated in isiXhosa, Kiswahili, English and any other language. This data was collected to determine communication and reading skills in the home language and in the commonly used languages in South Africa and Tanzania. Data on employment status was collected as it has been associated with the development of literacy skills, irrespective of the level of education obtained [245].

As an icebreaker, Section 2 enquired into lifestyle issues such as time of waking up and going to bed, and the favourite drink. The ability to tell time from either a clock face or a digital watch or both was also assessed; this is a basic indicator of numeracy literacy and an important skill to assess as some of the pictograms in the PIL incorporated clock faces.

Section 3 of the questionnaire aimed to evaluate the understanding of the PIL. The questions were designed based on the consumer testing methodology proposed by the EC guidelines for PIL testing. Each question consisted of two parts. The first part aimed to evaluate whether the participant could locate the appropriate information in the leaflet quickly and easily whilst the second part of the question aimed to evaluate if the participant understood the information correctly; thus each time they were asked, "Can you please tell me what it means in your own words?"

Section 4 aimed to assess acceptability of the PIL and thus it included a range of open-ended questions as proposed by the usability guidelines for evaluation of Australian CMIs

[11]. Section 5 was included to ascertain preference between the PIL and a standard CMI document containing ART information.

Approval for the study was obtained from the Rhodes University Departmental Ethical Standards Committee.

5.6.2 Development of interviewing and interpreting skills

Interviewing skills were developed initially by observing an experienced researcher conduct health-related interviews with the aid of an interpreter. Trial interviews in a related research area were then conducted in the target population under the supervision of an experienced researcher and supervisor of this project. A previously designed and validated questionnaire was used as the research tool and the interviews were conducted with the aid of an interpreter. Comments from the supervisor and the research colleague were noted.

In South Africa, which has 11 official languages, medical interpreting is quite common due to the society being both multilingual and multicultural. The constitution guarantees the right for all South Africans to be served in the language of their choice [309].

Some researchers have described interpreting as more than the oral translation of words [245,304]. It is a complex task involving the uncovering of meaning to make the message explicit to others and involves mediating between languages, cultures and people in particular contexts [245,304]. The interpreters used were from the Xhosa culture, who had isiXhosa as their home language; they were therefore of the same culture as that of the participants.

The main interpreter was a qualified teacher with tertiary education who had been previously trained by our group. The importance of reporting the exact answers given by the participants was emphasised as any deviations could potentially compromise the results. The interpreters were asked to ensure that participants were comfortable and at ease prior to commencing the interviews, they were asked not to be critical or judgemental in their communication so as to provide a safe and uncritical forum for the participants to respond to the questions, and they were requested to accurately and faithfully translate the complete communication between the interviewer and participant.

5.6.3 Evaluation of the PIL in the Pilot Study

5.6.3.1 Study site and study population

The pilot study was conducted in Grahamstown, a small town in the Eastern Cape, one of the nine South African provinces. According to the latest census report (2001), the Eastern Cape, which is the third largest province in the country, has a population of about 6.4 million, which is 14.4% of the total South African population. The Eastern Cape population consists of 87.5% Black African, 7.4% Coloured, 4.7% White and 0.3% Indian (Asian) [310].

For the pilot study, the interviews were conducted among the Xhosa population, which is one of the nine black ethnic groups in South Africa, with the highest concentration in the Eastern Cape. A large majority (83.4%) of the population in this province speak isiXhosa and this language is the second most commonly spoken home language in South Africa after isiZulu [310].

The Eastern Cape is one of the poorest provinces in the country with a high unemployment rate. An estimated 20.4% of the population aged 20 years and above are employed, 24.6% are unemployed and 55.6% are not economically active [310]. The educational qualifications of the people in this province range from 22.8% with no schooling at all, 7.4% with a primary school education and only 6.3% of the population aged 20 years and above holding a tertiary qualification [310].

The pilot study was conducted by interviewing 20 Xhosa participants of different educational levels. All participants were required to have an ability to read and understand English, and have isiXhosa as their stated home language. The interviews were conducted in Grahamstown with some participants recruited on the University campus and others from Joza Township.

5.6.3.2 The interview process

Most of these participants were fluent in English. The interviewer used the same standard approach each time. This included a greeting, after which the researcher briefly introduced herself and enquired if the person was interested in helping with the project. If a positive

response was received, they were asked if they could read in English. For those who replied in the affirmative, a time that was convenient for the interview was agreed upon. They were informed that the interview could take up to 45 minutes.

The interview commenced by first giving the participant a brief overview of the project and the reason for the interview. He/She was reassured that their intellectual ability was not being tested, as it was the PIL that was being evaluated. They were encouraged to relax and to take their time. Demographic information including their age, language proficiency, educational level and employment status was recorded. Their ability to tell time from either a conventional clock face or a digital watch or from both was determined.

The participant was then given the PIL, asked to read through it silently and to notify the interviewer once they had finished. The time they took to read the PIL was discreetly recorded using a stopwatch. Participants were then asked a number of questions concerning the information in the PIL and they were instructed to find the answers from the PIL Following this, a number of open-ended questions aimed at determining the acceptability of the PIL were asked. Participants were also encouraged to offer their comments and opinions regarding the PIL.

Participants were then handed the Australian version of the PIL, i.e. the 5-page CMI document on ART. They were asked to briefly examine the size, layout and style of the CMI document and then to compare the PIL and the CMI document in terms of size, style, presence of pictures and amount of information. Their preference between the two was also determined. At the conclusion of the interview, participants were thanked for their time and given a small honorarium (R15).

5.6.3.3 Analysis of data

A total understanding score was calculated based on the ability to locate the information for the 20 questions and correctly explain the information related to 19 of these questions. Acceptability was assessed qualitatively i.e., the responses were recorded and comments given were analysed and emergent themes extracted.

5.7 Modifications made to the research materials as a result of the pilot study

5.7.1 The questionnaire

The pilot study was invaluable in identifying problems with the existing questions and repetition in responses, and it indicated a need for additional data to be collected. In Section 1, two questions were included, which recorded how often a clinic or hospital was visited and how frequently medicines were taken (Appendix C2). This enabled any potential association between these questions and the understanding of the PIL to be explored.

It was also deemed necessary to include a sub-section evaluating the interpretation of the pictograms included in the PIL. Section 3, which dealt with locating and understanding information, was modified by combining certain questions to avoid repetition and by adding in new questions. However, the total number of questions remained at 20, which is the maximum number of questions that has been recommended for consumer testing [11,181].

In Section 4, an additional question that enquired about the language of choice in the PIL and that investigated the option of having it available in more than one language was included.

A question that enquired how the participants disposed of their unused medicines was added to the interview.

5.7.2 The PIL

The pilot study also resulted in extensive modification of the PIL, based on the comments made by the participants and observations recorded by the interviewer. Most of the participants could not locate information on how long to take the medicines and the need for lifelong, continuous use, thus the location of this information in the PIL was changed. The headings were identified as playing a major role in locating and using the information, so additional headings were included to highlight important instructions that had previously been ignored (Appendix B3).

Table 5.5 Changes made to the PIL

No changes were made to the uppermost section of the PIL.

- Heading 1: What is in this leaflet
  - No changes were made to the information under this heading.
- Heading 2: What your medicines are used for
  - Explanations on CD4 count and viral load where added by describing each of them in lay terms so as to aid the patient with an understanding of these two scientific terms.
- Heading 3: Before you take your medicines
  - An extra bullet separating breast feeding and contraception was added
- Heading 4: How to take your medicines
  - All the pictograms were left aligned;
  - Three sub - headings were added: 'how much to take', 'when to take them' and how long to take them.
    - 'How much to take' was added so as to draw more attention to the patient on how much they should take;
    - 'When to take them' was added so as to highlight the important message 'the same time everyday' in order to encourage the patient to associate their medicine taking with a particular time of the day, which may in turn reduce forgetfulness;
    - 'How to take them' was added to emphasize the information on taking with clean drinking water;
    - 'How long to take them' was added to stress that it is life - long therapy.
  - Information regarding taking the medicines after food was omitted because this instruction is important for treatment with AZT.
- Heading 5: While taking these medicines
  - Under this heading, two sub - headings,' things you must do' and 'things you must not do', were added so as to stress on the dos and don'ts that were ignored by some participants tested in the pilot study.
    - Things you must do
      - Tell your doctor if you are not taking the medicines as prescribed/instructed
    - Things you must not do
      - Do not share your medicines
      - Do not drink alcohol
- Heading 6: Possible side effects
  - No changes were made to the information under this heading.
- Heading 7: After taking your medicines
  - All pictograms were left aligned;
  - No changes were made to the information under this heading.
- Heading 8: Things to remember
  - No changes were made to the information under this heading.

5.8 Translation of the PIL into isiXhosa and Kiswahili

For the main study, the PIL was translated into isiXhosa and Kiswahili using a multistage approach involving translation, professional proofreading and back-translation. The translators were instructed to include familiar commonly used words and to avoid changing the context of the information, thus, ensuring that the meaning would remain the same. It was also emphasised that they should be cautious when translating medical-related terminology.

The PIL was translated into isiXhosa by two members of the Faculty of Pharmacy technical staff who had isiXhosa as their first language. The two isiXhosa versions of the PIL as well as the English version were then given to a professional isiXhosa language expert who compiled one isiXhosa version. In a meeting, the language expert highlighted why she had extracted the information from both isiXhosa PILs and comprehensively justified her preferred choice of words, phrases or sentences. This version was then translated back into English by two different isiXhosa speakers. They were asked to systematically communicate the meaning of each phrase and sentence to the researcher. All the sentences and words that did not match were reconstructed and compared to the English PIL with the aid of the language expert. The final isiXhosa version of the PIL was formatted to look similar to the English version.

The translation into Kiswahili followed a similar process. As the researcher is fluent in both Kiswahili and English, she independently translated, proofread and back translated the PIL. Two secondary level Kiswahili teachers who were fluent in English and Kiswahili initially translated the English PIL. The two translations were compiled into one document and submitted to translation experts for professional proofreading. The Kiswahili PIL was then translated back into English by two different individuals who were fluent in both languages and the final version formatted to look similar to the English version.

5.9 Evaluation of the PIL in the Main Study

For the main study, a standard interview protocol was followed to ensure consistency in the interview process across the two populations in which the PIL was to be evaluated.

5.9.1 Study sites and study population

The study was conducted in two different parts of Africa; Grahamstown, South Africa and Dar-es-Salaam, Tanzania.

Study site and study population for the South African arm of the study have been described previously (Section 5.6.3.1). A minor difference was that these interviews were conducted at Phumlani, Extension 2, in Joza Township, and a total of 60 Xhosa participants of different educational levels who could read in either isiXhosa or English were interviewed.

Tanzania is one of the poorest countries in the world. Dar-es-Salaam is one of the 26 regions of Tanzania and is made up of three mainly urban municipalities. The total Tanzanian population is estimated as 36 million [311]. Dar-es-Salaam is the largest city with an estimated population of 2.5 million people and is the commercial and economic centre and former capital city of Tanzania [311]. Almost 7% of the Tanzanian population lives in Dar-es-Salaam. The population of mainland Tanzania is 99% native African, of whom 95% are Bantu consisting of more than 130 tribes, and the other 1% consisting of Asians, Europeans, and Arabs [312].

The two main languages used in Tanzania are Kiswahili and English. Kiswahili is the national as well as the official language of Tanzania and is spoken by almost all Tanzanians. English is the official, primary language of commerce, administration and of higher education [312]. It is estimated that 78.2% of the total Tanzanian population aged 15 and over are literate in that they can read and write Kiswahili, English or Arabic [312].

Approval for this arm of the study was obtained from the Muhimbili University College of Health Sciences, School of Pharmacy Departmental Ethical Standards Committee.

The study population comprised 60 Tanzanian participants of different tribes and educational levels, who were interviewed in the Sinza B ‘Kwa Remy’ area, a semi-urban residential area in Dar-es-Salaam. All participants were required to be able to read either Kiswahili or English. They all stated that Kiswahili was the language they used daily, irrespective of their tribes or local vernaculars.

5.9.2 Recruitment of participants

Participants were randomly selected by the recruiters who were briefed on how to approach and recruit participants using a standard approach. They were told to convey a greeting and introduce themselves, after which they were to invite a potential candidate to participate. They were told to ask the participant if he/she could read in any of the languages in which the PIL was available i.e. English, isiXhosa and Kiswahili. Once a positive response was obtained, the recruiters established a time for the interview at the convenience of the participant.

5.9.3 The interview process

The interviews for the South African arm of the study had to be conducted with the aid of an interpreter, as the researcher could not speak isiXhosa. The interview protocol and procedure were clearly described to the interpreter and was similar to that used in the pilot study.

The same approach was used each time when commencing the interview. The interpreter was instructed to say the following:
Greetings: “Good morning/afternoon”.
Introduction: “my name is ….. and I stay in….. here in Phumlani. Here with me is Betty Mwingira from the Faculty of Pharmacy at Rhodes University. She is doing a project for her studies and needs your help in testing an information leaflet she has developed on the AIDS drugs. But we first need to know if you can read in isiXhosa or English, as you will need to read through the leaflet.” If the participant agreed to participate, the interpreter would then continue to say. “Betty needs to find out if people will understand the leaflet and if the information will help them understand better and remember their medicines instructions. The interview will take about 45 minutes, so please make yourself comfortable, and remember we are not testing you but the leaflet. Before you read the leaflet, we would first like to ask you a few questions about yourself”. At this point the interviewer started asking the questions as per the questionnaire and the interpreter translated all communications.

For the Tanzanian arm of the study, I conducted all the interviews as I am fluent in Kiswahili. The same interview protocol as described above was followed, apart from minor changes. Greetings: “How are you today?”
Introduction: “My name is Betty, I study in South Africa. For my Masters, I have developed a leaflet with information on the AIDS drugs and I need to know if it is understandable. That is why I need your help, to read it and then to tell me what you think about it. “I first need to know if you can read in Kiswahili or English”…….. “The interview will take about 45 minutes, so please make yourself comfortable, and remember I am not testing you but the leaflet. Before you read the leaflet, I would first like to ask you a few questions about yourself”. The interview then proceeded as outlined above. These interviews were all conducted in Kiswahili.

Any additional comments were recorded. Participants were then thanked for their time and given a small honorarium (R 20/TSH 3 000 equivalent to R 20) at the end of the interview.

5.10 Analysis of data

The SPSS Statistical software (Version 12) programme was used for analysis of the data. Frequency data were obtained for all variables. A total understanding score was calculated based on the ability to locate the information for the 20 questions and correctly explaining the information related to 19 of these questions. The aim was for 80% of the participants tested to be able to both locate and understand the information in the PIL. A regression analysis was conducted to investigate potential relationships between the understanding of the PIL and the variables of gender, age, education, employment, medicine-taking behaviour and self-reported ease in reading the PIL. The level of significance was set at 5%. The data were also analysed qualitatively by extracting emergent themes from the comments given by the participants. Acceptability of the PIL was also assessed as described in Section 5.6.3.3.

CHAPTER SIX
RESULTS

6.1 Introduction

In order for any kind of written information to be read and understood by its users, it must be well presented, readable and evaluated for understanding and acceptability [4,10,11,13,181]. The suitability of written patient educational materials may be dependent on a number of factors such as educational level, literacy level, socio-economic status, health status, perceptions and cultural background of the target population [10,168,199]. Studies have indicated the need to involve the end-user (consumer) of the material in the designing and evaluation processes [11,13,181]. Consumer testing of PILs is of great value in highlighting deficiencies in the information and in identifying possible solutions for the problem areas [11,181]. This enables the designer to effectively improve the PIL to better suit the target population [11,181].

This chapter presents the findings of readability, suitability and consumer testing of PILs for HAART.

6.2 Readability and suitability results

According to Fry's readability test, the PIL had a reading level suitable for Grade 7 learners. This implies that if the PIL was to be given to scholars, those in Grade 7 and above would theoretically be able to read the information in the PIL and would understand between 50% and 75% of the information.

On the Flesch Reading Ease score chart, with 10.91 words per sentence and 1.38 syllables per word, the PIL scored in the 'Fairly Easy' category. The Flesch Reading Ease score obtained from the Flesch formula was 78.5, which also categorises this material as suitable for 7^{th} grade readers.

From the computer generated reading statistics (Table 6.1), 9% of the sentences in the PIL were written in the passive voice. The Flesch Reading Ease score was found to be 65.7 and the Flesch–Kincaid grade level was 7, meaning that it is suitable for grade 7 learners.

All the three formulae used to calculate the readability of the PIL found it to be suitable for grade 7 learners. An exception was the computer generated Flesch Reading Ease score of 65.7 that translates to 8th and 9th grade level, higher than the result obtained using the formula manually. This may be attributed to the fact that the manual method only evaluated three selected sections of the PIL whereas the computerised test evaluated the whole document. These findings support the opinion of some researchers that more than one readability test should be used to evaluate the material [10,216].

Table 6.1 Readability statistics

Feature		Amount
Counts		
	Words	539
	Characters	2654
	Paragraphs	55
	Sentences	32
Averages		
	Sentences per paragraph	1.4
	Words per sentences	11.8
	Characters per word	4.5
Readability		
	Passive sentences	9%
	Flesch Reading Ease	65.7
	Flesch–Kincaid grade level	7.0

Application of the RAIN test to the PIL resulted in a score of 82% (Table 6.2), which classifies the material as readable [229,230]. This exceeded the recommended cut-off score of 80% to ensure readability.

Table 6.2 Results of the RAIN test

Criterion	Presence
Global coherence	Yes = 1
Local coherence	Yes = 1
Unity	Yes = 1
Audience appropriateness	Yes = 1
Adjunct questions	No = 0
Writing style	Yes = 1
Illustrations	Yes = 1
Typography	
Font style	Yes = 1
Font size	Yes = 1
Colour	No = 0
Titles highlighted	Yes = 1
Total score	9/11
Percent of overall criteria met	82%

The SAM analytical assessment tool [10] was used to measure the suitability of the PIL for the target population (Table 6.3). The PIL scored 94.4%, which categorises it in the "superior" material rating.

