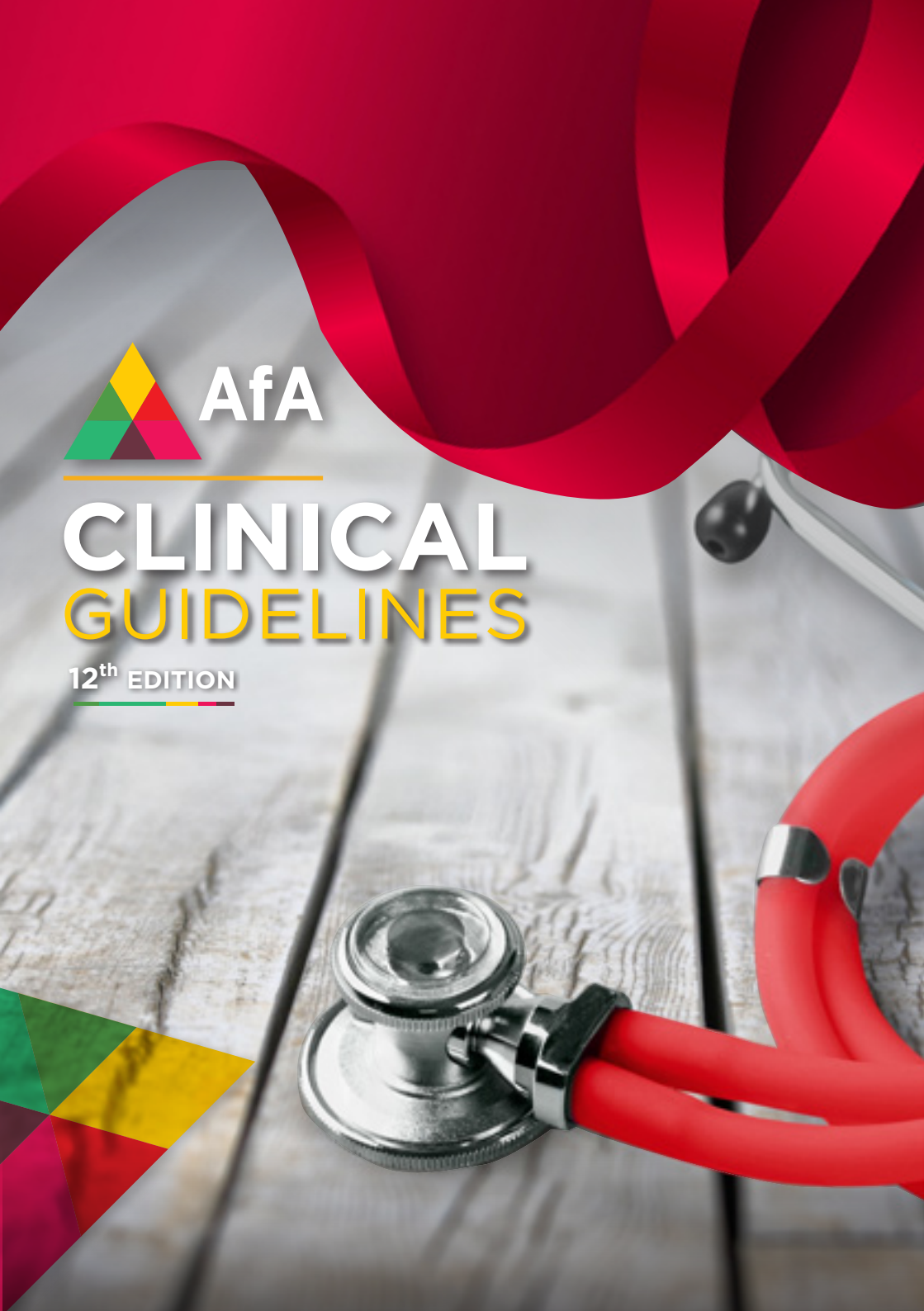
AfA

CLINICAL GUIDELINES

12th EDITION



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We acknowledge the contributions of Dr. Leon Regensberg and the late Dr. Steve Andrews to earlier editions of these guidelines.

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About AfA

As part of the greater Afrocentric Group of Companies, AfA designs, develops and delivers unique and encompassing programmes that help businesses and medical schemes care for individuals living with HIV/AIDS.

AfA was launched in May 1998 in response to the growing HIV pandemic and was the first private sector HIV Disease Management Programme (DMP) of its kind in Southern Africa. The establishment of this programme has assisted in improving the health outcomes of our members.

Many clients have been retained since 1998 – a testament to the value we bring and the quality of the relationships we take great care to develop.

Our model facilitates the integration of all services starting with prevention (HIV awareness education) to treatment and optimising the clinical wellbeing of beneficiaries registered on the programme. As the preferred partner in HIV disease management, AfA serves as care coordinator between the funder, doctors, pathology laboratories, pharmacists, and patients.

AfA's role in achieving UNAIDS targets

UNAIDS (United Nations Programme on HIV and AIDS) updated their 2025 AIDS targets. The revised 95-95-95 target proposes that 95% of people with HIV know their status, of those that know their status, 95% initiate antiretroviral therapy (ART), and of those on treatment, 95% are virally suppressed*.

The AfA HIV managed population has grown to over 400 000 lives in recent years and in 2023, 99.3% of its patients were on ART. Of these patients, 93.6% are virally suppressed. We therefore have a good understanding of the burden of HIV and are uniquely positioned to deliver an HIV management programme that achieves the desired outcomes.

The programme also started to mitigate the financial risk for its clients and proved that by funding the clinical management of HIV, schemes could prevent the unmitigated human and financial risk posed by their HIV-positive members becoming sick and requiring hospitalisation.

* *UNAIDS and WHO define viral suppression as <1,000 copies/mL as this is the threshold for transmitting HIV.*

Quick Facts

- 1st place PMR Africa Diamond Award for HIV Disease Management (2019 to 2021 consecutively).
- A successful HIV Management Programme is evidenced by clinical outcomes. 93.6% of our patients are virally suppressed.
- Dedicated team of experienced and internationally acknowledged HIV specialists and pharmacists ensuring expert reviews of clinical protocols and guidelines.
- Bespoke Disease Management System to manage HIV beneficiaries that integrates nationally with pathology laboratories.
- Clinical policy making and support for complex cases through our dedicated independent Clinical Advisory Committee comprising many of South Africa's leading HIV clinicians.
- Ongoing counselling and coaching for patients; adherence monitoring, management and risk stratification to trigger appropriate intervention.

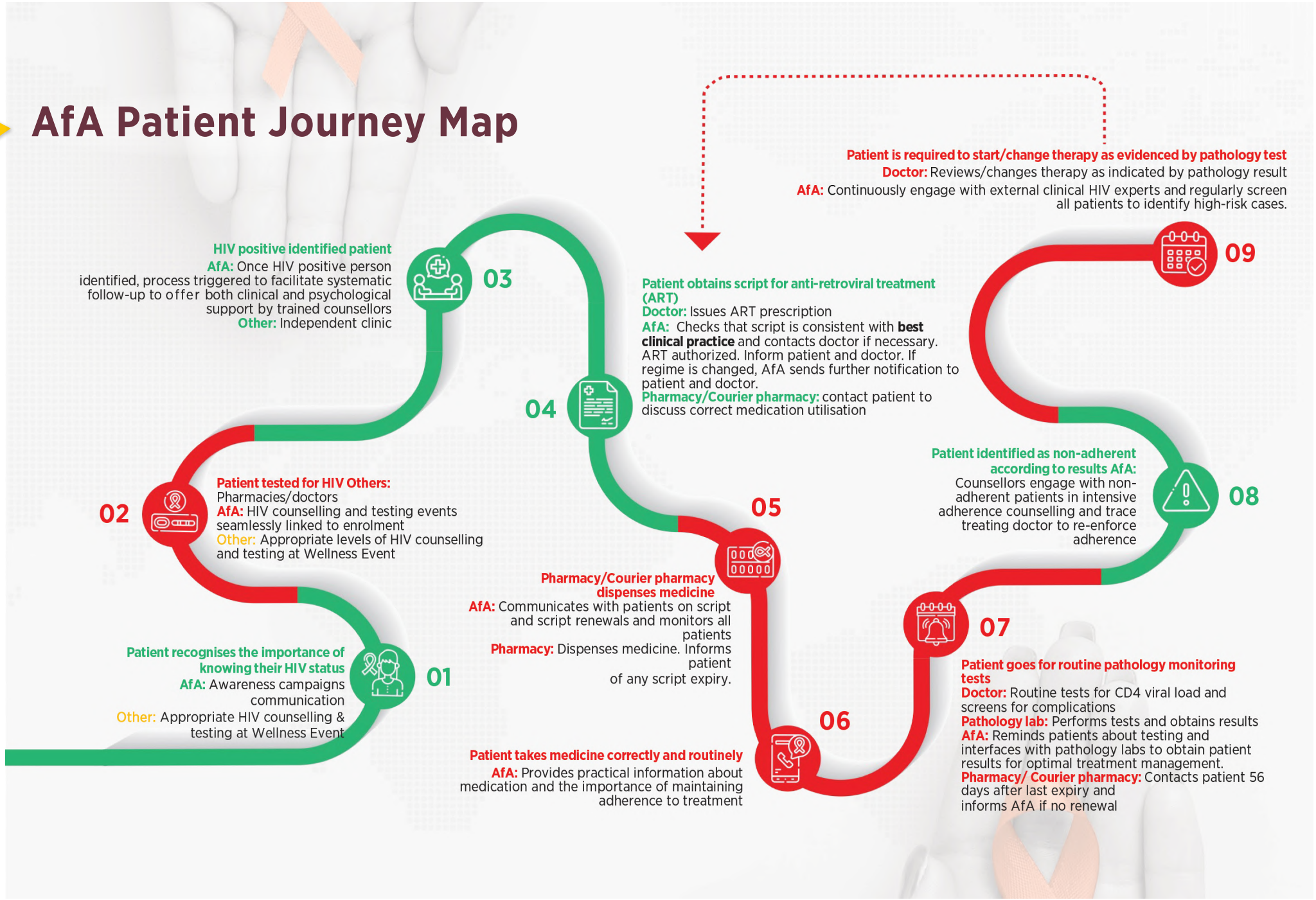
AfA takes care of the people on our programme and the organisations who bear the responsibility of funding that care.

For assistance in developing the best HIV/AIDS strategy that support your organisation and your employees, contact us.

Together, we can ensure healthier lives.

From prevention and patient care to treatment and medicine delivery.

AfA Patient Journey Map



Patient recognises the importance of knowing their HIV status
AfA: Awareness campaigns communication
Other: Appropriate HIV counselling & testing at Wellness Event

01

Patient tested for HIV Others:
Pharmacies/doctors
AfA: HIV counselling and testing events seamlessly linked to enrolment
Other: Appropriate levels of HIV counselling and testing at Wellness Event

02

HIV positive identified patient
AfA: Once HIV positive person identified, process triggered to facilitate systematic follow-up to offer both clinical and psychological support by trained counsellors
Other: Independent clinic

03

Patient obtains script for anti-retroviral treatment (ART)
Doctor: Issues ART prescription
AfA: Checks that script is consistent with **best clinical practice** and contacts doctor if necessary. ART authorized. Inform patient and doctor. If regime is changed, AfA sends further notification to patient and doctor.
Pharmacy/Courier pharmacy: contact patient to discuss correct medication utilisation

04

Pharmacy/Courier pharmacy dispenses medicine
AfA: Communicates with patients on script and script renewals and monitors all patients
Pharmacy: Dispenses medicine. Informs patient of any script expiry.

05

Patient takes medicine correctly and routinely
AfA: Provides practical information about medication and the importance of maintaining adherence to treatment

06

Patient goes for routine pathology monitoring tests
Doctor: Routine tests for CD4 viral load and screens for complications
Pathology lab: Performs tests and obtains results
AfA: Reminds patients about testing and interfaces with pathology labs to obtain patient results for optimal treatment management.
Pharmacy/ Courier pharmacy: Contacts patient 56 days after last expiry and informs AfA if no renewal

07

Patient identified as non-adherent according to results AfA:
Counsellors engage with non-adherent patients in intensive adherence counselling and trace treating doctor to re-enforce adherence

08

Patient is required to start/change therapy as evidenced by pathology test
Doctor: Reviews/changes therapy as indicated by pathology result
AfA: Continuously engage with external clinical HIV experts and regularly screen all patients to identify high-risk cases.

09

Introduction

The AfA Clinical Guidelines have been made available to all healthcare professionals since the inception of the programme. The Guidelines are regularly revised and updated by the expert consultants on the AfA Clinical Advisory Committee. The principle that is followed in the AfA Clinical Guidelines is to provide the best evidence that is appropriate for Southern Africa. Because patients transition between the public and private sectors, AfA has always recommended ART that is compatible with public sector regimens. However, AfA starting criteria were higher than in the public sector in the era before ART was made available to all, and there is more choice available in AfA.

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

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

Management of HIV Infection in Adults

Diagnosis

The diagnosis of HIV infection in adults is usually made by demonstrating the presence of HIV antibodies. The most frequently used method to detect antibodies in the laboratory is the enzyme-linked immunosorbent assay, or ELISA. The HIV ELISA can occasionally be false negative during the "window period" (see below). HIV ELISAs have 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. Rapid HIV antibody tests (used on whole blood, serum or saliva) have similar sensitivity and specificity to ELISA tests when performed in a laboratory; in the public sector two rapid tests from different manufacturers are used to confirm HIV, but the tests are usually done by nurses or counsellors. AfA requires laboratory confirmation of HIV infection with either an ELISA or viral load before approving ART. Currently used screening tests detect antibodies to both HIV-1 and HIV-2. HIV-2 is very rare in Southern Africa, but should be considered if HIV was acquired in West Africa. Special tests are required to diagnose HIV-2 – discuss with the laboratory.

As with other infectious diseases diagnosed by antibodies (e.g. tick-bite fever, primary syphilis), antibody tests may be negative in early HIV infection – this is the so-called "window period". In most individuals, antibodies develop within 3 – 6 weeks of infection. No test is available that will completely eliminate the "window period". Antigen tests (P24) are positive before antibodies appear, and have been incorporated into routine screening with current ELISAs that detect both antibody and antigen. The most sensitive tests in the window period are nucleic acid amplification tests (e.g. the qualitative PCR or the quantitative PCR, known as the viral load). In adults 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-positive and -negative people about prevention and limiting transmission of the virus. Prior to HIV testing, pre-test counselling is essential. Counselling should be done in the client's home language.

Issues that should be covered include:

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

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

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

Initial Examination and Staging

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

If the patient belongs to an AfA-contracted scheme or company, this examination will be part of their application to the programme. Please contact AfA for more information on how to apply.

Patients should be staged clinically according to the WHO disease staging system outlined below, which has prognostic value and is one of the criteria to initiate prophylaxis against opportunistic infections (OIs). Note that the staging system never improves – e.g. a patient who has recovered from pulmonary TB remains stage 3 for life.

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

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 (<8 g/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

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

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

Baseline Investigations

These should include the following:

- CD4 lymphocyte count
- HIV viral load
- Full blood count and differential count
- PAP smear
- ALT
- Syphilis serology
- Serum creatinine and eGFR
- Hepatitis B surface antigen
- Hepatitis C (if ALT is elevated)
- Pregnancy test
- Urine dipstix (if proteinuria is detected urine should be tested for protein:creatinine ratio)
- Serum cryptococcal antigen test if CD4 <200
- Sputum GeneXpert

CD4 and Viral Load Monitoring

The CD4 cell count, reported as the number of cells/µL, is a key laboratory indicator of the degree of immune suppression. The CD4 count is very useful in differential diagnosis e.g. cryptococcal meningitis (CM) is very unlikely if the CD4 count is above 200, and CMV disease is very unlikely if the CD4 count is above 100.

The percentage of lymphocytes which are CD4+ may be useful. The CD4 percentage is sometimes used 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 falls by about 25% during pregnancy due to dilution. The CD4 count varies by up to 20% from day to day. In HIV-negative individuals, the CD4 count is typically 500 – 1 500.

In HIV infection, mild immune suppression occurs once the count drops below 500 and patients may develop morbidity due to inflammatory dermatoses, herpes zoster and some HIV-related immune disorders (e.g. immune thrombocytopaenia). Tuberculosis (TB) may occur at any CD4 count, but the risk increases as CD4 counts fall. Once the CD4 count is below 200, there is significant immune suppression and a high risk of OIs and AIDS-defining conditions. Note that patients can be asymptomatic despite very low CD4 counts. On effective ART the CD4 count usually gradually rises until the normal range, but in some individuals there is very poor CD4 response – no change in ART is effective in this setting. If ART is interrupted the CD4 count rapidly drops to the count at baseline when ART was started. CD4 monitoring serves no purpose in virologically suppressed patients on ART whose CD4 count has risen to >200 cells/μL, confirmed on two counts.

