Chapter I

Prevention, Care and Treatment

OVERVIEW

HIV infection typically progresses from a prolonged asymptomatic stage, during which well-being can be maintained, through to a stage at which antiretroviral drugs (ARVs) become a critical part of the care and treatment strategy. The development of an effective programme to provide antiretroviral therapy is thus a critical component of the larger comprehensive plan to care for people living with HIV and AIDS (PLWHA). People living with HIV infection should be provided with a continuum of care and support services that respond to their changing needs over the course of their infection. Components of this continuum of care include: prevention-related interventions; voluntary counselling and HIV testing (VCT); medical care and treatment by a dedicated, trained medical team; psychosocial support; nutritional assistance; social supports; and as needed, community-based services and home-based care. At the stage at which ARVs are required to maintain health, medication should be made available and accessible through a coordinated programme across levels of the public health care system including primary health care clinics, community health centres, district hospitals, and regional and tertiary care institutions.

The HIV and AIDS care and treatment programme will integrate care and treatment with prevention efforts, and link to existing HIV interventions, such as voluntary counselling and HIV testing, prevention of mother-to-child transmission (PMTCT), and TB control. Treatment efforts will be further enhanced by involvement of community-based organisations, the private sector, and NGOs that provide assistance with education and adherence as well as practical support through a caring support network. In summary, South Africans should be able to access a full array of interventions and services to address HIV and AIDS within the context of a continuum of care.

The implementation of the HIV and AIDS care and treatment programme will also have far-reaching benefits beyond the delivery of treatment-related services. Many of the

interventions in this plan will strengthen the existing public health infrastructure, including pharmacies, laboratories, transportation, information technology, referral systems, facilities and staff capacity; surveillance systems; communication systems; monitoring and evaluation capacity; and research.

The comprehensive care and treatment plan will be located within the broader HIV and AIDS strategic framework. As a pillar of the strategic framework, it needs to align itself with the other three components: prevention; monitoring, evaluation and research; and legal and human rights. Monitoring and evaluation and research are addressed in Chapters XII and XIV, respectively.

BACKGROUND AND RATIONALE

In the context of its five-year HIV, AIDS and STI Strategic Plan, government has made a wide range of HIV and AIDS-related services available. These include voluntary counselling and testing[1-4], prevention of mother-to-child transmission of HIV[5], TB and STI management and HIV post-exposure prophylaxis (PEP) for both occupational exposures and survivors of sexual assault[6], orphan care programmes and nutritional supplementation[7]. These programmes have significantly improved the lives of South Africans living with HIV and AIDS.

The integration of HIV and AIDS care and treatment within existing efforts and interventions will avert the development of vertical systems of care, and will reinforce the national strategy emphasising primary health care. Health Promotion and Quality Assurance Training Centres will provide clinical training and support for the delivery of high quality care, including antiretrovirals when indicated.

A primary goal of the plan is to preserve recent gains made in slowing the spread of HIV in South Africa. Such gains have been validated by the United Nations Joint Programme on AIDS and confirmed, particularly in the youth of this country, by the 2002 antenatal HIV survey findings which show a decline in prevalence among the age group under 20 over the last 4 years.

The key prevention interventions are:

- VCT
- PMTCT
- Information, Education, and Communication (IEC)
- STI management
- Supply of barrier methods
- Life skills and HIV and AIDS education
- TB management
- Nutrition programmes

It becomes paramount, therefore, that in the context of the comprehensive care and treatment plan, these gains are not lost to a false sense of security. The plan offers the best locally and internationally accepted standards for the clinical management of people with HIV and AIDS. However, the currently available body of evidence and knowledge on HIV and AIDS still identifies prevention as the cornerstone of any country's response and programme. Hence, the importance of prevention interventions should not be lost. Newer interventions such as those proposed in this plan will ultimately augment or maximize the impact of established interventions, not undermine them.

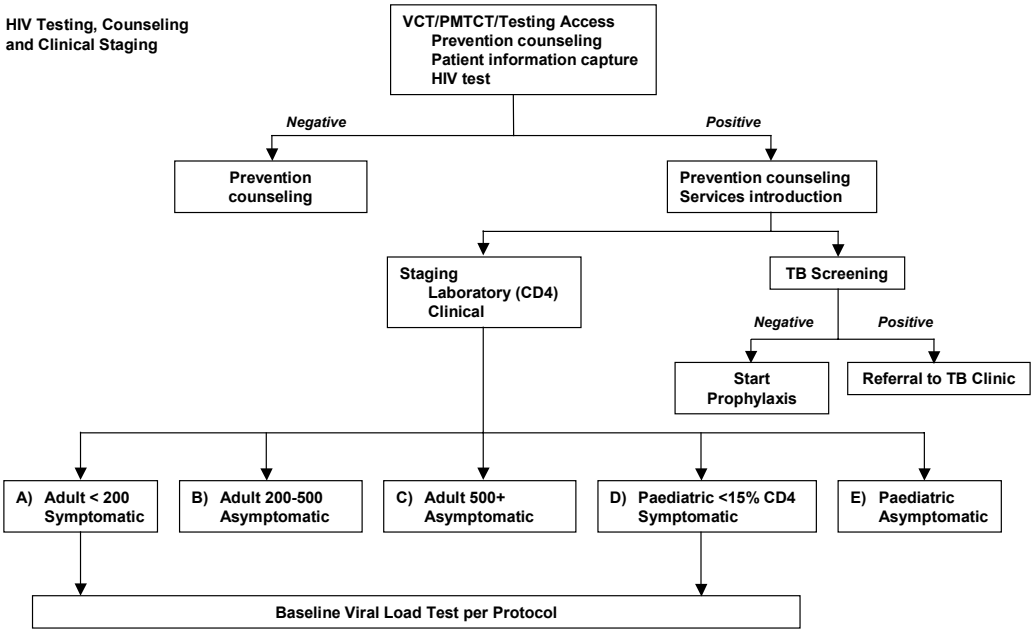
Against this background, the Joint Health and Treasury Task Team costed the implications of strengthening current prevention efforts as part of the requirements to improve our country's overall machinery in the fight against HIV and AIDS. The Joint Task Team estimated that an allocation of between R550 and R570 million per annum would achieve this objective. Such financial resources are available within the current Medium-Term Expenditure Framework and efforts have began to make them part of current initiatives, such as the national Khomanani IEC campaign.