Table 6.3 SAM scoring sheet

Factor to be rated	Score	Comments
CONTENT		
Purpose is evident	2	Information under what is in this leaflet
Content about behaviours	2	How to take medicines
Scope is limited	2	Yes, medicine instructions only
Summary or review included	2	Things to remember
LITRACY DEMAND		
Reading grade level	1	7th grade level (6 – 8 years of school)
Writing style, active voice	2	Active voice, easy text
Vocabulary uses common words	2	Terms explained
Context is given first	2	Consistent
Learning aids via "road signs"	2	Headings and sub-headings
GRAPHICS		
Cover graphic shows purpose	N/A	No cover
Type of graphics	2	Tested pictograms
Relevance of illustrations	2	Tested pictograms
List, tables, etc. explained	N/A	No tables
Captions used for graphics	2	Pictograms with explanation
LAYOUT AND TYPOGRAPHY		
Layout factors	2	3 columns, black print on white paper
Typography	1	Mixed caps and small letters, with bold text
Subheads ("chunking") used	2	Sub-headings present with enough information
LEARNING STIMULATION AND MOTIVATION		
Interaction used	N/A	One way instructions
Behaviours are modelled and specific	N/A	Information on medicines
Motivation, self - efficacy	2	Instructions organised in sub - headings
CULTURAL APPROPRIATENESS		
Match in logic, language, experience	2	With information on HIV transmission
Culture image and examples	2	Pictograms pre-tested in target population
Total SAM score	34	
Total possible score:	36	Percent score = 94.4%

All methods used objectively evaluated the PIL as 'theoretically' readable by and suitable for use in the target population.

6.3 Consumer testing of the PIL (Pilot study)

6.3.1 Demographic results

Twenty Xhosa participants were interviewed. Demographic data are presented in Table 6.4. There was a fairly even distribution of males to females. Just over half (55%) of the

participants had 11 years or less of formal education, 45% had between 5 - 11 years of schooling and none had less than five years of formal education. Nine of the 20 participants who had completed 12 years of schooling used the headings in the PIL appropriately to locate the information. Eleven participants had less than 10 years of formal education; of these, three were fairly good readers and nine did not use the headings to guide them in locating the information in the PIL.

Table 6.4 Demographic results (N = 20)

Demographic parameters		**Participants, N (%) (N = 20)**
Gender	Male	11 (55.0)
	Female	9 (45.0)
Age	< 21	1 (5.0)
	21 - 40	16 (80.0)
	41 - 65	3 (15.0)
Number of years in school	0 - 5	0 (0.0)
	6 - 11	11 (55.0)
	> 11	9 (45.0)
Language proficiency		
Home language:	Listen only	0 (0.0)
	Listen and speak	0 (0.0)
	Listen, speak and read	20 (100.0)
English:		
	Listen only	0 (0.0)
	Listen and speak	0 (0.0)
	Listen, speak and read	20 (100.0)
Other:		
	Listen only	1 (5.0)
	Listen and speak	0 (0.0)
	Listen speak and read	4 (20.0)
Employment	Yes	11 (55.0)
	No	9 (45.0)
Occupation	Clerical	6 (30.0)
	Domestic	3 (15.0)
	Unemployed	9 (45.0)
	Other	2 (10.0)

All the participants (100%) had isiXhosa as their home language. In assessing language proficiency the ‘Listen only’ category implies an ability to understand the spoken language, but not respond in this language. The ‘Listen and speak’ category assumes the ability to understand and communicate verbally, but not to read the language. The third category ‘Listen, speak and read’ indicates the highest level of proficiency with the ability to communicate and to read in that language. All the participants could listen, speak and read both isiXhosa and English. Only five of the 20 could communicate in a third language, with

one participant being able to understand but not speak isiZulu, whereas the remaining four could read in one of the other official South African languages, two in Afrikaans and the other two in isiZulu. Of the twenty, just under half (45%) were unemployed.

6.3.2 Time taken to read the PIL

The average time taken to read the PIL was 9 minutes. The majority of the participants (55%) took between 5 - 10 minutes to read the PIL (Table 6.5). Only one participant took more than 15 minutes to read it. Interestingly this participant had between 6 - 11 years of schooling, was unemployed and overall understood the information in the PIL very well (95%).

Table 6.5 Time taken to read the PIL

Time taken to read PIL (minutes)	**Participants, N (%) (N = 20)**
< 5	3 (15.0)
5 - 10	11 (55.0)
10 - 15	5 (25.0)
> 15	1 (5.0)

6.3.3 Understanding of the PIL

Of the 20 questions asked about the information in the PIL, four did not achieve the EC target of 80% of participants correctly locating and understanding the information (Table 6.6). Question 8 investigated understanding of the influence of medicines on the viral load. Many of the participants indicated that they did not understand the term ‘viral load’ which accounts for the lower results of 75% and 70% for location and understanding respectively. The lowest result was obtained for Question 12, which asked about the duration of therapy. Only 30% of the participants were able to locate it, which may be attributed to its position in the PIL, as it was not bulleted and it appeared after another instruction. This indicated the need for a modification in layout.

Table 6.6 Number (%) of participants correctly locating and understanding information in the PIL

Questions		Participants, N (%) N = 20
1. Using the leaflet, can you tell me the name of these medicines?	Located	20 (100.0)
2. Can you describe the medicines?	Located	19 (95.0)
3. Can one still spread HIV/AIDS while taking these medicines?	Located Understood	17 (85.0) 16 (80.0)
4. If you buy any medicine from a health shop or a traditional healer, what should you do before you take it?	Located Understood	19 (95.0) 19 (95.0)
5. According to the leaflet, how many times a day must you take Stavudine (d4T) capsules?	Located Understood	20 (100.0) 20 (100.0)
6. Looking at the leaflet, does it tell you what to do if you miss a dose of your medicines?	Located Understood	19 (95.0) 19 (95.0)
7. Suppose you start getting a fever, headaches and feel confused while taking these medicines. Does the leaflet tell you what to do?	Located Understood	18 (90.0) 18 (90.0)
8. What do these medicines do to the viral load?	Located Understood	15 (75.0) 14 (70.0)
9. What does the leaflet tell you to do if you take too much of these medicines by mistake?	Located Understood	20 (100.0) 19 (95.0)
10. Do these medicines cure HIV/AIDS?	Located Understood	17 (85.0) 17 (85.0)
11. According to the leaflet, if you are taking any other medicines, what should you do before taking these medicines?	Located Understood	20 (100.0) 20 (100.0)
12. How long do you have to take these medicines for?	Located Understood	16 (30.0) 17 (35.0)
13. According to the leaflet, if you have any allergies, what should you do before taking these medicines?	Located Understood	19 (95.0) 19 (95.0)
14. Does the leaflet tell you how many of Efavirenz (EFV) capsules you should take each time?	Located	20 (100.0)
15. Suppose you have been feeling better for the past month; Can you stop taking your medicines?	Located Understood	12 (60.0) 12 (60.0)
16. What should you do with left over medicines?	Located Understood	11 (55.0) 10 (50.0)
17. Suppose you start feeling weak and tired all the time while taking these medicines. Does the leaflet tell you what to do?	Located Understood	19 (95.0) 19 (95.0)
18. Does the leaflet tell you how to store these medicines?	Located Understood	20 (100.0) 20 (100.0)
19. Is there any advice in this leaflet about sharing your medicines with someone else who has HIV/AIDS?	Located Understood	19 (95.0) 19 (95.0)
20. If you want more information about your treatment and the medicines you are taking; Is there any information in this leaflet regarding who to talk to?	Located Understood	16 (80.0) 16 (80.0)

shading indicates questions that failed to achieve the target 80% overall understanding

Question 15 was located and understood by less than two thirds (60%) of the participants. This asked about the need to continue with taking medicines once the patient felt much better. This is an extremely important aspect of ART and it is crucial that there is excellent understanding of this point. As such, this information needed modifying. Only approximately half of the participants located (55%) and understood (50%) Question 16, which deals with disposal of unused medicines.

From closely observing the participants after asking the questions, I identified that they found the information required to answer Questions 3, 8, 12, 13 and 16 difficult to locate. This may be attributed to the following factors:

- location of words/phrases with no bullets was difficult especially the ones just after the pictograms
- more highlighting was required so as to make important points standout
- the order of the information was not easy to follow, highlighting a need for the inclusion of more sub-headings.

The overall percentage understanding score that was a composite of both locating and understanding the information was divided into 5 categories (Table 6.7). Three participants (15%) had a score of 100%, which means that they located and understood all the information in the PIL.

Table 6.7 Overall understanding of the PIL

% Understanding score	**Participants, N (%) N = 20**
< 60%	1 (5.0)
60 - 80%	6 (30.0)
81 - 94%	3 (15.0)
95%	7 (35.0)
100%	3 (15.0)

Only one participant (5%) had a total score of less than 60%. Although this particular participant had a reasonable educational level (6 - 11 years), she ignored the headings in the PIL but claimed that it was easy to read (falsely as it appears). The average rate of overall understanding of the PIL was 85%, thus the PIL was generally well understood in this group with varied reading skills.

6.3.4 Acceptability of the PIL

Results on acceptability of the PIL are presented in Table 6.8.

Table 6.8 Acceptability of the PIL

Questions	Response	Participants, N (%) (N = 20)
Readability		
1. How easy was it to read this leaflet?	Easy	8 (40.0)
	Average	9 (45.0)
	Difficult	3 (15.0)
2. Is the writing large enough?	Yes	19 (95.0)
	No	1 (5.0)
3. What do you think of the length of the sentences?	Too long	1 (5.0)
	Right	19 (95.0)
	Too short	0 (0.0)
4.Is there enough space between the lines?	Too wide	2 (10.0)
	Right size	17 (85.0)
	Too small	1 (5.0)
Amount of information		
5. If you had just started taking these medicines and this was all the information you were given about them, do you think it is enough?	Yes	14 (70.0)
	No	6 (30.0)
Pictograms		
6. Do you like having pictures in the leaflet?	Yes	20 (100.0)
	No	0 (0.0)
7. Do you think the pictures will help you understand and recall the information better?	Yes	20 (100.0)
	No	0 (0.0)
Words in the text		
8. Are there any words in the text that you did not understand?	No	6 (30.0)
	Yes, a few	11 (55.0)
	Yes, many	3 (15.0)
PIL size preference		
9. Is the size of the leaflet ok?	Yes	18 (90.0)
	No	2 (10.0)
10. What size would you prefer the leaflet to be?	Original PIL	8 (40.0)
	1 sheet - A-4	6 (30.0)
	1 sheet - A5	2 (10.0)
	Z-fold	4 (20.0)
Extra comments		
11. Did you like anything in particular about this leaflet?	Yes	17 (85.0)
	No	3 (15.0)
12. Is there anything else about this leaflet that we haven't talked about which you'd like to mention?	Yes	10 (50.0)
	No	10 (50.0)

Most of the participants found the leaflet to be either easy or of average difficulty to read (85%). Only three of the 20 (15%) found it difficult to read. Only one participant said the writing was not large enough and the sentences were too long. Most of the participants (75%) felt there was enough space between the lines. When questioned about the amount of information included in the PIL (Question 5), 70% of the participants felt it was sufficient to assist them in taking these medicines correctly.

All the participants (100%) approved of having pictograms incorporated into the leaflet (Question 6) and this agrees with findings from previous studies [83pt]. They all felt that the pictograms would help them understand and recall the information (Question 7). The participants also stated that they liked the presence of pictograms because they clearly illustrated the instructions and that they would aid even poor readers in understanding the information.

Most of the participants were happy with the size of the leaflet (Question 9). The majority (70%) preferred an A-4 size PIL because it was big enough; of these, eight preferred the 2-page PIL because it is easy to read, and six preferred the 1-page PIL, as it was less bulky.
Four participants (20%) stated that they would prefer a Z-fold PIL because it was small and easy to carry and store, and the folds helped with following the information in the PIL. Two participants stated that they would prefer the A-5 size PIL as it was small and easier to handle (Question 10).

Miscellaneous aspects of the PIL that elicited positive comments included the presentation of the information, the style of the PIL and the incorporation of pictograms in the text. Half of the participants (50%) had additional comments that were of value in aiding the improvement of the PIL. A summary of comments follows:
Comments on the PIL:

- no need to include the product description section
- the PIL should be in the patient's language of choice (the pilot PIL was in English only)
- a need to have coloured pictures of the actual medicines on the pictograms to help with identification.

Comments on the questionnaire:

- two participants highlighted the need to include a question on alcohol use as many people in this population engage in social drinking. They stated that it would be a good idea to ensure that the information on alcohol use is clearly stated and is understood, so that patients are reminded of the dangers of alcohol to their health.

The questions in the questionnaire were rephrased to improve their clarity based on this feedback.

In terms of the understanding of individual words contained in the PIL (Question 8), just under a third (30%) claimed to have understood all the words, whereas three participants (15%) admitted to not having understood many words. The identified problem words and the incidence of their lack of understanding are presented in Table 6.9.

Table 6.9 Words in the PIL not understood by the participants

Words	**Number of participants N = 20**
Allergy	1
ART	1
Burning	2
CD4 count	3
Chills	3
Confusion	4
Contraceptive	2
Diarrhoea	5
Drug names	6
Fever	1
Flu-like symptoms	1
Immune system	4
Indigestion	4
Injectable	1
Nausea	10
Numbness	11
Pharmacist	4
Precautions	3
Preservative	1
Product description	6
Side effects	4
Skin rash	1
Tingling	13
Viral load	13

shading indicates words not understood by more than half of the participants

The drug names Stavudine, Lamivudine and Efavirenz were explained to the patient as being just names like a person's name and therefore there was no need to understand them.

The terms ‘viral load’, ‘CD4 count’ and ‘Antiretroviral Therapy’ were briefly described in the PIL and participants were told they are HIV-related words and fairly new medical terms. Participants were told that most patients on or to be given ARVs are comprehensively educated prior to the commencement of therapy and most of the terminology becomes familiar to them. One of the participants who had some experience of taking ARVs confirmed this. This participant stated that the PIL was clear and would benefit PLWHAs on ARVs. The other words listed, especially the side effects (‘nausea’, ‘tingling’ and ‘numbness’) had no other substitutes, thus it was hoped that they might be understood if they are presented in the participants’ home language. Many participants referred to a ‘Pharmacist’ as a ‘Chemist’ (the term mostly used by this population).

6.3.5 Comparison of the PIL with the CMI document

When comparing preferences between our 2-page PIL and the standard 4-page Australian CMI document which had been developed for ART, the PIL was overwhelmingly preferred (Table 6.10).

Table 6.10 Results for comparison of the PIL with the CMI

Variable	**Participants, N (%) (N = 20)**	
	PIL	**CMI**
Print size	18 (90.0)	2 (10.0)
Font style	16 (80.0)	4 (20.0)
Length of the sentences	19 (95.0)	1 (5.0)
The space between the lines and white spaces	18 (90.0)	2 (10.0)
The number of pages	18 (90.0)	2 (10.0)
The presence/absence of pictures	20 (100.0)	0 (0.0)

All the participants thought that the PIL was easier to read as compared to the CMI document. Of the 20 participants, 11 (55%) stated that they would like to receive a 1-page document, whereas eight (40%) said they would prefer a 2-page document. Only one participant stated that they preferred a document with more than two pages. Of interest was the desire of 70% of the participants to initially receive basic information such as that in the PIL, but to then receive more comprehensive information such as that included in the CMI document later during future visits.

The results generated from the pilot study were invaluable in highlighting deficiencies in both the PIL and questionnaire design. The comments given, suggestions made and

problems highlighted by the participants, together with the observations made by the researcher, were used to guide the refinement of the questionnaire and the modification of the PIL.

6.4 Consumer testing of the PILs (Main study)

For the main study, a total of 120 participants were interviewed. The inclusion criteria were for a participant to have one of the African languages (i.e. isiXhosa or Kiswahili) as their home language and have the ability to read in their home language or in English.

6.4.1 Language of materials used

The PIL was available in English, isiXhosa and Kiswahili. The language the participants chose to read is presented in Table 6.11.

Table 6.11 Language of materials used

Language of materials	Participants, N (%) N = 120
English	18 (15.0)
IsiXhosa	42 (35.0)
Kiswahili	60 (50.0)

All the Tanzanian participants (50%) read the Kiswahili leaflet and 35% of the South African participants read the isiXhosa leaflet. The remaining 15% of the South African participants read the English version, although they were literate in isiXhosa. Some stated that they were more comfortable in English as they used it in their studies and at work, and that they preferred to read in English, as most of the words are better and more straightforward compared to isiXhosa. One participant said he read the English PIL because isiXhosa tends to have difficult words.

6.4.2 Overall demographic characteristics

The demographic results of the 120 participants are presented in Table 6.12. Of the 120, half of the participants (N = 60) were interviewed in Dar-es-Salaam, Tanzania, and the other half (N = 60) in Grahamstown, South Africa. There was a relatively even distribution of males and females. This can be attributed to the fact that the recruiters were instructed to invite an even number of participants of each gender.

Table 6.12 Demographic characteristics (N = 120)

Demographic Parameters	Participants, N (%)		
	Overall N = 120	**South Africa N = 60**	**Tanzania N = 60**
Gender			
Male	57 (47.5)	30 (50.0)	27 (45.0)
Female	63 (52.5)	30 (50.0)	33 (55.0)
Age			
< 21	21 (17.5)	3 (5.0)	18 (30.0)
21 - 40	84 (70.0)	48 (80.0)	36 (60.0)
41 - 65	15 (12.5)	9 (15.0)	6 (10.0)
> 65	0 (0.0)		
Home language:			
IsiXhosa	60 (50.0)	60 (100.0)	0 (0.0)
Kiswahili	60 (50.0)	0 (0.0)	60 (100.0)
Language proficiency			
Home language:			
Listen only	0 (0.0)	0 (0.0)	0 (0.0)
Listen and speak	0 (0.0)	1 (1.67)	0 (0.0)
Listen, speak and read	120 (100)	59 (98.3)	60 (100.0)
English:			
None	59 (49.1)	2 (3.3)	43 (71.8)
Listen only	1 (0.8)	1 (1.67)	13 (21.6)
Listen and speak	15 (12.5)	15 (25.0)	0 (0.0)
Listen, speak and read	45 (37.5)	42 (70.0)	4 (6.7)
Other language:			
None	100 (83.3)	46 (76.7)	54 (90.0)
Listen only	4 (3.3)	4 (6.7)	0 (0.0)
Listen and speak	4 (3.3)	3 (5.0)	1 (1.7)
Listen, speak and read	12 (10.0)	7 (11.7)	5 (8.3)
Number of years in school			
0 - 5	14 (11.6)	11 (18.3)	3 (5.0)
6 - 11	66 (55.0)	29 (48.3)	37 (61.7)
> 11	40 (33.3)	20 (33.3)	20 (33.3)
Employment[1]			
yes	57 (47.5)	18 (30.0)	39 (65.0)
no	63 (52.5)	42 (70.0)	21 (35.0)
Occupation			
clerical	11 (9.2)	8 (13.3)	3 (5.0)
domestic	2 (1.6)	0 (0.0)	2 (3.3)
mechanic	4 (3.3)	2 (3.3)	2 (3.3)
shop assistant	4 (3.3)	2 (3.3)	2 (3.3)
hospital worker	1 (0.8)	1 (1.67)	0 (0.0)
self-employed	22 (18.3)	5 (8.3)	17 (28.3)
unemployed	54 (45.0)	37 (61.7)	17 (28.3)
other	22 (18.3)	5 (8.3)	17 (28.3)

[1] Significant difference between the two groups ($p < 0.05$)

Our target population was black Africans from these two regions of Africa. The majority of the participants (70%) were from 21 - 40 years of age, 12.5% were aged from 41 - 65 and

17.5% were below 21 years of age. Of the 120 participants, 50% had Kiswahili as their home language and the other half had isiXhosa. Language proficiency was measured as described in Section 6.3.1. As can be observed, very few of the Tanzanian participants were fluent in English. There were no significant differences between the two groups with respect to gender, age, number of years in school and the frequency of hospital visits. The only significant difference was in their employment status ($p = 0.000124$).