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

Transient increases in VL occur with intercurrent infections and immunisations. VL results vary by up to three times (0.5 $\log_{10}$), 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 test should be repeated 6 – 8 weeks after starting ART. At this point the VL should show at least a 10-fold (1 $\log_{10}$) decrease. Thereafter the VL should be done every 6 months.

After 6 months of ART the VL should be below the limit of detection of the assay (typically VL <50). Failure of ART is defined by the VL. However, decisions to change ART for virological failure should not be based on the results of only one test.

HIV Disease Progression

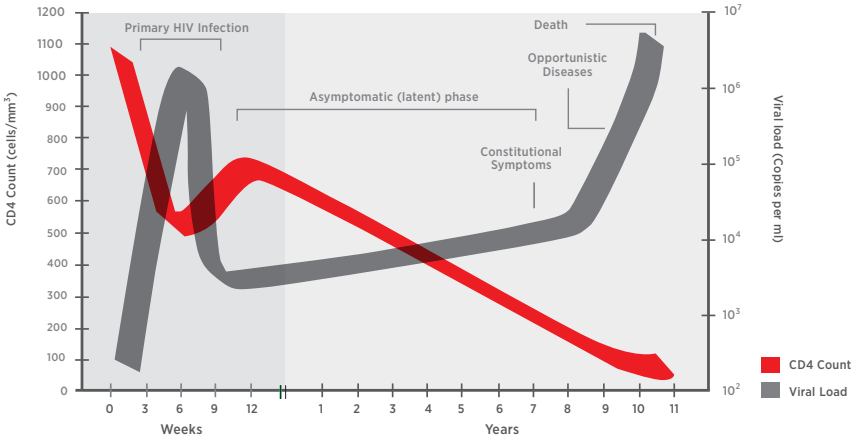
HIV infection is characterised by slowly progressive immune deficiency with a prolonged period of clinical latency. However, there is ongoing active viral replication and CD4 decline during clinical latency.

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 OIs, notably oropharyngeal candidiasis. Thrombocytopaenia and moderate elevation of liver enzymes occur commonly. The differential diagnosis of primary HIV includes acute Epstein-Barr virus infection, 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 VLs. Some of these long-term non-progressors, known as "elite controllers", have undetectable VLs without ART. Patients with high VLs progress more rapidly, as do older people. Long-term non-progressors and elite controllers are at higher risk of serious non-AIDS morbidity (e.g. vascular disease, chronic kidney disease, cancer) due to chronic immune activation; therefore, they require ART.

The natural history of untreated HIV infection



Minor HIV/AIDS-related Conditions

Oral Lesions

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

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

Oral Candidiasis

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

Topical therapy:

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

Systemic therapy (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

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 (an AIDS-defining condition) is made, which requires systemic treatment (fluconazole 200 mg daily for 14 days).

Oral Ulcers

Aphthous ulcers that are minor (<1 cm) or major (>1 cm) are commonly found in the oropharynx or, occasionally, in the oesophagus. Major aphthous ulcers are deep, painful ulcers that may cause considerable tissue destruction, are seen in advanced disease, and cause considerable morbidity.

Aphthous ulcers 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 if there is 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. The salivary gland enlargement usually regresses on ART.

Peripheral Neuropathy

Peripheral neuropathy is common in HIV infection. It occurs more commonly in late disease, affecting 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 e.g. isoniazid. 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.

The management of peripheral neuropathy should commence with a trial of B complex vitamins (or pyridoxine alone in patients on 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 integrase inhibitors (InSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Lamotrigine, pregabalin or gabapentin may also be of benefit, and do not have the same drug interaction problems as carbamazepine.

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 TB, which is a 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 should be done and the needle and syringe flushed with 1 – 2 ml of sterile saline and sent for rapid TB molecular test (Xpert MTB/RIF Ultra), which has a high diagnostic yield. There is little point in doing aspiration for cytology unless carcinoma is suspected, as lymphoma in particular may mimic the cytological features of TB. If caseous material is aspirated this is virtually diagnostic of TB, which should be confirmed on Xpert MTB/RIF Ultra or TB culture. If tests for TB are negative, an excision biopsy or Tru-Cut needle biopsy should be done for histology and TB culture.

Haematological Conditions

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

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

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 the number of lesions is limited – multiple lesions usually regress on ART.

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 poorly to therapy.

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

Herpes Simplex

Recurrent mucocutaneous ulcers are extremely common in HIV infection. Herpes simplex virus 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 500 mg 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. Multiple dermatomes may be involved and recurrences may occur. 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 may be of value (e.g. silver sulfadiazine).

Inflammation and co-morbidity

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

Major Opportunistic Infections and Conditions

Bacterial Pneumonia

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

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

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

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, ART is generally effective, disease is not life-threatening and azole-resistant Candida strains may be selected for on maintenance therapy.

Cryptococcosis

Diagnosis: Culture of *Cryptococcus neoformans* from any site or by positive cryptococcal antigen in blood or CSF. CSF Indian Ink stain is also useful to diagnose cryptococcal meningitis, but may be negative in around 20% of cryptococcal meningitis (CM) cases.

Induction Treatment:

Preferred regimen: 1 week of amphotericin B 1 mg/kg/day and flucytosine* 100 mg/kg/day in four divided doses, followed by 1 week of fluconazole 1200 mg/day.

The AMBITIONcm trial found that a novel regimen of a single high-dose of liposomal amphotericin B 10 mg/kg infusion given on day 1 together with 14 days of flucytosine 100 mg/kg/day and fluconazole 1200 mg/day orally, was non-inferior to the 7-day amphotericin-B plus flucytosine combination, with fewer side-effects. This is currently regarded as an alternative regimen. It is important to note that if this regimen is used and the patient is discharged from hospital earlier, they still require close monitoring for symptoms of raised intracranial pressure and therapeutic lumbar punctures (LPs) when indicated.

If flucytosine is unavailable: 2 weeks of amphotericin B 1 mg/kg/day and fluconazole 1200 mg/day.

*Flucytosine is not currently registered in South Africa and will need to be accessed via a Section 21 application.

All patients should have CSF opening pressure measured at diagnosis. Patients with raised intracranial pressure (>25 cm H_20) should have daily LPs, removing sufficient CSF (usually 10 – 20 ml) to lower pressure to <20 cm H_20. Failure to manage intracranial pressure can result in severe, permanent neurologic sequelae or death. LPs should be done daily until symptoms of raised intracranial pressure have 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. Steroids have been shown to be harmful in the management of raised intracranial pressure in cryptococcal meningitis. 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 prehydrating patients with normal saline. It also often causes hypokalaemia and hypomagnesaemia, which needs to be managed aggressively, and pre-emptive supplementation is advised. Finally, infusion reactions with fever and rigors occur commonly.

Consolidation treatment: Fluconazole 800 mg daily for 8 weeks.

Amphotericin B

The treatment of CM includes intravenous amphotericin B (AmB) 1 mg/kg/day for either 7 or 14 days. Amphotericin B has several potential toxicities, but these can usually be managed or prevented.

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

Maintenance treatment: Fluconazole 200 mg daily until CD4 count is >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; a positive antigen is not indicative of relapse. Patients experiencing culture-positive relapses should receive induction therapy as above, followed by fluconazole 800 mg for 8 weeks, then fluconazole maintenance. It is important to investigate the cause of the relapse. The most common cause is non-adherence. Where no history of poor adherence is apparent, such patients should have cryptococcal isolate tested for fluconazole susceptibility at a reference laboratory if possible. Long-term maintenance in such patients should be discussed with AfA.

Asymptomatic cryptococcal antigenaemia: 1–7% of patients starting ART with a CD4 count <200 have a positive serum (or plasma) cryptococcal antigen (CrAg) test despite not having symptoms of meningitis. However, these patients are at high risk of developing cryptococcal meningitis. Therefore, screening for serum CrAg should be done in all patients presenting with CD4 <200. Some patients with cryptococcal antigenaemia have presymptomatic meningitis. Therefore, all patients who are serum CrAg positive for the first time should have a LP done to exclude cryptococcal meningitis. For those with antigenaemia but no meningitis, treat pre-emptively with fluconazole 1200 mg daily for two weeks, followed by fluconazole 800 mg daily for 8 weeks, followed by fluconazole 200 mg daily until the CD4 count is >200 (minimum treatment duration of antifungal therapy is 12 months). If CM is excluded on LP in patients with positive serum CrAg then ART can be started without delay. In antigenaemic patients with no symptoms of meningitis, where LP is declined or not possible, we recommend deferring ART for 2 weeks (while treating with fluconazole as recommended above). Refer to: Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-positive persons: 2019 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.

The morbidity of CMV disease can be severe (e.g. retinitis, the commonest site, results in irreversible blindness). Early initiation of ART (within 2 weeks of diagnosis) is essential in all cases. Zidovudine in combination with valganciclovir is best avoided as this suppresses the bone marrow.

CMV retinitis

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

Treatment: Valganciclovir 900 mg orally bd for 2–3 weeks induction. (Requires pre-authorisation by AfA.)

This prevents CMV retinitis progression but does not reverse visual loss.

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

CMV GIT (colitis/oesophagitis/duodenitis)

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

Treatment: Valganciclovir 900 mg orally bd for 3 weeks. (Requires pre-authorisation by AfA.)

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

CMV CNS (encephalitis/polyradiculopathy/myelitis)

Diagnosis: PCR of CSF.

Treatment: Valganciclovir 900 mg orally bd for 2–3 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.

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.

Valganciclovir 900 mg orally bd for 3 weeks may be indicated in severe disease. (Requires pre-authorisation by AfA.)

Emergomyces

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

Diagnosis: Culture of *Emergomyces africanus* 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 PI-based ART). Note that there are important drug interactions between itraconazole and antiretrovirals. Itraconazole cannot be used safely with NNRTIs due to induction of itraconazole metabolism. A dose reduction (200 mg daily) is required with PIs. All patients on itraconazole for emergomyces

should therefore be treated with ART using dolutegravir or PIs.

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

Herpes Simplex Virus Ulcers

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

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

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

Histoplasmosis

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

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

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

Cystoisosporiasis (formerly Isosporiasis)

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

Treatment: Co-trimoxazole four single-strength (480 mg) tablets bd for 10 days. If the patient is unable to take oral medication use co-trimoxazole IVI. The alternative is ciprofloxacin 500mg bd.

Maintenance treatment: Co-trimoxazole 960 mg daily until CD4 count rises to >200 on ART. Recurrent cystoisosporiasis 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. 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 gastrointestinal 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 TB 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 TB, then TB treatment should be discontinued and MAC treated.

Treatment: Clarithromycin 500 mg bd plus ethambutol 15–25 mg/kg daily (usually 800 mg or 1200 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 daily should be used as an alternative. Similarly, if the patient is taking rifampicin for confirmed TB or any other reason, then azithromycin should be used in preference to clarithromycin due to drug-drug interactions. 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 300 mg daily when used with dolutegravir, 450 mg daily when used with efavirenz, and 150 mg daily when used with a PI. There may be increased toxicity with the daily dose of rifabutin due to accumulation of the metabolite – monitor closely for neutropaenia, uveitis and hepatitis.

Maintenance treatment: See above.

Pneumocystis Pneumonia (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 over several weeks, and hypoxia (at rest, or on effort as assessed by >5% desaturation). COVID-19 pneumonia should be excluded.

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 – Section 21 approval must be sought for any of these (primaquine is easier to get). 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.

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

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

Time	**Dose**
(hours)	(ml 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 IRIS (MRI lesions may be enhancing in this situation). ART has improved survival, but patients are left with residual disability.

Salmonella Bacteraemia

Diagnosis: Blood culture of non-typhoidal salmonella.

Treatment: Ciprofloxacin 500 mg bd for 4 – 6 weeks (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 OIs 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 be 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 TB have a better prognosis than other AIDS-defining illnesses. All forms of TB may occur at any CD4 count, but extrapulmonary, disseminated and non-cavitary pulmonary TB are typically seen when the CD4 count is <200. In advanced disease, the chest X-ray may be clear with a positive TB sputum culture.

The four 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-positive patients varies according to the CD4 count (Figure 1). Typical cavitary disease, as seen in HIV-seronegative patients, is rarely present at CD4 counts <200 cells/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.

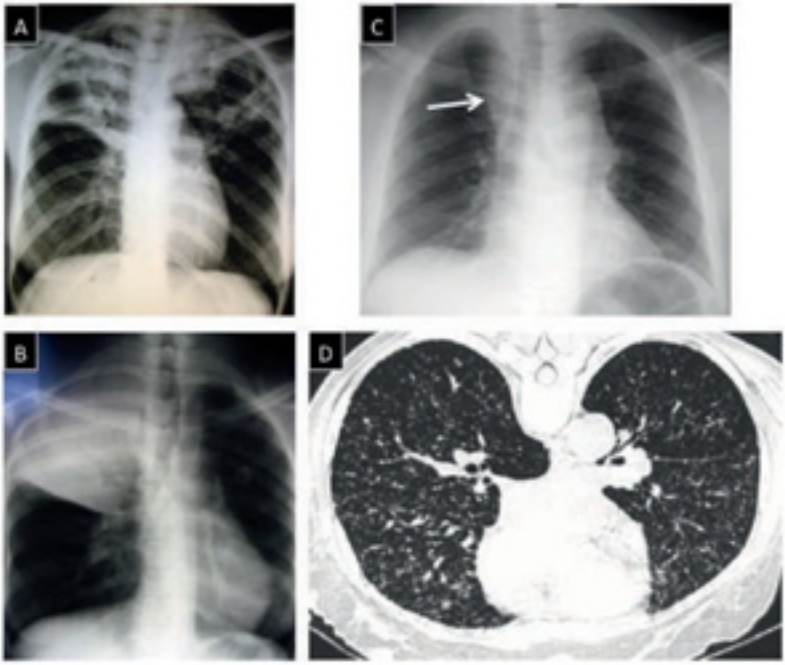


Figure 1. *Cavitary bilateral upper-lobe consolidation (A); right upper-lobe consolidation with air bronchogram (B); right para-tracheal lymphadenopathy with normal lung parenchyma (C); miliary TB pattern on CT scan (D).*

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

Diagnosis	Symptoms
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 shows 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 are usually apparent May present as bloody pleural effusion or linear opacities that follow the blood vessels on CXR in a predominant peri-hilar distribution with nodules of varying size
Lymphoid interstitial pneumonitis (LIP)	May be part of broader picture of diffuse inflammatory lymphocytosis syndrome (DILS) or associated with sicca syndrome (dry eyes, dry mouth) Bilateral reticulonodular 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 TB suggestive features on ultrasound or CT include splenomegaly with or without hypoechoic lesions, lymphadenopathy of >1.5 cm, and ascites, pleural or pericardial effusions (sometimes commented on during abdominal imaging). TB pericarditis often displays fibrous stranding on echocardiography. TB lymphadenopathy often has a hypodense centre from caseous necrosis on ultrasound/CT/MRI scans.

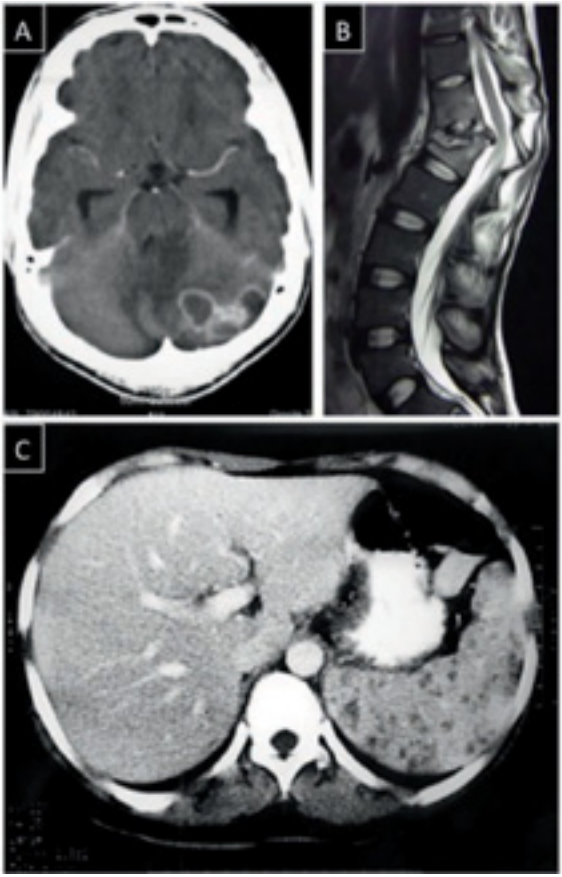


Figure 2. *Cranial CT showing multiple ring-enhancing space-occupying lesions (A); Pott's disease of the spine showing destruction of the disc space (B); and abdominal CT scan showing multiple splenic micro-abscesses (C).*

It is important to try and confirm the diagnosis of TB. In HIV-positive patients with PTB, 60–70% of sputum samples are 'smear-negative' by routine microscopy. Xpert MTB/RIF Ultra real-time PCR on sputum is now the diagnostic test of choice for HIV-positive 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, Xpert MTB/RIF Ultra will also confirm whether or not rifampicin resistance is present in sputum samples that are positive for *Mycobacterium tuberculosis*. Xpert MTB/RIF Ultra testing has been rolled out within the public sector in South Africa.