APPROACH

1. Continuum of Care

The continuum of care has as its basis an individual who seeks out care at different levels of the health system and follows him or her through diagnosis of HIV infection and throughout the duration of the illness (see Figure 1.1).

Figure 1.1: Entry into Continuum of Care



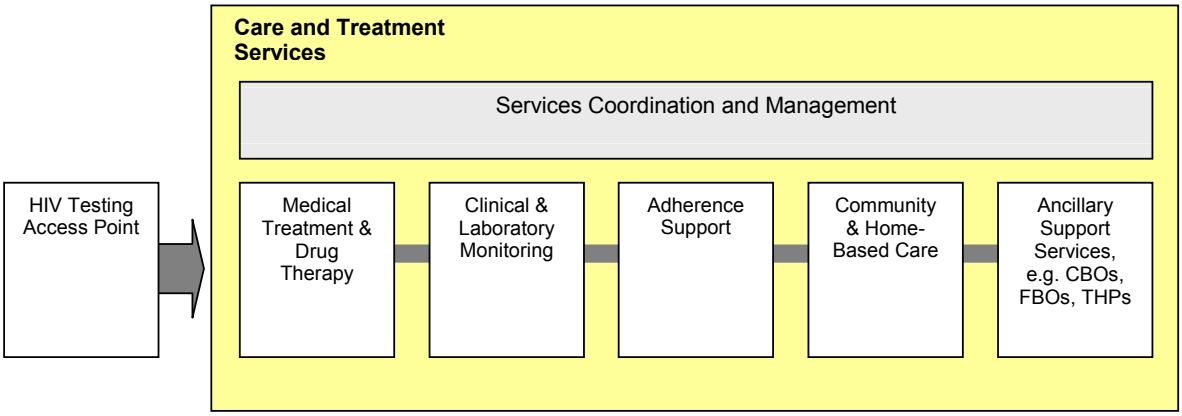
There are multiple entry points into the care delivery system, including voluntary counselling and testing venues, PMTCT programmes, clinics offering reproductive health and STI services, primary health care clinics, TB clinics, inpatient hospital settings and prisons. Following diagnosis and staging of HIV infection, individuals may be referred for antiretroviral therapy and/or prophylaxis for opportunistic infections, or routine follow-up and monitoring for patients with less advanced disease (Figure 1.1).

2. Service Coordination

Over the course of diagnosis and care for HIV and AIDS, numerous providers and delivery systems interface to address patient needs. The designation of a Care Coordinator maximizes coordination of patient services, including linkages with adherence and ancillary support systems, referrals, and follow-ups with diagnostic and consultant services at other locations. Other critical linkages facilitated by nurses/counsellors include those to ancillary community-based services such as home-based care, traditional health

practitioners, hospice, and palliative care provided by a full range of NGOs, CBOs, FBOs, and support groups run by persons living with HIV and AIDS (Figure 1.2).

Figure 1.2: Continuum of Care Services



3. Referral and Consultation

For patients with complex medical needs related to HIV, it is necessary that consultation and referral mechanisms are available to ensure that appropriate patient care is delivered. Clinicians from district hospitals will initiate most requests for consultation and patient referrals. Such requests will be channelled to the appropriate district or regional hospital, following a preliminary clinical assessment. Consultative capability in the referral hospital should include: Infectious Disease Control, Internal Medicine, Neurology, Ophthalmology, Gastroenterology, Oncology and Paediatrics. When the specialist is located in a different facility, issues around transportation and follow-up need to be formalised to ensure that the recommendations by the referring clinician are carried out. The patient should be referred back to the original referring provider for continuity of medical care wherever possible.

4. Home-Based Care

NGOs and CBOs can provide care services in the home. Home-based care is a particularly useful tool to assess and support patient adherence to ARV and other therapies, including locating and reaching out to patients who miss scheduled appointments, promoting continuity of care and adherence with ARV regimens. Palliative care services can also be provided through home-based programmes working to train and support the patients' families and friends to ensure the highest achievable quality of life.

5. Prevention Counselling and Support

a. Risk Reduction

Prevention counselling is a key element of routine care provided to all patients presenting for HIV testing. For patients who test HIV-positive, repeated interaction with trusted providers enables discussion on how to avoid transmission of the virus to family, friends and partners. This includes counselling around high-risk sexual behaviours, IV drug abuse, avoiding re-infection, the diagnosis and treatment of STIs, opportunistic infections and clinical screening for TB. Patients who undergo VCT and test HIV-negative will receive prevention counselling that emphasizes behaviours that keep this population HIV negative.

b. Maximizing Health and Slowing Progression

The majority of individuals who initially test HIV-positive are likely to be asymptomatic or in earlier stages of disease. All should be embraced into a constellation of health services focused on slowing progression and helping retain the individual in care throughout his or her life. This includes activities that reduce stress, promote adoption of healthy lifestyles including proper nutrition and the use of immune boosters, cessation of unhealthy habits (e.g. unsafe sex, use of tobacco, alcohol, illicit drugs and intravenous drug use), prophylaxis of preventable opportunistic infections and early identification and treatment of TB.

c. Community-Linked Prevention Strategies

Community groups including faith and community-based organisations, workplace programmes, NGOs, traditional health practitioners, associations of PLWHA, general practitioners, and home-based care providers have a role in carrying prevention messages forward. Community-based services can do a great deal to minimize fear and discrimination, providing and reinforcing accurate information to address stigma surrounding HIV infection. Together, these mechanisms better ensure that persons living with HIV will receive ongoing information, care and support to minimize the risk of transmitting the virus to others and to maintain good health and slow progression of disease.

