



CLINICAL GUIDELINES | 11th EDITION

ISENTRRESS



FOR LIFE

ISENTRRESS...

- ... is indicated for **adult and paediatric** HIV-1 infected patients¹
- ... is effective in **both treatment-naive and -experienced** HIV patients^{1,2}
 - ... with durable viral suppression and significant immunological response^{3,4}
- ... is **recommended as part of an initial combination regimen** by the DHHS, IAS and EU guidelines^{5,6,7}
- ... is generally **well-tolerated¹, with a lack of significant drug interactions²**
 - ... with a low impact on serum lipids^{3,4}
 - ... with few drug interactions expected between ISENTRESS and commonly prescribed co-medications⁸
 - ... with no dosage adjustment required in either renal impairment or mild-to-moderate hepatic impairment¹
- ... is **recommended as a preferred salvage therapy** by the SA HIV Clinicians Society guidelines⁹



No matter their stage of life or treatment consider the flexibility of...

ISENTRRESS[®]
raltegravir, MSD

REFERENCES: 1. ISENTRESS Package Insert (March 2014). 2. Sharma M, Wainwright SL. Raltegravir as antiretroviral therapy in HIV/AIDS. *Expert Opin Pharmacother* 2013;15(3):1-11. 3. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable Efficacy and Safety of Raltegravir Versus Efavirenz When Combined With Tenofovir/Emtricitabine in Treatment-Naive HIV-1-Infected Patients: Final 5-Year Results From STARTMRK. *J Acquir Immune Defic Syndr* 2013;63(11):77-85. 4. Martinez E, Larrousseau M, Litbre JM, et al. for the SPIRAL Study Group. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-1-infected patients: the SPIRAL study. *AIDS* 2010;24(18):1767-1797. 5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 10 June 2016. 6. European AIDS Clinical Society (EACS) Guidelines: Version 8.0, October 2015. Available at <http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html>. Accessed 10 June 2016. 7. Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral Treatment of Adult HIV Infection 2014 Recommendations of the International Antiviral Society—USA Panel. *JAMA* 2014;312(6):410-425. 8. European AIDS Clinical Society (EACS) guidelines 7.1, November 2014. Available from <http://www.europeanaidsclinicalsociety.org/>. Accessed January 2016. 9. Meininger G, Black J, Conardie F, et al. Guideline: Adult antiretroviral therapy guidelines 2014. Southern African HIV Clinicians Society. *S Afr J HIV Med* 2014;15(4):121-143.

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Introduction

Aid for AIDS (AfA) was launched in May 1998 in response to the growing HIV pandemic and was the first private sector HIV Disease Management Programme (DMP) of its kind. At the time, antiretroviral therapy (ART) was extremely expensive and healthcare funders provided little, if any HIV benefits, although it was clear that a strong case could be made for funding ART to prevent expensive hospitalisation due to opportunistic conditions.

Fortunately, a number of medical schemes and later companies acknowledged the value of sound evidence-based treatment combined with provider and patient support that could be provided by HIV managed care and this, together with significant reductions in the costs of ART and a sophisticated Disease Management System lead to AfA becoming a successful HIV DMP with clinical outcomes currently approaching the ambitious targets recently set by the WHO.

The success of AfA is largely the result of on-going collaboration between the programme, funders, providers and patients which ensures optimal use of expensive healthcare resources to achieve the best possible outcomes. Part of this collaboration is ensuring that providers have access to reliable and up to date user-friendly information about HIV management relevant to Southern Africa which reflects best possible clinical practice, both locally and internationally.

The AfA Clinical Guidelines are a response to this need and have been made available to all healthcare professionals since the inception of the programme. The Guidelines are regularly revised and updated by the expert consultants on the AfA Clinical Advisory Committee in the light of new developments in HIV management. As a result of the availability of new drugs and tests and changes in starting criteria, together with new approaches to HIV prevention using PrEP, it has become necessary to once again thoroughly revise the contents and publish a new edition of the Guidelines.

Due to the widespread use of tablets and smartphones, AfA took a decision to make the Guidelines available in App form to further simplify access to treatment information. The free App may be found in both the Apple and Android App Stores.

As before, AfA acknowledges the support of members of the pharmaceutical industry and others who have advertised in this publication. As a result, we are able to carry on making the Guidelines available to all healthcare providers, clinics and teaching institutions free of charge.

These Guidelines would also not be possible without the invaluable input and contributions made by the staff at AfA and the part-time infectious disease consultants on the AfA Clinical Advisory Committee, some of whom have been with AfA since its inception.

As always, feedback from colleagues is welcomed and the clinical staff at AfA may be contacted for assistance by the consultants with any aspect of HIV treatment.

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Management of HIV Infection in Adults



Diagnosis

The diagnosis of HIV infection in adults is usually made by demonstrating the presence of HIV antibodies on two different tests. The most frequently used method to detect antibodies in the laboratory is the enzyme-linked immunosorbent assay, or ELISA. Screening ELISAs include a test for P24 antigen, which enables early diagnosis of HIV before antibodies are produced. Although the HIV ELISA has 100% sensitivity (no false negatives – but see notes on the “window period” below) it has a specificity of 99.7%, i.e. rare false-positives may occur. A positive screening ELISA should therefore always be confirmed by a second test detecting different antibodies – no additional samples need to be sent as the laboratory will automatically do this. The rapid HIV antibody test (whole blood, serum or saliva) is an acceptable screening test with similar sensitivity and specificity to ELISA tests– in the public sector two rapid tests from different manufacturers are used to confirm HIV, but note that AfA requires laboratory confirmation of HIV infection with either an ELISA or viral load before approving ART. Currently used screening tests detect antibodies to both HIV-1 and HIV-2. HIV-2 is very rare in Southern Africa, but should be considered if HIV was acquired in West Africa – special tests are required to diagnose HIV-2, discuss with the laboratory. In adults alternative confirmatory tests, including HIV Western Blot and qualitative HIV PCR, are only indicated in special circumstances.

As with other infectious diseases diagnosed by antibodies (e.g. tick-bite fever, primary syphilis), antibody tests may be negative in early HIV infection – this is the so-called “window period”. In most individuals, antibodies develop within 3 – 6 weeks of infection. No test is available that will completely eliminate the “window period”. Antigen tests (P24) are positive before antibodies appear and have been incorporated into routine screening with current ELISAs that detect both antibody and antigen. The most sensitive tests in the window period are nucleic acid amplification tests (e.g. the qualitative PCR or the quantitative PCR, known as the viral load). However, the nucleic acid amplification tests have a very small false positive rate. HIV PCRs should generally only be requested when there is clinical evidence of primary infection and must always be confirmed by subsequent positive antibody tests.

Pre- and Post-Test Counselling

The purpose of HIV testing is not simply to identify infected individuals, but also to educate both HIV-infected and uninfected people about prevention and limiting transmission of the virus. Prior to HIV testing, pre-test counselling is essential. Counselling should always be done in the client's home language.

Triple Therapy **Trivenz**



Efavirenz + emtricitabine + tenofovir disoproxil fumarate
in a fixed dose combination for improved adherence and compliance.^{1,2}

Adcock Ingram, committed to the treatment of HIV

References: 1. Trivenz approved package insert, April 2013. 2. Southern African HIV Clinicians Society. Fixed-dose combination for adults accessing antiretroviral therapy. *Southern African Journal of HIV Medicine*. [Online] 2013. [cited 2015 May 14]; Available from URL: <http://www.sajhivmed.org.za/index.php/hivmed/article/view/104/168>.

[S4] Trivenz. Each film-coated tablet contains efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg. Reg. No. 47/20.2.8/0328. For full prescribing information, refer to the package insert approved by the Medicines Regulatory Authority. ZA.15.ARV.006 05/2015

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Issues that should be covered include:

- Confidentiality
- Transmission modes of HIV infection
- The concept of the “window period”
- Possible reactions to a negative or a positive result
- The social support available
- How to reduce risk and protect sexual partners
- The return appointment – as soon as possible, preferably within 24 hours

Post-test counselling is equally important. Issues that should be discussed include:

- The significance of either a negative or positive result
- If negative, suggest re-testing in three months
- If positive, explain that the person is both infected and infectious
- Possible routes of transmission and prevention strategies
- The person’s comprehension of the result and its significance
- Who s/he wishes to tell about the result
- The importance of notifying sexual partners
- Social support available
- The likely course of HIV and complications
- Medical follow-up
- Benefits and timing of ART

Initial Examination and Staging

A complete history should be taken and a physical examination should be performed, with particular attention to the skin, mouth, anogenital region, and lymph nodes. Evaluation of the mental state and peripheral nerves is also important. Body weight and height should be recorded.

If the patient belongs to an AfA-contracted scheme or company, this examination will be part of their application to the programme. Please contact Aid for AIDS on 086 0100 646/ +27 021 466 1769 for more information on how to apply.

Patients should be staged clinically according to the WHO disease staging system outlined below. This is valuable both in terms of prognosis and the initiation of ART or prophylaxis against opportunistic infections.

WHO Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection (2006)

Clinical stage I

- Asymptomatic
- Persistent generalised lymphadenopathy

Clinical stage II

- Unexplained moderate weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

Clinical stage III

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis

- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
- Acute necrotising ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (<8g/dl), neutropaenia (<0.5 × 10⁹ per litre) and/or chronic thrombocytopenia (<50 × 10⁹ per litre)

Clinical stage IV (AIDS)

- HIV-wasting syndrome*
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy**
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (extra-pulmonary histoplasmosis or coccidiomycosis)
- Recurrent severe bacterial infections (including non-typhoidal Salmonella)
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy

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

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

Baseline Investigations

These should include the following:

- Full blood count and differential count
- PAP smear
- ALT
- Mantoux (Tuberculin skin test)
- Syphilis serology
- Serum creatinine and eGFR
- Hepatitis B surface antigen
- Hepatitis C (if ALT is elevated)
- Pregnancy test
- Urine dipstick (proteinuria)
- Serum cryptococcal antigen test if CD4 <100 (Fluconazole treatment indicated if positive)

Other important baseline investigations include a **CD4 count** and a **viral load**.

CD4 and viral load monitoring

The CD4 cell count, reported as the number of cells/ μL , is the most clinically useful laboratory indicator of the degree of immune suppression. The CD4 count is very useful in differential diagnosis, e.g. cryptococcal meningitis is unlikely if the CD4 count is above 200, and CMV disease or disseminated non-tuberculous mycobacterial infection are unlikely if the CD4 count is above 100.

Apart from the absolute CD4 count, the percentage of lymphocytes which are CD4+ may be useful. The CD4 percentage is routinely used in preference to absolute counts in paediatrics (see paediatric section), as the normal CD4 counts in infants and young children are much higher. In adults the CD4 percentage is useful when evaluating significant changes in an individual's CD4 count, which may be associated with transient lymphopaenia due to intercurrent infection. In this case, the CD4 percentage will be unchanged.

The CD4 count may be reduced by intercurrent infections (e.g. tuberculosis). The CD4 count falls by about 25% during pregnancy due to dilution. The count may also vary by up to 20% from day to day. Due to this variability in CD4 counts, major therapeutic decisions should not be taken on the basis of a single count.

In uninfected individuals, the CD4 count is typically 500 – 1 500. In HIV infection, mild immune suppression occurs once the count drops below 500. These persons are at very low risk for major opportunistic infections, but may develop morbidity due to inflammatory dermatoses, herpes zoster

and some HIV-related immune disorders (e.g. immune thrombocytopenia). Tuberculosis may occur at any CD4 count. Once the CD4 count is below 200, there is significant immune suppression and a high risk of opportunistic infections and AIDS-defining conditions. It is important to note that patients can be asymptomatic despite very low CD4 counts.

The viral load measures the amount of HIV in the blood and is critically important for monitoring response to ART. Viral load measures are calculated and reported in copies/mL, as well as in \log_{10} values. The viral load also has some prognostic value as patients with high viral loads (>100 000) experience more rapid declines in CD4 count, whilst those with low viral loads (<1 000) usually have slow CD4 declines. In early HIV infection, the viral load may be in the millions – it settles to a plateau level (known as the “set point”) after 3 – 6 months.

Transient increases in viral load occur with intercurrent infections and immunisations, so the test should be done at least two weeks after any intercurrent infection or vaccination. Viral load results vary by up to three times (0.5 log), for example from 5 000 to 15 000, or 50 000 to 150 000. These changes appear to be large, but are within the margin of error of the test. The same laboratory and viral load test manufacturer should be used for follow-up tests if possible.

Viral loads are critically important for monitoring the response to ART. A baseline viral load is required prior to initiating ART. The test should be repeated 6 – 8 weeks after starting ART. At this point the viral load should show at least a 10 fold (1 \log_{10}) decrease. Thereafter the viral load should be done every 6 months. After 6 months of ART the viral load should be below the limit of detection of the assay (typically VL <50). Failure of ART is defined by the viral load. Decisions to change ART for virologic failure should not be based on the results of only one test. There is little point in monitoring the viral load if the patient is not on ART.

HIV Disease Progression

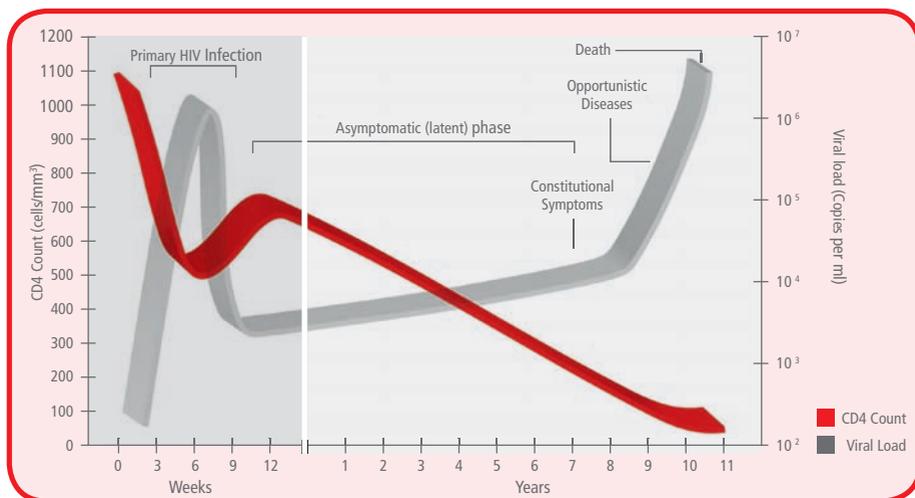
HIV infection is characterised by slowly progressive immune deficiency with a prolonged period of clinical latency. However, there is ongoing active viral replication during clinical latency.

Primary infection is symptomatic in more than 50% of cases, but the diagnosis is usually missed. The incubation period is typically 2–4 weeks after exposure. The duration of symptoms is variable, but is seldom longer than 2 weeks. The clinical manifestations resemble a glandular fever-type illness, but the presence of maculopapular rash or herpetiform orogenital ulceration strongly suggests primary HIV infection rather than the other viral causes of glandular fever. Atypical lymphocytosis occurs less frequently than in Epstein–Barr virus infection. Transient CD4 lymphopenia occurs, which may result in opportunistic infections, notably oropharyngeal candidiasis. Thrombocytopenia and moderate elevation of liver enzymes occur commonly. The differential diagnosis of primary HIV includes acute EBV, primary CMV infection, rubella, primary toxoplasmosis and secondary syphilis.

Disease progression is highly variable. AIDS develops on average after nine years with death occurring about a year later in adults not treated with ART. If untreated, most patients eventually develop one or more serious morbid events, which are known as AIDS-defining illnesses (WHO clinical stage 4). Death

occurs as a result of these illnesses, or from general cachexia. The rate of declining immunity is variable. A small proportion of patients don't experience disease progression. These patients (called long-term non-progressors) have a good immune response and have low viral loads. Some of these long-term non-progressors, known as "elite controllers", have undetectable viral loads without ART. Patients with high viral loads progress more rapidly, as do older people. The rate of disease progression is dependent in part on the viral load "set point" (the plateau level to which the viral load falls after seroconversion). If the set point is high, disease progression is likely to be rapid, whilst a low set point is associated with slow progression to AIDS.

The Natural History of Untreated HIV Infection



Eftenem

efavirenz | emtricitabine | tenofovir

FIXED DOSE COMBINATION OF EFV/ FTC/TDF



INDICATION¹

For use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults

Eftenem is a fixed-dose combination tablet containing 600 mg of EFV, 200 mg of FTC and 300 mg of TDF – **the preferred agents for use in treatment-naïve HIV patients**^{2,3,4}

EFV = efavirenz; FTC = emtricitabine; HIV = human immunodeficiency virus; TDF = tenofovir disoproxil fumarate

REFERENCES: **1.** EFTENEM package insert (13 August 2013). **2.** Killingley B, Pozniak A. The First Once-Daily Single-Tablet Regimen for the Treatment of HIV-Infected Patients. *Drugs of Today*. 2007;43(7):427-442. **3.** National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. National Department of Health, South Africa. April 2015. Available at: <http://www.sahivsoc.org/upload/documents/ART%20Guidelines%2015052015.pdf>. Accessed: 1 October 2015. **4.** Meintjes G, Black J, Conradie F, et al. Guideline: Adult antiretroviral therapy guidelines 2014 - Southern African HIV Clinicians Society. *S Afr J HIV Med*. 2014;15(4):121-143.

S4. Eftenem: Each film-coated tablet contains 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (tenofovir DF). Reg. No.: 47/20.2.8/0118. For full prescribing information refer to the package insert approved by the MCC. **HCR:** Specpharm (Pty) Ltd, Reg. No. 97/00203/07, Cor 15th and Pharmaceutical Road, Halfway House, Midrand, PO Box 651, Halfway House, Midrand, 1685, Gauteng. Telephone: + 27 11 652 0400.

CERTIFICATION NUMBER: EFTEN/22/28-09-2015.

...its all about trust

SPECPHARM

Minor HIV/AIDS-Related Conditions

Oral Lesions

Common conditions include thrush, aphthous ulcers and oral hairy leukoplakia. Oral hairy leukoplakia is generally asymptomatic and is an important prognostic sign.

Periodontal diseases, such as linear gingivitis and the more serious periodontal necrotising ulceration, occur commonly. Good dental hygiene is important and regular dentist visits are advised. Chlorhexidine rinses may also be useful.

Oral Candidiasis

Oropharyngeal candidiasis is common, and may manifest in one or more of the following ways: pseudomembranous plaques (white plaques which may be scraped off the mucosal surface with or without bleeding); erythematous candidiasis (presenting as single or multiple red patches); angular cheilitis (presenting as linear fissures or ulcers at the corners of the mouth); hyperplastic candidiasis (presenting as white, adherent plaques on the buccal mucosa); or median rhomboid glossitis.

Topical therapy:

- Nystatin suspension (100 000 IU/ml) 1 ml four times per day
- Daktarin® oral gel is helpful for angular cheilitis

Systemic therapy (only for lesions that fail to respond to topical therapy):

- Fluconazole 50 – 100 mg daily for seven days or 150 mg STAT
- Itraconazole oral solution: 200 mg daily for seven days

Relapses following topical and systemic treatment are common.

Systemic antifungals should be used judiciously as repeated use may result in infection with *Candida* species that are resistant to azole antifungals. In particular, routine prophylactic use of antifungals is not recommended because of the risk of developing resistance. In the presence of retrosternal dysphagia or odynophagia, a clinical diagnosis of oesophageal candidiasis is made, which requires systemic treatment (fluconazole 200 mg daily for 14 days).

Oral Ulcers

Oropharyngeal or oesophageal ulcers occur frequently. These are usually aphthous ulcers that are minor (<1 cm) or major (>1 cm). Major aphthous ulcers are deep, painful ulcers that may cause considerable tissue destruction, are seen in advanced disease, and cause considerable morbidity.

Aphthous ulcers may respond to topical steroids or a steroid inhaler aimed at the lesions, but a short course of prednisone 30 mg daily is required for severe lesions or with oesophageal involvement. Major aphthous ulcers typically resolve rapidly after ART is commenced. Other causes of mucosal ulcers include cytomegalovirus, histoplasmosis, and herpes simplex virus, which are diagnosed on biopsy (specimens should be taken from the edge of the lesion).

Salivary Gland Disorders

Salivary gland enlargement, especially the parotids, is common. It is usually due to a benign disorder of lymphocyte infiltration (with CD8+ cells) resulting in lympho-epithelial cysts. The sicca syndrome may co-exist. The salivary gland involvement is a marker for the diffuse infiltrative lymphocytic syndrome (DILS), which may cause lymphoid interstitial pneumonitis and a variety of auto-immune disorders (e.g. polymyositis, mononeuritis). Large cysts may be treated with aspiration and instillation of sclerosant. Alternative treatments include low dose irradiation or superficial parotidectomy. The salivary gland enlargement usually regresses on ART.

Peripheral Neuropathy

Peripheral neuropathy is common in HIV infection. It may present at any stage of the illness, but becomes more common in late disease, occurring in about a third of AIDS patients. It presents as a symmetrical mixed sensorimotor neuropathy in a typical “glove and stocking” distribution. It is slowly progressive. Paraesthesiae and depressed ankle jerks are seen in early disease, progressing to loss of sensation. Distal weakness may occur. It is important to exclude toxic neuropathy due to drugs. The drugs which most often cause peripheral neuropathy in HIV medicine are isoniazid and the antiretrovirals stavudine and didanosine. Drug-induced neuropathy progresses much more rapidly than HIV neuropathy and is usually more painful.

The management of peripheral neuropathy should commence with a trial of B complex vitamins (or pyridoxine alone with isoniazid). The most effective drug for painful neuropathy is regular analgesia, starting with paracetamol followed by adding a weak opioid such as tramadol. Analgesic adjuvants may be of benefit: amitriptyline starting at 10 – 25 mg at night and gradually increasing up to 100 mg if tolerated is preferred. Carbamazepine should be avoided as it has many drug interactions with non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Lamotrigine, pregabalin or gabapentin are also effective, and do not have the same drug interaction problems as carbamazepine.

Neuropathy induced or exacerbated by drugs generally reverses if the drug is stopped, but recovery may be partial. It is therefore important to stop the offending drug as soon as possible after neuropathy develops.

Lymphadenopathy

This is a common feature of HIV infection, typically occurring early in the illness and persisting for years. Lymphadenopathy may also be due to malignancy (e.g. Kaposi's sarcoma or lymphoma) or tuberculosis, which is an extremely common cause in Southern Africa. Rapid enlargement of a node, asymmetric enlargement, or lymphadenopathy associated with constitutional symptoms (even if the nodes are symmetrical) warrants further investigation. Lymph node needle aspiration (using a wide bore needle such as 19G) should be undertaken for microscopy. One slide should be air-dried and sent for staining for acid-fast bacilli (70 percent yield in tuberculosis). The other slide should be fixed and sent for cytology. If the node contains sufficient caseous liquid, this should be sent for TB culture. If this is unhelpful, excision biopsy should be done. Tru-cut needle biopsies of nodes also have a high diagnostic yield.

Haematological Conditions

Isolated thrombocytopaenia without coagulation abnormalities or haemolysis resembling immune thrombocytopaenia is a common problem in HIV infection. As with immune thrombocytopaenia unassociated with HIV, high dose steroids are often beneficial for severe thrombocytopaenia (<50). Thrombotic thrombocytopaenic purpura (a multisystem disorder with thrombocytopaenia and a micro-angiopathic haemolytic anaemia) is also HIV-associated and should be treated in conjunction with a haematologist. Both conditions usually respond to ART.

Bone marrow suppression is common in advanced disease. This may be due to bone marrow infiltration (e.g. TB or TB IRIS, malignancies, fungi) or due to HIV-induced hypoplasia/dysplasia – a bone marrow biopsy is usually necessary for accurate diagnosis. Pure red cell aplasia may complicate parvovirus infection and responds to high dose gamma globulin. Pure red cell aplasia is also a rare adverse effect of lamivudine and possibly emtricitabine. Drug-induced cytopaenias are common (especially zidovudine, which causes anaemia and neutropaenia, but not thrombocytopaenia). High dose co-trimoxazole may also cause bone marrow suppression, and prophylactic doses occasionally cause neutropaenia, usually without other cytopaenias. Filgrastim (Neupogen®) may be indicated if the neutrophil count is <0.5 in the presence of sepsis. If the cause is co-trimoxazole, add folic acid.

Skin Lesions

Skin lesions are very common and become more common as the CD4 count falls. If there is any uncertainty in diagnosis, the advice of a dermatologist should be obtained and a biopsy performed. Scabies should not be forgotten as a common cause of pruritus.

Common conditions include:

Xeroderma

Dry skin is very common in late-stage HIV infection and may be associated with pruritus. Therapy: emollients like cetomacrogol (note that aqueous cream is not an emollient).

Seborrhoeic Dermatitis

Lesions are commonly found in the hairline, nasolabial folds and eyebrows, but may be extensive. Therapy: low dose topical steroids and selenium sulphide shampoo.

Folliculitis

Several types are seen – infective, acneform and eosinophilic. Therapy: topical benzoyl peroxide and antibiotics (e.g. macrolides or doxycycline) may be effective. If severe or refractory, refer to dermatologist.

Papular, Pruritic Eruption (“Itchy red-bump disease”)

This is common and difficult to manage. Darker-skinned patients often experience marked post-inflammatory hyperpigmentation. Therapy: antihistamines (older sedating agents given at night are preferred) and steroid creams (10% hydrocortisone to body; 1% hydrocortisone to face or equivalents), often mixed with an emollient. The cause is thought to be an exaggerated response to insect bites and measures to reduce these (e.g. regular treatment of pets, mosquito nets) should be implemented.

Molluscum Contagiosum

This is commonly found with low CD4 cell counts. Therapy: local curettage if limited number of lesions.

Dermatophytosis (Tinea)

This may involve the skin, scalp or nails. Therapy: topical antifungals should be used for limited skin disease only. Extensive skin involvement or infection of the scalp or nails must be treated with oral antifungals as below:

Tinea corporis/cruris/pedis: terbinafine 250 mg daily for 2 weeks OR fluconazole 150 mg per week for 2 – 4 weeks.

Tinea capitis: terbinafine 250 mg daily for 4 weeks OR fluconazole 200 mg daily for 4 weeks.

Tinea unguium (fingernails): terbinafine 250 mg daily for 6 weeks OR itraconazole 200 mg bd for one week, repeat after 1 month.

Tinea unguium (toenails): terbinafine 250 mg daily for 12 weeks OR itraconazole 200 mg bd for one week, repeat monthly for 3 – 4 months. Note that big toe nail lesions respond very poorly to therapy.

NB: There are important drug interactions between certain ART and itraconazole.

Herpes Simplex

Recurrent mucocutaneous ulcers are extremely common in HIV infection. HSV is the commonest cause of genital ulceration in HIV. With advancing immune suppression, large chronic mucocutaneous ulcers develop, particularly in the anogenital region and around the mouth. The lesions may be very extensive. If they persist for longer than four weeks they are considered to be AIDS-defining (WHO Clinical Stage

4). Therapy: Oral acyclovir 400 mg 8 hourly or valaciclovir 500mg 12 hourly for 5 – 10 days. Frequent recurrences should be treated with suppressive therapy if they do not respond to ART: acyclovir 400 mg 12 hourly for six months.

Herpes Zoster

This may be the first sign of HIV infection. The average CD4 count at first episode of zoster is 350. It may affect multiple dermatomes and may be recurrent. Therapy: Valaciclovir 1 g 8 hourly or acyclovir 800 mg five times daily or famciclovir 250 mg 8 hourly – all for one week. Pain management is critically important – opiates are often necessary for acute pain. Amitriptyline 10 – 100 mg nocte is useful for prolonged pain (but should be started early if pain is not settling within a few days). Soothing antibacterial creams are useful (e.g. silver sulfadiazine).

Inflammation and co-morbidity

Untreated HIV infection is associated with marked immune activation. ART reduces immune activation, but this does not resolve completely, even with prolonged virologic suppression. There is increasing recognition that immune activation is implicated in a number of co-morbid illnesses that are not directly HIV-related; notably vascular disease, non-AIDS cancers and chronic kidney disease. It is important to address vascular risk factors in HIV-infected patients.

Major Opportunistic Infections and Conditions

Bacterial Pneumonia

Diagnosis: as for community-acquired pneumonia in HIV-negative patients. There is a higher rate of bacteraemia in HIV infection. Important to note that pulmonary TB can present as an acute pneumonia.

Treatment: ceftriaxone OR cefotaxime OR co-amoxiclav for 5 – 10 days. In severe pneumonia, add a macrolide (e.g. azithromycin). **NB: Fluoroquinolones should be avoided as this could mask TB and result in quinolone-resistant TB unless there are compelling reasons for their use (e.g. severe beta lactam allergy).**

Maintenance treatment: co-trimoxazole 960 mg daily until CD4 count rises to >200 on ART (reduces the incidence of bacterial pneumonia and prevents other opportunistic infections).

Candidiasis of Oesophagus/Trachea

Diagnosis: clinically with oropharyngeal thrush and retrosternal odynophagia/dysphagia or on endoscopy.

Treatment: fluconazole 200 mg daily for 14 days.

Maintenance treatment: not indicated. Although recurrences may occur the risk for this is reduced by ART, disease is not life-threatening and azole-resistant *Candida* strains develop on maintenance therapy.

Cryptococcosis

Diagnosis: culture of *Cryptococcus neoformans* from any site or by positive cryptococcal antigen in blood or CSF (Note: CSF cryptococcal antigen titres <1:8 may reflect a false positive or a low burden of infection). CSF Indian Ink stain is also useful to diagnose cryptococcal meningitis, but may be negative in around 20% of cryptococcal meningitis (CM) cases.

Treatment: amphotericin B 1 mg/kg/day IV + fluconazole 800mg/day for 14 days followed by fluconazole 400 mg daily for 8 weeks. All patients should have CSF opening pressure measured at diagnosis. Patients with raised intracranial pressure (>25 cm H₂O) should have daily lumbar punctures, removing sufficient CSF (usually 10 – 20 ml) to lower pressure to <20 cm H₂O. LPs should be done daily until symptoms of raised intracranial pressure has resolved. Raised intracranial pressure may develop on appropriate treatment, manifesting with headache, drowsiness or ophthalmoplegias. Patients presenting with these symptoms while on therapy should have repeat LPs. ART should be delayed for 4 – 6 weeks from the time of CM diagnosis – starting ART early in CM increases mortality. Amphotericin B can cause impaired renal function which can be minimised by pre-hydrating patients with normal saline. It also often causes hypokalaemia and hypomagnesaemia, which needs to be aggressively managed and pre-emptive supplementation is advised. Finally, infusion reactions with fever and rigors occur commonly.

Amphotericin B

The optimal treatment of cryptococcal meningitis includes intravenous amphotericin B (AmB) 1 mg/kg/day for 14 days. Amphotericin B has several potential toxicities, but monitoring and preventive strategies can reduce the effect of these.

Toxicity	Prevention	Monitoring	Treatment
Nephrotoxicity	Prehydrate with 1 litre normal saline given over 2 hours before AmB infusion	Creatinine twice weekly	Interrupt AmB and administer IV fluids if creatinine increases > 2 x baseline. Restart AmB with additional prehydration if creatinine normalises. Continue fluconazole 800 mg PO daily as monotherapy if it does not normalise (fluconazole dose may require adjustment for renal impairment)
Hypokalaemia	Routinely supplement with oral potassium	Potassium twice weekly	IVI potassium supplementation
Hypomagnasaemia	Routinely supplement with oral magnesium	Magnesium weekly	Increase oral supplementation or IVI supplementation
Chemical phlebitis (drip site)	Change IVI site regularly and flush drip after infusion	Drip site	Replace drip and monitor for secondary bacterial infection
Anaemia (expect 2 – 4 g/dl drop in Hb over 14 days on AmB)		FBC weekly	Consider transfusion if severe and symptomatic
Febrile reaction		Symptoms and temperature	Paracetamol prior to AmB infusion (if severe hydrocortisone 50 mg IVI prior to AmB infusion)
Cardiotoxicity	Infusion over 4 hours prevents cardiotoxicity		

Maintenance treatment: fluconazole 200 mg daily until CD4 count rises to >200 on ART (minimum treatment duration of antifungal therapy is 12 months). If relapse is suspected it is essential to send CSF for 14-day fungal culture as cryptococcal antigen can persist for years in the CSF thus a positive antigen is not itself indicative of relapse. Patients experiencing culture-positive relapses should receive 14 day induction therapy with amphotericin B and fluconazole as above, followed by fluconazole 800 mg for 8 weeks, then fluconazole maintenance. It is important to investigate the cause of the relapse. The most common cause is non-adherence. Where no history of poor adherence is apparent, such patients should have cryptococcal isolate tested for fluconazole susceptibility at a reference laboratory if possible. Long term maintenance in such patients should be discussed with AfA.

Asymptomatic cryptococcal antigenaemia: 2 – 10% of patients starting ART with a CD4 count <100 have a positive serum cryptococcal antigen (CrAg) test despite not having symptoms of meningitis. However, these patients are at high risk of developing cryptococcal meningitis during early ART. We thus suggest screening for serum CrAg in all patients presenting with CD4 <100. If feasible, all patients who are serum CrAg positive should be lumbar punctured, tested for cryptococcal meningitis and if meningitis is diagnosed treated appropriately. For those with antigenaemia but no meningitis, although there is no randomized controlled trial evidence to guide management, pending further research we suggest treating pre-emptively with fluconazole 800 mg daily for two weeks, followed by fluconazole 400mg daily for 8 weeks followed by fluconazole 200 mg daily until the CD4 count is > 200. If cryptococcal meningitis is excluded on LP in patients with positive serum CrAg then ART can be started without delay. In antigenaemic patients with no symptoms of meningitis where LP is declined or not possible, we recommend deferring ART for 2 weeks (while treating with fluconazole as recommended above). Such patients should be closely monitored for meningitis and if this develops then treated for CM as above. Refer to: Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update on the SA HIV Clinicians Society website (<http://www.sahivsoc.org>).

Cryptosporidiosis

Diagnosis: stool examination (request a modified acid fast stain).

Treatment: no effective therapy available – loperamide and oral rehydration solution. Responds well to ART.

Maintenance treatment: none.

Cytomegalovirus (CMV)

Disease outside the reticuloendothelial system is seen in advanced HIV (CD4 <100). The diagnosis and treatment of CMV differs by site of disease, so they will be discussed separately. Note that blood tests for CMV (serology, PP65 antigen or PCR) are not helpful in the diagnosis of CMV in AIDS patients as the vast majority of patients without CMV disease will be positive on one or more of these tests.

Treatment, especially valganciclovir, is currently extremely expensive, but the morbidity of CMV disease is severe (e.g. retinitis, the commonest site, results in irreversible blindness). Early initiation of ART (approximately 2 weeks after diagnosis) is essential in all cases. Zidovudine is best avoided in combination with ganciclovir or valganciclovir as these agents all suppress the bone marrow.

1. CMV retinitis

Diagnosis: funduscopy by an ophthalmologist (supported by PCR of vitreal fluid if necessary).

Treatment: ganciclovir 5 mg/kg bd IV for 14 days (patient should be admitted to hospital). This prevents CMV retinitis progression but does not reverse visual loss. Alternative valganciclovir

900 mg orally bd for 2 weeks induction. (Requires pre-authorisation by AfA).

Maintenance treatment: intravitreal ganciclovir 2 mg once a week. Discontinue when CD4 count is >100 on ART (in consultation with an ophthalmologist).

Alternative: valganciclovir 900 mg orally daily maintenance until CD4 count is >100 on ART. (Requires pre-authorisation by AfA).

2. CMV GIT (colitis/oesophagitis/duodenitis)

Diagnosis: histology of biopsy of ulcer showing typical inclusion bodies.

Treatment: ganciclovir 5 mg/kg bd IV for 14 – 21 days (patient should be admitted to hospital). Alternative valganciclovir 900 mg orally bd for 2 weeks. (Requires pre-authorisation by AfA).

Maintenance treatment: not necessary (unless there is a relapse).

3. CMV CNS (encephalitis/polyradiculopathy/myelitis)

Diagnosis: PCR of CSF.

Treatment: ganciclovir 5 mg/kg bd IV for 14 – 21 days. Alternative valganciclovir 900 mg orally bd for 2 weeks induction (Requires pre-authorisation by AfA).

Maintenance treatment: valganciclovir 900 mg orally daily. (Requires pre-authorisation by AfA). Discontinue when CD4 count is >100 on ART.

4. CMV pneumonitis

Diagnosis: histology of lung biopsy. Usually there is another pathogen causing disease (especially *Pneumocystis*).

Treatment: usually not necessary – treatment of co-pathogens usually results in resolution of disease.

Ganciclovir 5 mg/kg bd IV for 14 days may be indicated in severe disease. Alternative valganciclovir 900 mg orally bd for 2 weeks. (Requires pre-authorisation by AfA).

Emmonsiosis

This is a newly described dimorphic fungus that causes disseminated infection in patients with advanced HIV. It was first reported in South Africa.

Diagnosis: culture of *Emmonsia* spp. from any source (blood fungal culture, bone marrow or tissue biopsy cultures). Histology of biopsy of mucocutaneous lesions is suggestive.

Treatment: amphotericin B 1 mg/kg daily IV for 2 weeks or until improved, followed by itraconazole

200 mg 8 hourly for 3 days, then 200 mg bd (reduce to daily when on ART). Note that there are important drug interactions between itraconazole and antiretrovirals. Itraconazole cannot be used safely with NNRTIs due to induction of itraconazole metabolism. A dose reduction (200 mg daily) is required with protease inhibitors. All patients on itraconazole for emmonsiosis should therefore be treated with ART using protease inhibitors. Fluconazole 400mg daily appears to be active *in vitro* and could be considered instead of itraconazole and does not have important drug interactions with ART.

Maintenance treatment: itraconazole 200 mg daily (on PI-based ART) until CD4 count rises to >200 on ART (minimum of 12 months). Fluconazole 200mg daily may be an option.

Herpes Simplex Virus (HSV) Ulcers

Diagnosis: usually clinical – shallow, painful spreading muco-cutaneous ulcers. As HIV disease advances, spontaneous healing is delayed and eventually does not occur.

Treatment: acyclovir 400 mg 8 hourly OR valaciclovir 500 mg bd OR famciclovir 125 mg bd orally for 7 – 14 days.

Maintenance treatment: not usually indicated. Although recurrences are common, disease is not life-threatening and resistant mutant strains develop with chronic therapy. Recurrences can usually be dealt with by repeated treatment courses. In exceptional cases, acyclovir 400 mg bd for 6 months can be used (AfA pre-authorisation required).

Histoplasmosis

Diagnosis: culture of *Histoplasma capsulatum* from any source (blood fungal culture, bone marrow or tissue biopsy cultures). Histology of biopsy of mucocutaneous lesions is suggestive.

Treatment: amphotericin B 1 mg/kg daily IV for 2 weeks or until improved, followed by itraconazole 200 mg 8 hourly for 3 days, then 200 mg bd (reduce to daily when on ART). Note that there are important drug interactions between itraconazole and antiretrovirals. Itraconazole cannot be used safely with NNRTIs due to induction of itraconazole metabolism. A dose reduction (200 mg daily) is required with protease inhibitors. All patients with histoplasmosis should therefore be treated with ART using protease inhibitors.

Maintenance treatment: itraconazole 200 mg daily (on PI-based ART) until CD4 count rises to >150 on ART (minimum of 12 months).

Isosporiasis

Diagnosis: special stain of stool (request a modified acid fast stain).

Treatment: co-trimoxazole four single strength (480 mg) tablets bd for 14 days. If patient unable to take oral medications use co-trimoxazole IVI. Alternative ciprofloxacin 500mg bd.