6.4.2.1 Demographic characteristics of the Tanzanian participants

All the 60 participants interviewed were black Tanzanians of different tribes. There was an almost even distribution of males (45%) to females (55%). The majority of the participants (60%) were aged from 21 - 40 years. Kiswahili was the home language of all the participants; they could all listen, speak and read it and they all chose to read the Kiswahili PIL. A majority (61.7%) of the participants had between 6 - 11 years of schooling with 30 participants having completed primary school education (standard 7), 21 of whom were good readers. Only three participants had less than five years of schooling, two of whom were poor readers. A total of 27 participants had secondary school education and were all good readers. Overall, 47 participants were good readers, 40 of whom used the headings in the PIL appropriately to locate the information. Seven participants, who were poor readers, did not use the headings in the PIL appropriately. Fifteen of the participants read the drug name abbreviations in English.

Of the 31 participants who had a job, 13 were self-employed; this is a common thing in most residential areas, since most of the essential and basic items that residents need can be obtained from the surrounding area in local kiosks and tuck shops at any time of the day. Being self-employed, these participants had flexible working hours and willingly agreed to participate. All the participants were from Sinza area, a majority from Sinza B. Most took medicines infrequently and only two participants were on chronic medicines (Table 6.13).

6.4.2.2 Demographic characteristics of the South African participants

Of the 60 participants interviewed in Phumlani, 30 were male and the other 30 were female. All the participants in this group were black Xhosas and had isiXhosa as their home language. Eighty per cent of the participants were aged from 21 - 40years. Of the 60

participants, 11 (18.3%) had less than five years of schooling, of these, five were poor readers and all but one did not use the headings in the PIL to help locate the information. Twenty (33.3%) participants had more than 11 years of formal education. Almost all the participants 56 (93.3%) were good readers, 39 of whom also used the headings on the PIL appropriately to locate the information. Nineteen participants read the drug name abbreviations in English.

In this group, only 18 participants were employed and five participants (8.33%) were self-employed; over half (61.7%) were unemployed. This is in line with the high unemployment rate in the Eastern Cape, which is estimated at 32.5% [308].

Seven of the participants were on chronic daily medicines (Table 6.14). Nine said they never take medicines as they just drink lots of water when they have a minor ailment such as a headache (Table 6.13). There was a significant difference in the medicine-taking frequency between the two populations ($p = 0.000401$).

Table 6.13 Results of the reported health-related characteristics

Characteristics	**Participants, N (%)**		
	Overall	**South Africa**	**Tanzania**
	N = 120	**N = 60**	**N = 60**
Frequency of visit to clinic/hospital			
monthly	18 (15.0)	14 (23.3)	4 (6.7)
every 2 months	28 (23.3)	10 (16.7)	18 (30.0)
every 6 months	30 (25.0)	16 (26.7)	14 (23.3)
once per year	24 (20.0)	11 (18.3)	13 (21.7)
never	20 (16.6)	9 (15.0)	11 (18.3)
Frequency of medicine taking[1]			
every day	9 (7.5)	7 (11.7)	2 (3.3)
often	29 (24.1)	21 (35.0)	8 (13.3)
not very often	69 (57.5)	23 (38.3)	46 (76.7)
never	13 (10.8)	9 (15.0)	4 (6.7)

[1] Significant difference between the two groups ($p < 0.05$)

6.4.3 Understanding of pictograms

The interpretation and understanding of the six pictograms (Appendix A) incorporated into the PIL was recorded (Table 6.14). There were no significant differences in the interpretation of the pictograms across the two groups for all except one of the pictograms.

6.14 Correct interpretation of pictograms

Pictogram number and meaning	Participants, N (%)		
	Overall N = 120	**South Africa N = 60**	**Tanzania N = 60**
1. Take medicines twice daily	114 (95.0)	58 (96.7)	56 (93.3)
2. Take medicines once daily	115 (95.8)	58 (96.7)	57 (95.0)
3. Take medicines with a glass of water	120 (100.0)	60 (100.0)	60 (100.0)
4. Do not take alcohol while taking these medicines	119 (99.2)	60 (100.0)	59 (98.3)
5. Keep all medicines in a cool dry place, away from heat and direct sunlight	101 (84.2)	55 (91.7) [2]	46 (76.7) [2]
6. Keep all medicines out of reach of children	120 (100.0)	60 (100.0)	60 (100.0)

shading indicates questions that failed the ANSI 85% correct criterion
[2] Significant difference in interpretation of pictogram ($p < 0.05$)

- Pictogram 1. Take medicines twice daily

  This pictogram appeared twice in the PIL. It was generally well understood by 95% of the participants. Those who did not understand it were unable to recognise the sun and the moon as day and night. Some recommended having the words ‘day’ and ‘night’ written on this pictogram.

- Pictogram 2. Take medicines once daily

  Understanding of this pictogram was very high (95.8%). Some of the participants who misunderstood this pictogram said that it showed an AIDS patient sleeping on a bed about to die and did not associate the image with taking medicines. One participant was concerned as she stated that the man in bed, flat on his back, looked liked a corpse and it would be better if he were shown facing sideways to represent a sleeping figure.

- Pictogram 3. Take medicines with a glass of water

  This pictogram was understood by all the participants (100%).

- Pictogram 4. Do not take alcohol while taking these medicines

  This pictogram was understood by 99.2% of the participants. The one participant who did not understand it interpreted it as ‘do not keep medicines in bottles’. Another participant suggested that ‘this is alcohol’ be written on this pictogram.

- Pictogram 5. Keep all medicines in a cool dry place, away from heat and direct sunlight
  This pictogram was understood by 84% of the participants, the lowest score. It just failed to reach the ANSI 85% correct criterion. Some of the misinterpretations included: the picture shows sunrays and a dirty place therefore the medicines should be kept in a clean place/not in the fridge/not in the toilet/one should not smoke or expose themselves to the sun if taking medicines. Some participants did not recognise the sun or the fire. More of the Tanzanian participants misunderstood this pictogram as compared to the South Africans; there was a significant difference in the understanding of this pictogram across the groups ($p = 0.0261$).

- Pictogram 6. Keep all medicines out of reach of children
  All the participants (100%) understood this pictogram.

Some participants had comments concerning the pictograms. One participant suggested having the pictograms in colour for more clarity, others stated that non-readers might misinterpret the pictograms and that they need to be explained when the PIL is handed out. This emphasises the need to use pictograms in conjunction with other modes of communication to convey medicines instructions as has been suggested by other researchers [10,13,299,301]. Overall, the pictograms were generally well understood as only one failed to reach the ANSI 85% criterion in both groups.

The association between correct interpretation and understanding of the pictograms and a number of selected variables was investigated in the combined population. The variables of gender and medicine-taking behaviour had no significant associations with the interpretation of any of the pictograms (Table 6.15).

Table 6.15 Association between understanding of the pictograms and some variables

Pictograms	**Variables**				
	Gender	**Age**	**Education**	**Medicine-taking behaviour**	**Easiness to read**
Pictogram 1	0.1283	0.0138 [1]	0.2126	0.6523	0.0087 [1]
Pictogram 2	0.2150	0.0035 [1]	0.0688	0.6379	0.0058 [1]
Pictogram 3 [2]	-	-	-	-	-
Pictogram 4	0.4750	0.0293	0.6619	0.8625	0.7309
Pictogram 5	0.1024-	0.1011	0.0013 [1]	0.2939	0.0207 [1]
Pictogram 6 [2]	-	-	-	-	-

[1] Significant associations ($p < 0.05$)
[2] Pictograms understood by all participants (100%)

Age, educational level and self-reported ease of reading had a significant association with the interpretation of some of the pictograms ($p < 0.05$). The significant age association may be attributed to the fact that 'visual literacy', an ability to correctly interpret symbols [10,301] is better in the younger generations that are surrounded and better exposed to signs and symbols in everyday life, this is in line with previous findings [10,301]. Educational level has also been shown to influence visual literacy [10,289].

6.4.4 Time taken to read the PIL

The average time taken to read the PIL was 9 minutes. Overall, a majority (58.3%) of the participants took between 5 - 10 minutes to read the PIL. Eight participants took more than 15 minutes to read the PIL, seven of whom were Tanzanians (Table 6.16).

Table 6.16 Time taken to read the PIL

Time taken to read PIL (minutes)	**Participants, N (%)**		
	Overall N = 120	**South Africa N = 60**	**Tanzania N = 60**
< 5	6 (5.0)	3 (5.0)	3 (5.0)
5 - 10	70 (58.3)	41 (68.3)	29 (48.3)
10 - 15	36 (30.0)	15 (25.0)	21 (35.0)
> 15	8 (6.7)	1 (1.7)	7 (11.7)

6.4.5 Understanding of the PIL

Table 6.17 shows the results of participants correctly locating and understanding information in the PIL. Of the 20 questions that assessed the understanding of the PIL, six (Questions 1, 4, 6, 16, 17 and 20) were located and understood by all the participants. Some participants were able to locate the information for certain questions, but could not understand it.

The only question that failed to achieve the EC target of 80% in both groups was Question 3. This was a relatively complex concept, as it required an understanding of the consequences of an instruction that was not obeyed. The concept of developing resistance to medicines as a result of their misuse is a foreign one to many people and one not easily understood. There was a significant difference in the understanding of this information across the two groups ($p = 0.0071$). While 65% of the Tanzanian participants understood it, only 40% of the South African participants understood it.

A total of 115 of the 120 participants located the information pertaining to spreading HIV/AIDS while taking these medicines (Question 2), but only 105 understood it. The information for Question 7 regarding the effect of medicines on the viral load was located by 98.3% and understood by 95%. This may be due to the unfamiliarity of the term ‘viral load’. All 120 participants (100%) located the information regarding the effect of ART on AIDS outcomes (Question 9) and only three failed to understand it. The information concerning allergies (Question 12) was located by 99.1%, but understood by only 81.6%. This large difference may be due to a lack of awareness and concern about the importance of allergies in everyday life and health.

All except one of the instructions that were illustrated by pictograms scored 100%. One participant did not locate the information on how to take the EFV capsules (Question 13) and two did not understand this information.

Table 6.17 Number (%) of participants correctly locating and understanding information in the PIL

Questions		Participants, N (%)		
		Overall N = 120	South Africa N = 60	Tanzania N = 60
1. Using the leaflet, can you tell me the name of these medicines and describe them?	Located	120 (100.0)	60 (100.0)	60 (100.0)
2. Can one still spread HIV/AIDS while taking these medicines?	Located	115 (95.8)	59 (98.3)	56 (93.3)
	Understood	105 (87.5)	52 (86.7)	53 (88.3)
3. If you do not take your medicines as instructed, what may happen?	Located	115 (95.3)	59 (98.3)	56 (93.3)
	Understood	63 (52.5)	24 (40.0) [2]	39 (65.0) [2]
4. According to the leaflet, how many times a day must you take Stavudine (d4T) capsules	Located	120 (100.0)	60 (100.0)	60 (100.0)
	Understood	120 (100.0)	60 (100.0)	60 (100.0)
5. Looking at the leaflet, does it tell you what to do if you miss a dose of your medicines?	Located	114 (95.0)	58 (96.7)	56 (93.3)
	Understood	113 (94.1)	58 (96.7)	55 (91.7)
6. Like any other medicines, these medicines have both good and bad effects. Does the leaflet tell you what the bad effects are and what you should do if you experience any of them?	Located	120 (100.0)	60 (100.0)	60 (100.0)
	Understood	120 (100.0)	60 (100.0)	60 (100.0)
7. What do these medicines do to the viral load?	Located	118 (98.3)	58 (96.7)	60 (100.0)
	Understood	114 (95.0)	55 (91.7)	59 (98.3)
8. What does the leaflet tell you to do if you take too much of these medicines by mistake?	Located	109 (90.8)	56 (93.3)	53 (88.3)
	Understood	109 (90.8)	56 (93.3)	53 (88.3)
9. Do these medicines cure HIV/AIDS?	Located	120 (100.0)	60 (100.0)	60 (100.0)
	Understood	117 (97.5)	59 (98.3)	58 (96.7)
10. According to the leaflet, if you are taking any other medicines, what should you do before taking these medicines?	Located	119 (99.1)	59 (98.3)	60 (100.0)
	Understood	119 (99.1)	59 (98.3)	60 (100.0)
11. How long do you have to take these medicines for?	Located	108 (90.0)	59 (98.3)	49 (81.7)
	Understood	108 (90.0)	59 (98.3)	49 (81.7)
12. According to the leaflet, if you have any allergies, what should you do before taking these medicines	Located	119 (99.1)	59 (98.3)	60 (100.0)
	Understood	98 (81.6)	38 (63.3) [2]	60 (100.0) [2]
13. Does the leaflet tell you how many of Efavirenz (EFV) capsules you should take each time?	Located	119 (99.1)	60 (100.0)	59 (98.3)
	Understood	119 (98.3)	59 (98.3)	59 (98.3)
14. Suppose you have been feeling better for the past month; can you stop taking your medicines?	Located	111 (92.5)	58 (96.7)	52 (86.7)
	Understood	111 (92.5)	59 (98.3)	52 (86.7)
15. What should you do with left over medicines?	Located	116 (96.6)	58 (96.7)	57 (95.0)
	Understood	116 (96.6)	59 (98.3)	57 (95.0)
16. Some medicines can be taken with alcohol. Can you take alcohol while taking these medicines?	Located	120 (100.0)	60 (100.0)	60 (100.0)
	Understood	120 (100.0)	60 (100.0)	60 (100.0)
17. Does the leaflet tell you how to store these medicines?	Located	120 (100.0)	60 (100.0)	60 (100.0)
	Understood	120 (100.0)	60 (100.0)	60 (100.0)
18. Is there any advice in this leaflet about sharing your medicines with someone else who has HIV/AIDS?	Located	118 (98.3)	59 (98.3)	59 (98.3)
	Understood	117 (97.5)	59 (98.3)	58 (96.7)
19. Does it matter if you take these medicines at different times every day?	Located	114 (95.0)	56 (93.3)	58 (96.7)
	Understood	109 (90.8)	51 (85.0)	59 (98.3)
20. If you want more information about your treatment and medicines you are taking, who should you the talk to?	Located	119 (99.1)	60 (100.0)	59 (98.3)
	Understood	119 (99.1)	60 (100.0)	59 (98.3)

shading indicates questions that failed to reach the EC target of 80%

[2] Significant differences observed ($p < 0.05$)

Generally, the PIL was well understood by both groups. There were no significant differences between the two groups in locating and understanding the information for most questions (Table 6.17). Question 12 failed to reach the EC 80% criterion for understanding amongst the South African group. Even though this information was located by more than 80% of the group, it was only understood by 63.3% of the participants. A significant difference was observed for the understanding of this information across the groups ($p = 0.0000$), as all the Tanzanian participants understood it compared with only 63% of the South African participants.

The overall percentage understanding score was divided into six categories (Table 6.18). Only six of the 120 participants scored below 81%. A majority (59.2%) of the participants had a very high understanding score of more than 96% (Table 6.18).

Table 6.18 Overall percentage understanding of the PIL

% Understanding score	**Participants, N (%) N = 120-**
65 – 70%	1 (0.8)
71 – 75%	1 (0.8)
76 – 80%	4 (3.3)
81 – 85%	1 (0.8)
86 – 90%	16 (13.3)
91 – 95%	26 (21.7)
96 – 100%	71 (59.2)

6.4.6 Acceptability of the PIL

In terms of acceptability of the PIL, (Table 6.19), over half of the participants (61.7%) found the PIL to be of average difficulty to read and only 6.6% found it difficult to read. All the participants (100%) found the writing to be large enough, liked having pictures in the PIL and said the pictures would help with understanding and recall of instructions. They all also stated that the size of the PIL was adequate. Almost all the participants (95.3%) thought the length of the sentences was reasonable and 94.1% said the PIL had enough spacing between the lines and ample white space. A majority of the participants (92.5%) thought the information in the PIL was sufficient to enable them to take these medicines correctly. Those who disagreed with this commented that insufficient information was included to ensure a well-informed patient, particularly as these are dangerous medicines, whereas others expressed a desire for as much information as could be made available.