6. Levels of Care

a. Primary Health Care Level

Integration of HIV- and AIDS-related services into existing systems at the primary care level reinforces the national strategy for primary health care. Primary health care clinics and community health centres are the primary sites for diagnosis, staging and routine follow-up of HIV-positive patients. For patients who begin ARV treatment, these sites will provide the majority of ARV adherence monitoring and support. In some cases, where appropriate expertise exists, ARV treatment may also be initiated at the primary and community level. Additionally, individuals will receive counselling, nutritional assistance, psychosocial support and appropriate social welfare evaluation where necessary. The link between the primary health care facility and home- and community-based services is central to achieving good patient follow-up and continuity of care.

Patients who are early in the course of their infection will require less frequent laboratory monitoring, and will benefit primarily from counselling to promote prevention, good nutrition, stress reduction, and behavioural modification, as well as from appropriate immunizations against other preventable diseases. HIV-positive children should receive all routine immunizations according to standard paediatric protocols. Both adults and children should receive cotrimoxazole prophylaxis, an antibiotic which protects against pneumonia and diarrhoea, common conditions associated with HIV infection, when indicated by the degree of immune compromise. A schedule of health maintenance interventions and recommended prophylaxis is provided in Annex I.1.

For patients who meet criteria for ARV therapy (CD4<200 or symptomatic), referral to the district or regional hospital is required for the clinician's assessment and confirmation of eligibility for ARV therapy. Prior to initiation of ARV therapy, patients will be required to participate in a drug-readiness training programme and be assessed jointly by trained counsellors and/or nurses who have been closely involved with the patients and aware of individual social circumstances. This will include an assessment of any other therapies the patient may be on, such as the use of traditional medicines. Once the patient has been initiated and stabilized on ARV treatment, skilled primary health care nurses will be required to provide regular monitoring and follow-up of patients receiving ARVs in conjunction with the clinician. This will be guided by treatment protocols and training on

the side effect profiles of each antiretroviral medication. There should be ongoing communication between the primary health care facility and district hospital HIV and AIDS specialty clinic to ensure that patients are seen and monitored at appropriate intervals according to the national treatment guidelines.

Patient advocates (home-based carers, patient selected treatment 'buddies', and traditional health practitioners) will play a critical role in retention and follow-up of patients. The need for a dedicated cadre of advocates who have access to the patient on ARVs has been shown to be a critical ingredient to maximize adherence and to retain people in care[8]. These advocates also serve to help identify adverse drug events that occur between scheduled visits, and bring patients in for immediate medical attention.

b. District/Regional Hospital Level

District hospitals, and, where appropriate, regional hospitals, have been selected as the appropriate level for initiation and review of ARV treatment decisions in light of the following factors: twenty-four hour patient access; clinician availability; laboratory and diagnostic capability, either on-site or linked by a transportation system; pharmacy capability to secure and safely dispense ARVs; logistical support for regularly scheduled outpatient clinics; and clear consultation and referral lines both up to the reference hospitals and down to primary care facilities. In selected circumstances, where access to a district hospital is limited, ARV initiation may occur at lower level facilities and mobile clinics where the requisite expertise is available.

A team of health professionals with specialized training in the management and treatment of HIV infection should be responsible for delivery of care. This core team is comprised of clinicians, professional nurses, counsellors and pharmacists, with additional access to a psychologist and/or social worker, nutritionist and home-based carers. The delivery of care may take place in a dedicated HIV clinic, or be integrated within a general clinic where the full team is working together. The requirements of the HIV and AIDS care and treatment programme will necessitate the upgrading of basic infrastructure at these facilities. These upgrades will serve to strengthen the public health care system beyond HIV and AIDS.

Patients seen at district hospitals will typically be referred from primary health care facilities for initiation of ARV therapy. Patients presenting with more complex conditions can be evaluated and treated at the primary health care level, and patients referred to the outpatient department following inpatient admissions for opportunistic infections, should enter care at district hospital level. Following clinical assessment and review of laboratory data, clinicians will be able to prescribe the appropriate ARV regimen, which is to be dispensed through the hospital pharmacy. Upon the initial prescription, monthly ARV repeats should automatically be sent to the hospital pharmacy and a three-month supply maintained at the depot to eliminate risk of stock-outs. A reserve stock should be maintained at district hospitals (see Chapter VIII, *Drug Distribution*). It is necessary that patients on ARVs are seen at regular intervals by a clinician at the district hospital according to the national treatment protocol, including at least two visits during the first two months of therapy interspaced with clinic visits at the primary health care facility for side effect and adherence monitoring.

c. Tertiary Facilities

Tertiary hospitals have an important role in both training and expert clinical support to lower-level facilities. Expert clinicians should wherever possible, assist the providers at Level I and II hospitals for consultation and referral of complex patient care issues, including patients with multiple diagnoses, management of side effects and complications of therapy, and ARV regimen decision making. In any situation where treatment failure is suggested, these referral centres should guide decision-making and ARV management either directly or through consultation with the referring clinician.

