CHAPTER 3: ANTIRETROVIRAL THERAPY (ART)

3.1 Introduction

Since antiretroviral treatment was introduced in 1986, mortality and accompanying opportunistic infections in patients with advanced HIV infections have declined. Likewise, according to the guidelines of the World Health Organization (WHO:2002), on the use of antiretroviral therapy, mortality has dropped significantly in Europe and North America, due to access to HAART. The main obstacles with regard to the administration of antiretroviral drugs in developing countries have been the high cost and the lack of a healthcare infrastructure necessary to access these. There were also concerns that the difficulties with adherence to complicated medication regimens would lead to treatment failure and the accumulation of resistant viral strains that could promote the spread of drug resistance.

The researcher believes that great advances have been made in the treatment of patients with HIV infection. The use of appropriate potent combination antiretroviral therapy consisting of three different drug classes, as well as prophylactic interventions to prevent opportunistic infections, are of critical importance in providing each patient with the best opportunity to live a long and healthy life, despite the presence of HIV infection. In South Africa, a significant number of people also use alternative, complementary and traditional medicines. The use of such a myriad of potentially conflicting drugs calls for some education regarding drug use, as well as the prevention and management of their adverse effects, drug interactions and medication errors. (South Africa, 2006:16).

The management of HIV disease is supported by many pillars: lifestyle changes and support, treatment and prevention of opportunistic infections and antiretroviral therapy. Because of the complicated nature of HIV disease and the chronic nature of the treatment of HIV/AIDS and opportunistic infections, it is
imperative to make use of multidisciplinary teamwork and collaboration between various disciplines, more than ever before.

Kasper et al. (1999:1901) confirm that the treatment of patients with HIV infection requires not only a comprehensive knowledge of the possible disease process that may occur, but also the ability to deal with the problems of a chronic, potentially life-threatening illness. Furthermore, the said researcher asserts that the patients must also be educated concerning the potential development of resistance to antiretroviral drugs, and thus, the importance of constant and continued adherence. The researcher concurs that “The cornerstone of HIV prevention strategy is education, counselling and behaviour modification” (Isselbacher et al, 1999:1910).

The researcher believes that ART regimens have resulted in the reduction of mortality, retarded the progression of the HIV to AIDS and, also, reduced the incidence of opportunistic infections and hospitalisations, these results offer proof that ART contributes to the enhancement of the quality of life of HIV/AIDS positive individuals. These effects also contribute to increased productivity and therefore, to the economy, in general.

The matters that will be considered in this chapter are the goals of ART, different antiretroviral drugs, response to, and the prognosis of antiretroviral treatment, treatment failure, side effects, and drug interactions.

3.2 Goals of antiretroviral therapy

According to the National Department of Health’s guideline for Antiretroviral Treatment, (South Africa, 2003:2) the primary goal of ART is to decrease HIV-related morbidity and mortality. It further aims to provide maximal viral suppression, restore the immune function and improve the quality of life of HIV-positive patients.

The aforementioned guideline further stipulates the following goals for ART:
The patient should experience fewer HIV-related illnesses;
- The patient's CD4 count should rise and remain above the baseline count;
- The patient's viral load should become undetectable (<400 copies/ml) and remain undetectable on ARV therapy.
- The secondary goal is to decrease the incidence of HIV by:
  - An increased uptake in voluntary testing and counselling with more people knowing their status and practising safer sex;
  - The reduction of transmission in discordant couples;
  - Reducing the risk of transmission from mother-to-child.

The primary goals of ART, according to the (Southern African HIV Clinicians Society, 2004) are the:

- Improvement of quality of life;
- Reduction of HIV-related morbidity and mortality;
- Maximal and durable suppression of viral load; and
- Restoration and/or preservation of immunological function.

Botes (2005:119-124) also differentiates between primary and secondary goals of ART:

**Primary goals:**
- Decrease in the viral load to undetectable levels for as long as possible in order to halt disease progression and prevent/reduce resistant mutations;
- Increase and maintain a high CD4 T cell count;
- Improve duration and quality of life;
- Reduce HIV-related illnesses and death; and
- Reduce HIV transmission.

**Secondary goals:**
- Increase voluntary counselling and testing;
- Decrease HIV transmission rates in discordant couples;
- Reduce the risk of mother-to-child HIV transmission.
The researcher argues that the primary goal and indication for ART should be to improve the biopsychosocial functioning of patients in general, since HIV/AIDS, like many chronic diseases, affects all aspects of a patient’s life. In this respect Ross and Deverell (2004:211) assert the following regarding quality of life: “The pendulum of the pandemic has swung from dying from AIDS to living with HIV infection; a primary focus of therapeutic intervention is to enhance quality of life.” Such quality and the psychosocial consequences of illness and treatment have not always been considered a psychological issue of importance. By measuring the impact of treatment on the individual’s quality of life, one can assess whether the treatment is more harmful than the disease itself (Taylor, 2003:356). Patients should experience increased physical strength, gain independence, reclaim lost roles and take control of their lives.