If the Xpert MTB/RIF Ultra identifies rifampicin resistance, then a second sample should be sent to the laboratory for 'DR-TB: reflex DST testing'. First, a sputum smear microscopy is performed and sputum sent for culture. If the smear is positive, then first- and second-line line probe assays (LPAs) will be performed for genotypic resistance to rifampicin, isoniazid, ethambutol, fluoroquinolones and injectables. If the smear is negative, sputum is sent for culture and a first-line LPA is attempted. If the culture becomes positive, the second-line LPA will be done subsequently on that specimen. Further phenotypic tests can be performed on culture isolate, depending on results of the LPAs.

If for any reason Xpert MTB/RIF Ultra is not available, at least two sputum specimens should be sent for smear and culture. If the sputum is smear-positive, first-line LPA for rifampicin and isoniazid resistance can be requested directly on the specimen.

In disseminated TB, spread of *M. tuberculosis* to the genitourinary tract can lead to presence of the bacilli in urine. Lipoarabinomannan (LAM), a constituent of the bacillus' cell wall, can be detected in urine samples – ideally, early-morning urine to allow for concentration overnight. Urinary LAM in hospitalised patients with CD4 counts ≤200 has a sensitivity approaching 50% in smear-negative patients or those unable to produce sputum, and has high specificity (i.e. it is a good "rule in" test). Furthermore, bedside LAM-guided initiation of anti-TB treatment in HIV-positive hospital in-patients with suspected TB has been shown to be associated with reduced 8-week mortality. One caveat is that urinary LAM may be positive in disseminated non-tuberculous mycobacterial infections such as *Mycobacterium avium intracellulare*, and in infections due to *Nocardia* species. These infections are much rarer than TB, but referral for infectious diseases advice is suggested if any diagnostic concern exists.

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%.

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

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

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

Drug	Potency	Recommended dose (mg/kg)
First-line drugs		
Rifampicin (R)	High	10
Isoniazid (H)	High	5
Pyrazinamide (Z)	Low	25
Ethambutol (E)	Low	15
Second-line drugs		
Bedaquiline (Bdq)	High	400 mg daily for 2 weeks followed by 200 mg 3 x/ week for 22 weeks
Levofloxacin (Lfx)	Moderate	750 mg daily
Moxifloxacin (Mfx)	Moderate	400 mg daily
Linezolid (Lzd)	High	600 mg daily
Clofazamine (Cfz)	High	2 – 5
Terizidone (Trd)	Low	15 – 20
Para-aminosalicylic acid (PAS)	Low	150
Ethionamide (Eto)	Low	15 – 20

National guidelines for treatment of drug-sensitive TB 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 TB (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 one TB drug other than rifampicin and isoniazid
Multi-drug resistance (MDR)*	Drug resistance to rifampicin and isoniazid with or without resistance to other anti-TB drugs
Extensive drug resistance (XDR)	MDR plus resistance to fluoroquinolones and ≥1 of the three injectable second-line drugs (amikacin, kanamycin or capreomycin) – increasingly obsolete term as second-line injectable drugs are dropped from the DR-TB regimen
Pre-XDR	MDR and resistance to **either** fluoroquinolone **or** second-line injectable drugs

* *Xpert MTB/RIF Ultra 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, and should be counselled properly with regard to prolonged duration, toxicities, adherence and infection control. Directly observed, daily treatment is advised.*

Treatment of MDR-TB: In 2019, national guidelines for the 'Management of Rifampicin-Resistant Tuberculosis – a Clinical Reference Guide' were published, updating guidance from the January 2013 edition. Major changes in management reflect an interval period that has seen major shifts in diagnostic and therapeutic management.

The initial choice of regimen and duration of treatment for DR-TB in HIV-positive patients is determined by the presence or absence of the following factors:

1. History of previous treatment with second-line drugs for >1 month
2. Complicated extrapulmonary-TB (EPTB) – meningitis, osteoarticular, pericarditis, abdominal
3. Contact with XDR or pre-XDR
4. Younger than 6 years of age
5. Extensive disease on CXR
6. Both INH mutations (inhA and katG) present on LPA

Short course	Intensive phase: 4–6 months	Continuation phase: 5 months
	Linezolid – 2 months Bedaquiline – total 6 months High-dose Isoniazid Levofloxacin Clofazimine Pyrazinamide Ethambutol	Levofloxacin Clofazimine Pyrazinamide Ethambutol
Long course	**Intensive phase: 6 months**	**Continuation phase: 12 months**
Basic regimen	Bedaquiline Linezolid Levofloxacin Clofazimine Terizidone	Levofloxacin Clofazimine Terizidone
Fluroquinolone resistance	Bedaquiline Linezolid Delaminid Clofazimine Terizidone	Clofazimine Terizidone Linezolid, Bedaquiline and/ or Delaminid
Central nervous system involvement	***Extend intensive phase to 12 months*** Bedaquiline Linezolid Levofloxacin Delaminid Clofazimine Terizidone Pyrazinamide High-dose isoniazid or ethionamide	***Shorten continuation phase to 6 months*** Levofloxacin Clofazimine Terizidone Pyrazinamide Linezolid or high-dose isoniazid or ethionamide, depending on mutations

Adapted from 'Management of Rifampicin-Resistant Tuberculosis: A Clinical Reference Guide'

Presentation of the full guidelines for management of DR-TB is beyond the scope of this publication, but the prescriber is referred to the national **'Management of Rifampicin-Resistant Tuberculosis: A Clinical Reference Guide**.

Adverse events to TB drugs and ART

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

Adverse event	TB drug	ART
Drug-induced liver injury	Rifampicin, isoniazid, pyrazinamide, fluoroquinolones, ethionamide, PAS, linezolid	NNRTIs, PIs, integrase inhibitors
Cutaneous drug reaction	All	NNRTIs
Anaemia, leucopaenia, thrombocytopaenia	Linezolid	Zidovudine
Peripheral neuropathy	Isoniazid, ethionamide, linezolid, terizidone	
Nausea and vomiting	Ethionamide, pyrazinamide	Zidovudine, PIs
Psychosis	Isoniazid, terizidone, fluoroquinolones, ethionamide	Efavirenz

Coadministration of zidovudine with linezolid should be avoided, and zidovudine only introduced if necessary, after completion of linezolid in the TB regimen. Other important side-effects of second-line TB drugs include seizures (terizidone, fluoroquinolones and cycloserine), hypothyroidism (PAS, ethionamide), gastritis (PAS, ethionamide), arthralgia/arthritis (pyrazinamide and fluoroquinolones), tendonitis/tendon rupture (fluoroquinolones), reversible myelosuppression (linezolid), hypokalaemia/hypomagnesaemia (aminoglycosides), and QTc increase (clofazimine, fluoroquinolones, bedaquiline). Aminoglycosides are rarely used now, but ototoxicity from these drugs is usually irreversible. An audiogram should be performed prior to starting an aminoglycoside 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, while 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 restart after TB drug rechallenge is complete, and consider an integrase or PI-based regimen if the patient was previously on an NNRTI.

Management of severe CDR

STEP 1 Urgent action

Take accurate drug history

STOP ALL POTENTIALLY OFFENDING DRUGS. Check ALT

- ALT >5 x ULN → STOP ALL ART. Restart once LFTs have normalised. Consider an integrase or PI-based regimen
- ALT <5 x ULN → Switch to integrase or PI-based ART if on NNRTI

STEP 2 Review

REVIEW THE STRENGTH OF THE ORIGINAL TB DIAGNOSIS

Clinical, radiographic and laboratory evidence, plus response to treatment

- TB diagnosis likely/ confirmed AND DS-TB likely → Start TB backbone with three new drugs: Mfx/Lfx + linezolid + terizidone
- TB diagnosis unlikely → Do not restart TB therapy, monitor closely

STEP 3 Reintroduction

Reintroduce individual drugs with incremental dose increase sequentially

Day	Drug	Comment
1	Rifampicin 75 mg	
2	Rifampicin 300 mg	Evaluate for symptoms and signs of
3	Rifampicin full dose	anaphylaxis, for fever and skin daily
4		
5	Isoniazid 50 mg	
6	Isoniazid 100 mg	Monitor ALT and creatinine x 3 per week
7	Isoniazid 300 mg	
8		
9	Pyrazinamide 250 mg	Discontinue the drug as soon as the patient experiences minor skin involvement
10	Pyrazinamide 1 g	
11	Pyrazinamide full dose	
12	Ethambutol 100 mg	Rechallenge with ethambutol if intolerant to any of the above three drugs
13	Ethambutol 400 mg	
14	Ethambutol full dose	

INTOLERANCE: Z (RHE 9 months): R (H, E, Lfx 18 months): H (RZE 6 months)

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 zidovudine (if Hb allows) or abacavir, while on the nephrotoxic drug.

If renal dysfunction occurs following the start of TB treatment:

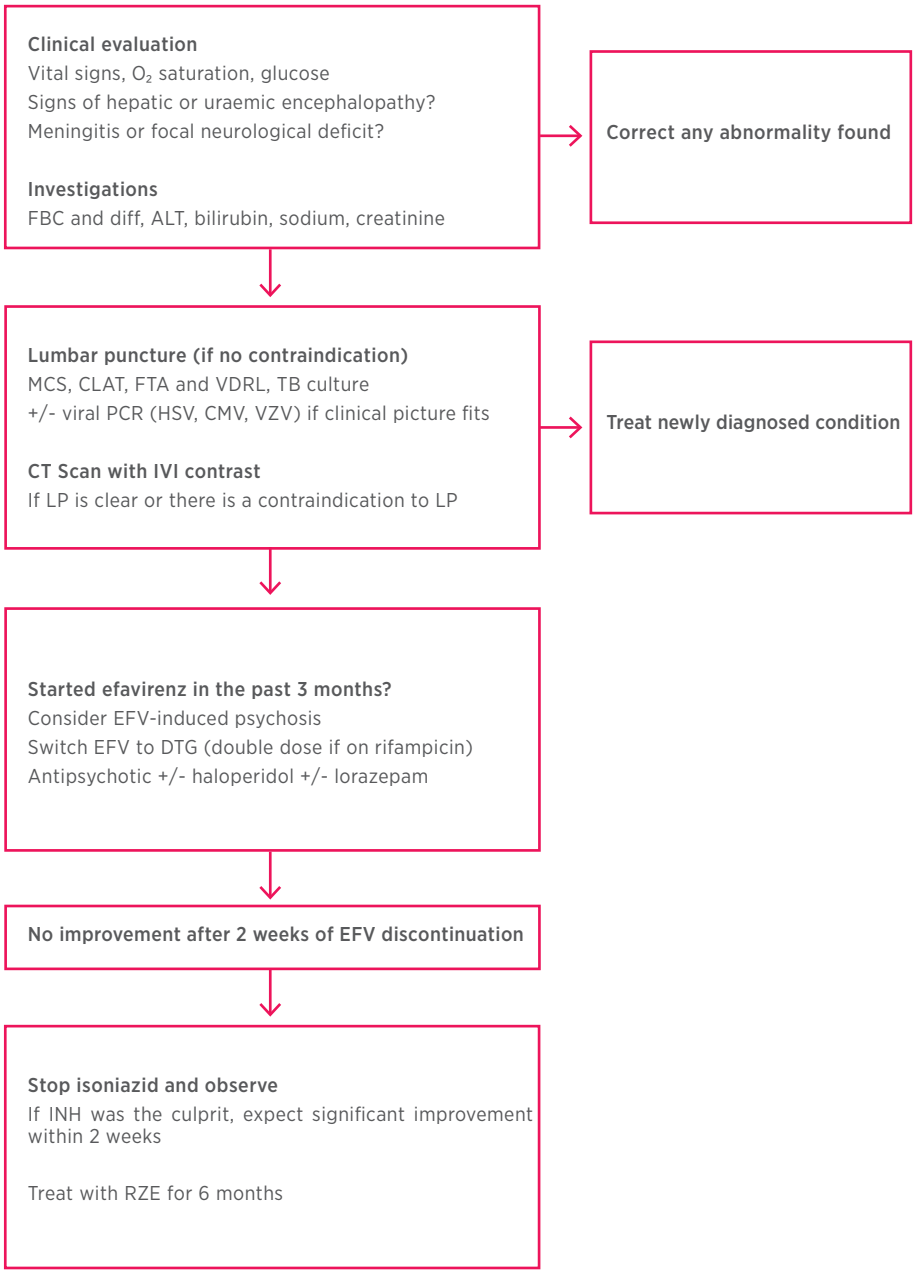
- STOP all agents commonly known to be nephrotoxic
- Correct dehydration as necessary
- Check urinary protein-creatinine ratio, serum electrolytes and creatinine. Renal ultrasound if renal dysfunction continues
- Monitor daily serum creatinine and fluid balance
- If the patient does not improve, refer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

Clinical algorithm for initial evaluation



Toxoplasmosis

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

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

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

HIV-associated Kaposi's Sarcoma (KS)

Background to HIV-associated KS:

- KS is a malignancy of lymphatic endothelial origin
- It is associated with human herpes virus-8 (HHV-8), also known as KS herpes virus (KSHV)
- KS may involve the skin, oral cavity, lymph nodes or viscera (especially lung and intestines). Lymphoedema is a common complication
- 80–90% of cases of visceral KS will have oral or skin involvement
- The CXR appearance of pulmonary KS involves nodules, consolidation and linear shadows, often spreading from the hilar regions bilaterally. The diagnosis is confirmed by visualising endobronchial KS lesions on bronchoscopy (biopsy poses a risk of haemorrhage). Pulmonary KS may be associated with intrathoracic adenopathy and/or pleural effusions, which are typically bloody or serosanguinous
- CXR is a useful screen for pulmonary KS in the setting of cutaneous disease
- KS is a WHO stage 4 defining illness, regardless of CD4
- The incidence of KS has been dramatically reduced by ART (92% reduction in Swiss cohort)
- Although the macroscopic appearance of skin and oral lesions may be very suggestive, if there is any uncertainty a biopsy should be performed to provide a definitive diagnosis. In particular, nodular vascular skin lesions that enlarge rapidly should be biopsied to exclude bacillary angiomatosis that is due to Bartonella infection and may mimic KS
- Atypical oral lesions should be biopsied to exclude other malignancies such as lymphoma, squamous carcinoma and salivary gland tumours

Treatment principles:

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

A suggested general approach is:

Limited cutaneous and oral lesions:

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

Extensive skin disease/visceral involvement:

- ART and systemic chemotherapy commenced simultaneously

Standard chemotherapy regimens

Options:

- Adriamycin (doxorubicin), bleomycin, vincristine combination therapy 2-weekly x 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. In a recent clinical trial conducted in LMICs, paclitaxel was shown to be superior to bleomycin/vincristine treatment for advanced KS in terms of one-year progression-free survival. Paclitaxel has also 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.

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.

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

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

Lymphoma

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

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

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

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

HIV-associated Nephropathy

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

It is important to diagnose HIVAN early, before there has been substantial loss of renal function. This is why we recommend serum creatinine and urine 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 reports of ART reversing the renal dysfunction associated with HIVAN. Cohort studies show that progression to ESRF is slowed down by ART. All patients with HIVAN should be started on ART without delay (renal failure dose adjustments may be required – see Drug Dosages in Renal Failure). Tenofovir should be avoided. ACE-inhibitors reduce the amount of proteinuria and are thought to slow disease progression.

A trial of corticosteroids is advised by some experts.

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

HIV-associated Dementia (HAD)

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

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

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

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

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 sequence 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.

N. Sacktor, et al.
Department of Neurology
Johns Hopkins University
Baltimore, Maryland
Sacktor NC, et al. *AIDS*. 2005;19(13): 1367-74.

Prevention of Opportunistic Infections

Primary prophylaxis is given to prevent common OIs. 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 960 mg daily. Prophylactic co-trimoxazole prevents pneumocystis pneumonia (PJP) and toxoplasmosis. Co-trimoxazole prophylaxis can be used in pregnancy as the benefits outweigh the risks. It also reduces the frequency of bacterial infections, including bacterial pneumonia, and some protozoal causes of diarrhoea *(Cystisospora 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 a CD4 >200 (e.g. because they develop TB), then co-trimoxazole can be discontinued after six months of ART, provided that the VL is suppressed.