7. Antiretroviral Therapy

a. Goals of Therapy

The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Plasma viral load is a strong prognostic indicator in disease progression, and reduction in viral load achieved with antiretroviral treatment and other therapies is correlated with substantial clinical benefits[9-15]. Suppression of plasma viral load to undetectable or low levels is a critical goal of

antiretroviral therapy, as this minimizes the degree of viral replication and potential development of resistance.

b. When to Start

The indication for antiretroviral treatment is based on clinical assessment and CD4 count. These important factors determine whether therapy should be started, or if it can be delayed. The lower the CD4 count, the higher the risk of AIDS and the more urgent the need for treatment. However, the risk of developing AIDS must be weighed against the risks of toxicity and development of resistance. Guidelines for eligibility criteria provide reference (See Table 1.1), but must be considered along with individual patient readiness for starting treatment. Patients must be prepared to make a lifelong commitment to taking ARVs, which may require not only education to gain understanding of potential side-effects and importance of adherence, but also psychosocial support to overcome fears. Well-informed and engaged patients are the most successful with adherence to therapy. The decision to initiate therapy must therefore be based not only on meeting the criteria and being ready to start, but also on being committed to adhering to treatment over the long term.

Patients who are acutely ill and severely immuno-compromised at the time of admission to a service point must be appropriately treated and stabilised clinically. Once stable, patients should be counselled and consent for HIV testing obtained; thereafter, treatment options must be made available, depending on clinical staging and the patient's choice.

Table 1.1: Criteria for ARV Initiation in Adults and Adolescents

ADULTS and ADOLESCENTS – including pregnant women
• CD4 $\leq$ 200 cells/ mm^3 and symptomatic, irrespective of stage, *or* • WHO stage IV AIDS defining illness, irrespective of CD4 count, *and* • Patient prepared and ready to take ARVs adherently

** Note: Treatment recommendations are based on increased (15%) probability of developing AIDS-related complications within 3 years.*

c. Adult ARV Drug Regimens

Due to the availability of approved drugs in South Africa and resource constraints, the choices of ARV regimens are not unlimited. Several factors have been considered in the selection of regimens, including safety profile, monitoring requirements, cold storage and potential for development of resistance (further elaborated in the notes for Table 1.5). A second-line regimen is available in the event of treatment failure of the first-line treatment. Men, and women of childbearing age, should be considered for regimen 1a therapy as outlined in Table 1.2. Special considerations around pregnancy are discussed below.

Table 1.2: Adult ARV Regimens and Routine Monitoring During Treatment

Regimen	Drugs	Test	Frequency
1a	d4T / 3TC / NVP	• CD4 • VL • ALT	• Staging, 6-monthly • Baseline, 6-monthly • Baseline
1b	d4T / 3TC / efavirenz	• CD4 • VL	• Staging, 6-monthly • Baseline, 6-monthly
2	AZT / DDI / Lopinavir / Ritonavir	• CD4 • FBC • Fasting cholesterol	• Staging, 6-monthly • Baseline, 1, 3, 6 mo, continue 6-monthly • Baseline only

- **Regimen 1a** – first-line for: (1) men (2) women of child bearing potential (3) pregnant women and (4) conditions where EFV is contraindicated (e.g.: psychiatric diagnosis)
- **Regimen 1b** – alternate first-line for persons who: (1) develop NVP intolerance (2) have evidence of hepatotoxicity and (3) other conditions where NVP is contraindicated. * *Avoid in pregnancy and women of childbearing potential*
- **Regimen 2** – use as (1) second-line for patients who 'fail' regimens 1a or 1b, or (2) first-line in patients who have evidence of NVP resistance prior to ARV initiation.
- ***Staging*** = initial testing for all patients after testing HIV-positive
- ***Baseline*** = testing for ARV eligible patients, at initiation of ARVs

d. Prior ARV Exposure

Individuals with prior exposure to ARVs may present for treatment. Some percentage may be at risk for the development of ARV resistance, if ARV therapy has been received for

short periods or in patterns of intermittent use, and/or if sub-optimal mono- or dual-therapy regimens were taken. These individuals should not be excluded from ARV access; however, a complete history of ARV and other therapies must be obtained to enable a rational approach to ARV regimen selection. Final decisions will largely be made at the district hospital level but should not be seen as only occurring at this level. The critical point is that recognized expert consultation be engaged in making any decisions that diverge from the written recommendations. Consultation with clinicians with experience in managing these patients is the best way to succeed in choosing the optimal regimens. This could occur at the community health centre or clinic level if the expertise is available. Decisions should be made on an individual basis. Where indicated and available, agents should be selected to which the patient has not been exposed, and/or from alternate categories where cross-resistance is unlikely[16].

e. Routine Monitoring

Regular monitoring and evaluation, both clinical and laboratory, is a critical component of management of HIV-positive patients at all stages of disease, and necessary to maximally prolong health and slow progression to AIDS-defining illnesses. Frequent monitoring affords the opportunity to reinforce messages of prevention, while enabling early detection and intervention for clinical, immunologic and psychological decline. As disease progresses, so too does the need for increased frequency of follow-up with all members and levels of the health care team. Once antiretroviral therapy is initiated, clinical and laboratory monitoring is needed to detect drug-intolerance, drug-reactions, drug toxicity, drug-drug interactions as well as treatment failure and the need to either reinforce adherence or switch regimens. Monitoring and evaluation of adherence is also critical to identify to eliminate potential or observed barriers to adherence. Thus, ongoing monitoring and evaluation, performed in the context of an integrated and comprehensive team approach to health care, will maximize the chance for treatment success.