Table 6.19 Participants' acceptability of the PIL

Questions	Response	Participants, N (%)		
		Overall N = 120	South Africa N = 60	Tanzania N = 60
Readability				
1. How easy was it to read this leaflet?	Easy	38 (31.7)	20 (33.3)	18 (30.0)
	Average	74 (61.7)	37 (61.7)	37 (61.7)
	Difficult	8 (6.6)	3 (5.0)	5 (8.3)
2. Is the writing large enough?	Yes	120 (100.0)	60 (100.0)	60 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)
3. What do you think of the length of the sentences?	Too long	4 (3.3)	2 (3.3)	2 (3.3)
	Right	115 (95.8)	57 (95.0)	58 (96.7)
	Too short	1 (0.8)	1 (1.7)	0 (0.0)
4. Is there enough space between the lines?	Too wide	5 (4.2)	1 (1.7)	4 (6.7)
	Right size	113 (94.2)	58 (96.7)	55 (91.7)
	Too small	2 (1.6)	1 (1.7)	1 (1.7)
Amount of information				
5. If you had just started taking these medicines and this was all the information you were given about them, do you think it is enough?	Yes	111 (92.5)	53 (88.3)	58 (96.7)
	No	9 (7.5)	7 (11.7)	2 (3.3)
Pictograms				
6. Do you like having pictures in the leaflet?	Yes	120 (100.0)	60 (100.0)	60 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)
7. Do you think the pictures will help you understand and recall the information better?	Yes	120 (100.0)	60 (100.0)	60 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)
Words in the text				
8. Are there any words in the text that you did not understand?	No	15 (12.5)	5 (8.3)	10 (16.7)
	Yes, a few	104 (86.7)	54 (90.0)	50 (83.3)
	Yes, many	1 (0.8)	1 (1.7)	0 (0.0)
PIL size preference				
9. Is the size of the leaflet ok?	Yes	120 (100.0)	60 (100.0)	60 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)
10. What size would you prefer the leaflet to be?	Original PIL	40 (33.3)	22 (36.7)	18 (30.0)
	1 sheet-A4	26 (21.7)	16 (26.7)	10 (16.7)
	1 sheet-A5	20 (16.7)	12 (20.0)	8 (13.3)
	Z-fold	34 (28.3)	10 (16.7)	24 (40.0)
PIL language preference				
11. In what language would you prefer to read the leaflet?	English	16 (13.3)	16 (26.7)	0 (0.0)
	IsiXhosa	44 (36.7)	44 (73.3)	0 (0.0)
	Kiswahili	60 (50.0)	0 (0.0)	60 (100.0)

On enquiring about the understanding of individual words contained in the PIL (Question 8), the majority (86.7%) admitted to not understanding a few of the words. One participant admitted to not have understood many of the words in the PIL. The identified problem words and their incidence are presented below (Table 6.20).

These words were significantly reduced in number, from 24 in the pilot study to only 7 in the main study. This decrease may be attributed to the PIL being in the home language as was anticipated in the pilot study.

Table 6.20 Words in the PIL not understood by the participants

Words	**Number of participants**	
	South Africa N = 60	**Tanzania N = 60**
ART	52	48
CD4 count	51	45
Capsules	3	5
Pharmacist	6	23
Product description	0	1
Resistance	7	1
Viral load	50	0

shading indicates words not understood by more than half of the participants

- ART is fairly new terminology and, although unfamiliar to these participants, it may be familiar to HIV/AIDS patients as most of them are informed about their treatment before commencing use.
- The word ‘Capsule’ not being understood was rather surprising. Most people in these societies refer to solid medicines as ‘vidonge’ (Kiswahili) or ‘pilisi’ (isiXhosa), irrespective of the formulation. Some also tend to get to know the generic names of the most commonly used medicines and use a general term for all the medicines in that group.
- CD4 count is an HIV-related term and again it is anticipated that HIV/AIDS patients would be familiar with this term.
- The word ‘Pharmacist’ had never been heard of by many of the Tanzanian participants, although they admitted to knowing the word ‘pharmacy’ (drug store). Most of the South African participants understood it, although the most commonly used term is ‘Chemist’.
- A few participants, most of whom read the English PIL, misunderstood the word ‘resistance’. One stated that he had never heard of it. It needs to be explained using simpler lay terms and was better understood in the home languages.
- Viral load is not a common term, and is one of the new words PLWHAs learn about their condition. Surprisingly, all the Tanzanian participants understood it while a majority (83.3%) of the South Africans did not. This may be attributed to the fact that AIDS-related terminology does exist in Kiswahili, but not in isiXhosa thereby requiring the use of English words. These words are called ‘borrowings’, an example of this being the Xhosa word ‘i-viral load’.

Reasons given for the preference for a particular PIL size and format were ease of reading (2-pages of A-4 format), less bulky and back to back printing (1-page of A-4 format); small, easier to follow and store and read in private (Z-fold); small, easier to handle and opens like a book (1-page of A-5 format).

General positive comments on the PIL included an appreciation of its simplicity and breadth of information. The PIL was regarded as well designed and easy to follow, user-friendly with the pictograms, and not intimidating, even to poor readers. The participants were enthusiastic about having this type of information made available to patients as they felt it would address many of the concerns and questions people have about their medicines and would contribute to correct medicine taking.

Generally, there were no significant differences between the two groups for acceptability of the PIL. A significant difference was observed ($p = 0.0054$) in the preference for the format of the PIL (Question 10), in that 40% of the Tanzanian participants preferred the Z-fold PIL, compared with only 16.7% of the South Africans.

A majority of the participants said they would prefer to receive a PIL in their home language. Those who preferred to receive an English PIL stated that they were much more comfortable reading the English version as they are more familiar with English technical and medical terminology compared to that in isiXhosa. Some participants stated that the PIL should be in both English and the home language so as to cater for foreigners. All the participants agreed upon the need to have the PIL in the patients' language of choice.

The Tanzanian participants tended to be more forthcoming with suggestions. Some of these were:

- including more information on HIV/AIDS and the medicines
- having the PIL in both English and Kiswahili so that the reader has a choice in both
- including the expiry dates of the medicines in the PIL
- showing a picture of an AIDS patient in the PIL to remind people what unsafe sex may lead to.

The product description section elicited several comments and was not understood by many participants. It was felt that this was not important information for patients and that it was too technical in nature.

An interesting issue that arose in the pilot study was the confusion surrounding the disposal of unused medicines. It was apparent that the concept of returning unused medicines to the clinic or doctor was a new one to many participants. The most common means of disposal of unused medicines seemed to be throwing them into the sewage or dumping them in the rubbish.

As this was an important issue about which the patients obviously need educating, an additional question was included in the main study enquiring about the disposal of unused medicines. Interestingly, different issues emerged in the two groups. Some South Africans appeared to be aware of the dangers of careless handling of medicines and they stated that they securely packaged the unused medicines before disposal in the sewage or rubbish. Others admitted to passing on their unused medicines to others with similar ailments. A fairly common approach in the Tanzanian group was to dispose the medicines by burying them. This feedback has highlighted the importance of educating patients on this issue.

6.4.7 Comparison of the PIL with the CMI document on ART

Most participants preferred all the design features of the PIL to those of the CMI document (Table 6.21) and they all felt that it was easier to read.

Table 6.21 Results for comparison of the PIL with a CMI document on ART

Variable	**Participants, N (%)**					
	Overall (N = 120)		**South Africa (N = 60)**		**Tanzania (N = 60)**	
	PIL	**CMI**	**PIL**	**CMI**	**PIL**	**CMI**
Print size	103 (85.8)	17 (14.2)	55 (91.7)	5 (8.3)	48 (80.0)	12 (20.0)
Font style	88 (73.3)	32 (26.7)	51 (85.0)	9 (15.0)	37 (61.7)	23 (38.3)
Length of the sentences	112 (93.3)	8 (6.7)	56 (93.3)	4 (6.7)	56 (93.3)	4 (6.7)
The space between the lines and white space	93 (77.5)	27 (22.5)	49 (81.7)	11 (18.3)	44 (73.3)	16 (26.7)
The number of pages	108 (90.0)	12 (10.0)	57 (95.0)	3 (5.0)	51 (85.0)	9 (15.0)
The presence/absence of pictures	120 (100)	0 (0.0)	60 (100.0)	0 (0.0)	60 (0.0)	0 (0.0)

A majority of the participants preferred the print size and text style used the PIL; of note was the greater number of the South Africans (85%) who preferred the Arial font in the PIL as compared to only 61.7% of the Tanzanians. The sentences in the PIL were generally shorter and were preferred, as was the spacing between the lines and the number of pages.

All the participants liked having pictures in a PIL, which supports previous findings [2]. When asked about the desired number of pages for the PIL, answers ranged from wanting a 1-page PIL (42.5%), a 2-page PIL (49.2%) and a PIL of longer than 2 pages (8.3%).

I was interested in assessing how much information about their medicines people ideally would like to receive, as there was a big difference between the length of the PIL and that of the CMI document. A third of the participants indicated that they would like to receive comprehensive information such as that contained in the CMI document the first time they receive their medicines. Interestingly some of these had poor reading skills. However, most of the participants were happy with brief, simplified information for new medicines but stated that they would like to receive additional information later in the course of their therapy, such as that in the CMI document, but with pictograms included.

6.4.8 Association between understanding of the PIL and miscellaneous variables

A regression analysis was conducted to investigate any significant associations between the overall per cent understanding of the PIL (which includes both locating and understanding the information) and the variables of gender, age, educational level, employment status medicine-taking behaviour and the stated easiness to read the PIL.

Two way sample t-tests for independent samples and two-way ANOVA tests were conducted, after the group difference was added as a factor. The level of significance was set at 5%. The results are presented in Table 6.22.

No significant association was found between the understanding of the PIL and the variables of gender, age, employment status and medicine-taking behaviour across the total population and within the two groups. Although there was a significant difference in the employment status of the participants between the two groups, it had no influence on the understanding of the PIL. However, education and self-reported ease of reading the PIL were found to correlate significantly with understanding ($p = 0.05$).

Table 6.22 Association between understanding of the PIL and miscellaneous variables

Variables		Overall % understanding of PIL		
		Participants, N (%) (N = 120)	Mean (+/-% SD)	p Value
Gender				
	Male	57 (47.5)	95.4 (5.62)	
	Female	63 (52.5)	94.4 (6.14)	0.5645
Age	< 21	21 (17.5)	94.73 (5.47)	
	21 - 40	84 (70.0)	95.37 (5.51)	
	41 - 65	15 (12.5)	94.18 (8.35)	0.7334
Education	0 - 5	14 (11.7)	90.64 (8.02)	
	6 - 11	66 (55.0)	94.90 (5.75)	
	> 11	40 (33.3)	97.03 (4.25)	0.0260 [1]
Employment	Yes	57 (47.5)	95.23 (6.09)	
	No	63 (33.3)	95.01 (5.73)	0.5760
Medicine-taking behaviour				
	Every day	9 (7.5)	92.87 (5.08)	
	often	29 (24.1)	93.88 (7.14)	
	not very often	69 (57.5)	95.71 (5.69)	
	never	13 (10.8)	96.23 (3.56)	0.2900
Ease to read				
	Easy	38 (31.7)	96.80 (4.09)	
	Average	74 (61.7)	95.23 (5.14)	
	Difficult	8 (6.6)	85.56 (10.15)	0.000001 [1]

[1] Significant influence on understanding ($p < 0.05$)

As anticipated, improved understanding was associated with an increase in the number of years of education. There was also a significant difference when the group effect was added. An analysis of variance (ANOVA) of the entire population revealed a significant education effect on the overall per centage of understanding, which included locating as well as understanding the information ($F=6.82$, (2,117) df, $p = 0.0015$).

When education and group were considered as variables in a two-way ANOVA, there was a significant education effect ($F = 9.76$, (2,114) df, $p = 0.000122$). When education and group were considered as variables in univariate tests of significance, there were significant group, education and interaction effects (Figure 6.1).

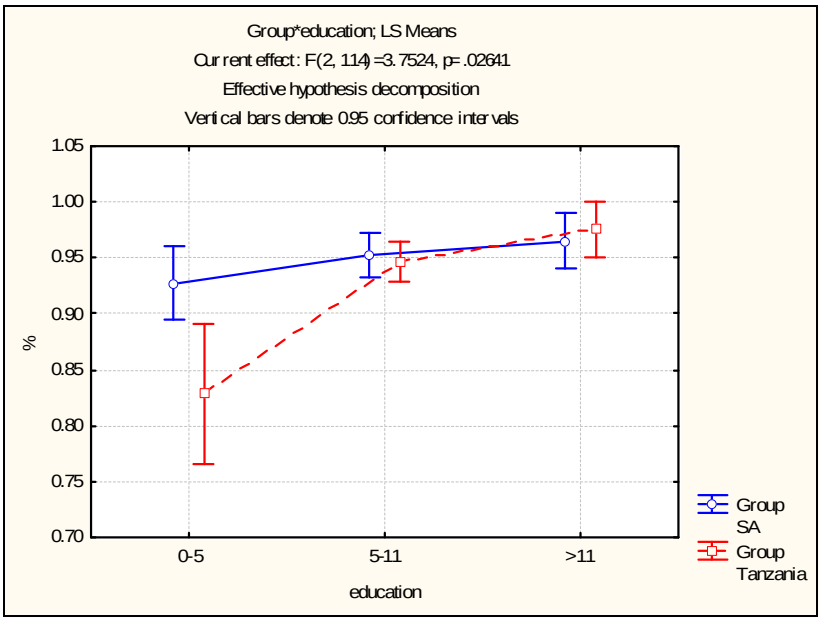


Figure 6.1 Interaction effect between understanding of the PIL and education

Figure 6.1 shows the significant difference in the understanding of the PIL with group and education effects combined. As can be observed, the Tanzanian participants with less than 5 years of formal education had a lower understanding score compared to their South African counterparts.

The stated easiness or difficulty in reading the PIL also showed a significant association with the overall per centage of understanding (F = 15.19, (2,117)df, p = 0.000001). None of the participants who reportedly found the PIL difficult to read scored 100%.

6.4.9 Association between individual questions and miscellaneous variables

The five most poorly answered questions (Questions 3,7,11,12,14 and 19) were individually analysed to investigate any association with the variables of education, employment status, self-reported ease to read and words not understood using Pearson Chi-squared (χ^2) tests.

As can be observed in Table 6.23, there was a significant association between understanding of the information on viral load (Question 7) and on allergies (Question 12) and the educational level of the participant. The employment status of the participants had a significant association with the understanding of Questions 3 and 12.

Table 6.23 Association between individual questions and miscellaneous variables

Questions	**Variables**			
	Education	Employment	Easiness to read	Words not understood
Q.3 If you do not take your medicines as instructed, what may happen?	0.7402	0.0096 [1]	0.5476	0.6304
Q.7 What do these medicines do to the viral load?	0.0064 [1]	0.4759	0.0404 [1]	0.6152
Q.11 How long do you have to take these medicines for?	0.2049	0.1612	0.0004 [1]	0.0047 [1]
Q.12 According to the leaflet, if you have any allergies, what should you do before taking these medicines	0.0000 [1]	0.0355 [1]	0.4976	0.4009
Q.14 Suppose you have been feeling better for the past month: Can you stop taking your medicines?	0.7394	0.0586	0.0876	0.0012 [1]
Q.19 Does it matter if you take these medicines at different times every day?	0.4505	0.1587	0.5092	0.8875

[1] Significant association with understanding of information ($p < 0.05$)

The self-reported ease in reading the PIL had a significant association with the understanding of Questions 7 and 11. A significant association was observed for the understanding of Questions 11 and 14 of the information with the words not understood.

The overall results clearly indicate that the educational level of a patient is a major determinant in influencing the reading and understanding of information, but the other variables are also of importance. These findings will be further discussed in the next chapter.

CHAPTER SEVEN
DISCUSSION

7.1 The importance of written medicines information for HAART

In healthcare, medicines are the major mode of treatment, and therefore the patient's role as an informed partner is crucial [134]. Although a well-informed patient is no guarantee of good adherence to therapy, it is important to avoid unintentional non-adherence through lack of information or because of inadequate understanding of the information.

After consultation with an HCP, patients typically retain only 20% of what they hear [156] however, this increases substantially when the verbal information is supplemented with written information in the form of a leaflet [156]. Written education materials are the most widely used method for conveying health and medicines information and are a useful resource in assisting patient recall of information. They are particularly valuable when a large volume of information is communicated verbally and when dealing with complex therapies. This is the case with HAART, which is chronic, complex therapy and which demands extremely high adherence levels. A well-informed patient is therefore essential to promote adherence in order to sustain efficacy of HAART and avoid the development of resistance.

Research into factors contributing to poor adherence to HAART has identified lack of patient education and the inability to identify their medicines as being of major importance [88,99-101]. This project attempted to address these issues by developing a user-friendly, comprehensive, readable PIL on a HAART regimen.

However, HAART consists of a minimum of three drugs, each with its own information. In southern and eastern Africa, many people requiring ART are likely to have limited reading skills and, when faced with three individual leaflets, each possibly two pages long, may find this information daunting and overwhelming. Our approach, therefore, was to design a medicines information document that integrated information from all three ARVs into one single PIL.

7.2 The use and applicability of visual aids in written medicines information

Poor health literacy and illiteracy are worldwide problems that are more pronounced in the developing countries [117,119,120,269,271]. A way to facilitate the conveyance of written information to poor readers is by means of the use of pictograms [13,283-288,295-297]. The success of pictograms, as a communication aid relies on a comprehensive design and evaluation process to produce lucid, culturally acceptable pictograms; their value in use depends on their appropriate use by the HCP who ought to give verbal reinforcement in conjunction with the pictograms [10,13,215,301-303]. Studies have demonstrated that the incorporation of pictograms into written medicines information is beneficial in that they reinforce recall of the illustrated instructions [4,13,256,287].

Previous research in a low-literate African population conclusively showed that medicines information incorporating pictograms was significantly better comprehended than documents containing text-only, and was the preferred format [13]. Taking this into account, pictograms were included in our ART PIL and were similarly enthusiastically received. All participants both South African and Tanzanian, indicated their liking of pictograms incorporated into the PIL and they were of the opinion that the pictograms would serve as a valuable aid in increasing understanding and recall of information. A number of researchers have shown this to be the case [13,290,295-297,301]. All except one of the instructions that were illustrated by pictograms were located and understood by all the participants in this study, which supports the notion that using pictograms to illustrate textual information appears to promote understanding.

It has been shown that personalised information handed directly to the patient is better accepted and appreciated than package inserts [134,162,168,199]. Pictograms in the ART PIL were used to communicate specific times at which the medicines should be taken. The blank clock faces were filled in after consultation with the patient, in order to ensure that the dosing schedule was convenient and fitted in with their daily routine. As well as minimising the uncertainty connected with the intervals between doses, this personalising of information engages the patient in a consultative, concordant process, offering choices and acknowledging that the patient voice is important in making health-related decisions.

7.3 Design and development of PILs for developing countries

Pharmacists are one of the HCPs responsible for influencing patient medicine-taking behaviour by empowering patients with medicines information and motivating them to take responsibility for their own health [13,61,253,254,258,304]. The quality and form of the information provided must, however, be appropriate for the patients' level of education and must also take into account their cultures, beliefs, attitudes, and expectations [10,13,168,199]. We as pharmacists designed this PIL with our role as medicines information providers in mind. All the aspects that have been highlighted in the literature of PIL design and development were taken into account to ensure that the final product was well understood and accepted by the end-users. This is apparent in our PIL, which scored highly in both understanding and acceptability in the target African populations.