Hypersensitivity to sulphonamides is common in HIV infection. Provided the reaction is mild (rash with no mucosal involvement or systemic symptoms), co-trimoxazole can be continued with antihistamine cover and close follow-up. If the reaction warrants stopping therapy, then rechallenge, or desensitisation may be attempted (success rates are about 60–70%). Alternatively, dapsone 100 mg daily can be used. Dapsone effectively prevents pneumocystis pneumonia, but does not protect against many of the other OIs 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 nor dapsone can be used, and the patient has a very low CD4 count, an alternative is atovaquone 1500 mg daily for a few months, until the CD4 count is clearly rising. It is less effective, extremely expensive and has significant drug interactions with rifampicin.

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

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

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

AfA endorses the simplified national guidelines on isoniazid preventive therapy (IPT) issued in the 2018 Standard Treatment Guidelines and Essential Medicines List, Primary Healthcare Level Care (**http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/285-phc**). The guidelines recommend isoniazid 300 mg daily together with pyridoxine (vitamin B6) 25 mg daily for 12 months. IPT should be started with ART or added to those on ART who have not yet received IPT. There is no need to test for latent TB infection (either tuberculin skin tests or interferon-gamma release assays [like QuantiFERON-TB gold test]).

The rationale for these simplified guidelines is from a South African trial, which showed that IPT for 12 months given to patients on ART, or starting ART, reduced the risk of TB by about a third and was well tolerated. The benefit of IPT in patients on ART was seen irrespective of tuberculin skin test (TST) status, which is unlike findings of studies done in the pre-ART era.

Patients must be followed up regularly while on IPT and asked specifically about symptoms of hepatotoxicity (nausea, vomiting, right upper-quadrant pain, and jaundice). If these symptoms occur, examine for jaundice and urgently check ALT. If significant hepatotoxicity (defined as ALT >5 times upper limit of normal (ULN) or >3 times ULN with symptoms or jaundice) occurs, discontinue IPT immediately. Pyridoxine should be given concurrently to reduce the risk of peripheral neuropathy.

Before commencing IPT, active TB should always be excluded. Further investigations to exclude TB must be done if any of the following symptoms are present (note that a screening CXR is not required before initiating IPT):

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

If any of the above symptoms are present, a sputum sample should be sent for GeneXpert MTB/RIF – if this is negative and symptoms persist, a second sputum sample should be sent for mycobacterial culture. IPT should be deferred until these results are known and the symptoms have resolved.

A trial of IPT in pregnant women on ART, the TB APPRISE study, showed that IPT resulted in worse pregnancy outcomes with no benefit. However, a large South African cohort study of 43 971 pregnant HIV-positive women, 16% of whom received IPT during pregnancy, has challenged the findings of the TB APPRISE study. In contrast to the TB APPRISE study, IPT reduced the risk of adverse pregnancy outcomes by 17% (95% confidence interval (CI) 13–22%). IPT during pregnancy reduced the risk of TB by 29% (95% CI 19–37%). Women with CD4 counts ≤350

cells/μL benefitted most from IPT during pregnancy, with a 49% reduction in the risk of TB, while IPT during pregnancy did not significantly reduce the risk of TB in women with higher CD4 counts. Based on this evidence, AfA recommends the use of IPT for pregnant women with CD4 counts ≤350 cells/μL. IPT should be deferred until after delivery in women with higher CD4 counts.

Hepatitis B Co-infection

Chronic hepatitis B virus (HBV) is endemic in sub-Saharan Africa, where hepatitis B surface antigen prevalence stands between 0.3% and 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 co-infection 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-positive 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 should start ART containing two agents with anti-HBV activity, namely tenofovir plus lamivudine or emtricitabine
- Tenofovir and lamivudine or emtricitabine should only be stopped in the face of severe adverse effects from these drugs precluding their use – stopping these is associated with the risk of a hepatitis 'flare'
- HIV-positive 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 to consider re-vaccination once the immune system is reconstituted if the response has been poor
- Vaccination should include a three-dose regimen at 0, 1, and 6 months using double-dose HBV vaccine
- All HIV-positive 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 first dose of HBV vaccine at two separate sites within 12 hours of birth. A four-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 cases where there is coinfection 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 2.4 MU IM STAT **PLUS** Azithromycin 1 g PO stat **PLUS** Acyclovir 400 mg 8-hourly for 5 days
Vaginal discharge (exclude candidiasis clinically)	Ceftriaxone 250 mg IM STAT **PLUS** Azithromycin 1 g PO STAT **PLUS** Metronidazole 2 g PO STAT
Urethral discharge	Ceftriaxone 250 mg IM STAT **PLUS** Azithromycin 1 g PO STAT

Management of specific infections

Syphilis (If there are no clinical signs for staging, regard as latent)	
Primary and secondary	Benzathine penicillin 2.4 MU IM as a single dose
Penicillin allergy	Doxycycline 100 mg 12-hourly for 14 days
Latent	Benzathine penicillin 2.4 MU 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 2.4 MU IM weekly for 3 weeks
Gonorrhoea	Ceftriaxone 250 mg IM STAT **PLUS** Azithromycin 1 g PO STAT
Penicillin allergy	Azithromycin 2 g PO STAT
Disseminated gonococcal arthritis	Ceftriaxone 1 g IM/IV daily for 7 days **PLUS** Azithromycin 1 g PO STAT
Chlamydial infection	Azithromycin 1 g PO STAT **OR** Doxycycline 100 mg 12-hourly for 7 days (14 days for lymphogranuloma venereum)
Chancroid	Ciprofloxacin 500 mg 12-hourly for 3 days **OR** Azithromycin 1 g PO STAT
Trichomonas	Metronidazole 2 g PO STAT
Bacterial vaginosis	Metronidazole 2 g PO 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-positive patients, and must be avoided in patients with a CD4 count of less than 200 as it could lead to life-threatening disease. Response to immunisation is very poor if the CD4 count is less than 200.

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

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

HIV-positive persons are at increased risk of severe outcomes from coronavirus disease-2019 (COVID-19). There is currently no published data on response to SARS-CoV-2 immunisation in HIV-positive persons, but as none of the current vaccine alternatives – adenoviral vector-based (Janssen; AstraZeneca; Sputnik), RNA (Pfizer; Moderna), protein (Novavax), or attenuated virus (Sinopharm, Sinovac) are live vaccines, safety profiles are likely to be similar to the HIV-negative population. Therefore, at the current time we recommend that HIV-positive persons be vaccinated against SARS-CoV-2.

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. OIs (especially those causing prolonged diarrhoea), TB 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 OIs or malignancy. In this context a C-reactive protein test is helpful, as it is raised >10 mg/l with many opportunistic diseases but not with HIV per se.

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

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

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

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

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

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

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

Antiretroviral Therapy in Adults

The goals of ART are:

- To prolong life expectancy
- To improve quality of life
- To prevent development of OIs and other AIDS-related conditions
- To reconstitute immune function
- To suppress viral replication
- 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 the host chemokine receptor CCR5, which blocks entry of the virus into the cell.

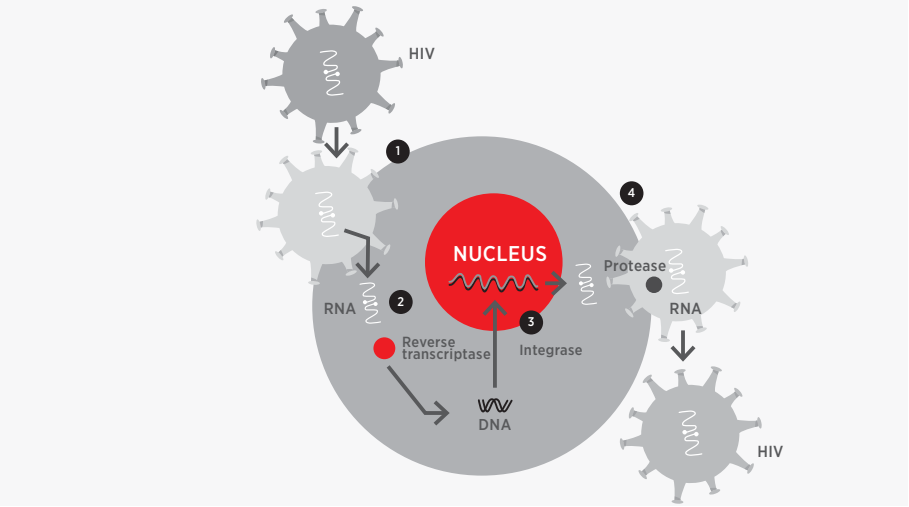
There are two classes of drugs that inhibit reverse transcriptase: nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These drugs block the conversion of viral RNA into proviral DNA, and thus genetic integration of the virus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

NRTIs resemble the natural nucleotide building blocks of DNA. When 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 and needs di-phosphorylation. 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.

PIs 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.

The HIV Lifecycle

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



Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Dual NRTIs form the backbone of most antiretroviral combinations: lamivudine or emtricitabine (these two NRTIs are interchangeable and are never used together) are always included.

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: zidovudine > lamivudine = emtricitabine = abacavir = tenofovir.

Tenofovir (TDF or TAF)

Tenofovir is a nucleotide analogue of adenosine. Two prodrugs are available: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). TAF has recently been registered in South Africa.

Side-effects: TAF is less toxic than TDF. The major concern is nephrotoxicity. Acute renal failure is rare, but mild reductions in GFR occur commonly with long-term use. Risk factors for nephrotoxicity include underlying renal impairment and coadministration of other nephrotoxic drugs. Hypokalaemia and hypophosphataemia due to renal tubular damage (Fanconi's syndrome) may rarely occur (measure serum phosphate and potassium if there are unexplained muscle symptoms such as myalgia). Nephrotoxicity is reversible when tenofovir is discontinued, but some residual damage may persist.

Regular monitoring of renal function (serum creatinine and eGFR) is recommended (at one, two, three and six months, then six-monthly). TDF should not be used if the eGFR is <50 ml/min; TAF can be used provided the eGFR is ≥30. Patients with heavy proteinuria (urine protein:creatinine ratio >0.1) should be referred to a nephrologist and both TDF and TAF should be deferred.

Severe flares of hepatitis B may occur if tenofovir is discontinued. Bone mineral density is mildly reduced (more common with TDF than TAF), which is of uncertain clinical significance. Hyperlactataemia risk – very low.

Dose: TDF 300 mg daily with food. TAF 25 mg daily with food (or 10 mg daily if used with ritonavir-boosted PIs).

Zidovudine (AZT)

AZT is a thymidine analogue and was the first effective antiretroviral drug.

Side-effects: Initial nausea, vomiting, headaches and myalgia, which improve as tolerance develops in a few weeks. Anaemia and neutropaenia (but not thrombocytopaenia) may occur, usually within 6 months; both are more common in advanced disease. Mild anaemia and neutropaenia are common and well tolerated. Monitor FBC at baseline, at one, two, three and six months, then six-monthly. AZT need only be discontinued if the Hb falls below 8.0 g/dl or the neutrophil count below 1.0×10^9/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. Myopathy with raised CK is a rare side-effect after long-term use. May cause lipoatrophy. Hyperlactataemia risk is moderate.

Dose: 300 mg bd.

Abacavir (ABC)

This is a guanosine analogue. ABC is currently recommended in first-line regimens in children in national guidelines. In adults ABC is reserved for patients with renal impairment.

Side-effects: The main problem is a severe systemic hypersensitivity reaction, which typically presents in the first 8 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, which is very uncommon in Africans. HLA-B*5701 should be tested prior to use of abacavir – if it is present, then abacavir should not be used as ~50% will develop hypersensitivity. Rechallenge should never be attempted, as this can be fatal. Some cohort studies have documented increased cardiovascular risk in patients on ABC; however, this finding was not confirmed in a meta-analysis of RCTs. Hyperlactataemia risk – very low.

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 tenofovir and AZT when mutations conferring resistance to these NRTIs are present. For this reason, 3TC (or the similar drug emtricitabine) is recommended in second-line and subsequent regimens, even when 3TC resistance is present.

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

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

Emtricitabine (FTC)

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

Side-effects: FTC may cause hyperpigmentation, particularly on the palms and soles. 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. Hyperlactataemia risk is very low.

Dose: 200 mg daily. FTC is only available in combination products.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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

Class side-effects:

All NNRTIs can cause a generalised hypersensitivity rash, but the incidence differs by individual drug: NVP > EFV = ETR > RPV. 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 is also on co-trimoxazole, stop this too Do not reintroduce co-trimoxazole

Antihistamines may be used for symptomatic treatment of NNRTI rash. The use of corticosteroids to treat the rash is not recommended, as there is evidence that prophylactic use of oral corticosteroids aggravates the risk and possibly the severity of the rash. If the NNRTI needs to be stopped for a hypersensitivity rash, a drug from another class should be used instead (e.g. dolutegravir) as there is a risk of cross-reaction.

Nevirapine (NVP)

Side-effects: NVP is associated with a high risk of severe hypersensitivity rash and hepatitis – for this reason it is no longer recommended for use in adults (except as single-dose therapy for PMTCT for selected women).

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. EFV should generally be avoided in shift workers. EFV can rarely cause a severe encephalopathy after long-term use in patients who are genetic slow metabolisers with high EFV concentrations. EFV can occasionally also cause drug-induced liver injury, which typically presents months after starting EFV.

Hypersensitivity rash is common in the first six weeks, but this is usually milder than with NVP (EFV has been discontinued because of rash in about 2% of patients in clinical trials). Gynaecomastia may occur; EFV should be permanently discontinued if it does. Patients on EFV 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.

Etravirine (ETR)

This second-generation NNRTI is only registered for use in ART-experienced patients. AfA restricts 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 always be given together with a boosted PI. Drug interactions are a bigger problem than with EFV or NVP e.g. it should not be used together with atazanavir or rifampicin.

Side-effects: Rash, hepatitis risk similar to EFV.

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

Rilpivirine (RPV)

This second-generation NNRTI can be used in first-line regimens, provided the baseline VL is <100 000 (a clinical trial of RPV versus EFV showed similar virologic suppression rates, but higher failure with RPV in participants with high VLs). It is better tolerated than EFV.

Not to be used with rifampicin or proton-pump inhibitors. Antacids or H_2 receptor antagonists should be administered 12 hours before or 4 hours after administration of RPV.

Side-effects: Rash, hepatitis risk lower than EFV.

Dose: 25 mg daily with food.

Protease Inhibitors (PIs)

All PIs 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. Some of the older PIs were associated with a risk of diabetes, but these are no longer recommended. PIs that are currently used are not associated with an increased risk of diabetes.

Diarrhoea, nausea and vomiting are common side-effects of all PIs. PI-induced diarrhoea may be successfully treated with loperamide/psyllium husk/calcium carbonate 900–1200 mg daily.

All PIs may rarely cause clinical hepatitis.

Lopinavir/ritonavir (LPV/r)

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

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

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

If used with rifampicin, the dose should be doubled (i.e. 4 tablets bd), but it is important to monitor ALT at baseline, 2 weeks, 4 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, but may be cosmetically unacceptable to patients. There is a low potential for dyslipidaemia with boosted ATV. GIT side-effects are uncommon. Nephrolithiasis (crystals of ATV may form in the urine) may occur uncommonly.

Dose: 300 mg plus ritonavir 100 mg daily (fixed-dose combination available). ATV should not be used with rifampicin and proton pump inhibitors.

Darunavir (DRV)

DRV has the highest barrier to resistance of all the PIs.

Side-effects: DRV is well tolerated at the once-daily dose, but GIT toxicity is common at the twice-daily dose used in salvage therapy. A skin rash may occur. There is moderate potential for dyslipidaemia.

Dose: In salvage therapy 600 mg bd plus ritonavir 100 mg bd with food. In PI-naïve patients or those without significant darunavir resistance mutations, a daily dose of 800 mg (plus 100 mg ritonavir) is preferred as it is better tolerated and equally effective. A daily dose of 400 mg (plus 100 mg ritonavir) has been shown to be effective when switching patients who are suppressed on another PI. Not to be used with rifampicin. There is a fixed-dose combination available with DRV 400 mg plus ritonavir 50 mg.

Integrase Inhibitors (InSTIs)

ART regimens including integrase inhibitors lower the VL faster than any other regimens, but the CD4 and long-term virologic responses are similar. Use of the first-generation integrase inhibitor raltegravir is strongly discouraged, as it has a low genetic barrier to resistance; if this develops, the second-generation integrase inhibitor dolutegravir (which has a high genetic barrier to resistance) is compromised.

Dolutegravir (DTG)

DTG is the preferred integrase inhibitor as it has a much higher genetic barrier to resistance than raltegravir (RAL), it is available as part of a fixed-drug combination tablet and can be taken once daily. DTG is now recommended as the preferred drug in first-line ART (replacing EFV) and also in second-line (replacing PIs) treatment.