The researcher is further of the view that the role of the social worker is to assess patients for ART, motivate them to adhere to it and to support them in adapting to the psychological and physical effects of living with a chronic illness. People living with HIV/AIDS need to make intermittent or permanent changes to their physical and social activities in order to undertake such an adaptation. The social worker can facilitate this process.

3.3 Initiating Antiretroviral Therapy

Recent studies indicate that there is no benefit in starting ART in asymptomatic patients with CD 4 cell counts > 350cells/cu mm. (Spencer, 2005:10); However, there is a general consensus that patients who suffer from an AIDS-defining disease, and who are severely symptomatic (even though they do not suffer from an AIDS-defining disease), and those whose CD4 cell counts are below 200 cells/mm, should be offered ART.

The medical criteria that the Gauteng Provincial Government’s Comprehensive Care and Treatment of HIV/AIDS and TB rollout plan for Antiretroviral Treatment (South Africa, 2004:4) stipulate are:

- Cd4 < 200 cells/mm3 irrespective of WHO stage; and
• WHO stage 4 irrespective of CD4+ cell count

Further to the above, the psychosocial considerations:

• Reliability of patients (i.e. the patient has attended three or more scheduled visits to an HIV clinic);
• No active alcohol or other substance abuse;
• No untreated active depression, emotional distress or any diagnosable mental illness;
• Social support. Patients should have disclosed their HIV status to a family member, a friend or joined a support group;
• Insight. Patients must have accepted their HIV status, understand HIV infection and the role of ART before starting treatment;
• Access to the clinic: Follow-up visits must be made regularly, so access to transport is essential;
• Regular place to stay, storage for medication and food; and
• Patients ready to commit themselves to treatment.

Research indicates that strict adherence to the ARV treatment regimen is essential in order to obtain the desired benefit, avoid the emergence of drug resistance, and clinical failure. The worldwide increase in the prevalence of ART resistance is of particular concern to researchers and practitioners.

Resistance can develop whenever the HIV continues to reproduce whilst ARV drugs are being taken. Since resistance remains one of the most significant threats to the long-term success of any HAART regimen, practitioners should be anxious to learn from past mistakes, translate new knowledge into appropriate treatment strategies, and develop new drugs that retain useful activity in the face of established resistance.

The researcher believes that the biopsychosocial model will provide insight into imposing factors with regards to adherence. Bearing this in mind, it is imperative that patients understand the need to strictly adhere to their ART medication
regimen and to take the drugs as directed. Good adherence to medication is the basis of effective viral control (Spencer, 2005:4). In order to render the services, indicated above, the social worker plays an essential role in the assessment of the patient’s biopsychosocial circumstances, and/or referral to the appropriate resources, prior to the initiation of ART.

3.4. Antiretroviral drugs (ART)

Antiretroviral treatment has moved from mono-therapy to triple drug, or, HAART, since the discovery that these drugs are more effective when three or more are taken at the same time. HAART is also known as combination therapy. (Kasper, et al., 2005:1071; Van Dyk, 2004: 69.)

Anti-HIV therapy consists of treatment by the administration of drugs that attack the virus itself. These drugs interfere with the manner in which the virus tries to reproduce itself inside a human cell, although anti-HIV drugs cannot destroy the virus completely. The ultimate purpose of ART is to reduce the HIV viral load (viral RNA levels) to below the level of detection (or at least as low as possible) as much as feasible – preferably to undetectable levels (<25 cells/ml) – for as long as possible (Spencer, 2005:4-13 and 14-26; Van Dyk, 2004:67).

Numerous new therapies have been introduced since 1996. The indications for ART have undergone dramatic changes in recent years, and recommendations for their use remain in flux (Spencer 2005:4-13 and 14-26; WHO, 2006; Van Dyk, 2004:67-73; The Foundation for Professional Development, 2004:175-221).

Combination therapy – HAART (Highly Active Antiretroviral Therapy) is recommended in order to obtain maximal antiviral treatment effects and to reduce the emergence of drug-resistant HIV. The drugs that are used belong to different pharmacological classes. Medication is taken every day and compliance with, and adherence to, the treatment regimen is mandatory (Spencer, 2005:14).
The appropriate use of potent combination antiretroviral therapy HAART and other treatment, as well as prophylactic interventions, is of critical importance in providing each patient with the best opportunity to live a long and healthy life, despite the presence of HIV infection. ART cannot cure HIV, but it can control the disease by reducing the viral load, followed by immune reconstitution (Isselbacher, et al., 1999:1473 & Gerberding and Sande, 1999:1470).

