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CLINICAL GUIDELINES | 10th EDITION

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Henry David Thoreau
Philosopher

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We acknowledge the contribution of the late Dr. Steve Andrews to earlier editions of these guidelines.

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Contents

Introduction

Sixteen years after the launch of Aid for AIDS (AfA) in May 1998, the programme continues to provide comprehensive HIV management solutions to medical aid schemes and companies. The value of HIV managed care is reflected in the clinical outcomes we are able to achieve in those on treatment, with viral load suppression rates well in excess of 80%.

With several million people now on antiretroviral therapy (ART) throughout Southern Africa, it is important that as many healthcare professionals as possible are familiar with the current management of HIV infection and the use of antiretrovirals, including the management of adverse effects and drug interactions.

Once again, the pace of new developments in both adult and paediatric HIV management, as well as the availability of new drugs, including fixed dose combinations, in both the private and public sectors has made it necessary to extensively revise and update these clinical guidelines, which are now in their 10th edition.

The face of the HIV epidemic is changing in Southern Africa due to the wider availability of ART which has resulted in improved survival, a prolonged lifespan and an overall ageing of the HIV-infected population. Because of this, and an increase in the number of new HIV infections in older people, a section on managing HIV infection in the elderly has been added.

HIV/TB co-infection remains an important problem and as before, an expanded and updated section on managing tuberculosis in HIV-infected patients has been included.

Hepatotoxicity is a common problem when managing HIV and so the section on Drug Induced Liver Injury (DILI) has also been extensively updated and revised.

As more patients experience treatment failure after long-term therapy, the appropriate use of resistance testing and salvage therapy has become critically important to ensure that patients do not run out of treatment options. Guidance is provided to assist practitioners in this regard.

The guidelines therefore remain an up-to-date, comprehensive and evidence-based guide to HIV management in Southern Africa. As always, we welcome feedback from colleagues, who are also encouraged to contact the clinical staff at AfA for assistance with any aspect of HIV treatment from the infectious disease experts on our Clinical Advisory Committee.

AfA once again would like to acknowledge 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 distributing copies to all healthcare providers, clinics and teaching institutions free of charge.

These guidelines would also not be possible without the on-going valuable input and contributions made by the part-time consultants who serve on the AfA Clinical Advisory Committee, some of whom have been with AfA since its inception.

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Management of HIV Infection in Adults

Diagnosis

The diagnosis of HIV infection is usually made by demonstrating the presence of HIV antibodies on two different tests. Screening tests will 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). 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 – in the public sector two rapid tests from different manufacturers are used to confirm HIV, but AfA requires laboratory confirmation of HIV infection with either an ELISA or viral load before approving ART. 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 viral load). However, the nucleic acid amplification tests have a very small but significant 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. Informed consent for HIV testing should ideally be obtained in writing. Short courses in basic counselling are available at organisations such as LifeLine and ATICC.

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Reference: 1. Department of Health, The South African antiretroviral treatment guidelines. 2013. Available from www.doh.gov.za <http://www.doh.gov.za>. Accessed 17 July 2013.

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Issues that should be covered include:

- Confidentiality
- Transmission 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 appropriate)
- 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
- The need for regular monitoring of CD4 counts

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 must 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 × 10^9 per litre) and/or chronic thrombocytopaenia (<50 × 10^9 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: 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 dipstix (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** (quantitative HIV PCR).

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 crucial in deciding when to start ART. The count is also 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. This is particularly important in deciding whether to initiate ART in patients without clinical evidence of advanced immune suppression.

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 thrombocytopaenia). Tuberculosis may occur at any CD4 count. Once the 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 CD4 count should be performed every 4 – 6 months in patients not yet eligible for ART.

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 should never be based on the results of only one test. There is no point in monitoring the viral load if the patient is not on ART.

Laboratory Tests

Test	Appropriate sample
HIV antibody test	Clotted blood
Viral load test	Blood in EDTA tube
CD4 cell count	Blood in EDTA tube
Hepatitis B surface antigen	Clotted blood
Syphilis serology	Clotted blood
Full blood count	Blood in EDTA tube
Serum chemistry (ALT, cholesterol, serum creatinine)	Clotted blood
PCR (qualitative)	Blood in EDTA tube
Serum lactate	Blood in fluoride tube

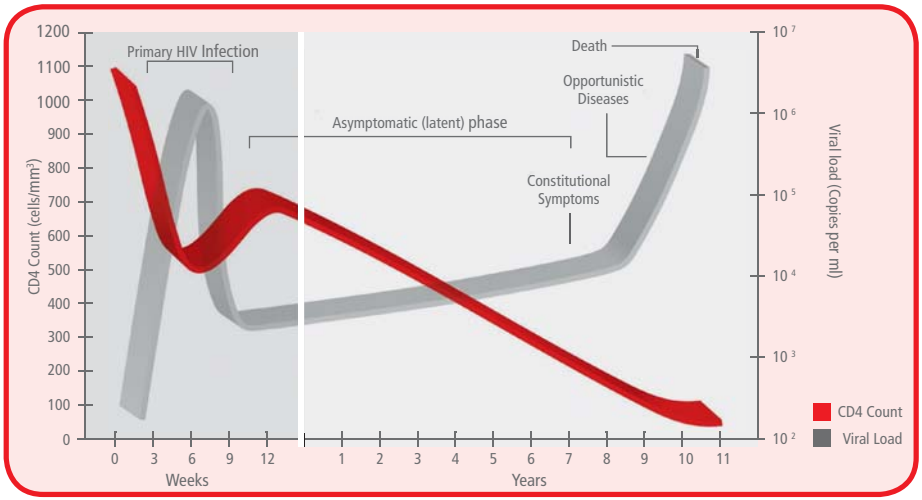
HIV Disease Progression

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 lymphopaenia occurs, which may result in opportunistic infections, notably oropharyngeal candidiasis. Thrombocytopaenia 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



Minor HIV/AIDS-Related Conditions

Oral Lesions

Common conditions include thrush, aphthous ulcers and oral hairy leukoplakia. Also common are periodontal diseases such as linear gingivitis and the more serious periodontal necrotising ulceration. As periodontal disease is common, good dental hygiene is important and regular dentist visits are advised. Chlorhexidine rinses may also be useful.

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.

Treatment of Oral Candidiasis

Topical (troches or lozenges are more effective because of the longer contact time):

- Amphotericin B lozenges 10 mg six-hourly for 5 days
- Nystatin suspension (100 000 IU/ml) 1 ml four times per day
- Daktarin® oral gel is helpful for angular cheilitis

Systemic (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).

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 may also regress 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 less effective than amitryptiline, but 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 has 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. Severe thrombocytopaenia (<50) is an indication for ART. 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. This is also an indication for ART irrespective of the CD4 count.

Bone marrow suppression is common in advanced disease. This may be due to bone marrow infiltration (TB or TB IRIS, malignancies, fungi) or due to HIV-induced hypoplasia/dysplasia – a bone marrow biopsy is necessary to distinguish these two disorders. 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. 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, but 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 folinic 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. See drug interaction table.

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).

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. clarithromycin). **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). 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 H_2O) should have daily lumbar punctures, removing sufficient CSF (usually 10 – 20 ml) to lower pressure to <20 cm H_20. LPs should be done daily until 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 of 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 rehydrate 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	Supplement with oral potassium	Potassium twice weekly	IVI potassium supplementation
Hypomagnasaemia	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
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 400 mg for maintenance as partial resistance may have developed. Such patients should also have cryptococcal isolate tested for fluconazole susceptibility at a reference laboratory if possible.

Asymptomatic cryptococcaemia: 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. A symptom screen for cryptococcal meningitis should be performed and if feasible, all patients who are CrAg positive with a CD4 <100 should be lumbar punctured, tested for cryptococcal meningitis and treated appropriately. There is no prospective evidence to guide management of patients found to have asymptomatic antigenaemia, but 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. ART should be started in asymptomatic patients after 2 – 4 weeks of fluconazole therapy. 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) 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: fundoscopy 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).

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 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 – see note below). 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 alternate days should be used.

Maintenance treatment: see above.

Pneumocystis Pneumonia (PCP)

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 <12 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 PCP and a history of intolerance to co-trimoxazole. The rapid desensitisation regimen listed 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.

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.

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-cavitatory 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 cavitatory disease as seen in HIV-seronegative patients is rarely present at CD4 counts <200 cells/mm^3. At CD4 counts <200 cells/mm^3 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.

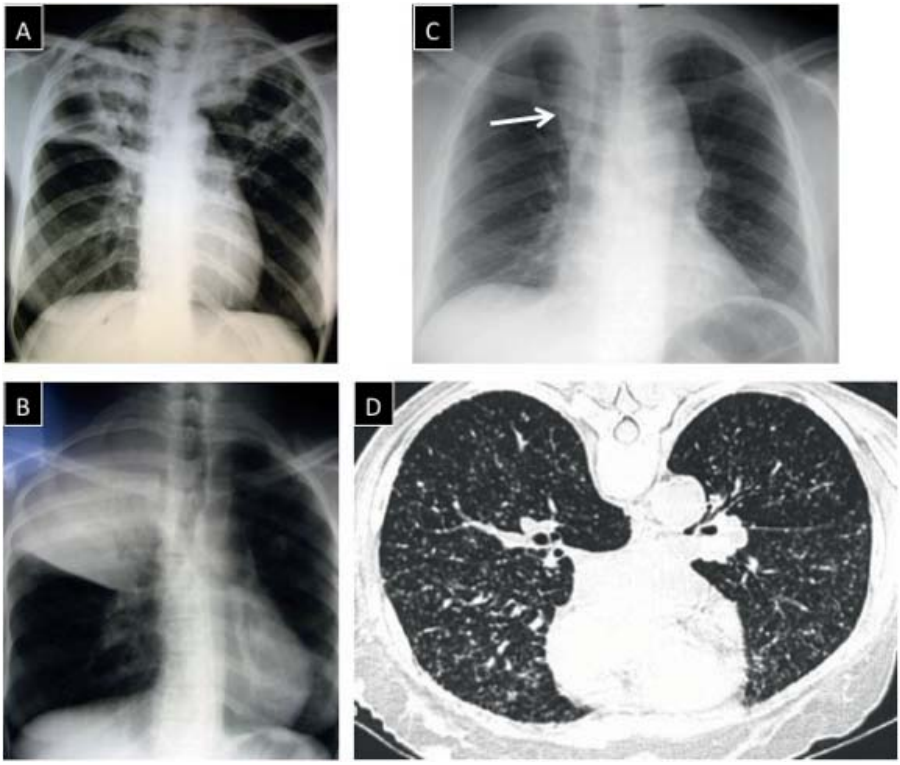


Figure 1. *Cavitatory bilateral upper lobe consolidation (A). Right upper lobe consolidation with air bronchogram (B). Right para-tracheal lymphadenopathy with normal lung parenchyma (C). Miliary TB pattern on CT scan (D).*

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 Cryptococossis	Can mimic PTB, but pleural effusions and lymphadenopathy are rare Serum CrAg and sputum fungal culture are usually positive
Pulmonary Nocardiosis	Predominantly upper lobe cavitary 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 usually present 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.

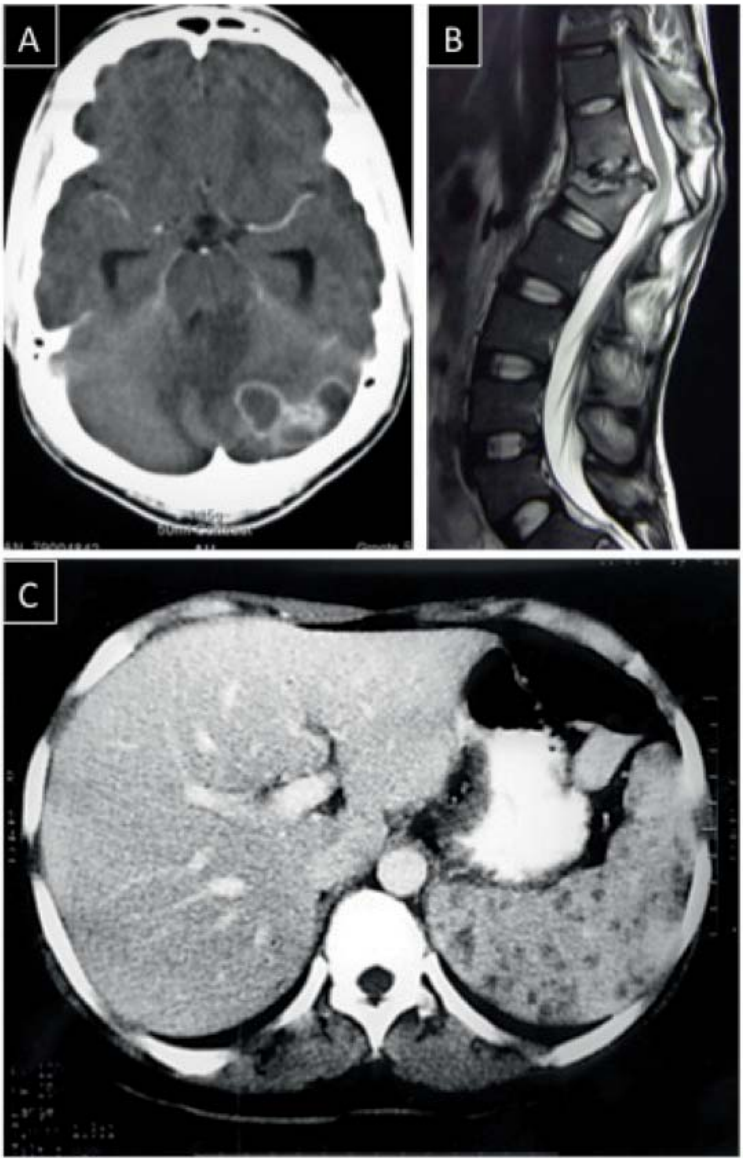


Figure 2: *Cranial CT showing multiple ring-enhancing space-occupying lesions (A). Potts disease of the spine showing destruction of the disc space (B) and abdominal CT scan showing multiple splenic micro-abscesses (C)*

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 is currently being 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).

In advanced disease, TB can progress rapidly. Therefore TB treatment will often be necessary before culture results are available. For pulmonary TB it is reasonable to commence TB treatment pending cultures if two sputum smears are 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

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 2nd line drugs (amikacin, kanamycin or capreomycin)
Pre-XDR	MDR and resistance to EITHER fluoroquinolone OR 2nd 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 Moxifloxacin Ethionamide Terizidone Pyrazinamide	15 – 20 mg/kg 400 mg 15 – 20 mg/kg 15 – 20 mg/kg 30 – 40 mg/kg	Moxifloxacin Ethionamide Terizidone Pyrazinamide	400 mg 15 – 20 mg/kg 15 – 20 mg/kg 30 – 40 mg/kg
33 – 50 kg	Kanamycin Moxifloxacin Ethionamide Terizidone Pyrazinamide	500 – 750 mg 400 mg 500 mg 750 mg 1 000 – 1 750 mg	Moxifloxacin Ethionamide Terizidone Pyrazinamide	400 mg 500 mg 750 mg 1 000 – 1 750 mg
51 – 70 kg	Kanamycin Moxifloxacin Ethionamide Terizidone Pyrazinamide	1 000 mg 400 mg 750 mg 750 mg 1 750 – 2 000 mg	Moxifloxacin Ethionamide Terizidone Pyrazinamide	400 mg 750 mg 750 mg 1 750 – 2 000 mg
>70 kg	Kanamycin Moxifloxacin Ethionamide Terizidone Pyrazinamide	1 000 mg 400 mg 750 – 1000 mg 750 – 1000 mg 2 000 – 2 500 mg	Moxifloxacin Ethionamide Terizidone Pyrazinamide	400mg 750 – 1 000 mg 750 – 1 000 mg 2 000 – 2 500 mg

Adapted from Management of Drug-Resistant Tuberculosis. Policy Guidelines. National Dept of Health 2011.

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	NNRTIs, PIs, Integrase inhibitors
Cutaneous drug reaction	All	NNRTIs
Peripheral neuropathy	Isoniazid, Ethionamide	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), tenonitis/tendon rupture (fluoroquinolones) and hypokalaemia/hypomagnesaemia (capreomycin and aminoglycosides). Ototoxicity from aminoglycosides or capreomycin is usually irreversible. An audiogram should be performed prior to starting an aminioglycoside 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.

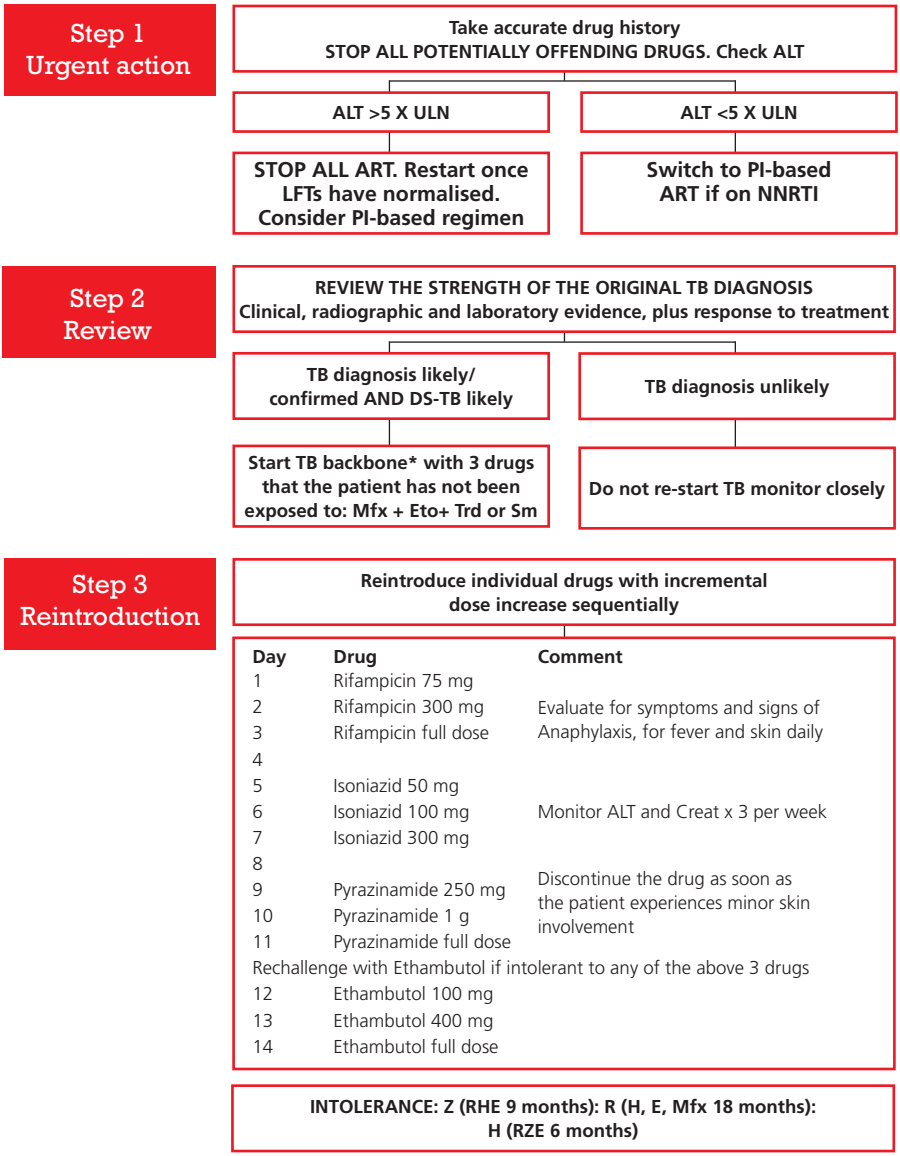
Mild rash in isolation without systemic symptoms, mucosal involvement or abnormal LFTs can be treated with oral antihistamines and skin moisturising agents, whilst continuing the drug under close observation.