Maintenance treatment: co-trimoxazole 960 mg daily until CD4 count rises to >200 on ART. Recurrent isosporiasis despite secondary prophylaxis and a good response to ART occurs in a small proportion of patients. Management in this situation is difficult – discuss with AfA.

Microsporidiosis

Diagnosis: demonstration of the organism on stool (modified trichrome stain or PCR) or on small bowel biopsy.

Treatment: some strains respond to albendazole 400 mg bd for 21 days – no therapy for other strains. Usually responds well to ART.

Maintenance treatment: none.

Non-tuberculous Mycobacterial Infection (disseminated)

Diagnosis: culture from blood (special mycobacterial blood culture bottle), bone marrow or other sterile site or gastro-intestinal biopsy – usual organism is *Mycobacterium avium* complex (MAC). Culture from sputum usually represents colonisation and is NOT an indication for treatment unless repeated cultures are positive in conjunction with CXR changes, and other causes are excluded. Although tuberculosis may occur concurrently with MAC, this is uncommon. If both OIs are confirmed then treat for both, but if MAC is diagnosed in a patient empirically treated for tuberculosis, then tuberculosis treatment should be discontinued and MAC treated.

Treatment: clarithromycin 500 mg bd plus ethambutol 15 – 25 mg/kg daily (usually 800 mg or 1 200 mg as ethambutol is available in 400 mg tablets) to be continued until the CD4 count has increased to >100 on ART, provided that the minimum duration of treatment is 12 months. When the non-nucleoside reverse transcriptase inhibitors and clarithromycin are used together, the clarithromycin levels are decreased; therefore azithromycin 500 mg/day should be used as an alternative. Similarly, if the patient is taking rifampicin for confirmed tuberculosis or any other reason, then azithromycin should be used in preference to clarithromycin due to drug-drug interactions. MAC is resistant to rifampicin. There is conflicting data on the added benefit of rifabutin to a macrolide + ethambutol. Under certain circumstances, such as failure to respond to dual therapy in proven MAC or severe disease, the addition of rifabutin may be considered – dosing of rifabutin is complex and all cases should be discussed with AfA for authorisation. The dose of rifabutin is 450 mg daily when used in conjunction with efavirenz, whereas with a protease inhibitor regimen, rifabutin 150 mg daily should be used. There may be increased toxicity with the daily dose of rifabutin due to accumulation of the metabolite – monitor closely for neutropaenia, uveitis and hepatitis.

Maintenance treatment: see above.

Pneumocystis Pneumonia (PJP)

Diagnosis: special stains of broncho-alveolar lavage or induced sputum (following ultrasonic nebulisation with hypertonic saline). Clinical diagnosis is suggested by bilateral interstitial (“ground glass”) infiltrate on CXR, history of progressive dyspnoea over several weeks, and hypoxia (at rest, or on effort as assessed by >5% desaturation).

Treatment: co-trimoxazole 480 mg per 4 kg body weight (maximum 16 single strength tablets/day) daily given in divided doses 6 – 8 hourly for 21 days. All hypoxic patients should be given adjunctive prednisone 40 mg bd for days 1 – 5, 40 mg daily for days 6 – 10 and 20 mg daily for days 11 – 21. There are extremely limited options available in South Africa for patients with co-trimoxazole intolerance. Pentamidine, trimethoprim (given with dapsone) and primaquine (given with clindamycin) are no longer registered in South Africa – MCC permission must be sought for any of these (primaquine is easier to get currently). The only available alternative therapy is atovaquone 750 mg bd for 21 days – this is only suitable for mild PCP and is extremely expensive. Atovaquone cannot be given with rifampicin (will result in subtherapeutic atovaquone levels). Some clinicians have used clindamycin plus dapsone, but there is no published evidence of efficacy with this combination.

Co-trimoxazole desensitisation should be considered for patients with PJP and a history of intolerance to co-trimoxazole. The rapid desensitisation regimen described below was successful in 19/22 patients with no significant problems in the three who failed. However, a further three patients had to subsequently discontinue due to the development of a rash (Clin Infect Dis 1995; 20:849).

Use co-trimoxazole suspension 240 mg/5 ml. Co-trimoxazole suspension will need to be diluted appropriately. Please consult your pharmacist. Desensitisation must be conducted in hospital and should be done WITHOUT antihistamine or steroid cover. Stop desensitisation if rash, skin symptoms (e.g. itch) or fever develop.

Time	Dose
(hours)	(mls of co-trimoxazole susp)
0	0.0005
1	0.005
2	0.05
3	0.5
4	5
5	Two single strength tablets followed by full dose

Maintenance treatment: co-trimoxazole 960 mg daily until CD4 count rises to >200 on ART.

Progressive Multifocal Leukoencephalopathy (PML)

Diagnosis: non-enhancing lesions on MRI, representing demyelination, together with positive PCR for JC virus on CSF. Definitive diagnosis requires brain biopsy (seldom necessary). If JC virus is negative, diagnosis is probably HIV leukoencephalopathy, which has a better prognosis, although CSF JC virus PCR may be false negative especially in patients on ART.

Treatment: no effective therapy available. Responds poorly to ART, with many cases experiencing exacerbation due to immune reconstitution (MRI lesions may be enhancing in this situation). ART has improved survival, but patients are left with residual disability.

Salmonella Bacteraemia

Diagnosis: blood culture of non-typhoidal salmonella.

Treatment: ciprofloxacin 500 mg bd for 4 – 6 weeks (very ill patients or vomiting – treat initially with ceftriaxone 1 g IVI daily).

Maintenance treatment: co-trimoxazole 960 mg daily until CD4 count rises to >200 on ART (even if the salmonella was resistant to co-trimoxazole – other opportunistic infections will be prevented).

Tuberculosis (TB)

HIV infection increases the risk of TB substantially, with the risk doubling shortly after seroconversion, and increasing further in advanced disease. TB may affect the lungs, be disseminated or limited to extrapulmonary sites. Disseminated or extrapulmonary TB is regarded as an AIDS-defining (stage 4) condition, although African cohort studies have shown that all forms of tuberculosis have a better prognosis than other AIDS-defining illnesses. All forms of TB may occur at any CD4 count, but extrapulmonary, disseminated and non-cavitary pulmonary TB are typically seen when the CD4 count is <200. In advanced disease, the chest x-ray may be clear with positive sputum TB culture.

The 4 cardinal features of TB are cough, fever, night sweats and weight loss. Every patient should be screened for these symptoms at each clinic visit. Symptoms of extrapulmonary TB (EPTB) will depend on location of TB disease. In comparison with HIV seronegative patients, the presentation of TB may be sub-acute or acute rather than chronic, sputum production is less common, and sputum smears are more likely to be negative. EPTB is more common, with TB lymphadenitis, TB meningitis, pleural and pericardial TB, disseminated TB and vertebral TB (Pott's disease) being the most common presentations.

The chest radiographic appearance of TB in HIV-infected patients varies according to the CD4 count (Figure 1). Typical cavitary disease as seen in HIV-seronegative patients is rarely present at CD4 counts <200 cells/mm³. At CD4 counts <200 cells/mm³ patchy mid and lower zone infiltrates are the commonest manifestation, often with associated hilar or mediastinal lymphadenopathy and pleural effusions. The typical miliary TB pattern may also occur. In advanced disease, pulmonary TB confirmed by sputum culture, may occur with a normal chest radiograph.

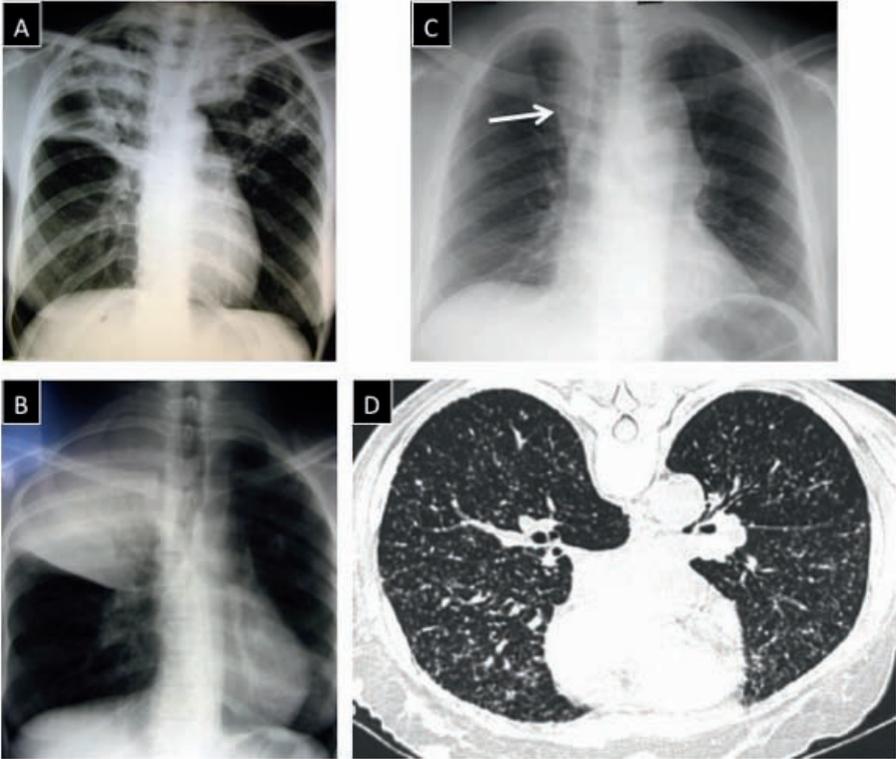


Figure 1. Cavitary bilateral upper lobe consolidation (A). Right upper lobe consolidation with air bronchogram (B). Right para-tracheal lymphadenopathy with normal lung parenchyma (C). Miliary TB pattern on CT scan (D).

There is a broad differential diagnosis for PTB in patients presenting with respiratory symptoms, particularly in those with advanced immunosuppression:

Bacterial Pneumonia	Short history, fever, consolidation on CXR ± air bronchogram ± para-pneumonic pleural effusion. Lymph nodes absent from CXR. Response to antibiotics
Bacterial super-infection of underlying bronchiectasis	Purulent sputum with CXR features of bronchiectasis i.e. cystic changes and parallel lines ± superimposed consolidation
Lung Abscess	Cough with purulent sputum and CXR showing cavity with air-fluid level on CXR. Requires 6 weeks co-amoxiclav and physiotherapy
Pneumocystis Pneumonia	Dry cough + progressive shortness of breath Hypoxia or >5% drop in saturation on exertion CXR classically show diffuse, ground-glass shadowing extending from peri-hilar region. Lymph nodes and effusions are not a feature Uncommon in patients with CD4 counts >200
Pulmonary Cryptococcosis	Can mimic PTB, but pleural effusions and lymphadenopathy are rare Serum CrAg and sputum fungal culture are usually positive
Pulmonary Nocardiosis	Predominantly upper lobe cavitory infiltrates. Rare diagnosis Branching, beaded Gram-positive bacilli on sputum microscopy Weakly positive on acid-fast staining, may be mistaken for TB
Pulmonary Kaposi's sarcoma	Mucocutaneous Kaposi's sarcoma lesions are usually apparent May present as bloody pleural effusion or linear opacities that follow the blood vessels on CXR in a predominant peri-hilar distribution with nodules of varying size
Lymphoid Interstitial Penumonitis (LIP)	May be part of broader picture of Diffuse Inflammatory Lymphocytosis Syndrome (DILS) or associated with sicca syndrome (dry eyes, dry mouth) Bilateral reticulo-nodular pattern on CXR

Imaging also plays an important role in diagnosis of EPTB, particularly in neurological, abdominal and vertebral TB (Figure 2). TB meningitis is characterised by basal meningeal enhancement on contrasted CT scan. Hydrocephalus, infarction, or intracranial tuberculomas may be present. Tuberculomas are either homogenous high signal density space-occupying lesions or more commonly, ring-enhancing lesions with a reduced signal within the lesion. The latter are a result of caseation forming a tuberculous abscess. In abdominal tuberculosis, suggestive features on ultrasound or CT include splenomegaly with or without hypoechoic lesions, lymphadenopathy of >1.5 cm, and ascites. TB pericarditis often displays fibrous stranding on echocardiography. TB lymphadenopathy often has a hypodense centre from caseous necrosis on ultrasound/CT/MRI scans.

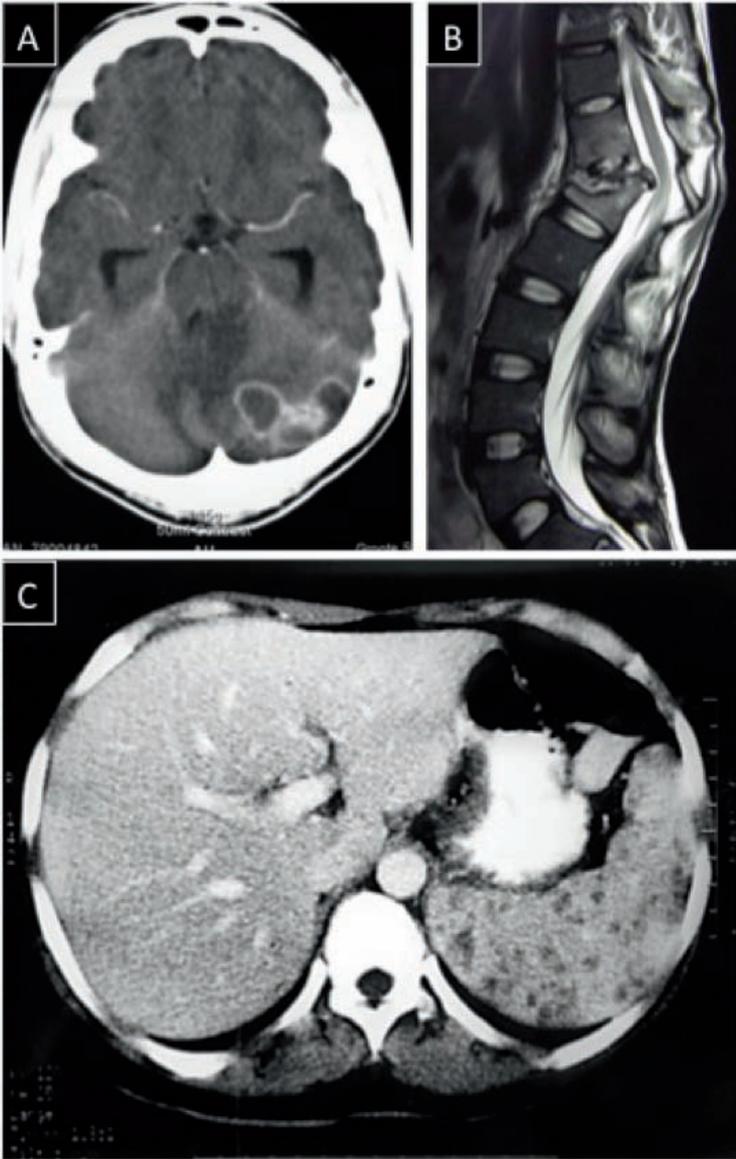


Figure 2: Cranial CT showing multiple ring-enhancing space-occupying lesions (A). Potts disease of the spine showing destruction of the disc space (B) and abdominal CT scan showing multiple splenic micro-abscesses (C)

It is important to try and confirm the diagnosis of TB. 60-70% of sputum samples from HIV-infected patients with PTB are 'smear-negative' by routine microscopy. GeneXpert real-time PCR on sputum is now the diagnostic test of choice for HIV-infected patients presenting with cough as it is more sensitive than sputum smear (70% of smear-negative, culture-positive sputum samples) and has 100% specificity. Furthermore, GeneXpert will also confirm whether or not rifampicin resistance is present in sputum samples that are positive for *Mycobacterium tuberculosis*. GeneXpert testing has been rolled-out within the South African public sector.

Where this test is not available, at least two sputum specimens should be sent for smear and culture. If the sputum is smear-positive, a rapid nucleic acid amplification test (HAIN MTBDR plus line probe assay) can be requested directly on the specimen, which detects rifampicin and isoniazid resistance, ensuring early optimal therapy. If drug resistance is confirmed, the Hain MTBDRsl test on sputum can be used to inform on sensitivity to ethambutol, quinolones and aminoglycosides.

Microscopy examination of lymph node aspirate smears also has a high yield (use a wide gauge needle e.g. 19G). Biopsy is also useful to obtain a rapid diagnosis – this can be from affected tissues (e.g. lymph node, lung pleura) or from bone marrow or liver if disseminated disease is suspected. All biopsy material should also be sent for mycobacterial culture, which has a high yield. Other specimens which give good culture yields are sputum, caseous material from cold abscesses/node aspirates or pleural/ascitic/pericardial fluid. In hospitalised patients early morning urine and blood (using special mycobacterial culture bottles) have a yield of around 30%.

A promising new test is urinary lipoarabinomannan (urinary-LAM), which in hospitalised patients with CD4 counts ≤ 200 , has a sensitivity approaching 50% in smear-negative patients, or those unable to produce sputum, and has high specificity (i.e. it is a good "rule in" test). Furthermore, bedside LAM-guided initiation of anti-tuberculosis treatment in HIV-positive hospital inpatients with suspected tuberculosis was recently shown to be associated with reduced 8-week mortality.

In advanced disease, TB can progress rapidly. Therefore TB treatment will often be necessary before culture results are available. For PTB it is reasonable to commence treatment pending cultures if a single Gene Xpert (or two smears) is negative, there has been no response to a course of antibiotics, and the chest x-ray is compatible with TB (as per national guidelines – it is important to point this out when referring patients to TB clinics for follow up). However, at least one and preferably two specimens should be sent for culture before starting TB therapy. As noted above, biopsy should also be considered.

HIV-positive patients respond well to TB treatment with the same drug combinations and duration of therapy used in HIV-seronegative individuals. Treatment should be initiated according to national guidelines (in South Africa: rifampicin, isoniazid, pyrazinamide and ethambutol in a fixed dose combination tablet [RHZE]) and all cases should be referred to their nearest TB clinic for management.

TB is a notifiable disease. Occasionally, drug side effects preclude the use of fixed dose combinations and individual drugs need to be used.

Action and dosage of individual anti-TB drugs

Drug	Action	Potency	Recommended dose (mg/kg)
First line drugs			
Rifampicin (R)	Bactericidal	High	10
Isoniazid (H)	Bactericidal	High	5
Pyrazinamide (Z)	Bactericidal	Low	25
Ethambutol (E)	Bacteriostatic	Low	15
Second line drugs			
Kanamycin (Km), Amikacin (Am), Streptomycin (Sm)	Bactericidal	Low	15
Ethionamide (Eto)	Bacteriostatic	Low	15 – 20
Moxifloxacin (Mfx)	Weakly bactericidal	Moderate	400 mg daily
Levofloxacin (Lfx)	Weakly bactericidal	Moderate	750 mg daily
Terizidone (Trd)	Bacteriostatic	Low	15-20
Cycloserine (Cs)	Bacteriostatic	Low	10-20
Para-aminosalicylic acid (PAS)	Bacteriostatic	Low	150
Capreomycin (Cm)		Low	15
Linezolid (Lzd)	Bactericidal	High	600 mg daily
Bedaquiline (Bdq)	Bactericidal	High	400 mg daily for 2 weeks followed by 200 mg 3x/week for 22 weeks

National guidelines for treatment of drug-sensitive tuberculosis with fixed dose combinations (FDC) are detailed in the following table:

Phase	Duration	Drug combination	Dose
Intensive	2 months	RHZE	30 – 37 kg 2 tabs
			38 – 54 kg 3 tabs
			55 – 70 kg 4 tabs
			>70 kg 5 tabs
Continuation	4 months	RH	30 – 37 kg 2 tabs (150/75)
			38 – 54 kg 3 tabs (150/75)
			55 – 70 kg 2 tabs (300/150)
			>70 kg 3 tabs (300/150)

Drug resistant tuberculosis (DR-TB) treatment depends on the type of resistance identified in the laboratory.

Resistance	Definition
Mono-resistance	Drug resistance to one drug only
Poly-resistance	Drug resistance to more than 1 TB drug other than rifampicin and isoniazid
Multi-drug resistance (MDR)*	Drug resistance to rifampicin and isoniazid
Extensive drug resistance (XDR)	MDR plus resistance to fluoroquinolones and one of the 3 injectable 2 nd line drugs (amikacin, kanamycin or capreomycin)
Pre-XDR	MDR and resistance to <u>EITHER</u> fluoroquinolone <u>OR</u> 2 nd line injectable drugs

* *GeneXpert MTB/RIF testing provides information about rifampicin resistance only. However, resistance to rifampicin is a good surrogate marker for multi-drug resistance (MDR). For patients who have isoniazid mono-resistance the intensive phase should be continued until sputum culture conversion has been achieved. Patients with DR-TB should never have a single drug added to a failing regimen, should be counselled properly with regard to prolonged duration, toxicities, adherence and infection control. Directly observed, daily treatment is advised.*

Treatment of MDR-TB: the intensive phase of treatment should continue for a minimum of 6 months, dosing at least 6 times/week. Conversion to the continuation phase may occur when 2 consecutive cultures are negative, taken one month apart. Continuation phase lasts at least 18 months after TB culture conversion. Patients with rifampicin mono-resistance should be treated in the same way as MDR-TB except that isoniazid (5 mg/kg) should be used instead of ethionamide.

	Intensive Phase		Continuation Phase	
Patient Weight	Drug	Daily Dosage	Drug	Daily Dosage
<33 kg	Kanamycin	15 – 20 mg/kg	Moxifloxacin	400 mg
	Moxifloxacin	400 mg	Ethionamide	15 – 20 mg/kg
	Ethionamide	15 – 20 mg/kg	Terizidone	15 – 20 mg/kg
	Terizidone	15 – 20 mg/kg	Pyrazinamide	30 – 40 mg/kg
	Pyrazinamide	30 – 40 mg/kg		
33 – 50 kg	Kanamycin	500 – 750 mg	Moxifloxacin	400 mg
	Moxifloxacin	400 mg	Ethionamide	500 mg
	Ethionamide	500 mg	Terizidone	750 mg
	Terizidone	750 mg	Pyrazinamide	1 000 – 1 750 mg
	Pyrazinamide	1 000 – 1 750 mg		
51 – 70 kg	Kanamycin	1 000 mg	Moxifloxacin	400 mg
	Moxifloxacin	400 mg	Ethionamide	750 mg
	Ethionamide	750 mg	Terizidone	750 mg
	Terizidone	750 mg	Pyrazinamide	1 750 – 2 000 mg
	Pyrazinamide	1 750 – 2 000 mg		
>70 kg	Kanamycin	1 000 mg	Moxifloxacin	400mg
	Moxifloxacin	400 mg	Ethionamide	750 – 1 000 mg
	Ethionamide	750 – 1000 mg	Terizidone	750 – 1 000 mg
	Terizidone	750 – 1000 mg	Pyrazinamide	2 000 – 2 500 mg
	Pyrazinamide	2 000 – 2 500 mg		

Adapted from Management of Drug-Resistant Tuberculosis. Policy Guidelines. National Dept of Health 2011 (Updated January 2013).

Management of XDR-TB or Pre-XDR TB should be under the guidance of a specialist in the field and should prompt immediate referral for inpatient care.

Adverse events to TB drugs and ART

Many of the common adverse events due to anti-tuberculosis drugs are shared by antiretrovirals

Adverse event	TB drug	ART
Drug-induced liver injury	Rifampicin, Isoniazid, Pyrazinamide, Fluoroquinolones, Ethionamide, PAS, Linezolid	NNRTIs, PIs, Integrase inhibitors
Cutaneous drug reaction	All	NNRTIs
Peripheral neuropathy	Isoniazid, Ethionamide, Linezolid	Stavudine, Didanosine
Nephrotoxicity	Aminoglycosides, Capreomycin	Tenofovir
Nausea and vomiting	Ethionamide, Pyrazinamide	Zidovudine, Didanosine, PIs
Psychosis	Isoniazid, Terizidone, Fluoroquinolones, Ethionamide	Efavirenz

Other important side effects of second line TB drugs include hearing loss (aminoglycosides and capreomycin), seizures (terizidone, fluoroquinolones and cycloserine), hypothyroidism (PAS, ethionamide), gastritis (PAS, ethionamide), arthralgia/arthritis (pyrazinamide and fluoroquinolones), tendonitis/tendon rupture (fluoroquinolones), reversible myelosuppression (linezolid), hypokalaemia/hypomagnesaemia (capreomycin and aminoglycosides), and QTc increase (fluoroquinolones, bedaquiline). Ototoxicity from aminoglycosides or capreomycin is usually irreversible. An audiogram should be performed prior to starting an aminoglycoside or capreomycin and regular audiometry should be done during treatment to detect high tone hearing loss, which is the first feature of hearing loss. The offending drug should be stopped immediately once hearing loss is identified, and patients with baseline hearing impairment should not be prescribed an ototoxic drug.

Management of cutaneous drug reactions after starting TB drugs

In addition to TB drugs causing cutaneous drug reactions (CDR), NNRTIs and co-trimoxazole should be suspected. Rash from NNRTIs almost always presents within two months of starting. Rashes due to co-trimoxazole typically present within three months of starting, but occasionally may present later. Moreover, a detailed history of traditional medicines and any over-the-counter medication should also be taken.

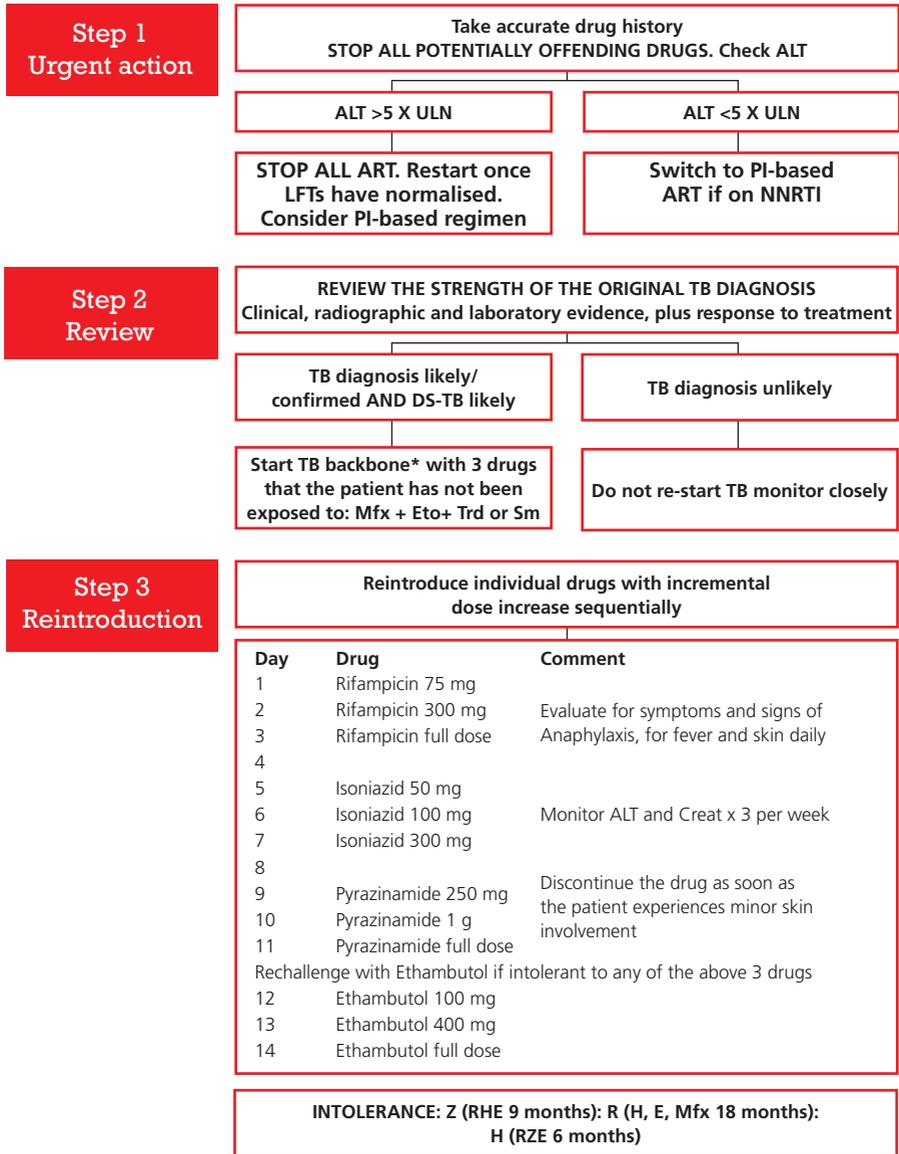
Mild rash in isolation without systemic symptoms, mucosal involvement or abnormal LFTs can be treated with oral antihistamines and skin moisturising agents, whilst continuing the drug under close observation.

Several are life-threatening:

- Stevens-Johnson Syndrome – <10% skin detachment and mucous membranes involved
- Toxic Epidermal Necrolysis – >30% skin detachment and mucous membranes involved
- DRESS syndrome – Drug rash eosinophilia and systemic symptoms

The following algorithm may be used for management of severe CDR. If ART also needs to be stopped, then re-start after TB drug rechallenge is complete and consider a PI-based regimen should the patient have previously been on an NNRTI.

Management of severe CDR



For management of drug-induced liver injury (DILI) in patients on ART and TB treatment refer to relevant section.

Management of renal dysfunction after starting TB drugs

TB drugs commonly causing nephrotoxicity are the aminoglycosides and, very rarely, rifampicin, which can cause an acute interstitial nephritis often together with flu-like illness, gastrointestinal symptoms, thrombocytopenia and anaemia. Tenofovir is the most important nephrotoxic ART causing renal failure, but co-trimoxazole may cause an interstitial nephritis. Other medications, notably non-steroidal anti-inflammatory drugs (NSAIDs), should also be considered.

DO NOT ADMINISTER tenofovir with other potentially nephrotoxic drugs like aminoglycosides. Consider switching tenofovir to stavudine, zidovudine (if Hb allows) or abacavir, whilst on the nephrotoxic drug.

If renal dysfunction occurs following the start of TB treatment:

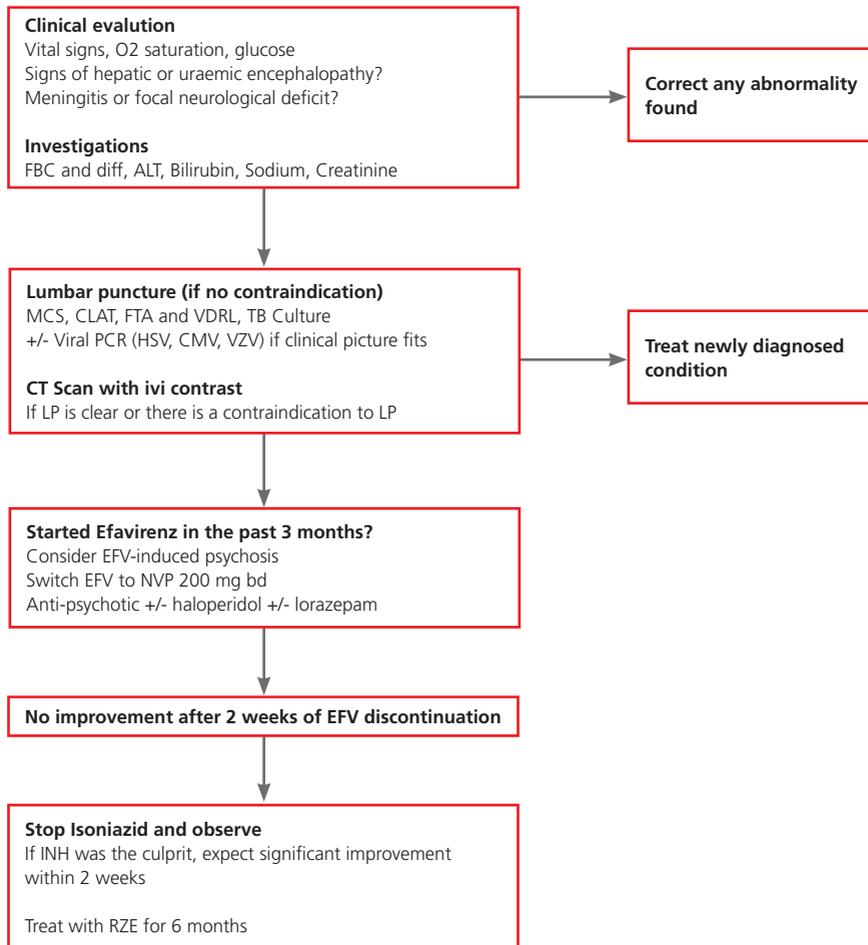
- STOP all agents commonly known to be nephrotoxic
- Correct dehydration as necessary
- Check urinary protein-creatinine ratio, serum electrolytes and creatinine. Renal ultrasound if renal dysfunction continues
- Monitor daily serum creatinine and fluid balance
- If the patient does not improve, refer for a specialist opinion +/- renal biopsy

Management of acute confusion after starting TB therapy

This is a medical emergency with a broad differential diagnosis:

Prior to starting ART	Acute superimposed infections (meningitis, sepsis, OI) Hypoxaemia (pneumothorax, pneumonia, embolus, heart failure) Metabolic cause (hypoglycaemia, hyponatraemia, hypernatraemia) Drug side effect (isoniazid psychosis, renal failure, liver failure) Paradoxical CNS TB reaction (hydrocephalus, tuberculoma) Substance abuse (alcohol withdrawal, illicit drug abuse)
Following ART start	Any of the above Drug side effect (efavirenz toxicity) CNS TB-IRIS Unmasking IRIS of another opportunistic infection

Clinical algorithm for initial evaluation



Toxoplasmosis

Diagnosis: is suggested with the following three features: CT/MRI scan showing contrast-enhancing mass lesions, CD4 count <200, and toxoplasma IgG positive. Note that toxoplasmosis IgG is positive in up to 40% of the general adult population and its value in this setting is as a rule-out test. (i.e. a negative toxoplasmosis IgG makes the diagnosis very unlikely). Rapid treatment response (clinical improvement in about one week and CT/MRI improvement after about two weeks) confirms the diagnosis (brain biopsy is definitive but seldom necessary).

Treatment: co-trimoxazole four single strength (480 mg) tablets bd for 4 weeks, then two bd for 12 weeks. For co-trimoxazole intolerance clindamycin 600 mg qid plus pyrimethamine 50 mg daily plus folinic acid 15 mg daily (to prevent bone marrow suppression from pyrimethamine – folinic acid is ineffective) for 6 weeks.

Maintenance treatment: co-trimoxazole 960 mg daily until CD4 count rises to >200 on ART.

In general, initiation of ART should be delayed until any active opportunistic infection is responding to treatment to avoid the development of immune reconstitution inflammatory syndrome (IRIS) – usually around two weeks for most infections. In cryptococcal and TB meningitis ART initiation should be delayed for 4 – 6 weeks.

HIV-Associated Kaposi's Sarcoma (KS)

Background to HIV-associated KS:

- KS is a malignancy of lymphatic endothelial origin
- It is associated with Human Herpes Virus-8 (HHV-8), also known as KS Herpes Virus (KSHV)
- KS may involve the skin, oral cavity, lymph nodes or viscera (especially lung and intestines). Lymphoedema is a common complication
- 80% – 90% of cases of visceral KS will have oral or skin involvement
- The CXR appearance of pulmonary KS involves nodules, consolidation and linear shadows often spreading from the hilar regions bilaterally. The diagnosis is confirmed by visualising endobronchial KS lesions on bronchoscopy (biopsy poses a risk of haemorrhage). Pulmonary KS may be associated with intrathoracic adenopathy and/or pleural effusions which are typically bloody or serosanguinous
- CXR is a useful screen for pulmonary KS in the setting of cutaneous disease
- KS is a WHO stage 4 defining illness, regardless of CD4
- The incidence of KS has been dramatically reduced by ART (92% reduction in Swiss cohort)

- Although the macroscopic appearance of skin and oral lesions may be very suggestive, if there is any uncertainty a biopsy should be performed to provide a definitive diagnosis. In particular nodular vascular skin lesions that enlarge rapidly should be biopsied to exclude bacillary angiomatosis that is due to Bartonella infection and may mimic KS
- Atypical oral lesions should be biopsied to exclude other malignancies such as lymphoma, squamous carcinoma and salivary gland tumours

Treatment principles:

- All HIV-positive patients with KS should be commenced on ART regardless of CD4 count
- Many patients with limited mucocutaneous KS will have complete resolution or substantial regression on ART alone. Nodular lesions in the mouth carry a poorer prognosis
- ART prolongs the time to treatment failure of KS chemotherapy
- It is important to investigate for and exclude co-existent opportunistic infections (particularly TB), if the patient is going to receive chemotherapy which will immunosuppress them further
- Treatment decisions need to be individualised and are based on: extent of disease, rate of growth of lesions and response to ART, symptoms, CD4 count and general condition. Quality of life is an important factor in decision-making regarding intensity of chemotherapy
- Radiotherapy is appropriate for symptomatic local lesions (e.g. lesion obstructing airway or swallowing)
- Systemic chemotherapy is indicated in the following patients:
 - Widely disseminated skin KS
 - Rapidly progressive disease
 - Visceral involvement
 - Significant lymphoedema
 - “B” symptoms (fever, night sweats, significant constitutional symptoms attributed to KS)
 - Failure to respond to ART or progression on ART

A suggested general approach is:

Limited cutaneous and oral lesions:

- Commence ART
- If lesions don't regress after 3 – 6 months or if they progress, then systemic chemotherapy

Extensive skin disease/visceral involvement:

- ART and systemic chemotherapy commenced simultaneously

Standard Chemotherapy Regimens

Options:

- Adriamycin (doxorubicin), bleomycin, vincristine combination therapy 2 weekly × 6 – 8 cycles
- Vincristine + bleomycin 2 weekly × 6 – 8 cycles is lower intensity option
- Liposomal anthracycline (daunorubicin or doxorubicin)
- Paclitaxel

Liposomal anthracyclines have been demonstrated to be superior to conventional combination chemotherapy (bleomycin and vincristine with or without non-liposomal doxorubicin) in terms of response rates and side effects. Paclitaxel has been found to be effective even in patients with anthracycline-resistant disease. Liposomal anthracyclines are better tolerated than paclitaxel in terms of side effects. Paclitaxel is associated with more neutropaenia, thrombocytopenia, myalgia and arthralgia. Paclitaxel is therefore usually reserved for salvage therapy.

ART with Chemotherapy

Given the increased risk of myelosuppression when combining chemotherapy with zidovudine, it is preferable to use tenofovir or abacavir rather than zidovudine. Stavudine and the vinca alkaloids share the common side effect of causing peripheral neuropathy.

There are several potential drug interactions when combining ART and the above chemotherapy agents:

- NNRTIs may reduce levels of paclitaxel and vincristine/vinblastine, but no dose adjustment advised
- PIs may increase levels of these agents potentially increasing toxicity, but no dose adjustment advised
- There is no interaction with the anthracyclines

Lymphoma

Non-Hodgkin's lymphoma (NHL) is 200 – 600 times more common in HIV-infected people compared with the general population. It is usually related to oncogenic viruses, EBV or HHV8. Systemic NHL typically presents with constitutional symptoms such as wasting and fever as well as symptoms related to site of disease. It may present with lymphadenopathy and/or GIT, hepatic, splenic, bone marrow, pulmonary or meningeal/nerve root involvement. Tissue biopsy is required for diagnosis. Common histologic types in HIV are diffuse large B-cell and Burkitt's lymphoma. Most are B cell in origin.

Primary CNS lymphoma presents with cerebral mass lesions. A positive EBV PCR on a CSF specimen in a patient with a mass lesion on brain imaging supports the diagnosis. Prognosis is poor even with optimal therapy.

Primary effusion lymphoma presents with lymphomatous effusions without mass lesions. It is diagnosed by pleural biopsy. It is related to HHV8.