Side-effects: Increases serum creatinine by 10-15 µmol/L due to inhibition of secretion, not nephrotoxicity. Headache, insomnia, nausea and diarrhoea. Hepatitis. Systemic hypersensitivity (rare). Initial reports of an increased risk of neural tube defects in women conceiving on DTG have not been confirmed in larger studies; national and WHO guidelines recommend the use of DTG in women of childbearing potential. More weight gain has been associated with DTG in randomised trials compared with first-generation integrase inhibitors, PIs or EFV; however, emerging evidence suggests that this is likely due to the other drugs impairing weight gain rather than DTG causing weight gain – this is an active area of research.

Dose: 50 mg daily. Rifampicin reduces the plasma concentrations of DTG, 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. Maraviroc is used very occasionally in salvage therapy.

Fixed-dose Combination (FDC) Products

TDF + FTC
TDF + 3TC
TAF + FTC
ABC + 3TC
AZT + 3TC
TDF + 3TC + DTG
TAF + 3TC + DTG
ABC + 3TC + DTG
TAF + FTC + DTG
TDF + FTC + EFV
TDF + 3TC + EFV
TDF + FTC + RPV
TAF + FTC + RPV
DTG + 3TC
DTG + RPV
ATV + RTV
LPV + RTV
DRV + RTV

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 products)	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
Rilpivirine (RPV)	25 mg daily	Rash, hepatitis (lower than efavirenz)
Protease inhibitors (PIs)		
Atazanavir (ATV)	300 mg + ritonavir 100 mg daily	Unconjugated hyperbilirubinaemia, dyslipidaemia (low potential)
Darunavir (DRV)	800 mg daily + ritonavir 100 mg daily or (if there is some DRV resistance) 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)

Chemical name	Dose	Common side-effects
Integrase inhibitors (InSTIs)		
Dolutegravir (DTG)	50 mg daily	Headache, GI side-effects, weight gain

Principles of Antiretroviral Therapy (ART)

Getting Started

The HIV-positive person's willingness to accept and adhere to ART is essential before embarking on therapy. Without this commitment, there is little chance of success. Including a patient-nominated "treatment buddy" in the counselling sessions is extremely helpful and has been shown to improve adherence.

All patients who are diagnosed with HIV infection should be advised that ART is indicated to treat their HIV infection, regardless of CD4 count or clinical stage. Patients should be adequately prepared for starting lifelong therapy with good adherence, and this may take a few counselling sessions. In those patients with a CD4 <200 or who are pregnant ART should be started as soon as possible.

Guidelines for starting ART:

ALL patients who are HIV-positive qualify to start ART

Adherence

Selection for resistant HIV mutants is likely to occur if adherence is poor, especially if not all of the drugs in a combination regimen are taken; for this reason fixed-dose combination formulations are preferred. Therefore, it is crucial that time is spent on carefully explaining the need to take the drugs correctly and to effectively manage adverse effects. Measuring adherence is difficult in clinical practice. Patients generally over-report adherence. A useful objective adherence 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. Healthcare professionals have been shown to have a poor ability to predict adherence. The factors listed below have been shown to increase the risk of poor adherence.

Factors which are associated with poor adherence:

- Untreated depression
- Active substance abuse
- Lack of insight
- Failure to disclose HIV status (a treatment supporter should be encouraged)
- Adolescents and young adults
- Central nervous system pathology (e.g. HIV dementia)

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

Methods to assist with maintaining adherence:

- Negotiate a plan with the patient to ensure commitment to a regimen
- Provide information to assist the patient in fully understanding their drug regimen, and in taking their medications adequately
- Depression is common in HIV/AIDS – assess and treat this if necessary
- Recruit patient-nominated ”treatment buddies” to support the patient
- Pay attention to “minor” side-effects, especially nausea, diarrhoea, and neuropsychiatric side effects, and consider treating them or switching the culprit drug where possible
- Memory aids such as diaries, pill-boxes and cellphone alarms, are useful for some patients
- Plan ahead for medication refills, financial assistance, etc.
- Assess and manage substance abuse
- Regularly monitor ART adherence at each clinical visit (the most pragmatic objective measure of adherence is whether patients have collected their medication on time)
- Plan regimens to avoid food restrictions where possible
- Avoid regimens with large pill burdens

Selecting Drug Combinations

Antiretroviral drugs must always be combined in order to delay or prevent the emergence of HIV resistance. Typical ART regimens consist of "triple therapy" with two NRTIs together with an InSTI, NNRTI or a boosted PI. AfA recommends first-line treatment with 2 NRTIs and DTG, because DTG has a much higher genetic barrier to resistance than EFV and is also better tolerated. This recommendation is in keeping with WHO and national public sector guidelines.

Recommended First-Line Combinations

Preferred regimen:	
TDF + 3TC+ DTG (TLD)	In patients on rifampicin the DTG dose needs to be increased to 50 mg bd until 2 weeks after stopping rifampicin
Alternate regimens:	
TDF + 3TC (or FTC) + EFV	Can be used if patient is on TB treatment
TDF + 3TC (or FTC) + RPV	RPV can be used provided the baseline VL is <100 000 or if DTG is not tolerated
TAF + 3TC (or FTC) + DTG or NNRTI	Renal impairment at baseline (eGFR 30 - 60 ml/min) or renal impairment develops on TDF
ABC + 3TC + DTG or NNRTI	Renal impairment at baseline (eGFR <50 ml/min) or renal impairment develops on TDF
AZT+ 3TC + DTG or NNRTI	Where both TDF and ABC are contraindicated and Hb > 8 g/dL

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

Dual NRTI Backbone Combinations

Recommended combinations:

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

We recommend tenofovir plus lamivudine or emtricitabine in first-line ART. Abacavir should be used when tenofovir is contraindicated (eGFR <50 ml/min) or not tolerated. Zidovudine is only recommended when both tenofovir and abacavir are contraindicated.

Patients with anaemia or neutropaenia should avoid zidovudine.

Monitoring Therapy

CD4 and VL Monitoring

Regular monitoring of the VL is important to identify treatment failure. The VL should be checked at 3 months then every 6 months. Vaccination and intercurrent infections can transiently increase the VL. VL tests should be deferred for a few weeks in these settings.

On ART the VL should be suppressed (defined as below the limit of quantification) on the VL assay i.e. undetectable after 24 weeks of therapy. The VL is the most important test for monitoring response to therapy. Virological failure is defined as a confirmed increase to >1000 (on two tests done 6–12 weeks apart) despite good adherence. This criterion should be used when deciding to change regimens – it is especially important not to delay switching the first-line regimen in patients on an NNRTI once failure has developed, as high-level resistance to NNRTIs develops rapidly and continuing a failing regimen results in the serial accumulation of resistant mutations to NRTIs.

CD4 counts should be assessed together with VLs, but once the CD4 count is confirmed to be >200 routine monitoring is not recommended, as it does not influence therapy and patients often become concerned due to irrelevant fluctuations in CD4 counts. CD4 counts should be repeated if virologic failure has occurred, to assess the need for co-trimoxazole prophylaxis. The CD4 count increases rapidly in the first month of ART (average rise of 75 cells/μL), followed by a more gradual rise thereafter (average rise of 80 cells/μL per year). However, CD4 responses are highly variable. Amongst patients who achieve and sustain virological suppression, a minority (10–20%) will experience no rise in CD4 or a very delayed or a suboptimal rise in CD4 count. There is no evidence that these patients benefit from switching or intensifying ART. Therefore, the same regimen should be continued with co-trimoxazole prophylaxis if the CD4 count remains <200 cells/μL.

It is important to note that an intercurrent clinical event is not an indication for changing therapy if the VL is suppressed. Furthermore, clinical deterioration and CD4 decline both occur after many months or even years of virological failure as defined above. Thus, clinical or immunological failure should not be used as a criterion for changing ART regimens.

Most patients failing their first boosted PI or DTG regimen have no major PI- or DTG-resistant mutations on resistance testing – they are failing due to poor adherence and need improved adherence rather than a change in regimen. Resistance to PIs or DTG occurs very slowly – with PIs at least two years of exposure with documented virologic failure is needed before resistance develops, and it is likely that a similar duration of exposure is required to develop resistance to DTG.

Viral Resistance and Changing Therapy

Resistance should be suspected if the VL starts increasing in a patient who is adhering to first-line ART. Ensure that the VL was not tested after vaccination or an acute infection. Minor transient increases in VL (less than 1000) – "viral blips" – are not indications to change therapy. A high VL should be confirmed with a second reading within three months.

Failure of therapy is defined as a sustained increase in VL >1000. Therapy should be switched for virological failure if two VLs are >1000, with the second being measured after an intervention to improve adherence, and where feasible a resistance test that demonstrates resistance to the current regimen. In patients who have been on a DTG first-line regimen for 2 years, we strongly advise a resistance test before switching to second-line treatment, because resistance to DTG when used in a first-line regimen is very uncommon and cannot be assumed based on two high VL readings. The reason is usually related to adherence problems.

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 increases susceptibility of the virus to TDF and AZT).

Recommended Second-line Combinations

AfA now recommends a second-line regimen of two NRTIs and DTG. DTG can be used with recycled TDF plus 3TC or FTC as trials have shown that outcomes are better than switching to AZT. The alternative is two NRTIs plus a ritonavir-boosted PI. AfA recommends darunavir/ritonavir or atazanavir/ritonavir as the PI in second-line treatment. Boosted darunavir and atazanavir are preferred to lopinavir as they have a lower potential for dyslipidaemia and gastrointestinal side-effects and are taken once daily.

The following second-line regimens are recommended

First-line regimen failing	Second-line regimen advised
2NRTIs + NNRTI	TDF + 3TC + DTG (preferred) 2 NRTIs + a boosted PI
2NRTIs + DTG	Only switch to second line if resistance test shows DTG resistance; second line should be two NRTIs (selected based on resistance test) + a boosted PI

Boosted PI = atazanavir with ritonavir or darunavir with ritonavir or lopinavir with ritonavir

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

Switching Patients from a Boosted PI to DTG in Second-Line when VL is <1000 or on regimen for <2 years

First-line regimen	Current second-line regimen	Alternate second-line regimen option
2 NRTIs + NNRTI	AZT + 3TC + boosted PI	TDF + 3TC + DTG (preferred) AZT + 3TC + DTG
	TDF + FTC + boosted PI	TDF + 3TC + DTG
	ABC + 3TC + boosted PI	TDF + 3TC + DTG (preferred unless TDF is contraindicated) TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG AZT + 3TC + DTG

Dual Therapy

Several dual therapy ART regimens are available as alternatives, primarily to avoid tenofovir-associated toxicity. Switching to DTG plus 3TC can be done in people who are virologically suppressed on a first-line ART regimen. DTG plus 3TC can be initiated in ART-naïve people if the VL is below 500 000. Two NRTI sparing regimens (DTG plus RPV or DTG plus a ritonavir-boosted PI) are also effective. AfA need to be contacted for approval of any of these dual therapy regimens.

NRTI-sparing Combinations

Patients who are unable to tolerate NRTIs can use a combination of DTG with the NNRTI rilpivirine (other NNRTIs reduce the concentrations of DTG) or a boosted PI. Most NNRTIs can be combined with a boosted PI; however, there are drug interactions that may require alterations of the PI dose (see table below):

PI	Efavirenz	Etravirine	Rilpivirine
Atazanavir/r	400 mg/100 mg daily	Not recommended	Standard dose
Darunavir/r	600 mg/100 mg twice daily*	Standard dose	Standard dose
Lopinavir/r	Standard dose	Standard dose	Standard dose

** The 800 mg/100 mg daily dose must not be used when DRV/r is coadministered with EFV.*

Third-line Combinations

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

ART Resistance, Genotype Resistance Testing and Archiving of Resistant Mutations

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

Other drugs have a high barrier to resistance (e.g. dolutegravir and boosted PIs), meaning either that it is difficult for the virus to develop resistance mutations to the drug or 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 VL at 3 months on ART then 6-monthly. If the VL is suppressed (lower than detectable limits or <50) it suggests good adherence and no resistance to that regimen. If the VL does not suppress then efforts should be made to improve adherence by counselling and support (e.g. treatment buddy in household). In any patient with a VL that is not less than 50 after 6 months on ART, a repeat measurement should be taken in 2 to 3 months' time after such an adherence intervention.

If the VL remains above 1000 on two or more occasions (preferably 2–3 months apart) despite improved adherence, this suggests viral resistance may have developed and the regimen may need to be changed. In the case of a DTG-containing first-line regimen, patients must have a resistance test that demonstrates resistance to DTG before a switch to second-line treatment. With an NNRTI first-line regimen, a switch to second-line is important after two VLs >1000 and a resistance test may help inform the choice of second-line regimen. As stated above, in patients failing second-line treatment it is essential to do a resistance test before switching to a third-line regimen. There are two reasons for this. First, many patients failing second line do not have significant resistance, and in such patients there is a need to improve adherence to the second-line regimen rather than switching to third-line. Second, if patients do have significant second-line resistance the genotype is important in guiding the choice of drugs in the third-line regimen.

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

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

1) In children <2 years who have been HIV infected despite their mother receiving PMTCT.
2) In adult patients where there is a strong suspicion that the patient has been infected with a resistant virus (e.g. sexual partner failing ART).
3) Patients who seroconvert while taking TDF/FTC for PrEP.

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
- The test can only be performed in commercial laboratories if the VL is >500–1000
- If the resistance mutation is present, but in fewer than 20% of viruses in the viral population, it will not be detected. This is termed "archiving". This typically occurs when a patient has developed drug-resistant mutations, but then stops ART. What happens over the next few weeks for most mutations is that the wild type virus (without the mutation) replicates faster than the resistant mutant (because most resistant mutants have a fitness cost to the virus), and thus the wild type comes to dominate the viral population in the absence of ART and the resistant mutant becomes archived. It is thus essential that the genotype resistance test is performed while the patient is taking the failing regimen, in order that the result detects all the mutations to that regimen that have been selected
- The genotype resistance test may not detect mutations that developed during the failure of a previous regimen because they are now archived. This may be the case when a patient fails an NNRTI-containing first line and then has a genotype resistance test performed after second-line failure a few years later. The NNRTI-resistance mutations may be archived, but we assume that they are present based on the treatment history. Thus in deciding about the next ART regimen the genotype resistance test should always be interpreted together with a full treatment history
- All genotype resistance test results should be referred to AfA for advice regarding the best subsequent regimen

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

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

Less than one year: In the first year of ART we advise that adherence support be enhanced and that patients are not switched to second-line treatment. Studies have shown that about 70% of patients who have a detectable VL 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 pill boxes. Psychological and substance abuse issues contributing to poor adherence should be addressed (e.g. 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 VL, 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 VL even if adherence was improved to 100%. In this situation we thus advise switching to second-line ART. The benefit of a second-line

regimen containing DTG or a boosted PI in these patients is that this regimen has a 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 or DTG second-line regimen if they do not suppress after 1 year, is likely to ensure that they gain at least partial clinical benefit from ART.

Management of Detectable HIV VLs in a Patient who has been Receiving Dolutegravir for >6 Months

Dolutegravir is a very robust drug in InSTI-naïve patients when paired with 2 NRTIs i.e. TDF + 3TC/FTC or AZT + 3TC – resistance has very rarely been reported in this situation. Therefore, although a VL >1000 on two occasions after 6 months on therapy has traditionally been a marker of possible resistance, this paradigm no longer applies in patients on DTG unless:

1. The patient has had previous exposure to raltegravir as part of a failing regimen.
2. The patient was exposed to a scenario where a drug–drug interaction could have decreased DTG concentrations.

Provided that none of the above conditions are met, a detectable VL or repeated detectable VLs should not be assumed to reflect possible resistance. Rather, it can be assumed that the detectable VLs represent poor adherence, and efforts to address this should be instituted. We do not recommend performing resistance testing for patients on a DTG-based regimen within 2 years of commencing the drug, provided none of the above points apply. If a patient has a VL >1000 on more than one occasion after 2 years on a DTG-regimen, despite adherence interventions having been implemented, then please discuss with AfA regarding a request for a resistance test.