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, thrombocytopaenia 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:

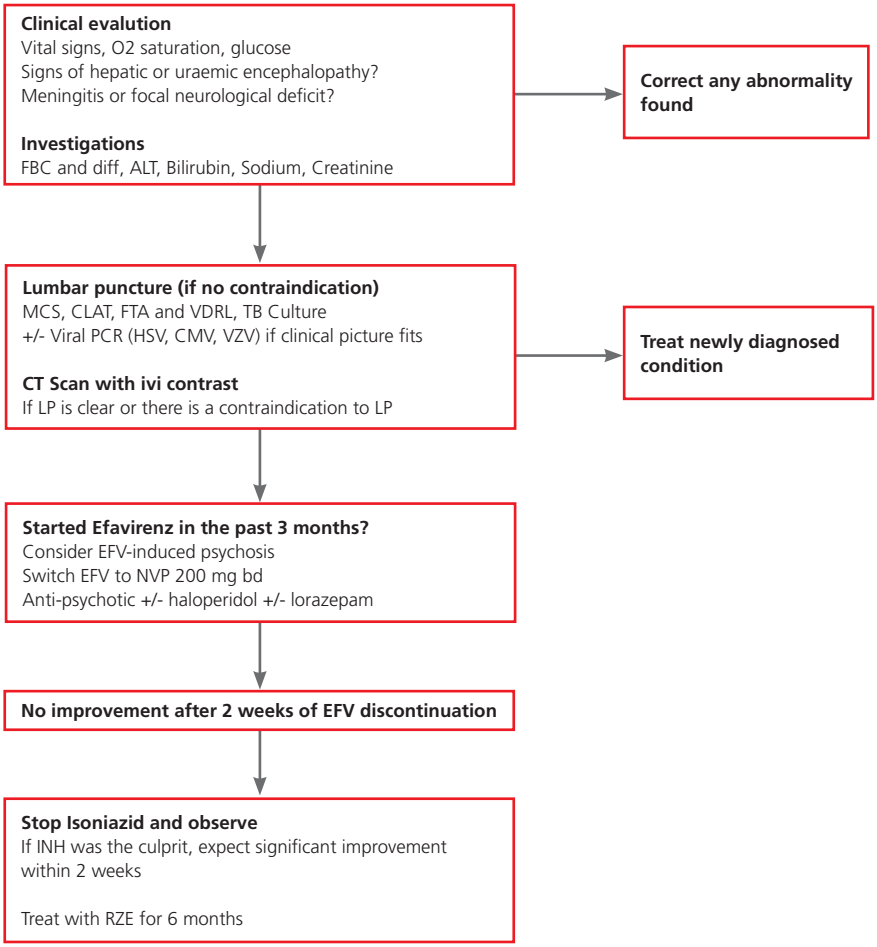
- STOP all agents commonly known to be nephrotoxic
- Correct dehydration as necessary
- Check urinary protein-creatinine ratio, serum electrolytes and creatinine. Renal ultrasound if renal dysfunction continues
- Monitor daily serum creatinine and fluid balance
- If the patient does not improve, refer 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 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 – folic 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, as KS is a stage 4 defining illness
- Co-trimoxazole prophylaxis should also be commenced given that this is a stage 4 defining illness
- 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, 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 (eg. lesion obstructing 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)
  - 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

Disfiguring or symptomatic (pain, obstructing airway/swallowing, etc) local lesions:

- Commence ART and local therapy
- If lesions don't regress after 3 – 6 months or if they progress, then systemic chemotherapy should be used

Extensive skin disease/visceral involvement:

ART and systemic chemotherapy, with the commencement staggered a few days apart

Standard Chemotherapy Regimens

Options:

- Adriamycin (doxorubicin), bleomycin, vincristine combination therapy 2 weekly × 6 – 8 cycles
- Vincristine + bleomycin 2 weekly x 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, thrombocytopaenia, 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 when commencing ART around the time of chemotherapy. It is worth noting that 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
- PIs may increase levels of these agents potentially increasing toxicity
- 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 are immunoblastic 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 dipstix as part of the initial assessment of HIV-positive patients. Any patient who has proteinuria on dipstix 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 (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. AZT may be a better choice than TDF because of better CNS penetration (although there is no prospective evidence that this has clinical benefit but trials are underway). 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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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 (PCP) 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 (see below) 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 PCP section for rapid desensitisation regimen when patients present with acute infections such as toxoplasmosis and PCP):

(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. A recent trial in Botswana 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 coinfected 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 coinfected patients with a CD4 count <500, or any patient with symptomatic liver disease should start ART containing 2 agents with anti-HBV activity, namely tenofovir plus lamivudine or emtricitabine, in addition to efavirenz or protease inhibitor or raltegravir
- Due to its propensity to cause hepatitis, use of nevirapine should be avoided in HIV-HBV coinfected 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'
- Asymptomatic coinfected patients whose CD4 count is >500 may still be eligible for tenofovir and lamivudine or emtricitabine-based ART at the discretion of the prescribing physician
- 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 coinfected 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
- Coinfected babies should be referred to a specialist paediatrician for further management
- All coinfected 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 coinfected patients should be tested for hepatitis C virus (HCV) infection, and those coinfected should be discussed with a specialist for advice on management
- All HIV-HBV coinfected 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 **OR** Cefixime 400 mg PO STAT **OR** Cefpodoxime 200 mg PO STAT **PLUS** Doxycycline 100 mg 12 hourly for 7 days (or azithromycin 1 g single dose) **PLUS** Metronidazole 2 g STAT
Urethral discharge	Ceftriaxone 250 mg IM STAT **OR** Cefixime 400 mg PO STAT **OR** Cefpodoxime 200 mg PO STAT **PLUS** Doxycycline 100 mg 12 hourly for 7 days (or azithromycin 1 g single dose)

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 **OR** Cefixime 400 mg PO STAT **OR** Cefpodoxime 200 mg PO STAT
Penicillin allergy	Ciprofloxacin 500 mg PO STAT (NB: High rates of resistance in SA currently) **OR** Spectinomycin 2 g IM STAT
Disseminated gonococcal arthritis	Ceftriaxone 1 g IM/IV daily for 7 days
Chlamydial infection	Doxycycline 100 mg 12 hourly for 7 days (14 days for lymphogranuloma venereum) **OR** Azithromycin 1 g single dose
Chancroid	Erythromycin 500 mg 6 hourly for 7 days **OR** 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.

Use of the currently available polysaccharide pneumococcal vaccine has been shown to be harmful in a large Ugandan study, and should thus not be given unless there are other indications (e.g. splenectomy or chronic lung disease). The new 7-valent conjugate pneumococcal vaccine was shown to be protective in HIV-infected adults with a previous episode of invasive pneumococcal disease.

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.

Centrum®, the world's most clinically studied multivitamin[1]

Researchers have found that people with HIV are more likely to show signs of micronutrient deficiencies, compared to uninfected people[2,3]. Micronutrients play an important role in HIV infection. HIV infection seems to impair micronutrient status, thus micronutrient status/ intake may affect HIV transmission, progression and morbidity[4].

Many experts recommend multivitamins for people living with HIV, particularly those who are undernourished and have advanced disease[5]. With specially balanced blends of nutrients to help unlock energy, strengthen immunity and maintain good health, the **Centrum®** range of scientifically formulated multivitamin and mineral supplements help bridge dietary nutritional gaps, helping you to live life at 100%[6].

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A varied, balanced diet and a healthy lifestyle are important. This product should not be used as a substitute for a balanced diet. For a list of ingredients, refer to product labelling. Marketed by: Pfizer Consumer Healthcare. Applicant: Pfizer Laboratories (Pty) Ltd. Co. Reg. No.: 1954/000781/07. 85 Bute Lane, Sandton, 2196, South Africa. Tel: 0860 Pfizer (734 937). CEN596

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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 recent meta-analysis failed to show conclusive benefit, but supported the use of a supplement at doses of RDA (recommended daily allowance).

Any affordable, balanced multivitamin/mineral formulation can be used, and will be funded by most medical schemes and companies contracted to Aid for AIDS. Preparations containing very high doses of fat-soluble vitamins (A, D, E and K) and zinc should be avoided as these are harmful. The benefit appears to be limited to patients with a CD4 count of <200.

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 primary 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.

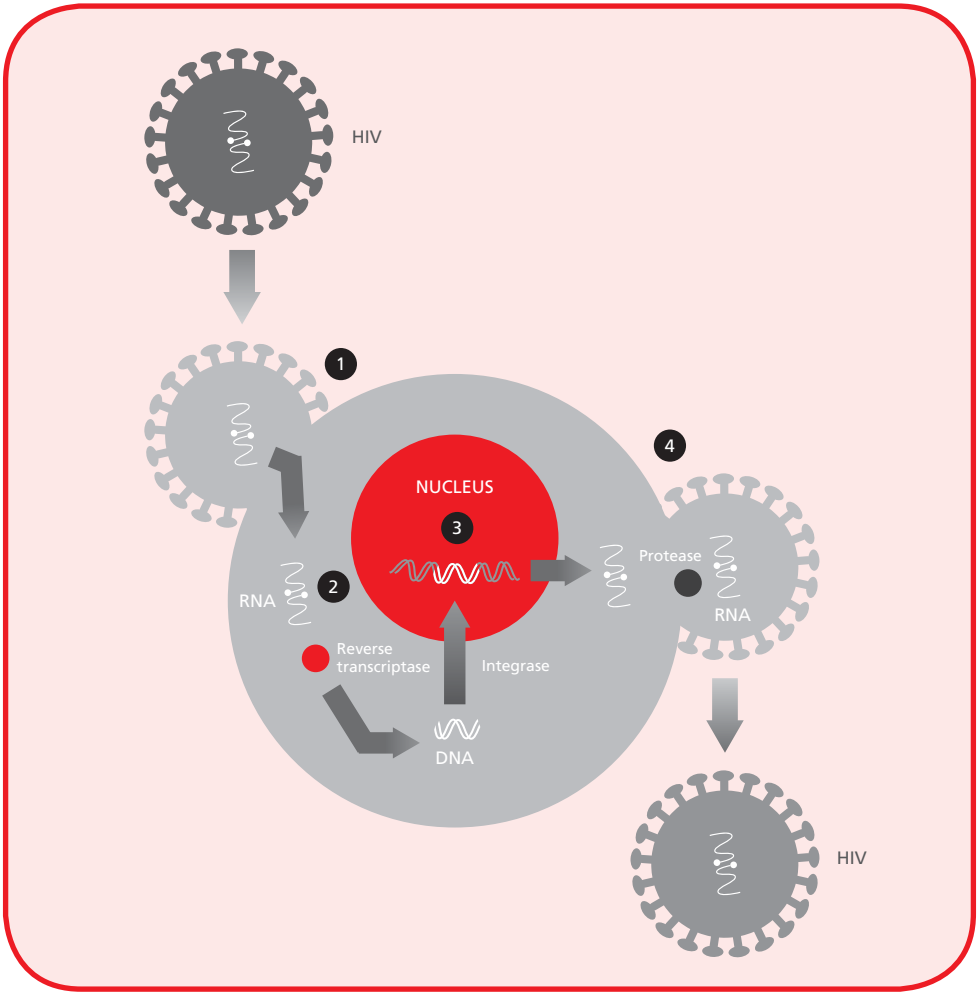
The HIV Lifecycle

1. After HIV binds to receptors 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 dipstix 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 – of unknown 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 many 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 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 0.5×10^9/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. The dose may be reduced to 200 mg bd if a significant drop in the Hb or neutrophil count occur.

Abacavir (ABC)

This is a guanosine analogue. ABC is currently recommended in first line regimens in children in national guidelines. However, tenofovir is preferred in adults as it is more effective, especially in patients with viral loads >100,000. ABC is also 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 – see below), 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. We advise that ABC be avoided in patients with significant cardiovascular risk factors and those with established cardiovascular disease.

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 is rare and has only been reported in paediatric patients. 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 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 (ddI)

This is an adenosine analogue. ddI should not be combined with stavudine as both have a high potential for hyperlactataemia and neuropathy. ddI should also not be combined with tenofovir as there are interactions that enhance ddI'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. ddI 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 ddI use. Hyperlactataemia risk – high. Cirrhosis is a rare complication of long-term ddI 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 single 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 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. All four NNRTIs induce several metabolising enzymes and drug transporters, and efavirenz and etravirine also inhibit some isoenzymes of the cytochrome P450 system. There are thus many potential drug interactions.

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/arthralgia	Permanent discontinuation. No reintroduction If patient also on co-trimoxazole, stop this too. Do not reintroduce co-trimoxazole

Antihistamines (see Drug Interactions table) may be used for symptomatic treatment of NNRTI rash. As there is evidence that prophylactic use of oral corticosteroids aggravates the risk and possibly the severity of the rash, the use of corticosteroids to treat the rash is not recommended. 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.

CELSENTRI® (maraviroc) tablets

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Celsentri® supports you in achieving your treatment goals with CCR5-tropic virus

- Significant virological response to week 48, sustained to week 96[1]
- Significant CD4+ cell increase to week 48, sustained to week 96[2,3]

Patients who may benefit from Celsentri®:

- Patients experiencing virological failure on 2 NRTI + NNRTI with M184V and K103N mutations
- Patients who are triple class-experienced
- Patients currently on 2 NRTI + NNRTI and experiencing CNS side effects[4,5]
- Patients currently on PI-based regimen and experiencing GI side effects[4,5]
- Tropism testing, resistance testing and treatment history should guide the use of Celsentri®

Use of Celsentri® is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group

References: 1. Hardy WD, Gulich RM, Mayer H, *et al.* Two-Year Safety and Virologic Efficacy of Maraviroc in Treatment-Experienced Patients With CCR5-Tropic HIV-1 Infection: 96-Week Combined Analysis of MOTIVATE 1 and 2. *J Acuir Immune Defic Syndr* 2010; **15**;55(5):558-564. **2.** Asmuth DM, Goodrich J, Cooper DA, *et al.* CD4+ T-Cell Restoration After 48 Weeks in the Maraviroc Treatment-Experienced Trials MOTIVATE 1 and 2. *J Acquir Immune Defic Syndr* 2010; **54**:394-397. **3.** Lazzarin A Sierra-Madero JG, Frank I, *et al.* Maraviroc (MVC) Increases CD4+ and CD8+ Cells - Long-term Data from The MVC Clinical Development Program. Poster 0422 presented at HIV10, 7-11 November 2010, Glasgow, UK. **4.** Guidelines for antiretroviral therapy in adults. Southern African HIV Clinicians Society. *The Southern African Journal of HIV Medicine* 2008; 18-21. **5.** Sorianoa V, Pernob CF, Rolf Kaiserc R, *et al.* When and how to use maraviroc in HIV-infected patients. *AIDS* 2009, **23**:2377-2385.

All adverse events should be reported by contacting the Aspen Hotline or directly to GSK on +27 11 745 6000.

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WARNINGS: HEPATOTOXICITY: Hepatotoxicity has been reported with CELSENTRI use. Evidence of a systemic allergic reaction (e.g. pruritic rash, eosinophilia or elevated IgE) prior to the development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or allergic reaction following use of CELSENTRI should be evaluated immediately.

To be taken as part of an ARV combination regimen. **Dose Adjustment:** Appropriate dose adjustment of CELSENTRI when co-administered with CYP3A4 inhibitors and/or inducers. **Cardiovascular Safety:** Caution in patients at increased risk for cardiovascular events. **Immune Reconstitution Syndrome:** Reactions observed within the 1st few weeks or months of initiation of HAART. **Hepatic Safety:** Discontinuation considered in any patient with signs or symptoms of acute hepatitis. **Renal Impairment:** CELSENTRI used with caution in patients with renal impairment (CLcr < 80 ml/min) taking potent CYP3A4 inhibitors. **Soya lecithin:** Hypersensitivity to peanuts or soya - CELSENTRI should not be used. **Effects on ability to drive and use machines:** CELSENTRI may cause dizziness. **INTERACTIONS:** Dose adjustment of CELSENTRI recommended when co-administered with CYP3A4 inhibitors and/or inducers (see package insert). **PREGNANCY AND LACTATION: Pregnancy:** Safety has not been proven. **Lactation:** It is not known whether CELSENTRI is secreted into human milk. Mothers should be instructed not to breastfeed because of the potential for HIV transmission and any possible undesirable effects in breastfed infants. **DOSAGE AND DIRECTIONS FOR USE: Adults:** 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered ARV therapy and other medicinal products (see package insert). **Children:** Not recommended. **Elderly:** Caution should be exercised when administering CELSENTRI in elderly patients. **Renal impairment:** Dosage adjustment recommended in patients with renal impairment who are receiving potent CYP3A4 inhibitors. **Hepatic impairment:** CELSENTRI should be used with caution in patients with hepatic impairment. **SIDE EFFECTS AND SPECIAL PRECAUTIONS:** Common: diarrhoea, nausea, headache; dizziness, paraesthesia, dysgeusia, somnolence; cough; vomiting, abdominal pain, abdominal distension, dyspepsia, constipation; rash, pruritus, muscle spasms, back pain, asthenia, insomnia. **MANAGEMENT OF OVERDOSAGE:** General supportive measures including keeping the patient in a supine position, careful assessment of patient vital signs, blood pressure and ECG. Elimination of unabsorbed active CELSENTRI by emesis or gastric lavage. Administration of activated charcoal used to aid in removal of unabsorbed active substance. **HCR:** GlaxoSmithKline South Africa (Pty) Ltd, Co, Reg. No.1948/030135/07, 39 Hawkins Avenue, Epping Industria 1, 7460. For full prescribing information see package insert approved by the medicine's regulatory authority. A17416 01/14.

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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 generally be avoided in these patients. 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 (one study reported that the risk was increased if the baseline, but not the current, CD4 counts were above these levels).

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 myelomeningocoele have been reported in humans. However, a recent 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

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).

Side effects: rash, hepatitis risk lower than efavirenz.

Dose: 25 mg daily with food.

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: 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 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 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 is recommended to give ritonavir and indinavir in combination, 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.

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. Rifampicin reduces the plasma concentrations of raltegravir, but a clinical trial has shown that a dose adjustment is not necessary.

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

Dose: 400 mg bd.

Dolutegravir

This drug is expected to be registered in South Africa soon. It is more robust than raltegravir from a resistance perspective. There is limited experience with it to date.

Side effects: Increases serum creatinine by 10-15 µmol/L due to inhibition of secretion, not nephrotoxicity. Headache, 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 + ABC
AZT + 3TC + NVP
d4T + 3TC + NVP

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Reference: 1. Guidelines for antiretroviral therapy in adults. Southern African HIV Clinicians Society. *The Southern African Journal of HIV Medicine* 2012; 13(3):114-133.

S4 Tenarenz®. Reg. No: 44/20.2.8/1051. Each film-coated tablet contains tenofovir disoproxil fumarate 300 mg, efavirenz 600 mg, and lamivudine 300 mg. 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. A15350 10/12.

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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
Protease inhibitors (PIs)		
Atazanavir (ATV)	300 mg + ritonavir 100 mg daily	Unconjugated hyperbilirubinaemia, dyslipidaemia (low potential)

Chemical name	Dose	Common side effects
Darunavir (DRV)	600 mg bd + ritonavir 100 mg bd with food	Diarrhoea, nausea, rash, dyslipidaemia (moderate potential)
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

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.

Timing of when to commence ART is not a simple decision. The key determinant of outcome on ART is the CD4 count when ART is initiated. Cohort studies show that provided ART is started using a CD4 threshold of 350, outcome is excellent and immune reconstitution occurs in most cases. Some guidelines advocate starting ART at higher CD4 counts based on retrospective studies. Such studies are prone to bias and the benefit of starting at higher CD4 counts, if present, are relatively small. We await the results of a large randomised controlled trial addressing the question of benefits and risks of earlier initiation of ART (the START study). Some international guidelines also use a high viral load as an indication to commence therapy. However CD4 decline is very variable and we do not support initiating ART only on the basis of a high viral load – these patients should have their CD4 count monitored more frequently (e.g. three monthly).

Guidelines for starting ART:

The patient MUST be ready for treatment

AND

- CD4 <500 (preferably confirmed on 2 occasions)

  OR

- Confirmed WHO Clinical Stage 3 or 4 condition or other serious morbidity*

* *HIV-related e.g.lymphocytic interstitial pneumonitis, polymyositis, HIV vasculopathy, or HIV-unrelated e.g. active chronic hepatitis B or C, non-AIDS malignancies.*

Please note that this list is not exhaustive – any severe HIV-related disorder, as well as any condition requiring long-term immunosuppressive therapy could be considered an indication for ART.

As untreated HIV appears to be a risk factor for vascular disease, patients with symptomatic vascular disease may also be considered for earlier ART.

The HIV-infected partner in a sero-discordant couple may be offered early ART regardless of CD4 count to protect the HIV-uninfected partner.

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, with a progressive reduction in response for adherence below 95%. 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), such 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.

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 before ART or if adherence is poor
- 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 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 or NVP).

Recommended First Line Combinations

First line
TDF + FTC + NNRTI*
AZT + 3TC + NNRTI*

* *EFV or NVP. EFV is the preferred agent if on TB treatment. NVP should be avoided in females with a CD4 count >250 and males with a CD4 count >400. Some experts recommend NVP as the preferred agent for women who intend to fall pregnant, but WHO and Department of Health guidelines recommend EFV. Abacavir can be used as an alternative NRTI if there are intolerances/ contra-indications to TDF and AZT, but is not recommended in first line as it has inferior virologic efficacy to TDF.*

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
- Zidovudine + lamivudine
- Abacavir + lamivudine (alternative regimen)

In terms of the recommended combinations we favour tenofovir plus lamivudine or emtricitabine. Zidovudine should be used when tenofovir is contra-indicated (creatinine clearance <50ml/min) or not tolerated. Several studies have demonstrated lower rates of virological suppression with abacavir

regimens compared with tenofovir regimens in patients with baseline viral load >100 000 copies/ml. Abacavir may possibly be associated with an increased risk of MI and may cause a hypersensitivity reaction. Patients with anaemia or neutropaenia should avoid zidovudine. Abacavir use is restricted because of expense and the reasons discussed above – it may be substituted if toxicity occurs and no other options are available (discuss with AfA).

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. 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. These tests should not be done following vaccination or if an intercurrent infection is present, as these will transiently increase the viral load.

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 sustained increase to >1 000 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.

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 should not be 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.

Patients failing their first boosted PI regimen (i.e. the currently advised second line ART) usually 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. 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 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 (at least one a new NRTI) and a ritonavir-boosted PI. Ideally, changing therapy should include at least two "clean" drugs (never used before or unlikely to be cross-resistant). Constructing a new regimen may be difficult if the patient has been exposed to multiple agents, particularly since there is often cross-resistance within classes of antiretrovirals.

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 stavudine, 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

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 several observational studies have shown outcomes on 2nd line regimens are similar in patients with or without resistance in the NRTI backbone.