Most of the research on the use of PILs is from developed countries [6,8,128-130,168,199,207-209], a limited number of studies have investigated the value and use of PILs in developing countries [12,13,219]. Properly designed and evaluated patient educational materials have been shown to be well understood and accepted by consumers [168,181], if they are designed in collaboration with, and comprehensively evaluated for understanding and acceptability in, the target population [11,13,181]. We designed our PIL in close collaboration with focus groups with members from the target population and subsequently evaluated it in the target population. Our findings support the literature as our PIL was very well understood and highly accepted by the target population.

7.4 Development of PILs for South Africa

Regulation 10 of the South African Medicines and Related Substances Control Act, Act 101, as amended, published in April 2003 made the provision of PILs mandatory with all medicines, and outlines the information that is to be included in PIL, but with no mention of their format, design or evaluation [9]. The PIL designed in this study incorporated all the stated legal requirements. The legislation also requires the inclusion of compulsory statements, but makes a provision for any deviations that are deemed necessary to improve the comprehension of the PIL. The inclusion of the product description section elicited both negative and positive comments. The general consensus was that this section is too technical and of no value to the patient in aiding the safe and effective taking of their medicines. This

suggests that the current guidelines on PIL content need to be reviewed so as to ensure that PILs will be acceptable to the end-users. Preliminary guidelines on PIL design and format for South Africa published in May 2004 by the South African Medicines Control Council clearly outline the sequence of information to be included, as well as the format and layout, and suggesting the use of illustrations such as pictograms [203]. There is no requirement for the development in collaboration with the target population nor that the final product be tested prior to distribution. There is no evidence that PILs developed using these guidelines will appropriately cater for the enormous diversity of the South African population. This study thus highlights the need for consumer testing to be made mandatory prior to PIL distribution. The need to have set guidelines for PIL evaluation is also evident from studies conducted in Europe [181].

In the design phase, particular attention was paid to both the amount of information included and the difficulty of the words used. Linguistically transparent words and commonly used phrases that were familiar to the target population were incorporated. Most of the medical-related terminologies on HIV/AIDS are fairly new. Although the terms ‘viral load’, ‘CD4 count’ and ‘antiretroviral therapy’ were poorly understood, there are no substitutes. Explanations describing these words in lay terms were included so as to aid their comprehension. These problem words may have contributed to a lack of continuity in reading the PIL and a subsequent lack of understanding of the entire meaning of some of the sentences. ‘Resistance’ also presented problems and was ignored. The inclusion of a subordinate clause ‘if’ in the question that enquired about the development of resistance ((Question 3.3.3) – (Appendix C2)) made the structure of that question more abstract, and may have contributed to the poor understanding of the information on resistance. This was the only information that did not reach the required EC criterion of 80% in this study.

The final choice of text style and size of the PIL was guided by the focus groups as it was vital to ensure optimal appeal to the target population. This careful selection was vindicated by the results of consumer testing, as a majority of the participants preferred the text style and size used in the PIL over that used in the CMI ART document.

The distribution of PILs in the home language of patients has been shown to be superior in aiding their utility and acceptance by the consumers [4,10,214]. In this study, a general consensus was that PILs be distributed in the patients’ language of choice implying that it has

to be available in the home language of the target population. Ideally, PILs should be designed in the language in which they are distributed [4]. However, in a country such as South Africa, with 11 official languages, it is unlikely that information design experts would be fluent in all 11 languages. The translation process is thus a crucial ingredient of the development of PILs for South Africa and needs be executed with great care to ensure that the context and meaning of the information remain the same, particularly given the unavoidable use of medical jargon. A three-step procedure was followed in this study to ensure consistency of meaning after translation. Initial translation by laypersons, professional proofreading by a language expert and then back translation proved to be essential and invaluable in detecting inconsistencies and inappropriate language usage. This multistage rigorous approach is recommended for the translation of all health-related materials [10].

7.5 Readability of PILs in relation to the reading skills of the target population

It has been observed that the reading level of most written health-related material is higher than that of the average consumer [4,10,173-175,217], therefore, the objective assessment of readability is essential to ensure that they match the reading skills of the target population. The use of more than one method of evaluation has thus been advocated, an approach used in this study. A number of objective tests were used to evaluate the readability of the PIL, and consumer testing confirmed the suitability of the PIL for the target population.

Readability formulae do not take into account numerous variables that also influence the readability of a material. These include legibility, motivation of the reader, learnability of the text, usability, the relationship among words, sentences and sentences parts and the level of abstraction required of the reader by the material [10]. Some researchers have long argued that readability formulae should not be too heavily relied on and that they should be used as quick guides rather than as the sole instrument to determine readability levels as they only provide an estimate of reading grade level [216]. In this study, two manual readability formulae were used, as well as a computerised test, and the results obtained graded the PIL as being suitable for grade 7 learners. As all the formulae were developed in the US, the grading pertains to the American schooling system and its applicability to local grade levels is uncertain. For this study, an assumption was made that the years of schooling (and thus grade levels) for the US and South Africa were equivalent. In the Tanzanian schooling system,

grade 7 (equivalent to the local Standard 5) is part of the primary school education. The majority of Tanzanians have attained Standard 7 as their minimum level of schooling.

When assessed for variables that influence readability, the PIL scored highly overall and was categorised as 'superior'. This is a good reflection of the rigorous process that was adopted in designing this PIL.

7.6 Consumer evaluation of the format, content and general design of the PIL

In order to stimulate interest, and aid in responsible medicines-taking behaviour, medicines information should be attractive, of the appropriate tone and length, user-friendly, easily readable and accessible [4,10,13,168]. The evaluation of consumer preference using open-ended questions best assesses these features and forms a vital part of the design process as it provides the designer with invaluable feedback on how to improve both the readability and the appearance of the material.

Some studies have shown that the Z-fold [13] and A-5 size [183] leaflets were preferred and acceptable; in this study it was evident that the A-4 size was the preferred format and design. The three-column format adopted from the Australian CMI Usability guidelines also proved to be acceptable to most of the participants.

7.7 Factors that may influence the understanding of PILs

The demographic characteristics of the patient as well as cultural beliefs and perceptions concerning the treatment and the disease have been associated with health behaviour. In this study, the variables of gender, age, and medicine-taking behaviour did not have any significant associations with the understanding of the information in the PIL. Understanding of the PIL had a significant association with the educational level of the patient, a finding supported by other researchers [168]. The educational level in this study was determined by the number of years of formal education attained. A better predictor would have been the functional health literacy of participants, as the PIL contained health-related terminology. Functional health literacy can be determined using US health literacy tests. However, those in current use were developed for an English-speaking US population and have been shown to be inapplicable for use in the local Xhosa population [245] who have English as a second

language. The modified REALM-M tool [246] that was developed for use in the Xhosa population has not been validated and was thus not suitable for use in this study. A local validated health literacy assessment tool is required, as a mere translation of the REALM has been shown to be unsatisfactory and unreliable [246].

Self-reported ease of reading the PIL also showed a significant association with its understanding. Not surprisingly, those who claimed the PIL was difficult to read did not achieve a high understanding as they displayed a lack of reading continuity that may have disrupted the information flow and in turn reduced the understanding of the information.

7.8 Expected versus observed results for consumer testing of the PIL

The levels of understanding obtained in this study were higher than the values reported in previous research [181] and similar to those obtained by Mansoor *et al* [13]. This excellent understanding may be due to the collaboration with the target population throughout the design and evaluation process, as a result of which deficiencies and problems were identified and addressed. In line with previous findings [4,13,135], our study has demonstrated the usefulness and beneficial outcome of the use of focus groups constituted of members from the target population to help design and evaluate patient educational materials.

The PIL was designed with reference to various validated guidelines, and taking cognisance of previous research. The well-defined target population was the Xhosa ethnic group. Its transferability to other population groups was uncertain, as it has been proposed that PILs be designed and tailored for a specific group [4,13,135]. However, our results showed that the PIL, after translation, was extremely well understood and accepted by a totally different population in East Africa. Although there were no significant demographic differences between the groups in terms of age, gender and educational level, the participants in Tanzania, an East African country, belonged to a different ethnic group, with very different customs, habits, lifestyle and health-related perceptions. This study has demonstrated that it is possible to produce ‘customised’ PILs that may be successfully used in various African countries, as long as the two populations show no significant demographic differences. Thus standardising the approach to designing and evaluating PILs will result in a product that should be suitable for use in diverse population groups in Africa or in all developing countries.

Of note was that the Tanzanian participants with less than 5 years of schooling scored less than their South African counterparts. This may be attributed to the difference in the history of the two countries with respect to formal training. In the analysis of results, only formal education was considered; however the fact that people also tend to acquire literacy through apprenticeship learning, by informal skills acquisition in everyday activities from peers and from family members tends to be ignored. This type of acquired functional literacy is commonplace in South Africa, where data indicate that the lack of formal training opportunities and socio-economic pressures has led to apprenticeship learning in various work and community contexts [245]. The need for survival forces people to acquire various skills informally, and this may be the case with reading skills.

7.9 Strengths and weaknesses of the PIL

Consumer testing is known to play a crucial role in evaluating consumer understanding and acceptability of written information [11,181]. This process, which was applied in this study, enabled the identification of the strengths and weaknesses of the PIL both through formal questioning of understanding and acceptability, and from informal observation of individual participants as they read and then attempted to locate and retrieve information from the PIL.

The overall presentation of the information on PILs influences their usability and acceptability by consumers [4,168,199]. A number of factors increased the attractiveness of our PIL and in turn rendered it acceptable by the target population. It has been shown that people prefer easy-to-read materials, irrespective of their educational level [10,168]. The three columns in which the information was formatted, the short, easy-to-read and highlighted headings together with the bullet points gave it a generally good aesthetic appeal, and enabled easy navigation through the PIL. Broken paragraphs as opposed to solid text and sufficient space between the paragraphs and important points in the PIL made the document ‘inviting’ to read, attracted attention, and made it less intimidating, especially to poorly skilled readers.

A common problem of PILs is the small font size, which makes them appear difficult to read [162,168]. The reasonable print size used in our PIL enhanced its legibility and minimised the perception that it would be difficult to read after the first glance. The incorporation of pictograms in text has been shown to enhance the appeal of PILs, making them more likely to be read [13,168] and assisting with location of the information [13,168]. Our PIL successfully

incorporated pictograms in the text, which positively influenced both comprehension and acceptability.

The length of the 2-page PIL was daunting to the lesser educated participants, who then required more encouragement and reassurance of their ability to read the document; it was also a deterrent that sometimes hindered attention span. When people with poor reading skills are faced with a page of written information, their eyes tend to wander about the page without finding the central focus of the visual, and miss the main message; unlike skilled readers who systematically scan through the visual, finding the central concept and subsequently identifying the principal features [10].

Although the time taken to read the PIL was not associated with its understanding, the average time of 9 minutes required to read the PIL may have exhausted some the participants. This may present problems in practice, but since patients will be verbally counselled and educated on medicine use and on the importance of adherence, the PIL will serve as a take-home reference document.

The avoidance of the use of medical terms and jargon has been advocated as they tend to be misunderstood by most lay readers [10,226]. In the PIL, the use of HIV/AIDS related terminology was inevitable. Most of these terms were defined in words familiar to lay persons, but the information was still not understood by some of the participants. Prior to the provision of ART, the public health patients in South Africa receive comprehensive training and are educated on HIV/AIDS and its treatment, so these words should not pose as much of a problem to PLWHAs on ART for whom the PIL is intended.

The size of the PIL although well accepted by the majority of the participants, was regarded by some as too big to store. Given the resource constraints in most of the African countries, this size is the easiest to print and can be photocopied using the most commonly used paper size, rendering it the most economical form to reproduce.

7.10 Study limitations

The PIL was designed and tested in only one ethnic group in South Africa with all the participants being from a peri-urban setting in a small town. The majority of the participants

were between the middle and lower end of the socio-economic scale. Caution would therefore have to be exercised in extrapolating these results to other ethnic groups and to people living in different settings such as in the many isolated, rural areas of South Africa. The PIL was tested amongst a very diverse group of Tanzanians of different tribes all of whom were living in an urban setting in a large city. The majority were from the middle and low levels of the socio-economic scale, and any extrapolation of these results should also be done with caution.

The PIL was not tested on PLWHAs who were actually taking ART. The participants had no personal vested interest in making a real effort to understand the information and this may have resulted in bias; therefore testing the PIL using patients on HAART would have been the best method of evaluation. At the commencement of this study, the provision of ART in the South African public health sector had not been implemented and it would have been difficult to obtain enough participants who were on the regimen for whom the information was designed.

The study did not investigate cultural beliefs and perceptions regarding health and medicine-taking behaviour in the two diverse African populations. These findings may have enabled us to comprehensively compare the two populations and identify any significant similarities or differences that may exist, and also provide a reliable opinion about the attitudes regarding the use of medicines information across these two Africa populations. Even without collecting data of this sort, the interviews took about 45 minutes, which is longer than the 30 minutes maximum time recommended by most researchers [11].

7.11 Participants' attitudes towards the interviews and the study

The people interviewed in this study were interested and willing participants and there was no shortage of recruits. No hostility or resistance from these participants or the associated surrounding communities was encountered. Of interest was the vociferousness and enthusiasm of the Tanzanian participants compared with their South African counterparts. The Tanzanians were more willing to offer their own opinions; they asked more questions and were keen to learn more about the whole area of HIV/AIDS. Their need and desire for information appeared to be greater than that of the South Africans. This may be attributed to the fact that the South African study site was in Grahamstown, a small university town, where

community research is very common; many members of the Grahamstown community have had exposure to these projects and learnt from them.

In Tanzania, community research is mainly conducted in other regions with more definable sample groups of the same dialects. In contrast, most of the residents of Dar-es-Salaam are of different tribes and, because community research is not common in Dar-es-Salaam, many of the participants took this opportunity to attain more knowledge.

Some health-related information is available in most of the South African public sector primary healthcare centres with take-home pamphlets and many posters on display to educate the general public on different health-related issues. In contrast, minimal health-related information is available to Tanzanians public sector patients. These facilities are also mostly used for maternity issues and childcare, and the majority of patients attend private clinics in residential areas that are affordable to the average Tanzanian. This might have contributed to the greater quest for knowledge displayed by the Tanzanian participants.

CHAPTER EIGHT
CONCLUSION

This research has shown that PILs designed in collaboration with the target population and evaluated using consumer testing are subsequently highly understood and accepted by them. This PIL, that was piloted in South Africa was surprisingly also well understood by randomly selected participants from a different African region. It is evident that consumers would like to receive medicines information in the language of their choice, and thus it needs to be available in all the languages used in a particular area. Information incorporating pictograms is the format of choice in these two populations and it may be predicted that other African populations may also prefer this format.

The educational level of a participant has been shown to have an influence on the understanding of health-related information, and thus the need to ascertain that the information provided matches the average reading level of the intended end-users is paramount. The perceived ease or difficulty with which the material is read has also been shown to have a significant association with its understanding. Therefore information materials should be designed to ensure acceptability and attract positive attention so as to make sure that readers can navigate through the information contentedly. This written information is meant to supplement and not replace verbal counselling and any clarification can be obtained from a HCP.

Ours is the first group to conduct a comparison study of the understanding and acceptability of PILs between a South African and a Tanzanian population. Although the two groups are from very diverse parts of Africa, the general consensus was that medicines information should be distributed in the patients' language of choice and it should incorporate pictograms. The PIL was extremely well understood and accepted by both population groups, whereas the Australian CMI based document, containing information on the same medicines, was considered too bulky and intimidating to read.

The design template we developed in this project was communicated to and reviewed by the PIL task team of the South African MCC. The layout and format, of two A-4 pages with three columns each, have been included in the May 2004 MCC guidelines for PIL design in South

Africa. Recommendations for the inclusion of a method to evaluate PILs prior to distribution such as consumer testing will be communicated to this PIL task team.

The findings obtained from the Tanzanian arm of this study will be presented to the relevant Tanzanian authority involved in patient education. Included will be a recommendation that PILs be made available to consumers, particularly those patients using HAART where high adherence levels are crucial. I believe that research into pharmacy practice must in some way, ultimately, impact on the practice of pharmacy, either by influencing the practice of individual pharmacists, or by influencing healthcare decisions taken by policy makers involved in healthcare decisions. Eventually this type of research should benefit the health of the general community.

The PIL may be used as a generic template for design, layout and format. Consumer testing of PILs confirms their acceptability and usability in the target population and has no substitute. This evaluation method is of superior value and is recommended for use in developing countries.

HAART is complex therapy that needs an informed patient who has the knowledge and competence to adhere to the instructions, particularly as adherence is a crucial determinant of successful treatment outcomes. Properly designed and tested medicines information may improve adherence rates, satisfy patient information needs, educate patients on the correct use of their medicines and also play a significant role in empowering patients to become more active participants in their healthcare. A more informed patient enables greater participation in the decision-making process, resulting in a positive impact on medicine-taking behaviour and health outcomes. PILs do not replace verbal counselling by the pharmacist, but should be considered a useful adjunct to this process.

From the findings obtained in this study, some recommendations for the future of PIL design and evaluation in the developing countries are suggested. PILs for the developing countries should have culturally appropriate pictograms incorporated in the text. To aid with the identification of medicines, as per the instructions, all multiple therapy medicine products should be produced with their colour pictures in the form of stickers that can be placed on the relevant pictograms. PILs need be designed in collaboration with and be evaluated in the target population prior to distribution. Each country should develop guidelines for the design,

development and assessment of PILs so as to ensure that the final product is of value to the end-user and not merely satisfaction of a legal requirement.

In light of the findings of this project, directions for future research are suggested; a subsequent translation of the PIL into one of the other South African languages and its evaluation, and a comparison of the results with those obtained in this study, to establish if it could be of universal use in South Africa. To ascertain the applicability of this research to pharmacy practice, an adherence follow-up study needs to be conducted amongst PLWHAs on this ARV regimen, in which the PIL will be provided as an adherence-aiding tool and its impact on medicine-taking behaviour will be investigated over a period of time. This follow-up study will then serve to show if the PIL will have a significant impact on adherence to HAART. The development and validation of an objective readability assessment tool that will produce results for an African schooling system will also help with the evaluation of educational materials to ensure that they suit the target African population.

The design, evaluation and use of PILs is an initiative that is rapidly gaining importance in many developing countries. As it is a growing field in healthcare, guidelines need to be established to ensure that this kind of information is written and designed to suit the target population, and that draft written material is evaluated in the target population before its final preparation and distribution.