f. CD4 and Viral Load Testing

Progression of disease and decreased durability of benefit from antiretroviral treatment and other therapies correlates with CD4 count below 200 cells/mm^3. The standard of care highlights the importance of intervening with ARV therapy before patients fall significantly below 200 CD4 cells[17]. Current recommendations do not include an

increased frequency of CD4 monitoring for patients whose CD4 count falls between 200-350 cells/mm^3; therefore, provider discretion will be necessary to consider the patients' overall rate of decline of CD4 count and duration of time before their next recommended follow-up and CD4 repeat (see Table 1.3). Acute illness or vaccination has a transient effect on both CD4 (decrease) and viral load (increase) values. Therefore, patients who present for routine CD4/VL monitoring should be re-scheduled for testing if there is a likelihood of aberrant values [1 month or more following acute illness, more than 2-3 months for TB].

Table 1.3: Staging CD4 and Viral Load Monitoring

CD4 count	Test	Frequency
> 500 cells/ mm^3	CD4	• Staging, 12-monthly
200 – 499 cells/ mm^3	CD4	• Staging, 6-monthly
< 200 cells/ mm^3 *and/or on ARVs*	CD4 VL	• Staging, 6-monthly • Baseline, 6-monthly (for regimen 1 only)

- *Staging – initial testing for all patients after HIV+ test*
- *Baseline – testing for ARV-eligible patients prior to initiation of ARVs*

g. Management of TB and HIV

TB is likely the leading cause of death among HIV-infected persons[18]. TB accounted for an estimated 30% of the all AIDS related death in 1999[19]. It has been suggested by WHO that from a global public health perspective, the effective treatment and control of TB must remain a central priority when treatment strategies for co-infected patients are being developed. However, the use of antiretroviral drugs among persons being treated for TB is complicated by overlapping toxicity profiles of some antiretroviral and anti-TB drugs, namely protease inhibitors and non-nucleoside reverse transcriptase inhibitors and the rifampicin-containing anti-TB regimen. Similarly there are concerns about drug malabsorption and complex drug-drug interactions and the occurrence of paradoxical reactions among co-infected patients (TB and HIV).

Due to the high TB and HIV co-infection rates in South Africa, many individuals who meet the criteria to receive ARVs through the Plan will have pulmonary TB[20]. Similarly, patients started on ARVs often flare with symptomatic TB as their immune status

improves (see *Immune Reconstitution Syndrome*). It is for these reasons that the antiretroviral regimens selected for this programme have options that are compatible with current TB regimens.

The current WHO guidelines for use of antiretroviral therapy in TB and HIV high burden countries recommend that until more information is available, ARVs should be initiated in TB patients with ongoing TB treatment if there is a very high risk of HIV disease progression and mortality[21]. This would occur mainly among TB patients with low CD4 T-cell count (<200 cells/mm^3). Therefore, individuals who are diagnosed with acute pulmonary TB prior to ARV initiation, should be started on appropriate anti-TB treatment (4-drug combination therapy with Rifafor) and should complete two months of therapy or longer until clinically stable, prior to starting ARV treatment. Individuals who develop pulmonary TB while on the first-line ARV regimen should be continued on their ARVs (as long as the ARVs are compatible with TB treatment): however, they should be monitored closely for development of hepatic (liver) toxicity in the context of co-administration of isoniazid (a component of the TB therapy) and a non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz).

The usual symptoms of liver damage are non-specific initially, with fatigue and malaise predominating. This progresses to increasing fatigue, darkening of the urine colour (*coca cola* or tea coloured), lightening of the stool and jaundice. This would be preceded by elevations in ALT. If significant hepatotoxicity does develop, a switch to a rifampicin-compatible second-line protease inhibitor containing regimen may be required. This should be done in consultation with an HIV experienced provider. In patients presenting with active TB in late stage HIV (moribund) the treating clinician may not feel the patient can wait for two months of anti-TB treatment before initiating ARV treatment. This is a situation that may warrant starting both TB treatment and HIV treatment concomitantly. This should be discussed with an experienced HIV provider.

h. Immune Reconstitution Syndrome

Exacerbation of clinically occult infections (e.g. TB, CMV, fungal, toxoplasmosis) in an immunodeficient patient must be anticipated after beginning antiretroviral therapy. Patients can 'flare' with signs and symptoms of an acute opportunistic infection during the

first few weeks of ARV therapy due to an enhanced immune response. This immune reconstitution with associated clinical symptoms is not indicative of a drug failure or adverse events as a consequence of the treatment, and should not warrant considerations around switching regimens. The focus should be on diagnosing and treating the opportunistic infection. In these situations consultation with an experienced provider is warranted. It is important that a full drug history be obtained to exclude the possibility of interaction with traditional or alternative therapies.

i. Pregnant Women

Eligibility criteria for starting antiretroviral therapy (see Table 1.1) in pregnancy will not differ from other adults; however, the default first-line regimen for all women will include nevirapine as the NNRTI (non-nucleotide reverse transcriptase inhibitor) agent rather than efavirenz due to the potential of efavirenz to cause foetal abnormalities (see Table 1.2 footnote 1a/1b). All pregnant women with a CD4 <200 cells/mm3 should be started on ARVs after the first trimester. Pregnant women with CD4 counts between 200 and 350 CD4 cells/mm3 should be strongly considered for initiation of antiretroviral therapy after the first trimester, with therapy to be continued for life. Women who become pregnant while on ARVs should continue therapy without interruption, including during the first trimester. For pregnant women who test HIV-positive during labour, single-dose nevirapine will be used for PMTCT per guidelines.