Practical Tips for Interpreting Genotype Resistance Testing

General points

- Patient must be on a failing ART regimen when a 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 >500–1000 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 select for K65R, which compromises TDF and ABC 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, but increases susceptibility to AZT and TDF. For this reason, and because M184V reduced viral fitness, 3TC or FTC are often used even if M184V is present
- Abacavir selects for L74V, which compromises ABC
- Abacavir also selects for Y115F, which decreases its susceptibility
- AZT selects for thymidine analogue mutations (TAMs), which may compromise all NRTIs. There are six TAMs: M41L, D67N, K70R, L210W, T215Y/F, and 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. Rilpivirine can be compromised by certain mutations selected by EFV or NVP
- Etravirine often remains active when there is efavirenz and nevirapine resistance, but etravirine resistance may result from certain mutations selected by nevirapine and efavirenz. It is unpredictable whether efavirenz or nevirapine exposure will result in etravirine resistance in an individual patient: it depends which mutations are present and how many. For example, K103N does not cause etravirine resistance, whereas the mutations L100I, K101P and Y181C/I/V are the main mutations that reduce etravirine susceptibility, particularly in combination. A weighted scoring system is used for determining etravirine susceptibility based on which NNRTI mutations are present

PI-resistance mutations

- Most PIs require multiple PI-resistance mutations before there is high-level resistance. PI-resistance patterns are complex, and interpreting the genotype usually requires an algorithm such as the Stanford Database
- The most important (or “major”) PI mutations occur at positions 30, 32, 46, 47, 48, 50, 54, 76, 82, 84, 88 and 90 in the protease gene
- A single mutation (I50L) can compromise atazanavir, but this mutation tends not to occur with ritonavir-boosted atazanavir
- Darunavir and tipranavir have the highest genetic barrier to resistance (i.e. they tend to remain active even when other PIs are compromised)
- Response to darunavir regimens is dependent on the 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 three 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 and N155H
- Dolutegravir may be compromised by mutations that accumulate in patients failing raltegravir (e.g. Q148H). When dolutegravir is used as the first integrase inhibitor it appears to have a very high barrier to resistance, with no dolutegravir resistance reported

to date when it has been used in first-line ART clinical trials and a few cases reported in clinical practice

- Dolutegravir may select for resistance when it is the first integrase inhibitor used (e.g. R263K and G118R), although this is uncommon
- When a resistance test is requested in South Africa currently the integrase gene is not routinely sequenced, but this can be specifically requested in patients failing an integrase inhibitor

Managing Drug Toxicity

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

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) it may be necessary to stop all antiretrovirals. In patients with severe NNRTI-related toxicity an integrase inhibitor or PI should be substituted.

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

Haematological Toxicity

Patients on zidovudine or co-trimoxazole may experience abnormalities in their FBC. 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. Significant anaemia and neutropaenia (NOT thrombocytopaenia) are commonly seen with zidovudine 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 3 months of therapy and then at 6 months, thereafter 6-monthly) is essential for all patients on zidovudine. 3TC and FTC are rare causes of red cell aplasia – parvovirus B19 infection should be excluded (positive parvovirus B19 PCR in blood).

Haematological toxicity with co-trimoxazole is more frequent with high doses used for treating OIs. 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 the dose reduced to 480 mg daily, depending on the severity of neutropaenia.

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

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

Management of drug-induced anaemia and neutropaenia

Hb <8 or neutrophils <1	Switch AZT to alternative
Neutrophils <1	Stop co-trimoxazole (discuss alternative with AfA)

Hepatotoxicity

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

It is important to distinguish drug-induced liver injury from viral hepatitis. Hepatitis A, B and C should always be checked when hepatitis occurs. Infection with hepatitis B is common in HIV-positive 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).

NNRTIs, PIs and InSTIs 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 may develop isolated unconjugated hyperbilirubinaemia resembling Gilbert's syndrome, which is not accompanied by liver injury, but the drug should be substituted if jaundice is marked or not tolerated by the patient. Atazanavir/ritonavir can also cause liver injury – in such cases transaminases will be elevated.

NVP was a frequent cause of hepatitis in the first 3 months of initiating the drug. We no longer recommend the use of NVP in ART regimens.

Many other drugs commonly used in HIV-positive 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 2 weeks
- ALT 100–200, repeat in 1 week. But if there are symptoms of hepatitis or jaundice, stop the relevant drugs, do hepatitis screen and full LFT. INR should also be checked in patients with jaundice
- ALT >200, stop relevant drugs, do hepatitis screen and full LFT. INR should also be checked 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 an efavirenz-based regimen develops hepatitis, the efavirenz should be switched to DTG, 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 (switching efavirenz to DTG) may be introduced, with monitoring of ALT.

Where canalicular 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 are fatty liver due to NRTIs and TB infiltration of liver. Fatty liver can be visualised on ultrasound or CT scan and may result in fibrosis and chronic liver disease. Drug-induced cholestasis or cholestatic hepatitis may be due to macrolides, rifampicin, co-amoxiclav or co-trimoxazole – and it takes much longer to resolve than hepatitis with elevated transaminases.

Suggested substitutions if antiretroviral drug-induced hepatitis occurs on:

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

Hepatitis in Patients on ART and TB Therapy

The priority in patients developing hepatitis on ART and TB drugs is to sort out the TB therapy first, followed by the ART. If hepatitis develops, as defined above, stop all antiretrovirals, co-trimoxazole and all potentially hepatotoxic TB drugs (isoniazid, rifampicin and pyrazinamide). Three TB drugs (e.g. linezolid 600 mg daily (avoid if Hb <10), moxifloxacin 400 mg daily or levofloxacin 1000 mg daily (unless body weight very low, then use 750 mg daily), and ethambutol 800–1200 mg daily) should be started and continued throughout rechallenge to prevent the development of resistance and provide treatment for TB. Other causes of hepatitis, especially viral hepatitis, should also be excluded. TB immune reconstitution inflammatory syndrome (TB-IRIS) with worsening granulomatous hepatitis should be considered in the differential diagnosis. TB-IRIS typically presents a few weeks after starting ART in TB patients. The GGT and alkaline phosphatase are typically elevated more than the transaminases; if there is jaundice it is mild and bilirubin is predominantly conjugated and tender hepatomegaly is usually present. However, this diagnosis can be difficult as there is no confirmatory diagnostic test. An ultrasound (to exclude extrahepatic cholestasis) should be done and a liver biopsy should be considered.

Once the ALT has settled to <100 and jaundice has resolved then rechallenge with certain TB drugs may be considered. It is important to review the diagnosis of TB before attempting rechallenge – if the diagnosis was not made on good grounds, TB therapy should be stopped and the patient carefully monitored. If the hepatitis resulted in hepatic failure (encephalopathy and 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 – consult AfA for advice.

When possible, drug rechallenge is important because outcomes on second-line TB treatment are significantly worse than with first-line drugs (6 months of rifampicin has key sterilising activity that prevents relapse). TB drug rechallenge has been found to be successful without recurrence in 60–90% of patients, and provided ALT and symptoms are frequently monitored during rechallenge, it is usually safe. Several rechallenge regimens have been suggested and many local institutions have developed their own regimens. Many South African experts do not attempt rechallenge with pyrazinamide (PZA), 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 the intensive phase. A randomised controlled trial of different rechallenge regimens was conducted in India, but only HIV-seronegative patients were studied. Three rechallenge regimens were tested (reintroducing 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)

DAYS 4-6 Add isoniazid (normal dose)

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

During rechallenge ALT should be monitored twice weekly for the first 3 weeks, then every 2 weeks for a month, then monthly until 3 months. Also monitor for hepatitis symptoms and jaundice.

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

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

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

- **Pyrazinamide not rechallenged/not tolerated:** Stop both moxifloxacin/levofloxacin and linezolid, continue isoniazid, rifampicin and ethambutol for total duration of 9 months
- **Rifampicin not tolerated:** Discuss with AfA
- **Isoniazid not tolerated**: Stop linezolid and continue levofloxacin (not moxifloxacin), rifampicin, ethambutol and pyrazinamide and treat for total duration of 6 months

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

- **Rifampicin not tolerated:** Discuss with AfA
- **Isoniazid not tolerated:** Stop linezolid and continue levofloxacin (not moxifloxacin), rifampicin and ethambutol and treat for total duration of 6 months

ART can be recommenced 2 weeks following successful rechallenge with TB therapy:

- If nevirapine was used, this should be replaced with dolutegravir 50 mg 12-hourly if on rifampicin
- If efavirenz was used, this should be replaced with dolutegravir 50 mg 12-hourly if on rifampicin
- If double-dose lopinavir/ritonavir was used, the options are to rechallenge this with slow dose escalation over 2 weeks or dolutegravir (50 mg 12-hourly if on rifampicin) could be considered depending on treatment history – discuss with AfA

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

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

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

Hyperlactataemia

NRTIs can cause mitochondrial toxicity by inhibiting the human mitochondrial DNA gamma polymerase enzyme. One manifestation of mitochondrial toxicity is hyperlactataemia. Symptomatic hyperlactataemia has become very uncommon since the NRTIs stavudine and didanosine are no longer used.

The risk of hyperlactataemia with different NRTIs is:

zidovudine > lamivudine = abacavir = tenofovir = emtricitabine

The most severe manifestation is overt lactic acidosis, which is life-threatening. There is no need to monitor lactate levels in asymptomatic patients as this does not predict the development of symptomatic hyperlactataemia. Symptomatic hyperlactataemia typically occurs after patients have been on ART for at least 6 months. Early recognition of symptomatic hyperlactataemia is important.

Signs and symptoms of hyperlactataemia are non-specific:

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

Other causes of lactic acidosis should be considered (e.g. severe sepsis). Lactate elevation in NRTI-induced hyperlactataemia persists for weeks, while with other causes it resolves rapidly when the underlying condition is treated. NRTIs should be permanently discontinued if symptomatic hyperlactataemia occurs (see NRTI-sparing ART regimens table).

Dyslipidaemia and Lipid Lowering Drugs

PIs 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. Efavirenz can cause elevated total cholesterol and mild hypertriglyceridaemia. Dolutegravir does not significantly affect lipids.

Fasting lipids (total cholesterol and triglycerides) should be done at baseline in all patients starting PIs. This should be repeated in 3 months. Lifestyle modification should be advised for all elevations (stop smoking, lose weight if relevant, increase aerobic exercise, reduce cholesterol and saturated fat intake). Boosted atazanavir is associated with a lower risk of dyslipidaemia and patients should be switched to this PI if possible. Darunavir/r has a more favourable lipid profile than lopinavir/r. Marked elevation of triglycerides (>11 mmol/L) can cause pancreatitis and should urgently be treated with fibrates and switching the PI.

Elevated cholesterol levels should be treated with statins according to the calculated risk as in HIV-uninfected patients, based on Framingham risk score. The recently published REPRIEVE

study showed that statins reduce the risk of major vascular events in people with HIV ≥40 years of age who do not qualify for statins on the Framingham score – this is the first evidence-based intervention showing that the increased risk of vascular events in HIV, which is independent of other risk factors, can be reduced.

Fibrates are not associated with drug interactions. There are marked drug interactions between the PIs and 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 was 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 PIs, but prospective trials have shown that rates of fat accumulation are similar with the use of NNRTIs or PIs. Furthermore, a longitudinal study in the USA showed that visceral and trunk fat increased at similar rates in patients on ART and HIV-negative controls from the general population. Randomised controlled trials have shown that antiretroviral drug substitutions of PIs 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 three of the following five traits:

- Waist circumference >102 cm in men and >88 cm in women
- Triglycerides ≥1.7 mmol/L
- HDL cholesterol <1 mmol/L in men and <1.3 mmol/L 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.

Managing Weight Gain Associated with Dolutegravir

Dolutegravir and other integrase strand transfer inhibitors have been associated with more weight gain in people living with HIV (PLHIV) starting antiretroviral therapy than other classes of ART. Weight gain is more marked among women.

Recent evidence has shown that the greater weight gain with dolutegravir compared with efavirenz is due to efavirenz impairing weight gain in patients who are slow metabolisers of this drug due to polymorphisms in the main metabolising enzyme of efavirenz, the cytochrome P450 enzyme CYP2B6, which is common in South Africa. Patients on efavirenz with wild type CYP2B6 gained the same amount of weight as those on dolutegravir. CYP2B6 slow

metabolisers have high concentrations of efavirenz, which could impair weight gain either through metabolic effects (mitochondrial toxicity and impaired adipocyte differentiation) or through neuropsychiatric effects impairing appetite.

Antiretroviral drugs that have more metabolic toxicity are associated with less weight gain in randomised controlled trials, suggesting that, like efavirenz, they impair weight gain. One example is the NRTIs: weight gain is progressively higher with zidovudine, tenofovir disoproxil, abacavir, and tenofovir alafenamide; a ranking of NRTIs with most to least metabolic toxicity would follow the same order. Newer, safer antiretroviral drugs are associated with more weight gain because they allow a better return to health, which could include excessive weight gain for PLHIV with unhealthy lifestyles.

PLHIV who experience marked weight gain on dolutegravir-based ART should be screened for other features of the metabolic syndrome and treated accordingly. The weight gain should be addressed by appropriate lifestyle interventions. Switching to more toxic antiretrovirals like efavirenz is not evidence-based and could cause harm.

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 efavirenz, so patients should be switched to an alternative if this 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 OIs have been associated with pancreatitis (e.g. MAC, CMV, TB). Pancreatitis may occur in patients with severe symptomatic hyperlactataemia. Severe hypertriglyceridaemia >10 mmol/l (which may be caused by PIs) can cause pancreatitis. Other drugs used in HIV can rarely cause pancreatitis (e.g. co-trimoxazole).

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

PI-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 or boosted darunavir) 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 ART

Therapy with antiretroviral drugs should not be completely interrupted except in exceptional circumstances (e.g. life-threatening toxicity). Interruptions of long-term therapy have been shown to increase the risk of resistance and even death (in trials of repeated structured treatment interruptions).

HIV and the Elderly

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

The prevalence of HIV in older people will thus continue to increase over time, and it has been estimated that around 50% of PLHIV in high-income countries are older than 50.

In a 2022 national HIV survey in South Africa, HIV prevalence was above 20% among people aged 50–54 years, and 16.1% among women and 15.1% among men aged 55–59 years (compared to 17.0% among men and women aged 15–49 years). HIV infection is not uncommon in even older individuals; there are over 5000 people over the age of 60 currently registered on AfA (including nonagenarians).

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

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

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

When ART is started 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 South African study 30% of people aged 50 years and over had two or more chronic conditions. It is also possible that HIV infection itself increases the risk of developing some of the degenerative diseases associated with ageing, including dementia due to vascular events.

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

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

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

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

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

Once-a-day dosing with fixed-dose combinations (e.g. TDF/3TC/DTG), where this is possible, is an attractive option to simplify therapy and improve treatment adherence.

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

Drug Dosages in Renal Insufficiency

Most NRTIs require dose reductions in patients with renal insufficiency, but NNRTIs, PIs and InSTIs do not need dose adjustments.

The extent of renal insufficiency can be assessed either by the estimated glomerular filtration rate (eGFR), which most laboratories calculate routinely, or by the creatinine clearance using the formula below:

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

Good estimate for men, for women multiply total by 0.85

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

Drug	Creatinine clearance/ eGFR 10–50	Creatinine clearance/ eGFR <10
Zidovudine	Unchanged	300 mg daily
Emtricitabine[#]	Unchanged if >30	AVOID
Abacavir	Unchanged	Unchanged
Lamivudine	150 mg daily	50 mg daily (150 mg daily is preferred by some experts as this allows tablets rather than syrup to be used – this dose appears to be well tolerated)
Tenofovir (TDF)	AVOID	AVOID*
Tenofovir (TAF)	Unchanged if >30	AVOID
Atazanavir	Unchanged	Unchanged
Darunavir	Unchanged	Unchanged
Lopinavir	Unchanged	Unchanged

Drug	Creatinine clearance/ eGFR 10–50	Creatinine clearance/eGFR <10
Nevirapine	Unchanged	Unchanged
Efavirenz	Unchanged	Unchanged
Etravirine	Unchanged	Unchanged
Rilpivirine	Unchanged	Unchanged
Dolutegravir	Unchanged	Unchanged
Maraviroc	Should be used with caution in patients with renal impairment who are taking potent CYP3A4 inhibitors – see package insert for details	
Co-trimoxazole	480 mg daily	480 mg three times a week
Fluconazole	Half dose	Quarter dose
Dapsone	Unchanged	Unchanged

Only available in fixed-dose combination formulations with tenofovir – dose adjustments do exist, but are different from tenofovir

* *In patients on dialysis 300 mg once a week may be considered e.g. if they have hepatitis B*

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. The 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
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*
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
Rilpivirine	No dose adjustment is required in patients with mild or moderate hepatic impairment Rilpivirine has not been studied in patients with severe hepatic impairment
PIs	
All	Use with caution
InSTIs	
Dolutegravir	Can use standard doses with moderate liver impairment. No dosage recommendations available for severe liver impairment

Drug	Prescribing with liver impairment
CCR5 antagonist	
Maraviroc	Use with caution – see package insert for details

* *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 and DTG.*

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.