Treatment: Chemotherapy and ART. Radiotherapy to relieve compressive symptoms and for primary CNS lymphoma.

HIV-Associated Nephropathy

HIV-associated nephropathy (HIVAN) results from direct infection of renal epithelial cells by HIV. It typically occurs when the CD4 count is less than 200, but may occur earlier in the course of HIV infection. It is a WHO clinical stage 4 defining condition. It manifests with heavy proteinuria and may progress to end-stage renal failure (ESRF) over the course of months. Patients usually do not have oedema or hypertension because the condition also results in salt wasting. Microscopic examination of urine is usually bland and renal ultrasound shows enlarged echogenic kidneys. A definitive diagnosis is made by renal biopsy which shows focal segmental glomerulosclerosis and cystic tubular dilatation.

It is important to diagnose HIVAN early before there has been substantial loss of renal function. This is why we recommend serum creatinine and urine dipstick as part of the initial assessment of HIV-positive patients. Any patient who has proteinuria on dipstick should have a spot urine sent for protein-creatinine ratio. Patients with significant proteinuria (>1 g/day) or abnormal creatinine should be referred to a nephrologist for assessment. There are anecdotal case reports of ART reversing the renal dysfunction associated with HIVAN. Cohort studies show that progression to end stage renal failure is slowed down by ART. All patients with HIVAN should be started on ART without delay (renal failure dose adjustments may be required – see Drug Dosages in Renal Failure). Tenofovir should be avoided. ACE-inhibitors reduce the amount of proteinuria and are thought to slow disease progression.

A trial of corticosteroids is advised by some experts.

Patients may still progress to ESRF despite the above therapy, particularly if ART is only started once there has been significant loss of renal function. In such patients, where available, dialysis and transplantation should be considered.

HIV-Associated Dementia (HAD)

This usually presents in patients with advanced HIV disease (CD4 count typically <200). It is a WHO stage 4 defining condition. It results from the direct effects of HIV on the CNS. Patients manifest with a progressive subcortical dementia with common early manifestations being forgetfulness, difficulty concentrating and performing complex tasks. Motor problems such as difficulty with rapid alternating movements, tremor and unsteady gait are frequent, as are behavioural changes (apathy or agitation). As HAD advances, patients develop extreme apathy and marked motor slowing and may progress to a vegetative state. A vacuolar myelopathy presenting with slowly progressive paraplegia and incontinence due to HIV's effect on the spinal cord may be associated with HAD.

HAD is a diagnosis of exclusion. At the very least all patients should have a lumbar puncture, CT scan and syphilis serology performed in order to exclude opportunistic infections. CSF in HAD may show minor elevations of protein and lymphocytes. The CT scan in advanced HAD shows cerebral atrophy.

A useful screening test for HAD is the International HIV Dementia Score. This test is less influenced by education status compared to other dementia scales. Patients with a low score on this screen (10/12 or less) should have more detailed neuropsychiatric assessment where this is available.

All patients with HAD (even early manifestations) should be commenced on ART without delay. Dramatic reversal of cognitive and neurological disability may be experienced on ART, but many patients will be left with residual (sometimes subtle) cognitive or neurological deficits, particularly if ART is started when HAD is advanced. Patients with HAD have increased sensitivity to the extra-pyramidal side effects of neuroleptics and low doses should be used.

INTERNATIONAL HIV DEMENTIA SCALE (IHDS)

Memory Registration – Give four words to recall (dog, hat, bean, red) – one second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

- 1. Motor Speed:** Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible:
4 = 15 in 5 seconds
3 = 11 – 14 in 5 seconds
2 = 7 – 10 in 5 seconds
1 = 3 – 6 in 5 seconds
0 = 0 – 2 in 5 seconds
- 2. Psychomotor Speed:** Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice:
4 = 4 sequences in 10 seconds
3 = 3 sequences in 10 seconds
2 = 2 sequences in 10 seconds
1 = 1 sequences in 10 seconds
0 = unable to perform
- 3. Memory Recall:** Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); colour (red):
Give 1 point for each word spontaneously recalled.
Give 0.5 points for each correct answer after prompting.
Maximum – 4 points.

Total International HIV Dementia Scale Score: This is the sum of scores on items 1 – 3. The maximum possible score is 12 points. A patient with a score of ≤ 10 should be evaluated further for possible dementia.

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Sacktor NC, et al. AIDS. 2005;19(13): 1367-74.

Prevention of Opportunistic Infections

Primary prophylaxis is given to prevent common opportunistic infections. This is a critically important component of care.

Co-trimoxazole Prophylaxis

All patients with either CD4 counts of less than 200 OR with WHO clinical stage 3 or 4 disease (irrespective of CD4 count) should receive co-trimoxazole 480 – 960 mg daily. The lower dose causes fewer side effects, but there is more evidence for the higher dose. Prophylactic co-trimoxazole prevents *Pneumocystis pneumonia* (PJP) and toxoplasmosis. Co-trimoxazole prophylaxis can be used in pregnancy as the benefits outweigh the risks. It also reduces the frequency of bacterial infections, including bacterial pneumonia, and some protozoal causes of diarrhoea (*Isospora belli* and *Cyclospora* species). Outside of malaria endemic settings, if the patient is on ART and the CD4 count is rising, it has been shown to be safe to withdraw the drug once the CD4 count is above 200. This also applies to co-trimoxazole used as secondary prophylaxis. If patients start ART and co-trimoxazole prophylaxis with CD4 >200 (e.g. because they develop TB), then co-trimoxazole can be discontinued after six months of ART, provided that the viral load is suppressed.

Hypersensitivity to sulphonamides is common in HIV infection. Provided the reaction is mild (rash with no mucosal involvement or systemic symptoms) co-trimoxazole can be continued with antihistamine cover and close follow-up. If the reaction warrants stopping therapy, then rechallenge, or desensitisation may be attempted (success rates are about 60% – 70%). Alternatively dapsone 100 mg daily can be used. Dapsone effectively prevents pneumocystis pneumonia, but does not protect against many of the other opportunistic infections prevented by co-trimoxazole. If the allergic reaction took the form of a life-threatening reaction like Stevens-Johnson syndrome, neither co-trimoxazole nor dapsone should be used as cross reactions may occur. If neither co-trimoxazole or dapsone can be used, and the patient has a very low CD4 count, an alternative is atovaquone 1 500mg daily for a few months until the CD4 count is clearly rising. It is less effective, extremely expensive and has significant drug interactions with rifampicin.

A simple slow method for co-trimoxazole desensitisation (safe and effective in about two-thirds of cases) appropriate for prophylaxis is as follows (see PJP section for rapid desensitisation regimen when patients present with acute infections such as toxoplasmosis and PJP):

(Use co-trimoxazole suspension 240 mg/5ml)

- DAY 1** 1.25 ml daily
- DAY 2** 1.25 ml bd
- DAY 3** 1.25 ml tds
- DAY 4** 2.5 ml bd
- DAY 5** 2.5 ml tds
- DAY 6** 1 tablet (480 mg) daily

Rechallenge and desensitisation should be done under antihistamine cover, starting the day before. After the initial rechallenge dose the patient should be observed for several hours.

If the patient is on ART and the CD4 count is >100 the risks of desensitisation may not be justified as it can be anticipated that the CD4 will rise to >200 soon in most patients.

Tuberculosis Preventive Therapy

Isoniazid preventive therapy (IPT) is effective, but trials in antiretroviral naïve patients have shown that only patients with a positive tuberculin skin test (TST) benefit from preventive therapy (in HIV infection a Mantoux of over ≥ 5 mm induration is considered positive). The Department of Health and WHO recommend IPT for all HIV-infected people in whom TB has been excluded (see symptom screening below) if TST cannot be done, but recommend that TST be done if possible, with IPT only being given to those who are TST positive. TST is readily available in the private sector through pathology laboratories. A recent South African trial has shown that IPT for 12 months given to patients on ART irrespective of TST status reduced the risk of TB by about a third. IPT should also be offered to HIV-infected patients irrespective of TST status who have had recent contact with open tuberculosis, or are at high risk (e.g. healthcare workers and underground miners). There is currently no controlled data on the use of IPT in pregnancy, but its use is recommended by the WHO.

Isoniazid (INH) 300 mg daily for six months is the best studied regimen. Unfortunately the duration of benefit of 6 months IPT is short. The BOTUSA study showed that INH for 36 months was much more effective than 6 months in patients with positive TST. Importantly, the Botswana trial showed threefold increase in mortality in patients with a negative TST who received 36 months of INH, therefore prolonged IPT should not be given if TST is not done or is negative. AfA strongly encourages 36 months of INH in patients with a positive TST.

Patients must be followed up regularly whilst on IPT and asked specifically about symptoms of hepatotoxicity (nausea, vomiting and jaundice). If these symptoms occur examine for jaundice and check ALT. If significant hepatotoxicity occurs discontinue IPT. Pyridoxine (vitamin B6), 25 mg daily, should be given concurrently to reduce the risk of peripheral neuropathy.

Before commencing IPT, active tuberculosis should always be excluded. Further investigations to exclude TB must be done if any of the following symptoms are present:

- Current cough
- Fever
- Weight loss
- Drenching night sweats

If any of the above symptoms are present, two sputum samples should be sent; one for GeneXpert and the other for smear and culture. IPT should be deferred until these results are known and the symptoms have resolved.

A screening chest x-ray is not required before initiating IPT.

	Pre-ART	On ART
TST not done	IPT for 6 months	IPT for 12 months
TST negative	Nil	IPT for 12 months
TST positive	IPT for at least 36 months	IPT for at least 36 months

Hepatitis B Coinfection

Chronic hepatitis B virus (HBV) is endemic in sub-Saharan Africa where hepatitis B surface antigen prevalence stands between 0.3 – 15% and rates of exposure to the virus are 5 – 80% depending on the socioeconomic group and geographical location. HIV infection adversely affects the course of HBV in coinfecting patients resulting in higher rates of chronicity, reduced rates of spontaneous HBsAg and HBeAg seroconversion, increased rate of HBV replication, liver-related mortality and risk of HBV flare after starting ART due to HBV-IRIS. HIV-HBV coinfection rates in urban clinics in Johannesburg as judged by HBsAg-positivity in HIV patients were ~5%, with a higher rate of 17% reported from an industrial clinic setting (Hoffman 2007).

- All children should receive HBV vaccination as part of the extended programme of immunisation (EPI)
- All HIV-infected patients should be screened for HBV by HBsAg testing at the time of HIV diagnosis
- Suspected acute HBV – wait for enzymes to settle before starting ART. The presence of core antibody IgG excludes acute infection
- All HIV-HBV coinfecting patients should start ART containing 2 agents with anti-HBV activity, namely tenofovir plus lamivudine or emtricitabine
- Due to its propensity to cause hepatitis, use of nevirapine should be avoided in HIV-HBV coinfecting patients
- Tenofovir and lamivudine or emtricitabine should only be stopped in the face of severe adverse effects from these drugs precluding their use – stopping these is associated with the risk of a hepatitis ‘flare’
- HIV-infected patients who are HBsAg negative on screening, should be tested for the presence of hepatitis B core IgG antibody (HBcIgG) and if negative, should be offered vaccination against HBV
- Vaccination should not be attempted in patients with CD4 counts <200 as protective efficacy is poor. Rather, withhold vaccination until the CD4 count increases to >200 on ART. If the decision is taken to vaccinate a patient with low CD4 counts, then it is essential to test for HBsAb levels following vaccination and consider re-vaccination once the immune system is reconstituted if the response has been poor
- Vaccination should include a total of 3 doses administered at 0, 1 and 6 months. Double-dose vaccination should be considered in patients with CD4 counts of <350, as studies have shown a better response above 350. If using the rapid schedule, for example for post-exposure prophylaxis or for babies born to infected mothers, a 4 dose schedule is used, administered at 0, 6, 10 and 14 weeks
- All HIV-infected pregnant women must be tested for HBV, as should all HIV-negative pregnant women

- Babies born to mothers who are HIV-HBV coinfecting must receive hepatitis B immunoglobulin (HBIG) and the 1st dose of HBV vaccine at two separate sites within 12 hours of birth. A 4-dose vaccination course should be completed and the baby tested for presence of HBsAg and HBsAb at 6 months of age. HBIG should be repeated at 1 month if the mother is HBeAg positive. If the baby is HBsAb negative at 6 months of age, a repeat vaccination course is required
- Coinfecting babies should be referred to a specialist paediatrician for further management
- All coinfecting patients should be counselled with regard to lifestyle modifications to reduce hepatotoxicity, including alcohol, substance abuse, and co-prescription of herbal and traditional medicines
- All coinfecting patients should be tested for hepatitis C virus (HCV) infection, and those coinfecting should be discussed with a specialist for advice on management
- All HIV-HBV coinfecting patients should be immunised with Hepatitis A vaccine if no evidence of immunity exists
- HBV-seronegative partners of patients with chronic hepatitis B should be offered HBV vaccination. Sexual partners of patients with acute hepatitis B should be offered HBIG and vaccination

Management of Sexually Transmitted Infections (STIs)

Syndromic management for common presentations:

Genital ulcer (exclude genital herpes clinically) Check Syphilis serology	Benzathine penicillin 2.4MU IM STAT PLUS Azithromycin 1 g single dose PLUS Acyclovir 400 mg 8 hourly for 5 days
Vaginal discharge (exclude candidiasis clinically)	Ceftriaxone 250 mg IM STAT PLUS Azithromycin 1 g PO STAT PLUS Metronidazole 2 g PO STAT
Urethral discharge	Ceftriaxone 250 mg IM STAT PLUS Azithromycin 1 g PO STAT

Management of specific infections:

Syphilis (If there are no clinical signs for staging, regard as latent)	
Primary and secondary	Benzathine penicillin 2.4MU IM as a single dose
Penicillin allergy	Doxycycline 100 mg 12 hourly for 14 days
Latent	Benzathine penicillin 2.4MU IM at weekly intervals for 3 weeks
Penicillin allergy	Doxycycline 100 mg 12 hourly for 28 days
Neurosyphilis	Penicillin G 5 MU 6 hourly IV for 10 days followed by benzathine penicillin 2.4MU IM weekly for 3 weeks
Gonorrhoea	Ceftriaxone 250 mg IM STAT PLUS Azithromycin 1 g PO STAT
Penicillin allergy	Azithromycin 2 g PO STAT
Disseminated gonococcal arthritis	Ceftriaxone 1 g IM/IV daily for 7 days PLUS Azithromycin 1 g PO STAT
Chlamydial infection	Doxycycline 100 mg 12 hourly for 7 days (14 days for lymphogranuloma venereum) OR Azithromycin 1 g single dose
Chancroid	Ciprofloxacin 500 mg 12 hourly for 3 days OR Azithromycin 1 g single dose
Trichomonas	Metronidazole 2 g STAT
Bacterial vaginosis	Metronidazole 2 g STAT OR Metronidazole 400 mg 12 hourly for 7 days

There is a slow, but global rise in cephalosporin-resistant *Neisseria gonorrhoea*. Patients with suspected gonorrhoea and treatment failure should have discharge cultured and antibiotic sensitivities requested.

Immunisations

Live vaccines (e.g. yellow fever) should be used with caution in all HIV-infected patients and must be avoided in patients with a CD4 count less than 200 as they could lead to life-threatening disease. Response to immunisation is very poor if the CD4 count is less than 200.

HIV-infected persons are at increased risk of invasive pneumococcal disease. All HIV-infected adults should receive pneumococcal vaccination using the Pneumococcal Conjugate Vaccine (PCV)-13 and boosting with pneumococcal polysaccharide vaccine (PPV)-23 (see Immunisations for HIV-infected adults table).

HIV-infected persons infected with influenza have higher rates of hospitalisation, secondary bacterial infections, prolonged illness and increased mortality. Even once on ART, risk is still greater than the general population. Therefore annual influenza immunisation should be given to all HIV-infected adults. Hepatitis B immunisation should be given if the person is core antibody negative (see hepatitis B section for further guidance).

Nutritional Support

HIV infection is a protein-wasting illness in the late stages and weight loss is common. In addition, there are a number of treatable causes of weight loss. These include unrecognised depression, poor dentition and HIV-associated oral conditions, for example thrush. Opportunistic infections (especially those causing prolonged diarrhoea), tuberculosis and malignancies can cause rapid weight loss. Antiretroviral drugs may also cause weight loss by several mechanisms: anorexia, nausea, diarrhoea or symptomatic hyperlactataemia.

The HIV-wasting syndrome is an AIDS-defining condition and is defined as weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>one month) or chronic weakness and unexplained prolonged fever (>one month). This is a diagnosis of exclusion. If the weight loss is rapid (>1 kg/month) then investigations should be done to rule out underlying TB, other opportunistic infections or malignancy. In this context a C-reactive protein is helpful, as it is raised > 10 mg/l with many opportunistic diseases but not with HIV per se.

Nutritional support with protein and carbohydrate supplements may be indicated if there is documented weight loss of greater than 10% of body weight over any period. This seems to improve well-being, but does not increase life expectancy. The use of anabolic steroids should not be considered unless serum testosterone levels are low.

People living with HIV should be encouraged to eat a balanced diet, but increased calorie and protein intake should be taken to counter the increased energy requirements and protein-wasting in advanced disease.

Micronutrients, especially zinc and selenium, have an important role in immunity. Increased oxidative stress and immune dysfunction are common in HIV infection. A number of studies have confirmed low levels of micronutrients, especially in patients with advanced disease. Trials assessing the benefits of micronutrient supplementation have generally been inconclusive, with the possible exception of patients with advanced disease where there may be some benefit. There is evidence that high doses of vitamin A and zinc are harmful. A meta-analysis failed to show conclusive benefit, but supported the use of a supplement at doses of RDA (recommended daily allowance).

AfA have revised guidelines for micronutrient supplementation. Multivitamin supplementation at RDA is recommended for all pregnant and lactating women, preferably with added selenium. In non-pregnant adults micronutrient supplementation is recommended only for patients with CD4 counts <200 cells/ μ L or an active opportunistic infection. Preparations containing very high doses of fat-soluble vitamins (A, D, E and K) and zinc should be avoided as these are harmful.

Patients should be discouraged from using unconventional nutritional supplements or alternative remedies, which are scientifically unproven. Some of these have turned out to be toxic to the liver or bone marrow and have significant drug interactions with ART.

Of particular concern is the African wild potato (hypoxis), which has been reported to cause bone marrow depression and CD4 count decline. Patients should be advised to avoid these products, pending the outcome of properly conducted efficacy and safety studies.

Management of weight loss and the maintenance of adequate nutrition become particularly difficult in advanced disease. The advice of a dietician is recommended.

Antiretroviral Therapy in Adults

The goals of ART are:

- To prolong life expectancy
- To improve quality of life
- To prevent development of opportunistic infections and other AIDS-related conditions
- To reconstitute immune function
- To suppress viral replication as far as possible and for as long as possible. Specifically to durably suppress plasma viral load < 50 copies/ml
- To prevent transmission of the virus

Antiretroviral Drugs

Antiretroviral drugs currently available in Southern Africa block viral replication by inhibiting three viral enzymes (reverse transcriptase, protease or integrase) or by inhibiting chemokine receptor CCR5, which blocks entry of the virus into the cell.

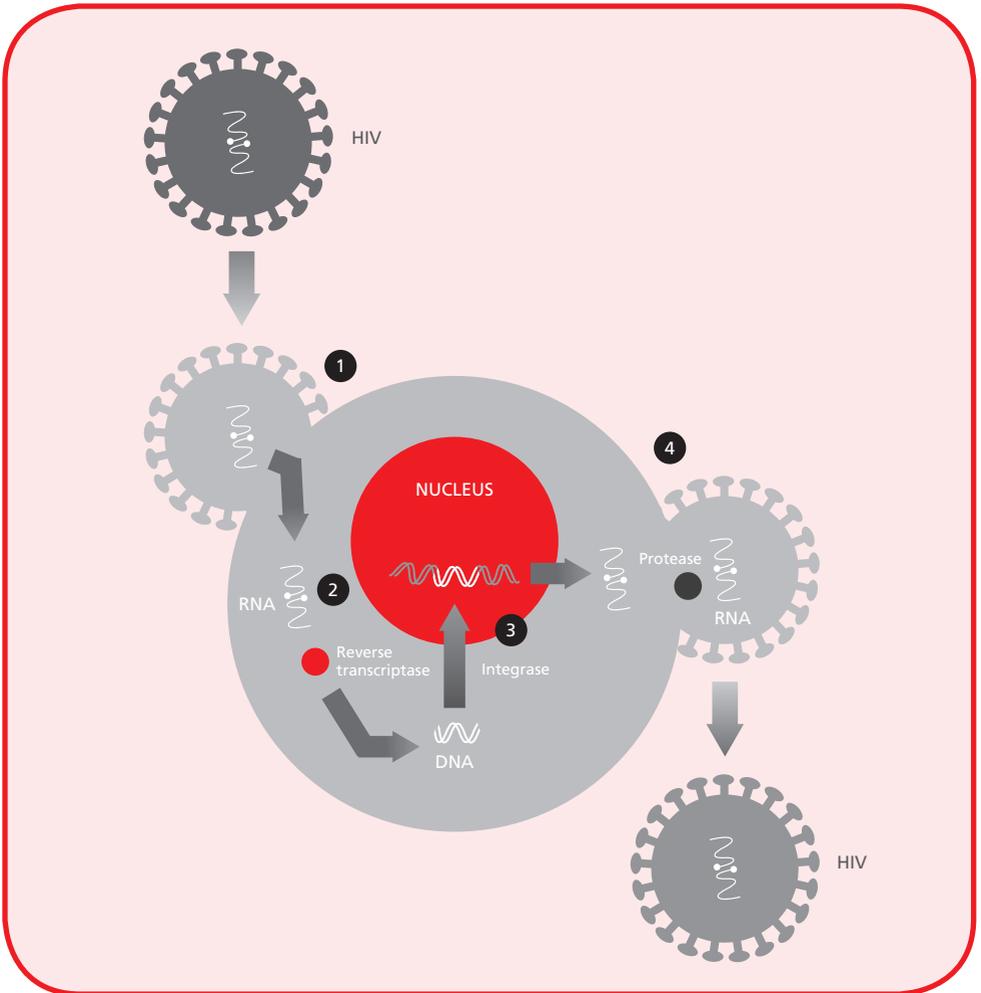
There are two classes of drugs that inhibit reverse transcriptase: nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These drugs block the conversion of viral RNA into proviral DNA and thus genetic integration of the virus into host DNA cannot occur.

NRTIs resemble the natural nucleotide building blocks of DNA. When the reverse transcriptase adds the drug to a developing strand of DNA, it prevents further reverse transcription of RNA into DNA. NRTIs need to be activated intracellularly by tri-phosphorylation. The nucleotide RTI tenofovir already contains one phosphate group. NNRTIs inhibit activity of the reverse transcriptase by binding to the reverse transcriptase enzyme, which changes the conformation of the active site thereby preventing reverse transcription.

Protease inhibitors inhibit the activity of HIV protease, which cleaves viral polypeptides into functional proteins. This prevents the formation of mature infectious viruses. Integrase inhibitors block integration of proviral DNA into the CD4 cell chromosomal DNA. As many of the antiretroviral drugs now have generic equivalents, trade names have been omitted from the section which follows.

The HIV Lifecycle

1. After HIV binds to receptors, including a co-receptor (CCR5 or CXCR-4) on the CD4 cell surface, the viral contents enter the cytoplasm
2. The HIV genome is then reverse transcribed to viral DNA by reverse transcriptase
3. HIV DNA enters the nucleus of the CD4 cell and inserts itself into the genome using integrase
4. Protease is used to assemble new HIV particles which leave the cell, ready to infect other CD4 cells



Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Dual NRTIs form the backbone of most antiretroviral combinations.

Class side effect

All NRTIs impair mitochondrial function by inhibiting mitochondrial DNA γ -polymerase. This can cause steatohepatitis, symptomatic hyperlactataemia or lactic acidosis. The NRTIs vary in their ability to do this: stavudine = didanosine >> zidovudine > lamivudine = abacavir = tenofovir.

Tenofovir (TDF)

Tenofovir is a nucleotide analogue of adenosine. It is formulated as a prodrug (tenofovir disoproxil fumarate – TDF) to improve bioavailability. It is best combined with either lamivudine or emtricitabine. Tenofovir is also effective against hepatitis B. There is a significant interaction between tenofovir and didanosine that results in increased toxicity. Because of this and concerns about efficacy this combination is not recommended.

Side effects: The major concern is nephrotoxicity. Acute renal failure develops in <1% on TDF and mild reductions in creatinine clearance may occur with long-term use. Risk factors for nephrotoxicity include underlying renal impairment and co-administration of other nephrotoxic drugs (e.g. aminoglycosides, chronic NSAIDs). Tenofovir should not be used in patients on intensive phase of MDR TB treatment as this includes an aminoglycoside. Hypokalaemia and hypophosphataemia due to renal tubular damage (Fanconi's syndrome) are other complications (test phosphate and potassium levels if there are unexplained muscle symptoms such as myalgia). Nephrotoxicity is reversible when TDF is discontinued, but some residual damage may persist.

Regular monitoring of renal function (serum creatinine and eGFR) is recommended (one, two, three, six months, then six monthly). The drug should not be used if the estimated creatinine clearance (or eGFR) is <50 ml/min. A urine dipstick should be performed prior to starting TDF and if this shows proteinuria a urinary protein/creatinine ratio should be requested. Mild proteinuria is not usually a contra-indication to TDF, but renal function should be monitored closely as it may be an indication of early HIVAN. If the protein/creatinine ratio is >0.1, refer patient to a nephrologist and defer use of TDF. Most clinicians would avoid use of TDF if there is heavy proteinuria.

Severe flares of hepatitis B may occur if the drug is discontinued. Bone mineral density is mildly reduced, which is of uncertain clinical significance. Hyperlactataemia risk – very low.

Dose: 300 mg daily with food.

Zidovudine (AZT)

AZT is a thymidine analogue and was the first effective antiretroviral drug. AZT is preferred by some guidelines as part of ART regimens in pregnant women as it has been the most widely used antiretroviral in pregnancy.

Side effects: initial nausea, vomiting, headaches and myalgia, which improve as tolerance develops in a few weeks. Anaemia and neutropaenia (but not thrombocytopenia) may occur, usually within six months and more frequently in advanced disease. Mild anaemia and neutropaenia are common and well tolerated. Monitor FBC at baseline, 1, 2, 3 and 6 months, then 6 monthly. AZT need only be discontinued if the haemoglobin (Hb) falls below 6.5 g/dl or the neutrophil count below $0.5 \times 10^9/l$, but many clinicians would switch to an alternative drug at lesser degrees of haematological toxicity unless there were compelling reasons to use AZT. Macrocytosis (not related to vitamin B12/folate deficiency) occurs in nearly all patients, and may in fact be used to confirm compliance. Myopathy with raised CK is a rare side effect after long-term use. May cause lipoatrophy. Hyperlactataemia risk – moderate.

Dose: 300 mg bd.

Abacavir (ABC)

This is a guanosine analogue. ABC is currently recommended in first line regimens in children in national guidelines. ABC is expensive.

Side effects: The main problem is a severe systemic hypersensitivity reaction, which occurs in approximately 3% of patients in clinical trials (though the risk is lower in patients of African descent), which typically presents in the first eight weeks of therapy. The hypersensitivity reaction has protean manifestations including rash, fever, GIT symptoms and even cough. The hypersensitivity reaction is limited to people with HLA-B*5701, if possible this should be tested for prior to use of abacavir – if it is present, then abacavir should not be used (HLA- B*5701 is very uncommon in Africans). Rechallenge should never be attempted, as this can be fatal. Hyperlactataemia risk – very low. Some cohort studies have documented increased cardiovascular risk in patients on ABC, however this finding was not confirmed in a meta-analysis of RCTs.

Dose: 300 mg bd OR 600 mg daily.

Lamivudine (3TC)

This is a cytosine analogue which is also active against hepatitis B. Unlike most other NRTIs, a single point mutation confers high level resistance. However, this resistance mutation slows down viral replication and also partially restores sensitivity to stavudine, tenofovir and zidovudine when mutations conferring resistance to these NRTIs are present. For this reason 3TC (or the similar drug emtricitabine) is usually recommended in second line and subsequent regimens even when 3TC resistance is present.

Side effects: Generally well tolerated. Pure red cell aplasia is a rare but important side effect (investigate with bone marrow biopsy and exclude other potential causes including parvovirus B19 with PCR test on blood or bone marrow). Severe flares of hepatitis B may occur if the drug is discontinued. Pancreatitis has only been reported in paediatric patients and it is questionable whether 3TC is responsible. Hyperlactataemia risk – very low.

Dose: 150 mg bd or 300 mg daily (when given with other once-daily drugs e.g. tenofovir or abacavir).

Emtricitabine (FTC)

Emtricitabine is a cytosine analogue, which is similar to 3TC in that it is well tolerated, shares the same resistance mutation and also has activity against hepatitis B.

Side effects: Emtricitabine may cause hyperpigmentation, particularly on the palms and soles. Severe flares of hepatitis B may occur if the drug is discontinued. Hyperlactataemia risk – very low.

Dose: 200 mg daily. FTC is only available co-formulated with TDF.

Stavudine (d4T)

Stavudine is also a thymidine analogue. Stavudine and zidovudine must never be combined as they interact antagonistically. The two drugs have a very similar resistance profile and there is extensive cross-resistance. Stavudine is associated with significant toxicity, and national and international guidelines recommend against its use, unless other NRTIs are contra-indicated or not tolerated.

Side effects: Stavudine is usually well tolerated for the first 4-6 months, but major mitochondrial toxicities then become increasingly common. Peripheral neuropathy is common. Anaemia and neutropaenia have been reported, but are mild and much less common than with zidovudine. Macrocytosis also occurs commonly as with AZT. Lipoatrophy (loss of subcutaneous fat, most noticeable in the face/limbs/buttocks) is a common and cosmetically distressing side effect. Hyperlactataemia risk – high. Stavudine should be avoided in women with a body mass index >28 or weight >75kg due to the increased risk of hyperlactataemia. Also causes steatohepatitis and pancreatitis.

Dose: 30 mg bd irrespective of body weight (package insert recommends 40 mg bd if >60 kg, but a meta-analysis showed that a lower dose is as effective and less toxic).

Didanosine (ddl)

This is an adenosine analogue. ddl should not be combined with stavudine as both have a high potential for hyperlactataemia and neuropathy. ddl should also not be combined with tenofovir as there are interactions that enhance ddl's toxicity and reduces its efficacy. The bioavailability of the drug is reduced by stomach acid and it therefore needs to be given in a buffered or enteric-coated formulation. The buffered tablets must be chewed or crushed and dissolved in water before swallowing. The drug must be given on an empty stomach. The enteric coated formulation should be used where possible as it has fewer side effects. These capsules must not be chewed, but still need to be taken on an empty stomach. ddl is associated with significant toxicity, and national and international guidelines recommend against its use, unless other NRTIs are contra-indicated or not tolerated.

Side effects: Peripheral neuropathy, nausea, headache and pancreatitis. As abdominal discomfort is common with didanosine, a diagnosis of pancreatitis should only be made if there is a significant increase in serum lipase levels. The serum lipase level rather than the amylase level should be used in the diagnosis of pancreatitis because the serum amylase level may be chronically elevated in HIV-infected patients due to salivary gland disease. Self-limiting gynaecomastia has been associated with ddl use. Hyperlactataemia risk – high. Cirrhosis is a rare complication of long-term ddl use.

Dose: 400 mg daily if weight >60 kg, 250 mg daily if weight <60 kg. The dose can also be given as 200 mg bd (125 mg bd if weight <60 kg).

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Resistance to the first generation NNRTIs efavirenz (EFV) and nevirapine (NVP) can arise very rapidly, as one of several mutations confers high level resistance. There is cross-resistance between both EFV and NVP. These drugs should NEVER be used as single agents or added as a sole new agent to a failing regimen. Etravirine and rilpivirine are second generation NNRTIs that have some different resistant mutation patterns to EFV and NVP, and retain activity in the presence of some, but not all, resistance mutations to EFV and NVP. NNRTIs are metabolised by the liver. Efavirenz and etravirine induce several metabolising enzymes and drug transporters, and also inhibit some isoenzymes of the cytochrome P450 system. There are thus many potential drug interactions. Nevirapine is a weak enzyme inducer.

Class side effects:

All NNRTIs can cause a generalised hypersensitivity rash, but the incidence differs by individual drug: NVP > EFV = etravirine > rilpivirine. Provided there are no danger signs (see table), the NNRTI should be continued and the rash will resolve in most patients. Life-threatening skin rashes may occur. Patients with rash and mucosal involvement or extensive (>10% surface area) desquamation have Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, and should be urgently admitted, preferably under the care of a dermatologist.

Managing NNRTI rash:

Description of rash	Action
Mild to moderate rash without systemic features	Continue dosing without interruption. No dose escalation of NVP during lead-in until rash resolves
Any rash with one or more of the following associated features: Elevated ALT Fever ≥38°C Blistering/moist desquamation Mucosal lesions (oral/conjunctival/genital) Angioedema Myalgia/arthritis	Permanent discontinuation. No reintroduction If patient also on co-trimoxazole, stop this too. Do not reintroduce co-trimoxazole

Antihistamines may be used for symptomatic treatment of NNRTI rash. The use of corticosteroids to treat the rash is not recommended as there is evidence that prophylactic use of oral corticosteroids aggravates the risk and possibly the severity of the rash. There does not appear to be an increased risk of developing a rash with efavirenz in patients discontinuing nevirapine because of hypersensitivity. Most experts advise against switching to efavirenz if the skin rash was life-threatening (e.g. Stevens-Johnson syndrome), but switching is reasonable for milder reactions after the rash has resolved. There is insufficient evidence to recommend switching from efavirenz to nevirapine or rilpivirine because of a rash.

Nevirapine (NVP)

Side effects: The most important is a generalised hypersensitivity rash. This occurs in about 15% of patients, almost always within the first six weeks of therapy. In clinical trials, nevirapine has been discontinued because of a rash in about 5% of patients. Abnormal liver enzymes occur commonly (10 – 20%), especially in the first eight weeks, but clinical hepatitis is uncommon (2%). About 50% of patients who develop a rash on NVP also develop elevated ALT, which usually occurs about 10 days after the rash commences. Liver failure due to nevirapine is a rare complication. Liver function (sufficient to measure ALT only) should be monitored at two, four, eight and twelve weeks – see section for managing abnormal liver function tests.

Hepatitis associated with a rash occurs more commonly in women with a CD4 count >250 and in men with a CD4 count >400 – nevirapine should be avoided in these settings. Note that when switching to a NVP-based regimen in patients on ART CD4 counts above these levels are not associated with an increased risk of hypersensitivity reactions.

Dose: One 200 mg tablet daily for two weeks, then 200 mg bd. The dose needs to be increased as the drug induces its own metabolism and the lower lead in dose is also associated with a lower risk of hypersensitivity. If the patient is switching from efavirenz to nevirapine the lead-in dose is not necessary as efavirenz is a hepatic enzyme inducer (i.e. start with 200 mg bd). If the patient is already on rifampicin for at least a week the lead-in dose should also be omitted (avoid nevirapine with rifampicin because it induces NVP metabolism, which reduces efficacy, unless other options are unavailable or not tolerated).

Efavirenz (EFV)

Side effects: Transient neuropsychiatric side effects are very common, including insomnia, dizziness, anxiety, impaired concentration, and abnormal dreams. Less common neuropsychiatric side effects include delusions, inappropriate behaviour, psychosis and mood disorders. The symptoms usually begin during the first few days of therapy, are generally mild and resolve despite ongoing EFV use after several weeks. Once tolerance to these side effects has developed the drug is generally well tolerated in the long term. Dosing at bedtime improves the tolerability. Efavirenz should generally be avoided in shift workers. Efavirenz CNS side-effects can be reduced by taking the drug on an empty stomach (a fatty meal increases absorption).

Hypersensitivity rash is common in the first six weeks, but this is usually milder than with nevirapine (efavirenz has been discontinued because of rash in about 2% of patients in clinical trials). Teratogenicity has been noted in animal studies and a few cases of myelomeningocele have been reported in humans. However, a meta-analysis showed no excess risk of birth defects among children who had first trimester exposure to efavirenz. These findings resulted in the recommendation by WHO, which has been implemented in public sector programmes in Southern Africa, to use efavirenz in early pregnancy or in women intending to conceive. While reassuring, the numbers included in the meta-analysis did not have sufficient power to confirm that the drug is definitely safe to use in pregnancy, and it remains

an FDA category D drug with the appropriate warning in the package insert. Some experts still prefer to avoid efavirenz in the 1st trimester.

Self-limiting gynaecomastia has been described. Patients on efavirenz may have false positive urinary cannabis tests.

Dose: 600 mg at night. A clinical trial has shown similar outcomes with 400 mg at night. This dose reduction should be considered if neuropsychiatric side effects don't resolve, but there is insufficient data on whether adequate concentrations are achieved in pregnancy and with TB therapy.

Etravirine (ETR)

This second generation NNRTI has only been registered for use in ART-experienced patients. AfA restrict its use for salvage therapy, guided by the results of resistance testing, as some combinations of first generation NNRTI resistant mutations impair its efficacy. It must also always be given together with a boosted protease inhibitor. Drug interactions are a bigger problem than with efavirenz or nevirapine e.g. it should not be used together with atazanavir or rifampicin.

Side effects: Rash, hepatitis risk similar to efavirenz.

Dose: 200 mg (two 100 mg tablets) twice daily following a meal.

Rilpivirine (RPV)

This second generation NNRTI can be used in first-line regimens, provided the baseline viral load is <100,000 (a clinical trial of rilpivirine versus efavirenz showed similar virologic suppression rates, but higher failure with rilpivirine in participants with high viral loads). It is better tolerated than efavirenz. Not to be used with rifampicin.

Side effects: Rash, hepatitis risk lower than efavirenz.

Dose: 25 mg daily with food.

For patients new to ARV therapy with a VL \leq 100,000 copies/mL

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References: 1. Ghosh J, Chaix ML, Delaugerre C. HIV-1 Resistance to First- and Second Generation Non-nucleoside Reverse Transcriptase Inhibitors. *AIDS Reviews* 2009; 11:165-178. 2. Pillbox. US National Library of Medicine. <http://pillbox.nlm.nih.gov>. Accessed December 3, 2013.

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Protease Inhibitors (PIs)

All protease inhibitors are inhibitors of many drug metabolising enzymes and the drug efflux pump p-glycoprotein, the most potent of which is ritonavir. In addition, some cytochrome P450 isoenzymes are induced by ritonavir. This results in clinically significant drug interactions with many drugs metabolised by the liver, including other PIs. This enzyme inhibition is exploited therapeutically by combining low dose ritonavir with other PIs, prolonging their half-lives and often also increasing the peak drug levels. This so-called “PI boosting” results in better outcomes and is the standard of care.

There is a degree of cross-resistance between currently available PIs. Among the available PIs, darunavir has the highest barrier to resistance (i.e. requires the most PI mutations for the virus to be resistant).

Class side effects:

PIs may cause dyslipidaemia (elevated triglycerides and LDL-cholesterol, especially the former). Fasting lipograms should be done before initiating PIs and at 3 months, then repeated annually in those with dyslipidaemia or those with ischaemic heart disease or other risk factors for ischaemic heart disease. Indinavir was associated with a risk of diabetes, but this is not the case with newer PIs.

Diarrhoea, nausea and vomiting are common side effects of all PIs. PI-induced diarrhoea may be successfully treated with loperamide/psyllium husk/calcium carbonate 900 – 1 200 mg daily.

All PIs may cause hepatitis.