In South Africa, the Government has compiled a standardized National ARV rollout programme, based on international best practices (South Africa, 2003).

Medical and psychosocial considerations are taken into account when deciding when to initiate ARTs. The initiation of HAART is never an emergency, unless administered as post-exposure prophylaxis. ART should be deferred until patients are prepared to commit themselves to long-term treatment and to maintaining good adherence to treatment. The Gauteng Provincial Government Comprehensive Care and treatment of HIV/AIDS and TB rollout plan for Antiretroviral Treatment advocates that:

- Strengthening of the prevention interventions is a priority;
- Not everyone who is HIV-positive needs ART; and
- Decisions regarding whether or not to put a patient on ART are based on medical and psychosocial criteria. (South Africa, 2004:4)


The researcher opines that the biopsychosocial model will be of great value in assessing the circumstances of the patients regarding adherence to ART. The pursuit of an AIDS vaccine remains a critical international goal. Until there is an effective vaccine, social mobilisation toward healthier and safer sexual behaviour should be significantly increased and sustained. The high rate of HIV
infection in the sexually active population indicates continued high-risk behaviour.

During the last few years, a rapid change in the treatment strategies for HIV infection has taken place. ART currently available falls into two main categories:

- Nucleoside and Non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs); Protease inhibitors (PI).

In order to understand the modes of action of the above therapies, it is important to review the method of viral replication inside the human cell. Once the HIV has locked onto, and invaded a human cell, it uses an enzyme called reverse transcriptase (RT) to convert its genetic code (RNA) into the same form as the genetic code of human cells (DNA). This viral DNA then merges with the human DNA, converting the cell into a factory for producing the building blocks of the new virus. This new DNA is called "proviral DNA." Reverse transcription can be blocked by Nucleoside Reverse Transcriptase Inhibitors (NRTIs), and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Gerberding and Sande, 1999:1470; Isselbacher, et al., 1999:1853 & Kasper, et al. 2005:1901).

3.4.1 Nucleoside Reverse Transcriptase Inhibitors. (NRTIs)

NRTIs were the first ARV agents used to treat HIV infection. Their structures mimic those of natural nucleosides, which serve as building blocks for RNA/DNA synthesis. Drugs in this class act as false building blocks and they therefore terminate the DNA chain and prevent DNA synthesis from taking place (South Africa, 2006).

The NRTIs currently available in South Africa are:

- Zidovudine (ZDV or AZT);
- Didanosine (ddl);
- Zalcitabine (ddc);
- Lamivudine (3TC);
• Stavudine (d4T); and
• Abacavir (ABC)

3.4.2 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)

NNRTIs are structurally distinct from the NRTIs and act by binding to the enzyme, reverse transcriptase, directly, downstream from the active catalytic site, thereby interfering with its transcriptional activity (South Africa, 2006).

• Two NNRTIs are currently available in South Africa: Nevirapine (NVP); and Efavirenz (EFV).

3.4.3 Protease inhibitors

Protease is a different HIV enzyme. After the HIV has successfully merged its DNA with the DNA of the human cell, the cell produces a string of protein. These long strings of proteins are cut up into smaller proteins by a viral enzyme, protease. These proteins serve a variety of functions; some become structural elements of new HI viruses, while others become enzymes, such as reverse transcriptase. Once the new viral particles are assembled, they bud off the host cell, and create a new virus. This virus is then able to infect new cells. Each infected cell can produce many new viruses. By blocking protease, protease inhibitors help to prevent an infected cell from producing new infectious virus particles (South Africa, 2006).

Six PIs are currently available in South Africa:

• Saquinavir, Ritonavir, Lopinavir, Indinavir, Nelfinavir; and Amprenavir

In addition to the above, there are also other classes of drugs that intervene with the functioning of the HIV and are currently in the process of being tested:

• Fusion inhibitors;
• Nucleotide Reverse Transcriptase Inhibitors (NtRTIs);
• HIV-entry inhibitors;
- Co-receptor antagonists (e.g. CCR5 inhibitors)
- Integrase inhibitors;

**Figure 2:** The life-cycle of the HIV-1 virus and the role of therapy in its control. Spencer (2005:6, 7)

![Diagram of HIV life cycle with drug targets](image-url)
The author explains the working of the different ART drugs, NRTIs/NNRTIs and PIs with the assistance of Spencer’s illustration above:

- Free virus (HIV);
- Fusion with CD4 receptor/co-receptor and cell membrane; (Here the drug class HIV – entry inhibitors – with direct viral interaction, fusion inhibitors and co-receptor inhibitors, interfere with the functioning of the virus);
- Penetration and entry of HIV into cytoplasm of cell;
- “Uncoating” of virus and liberation of ‘free’ virus and its associated viral enzymes;
- Transformation of viral RNA into viral DNA; Reverse Transcription. (Here the drugs NNRTIs, and NNRTIs are able to block the functioning of the virus);
- Penetration of the nucleus of the cell and integration of viral DNA into host (genomic) DNA to form proviral DNA: Integration. (Drugs working here are the Integrase inhibitors);
- Activation of the CD4 cell leads to the transcription of proviral DNA into its original (genomic) viral RNA and messenger, mRNA: Viral Transcription;
- Viral RNA leaves the nucleus together with viral mRNA. mRNA is translated into appropriate viral proteins (structural, enzymic) on the Ribosomes of the endoplasmic reticulum:
- Translation - Translated viral proteins and genomic viral RNA are processed, assembled, packaged and released in the form of a new infectious virus: (By blocking protease, PIs help to prevent an infected cell from producing new infectious virus particles; and new viral assembly).

3.5 Response to antiretroviral treatment and Treatment failure

The advent of combination ART has substantially improved the prognosis of patients with HIV-infection and transformed HIV/AIDS into a treatable chronic condition for a significant proportion of those who have access to ART.

Response to ART can be assessed clinically, immunologically and virologically. Studies have proven adherence to be crucial to the sustained virological, immunological and clinical benefits of ART.
3.5.1 Clinical response

A person who responds to ART should indicate a reduction in HIV-related symptoms or opportunistic conditions as well as a generally slower progression towards AIDS, and hence, fewer episodes of hospitalisation.

Immune reconstitution inflammatory syndrome (IRIS) occurs when an improving immune function unmasks a previously occult opportunistic infection. Events occurring within three months of the commencement of ARVs might be immune reconstitution disease and not treatment failure. The aforementioned syndrome indicates that an infection was present in the patient’s body, but was not clinically evident. Patients become ill during the first weeks of ARV, particularly those with a CD4 count of less than 50 cells/mm3, i.e. advanced HIV disease. Mostly patients present with fever of unknown origin. The immune system reconstitutes itself once the patient commences ARV. Initially, a response takes place in the memory cells, followed by a response in naïve cells, including those of thymic origin. An immune reconstitution illness is not indicative of drug failure or drug side effects. It is not a reason to stop ARV, or to change the ART regimen (South Africa, 2006).

If a patient develops new or recurring HIV-related symptoms or opportunistic conditions while taking ARTs, this might however also be due to treatment failure. This can be distinguished from IRIS by the timing of the onset of symptoms and the CD4 and Viral Load measurement. Treatment failure is defined as disease progression with a decrease in CD4 count and an increase in Viral Load, with the subsequent development of new opportunistic infections or malignancy (WHO, 2006).

In addition to immune reconstitution, clinical success is also realised by means of enhancing quality of life and improving the daily performance of a patient. It can be measured by applying the Karnofsky Score (WHO, 2004.)

*The Karnofsky Score* (WHO, 2004) is a widely accepted and appropriate measure to establish the physical wellness or performance status of
respondents. The Karnofsky Scale (Karnofsky index) was devised by two American doctors in the 1940s (David Karnofsky and Joseph Burchenal) in an attempt to try and measure the more subjective side of the outcome of cancer treatment. Nowadays it continues to be employed with regards to other chronic diseases. This scale has also been adopted in the South African National Antiretroviral Guidelines (South Africa, 2003): http://www.cancerbacup.org.uk/Qas/AboutcancerQAs/AllQAs/related_faqs/Qas/993:28.02.2006

Table 6: Karnofsky Score, HIV/AIDS and antiretroviral therapy

<table>
<thead>
<tr>
<th>Physical Ability</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>100</td>
</tr>
<tr>
<td>Independent with minimal symptoms</td>
<td>90</td>
</tr>
<tr>
<td>Independent with more effort and symptoms</td>
<td>80</td>
</tr>
<tr>
<td>Can do only activity of daily living</td>
<td>70</td>
</tr>
<tr>
<td>Partially independent</td>
<td>60</td>
</tr>
<tr>
<td>Partially dependent, requires more medical treatment</td>
<td>50</td>
</tr>
<tr>
<td>Dependent with specific care</td>
<td>40</td>
</tr>
<tr>
<td>Totally dependent, requires hospitalisation, death not impending</td>
<td>30</td>
</tr>
<tr>
<td>Moribund, needs hospitalisation with full medical treatment</td>
<td>20</td>
</tr>
<tr>
<td>Comatose</td>
<td>10</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

(WHO, 2004)

An explanation of the above table follows. The scale relates purely to physical ability and covers 11 points, from normal health to death, each scored as a percentage. The researcher is aware that the definitions of each stage are not very precise, since they do not include feelings and emotions. Nevertheless, this remains a very useful scale against which to measure the functioning of the HIV/AIDS patient.