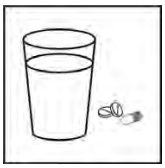
New refs

1. [ref no 5 ADHERENCE to long term therapies-].
2. [ref no 50- 9C-smith, information needs of patients].
3. ref no 213-bandesha+raynor-prelininary invest into PIs,
4. ref no 151-buck-8D,]. providing pts with WMI
5. [ref no 133 - Raynor adherence report-1998-ref,
6. ref no 131-kitching-22D,
7. [refs 165- Gibbs the benefits of prescription medicines, doc,
8. ref no 127- kenny- PIL for every ILL,].
9. [ref no 172- act 101 ref].
10. [refs-doak= 167,
11. CMI,
12. to add : http://www.fhi.org/en/Publications/index.htm-patient education
13. http://www.fip.org/- patient education
14. http://www.wma.net/e/policy/l4.htm- patient education
15. optimising pt comp- Ruth Day etc. optimizing patient comp thru medicines information leaflets- NEW REF to add

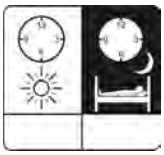
APPENDIX A

Pictograms incorporated into the PIL.

Pictogram 6: Take medicines with a glass of water



Pictogram 7a: Take twice daily



Pictogram 7b: Take once daily

Pictogram8: Store all medicines in a cool dry place, away from heat and direct sunlight

Pictogram 9: Do not take alcohol while taking these medicines

Pictogram 10: Keep all medicines out of reach of children

APPENDIX B

Patient Information Leaflets (PILs)

APPENDIX B1

Pilot study PIL

ANTIRETROVIRAL THERAPY

Stavudine, Lamivudine and Efavirenz (S4)

Patient information leaflet

What is in this leaflet?

Please read this leaflet carefully before you start taking your medicines.

This leaflet answers some common questions about your medicines.

It does not take the place of talking to your doctor, pharmacist or nurse.

Keep this leaflet with the medicines. You may need to read it again.

What your medicines are used for

These medicines will help you feel better and help you live a longer, healthier life if you take them correctly.

These medicines do not cure HIV/AIDS.
They work by slowing down the production of HIV. They stop the damage HIV does to the body's immune system, which fights infection. They increase your (good) CD4 count and reduce your (bad) viral load.

You can still spread HIV/AIDS by having unprotected sex.
These medicines do not reduce the risk of passing on HIV infection to others. You should continue to take all the proper precautions.

While taking these medicines, you may continue to develop other infections.

You should keep in regular contact with your doctor.

Before you take your medicines

You must tell your doctor, pharmacist or nurse if:

- you are taking or have taken any other medicines
- you have anything else that is wrong with you
- you are allergic to any medicine, food or preservative
- you are pregnant, or trying to fall pregnant
- you are breastfeeding or are on an oral or injectable contraceptive.

Taking other medicines

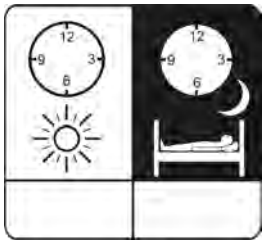
You must not take any other medicines, natural products or herbal and traditional remedies without first telling your doctor, pharmacist or nurse.

This includes any medicine you buy from the pharmacy, health food shop or supermarket.

How to take your medicines

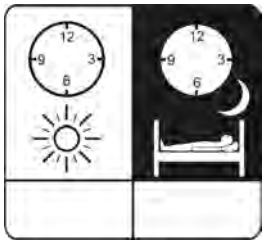
You must take your medicines as your doctor, pharmacist or nurse instructs you.

1. Stavudine (d4T)
(dark orange capsules)



Take 1 capsule in the morning and 1 capsule at night

2. Lamivudine (3TC)
(white tablets)

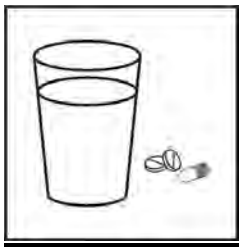


Take 1 tablet in the morning and 1 tablet at night

3. Efavirenz (EFV)
(gold capsules)

Take 3 capsules at night.

You should take your medicines at the same time every day, after food.
Taking your medicines after food will reduce bad side-effects the medicines may have on your stomach resulting in nausea and vomiting



You must take your medicines with a full glass of clean water.

You should not drink any alcohol at any time when taking these medicines.
Alcohol will increase the bad side-effects from these medicines.

You will be taking these medicines for a long time.

Do not stop taking your medicines even if you feel better.

If you forget to take them

Take them as soon as you remember. If you only remember just before your next dose, leave it out and continue as normal

Never take two doses at the same time.

If you take too much (overdose)

Immediately consult your doctor pharmacist or nurse. If they are not available, contact the nearest hospital or clinic or poison control centre.

While taking these medicines

Tell your doctor, pharmacist or nurse if, for any reason, you have not taken your medicines exactly as instructed.

If you do not tell them this

- your doctor may think that the medicines are not effective
- you may develop resistance to them.

Do not share your medicines with anyone even if they have HIV/AIDS and feel as sick as you do.

Possible side-effects

Check with your doctor as soon as possible if you have any problems while taking your medicines, even if you do not think the problems are connected with the medicines, or are not listed in this leaflet.

These side-effects have been reported

- nausea, vomiting, diarrhoea, indigestion, cough
- tingling, burning, numbness, or pain in the hands or feet
- skin rash, chills with fever
- general ill feeling
- feeling weak, dizzy and tired all the time, weight loss
- trouble in sleeping, hair loss
- headache, confusion
- pain in the chest, stomach back, muscles and joints
- flu-like symptoms.

You may not experience any of these side-effects. If you do experience any of these side-effects and they worry you, see your doctor, pharmacist or nurse.

This is not a complete list of all the side-effects. Others may occur in some people and there may be some side-effects not yet known.

After taking your medicines

Storage

Keep these medicines in a safe, dry and cool place that is away from heat and direct sunlight.

Do not store them in a bathroom or near a sink, or leave them in the car or on a windowsill.

Keep all medicines where children cannot see or reach them.

Disposal

Return all unused medicines to the clinic or to your pharmacist.

Things to remember

- **You must always take your medicines as you are told to.**
- **You must see your doctor regularly for a check up.**
- **Please ask your doctor, pharmacist or nurse if you have any questions.**

Product description

d4T: Active ingredient: 40 mg of Stavudine per capsule. A bottle contains 60 capsules
Registration number: 32/20.2.8/265/6/7

3TC: Active ingredient: 150 mg of Lamivudine per tablet. They are supplied in a white high-density polyethylene bottle, with a plastic cap. Each bottle contains 60 tablets.

Registration number: 30/20.2.8/0366

EFV: Active ingredient: 200 mg of Efavirenz per capsule. A box contains 90 capsules.

Registration number-0056-0474-92

They are all 'sugar free'

Name and business address of the applicant:

d4T: Glaxo WellSouth Africa (Pty) Ltd, Old Pretoria Road, Midrand, South Africa.Tel: 011 745 6000
3TC: Bristol-Meyers Squibb, 47 Van Buuren Road, Bedfordview, South Africa. Tel: 011 4656400
EFV: Merck (Pty) Ltd, 1685, Midrand, South Africa. Tel: 011372 5000

Date published: November 200

APPENDIX B2

Consumer Medicines Information (CMI) document

ANTIRETROVIRAL THERAPY

Stavudine, Lamivudine and Efavirenz

Patient Information Leaflet

What is in this leaflet?

Please read this leaflet carefully before you start taking your medicines.

Your medicines are:

- Stavudine (d4T),
- Lamivudine (3TC), and
- Efavirenz (EFV).

This leaflet answers some common questions about your medicines. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Sometimes new risks are found even when the medicine has been used for many years. Your doctor has weighed the risks of you taking these medicines against the benefits these medicines are expected to have for you.

If you have any concerns about taking these medicines, ask your doctor or pharmacist.

Keep this leaflet with the medicines.
You may need to read it again.

What these medicines are used for?

These are three different medicines used in combination to slow down the progression of human immuno-deficiency virus (HIV) infection, which can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

These medicines do not cure AIDS or HIV infection, but they slow the production of HIV.

In this way they stop ongoing damage to the body's immune system, which fights infection.

These medicines do not reduce your risk of passing HIV infection to others. You will still be able to pass on the HIV virus by sexual activity or by passing blood or bodily secretions, which carry the HIV. You should continue to take all appropriate precautions

While taking these medicines, you may continue to develop other infections and other complications of HIV infection. You should keep in regular contact with your doctor.

These medicines have been extensively studied but for limited periods of time. The long-term risks and benefits of taking them are not known; especially in patients without symptoms of HIV infection, or with early HIV disease.

Ask your doctor if you have any questions about why you have been prescribed these medicines.

Before you take these medicines

When you must not take them

- **Do not take these medicines if you have ever had an allergic reaction to Stavudine, Lamivudine or Efavirenz, or any other ingredients listed at the end of this leaflet.**
  Symptoms of an allergic reaction may be mild or severe. Read the Side-Effects section to find out symptoms of allergy.
- **Do not take these medicines if you are pregnant, trying to become pregnant or are breastfeeding, unless your doctor says you should.**
  Your doctor will discuss the risks and benefits of using these medicines if you are pregnant or breastfeeding.
- **Do not give your medicines to anyone else, even though their symptoms may sound similar to yours.**
- **Do not take these medicines if you have**
- **kidney disease**
- **liver disease**
- **reduced red blood cell count (anaemia),**

- **reduced white blood cell count (neutropenia).**

  If you have certain conditions your doctor may advise that you take a lower dose of these medicines.

- **Do not take any of these medicines after the expiry date (EXP) printed on the pack.**

  If you take them after the expiry date has passed, they may not work as well.

- **Do not take these medicines if the packaging is torn or shows signs of tampering.**

If you are not sure you should be taking these medicines, talk to your doctor or pharmacist.

Before you start to take them

You must tell your doctor if:

- **you are allergic to foods, dyes, preservatives or any other medicines.**
- **you are taking or have taken any other medicines.**
- **you have or have ever had, medical conditions, especially the following:**
- **liver disease, including hepatitis B or C**
- **high cholesterol**
- **mental illness**
- **seizures or fits**
- **you consume large amounts of alcohol or use recreational drugs.**

When you stop taking these medicines

If you have a long-standing viral infection of the liver (hepatitis B) it may flare up. This can cause serious illness particularly if your liver is already not working well. If you have both HIV and Hepatitis B, when you stop taking these medicines, your doctor is likely to arrange tests from time to time to check how well your liver is working and to measure virus levels.

Taking other medicines

Tell your doctor if you are taking any other medicines, including medicines you buy without a prescription from a pharmacy, supermarket or health food shop.

This includes herbal remedies and herbal products like St. John's wort, which is sold as a dietary supplement.

Some medicines have major interactions with these medicines and may affect the way they work.

Make sure your doctor and pharmacist know about all the medicines you are taking, as they have more information on medicines to be careful with or to avoid while taking these medicines.

How to take your medicines

Your doctor or pharmacist will tell you how many of each and how often to take them.

You will also find this information on the labels of your medicines.

Do not take extra tablets. Do not take the tablets more than you have been told.

How much to take

Take two d4T capsules per day, one in the morning and one at night.

Taking your d4T after food will reduce abdominal side effects it can cause when taken on an empty stomach.

Take two 3TC tablets per day, one in the morning and one at night.

Take three EFV tablets per day, all three at night before you sleep.

Taking EFV at bedtime will avoid or reduce certain side effects such as dizziness and sleepiness.

Carefully follow all the directions given to you by your doctor.

They may differ from the information contained in this leaflet.

If you do not understand the instructions on your medicines, ask your doctor or pharmacist for help.

How to take them

Your medicines should be swallowed with a full glass of water.

When to take them

You should take your medicines about the same time each day.

Taking your medicines at the same time each day is important because keeping a constant level of the medicines in your body helps to prevent resistance. Resistance means that the medicine may lose its effectiveness over time.

How long to take them

Because your medicines help control your condition, but do not cure it, you will need to take your medicines everyday. Continue taking your medicines as long as your doctor prescribes.

Do not stop taking your medicines or change the dose without first checking with your doctor. Do not let yourself run out of medicine over weekends or on holidays.

If you have a break in therapy or reduce your dose temporarily, the virus may develop resistance and your medicines may not be effective.

If, for any reason, your therapy is interrupted or stopped, tell your doctor.

If you forget to take them

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to. Otherwise, take it as soon as you remember, then go back to taking it as you would normally.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering to take your medicines, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately call your doctor, pharmacist or a poison center, for advice, even if there are no signs of discomfort or poisoning. You may need medical attention.

Keep the telephone numbers for these places handy.

If you are not sure what to do, contact your doctor or pharmacist.

While you are taking these medicines

Things you must do

Tell your doctor or pharmacist that you are taking these medicines if you are about to be started on any new medicines.

There is little information about the way other medicines may affect how d4T, 3TC and EFV work. You must tell your doctor, pharmacist, traditional healer or herbalist that you are taking these medicines before you buy from a pharmacy, health food shop, supermarket or other clinic This is especially important regarding medicines which might have an effect on the kidneys, liver, red or white blood cells or other body cells.

Tell your doctor if you become pregnant or are trying to become pregnant.

Tell your doctor if, for any reason, you have not taken your medicine exactly as prescribed.

Otherwise, your doctor may think that it was not effective and change your treatment unnecessarily.

Things you must not do

Do not stop taking your medicines or change the dose without first checking with your doctor.

Do not give these medicines to anyone else, even if their symptoms seem similar to yours.

Things to be careful of

Be careful driving or operating machinery until you know how these medicines affect you.

EFV may cause dizziness, drowsiness or affect concentration in some people, especially during the first few days. Make sure you know how you react to EFV before you drive a car or operate machinery.

If you drink alcohol, dizziness may be worse.

d4T may cause headaches and tiredness in some people.

Side-Effects

Check with your doctor as soon as possible if you have any problems while taking your medicines, even if you do not think the problems are connected with the medicines or are not listed in this leaflet.

Like other medicines d4T, 3TC and EFV can cause some side-effects. If they occur, they are most likely to be minor and temporary. However, some may be serious and need medical attention.

It is not known whether many of these side-effects are due to taking these medicines. Some of these symptoms may occur as part of HIV infection, AIDS or AIDS-related Complex.

Tell your doctor or pharmacist if you notice any of the following and they worry you:

- severe headache, dizziness,
- sleeplessness, confusion, depression, nervousness, fainting, loss of mental clarity, seizures,
- fatigue/tiredness, weakness, weight loss, generally feeling unwell,
- diarrhea, abdominal discomfort and pain, constipation, difficulty in swallowing, gas from stomach or bowel, bleeding gums or nose, blood in stools, mouth ulcers, heartburn, vomiting, loss or reduction in appetite, nausea,
- skin rash, itchiness, acne,
- changes in nail, skin or mouth colour,
- fever, chills, body odour, swelling of lips and/or tongue, flu-like symptoms, increased sensitivity to pain, back pain, enlarged glands, chest pain,
- unusual feelings in any part of the body, such as numbness, burning, tingling or pins and needles,
- increased bruising or bleeding,
- muscle aches or pains, muscle shaking or spasm or twitching, muscle disease,
- reduction in all blood cells,
- enlarged fatty liver ,abnormal results of blood tests of liver function, inflammation of the pancreas,
- cough, sore throat, hay fever, sinus problems, hoarseness,
- vision problems, hearing loss, sensitivity to light,
- passing too much urine, pain, difficulty or increased frequency of passing urine,
- blood chemistry changes with excess acidity of the blood,
- hair loss.

Ask your doctor or pharmacist to answer any questions you may have.

Some of these side effects may be worse if you:

- drink alcohol
- take medicines for certain illnesses, including depression, schizophrenia, psychoses, anxiety
- take recreational drugs

If you think you have any allergic reaction to these medicines, TELL YOUR DOCTOR IMMEDIATELY or go to the nearest clinic.

Symptoms usually include some or all of the following:

- **wheezing**
- **swelling of the lips/mouth**
- **difficulty in breathing**
- **hay fever**
- **lumpy rash (hives)**
- **fainting**
- **severe stomach cramps or pain**
- **nausea**
- **vomiting**

If you have any of the following symptoms soon after starting taking your medicines, DO NOT TAKE ANY MORE and tell your doctor IMMEDIATELY or go to the nearest clinic

- **Severe stomach pain or cramps**
- **Nausea**
- **Vomiting.**

These side effects may be due to a condition called pancreatitis.

If you are on medication for HIV and become very sick, with fast breathing, stop taking these medicines and consult your

doctor immediately. You may have a condition known as "lactic acidosis". The fast breathing is due to high acid levels in the blood.

Your liver may not be working properly and gets big and fatty. This can be life threatening. This illness occurs more in women than men.

Tell your doctor immediately or go to the nearest clinic if you develop any of the following:

- any severe skin reaction
- fast or irregular heart beat
- convulsions or fits
- liver disease with nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and/or dark coloured urine

Because these side-effects are serious, you may need urgent medical attention.

This is not a complete list of all the side-effects. Others may occur in some people and there may be some side-effects not yet known.

Tell your doctor if you notice anything else that is making you feel unwell, even if it is not on this list

Ask your doctor or pharmacist if you don't understand anything in this list.

Do not be alarmed by this list of possible side-effects. You may not experience any of them.

After taking your medicines

Storage

Keep these medicines where children cannot reach them.
A locked cupboard at least one-and-a half meters above the ground is a good place to store medicines.

Keep your medicines in a cool, dry place where they stay below 30^0 C.

Do not store them, or any other medicines, in a bathroom or near a sink. Do not leave them in the car or on the windowsills.

Heat and dampness can destroy some medicines.

Keep your medicines in their packs until it is time to take them.
If you take them out of their packs, they may not keep well.

Disposal

If your doctor tells you to stop taking these medicines, or that they have passed their expiry date, ask you pharmacist what to do with any medicines left over.

Product description

What your medicines look like

d4T: 250 mg capsules are white and pale blue with a dark blue band and printed with "WELLCOME", "250" and a unicorn logo. A box contains 60 capsules.

3TC: 150 mg tablets are white, film-coated, modified diamond shaped tablets engraved "GX CJ7" on the face.They are supplied in a white high-density polyethylene bottle, with a plastic cap. Each bottle contains 60 tablets and is in a carton.