Lopinavir/ritonavir (LPV/r)

This is a fixed combination of lopinavir and ritonavir. It is a robust drug in terms of resistance in that it needs several mutations (that generally accumulate slowly) in the virus for high-level resistance to occur.

Side effects: Not well tolerated. Diarrhoea, nausea and vomiting, hepatitis. Dyslipidaemia (high potential).

Dose: 400 mg/100 mg (2 tablets) bd or 800 mg/200 mg (4 tablets) daily (the daily dose is not recommended in pregnancy or in patients with prior PI experience).

If used with rifampicin, the dose should be doubled (i.e. 4 tablets bd), but it is important to monitor ALT at baseline, two weeks, four weeks, then monthly in this setting as there is a high risk of hepatotoxicity.

Atazanavir (ATV)

Side effects: Unconjugated hyperbilirubinaemia (drug-induced Gilbert's syndrome) is very common – this is not associated with liver injury. There is a low potential for dyslipidaemia (with boosted atazanavir) and the GIT side effect profile is lower than many other PIs.

Dose: 300 mg plus ritonavir 100 mg daily. An unboosted dose of 400 mg daily may be used in patients who have achieved virologic suppression with boosted atazanavir, unless the patient is also on tenofovir. Ritonavir boosting is essential if coadministered with tenofovir as tenofovir lowers atazanavir concentrations. ATV should not be used with rifampicin.

Darunavir (DRV)

Darunavir is used primarily in salvage therapy as it is usually effective when resistance has developed to other available PIs, but can be considered in patient's unable to tolerate other PIs.

Side effects: The most frequent side effect is diarrhoea. Other side effects include skin rash (there may be a cross-reaction in patients allergic to sulphonamides as it contains a sulpha group), nausea, vomiting and headache. There is a moderate potential for dyslipidaemia.

Dose: In salvage therapy 600 mg bd plus ritonavir 100 mg bd with food. In PI naïve patients a daily dose of 800 mg (plus 100 mg ritonavir) is preferred as it is better tolerated and equally effective - the 400 mg tablets are not currently available in SA, so 825mg or 900 mg daily can be used. Not to be used with rifampicin.

Indinavir (IDV)

Side effects: IDV is seldom used as side effects are frequent and include nephrolithiasis (patients need to drink at least 1.5 litres of fluid daily, with increased fluid intake in summer), unconjugated hyperbilirubinaemia, diabetes and hair loss. Nephrolithiasis should be managed by increasing fluid intake. There is a moderate potential for dyslipidaemia. It should be combined with ritonavir, which prolongs the half-life of indinavir and allows for 12 hourly dosing with no food restrictions.

Dose: 800 mg bd plus ritonavir 100 mg bd with plenty of fluids. Not to be used with rifampicin.

This drug is no longer available in South Africa.

Ritonavir (RTV)

Ritonavir is well absorbed orally. Its properties as a powerful liver enzyme inhibitor are utilised in PI boosting where it is used in low doses. It is no longer used on its own because of its toxicity in full doses. AfA strongly discourages the use of ritonavir as the sole PI in adults and children as it selects for mutations that compromise other PI options such as lopinavir/ritonavir.

Saquinavir (SQV)

Saquinavir should never be used without boosting by ritonavir as it has very poor oral bioavailability. Seldom used unless adjusted doses of lopinavir with rifampicin are not tolerated.

Side effects: These include diarrhoea, nausea and abdominal pain. There is a low potential for dyslipidaemia.

Dose: Saquinavir 1 000 mg bd plus ritonavir 100 mg bd. Alternatively 400 mg bd plus ritonavir 400 mg bd (this regimen may be used with rifampicin together with frequent monitoring of ALT at baseline, two weeks, four weeks, then monthly).

Integrase Inhibitors

ART regimens including integrase inhibitors lower the viral load faster than any other regimens, but the CD4 and long-term virologic responses are similar. The major route of metabolism of dolutegravir and raltegravir is glucuronidation.

Raltegravir (RAL)

Because of its price, its use is restricted to salvage therapy in combination with a boosted PI, but may be used in second-line or even first-line if there is intolerance to other drug classes, provided there is a fully active NRTI backbone available.

Side effects: Headache, nausea and diarrhoea. Hepatitis. Rash, with rare reports of Stevens Johnson Syndrome. Rhabdomyolysis (rare).

Dose: 400 mg bd. Rifampicin induces the metabolism of raltegravir, but a phase 2 study showed that virologic outcomes were similar with standard dosing and double dosing.

Dolutegravir (DTG)

This drug has recently been registered in South Africa. It has a much higher genetic barrier to resistance than raltegravir.

Side effects: Increases serum creatinine by 10-15 $\mu\text{mol/L}$ due to inhibition of secretion, not nephrotoxicity. Headache, insomnia, nausea and diarrhoea. Hepatitis.

Dose: 50 mg daily. Rifampicin reduces the plasma concentrations of dolutegravir, but this is overcome by increasing the dose to 50 mg 12 hourly.

CCR5 antagonist

Maraviroc

Inhibits HIV entry into cells by blocking the host chemokine receptor-5. Unfortunately viruses may mutate to use an alternative chemokine receptor CXCR-4. Therefore it is essential to determine the receptor tropism in individual patients before using maraviroc. The tropism assay is expensive, as is the drug. Its place in therapy is unclear, even in high income countries where it is affordable.

Table: Fixed Dose Combination (FDC) Products

TDF + FTC

AZT + 3TC

ABC + 3TC

TDF + FTC + EFV

TDF + 3TC + EFV

AZT + 3TC + NVP

d4T + 3TC + NVP

Table: Summary of currently recommended antiretroviral drugs

Chemical name	Dose	Common side effects
Nucleos(t)ide analogue reverse transcriptase inhibitors (NRTIs)		
Tenofovir (TDF)	300 mg daily with food	Nephrotoxicity
Zidovudine (AZT)	300 mg bd	Nausea, headache, fatigue, neutropaenia, anaemia, myalgia, lipoatrophy
Abacavir (ABC)	300 mg bd 600 mg daily	Hypersensitivity reaction
Emtricitabine (FTC – only available in combination with TDF)	200 mg daily	Hyperpigmentation (palms/soles)
Lamivudine (3TC)	150 mg bd 300 mg daily	Generally well tolerated
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV)	600 mg nocte	CNS effects, rash, hepatitis, gynaecomastia
Etravirine (ETR)	200 mg bd	Rash, hepatitis
Nevirapine (NVP)	200 mg daily for two weeks, then 200 mg twice daily	Rash, hepatitis (high risk)
Rilpivirine (RPV)	25mg daily	Rash, hepatitis (lower than efavirenz)
Protease inhibitors (PIs)		
Atazanavir (ATV)	300 mg + ritonavir 100 mg daily	Unconjugated hyperbilirubinaemia, dyslipidaemia (low potential)
Darunavir (DRV)	600 mg bd + ritonavir 100 mg bd with food	Diarrhoea, nausea, rash, dyslipidaemia (moderate potential)

Chemical name	Dose	Common side effects
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg (2 tablets) bd	Diarrhoea, nausea and dyslipidaemia, (high potential)
Ritonavir (RTV)	100 mg daily or bd for boosting (use of full doses not advised)	Diarrhoea, nausea, abdominal pain, dyslipidaemia (high potential if full dose is used)
Integrase inhibitors		
Raltegravir (RAL)	400 mg bd	Headache, GI side effects
Dolutegravir (DTG)	50 mg od	Headache, GI side effects

Principles of Antiretroviral Therapy (ART)

Getting Started

The HIV-infected person's willingness to accept and adhere to ART is essential before embarking on therapy. Without this commitment, there is little chance of success. It is recommended that therapy only be commenced after at least two consultations with extensive counselling. Including a patient-nominated "treatment buddy" in the counselling sessions is extremely helpful and has been shown to improve adherence.

AfA updated its criteria for when to initiate ART in August 2015. This was based on findings of the TEMPRANO and START trials showing clinical benefit when patients start ART at CD4 counts greater than 500, and the HPTN 052 trial which demonstrated that ART prevents transmission of HIV from an HIV-infected partner to an uninfected sexual partner. We now advise that all patients who are diagnosed with HIV infection should be advised that ART is indicated to treat their HIV infection regardless of CD4 count or clinical stage. Patients should be adequately prepared for starting lifelong therapy with good adherence and this may take a number of counselling sessions. In those patients with CD4 < 350 undue delays in starting ART should be avoided.

Guidelines for starting ART:

ALL patients who are HIV-infected would qualify to start provided they have had adequate counselling to prepare them for lifelong ART with optimal adherence

Adherence

If the individual drugs of an antiretroviral regimen are not taken correctly or omitted, there is a considerable risk of selection for resistant HIV strains. High levels of adherence have been shown to be associated with the best virological response. Adherence also predicts survival – 80% adherence or greater is associated with the lowest death rates. Measuring adherence is difficult in clinical practice. Patients generally over-report adherence. A useful measure is the proportion of monthly prescriptions filled in the last 6 months. (AfA may be contacted for a claims history report for specific patients). Therefore, it is crucial that time is spent on carefully explaining the need to take the drugs correctly and how to deal with possible adverse effects. It is difficult to predict who is likely to be compliant.

Factors which are associated with poor adherence include:

- Untreated depression
- Active substance abuse
- Lack of insight
- Failure to disclose HIV status (especially failure to have a treatment buddy)
- Adolescents and young adults
- Central nervous system pathology (e.g. HIV dementia). These patients especially need a treatment supporter

It is critical that adherence to therapy is assessed before drug combinations are changed because of suspected viral resistance.

The doctor should ensure that the patient is ready and prepared to commit to lifelong therapy and spend time explaining what is required and the need to take therapy exactly as prescribed. There should be no rush to initiate therapy in the vast majority of patients.

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Methods to assist with maintaining adherence:

- Negotiate a plan with the patient to ensure commitment to a regimen
- Take time – do not rush into beginning an ART regimen
- Depression is common in HIV/AIDS – always assess and treat this if necessary
- Recruit patient-nominated “treatment buddies” to support the patient (this has been shown to make a big difference to outcomes and is strongly recommended)
- Pay attention to “minor” side effects and consider treating them or switching the culprit drug where possible, – especially nausea, diarrhoea, and neuropsychiatric side effects
- Use memory aids such as diaries, pill-boxes and cell phone alarms, etc
- Provide information to assist the patient in fully understanding their drug regimen, and in taking their medications adequately
- Plan ahead for medication refills, financial assistance, etc
- Avoid recreational drug and alcohol abuse
- Regularly monitor ART adherence at each clinical visit (the most pragmatic objective measure of adherence is whether patients have collected their medication on time)
- Plan regimens to avoid food restrictions where possible
- Attempt to avoid regimens which require large pill burdens (the number of pills is associated with poor adherence – try to minimise non-ART medication)

Selecting Drug Combinations

Antiretroviral drugs must always be combined in order to delay or prevent the emergence of HIV resistance. A number of different combinations have been shown to be effective in preventing opportunistic infections and other HIV-related conditions, and preventing the onset of AIDS. In order to achieve virological suppression, it is essential to use combinations of potent drugs, typically “triple therapy” with two NRTIs and an NNRTI or two NRTIs and a boosted PI. AfA recommends first line of 2 NRTIs and an NNRTI (EFV, RPV or NVP) in keeping with WHO and public sector guidelines.

Recommended First Line Combinations

First line

TDF + FTC + NNRTI*

ABC + 3TC + NNRTI*

AZT + 3TC + NNRTI*

* *EFV or RPV. EFV is the preferred agent if on TB treatment. RPV can be used provided the baseline VL is < 100,000 or if EFV is not tolerated. NVP should generally be avoided, particularly in females with a CD4 count >250 and males with a CD4 count >400, because of its high risk of severe rashes and hepatitis.*

NB: If hepatitis B surface antigen positive, include TDF and FTC/3TC in the combination

Dual NRTI Backbone Combinations

Recommended combinations:

- Tenofovir + lamivudine or emtricitabine
- Abacavir + lamivudine (alternative regimen)
- Zidovudine + lamivudine

We favour tenofovir plus lamivudine or emtricitabine in first-line ART. Abacavir or zidovudine should be used when tenofovir is contra-indicated (creatinine clearance <50ml/min) or not tolerated.

Patients with anaemia or neutropaenia should avoid zidovudine.

The addition of a PI or NNRTI to the dual NRTI backbone (“triple therapy”) results in a potent combination, which should result in sustained suppression of viral replication in adherent patients. The preferred initial regimen is to add an NNRTI to the dual NRTIs because the protease inhibitors have significant long-term toxicity, NNRTI-based regimens are at least as effective as PI-based regimens in randomised controlled trials, and NRTI resistance mutations in patients failing a first-line PI-based regimen would compromise NNRTI-based regimens (the reverse is not true - PI-based therapy is very effective even in the presence of NRTI resistance mutations).

Monitoring Therapy

CD4 and VL Monitoring

Regular monitoring of the viral load is critically important to identify poor adherence to therapy or treatment failure early. The viral load should be done at 3 months then every 6 months. Vaccination and intercurrent infections can transiently increase the viral load; viral loads should be deferred for a few weeks in these settings.

On ART the viral load should be undetectable (<50) after 16 – 24 weeks of therapy. The viral load is the most important test for monitoring response to therapy. Virological failure is defined as a confirmed increase to >1 000 (on two tests done 6-12 weeks apart) despite good adherence. This criterion should be used when deciding to change regimens – it is especially important not to delay switching the first line regimen once failure has developed as high level resistance develops rapidly to NNRTIs and continuing a failing regimen results in the serial accumulation of resistant mutations to NRTIs.

CD4 counts should be done together with viral loads, but once the CD4 count is confirmed to be >200 routine monitoring is not recommended as it does not influence therapy and patients often become concerned due to irrelevant fluctuations in CD4 counts. CD4 counts should be repeated if virologic failure has occurred to assess the need for cotrimoxazole prophylaxis.

The CD4 count rises rapidly within four weeks on starting ART and then more gradually. The average rise in CD4 is about 150 in the first year and about 80 per annum thereafter, but this is extremely variable. In some patients (about 10 – 20%), especially elderly patients, the CD4 count fails to rise despite a suppressed viral load. When the viral load is suppressed and CD4 counts fail to rise there is no evidence that changing their ART regimens will make a difference – in some patients the CD4 count will eventually increase.

Clinical monitoring is also important, including general well-being and sustained weight gain. It is important to note that an intercurrent clinical event is not an indication for changing therapy if the viral load is suppressed. Furthermore, clinical deterioration and CD4 decline both occur after many months or even years of virological failure as defined above. Thus, clinical or immunological failure should not be used as a criterion for changing ART regimens.

Most patients failing their first boosted PI regimen (i.e. the currently recommended second line ART) have no major PI resistant mutations on resistance testing – they are failing due to poor adherence and need improved adherence rather than third line. However, there are an increasing number of patients failing second line who do have PI resistance (see section below). With newer third line treatment options viral suppression on third line is possible for the majority of adherent patients. However, if patients develop resistance to third line and even if there is substantial PI resistance they often continue benefiting clinically and immunologically despite virologic failure. One explanation for this is that the viral mutations necessary for the development of PI resistance cripple the virus.

Viral Resistance and Changing Therapy

Resistance should be suspected if the viral load starts increasing in a patient who is adhering to first line ART. Ensure that the viral load was not done after vaccination or an acute infection. Minor transient increases in viral load (less than 1 000), “viral blips”, are not indications to change therapy. A high viral load should be confirmed with a second reading within three months.

Failure of therapy is defined as a sustained increase in viral load $>1\ 000$. Therapy should be switched for virological failure if two viral loads are $>1\ 000$ with the second being measured after an intervention to improve adherence, and where feasible a resistance test that demonstrates resistance to the current regimen.

If treatment failure has occurred, then a new combination should be selected (but note that 3TC/FTC is often continued in subsequent regimens even if the mutation conferring resistance has developed as this slows viral replication and improves susceptibility of the virus to TDF, AZT and d4T). For example, if a patient fails therapy with two NRTIs and an NNRTI, one could change to two NRTIs (preferably one a new NRTI) and a ritonavir-boosted PI.

Recommended Second Line Combinations

Two NRTIs plus a ritonavir-boosted protease inhibitor are recommended if the first line NNRTI regimen fails. AfA recommends either atazanavir/ritonavir or lopinavir/ritonavir as the PI in second line. Lopinavir/ritonavir has a very high barrier to resistance; whereas boosted atazanavir has a lower potential for dyslipidaemia and gastro-intestinal side effects and is taken once daily.

For example, a patient failing an initial regimen of zidovudine, lamivudine and nevirapine is likely to have resistance to NNRTIs and lamivudine, thus tenofovir, 3TC (or FTC) plus lopinavir/ritonavir should be effective. Although this combination has only two new drugs the potency of TDF and a boosted-PI will result in suppression of VL in the vast majority of adherent patients.

First line	Second line advised
d4T + 3TC + NNRTI	TDF + FTC (or 3TC) + boosted PI
AZT + 3TC + NNRTI	TDF + FTC (or 3TC) + boosted PI
TDF + FTC + NNRTI	AZT + 3TC + boosted PI If AZT not tolerated, can consider TDF or ABC

Boosted PI = lopinavir with ritonavir or atazanavir with ritonavir

NB: If hepatitis B surface antigen positive, do not stop TDF and FTC/3TC (if need to change HIV treatment regimen then continue these drugs and construct the next HIV regimen around them in consultation with AfA).

Even if a resistance test shows high-level resistance to TDF and AZT we still recommend a regimen consisting of 2 NRTIs + a boosted PI, because clinical trials have shown virological outcomes on 2nd line regimens are similar in patients with or without resistance in the NRTI backbone. In fact in the EARNEST trial, those patients with more extensive NRTI resistance after failing first-line were more likely to achieve virological suppression on second-line, perhaps because relatively better adherence is associated with accumulation of more resistance mutations.

Unusual Combinations

Patients who are unable to tolerate NRTIs (e.g. because of lactic acidosis) can use a combination of an NNRTI with a boosted PI. However there are drug interactions that may require alterations of the PI dose (ritonavir-boosted PIs must always be used when coadministered with NNRTIs), with higher doses being recommended in some instances for PI-experienced patients because a modest reduction in PI concentrations, which is unimportant with PI-naïve patients, may be important if there are mutations conferring PI resistance (see table below):

PI	Dose for PI-naïve			
	Nevirapine	Efavirenz	Etravirine	Rilpivirine
Atazanavir/r	Not recommended	400 mg/100 mg daily	Not recommended	Standard dose
Darunavir/r	Standard dose	Standard dose	Standard dose	Standard dose
Lopinavir/r	Standard dose	Standard dose	Standard dose	Standard dose

PI	Dose for PI-experienced			
	Nevirapine	Efavirenz	Etravirine	Rilpivirine
Atazanavir/r	Not recommended	400 mg/100 mg daily	Not recommended	Standard dose
Darunavir/r	Standard dose	Standard dose	Standard dose	Standard dose
Lopinavir/r	500 mg/125 mg bd	500 mg/125 mg bd	Standard dose	Standard dose

The combination of lopinavir/ritonavir + efavirenz has the best evidence for use as an alternate first line ART regimen. Another alternative combination is a boosted PI plus raltegravir or dolutegravir which may be considered in instances where there is resistance and/or intolerance to multiple drugs.

Third Line Combinations

Third line treatment choices need to be individualised and decided upon in consultation with the AfA clinical committee who take into account the treatment history and results of a resistance test done while failing on second line ART. A resistance test that demonstrates resistance to second line is a prerequisite for being considered for third line therapy. Drugs used in third line include darunavir/ritonavir, dolutegravir, etravirine and NRTIs. In selected patients with extensive drug resistance maraviroc may be considered. In patients currently on raltegravir third line, we suggest switching raltegravir to dolutegravir if the viral load is suppressed. If the viral load is not suppressed – discuss with AfA before making this switch.

ART Resistance, Genotype Resistance Testing and Archiving of Resistant Mutations

When adherence to ART is sub-optimal there is a risk that there will be ongoing viral replication in the presence of low drug concentrations. This may result in the selection of drug resistant mutants in the viral population. If resistance mutations accumulate, virological failure ensues and then even if adherence subsequently improves the viral load will not suppress and further accumulation of drug resistance mutations will develop. Certain drugs have a low barrier to resistance (e.g. 3TC, FTC, nevirapine and efavirenz) meaning that a single mutation in the viral genome at a key site will result in high level resistance to that drug and closely related drugs.

Other drugs have a high barrier to resistance (e.g. boosted protease inhibitors) meaning that many resistance mutations in the viral genome are required for high level resistance. Resistance to drugs with a low barrier to resistance develops relatively early if there is poor adherence.

We advise monitoring the viral load at 3 months on ART then 6 monthly. If the viral load is suppressed (lower than detectable limits or <50) it suggests good adherence and no resistance to that regimen. If the viral load does not suppress then efforts should be made to improve adherence by counselling and support (e.g. treatment buddy in household). In any patient with a VL that is not less than 50 after 6 months on ART a repeat measurement should be taken in 2 to 3 months time after such an adherence intervention.

If the viral load remains above 1 000 on two or more occasions (preferably 2-3 months apart) despite improved adherence, this suggests viral resistance has developed and the regimen needs to be changed. Ideally a resistance test is done to confirm presence of resistance mutations and to guide decisions regarding the next regimen, but the resistance profile at first line failure is relatively predictable and genotyping is therefore often not essential. As stated above, in patients failing second line it is essential to do a resistance test before switching to third-line. There are two reasons for this. First, many patients failing second line do not have significant resistance and in such patients there is a need to improve adherence to second-line rather than switching to third-line. Second, if patients do have significant second-line resistance the genotype is important in guiding the choice of drugs in the third-line regimen.

AfA advises genotype resistance testing in patients with confirmed virological failure on first or second line, provided funds permit and adherence has been confirmed.

In addition, there are certain situations where AfA advises a genotype be done before ART is started:

- 1) In children < 2 years who have been HIV infected despite their mother receiving PMTCT.
- 2) In adult patients where there is a strong suspicion that the patient has been infected with a resistant virus (e.g. sexual partner failing ART).

Important points regarding genotype resistance testing:

- The test involves sequencing the viral gene coding for reverse transcriptase and protease enzymes (the target of the ART drugs) to detect resistance mutations at key points in these enzymes that are known to confer resistance to specific drugs. Resistance tests can also test for mutations in the integrase enzyme, but this is not routinely done in SA currently
- The test can only be performed in commercial laboratories if the viral load is >1 000
- If the resistance mutation is present, but in fewer than 20% of viruses in the viral population it will not be detected. This is termed “archiving”. This typically occurs when a patient has developed drug resistant mutations, but then stops ART. What happens over the next few weeks for most mutations is that the wild type virus (without the mutation) replicates faster than the resistant mutant (because most resistant mutants have a fitness cost to the virus) and thus the wild type comes to dominate the viral population in the absence of ART and the resistant mutant becomes archived. It is thus essential that the genotype resistance test is performed while the patient is taking the failing regimen in order that the result detects all the mutations to that regimen that have been selected
- The genotype resistance test may not detect mutations that developed during the failure of a previous regimen because they are now archived. This may be the case when a patient fails an NNRTI-containing first line and then has a genotype resistance test performed after second line failure a few years later. The NNRTI resistance mutations may be archived, but we assume that they are present based on the treatment history. Thus in deciding about the next ART regimen the genotype resistance test should always be interpreted together with a full treatment history
- All genotype resistance test results should be referred to the AfA Clinical Committee for advice regarding the best subsequent regimen

Even when there is viral resistance on a PI regimen it is worthwhile continuing with therapy in the face of resistance if there are no other treatment options whilst awaiting new drugs – studies have shown that continuing therapy (apart from NNRTIs) in this situation confers significant clinical benefit. This is due to reduced viral fitness as a result of the mutations that confer resistance.

Patients with Poor Adherence to First Line ART (2 NRTIs + 1 NNRTI) who have a Persistently Non-suppressed Viral Load

The approach to these patients should be based on how long they have been taking first line therapy.

Less than 1 year: In the first year of ART we advise that adherence support be enhanced and that patients are not switched to second line. Studies have shown that about 70% of patients who have a detectable viral load during early ART may subsequently suppress with improved adherence support. Improved adherence support may include interventions such as: motivational counselling, strategies to remind patients (e.g. cellphone alarms), treatment buddies and pillboxes. Psychological and substance abuse issues contributing to poor adherence should be addressed (eg. refer to psychologist or for substance abuse counselling).

More than one year: If the patient has been on first line ART intermittently or with poor adherence for more than one year and has a persistently non-suppressed viral load it is very likely that they will have developed resistance to at least the NNRTI and 3TC or FTC as these drugs have a low barrier to resistance. It thus seems futile to attempt to improve adherence to a regimen that is very unlikely to suppress the viral load even if adherence was improved to 100%. In this situation we thus advise switching to second line ART. The benefit of second line regimen containing a boosted PI in these patients is that this regimen has a much higher barrier to resistance and all the drugs have a similar half-life, meaning that resistance is less likely to develop rapidly in patients who “stop and start” ART.

We would strongly advise against a punitive approach (e.g. clinician stopping ART prescription) in these patients. Such an approach is counterproductive and harmful. There is evidence that even if patients take ART above a threshold of 20% their survival is improved, thus stopping ART in such patients would result in reduced survival. A subgroup of patients find taking lifelong therapy with good adherence impossible. In these patients ongoing support and counselling aimed at maximising adherence, and switching to a boosted PI regimen if they do not suppress after 1 year, is likely to ensure that they gain at least partial clinical benefit from ART.



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References: 1. WHO guidelines 2. Raffi F et al. *Lancet Infect Dis.* 2013;13(11):927-935. 3. Wolmsley SL et al. *N Engl J Med.* 2013;369(19):1807-1818. 4. Clotet B et al. *Lancet.* 2014;383:2222-2231. 5. Raffi F et al. *Lancet.* 2013;381:735-743.

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Practical Tips for Interpreting Genotype Resistance Testing

General points

- Patient must be on a failing ART regimen when resistance test is performed (this is because when ART is stopped many resistance mutations become overrun by wild-type and are not detected, termed “archiving”)
- Commercial assays usually require VL >1000 copies/ml to perform test
- If no resistance mutations are shown (i.e. wild type) in a patient failing an ART regimen this suggests that non-adherence is the cause of virological failure
- The resistance test must always be interpreted together with a treatment history. In a patient who has failed a first-line NNRTI regimen who then fails a second-line PI regimen, if a resistance test is done at second-line failure the NNRTI mutations that developed at first-line failure may be “archived”, but must be assumed to be present given the treatment history
- If there are mixed populations of drug resistant and wild type viruses at given allele(s) (e.g. M184M/V) this suggests partial adherence that allows both populations to remain in circulation without enough differential selection pressure to make the resistant virus dominate
- Nomenclature: resistance mutations are denoted with a letter-number-letter. For example, “M184V” where the number stands for the amino acid position in the enzyme where the mutation occurs (“184”), the first letter stands for the amino acid present at the position in the wild type (“M”=methionine) and the last letter stands for the amino acid present in the resistant mutant (“V”=valine)
- We use the Stanford HIV Drug Resistance Database for interpreting genotype results:
<http://hivdb.stanford.edu/>

NNRTI resistance mutations

- Tenofovir and abacavir (and sometimes d4T with subtype C virus) select for K65R which compromises TDF, ABC, ddI and d4T, but increases susceptibility to AZT
- Tenofovir also selects for the mutation K70E
- 3TC and FTC select for M184V, which compromises both 3TC and FTC, and impairs the activity of ABC and ddI, but increases susceptibility to AZT, d4T and TDF. For this reason, and because M184V reduced viral fitness, 3TC or FTC are often used even if M184V is present
- Abacavir and ddI select for L74V which compromises ABC and ddI
- Abacavir also selects for Y115F which decreases its susceptibility

- AZT and d4T select for thymidine analogue mutations (TAMs) which may compromise all NRTIs. There are 6 TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E. TAMs may cause cross-resistance to all NRTI drugs. The more TAMs there are, the more the NRTI class is compromised. The pattern of TAMs accumulated affects the degree to which individual drugs are affected
- Tenofovir is not thought to select for TAMs itself, but certain TAMs can compromise tenofovir. The presence of ≥ 3 TAMs, including M41L and L210W, confers intermediate- to high-level tenofovir resistance
- The SSS insertion at position 69 in the NRTI gene causes broad resistance in the NRTI class
- The Q151M mutation causes broad resistance in the NRTI class (apart from tenofovir)

NNRTI resistance mutations

- A single NNRTI resistance mutation causes high level resistance to both efavirenz and nevirapine
- Efavirenz most frequently selects for K103N
- Nevirapine most frequently selects for Y181C
- Rilpivirine frequently selects for E138K, often together with the NRTI mutation M184I resulting in failure of rilpivirine-containing first line regimens
- Etravirine often remains active when there is efavirenz and nevirapine resistance, but etravirine resistance may result from certain mutations selected by nevirapine and efavirenz. It is unpredictable whether efavirenz or nevirapine exposure will result in etravirine resistance in an individual patient: it depends which mutations and how many are present. For example, K103N does not cause etravirine resistance whereas the mutations L100I, K101P and Y181C/I/V are the main mutations that reduce etravirine susceptibility, particularly in combination. A weighted scoring system is used for determining etravirine susceptibility based on which NNRTI mutations are present

PI resistance mutations

- Most PIs require multiple PI resistance mutations before there is high level resistance. PI resistance patterns are complex and interpreting the genotype usually requires an algorithm such as the Stanford Database
- The most important (or “Major”) PI mutations occur at positions 30, 32, 46, 47, 48, 50, 54, 76, 82, 84, 88 and 90 in the protease gene
- A single mutation (I50L) can compromise atazanavir, but this mutation tends not to occur with ritonavir-boosted atazanavir
- Darunavir and tipranavir have the highest genetic barrier to resistance (i.e. they tend to remain active even when other PIs are compromised)
- Response to darunavir regimens is dependent on presence or absence of 11 specific PI mutations at baseline (a scoring system has been developed that predicts response based on the number of these mutations present: more than 3 of these mutations is associated with reduced virological response)

Integrase inhibitor resistance mutations

- The major mutations in the integrase gene associated with raltegravir resistance are: Y143R/H/C, Q148H/K/R, N155H
- Dolutegravir may be compromised by mutations that accumulate in patients failing raltegravir (e.g. Q148H). When dolutegravir is used as the first integrase inhibitor it appears to have a very high barrier to resistance with no dolutegravir resistance reported to date when it has been used in first-line ART clinical trials
- When a resistance test is requested in South Africa currently the integrase gene is not routinely sequenced, but this can be specifically requested in patients failing an integrase inhibitor

Managing Drug Toxicity

Currently recommended antiretrovirals are generally well tolerated. Most adverse drug reactions are mild and occur only in the first few weeks of therapy. If toxicity doesn't resolve, or is severe, then the offending drug should be substituted. It is important to ensure that the viral load is suppressed before substituting a single drug otherwise resistance may develop to the new drug, compromising future regimens. Single drug substitutions can safely be done in the first 6 months of ART without measuring the viral load.

It is rarely necessary to stop the whole ART regimen for toxicity. Switch only the culprit drug and continue the rest of the ART regimen. In certain life-threatening situations (e.g. hepatitis with liver failure, lactic acidosis) it may be necessary to stop all antiretrovirals. In patients with severe NNRTI-related toxicity an integrase inhibitor or PI should be substituted. If it is necessary to stop an NNRTI-based regimen, if feasible, stop the NNRTI and continue the two NRTIs for 7 days in order to reduce the risk of resistance developing to NNRTIs, which have a long half-life.

It is important to distinguish whether morbidity or laboratory abnormalities are due to HIV complications or drug toxicity.

Haematological Toxicity

Patients on zidovudine, stavudine, or co-trimoxazole may experience abnormalities in their full blood counts. Macrocytosis (unrelated to vitamin B12/folate deficiency – there is no point in testing for this unless macrocytosis was present at baseline) is seen with zidovudine and stavudine. Significant anaemia and neutropaenia (NOT thrombocytopaenia) are commonly seen with zidovudine and occasionally with stavudine, and may respond to reduced doses (zidovudine 200 mg bd), but most clinicians would switch to an alternative agent unless there are compelling reasons to continue. Regular FBC monitoring (monthly for the first three months of therapy and then at six months, thereafter six monthly) is essential for all patients on zidovudine. 3TC and FTC are rare causes of red cell aplasia – parvovirus B19 infection should be excluded (positive parvovirus B19 PCR in blood).

Haematological toxicity with co-trimoxazole is more frequent with high doses used for treating opportunistic infections. This can result in pancytopenia and may respond to folinic (not folic) acid. Neutropenia may occasionally occur with prophylactic doses of co-trimoxazole, and if this occurs co-trimoxazole should be discontinued or dose reduced to 480 mg daily depending on severity of neutropenia.

If the baseline Hb is < 10 or the neutrophil count is < 1.5 AZT should be avoided.

Before blaming drugs for haematological toxicity it is important to recognise that advanced HIV disease and many opportunistic diseases (especially TB) can be associated with cytopenias.

Management of drug-induced anaemia and neutropenia	
Hb <8 or Neutrophil <1	Switch AZT to alternative
Neutrophil <1	Stop co-trimoxazole (discuss alternative with AfA)

Hepatotoxicity

The full panel of liver function tests is expensive; therefore it is recommended that only the alanine transferase (ALT) is monitored, as this is a sensitive and specific indicator of drug-induced liver injury. Minor derangements of liver enzymes are common and drug substitutions are not warranted unless the patient has symptoms of hepatitis. ALT elevations greater than five times the upper limit of normal (typically >200) are significant and warrant action as indicated below. The full LFT profile should be requested in patients with symptoms suggestive of hepatitis or if the ALT is >200. The presence of jaundice together with transaminitis in patients with suspected drug-induced liver injury is an indication of severe hepatotoxicity – these patients should be admitted and INR should be checked.

It is important to distinguish drug-induced liver injury from viral hepatitis. Hepatitis A, B and C should always be checked when hepatitis occurs. Infection with hepatitis B is common in HIV-infected patients and flares of viral hepatitis occur commonly shortly after commencing ART (part of immune reconstitution). In patients with hepatitis B withdrawing antiretrovirals with activity against hepatitis B (lamivudine, emtricitabine and tenofovir) may cause hepatitis flares, which can be life threatening (see Hepatitis B coinfection section).

Nevirapine is most often associated with hepatotoxicity (subclinical significant increase in liver enzymes 5 – 15%, clinical hepatitis in 2%). Patients starting nevirapine should have their ALT monitored regularly – after 2 weeks, 4 weeks, 8 weeks and 12 weeks, and then at six months, thereafter six monthly (hepatitis is very uncommon after 12 weeks). Other NNRTIs, all PIs and integrase inhibitors can also cause hepatitis. NRTIs may result in steatohepatitis – this develops after prolonged use and

generally causes mild elevation of liver enzymes, affecting GGT and alkaline phosphatase more than the transaminases, and ALT more than AST. Patients on atazanavir or indinavir may develop isolated unconjugated hyperbilirubinaemia resembling Gilbert's syndrome, which is not accompanied by liver injury, but the drug should be substituted if jaundice is marked or not tolerated by the patient. Atazanavir/ritonavir can also cause liver injury – in such cases transaminases will be elevated.

Many other drugs commonly used in HIV-infected patients, notably anti-tuberculous therapy (including prophylactic isoniazid), fluconazole and occasionally co-trimoxazole may also cause hepatitis. Some drugs used in HIV can cause cholestatic hepatitis (e.g. macrolides, co-trimoxazole).

Management of suspected antiretroviral drug-induced hepatitis:

- ALT 40 – 100, repeat in two weeks
- ALT 100 – 200, repeat in one week. But if symptoms of hepatitis or jaundice – stop relevant drugs, do hepatitis screen and full LFT. INR should also be done in patients with jaundice
- ALT >200, stop relevant drugs, do hepatitis screen and full LFT. INR should also be done in patients with jaundice

In summary: ALT > 200 is the threshold for stopping hepatotoxic drugs, but hepatotoxic drugs should be discontinued at lower levels of LFT abnormalities if there are symptoms of hepatitis (RUQ pain, anorexia, nausea/vomiting) or jaundice.

Consider other causes and investigate for:

- Other drugs (e.g. TB treatment, co-trimoxazole, fluconazole)
- Hepatitis A, B and C
- TB/TB – IRIS in liver
- Alcohol
- Alternative remedies
- Sepsis
- HIV cholangiopathy
- Fatty liver

If a patient on a NNRTI-based regimen develops hepatitis the NNRTI should be discontinued and the NRTI backbone continued for 7 days to prevent NNRTI resistance from developing (because NNRTIs have a very long half-life), unless the hepatitis is severe (features of hepatic failure), in which case all drugs should be stopped. The ALT should be monitored once or twice weekly. Once the ALT has settled to <100 and the bilirubin has normalised a modified ART regimen may be introduced with frequent monitoring of ALT (twice weekly for the first two weeks, then weekly until 4 weeks). Rechallenge with efavirenz may be considered, but is not recommended with nevirapine.

Where cannalicular liver enzymes are very significantly elevated (GGT or alkaline phosphatase) or if conjugated bilirubin is elevated, a liver ultrasound should be done to exclude extrahepatic biliary obstruction. Other common causes of this picture are fatty liver due to NRTIs (especially stavudine and didanosine), and TB infiltration of liver. Fatty liver can be visualised on ultrasound or CT scan and may result in fibrosis and chronic liver disease. Drug-induced cholestasis or cholestatic hepatitis may be due to macrolides, rifampicin, co-amoxiclav or co-trimoxazole – it takes much longer to resolve than hepatitis with elevated transaminases.

Suggested substitutions if antiretroviral drug induced hepatitis occurs on:

- Nevirapine → Efavirenz or Rilpivirine
- Efavirenz → boosted PI or integrase inhibitor
- Boosted PI → different boosted PI (or dolutegravir in select cases depending on treatment history – discuss with AfA)
- NRTI fatty liver – safer NRTI combination (TDF, ABC, 3TC, FTC)

Hepatitis in Patients on ART and TB Therapy

The priority in patients developing hepatitis on ART and TB drugs is to sort out the TB therapy first, followed by the ART. If hepatitis develops, as defined above, stop all antiretrovirals (if on a NNRTI-based regimen the NRTIs should be continued for a week), co-trimoxazole and all potentially hepatotoxic TB drugs (isoniazid, rifampicin and pyrazinamide). Three TB drugs (e.g. amikacin 15 mg/kg daily, moxifloxacin 400 mg daily or levofloxacin 1000 mg daily (unless body weight very low, then use 750 mg daily), and ethambutol 800 – 1 200 mg daily) should be started and continued throughout rechallenge to prevent the development of resistance and provide treatment for TB. Other causes of hepatitis, especially viral hepatitis, should also be excluded. TB immune reconstitution inflammatory syndrome (TB-IRIS) with worsening granulomatous hepatitis should be considered in the differential diagnosis. TB-IRIS typically presents a few weeks after starting ART in TB patients. The GGT and alkaline phosphatase are typically elevated more than the transaminases, if there is jaundice it is mild and bilirubin is predominantly conjugated and tender hepatomegaly is usually present. However, this diagnosis can be difficult as there is no confirmatory diagnostic test. An ultrasound (to exclude extrahepatic cholestasis) should be done and a liver biopsy should be considered.

Once the ALT has settled to <100 and jaundice has resolved then rechallenge with certain TB drugs may be considered. It is important to review the diagnosis of TB before attempting rechallenge – if the diagnosis was not made on good grounds TB therapy should be stopped and the patient carefully monitored. If the hepatitis resulted in hepatic failure (encephalopathy and/or coagulopathy) then rechallenge should not be done – in this setting a regimen containing ethambutol and second line TB drugs should be introduced and treatment should be prolonged for 18 months – consult AfA for advice.