The researcher is of the opinion that counsellors in general are not familiar with the Karnofsky Scale and thus do not use it to motivate patients with regard to their adherence to ART and how this will affect their quality of life. She further holds the view that the counsellors should be more aware of the clinical facts
and how these influence quality of life. This knowledge would assist with the process of motivating patients to adhere to treatment. The aforementioned is a further indication for the reason why counsellors dealing with ART and adherence issues should be well-trained and experienced.

3.5.2 Virological response

One of the goals of ART is to suppress the viral load. The anticipated response to ART in a treatment-naïve patient, who adheres to treatment, is a viral load of less than 50 copies/ml at 24 weeks (6 months) of treatment (WHO, 2006).

If the viral load has not been suppressed after a few months of therapy, or, if it increases again after initially having been suppressed, it is a cause for concern, since it might indicate treatment failure. A detectable viral load measurement, on two separate occasions, in an individual who has had a previously undetectable viral load, needs further investigation and assessment.

Virological failure should also be considered in the following scenarios:

- A decline in viral load of not more than one log within 8 weeks after commencing therapy; and
- A sustained increase in viral load of greater than 0.6 log from its lowest point or a return to 50% of the pre-treatment value (WHO, 2006).

Poor adherence is the major cause of failure to achieve viral suppression with existing ART regimens. The greater the number of doses taken correctly, the more likely it is that virological suppression will be achieved, and therefore, maintained.

Table 7: Correlation between Adherence and Virological Response to ART

<table>
<thead>
<tr>
<th>Adherence to ART</th>
<th>Viral load &lt;400 copies/mm³</th>
</tr>
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<tbody>
<tr>
<td>&gt;95% adherence</td>
<td>78%</td>
</tr>
<tr>
<td>90% to 95% adherence</td>
<td>45%</td>
</tr>
<tr>
<td>80% to 90% adherence</td>
<td>33%</td>
</tr>
</tbody>
</table>
**70% to 80% adherence**  
29%

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Number of doses dispensed minus tablets returned over number prescribed e.g. \((30-5)/28=25/28=0.9\) (90%)

(Chesney, 1997:2 and Friedland, 2003:35)

The above table can be explained as follows: To achieve an 80% chance of complete viral suppression, more than 95% of doses need to be taken; for a twice daily regimen this means missing less than one dose every second week. There is a rapid decline in virological benefit as adherence drops. Someone taking 70% of the doses has only a 6% chance of achieving viral suppression at 1 year. The present writer firmly believes that it is important for the counsellors to understand the above and to be able to explain this to patients during their assessment for ART.

### 3.5.3 Immunological response

The researcher argues that the CD4 count is one of the most useful markers of the state of the immunity in a person with HIV/AIDS and remains the cornerstone of judgment of the progression of HIV/AIDS in order to indicate to patients the restoration of their immune system; and thus motivates them to continue with ARV medication.

One of the goals of ART is that the CD4 count of the patient should rise and remain above the baseline count. According to the selection criteria of the National Antiretroviral Treatment Guidelines (2003:4), as previously mentioned above, the following patients are candidates for ARV treatment:

- CD4 count <200 cell/mm³, irrespective of WHO stage; or
- WHO stage IV disease, irrespective of CD4 count

In other words, treatment can only be initiated for patients who are diagnosed with AIDS. Patients whose CD4 count are >200, but who suffer from an AIDS-
related cancer, and possibly need chemo- or radiation therapy, also qualify for ART.

The CD4 response is generally a mirror image of the HIV/RNA decay curve, with increases that average 50-60 cells/mm³ in the first 4 months on ARV, with subsequent increases at a rate of 8-10 cells mm³/month or 100-150 cells/mm³ per year with good viral suppression. However, a discrepancy can exist between the viral load and CD4 count, where the viral load is at a lower than detectable level, but the CD4 count fails to rise. The cause of this cannot always be found, but probabilities are TB infection or CMV (cytomegalovirus) and EBV (Epstein-Barr virus) infection.

It is reported in Bartlett, Gallant & Joel, (2005:3) that a CD 4 count should increase by 50% after 8 months of treatment. However, this count has two major limitations, namely it is subject to considerable variation and it only reflects existing damage to the immune system. The CD4 cell count is therefore not ideal for predicting future damage to the immune system in any given individual. Patients on ART should be monitored regularly:

- Where possible at 6 to 8 weeks after commencing ART in order to assess initial response to therapy;
- Four- to six-monthly thereafter if the patient has responded to therapy or is clinically stable; and
- A repeat assessment of both CD4 cell count and viral load is indicated if routine measurements yield unexpected results, or the individual’s clinical condition changes (South African, 2003).