Unusual Combinations

Patients who are unable to tolerate NRTIs (e.g. because of lactic acidosis) can use a combination of an NNRTI (efavirenz, nevirapine or etravirine) 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			Dose for PI-experienced		
	Nevirapine	Efavirenz	Etravirine	Nevirapine	Efavirenz	Etravirine
Atazanavir/r	Not recommended	400 mg/ 100 mg daily	Not recommended	Not recommended	400 mg/ 100 mg daily	Not recommended
Darunavir/r	Standard dose	Standard dose	Standard dose	Standard dose	Standard dose	Standard dose
Lopinavir/r	Standard dose	Standard dose	Standard dose	500 mg/ 125 mg bd	500 mg/ 125 mg bd	Standard dose

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

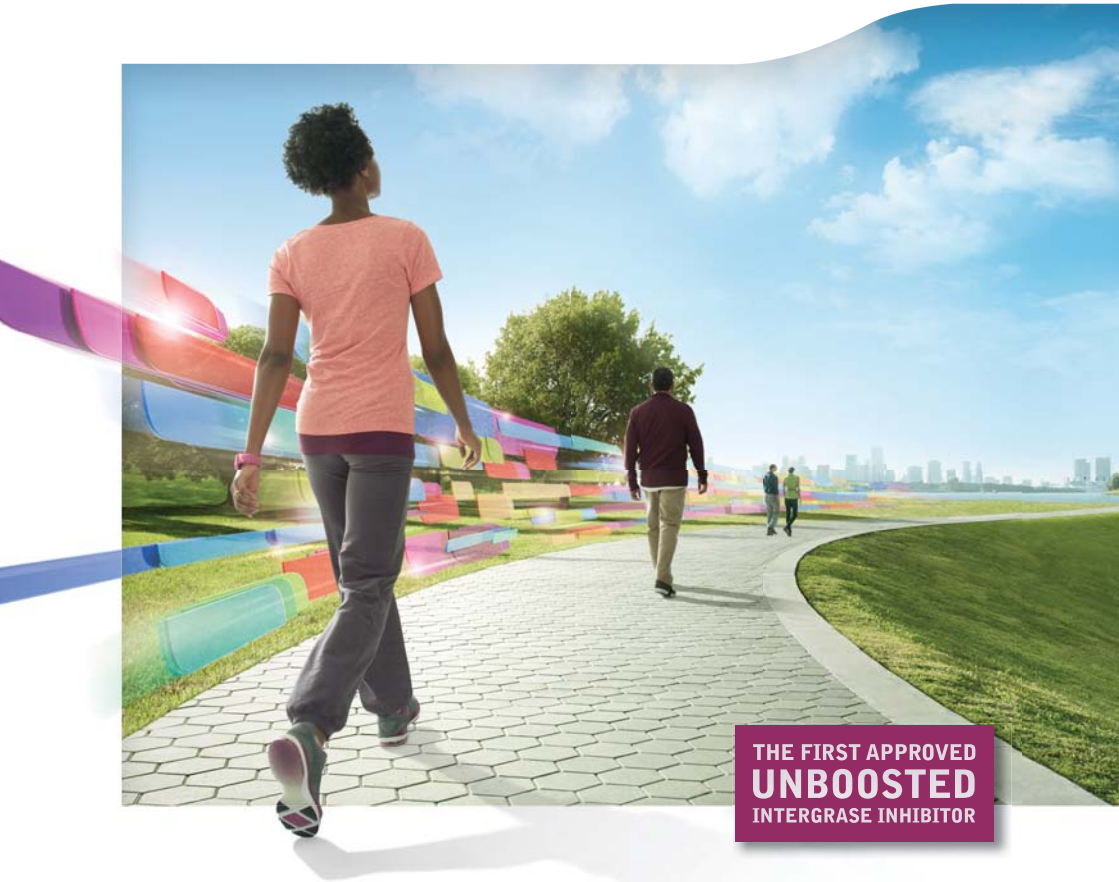
Third Line Combinations

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 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, raltegravir and NRTIs.

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.

ENVISION A PATH FORWARD – TODAY AND TOMORROW



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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 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, but the resistance profile at first line failure is relatively predictable and genotyping is therefore often unnecessary.

In patients failing an ART regimen it is sometimes necessary to do a genotype resistance test to guide decisions regarding the next 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 infants 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. 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. In this situation one may consider interrupting raltegravir, because continuing raltegravir in a failing regimen may result in accumulation of further integrase mutations that may compromise second line integrase inhibitors such as dolutegravir which will be available in the future.

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.

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/

NRTI 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. This is unpredictable: 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 (see above)
- 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
- Commercial assays currently available in South Africa do not sequence the integrase gene, but this is likely to change when this class of drugs becomes more widely used

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 a PI should be substituted. If it is necessary to stop an NNRTI-based regimen 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 is a rare cause 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 pancytopaenia and may respond to folinic (not folic) acid. Neutropaenia 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 neutropaenia.

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 cytopaenias.

Management of drug-induced anaemia and neutropaenia	
Hb <10 Neutrophil <1.5	Avoid AZT if possible otherwise decrease the dose to 200 mg bd
Hb <8 Neutrophil <1	Switch AZT to alternative
Neutrophil <1	Stop co-trimoxazole

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 the most sensitive 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 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).

All currently available antiretrovirals can cause hepatotoxicity. 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 raltegravir 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 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.

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*
- ALT >200, stop relevant drugs, do hepatitis screen and full LFT. INR should also be done in patients with jaundice.

** If symptoms of hepatitis or jaundice – 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 (as suggested

below) 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 may be due to macrolides, 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
- Efavirenz ⇨ boosted PI or raltegravir
- Boosted PI ⇨ different boosted PI
- 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 activity against 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 extra-hepatic 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.

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 recently published, 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.

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, 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, 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
- If double dose lopinavir/ritonavir was used this should be recommenced with slow dose escalation over two weeks. After ART rechallenge, monitor ALT every 2 weeks for 2 months. If this is not tolerated on rechallenge discuss with AfA regarding alternative treatment strategies.

Do not rechallenge co-trimoxazole unless there are compelling reasons (e.g. history of PCP 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 (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 – see below. 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 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 (see under treatment below).

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 (see above), 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 - PI + NNRTI table). If the patient has failed an NNRTI regimen and was on a boosted PI this should be continued alone – many patients will remain suppressed when treated only with a boosted PI. If they do not suppress then AfA should be contacted for advice on which drugs may be added (using safer NRTIs after lactic acidosis is controversial; adding integrase inhibitors in such a scenario may be an option). 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 Clinician 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 or saquinavir (1 600 mg/100 mg daily) are associated with a lower risk of dyslipidaemia and patients should be switched to these PIs 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, raltegravir or PIs. Furthermore, a longitudinal study in the USA showed that visceral and trunk fat increased at similar rates in patients on ART and 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 >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 ≥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. 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 interrupted except in exceptional circumstances (e.g. severe toxicity), or if ART was only prescribed to prevent mother-to-child transmission. 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 or efavirenz, 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 (can also 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.

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 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 sex.

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 will be older than 50 by 2015. 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 1,717 people over the age of 60 currently registered on AfA (including eight 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. 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 co-morbidities. 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 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 serious 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 impairment in renal function and hepatic metabolism. 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).

There is no evidence that starting ART earlier than in younger patients results in better outcomes and the usual criteria for initiating therapy should apply. When selecting the most appropriate ART

combination to use in older patients, the possibility of pre-existing renal or hepatic insufficiency and hyperlipidaemia should be considered. The relevant baseline tests, e.g. serum creatinine should be carried out, and after starting ART patients should be regularly monitored for evidence of toxicity.

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 decreased hepatic and renal function should always be considered as indicated above. It is not clear if the elderly are more likely to develop CNS toxicity with efavirenz, but caution should be exercised in those with early cognitive impairment.

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 support and care.

Drug Dosages in Renal Failure

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.

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

$$\frac{\textbf{(140 – age) × weight (kg)}}{\textbf{serum creatinine (µmol/L)}}$$

Good estimate for men, for women multiply total by 0.85

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
Raltegravir	Unchanged	Unchanged
Dolutegravir	Unchanged	Unchanged
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 coinfected 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 coinfected 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
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

* *Patients coinfected 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 raltegravir.

ART and Porphyria

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.

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
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 on alternate days can be used as an alternative to rifampicin
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

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.

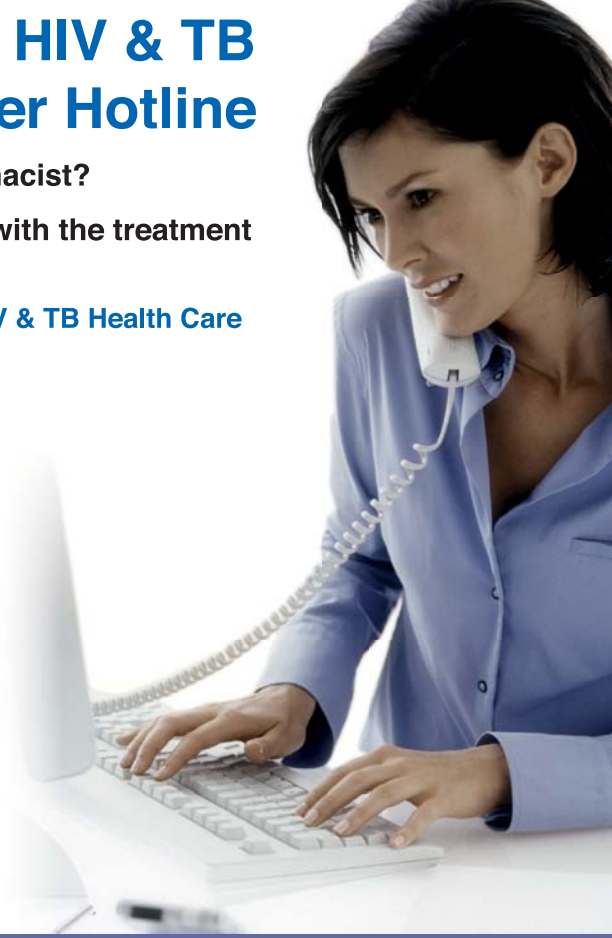
The basis of most of these drug interactions is interference with hepatic metabolism. PIs and NNRTIs are metabolised by the liver and other drugs that induce and/or inhibit hepatic enzymes which affect the levels of PIs or NNRTIs. Both PIs and NNRTIs induce and/or inhibit hepatic enzymes, which leads 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.

The accompanying tables list drugs interacting with ART. The list is not comprehensive. Drugs have been omitted where there is either no documented interaction, or no data available. 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.

We would like to acknowledge the assistance of the Medicines Information Centre, University of Cape Town in drawing up these tables.

Toll-Free National HIV & TB Health Care Worker Hotline



Are you a doctor, nurse or pharmacist?

Do you need clinical assistance with the treatment of your HIV or TB patients?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE
0800 212 506

0800 212 506 / 021 406 6782

Alternatively send an SMS or "Please Call Me" to 071 840 1572

www.hivhotline.uct.ac.za

The Medicines Information Centre (MIC) situated within the Division of Clinical Pharmacology, Department of Medicine at the University of Cape Town is the largest and only clinically-based medicine information centre in South Africa.

In collaboration with the Foundation for Professional Development and USAID/PEPFAR, the MIC provides a toll-free national HIV & TB hotline to all health care workers in South Africa for patient treatment related enquiries.

What questions can you ask?

The toll-free national HIV & TB health care worker hotline provides information on queries relating to:

- HIV testing
- Post exposure prophylaxis: health care workers and sexual assault victims
- Management of HIV in pregnancy, and prevention of mother-to-child transmission
- Antiretroviral Therapy
  - When to initiate
  - Treatment selection
  - Recommendations for laboratory and clinical monitoring
  - How to interpret and respond to laboratory results
  - Management of adverse events
- Drug interactions
- Treatment and prophylaxis of opportunistic infections
- Drug availability
- Adherence support
- Management of tuberculosis and its problems

When is this free service available?

The hotline operates from Mondays to Fridays 8.30am – 4.30pm.

Who answers the questions?

The centre is staffed by specially-trained drug information pharmacists who share 50 years of drug information experience between them. They have direct access to:

- The latest information databases and reference sources
- The clinical expertise of consultants at the University of Cape Town's Faculty of Health Sciences, Groote Schuur Hospital and the Red Cross War Memorial Children's Hospital

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MEDICINES INFORMATION CENTRE

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	Interaction	Management
Acetazolamide		
Lamivudine/Emtricitabine	Potential for competition with lamivudine/emtricitabine for active renal transport mechanisms, which may lead to increased levels of either drug.	Monitor for adverse effects.
Stavudine	Potential for competition with stavudine for active renal transport mechanisms, which may lead to increased levels of either drug.	Monitor for adverse effects.
Tenofovir	Potential for competition with tenofovir for active renal transport mechanisms, which may lead to increased levels of either drug.	Monitor for adverse effects.
Zidovudine	Additive myelosuppression.	If concomitant treatment with potentially myelosuppressive drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters.
Aciclovir		
Tenofovir	Levels of tenofovir or aciclovir may be increased.	Weekly monitoring of renal function when used concomitantly.
Zidovudine	One case report of profound lethargy.	No dosage adjustment required.
Activated Charcoal		
	May prevent absorption of antiretroviral.	Do not take antiretroviral for 2 hours before or 2 hours after having taken activated charcoal.
Albendazole		
Efavirenz	Theoretically levels of the active metabolite albendazole sulfoxide may be reduced.	Monitor response, this is likely to be clinically important when used to treat systemic worm infections.
Etravirine	Theoretically levels of the active metabolite albendazole sulfoxide may be reduced.	Monitor clinical effect of albendazole.
Lopinavir/Atazanavir/Darunavir+ritonavir	Ritonavir reduces the exposure to albendazole and its active metabolite, albendazole sulfoxide significantly.	Monitor response, this is likely to be clinically important when used to treat systemic worm infections.
Nevirapine	Theoretically levels of the active metabolite albendazole sulfoxide may be reduced.	Monitor clinical efficacy of albendazole.
Zidovudine	Additive bone marrow suppression.	Monitor FBC every two weeks.
Alfentanil		
Efavirenz	Potential decrease in alfentanil concentration.	Monitor for effectiveness of alfentanil.
Etravirine	Etravirine may decrease alfentanil level.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential increase in alfentanil concentration.	Monitor closely for increased respiratory depression and adjust dose of alfentanil if needed.
Nevirapine	Potential decrease in alfentanil concentration.	Monitor response and adjust dose if needed.
Alfuzosin		
Etravirine	Potential decrease in alfuzosin exposure.	Monitor clinical effect and increase dosage if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased plasma concentrations of alfuzosin.	Contraindicated.
Alimemazine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically concentrations of alimemazine and ritonavir may be increased.	Monitor closely.

	Interaction	Management
Allopurinol		
Didanosine	Increased didanosine effects.	Avoid combination.
Alprazolam		
Efavirenz	Efavirenz could potentially decrease alprazolam exposure.	Monitor clinical effect and withdrawal symptoms.
Etravirine	Etravirine, an inducer of CYP3A4, could potentially decrease alprazolam exposure.	Monitor clinical effect and withdrawal symptoms.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased alprazolam effect when lopinavir/ritonavir or atazanavir/ritonavir is started. (After 10 days no significant interaction).	Use safer alternative e.g. oxazepam, temazepam, lorazepam.
Nevirapine	Theoretical risk of reducing alprazolam effects.	Monitor for alprazolam effects, and withdrawal symptoms when adding nevirapine to patient already on alprazolam.
Aluminium hydroxide		
Lopinavir/Atazanavir/Darunavir+ritonavir	Atazanavir solubility/absorption decreases as pH increases.	Atazanavir should be administered 2 hours before or 1 hour after antacids.
Raltegravir	Decreased raltegravir exposure.	Do not coadminister.
Amikacin		
Lamivudine/Emtricitabine	Amikacin is nephrotoxic.	Monitor renal function periodically and adjust lamivudine dosage accordingly.
Stavudine	Amikacin is nephrotoxic.	Monitor renal function periodically and adjust stavudine dosage accordingly.
Tenofovir	Potential for additive nephrotoxicity.	Avoid if possible or monitor renal function weekly if concurrent use unavoidable.
Amiodarone		
Efavirenz	Theoretically efavirenz may decrease or increase levels of amiodarone.	Combination best avoided until more data becomes available, alternatively close monitoring of the therapeutic effect is recommended.
Etravirine	Etravirine is expected to decrease plasma concentrations of amiodarone.	Caution is warranted and therapeutic concentration monitoring, if available, is recommended.
Lopinavir/Atazanavir/Darunavir+ritonavir	Ritonavir increases amiodarone levels significantly.	Avoid lopinavir/ritonavir combination. Atazanavir/darunavir + ritonavir can be used with caution, if cardiac function and amiodarone levels can be monitored.
Nevirapine	Potential for decrease in amiodarone plasma concentrations.	Dose adjustment of amiodarone may be needed due to possible decrease in clinical effect.
Amitriptyline		
Lopinavir/Atazanavir/Darunavir+ritonavir	Plasma concentration and effects of amitriptyline may be increased. Concurrent use of amitriptyline and lopinavir/ritonavir may result in an increased risk of QT interval prolongation.	Careful monitoring of therapeutic and adverse effects is recommended.
Amlodipine		
Efavirenz	Theoretically amlodipine levels may be decreased.	Monitor effect closely and increase dose of amlodipine if needed.
Etravirine	Potential decrease in amlodipine exposure.	Monitor clinical effect and increase dose of amlodipine if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Amlodipine levels significantly increased by ritonavir and atazanavir. Both can prolong PR interval.	Use lower starting dose of amlodipine and titrate to effect. Monitor closely.
Nevirapine	Theoretically amlodipine levels may be reduced.	Monitor effect closely and increase dose of amlodipine if needed.

	Interaction	Management
Amphotericin B		
Didanosine	Amphotericin is nephrotoxic.	Renal function should be monitored and didanosine dosage adjusted accordingly.
Lamivudine/Emtricitabine	Amphotericin B is nephrotoxic.	Renal function should be monitored and lamivudine dosage adjusted accordingly.
Stavudine	Amphotericin B is nephrotoxic.	Renal function should be monitored and stavudine dosage adjusted accordingly.
Tenofovir	Additive nephrotoxicity.	Avoid concurrent use if possible. Monitor renal function weekly if concomitant use is unavoidable.
Zidovudine	Similar toxicity profile.	Monitor FBC and renal function closely. Consider dose reduction if required.
Artemether/lumefantrine		
Efavirenz	Efavirenz decreases artemether and lumefantrine levels.	Monitor for efficacy.
Etravirine	Artemether AUC: decreased by 38%; Lumefantrine AUC: decreased by 13%	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Decreased artemether/DHA exposure. Increased AUC of lumefantrine.	Use with caution and monitor for toxicity and efficacy.
Nevirapine	NVP-based ART decreased artemether and dihydroartemisinin AUCs but effect on lumefantrine exposure is variable in different studies. Nevirapine exposure also reduced.	Monitor response closely.
Aspirin		
Tenofovir	Additive nephrotoxicity has been reported with NSAIDs.	Use with caution. The risk is increased if an NSAID is used for a long duration, if the patient has a pre-existing renal dysfunction, has a low body weight, or receives other drugs that may increase tenofovir exposure. Monitor renal function.
Zidovudine	In vitro study showed possible increase in AZT concentration. Further research needed. Not yet shown to be a clinically significant interaction.	No dosage adjustment required.
Atenolol		
Lopinavir/Atazanavir/Darunavir+ritonavir	Cardiac and neurological events have been reported when ritonavir was coadministered with beta blockers. Possible prolongation of PR interval. No clinically significant drug interaction or additive effect of atazanavir and atenolol.	Use with caution.
Atorvastatin		
Efavirenz	Decreased concentrations of atorvastatin due to enzyme induction by efavirenz. AUC decreased by 30 to 40 percent.	Some patients may need higher doses of atorvastatin to achieve target lipid goals, but only with increased monitoring of toxicities.
Etravirine	Etravirine slightly lowers atorvastatin exposure.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Markedly increased levels of atorvastatin (5-fold).	Avoid combination if possible. May consider low dose atorvastatin or normal dose pravastatin, monitor for myopathy.
Nevirapine	Potential for decreased concentrations of atorvastatin due to enzyme induction by nevirapine.	Monitor therapeutic response.
Atovaquone		
Efavirenz	Atovaquone AUC decreased by 75%.	Dose adjustment not established.
Lopinavir/Atazanavir/Darunavir+ritonavir	Lopinavir/ritonavir may decrease atovaquone drug levels. Atazanavir decreases atovaquone AUC by 46%.	Clinical significance is unknown, however, an increase in atovaquone dose may be needed. Monitor therapeutic effect.
Nevirapine	Possible reduction of atovaquone levels.	Use with caution. Monitor response.
Zidovudine	Increased zidovudine effects possible due to inhibition of glucuronidation by atovaquone.	No dose adjustment required. Monitor for AZT toxicity.
Aurothioglucose		
Didanosine	Both drugs may cause peripheral neuropathy.	Avoid combination where possible, monitor closely for peripheral neuropathy.
Stavudine	Both drugs may cause peripheral neuropathy.	Avoid combination where possible, monitor closely for peripheral neuropathy.
Azithromycin		
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased risk of QT interval prolongation.	No dosage adjustment required. Monitor.
BCG vaccine		
	No kinetic interaction reported.	HIV-positive children are at high risk of disseminated BCG disease following BCG vaccination. Where HIV services provide early identification and antiretroviral therapy, BCG vaccination in infants born to HIV-positive mothers should be delayed until these infants are confirmed to be HIV negative. In areas with a high prevalence of TB and HIV, where diagnostic and treatment services for mother and infants are limited, the current recommendation is that BCG vaccination should be given at birth to all infants regardless of HIV exposure.
Beclomethasone		
Efavirenz	No interaction reported.	When very high doses are used and systemic absorption is higher, monitor for steroid effect and ideally efavirenz levels should be monitored.
Lopinavir/Atazanavir/Darunavir+ritonavir	Coadministration of darunavir/ritonavir (600/100 mg twice daily) and inhaled beclomethasone diproprionate (160 mg twice daily) decreased the AUC and Cmax of the active metabolite by 11% and 19%, respectively. No significant effect on adrenal function was seen.	No dosage adjustment required.
Nevirapine	No interaction reported.	When very high doses are used and systemic absorption is higher, monitor for steroid effect and ideally nevirapine levels should be monitored.
Betamethasone		
Efavirenz	Theoretically betamethasone levels may be reduced and efavirenz levels may be reduced.	Monitor for steroid effect. Ideally, efavirenz levels should be monitored.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically betamethasone levels may be increased and PI levels reduced.	Monitor for steroid effect and consider dose reduction of systemic betamethasone. Ideally, PI levels should be monitored.
Nevirapine	Theoretically betamethasone and nevirapine levels may be reduced.	Monitor for steroid effect and consider dose increase of corticosteroid. Ideally, nevirapine levels should be monitored.
Budesonide		
Efavirenz	Theoretically oral budesonide levels may be decreased. Theoretically, efavirenz levels may be decreased.	Monitor for steroid effect. Ideally, efavirenz levels should be monitored.
Etravirine	Theoretically oral budesonide and etravirine levels may be decreased.	Monitor therapeutic outcome.