EFV: 200 mg capsules are gold with 3809 marked in purple on the capsule
A bottle of 200mg contains 90 capsules

Ingredients

d4T:

Active ingredient- 250 mg of Stavudine per capsule.

Capsules contain maize starch, microcrystalline cellulose, sodium starch glycollate, magnesium strearate, gelatin, titanium dioxide, indigo carmine C173015,polysorbate 80 and Opacode S-1-8100HV Black.

It does not contain Gluten.

3TC:

Active ingredient- 150mg of Lamivudine per tablet

Tablets also contain microcrystalline cellulose (460), magnesium stearate (572), titanium dioxide(171), hypromellose (464), sodium starch glycollate, macrogol 400 and polysorbate 80 (433) an purified water.

EFV:

Active ingredient: 200mg of Efavirenz per capsule

Capsules also contain lactose, magnesium stearate, sodium lauryl sulfate, sodium starch glycollate, gelatin,titanium dioxide, yellow iron oxide,silicon dioxide, indigo carmine CI73015.

Manufacturer

d4T-Glaxo Wellcome
South Africa (Pty) Ltd,
Old Pretoria Road, Midrand, SA
3TC*:* Glaxo Wellcome
South Africa (Pty) Ltd, Old Pretoria Road, Midrand, SA
EFV: Merck Sharp & Dohme Ltd, South Africa.

Further information

This is not all the information that is available for your medicines: d4T, 3TC and EFV. If you do have any more questions or are not sure about anything, ask your doctor or pharmacist.

Pharmaceutical companies are not in a position to give people an individual diagnosis or medical advice. Your doctor or pharmacist is the best person to give you advice on the treatment of your condition You may also be able to find general information about your disease and its treatment from books, for example from public libraries.

Do not throw this leaflet away.

You may need to read it again.

This leaflet was prepared on the 22nd October 2003.
The information provided only applies to: Stavudine (d4T)-250 mg, Lamivudine (3TC)-150 mg and Efavirenz (EFV)- 200 mg.

APPENDIX B

Patient Information Leaflets (PILs)

APPENDIX B4

Main Study PIL: Kiswahili Version

TIBA DHIDI YA VIRUSIGEUZI

Stavudini, Lamivudini na Efavirenzi

Kijarida cha maelezo kwa mgonjwa

Kijarida hiki kina nini?

Tafadhali soma kijarida hiki kwa makini kabla ya kuanza kutumia dawa zako.

Kijarida hiki kinajibu baadhi ya maswali kuhusu dawa zako.

Maelezo haya hayachukui nafasi ya kuongea na daktari wako, mfamasia au muuguzi.

Tafadhali hifadhi kijarida hiki pamoja na dawa zako kwani unaweza kuhitaji kukisoma tena.

Matumizi ya dawa zako

Dawa hizi zitakupa nafuu na kuongeza muda wa kuishi na maisha yenye afya iwapo utazitumia ipasavyo.

Dawa hizi hazitibu UKIMWI. Zinafanya kazi kwa kupunguza kasi ya ongezeko la virusi vya UKIMWI mwilini. Zinakomesha uharibifu unaofanywa na virusi vya UKIMWI kwenye kinga ya mwili inayopigana na maradhi.

Zinaongeza chembe za CD4 (ambazo ni nzuri na huukinga mwili dhidi ya uambukizo). Zinapunguza virusi mwilini (virusi ambavyo hudhoofisha kinga mwilini, idadi kubwa ya virusi ni mbaya).

Bado unaweza kuambukiza UKIMWI kwa kufanya ngono isiyo salama (kufanya ngono bila kutumia kondomu). Dawa hizi hazipunguzi hatari ya kuwaambukiza wengine virusi vya UKIMWI.
Unapaswa kuendelea kuchukua tahadhari zinazofaa.

Unapotumia dawa hizi, unaweza kuendelea kupata uambukizo mwingine.

Kwa hiyo, unashauriwa kuendelea kumuona daktari wako mara kwa mara.

Kabla ya kutumia dawa zako

Ni lazima umuambie daktari wako, mfamasia au muuguzi kama:

- unatumia au umekwisha tumia dawa nyingine zozote
- una tatizo lingine lolote
- kuna dawa, vyakula au dawa ya kuhifadhi inayokudhuru
- ni mjamzito au unatarajia kuwa mjamzito
- unanyonyesha
- unatumia dawa au sindano za uzazi wa mpango.

Utumiaji dawa nyingine

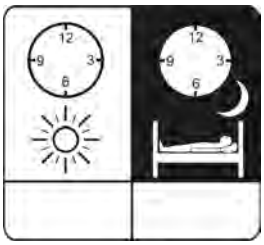
Usitumie dawa nyingine yoyote, ya kiasili, mitishamba au tiba za jadi bila kumtaarifu daktari wako, mfamasia au muuguzi. Hii inajumuisha dawa zote unazonunua kwenye maduka ya dawa, ya vyakula na makubwa.

Jinsi ya kutumia dawa zako

Ni lazima utumie dawa zako kama ulivyoelekezwa na daktari wako, mfamasia au muuguzi.

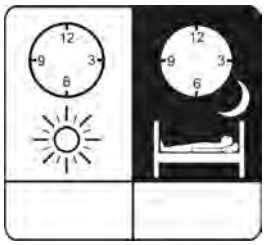
Kiasi cha kutumia

1. Stavudini (d4T)
(kapsuli za rangi ya chungwa iliyokolea)



Meza kapsuli moja asubuhi na kapsuli moja usiku.

2. Lamivudini (3TC)
(vidonge vyeupe)



Meza kidonge kimoja asubuhi na kidonge kimoja usiku.

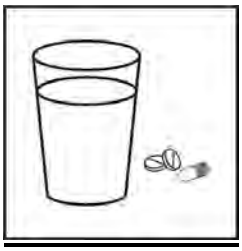
3. Efavirenzi (EFV)
(kapsuli za rangi ya dhahabu)

Meza kapsuli tatu usiku

Muda wa kutumia

Unashauriwa kumeza dawa zako muda huo huo kila siku.

Jinsi ya kutumia



Ni lazima umeze dawa zako kwa glasi moja nzima ya maji masafi

Kipindi cha kutumia

Ni lazima kutumia dawa hizi kila siku, kwa maisha yako yote.

Usiache kutumia dawa hata kama unajisikia nafuu.

Endapo umesahau kumeza dawa

Meza mara tu ukumbukapo. Iwapo muda wa kumeza dozi inayofuatia umekaribia, acha uliyosahau na meza inayofuatia, kama kawaida.

Usimeze dozi mbili kwa wakati mmoja.

Ukimeza dawa nyingi (kuzidisha kipimoi)

Muone daktari, mfamasia au muuguzi haraka iwezekanavyo. Kama hawapo nenda kwenye hospitali au zahanati ya karibu.

Wakati unapotumia dawa hizi

Mambo usiyotakiwa kufanya

Usichangie matumizi ya dawa zako na mtu mwingine hata kama ni muathirika wa UKIMWI na anaumwa kama wewe.

Usinywe pombe wakati wote unapotumia dawa hizi.
Pombe itaongeza madhara ya dawa hizi mwilini.

Mambo muhimu ya kufanya

Kama kwa sababu yoyote hujatumia dawa zako ipasavyo mwambie daktari mfamasia au muuguzi.
Kama usipowaambia

- daktari wako anaweza kufikiri kuwa dawa hazifanyi kazi vizuri
- virusi mwilini vitakuwa sugu dhidi ya dawa.

Madhara mengine

Muone daktari haraka iwezekanavyo kama utapata matatizo yoyote unapotumia dawa hizi, hata kama unadhani matatizo hayo hayajasababishwa na dawa hizi au hayapo kwenye orodha ifuatayo.

Madhara haya yameripotiwa

- kichefuchefu na kutapika
- kuharisha, kuvimbiwa
- kupoteza hamu ya kula
- kusikia uchovu, udhaifu na kizunguzungu wakati wote
- kukosa usingizi, maumivu ya kichwa na kuchanganyikiwa
- kunyonyoka nywele, kikohozi
- maumivu ya kifua, misuli, mgongo, tumbo na viungo
- homa, vipele mwilini
- mikono na miguu kufa ganzi, kuwaka moto na kuuma
- kupungua uzito, dalili ya mafua.

Inawezekana usipatwe na madhara yoyote kati ya haya. Lakini iwapo unapatwa na madhara haya na yanakutia shaka muone daktari wako, mfamasia au muuguzi mara moja.

Hii siyo orodha yote ya madhara. Mengine hujitokeza kwa baadhi ya watu, na huenda madhara mengine bado hayajajulikana.

Baada ya kumeza dawa zako

Kuhifadhi

Hifadhi dawa hizi mahali, salama, pakavu na pasipo na joto, mbali na moto na mwanga wa jua.

Usihifadhi bafuni au karibu na sinki, au kuziacha ndani ya gari au kwenye kizingiti cha dirisha.

Hifadhi dawa zote mahali ambapo watoto hawawezi kuona wala kufikia.

Utupaji

Rudisha dawa zote zilizobaki zahanati au kwa mfamasia.

Mambo ya kukumbuka

- **Ni lazima utumie dawa zako kufuatana na maelezo ya daktari.**
- **Muone daktari mara kwa mara ili akuchunguze afya yako.**
- **Kama una maswali, tafadhali usisite kumuuliza daktari wako, mfamasia au muuguzi.**

Maelezo ya dawa

d4T: Dawa yenyewe: Mg 40 za Stavudini kila kapsuli. Chupa moja ina kapsuli 60.

Namba ya usajili: 32/20.2.8/265/6/7

3TC: Dawa yenyewe:Mg 150 za Lamivudini kila kidonge. Zinaletwa kwenye chupa ya plastiki yenye kifuniko cheupe. Kila chupa ina vidonge 60.

Namba ya usajili: 30/20.2.8/0366

EFV: Dawa yenyewe: Mg 200 za Efavirenzi kila kapsuli. Boksi lina kapsuli 90.

Namba ya usajili: 0056-0474-92

'Dawa hizi hazina sukari'

Jina na anuani ya mtengenezaji

d4T: Bristol-Meyers Squibb, 47 Van Buuren Road, Bedfordview, Afrika Kusini. Simu: +27114656400
3TC: Glaxo Wellcome South Africa (Pty) Ltd, Old Pretoria Road, Midrand, Afrika Kusini. Simu: +27117456000
EFV: Merck (Pty) Ltd, 1685, Midrand, Afrika Kusini. Simu: +27113725000

Tarehe kilipochapishwa: Desemba 2003

APPENDIX B5

Main Study PIL: IsiXhosa Version

UNYANGO LWE-ANTIRETROVAYIRALI

(ANTIRETROVIRAL THERAPY)

iStavudine, Lamivudine ne-Efavirenz (S4)

Iphetshana eliqulethe ulwazi olwenzelwe izigulana

Liqulathe ni eli phetshana?

Nceda funda eli phetshana ngokulumkileyo phambi kokuba uqale ukusebenzisa amayeza akho.

Eli phetshana liphendula eminye imibuzo eqhelekileyo malunga namayeza akho.

Aliyithathi indawo yokuthetha nogqirha, usokhemisti okanye umongikazi wakho.

Ligcine eli phetshana namayeza.Usenokuphinda udinge ukulifunda kwakhona.

Into asetyenziselwa yona amayeza akho

La mayeza aya kunceda uzive ngcono, kwaye uphile ubomi obude, obusempilweni ukuba uwasebenzisa ngendlela eyiyo.

La mayeza awayinyangi iHIV/AIDS.
Asebenza ngokuthomalalisa ukukhula kwegciwane le-HIV anqanda, umonakalo obangelwa yi-HIV kumajoni omzimba alwa nezifo. Anyusa isibalo se-CD4 (la ngamajoni alungileyo akhusela umzimba kwizifo). Anciphisa I-"viral load" (ubungakanani be HIV emzimbeni, umthwalo wentsholongwane akulunganga ube phezulu).

Usengayisasaza iHIV/AIDS ngokwabelana ngesondo ungazikhuselanga (ngokungasebenzisi ikondom ngexesha lesondo).
La mayeza akanqandi ubungozi bokosulela abanye abantu nge-HIV. Qhubeka uthatha amanyathelo okukunqanda oku. Ngethuba usebenzisa la mayeza usenokuqhubeka ngokuvela ezinye izifo.

Yithi rhoqo unoqhagamshelwano nogqirha wakho.

Phambi kokusebenzisa amayeza akho

Xelela ugqirha, usokhemisti okanye umongikazi ukuba:

- unamanye amayeza owasebenzisayo okanye ubuwasebenzisa
- unokunye ukugula onako
- akulungelwa ngamayeza athile, ukutya nezikhuseli-kubola
- ukhulelwe okanye uzama ukukhulelwa
- uyancancisa okanye uyacwangcisa, ngepilisi okanye inaliti.

Ukusebenzisa amanye amayeza

Musa ukutya amanye amayeza, iimveliso zendalo okanye amayeza esintu, awamaxhwele namagqirha ungaxelelanga ugqirha, usokhemisti okanye umongikazi.

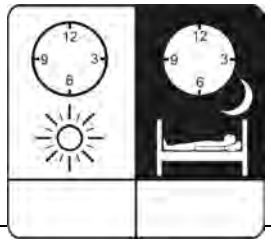
Oku kuquka nawaphi amayeza owathenga ekhemesti nakwivenkile zempilo okanye zokutya.

Imigaqo yokutya amayeza akho

Watye amayeza ngokwemiyalelo kagqirha, usokhemisti okanye umongikazi.

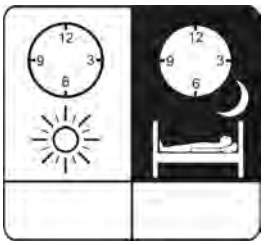
Imilinganiselo oyitya ngayo I -

1.Stavudine (d4T)
(iikhapsuli ezimdaka bu-orenji)



Thatha ikhapsuli ibenye kusasa, ibenye nangokuhlwa.

2.Lamivudine (3TC)
(Iipilisi ezimhlophe)



Thatha ipilisi ibenye kusasa, kwakhona ibenye ebusuku.

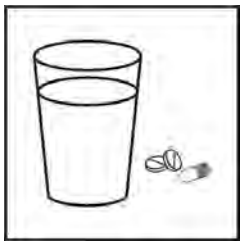
3.Efavirenz (EFV)
(iikhapsuli ezibugolide)

Thatha iikhapsuli zibentathu ebusuku.

Uzithatha nini ezi pilisi

Watye amayeza rhoqo ngamaxesha amanye ntsuku zonke.

Uzisebenzisa njani



Zisele ipilisi ngeglasi ezeleyo yamanzi acocekileyo.

Uzisela ixesha elingakanani

Zisele yonke imihla ubomi bakho bonke.

Musa ukuyeka ukuzisela nokuba uziva ungcono.

Xa ulibele ukuzisela

Zisele kwangoko wakuzikhumbula phambi kokuba usele ezilandelayo
Ukuba ukhumbule seyiza kuba lixesha lomlinganiselo olandelayo, sowuyeka lowo, uqhubekeke ngalowo welo xesha.
Ungaze usele iipilisi zamaxesha amabini ahlukeneyo ngexesha elinye.

Ukuba uthe wathatha ngaphezulu komlinganiselo

Ngoko nangoko dibana nogqirha, usokhemisti okanye umongikazi akuncede. Ukuba awubafumani yiya esibhedlele, okanye kwikliniki efutshane nawe, kungenjalo kwindawo enokulwa netyhefu.

Ngethuba usebenzisa la mayeza

Izinto omawungazenzi

Musa ukwabelana naye nabanina ngamayeza akho, nokuba nabo bane-

HIV/AIDS okanye bagula njengawe.

Akufuneki usele utywala nanina usasebenzisa la mayeza.
Utywala bunganyusa okungalunganga kula mayeza.

Izinto omawuzenze

Xelela ugqirha, usokhemisti okanye umongikazi, ukuba uthe akwawasebenzisa

ngokwemiyalelo amayeza akho.

Ukuba akubaxeleli oku

- Ugqirha usenokucinga ukuba awasebenzi kakuhle amayeza
- Umzimba wakho unokuthi uvukwe kukungamelani namayeza

Imiphumela engeyiyo

Dibana nogqirha ngokukhawuleza ukuba uthe wavukwa naziphina

iinkathazo ngethuba usebezisa la mayeza, nokuba sowucinga ukuba ezo nkathazo azinanto yakwenza nala mayeza okanye azibhalwanga kweli phetshana.

Le miphumela ilandelayo iyabikwa

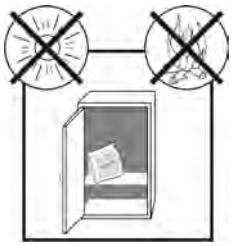
- isicefu-cefu, ukugabha, urhudo, ukuqhina, ukhohlokhohlo
- untlontlozelo,isitshisa, inkantsi,ukuqaqamba kwezandla neenyawo
- ukurhawuzela kolusu, ukugodola nefiva
- ukuziva ungekho mpilweni
- ukuziva utyhafile, unesiyezi, kwaye udiniwe lonke ixesha nokuhla kobunzima
- ukulala nzima, ukulahlekelwa ziinwele
- intloko ebuhlungu, ukuphazamiseka engqondweni
- iintlungu esifubeni, esiswini, emqolo,kwizihlunu nasekudibaneni kwamalungu
- Iimpawu zokuba ngathi uza kuba nomkhuhlane

Usenokungabi nazo ezi mpawu zibaliweyo. Ukuba uthe wanayo enye yezi zinto zibaliweyo, yaye iyakukhathaza bonana nogqirha wakho, usokhemisti okanye unesi.

Asiloluhlu lupheleleyo lwemiphumela engalunganga olu. Eminye isenokuvakala kwabanye abantu, ikhona neminye engekaziwa.

Emva kokusebenzisa amayeza akho

Ukuwagcina



Wagcine la mayeza kwindawo ekhuselekileyo, eyomileyo nepholileyo kude ebushushwini nemitha yelanga.

Musa ukuwagcina egumbini lokuhlamba okanye kwisitya sokuhlanbela, ungawashiyi emotweni okanye efestileni.

Gcina onke amayeza apho abantwana bangenakufikelela khona.

Ukuwalahla

Buyisela onke amayeza angasebenzanga ekliniki okanye kusokhemisti.