8. Antiretroviral Therapy in Paediatrics

a. Diagnosing HIV in Paediatrics

Using the most widely available HIV test (ELISA), it is not possible to tell whether a newborn infant has been infected with HIV. Maternal antibodies may be present in the infant's blood for 12-18 months after birth. Thus, a child may test HIV ELISA positive prior to 15 months when they are not actually infected. Confirmation of HIV-positive status is required for ARV treatment consideration. Infants aged below 18 months presenting with suspected AIDS will require an HIV p24 Antigen test (current cost R 52.63 per test) to determine their true HIV status, due to the risk that ELISA or rapid tests may react to residual maternal antibodies. Likely numbers of babies requiring treatment in this age group have been estimated with reference to the ASSA2000 model's one-year age-band projections.

Confirmation of HIV-positive status in children over 18 months of age still requires two positive ELISA tests until HIV DNA PCR or p24 antigen test can be integrated into the system of care. HIV-infection must be suspected in children who have more than 2 hospital admissions per year for HIV complications or a prolonged hospitalisation (> 4 weeks).

b. When to Start ARVs in Children

Just as with adults, the decision to start treatment in children must take into account patient readiness along with the clinical and CD4 eligibility criteria. In the case of infants and children, 'patient readiness' refers to readiness of the responsible person who will be administering the ARV drugs. It is mandatory that at least one responsible person be present who is capable of ensuring adherence to the child's ARV schedule. Other factors that may be considered by the health care team to determine treatment readiness, include: primary health clinic attendance record, immunization record, and previous history of medication compliance (anti-TB, nutritional supplementation). Clinical and CD4 eligibility criteria for starting therapy are listed in Table 1.4.

Table 1.4: Criteria for ARV Initiation in Children < 6 Years Old

PAEDIATRIC
• CD4 < 15% and symptomatic *or* • WHO Paediatric Stage III AIDS defining illness, irrespective of CD4 % *and* • At least one responsible person capable of administering child's medication

** Note: Treatment recommendations are based on increased (15%) probability of developing AIDS- related complications within 3 years.*

c. Paediatric ARV Drug Regimens

As is the case for adults, there are a limited number of ARV agents currently approved and available for use in children. Given these limitations, factors considered in the selection of the paediatric regimens included safety profile, monitoring requirements and potential for

development of resistance (see Table 1.5). A second-line regimen is available in the event of failure of the first-line treatment. Government will maintain one national protocol, allowing for regimens to be changed over time as clinical assessment and practice evolve.

Table 1.5: Paediatric ARV Regimens and Routine Monitoring on ARVs

Regimen	Drugs	Test	Frequency
1a	d4T/ 3TC Lopinavir/Ritonavir	• CD4 • VL • ALT • Chol/TG	Staging, 6-monthly Baseline, 6-monthly Baseline Baseline, 12-monthly
1b	d4T/ 3TC / NVP	• CD4 • VL • ALT	Staging, 6-monthly Baseline, 6-monthly Baseline, 1 m, 6-monthly
1c	d4T / 3TC efavirenź	• CD4 • FBC	Staging, 6-monthly Baseline, 1, 3, 6 mo, 6-monthly
2a	AZT / ddI Lopinavir/Ritonavir	• CD4 • FBC • Chol/TG	Staging, 6-monthly Baseline, 1, 3, 6 mo, 6-monthly Baseline, q 12 monthly
2b	AZT / ddI efavirenz or NVP	• CD4 • ALT • FBC	6-monthly Baseline, 1 mo, 6-monthly (NVP only) Baseline, 1,3,6 months, then 6-monthly

Notes:

- *d4T syrup requires refrigeration. If no refrigerator at home, switch d4T to AZT. Clinician discretion to substitute ABC for d4T in infants > 3 months of age.*
- *NVP - Choice between first-line regimens is informed by: (a) previous exposure to NVP within last 12 months consider lopinavir/ritonavir; (b) children without history of NVP exposure can receive regimen 1b or 1c, 2b is 2nd line if regimen 1a was given*
- *efavirenz - limited to children >3 yrs of age and >13 kg.*
- *For drug failure criteria in paediatrics refer to: Continuum of Care Building for HIV - Paediatric Section, developed by the national Department of Health*
- *'Staging' – initial testing for all infants/children after confirmed HIV-positive*
- *'Baseline' – for ARV eligible children at time of ARV initiation*
- *(See Annex I.6 for paediatric ARV detailed dosing and drug information)*

d. Cotrimoxazole Prophylaxis

There is overwhelming evidence that cotrimoxazole prophylaxis prevents *pneumocystis carinii* pneumonia, a common opportunistic infection in HIV infected infants. Cotrimoxazole prophylaxis also protects against selected invasive bacterial disease. Prophylaxis should start in infants born to HIV-positive mothers after 6 weeks of age (See Table 1.6), and should be continued until risk of HIV exposure has ceased and HIV infection has been ruled out (e.g. negative ELISA after 15 months of age or HIV PCR after 1 month of age).