	Interaction	Management
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible increase in budesonide levels as a result of enzyme inhibition by ritonavir. Theoretically, oral budesonide may decrease PI levels.	Use with caution. Patients on oral budesonide should be closely monitored for increased signs and symptoms of hypercorticism and reduction of budesonide dosage should be considered. Ideally, PI levels should be monitored if oral budesonide used.
Nevirapine	Theoretically budesonide and nevirapine levels may be reduced if oral budesonide is used.	Monitor for steroid effect. Ideally, nevirapine levels should be monitored.
Bupivacaine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible increased bupivacaine concentrations.	Monitor for increased or prolonged therapeutic and adverse reactions.
Bupropion		
Efavirenz	Bupropion AUC decreased by 55% due to induction of CYP2B6 by EFV.	Titrate bupropion to clinical effect. Do not exceed maximum recommended dose.
Lopinavir/Atazanavir/Darunavir+ritonavir	Ritonavir decreases the level of bupropion. Atazanavir alone is unlikely to alter bupropion concentrations.	Start at recommended starting dose and titrate to effect. Do not exceed maximum recommended doses.
Nevirapine	Theoretically bupropion levels may be decreased as NVP induces CYP2B6.	Titrate bupropion to clinical effect.
Captopril		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically captopril levels may be increased.	Monitor closely.
Carbamazepine		
Abacavir	May increase carbamazepine concentrations due to competition for glucuronidation.	Perform TDM for carbamazepine.
Efavirenz	When efavirenz is administered concomitantly, there is a reduction in the plasma concentrations of both drugs.	Avoid combination. Valproic acid or lamotrigine can be used as an alternative.
Etravirine	Reduced plasma concentrations of etravirine.	Avoid combination. Valproic acid or lamotrigine can be used as an alternative.
Lopinavir/Atazanavir/Darunavir+ritonavir	Coadministration of carbamazepine and protease inhibitors may result in decreased concentrations of protease inhibitors. Also, PIs may increase the levels of carbamazepine.	Avoid combination. Valproic acid or lamotrigine (may require higher dose) can be used as an alternative to carbamazepine.
Nevirapine	Nevirapine may cause decreased carbamazepine plasma concentrations. Also, carbamazepine may lower nevirapine concentrations.	Avoid combination. Valproic acid or lamotrigine can be used as an alternative.
Raltegravir	Theoretically raltegravir concentrations may be reduced via induction of glucuronidation.	Consider therapeutic drug monitoring for raltegravir.
Zidovudine	May increase carbamazepine concentrations due to competition for glucuronidation.	Perform TDM for carbamazepine and monitor for potential additive haematological toxicity.
Carvedilol		
Etravirine	Etravirine could potentially increase carvedilol concentrations via CYP2C9 inhibition or decrease carvedilol concentrations via induction of glucuronidation (UGT1A1).	Monitor clinical effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Possibility of prolonged PR interval. Also darunavir/ritonavir could potentially increase carvedilol concentrations via CYP2D6 inhibition or decrease carvedilol concentrations via induction of glucuronidation.	Use with caution. Clinical monitoring is recommended.

	Interaction	Management
Cetirizine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased exposure and half-life of cetirizine.	No dosage adjustment required. Monitor patients for increased cetirizine side effects including drowsiness.
Chloramphenicol		
Didanosine	No kinetic interaction reported, but both drugs may cause peripheral neuropathy.	Monitor closely for peripheral neuropathy.
Efavirenz	Theoretically chloramphenicol may increase efavirenz levels.	Monitor for efavirenz toxicity.
Etravirine	Theoretically etravirine levels may be increased.	Monitor for adverse effects.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically chloramphenicol may increase PI levels.	Monitor for PI toxicity.
Nevirapine	Theoretically chloramphenicol may increase nevirapine levels.	Monitor for nevirapine toxicity.
Stavudine	No kinetic interaction reported, but both drugs may cause peripheral neuropathy.	Monitor closely for peripheral neuropathy.
Zidovudine	Theoretically both chloramphenicol and zidovudine effects may be increased due to inhibition of glucuronidation. Also, both agents are bone marrow toxins.	Monitor FBC frequently.
Chlordiazepoxide		
Efavirenz	The action of chlordiazepoxide may be decreased.	Monitor clinical effect.
Etravirine	The action of chlordiazepoxide may be decreased.	Monitor clinical response.
Lopinavir/Atazanavir/Darunavir+ritonavir	The activity of chlordiazepoxide may be increased.	Monitor closely and consider lowering the dose or use safer alternative e.g. oxazepam, temazepam, lorazepem.
Nevirapine	The action of chlordiazepoxide may be decreased.	Monitor clinical response.
Chloroquine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically PIs may increase chloroquine levels. Increased risk of QT interval prolongation.	No dosage adjustment required. Monitor for ophthalmological toxicity in patients on long-term chloroquine therapy. Avoid/closely monitor in patients with risk of QT interval prolongation.
Chlorphenamine/ chlorpheniramine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically chlorpheniramine levels may be increased.	Clinical significance of this interaction is unknown. Monitor for adverse effects.
Chlorpromazine		
Didanosine	No interaction reported with EC caps. Buffer in tablets may reduce chlorpromazine absorption.	No dosage adjustment required. If using tablets give at least two hours apart.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretical interaction resulting in increased chlorpromazine levels.	Use with caution due to the risk of QT interval prolongation reported for both drugs.
Zidovudine	Additive haematological toxicity.	Monitor FBC.
Cimetidine		
Didanosine	May increase didanosine levels.	Monitor for didanosine toxicity.
Efavirenz	No drug interaction reported, but theoretically cimetidine could increase efavirenz levels.	No dosage adjustment required, but monitor for side effects of efavirenz.
Lopinavir/Atazanavir/Darunavir+ritonavir	No clinically significant interaction with lopinavir/ritonavir/darunavir, but cimetidine significantly reduces absorption of atazanavir.	Atazanavir: management complicated and dependent on ARV regimen and dose of cimetidine. Call 0800 212506 for advice.
Zidovudine	Inhibition of AZT clearance.	No dosage adjustment required.

	Interaction	Management
Ciprofloxacin		
Didanosine	Decreased ciprofloxacin effect caused by chelation and adsorption of ciprofloxacin by cations contained in didanosine buffer.	Give ciprofloxacin 2 hours before or 6 hours after didanosine. If available use enteric coated formulation of didanosine which may then be given with ciprofloxacin.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased risk of QT interval prolongation.	Use with caution. Monitor closely.
Cisapride		
Efavirenz	Possible increase of cisapride levels and cardiotoxicity.	Avoid combination. Alternative: Metoclopramide
Etravirine	Cisapride levels may potentially be decreased.	A dose adjustment may be needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible increase of cisapride levels and cardiotoxicity.	Avoid combination.
Nevirapine	Possible decrease in cisapride clinical effects.	Dosage adjustment may be needed.
Cisplatin		
Didanosine	Increased risk of peripheral neuropathy.	Monitor closely for peripheral neuropathy.
Lamivudine/Emtricitabine	Cisplatin and lamivudine/emtricitabine could potentially compete for OCT2 which could slow their renal elimination. Furthermore, cisplatin may impair the renal function.	Closely monitor creatinine clearance and adjust lamivudine dosage accordingly.
Stavudine	Increased risk of peripheral neuropathy.	Monitor closely for peripheral neuropathy.
Tenofovir	Increased risk of nephrotoxicity.	Closely monitor renal function.
Zidovudine	Additive haematotoxicity.	Monitor FBC closely.
Citalopram		
Efavirenz	Citalopram is extensively metabolised by CYP450 enzymes. No interaction data available.	Use with caution.
Lopinavir/Atazanavir/Darunavir+ritonavir	Coadministration may increase citalopram concentrations. In addition, concurrent use may result in an increased risk of QT interval prolongation.	Use with caution, monitor closely.
Nevirapine	Citalopram is extensively metabolised by CYP450 enzymes. No interaction data available.	Use with caution.
Clarithromycin		
Efavirenz	Potential induction of CYP3A4 by efavirenz resulting in decreased clarithromycin levels. High incidence of rash in patients receiving both drugs.	Clinical significance unknown, if macrolide is needed consider using azithromycin which does not interact.
Etravirine	Etravirine reduces clarithromycin exposure, and increases that of its hydroxy metabolite. Clarithromycin slightly increases etravirine exposure.	Avoid combination if possible; consider use of azithromycin
Lopinavir/Atazanavir/Darunavir+ritonavir	Lopinavir/ritonavir: Potential for increased clarithromycin levels and effects, particularly prolongation of QT interval. (Cardiac toxicity). Atazanavir: increased atazanavir and clarithromycin exposure and reduced exposure of the active metabolite, 14-OH clarithromycin by 70%. Darunavir/ritonavir: AUC, maximum plasma concentration, and minimum plasma concentration of clarithromycin were increased by 57%, 26%, and 174%, respectively. The metabolite, 14-hydroxyclarithromycin, was not detectable.	Lopinavir/ritonavir: For patients with renal impairment dose reduction of clarithromycin should be considered. No data for atazanavir/ritonavir. Atazanavir: a dose reduction of clarithromycin by 50% should be considered. Due to the reduced exposure of active metabolite, possibly not effective for infections other than MAC.
Nevirapine	Nevirapine decreases clarithromycin levels, but increases levels of its active metabolite. Also, nevirapine levels are increased slightly.	No dose adjustment is necessary, but close monitoring of hepatic abnormalities is advised. Activity against Mycobacterium avium-intracellular complex (MAC) may be impaired. Use azithromycin instead.
Zidovudine	Some reduction in zidovudine levels is likely if the two drugs are taken at the same time.	No dosage adjustment required, but give clarithromycin either 2 hours before or 2 hours after the zidovudine. Monitor for AZT efficacy.
Clindamycin		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically ritonavir may increase clindamycin levels.	Monitor for adverse events.
Clonazepam		
Efavirenz	Possible decrease in clonazepam levels.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased clonazepam effects.	Avoid combination. Use safer alternative e.g. oxazepam, temazepam, lorazepam.
Nevirapine	Possible decrease in clonazepam concentrations and symptoms of withdrawal.	Monitor for clonazepam effects, and withdrawal symptoms when adding nevirapine to patient already on clonazepam.
Clopidogrel		
Lopinavir/Atazanavir/Darunavir+ritonavir	Atazanavir and atazanavir/ritonavir are predicted to decrease the activation of clopidogrel to its active metabolites.	An alternative to clopidogrel should be considered.
Clozapine		
Efavirenz	Efavirenz may decrease clozapine concentrations.	Monitor therapeutic effect.
Etravirine	Etravirine may decrease clozapine concentrations.	Monitor therapeutic effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Atazanavir and atazanavir/ritonavir or lopinavir/ritonavir or darunavir/ritonavir may cause increases in clozapine plasma concentrations increasing risk of arrythmias, haematological abnormalities, seizures or other serious adverse effects.	Use with extreme caution only. Monitor patients closely for response to and toxicity of clozapine.
Nevirapine	Nevirapine may decrease clozapine concentrations.	Monitor therapeutic effect.
Zidovudine	Additive haematotoxicity.	Use with caution and monitor FBC closley.
Codeine		
Efavirenz	Efavirenz could potentially decrease codeine exposure.	Monitor analgesic effect.
Etravirine	Etravirine could potentially decrease codeine exposure.	Monitor analgesic effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretical possibility that analgesic efficacy may be decreased.	Monitor for efficacy of codeine.
Nevirapine	Nevirapine could potentially decrease codeine exposure.	Monitor analgesic effect.
Colchicine		
Efavirenz	Efavirenz may reduce colchicine concentrations.	Monitor therapeutic effect.
Etravirine	Etravirine may reduce colchicine concentrations.	Monitor therapeutic effect.

	Interaction	Management
Lopinavir/Atazanavir/Darunavir+ritonavir	Significant increases in colchicine levels.	Concomitant use not recommended. If concurrent use unavoidable: For treatment of gout, reduce colchicine dosage to 0.6 mg x 1 then 0.3 mg one hour later. Dose not to be repeated within 3 days. For prophylaxis of gout, reduce colchicine dosage to 0.3 mg once per day if on 0.6 mg BID prior to PI therapy or reduce colchicine dose to 0.3 mg once per day if on 0.6 mg once per day prior to PI therapy. Patients with renal or hepatic impairment should not be given colchicine with ritonavir.
Contraceptives, oral		
Efavirenz	Efavirenz did not change ethinylestradiol AUC, but significantly reduced exposure to the active metabolites of norgestimate. In another study levonorgestrel levels were significantly reduced.	Use with caution. Oral or injectable contraceptive or IUD are options. In addition, a barrier method must be used.
Etravirine	Slightly increases ethinyl oestradiol exposure, but did not change norethisterone exposure or the suppression of ovulation.	No dosage adjustment required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Ethinylestradiol AUC decreased by 42% and norethisterone concentration also decreased by lopinavir/ritonavir. Unboosted atazanavir may increase ethinylestradiol (EE) levels. Atazanavir boosted with ritonavir decreased EE levels. Darunavir decreased EE AUC by 44%.	Use with caution. Lopinavir/atazanavir/darunavir + ritonavir: Avoid low-dose OCs. High-dose oral or injectable contraceptive or IUD are options. In addition, a barrier method must be used. Atazanavir (unboosted): use no more than 30 mcg EE.
Nevirapine	Ethinylestradiol and norethisterone AUCs are decreased by 29% and 18% respectively by nevirapine.	Use with caution. Avoid low-dose OCs. High-dose oral or injectable contraceptive or IUD are options. In addition, a barrier method must be used.
Zidovudine	Theoretically ethinylestradiol may increase AZT concentration via inhibition of glucuronidation.	Monitor for AZT toxicity.
Corticosteroids		
Efavirenz	In one small study prednisolone half-life was reduced. Also, efavirenz levels may be decreased.	Monitor for steroid effect. Ideally, efavirenz levels should be monitored.
Lopinavir/Atazanavir/Darunavir+ritonavir	There are numerous case reports of Cushing's syndrome with combination of inhaled fluticasone and ritonavir. Combination of prednisone and ritonavir resulted in approximately 30% increase in prednisolone AUC. Levels of other systemic corticosteroids theoretically also increased. Theoretically corticosteroids may reduce lopinavir/ritonavir levels.	Avoid inhaled fluticasone, but other topical corticosteroids have less systemic absorption & can probably be used without dosage adjustment. Use caution with high dose topical corticosteroids. Consider dose reduction for systemic corticosteroids if they are used. Ideally, lopinavir/ritonavir levels should be monitored.
Nevirapine	Theoretically corticosteroid and nevirapine levels may be reduced.	Monitor for steroid effect. Ideally, nevirapine levels should be monitored.
Cyclophosphamide		
Efavirenz	Possible increase in efficacy or toxicity.	Use with caution and monitor closely.
Etravirine	Etravirine could potentially increase the amount of drug converted to the inactive neurotoxic metabolite.	Careful monitoring of cyclophosphamide efficacy and toxicity is recommended.
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible increase in efficacy or toxicity.	Use with caution and monitor closely.
Nevirapine	Possible increase in amount of active metabolite and increased neurotoxicity.	Use with caution.
Zidovudine	Additive myelosuppression.	Monitor haematological parameters closely.

	Interaction	Management
Cyclosporin		
Efavirenz	Potential reduction in the effect of cyclosporin.	Close monitoring is recommended with appropriate dose adjustment of cyclosporin.
Etravirine	Etravirine may reduce plasma concentrations of cyclosporin.	Monitor closely.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential increase in cyclosporin levels and effects resulting in increased adverse effects of immunosuppression and renal toxicity.	Monitor and adjust cyclosporin as indicated.
Nevirapine	Possible decrease in the clinical effects of cyclosporin.	Monitor and adjust cyclosporin as indicated.
Tenofovir	Additive nephrotoxicity.	Renal function should be monitored during coadministration.
Dabigatran		
Lopinavir/Atazanavir/Darunavir+ritonavir	Dabigatran is a substrate of P-glycoprotein. PIs may inhibit or induce P-glycoprotein. No studies available.	Co-administration not recommended.
Dapsone		
Didanosine	Potential for additive neuropathy.	No dosage adjustment required. Monitor closely.
Lopinavir/Atazanavir/Darunavir+ritonavir	Concurrent use of atazanavir and dapsone may result in an increased risk of hemolytic anaemia and symptomatic hyperbilirubinemia.	No dosage adjustment required, monitor.
Stavudine	Potential for additive neuropathy.	No dosage adjustment required. Monitor for neuropathy.
Zidovudine	Additive haematological toxicity.	No dosage adjustment required. Monitor for haematological toxicity.
Daunorubicin		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretical possibility of increased daunorubicin concentrations increasing the risk of cardiotoxicity.	No dosage adjustment required. Monitor for adverse effects.
Zidovudine	Additive myelosuppression.	If concomitant treatment with potentially myelosuppressive drugs is necessary, care should be taken in monitoring haematological parameters.
Dexamethasone		
Didanosine	Didanosine chewable/dispersible tablets and powder for oral solution contain an antacid which may decrease the absorption of dexamethasone.	Dexamethasone should be taken at least two hours apart from antacids.
Efavirenz	Possible decrease in efficacy of dexamethasone and decrease in the levels of efavirenz.	Monitor for steroid effect. Ideally, efavirenz levels should be monitored.
Etravirine	Dexamethasone is predicted to decrease the plasma concentrations of etravirine. Etravirine may decrease dexamethasone levels.	Use with caution or consider an alternative.
Lopinavir/Atazanavir/Darunavir+ritonavir	Dexamethasone may decrease lopinavir or ritonavir or darunavir levels. Possible increase in levels and effects of dexamethasone.	Monitor for steroid effect and consider dose reduction of dexamethasone. Clinical monitoring of antiviral efficacy is recommended.
Nevirapine	Possible decrease in efficacy of dexamethasone and nevirapine.	Monitor for steroid effect and consider increase of dexamethasone dose. Ideally, nevirapine levels should be monitored.
Diazepam		
Efavirenz	Risk of prolonged sedation.	Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives.
Etravirine	Etravirine is predicted to increase diazepam exposure.	Alternatives to diazepam should be considered.

	Interaction	Management
Lopinavir/Atazanavir/Darunavir+ritonavir	Unpredictable.	Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives.
Nevirapine	Theoretically nevirapine may reduce diazepam levels.	Monitor for diazepam effects, and withdrawal symptoms when adding nevirapine to patient already on diazepam.
Digoxin		
Etravirine	Moderate increase in exposure and plasma concentrations of digoxin.	Monitor digoxin levels.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased digoxin effects and theoretically an additive effect on PR interval prolongation.	Start with lowest dose of digoxin and monitor or if patient already on digoxin the dose should be halved and levels monitored.
Diltiazem		
Efavirenz	Decreased diltiazem levels (AUC decreased by 69%).	Adjust dose according to clinical response.
Etravirine	Theoretically diltiazem could increase etravirine concentrations and etravirine could potentially decrease diltiazem concentrations.	No dosage adjustment required for etravirine. Monitor diltiazem clinical effect and adjust dosage if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Plasma concentrations of diltiazem may be increased. Unboosted atazanavir increased diltiazem AUC by 2.25-fold. Also, possible increased risk of PR interval prolongation.	Initiate diltiazem at low dose. Monitor and adjust dose if required. Unboosted atazanavir: reduce diltiazem dose by 50%.
Nevirapine	Possible decrease in diltiazem plasma concentrations with a possible decrease in clinical effects.	Monitor closely and adjust dosage as required.
Disopyramide		
Efavirenz	Theoretically levels of disopyramide may be decreased.	The magnitude and therapeutic consequences of this interaction cannot be predicted with any certainty. Dose adjustment may be needed.
Etravirine	Etravirine is expected to decrease plasma concentrations of disopyramide.	Use with caution and monitor.
Lamivudine/Emtricitabine	Potential decrease in lamivudine renal elimination.	No dosage adjustment required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Plasma concentrations of disopyramide may be increased.	The magnitude and therapeutic consequences of this interaction cannot be predicted with any certainty. Dose adjustment may be needed due to possible increase in clinical effect.
Nevirapine	Clinical effect of disopyramide may be reduced due to decreased plasma concentrations.	Disopyramide dose adjustment may be needed due to possible decrease in clinical effect.
Disulfiram		
Abacavir	Abacavir concentrations may increase due to inhibition of alcohol dehydrogenase by disulfiram.	No dosage adjustment required.
Didanosine	Possible increase in peripheral neurophathy as didanosine and disulfiram have similar toxicity profiles.	No dosage adjustment required. Monitor for peripheral neuropathy.
Lopinavir/Atazanavir/Darunavir+ritonavir	Lopinavir/ritonavir oral solution contains alcohol. Disulfiram reaction (e.g. nausea, vomiting, hypotension, headache). Inhibition of alcohol- and aldehyde dehydrogenase by disulfiram.	Do not coadminister disulfiram and lopinavir/ritonavir oral solution; consider lopinavir/ritonavir tablets.
Stavudine	Possible increase in peripheral neurophathy as stavudine and disulfiram have similar toxicity profiles.	No dosage adjustment required. Monitor for peripheral neuropathy.
Doxorubicin		
Stavudine	Decreased stavudine efficacy.	Use with caution only if potential benefit outweighs potential risks.

	Interaction	Management
Zidovudine	Additive haematologic toxicity (neutropaenia).	Use with caution and close monitoring is required.
Doxycycline		
Didanosine	Buffered tablet formulations of didanosine contain antacids which may impair absorption of doxycycline.	Separate doses or use enteric coated didanosine.
Efavirenz	Theoretically doxycycline levels may be decreased.	Monitor response.
Etravirine	Theoretically doxycycline levels may be decreased.	Monitor response.
Nevirapine	Theoretically doxycycline levels may be decreased.	Monitor response.
DTP vaccine		
	No kinetic interaction reported.	Immunisation according to usual recommended schedules, however immunisation may be less effective in individuals with HIV infection.
Ergometrine		
Efavirenz	Ergot toxicity possible.	These drugs should not be coadministered.
Lopinavir/Atazanavir/Darunavir+ritonavir	Acute ergot toxicity has been reported with combination. (Peripheral vasospasm and ischemia of the extremities and other tissues).	These drugs should not be coadministered.
Nevirapine	Theoretically nevirapine may reduce effects of ergometrine.	Monitor response.
Ergotamine		
Efavirenz	Increased ergotamine toxicity.	These drugs should not be coadministered.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased ergotamine toxicity.	These drugs should not be coadministered.
Nevirapine	May result in decreased ergotamine concentrations.	Monitor response.
Erythromycin		
Lopinavir/Atazanavir/Darunavir+ritonavir	Lopinavir/ritonavir, atazanavir/ritonavir and darunavir/ritonavir could increase concentrations of erythromycin and this may result in an increase in toxicity, especially cardiac adverse events (QT interval prolongation).	Use with caution and if possible an alternative antibiotic should be used.
Esomeprazole		
Efavirenz	Efavirenz halves omeprazole exposure.	Monitor response.
Etravirine	Omeprazole slightly increases etravirine exposure, and etravirine inhibits omeprazole metabolism.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Atazanavir: 75% decrease in AUC of atazanavir with omeprazole	Coadministration of atazanavir and proton pump inhibitors is not recommended.
Ethambutol		
Didanosine	No clinically significant kinetic interaction found, but both drugs may cause peripheral neuropathy.	No dosage adjustment required.
Stavudine	No clinically significant kinetic interaction found, but both drugs may cause peripheral neuropathy.	No dosage adjustment required.
Ethanol		
Abacavir	Ethanol may increase levels of abacavir. Abacavir may decrease alcohol tolerance.	Usually not clinically significant.
Didanosine	Increased risk of pancreatitis.	Monitor clinically.