When possible, drug rechallenge is important because outcomes on second line TB treatment are significantly worse than with first line drugs (6 months rifampicin has key sterilising activity that prevents relapse). TB drug rechallenge has been found to be successful without recurrence in 60 – 90% of patients and, provided ALT and symptoms are frequently monitored during rechallenge, it is usually safe. Several rechallenge regimens have been suggested and many local institutions have developed their own regimens. Many South African experts do not attempt rechallenge with pyrazinamide, but this should be considered in patients with TB meningitis, miliary TB or if there is resistance to INH, or if rechallenge with INH or rifampicin is not tolerated. Only consider PZA rechallenge if hepatitis occurred during intensive phase. A randomised controlled trial of different rechallenge regimens was conducted in India, but only HIV seronegative patients were studied. Three rechallenge regimens were tested (re-introducing rifampicin, INH and PZA simultaneously vs commencing one at a time at full dose vs commencing one at a time at increasing dose), and the proportion of patients who had recurrence was similar in the three arms.

We favour the following approach to rechallenge in line with the American Thoracic Society guidelines:

Day 1: Start rifampicin (normal dose)

Day 4-6: Add isoniazid (normal dose)

Day 8-10: Consider adding pyrazinamide (normal dose – see above)

During rechallenge ALT should be monitored twice weekly for the first 3 weeks, then every two weeks for a month, then monthly until 3 months. Also monitor for hepatitis symptoms and jaundice.

The duration of TB therapy after rechallenge depends on how much TB therapy has been completed and which drugs were successfully rechallenged.

The following durations are rough guidelines for alternative regimens – contact AfA for advice if necessary:

If the DILI occurred during the intensive phase, we recommend the following alternative regimens (with duration counted from date TB treatment was originally started, but adding in number of days taken for DILI resolution and the rechallenge):

- **Pyrazinamide not rechallenged/not tolerated:** stop moxifloxacin/levofloxacin and stop amikacin, continue isoniazid, rifampicin and ethambutol for total duration 9 months
- **Rifampicin not tolerated:** continue amikacin (for 2 months) and pyrazinamide, moxifloxacin/levofloxacin, isoniazid, and ethambutol for total duration of 18 months
- **Isoniazid not tolerated:** stop amikacin and continue levofloxacin (not moxifloxacin), rifampicin, ethambutol and pyrazinamide and treat for total duration of 6 months

If DILI occurred during the continuation phase, we recommend the following alternative regimens (with duration counted from date TB treatment was originally started, but adding in number of days taken for DILI resolution and the rechallenge):

- **Rifampicin not tolerated:** moxifloxacin/ levofloxacin, isoniazid, and ethambutol for total duration of 18 months
- **Isoniazid not tolerated:** stop amikacin and continue levofloxacin (not moxifloxacin), rifampicin and ethambutol and treat for total duration of 6 months

ART can be recommenced two weeks following successful rechallenge with TB therapy:

- If nevirapine was used this should be replaced with efavirenz.
- If efavirenz was used this should generally be rechallenged with close monitoring of ALT. Alternative is to replace with an integrase inhibitor.
- If double dose lopinavir/ritonavir was used the options are to rechallenge this with slow dose escalation over two weeks or dolutegravir (50mg 12 hourly if on rifampicin) could be considered in select cases depending on treatment history – discuss with AfA.

After ART rechallenge, monitor ALT every 2 weeks for 2 months.

Do not rechallenge co-trimoxazole unless there are compelling reasons (e.g. history of PJP and CD4 count <200).

For more detailed guidelines on TB drug-induced liver injury (and in particular cholestatic liver derangements) we refer clinicians to the SA HIV Clinicians Society Consensus Statement on their website (<http://www.sahivsoc.org>).

Hyperlactataemia

NRTIs can cause mitochondrial toxicity by inhibiting the human mitochondrial DNA gamma polymerase enzyme. One manifestation of mitochondrial toxicity is hyperlactataemia. Asymptomatic elevated lactate is common in patients on certain NRTIs such as stavudine (10 – 20%). Provided this is asymptomatic, there is no reason to stop NRTIs. There is in fact no need to monitor lactate levels in asymptomatic patients as this does not predict the development of lactic acidosis. Symptomatic hyperlactataemia without acidosis occurs in 1 – 2% per annum with NRTIs that are most toxic to mitochondria. Lactic acidosis is rare and presents as a life-threatening acute illness with acidosis. Lactic acidosis carries a poor prognosis (up to 50% mortality). Obese women are at high risk of developing symptomatic hyperlactataemia and lactic acidosis.

The risk of lactate elevation is as follows:

Stavudine = didanosine >> zidovudine > lamivudine = abacavir = tenofovir = emtricitabine

The combination of didanosine and stavudine should be avoided as it is associated with a very high risk of symptomatic hyperlactataemia/lactic acidosis.

Early recognition of symptomatic hyperlactataemia is the most important safeguard against lactic acidosis. If NRTI therapy is discontinued or switched to safer options like TDF, ABC and 3TC after early detection, symptoms resolve in most cases. Patients with symptomatic hyperlactataemia often have some other evidence of toxicity thought to be mediated by mitochondrial toxicity (especially peripheral neuropathy). Hyperlactataemia typically occurs after patients have been on ART for at least 6 months.

Signs and symptoms of hyperlactataemia are non-specific and may include:

- Nausea and vomiting (of new onset)
- Abdominal pain
- Weight loss
- Malaise
- Liver dysfunction (due to steatosis)
- Tachycardia
- Lethargy

More severe features may be seen in patients with lactic acidosis:

- Kussmaul's breathing as a result of metabolic acidosis
- Hypotension
- Decreased level of consciousness

Other causes of lactic acidosis should be considered (e.g. severe sepsis). An important clue that the cause of hyperlactataemia is NRTI-induced is that the lactate elevation persists for weeks, whilst with other causes it resolves rapidly when the underlying condition is treated. Procalcitonin levels will be elevated in severe sepsis.

Laboratory diagnosis

Plasma lactate level needs to be taken without a tourniquet in a fluoride tube, sent to the laboratory on ice. Laboratories require the sample to be received within a certain time period – liaise with your laboratory. The normal level is <2 mmol/l (arterial) or <2.5 mmol/l (venous). Levels of 2.5 to 5 are moderate and more than 5 is severe hyperlactataemia.

Lactic acidosis is diagnosed when lactate levels >5 are associated with acidosis (characterised by low pH, low serum bicarbonate, <20 mmol/l, and increased anion gap – serum bicarbonate is the most sensitive test). Other useful tests include serum lipase, LFTs, arterial blood gas analysis and serum glucose. Tests to look for other causes or triggers of acidosis should be done.

Treatment of symptomatic hyperlactataemia/lactic acidosis

Early intervention with discontinuation of NRTIs is essential. It is also essential to establish whether lactic acidosis is present, as patients with severe lactic acidosis need intensive care admission and a careful search for other causes or triggers of lactic acidosis (e.g. sepsis, myocardial infarction, pancreatitis – but note that pancreatitis can co-exist with NRTI-induced hyperlactataemia). Treatment of lactic acidosis should include:

- Maintenance of airway patency
- Delivery of oxygen
- Monitoring cardiac rhythm
- Respiratory and/or haemodynamic support to improve tissue perfusion
- Most clinicians would empirically add a broad spectrum antibiotic, e.g. third generation cephalosporin, pending cultures as sepsis is a common cause of lactic acidosis that may mimic NRTI-associated lactic acidosis

There is no evidence to support any particular therapy in lactic acidosis, but good supportive care in an intensive care unit should be instituted.

Bicarbonate replacement is controversial. High dose vitamin B complex (riboflavin and thiamine are thought to be important) may have a role in therapy.

In cases without acidosis and if lactate <5 the NRTIs should be switched to safer options like TDF, ABC and 3TC. In patients with acidosis or with severe symptomatic hyperlactataemia (lactate >5) NRTIs should be stopped. If the patient was on an NNRTI add a boosted PI and treat with an NNRTI + boosted PI regimen (beware of drug interactions– refer to Unusual combinations table). If the patient has failed an NNRTI regimen and was on a boosted PI then the boosted PI should be continued and discuss with AfA regarding what additional drugs to add to the regimen. In critically ill patients with multiorgan failure it may be necessary to discontinue all ART and only re-introduce when lactic acidosis has resolved with a regimen that does not include an NRTI.

After withdrawal of NRTIs or substitution with safer NRTIs lactate levels resolve slowly over 12 weeks and may fluctuate, but symptoms generally resolve more rapidly. Lactate should be monitored regularly if safer NRTIs have been substituted until the levels are decreasing. If lactate increases substantially and patient remains symptomatic interrupt NRTIs and switch to boosted PI +/- NNRTI.

See SA HIV Clinicians Society guidelines (<http://www.sahivsoc.org>).

Dyslipidaemia

PIs, with the exception of unboosted atazanavir, can cause fasting hypertriglyceridaemia and elevated LDL cholesterol. Boosted atazanavir is associated with less severe dyslipidaemia. Lopinavir is associated with the most marked elevation of triglycerides. Stavudine can cause mild hypertriglyceridaemia. Efavirenz can cause elevated total cholesterol and mild hypertriglyceridaemia.

Fasting lipids (total cholesterol and triglycerides) should be done at baseline in all patients starting protease inhibitors. This should be repeated in 3 months. Lifestyle modification should be advised for all elevations (stop smoking, lose weight if relevant, increase aerobic exercise, reduce cholesterol and saturated fat intake). Boosted atazanavir is associated with a lower risk of dyslipidaemia and patients should be switched to this PI if possible.

Elevated cholesterol and triglyceride levels should be treated with lipid lowering agents according to the calculated risk as in HIV-uninfected patients, based on Framingham risk score.

Fibrates are the drugs of choice for PI-induced dyslipidaemia as they are more potent than statins at reducing triglycerides (which is the commonest PI-induced dyslipidaemia) and are not associated with drug interactions. There are marked drug interactions with most of the statins, which should be avoided EXCEPT for low dose atorvastatin (5 – 10 mg) or pravastatin.

Lipodystrophy

Changes in body fat distribution may result from long-term use of ART. This can present either with fat accumulation (visceral obesity, breast enlargement, “buffalo hump”, lipomata) or with fat loss (lipoatrophy, presenting as facial, limb and buttock wasting) or with both fat loss and accumulation.

Lipoatrophy is particularly associated with stavudine and zidovudine use. Some reversal of lipoatrophy occurs on switching to NRTIs that are not associated with this problem (tenofovir or abacavir), but resolution is seldom complete and is very slow.

Previously fat accumulation was thought to be due to protease inhibitors, but prospective trials have shown that rates of fat accumulation are similar with the use of NNRTIs, integrase inhibitors or PIs (i.e. this is not a side effect of a specific drug or class). Furthermore, a longitudinal study in the USA showed that visceral and trunk fat increased at similar rates in patients on ART and HIV-negative controls from the general population. Randomised controlled trials have shown that antiretroviral drug substitutions are not effective for altering fat accumulation. Metabolic disorders (increased glucose and increased lipids) may be associated with visceral fat accumulation. Diet and aerobic exercises help for visceral fat accumulation. Metformin has been shown to be beneficial in patients with insulin resistance or the metabolic syndrome, which is defined as any 3 of the following 5 traits:

- Waist circumference >102 cm in men and >88 cm in women
- Triglycerides ≥ 1.7 mmol/L
- HDL cholesterol <1 mmol/L in men and <1.3 in women
- Blood pressure $\geq 130/85$ mmHg
- Fasting glucose ≥ 5.6 mmol/L

In extreme cases with focal fat accumulation (e.g. buffalo humps) surgery may be necessary.

Gynaecomastia

Gynaecomastia involves the development of breast tissue in men. This is not related to lipodystrophy. It may be bilateral or unilateral. Serum testosterone should be measured and replacement therapy given if this is low. Gynaecomastia is most consistently associated with EFV, so patients should be switched to an alternative if the side effect is distressing for the patient. Some cases may resolve without a change in therapy.

Pancreatitis

HIV infection is associated with an increased risk of idiopathic pancreatitis. Some opportunistic infections have been associated with pancreatitis (e.g. MAC, CMV, tuberculosis). Some antiretroviral drugs can cause pancreatitis, notably ddI and d4T. Pancreatitis may occur in patients with severe symptomatic hyperlactataemia. Severe hypertriglyceridaemia > 10 mmol/l (which may be caused by PIs) can cause pancreatitis. Other drugs used in HIV can rarely cause pancreatitis (e.g. co-trimoxazole).

Amylase concentrations are often elevated in HIV due to salivary gland disease – lipase or pancreatic amylase should be requested in order to diagnose pancreatitis.

Protease Inhibitor Induced Diarrhoea

PI-induced diarrhoea is more common in patients treated with lopinavir/ritonavir than other boosted PIs. If diarrhoea occurs on lopinavir/ritonavir then switching to a PI less associated with diarrhoea (e.g. boosted atazanavir) should be tried first. The following treatments of PI-induced diarrhoea have shown benefit in small clinical trials: bulk forming agents (oat bran, psyllium husk), calcium carbonate, and loperamide.

Interrupting Antiretroviral Therapy

Therapy with antiretroviral drugs should not be completely interrupted except in exceptional circumstances (e.g. life threatening toxicity). Interruptions of long-term therapy have been shown to increase the risk of resistance and even death (in trials of repeated structured treatment interruptions). If ART has to be interrupted and the combination includes the NNRTIs nevirapine, efavirenz or rilpivirine, which have long half-lives, the dual NRTI combination should be continued for a week after stopping the NNRTI to reduce the risk of resistance developing (other option is to cover the tail with a week of LPV/r). An exception to this is when NRTIs are the cause of severe toxicity (e.g. pancreatitis or lactic acidosis) then the NRTIs and NNRTIs should be stopped simultaneously (with or without boosted PI cover). With a dual NRTI and a boosted PI regimen all drugs can be stopped simultaneously as they have similar half-lives.

HIV and the Elderly

The wide availability of effective antiretroviral therapy has resulted in increased survival and an overall ageing of the HIV-infected population. In addition, there appears to be an increase in the number of new HIV infections in older people. People aged 50 and older may exhibit the same risk behaviours found among younger people, but are seldom targeted with prevention messages because they are assumed to be at low risk. Biological changes in older women after the menopause may also increase the risk of HIV transmission during sexual intercourse.

The prevalence of HIV in older people will thus continue to increase over time and it has been estimated that around 50% of people living with HIV in high income countries are older than 50. According to UNAIDS, in 2012 there were an estimated 2.9 million people aged 50 years and over living with HIV in low and middle income countries.

In a 2012 national HIV survey in South Africa, HIV prevalence was 13% among people aged 50-54 years, and 12% among women and 6.9% among men aged 55-59 years (compared to 18% among men and women aged 15-49 years). HIV infection is not uncommon in even older individuals; there are close to 2000 people over the age of 60 currently registered on AfA (including a few octogenarians).

There are indications that older adults are less knowledgeable about HIV and its transmission and are less likely to take an HIV test compared with younger people. Nevertheless, the possibility of HIV infection should always be considered in older patients and appropriate education, counselling and testing provided.

Is the natural history of HIV infection different in older adults?

Prior to the widespread availability of effective ART combinations, older patients had higher morbidity, higher mortality and a much shorter AIDS-free survival than younger patients. This may partly have been due to late diagnosis as a result of a perception of low HIV prevalence in the elderly and inadequate screening, as well as biological factors – the CD4 count declines faster over the age of 40.

With ART started at the appropriate time, older people are in fact more likely to achieve virological suppression than younger people, probably due to improved adherence although they may have a lower CD4 count response, and survival has improved substantially.

Ageing individuals experience HIV as a chronic disease which is often complicated by multiple comorbidities. With currently available ART regimens the causes of death are shifting from mainly AIDS-related complications to non-HIV related conditions.

There are a number of reasons why managing HIV in older people can be challenging.

Older people are more likely to have multiple pathologies such as cardiovascular disease, renal disease or diabetes. In a recent South African study, 30% of people 50 years and over had two or more chronic conditions. It is also possible that HIV infection itself increases the risk of developing some of the degenerative diseases associated with ageing, including dementia due to vascular events.

While there is evidence that people over 50 are in general more likely to adhere to ART, there is also evidence that adherence may be adversely affected in later life by neurocognitive impairment and polypharmacy as a result of receiving treatment for other chronic conditions, often from different healthcare providers, or self-medication. This polypharmacy also increases the potential for drug-drug interactions.

It is thus important to be aware of all the medications the patient is taking (including over the counter products and traditional remedies). An attempt should be made to reduce the patient's overall pill burden as far as possible.

ART has a number of potential adverse effects and older patients are more likely to develop toxicity as a result of age-related changes in pharmacokinetics (including a reduction in renal and hepatic clearance) and pharmacodynamics (increased sensitivity to several classes of drugs). Certain antiretrovirals may additionally be associated with an increased risk of renal disease (e.g. tenofovir), hepatotoxicity (e.g. nevirapine), hyperlipidaemia (e.g. lopinavir/r) and cardiovascular disease (e.g. abacavir). Tenofovir should also be used with caution in elderly patients with established osteoporosis due to its potential bone toxicity. It is not clear if the elderly are more likely to develop CNS toxicity with efavirenz but, this may be a problem in patients with early cognitive impairment.

There is no evidence that when to start ART should be any different in older patients and the current approach of initiating therapy on diagnosis should apply, provided that there is a willingness to accept and adhere to treatment.

When selecting the most appropriate ART combination to use in older patients, the possibility of pre-existing renal or hepatic insufficiency should be considered. The relevant baseline tests, e.g. serum creatinine and ALT should be carried out, and after starting ART patients should be regularly monitored for evidence of toxicity. As mentioned earlier, the possibility of drug-drug interactions should always be considered if other medications are being taken on a regular basis.

Once a day dosing with fixed dose combinations (e.g. TDF/FTC/EFV), where this is possible, is an attractive option to simplify therapy and improve treatment adherence. However, the pharmacokinetics of the component drugs have not been evaluated in patients over 65 and the possibility of adverse effects should always be considered.

Healthcare providers should also be aware that elderly people living with HIV may have difficulty coming to terms with the diagnosis and feel isolated and marginalized. Issues around managing disclosure to family members, as well as anxiety and depression are not uncommon and it is important to provide at-risk older patients with appropriate additional support and care.

Drug Dosages in Renal Failure

Most NRTIs require dose reductions in renal failure.

Formula to estimate creatinine clearance (most labs report "eGFR", which uses a different formula but is also a good approximation of creatinine clearance):

<u>(140 – age) × weight (kg)</u>	Good estimate for men, for women multiply
serum creatinine (µmol/L)	total by 0.85

For peritoneal dialysis the dose given under creatinine clearance <10 should be given daily. For haemodialysis the dose given under creatinine clearance <10 should be given daily, but must be given after dialysis on dialysis days as some of the drug will be dialysed out.

Drug	Creat. clearance 10 – 50	Creat. clearance <10
Zidovudine	Unchanged	300 mg daily
Didanosine	>60 kg 200 mg daily <60 kg 150 mg daily	>60 kg 100 mg daily <60 kg 75 mg daily
Lamivudine	150 mg daily	50 mg daily
Stavudine	15 mg 12 hourly	15 mg daily
Abacavir	Unchanged	Unchanged
Tenofovir	AVOID	AVOID*
PIs	Unchanged	Unchanged
Nevirapine	Unchanged	Unchanged
Efavirenz	Unchanged	Unchanged
Etravirine	Unchanged	Unchanged
Rilpivirine	Unchanged	Unchanged
Raltegravir	Unchanged	Unchanged
Dolutegravir	Unchanged	Unchanged
Maraviroc	Should be used with caution in patients with renal impairment who are taking potent CYP3A4 inhibitors – see package insert for details	
Co-trimoxazole	480 mg daily	480 mg three times a week
Fluconazole	Half dose	Quarter dose
Dapsone	Unchanged	Unchanged

* In patients on dialysis 300 mg once a week may be considered.

Sources:

Bartlett JG. *Medical care of patients with HIV Infection.*
The Sanford guide to antimicrobial therapy

ART Dosages in Liver Impairment

Assessing the degree of liver impairment is difficult. Liver function tests are of minimal value. Degree of hepatic impairment should be assessed clinically together with the INR.

Drug	Prescribing with liver impairment
NRTIs	
Abacavir	Reduce adult dose to 200 mg bd for mild to moderate liver impairment Contraindicated in severe hepatic impairment
Didanosine	Use with caution. Recent reports implicate didanosine use as a risk factor for the development of hepatic decompensation in patients being treated for cirrhosis due to hepatitis C. Avoid coadministration of didanosine with stavudine in patients with liver disease in view of the likely increased risk of lactic acidosis
Lamivudine/ Emtricitabine	No adjustment necessary. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV and have discontinued lamivudine*
Stavudine	No adjustment of dose is necessary. Avoid coadministration of didanosine with stavudine in patients with liver disease in view of the likely increased risk of lactic acidosis. Many clinicians would avoid d4T in patients with liver disease because of the risk of steatohepatitis
Tenofovir	No dosage adjustment necessary. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV and have discontinued tenofovir*
Zidovudine	Decrease dose to 200 mg bd
NNRTIs	
Efavirenz	Use with caution
Nevirapine	Use with caution. Contraindicated in severe hepatic impairment and most clinicians would avoid in patients with any liver disease
Etravirine	Can use standard doses with moderate liver impairment. No dosage recommendations available for severe liver impairment
Rilpivirine	No dose adjustment is required in patients with mild or moderate hepatic impairment Rilpivirine has not been studied in patients with severe hepatic impairment
PIs	
All	Use with caution
Integrase Inhibitors	
Raltegravir	Can use standard doses with moderate liver impairment. No dosage recommendations available for severe liver impairment
Dolutegravir	Can use standard doses with moderate liver impairment. No dosage recommendations available for severe liver impairment
CCR5 antagonist	
Maraviroc	Use with caution – see package insert for details

* Patients coinfecting with chronic hepatitis B should be treated with the dual NRTI backbone of tenofovir plus lamivudine (or emtricitabine). This dual NRTI therapy should not be discontinued even if HIV resistance develops as flare-up of hepatitis B may occur, which can be life-threatening.

In patients with liver impairment the safest ARTs are probably tenofovir, FTC, 3TC, efavirenz and integrase inhibitors.

ART and Porphyrria

There is very limited information on the safety of antiretrovirals in patients with porphyria. Before commencing therapy the patient should be discussed with AfA. The concern regarding using ART drugs in patients with porphyria applies to those forms of porphyria that are associated with acute attacks.

It is likely that most nucleoside reverse transcriptase inhibitors will be safe. The one exception is zidovudine, which is regarded as probably porphyrinogenic. Dolutegravir and raltegravir are both classified as probably not porphyrinogenic.

Most of the protease inhibitors are regarded as probably porphyrinogenic and full dose ritonavir is definitely porphyrinogenic. Efavirenz and nevirapine are regarded as probably porphyrinogenic.

Therefore, the major difficulty rests with the NNRTI or PI component. Here the safest regimen on theoretical grounds is saquinavir 1 600 mg plus ritonavir 100 mg daily, followed by lopinavir/ritonavir and efavirenz.

Some experts have recommended using unboosted atazanavir 400 mg, which on theoretical grounds may have a low porphyrinogenic potential.

Close monitoring of urine porphobilinogen after introduction of ART is advised.

Contact the Medicines Information Centre at the University of Cape Town for up to date advice.

ART in the Patient with TB

- If the patient is already on ART, the regimen should be changed to be compatible with rifampicin
- A patient already on a nevirapine-based regimen who is virologically suppressed, and needs to start TB therapy, should have nevirapine switched to efavirenz unless contraindications are present
- Tenofovir and aminoglycosides should not be prescribed together. Any patient on a tenofovir-containing regimen who is virologically suppressed and who requires streptomycin, amikacin, kanamycin or capreomycin should have the tenofovir switched to an alternative NRTI for the duration of aminoglycoside treatment. If the patient is failing their current ART regimen, then switching the NRTI should be accompanied by introduction of a suppressive regimen
- When ART is commenced in a patient on TB therapy, the patient's symptoms may temporarily worsen as part of immune reconstitution – the patient should be specifically warned about this
- For patients not yet on ART: The patient should be stabilised on TB treatment before starting ART. Patients with CD4 counts <50 should be commenced on ART after 2 weeks of TB treatment, patients with higher CD4 counts should commence ART around 8 weeks

TB therapy and ART share certain side effects, the most serious of which is drug-induced hepatitis. Patients should therefore be monitored for symptoms of hepatitis (nausea, anorexia and RUQ pain).

The paradoxical tuberculosis-associated TB-immune reconstitution inflammatory syndrome (IRIS) following commencement of ART may cause a flare up of the tuberculosis. It commonly occurs when ART is commenced within the first two months of anti-tuberculous therapy, and in patients with advanced disease. Paradoxical TB-IRIS onset is typically 1 – 4 weeks after starting ART. Return of TB symptoms and paradoxical enlargement of previous or new TB lesions (nodes, pulmonary infiltrates, effusions, tuberculomas, etc.) are usual manifestations. TB drug-resistance should be excluded in all IRIS cases. TB-IRIS symptoms can be successfully treated with prednisone starting with a dose of 1.5 mg/kg/day and tailoring over 1 – 2 months. Steroids should only be prescribed once the diagnosis is certain and other causes for deterioration are excluded (e.g. MDR TB or pneumonia). Steroids must not be given to patients with Kaposi's sarcoma.

Rifampicin has significant drug interactions with the protease inhibitors and NNRTIs. When ART is indicated it is preferable to use a regimen which does not interact significantly with rifampicin (see table below). If the patient is already on ART, therapy should be changed to allow rifampicin to be used.

If double dose lopinavir/ritonavir is used with rifampicin, a gradual increase in the dose is recommended to improve tolerability (two tablets twice a day for five days, then three tablets twice a day for five days, then four tablets twice a day until one week after completing TB medication).

ART Interactions with Rifampicin

NRTIs	No significant interactions
Efavirenz	Minimal reduction in efavirenz levels, no dose adjustment necessary Preferred regimen is EFV plus 2 NRTIs
Nevirapine	Moderate reduction in nevirapine levels. Only consider starting NVP if EFV is contraindicated or not tolerated – omit lead-in dose
Etravirine	Avoid. Significant decreases in etravirine concentrations
Rilpivirine	Avoid
Lopinavir/ritonavir	Lopinavir/ritonavir double dose (increase the dose gradually – 3 tablets bd for a week, then 4 tablets bd) needs to be given to counteract the enzyme-inducing effect of rifampicin. Close monitoring of liver function essential (at weeks two and four, then monthly until TB treatment completed)
Ritonavir + saquinavir both 400 mg bd	No significant interaction. Close monitoring of liver function essential (as above)
All other ritonavir-boosted PIs	Marked reduction in PI levels - avoid. Rifabutin 150 mg daily can be used as an alternative to rifampicin. There may be increased toxicity with the daily dose of rifabutin due to accumulation of the metabolite – monitor closely for neutropaenia, uveitis and hepatitis
Raltegravir	Modest reduction in raltegravir levels, but a small clinical trial has shown that dose increase is not necessary
Dolutegravir	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when coadministered with rifampicin
Maraviroc	Complex. See package insert for details

Interactions with Antiretroviral Drugs

Patients receiving ART frequently take other medication, including over the counter drugs. There are numerous potential drug interactions with ART. Interactions could be on the basis of shared side effects, impaired absorption or altered metabolism.

In general, the nucleoside reverse transcriptase inhibitors do not interact with the pharmacokinetics of other drugs with the exception of the old buffered formulation of didanosine, which has an antacid that may interfere with absorption of other drugs (the enteric coated formulation is free of interactions) and tenofovir, which increases the toxicity of didanosine and reduces the concentrations of atazanavir. Most drug interactions are with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

The basis of most of these drug interactions is interference with hepatic metabolism. PIs and NNRTIs are metabolised by the liver and other drugs that induce and/or inhibit hepatic enzymes which affect the levels of PIs or NNRTIs. Both PIs and NNRTIs induce and/or inhibit hepatic enzymes, which leads to potential problems with many other drugs. Enzyme induction may lead to sub-optimal drug levels – when this involves antiretroviral drugs this could lead to the development of HIV resistance. Enzyme inhibition leads to elevation of drug levels, potentially causing toxicity.

When the drug interaction leads to marked alteration of drug levels, coadministration should be avoided. In other instances a dose adjustment of the interacting drug MAY be necessary. If the patient is clinically stable on the coadministered medication with no evidence of toxicity, then a dose adjustment may not be necessary. Drug levels (e.g. theophylline) or effects (e.g. INR with warfarin) should be checked where this is possible. Alternative and complementary medications may also have interactions with ART.

Further information on drug interactions can be obtained from the package inserts, the South African Medicines Formulary, the National HIV Hotline (run by the Medicines Information Centre, phone 0800 212 506), by contacting an AfA pharmacist or from the following website: www.hiv-druginteractions.org.

Guidelines on Artificial Ventilation, ICU Care and Withdrawal of Therapy

- Criteria for withholding or discontinuing ventilation in HIV-infected individuals should be the same as those for individuals without HIV. The doctor treating the patient must ultimately make these decisions
- Patients who require ventilation for conditions which are not directly related to HIV have a similar outcome to patients without HIV
- The commonest HIV-related indication for ventilation is pneumonia, either due to conventional bacteria or *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*). Both have similar in-hospital mortality to patients without HIV who require ventilation for community-acquired pneumonia
- ART has dramatically improved the outcome of patients with advanced HIV disease. All patients registered with AfA have access to ART. Thus, provided there is a reasonable prospect of surviving intensive care unit admission, patients should receive artificial ventilation. The exception is patients who have documented failure of all available ART regimens – this should be discussed with AfA in each case
- ART takes weeks to months to achieve clinical benefit, so introducing ART in a newly-diagnosed HIV-infected patient on a ventilator is unlikely to affect their outcome. It may in fact worsen outcome due to the early paradoxical deterioration of opportunistic infections (IRIS) seen in the first few weeks of starting ART in patients with advanced HIV. In HIV-infected patients who have prolonged ICU admissions ART initiation should be considered (discuss with AfA)
- Nearly all of the HIV-related conditions are either treatable or will regress on ART. However, if a progressive condition has failed to respond to a reasonable trial of ART or specific therapy then ventilation would be futile. Examples of conditions that fall into this category are visceral Kaposi's sarcoma, lymphoma and progressive multifocal leukoencephalopathy
- Under the following circumstances, it would be reasonable to consider withdrawing active therapy, apart from supportive/nursing care:
 - If the patient requests it
 - If the patient has an untreatable AIDS condition
 - If there has been no response to an adequate trial of ART
 - If the patient has a poor quality of life

The views of the patient, involved healthcare professionals and relatives should always be taken into account.

NB: The use of laboratory tests e.g. CD4 count or viral load to determine when to withhold or stop therapy is not acceptable as benefit can still be gained from ART even in patients with advanced disease and both CD4 counts and viral loads are dramatically altered in critical illness.

Infection Prevention and Control (IPC)

Preventing Exposure to Pathogens

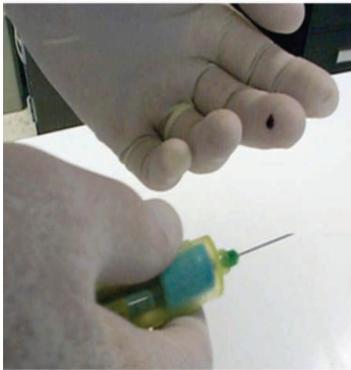
Hospital acquired infections (HAI) also termed 'nosocomial' infections, are transmitted person-to-person via the airborne route (either on small droplets such as for *Mycobacterium tuberculosis* and measles, or large droplets for influenza or *Neisseria meningitidis*) or through skin contact. Signs should be available that indicate the type of precaution(s) that must be taken for a particular mode of transmission and should be clearly visible to all staff and visitors ideally on the door of the patient's isolation room.

IPC Warning Signs

Mode of transmission	Signage	Pathogens/PPE
Airborne Small droplet nuclei	 <p>STOP! - WARNING AIRBORNE PRECAUTIONS ALL STAFF AND VISITORS WEAR MASKS DISINFECT / WASH YOUR HANDS BEFORE ENTERING WHEN YOU LEAVE</p>	Tuberculosis Measles Chickenpox (pneumonitis) N95 mask
Droplet Large droplets from upper respiratory tract	 <p>STOP! - WARNING DROPLET PRECAUTIONS ALL STAFF AND VISITORS WEAR MASKS AND GOGGLES BEFORE ENTERING WHEN YOU LEAVE</p>	Meningococcal infections Influenza Surgical mask
Contact	 <p>STOP! - WARNING CONTACT PRECAUTIONS ALL STAFF AND VISITORS WEAR GLOVES AND APRONS FOR ALL PATIENT CONTACT WASH/DISINFECT YOUR HANDS BEFORE & AFTER PATIENT CONTACT</p>	Drug-resistant pathogens on skin, wounds, GIT <i>Clostridium difficile</i> -associated diarrhoea Apron and gloves

Prevention of Sharp Injuries

Greater than 80% of sharps injuries are preventable. Use of safety devices for blood taking reduces needlestick injuries.



Wear gloves wherever contact with blood is anticipated.

Use safety equipment for blood taking. If this is not available use a conventional needle and syringe, remove the needle using the allocated slot in the lid of the sharps bin and transfer blood to the uncapped specimen tubes.

Clean up properly and do not leave needles or other sharp objects in the bed or around the patient area.

Never walk with an unprotected sharp to reach the nearest container, rather, get someone to bring you a container.

DO NOT resheath needles as this increases risk.

Only in extreme circumstances, should you consider resheathing a sharp, using a 'safe' technique whereby you do not hold the sheath in your hand while resheathing.

Prevention of Mycobacterium Tuberculosis Transmission

Mycobacterium tuberculosis is transmitted by small aerosol nuclei generated by coughing. Due to small droplet size, aerosols remain suspended in the atmosphere for a long time before falling to the ground.

Active case finding is critical to correct placement of patients. Most private facilities will have single-bedded isolation rooms.

If isolation rooms are unavailable, the following patients are at less risk to others if nursed on an open ward:



1. Proven or suspected extrapulmonary tuberculosis, without pulmonary involvement.
2. Proven drug-sensitive pulmonary tuberculosis when the patient has completed >2 weeks of uninterrupted intensive phase treatment.
3. Any PTB suspect (clinical and/or radiological grounds) without microbiological proof, who has completed >2 weeks of uninterrupted intensive phase treatment.
4. Any patient with multi-drug resistant (MDR) PTB, who has completed a minimum of 4 months intensive phase therapy and has had 2 negative sputum cultures 1 month apart (culture conversion).

All staff and visitors should be taught how to wear an N95 mask.

An airborne precautions sign must be fixed to the door of each isolation cubicle.

When entering the room of a patient with proven or suspected tuberculosis, an N95 mask should be worn.

If a patient is moved from an isolation area, then he/she should wear a surgical mask or an N95 mask depending on resources.

Patients with respiratory compromise may have difficulty wearing an N95 mask, which further restricts respiration.

1. Open the mask and separate the two blue elastic straps.
2. Place the mask over your nose, mouth and chin, ensuring that the two elastic straps are positioned as shown.
3. Firmly mould the metal strip against each side of your nose to create a proper seal.
4. The mask should fit firmly against your face.
5. When breathing out, you should not feel air escaping.



HIV and the Traveller

A number of factors impact on the advice given to HIV-infected people wishing to travel. First and foremost, entry into some countries is prohibited if a person is known to be HIV positive which may require re-thinking the trip at the outset. The advice given on immunisation against communicable diseases will depend on the person's immune status and whether the vaccine contains live attenuated virus, an inactivated pathogen or a toxin. Special consideration and counselling needs to be given to persons entering a malaria endemic area and an assessment of the likely drug interactions between antimalarials and antiretrovirals for those persons taking ART is crucial if adequate protection against malaria is to be achieved.

Patients planning a trip abroad should consult a travel health practitioner or their own doctor well in advance of travelling. Table 1 shows the current restrictions imposed by a number of countries that prohibit or restrict travel of HIV-infected people. Up-to-date information can be obtained from The Global Database on HIV-specific travel and residence restrictions (<http://www.hivtravel.org>).

Table 1: Travel restrictions imposed on HIV-infected travellers

Entry into the country denied to HIV-infected persons	Proof of HIV seronegative status even for short-term stays (10 – 90 days)	Deported if HIV serostatus found to be positive
Brunei Oman Sudan United Arab Emirates Yemen	Egypt Iraq Qatar Singapore Turks & Caicos	Bahrain Brunei Egypt Iraq Jordan Kuwait Malaysia Mongolia North Korea Oman Qatar Russian Federation Saudi Arabia Singapore Sudan Syria Chinese Taipei United Arab Emirates Yemen

Immunisation for HIV-infected Travellers

General principles that apply to vaccination in adults with HIV-infection are:

1. HIV-infected persons should avoid live vaccines, although Yellow Fever and MMR may be given to patients with CD4 cell counts >200.
2. Vaccine efficacy is reduced in HIV-infected persons with advanced immunosuppression. Some vaccine courses will require extra or booster doses, depending on the individual vaccine.
3. Duration of vaccine efficacy may be reduced in HIV infection, particularly in those with advanced immunosuppression.
4. A lack of antibody response does not always equate with lack of efficacy.

5. When considering vaccinations for HIV-infected travellers, the need for travel to a high risk area should be balanced with the risk of increased disease severity in HIV-infected travellers, particularly in those with advanced immunosuppression. If travel can be avoided or delayed until immune reconstitution has taken place following instigating ART, then this should be discussed at every opportunity.