Table 1.6: Cotrimoxazole Use in HIV-positive Children

Who Should Receive Cotrimoxazole Prophylaxis?	
• Infants (> 6 weeks) born to an HIV-infected woman irrespective NVP use for PMTCT • Infants (> 6 weeks) confirmed HIV-positive during first year of life by DNA PCR • Clinical diagnosis of HIV infection and positive serology • Children (> 12 months), with symptomatic HIV disease or AIDS-defining illness (WHO category II or III) should continue Cotrimoxazole prophylaxis for life.	
When Should You Start Cotrimoxazole Prophylaxis?	
• At 6 weeks of age for infants born to an HIV-positive mother • At any time when the infant/child fulfils the initiation criteria	
Cotrimoxazole Dosage (5mg/kg trimethoprim + 20mg/kg sulphamethoxazole)	
Weight	**Dose**
• < 5 kg • 5 – 9.9 kg • 10 – 14.9 kg • 15 – 21.9 kg • > 22 kg	• 2.5 ml daily • 5 ml daily • 7.5 ml daily • 10 ml or 1 tablet daily • 15 ml or 1.5 tablets daily

e. Nevirapine resistance

Resistance monitoring is critical in infants exposed to nevirapine in the PMTCT programme, as nevirapine resistance mutations have been seen in almost half of babies exposed to nevirapine through PMTCT[22]. Guidelines and recommendations will be updated as new information from sound studies becomes available. Until further

evidence, nevirapine will remain available as an agent in the first-line regimen recommended for use in children but lopinavir/ritonavir may be substituted for nevirapine in first line regimen when clinically indicated (Table 1.5 footnotes 1 and 2).

9. Changing or Stopping Antiretroviral Treatment

a. Treatment Failure – Changing Regimens

Treatment failure can be defined as virologic, immunologic and/or clinical. Treatment failure results from failure to suppress viral replication with the development of viral resistance. Primary virologic failure is less than 1-log (10 fold) drop in viral load after 6-8 weeks of therapy. Secondary virologic failure is 1-log (10 fold) increase in from lowest recorded level. Immunologic failure is defined as a 30% drop in CD4 count from peak value or a return to pre-ARV baseline or lower. Clinical failure is progression of disease with the development of opportunistic infections or malignancy occurring 3 months or more after initiation of ARV therapy.

Clinical failure must be distinguished from Immune Reconstitution Syndrome. A favourable CD4 T-cell response can occur with incomplete viral load suppression and might not indicate an unfavourable prognosis. The urgency of changing therapy in the presence of low-level viraemia is tempered by this observation. Continuation of existing therapy does not lead to rapid accumulation of drug-resistant virus in every patient. A reasonable strategy is maintenance of the regimen, with redoubled efforts at optimising adherence and increased monitoring. If it is determined that a patient should switch regimens due to treatment failure, there should be a switch from their first-line combination to a completely new standardized second-line regimen.

b. Drug Toxicity or Intolerance – Single Substitutions and Interruptions

Patients with a good response to an ARV regimen including adequate viral suppression may develop signs of drug intolerance or drug toxicity. If this toxicity is clearly linked with a single drug in the regimen, that drug can be discontinued and replaced with a substitute according to the national protocol. Should toxicities develop or side effects occur which are intolerable enough to compromise adherence, and a specific agent cannot be identified, switching the entire regimen may be appropriate.

In the situation where a patient does not have adequate viral suppression, and a serious toxicity or intolerance develops, it is recommended that the entire regimen be switched. If a low-grade toxicity or intolerance occurs and a temporary interruption in therapy is planned, the entire regimen must be stopped at the same time regardless of whether the offending agent is identified. On resolution of the side effect, all agents should be restarted together under close monitoring.

c) Salvage Regimens

A patient's best chance of good clinical outcomes is when the first line treatment is successful. A second line regimen, whilst still effective, is typically less so than the first line, as the virus may have developed resistance to this class of drugs. If the second line of drugs fails, then salvage therapy may have to be considered. This is highly specialised treatment, requiring referral to a higher-level facility. Salvage regimens are expensive and their clinical benefit may be limited.

From a cost and equity point of view, the greater the number of patients that go on salvage therapy, the fewer the number of patients who will be put onto basic treatment. Hence it would currently not be advisable to provide salvage therapy in the South African public sector. It may be considered as a future option when new laboratory technologies and new drugs become available.

10. Adverse Events Reporting

Identification of a potential adverse drug event by any member of the health care team should be brought to the attention of the primary provider, and when deemed appropriate, reported by the provider to the Pharmacovigilance Unit at the national level using the Medicines Control Council (MCC) adverse drug reaction reporting protocol. The Pharmacovigilance Unit will provide a standardized protocol outlining the grading and reporting criteria for adverse events (AEs). (See Chapter XIII, *Pharmacovigilance*.)

11. Patient Drug-Readiness Training

For individuals who are ARV eligible (CD4 $\leq$ 200 and/or symptomatic) and preparing to begin treatment, specific education or drug-readiness training is essential to provide the knowledge to enable individuals to take ownership of their own health and prolongation of

their lives. Adequate time, qualified knowledgeable staff, well developed training materials and adequate facilities are needed to conduct such programmes. Nurses and/or counsellors may facilitate training. Current recommendations suggest 3-times weekly training sessions to occur prior to drug initiation. Basic topics recommended for inclusion:

- Positive living – dealing with stigma and discrimination, legal issues, disclosure, and healthy lifestyle including good nutrition.
- Basics of HIV and AIDS
- Opportunistic infections – prophylaxis and treatment
- Care and treatment for HIV and AIDS – including ARVs
- ARV side effects
- ARV adherence

12. Adherence

a. Purpose

Adherence to ARV treatment is essential to maintain long-term health benefit and avoid development of drug resistance[23, 24]. It is not possible for health care providers to reliably predict which individuals will ultimately be adherent to their treatment plan, as adherence does not correlate with gender, cultural background, socio-economic or education level, or language barriers between provider and patient. It is therefore essential to provide all patients with a comprehensive plan to support adherence that utilizes multiple strategies and all members of the health care team, as well as family and community.