	Interaction	Management
Ethionamide		
Didanosine	Similar toxicity profile.	Monitor closely for peripheral neuropathy.
Stavudine	Similar toxicity profile.	Monitor closely for peripheral neuropathy.
Ethosuximide		
Efavirenz	Potential decreased levels of ethosuximide.	Monitor individual response. The ethosuximide dosage may need to be altered.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential for increased ethosuximide concentrations.	Individual monitoring required. Decrease ethosuximide dose if required.
Nevirapine	Potential for decreased ethosuximide concentrations therefore decreased efficacy.	Monitor individual response. Increase ethosuximide dosage if required.
Fentanyl		
Efavirenz	Potential decrease in fentanyl concentrations.	Monitor individual response. Alter the drug dosage if required.
Etravirine	Possible decrease in fentanyl plasma concentrations decreasing the clinical effect.	Monitor individual patients. Adjust dosage of fentanyl if required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Fentanyl clearance decreased. Increase in fentanyl effects e.g. sedation, confusion, respiratory depression.	Monitor closely. Start with a low dose and titrate. These drugs should not be used together without careful risk benefit assessment and careful monitoring of therapeutic and adverse effects.
Nevirapine	Possible decrease in fentanyl plasma concentrations decreasing the clinical effect.	Monitor individual patients. Adjust dosage of fentanyl if required.
Flecainide		
Etravirine	Possible decrease in flecainide plasma concentrations.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Flecainide levels may be increased, resulting in an increased risk of cardiac arrhythmias.	Do not coadminister.
Fluconazole		
Efavirenz	No clinically significant interaction.	No dosage adjustment required.
Etravirine	Etravirine AUC increased by 86%.	No dose adjustment established.
Lopinavir/Atazanavir/Darunavir+ritonavir	No clinically significant kinetic interaction. However may result in an increased risk of QT interval prolongation.	No dosage adjustment required. Monitor.
Nevirapine	Co-administration of fluconazole and nevirapine resulted in approximately 100% increase in nevirapine exposure compared with historical data where nevirapine was administered alone. High incidence of raised ALT reported.	Use combination with caution. Monitor patients closely for nevirapine adverse effects.
Zidovudine	Increased zidovudine effects.	No dosage adjustment required, but monitor for AZT toxicity.
Fluoxetine		
Efavirenz	A case of serotonin syndrome has been reported due to efavirenz possibly inhibiting the metabolism of fluoxetine.	Use with caution.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential increase in fluoxetine and protease inhibitor concentrations and toxicity. Serotonin syndrome reported with ritonavir and fluoxetine.	Careful monitoring of therapeutic and adverse effects is recommended when concomitantly administered with ritonavir.
Nevirapine	Decreased fluoxetine levels.	Monitor clinical response to fluoxetine and increase the dose if needed.

	Interaction	Management
Fluphenazine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically both ritonavir and fluphenazine levels may be increased. Additive QT prolongation.	Monitor closely for side effects.
Flurazepam		
Efavirenz	Efavirenz may increase levels of flurazepam.	Do not coadminister these drugs. Use safer alternatives e.g. oxazepam, temazepam, lorazepam.
Etravirine	Etravirine could potentially decrease flurazepam exposure.	Monitor clinical effect and withdrawal symptoms.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased risk of sedation, respiratory depression and confusion.	Do not coadminister these drugs. Use safer alternatives e.g. oxazepam, temazepam, lorazepam.
Nevirapine	Theoretical risk of reducing flurazepam levels.	Monitor for flurazepam effects, and withdrawal symptoms when adding nevirapine to patient already on flurazepam.
Fluticasone		
Efavirenz	Theoretically fluticasone levels may be decreased. Theoretically, efavirenz levels may be decreased.	Monitor for steroid effect. Ideally, efavirenz levels should be monitored.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased fluticasone levels possibly resulting in decreased plasma cortisol concentrations (e.g. Cushing's syndrome, adrenal suppression) .	Avoid combination. Safer alternative is beclomethasone.
Nevirapine	Theoretically fluticasone and nevirapine levels may be reduced.	Monitor for steroid effect. Ideally, nevirapine levels should be monitored.
Furosemide		
Tenofovir	Furosemide could potentially decrease tenofovir renal elimination.	No dosage adjustment required, but renal function needs to be closely monitored.
Fusidic acid		
Lopinavir/Atazanavir/Darunavir+ritonavir	One case report states significant elevation of fusidic acid and ritonavir levels and hepatotoxicity.	Use with caution.
Ganciclovir		
Didanosine	Significantly increased didanosine serum concentrations and increased risk of didanosine toxicity (neuropathy, diarrhoea, pancreatitis). Decreased oral absorption of ganciclovir due to reduced gastric acidity from antacid buffer in ddI.	For both IV and PO ganciclovir, check blood counts and monitor for didanosine toxicity (pancreatitis, neuropathy). Didanosine doses may need to be reduced. Use EC tablets. Monitor for ganciclovir efficacy.
Stavudine	No significant change in ganciclovir levels. Possible additive haematological toxicity.	No dosage adjustment necessary. Monitor.
Tenofovir	Additive nephrotoxicity.	If possible avoid concurrent use. If concomitant use is unavoidable monitor renal function weekly.
Zidovudine	Additive haematotoxicity.	Avoid combination. If possible, use stavudine instead of zidovudine.
Garlic supplements		
Efavirenz	Theoretically garlic supplements containing allicin may reduce efavirenz levels.	Until more is known about this potential interaction garlic should be avoided.
Etravirine	Theoretically garlic supplements containing allicin may reduce etravirine levels.	Until more is known about this potential interaction garlic should be avoided.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically garlic supplements containing allicin may reduce protease inhibitor levels.	Until more is known about this potential interaction garlic should be avoided.

	Interaction	Management
Nevirapine	Theoretically garlic supplements containing allicin may reduce nevirapine levels.	Until more is known about this potential interaction garlic should be avoided.
Gemfibrozil		
Lopinavir/Atazanavir/Darunavir+ritonavir	In one study lopinavir/ritonavir decreased gemfibrozil AUC by 41%.	Monitor for clinical response.
Raltegravir	Gemfibrozil may increase raltegravir concentrations.	Perform TDM for raltegravir.
Glibenclamide		
Efavirenz	Efavirenz could potentially decrease glibenclamide concentrations.	Monitor clinical effect and increase glibenclamide dosage if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically ritonavir can increase plasma concentrations of glibenclamide.	Monitor therapeutic effect of glibenclamide and reduce dosage if needed.
Nevirapine	Nevirapine could potentially decrease glibenclamide concentrations.	Monitor clinical effect and increase glibenclamide dosage if needed.
Gliclazide		
Efavirenz	No interaction reported, however theoretically efavirenz inhibits the enzyme which breaks down gliclazide, which may result in higher gliclazide levels.	Monitor clinical effect and decrease gliclazide dosage if needed.
Etravirine	No interaction reported, however theoretically etravirine inhibits the enzyme which breaks down gliclazide, which may result in higher gliclazide levels.	Monitor clinical effect and decrease gliclazide dosage if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	No interaction reported. Theoretical possiblity of decreased gliclazide concentrations via ritonavir's potential to induce CYP2C9 of which gliclazide is a substrate.	No dosage adjustment required. Monitor individual response to concomitant therapy.
Griseofulvin		
Efavirenz	Theoretically griseofulvin as an enzyme inducer may decrease plasma levels of efavirenz.	Use with caution.
Etravirine	Theoretically griseofulvin as an enzyme inducer may decrease plasma levels of etravirine.	Use with caution.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically griseofulvin as a liver enzyme inducer may decrease plasma levels of protease inhibitors.	Use with caution.
Nevirapine	Theoretically griseofulvin as a liver enzyme inducer may decrease plasma levels of nevirapine.	Use with caution.
Haemophilus influenzae b, conjugated		
	No kinetic interaction reported.	Immunisation according to usual recommended schedules, however immunisation may be less effective in individuals with HIV infection.
Haloperidol		
Efavirenz	Efavirenz could potentially decrease haloperidol exposure.	No dosage adjustment required, but monitor therapeutic effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors may increase serum levels of haloperidol although to a moderate extent.	Use with caution due to the risk of QT interval prolongation reported for both drugs and monitor side effects.
Nevirapine	Nevirapine could potentially decrease haloperidol exposure.	No dosage adjustment required, but monitor therapeutic effect.

	Interaction	Management
Hepatitis B, purified antigen		
	No kinetic interaction reported.	Immunisation according to usual recommended schedules, however immunisation may be less effective in individuals with HIV infection.
Hydrocortisone (oral)		
Efavirenz	Theoretically hydrocortisone levels may be decreased. Efavirenz levels may also be reduced.	Monitor for steroid effect. Ideally, efavirenz levels should be monitored.
Etravirine	Etravirine may decrease hydrocortisone concentrations. Etravirine levels may also be reduced.	A dose adjustment of hydrocortisone may be required. Ideally, etravirine levels should be monitored.
Lopinavir/Atazanavir/Darunavir+ritonavir	Corticosteroid levels may be increased and protease inhibitor levels may be reduced.	Monitor for steroid effect and consider dose reduction of hydrocortisone. Ideally, protease inhibitor levels should be monitored.
Nevirapine	Theoretically hydrocortisone and nevirapine levels may be reduced.	Monitor for steroid effect and consider increase in hydrocortisone dose. Ideally, nevirapine levels should be monitored.
Ibuprofen		
Etravirine	Theoretically etravirine may increase ibuprofen levels.	Use the lowest recommended dose of ibuprofen especially in high risk patients.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically protease inhibitors may decrease ibuprofen levels.	Monitor effects of ibuprofen.
Tenofovir	Coadministration of NSAIDs and tenofovir may increase the risk of nephrotoxicity in particular if an NSAID is used for a long duration, if the patient has a pre-existing renal dysfunction, has a low body weight, or receives other drugs that may increase tenofovir exposure.	Use with caution and monitor renal function.
Zidovudine	Additive risk of haematological toxicity.	Monitor.
Ifosfamide		
Efavirenz	Theoretically may reduce efficacy of ifosfamide and increase toxicity.	Use with caution.
Etravirine	Increased risk of ifosfamide toxicity.	Use with caution.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically may reduce efficacy of ifosfamide. Potential for ifosfamide to decrease protease inhibitor levels.	Use with caution.
Nevirapine	Increased risk of ifosfamide toxicity.	Use with caution.
Zidovudine	Additive haematotoxicity.	Monitor haematological parameters.
Imipramine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors could potentially increase imipramine concentrations.	Monitor side effects and consider dose reduction if needed.
Interferon-alpha		
Abacavir	Some data suggest lower response rate to pegylated interferon therapy if on abacavir.	Monitor closely for treatment-associated toxicities, especially hepatic decompensation and anaemia.
Lamivudine/Emtricitabine	No significant kinetic interaction.	Monitor closely for treatment-associated toxicities, especially hepatic decompensation.
Nevirapine	No clinically significant interaction reported.	No dosage adjustment required.
Stavudine	Similar toxicity profile.	Monitor for treatment-associated toxicities, especially hepatic decompensation.
Tenofovir	Pharmacokinetic interaction unlikely.	Closely monitor for treatment-associated toxicities, especially hepatic decompensation and anaemia.
Zidovudine	Similar toxicity profiles. Interferon-alpha increases zidovudine exposure.	Monitor for haematological toxicity, renal function and for hepatic decompensation.

	Interaction	Management
Isoniazid		
Didanosine	No kinetic interaction found, but both drugs may cause peripheral neuropathy.	Monitor closely for development of peripheral neuropathy.
Stavudine	No kinetic interaction, but both drugs can cause peripheral neuropathy.	Monitor closely for development of peripheral neuropathy.
Isosorbide dinitrate		
Etravirine	Inducers of CYP3A4 such as etravirine may increase production of the active substance nitric oxide.	The clinical relevance of this potential interaction is unknown.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically HIV protease inhibitors may reduce production of the active substance nitric oxide, decreasing clinical effect. The clinical relevance of this potential interaction is unknown.	Monitoring for clinical effect of isosorbide dinitrate is advised.
Isotretinoin		
Efavirenz	Efavirenz could potentially increase isotretinoin level (inhibition 2C8) or decrease isotretinoin level (induction 3A4).	Monitoring of side effects is recommended.
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors could potentially increase isotretinoin concentrations by inhibition of CYP2C8 and CYP3A4.	Monitor therapeutic response and toxicity.
Itraconazole		
Didanosine	Decreased itraconazole effects.	Administer itraconazole capsules at least 2 hours after didanosine tablets/suspension. Alternatively use itraconazole solution or didanosine EC.
Efavirenz	Itraconazole effects decreased.	Use a safer alternative such as fluconazole.
Etravirine	Etravirine is predicted to decrease itraconazole concentrations, and itraconazole is expected to increase etravirine plasma concentrations.	Use with caution.
Lopinavir/Atazanavir/Darunavir+ritonavir	Effects of both itraconazole and protease inhibitors may be increased.	High doses of itraconazole (greater than 200 mg/day) are not recommended. Monitor for toxicity. Suggested alternative is fluconazole.
Nevirapine	Itraconazole levels reduced.	Do not coadminister.
Kanamycin		
Lamivudine/Emtricitabine	Kinetic interaction unlikely.	As kanamycin is nephrotoxic (risk is dose and treatment duration related), renal function should be monitored periodically and lamivudine/emtricitabine dosage adjusted accordingly.
Tenofovir	Potential for additive nephrotoxicity.	Avoid concurrent use or monitor renal function weekly if concurrent use unavoidable.
Ketoconazole		
Didanosine	No significant interaction with didanosine EC. With didanosine buffered preparations possible decrease in didanosine effects and decreased ketoconazole absorption.	If didanosine enteric coated capsules are used, no dose adjustment required. If didanosine buffered solution is used administer ketoconazole at least 2 hours prior to or after didanosine tablets or suspension.
Efavirenz	Potential decrease in ketoconazole effects.	Use with caution and monitor efficacy of ketoconazole closely. Safer alternative is fluconazole.
Etravirine	Increased etravirine plasma concentrations and decreased ketoconazole plasma concentrations.	Do not coadminister.
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible increased ketoconazole effects and decreased or increased protease inhibitor effects.	Manufacturer recommends against using high doses of ketoconazole (>200mg daily). Suggested alternative is fluconazole. Unboosted atazanavir does not require a dose adjustment.
Nevirapine	Decreased ketoconazole effects and increased nevirapine effects.	Do not coadminister.
Lamotrigine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Decrease in lamotrigine levels by about 50% due to induction of glucuronidation. For atazanavir alone, no clinically significant interaction would be expected.	Monitor therapeutic effect. An increase in lamotrigine dosage may be required.
Lansoprazole		
Efavirenz	No interaction reported. Theoretically efavirenz may increase lansoprazole levels.	No dosage adjustment required. Monitor patients.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically lopinavir/ritonavir may decrease lansoprazole levels. Atazanavir AUC decreased by 94%.	Monitor therapeutic response with lopinavir/ritonavir. Atazanavir: concurrent use not recommended.
Levodopa		
Lopinavir/Atazanavir/Darunavir+ritonavir	Severe dyskinesias have been reported in combination with indinavir.	Monitor for enhanced levodopa effects, including severe dyskinesias. Doses of levodopa may need to be reduced.
Levothyroxine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased TSH levels. Look for signs and symptoms of hypothyroidism.	Monitor and adjust levothyroxine as indicated.
Lidocaine (Lignocaine)		
Efavirenz	Theoretically efavirenz may decrease lidocaine levels.	Monitor closely.
Etravirine	Decreased plasma concentrations of lidocaine.	Use with caution and monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Concentrations of systemic lidocaine may be increased and has the potential to produce serious adverse effects (hypotension, cardiac arrhythmias).	Monitor and adjust lidocaine as indicated.
Nevirapine	Potential decrease in lidocaine levels.	Dose adjustment may be needed due to possible decrease in clinical effect.
Liquid paraffin (mineral oil)		
	Liquid paraffin may impair absorption of many orally administered drugs.	Space at least 2 hours from any other drugs.
Lithium		
Lopinavir/Atazanavir/Darunavir+ritonavir	Two case reports of decreased lithium concentrations with atazanavir/ritonavir. Increased risk of QT prolongation.	Use with caution. Monitor lithium levels.
Loperamide		
Lopinavir/Atazanavir/Darunavir+ritonavir	Ritonavir substantially increases the levels of loperamide, but did not result in opioid CNS effects. Further studies required.	Loperamide dosage reduction may be needed, which should not affect antidiarrhoeal activity which is outside the CNS compartment. Monitor and reduce dosage if needed.
Loratadine		
Efavirenz	No interaction reported. Theoretically, efavirenz may decrease the concentration of loratadine.	Monitor patients closely.
Etravirine	Decreased loratadine level.	Monitor therapeutic response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically protease inhibitors may increase levels of loratadine.	No dosage adjustment required.

	Interaction	Management
Lorazepam		
Zidovudine	Theoretically a modest increase in the bioavailability of zidovudine. Concurrent use can increase the incidence of headaches.	If headaches occur, discontinue lorazepam.
Magnesium hydroxide		
Didanosine	Antacids may increase didanosine levels. Additive side effects such as diarrhoea.	Monitor closely and separate doses by as much as possible.
Lopinavir/Atazanavir/Darunavir+ritonavir	Atazanavir solubility/absorption decreases as pH increases, no interaction with other protease inhibitors.	Atazanavir should be administered 2 hours before or 1 hour after antacids. No dosage adjustment required.
Raltegravir	Raltegravir concentration reduced.	Coadministration not recommended.
Measles vaccine		
	No kinetic interaction reported.	Immunisation according to usual recommended schedules, however immunisation may be less effective in individuals with HIV infection.
Mebendazole		
Efavirenz	Theoretically efavirenz may reduce mebendazole levels. This may be clinically important in patients on high doses for echinococcosis.	Monitor response.
Etravirine	Theoretically etravirine may reduce mebendazole levels. This may be clinically important in patients on high doses for echinococcosis.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	In one small study mebendazole exposure was reduced when coadministered with ritonavir. The effect of administering a ritonavir-boosted protease inhibitor on mebendazole pharmacokinetics is not known.	Monitor response.
Nevirapine	Theoretically nevirapine may reduce mebendazole levels. This may be clinically important in patients on high doses for echinococcosis.	Monitor response.
Medroxyprogesterone, oral		
Efavirenz	Theoretically medroxyprogesterone levels may be decreased.	Monitor clinical effect.
Etravirine	Theoretically medroxyprogesterone levels may be decreased.	Monitor clinical effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically concentration of medroxyprogesterone may be decreased.	Monitor clinical effect.
Nevirapine	Theoretically concentration of medroxyprogesterone may be decreased.	Monitor clinical effect.
Mefloquine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Mefloquine decreases steady-state ritonavir exposure. Also, concurrent use may result in an increased risk of QT interval prolongation.	Use with caution, no dosage adjustment recommended.
Metformin		
Didanosine	Limited data suggests an increased risk of lactic acidosis.	No dosage adjustment required. Monitor patients clinically.
Stavudine	Limited data suggests an increased risk of lactic acidosis.	No dosage adjustment required. Monitor patients clinically.
Tenofovir	Limited data suggests an increased risk of lactic acidosis.	No dosage adjustment required. Monitor patient clinically.

	Interaction	Management
Methotrexate		
Abacavir	No kinetic interaction.	Use with caution in HIV patients and monitor closely.
Didanosine	Additive liver toxicity.	Use with caution in HIV patients and monitor closely.
Efavirenz	No kinetic interaction.	Use with caution in HIV patients and monitor closely.
Etravirine	No kinetic interaction.	Use with caution in HIV patients and monitor closely.
Lamivudine/Emtricitabine	There is potential for competition for active renal transport mechanisms if lamivudine and methotrexate are coadministered, which may lead to increased exposure to either drug and potential for toxicity.	Use with caution in HIV patients and monitor closely.
Lopinavir/Atazanavir/Darunavir+ritonavir	No kinetic interaction.	Use with caution in HIV patients and monitor closely.
Nevirapine	Additive liver toxicity.	Use with caution in HIV patients and monitor closely.
Raltegravir	Kinetic interaction unlikely.	Use with caution in HIV patients and monitor closely.
Stavudine	There is potential for competition for active renal transport mechanisms if stavudine and methotrexate are coadministered, which may lead to increased exposure to either drug, and potential for toxicity. Also, additive hepatotoxicity.	Use with caution in HIV patients and monitor closely.
Tenofovir	There is potential for competition for active renal transport mechanisms if tenofovir and methotrexate are coadministered, which may lead to increased exposure to either drug and potential for toxicity. Methotrexate and tenofovir may both cause renal toxicity, if coadministered, close monitoring of renal function is recommended.	Use with caution in HIV patients and monitor closely.
Zidovudine	Additive haematotoxicity.	Use with caution in HIV patients and monitor closely.
Methyldopa		
Didanosine	Both agents can cause pancreatitis.	Use with caution and monitor closley.
Stavudine	Both agents can cause pancreatitis.	Use with caution and monitor closley.
Zidovudine	Additive haematotoxicity.	Monitor closely.
Metoprolol		
Lopinavir/Atazanavir/Darunavir+ritonavir	Plasma concentrations of metoprolol may be increased, increasing the risk of cardiovascular and neurological side effects. The interaction cannot be predicted. Potential for additive PR interval prolongation.	Use with caution and monitor the patient for increased side effects of metoprolol and decrease the metoprolol dose if needed.
Nevirapine	No clinically significant interaction reported.	No dosage adjustment required.
Metronidazole		
Abacavir	Metronidazole may increase abacavir concentrations due to inhibition of alcohol dehydrogenase.	No dosage adjustment required.
Didanosine	Both drugs may cause peripheral neuropathy.	Monitor closely.
Lopinavir/Atazanavir/Darunavir+ritonavir	Oral lopinavir/ritonavir solution contains alcohol. Concomitant use may result in disulfiram-like reaction.	Do not coadminister, may consider lopinavir/ritonavir capsules or tablets.