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

ART in the Patient with TB

- Many ARTs cannot be taken with rifampicin; some ARTs can be used with dose increases – see table
- If the patient is already on ART, the regimen should be changed to be compatible with rifampicin if possible
- EFV-based ART is preferred as there is no significant interaction with rifampicin, but this option should only be used in ART-naïve patients or those with virologic suppression on EFV-based ART
- When ART is commenced in a patient on TB therapy, the patient's symptoms may temporarily worsen as part of immune reconstitution – they should be specifically warned about this
- For those 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 at around 8 weeks

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

ART Interactions with Rifampicin

NRTIs	No significant interactions
Efavirenz	Minimal reduction in efavirenz levels, no dose adjustment necessary. Preferred regimen is EFV plus two NRTIs
Etravirine	Avoid
Rilpivirine	Avoid
Lopinavir/ritonavir	Double the dose of lopinavir/ritonavir (increase the dose gradually – 3 tablets twice daily for 5 days, then 4 tablets twice daily) needs to be given to counteract the enzyme-inducing effect of rifampicin. Close monitoring of liver function is essential (at weeks 2 and 4, then monthly until TB treatment is completed)
All other ritonavir- boosted PIs	Marked reduction in PI levels – avoid. Rifabutin 150 mg daily can be used as an alternative to rifampicin. Monitor for neutropaenia, uveitis and hepatitis
Dolutegravir	Increase the dose of dolutegravir to 50 mg twice daily
Maraviroc	Complex. See package insert for details

The paradoxical TB-associated TB-immune reconstitution inflammatory syndrome (IRIS) following commencement of ART may cause a flare-up of TB. TB-IRIS commonly occurs when ART is commenced within the first 2 months of anti-TB 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 KS. Steroids (prednisone 40 mg daily for 2 weeks, then 20 mg daily for 2 weeks) have also been shown to safely reduce the risk of TB-IRIS in patients starting ART while still on TB therapy with CD4 counts <100.

Rifampicin has significant drug interactions with DTG, the PIs and NNRTIs. When ART is indicated it is preferable to use a regimen which does not interact significantly with rifampicin (see table). 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 (2 tablets twice a day for 5 days, then 3 tablets twice a day for 5 days, then 4 tablets twice a day until 2 weeks after completing TB medication). If the dolutegravir dose is increased to 50 mg twice daily the dose can be reduced to 50 mg daily 2 weeks after completing TB medication.

Antiretroviral Drug-Drug Interactions

Patients receiving ART frequently take other medication, including over-the-counter drugs. There are numerous potential drug interactions with ART. Interactions can be pharmacokinetic (affecting absorption, distribution, metabolism or elimination) or pharmacodynamic (e.g. additive toxicity).

Antiretroviral drugs can be the victims and/or perpetrators of pharmacokinetic interactions. Antiretroviral drugs that are perpetrators of pharmacokinetic interactions are either inducers (e.g. efavirenz) or inhibitors (e.g. ritonavir, which also has some inducing activity) of drug-metabolising enzymes. Efflux pump inducers can result in sub-therapeutic concentrations of victim drugs, while inhibitors can cause toxic concentrations of victim drugs.

Summary of clinically important pharmacokinetic interactions with ART (an overview)

Antiretroviral drug	Perpetrator of PK interactions	Victim of PK interactions
NRTIs	No	No
NNRTIs		
Efavirenz	Strong inducer	No
Rilpivirine	No	Avoid with strong inducers*
Etravirine	Mixed inducer and inhibitor	Avoid with strong inducers*
INSTIs		
Dolutegravir	Inhibits transport of metformin	Increase dose to 50 mg 12-hourly with strong inducers* Di-/trivalent cations impair absorption
PIs	Strong inhibitor Inducer	Avoid with strong inducers*

* *Strong inducers include rifampicin, carbamazepine, phenobarbitone and phenytoin*

When the drug-drug interaction leads to marked alteration of levels of the victim drug, coadministration should be avoided. In some instances a dose adjustment of the victim drug MAY 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/checker**.

Guidelines on Artificial Ventilation, ICU Care and Withdrawal of Therapy

- Criteria for withholding or discontinuing ventilation in HIV-positive individuals should be the same as 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 as in 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 ICU 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-positive patient on a ventilator is unlikely to affect their outcome. It may in fact worsen outcome, due to the early paradoxical deterioration of OIs (IRIS) seen in the first few weeks of starting ART in patients with advanced HIV. In HIV-positive 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 VL) 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 VLs are dramatically altered in critical illness.

Infection Prevention and Control (IPC)

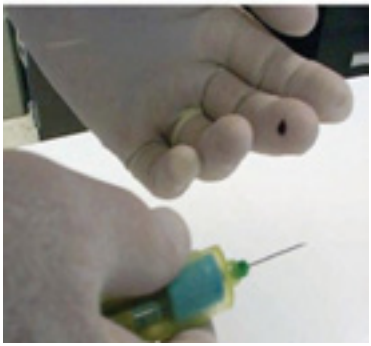
Preventing Exposure to Pathogens

Hospital-acquired infections, also termed 'nosocomial' infections, are transmitted from person to person via the airborne route (either on small droplets such as for *M. tuberculosis* and measles, or large droplets for influenza, SARS-CoV-2 or *Neisseria meningitidis*) or through skin contact. Signs should be available that indicate the type of precaution(s) that must be taken for a particular mode of transmission, and should be clearly visible to all staff and visitors, ideally on the door of the patient's isolation room.

IPC Warning Signs

Mode of transmission	Signage	Pathogens/PPE
Airborne Small droplet nuclei		TB Measles Chickenpox (pneumonitis) SARS-CoV-2 (for aerosol generating procedures) **N95 mask**
Droplet Large droplets from upper respiratory tract		Meningococcal infections Influenza SARS-CoV-2 **Surgical mask**
Contact		Drug-resistant pathogens on skin, wounds, GIT *Clostridioides difficile*-associated diarrhoea **Apron and gloves**

Prevention of Sharps Injuries



More 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 re-sheath needles, as this increases risk.

Only in extreme circumstances should you consider re-sheathing a sharp, using a 'safe' technique where you do not hold the sheath in your hand while re-sheathing.

Prevention of *M. tuberculosis* Transmission

M. tuberculosis is transmitted by small aerosol nuclei generated by coughing. Due to the 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 TB, without pulmonary involvement.
2. Proven drug-sensitive pulmonary TB when the patient has completed >2 weeks of uninterrupted intensive-phase treatment.

3. Any PTB suspect (on 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 of intensive-phase therapy and has had two negative sputum cultures 1 month apart (culture conversion).

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

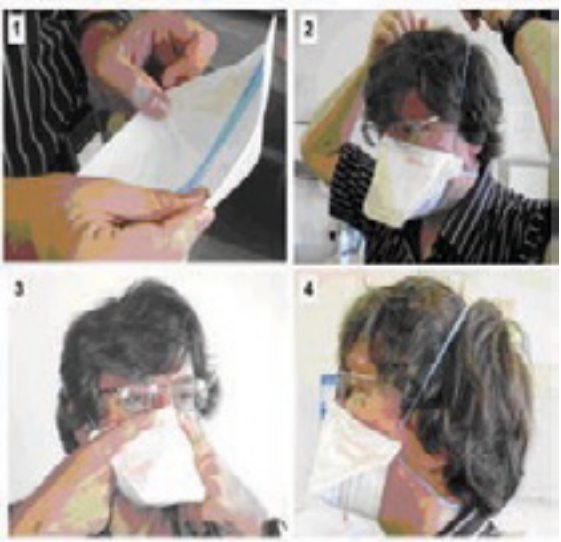
An airborne precautions sign must be fixed to the door of each isolation cubicle.

When entering the room of a patient with proven or suspected TB, 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-positive 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 need 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. The table shows the current restrictions imposed by a number of countries that prohibit or restrict travel of HIV-positive people. Up-to-date information can be obtained from The Global Database on HIV-specific travel and residence restrictions (**http://www.hivtravel.org**).

Travel restrictions imposed on HIV-positive travellers

Countries, territories and areas that require HIV testing or disclosure for certain types of entry, study, work, and/or residence permits	**Countries, territories and areas that prohibit short and/or long stays on the basis of HIV status AND require HIV testing or disclosure for certain types of entry, study, work and/or residence permits**	**Countries that deport non-nationals on the basis of HIV status AND prohibit short- and/or long-term stays on the basis of HIV status AND require HIV testing or disclosure**
Angola	Aruba	Bahrain
Australia	Bosnia and Herzegovina	Brunei Darussalam
Azerbaijan	Dominican Republic	Cook Islands
Belize	Indonesia	Egypt
Cayman Islands	Kyrgyzstan	Iraq
Cuba	Maldives	Jordan
Israel	Marshall Islands	Kuwait
Kazakhstan	Mauritius	Malaysia
Lebanon	Saint Vincent & the Grenadines	Oman
New Zealand	Tunisia	Qatar
Palau	Ukraine	Russian Federation
Papua New Guinea		Saudi Arabia
Paraguay		Singapore
Samoa		Solomon Islands
Saint Kitts and Nevis		Sudan
Tonga		Syrian Arab Republic
Turks and Caicos		Turkmenistan
Tuvalu		United Arab Emirates
		Yemen

Immunisation for HIV-positive Travellers

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

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

Immunisations for HIV-positive adults

Vaccine	Indication	Notes
Live vaccines/toxoids		
Cholera (CVD103-HgR)	Contraindicated	Use inactivated oral vaccine
Influenza (intranasal)	Contraindicated	Use inactivated parenteral vaccine Avoid vaccination in household contacts
Measles, mumps, rubella (MMR)	Indicated for measles IgG-seronegative persons with CD4 count >200 Contraindicated if CD4 ≤200	Avoid pregnancy for 1 month after vaccination Breastfeeding not contraindicated Administer two 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
TB (BCG)	Contraindicated	
Typhoid (Ty21a)	Contraindicated	Use inactivated typhoid ViCPS vaccine

Vaccine	Indication	Notes
Live vaccines/toxoids (continued)		
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-positive travellers: - with CD4 ≤200 - who are >60 years of age on CCR5 inhibitors† - with egg allergy - pregnant or breastfeeding	Decisions regarding YF vaccination should always be taken in light of likely risk of acquisition of infection An exemption certificate should be provided to all travellers not vaccinated, but travelling to a YF endemic country Focused advice on avoidance of mosquito bites must be stressed Safe for household contacts Re-vaccinate after 10 years
Zoster (shingles)	Contraindicated	VZV titre ≥5 times that of chickenpox vaccine
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-positive patients
Diphtheria/tetanus/ polio (parenteral Td/ IPV)	Booster dose every 10 years	No need to restart a course, irrespective of the time elapsed since last dose
Hepatitis A	Should be considered for all HIV-positive 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

Vaccine	Indication	Notes
Inactivated vaccines/toxoids (continued)		
Hepatitis B	Recommended for all non-immune HIV-positive adults	Three-dose regimen at 0, 1, and 6 months using double-dose HBV vaccine. Check anti-HBs antibodies 1 month after final vaccine dose: - If anti-HBs titre <10 milli-international units/mL, then repeat the vaccine series with double-dose vaccine - If anti-HBs titre remains <10 milli-international units/mL after repeat vaccination series, do not revaccinate, but ensure optimised compliance with non-vaccine preventative measures
Influenza	Annual vaccination for all HIV-positive patients	
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 JEV vaccine, Ixiaro®, an inactivated virus strain derived from tissue culture has been licensed by the FDA. No information is available yet for HIV-positive persons
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'	Two doses given 8 to 12 weeks apart and boosted every 5 years Quadrivalent (ACWY) vaccine recommended No evidence of increased risk of adverse events in HIV-positive persons
Pneumococcus	Indicated for children as part of the extended programme of immunisation, and all HIV-positive persons: 1. No prior immunisation against pneumococcus with either PCV-13 or PPV-23	

Vaccine	Indication	Notes
Inactivated vaccines/toxoids (continued)		
Pneumococcus (continued)	a. A single dose of PCV-13 should be given irrespective of CD4 count, followed by a single dose of PPV-23 at least 8 weeks later b. If the patient's CD4 count is <200 cells/mm^3, then PPV-23 should be deferred until the patient has been started on ART and achieved a CD4 count ≥200 cells/mm^3 c. A second dose of PPV-23 should be given 5 years after the initial PPV-23 dose 2. For HIV-positive persons who have previously received one or more doses of PPV-23: a. A single dose of PCV-13 should be administered a minimum of 1 year after the last PPV-23 dose	
Rabies	Indicated for all travellers to dog rabies endemic areas	Intramuscular immunisation recommended rather than intradermal Assess response to immunisation in travellers with CD4 ≤200, if resources allow ± further boosting if antibody response >0.5 IU.ml not achieved Counsel all travellers to endemic areas on wound treatment and post-exposure prophylaxis
SARS-CoV-2	Indicated for all HIV-positive persons	

Vaccine	Indication	Notes
Inactivated vaccines/toxoids (continued)		
Tick-borne encephalitis	Indicated for HIV-positive 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 avoidance of tick bites and consumption of unpasteurised milk
Typhoid (ViCPS)	Indicated for HIV-positive 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-positive 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 there should be liberal use of high-factor sunscreen and protective clothing. For patients not on ART, either of the three 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 the tablets with food.

Antimalarial chemoprophylaxis for HIV-positive travellers on ART

	Adverse effects	PIs	NRTIs	NNRTIs	InSTIs
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: 541-556

Antimalarial treatment for HIV-positive travellers on ART

	PIs	NRTIs	NNRTIs	InSTIs
Quinine	Decrease quinine levels	No interactions expected	Decrease quinine levels	No interactions expected
Artemisinins	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 co-administer EFV increases amodiaquine levels**	No interactions expected

www.hiv-druginteractions.org

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

Lancet ID 2011; 11: 541-556

Hospitalisation

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

Emergency Post-Exposure Prophylaxis

Post-exposure prophylaxis (PEP) is indicated after exposure to HIV-positive 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 4 weeks. Please contact AfA immediately for authorisation, but do not delay initiation of PEP. If exposure occurs on the weekend, please ensure that your patient gets the necessary medication after exposure. You can then contact AfA first thing on Monday morning to complete the PEP application to arrange reimbursement for further PEP medication.

PEP regimens are not well tolerated. Where PEP is felt to be justified, a three-drug strategy is advocated for all percutaneous exposures, and mucocutaneous exposure with potentially infectious material. 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. We recommend TDF/3TC/DTG based on mechanism of action, ease of administration and tolerability. A PI may be used in place of DTG if contraindicated for any reason. Boosted ATV is associated with unconjugated hyperbilirubinaemia. The neuropsychiatric side-effects of EFV make this drug less suitable, as stress related to possible HIV exposure is often considerable. NVP 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. **Nucleos(t)ide backbone:**
   a. Tenofovir and lamivudine/emtricitabine
   b. Zidovudine and lamivudine
2. **Third agents:**
   a. Dolutegravir
   b. Atazanavir/ritonavir
   c. Darunavir/ritonavir
   d. Rilpivirine

The list of preferred third agents above are all well tolerated. 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 the first dose of standard PEP without delay.

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

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

Recommendations for PEP after exposure to potentially infectious material*

Exposure	HIV status of source patient	
	Positive or unknown**	Negative
Intact skin	No PEP	No PEP
Mucosal splash or non-intact skin	Three drugs	No PEP
Percutaneous injury	Three drugs	No PEP

* *Includes blood, CSF, semen, vaginal secretions and synovial/pleural/pericardial/peritoneal/ amniotic fluid*

** *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 HIV status of the source remaining unknown, the full 28-day course of PEP should be completed.*

After sexual exposure, remember to also prescribe emergency contraception if necessary. Following rape empiric treatment for sexually transmitted infections should be given (ceftriaxone 250 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: it is necessary at the time of exposure to ascertain the patient's HIV status. Follow-up HIV testing should be done 6 weeks and 3 months after exposure to determine whether the patient has become infected. Current laboratory antibody tests (ELISA) should be positive within 3 months.

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

Baseline and follow-up FBC and creatinine clearance should be done if zidovudine or tenofovir respectively are selected. If a patient has been exposed to HIV, condoms should be used until the 3-month HIV ELISA test is negative. Patients should be counselled regarding the need to complete the 4-week course of prophylaxis, as side-effects to treatment are common.

Pre-exposure Prophylaxis

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

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

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

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

Pregnancy and Mother-to-Child Transmission Prophylaxis

HIV can be transmitted to the infant in utero, perinatally or by breastfeeding. Without intervention the risk of transmission is 20 – 40% but it is dramatically reduced to <2% with antiretroviral therapy for mother and baby and with interventions to reduce the risk of HIV transmission through breastfeeding (see infant feeding section). Women living with HIV (WLHIV) should ideally be virally suppressed before planning a pregnancy. ART should be initiated as soon as possible in women diagnosed in pregnancy or reinitiated as soon as possible if treatment was interrupted.