Table 2: Immunisations for HIV-infected adults

Vaccine	Indication	Notes
Live Vaccines/Toxoids		
Cholera (CVD103-HgR)	Contraindicated	Use inactivated oral vaccine
Influenza (intranasal)	Contraindicated	Use inactivated parenteral vaccine Avoid vaccination in household contacts
Measles, Mumps, Rubella (MMR)	Indicated for measles IgG-seronegative persons with CD4 count >200 Contraindicated if CD4 ≤200	Avoid pregnancy for 1 month after vaccination Breastfeeding not contraindicated Administer 2 doses at least 1 month apart to increase likelihood of protection against measles Safe for household contacts
Poliomyelitis (oral; OPV)	Contraindicated	Avoid vaccination in household contacts
Tuberculosis (BCG)	Contraindicated	
Typhoid (Ty21a)	Contraindicated	Use inactivated Typhoid ViCPS vaccine
Varicella-zoster (Chickenpox)	Varicella seronegative patients with CD4 count >200	Pregnancy should be avoided for 1 month after vaccination
Yellow fever	Indicated if significant risk of contracting YF for travellers with CD4 count >200, whether or not on ART Contraindicated in HIV-infected travellers: with CD4 ≤200 who are >60 years of age on CCR5 inhibitors [†] with egg allergy pregnant or breastfeeding	Decisions regarding YF vaccination should always be taken in light of likely risk of acquisition of infection An exemption certificate should be provided to all travellers not vaccinated, but travelling to a YF endemic country Focused advice on avoidance of mosquito bites must be stressed Safe for household contacts Re-vaccinate after 10 years
Zoster (Shingles)	Contraindicated	VZV titre ≥5 times that of chickenpox vaccine

Vaccine	Indication	Notes
Inactivated Vaccines/Toxoids		
Cholera (WC/rBS)	Indicated in travellers to high risk areas during epidemics or after natural disasters	Limited efficacy and safety data Responses in travellers with CD4 <100 are poor Stress good food and water hygiene
Cholera (Dukoral®)	Protects against <i>V.cholerae</i> -O1 subtype	No efficacy data available specifically in HIV-infected patients
Diphtheria/Tetanus/ Polio (parenteral Td/ IPV)	Booster dose every 10 years	No need to re-start a course, irrespective of the time elapsed since last dose
Hepatitis A	Should be considered for all HIV-infected individuals without evidence of immunity, but particularly in patients with comorbid liver disease, non-immune travellers to endemic areas and MSM	If resources allow, check for serological evidence of natural infection before vaccination Serological responses reduced in immunosuppressed patients, but good efficacy even at low CD4 count Two or three doses required May be given as single vaccine or as combination with Hepatitis B
Hepatitis B	Recommended for all non-immune HIV-infected adults	4 dose schedule (0,1,2,12 months) ± booster doses as dictated by serological response Those who fail to respond to 1 st vaccination course should either receive a 2 nd course with single or double-dose vaccine Stress advice on risk reduction, especially in high risk groups such as MSM
Influenza	Annual vaccination for all HIV-infected patients with CD4 cell count >100 and those on ART whose CD4 count does not rise above 100	Patients whose CD4 count <100, who are ART-naïve should start ART and be vaccinated once CD4 count rises
Japanese B encephalitis	Indicated for travellers to south-east Asia and Far East staying >1 month in endemic areas, particularly for those travellers whose work puts them at high risk [†]	Formalin-inactivated JEV vaccine linked with severe neurological adverse events A new JEV vaccine, Ixiaro®, inactivated virus strain derived from tissue culture has recently been licensed by the FDA. No information is available yet for HIV-infected persons

Vaccine	Indication	Notes
Inactivated Vaccines/Toxoids (continued)		
Neisseria meningitidis	Consider in young adults and patients with functional or anatomic asplenia. Mandatory for visitors to the Hajj. Indicated for travellers to the 'Meningitis belt'	Single dose quadrivalent (ACWY) vaccine recommended No evidence of increased risk of adverse events in HIV-infected persons
Pneumococcus	Indicated for children as part of the extended program of immunisation, and all HIV-infected persons: 1. No prior immunisation against Pneumococcus with either PCV-13 or PPV-23 a. A single dose of PCV-13 should be given irrespective of CD4 count, followed by a single dose of PPV-23 at least 8 weeks later b. If the patient's CD4 count is <200 cells/mm ³ , then PPV-23 should be deferred until the patient has been started on antiretroviral therapy and achieved a CD4 count ≥200 cells/mm ³ c. A second dose of PPV-23 should be given five years after the initial PPV-23 dose 2. For HIV-infected persons who have previously received one or more doses of PPV-23: a. A single dose of PCV-13 should be administered a minimum of 1 year after the last PPV-23 dose	
Rabies	Indicated for all travellers to dog-rabies endemic areas	Intramuscular immunisation recommended rather than intradermal Assess response to immunisation in travellers with CD4 ≤200, if resources allow ± further boosting if antibody response >0.5IU.ml not achieved Counsel all travellers to endemic areas on wound treatment and post-exposure prophylaxis

Vaccine	Indication	Notes
Inactivated Vaccines/Toxoids (continued)		
Tick-borne Encephalitis	Indicated for HIV-infected travellers intending to walk, camp or work in heavily forested regions in endemic areas	Limited efficacy data available. Highest risk in late spring/early summer Travellers with CD4 count >400 had better serological response Stress avoid tick bites and consumption of unpasteurised milk
Typhoid (ViCPS)	Indicated for HIV-infected travellers at risk of exposure, particularly to highly endemic areas	Booster every 3 years. Serological response reduced in travellers with CD4 count ≤200 Stress importance of food and water hygiene

† A severe viscerotropic disease after YF vaccination described in an HIV-negative person with genetically determined disruption of the CCR5-RANTES axis.

‡ Participants in extensive outdoor activities in rural areas.

¹ Dworkin et al. *Clin Infect. Dis* 2001;32: 794-800.

² Watera et al. *AIDS* 2004; 18: 1210-13.

Antimalarial Chemoprophylaxis and Treatment

HIV-infected travellers are at increased risk of severe falciparum malaria if infected and advice for travellers to an endemic malaria area should go far beyond the use of chemoprophylaxis. All efforts should be made to avoid being bitten between dusk and dawn, including use of DEET-based mosquito repellents, long-sleeved shirts and long trousers, and impregnated bed nets. Three choices exist for antimalarial chemoprophylaxis; mefloquine, atovaquone-proguanil and doxycycline. Only doxycycline is free of interactions with ART and is therefore a good choice for patients already on ART. Doxycycline may cause photosensitivity in ~3% of patients, so the liberal use of high factor sun-screen and protective clothing should be used. For patients not on ART, either of the 3 chemoprophylactic agents can be used. Side effects of mefloquine include neuropsychiatric effects and atovaquone-proguanil may be associated with gastrointestinal disturbance, which is decreased by taking tablets with food.

Antimalarial Chemoprophylaxis for HIV-Infected Travellers on ART

	Adverse effects	Protease inhibitors	NRTIs	NNRTIs	Integrase inhibitors
Mefloquine	Neuropsychiatric	Ritonavir levels reduced (+ other PIs)	No interactions expected	No data available Avoid EFV co-administration	No interactions expected
Atovaquone proguanil	Gastrointestinal	Atovaquone levels reduced by RTV, LPV, ATV	No interactions expected	Atovaquone levels reduced by EFV + NVP	No interactions expected
Doxycycline	Photo-sensitivity Gastrointestinal	No interactions expected	No interactions expected	No interactions expected	No interactions expected

www.hiv-druginteractions.org

Am J Med 2007; 120: 574-580

Lancet ID 2011; 11:541-56

Antimalarial Treatment for HIV-infected Travellers on ART

	Protease inhibitors	NRTIs	NNRTIs	Integrase Inhibitors
Quinine	Decrease quinine levels	No interactions expected	Decrease quinine levels	No interactions expected
Artemesinins	May increase artemisinin levels, but decrease levels of more active metabolite DHA	No interactions expected	Artemether levels decreased by EFV and NVP, but increased levels of more active metabolite DHA	No interactions expected
Lumefantrine	Lumefantrine levels increased	No interactions expected	Lumefantrine levels reduced by EFV and NVP	No interactions expected
Amodiaquine	No known interactions	Avoid AZT	Do not coadminister EFV increases Amodiaquine levels	No interactions expected

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Trends Parasitol 2008; 24(6):264-271

Lancet ID 2011; 11:541-56

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Reference: 1. Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. *Patient Preference and Adherence* 2012; 6:427-433.

[S4] Tribuss[®]. Reg. No: 44/20.2.8/0980. Each film coated tablet contains 300 mg tenofovir disoproxil fumarate, 200 mg emtricitabine and 600 mg efavirenz. For full prescribing information, refer to the package insert approved by the medicines regulatory authority. Applicant: Pharmacare Limited. Co. Reg. No.: 1898/000252/06. Building 12, Healthcare Park, Woodlands Drive, Woodmead 2191. Tel (011) 239 3400, Fax (011) 239 3438. A 19143 03/15.

A Guide to Antiretroviral Therapy in Adults

PRE-ART

Counselling checklist

- Understanding of HIV and transmission
- HIV incurable and ART lifelong
- Need for 100% adherence and risk of resistance
- Side effects (including IRIS) and how they will be managed
- Beneficial effects of ART
- Assess for depression and substance abuse
- Disclosure and treatment buddy
- Other adherence strategies
- Need for ongoing use of condoms

Criteria for ART

- ALL patients who are HIV-infected once they have had adequate counselling to prepare for lifelong ART with optimal adherence

OI prophylaxis

- Co-trimoxazole: CD4 < 200 or WHO Stage 3 or 4 condition
- INH: Assess for IPT - refer to Tuberculosis Preventive Therapy in guidelines (NB: Need to exclude active TB first)
- 2^o prophylaxis as required

ART

Switching to 2nd line

- VL > 1000 x 2
- Adequate adherence

2nd line combinations

If failed TDF, FTC or 3TC, NNRTI: AZT*, 3TC, boosted PI
 If failed AZT or d4T, 3TC, NNRTI: TDF, FTC, boosted PI
 * If AZT not tolerated, can consider TDF or ABC

VISIT
1

VISIT
2

VISIT
3

4/52
Creatinine
(if on TDF)
FBC (if on AZT)

8/52
Creatinine
(if on TDF)
FBC (if on AZT)

12/52
Creatinine
(if on TDF)
FBC (if on AZT)
Lipogram
(if on PI)
VL

6/12 then
6 monthly
Creatinine
(if on TDF)
FBC (if on AZT)
VL

Baseline evaluation

- CD4
- VL
- TB symptom screening
- FBC + diff
- PAP smear
- ALT
- Mantoux (Tuberculin skin test)
- Syphilis serology
- Serum creatinine + eGFR
- HepBsAg
- Pregnancy test
- Urine dipstix
- Serum cryptococcal antigen test if CD4 < 100

1st line combinations

1. **TDF**
 - ABC if eGFR < 50 or AZT
 2. **FTC or 3TC**
 3. **EFV**
 - Preferred agent if on TB meds
 - Caution if active psychiatric disease
 - Provided the baseline VL is < 100,000
- or **RPV**

Long term issues

- Prevention of transmission
- Family planning
- Cardiovascular risk factors
- Mental health issues
- PAP smear
- Monitor adherence (pharmacy refills)

ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral therapy
AZT	Zidovudine
CTMX	Co-trimoxazole
d4T	Stavudine
EFV	Efavirenz
FTC	Emtricitabine
INH	Isoniazid
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
KS	Kaposi's sarcoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
PI	Protease inhibitor
PML	Progressive multifocal leukoencephalopathy
RPV	Rilpivirine
TDF	Tenofovir

With severe opportunistic diseases

Generally wait 2 weeks after starting treatment for OI before initiating ART except PML, KS, cryptocosporidium, lymphoma (start earlier). Cryptococcal meningitis start after 4-6 weeks.

REMEMBER: Drug interactions are common with ART

Consider acute, chronic (e.g. antiepileptic drugs) and TB medication, OTC medication and "natural" remedies. Further information on drug interactions can be obtained from the package inserts, the South African Medicines Formulary, the National HIV Hotline (run by the Medicines Information Centre, phone 0800 212 506), by contacting an AFA pharmacist or from the following website: www.hiv-druginteractions.org



POSITIVE CONTRIBUTIONS

We began our clinical HIV research more than 30 years ago, in response to what we perceived as a potential epidemic – **our scientists were among the first to discover and develop medicines for the treatment of HIV**

POSITIVE ABOUT THE FUTURE

We believe that a future where **HIV/AIDS is a manageable chronic illness is closer**, in part, because of MSD's response to the crisis

POSITIVELY COMMITTED

We have never wavered in **our commitment to develop meaningful therapeutic options for people with HIV infection**

POSITIVELY COMMITTED TO A BETTER TOMORROW



Once Daily
STOCRIN®
(efavirenz)

A first generation NNRTI recommended for initial therapy, and is **regarded as the preferred NNRTI in South Africa**^{1,2}



ATRIPLA™
(efavirenz 600 mg/emtricitabine 200 mg/
tenofovir disoproxil fumarate 300 mg) Tablets

A fixed dose combination of TDF, FTC & EFV, with a once daily dosing³. The combination is a **preferred first line regimen** recommended by the **Southern African HIV Clinicians Society**¹



ISENTRESS®
raltegravir, MSD

A welcome addition to the ARV drug armamentarium due to its **good tolerability, low potential for drug–drug interactions and good clinical efficacy** in both treatment-naïve and -experienced patients^{1,4,5}

ARV = antiretroviral; EFV = efavirenz; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate

For full prescribing information refer to the package insert approved by the medicines regulatory authority.

REFERENCES: 1. Meinijnges G, Black J, Conradie F et al. Guidelines: Adult antiretroviral therapy guidelines 2014. Southern African HIV Clinicians Society. *S Afr J HIV Med*. 2014;15(4):121-143. 2. Rakhmanina NV, van den Anker JN. Efavirenz in the therapy of HIV infection. *Expert Opin Drug Metab Toxicol*. 2010;6(1):95-103. 3. ATRIPLA Package Insert, May 2015. 4. Sharma M, Wainwiler SL. Raltegravir as antiretroviral therapy in HIV/AIDS. *Expert Opin Pharmacother*. 2013;15(8):1-11. 5. ISENTRESS® Package Insert, March 2014.

SELECTED SAFETY INFORMATION: ATRIPLA is contra-indicated in patients with demonstrated hypersensitivity to any of the components of the product; in patients with moderate to severe renal impairment; during pregnancy. ATRIPLA should not be administered concurrently with voriconazole, amoxicillin, bepridil, cisapride, midazolam, piroxicam, triazolam or ergot derivatives. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued emtricitabine or tenofovir DF. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA. Mothers should be instructed not to breastfeed if they are receiving ATRIPLA. ISENTRESS is contra-indicated in patients who are hypersensitive to any component of this medicine. Immune and Reconstitution Syndrome: During the initial phase of treatment, patients responding to antiretroviral therapy such as ISENTRESS may develop an inflammatory response to incident or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis carinii* pneumonia, and tuberculosis, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment. Caution should be used when co-administering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g. rifampin) due to reduced plasma concentrations of raltegravir. ISENTRESS is contra-indicated in patients with clinically significant hypersensitivity to any of its components and in patients who are pregnant or lactating. STOCRIN should not be administered concurrently with dofetilide, astemizole, cisapride, midazolam, triazolam or ergot derivatives because competition for CYP2A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation or respiratory depression). Resistant virus emerges rapidly when NNRTIs are administered as monotherapy. Therefore, STOCRIN must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. Pregnancy should be avoided in women receiving STOCRIN.

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ATRIPLA®: Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (DF) which is equivalent to 245 mg of tenofovir disoproxil. Reg. No. 42/20.2.8/029.

STOCRIN®: Each tablet contains 50 mg, 200 mg or 600 mg of efavirenz. Reg. Nos: 50 mg – 46/20.2.8/0736, 200 mg – 46/20.2.8/0737, 600 mg – 37/20.2.8/0628. ISENTRESS®: Each chewable tablet contains either 25 mg or 100 mg of raltegravir. Each film-coated tablet contains 400 mg of raltegravir. Reg. Nos: 25 mg – 46/20.2.8/0863, 100 mg – 46/20.2.8/0864, 400 mg – 42/20.2.8/0867.

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Hospitalisation

The need for hospitalisation is dramatically reduced by the use of effective ART. The duration of hospitalisation can be shortened by the judicious use of step-down facilities and home nursing. Hospitalisation always requires reimbursement authorisation. Please refer to individual scheme rules for details regarding hospital case management. Hospitalisation is not covered for members of corporate programmes. Such patients should either contact their medical schemes or be referred to a state hospital.

Emergency Post-Exposure Prophylaxis (e.g. needlestick injury, rape)

Post-exposure prophylaxis (PEP) is indicated after exposure to HIV-infected body fluids (e.g. sexual intercourse or needlestick injury) and should commence as soon as possible. It is unclear whether delayed initiation of PEP is of benefit – animal models suggest that there is no benefit after 24 hours for percutaneous injury, but most guidelines allow use up to 72 hours after exposure. The duration of prophylactic treatment should be four weeks. Please contact AfA immediately for authorisation, but do not delay initiation of PEP. If exposure occurs on the weekend, please ensure your patient gets the necessary medication after exposure. You can then contact AfA, first thing on Monday morning, to complete the post-exposure prophylaxis (PEP) application to arrange reimbursement for further PEP medication.

PEP regimens are not well tolerated. Where PEP is felt to be justified, a 3-drug strategy is advocated for all percutaneous exposures, and a 2-drug strategy for mucocutaneous exposure. The standard dual NRTI combination has historically been AZT plus 3TC, but many experienced clinicians avoid AZT, as this causes nausea and headache in many patients, and use tenofovir instead. The third drug should be either a boosted PI, raltegravir, dolutegravir or efavirenz. Although there is less experience using raltegravir, there is good rationale for its use. The neuropsychiatric side effects of efavirenz make this drug less suitable, as stress related to possible HIV exposure is often considerable. Nevirapine should never be used for PEP as it has been associated with severe and fatal hepatotoxicity in this setting. There is no data supporting the use of rilpivirine in PEP.

ART regimens for PEP are suggested as follows:

1. Nucleos(t)ide backbone:

- a. Tenofovir and emtricitabine
- b. Stavudine and lamivudine
- c. Zidovudine and lamivudine

2. Third agents:

- a. Dolutegravir or Raltegravir
- b. Atazanavir/ritonavir
- c. Lopinavir/ritonavir
- d. Efavirenz

If the source patient is already on ART, an alternative combination should be considered if the patient is known to be failing therapy – specialist advice is recommended, but give first dose of standard PEP without delay.

Establishing that the exposed person is HIV-negative is critically important.

PEP should never be offered to known HIV-positive people as there is no benefit and it could result in the development of ART resistance, which will impair success of future regimens.

Recommendations for post exposure prophylaxis (PEP) after exposure to potentially infectious material (includes blood, CSF, semen, vaginal secretions and synovial/pleural/pericardial/peritoneal/amniotic fluid)

Exposure	HIV status of source patient	
	Positive or unknown*	Negative
Intact Skin	No PEP	No PEP
Mucosal splash or non-intact skin	2 or 3 Drugs**	No PEP
Percutaneous injury	3 Drugs	No PEP

* *If subsequent testing reveals the source to be HIV seronegative, PEP can be stopped, unless symptoms and signs suggestive of acute HIV seroconversion illness are present in the source patient at the time of injury. In the event of the source HIV status remaining unknown, the full 28-day course of PEP should be completed*

** *If the source patient is already on 2nd line therapy, increasing the risk of resistance to NRTIs*

Following sexual exposure remember to also prescribe emergency contraception if necessary. Following rape empiric treatment for sexually transmitted infections should be given (cefepodoxime 200 mg stat, azithromycin 1 g stat, metronidazole 2 g stat). Hepatitis B vaccination should also be offered if hepatitis B surface antigen and antibody is negative.

Follow-up Monitoring

HIV serology must be done in the laboratory for medico-legal reasons: necessary at the time of exposure to ascertain the patient's HIV status. Follow up HIV testing should be done six weeks and three months after exposure to determine whether the patient has become infected. Current laboratory antibody tests (ELISA) should be positive within three months.

NOTE: Tests for diagnosing HIV infection before the antibody becomes positive (e.g. PCR) should NOT be done unless there are features of seroconversion illness as these tests are too sensitive with most of the positive results being false positives. This causes unnecessary stress.

Baseline and follow up FBC and creatinine should be done if zidovudine or tenofovir respectively are selected. If a patient has been exposed to HIV, condoms should be used until the three-month HIV ELISA test is negative. Patients should be counselled regarding the need to complete the four-week course of prophylaxis, as side effects to treatment are common.

Pre-exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) involves the use of ART to prevent HIV infection. It should only be used as part of a package of HIV prevention services, and is intended for intermittent use during periods of perceived increased risk, rather than continuous treatment as is the case of ART. It is indicated for any HIV-seronegative person who is at perceived risk of acquiring HIV, and has been most extensively studied in MSM.

Baseline screening for HIV infection, renal function (creatinine clearance) and a pregnancy test for female users must be undertaken. Screening for STI is recommended and Hepatitis B vaccination should be offered to any person requesting PrEP, who is found to be Hepatitis B seronegative.

Daily oral tenofovir and emtricitabine combination is the regimen of choice for PrEP. It is contraindicated in those with abnormal renal function and any person presenting with an acute viral syndrome, until it is ensured that this is not an HIV seroconversion illness.

Follow-up visits should be 3-monthly, at which time the following screening should be undertaken; HIV, pregnancy and renal function re-testing, and repeat counselling for adherence and side effects. Six-monthly re-screening for STIs is recommended.

Pregnancy and Mother-to-Child Transmission Prophylaxis

HIV can be transmitted to the infant in utero, perinatally or by breastfeeding. Without intervention the risk of transmission is 20 – 40% but is dramatically reduced to <2% with antiretroviral therapy for mother and baby and with interventions to reduce the risk of HIV transmission through breastfeeding (see infant feeding section). AfA recommends triple antiretroviral therapy, which has the lowest risk of transmission, for all pregnant women. It is very important to achieve viral suppression before delivery and therefore every attempt should be made to maximize the duration of a suppressive ART regimen antenatally. Elective Caesarean section before the onset of labour also reduces the risk of HIV transmission, but provides no additional benefit if the viral load is <1000 copies/mL. Women becoming pregnant while taking antiretrovirals should continue with their drug regimen.

Viral load management is essential for a successful outcome for mother and infant. For mothers on ART for >6 months, confirm that the viral load is below detectable limits and then repeat 3 monthly during pregnancy. For any detectable viral load, confirm with 2nd assay and address adherence. A change to second-line ART is strongly recommended (refer to adult section on changing therapy) for pregnant women with confirmed virologic failure who have been on first-line ART for >6 months. For mothers in whom HIV is diagnosed during the pregnancy, see after a month to check adherence and exclude intolerance of medications. Viral load should be <1000 copies/mL by 3 months. If viral load is >1000 copies/mL at 3 months, step up adherence support and repeat viral load after a month. If still not <1000 copies/mL by 3 months seek advice from AfA.

A fixed dose combination comprising efavirenz, tenofovir and emtricitabine is commonly used as first-line ART in pregnancy. The South African package insert warns against using efavirenz in pregnancy, but the FDA and international guidelines state that its use may be considered after the first trimester. Recent studies have failed to show an increased risk of teratogenicity with efavirenz exposure in pregnancy, however, studies with larger sample sizes, especially with first trimester exposure, are required before it can be definitively shown that efavirenz is not teratogenic.

Public sector South African and WHO guidelines now recommend efavirenz even in the first trimester as the potential low risk of teratogenicity is thought to be outweighed by the harm caused by using nevirapine, which is more toxic. Nevirapine has a higher risk of hepatitis and rash in women with a CD4 count >250, so should be avoided in this setting.

A foetal ultrasound is recommended at 18 – 20 weeks gestation when there was efavirenz exposure in the first trimester.

Two 2nd generation NNRTIs, etravirine and rilpivirine, have been used in pregnancy but there is insufficient data to exclude teratogenicity. Rilpivirine should not be used if the baseline viral load is > 100,000. When HIV is diagnosed in the 3rd trimester, raltegravir (with 2 NRTIs) is increasingly used because of its rapid reduction in viral load.

Lopinavir/ritonavir is the best studied boosted PI in pregnancy, but boosted atazanavir is an alternative.

Zidovudine is the best studied NRTI in pregnancy. There are some concerns that tenofovir, which reduces bone mineral density to a small extent in adults, may affect skeletal development in exposed infants. Recent data from a cross-sectional study, showing reduced bone mineral content in newborn infants, reinforces this concern. Despite this, the use of a TDF, FTC and EFV combination tablet has become the standard of first line care even in pregnancy. Stavudine and didanosine should be avoided as the risk of hyperlactataemia is higher in pregnancy.

The pharmacokinetics of many drugs are altered in pregnancy. Studies have shown a significant reduction in the concentrations of lopinavir, but the standard doses achieve adequate concentrations and AfA does not recommend dose increases. Once daily lopinavir dosing should not be done in pregnancy. Similarly the concentrations of boosted atazanavir are somewhat reduced, but no dose adjustment is recommended. Efavirenz concentrations are mildly reduced – no dose adjustment is recommended.

CD4 counts are about 25% lower in pregnancy due to dilution, falling to a nadir at the end of the first trimester. The CD4 percentage remains unchanged. The CD4 count rises to pre-pregnant levels three months after delivery. If the count is less than 200, daily co-trimoxazole should be given as primary prophylaxis. Women requiring co-trimoxazole should receive folate supplements as trimethoprim is linked to neural tube defects.

ART in Pregnancy

- All women now qualify for ongoing ART regardless of WHO stage or CD4 count. If the woman has WHO stage 1 or 2 and a CD4 count >350, it is reasonable to delay starting ART until the beginning of the second trimester
- ART-naïve women who present in labour should be given nevirapine 200 mg stat and a single dose of TDF combined with FTC to reduce the risk of NNRTI resistance

Antiretroviral Therapy for Infants to Prevent MTCT

Increased Risk for Transmission

A “one size fits all” approach to infant prevention is inappropriate. There are clearly infants at higher risk of perinatal transmission. In these cases expanded prevention is indicated. Where breastfeeding is practiced, additional measures should be considered.

A PCR at birth is now standard practice. For non-breastfed infants or where mothers commenced ART late in pregnancy or with detectable viral loads on 2 or more occasions antenatally, we recommend an additional PCR at 4 months of age as ART may complicate identifying infected infants with current PCR assays. Clinicians managing HIV-infected pregnant women and their infants should consider the following:

- First, is the mother’s viral load fully suppressed? Viral load remains the primary driver of transmission. Duration on effective ART and adherence to therapy must be addressed in pregnancy
- Second, is there a risk for resistance in the mother? Mothers on ART for >6 months whose viral loads are not suppressed may have drug resistance. In these mothers all attempts should be made to achieve suppression and a resistance test should be considered

Neonatal post-exposure prophylaxis in situations where there is a high risk of transmission

Situation	Mother	Exposed Neonate
Viral load detectable (> 400) between 28 – 40 weeks gestation	Check adherence and repeat viral load Consider drug resistance assay if on ART >6 months and VL > 1000	Initiate AZT, 3TC and nevirapine (we recommend nevirapine twice daily at therapeutic doses) for 4 weeks as soon as possible after birth
ART initiated during pregnancy and <12 weeks before delivery (late presentation)	Consider raltegravir (twice daily) with 2 NRTIs	
Defaulted ART for at least one month at any stage during pregnancy	Resume or change therapy	
Mothers diagnosed with TB during pregnancy	Do not delay TB treatment	
Failure of 1 st or 2 nd line ART is identified after the 2 nd trimester	Change therapy or consider resistance testing Improve adherence	
		AZT, 3TC and NVP may still be beneficial Consult AfA if a resistance test indicates alternative therapy is required

Minimal Risk for Transmission

If the maternal viral load is suppressed between 28 – 40 weeks and adherence is confirmed, we recommend AZT or NVP for 6 weeks. If there is uncertainty triple therapy is preferable (see above).

Breastfeeding should only be considered for mothers with full virological suppression. Breastfed infants should receive daily NVP for the duration of breastfeeding and until the infant is fully weaned for 2 weeks.

Neonatal post-exposure prophylaxis in situations where there is a minimal risk for transmission

Neonatal AZT dose	
AZT Oral	<ul style="list-style-type: none"> • 35 weeks to Term: 4 mg/kg 12 hourly for 6 weeks • 30 – 35 weeks: Birth to 2 weeks 2 mg/kg 12 hourly then 3 mg/kg 12 hourly for 4 weeks • <30 weeks: Birth to 4 weeks 2 mg/kg 12 hourly; then 3mg/kg 12 hourly for 2 weeks
AZT IVI (If infant nil per mouth)	<ul style="list-style-type: none"> • Preterm 1.5 mg/kg 12 hourly • Term 1.5 mg/kg 6 hourly

Women who elect to breastfeed should be counselled to exclusively breastfeed without addition of water, formula milk, juices, cereals or solids for the first 4 to 6 months. Weaning should be gradual. Abrupt weaning causes engorgement and increases transmission. As transmission is more associated with solids, wean to replacement milk first (see infant feeding section for further information).

NVP Infant Dosing Guide for prophylaxis during breastfeeding

Birth Weight	Age	Dose	Volume
<2.0kg	Birth to 2 weeks 2 to 6 weeks	2mg/kg 4mg/kg	0,2 ml/kg 0,4 ml/kg
2.0 – 2.5kg	Birth to 6 weeks	10mg	1ml
>2.5kg	Birth to 6 weeks	15mg	1.5ml
N/A	4 weeks to 6 months	20 mg/d	2 ml
N/A	6 months to 9 months	30 mg/d	3 ml
N/A	9 months to end breastfeeding	40 mg/d	4 ml

Diagnosis of HIV in Infancy

The diagnosis of HIV in an infant is done by a qualitative PCR. The first PCR should be done on day one of life and repeated at 4 months especially where there has been sub-optimal antenatal ART. Note: never request the PCR on cord blood as this may give a false positive result. The HIV ELISA may be positive for up to 18 months because of maternal antibodies.

A resistance test should be done on children under 2 years of age who become HIV-infected, regardless of the kind of PMTCT given (requires pre-approval by AfA). For breastfed infants, perform the PCR every three months and also if infants develop symptoms. The last PCR should be done 12 weeks after fully weaned.

Family Planning

HIV infection reduces fertility and ill patients often have reduced libido. However, both libido and fertility improve with effective ART. Patients often initially decide not to have children, but change their mind as they recover on ART. Contraception and family planning are important components of care, which should be discussed with all women, both at initial and follow-up visits. The negative view of HIV-infected women having children is untenable, given the good results of regimens to prevent mother-to-child transmission and the good long-term survival on ART. The main aim of ART is to improve the quality of life of individuals, and having children is a very important component of quality of life for most people.

Drug interactions with ART are important considerations with hormonal contraception. Sterilisation should be offered to those who have completed their families.

Contraception

- **Barrier method.** There are compelling reasons to always recommend barrier methods together with other contraceptive measures as this will reduce the risk of transmission of HIV, the acquisition of super-infection with ART-resistant HIV, and infection with other pathogens (notably herpes simplex). However, the contraceptive efficacy of barrier methods is sub-optimal, with annual failure rates of approximately 5%. Thus, additional contraception methods should always be taken
- **Intrauterine devices.** Early fears that these would be associated with increased risk of infection in HIV-seropositive women have not been confirmed in prospective studies. The progestogen-eluting devices are effective when used with enzyme-inducing drugs as they have a local action. Thus, these should be effective when used with ART
- **Hormonal contraception.** There are important drug interactions with some ART (notably the protease inhibitors and the NNRTIs) and hormonal contraception, resulting in alteration in the hormone concentrations. There is limited data on the contraceptive efficacy of hormonal agents when coadministered with ART, but depot progestogen preparations are not significantly affected

by drug interactions (see table for recommendations). The combined oral contraceptive pill (COCP) may be less effective when coadministered with nevirapine or a ritonavir-boosted PI (both of which induce the metabolism of oestrogen and, to a lesser extent, progesterone), but provided that high dose oestrogen formulations are used, these should be effective – another method (e.g. barrier) should be used in conjunction. Low dose COCP should be used with efavirenz, as this inhibits the metabolism of oestrogen. There is insufficient data on progestogen-only pills and on patches to make a recommendation. New evidence has found that efavirenz, together with other enzyme inducing drugs, can interfere with the action and effectiveness of progestin subdermal implants and they should therefore not be used

ART	Recommendation
Ritonavir-boosted PI	COCP not recommended*. Depot progestogens
Efavirenz	COCP or depot progestogens other than progestin subdermal implants
Nevirapine	COCP not recommended*. Depot progestogens

* *High dose COCP may be adequate, but should be used in conjunction with another method.
COCP = combined oral contraceptive pill.*

Management of HIV infection in Children



HIV infection in children is preventable through highly effective strategies for PMTCT.

There are key diagnostic, clinical, immunological, virological and therapeutic differences between HIV infected children and adults:

- Diagnosis in infants is complicated by transplacental crossing of maternal HIV antibodies
- Disease follows a more rapid course than in adults due to an immature immunological system. In the absence of antiretroviral therapy, more than 50% of HIV-infected children die by two years of age. The risk of death and disease progression is highest in the first few months of life. Nevertheless, a small but significant minority present late and even in adolescence. The developing brain is especially vulnerable to HIV
- The interpretation of CD4 counts and percentage alters with the age of the infant. The younger the child, the higher the CD4 at which morbidity and mortality occur
- Young infants often have higher viral loads
- Using NNRTIs for PMTCT causes resistance in infected infants. Therefore protease inhibitors are the mainstay of initial therapy in young children. There are fewer therapeutic options for children

The emphasis is on prevention, early establishment of HIV status immediately after birth, early institution of antiretroviral therapy and co-trimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) and bacterial infections.

Routes of Infection

- Mother-to-child transmission – this is by far the most important route, accounting for 95% of paediatric HIV. Breastfeeding contributes up to 44% where prolonged breastfeeding is practiced in the absence of antiretroviral therapy to either the mother or the infant or poor adherence
- Sexual abuse
- Blood product transfusion – this route is now extremely rare but is possible where a donor donated blood in the window period
- Unexplained – in a small number of children, no obvious cause is found. Investigations of such children suggest the following possible causes:
 - Not the genetic offspring of the parents
 - In healthcare facilities: Use of contaminated equipment such as disposable razor blades or breast milk pumps, poorly labelled expressed breast milk given to the wrong infant
 - Surrogate breastfeeding
 - Premastication of food by an HIV infected adult or older child given to a toddler being weaned onto solid foods
 - Household transmission – shared toothbrushes or shaving equipment
 - Scarification and traditional circumcision
 - Covert sexual abuse may be subtle and difficult to confirm

Diagnosis of HIV in Infants and Children

Passively acquired maternal antibodies persist for up to 18 months. Detection of HIV antibodies in children only confirms infection after 18 months of age. In reality, antibodies detected after the first year of life are highly predictive of HIV infection but are not conclusive.

To determine the infection status of an HIV-exposed infant before 18 months of age, the qualitative polymerase chain reaction (PCR) test for HIV specific DNA/RNA must be performed. This can already detect in utero and early intrapartum HIV infection in 70% of newborn infants on day one of life and up to 90% by two weeks of age. A quantitative HIV RNA (viral load) assay should be done to confirm a positive qualitative HIV DNA/RNA PCR.

A more aggressive testing strategy is indicated where there is an increased risk of in utero and intrapartum infection; for instance, late antenatal diagnosis and/or short durations of triple ART or zidovudine (AZT). Premature infants therefore are at highest risk for transmission. We recommend a PCR on day one of life for any infant at high risk of infection.

It is already becoming apparent that antenatal and post partum antiretroviral drugs may influence the early detection of HIV DNA or RNA. All infants require a minimum of two PCR tests prior to declaring them uninfected or infected. For formula fed infants, the 2nd PCR should be done at 4 months of age and in breastfed infants 12 weeks after cessation of breastfeeding.

The following strategy should be adopted for infant diagnosis where the HIV exposure status is known:

- In neonates where mothers have been on adequate antenatal ART prophylaxis (≥ 20 weeks of ART or AZT where antenatal viral load $\leq 1\ 000$):
 - A HIV DNA/RNA PCR should be performed at 4-6 weeks of age **and**
 - If negative, repeat at 4 months
 - If **positive**, confirm with a viral load (which, if detectable, will confirm HIV infection), full blood count, ALT and CD4 count. Also request a resistance test for the baby (requires preapproval by AfA)
 - If the infant is breastfed, further testing is required
- Where antenatal ART administration has been inadequate:
 - Counsel in pregnancy, delivery and immediately post partum on risk of vertical transmission and need for intensive early testing and prophylaxis (which may convert to treatment)
 - Perform the first HIV-PCR on day one and store a sample in case needed to confirm a positive test
 - Commence triple ART post exposure prophylaxis as soon as possible on day one of life, preferably within 6 to 12 hours of birth
 - If HIV PCR is negative, repeat at 4-6 weeks and then at four months of age to exclude either laboratory errors or prolonged incubation
 - If any test is positive
 - Do a baseline viral load to confirm HIV infection
 - Prepare for rapid initiation of ART – full blood count, ALT and CD4 count
 - Also request a resistance test for the baby (requires pre-approval by AfA)
 - If the child is on triple prevention, urgently consult an expert as the patient may already be on effective therapy. An expert should also be consulted if the child is on monotherapy
- For breastfed infants with initial negative PCR – repeat qualitative HIV DNA/RNA PCR 3 monthly during breastfeeding and 12 weeks after the infant has been fully weaned. If older than 18 months of age, an antibody test is adequate

HIV testing should be done on any symptomatic infant at any age regardless of algorithms should HIV infection be suspected.

The following strategy should be adopted for infant diagnosis where HIV exposure status is not known during the antenatal and immediate post partum period:

- In newborn infants, first screen the mother for HIV antibodies

Screen all children with HIV antibody test – if the screening is positive:

- **In children >18 months:**
 - Viral load can be performed as a confirmatory test
- **In children <18 months:**
 - A qualitative HIV DNA/RNA PCR should be done and if positive, confirm with a viral load test

Take note that a negative antibody test in a child does not exclude maternal HIV and potential exposure in the breastfeeding infant.

Resistance Testing Prior to Initiation of Therapy

Antiretroviral resistance testing by genotyping is indicated in the infant prior to starting ART for the following situations:

- < 2 years of age and exposed to ART for PMTCT
- Infected during breastfeeding
 - When the mother is on antiretroviral therapy
 - When infant is receiving prophylactic nevirapine (NVP)

Note: Resistance tests only detect the majority of mutations and may not reflect prior regimens. Interpretation includes assessment of the full drug exposure history of the mother and infant.

The resistance test must be preapproved by AfA.

NB: The child must be registered with the medical scheme before AfA can authorise any investigations.

Management of HIV-Exposed Infants

Commence co-trimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) at four to six weeks of age on all exposed infants. Prophylaxis should be continued for the duration of breastfeeding exposure AND until HIV infection is excluded completely. As PJP can occur in HIV-exposed uninfected infants in the first 6 months of life, we recommend continuing PJP prophylaxis until the infant is thriving and the HIV status is confirmed negative.

Feeding HIV-exposed Infant

With increased evidence, views have changed on the feeding of infants in low-resource families with poor access to clean water and ability to sterilise bottles, as well as where there are social pressures to breastfeed. This is particularly important where disclosure has not occurred.

What we now know:

- The risk of transmission relates to the levels of HIV in breast milk. Higher maternal plasma viral load, lower CD4 count, lower maternal vitamin A, infrequent emptying and mastitis are also risk factors
- Although the majority of transmission occurs early in breastfeeding, the risk is cumulative
- Where breastfed infants are exposed to mixed feeding in the first 2 months of life, the risk of transmission increases. Mixed feeding with solids has a 2,9 fold increase in transmission risk in the first 6 months of life
- The viral load in breast milk increases during weaning with a potential increase in the risk of transmission in this time, especially when the weaning is accelerated
- Several studies in low resource settings showed that infants who receive replacement feeding or cease breastfeeding early are at high risk of malnutrition and non-HIV related morbidity and mortality due to infections

Can Breastfeeding be Made Safer?

Giving either the mother combination antiretroviral therapy or individual antiretroviral drugs to the infant reduces the risk of HIV transmission.

Infant nevirapine (NVP) is a safe and cost effective public health intervention. This strategy, now also used in the South African public sector, advises once daily NVP for the first 6 weeks of life in all infants and for 12 weeks where there are antenatal risk factors. Women are now initiating life-long ART from diagnosis in pregnancy, regardless of health status or CD4 count. If the breastfeeding mother has an undetectable viral load, transmission should not be occurring. However, women who wish to continue giving nevirapine prophylaxis may do so for the duration of breastfeeding. Dosages for preterm and low

birth weight infants should follow the recommendations from the public sector (see PMTCT section).

For breastfeeding mothers, early diagnostic testing is still recommended. Where the 6-week PCR is negative, breastfeeding is encouraged for the first year of life, followed by weaning and retesting 12 weeks after the last breastfeed.

Breastfeeding should be exclusive until 6 months of age, after which supplemental feeding, including solids should be commenced.

Co-trimoxazole should continue throughout breastfeeding regardless of the results of the early HIV PCR and only discontinued after complete weaning and a negative follow-up test.

Although this strategy is attractive in low resource settings where the morbidity and mortality associated with replacement feeding is very high, HIV transmission still occurs rarely. With extended NVP and maternal ART breastfeeding-associated transmission between 6 weeks and 6 months was 2,6% and 1,1% respectively in one large study.