	Interaction	Management
Stavudine	Both drugs may cause peripheral neuropathy.	Monitor closely.
Mianserin		
Efavirenz	Theoretically efavirenz could decrease mianserin concentrations to a moderate extent.	Monitor clinical effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically protease inhibitors could increase mianserin concentrations to a moderate extent.	Monitor adverse effects.
Nevirapine	Theoretically nevirapine could decrease mianserin concentrations to a moderate extent.	Monitor clinical effect.
Midazolam		
Efavirenz	Risk of prolonged sedation or respiratory depression.	Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives. Single dose parenteral administration may be used with caution.
Etravirine	Etravirine, an inducer of CYP3A4, could potentially decrease midazolam exposure.	Monitor clinical effect and withdrawal symptoms.
Lopinavir/Atazanavir/Darunavir+ritonavir	Midazolam levels may be raised, increasing risk of prolonged sedation, confusion and respiratory depression.	Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives. Single dose parenteral administration may be used with caution.
Nevirapine	Theoretically nevirapine may decrease levels of midazolam.	Monitor for midazolam effects and withdrawal symptoms when adding nevirapine to patient already on midazolam.
Morphine		
Efavirenz	Theoretically efavirenz could potentially increase morphine concentrations via competition or inhibition of UGT2B7.	Monitor for signs of opiate toxicity.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically lower levels of morphine may be expected.	Monitor response.
Moxifloxacin		
Didanosine	Chewable/buffered preparations may interfere with biovailability of moxifloxacin.	Administer moxifloxacin four hours before or eight hours after these formulations of didanosine. Alternatively use EC tablets.
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors may result in QT interval prolongation and increased moxifloxacin levels. This may result in additive QT prolongation with moxifloxacin.	Use with caution.
Mycophenolate mofetil		
Abacavir	Abacavir could alter mycophenolate levels.	Concentration monitoring of mycophenolate is recommended.
Efavirenz	Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA). MPA undergoes glucuronidation; coadministration of inducers or inhibitors of glucuronidation, such as some PIs and NNRTIs, could alter mycophenolate levels.	Concentration monitoring of mycophenolate is recommended.
Lopinavir/Atazanavir/Darunavir+ritonavir	Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA). MPA undergoes glucuronidation; coadministration of inducers or inhibitors of glucuronidation, such as some PIs and NNRTIs, could alter mycophenolate levels.	Concentration monitoring of mycophenolate is recommended.
Nevirapine	In one small study nevirapine exposure was reduced moderately (AUC by 13%). Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA). MPA undergoes glucuronidation; coadministration of inducers or inhibitors of glucuronidation, such as some PIs and NNRTIs, could alter mycophenolate levels.	Concentration monitoring of mycophenolate is recommended.
Tenofovir	Concentrations of both substances could be possibly increased due to competition for active tubular secretion. In vitro data suggest that mycophenolic acid (active metabolite) inhibits the renal transporters OAT1/OAT3.	Closely monitor renal function due to the risk of tubular necrosis that may occur with both drugs.
Zidovudine	AZT could alter mycophenolate levels.	Concentration monitoring of mycophenolate is recommended.
Nalidixic acid		
Didanosine	Decreased nalidixic acid serum concentrations when using buffered didanosine preparations.	Use EC didanosine.
Naloxone		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically lower levels of naloxone may be expected.	Monitor response.
Nifedipine		
Efavirenz	Theoretically nifedipine concentrations may be decreased.	Dose adjustment may be needed due to possible decrease in clinical effect.
Etravirine	Etravirine, an inducer of CYP3A4, could potentially decrease nifedipine exposure.	Monitor clinical effect and increase dose if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically nifedipine levels may be increased as well as the risk of cardiotoxicty. (prolonged PR interval)	Use with caution. Monitor and adjust nifedipine as indicated.
Nevirapine	Theoretically nevirapine can lower nifedipine levels.	Dose adjustment may be needed due to possible decrease in clinical effect.
Nitrofurantoin		
Didanosine	Potential for increased risk of peripheral neuropathy.	Monitor closely for peripheral neuropathy.
Stavudine	Potential for increased risk of peripheral neuropathy.	Monitor closely for peripheral neuropathy.
Zidovudine	Additive myelosuppression.	Monitor haematological parameters.
Ofloxacin		
Didanosine	Chewable/buffered preparations may interfere with biovailability of ofloxacin.	Administer ofloxacin four hours before or eight hours after these formulations of didanosine. Alternatively use EC tablets.
Lamivudine/Emtricitabine	Potential decrease in lamivudine/emtricitabine renal elimination as in vitro data suggest that ofloxacin inhibits the renal transporter OCT2.	Monitor for side effects.
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors may result in QT interval prolongation and increased ofloxacin levels. This may result in additive QT prolongation with ofloxacin.	Use with caution.
Olanzapine		
Efavirenz	Olanzapine is metabolized by CYP1A2 (major) and glucuronidation (UGT1A4). Efavirenz has been shown to induce UGT1A4 and could potentially decrease olanzapine exposure.	Monitor the clinical effect and increase dosage if needed.

	Interaction	Management
Lopinavir/Atazanavir/Darunavir+ritonavir	Olanzapine AUC decreased by 53% by ritonavir, therefore effects may be decreased.	Monitor patients as higher olanzapine dosages may be needed to maintain therapeutic effect.
Omeprazole		
Efavirenz	Efavirenz halves omeprazole exposure.	Monitor response where a high degree of acid suppression is required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential for an increase in omeprazole metabolism. Atazanavir: 94% reduction in AUC of atazanavir.	Monitor therapeutic response with darunavir/lopinavir/ritonavir. Atazanavir: concurrent use not recommended.
Raltegravir	Raltegravir exposure (AUC) increased 3 fold.	Clinical relevance unknown, UK and US manufacturers no dosage adjustment.
Oxazepam		
Zidovudine	A modest increase in the bioavailability of zidovudine. Concurrent use can increase the incidence of headaches.	If headaches occur, discontinue oxazepam.
Paclitaxel		
Didanosine	Possible additive peripheral neuropathy.	Use with caution and monitor closely.
Efavirenz	Possible increase in paclitaxel levels due to inhibition of CYP2C8.	Use with caution and monitor paclitaxel induced toxicity.
Etravirine	Potential moderate decrease in paclitaxel exposure. Also potential decrease in etravirine concentrations.	Monitor response to antiretroviral therapy.
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible increase in paclitaxel levels and toxicity with increased risk and severity of myelosuppression, constitutional symptoms and peripheral neuropathy.	Use with caution and monitor closely for paclitaxel toxicity.
Nevirapine	Possible decrease in paclitaxel levels. In one patient no pharmacokinetic interaction was found.	Monitor response.
Raltegravir	Potential reduction of raltegravir concentration.	Monitor response to antiretroviral therapy.
Stavudine	Possible additive peripheral neuropathy.	Use with caution and monitor closely.
Zidovudine	Possible additive haematotoxicity.	Monitor FBC closely.
Paracetamol		
Didanosine	One case report of hepatotoxicity.	No dosage adjustment required.
Zidovudine	Some reports of increased haematological and hepatotoxicity, but clinical importance unclear from available data.	No dosage adjustment required.
Pethidine		
Efavirenz	Efavirenz induces CYP2B6 and CYP3A4 which could potentially increase concentrations of norpethidine. Norpethidine has analgesic and CNS stimulant activity which may increase the risk of CNS effects (e.g. seizures). There is a risk of toxicity with long term therapy.	Monitor for toxicity.
Lopinavir/Atazanavir/Darunavir+ritonavir	Decreased pethidine AUC but increased AUC of norpethidine (a neurotoxic metabolite).	Long term use of pethidine and PIs is not recommended due to the increased concentration of norpethidine which may increase the risk of seizures. Some sources recommend avoiding concurrent use.
Nevirapine	Nevirapine induces CYP2B6 and CYP3A4 and could potentially increase concentrations of norpethidine. There is a risk of toxicity with long term therapy.	Use with caution and avoid long term use.
Phenobarbital (phenobarbitone)		
Abacavir	Possible slight decrease in abacavir concentrations due to induction of UDP-glucuronyltransferases.	Monitor response.
Efavirenz	Possible decrease in efavirenz and phenobarbital concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine.
Etravirine	Decreased etravirine concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine.
Lopinavir/Atazanavir/Darunavir+ritonavir	Phenobarbital induces CYP3A4 and may decrease protease inhibitor concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine (may require higher dose).
Nevirapine	Possible decrease in nevirapine levels.	Avoid combination. Safer alternatives are valproic acid or lamotrigine.
Raltegravir	The impact of phenobarbital on UGT1A1 is unknown.	Monitor antiviral efficacy closely.
Zidovudine	May decrease zidovudine concentrations as phenobarbital has been shown to induce zidovudine glucuronidation by 4-fold in rats.	Monitor response.
Phenytoin		
Abacavir	Slight decrease in plasma concentration of abacavir.	Monitor response.
Didanosine	Possible increased risk of peripheral neuropathy.	Monitor closely.
Efavirenz	Theoretically there is the potential for reduction or increase in the plasma concentrations of phenytoin and decrease in efavirenz concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine.
Etravirine	Decreased etravirine concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine.
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible decrease in protease inhibitor and phenytoin concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine (may require higher dose).
Nevirapine	Potential for decreased nevirapine concentrations.	Avoid combination. Safer alternatives are valproic acid or lamotrigine.
Raltegravir	Impact of phenytoin on UGT1A1 is unknown.	Monitor antiviral efficacy closely.
Stavudine	Possible increased risk of peripheral neuropathy.	Monitor closely.
Zidovudine	Moderated decrease in AZT clearance and altered phenytoin levels.	Monitor FBC for AZT toxicity and monitor phenytoin levels.
Pimozide		
Efavirenz	Concurrent use may result in an increased risk of cardiac arrhythmias.	Do not coadminister.
Etravirine	Etravirine may decrease pimozide levels.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased pimozide effects such as cardiac arrhythmias are possible.	Do not coadminister.
Nevirapine	Theoretically nevirapine may decrease pimozide levels.	Monitor response closely.
Piroxicam		
Efavirenz	No interaction reported, but theoretically efavirenz could increase piroxicam levels.	Monitor for side effects of piroxicam, especially GI and CNS.
Etravirine	No interaction reported, but theoretically piroxicam levels could be slightly increased.	Monitor for adverse effects.
Lopinavir/Atazanavir/Darunavir+ritonavir	Modest reduction in piroxicam levels possible.	Dose adjustment unlikely.
Tenofovir	Additive nephrotoxicity has been reported with NSAIDs.	Use with caution and monitor renal function.

	Interaction	Management
Polio Vaccine, oral		
	No kinetic interaction reported.	Immunisation according to usual recommended schedules, however immunisation may be less effective in individuals with HIV infection. Also, risks attached to live vaccines in immunocompromised patients should be considered.
Pravastatin		
Efavirenz	Efavirenz administration resulted in a median 40% decrease in pravastatin exposure.	Monitor response. Pravastatin dose may need to be increased.
Lopinavir/Atazanavir/Darunavir+ritonavir	No clinically significant interaction with lopinavir/ritonavir. However with darunavir/ritonavir AUC increased by 81%, but an up to 5-fold increase was seen in a limited subset of subjects.	No dosage adjustment required for lopinavir/ritonavir. For darunavir/ritonavir it is recommended to start with the lowest possible dose of pravastatin and titrate it up to the desired clinical effect while monitoring for safety.
Nevirapine	Slight reduction in pravastatin exposure possible.	Monitor response.
Raltegravir	Pravastatin appears to reduce the minimum concentration of raltegravir by 41%. AUC increased by 13%. Unlikely to be clinically important.	No dosage adjustment required.
Praziquantel		
Efavirenz	Theoretically efavirenz may decrease praziquantel levels.	Monitor response.
Etravirine	Theoretically etravirine may decrease praziquantel exposure.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically protease inhibitors may increase praziquantel exposure.	Monitor for praziquantel adverse events.
Nevirapine	Theoretically nevirapine may lower praziquantel levels.	Monitor for effectiveness of praziquantel.
Prednisone		
Efavirenz	One small study shows a shorter half-life of prednisolone, AUC decreased by 21-40%. Also, efavirenz levels may be reduced.	Monitor for steroid and efavirenz effect.
Etravirine	Theoretically prednisone and etravirine levels may be reduced.	Monitor therapeutic response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Combination of prednisone and ritonavir resulted in approximately 30% increase in prednisolone levels. Theoretically, protease inhibitor levels may be reduced.	Monitor for steroid effect and consider dose reduction for systemic corticosteroids. Ideally, protease inhibitor levels should be monitored.
Nevirapine	Theoretically corticosteroid and nevirapine levels may be reduced.	Monitor for steroid effect and consider dose increase of corticosteroids. Ideally, nevirapine levels should be monitored.
Prochlorperazine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically ritonavir may increase prochlorperazine levels.	Monitor for adverse events and lower dose of prochlorperazine if required.
Zidovudine	Additive haematotoxicity.	Monitor FBC.
Promethazine		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretical interaction possibly resulting in increased promethazine levels. Increased risk of QT interval prolongation.	Monitor adverse events of promethazine.
Propafenone		
Efavirenz	Efavirenz theoretically can decrease propafenone levels.	Closely monitor response and adjust dose accordingly.
Etravirine	Concentrations of propafenone may be decreased.	Use with caution. Drug concentration monitoring is recommended, if available.
Lamivudine/Emtricitabine	No interaction found.	No dosage adjustment required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Propafenone levels may be increased. In addition, propafenone may increase ritonavir levels. Increased risk of QT interval prolongation and torsade de pointes.	Do not coadminister.
Nevirapine	Theoretically nevirapine may lower propafenone levels via enzyme induction.	Monitor response and increase dose of propafenone if required.
Propranolol		
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors may increase propranolol levels although to a moderate effect. Potential for additive PR prolongation.	Use with caution and clinical monitoring recommended.
Pyrazinamide		
Didanosine	Possible increase in pyrazinamide exposure and risk of arthralgia.	No dosage adjustment required but monitoring for side effects suggested.
Zidovudine	Limited evidence suggests that zidovudine may lower pyrazinamide levels.	Clinical significance unknown.
Quetiapine		
Efavirenz	Possible decrease in quetiapine levels.	Monitor response and increase dose if needed.
Etravirine	Etravirine may decrease quetiapine levels.	Monitor response and increase dose if needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically quetiapine levels may be raised due to inhibition of CYP3A4-mediated quetiapine metabolism by protease inhibitors. Serious quetiapine adverse effects have been reported.	Some sources state that concomitant use is contraindicated, while others recommend use with extreme caution and that quetiapine should be reduced to one sixth of the original dose.
Nevirapine	Possible decrease in quetiapine levels.	Monitor response and increase dose if needed.
Quinidine		
Efavirenz	Theoretically efavirenz can decrease quinidine levels.	Monitor response, drug concentration monitoring is recommended if available.
Etravirine	Concentrations of quinidine may be decreased.	Drug concentration monitoring is recommended, if available.
Lopinavir/Atazanavir/Darunavir+ritonavir	Coadministration may result in increased quinidine levels and an increase of the associated cardiac adverse effects. Increased risk of QT interval prolongation.	Caution is warranted and therapeutic concentration monitoring is recommended when available.
Nevirapine	Theoretically nevirapine can lower quinidine levels.	Monitor response and drug concentration monitoring is recommended if available.
Quinine		
Efavirenz	No interaction reported. Theoretically efavirenz can decrease quinine levels due to induction of CYP3A4.	Monitor response. If possible monitor quinine levels.
Etravirine	Possible decreased exposure to quinine.	Monitor response. If possible monitor quinine levels.
Lopinavir/Atazanavir/Darunavir+ritonavir	With ritonavir alone the AUC of quinine increased 4-fold and half life increased by 20%. Also, increased risk of QT interval prolongation. The combination of lopinavir/ritonavir reduced the AUC of quinine by 50%.	Use with caution. Monitor closely for adverse effects. If possible monitor quinine levels.
Nevirapine	Possible decrease in quinine levels.	Monitor response. If possible monitor quinine levels.

	Interaction	Management
Ranitidine		
Lopinavir/Atazanavir/Darunavir+ritonavir	No clinically significant interaction with lopinavir/ritonavir/darunavir. Atazanavir absorption significantly reduced.	No dosage adjustment required with lopinavir/ritonavir/darunavir. Avoid use with atazanavir or if essential consult the HIV hotline.
Ribavirin		
Abacavir	Increased risk of lactic acidosis. Some data suggest a risk of a lower response rate to pegylated interferon/ribavirin therapy.	Use with caution.
Didanosine	Mitochondrial toxicity substantially increased. (i.e.pancreatitis, hyperlactatemia, lactic acidosis, peripheral neuropathy and hepatic failure).	Avoid combination if at all possible. Monitor patients closely for didanosine related toxicities if combined.
Lamivudine/Emtricitabine	Increased risk of lactic acidosis and hepatic decompensation.	Use combination with caution only if the potential benefit outweighs the risks.
Stavudine	Increased risk of lactic acidosis and hepatic decompensation.	Use combination with caution only if the potential benefit outweighs the risks.
Tenofovir	Increased risk of lactic acidosis.	Use with caution.
Zidovudine	Increased risk for developing lactic acidosis, hepatic decompensation, neutropaenia and anaemia.	Avoid combination if at all possible. Monitor closely for lactic acidosis, hepatic decompensation, neutropaenia and anaemia.
Rifabutin		
Didanosine	Possible decreased rifabutin levels with buffered didanosine.	Separate once daily buffered didanosine from rifabutin by at least 2 hours to avoid interaction.
Efavirenz	Decreased rifabutin effects.	Increase rifabutin to 450mg/day or 600 mg three times per week with concomitant efavirenz.
Etravirine	Etravirine AUC decreased 37%.	No dosage adjustment required, unless coadministered with a boosted PI. With boosted PI: caution and monitoring recommended and the US guidelines suggest etravirine and rifabutin should not be coadministerd with boosted darunavir, lopinavir or saquinavir.
Lopinavir/Atazanavir/Darunavir+ritonavir	Significantly increased rifabutin levels.	Reduce rifabutin dose to 150mg every other day or 150mg 3 times per week and monitor for adverse events such as neutropaenia and uveitis.
Nevirapine	No clinically significant interaction in most patients. Some patients may experience large increases in rifabutin exposure and may experience toxicity.	Use with caution. No dosage adjustment required.
Raltegravir	Raltegravir minimum concentration reduced by 20%. AUC and maximum plasma concentration increased by 19% and 39% respectively. Unlikely to be clinically important.	No dosage adjustment required.
Stavudine	No significant interaction.	No dosage adjustment required.
Zidovudine	Slight decrease in AZT levels.	No dosage adjustment recommended, but monitor effects of AZT.
Rifampicin		
Abacavir	Slight decrease in plasma concentration of abacavir.	Monitor response.
Efavirenz	Efavirenz AUC reduced by 26%.	No dosage adjustment currently recommended.
Etravirine	Decreased etravirine concentrations.	Contraindicated.
Lopinavir/Atazanavir/Darunavir+ritonavir	Rifampicin reduces atazanavir, darunavir and lopinavir levels. Increases ALT/AST.	Dosage adjustment required. Monitor liver function. Adults: The dose of lopinavir/ritonavir should be doubled slowly over 2 weeks (to 800/200mg bd). Monitor ALT monthly while on double-dose. Children: Extra ritonavir should be added at a dose of 0.75X the volume of the lopinavir/ritonavir dose. (See Paediatric dosing table) Avoid concurrent use with atazanavir and darunavir as dose adjustment not established.
Nevirapine	Decreased nevirapine levels. (AUC decreased by 58%)	For adults and children over 3 years old and over 10kg, switch to efavirenz if possible. If switch not possible, then consider monitoring trough nevirapine levels and adjusting dose accordingly. Monitor liver function closely.
Raltegravir	Raltegravir AUC and minimum plasma concentration decreased by 40% and 61% respectively.	Although the manufacturer states that doubling of raltegravir dose to 800mg bd can be considered, a clinical trial has shown that a dose adjustment may not be necessary. Monitor virological response closely. No data in children.
Zidovudine	Reduced levels of zidovudine. (AUC decreased by 47%)	Monitor efficacy closely.
Risperidone		
Efavirenz	Efavirenz may decrease risperidone concentrations.	No dosage adjustment required, but monitor therapeutic effect.
Etravirine	Etravirine may decrease risperidone concentrations.	No dosage adjustment is required, but monitor therapeutic response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential increase in risperidone levels.	A decrease of the risperidone dose may be needed. Careful monitoring of therapeutic and adverse effects is recommended.
Sildenafil		
Efavirenz	Theoretically efavirenz may decrease sildenafil levels.	The efficacy of sildenafil should be closely monitored and dose adjustments may be required.
Etravirine	AUC of sildenafil decreased by 37%.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors substantially increase sildenafil concentrations.	Avoid combination if possible. If coadministration is absolutely necessary, do not take more than 25mg of sildenafil within a 48 hour period. Monitor for adverse effects such as hypotension, syncope, visual changes and prolonged erection.
Nevirapine	Theoretically nevirapine may decrease sildenafil levels.	Titrate sildenafil dose based on patient response and tolerability.
Simvastatin		
Efavirenz	Efavirenz significantly reduces the concentrations of simvastatin.	Patients should be closely monitored for anti-lipid activity and the simvastatin dose may need to be increased.
Etravirine	Decreased simvastatin exposure.	Monitor response. Dose adjustments for simvastatin may be needed.
Lopinavir/Atazanavir/Darunavir+ritonavir	Significantly increased simvastatin levels.	Do not coadminister due to an increased risk of myopathy including rhabdomyolysis.
Nevirapine	Potential for decreased concentrations of simvastatin due to enzyme induction by nevirapine.	Patients should be closely monitored for anti-lipid activity and the simvastatin dose may need to be increased.
Sirolimus		
Efavirenz	Efavirenz may markedly reduce sirolimus levels in some patients.	Monitor sirolimus levels and adjust dose accordingly.
Etravirine	Sirolimus plasma concentrations may be	More frequent therapeutic concentration