**Immunological failure** Is defined as a 30% drop in the CD4+ cell count from the peak value or a return to the pre-treatment baseline or lower. Some patients obtain virological suppression but the immune system is so severely compromised that it is impossible to regenerate and as a result immunological and clinical treatment success is not achieved. Furthermore, it is important to understand that the CD4 count is affected by numerous other conditions, where
a marked diurnal and seasonal variation occurs, and also, any intercurrent infection, for instance influenza, can also cause a temporary decrease in the CD4 count according to the HIV/AIDS Bureau: Women’s HIV Care Guide, 2005: http://hab.hrsa.gov/publications/womencare05/WG05chap4.htm

The CD4 cell count is one of the methods used to assess effectiveness of ARV therapy. Throughout this assessment, the multidisciplinary team involved in the field of HIV/AIDS’s, faces additional challenges with regards to the availability of ART and in particular, issues of adherence. The present researcher contends that the issue of adherence to ART has brought the importance of multidisciplinary teamwork in health settings to the forefront, and calls for health providers to work together towards one common goal. Patients must be educated about the importance of adherence, which is an indication for teamwork since each team member, as a specialist in his/her field, will be able to contribute to adherence issues.

3.6 Strategies in Treatment Failure

Literature differentiates between three types of treatment failure: virological, clinical and immunological, as explained above (Abdool Karim and Abdool Karim, 2005:514). In many cases, the effects of anti-HIV drugs decrease over time and possible causes of treatment failure are as follows:

- HIV develops resistance to one or more of the drugs;
- Cross-resistance (resistance to a specific drug can afford resistance to the whole class);
- Low blood-levels because of decreased absorption of the drug – e.g. due to persistent vomiting or chronic diarrhoea, as found in HIV enteropathy; and
- Problems with adherence.

The optimal response to treatment failure will depend on the reason for the failure of the current regimen. If it seems likely that the patient has developed resistance to some or all of the current drugs, the best course of action may be to switch to new drugs. Switching to a new regimen as soon as the current
therapy seems to be failing is recommended, because the longer one remains on drugs to which the HIV is becoming resistant, the greater the risk of developing cross-resistance to other drugs (South Africa, 2006).

However, switching to a new regimen as soon as possible poses the risk of going through the available drugs too quickly. It is important to consider to which of the other drugs the HIV may have developed a cross-resistance, and to aim to select a new combination consisting of at least two drugs to which the HIV is still likely to be susceptible.

If problems concerning adherence or side effects do present, it is possible to switch medication to a more convenient regimen. If the patient regularly fails to take his/her medication correctly, the risk may simply escalate to the development of drug-resistant HIV strains. This may shorten the duration of benefits gained from the current regimen, and also limit future treatment options (South Africa, 2003).

Adding or changing a single new drug, within a combination, that does not suppress the viral load, is likely to lead to the development of drug resistance, because the impact of that single new drug is likely to be insufficient to block repetition. Experts now advise that wherever possible, changes in treatment should always include at least two new drugs, because resistance to some drugs develops progressively and as more resistance mutations accumulate, sensitivity to the drug will decrease. However, resistance to drugs emerges at varying rates. In many cases, the effects of ARV medication decrease over time. At some point, the patient and the ARV team may decide that the current treatment is failing and that it is time to switch to other drugs.

A blood test that measures whether the patient is receiving sufficiently high levels of the drug, called the plasma concentration test, is not readily available. Furthermore, the therapeutic and adverse effects are not precisely quantifiable for all tests (Isselbacher et al., 1999:403). If treatment failure occurs, despite taking drugs in the recommended manner, it may be necessary to increase the doses or attempt other ways to improve drug levels; for example, to take a
combination of drugs which interact and boost the levels of one or more of these. The class of PIs lend themselves to this type of intervention. The PI, Ritonovir, a very strong inhibitor of the liver enzyme system called p450, is responsible for the elimination of drugs from the body. By slowing down the metabolism and elimination of the other PIs, it increases their levels in the blood. It is thus a useful addition to any PI-containing regimen (South African, Medicine Formulary, 2006).

3.7 Side Effects and Drug Interactions of Art

A wide variety of ART drugs are currently available, but ARV drugs, like most chronic medications, do not come without their negative aspects such as a heavy pill burden (having to take too large a number of pills), drug interactions, drug toxicity and side effects. All these adverse event, coupled with adherence issues and individual factors, such as pill fatigue (patients become tired of taking medication on a daily basis), transport problems, long clinic queues and issues concerning disclosure, make ART a very complex issue.