b. Adherence Assessment and Monitoring - Role of the Health Care Team

Evidence indicates that adherence wanes as time progresses. Thus, monitoring and support of adherence is essential. New diagnoses or symptoms can influence adherence. For example, depression might require referral, management, and consideration of the short- and long-term impact on adherence. A trusting relationship between the patient and members of the health care team is essential. Optimal adherence requires full participation by the health-care team, with every patient interaction representing an opportunity for reinforcement. Supportive and non-judgmental attitudes and behaviours will encourage patient honesty regarding adherence and problems. Clinicians should commit to communication between clinic visits, ongoing adherence monitoring, and timely response

to adverse events or interim illness. Interim management during clinician vacations or other absences must be clarified with the patient. Adherence support must be intensified when sub-optimal adherence is identified (e.g. investigate new barriers, more frequent visits, enlist support of family/friends, review teaching, increase home visits, etc.). For all health care team members, specific training regarding ARV treatment and adherence should be offered and updated periodically. (See Table 1.7 for adherence support methods)

Table 1.7: Adherence Strategies

Strategies to Promote Adherence
• Spend time and have multiple encounters to explain goals of therapy and need for adherence. • Consider monitoring of medications such as cotrimoxazole or other surrogate prior to ARV initiation. • Negotiate a treatment plan that the patient can understand and to which he/she commits. • Encourage disclosure to family or friends who can support the treatment plan. • Inform patient of potential side effects – severity, duration, and coping mechanisms. • Establish 'readiness' to take medications before ARV initiation. • Provide adherence tools where available: written calendar of medications, pill boxes. • Encourage use of alarms, pagers or other available mechanical aids for adherence. • Avoid adverse drug interactions; full disclosure for over-the-counter drugs and traditional medicines. • Anticipate, monitor and treat side effects. • Include adherence discussions in support groups. • Develop links with community-based organizations to support adherence. • Encourage links with support groups. • Create links with patient advocates.

13. Traditional Medicine

Health seeking behaviours are largely affected by cultural norms and personal belief systems. A large percentage of patients have deeply rooted traditions around maintenance of health and treatment of illness, and utilise traditional health practitioners as their first

point of contact for health care. Traditional health practitioners hold positions of authority within the community and their advice is widely respected. As a well-established and accepted form of health care in South Africa, it is essential that traditional medicine and its practitioners be recognized, respected, and engaged in coordinating care for HIV-positive patients that wish to utilize both disciplines. Traditional practitioners may play an important role in raising public awareness and promoting acceptance of VCT as well as adherence to TB and antiretroviral therapy. (See Chapter III, *Traditional Medicine.*)

14. Care for Caregivers

For persons involved in care for patients with HIV and AIDS, both paid and volunteer, burnout is a common issue due to the tremendous emotional and psychological stress that accompanies work where recurrent illness, hardship and death is a constant. Due to the acute needs of the patients, the needs of staff looking after them are often overlooked. Additionally, many staff members are themselves infected and affected by HIV and AIDS, making their work doubly challenging. Provision of time and structured programmes for debriefing and grief management for staff members, especially after loss of patients who were well known and close to staff, is particularly helpful. Given constraints on time, resources, and availability of trained psychologists and counsellors, co-workers and peers can play an important role in support. Developing staff support programmes will help facilities attract and retain personnel and will have benefits that stretch far beyond the HIV and AIDS care and treatment programme (See Chapter V, *Human Resources and Training*). The Department of Health is currently developing guidelines to improve working conditions for caregivers.

Motivated and talented persons who have committed their lives to caring for persons living with HIV and AIDS are essential and precious commodities; therefore, these persons should be supported to the extent that resources allow. Each facility and HIV health care team must develop strategies and programmes that meet the individual needs of their site and team members. Availability of antiretroviral treatment for all persons in advanced stages of HIV infection, including health care professionals, may decrease stigma and discrimination for staff who are HIV-positive, and promote disclosure and support amongst peers.

SPECIAL CONSIDERATIONS

South African Military Health Service

The South African Military Health Service (SAMHS) plans to implement a comprehensive HIV and AIDS care and treatment programme for military personnel and their dependents. This programme will complement existing programmes focused in SAMHS on prevention, diagnosis and treatment of opportunistic infections and sexually transmitted infections, prophylaxis in instances of occupational exposures such an injuries and in instances of sexual assault, PMTCT, and nutritional supplementation. SAMHS is participating in a research project that will involve ARVs. The implementation of antiretroviral treatment is expected to commence in January 2004. Prior to that time, training of SAMHS medical personnel in the safe and correct use of ARVs will take place, in collaboration with the national Department of Health. Plans will also be finalized for the purchase of necessary laboratory equipment and antiretroviral drugs in concert with the Department. Those HIV-positive persons completing their military service will be referred into ongoing care to ensure the continued benefit from care and treatment services.

Correctional Services

There are approximately 180,000 prisoners in South Africa. The number of HIV-positive prisoners is unknown. Correctional Services is not currently within the public health sector, but relies on referrals to public facilities for clinician care. In order to offer HIV and AIDS care and treatment, tight linkages with the public health system will be needed, so that patients requiring evaluation for antiretroviral therapy can be appropriately assessed and started on ARVs by skilled clinicians. The health care team will refer prisoners back to Correctional Services for ongoing primary care follow-up for HIV, with referrals for specialized care in public facilities according to national treatment guidelines. Upon discharge from Correctional Services, clear referral to ongoing care is to be formalized to ensure continuation of therapies and reinforcement of prevention counselling and support.

ADMINISTRATIVE STRUCTURE

Administrative systems will be put in place to support the planning, implementation, monitoring and evaluation of the integration of antiretroviral treatment within comprehensive integrated systems of care (see Chapter XV, *Programme Management*).