	Interaction	Management
Lopinavir/Atazanavir/Darunavir+ritonavir	Sirolimus levels may be markedly increased when coadministered with protease inhibitors.	More frequent therapeutic concentration monitoring is required.
Nevirapine	Potential decrease in sirolimus plasma concentrations, although in one case series no changes were observed.	More frequent therapeutic concentration monitoring is required.
Tenofovir	Additive tubular (renal) toxicity.	Use with caution and monitor renal function.
St John's wort		
Efavirenz	St John's wort may reduce the plasma concentrations and clinical effects of efavirenz.	Avoid combination.
Etravirine	Etravirine levels may be decreased.	Avoid combination.
Lopinavir/Atazanavir/Darunavir+ritonavir	St John's wort may reduce the plasma concentrations and clinical effects of protease inhibitors.	Avoid combination.
Nevirapine	St John's wort may reduce the plasma concentrations and clinical effects of nevirapine.	Avoid combination.
Streptomycin		
Tenofovir	Additive nephrotoxicity.	Avoid combination if possible. Monitor renal function weekly if concurrent use unavoidable.
Sulfadoxine/Pyrimethamine		
Didanosine	Pyrimethamine needs an acidic pH for absorption.	Administer 2 hours before or 1 hour after didanosine.
Lamivudine/Emtricitabine	Pyrimethamine could potentially decrease lamivudine renal elimination as in vitro data suggest that pyrimethamine inhibits the renal transporters OCT2 and MATE1.	No dosage adjustment required, but monitor for side effects.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically pyrimethamine may increase ritonavir levels.	No dosage adjustment required. Monitor for increased ritonavir side effects.
Zidovudine	Increased risk of haematotoxicity.	Monitor FBC closely.
Sulphasalazine		
Zidovudine	Additive haematotoxicity.	Monitor FBC.
Tacrolimus		
Efavirenz	Efavirenz may reduce tacrolimus levels in some patients.	Monitor tacrolimus levels and adjust dosage as required.
Etravirine	Etravirine may reduce tacrolimus levels in some patients.	Monitor tacrolimus levels and adjust dosage as required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Tacrolimus concentrations may be increased significantly when coadministered with protease inhibitors.	More frequent therapeutic concentration monitoring is recommended until plasma levels of tacrolimus have been stabilised.
Nevirapine	Potentially tacrolimus levels may be reduced.	Monitor tacrolimus levels and adjust dosage as required.
Tenofovir	Additive nephrotoxicity.	Monitor renal function weekly or consider alternative antiretroviral.
Tamoxifen		
Efavirenz	Theoretically tamoxifen active metabolite levels may be increased.	Use with caution and monitor efficacy and toxicity.
Etravirine	Theoretically tamoxifen active metabolite levels may be increased.	Use with caution and monitor efficacy and toxicity.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential decrease of tamoxifen efficacy by inhibiting conversion to active metabolite.	Use with caution.
Nevirapine	Theoretically tamoxifen levels may be decreased and active metabolite levels increased.	Use with caution and monitor efficacy and toxicity.

	Interaction	Management
Tetracyclines		
Didanosine	Possibility of decreased tetracycline levels due to chelation.	Didanosine chewable/dispersible tablets should not be co-adminstered with tetracycline antibiotics.
Theophylline		
Lopinavir/Atazanavir/Darunavir+ritonavir	Possible decrease in theophylline levels.	Monitor theophylline levels and increase theophylline dosage as indicated.
Timolol		
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically ritonavir may increase the levels of timolol. Also additive risk of PR prolongation.	Monitor for signs of increased timolol levels (hypotension, bradycardia) and adjust dose if required.
Tramadol		
Efavirenz	Efavirenz could potentially reduce tramadol exposure but may not affect the metabolic pathway leading to the more potent active metabolite.	No initial dosage adjustment required, but monitor analgesic effect.
Etravirine	No interaction reported.	Monitor analgesic effect.
Lopinavir/Atazanavir/Darunavir+ritonavir	Protease inhibitors may increase tramadol exposure but also reduce the conversion to the more potent active metabolite.	Monitor tramadol related side effects and the analgesic effect. Adjust tramadol dosage if needed.
Trazodone		
Efavirenz	Theoretically trazodone levels could be decreased.	Monitor response and adjust trazodone dose accordingly.
Etravirine	Theoretically trazodone levels may be decreased.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Increased trazodone concentrations with increased effects such as nausea, hypotension and syncope.	Use with caution. If benefit outweighs risk initiate trazodone at a lower dose.
Nevirapine	Theoretically trazodone levels could be lowered.	Monitor response.
Triazolam		
Efavirenz	Theoretically efavirenz may increase or decrease triazolam levels.	Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives.
Etravirine	Etravirine could potentially decrease triazolam exposure.	Monitor clinical effect and withdrawal symptoms.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically protease inhibitors can significantly increase triazolam levels.	Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives.
Nevirapine	Possible decrease in triazolam concentration, resulting in withdrawal symptoms.	Monitor patient for symptoms of withdrawal and adjust dosage if needed.
Trimethoprim/sulfamethoxazole		
Didanosine	No clinically significant kinetic interaction, but additive risk for developing pancreatitis.	No dosage adjustment required.
Lamivudine/Emtricitabine	Possible increase in lamivudine/emtricitabine exposure.	No dosage adjustment required, unless renal impairment present. Co-administration of lamivudine/emtricitabine with high doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided.
Nevirapine	No clinically significant kinetic interaction. Combination may increase risk of rash.	No dosage adjustment required.
Stavudine	Potential interaction due to competition for active renal secretion as well as additive risk for developing pancreatitis.	No dosage adjustment required. Monitor for side effects.

	Interaction	Management
Zidovudine	Possible increased risk of AZT toxicity. May be more pronounced in hepatic failure.	Monitor for AZT toxicity.
Valproic acid		
Didanosine	Additive risk of fatty liver.	No dosage adjustment required. Monitor liver function.
Efavirenz	No significant kinetic interaction between valproate and efavirenz.	No dosage adjustment required.
Lamivudine/Emtricitabine	Additive risk of fatty liver.	No dosage adjustment required. Monitor liver function.
Lopinavir/Atazanavir/Darunavir+ritonavir	Lopinavir levels increased and valproic acid concentrations may be decreased (induction of glucuronidation by ritonavir).	No dosage adjustment required. Increased monitoring for lopinavir/ritonavir toxicity (lipid profile and glucose). Careful monitoring of valproate concentrations and/or therapeutic effect is recommended.
Stavudine	Additive risk of fatty liver.	No dosage adjustment required. Monitor liver function.
Zidovudine	Valproic acid inhibits breakdown of zidovudine resulting in increased zidovudine effects (AUC increased by 80%) Additive risk of fatty liver.	Monitor closely for AZT toxicity and consider dose reduction to 200mg bd if necessary. Monitor liver function.
Verapamil		
Efavirenz	Theoretically efavirenz may decrease the concentrations of verapamil.	Monitor therapeutic effect closely and adjust dose accordingly.
Etravirine	Theoretically etravirine may decrease the concentrations of verapamil.	Monitor therapeutic effect closely and adjust dose accordingly.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential for significant elevation of verapamil serum levels and additive PR prolongation.	Combination best avoided and careful monitoring of therapeutic and adverse effects is recommended if administered concomitantly.
Nevirapine	Potential for decrease in verapamil levels.	Monitor therapeutic effect closely and adjust dose accordingly.
Vincristine		
Didanosine	Both drugs may cause peripheral neuropathy.	Avoid combination if possible, monitor closely if used concomitantly.
Efavirenz	Theoretically efavirenz may decrease vincristine levels.	Monitor closely for reduced effectiveness of vincristine.
Etravirine	Potential decrease in vincristine exposure.	Monitor response.
Lopinavir/Atazanavir/Darunavir+ritonavir	Theoretically protease inhibitors may increase the levels of vincristine. An increased risk of neurotoxicity has been observed in studies.	Patients should be closely monitored for the signs and symptoms of sensory and autonomic neuropathy, and dosage adjustments made as needed.
Nevirapine	Theoretically nevirapine may reduce vincristine levels.	Monitor closely for reduced effectiveness of vincristine.
Stavudine	Both drugs may cause peripheral neuropathy.	Avoid combination if possible, monitor closely if used concomitantly.
Zidovudine	Additive myelosuppression.	Monitor closely.
Voriconazole		
Efavirenz	Increased efavirenz effects and significantly decreased voriconazole effects.	Voriconazole maintenance dose must be increased to 400mg bd and EFV dose should be decreased by 50%. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.
Etravirine	Etravirine AUC increased by 36%; voriconazole AUC increased by 14%.	No dosage adjustment required.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential decrease or increase in voriconazole levels and increase in lopinavir/ritonavir levels. Levels of unboosted atazanavir may be increased.	Avoid combination unless benefit outweighs risk. Unboosted atazanavir may be used with caution.
Nevirapine	Theoretically voriconazole levels may be reduced and nevirapine levels increased.	Monitor patients closely.
Warfarin		
Efavirenz	Warfarin levels may be increased or decreased increasing the risk of bleeding or clotting.	Monitor INR and adjust warfarin as indicated.
Etravirine	Etravirine is expected to increase plasma concentrations of warfarin.	Monitor INR closely.
Lopinavir/Atazanavir/Darunavir+ritonavir	Warfarin levels may be increased or decreased increasing the risk of bleeding or clotting.	Monitor INR and adjust warfarin as indicated.
Nevirapine	Possibility of decreased or increased warfarin levels.	Monitor INR and adjust warfarin as indicated.
Zolpidem		
Efavirenz	Possible decrease in zolpidem concentration.	Monitor clinical effect and withdrawal symptoms.
Etravirine	Etravirine could potentially decrease zolpidem exposure.	Monitor clinical effect and withdrawal symptoms.
Lopinavir/Atazanavir/Darunavir+ritonavir	Potential increase in zolpidem exposure, resulting in risk of increased and prolonged sedation.	Monitor carefully for sedation. Dose decrease of zolpidem may be necessary.
Nevirapine	Possible decrease in zolpidem concentration.	Monitor response. Patients on long-term zolpidem may show withdrawal symptoms after nevirapine is commenced. Lorazepam, oxazepam and temazepam are safer alternatives.

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

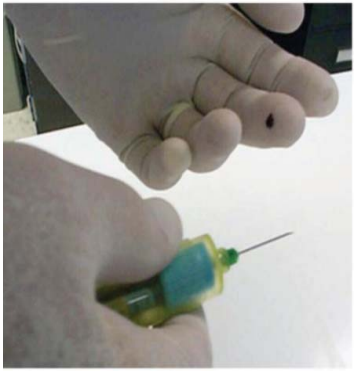
Hospital acquired infections (HAI) also termed 'nosocomial' infections, are transmitted person to person via the airborne route or through skin contact. Signs should be available that indicate the type of precaution(s) that must be taken for a particular mode of transmission and should be clearly visible 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		Tuberculosis Measles Chickenpox (pneumonitis) **N95 mask**
Droplet Large droplets from upper respiratory tract		Meningococcal infections Influenza **Surgical mask**
Contact		Drug-resistant pathogens on skin, wounds, GIT Influenza **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 resheathe needles as this increases risk.

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

Prevention of Mycobacterium Tuberculosis Transmission

M. 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.

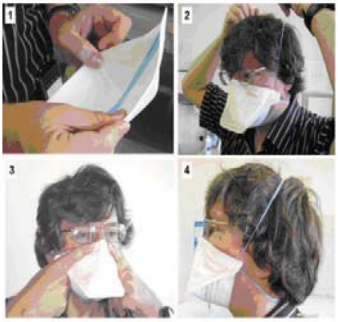
An airborne precautions sign must be fixed to the door of each isolation cubicle.

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	Egypt	Bahrain
Oman	Iraq	Brunei
Sudan	Qatar	Egypt
United Arab Emirates	Singapore	Iraq
Yemen	Turks & Caicos	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 travellers

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 traveling 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 *V.cholerae*-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 1st vaccination course should either receive a 2nd 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	PCV-13 should be offered to all HIV-infected persons independent of CD4 count to reduce incidence of invasive pneumococcal disease	Patients with CD4 count <200, delay PPV-23 boost until on ART and CD4 reconstituted
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
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

www.hiv-druginteractions.org
Trends Parasitol 2008; 24(6):264-271
Lancet ID 2011; 11:541-56

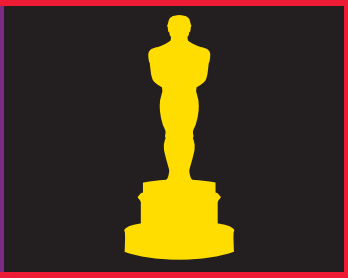
Hospitalisation

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.

Be Original

Why Substitute?

The original, once-daily, single-tablet regimen for the treatment of HIV-1 infected patients[1]



ATRIPLA™ SELECTED SAFETY INFORMATION.
ATRIPLA™ is contra-indicated in patients with previously demonstrated hypersensitivity to any of the components of the product. ATRIPLA™ should not be administered concurrently with astemizole, bepridil, cisapride, midazolam, pimozide, triazolam or ergot derivatives. ATRIPLA™ should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations. ATRIPLA™ is contra-indicated in patients with moderate to severe renal impairment (Creatinine Clearance less than 50 ml/min). 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. ATRIPLA™ should not be used in pregnancy. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA™. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving ATRIPLA™.

Before prescribing, please consult the package insert.

References: 1. 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.

MSD

ATRIPLA™
(efavirenz 600 mg/emtricitabine 200 mg/
tenofovir disoproxil fumarate 300 mg) Tablets
One pill. All HAART.

Pill shown in "substitute" is not actual size.

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

- The patient must be ready for treatment

AND

- Confirmed Stage 3 or 4 condition
  or any serious co-morbidity
- Partner is HIV negative

} Any CD4 count

OR

- Asymptomatic or Stage 2 condition (preferably confirmed on 2 occasions) — CD4 < 500

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° 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

VISIT 1

VISIT 2

VISIT 3

2/52
ALT
(if on NVP)

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

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

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

6/12 then 6 monthly
ALT (if on NVP)
Creatinine
(if on TDF)
FBC (if on AZT)
CD4 + 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
- **AZT** or **ABC** if eGFR < 50
- Avoid AZT if anaemic

2. FTC or **3TC**

3. EFV
- Preferred agent if on TB meds
- Caution if active psychiatric disease

or **NVP**
- Avoid in females with CD4 > 250, males with CD4 > 400

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
NVP	Nevirapine
OI	Opportunistic infection
PI	Protease inhibitor
PML	Progressive multifocal leukoencephalopathy
TDF	Tenofovir

With severe opportunistic diseases

Generally wait 2 weeks after starting treatment for OI before initiating ART except PML, KS, cryptosporidium, 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. Refer to: Interactions with Antiretroviral Drug Tables in guidelines, National HIV Hotline: 0800 212 506, http://www.hiv-druginteractions.org

There's *Help* and then there's Aid for AIDS

Aid for AIDS offers an integrated approach to HIV management. We provide the necessary care, counselling and support to help people living with HIV lead productive, fulfilling and healthy lives. We achieve this by fulfilling an integrated care-coordinator role between the employer, medical scheme, doctors, pharmacies, pathology labs and patients.

We are uniquely able to demonstrate our clinical and financial value to a funder and offer a comprehensive and holistic range of solutions to manage HIV/AIDS in the workplace. These services are flexible and can be customised enabling us to partner with you in developing unique solutions especially for you.

Please contact
Aid for AIDS Management (Pty) Ltd
Tel 021 466 1700 email connect@afadm.co.za
www.aidforaids.co.za

afa AidforAids
Your life. Our life.
A Member of AfroCentric Group

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 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.

ART regimens for PEP are suggested as follows:

1. **Nucleoside backbone:**
    a. Tenofovir and emtricitabine
    b. Stavudine and lamivudine
    c. Zidovudine and lamivudine
2. **Third agents:**
    a. Lopinavir/ritonavir
    b. Atazanavir/ritonavir
    c. Raltegravir
    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 (cefpodoxime 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, three months and six months after exposure to determine whether the patient has become infected. Current laboratory antibody tests (ELISA) should be positive within three months, but the six month test is retained for medico-legal reasons.

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.

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%. This risk can be 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 is associated with the lowest risk of transmission, for all pregnant women. It is very important to achieve viral suppression at the time of delivery and therefore every attempt should be made to maximize the duration of a suppressive 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 generally continue with their drug regimen. Though efavirenz may be teratogenic, recent studies have failed to show an increased risk of teratogenicity, but larger sample sizes are required before it can be definitively shown that efavirenz is not teratogenic. 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. New

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.

Zidovudine/tenofovir, lamivudine (or emtricitabine) and lopinavir/ritonavir or efavirenz are recommended. A fixed dose combination comprising efavirenz, tenofovir and emtricitabine is commonly used. Nevirapine has a higher risk of hepatitis and rash in women with a CD4 count >250, so should be avoided. Lopinavir/ritonavir is the best studied boosted PI in pregnancy, but boosted atazanavir is an alternative. Stavudine and didanosine should be avoided as the risk of hyperlactataemia is higher in pregnancy. There are some concerns that tenofovir, which reduces bone mineral density to a small extent in adults, may affect 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.

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. Once daily dosing should not be done in pregnancy. Similarly the concentrations of boosted atazanavir are somewhat reduced - no dose adjustment is recommended. Efavirenz concentrations are only 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.

Women Who Qualify for Ongoing ART

ART should be initiated in pregnant women regardless of CD4 count. If the woman has WHO stage 1 or 2 and a CD4 count >350, it is reasonable to delay starting until the beginning of the second trimester.

Women Who do not Qualify for Ongoing ART

- ART commencing early in the second trimester is the most effective form of mother-to-child transmission prophylaxis
- ART is continued until delivery if the mother elects to use formula feeding, or until two weeks after weaning if she elects to breastfeed. If efavirenz was used the dual NRTIs should be continued for a week after stopping efavirenz to reduce the risk of NNRTI resistance
- It is important to explain to women who do not qualify for long-term ART that ART is only being given for PMTCT and that it will be stopped after delivery. ART can be recommenced when criteria for initiating therapy are fulfilled
- Zidovudine monotherapy from week 14 of pregnancy is an option for women who do not wish to take ART and who have CD4 counts >350 and viral loads below 1 000, but this may not be as effective as short course ART. Resistance to AZT rarely develops with monotherapy used for PMTCT. Women should receive a single dose of nevirapine in labour with a single dose of TDF combined with FTC to minimise the risk of NNRTI resistance
- Women who present late (in labour) should be given nevirapine 200 mg stat and a single dose of TDF combined with FTC to reduce the risk of nevirapine resistance

Dual nucleoside therapy only (e.g. zidovudine and lamivudine) as MTCT prophylaxis is discouraged because of a high risk of lamivudine 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 and very early PCR are indicated. Where breastfeeding is practiced, measures should be considered.

Clinicians managing infected pregnant women and their infant should consider the following:

- Firstly, is the mother's viral load fully suppressed? Viral load remains the primary driver of transmission. Duration on effective therapy and adherence to therapy must be assessed and ensured in pregnancy.
- Secondly, is there a risk for resistance in the mother? Mothers not suppressed may not necessarily have drug resistance. Where there is late initiation of therapy, mothers may not be suppressed, but resistance will be unusual if they are adherent. However, where mothers are on first or second line therapy for > 4 months and are not suppressed, there is a risk of drug resistance. In these mothers all attempts should be made to achieve suppression. Where mothers are failing second and third line therapy during pregnancy a resistance test must be considered. Where appropriate, a prevention strategy should be planned prior to delivery for the infant.

Situations with an increased risk of transmission include mothers with any of the following:

1. Viral load detectable (> 400 copies/ml) between 28 – 40 weeks gestation
2. ART initiated during pregnancy and <12 weeks before delivery (late presentation)
3. Defaulted ART for at least one month at any stage during pregnancy
4. Failure of second line or subsequent regimens – consider resistance testing and switching to a suppressive regimen during pregnancy
5. Mothers diagnosed with TB during pregnancy

For any of above – initiate AZT, 3TC and nevirapine (we recommend nevirapine twice daily at therapeutic doses) for 4 weeks as soon as possible after birth.

The duration of further prevention will be determined by the breastfeeding status of the infant and viral load of mother.

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).

Neonatal AZT dose	
AZT Oral	• Term: 4 mg/kg 12 hourly • 30 – 34 weeks 2 mg/kg bd for 2/52 then 2 mg/kg 8 hourly for 2/52 • <30 weeks 2 mg/kg 12 hourly for 4/52
AZT IVI (If infant nil per mouth)	• Preterm 1.5 mg/kg 12 hourly • Term 1.5 mg/kg 6 hourly

Although breastfeeding increases the risk of transmission, interventions will reduce this risk if the woman chooses to breastfeed. If the mother is on ART and the viral load is undetectable, then transmission via breast milk will be negligible. If the breastfeeding mother's viral load is not suppressed on ART, or if the mother is not on ART the infant should be given daily nevirapine until two weeks after weaning.

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 highly associated with solids, wean to replacement milk first (see infant feeding section for further information).