3.7.1 Medication or drug interactions

These can be classified as pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions involve the interaction of the medication with the body and may manifest in changes in drug absorption, distribution, metabolism and excretion. Pharmacodynamic interactions refer to interactions between different medications, in the body, and may result from competition at receptor sites, or the activity of two drugs in the same physiological system. The effect may be additive, synergistic or antagonistic. An additive effect occurs when the action of one drug is strengthened by the action of another. A synergistic effect occurs when the action of one drug enhances the action of another. Lastly, an antagonistic effect occurs when the action of one drug interferes with, or antagonizes, the action of another, thereby diminishing its effect (Isselbacher, et al., 1999:403).

Interaction between medications is a frequent occurrence since not only is ARV medication prescribed for HIV-infected patients, but, also, multiple drugs for the
prophylaxis of opportunistic infections, side-effects, or the treatment of concomitant illnesses, both acute and chronic. All these medications can interact on different levels and cause additional problems. Patients may also seek medical care from more than one practitioner or healthcare facility, often causing duplication of medication with additive toxicity or significant drug interactions. Furthermore, patients make use of over-the-counter and traditional, or herbal, remedies, as well as illicit and recreational drugs that might interfere with prescribed medication.

As access to ART expands in South Africa, the potential for drug interactions with ARV medication becomes increasingly important (Cohen, Andrews & Maartens, 2002:42). In South Africa, an additional factor exists: many people believe in traditional medicine, and according to the National Comprehensive Treatment Plan in South Africa, about 90% of HIV-positive patients take some complementary, herbal, or traditional medicine together with ARV medication. Research regarding herbal or traditional medicine is still very limited and patients should be counselled with regards to the possibility of drug interactions and toxicities (South Africa, 2006).

With the increasing availability of ART in South Africa, questions have arisen with regards to drug toxicity. Jones & Nelson (2005:18) state that drug resistance and ARV toxicities are emerging as major treatment challenges in the HAART era. Novel ARV drugs should be designed to overcome the resistance evoked by current agents and reduce toxicity, thus enhancing adherence. The National Antiretroviral Treatment Guidelines (South Africa, 2004) recommends the following principles for managing the adverse events of ART:

- Establish whether the adverse event is due to ARV agents, other medication, or illness;
- Never to stop only one ARV drug - if there is a need to discontinue ART, all ARV medication must be stopped together; and
- This is to prevent the development of resistance.
One of the major factors that influence adherence to ART is the treatment regimen, since pill burden and complexity of regimen are important contributors to poor adherence. Heyer and Ogunbanjo (2006:5-9), postulate that good adherence is associated with a low pill burden and optimum treatment regimens selected by patients include: two or less pills per day, no dietary restrictions, small pills, all drugs combined into one pill and once-a-day dosing. In the developing world, we are still very far from this ideal, with some patients taking up to 10 different medications daily, and some regimens requiring dosing three times a day. It is for this reason that support, counselling and monitoring patients on ARV is mandatory.

3.7.2 Adverse drug reactions and side effects

These side-effects of ART are realities of HIV treatment. The side-effects can be classified as acute- and long-term, and as mild to severe (rarely fatal) reactions. Pharmacokinetic variability of absorption, distribution and elimination of drugs varies from patient to patient, and flexibility in dosages is necessary (Davidson, 2002:153). Some of the most commonly reported side effects reported according to the Department of Health (South Africa, 2006), follow:

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
Efavirenz is associated mostly with psycho-neurological side-effects, which include dizziness, insomnia, impaired concentration, drowsiness, abnormal dreams and hallucinations, and in more severe cases, manic and paranoid reactions, as well as severe depression or anxiety. This class is also prone to cause hepatic toxicity, and Nevirapine, in particular, is known for its association with a skin rash and systemic hypersensitivity (Rossouw, 2006).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
This class can be divided into the D-drugs and non-D-drugs. The most commonly used D-drugs are d4T and ddI which are associated with mitochondrial toxicity, manifesting as myopathy (weakening of the muscles), peripheral neuropathy, pancreatitis, hepatic steatosis (fattening of the liver),
lipoatrophy and hyperlactataemia (build-up of lactic acid in the blood) and lactic acidosis (Rossouw, 2007).

AZT is mostly well-tolerated but can cause bone-marrow suppression with subsequent anaemia (reduction in the body’s oxygen-carrying capacity leading to fatigue) and neutropenia (reduction in infection-fighting cells in the body leading to an increased susceptibility to infections) (Rossouw, 2007).

3TC is the best tolerated of the class, but can lead to the same non-specific side-effects of the class, such as headache, malaise, myalgia, anorexia and nausea (Rossouw, 2007).

**Protease Inhibitors (PI)**

This class of ART is very potent and has mostly long-term metabolic side-effects, such as dislipidaemia (increase in total cholesterol, especially an increase in low density lipoprotein – LDL – that is associated with an increased risk of cardiovascular events like heart attacks and strokes), insulin resistance leading to type 2 diabetes mellitus, hyperurisaemia (leading to gout), and lipodystrophy (where fat in the body is taken away from the legs, arms and face and redistributed to the abdomen, neck and breasts, leading to a characteristic appearance that is increasingly being recognised as the ‘new’ face of HIV (Rossouw, 2007).