These strategies do not consider maternal viral suppression or prior failure of maternal therapy. In addition, children who seroconvert while breastfeeding and taking extended NVP will not only have NVP and efavirenz (EFV) resistance, but may also develop mutations to second generation NNRTIs such as rilpivirine (RPV) and etravirine (ETR).

For mothers on ART, babies are exposed to low levels of ART secreted in the milk, possibly contributing to resistance if they become HIV-infected. This resistance will limit therapeutic options for the infants. Also, the long-term implications of prolonged ART exposure over months through breast milk are unknown.

In the public sector in South Africa, free formula has been phased out and all HIV-infected women are advised to breastfeed.

Despite the reduced risk, breastfeeding remains a potential (but diminishing) source of postnatal HIV infection. Mothers choosing to breastfeed should be very carefully counselled. An intervention strategy should be developed for the mother if on ART, and regular viral load assessment throughout breastfeeding should be performed.

Indications for Co-trimoxazole Prophylaxis

	Start	Stop
Exposed formula fed	4 – 6 weeks	PCR negative ≥6 weeks after weaning and clinically uninfected
Exposed breastfed	4 – 6 weeks	PCR negative ≥6 weeks after weaning and clinically uninfected
HIV infected <12 months	4 – 6 weeks	Provide regardless of CD4
HIV infected 1 – 5 yrs	Clinical stage II/III/IV CD4 <15% or <500	Continue until no longer clinically indicated
HIV infected >5yrs	Clinical stage II/III/IV CD4 <15% or <200	Continue until no longer clinically indicated

Recommended daily dose	Suspension (200 mg/40 mg per 5 ml)	Single-strength adult tablet (400 mg/80 mg)	Double-strength adult tablet (800 mg/160 mg)
<6 months 100 mg sulfamethoxazole/ 20 mg trimethoprim	2,5 ml	¼ tablet, possibly mixed with feeding	–
6 months – 5 years 200 mg sulfamethoxazole/ 40 mg trimethoprim	5 ml	½ tablet	–
6 – 14 years 400 mg sulfamethoxazole/ 80 mg trimethoprim	10 ml	1 tablet	½ tablet

Commence an appropriate multivitamin preparation daily.

Clinical Grounds to Suspect HIV Infection

Although the majority of HIV-infected children will be detected through mother-to-child transmission prevention programmes, many older children are still diagnosed with HIV. All children of a newly diagnosed mother should be tested for HIV regardless of their age and the presence of symptoms.

Clinicians should maintain a low threshold for testing and should suspect HIV in the following circumstances:

- Failure to thrive
- Recurrent or chronic diarrhoea
- Infection with unusual organisms
- Recurrent oral candidiasis
- Recurrent infections
- Recurrent pneumonia
- Tuberculosis
- Unexplained anaemia or thrombocytopenia
- Generalised lymphadenopathy, hepatomegaly, splenomegaly and hepatosplenomegaly
- Severe herpes simplex stomatitis, varicella zoster or chicken pox
- Unexplained neurodevelopmental delay
- Cardiomyopathy
- Nephropathy
- Malignancies
- Bronchiectasis
- Severe pneumonitis in the first year of life
- Invasive bacterial disease such as arthritis, osteitis, mastoiditis
- Unexplained arthropathy
- Enlarged parotids or digital clubbing (older child)
- Severe dermatitis
- Recto-vaginal and peri-anal fistulae
- Chronic otorrhoea

Classification

Table 1: WHO clinical staging of HIV for infants and children with established HIV infection

Clinical stage 1
Asymptomatic Persistent generalised lymphadenopathy
Clinical stage 2 ⁽ⁱ⁾
Unexplained persistent hepatosplenomegaly Oral candidiasis beyond neonatal age (persistent or recurrent) Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Fungal nail infections
Clinical stage 3 ⁽ⁱ⁾
Unexplained moderate malnutrition, not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one month) Persistent oral candidiasis (after first six weeks of life) Oral hairy leukoplakia Acute necrotising ulcerative gingivitis/periodontitis Lymph node TB Pulmonary TB Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease including bronchiectasis Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.50 x 10 ⁹ /L ³) or chronic thrombocytopaenia (<0.50 x 10 ⁹ /L ³)

Clinical stage 4^{(i) (ii)}

Unexplained severe wasting, stunting or severe malnutrition, not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration, or visceral at any site)
Extrapulmonary TB
Kaposi's sarcoma
Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy
Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over one month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated non-tuberculous mycobacteria infection
Cerebral or B cell non-Hodgkin's lymphoma
Progressive multifocal leukoencephalopathy
HIV-associated cardiomyopathy or nephropathy

- (i) *Unexplained refers to where the condition is not explained by other causes.*
- (ii) *Some additional specific conditions can be included in regional classifications (e.g. Penicilliosis in Asia, HIV-associated rectovaginal fistula in Africa).*

Immunological Classification

Because there is a gradual decline in CD4 cell numbers up to five years of age whilst CD4 cell percentages remains constant, CD4% is used to simplify matters. However clinicians should remember that CD4 percentage is influenced by the total lymphocyte count which may lead to a false impression. Be sure to exclude lymphopaenia, which may give a falsely elevated percentage but low absolute CD4 count.

Always note percentage and absolute numbers as well as the CD4/CD8 ratio to gain a full appreciation of immunological status. CD8 cells may be elevated in response to HIV and a low CD4 cell percentage may give a false impression of immune suppression. After five years of age, one can use the CD4 count instead of percentage. The immunological indications for ART in children above 12 months of age are shown in the table on the next page.

Revised CDC Immunological Classification (2014) based on CD4 count or percentage

	Age					
	<1 year		1-5 years		≥6 years	
Stage*	Cells/ μ l	%	Cells/ μ l	%	Cells/ μ l	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

* The stage is based primarily on the CD4 count

The Management of a Newly Diagnosed Child

HIV Infection is a Disease of the Family

ART should be initiated as soon as possible, preferably on day of diagnosis. Counselling on adherence must continue after therapy has been initiated.

Important points when counselling parents of HIV-infected children:

- Survival of infected and uninfected children is intimately linked with health of the parents. Every effort should be made to screen and counsel family members and refer for appropriate therapy. This includes fathers and older siblings who may be untested
- Disclosure should be extended to other significant family members like parental siblings and grandparents
- Be hopeful. HIV is a chronic disease with many opportunities for positive intervention
- Encourage economic advancement
- Discuss the routes of acquisition of HIV in children
- Discuss infant feeding. Breastfeeding in an already infected infant should continue. Lactation can also be re-initiated in an infected infant
- The parents should contemplate the need for planning for the child in the event of advanced disease in the parent

- **Adherence to all medical interventions including ART, co-trimoxazole, immunisations, TB treatment, etc. MUST BE METICULOUS**
- Always consider TB

History

- Carefully note details of maternal and infant ART use, including drugs and duration
- Also note feeding choices for neonates and infants

Clinical Assessment

- Record the child's weight, height and head circumference. All these values should be noted on the appropriate centile charts. In children >3 years, head circumference does not have to be recorded at follow-up visits
- Check the perinatal details, including maternal syphilis results and previous weights on the "Road to Health" card. Also check mother's Hepatitis B status
- Check the immunisation status on the "Road to Health" card
- Check for generalised lymphadenopathy, hepatosplenomegaly, parotid enlargement, digital clubbing or oral thrush
- Check dental hygiene and refer to dentist if necessary
- Actively exclude tuberculosis (TB) in family members. Always inquire about the possibility of TB or coughing and weight loss in family members or friends. If a family member has active tuberculosis, the child should be fully investigated for TB, with chest x-ray, gastric washing (or induced sputum) etc. If negative, tuberculosis prophylaxis should be given. If positive, the child should be referred to a TB clinic for treatment. The Mantoux skin test is the preferred test in HIV infected-children. Induration of ≥ 5 mm is considered positive. Interferon gamma release assays (IGRAs) are gaining in popularity. The 2 tests are equivalent. Positive skin tests and IGRAs indicate TB infection rather than disease and negative tests cannot exclude infection. For positive skin tests and IGRAs without TB-disease, give INH 10 – 15 mg/kg daily for six months
- **The possibility of TB infection should be reassessed with ANY new TB source case and if disease is excluded INH preventative therapy should be provided**

Baseline Investigations

- Hepatitis B serology, even if partially or fully immunised. If surface antigen positive, check mother. If surface antibody negative and not fully immunised (6, 10, 14 weeks and 18 months), complete the series and then check antibody levels after 1 month. If fully vaccinated and antibody negative revaccinate and consider an increase in the dose
- Mantoux or IGRA
- Chest radiograph – this is extremely valuable as many children develop chronic lung disease or TB
- Full blood count and differential
- ALT
- CD4 count
- Urinalysis (dipstick)
- Viral load should be done in all children to confirm diagnosis before starting treatment
- Consider retesting for syphilis – only necessary if mother’s status during pregnancy is uncertain
- Stool for microscopy, culture and sensitivity, and parasites if diarrhoea is present
- Gastric aspirates – daily x 2 or induced sputum x 2 where TB is suspected
- Baseline electrolytes, urea and creatinine and non-fasting lipid profile (fasting profile only if non-fasting values abnormal)

Immunisations

There is increasing evidence on the lack of appropriate responses to vaccinations in infants and children prior to ART and after initiation of therapy; this leads to morbidity and mortality from vaccine preventable illness.

Guidelines from developed countries increasingly suggest that clinicians use vaccine specific antibody levels to guide actions; however this may not be practical. For Hepatitis B, we should measure HBV surface antibodies to confirm seroconversion and if absent or low, to repeat vaccination. In general all childhood vaccinations should be given. Revaccination is not universally recommended but there is increasing evidence that it should be considered. We recommend repeating the MMR in childhood e.g. >5 years of age. HPV vaccination is being rolled out by the National Department of Health and is recommended. Influenza vaccination should be given annually from 6 months of age during flu season despite concern regarding its efficacy. Where children have missed vaccinations a full catch up schedule should be given, the exception is rotavirus vaccine. BCG vaccination is contraindicated in children with confirmed HIV infection. However most infants will receive this vaccine prior to the availability of test results and there is no guidance on the actions to be taken in children who did not receive this vaccine.

Note that vaccinations may cause transient increases in viral load. This should be kept in mind when planning these investigations and interpreting the results.

Age of Child	South African EPI schedule	Private sector	Suggested Addition
At birth	OPV (0) BCG	OPV (0) BCG	
6 weeks	OPV (1) RV (1) PCV (1) DTaP-IPV-Hib—HBV (1)	OPV (1) RV (1) PCV (1) DTaP-IPV-Hib—HBV (1)	
10 weeks	DTaP-IPV-Hib—HBV (2)	RV (2) PCV (2) DTaP-IPV-Hib—HBV (2)	
14 weeks	RV (2) PCV (2) DTaP-IPV-Hib—HBV (3)	RV (3) PCV (3) DTaP-IPV-Hib—HBV (3)	
6 months	Measles* (1)		Flu vaccine given after 6 months in the first flu season followed by a second vaccination 1 month later and then annually
9 months	PCV (3)	MMR (1) MCV (1)	
12 - 15 months	Measles (2) at 12 months	PCV (4) MMR (2) Varicella (1) Hep A (repeat 6 months later) MCV (2)	
18 months	DTaP-IPV-Hib—HBV (4)	DTaP-IPV-Hib—HBV (4)	
5-6 years	Td vaccine (6 years)	DTaP or Tdap-IPV MMR (3) Varicella (2)	
9 years (girls and desirable in boys)	HPV	HPV	HPV vaccine 3 doses – Month 0, 2 and 6
12 years	Td vaccine	Tdap-IPV	

* MeasBio® (Biovac) should not be given at the same time as any other vaccine AND there should be a 4 week interval between receiving MeasBio® and any other vaccine

Routine Medication

- Parasite infestations: mebendazole or albendazole every six months (start from 12 months)
 - Mebendazole: 100 mg twice daily for three days (100 mg = 5 ml or one tablet) or 500 mg stat if over five years of age
 - Albendazole: if under 10 kg, 200 mg stat (suspension 20 mg/ml). If over 10 kg, give 400 mg stat (tablets 200 mg)
- **PCP prophylaxis: This should continue in childhood until no longer indicated**

Dapsone can be used for adverse events thought to be due to co-trimoxazole, but is inferior to co-trimoxazole and should not be used in the absence of a specific indication. The dose is 2 mg/kg daily or 4 mg/kg/week. Co-trimoxazole may be of benefit to children with recurrent bacterial infections.

Nutritional Support

- A balanced diet should be given. Advice from a dietician should be sought if dietary problems or inadequate intake is suspected. Children with chronic lung disease require additional nutrition
- Multivitamins (vitamin A 3 000*iu* per day)
- Iron should be given only if iron deficiency is suspected
- Folic acid – 2,5 mg daily may benefit symptomatic children

(Note: there are no data to support giving anabolic steroids)

Dietetic advice must also be sought for children with hypercholesterolaemia secondary to protease inhibitors.

Follow-Up

All HIV-exposed infants should be seen at four – six weeks of age. Thereafter, patients should be seen every three – six months. The patient should be seen at monthly intervals on initiation of ART or if there is a change of clinical importance.

Monitoring

Clinical Monitoring, Height, Weight and Head Circumference

The clinical progress of children both on and off ART should be monitored carefully.

Growth: The “Road to Health” chart is a valuable tool for monitoring wellbeing. Failure to gain weight is common among untreated HIV infected children and may indicate an opportunistic infection such as TB or a poor response to ART. Stunting (height for age <-2 Z-score) is common among HIV infected children and may not correct when ART is started. Children who initiate ART may also gain too much fat and have a very high BMI often due to very unhealthy diets. Long term cardiac health outcome is not known, but a healthy lifestyle must be encouraged. Nutritional assessment and advice is an essential component of the chronic care of HIV infected children and referral to a dietician may be needed.

Neurocognitive: The neurotropic nature of HIV makes assessment of both children on and off ART essential. This is especially so for children not on ART, however it has become clear that slower progressors and children on ART may also experience cognitive problems. There is a higher risk of school failure and ADD/ADHD. Children failing ART may also experience cognitive decline. Although school performance and behaviour is a complex interplay between intellect and the environment, clinicians should always consider the role of HIV. Early recognition and early referral where needed may change the outcomes of these children. Interventions include cognitive and hearing assessment, assessment for ADD/ADHD and if established encephalopathy, mobility support. The help of a developmental paediatrician should be sought where needed.

Head circumference: This should be measured and plotted on a growth chart in the first 3 years of life as it reflects brain growth. Flattening of the curve is highly suggestive of encephalopathy.

Lung health: Lung health in HIV infected children is still poorly understood for both children with access to early ART and for those with delayed therapy. With increasing access to ART in younger children LIP is now rare. Later progressing older children and adolescents with delayed access to ART often present with complex severe chronic lung disease previously unrecognised. These children often experience progressive respiratory failure despite ART. Careful clinical assessment of pulmonary disease is essential in all children with HIV.

Psychiatric illness: With use of ART the general health of HIV infected children have improved dramatically. However, as the paediatric population ages into adolescence there is an increasing risk for depression and other psychiatric disorders. This is in part due to the nature of the HIV infection, but also because older children and adolescents may struggle with transitioning to adulthood whilst chronically ill, adaptation and coping skills may be poor. Clinicians should look for these problems and intervene early.

CD4 Lymphocytes

CD4 counts are much higher in infancy than in adults but the percentage remains constant. Absolute CD4 counts are useful for monitoring response to antiretrovirals and are a better indicator of immunological reserve than CD4%.

Children >2 years of age and not on ART should have their CD4 count checked every three to six months.

Viral Load

Levels in infants are far higher in the first year of life than in adults and decline to adult values by two to three years of age. By two months of age most infected infants have viral loads above 100 000, ranging from undetectable to 10 million. Levels >299 000 correlate with rapid disease progression and death in infants below one year of age. Viral loads are useful to monitor adherence to antiretrovirals.

Initiation Criteria for ART

AfA updated its criteria for when to initiate ART in August 2015 in light of data from two major randomised controlled trials. **ALL children who are HIV-infected would qualify to start provided carers have had adequate counselling to prepare for lifelong ART with optimal adherence.** For children 3-5 years of age (or older) in clinical stage 1 or 2 without immune suppression in whom there are concerns about the ability to adhere or where there are significant social problems it may still be better to address these issues prior to initiating therapy whilst carefully monitoring the child.

For long-term non-progressor children with CD4 counts well within normal range and viral load < 1000 copies/mL, ART may be withheld provided 3 to 6 monthly follow-up is undertaken, all immunisations are up to date and CD4 and viral loads repeated every 6 months. Annual neurodevelopmental assessment is also recommended.

Viral load for monitoring ART

Although excellent and sustained clinical and immunological responses are seen in the absence of fully suppressed viral loads, there is growing concern that these infants and children are at high risk to accumulate resistance mutations. Initial virological response may be slower than in adults (8 – 12 weeks), especially if the initial viral load is >1 million.

The overall aim of treatment is to reduce the viral load to levels below the lowest detection threshold (<50) rapidly and to maintain undetectable levels throughout life. Suppression to an undetectable viral load occurs in more than 70% of children. A baseline value followed by a second value at three months, and thereafter six monthly is a reasonable approach.

Which ART Regimen to Start

There is clear evidence that children who failed NVP-based PMTCT should receive a boosted protease inhibitor. Integrase inhibitors are now available with dosage and formulations for children, including infants from a month of age. A randomised study recently found that boosted protease inhibitors are superior in infants both with or without PMTCT exposure to NNRTIs. For older children one randomised study showed no difference between NNRTIs and boosted PIs. For NRTIs, abacavir (ABC) combined with 3TC has a favourable toxicity profile and in one study was superior to AZT + 3TC. A trial conducted at Rahima Moosa Mother and Child Hospital released in 2014 supports switching children who received single dose nevirapine for PMTCT and then LPV/r-containing ART in the first 3 years of life to efavirenz-based ART at the age of 3 years. This strategy can be implemented if good virological control was shown in the first 3 years of life and if viral load testing is repeated within 6 to 8 weeks of the switch.

Stavudine (d4T) is no longer recommended. ABC is associated with a rare but serious hypersensitivity reaction. The majority of the risk is related to HLA-B*5701 genotype. Testing can be performed to exclude patients with this genotype from initiating ABC. The risk in African children is thought to be low.

Discussion with the family about which antiretroviral drugs to start should include consideration of the taste and volume of syrups, pill size and numbers, crushability, storage and food requirements, and number of times a day drugs must be taken. It is good practice to show the family the medicines at an early stage. Details of early (e.g. nausea, vomiting, diarrhoea) and late side effects of drugs should be discussed and documented.

Treatment in infants is not difficult provided that meticulous attention is given to adherence and adequate dosing, readjusted as the child enters a new weight band. For young infants, initiate ART early, preferably immediately if possible after confirmation within the first week of diagnosis and continue educating about the medicines over the next few weeks.

Summary of Recommendations on Which ART to Start

Infants and children <36 months

In infants with baseline resistance to any drugs apart from non-nucleoside reverse transcriptase inhibitors advice from an expert should be sought.

In children on anti-tuberculosis regimens that contain rifampicin, the regimen should be adjusted accordingly.

ABC and lamivudine (3TC) + lopinavir/r (LPV/r)

Raltegravir can be considered for LPV/r intolerance (discuss with AfA)

Children >36 months

The decision should be based on knowledge of PMTCT prophylaxis and the baseline resistance test, if performed. In children on anti-tuberculosis regimens that contain rifampicin, the regimen should be adjusted accordingly. In children where therapy was previously interrupted expert advice should be sought.

Initiate

ABC and 3TC + LPV/r

OR

ABC and 3TC + Efavirenz¹

Raltegravir or ATV/r may be considered if adverse effects occur (discuss with AfA)

For ABC, remember to counsel about possible hypersensitivity reaction in the first 6 weeks. Ensure that you are contactable as the reaction may be severe.

¹ EFV is now licensed for children < 3 years in the USA. However toxic levels are associated with some CYP2B6 variants (especially the TT). Currently the drug is not licenced for these children is SA.

Switch to solid formulations as soon as developmentally appropriate (3 to 5 years of age).

Summary of suggested routine monitoring of a child on ART

Every 3 months	Every 6 months	Annual
<ul style="list-style-type: none">• Height, weight and head circumference• Formal adherence questionnaire and pill count if possible• Clinical examination	<ul style="list-style-type: none">• FBC• ALT• CD4 count and percentage• Viral load	<ul style="list-style-type: none">• Tanner pubertal stage• Non-fasting blood lipids if on ritonavir boosted PI (fasting if abnormality detected)

Treatment Failure

Treatment failure is usually first virological, followed by immunological and clinical failure. Clinical failure is the recurrence or non-disappearance of stage 3 or 4 disease. There are exceptions: for example, pneumonia can recur in children with underlying bronchiectasis. Similarly, immunological failure is the reappearance of low CD4 percentage (generally 20%, but could be lower in older children, or CD4 count in adolescents). For virological failure, we consider any persistently detectable viral load after prior full suppression to be failure.

It is not yet clear at which level to switch therapy and the actions may depend on the age as well as the first line therapy. It is well known that 3TC, raltegravir and the non-nucleoside reverse transcriptase inhibitors have a low resistance threshold and that resistance may accumulate in these children rapidly. This happens to a lesser extent in children failing a LPV/r-based regimen. Many children on treatment with a detectable VL between 1 000 and 50 000 still have an excellent clinical response and maintain high CD4 percentage values. However, continued viral replication is associated with increasing cumulative risk of the acquisition of resistance mutations, which will eventually drive immunological and clinical failure and compromise subsequent therapy.

If the viral load persists above 1 000 (on a NNRTI or RAL-containing regimen) or 5 000 (on a PI containing regimen), intervention is needed. For the PI, improved adherence should lead to viral suppression. For the NNRTI or RAL, resistance is almost invariable, but a switch should not be made until adherence has been optimised over 3 months. A repeat viral load is required and if below detectable limits, the current regimen may be continued. If adherence remains problematic one can consider using 3TC monotherapy (3TC resistance is already invariable, but it will cripple the virus for some time) until adherence has improved to facilitate second line therapy. AfA should be consulted.

Low CD4 percentage in the presence of undetectable viral load occurs in children with severe immunosuppression and does not indicate clinical failure.

Causes of Failure

The most important cause is poor adherence. Occasionally, inadequate drug levels or inadequate potency of the drugs chosen can all contribute. Genetic differences in drug metabolism are also likely to be important. Drug level variability is high in children, who may benefit from individual “tailoring” of drug doses following drug level measurement. If poor adherence is identified and improved early, it may not necessarily lead to resistance, especially for PIs. Regrettably, first generation NNRTIs, however, are particularly likely to select mutations conferring complete resistance to the class within only a few days of viral replication.

Second-line Treatment after Initial Treatment Failure

The choice of treatment should be based on careful analysis of the causes of failure, the previous regimen used and possibly on the results of resistance genotyping (requires preapproval by AfA).

Resistance Assays

Remember to keep the child on the failing regimen until the genotyping assay has been done.

Drug resistance may develop after only one mutation or may require several. Single mutants are often present within the virus quasi-species prior to treatment, and are selected by replication in the presence of the antiretroviral drug. For some drugs, a single point mutation is associated with resistance (3TC, RAL or NNRTIs), while for other drugs (AZT or PIs) more mutations may be required. Resistance can be overcome for certain drugs by increasing drug levels, for example PIs with RTV boosting.

Genotypic resistance assay should be performed in all HIV-infected children (less than two years) exposed to any ART during pregnancy. The resistance test must be preapproved by AFA.

Therapeutic Drug Monitoring (TDM)

At present, drug monitoring should be considered in children failing a PI and going back onto a PI after previous exposure. If malabsorption is suspected or the patient is on rifampicin and NVP, TDM may also be useful.

Adherence

An important challenge when starting therapy is to convince parents and children to be fully adherent. Lack of disclosure of the child's HIV status is the most important barrier to optimal adherence. Disclosure to all caregivers administering medication should be encouraged.

Poor family social circumstances compound adherence difficulties, and careful social assessment and plans for family support should always precede starting or changing therapy.

Poor adherence to PI drugs is related to poor palatability leading to children refusing to take them. There is no gold standard method for measuring adherence. Receipt of medication should be monitored using pharmacy records. Regular viral load measurement and occasionally drug levels are useful.

Three-day recall and diary cards are useful tools to assess adherence.

Adolescents are particularly challenging and between 10 and 18 years even children previously adherent to therapy become non-adherent. In this period vigilance and intensive support is needed.

Immune Reconstitution Inflammatory Syndrome (IRIS)

In the first year of life, the most common IRIS event is BCG. The infant develops painful, right axillary suppurative lymphadenopathy, usually after two to three weeks of ART. This can usually be managed symptomatically. For pus formation, repeated aspiration is helpful. Anti-mycobacterial drugs are only indicated where disseminated BCG is suspected. As in adults, an IRIS reaction may occur with other opportunistic infections as paradoxical deterioration of unmasking events.

Toxicity

Although there are fewer data on toxicity in children than in adults, the complete spectrum of metabolic complications observed in adults has been reported in children. The increasing prevalence of metabolic abnormalities observed in children treated with ART is now of major concern.

Lipodystrophy Syndrome (LDS) and Altered Blood Lipids

Fat redistribution in LDS is increasingly recognised in children. The impact that body changes may have on self-image leads to poor adherence and treatment failure. The commonest clinical picture seen is facial and limb lipoatrophy, but truncal obesity and buffalo hump also occur, with or without elevations in blood lipid levels. The prevalence of LDS ranges from 2% to 33%. Risk factors include puberty, female sex, advanced disease and duration of time on ART.

A single drug switch away from the probable offending drug can be made provided that the child is virologically suppressed. Usually this involves a switch from AZT or d4T to ABC. In children with prior failure the previous circumstances should be considered and advice should be sought.

In children, hypercholesterolaemia is more common than hypertriglyceridaemia. RTV-boosted PIs have been most associated with abnormal blood lipids, cholesterol, triglycerides and low density lipoproteins. All children on RTV-boosted PIs including LPV should have non-fasting blood lipids measured at least annually. Do fasting lipogram if any abnormality detected. Consider switching LPV to an NNRTI, atazanavir or raltegravir depending on the age, weight and circumstances. Confirm suppression prior to switching therapy. There is very limited experience of statins in children but referral to a paediatrician with experience in this field may be needed. Refer to a dietician and encourage physical exercise.

Peripheral lipoatrophy is linked to d4T, especially if combined with didanosine (ddl). d4T + ddl combinations should be avoided if at all possible. Management also requires drug switching and supportive care.

Mitochondrial Toxicity

Mitochondrial toxicity may result from therapy with NRTIs especially AZT, d4T and ddI. A high index of suspicion is necessary for mitochondrial toxicity because early symptoms are non-specific. A special situation occurs in children born to HIV-infected mothers exposed to NRTIs in utero in whom the prevalence of transient hyperlactataemia is greater, suggesting reversible mitochondrial dysfunction.

Severe lactic acidosis is a rare but serious toxicity. The incidence of symptomatic hyperlactataemia is 0,4 – 0,8 per 100-patient-years. The predictive value of random lactate determinations is low, so should not be done routinely. Fulminant severe lactic acidosis and death have been seen in children. When this does occur therapy should be interrupted and supportive care instituted.

Although the great majority of children are asymptomatic, these infants may have a slightly higher risk of mitochondrial disorders, including neurological dysfunction.

Osteoporosis

There have been increasing reports of osteonecrosis and abnormalities of bone mineral metabolism in patients on ART. Osteonecrosis usually results from circulatory insufficiency, and the areas most involved are the femoral and humeral heads. In children, a large case-controlled study has suggested that Legg-Calve-Perthes disease is nine-fold more frequent in HIV-infected children than in the general population.

The incidence of osteopaenia and osteoporosis is increased in adults treated with ART, although the association with PIs is not clear. The pathogenesis is not obvious, although decreased bone mineral content may be a result of mitochondrial toxicity (and associated with NRTI use).

An association has been reported between osteopaenia in children and ART, including duration of time on ART.

Diabetes

Altered glucose homeostasis is seen in adult patients treated with ART. Although fasting glucose levels remain normal in most adults, impaired glucose tolerance and hyperinsulinaemia are not uncommon in PI-treated patients, and the incidence of diabetes mellitus is increased in PI-treated compared with untreated HIV-patients.

In contrast, impaired glucose tolerance has been infrequently reported in children and diabetes is very rare. The true prevalence of insulin resistance is difficult to assess in clinical practice, but may assume greater importance as children remain on ART for longer periods of time.

Summary of Prescribing and Administration Information for Antiretrovirals

Dosage (oral unless specified)

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs/NRTTIs)						
Zidovudine (AZT)	<p>Oral: Term: 4 mg/kg b.d or 2 mg/kg q.d.s</p> <p>Premature: ≥30 weeks: 2 mg/kg b.d for 2 weeks then 2 mg/kg t.d.s</p> <p>≤30 weeks: 2 mg/kg b.d for 4 weeks then 2 mg/kg t.d.s</p> <p>IV: Term: 1,5 mg/kg q.d.s Premature: 1,5 mg/kg b.d</p>	<p>Oral: 1 – 3 months: 4 mg/kg b.d or 2 mg/kg q.d.s</p>	<p>Oral: Over 3 months: 360 mg – 480 mg/m²/day in two divided doses</p> <p>Intravenous (IV) infusion: Over 3 months: Intermittent: 120 mg/m² q.d.s or continuous: 20 mg/m²/h</p>	250 – 300 mg b.d	<p>Capsules: 100 mg, 250 mg</p> <p>Tablets: 300 mg</p> <p>Syrup: 10 mg in 1 ml</p> <p>Infusion: 10 mg in 1 ml, 20 ml vials</p>	<p>Large volume of syrup not well tolerated in older children.</p> <p>Infusion: Dilute with 5% dextrose to a concentration of ≤4 mg/ml.</p> <p>Intermittent infusion is given over 1 hour.</p>

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs/NRTTs) (continued)						
Didanosine (ddI, dideoxyinosine)	<3 m of age: 50 – 100 mg/m ² every 12 hours >3 m of age: 90 – 120 mg/m ² every 12 hours (Can give total daily dose once daily if adherence problematic)	1 to 8 months of age: 100 mg/m ² every 12 hours After 8 months of age: 120 mg/m ² every 12 hours		<60 kg: 250 mg o.d or 125 mg b.d ≥60 kg: 400 mg o.d or 200 mg b.d	Capsules: 250 mg, 400 mg Tablets: 25 mg, 50 mg, 100 mg, 150 mg	Enteric coated capsules ideally to be taken at least 2 hours before or after food but can be given with Pl. Tablets: Rarely used in children. To ensure sufficient antacid each dose to be taken as 2 tablets, chewed, crushed or dispersed in water or clear apple juice.
Stavudine (d4T)		Over 3 months and <30 kg: 1 mg/kg b.d ≥30: 30 mg b.d		30 mg b.d	Capsules: 15 mg, 20 mg, 30 mg	No longer recommended unless as a substitute.
Lamivudine (3TC)	2 mg/kg b.d	Over 1 month: 4 mg/kg b.d or 8 mg/kg o.d (PENTA 13). Maximum 300 mg daily		150 mg b.d or 300 mg o.d	Tablets: 150 mg, 300 mg Oral solution: 10 mg in 1 ml	Well tolerated. Use oral solution within 1 month of opening.

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs/NRRTIs) (continued)						
Abacavir (ABC)		<p>1 – 3 months: 8 mg/kg b.d under study</p> <p>Over 3 months: 8 mg/kg b.d or 16 mg/kg o.d (PENTA 13) Maximum 600 mg daily</p>		<p>300 mg b.d or 600 mg o.d Daily dosing if >14kg</p>	<p>Tablets: 60 mg, 300 mg</p> <p>Oral solution: 20 mg in 1 ml</p>	<p>Must caution parents about risk of serious hypersensitivity.</p> <p>Patients should not interrupt therapy without consulting their doctor.</p>
Tenofovir (TDF)			<p>>2 yrs: 8 mg/kg once daily (max dose 300 mg/day) TDF has been approved for children >2 years of age by the FDA. In South Africa the drug is not licensed for children this young and appropriate formulations are not yet available</p>	<p>8mg/kg once daily (max dose 300 mg/day)</p> <p>In children ≥12 years of age (35kg or more) – TDF can be considered as 1st line therapy</p>	<p>Tablets: 300mg</p>	<p>In children <12 years should be considered for specific indications i.e. hepatitis B infection.</p> <p>Monitor serum creatinine and urine dipstick monthly for first 3 months, at 6 months and then 6 monthly.</p> <p>A DXA scan may be of value at baseline & after 6 months. Refer if reduced bone density.</p>

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)						
Nevirapine (NVP)	<i>Investigational dose not FDA approved</i> 34–37 weeks: 4 mg/kg/dose b.d for the first week increasing to 6 mg/kg/dose b.d ≥37 weeks: 6 mg/kg/dose b.d	Inadequate data. 150 – 200 mg/m ² /day o.d for 14 days then, if no rash, increase to 300 – 400 mg/m ² /day in 2 divided doses ≥50 kg: adult dose	Over 16 years: 200 mg o.d for 14 days then 200 mg b.d	Over 16 years: 200 mg o.d for 14 days then 200 mg b.d	Tablets: 200 mg Suspension: 10 mg in 1 ml	Few data on use with PI. Practice is to increase PI dose by about 30%. Suspension: shake well. Store at room temperature.
Efavirenz (EFV)	Unknown	Inadequate data in children <3 years or <13 kg <i>Over 3 years:</i> 13 – 15 kg, 200 mg o.d 15 – 20 kg, 250 mg o.d 20 – 25 kg, 300 mg o.d 25 – 32.5 kg, 350 mg o.d 32.5 – 40 kg, 400 mg o.d ≥40 kg: 600 mg o.d	Inadequate data in children <3 years or <13 kg	600 mg o.d	Capsules: 50mg, 200 mg Tablets: 50 mg, 200 mg, 600 mg	Bedtime dosing is recommended, especially during the first 2 – 4 weeks to improve tolerability of CNS side effects. Capsules may be opened and added to food. Contents have a peppery taste.
Etravirine (ETR)	6 to less than 18 years: <16kg: Safety and efficacy not established 16 kg to less than 20 kg: 100 mg b.d 20 kg to less than 25 kg: 125 mg b.d 25 kg to less than 30 kg: 150 mg b.d 30 kg or more: 200 mg b.d				Tablets: 100mg	To be taken after a meal. Should only be considered for salvage therapy.
Rilpivirine	The safety and efficacy of rilpivirine have not been proven in adolescents and children. Treatment with rilpivirine is not recommended for children ≤12 years			For adolescents ≥35kg: 25mg o.d	Tablets: 25mg	Provided baseline viral load ≤ 100,000 copies.

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Protease inhibitors (PIs)						
Ritonavir (RTV) DO NOT USE AS SINGLE AGENT		<p>>1 month of age: 350 to 400 mg/m² of body surface area twice daily with a maximum dose of 600 mg twice daily</p>	<p>Start with 250 mg/m² to minimise risk of nausea and vomiting Increase stepwise to full dose over 5 days as tolerated</p> <p>Dose range 300 – 400 mg/m² b.d</p>	<p>600 mg b.d starting with 300 mg b.d and escalating over 5 days or more as tolerated Low dose to boost other PIs: e.g. 100 mg b.d</p>	<p>Tablets: 100 mg</p> <p>Oral solution: 80 mg in 1 ml</p>	<p>Take with food to increase absorption and reduce gastrointestinal side effects. If RTV is given with ddI there should be 2 hours between taking each of the drugs. Oral solution must be kept in the fridge and stored in the original container. Can be kept at room temperature if used within 30 days. To minimise nausea and vomiting, escalate dose over 5 days or so, as tolerated. Oral solution contains 43% alcohol and is very bitter. Do not mix it with water. To increase tolerability: Mix solution with milk, chocolate milk or ice cream. Dull the taste buds before giving, with ice or lollies. Coat the mouth with peanut butter before the dose. Give strong tasting food straight after the dose e.g. cheese, chewing gum.</p>

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Protease inhibitors (PIs) (continued)						
Saquinavir (SQV)	Unknown	Unknown	Under study: 50 mg/kg t.d.s	Over 16 years: With low dose ritonavir: SQV 1 g b.d with ritonavir 100 mg b.d	Capsules: 200 mg hard gelatine	Take within 2 hours after a meal. SQV concentration increased by giving with grapefruit juice. Photosensitivity can occur – sunscreen or protective clothing advised.
Lopinavir/ritonavir (LPV/r)	300 mg/m ² b.d <6 months old	6 months – 12 years: All doses given b.d with food 300/75 mg/m ² b.d With NVP or EFV or decreased PI susceptibility dose needs to be increased. Use therapeutic drug monitoring Contact AFA if assistance is required		Without NVP or EFV: 400/100 mg b.d With NVP or EFV: 533/133.3 mg (6,67 ml) b.d	Oral solution: lopinavir 80 mg with ritonavir 20 mg in 1 ml LPV/r tablets: 100 mg/25 mg, 200 mg/50 mg	Higher doses used with NNRTIs or if previously PI experienced. Liquid formulation has a low volume but a bitter taste. Tablets are large. Take with food to enhance absorption – especially the liquid. Store in the fridge. Can be kept at room temperature for 6 weeks. ddl should be taken 1 hour before or 2 hours after LPV/r. 5 ml oral solution = 2 tablets. LPV/r and rifampicin: Add extra ritonavir so that the lopinavir and ritonavir doses are the same i.e. add 60 mg ritonavir per 1 ml LPV/r.

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Protease inhibitors (PIs) (continued)						
Atazanavir (ATV)	6 years to less than 18 years: 15 kg to less than 20 kg: Atazanavir once a day 20 kg to less than 40 kg: Atazanavir once a day 40 kg or more: Atazanavir 300 mg plus ritonavir 100 mg once a day Ritonavir intolerance: For therapy-naive patients at least 13 years of age and weighing at least 40 kg, atazanavir 400 mg (without ritonavir) once a day		150 mg plus ritonavir 100 mg 200 mg plus ritonavir 100 mg 300 mg plus ritonavir 100 mg once a day	100 mg 100 mg 100 mg once a day	Capsules: 150 mg, 200 mg, 300 mg	Should be taken with food to enhance absorption. Atazanavir should be taken at least 1 hour before or after antacid or ddi.
Darunavir (DRV)			<i>15 to less than 30 kg:</i> darunavir 375 mg plus ritonavir 50 mg b.d <i>30 to less than 40 kg:</i> darunavir 450 mg plus ritonavir 60 mg b.d 40 kg or more: darunavir 600 mg plus ritonavir 100 mg b.d		Tablets: 75 mg, 150 mg, 600mg	Should only be used if patient is resistant to lopinavir.

Names of drug	Neonatal (<30 days)	Infant (1 – 12 months)	Paediatric (Tanner stages 1 – 3)	Adolescent (Tanner stages 4 – 5)/adult	Formulations	Special instructions
Integrase Inhibitors						
Raltegravir (RAL)	Raltegravir can be used in children from 4 weeks and weighing at least 3 kg Note: Film-coated tablets, chewable tablets and oral suspension are not interchangeable. The formulation used will influence the dose Patients can remain on the oral suspension as long as their weight is below 20 kg See table below for recommended doses				For Oral suspension: Single-use packet of 100 mg (not yet available in SA) Tablets: 25 mg , 100 mg 400 mg	Should only be considered for salvage therapy. Should not be added as the only active drug to a failing regimen.