NVP Infant Dosing Guide for LOW risk prophylaxis

Birth Weight	Age	Dose	Volume
<2.0kg	Birth to 2 weeks 2 to 4 weeks	2mg/kg 4mg/kg	0,2 ml/kg 0,4 ml/kg
2.0 – 2.5kg	Birth to 4 weeks	10mg	1ml
>2.5kg	Birth to 4 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. Where mothers have had inadequate antenatal antiretrovirals or have severe HIV-related disease, the first PCR should be done on day one of life. 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.

Genotyping should be done on infants under 6 months of age who become HIV-infected, regardless of the kind of PMTCT given (requires preapproval by AfA). For breastfed infants, perform the PCR every three months and also if infants develop symptoms. The last PCR should be done six weeks after fully weaned. Performing a single PCR at 6 weeks of age only is sub-optimal.

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 get well 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. It is especially important to use effective contraception in women on efavirenz, which may have teratogenic potential in the first trimester. 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 are likely to 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 will probably 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

ART	Recommendation
Ritonavir-boosted PI	COCP not recommended*. Depot progestogens
Efavirenz	COCP or depot progestogens
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

In the majority of cases 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 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 after birth, early institution of antiretroviral therapy and co-trimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) 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
- 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 1 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 1 of life for any infant at high risk of infection.

It is unclear exactly how antenatal and post partum antiretroviral drugs may influence the early detection of HIV DNA or RNA. All infants require a minimum of 2 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 6 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 ≤1 000):
  - HIV DNA should be performed at four to six 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 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 preapproval 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 six 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:

- < six months 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 baby 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 (PCP) 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 PCP can occur in HIV-exposed uninfected infants in the first 6 months of life, we recommend continuing PCP 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 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. Where the

mothers do not require ART for their own health, NVP is continued in the infant for the duration of breastfeeding. If mothers are on ART and are virally suppressed, NVP is discontinued at 6 weeks. Initial NVP dosing is based on birth weight and subsequent dosing on age. 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 6 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 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 is being phased out and all HIV-infected women will be 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	>6 months therapy AND CD4 ≥15%/350 on 2 occasions 3 months apart
HIV infected >5yrs	Clinical stage II/III/IV CD4 <15% or <200	>6 months therapy AND CD4 ≥15%/200 on 2 occasions 3 months apart

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 thrombocytopaenia
- 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.

WHO Immunological Classification

Extent of immuno-deficiency	Age-related CD4 values			
	<11 months (%)	12 – 35 months (%)	36 – 59 months (%)	>5 years (cells/mm^3)
Not significant	>35	>30	>25	>500
Mild	30 – 35	25 – 30	20 – 25	350 – 499
Advanced	25 – 30	20 – 25	15 – 20	200 – 349
Severe	<25	<20	<15	<200 or <15%

The Management of a Newly Diagnosed Child

HIV Infection is a Disease of the Family

For young infants and children with severe immune suppression and or significant illness, prepare to initiate antiretroviral therapy as soon as possible (aim for less than 2 weeks). Counselling on adherence can 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 RPR 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. There is no evidence of superiority to the Mantoux in infants and HIV-infected children. 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 between six and nine 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 and 14 weeks), 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 with clinical criteria to start treatment and may aid clinical decision-making in other children
- Consider RPR – 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 are increasingly suggesting 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. Emerging data suggest repeating the MMR in childhood e.g. >5 years of age. HPV vaccination is also in the process of 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.

	South African EPI vaccinations	Suggested addition
Birth	BCG OPV (0)	
6 weeks	OPV (1) RV (1) DTaP-IPV//Hib (1) Hep B (1) PCV (1)	
10 weeks	DTaP-IPV//Hib (2) Hep B (2)	
14 weeks	RV (2) DTaP-IPV//Hib (3) Hep B (3) PCV (2)	
6 months		Flu vaccine given after 6 months in the first flu season followed by a second vaccination 1 month later and then annually
9 months	Measles (1) PCV (3)	Varicella vaccine
12 months		Hep A (1) Varicella vaccine if CD4 %>15

	South African EPI vaccinations	Suggested addition
18 months	DTaP-IPV//Hib (4) Measles (2)	 Consider MMR rather than Measles Varicella vaccine Hep A (2)
2 years		Meningococcal polysaccharide vaccine
5 years		PCV
>5 years		MMR
6 years	Td	TdP to be considered rather than Td Meningococcal vaccine
9 years (girls and desirable in boys)		HPV vaccine 3 doses 0, Month 2 and Month 6
12 years	Td	TdP to be considered rather than Td Meningococcal polysaccharide 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: All children under the age of 1 year should receive co-trimoxazole prophylaxis. Children older than a year should receive prophylaxis for CD4 <15% (or if they have a stage III or IV condition)**

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 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 becoming 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. In children >1 year, CD4 percentage <15% should be viewed in the same light as a CD4 count <350 in adults. Absolute CD4 counts are useful for monitoring response to antiretrovirals.

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

There is strong evidence that all children < 24 months newly diagnosed with HIV should be offered ART regardless of clinical and immunological state. Evidence for initiation of therapy in children > 3 years of age with mild to moderate symptoms and without significant immune decline is less robust and with 1 study suggesting no additional benefit. Despite this WHO and the South African NDOH now recommend therapy to all children < 5 years to potentially prevent exacerbation of subtle clinical disease such as lung disease and neurocognitive decline. For children 3-5 years of age in clinical stage 1 or 2 without immune suppression in who 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.

- **<5 years of age – All**

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

- **≥ 5 years of age**
  - CD4 < 500
  - Stage 3 or 4 diseases

Other indications and considerations – discuss with AfA

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 as long as possible. 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. A randomised study recently found that boosted protease inhibitors are superior in infants without PMTCT exposure to NNRTIs. For older children one randomised study showed no difference between NNRTIs and unboosted PIs. For NRTIs, abacavir (ABC) combined with 3TC has a favourable toxicity profile and in one study was superior to AZT + 3TC. A recent 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 required repeat viral load testing within 6 to 8 weeks of the switch.

There is growing concern regarding the long-term side effects of stavudine (d4T), which should now be avoided. 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. 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 <24 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)

Children >24 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 + EFV[1] or NVP

For ABC, remember to counsel about possible hypersensitivity reaction in the first 6 weeks. Ensure that the parent has your telephone number.

[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
• Height, weight and head circumference • Formal adherence questionnaire and pill count if possible • Clinical examination	• FBC • ALT • CD4 count and percentage • Viral load	• 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 a case of virological 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 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. A large number of children on treatment with a detectable VL between 1 000 and 50 000 continue to have excellent clinical response and maintain high CD4 percentage values, but 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.

Children where the viral load persists above 1 000 (on a NNRTI containing regimen) or 5 000 (on a PI containing regimen) need intervention. For the PI, improved adherence should lead to viral suppression. For the NNRTI, resistance is almost invariable, but a switch should not be made until adherence has been optimised over 3 months. If adherence continues to be problematic one could 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 with 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 or NNRTIs), while for other drugs (AZT or PIs) a number of 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 infants (less than six months) 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 who are going to administer 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 with repeated aspiration. Anti-mycobacterial drugs are 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 reported 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 the PI to an NNRTI (unless child has already failed this drug class) or ABC in children with markedly elevated blood lipids. There is very limited experience of statins in children. Refer to a dietician and encourage physical exercise.

Peripheral lipoatrophy is linked to d4T, especially if combined with didanosine (ddI). d4T + ddI 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/NtRTIs)						
Zidovudine (AZT)	**Oral:** *Term:* 4 mg/kg b.d. or 2 mg/kg q.d.s **Premature:** ≥30 weeks: 2 mg/kg b.d for 2 weeks then 2 mg/kg t.d.s. *≤30 weeks:* 2 mg/kg b.d. for 4 weeks then 2 mg/kg t.d.s. **IV:** *Term:* 1,5 mg/kg q.d.s Premature: 1,5 mg/kg b.d	**Oral:** *1 – 3 months:* 4 mg/kg b.d. or 2 mg/kg q.d.s. **IV:** *1 – 3 months:* 1,5 mg/kg q.d.s.	**Oral:** *Over 3 months:* 360 mg – 480 mg/m^2/day in two divided doses **Intravenous (IV) infusion:** *Over 3 months:* Intermittent: 120 mg/m^2 q.d.s. or continuous: 20 mg/m^2/h	250 – 300 mg b.d	**Capsules:** 100 mg, 250 mg **Tablets:** 300 mg **Syrup:** 10 mg in 1 ml **Infusion:** 10 mg in 1 ml, 20 ml vials	Large volume of syrup not well tolerated in older children. **Infusion:** Dilute with 5% dextrose to a concentration of ≤4 mg/ml. Intermittent infusion is given over 1 hour.

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/NtRTIs) *(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 PI. **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	
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/NtRTIs) ***(continued)***						
Abacavir (ABC)		*1 – 3 months:* 8 mg/kg b.d. under study. *Over 3 months:* 8 mg/kg b.d. or 16 mg/kg o.d. (PENTA 13) Maximum 600 mg daily.		300 mg b.d. or 600 mg o.d.	**Tablets:** 60 mg, 300 mg **Oral solution:** 20 mg in 1 ml	Must caution parents about risk of serious hypersensitivity. Patients should not interrupt therapy without consulting their doctor.
Tenofovir (TDF)			*>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.	8mg/kg once daily (max dose 300 mg/day) In children ≥12 years of age (35kg or more) – TDF can be considered as 1st line therapy.	**Tablets:** 300mg	In children <12 years should only be used for salvage therapy after resistance testing. Monitor serum creatinine and urine dipstix monthly for first 3 months, at 6 months and then annually. A DXA scan may be of value at baseline & repeat annually.

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)	Inadequate data but 2 – 5 mg/kg o.d. has been used. P1115 will use 6mg/kg b.d. for prevention and treatment	Inadequate data. 150 – 200 mg/m²/day o.d. for 14 days then, if no rash, increase to 300 – 400 mg/m²/day in 2 divided doses *≥50 kg:* adult dose		*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. *Over 3 years:* 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.		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.

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		*>1 month of age:* 350 to 400 mg/m^2 of body surface area twice daily with a maximum dose of 600 mg twice daily.	Start with 250 mg/m^2 to minimise risk of nausea and vomiting. Increase stepwise to full dose over 5 days as tolerated. Dose range 300 – 400 mg/m^2 b.d.	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.	**Capsules:** 100 mg **Oral solution:** 80 mg in 1 ml	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.

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 bd. 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. ddI 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 150 mg plus ritonavir 100 mg once a day 20 kg to less than 40 kg: Atazanavir 200 mg plus ritonavir 100 mg 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				**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)			*15 to less than 30 kg:* darunavir 375 mg plus ritonavir 50 mg b.d. *30 to less than 40 kg:* 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, 300 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 (not yet available in SA) 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 (± 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
≥ 40		300mg (3 x 100mg) twice daily	400mg (1 x 400mg) twice daily

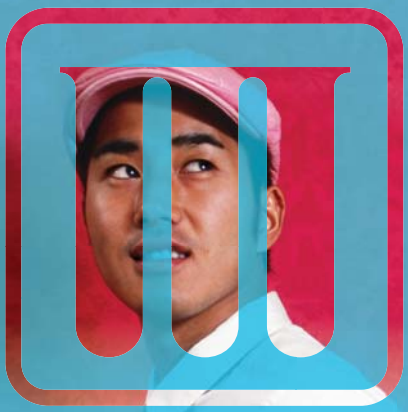
Summary of the Major Toxicities of Antiretrovirals

Names of drug	More common side effect	Less common (more severe)	Rare
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)			
Zidovudine (AZT)	Haematologic toxicity, including anaemia and granulocytopaenia. Headache, nausea	Myopathy, myositis and liver toxicity	Unusual (severe): cases of mitochondrial toxicity have been reported. Some of these have been fatal
Didanosine (ddI)	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) ***continued***			
Abacavir (ABC)		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 Hypersensitivity can occur without a rash Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase and lymphopaenia Most common in first 6 weeks of therapy In patients with suspected hypersensitivity, abacavir should be stopped Do not rechallenge as hypotension and death have occurred on rechallenge 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) *continued*			
Tenofovir disoproxil fumarate (TDF)	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 Hypophosphataemia in >10%. Patients at risk of renal impairment should be monitored closely	Approximately 1% discontinued due to gastrointestinal side effects	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 Cases of lactic acidosis and severe hepatomegaly with steatosis have been reported with use of the nucleoside analogues. Some of these have been fatal
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)			
Nevirapine (NVP)	Skin rash in 10%. If mild and systemically well can sometimes treat through with antihistamines. Some are severe requiring hospitalisation. Can be life-threatening including Stevens- Johnson syndrome, toxic epidermal necrolysis, fever, nausea, headache and abnormal liver function tests	Hepatitis may rarely lead to severe and life-threatening and in some cases fatal liver damage. Very rarely – liver failure and granulocytopaenia. 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	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)	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		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
Intergrase Inhibitors			
Raltegravir (RAL)	Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis Nausea, diarrhoea, headache, insomnia, fever, creatine phosphokinase elevation		



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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 ß 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 0.7 – 1 mg/kg/day IV for up to 14 days followed by 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 H_20.

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 PCP. 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: ganciclovir dosage 10 mg/kg/day in two divided doses IVI for 14 days. Treat for PCP and bacterial pneumonia.

Congenital CMV

Diagnosis: isolation of CMV 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 should be the 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 has recently become 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: ganciclovir 5 mg/kg/day. Discontinue when CD4 percentage is >15% on ART.

Oral valganciclovir may be considered, a commercially available preparation has recently become available for children.

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.

AZT is best avoided in combination with ganciclovir as both agents suppress the bone marrow. Early initiation of ART essential, preferably while still receiving ganciclovir to avoid Immune Reconstitution Inflammatory Syndrome (IRIS).

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
- A typical 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 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 (PCP), which is more common below one year of age. Median survival is five times longer for children with lymphoid interstitial pneumonitis (LIP) than PCP.

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.

Diagnosis: the least invasive is obviously a diagnosis of exclusion. A lung biopsy may be needed to exclude tuberculosis. A CT scan of the lungs may be necessary to exclude bronchiectasis (consult 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: prednisone 2 mg/kg/day for 4 – 6 weeks. Wean to 0,5 mg/kg on alternate days if possible and according to symptoms. Treat only if the child is symptomatic.

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: clarithromycin 15 mg/kg/day in two divided doses plus ethambutol 20 mg/kg/day (Azithromycin should be used if patient is on an NNRTI). For extensive disease, add ciprofloxacin 30 mg/kg/day in two divided doses. Consider adding amikacin 15 mg/kg daily until good response. 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.

Congenital Tuberculosis

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: ceftriaxone OR cefotaxime OR co-amoxiclav for five to ten days. In severe pneumonia add aminoglycoside. Consider treating for PCP.

Maintenance treatment: ensure that co-trimoxazole prophylaxis continues if frequent.

Pneumocystis pneumonia

The onset of illness is often abrupt, but may be insidious. In HIV-infected children with pneumonia, four clinical variables independently associated with PCP are: age <6 months, respiratory rate >59 breaths per minute, arterial percentage haemoglobin saturation ≤92%, and the absence of vomiting.

Diagnosis: PCP 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. Most common where antenatal screening had not been done and where co-trimoxazole prophylaxis was not given. Special stains of broncho-alveolar lavage or induced sputum (following nebulisation of hypertonic saline). Suspect in any infant presenting with severe pneumonitis and requiring oxygen. Clinical diagnosis is suggested by bilateral interstitial ("ground glass") infiltrate on CXR. Hypoxia is common (spontaneous or on effort as assessed by >5% desaturation).

Treatment: co-trimoxazole 20 mg/kg/day in four divided doses intravenously for 21 days. Change to oral therapy at same dosage once patient is stable. Consider giving hypoxic patients prednisone 2 mg/kg/day for seven days and then wean, over a week (may exacerbate concomitant CMV pneumonitis).

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.

Treatment of Major Morbid Events in Children

Condition	Treatment options	Dosage	Duration	Prophylaxis
Herpes simplex Gingivo-stomatitis	Acyclovir	30 mg/kg/day IVI in 3 divided doses; 60 mg/kg/day in 3 doses (max 1 g/d)	5 – 10 days	N/R
Chicken pox and Zoster	Acyclovir	50 mg/kg/day IVI in 3 divided doses or 1500 mg/m^2/day. Oral: 80 mg/kg/day qid once patient is stable (not to exceed 80 mg/kg/day)	7 – 10 days 7 – 10 days	
Candida oesophagitis	Fluconazole	6 mg/kg stat and then 3 mg/kg	14 – 21 days	N/R
Pneumocystis jiroveci pneumonia	Co-trimoxazole OR primaquine + clindamycin	15 – 20 mg/kg/day qid IVI (trimethoprim component) (can switch to po)*; 0.5 mg (base)/kg/day. (not available in RSA) 20 – 40 mg/kg/day	21 days	Co-trimoxazole 5 mg/kg of trimethoprim daily; dapsone 2 mg/kg/day or 4 mg/kg/week (max 100 mg)

Condition	Treatment options	Dosage	Duration	Prophylaxis
Shigellosis	Cefuroxime	150 mg/kg/dose tds IV 50 mg/kg/dose qid	7 – 10 days	
Salmonella bacteraemia	Ceftriaxone	50 mg/kg/day (can change to po and adjust according to sensitivity of organism)	7 to 10 days (4 – 6 weeks if recurrent)	N/R
Tuberculosis	Standard short-course		6 – 9 months	INH 10 – 15 mg/kg
Cytomegalovirus	Short-course ganciclovir. Long-term ganciclovir for retinitis not supported	5 mg/kg bd for one day then 5 mg/kg/day	2 – 3 weeks	N/A
Isosporiasis	Co-trimoxazole	10 mg/kg/day (trimethoprim) qid x 10 days, then 5mg/kg/day bd x 3 weeks	4 weeks	Co-trimoxazole 5 mg/kg trimethoprim daily
Crypto-sporidiosis	None available	N/A	N/A	N/A
Bacterial pneumonia	Cefuroxime + Gentamicin	150 mg/kg/day tds IV 5 mg/kg/day tds	10 days	
Myco-bacterium avium-intracellulare	Best results clarithromycin + ethambutol + rifabutin (adults) Clarithromycin Ethambutol Rifabutin Ofloxacin Amikacin or streptomycin	15 mg/kg/day bd 25 mg/kg/day 5 mg/kg/day-dosage under study. If cannot obtain, use rifampicin 20 mg/kg/day 20 mg/kg/day 20 mg/kg/day.	Ongoing	
Bacterial meningitis	Cefotaxime or ceftriaxone Consider adding vancomycin if S. pneumoniae suspected or cannot be excluded	200 mg/kg/day tds IVI 100 mg/kg/day daily IVI 60 mg/kg/day qid IVI	7 – 14 days 7 – 14 days	

**Adjunctive prednisone 2 mg/kg for seven days should be given to hypoxic patients.*

Specific Issues for Adolescents

What About Adolescents?

There is little expertise in treating adolescents in South Africa. They are at high risk for acquiring HIV and more vertically infected children can be expected to survive to this age. Compliance may be an especially important issue. Also the issue of disclosure of diagnosis has ramifications on compliance. 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. 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

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

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/m²/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							
5-5.9	3ml bd		3ml bd			*1.5ml bd	1.5ml bd
6-6.9							
7-7.9	4ml bd		4ml bd				
8-8.9							
9-9.9							
10-10.9	Choose only one option: 6ml bd OR 2x60mg tabs bd	Choose only one option: 12ml od OR 4x60mg tabs od	Choose only one option: 6ml bd	12ml od	200mg nocte *(1x200mg cap/tab)*	2ml bd	1.5ml bd
11-13.9							
14-16.9	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	300mg nocte: *(200mg cap/tab + 2x50mg cap/tab)*	Choose one option: -2.5ml bd -100/25mg **paeds tabs:** 2 bd -200/50mg **adult tabs:** 1 bd	2ml bd
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		Choose one option: -3ml bd - 100/25mg **paeds tabs:** 2 bd - 200/50mg **adult tabs:** 1 bd	2.5ml bd
23-24.9		1x300mg tab + 2x60mg tabs od					
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						Choose one option: - 4ml bd - 100/25mg **paeds tabs:** 3 bd - **#**200/50mg **adult tabs:** 1 bd + 100/25mg **paeds tabs:** 1 bd	
35-39.9						Choose one option: - 5ml bd - 200/50mg **adult tabs:** 2 bd	4ml bd
>40					600mg tab nocte		

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)	
1mg/kg/dose **TWICE** daily	180-240mg/m²/dose **ONCE** daily	160-200 mg/m²/dose **TWICE** daily (after once daily lead-in x 2 wks)	180-240mg/m²/ dose **TWICE** daily	**Target Dose**
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)*			**5-5.9**
	125mg od: *(1x100mg + 1x25mg tabs)*	8ml bd	9ml bd	**6-6.9**
10mg bd: open 20mg capsule into 5ml water: give 2.5ml				**7-7.9**
			1 cap bd OR 12ml bd	**8-8.9**
				9-9.9
15mg bd: open 15mg capsule into 5ml water	150mg od: *(1x100mg +1x50mg tabs)*	10ml bd		**10-10.9**
				11-13.9
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	**14-16.9**
				17-19.9
	200mg od: *(2x100mg tabs)*		2 caps bd OR 20ml bd	**20-22.9**
				23-24.9
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	**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

Index

A

B / C

D

E / F / G

H

I

J / K / L

M

N

O

P/Q

R / S

T

U / V / W

Index

J / K / L

M

N

O

P/Q

R / S

T

U / V / W

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
Optipharm	Tel: 0860 906 090 • Fax: 0865 009 822 Email: info@optipharm.co.za
PSSA Medicine Depot Dispensary	Tel: 031 208 4590 or 031 208 5612 • Fax: 031 207 5653
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	www.hopkins-hivguide.org
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/ClinicalGuidelines.aspx
AIDSinfo	http://www.aidsinfo.nih.gov/guidelines/
WHO	http://www.who.int/hiv/pub/guidelines/en/

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Notes

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Notes

Single Tablet Regimens Improve Patient Adherence[1]

tribuss®

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Emtricitabine 200 mg
Efavirenz 600 mg

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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. A16771 08/13.

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