Izinto omawuzikhumbule

- **Wathathe amayeza akho kanye ngendlela oyalelwe ngayo.**
- **Kufuneka ubonane nogqirha wakho rhoqo akuxilonge.**
- **Nceda buza ugqirha wakho, usokhemisti okanye unesi ukuba unemibuzo.**

Inkcazelo ngemveliso

d4T: Active ingredient: 40 mg of Stavudine per capsule. A bottle contains 60 capsules
Registration #:32/20.2.8/265/6/7
3TC: Active ingredient: 150 mg of Lamivudine per tablet. They are supplied in a white high-density polyethylene bottle, with a plastic cap. Each bottle contains 60 tablets.
Registration # 30/20.2.8/0366
EFV: Active ingredient: 200 mg of Efavirenz per capsule. A box contains 90 capsules.
Registration #: 0056-0474-92.
Zonke 'azinaswekile'

Igama nedilesi yeshishini lomceli:
d4T: Bristol-Meyers Squibb, 47 Van Buuren Road, Bedfordview, South Africa. Tel: 011 4656400
3TC: Glaxo Wellcome South Africa (Pty) Ltd, Old Pretoria Road, Midrand, South Africa. Tel: 011 745 6000
EFV: Merck (Pty) Ltd, 1685, Midrand, South Africa. Tel: 011372 5000

Umhla eshicilelwe ngawo:
Matshi 2004

APPENDIX C1

Pilot Study Questionnaire

Questionnaire - Antiretroviral Therapy

(Assessment of a PIL)

Name of respondent: _____ | | | | 1

Language of materials used: | English [1] | IsiXhosa [2] | Kiswahili [3] | | 2

Section 1: Demographics

1.1 Gender			Male [1]	Female [2]		3
1.2 Race	Black [1]	White [2]	Coloured [3]	Indian [4]		4
1.3 Age	< 21 [1]	21- 40 [2]	41- 65 [3]	> 65 [4]		5
1.4 Home Language	IsiXhosa [1]	Kiswahili [2]	English [3]	Other [4]		6

1.5 Language proficiency	Home language	Listen[1]	Speak[2]	Read[3]		7
	English	Listen[1]	Speak[2]	Read[3]		8
	Other	Listen[1]	Speak[2]	Read[3]		9

If other, please specify: _____

1.6 Number of years in school	0-5 [1]	6-11 [2]	>11 [3]		10
1.7 Are you currently employed?		Yes[1]	No[2]		11

1.8 What work do you do?

Clerical[1]	Farm[2]	Domestic[3]	Education[4]	Mechanic[5]	
Shop assistant[6]	Hospital worker[7]	Self-employed[8]	Unemployed[9]	Other[10]	12

If other, please specify: _____

Section 2: Lifestyle

2.1 What time do you wake up in the morning?		Same time [1]	Irregular [2]	13
2.2 What time do you go to bed at night?		Same time [1]	Irregular [2]	14
2.3 What is you favourite drink?	Cool drink [1]	Hot drink [2]	None [3]	15
2.4 Can you tell the time from a clock face?	Yes [1]	No [2]	Digital time only [3]	16

Section 3: Understanding of the Leaflet

(Participants will now be given the leaflet and asked to read it. They will be timed using a stopwatch)

3.1 Time taken to read it (in mins)

< 5mins[1]	5-10 mins[2]	10-15 mins[3]	> 15mins[4]	17

3.2 Finding and Understanding of Instructions (according to the leaflet)

3.2.1 Using the leaflet, can you tell me the name of these medicines?	Located [1]	Not Located [2]		18
3.2.2 Can you describe the medicines?	Located [1]	Not Located [2]		19
3.2.3 a. Can one still spread HIV/AIDS while taking these medicines?	Located [1]	Not Located [2]		20
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		21
3.2.4 a. If you buy any medicine from a health shop or a traditional healer, what should you do before you take it?	Located [1]	Not Located [2]		22
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		23
3.2.5 a. According to the leaflet, how many times a day must you take Stavudine (d4T) capsules?	Located [1]	Not Located [2]		24
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		25
3.2.6 a. Looking at the leaflet, does it tell you what to do if you miss a dose of your medicines?	Located [1]	Not Located [2]		26
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		27
3.2.7 a. Suppose you start getting a fever, headaches and feel confused while taking these medicines. Does the leaflet tell you what to do?	Located [1]	Not Located [2]		28
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		29
3.2.8 a. What do these medicines do to the viral load?	Located [1]	Not Located [2]		30
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		31
3.2.9 a. What does the leaflet tell you to do if you take too much of these medicines by mistake?	Located [1]	Not Located [2]		32
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		33
3.2.10 a. Do these medicines cure HIV/AIDS?	Located [1]	Not Located [2]		34
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		35
3.2.11 a. According to the leaflet, if you are taking any other medicines, what should you do before taking these medicines?	Located [1]	Not Located [2]		36
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		37
3.2.12 a. How long do you have to take these medicines for?	Located [1]	Not Located [2]		38
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		39
3.2.13. a. According to the leaflet, if you have any allergies,what should you do before taking these medicines?	Located [1]	Not Located [2]		40
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]		41
3.2.14 a. Does the leaflet tell you how many of Efavirenz (EFV) capsules you should take each time?	Located [1]	Not Located [2]		42
	Correct [1]	Incorrect [2]		43

3.2.15 a. Suppose you have been feeling better for the past month;
Can you stop taking your medicines? | Located [1] | Not Located [2] | | 44

b. Can you tell me what it says in your own words? | Correct [1] | Incorrect [2] | | 45

3.2.16 a. What should you do with left over medicines? | Located [1] | Not Located [2] | | 46

b. Can you tell me what it says in your own words? | Correct [1] | Incorrect [2] | | 47

3.2.17 a. Suppose you start feeling weak and tired all the time while taking these medicines. Does the leaflet tell you what to do? | Located [1] | Not Located [2] | | 48

b. Can you tell me what it says in your own words? | Correct [1] | Incorrect [2] | | 49

3.2.18 a. Does the leaflet tell you how to store these medicines? | Located [1] | Not Located [2] | | 50

b. Can you tell me what it says in your own words? | Correct [1] | Incorrect [2] | | 51

3.2.19 a. Is there any advice in this leaflet about sharing your medicines with someone else who has HIV/AIDS? | Located [1] | Not Located [2] | | 52

b. Can you tell me what it says in your own words? | Correct [1] | Incorrect [2] | | 53

3.2.20 a. If you want more information about your treatment and the medicines you are taking; Is there any information in this leaflet regarding who to talk to? | Located [1] | Not Located [2] | | 54

b. Can you tell me what it says in your own words? | Correct [1] | Incorrect [2] | | 55

3.3 Questions Answered Correctly

3.3.1 No. of questions answered correctly

a. Located (total = 20) _____ | | 56

b. Understood (total = 18) _____ | | 57

3.4 Rating for Understanding of the Leaflet : _____ | | 58

Both located and understood
Total score = 36

Additional Notes:

_____

_____

_____

_____

_____

_____

_____

Section 4: Acceptability of the PIL

4.1 How easy was it to read this leaflet?	Easy[1]	Average[2]	Difficult[3]		59
4.2 Is the writing large enough?		Yes[1]	No[2]		60
4.3 What do you think of the length of the sentences?	Too long[1]	Right[2]	Too short[3]		61
(Participants are asked if they are too long, ok or too short)					
4.4 Is there enough space between the lines?	Too wide[1]	Right size[2]	Too small[3]		62
4.5 If you had just started taking these medicines and this was all the information you were given about them, do you think it is enough?		Yes[1]	No[2]		63
(Participants must be reminded that these are dangerous medicines and they need to know all the important information about them)					
4.6 Do you like having pictures in the leaflet?		Yes[1]	No[2]		64
4.7 Do you think the pictures will help you understand and recall the information better?		Yes[1]	No[2]		65
4.8 Are there any words in the text that you did not understand?	No[1]	Yes, a few[2]	Yes, many[3]		66

(If there are some words the participant did not understand, they should mention some of them)

Words not understood: _____

_____

4.9 Is the size of the leaflet ok?			Yes[1]	No[2]	67
If not, what size would you prefer it to be?					
(The participant should be told to consider both print size and layout)					
	2 sheets-A4[1] *Original PIL*	1 sheet-A4[2] *Arial 10pts,2 pgs Portrait*	1 sheet-A5[3] *Arial 9pts,2pgs Landscape*	Z-fold[4] *Arial 9pts,2 pgs Landscape*	68
4.10 Did you like anything in particular about this leaflet?			Yes[1]	No[2]	69
If yes, please elaborate:					

_____

_____

4.11 Is there anything else about this leaflet that we haven't talked about which you'd like to mention?		Yes[1]	No[2]	70
If yes, what is it?				

_____

_____

Section 5: Comparison of PIL with CMI

(The participant is shown both the PIL and CMI on ART)

5.1 Which of the two leaflets would you prefer, with respect to:				
5.1.1 Print size	PIL[1]	CMI[2]		71
5.1.2 Font style	PIL[1]	CMI[2]		72
5.1.3 Length of the sentences	PIL[1]	CMI[2]		73
5.1.4 The space between the lines and white space	PIL[1]	CMI[2]		74
5.1.5 The number of pages	PIL[1]	CMI[2]		75
5.1.6 The presence/absence of pictures	PIL[1]	CMI[2]		76
5.2 Which leaflet do you think is easier to read?	PIL[1]	CMI[2]		77

5.3 How many pages would you prefer to receive?	1 page[1]	2 pages[2]	> 2 pages[3]	78

5.4 The CMI gives much more information about your medicines; would you like to receive this extra information:				
5.4.1 The first time you receive your medicines?	Yes[1]	No[2]		79
5.4.2 After you start taking the medicines?	Yes[1]	No[2]		80

Additional notes:

Thank You.

APPENDIX C2

Main Study Questionnaire

Questionnaire - Antiretroviral Therapy

(Assessment of a PIL)

Name of respondent: _____ 1

Language of materials used: English [1] | IsiXhosa [2] | Kiswahili [3] 2

Section 1: Demographics

1.1 Gender			Male [1]	Female [2]	3
1.2 Race	Black [1]	White [2]	Coloured [3]	Indian [4]	4
1.3 Age	< 21 [1]	21- 40 [2]	41- 65 [3]	> 65 [4]	5
1.4 Home Language	IsiXhosa [1]	Kiswahili [2]	English [3]	Other [4]	6

1.5 Language proficiency	Home language	Listen[1]	Speak[2]	Read[3]	7
	English	Listen[1]	Speak[2]	Read[3]	8
	Other	Listen[1]	Speak[2]	Read[3]	9

If other, please specify: _____

1.6 Number of years in school	0-5 [1]	6-11 [2]	>11 [3]	10
1.7 Are you currently employed?		Yes[1]	No[2]	11

1.8 What work do you do?

Clerical[1]	Farm[2]	Domestic[3]	Education[4]	Mechanic[5]	
Shop assistant[6]	Hospital worker[7]	Self-employed[8]	Unemployed[9]	Other[10]	12

If other, please specify: _____

1.9 How often do you visit a clinic/hospital?

Every:	Month [1]	2 Months[2]	6 months[3]	Once per year[4]	13

1.10 How often do you take medicines?

Every day[1]	Often[2]	Not very often[3]	Never[4]	14

Section 2: Lifestyle

2.1 What time do you wake up in the morning?	Same time [1]	Irregular [2]	15
2.2 What time do you go to bed at night?	Same time [1]	Irregular [2]	16

2.3 What is your favourite drink?	Cool drink [1]	Hot drink [2]	None [3]	17
2.4 Can you tell the time from a clock face?	Yes [1]	No [2]	Digital time only [3]	18

Section 3: Understanding of the Leaflet

(Participants will now be given the leaflet and asked to read it. They will be timed using a stopwatch)

3.1 Time taken to read it (in mins)

< 5mins[1]	5-10 mins[2]	10-15 mins[3]	> 15mins[4]	
				19

3.2 Pictograms

(Participants will be asked to look at individual pictograms and explain what they think they mean)

3.2.1 a.What is this picture showing? b. What do you think it means?	Correct [1]	Incorrect [2]	*(Twice daily)*	20
3.2.2 a.What is this picture showing? b. What do you think it means?	Correct [1]	Incorrect [2]	*(Once daily)*	21
3.2.3 a.What is this picture showing? b. What do you think it means?	Correct [1]	Incorrect [2]	*(Water)*	22
3.2.4 a.What is this picture showing? b. What do you think it means?	Correct [1]	Incorrect [2]	*(Alcohol)*	23
3.2.5 a.What is this picture showing? b. What do you think it means?	Correct [1]	Incorrect [2]	*(Heat)*	24
3.2.6 a.What is this picture showing? b. What do you think it means?	Correct [1]	Incorrect [2]	*(Children)*	25

Additional notes:

3.3 Finding and Understanding of Instructions (according to the leaflet)

3.3.1 Using the leaflet, can you tell me the name of these medicines and describe them?	Located [1]	Not Located [2]	26
3.3.2 a. Can one still spread HIV/AIDS while taking these medicines?	Located [1]	Not Located [2]	27
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	28
3.3.3 a. If you do not take your medicines as instructed, what may happen?	Located [1]	Not Located [2]	29
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	30
3.3.4 a. According to the leaflet, how many times a day must you take Stavudine (d4T) capsules?	Located [1]	Not Located [2]	31
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	32
3.3.5 a. Looking at the leaflet, does it tell you what to do if you miss a dose of your medicines?	Located [1]	Not Located [2]	33
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	34
3.3.6 a Like any other medicines, these medicines have both good and bad effects. Does the leaflet tell you what the bad effects are and what you should do if you experience any of them?	Located [1]	Not Located [2]	35
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	36
3.3.7 a. What do these medicines do to the viral load?	Located [1]	Not Located [2]	37
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	38
3.3.8 a. What does the leaflet tell you to do if you take too much of these medicines by mistake?	Located [1]	Not Located [2]	39
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	40
3.3.9 a. Do these medicines cure HIV/AIDS?	Located [1]	Not Located [2]	41
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	42
3.3.10 a. According to the leaflet, if you are taking any other medicines, what should you do before taking these medicines?	Located [1]	Not Located [2]	43
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	44
3.3.11 a. How long do you have to take these medicines for?	Located [1]	Not Located [2]	45
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	46

3.3.12. a. According to the leaflet, if you have any allergies, what should you do before taking these medicines?	Located [1]	Not Located [2]	47
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	48
3.3.13 a. Does the leaflet tell you how many of Efavirenz (EFV) capsules you should take each time?	Located [1]	Not Located [2]	49
	Correct [1]	Incorrect [2]	50
3.3.14 a. Suppose you have been feeling better for the past month; Can you stop taking your medicines?	Located [1]	Not Located [2]	51
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	52
3.3.15 a. What should you do with left over medicines?	Located [1]	Not Located [2]	53
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	54
3.3.16 a. Some medicines can be taken with alcohol. Can you take alcohol while taking these medicines.?	Located [1]	Not Located [2]	55
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	56
3.3.17 a. Does the leaflet tell you how to store these medicines?	Located [1]	Not Located [2]	57
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	58
3.3.18 a. Is there any advice in this leaflet about sharing your medicines with someone else who has HIV/AIDS?	Located [1]	Not Located [2]	59
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	60
3.3.19 a. Does it matter if you take these medicines at different times every day?	Located [1]	Not Located [2]	61
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	62
3.3.20 a. If you want more information about your treatment and the medicines you are taking, who should you talk to?	Located [1]	Not Located [2]	63
b. Can you tell me what it says in your own words?	Correct [1]	Incorrect [2]	64

3.4 Questions Answered Correctly

3.4.1 No. of questions answered correctly

a. Located (total = 20) _____ 65

b. Understood (total = 19) _____ 66

3.5 Rating for Understanding of the Leaflet : _____ 67

Both located and understood
Total score = 39

Additional Notes:

_____

_____

_____

_____

_____

_____

_____

Section 4: Acceptability of the PIL

4.1 How easy was it to read this leaflet?	Easy[1]	Average[2]	Difficult[3]		68
4.2 Is the writing large enough?		Yes[1]	No[2]		69
4.3 What do you think of the length of the sentences?	Too long[1]	Right[2]	Too short[3]		70
(Participants are asked if they are too long, ok or too short)					
4.4 Is there enough space between the lines?	Too wide[1]	Right size[2]	Too small[3]		71
4.5 If you had just started taking these medicines and this was all the information you were given about them, do you think it is enough?		Yes[1]	No[2]		72
(Participants must be reminded that these are dangerous medicines and they need to know all the important information about them)					
4.6 Do you like having pictures in the leaflet?		Yes[1]	No[2]		73
4.7 Do you think the pictures will help you understand and recall the information better?		Yes[1]	No[2]		74
4.8 Are there any words in the text that you did not understand?	No[1]	Yes, a few[2]	Yes, many[3]		75

(If there are some words the participant did not understand, they should mention some of them)

Words not understood: _____

_____

4.9 Is the size of the leaflet ok?

Yes[1]	No[2]		
			76

4.10 What size would you prefer the leaflet to be?

(Participant is shown 3 other PILs and told to consider both print size and layout)

2 sheets-A4[1] *Original PIL*	1 sheet-A4[2] *Arial 10pts,2 pgs Portrait*	1 sheet-A5[3] *Arial 9pts,2pgs Landscape*	Z-fold[4] *Arial 9pts,2 pgs Landscape*		
					77

4.11 In what language would you prefer to read the leaflet ?

English [1]	IsiXhosa [2]	Kiswahili [3]		
				78

4.12 Did you like anything in particular about this leaflet?

Yes[1]	No[2]		
			79

If yes, please elaborate:

_____

_____

4.13 Is there anything else about this leaflet that we haven't talked about which you'd like to mention?

Yes[1]	No[2]		
			80

If yes, what is it?

_____

_____

Section 5 : Comparison of PIL with CMI

(The participant is shown both the PIL and CMI on ART)

5.1 Which of the two leaflets would you prefer, with respect to:

	PIL[1]	CMI[2]		
5.1.1 Print size				1
5.1.2 Font style				2
5.1.3 Length of the sentences				3
5.1.4 The space between the lines and white space				4
5.1.5 The number of pages				5
5.1.6 The presence/absence of pictures				6

5.2 Which leaflet do you think is easier to read?

PIL[1]	CMI[2]		
			7

5.3 How many pages would you prefer to receive?

1 page[1]	2 pages[2]	> 2 pages[3]		
				8

5.4 The CMI gives much more information about your medicines; would you like to receive this extra information:

5.4.1 The first time you receive your medicines?	Yes[1]	No[2]	9
5.4.2 After you start taking the medicines?	Yes[1]	No[2]	10

Additional notes:

Thank You.