Raltegravir dose from 4 weeks to 12 years (\pm 6 mg/kg)

Weight (kg)	Dose of Suspension to be administered	Chewable tablets (25mg and 100mg)	Film-coated tablet (400mg)
3 to < 4	20mg twice daily		
4 to < 6	30mg twice daily		
6 to < 8	40mg twice daily		
8 to < 11	60mg twice daily		
11 to < 14	80mg twice daily	75mg (3 x 25mg) twice a day	
14 to < 20	100mg twice daily	100mg (1 x 100mg) twice daily	
20 to 25		150mg (1.5 x 100mg) twice daily	
25 to 28		150mg (1.5 x 100mg) twice daily	400mg (1 x 400mg) twice daily
28 to < 40		200mg (2 x 100mg) twice daily	400mg (1 x 400mg) twice daily
\geq 40		300mg (3 x 100mg) twice daily	400mg (1 x 400mg) twice daily

Summary of the Major Toxicities of Antiretrovirals

Names of drug	More common side effect	Less common (more severe)	Rare
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)			
Zidovudine (AZT)	Haematological toxicity, including anaemia and granulocytopenia Headache, nausea	Myopathy, myositis and liver toxicity	Unusual (severe): cases of mitochondrial toxicity have been reported Some of these have been fatal
Didanosine (ddl)	Diarrhoea, abdominal pain, nausea, vomiting	Pancreatitis (dose related, less common in children than adults). Cases of mitochondrial toxicity have been reported Some of these have been fatal	Peripheral neuropathy (dose related), electrolyte imbalance and hyperuricaemia Increased liver enzymes and retinal depigmentation
Stavudine (d4T)		Peripheral lipoatrophy as part of lipodystrophy syndrome (LDS) Peripheral neuropathy Cases of mitochondrial toxicity have been reported. Some of these have been fatal	Increased liver enzymes
Lamivudine (3TC)		Pancreatitis (mainly seen in children with advanced HIV infection receiving many other medications) Cases of mitochondrial toxicity have been reported. Some of these have been fatal	

Names of drug	More common side effect	Less common (more severe)	Rare
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs) <i>continued</i>			
Abacavir (ABC)		<p>Approximately 1 – 3% of children develop a potentially fatal hypersensitivity reaction. Symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhoea and abdominal pain or respiratory symptoms e.g. shortness of breath. Physical findings include lymphadenopathy, ulceration of mucous membranes and maculopapular or urticarial skin rash.</p> <p>Hypersensitivity can occur without a rash.</p> <p>Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase and lymphopaenia.</p> <p>Most common in first 6 weeks of therapy.</p> <p>In patients with suspected hypersensitivity, abacavir should be stopped.</p> <p>Do not rechallenge as hypotension and death have occurred on rechallenge.</p> <p>Cases of mitochondrial toxicity have been reported. Some of these have been fatal.</p>	

Names of drug	More common side effect	Less common (more severe)	Rare
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs) continued			
Tenofovir disoproxil fumarate (TDF)	<p>Evidence of tubular leak syndrome i.e. renal toxicity including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calcuria and decreases in serum phosphate have been seen</p> <p>Hypophosphataemia in >10%. Patients at risk of renal impairment should be monitored closely</p>	Approximately 1% discontinued due to gastrointestinal side effects	<p>At high doses tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals. These effects have not been seen in adults taking tenofovir for up to 1 year. It is unknown if these effects will occur in the longer term or in children</p> <p>Cases of lactic acidosis and severe hepatomegaly with steatosis have been reported with use of the nucleoside analogues. Some of these have been fatal</p>
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)			
Nevirapine (NVP)	<p>Skin rash in 10%. If mild and systemically well can sometimes treat through with antihistamines</p> <p>Some are severe requiring hospitalisation. Can be life-threatening including Stevens- Johnson syndrome, toxic epidermal necrolysis, fever, nausea, headache and abnormal liver function tests</p>	<p>Hepatitis may rarely lead to severe and life-threatening and in some cases fatal liver damage</p> <p>Very rarely – liver failure and granulocytopenia</p> <p>Hypersensitivity reactions including, but not limited, to severe rash or rash with fever, blisters, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, general malaise and/or significant hepatic abnormalities</p>	Manufacturers recommend frequent monitoring of LFTs for the first 3 months. The risk of hepatic events is greatest in the first 6 weeks, but the risk continues past this period and monitoring is recommended throughout treatment
Efavirenz (EFV)	<p>Skin rash, CNS system (somnolence, insomnia, abnormal dreams, 'spacey kids', confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalisation, hallucinations, euphoria). Best avoided if previous psychological problems</p>		Teratogenic in primates

Names of drug	More common side effect	Less common (more severe)	Rare
Protease inhibitors (PIs)			
Ritonavir (RTV)	Nausea, vomiting, diarrhoea, headache, abdominal pain and anorexia	Circumoral paresthesias and increases in liver enzymes. Lipodystrophy syndrome	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis
Saquinavir (SQV)	Diarrhoea, abdominal discomfort, headache, nausea, paresthesias and skin rash	Lipodystrophy syndrome	Hyperglycaemia, ketoacidosis and diabetes
Lopinavir/ritonavir (LPV/r)	Diarrhoea, nausea and vomiting	Lipodystrophy syndrome	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis
Atazanavir (ATV)	Asymptomatic elevations in unconjugated bilirubin (30% patients), jaundice (10% patients), headaches, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhoea and paresthesias	Prolongation of PR interval on ECG	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis
Darunavir (DRV)	Diarrhoea, nausea and vomiting, headache, skin rash		Hyperglycaemia
Integrase Inhibitors			
Raltegravir (RAL)	Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis Nausea, diarrhoea, headache, insomnia, fever, creatine phosphokinase elevation		

Mylan ARVs, connecting with and touching lives



Approximately 50 % of people living with HIV/AIDS in the developing world who are receiving treatment depend on a Mylan ARV product¹

Reference: 1. Mylan corporate communication.

[S4] **ATRIOZA** (Film-coated tablets). Reg. No.: 45/20.2.8/0172. Each film-coated tablet contains tenofovir disoproxil fumarate 300 mg, efavirenz 600 mg and emtricitabine 200 mg. Lactose monohydrate 120 mg. [S4] **DUMIVA** (Film-coated tablets). Reg. No.: 46/20.2.8/0012. Each film-coated tablet contains abacavir 600 mg and lamivudine 300 mg. Sugar free. [S4] **EFLATEN** (Film-coated tablets). Reg. No.: 45/20.2.8/0171. Each film-coated tablet contains tenofovir disoproxil fumarate 300 mg, lamivudine 300 mg and efavirenz 600 mg. Lactose monohydrate 60 mg. [S4] **TENEMINE** (Film-coated tablets). Reg. No.: 45/20.2.8/0112. Each film-coated tablet contains tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg. Lactose monohydrate 136 mg.

For full prescribing information refer to the package insert approved by the medicines regulatory authority.

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Opportunistic Conditions

Bacterial Infections (Recurrent)

Febrile episodes should be managed similarly to those occurring in other immunocompromised children. There is a reasonable chance that a febrile episode may indicate serious invasive bacterial disease, including pneumonia, meningitis, septicaemia and osteitis. Where this is suspected, blood cultures should be drawn and parenteral antibiotics given, pending the results. Generally, an aminoglycoside should be given with a β lactam antibiotic.

Viral upper and lower respiratory tract infections are also common as are secondary bacterial complications such as otitis media and sinusitis. A useful approach is to use amoxicillin/clavulanate or amoxicillin (amoxicillin component should be 45 – 90 mg/kg/day) in order to give high enough levels of amoxicillin for activity against *S. pneumoniae* with intermediate penicillin resistance (also useful as follow-up therapy for pneumonia).

Disseminated BCG Infection

BCG is given at birth to all neonates in South Africa by intradermal injection in the area of the right deltoid. Disseminated BCG has been seen in HIV-infected infants in the presence of delayed HIV-diagnosis, severe immunosuppression and delayed initiation of ART. It usually, but not always, occurs in the absence of right axillary adenopathy. Gastric aspirates, mycobacterial blood cultures and bone marrow aspirates may be helpful. If mycobacterial species are found further identification should be requested if you suspect BCG. **NB: Hain Line Probe and GeneXpert diagnose mycobacterial species and not MTB.**

Treatment:

- Antimycobacterial drugs: for suspected or confirmed systemic disease
 - Isoniazid (INH) 15 mg/kg/day
 - Rifampicin (RIF) 15 mg/kg/day
 - Pyrazinamide (PZA) 20 – 25 mg/kg/day (2 months, or until tuberculosis excluded, as TB often co-exist; BCG is PZA-resistant)
 - Ethambutol (EMB) 20 – 25 mg/kg/day
 - Fluoroquinolone depending on age and weight – levofloxacin for younger children or moxifloxacin for adolescents

Bronchiectasis

Bronchiectasis and other forms of chronic lung disease are common in children where initiation of ART has been delayed and is often the presenting feature in older children and adolescents with slowly progressing vertically acquired HIV.

A history of chronic cough is common in HIV infected children. Bronchiectasis should be suspected when the cough is productive and worse at night or when there are clinical features of a chronic pulmonary illness. Children may also present acutely with secondary bacterial pneumonia or tuberculosis. CT scan is useful to confirm the diagnosis.

Patients should be managed by treating infections aggressively and clearing secretions with home based chest physiotherapy. Specialist consultation may be helpful to assess whether long-term macrolide therapy or surgery should be considered. Most importantly a suppressive ART regimen should be implemented.

Candidiasis

Oral

Miconazole gel, 4 – 6 hourly is effective for the treatment of oral thrush OR nystatin suspension. Infants should receive 1 ml (100 000u) and older children 2 ml (200 000u) 4 – 6 hourly.

Oesophagus/trachea

Diagnosis: clinical with oropharyngeal thrush and odynophagia/dysphagia. Suspect in patients with drooling. Infants are irritable and appear uncomfortable. They often clearly struggle to swallow when feeding and pool milk in the back of the throat. They may cough while feeding.

Since endoscopy is often not feasible a trial of therapy is always acceptable. Rapid improvement may be noticed. If difficulty persists, a barium swallow with fluoroscopy should be considered to look for incoordination of swallowing and structural abnormalities of the oesophagus.

Treatment: fluconazole 6 – 12 mg/kg/day for 14 – 21 days.

Maintenance treatment: not indicated. Although recurrences are common, disease is not life-threatening and azole-resistant Candida strains develop.

Nappy Rash

Often associated with a *Candida* infection. They can usually be treated topically with nystatin cream bd. The nappy area needs meticulous attention, as it may be a nidus for bacterial superinfection.

Cryptococcosis

Diagnosis: culture of *Cryptococcus neoformans* from any site or by positive cryptococcal antigen in blood or CSF.

Treatment: amphotericin B 1 mg/kg/day IV for 14 days and fluconazole 10 – 20 mg/kg/day for 8 weeks. Patients with initial raised intracranial pressure should have daily lumbar puncture, removing sufficient CSF to lower pressure to <20 cm H₂O.

Maintenance treatment: fluconazole 10 mg/kg/day until CD4 percentage >20% if >6 years of age and >25% if 2 to 6 years of age on ART (minimum of 6 months). Co-trimoxazole 5 mg/kg/day (to prevent other opportunistic infections) until CD4 percentage >20% if >6 years of age and >25% if 2 to 6 years of age on ART (minimum of 6 months).

Cryptosporidiosis

Diagnosis: stool examination.

Treatment: no effective therapy available – loperamide and oral rehydration solution helpful. May respond well to ART. Aggressive nutritional and fluid support.

Maintenance treatment: none. Co-trimoxazole prophylaxis (to prevent other opportunistic infections).

Cytomegalovirus (CMV)

The majority of children born in Africa probably become infected with CMV in early life. Due to its ubiquitous presence and its tendency to reactivate during acute illness it may be very difficult to make a diagnosis of active CMV infection without obtaining tissue specimens, which in most cases is impractical.

A number of tests are used to diagnose the presence of CMV:

- Culture of CMV in urine and respiratory secretions – a positive test confirms infection but not active disease. Urine culture prior to 3 weeks of age may be useful to diagnose congenital infection
- PP65 antigen in blood measures the expression of CMV in neutrophils; often false negative in neutropaenic patients. A positive result indicates viraemia but not necessarily active disease. We do not recommend this test

- A positive qualitative CMV PCR in the blood confirms the presence of CMV infection but not active disease. The quantitative PCR may be helpful in that it is thought to be higher in disease and can be used to monitor therapy. There may however be inter-laboratory variation in the quantitative test
- A positive qualitative CMV PCR in the CSF may occur if there is a bloody tap or lymphocytes in the CSF due to another cause
- CMV serology – bear in mind that a positive IgG in a young infant may be maternal in origin and this indicates infection not disease
- Tissue PCR and histology may be helpful

Pneumonitis

Severe interstitial pneumonitis may occur, often with PJP. Occurs most commonly in the first year of life in infants not on co-trimoxazole prophylaxis. The most common situation is where the mother had not been tested in pregnancy or had a negative test in pregnancy. It is a major contributor to early mortality. CMV should be considered in infants with severe pneumonitis. In children with CMV pneumonia screening for retinitis should be done.

Diagnosis: quantitative PCR is the test of choice with higher levels indicating an increased likelihood of disease. Lung biopsy is definitive but seldom done.

Treatment: see adult section.

Congenital CMV

Diagnosis: isolation of CMV or a positive PCR from urine, stool, respiratory tract secretions or CSF within the first three weeks of life.

Treatment: indications and duration of therapy are controversial with many experts suggesting prolonged suppressive treatment. Where possible a paediatrician with expertise should be consulted.

Intravenous ganciclovir therapy (6 mg/kg/dose 12 hourly) for six weeks should be offered to HIV-exposed or HIV-infected babies with symptomatic congenital CMV disease.

Oral valganciclovir may be considered, a commercially available preparation is available for children.

CMV retinitis

Diagnosis: fundoscopy by an ophthalmologist. No special investigations are needed if clinical features are present and there are no systemic symptoms.

Treatment: ganciclovir 5 mg/kg bd IV for 14 days (patient should be admitted to hospital).

Maintenance treatment: oral valganciclovir (Requires pre-authorisation by AfA).

CMV GIT (colitis/oesophagitis)

Seldom diagnosed in infants.

Diagnosis: histology of biopsy of ulcer.

Treatment: ganciclovir 5 mg/kg bd IV for 14 -21days (patient should be admitted to hospital).

Maintenance treatment: not necessary.

Diarrhoea (non-specific)

May be persistent and associated with failure to thrive.

Investigations

Often no pathogen is found on stool culture. Culture for bacterial pathogens. Stool microscopy for giardia and cryptosporidium.

HIV Encephalopathy

Signs and symptoms include:

- Regression of or failure to achieve developmental milestones
- Motor signs, including spastic diplegia, ataxia and pseudobulbar palsy
- Acquired microcephaly
- Expressive language delay in toddlers
- Behavioural and concentration difficulties in older children

Differential diagnosis

Tuberculosis, CNS lymphoma and toxoplasmosis should be excluded.

Investigations

CT or MRI – former for cerebral atrophy and/or calcification of basal ganglia; and latter for white matter changes (all features of HIV encephalopathy). Lumbar puncture may need to be done to exclude subacute meningitis (bacterial, mycobacterial or cryptococcal).

Herpes Simplex Virus Ulcers (Including Stomatitis)

Diagnosis: usually clinical – shallow, painful spreading mucocutaneous ulcers. As disease advances, spontaneous healing is delayed and then does not occur.

Treatment: acyclovir, two years and over give 400 mg eight hourly for five days; Under two years, give 200 mg eight hourly for five days. Give intravenously at 25 mg/kg/day in three divided doses if unable to swallow. Analgesia – paracetamol 10 – 15 mg/kg six hourly.

Isosporiasis

Diagnosis: special stain of stool.

Treatment: co-trimoxazole 10 mg/kg/day of trimethoprim 12 hourly for three weeks.

Maintenance treatment: co-trimoxazole 5 mg/kg/day of trimethoprim until CD4% >15%.

Management of HIV-Associated Kaposi's Sarcoma (KS) in Children

Background to HIV-associated KS

- KS is a malignancy of lymphatic endothelial origin and is the most common malignancy seen in children
- Almost 100% of cases are associated with Human Herpes Virus-8 (HHV-8) also known as KS Herpes Virus (KSHV)
- KS may involve the skin, oral cavity, lymph nodes or viscera (lung, intestines and rarely other organs such as the liver and bone marrow). Lymphoedema is a potential complication. Skin lesions usually subcutaneous
- The typical CXR appearance of pulmonary KS is a reticulonodular appearance spreading from the hilar regions bilaterally. The diagnosis is confirmed by visualising endobronchial KS lesions on bronchoscopy (biopsy poses a high risk of haemorrhage). Pulmonary KS may be associated with intrathoracic adenopathy and/or pleural effusions which are typically bloody or serosanguinous
- CXR is a useful screen for pulmonary KS. Faecal occult blood is a useful screen for GIT involvement
- KS is a WHO stage 4 defining illness
- Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions, certain cases should have biopsy confirmation. Atypical skin lesions should be biopsied
- Lymph nodes >2 cm should be biopsied to exclude TB and lymphoma
- Atypical oral lesions should be biopsied to exclude other malignancies such as lymphoma, squamous carcinoma and salivary gland tumours

Treatment principles

- Refer to adult section. All HIV-positive patients with KS should be commenced on ART regardless of CD4 as KS is a stage 4 defining illness. This should always be the first-line therapeutic intervention
- Regression and resolution of mucocutaneous KS on ART alone is well described. There are also case reports of regression of pulmonary KS lesions on ART alone
- ART prolongs the time to treatment failure of KS chemotherapy
- It is important to investigate for and exclude co-existent opportunistic infections (particularly TB), especially if the patient is going to receive chemotherapy, which will immunosuppress them further
- Refer to paediatric oncologist

Lymphoid Interstitial Pneumonitis (LIP)

Occurs in at least 40% of children with perinatal HIV. Usually diagnosed in children over one year of age. This is in contrast to *pneumocystis jiroveci* pneumonia (PJP), which is more common below one year of age. Median survival is five times longer for children with lymphoid interstitial pneumonitis (LIP) than PJP.

LIP is characterised by diffuse infiltration of pulmonary interstitium with CD8 plus T lymphocytes and plasma cells. It may progress to hypoxaemia. Superimposed bacterial infections are common and bronchiectasis may develop.

Clinical

Symptoms include: slowly progressive tachypnoea, cough and wheezing.

Signs include: clubbing, parotid enlargement, generalised adenopathy, hepatosplenomegaly. Bacterial superinfection is common.

Radiological: reticulonodular infiltrates associated with hilar adenopathy. Bronchiectasis may occur.

Diagnosis: the diagnosis is usually made by clinical assessment and a CXR. Often TB needs to be excluded. CT scan may be valuable but should be discussed with a pulmonologist.

Management

Lung function in older children may identify those with reversible bronchoconstriction that may benefit from an inhaled bronchodilator and inhaled steroid therapy.

Treatment: ART essential. For children with chronic hypoxia steroids can be considered.

Microsporidiosis

Diagnosis: demonstration of the organism on stool (special stains or PCR) or on small bowel biopsy.

Treatment: one strain (*E. intestinalis*) responds to albendazole 400 mg bd for five days – if >2 years. Responds well to ART.

Maintenance treatment: none.

Mycobacterium Avium Complex (MAC Infection Disseminated)

Diagnosis: culture from blood, lymph node biopsy or bone marrow – usual organism is *mycobacterium avium* complex. Culture from sputum is unhelpful and is NOT an indication for treatment.

Treatment: a macrolide (clarithromycin 15mg/kg/day in two divided doses or azithromycin 10-12mg/kg/day) plus ethambutol (15mg/kg/day). Under certain circumstances, such as failure to respond to dual therapy in proven MAC or severe disease, the addition of a rifamycin (preferably rifabutin 20mg/kg/day. Monitor white cell count) may be considered. Dosing of rifabutin is complex.

Management should be discussed with an experienced clinician.

Drug interactions with ART is a problem for macrolides and rifamycins. Azithromycin and not clarithromycin should be used if patient is on an NNRTI. Initiate ART and stop MAC treatment after 12 months if CD4 percentage >15.

Maintenance treatment: see above. Co-trimoxazole.

Mycobacterium Tuberculosis

Diagnosis:

History

In children with HIV, pulmonary tuberculosis may present like an acute pneumonia. Fever is a common symptom. New onset of cough for >14 days OR in children with chronic lung disease a worsening cough.

History of exposure to adolescent or adult with tuberculosis. In the source case: always ask for a history suggestive of resistance i.e. retreatment, poor compliance, poor response or confirmed resistance.

Examination: generalised lymphadenopathy, hepatosplenomegaly, consolidation and pleural effusion, unusual features of PTB in HIV disease include otorrhoea, finger clubbing and presentation as an acute lung infection.

Chest x-ray: bronchopneumonia with hilar adenopathy, miliary changes and pleural effusions. Mantoux ≥ 5 mm or positive IGRA.

Microbiology: acid fast bacilli on Ziehl-Neelsen or Auramine, confirmed by culture on early morning gastric aspirate, induced sputum, CSF pleural and ascitic fluids.

Management: the source/index case should be identified and treated. All contacts should be screened for tuberculous infection. Monitor the nutritional status of the child to assess response to treatment. Only symptomatic pleural effusions should be drained.

Treatment: refer to state sector clinic. Directly observed therapy short course using fixed drug combination is recommended to avoid drug resistance. Treatment should be given every day of the week in both the intensive and the continuation phases.

HIV-infected children with tuberculosis should be treated as per standard treatment protocol and fixed drug combinations should be used wherever possible and the doses should be adjusted according to weight gain.

All children with HIV should receive 4 anti-TB drugs regardless of the severity of disease. In children <4 kg ethionamide is preferred due to dosing difficulties of ethambutol. In all other children except those with TB-meningitis ethambutol is the fourth drug of choice.

All HIV-infected children of any age in contact with an adult who is TB infected should be screened for tuberculosis. If negative, the child should receive chemoprophylaxis.

Tuberculosis in the infant younger than 3 months

Acquired through placental blood flow or via the passage of swallowed maternal blood during delivery or via inhalation of the bacilli during the neonatal period. The incidence is increasing in the HIV era.

Diagnosis: positive vaginal swabs or sputum for *M. tuberculosis* in the mother. Hepatosplenomegaly and a suggestive chest x-ray.

Treatment: neonates born to mothers with active tuberculosis who do not have signs of TB: INH for 6 months. In HIV uninfected infants the BCG can be given after completion of chemoprophylaxis. If at any stage the child should have symptoms of TB a full screen should be performed including relevant cultures and therapy instituted.

Pneumonia

Bacterial

Diagnosis: as for community-acquired pneumonia in HIV negative.

Treatment: similar to therapy in children without HIV, but opportunistic and gram negative infections should be considered.

Maintenance treatment: ensure that co-trimoxazole prophylaxis continues if frequent.

Pneumocystis pneumonia

PJP occurs most commonly in infants younger than one year with a peak from three to six months. However, clinicians should maintain a high index of suspicion in all HIV exposed and infected infants, particularly if they are not on ART and/or preventative therapy. In young infants the disease is particularly seen where HIV risk was not identified antenatally and where co-trimoxazole prophylaxis was not given. Unlike adults, onset of illness is often abrupt, but may be insidious. In HIV-infected children with pneumonia, four clinical variables independently associated with PJP are: age <6 months, respiratory rate >59 breaths per minute, arterial percentage haemoglobin saturation $\leq 92\%$, and the absence of vomiting.

Diagnosis: CXR shows bilateral interstitial (“ground glass”) infiltrates. Special stains of broncho-alveolar lavage or induced sputum (following nebulisation of hypertonic saline).

Treatment: co-trimoxazole 20 mg/kg/day in four divided doses. Initial intravenous therapy can be changed to oral therapy once the infant is stable. Treatment is for 21 days. Adjuvant therapy includes prednisone 2 mg/kg/day for seven days.

There are limited options available in South Africa for patients with co-trimoxazole intolerance – rechallenge should be attempted. Rechallenge or desensitise rapidly with co-trimoxazole under antihistamine cover. This option is risky if the original co-trimoxazole hypersensitivity was life-threatening.

Maintenance treatment: co-trimoxazole 6 mg/kg/day until CD4 percentage >20% if >6 years of age and >25% if two to six years of age on ART (minimum of six months).

Progressive Multifocal Leukoencephalopathy

Diagnosis: non-enhancing lesions on MRI together with positive PCR for JC virus on CSF. Definitive diagnosis requires brain biopsy (seldom necessary).

Treatment: no effective therapy available. Case reports suggest good response to ART when manifests as immune reconstitution inflammatory syndrome.

Toxoplasmosis

Uncommon in children.

Diagnosis: is made on CT/MRI scan showing enhancing mass lesions. CD4 count is nearly always <200 (<15%). Toxoplasma IgG (not IgM) positive. Rapid treatment response confirms the diagnosis (brain biopsy is definitive but seldom necessary).

Treatment: pyrimethamine 2 mg/kg/d PO divided q12h for two to four days initially, then 1 mg/kg/day PO daily or divided twice daily not to exceed 25 mg/day for one month with clindamycin 30 mg/kg/day in three divided doses. Add folinic acid 5 – 10 mg/day (use folic acid 10 mg/day if folinic acid unavailable).

Maintenance treatment: co-trimoxazole 5 mg/kg/day of trimethoprim component until CD4 count rises to >200 (>15%) on ART.

In general, initiation of ART should be delayed until any active opportunistic infection is under control to avoid the development of immune reconstitution inflammatory syndrome (IRIS). This may not be possible in young infants – ask for advice when in doubt.

Specific Issues for Adolescents

What About Adolescents?

There is increasing expertise in treating adolescents in South Africa. They are at high risk for acquiring HIV and most vertically infected children are now surviving to this age. Compliance is an especially important issue. For adolescents with early sexual development (Tanner stage 1 and 2) paediatric dosages should be used and for more advanced sexual maturity (Tanner stage 3 and 4), adult dosages are indicated.

Sexually active adolescents are at risk of contracting HIV. Pre-emptive counselling should take place. Those perinatally infected children who reach adolescence will need counselling regarding modes of transmission and prevention of transmission. Disclosure of HIV status must occur prior to sexual debut. Open discussion is encouraged. Adult treatment guidelines are appropriate for post-pubertal adolescents (Tanner 5). Non-compliance is problematic. Strategies such as more frequent visits and intensive counselling should be introduced to promote adherence.

Tanner Staging for Boys

Stage	Pubic hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Slight enlargement	Enlarged scrotum, pink texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult, less than adult	Larger, glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult	Adult

Tanner Staging for Girls

Stage	Pubic hair	Breasts
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border labia	Breast and papilla elevated as small mound; areola diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature; nipple projects, areola part of general breast contour



ANTIRETROVIRAL DRUG DOSING

Compiled by the Child and Adolescent Committee of the SA

	Abacavir (ABC)	Lamivudine (3TC)	Efavirenz (EFV)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)		
Target Dose	8mg/kg TWICE daily OR ≥10kg: 16mg/kg ONCE daily	4mg/kg TWICE daily OR ≥10kg: 8mg/kg ONCE daily	By weight band ONCE daily	300/75mg/m ² /dose LPV/rtv TWICE daily	ONLY as booster for LPV/ rtv when on Rifampicin TWICE daily (0.75xLPV dose bd)		
Available Formulations	Sol 20mg/ml Tabs 60mg (scored dispersible), 300mg (not scored), ABC/3TC 600/300mg	Sol. 10mg/ml Tabs 150mg (scored), 300mg, ABC/3TC 600/300mg	Caps 50,200mg Tabs 50,200, 600mg (not scored)	Sol. 80/20mg/ml Adult Tabs 200/50mg, Paeds Tabs 100/25mg	Sol. 80mg/ml		
Wt. (kg)	Currently available tablet formulations of abacavir (except 60mg), efavirenz, LPV/rtv						
<3	Consult with a clinician experienced in paediatric ARV prescribing						
3-3.9	2ml bd	2ml bd	Avoid using when <10kg or <3 years: dosing not established	*1ml bd	1ml bd		
4-4.9	3ml bd	3ml bd		*1.5ml bd	1.5ml bd		
5-5.9							
6-6.9							
7-7.9							
8-8.9	4ml bd	4ml bd					
9-9.9	Choose only one option: 6ml bd OR 2x60mg tabs bd	Choose only one option: 6ml bd OR 12ml od	200mg nocte (1x200mg cap/tab)			2ml bd	1.5ml bd
10-10.9							
11-13.9	8ml bd OR 2.5x60mg tabs bd	5x60mg tabs od OR 1x300mg tab od OR 15ml od	½ x150mg tab bd OR 8ml bd	1x150mg tab od OR 15ml od	Choose one option: -2.5ml bd -100/25mg paeds tabs: 2 bd -200/50mg adult tabs: 1 bd	2ml bd	
14-16.9							
17-19.9							
20-22.9	10ml bd OR 3x60mg tabs bd	1x300mg tab + 1x60mg tab od	1x150mg tab bd OR 15ml bd	2x150mg tab od OR 1x300mg tab od OR 30ml od	300mg nocte: (200mg cap/tab + 2x50mg cap/tab)	Choose one option: -3ml bd -100/25mg paeds tabs: 2 bd -200/50mg adult tabs: 1 bd	2.5ml bd
23-24.9							
25-29.9	1x300mg tab bd	2x300mg tabs od OR 1xABC/3TC 600/300mg tab od	1x150mg tab bd	2x150mg tabs od OR 1x300mg tab od OR 1xABC/3TC 600/300mg tab od	400mg nocte: (2x200mg caps/ tabs)	Choose one option: -3.5ml bd -100/25mg paeds tabs: 3 bd -#200/50mg adult tabs: 1 bd + 100/25mg paeds tabs: 1 bd	3ml bd
30-34.9							
35-39.9							
>40							

od = once a day
(usually at night)
bd = twice a day

* Avoid LPV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.
Children 25-34.9kg may also be dosed with LPV/rtv 200/50mg adult tabs: 2 tabs am; 1 tab pm

CHART FOR CHILDREN 2013

HIV Clinicians Society in collaboration with the Department of Health



Stavudine (d4T)	Didanosine (ddI)	Nevirapine (NVP)	Zidovudine (AZT)	Target Dose
1mg/kg/dose TWICE daily	180-240mg/m ² /dose ONCE daily	160-200 mg/m ² /dose TWICE daily (after once daily lead-in x 2 wks)	180-240mg/m ² / dose TWICE daily	
Sol. 1mg/ml Caps 15,20,30mg	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored), AZT/3TC 300/150mg	Available Formulations

and AZT must be swallowed whole and NOT chewed, divided or crushed Wt. (kg)

for neonates (<28 days of age) and infants weighing <3kg				<3
6ml	Avoid	5ml bd	6ml bd	3-3.9
				4-4.9
7.5mg bd: open 15mg capsule into 5ml water: give 2.5ml	100mg od: (2x50mg tabs)	8ml bd	9ml bd	5-5.9
10mg bd: open 20mg capsule into 5ml water: give 2.5ml	125mg od: (1x100mg + 1x25mg tabs)			6-6.9
				7-7.9
15mg bd: open 15mg capsule into 5ml water	150mg od: (1x100mg + 1x50mg tabs)	10ml bd	1 cap bd OR 12ml bd	8-8.9
				9-9.9
				10-10.9
20mg bd: open 20mg capsule into 5ml water (if the child is unable to swallow a capsule)	175mg od: (1x100mg + 1x50mg + 1x25mg)	1 tab am ½ tab pm OR 15ml bd	2 caps am 1 cap pm OR 15ml bd	11-13.9
				14-16.9
	200mg od: (2x100mg tabs)		2 caps bd OR 20ml bd	17-19.9
				20-22.9
30mg bd	250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od	1 tab bd	1x300mg tab bd OR 1xAZT/3TC 300/150mg tab bd	23-24.9
				25-29.9
				30-34.9
				35-39.9
				>40

Weight (kg)	3-4.9	5-9.9	10-13.9	14-29.9	≥30
Cotrimoxazole Dose	2.5ml od	5ml od	5ml od	10ml or 1 tab od	2 tabs od
Multivitamin Dose	2.5ml od	2.5ml od	5ml od	5ml od	10ml or 1 tab od



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General Information

Contact information	
Medicines Information Centre	Toll-free National HIV & TB Healthcare Worker Hotline Tel: 021 406 6782 or 0800 212 506 Email: pha-mic@uct.ac.za
Clicks Direct Medicines	Tel: 0861 444 405
Pharmacy Direct	Tel: 0860 027 800 • Fax: 0866 114 000/1/2/3 Email: care@pharmacydirect.co.za
Medipost	Tel: 012 426 4000 • Fax: 0866 488 446
Ampath	Tel: 011 929 9800
Global	Tel: 031 904 0500
Lancet	Tel: 011 358 0800
Pathcare	Tel: 0860 410 3392
Vermaak & Partners	Tel: 012 404 2300
Useful web addresses	
Aid for AIDS	www.aidforaids.co.za
The Body	www.thebody.com
AIDSMAP	www.aidsmap.com
AVERT	www.avert.org
CDC	www.cdc.gov/hiv
Drug interactions	www.hiv-druginteractions.org
Johns Hopkins HIV Guide	http://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_HIV_Guide
SA HIV Clinicians Society	www.sahivsoc.org
UNAIDS	www.unaids.org
Medscape	www.medscape.com/hiv
Aids Information	www.ashastd.org
BHIVA	http://www.bhiva.org/guidelines.aspx
AIDSinfo	http://www.aidsinfo.nih.gov/guidelines/
WHO	http://www.who.int/hiv/pub/guidelines/en/

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activo

...the house of ARV's

TRUNO

600 mg Efavirenz
200 mg Emtricitabine
300 mg Tenofovir



FDA APPROVED ✓

ATAZOR

150 mg Atazanavir
200 mg Atazanavir
300 mg Atazanavir



FDA APPROVED ✓

ZENVIR

50 mg Efavirenz
200 mg Efavirenz



FDA APPROVED ✓

WHO PREQUALIFIED ✓

BAVIR

300 mg Abacavir
20 mg/ml Abacavir



FDA APPROVED ✓

WHO PREQUALIFIED ✓

EMTROC

200 mg Emtricitabine
300 mg Tenofovir
Disoproxil Fumarate



WHO PREQUALIFIED ✓

HETLAM

150 mg Lamivudine



FDA APPROVED ✓

WHO PREQUALIFIED ✓

HEVAZ

600 mg Efavirenz



FDA APPROVED ✓

WHO PREQUALIFIED ✓

HETEMCIT

200 mg Emtricitabine
300 mg Tenofovir
Disoproxil Fumarate



FDA APPROVED ✓

WHO PREQUALIFIED ✓

NEVIVIR

200 mg Nevirapine



FDA APPROVED ✓

WHO PREQUALIFIED ✓

HEFTENAM

600 mg Efavirenz
200 mg Emtricitabine
300 mg Tenofovir
Disoproxil Fumarate



FDA APPROVED ✓

WHO PREQUALIFIED ✓

COMBOZIL 150/300

150 mg Lamivudine
300 mg Zidovudine



FDA APPROVED ✓

WHO PREQUALIFIED ✓

HETERO TENFOVIR

300 mg Tenofovir
Disoproxil Fumarate



FDA APPROVED ✓

WHO PREQUALIFIED ✓

TRUNO 600/200/300 (tablets). Reg. No. 47/20.2.8/0572. Each film-coated tablet contains Efavirenz 600 mg, Emtricitabine 200 mg and Tenofovir disoproxil fumarate 300 mg, equivalent to 245 mg of Tenofovir disoproxil. Applicant: Aurobindo Pharma (Pty) Ltd, Woodhill Office Park, Building 1, 53 Philip Engelbrecht Avenue, Meyersdal, Ext. 12, 1448, Johannesburg, South Africa. ZENVIR CAPSULES 50 mg and 200 mg (capsules). Reg. Nos. 41/20.2.8/0538, 41/20.2.8/0540. Each capsule contains 50 mg or 200 mg Efavirenz respectively. Applicant: Aurobindo Pharma (Pty) Ltd, Woodhill Office Park, Building 1, 53 Philip Engelbrecht Avenue, Meyersdal, Ext. 12, 1448, Johannesburg, South Africa. EMTROC, Reg. No. 47/20.2.8/0188. Each film-coated tablet contains 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate. Applicant: Macekeds Pharmaceuticale SA (Pty) Ltd, Stand 6D & E, Growthpoint Business Park, Tonelli Street, Halfway House, Midrand. HEVAZ 600, Reg. No. 43/20.2.8/0363. Each tablet contains 600 mg Efavirenz. Applicant: Hetero Drugs SA, Co. Reg. No. 2008/00174910. 252 Jean Avenue, Jean Park Chambers, Building 6, Unit 19, Centurion, 0157. NEVIVIR, Reg. No. 43/20.2.8/0230. Each tablet contains 200 mg Nevirapine. Applicant: Hetero Drugs SA, Co. Reg. No. 2008/00174910. 252 Jean Avenue, Jean Park Chambers, Building 6, Unit 19, Centurion, 0157. COMBOZIL 150/300, Reg. No. 43/20.2.8/0362. Each tablet contains 150 mg Lamivudine and 300 mg Zidovudine. Applicant: Hetero Drugs SA, Co. Reg. No. 2008/00174910. 252 Jean Avenue, Jean Park Chambers, Building 6, Unit 19, Centurion, 0157. ATAZOR 150, ATAZOR 200 and ATAZOR 300 (capsules). Reg. No. 43/20.2.8/0235; 46/20.2.8/0382. Each hard gelatin capsule contains Atazanavir sulphate equivalent to 150 mg or 200 mg or 300 mg of Atazanavir respectively. Applicant: Emure Pharmaceuticals SA (Pty) Ltd, Co. Reg. No. 2010/01517/07, 65 Philip Engelbrecht Ave, Meyersdal Office Park, Building 1, Meyersdal, 1448. BAVIR ORAL SOLUTION 20 mg/ml (oral solution). Reg. No. 41/20.2.8/0387. Each 1 ml contains Abacavir sulphate equivalent to 20 mg of Abacavir. BAVIR TABLETS 300 mg (tablets). Reg. No. 41/20.2.8/0917. Each film-coated tablet contains Abacavir sulphate equivalent to 300 mg of Abacavir. Applicant: Aurobindo Pharma (Pty) Ltd, Woodhill Office Park, Building 1, 53 Philip Engelbrecht Avenue, Meyersdal, Ext. 12, 1448, Johannesburg, South Africa. HETLAM, Reg. No. 43/20.2.8/0831. Each tablet contains 150 mg Lamivudine. Applicant: Hetero Drugs SA, Co. Reg. No. 2008/00174910. 252 Jean Avenue, Jean Park Chambers, Building 6, Unit 19, Centurion, 0157. HETEMCIT (Tablet). Reg. No. 47/20.2.8/0232. Each film-coated tablet contains: 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate. Applicant: Hetero Drugs S.A., Jean Park Chambers, 252 Jean Avenue, Building 6, Unit 19 Centurion. HEFTENAM (efavirenz 600 mg / emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg) film coated tablets. Reg. No. 46/20.2.8/0757. Each film coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir (which is equivalent to 245 mg of tenofovir disoproxil). Applicant: Hetero Drugs South Africa, Jean Park Chambers, 252 Jean Avenue, Centurion, Building 6, Unit 19. HETERO TENFOVIR (tablets). Reg. No. 46/20.2.8/0019. Each film-coated tablet contains 300 mg of tenofovir disoproxil fumarate. Applicant: Hetero Drugs SA, 252 Jean Avenue, Jean Park Chambers, Building 6, Unit 19, Centurion, South Africa, 0157, Tel: +27 12 644 2120. Marketed by: Active Health (Pty) Ltd t/a Active Pharmaceuticals, Co. Reg. No. 2009/00954107. Active House, 147 Garfontein Road, Alphen Park, Pretoria, South Africa, 0081, Tel: +2712 460 9919 / 0800 ACTIVE (228486), www.active.co.za. For full prescribing information refer to the respective package inserts approved by the Medicines Regulatory Authority.



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