Charalambous’ study, as quoted by Churchyard and Metcalf (2005:10), found that adverse events were common in patients (41%) but that the majority of adverse events were mild to moderate (88%) and transient, usually only lasting two to four weeks. The most common side-effects were anaemia and elevated liver enzymes. Severe adverse events, which resulted in hospitalisation and death, occurred in only 1.2% of cases (Rossouw, 2007).

The researcher contends that the prevention and management of side-effects of ARV drugs offer an essential challenge to all involved in ART management. Side-effects and adverse reactions continue to affect the patient’s decision to commence treatment, to continue, and to adhere to the prescribed regimens. It
is the responsibility of the treating clinic to educate and counsel patients with regards to the possible side effects. While a single dose of aspirin may be enough to treat a headache, in contrast, life-long, continuous adherence to ART is required in the treatment of HIV. This daily burden of taking pills and pill fatigue is a problem reported by ART patients, which is a serious factor that should not be underestimated when addressing adherence issues.

### 3.8 Other Uses of Antiretroviral Therapy

Prophylaxis can be defined as a means to prevent HIV infection from occurring. Since 1988, post-exposure prophylaxis, for occupational exposure to HIV, has been prescribed by doctors.

#### 3.8.1 Post-exposure prophylaxis

Post-exposure prophylaxis is indicated in healthcare workers after exposure to infected blood products or fluid, and also in the general population after traumatic or sexual exposure (Spencer, 2005:235). *The National Antiretroviral Treatment Guidelines* (South Africa, 2004:72), acknowledge the fact that healthcare workers have a low, but measurable risk of HIV infection after accidental exposure to infected blood or body fluid. Accidental exposure to HIV, following a hollow needle-stick injury and percutaneous exposure to infected blood, remains frequent within the context of healthcare. The risk remains low at 0.3 % (Van Dyk, 2004:72).

Healthcare workers at risk are doctors, nurses, hospital cleaners, allied workers, such as physiotherapists, ambulance personnel and healthcare students, while non-healthcare workers at risk include rescue teams, police, crime scene attendants and sewerage-plan workers.

#### 3.8.2 Sexual exposure or raped victims

All women and men presenting to a health facility after being raped or sexually assaulted, should be counselled concerning the potential risks of HIV transmission post-rape. It is important to know the HIV status of the patient prior to administering any anti-retroviral treatment, although it should always be kept
in mind that the patient might still be in the window period, and hence exhibit a false-negative HIV test.

There is strong non-experimental support that the use of ART in preventing HIV sero-conversion could be effective in preventing HIV transmission caused by exposure. The medication is used for a period of 28 days as prophylaxis. The importance of adherence should be explained to patients. Patients should present themselves to a health facility within 72 hours of being sexually assaulted. All post-rape prophylaxis cases should be carefully monitored and evaluated (Grimwood, 2004:73).

3.8.3 Prevention of Maternal-To-Child Transmission (PMTCT)

Programmes to prevent mother-to-child transmission of HIV (PMTCT) were initiated by the National Government in December 2000. PMTCT counselling and testing is the most common entry point into HIV care for women. Pregnant women have an opportunity to initiate ART treatment during pregnancy in order to experience the dual benefits of the reduction of vertical transmission as well as sustaining health, according to the National Antiretroviral Treatment Programme guideline for carers (Grimwood, 2004:66).

Notwithstanding the availability of prophylaxis, a sound support programme must be in place. The exposed person must be monitored and fully informed regarding ARV drugs, side effects, and sero-conversion. Counselling is a critical component of the management of the use of ARV drugs for the exposed, as well as PMTCT.

3.9 Summary

The worldwide increase in the prevalence of ARV resistance is of particular concern to researchers and practitioners. Since resistance remains one of the most significant threats to the long-term success of any HAART regimen, practitioners are anxious to learn from past mistakes, translate new knowledge into appropriate treatment strategies and develop new drugs that retain useful activity in the face of established resistance (Miller, 2004:23).
In this chapter, matters related to ARV that were considered are: the goals of ART, different ARV drugs, response and prognosis to ARV treatment, and treatment failure. The present researcher believes that it is only when one understands the pathophysiology of HIV/AIDS, the pharmacology of ARVs, and the response of the body of the patient to ART, coupled with the importance of adherence, that long-term strategies can be developed.

She will proceed to discuss resistance; adherence; predicting adherence; special adherence groups; patient, providers and regime matters influencing ART; placing a specific focus on the adherence team. Adherence support in the different adherence phases and strategies to support adherence, such as medication alerts and measuring adherence, will also be discussed in the following chapter.