Viral load management is essential for a successful outcome for mother and infant.
AfA recommends the following:

1) Women becoming pregnant while taking antiretrovirals should continue with their drug regimen.
2) For mothers on ART for >3 months: a viral load should be performed to confirm that the viral load is below detectable limits and then repeated 3 monthly during pregnancy. For any detectable viral load, confirm with a 2nd assay as soon as possible and address adherence. A change in ART regimen for the mother would depend on her treatment history. Refer to adult section on changing therapy for guidance and contact AfA for advice.
3) For mothers who are diagnosed during pregnancy: adherence should be emphasised and the viral load should be <50 copies/mL after 3 months. If the viral load is >50 copies/mL at 3 months, step-up adherence support and repeat the viral load after a month. If repeat viral load is still not <50 copies/mL seek advice from AfA.
4) 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 <50 copies/mL.

AfA recommends that all pregnant women be screened and tested for syphilis using rapid tests. Testing should be repeated throughout pregnancy.

ART in Pregnancy

A fixed-dose combination comprising tenofovir, lamivudine and dolutegravir (TLD) is the preferred first-line regimen in pregnancy. There are some concerns that tenofovir, which reduces bone mineral density to a small extent in adults, may affect skeletal development in exposed infants. Data from a cross-sectional study, showing reduced bone mineral content in newborn infants, reinforces this concern. Despite this, using a regimen which contains tenofovir is the standard of first-line care even in pregnancy.

Lopinavir/ritonavir is the best studied boosted PI in pregnancy, but boosted atazanavir and boosted darunavir are alternatives. The pharmacokinetics of many drugs are altered in pregnancy. Although studies have shown significant reductions in the total drug concentrations of PIs in the second and third trimesters, unbound drug concentrations, which exert the pharmacological effects, are not affected. Therefore, standard doses of PIs should be used.

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

Situation	Therapy	Monitoring
Newly diagnosed OR treatment naïve	Initiate ART	VL after 3 months • VL >50 copies/mL – emphasise adherence support and repeat in one month. If repeat VL is still >50 copies/mL seek advice from AfA • VL <50 copies/mL repeat every 3 months and again just before or at delivery
ART >3 months and first-line therapy	Continue ART	Viral load when pregnancy confirmed • VL <50 copies/mL - repeat every 3 months and just before or at delivery • VL >50 copies/mL AND <6 months on therapy - emphasise adherence support and repeat in one month. If still not suppressed seek advice from AfA • VL >50 copies/mL AND >6 months on therapy - seek advice from AfA
Interrupted ART	Resume or change ART (TLD may be considered - seek advice from AfA)	VL after 3 months • VL >50 copies/mL - emphasise adherence support and repeat VL in one month and if still >50 copies/mL seek advice from AfA • VL <50 copies/mL - repeat every 3 months and again just before or at delivery
Presenting in labour not on therapy	Nevirapine 200mg stat plus commence TLD at same time to reduce the risk of NNRTI resistance	VL at delivery and every 3 months if breastfeeding
Failure of 1st or 2nd line ART after the 2nd trimester	Consider resistance testing – seek advice from AfA as a change in regimen may be necessary Emphasise adherence support	

Antiretroviral Therapy for Infants to Prevent MTCT

A "one size fits all" approach to infant prevention is inappropriate. Infants at higher risk of perinatal transmission require expanded prevention provided the birth PCR is negative. Clinicians managing HIV-positive pregnant women and their infants should consider the following:

- First, is the mother's viral load suppressed (<50 copies/mL)? Viral load remains the primary driver of transmission. Effective ART and adherence to therapy must be addressed in pregnancy.
- Second, is there a risk for resistance in the mother? Mothers on ART for >6 months whose viral loads are not suppressed may have drug resistance. In these mothers all attempts should be made to achieve suppression during pregnancy and a resistance test should be considered. Timing of the test will be determined by previous and current regimens and duration on therapy.

A maternal viral load at the time of delivery is now standard of care and needed to assess the risk profile of infants. If the maternal viral load is <50 copies/mL just before or at delivery and adherence is confirmed, we recommend twice daily AZT or daily NVP for 6 weeks. If the mother's history or viral load just before or at delivery is NOT available or if viral load is >50 copies/mL prevention should be initiated with AZT, 3TC and NVP until the result at delivery is known.

Where mothers are failing second-line or third-line therapy, infant prevention should be discussed with AfA prior to delivery of the baby. However, if this was not done, prevention with AZT, 3TC and NVP should be initiated and infant prevention discussed with AfA to decide if additional therapy can be considered.

SUGGESTED PREVENTION	
Mother	**Infant**
Viral load known to be <50 copies/mL just before or at delivery and low risk of resistance	Low risk prevention • AZT or NVP for 6 weeks
Viral load unknown just before or at delivery but suspected to be suppressed, low risk of resistance	High risk prevention • AZT, 3TC, NVP with review of maternal viral load and step down to lower risk if mother's viral load <50 copies/mL

Viral load known to be >50 copies/mL just before or at delivery and low risk of resistance	High risk prevention - formula feeding women • AZT, 3TC, NVP for 4 weeks High risk prevention - breastfeeding women • AZT, 3TC, NVP for 6 weeks, then stop AZT and 3TC and continue NVP at the prophylactic daily dose until mother's viral load is <50 copies/mL or until 4 weeks after the infant is fully weaned
Viral load known to be >50 copies/mL just before or at delivery and risk of resistance or failing second-line therapy	High risk prevention Alternative drugs (such as LPV/r and raltegravir) may be needed; ideally should be discussed prior to delivery • Start AZT, 3TC and NVP and contact AfA for advice
Post-partum diagnosis in the breastfeeding mother	High risk prevention and urgent diagnostic test

Neonatal AZT dose for post exposure prevention in infants		
AZT Oral	35 weeks to Term	• Birth to 6 weeks: 4 mg/kg 12 hourly
	30 – 35 weeks	• Birth to 2 weeks: 2 mg/kg 12 hourly then • 2 weeks to 6 weeks: 3 mg/kg 12 hourly
	<30 weeks	• Birth to 6 weeks: 2 mg/kg 12 hourly
AZT IVI (If infant nil per mouth)		• Preterm: 1.5 mg/kg 12 hourly • Term: 1.5 mg/kg 6 hourly

Neonatal 3TC dose for HIGH RISK exposure prevention		
3TC oral	All gestations	• Birth to 4 weeks: 2 mg/kg/dose twice a day, round up to the closest 0.5mg • More than 4 weeks: 4 mg/kg/dose twice a day

Neonatal NVP dose for HIGH RISK exposure prevention		
NVP oral	<35 weeks	• 2 mg/kg twice a day
	>35 weeks 2-3 kg	• 4 mg/kg twice a day
	>35 weeks >3 kg	• 6 mg/kg twice a day

NVP Infant Dosing Guide for prophylaxis during breastfeeding. NVP to be continued until mother's VL is < 50 copies/mL or continued until 4 weeks after the infant is fully weaned

Birth Weight	Age	Daily Dose	Volume
<2.0 kg	Birth to 2 weeks 2 to 6 weeks	2 mg/kg 4 mg/kg	0,2 ml/kg 0,4 ml/kg
2.0 – 2.5 kg	Birth to 6 weeks	10 mg	1 ml
>2.5 kg	Birth to 6 weeks	15 mg	1.5 ml
N/A	6 weeks to 6 months	20 mg	2 ml
N/A	6 months to 9 months	30 mg	3 ml
N/A	9 months to 24 months	40 mg	4 ml

Breastfeeding

Breastfeeding remains a potential source of postnatal HIV infection, especially if the viral load is not suppressed. In low resource settings where the morbidity and mortality associated with replacement feeding is very high breastfeeding is preferred with extended NVP to infants of mothers who are not virally suppressed. Maternal ART and extended NVP both reduce the risk of breastfeeding-associated transmission. Though the majority of the risk of transmission is in the first 6 weeks the risk is cumulative and throughout the course of breastfeeding.

The risk of breastfeeding transmission is lowest in mothers who are suppressed prior to conception and remain suppressed with the target viral load being <50 copies/mL. Breastfeeding-associated HIV transmission still occurs, especially in unsuppressed mothers who struggle to remain on ART, women who are not suppressed due to late initiation of ART in pregnancy and those who seroconvert while breastfeeding. In these infants access to infant prevention is crucial if mothers breastfeed, but it needs to be emphasised that maternal therapy and viral suppression is the preferred breastfeeding transmission prevention strategy.

In the South African public sector, all women with HIV are advised to breastfeed as all mothers are on ART. Infants of unsuppressed mothers can access prolonged NVP, a safe and cost-effective public health intervention. Women on second and third-line ART who fail to suppress may be an exception if effective infant prevention is not possible.

Careful counselling is needed about the risks and benefits of breastfeeding - the personal situation of mothers should also be considered. Ideally only mothers who have a viral load of <50 copies/mL and good adherence should breastfeed. However other women may also express desire to breastfeed for various reasons. If women with viral loads of <50 copies/mL elect to breastfeed, they should be supported but reminded that maintaining viral suppression is essential. Both she and her baby require careful monitoring. While breastfeeding, viral loads should be performed every 3 months and intensive adherence support provided. If mothers who are not virally suppressed elect to breastfeed, the risk and benefits of breastfeeding should be explained to the mother and it should be emphasised that maternal virologic suppression and not infant prevention is the most appropriate way to prevent breastfeeding-associated HIV transmission. All efforts should be made to assist women to suppress and infant prevention should be provided with regular follow-up of both mother and baby.

Women who are failing second and third-line ART should be carefully counselled about the risk of breastfeeding and formula feeding should be encouraged.

All women who elect to breastfeed should be counselled about the benefit of exclusive breastfeeding for 4-6 months with gradual weaning. Abrupt weaning causes breast engorgement and increases transmission. For those rare cases where breastfeeding transmission has occurred, breastfeeding can continue. Mothers who would like to breastfeed but need to return to work within 6 months and would like to mix feed with formula can consider this provided they are suppressed and on effective ART with careful counselling.

For breastfeeding women who are not suppressed on first-line ART we suggest the following for their infants:

1) Step 1 – continue high risk prevention for up to 6 weeks
2) Step 2 - repeat the mother's viral load and the baby's PCR 4 to 6 weeks after delivery
    a. If the mother's repeat viral load is <50 copies/mL, infant prevention can stop at 6 weeks, the mother should be supported to remain adherent and suppression should be monitored carefully. Gradual weaning at 4-6 months is recommended
    b. If the mother's viral load is >50 copies/mL, the mother should be counselled and weaning considered. The infant should switch to breastfeeding prevention
        i. NVP only as breastfeeding prevention for a further 6 weeks if there is low risk for NNRTI resistance
        ii. If NNRTI resistance is a consideration, discuss with AfA and consider alternative ART for prevention after expert advice

At 12 weeks, the mother's viral load should be repeated. If the viral load is still not suppressed, infant weaning should be recommended and prevention should be supported during the weaning process. If the infant PCR is positive, perform resistance testing and initiate appropriate ART once this result is available.

Children who seroconvert while breastfeeding and taking extended NVP will not only have NVP and efavirenz resistance, but may also develop mutations to second generation NNRTIs such as rilpivirine and etravirine. Babies are also exposed to low levels of antiretrovirals secreted in the milk, possibly contributing to resistance if they become HIV-infected, thus limiting therapeutic options for the infants. The long-term implications of prolonged ART exposure over months through breast milk are unknown. In viraemic mothers with resistance, the infant may also be infected with a resistant strain.

Co-trimoxazole Prophylaxis

New data confirms that thriving HIV exposed uninfected infants do not require co-trimoxazole at 6 weeks of age if their mothers are in care and on ART.

Diagnosis of HIV in Infancy

The diagnosis of HIV in an infant is done by a qualitative PCR. The first PCR should be done on day one of life and repeated at 10 weeks, at 6 months and 4 weeks after prevention is stopped. If the infant is unwell at any time the PCR should be repeated especially where there has been sub-optimal antenatal ART.

NOTE: never request the PCR on cord blood as this may give a false positive result. The HIV ELISA may be positive for up to 24 months because of maternal antibodies.

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

Family Planning

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

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

Contraception

- **Barrier method.** There are compelling reasons to always recommend barrier methods together with other contraceptive measures as this will reduce the risk of transmission of HIV, the acquisition of super-infection with ART-resistant HIV, and infection with other pathogens (notably herpes simplex). However, the contraceptive efficacy of barrier methods is sub-optimal, with annual failure rates of approximately 5%. Thus, additional contraception methods should always be taken.
- **Intrauterine devices.** Early fears that these would be associated with increased risk of infection in HIV-positive women have not been confirmed in prospective studies. The progestogen-eluting devices are effective when used with enzyme-inducing drugs as they have a local action. Thus, these should be effective when used with ART.
- **Hormonal contraception.** There are important drug interactions with some ART (notably the protease inhibitors and the NNRTIs) and hormonal contraception, resulting in alteration in the hormone concentrations. There is limited data on the contraceptive efficacy of hormonal agents when coadministered with ART, but depot progestogen preparations are not significantly affected by drug interactions (see table for recommendations). The combined oral contraceptive pill (COCP) may be less effective when coadministered with a ritonavir-boosted PI which induce the metabolism of oestrogen and, to a lesser extent, progesterone, but provided that high dose oestrogen formulations are used, these should be effective. Another method e.g. barrier should be used in conjunction. High dose COCP and a barrier method 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. Evidence has found that efavirenz, together with other enzyme inducing drugs, can interfere with the action and effectiveness of progestin subdermal implants and they should therefore not be used. Rilpivirine can be used with progestin subdermal implants.

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

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

Diagnosis and Management of HIV Infection in Children

Key differences between adults and children with HIV

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

1) **Routes of infection**

- Vertical transmission accounts for 95% of paediatric HIV with transmission occurring in utero, during delivery and through breastfeeding. Good maternal care and controlling maternal viraemia are the mainstay of prevention
- Sexual abuse
- Blood product transfusion – this route is 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 adult or older child living with HIV 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

2) **Diagnosis in infants is complicated by transplacental crossing of maternal HIV antibodies**

3) **Disease follows a more rapid course than in adults due to an immature immunological system.** In the absence of ART, more than 50% of children with HIV 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

4) **The clinical disease staging differs from that used in adults.** The developing brain is especially vulnerable to HIV

5) **The interpretation of CD4 counts and percentage alters with the age of the child.** In infants and younger children morbidity and mortality occur at higher CD4 counts

6) **Infants have higher viral loads.** At the beginning of the epidemic young infants had higher viral loads than adults. Now particularly infants accessing aggressive prevention programmes may have lower viral loads while still on ART used for vertical transmission prevention than historic cohorts. Higher viral loads take longer to suppress

7) **Infants acquiring HIV despite ART used for vertical transmission prevention may have resistant virus.** NNRTI resistance is common and other maternal resistance may also be transmitted. Therefore, integrase inhibitors or protease inhibitors are the mainstay of initial therapy in young children. Resistance tests should be requested in infants newly diagnosed with HIV (requires preapproval by AfA)

8) **There are fewer therapeutic options for children than adults**. The emphasis is on prevention, early establishment of HIV status immediately after birth, early institution of antiretroviral therapy and co-trimoxazole prophylaxis against Pneumocystis jirovecii pneumonia (PJP) and bacterial infections

Diagnosis of HIV in Infants and Children

Passively acquired maternal antibodies persist for up to 24 months in infants who were exposed to HIV in utero. In reality, antibodies detected after the first year of life are highly predictive of HIV infection but are not conclusive. HIV antibody tests in children only confirms infection after 24 months of age.

To determine the infection status of children before 24 months of age, the qualitative polymerase chain reaction (PCR) test for HIV specific DNA/RNA must be performed. This can detect in utero and early intrapartum HIV infection in 70% of newborn infants on day one of life and up to 90% by two weeks of age in the absence of maternal ART. A quantitative HIV RNA (viral load) assay can be done to confirm a positive qualitative HIV DNA/RNA PCR. In children < 24 months of age 2 positive nucleic acid tests are required to confirm HIV infection.

More recently, it has become evident that antenatal and post-partum antiretroviral drugs may influence the early detection of HIV DNA or RNA. Rarely, qualitative PCR results may be indeterminate. Under these circumstances, consult with the virology laboratory and with AfA.

The following strategy should be adopted for infant diagnosis where the HIV exposure status at birth is known - routine testing at specific timepoints are recommended:

- Testing starts at birth with a DNA/RNA PCR (note that cord blood should NOT be used) with repeated PCR testing at 10 weeks and 6 months and an antibody test between 18 and 24 months
- Breastfed children require more frequent testing to exclude HIV infection. They require a PCR test every 3 months between 6 and 18 months and an antibody test thereafter for as long as they breastfeed. An age appropriate test should also be done at 6 weeks and then 6 months after breastfeeding has stopped. If at any stage a child presents with features of HIV, an age appropriate test should be done regardless of previous test results

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, urgently screen the mother for HIV

The following strategy should be adopted for infant or child diagnosis where HIV exposure status is not known or negative during the antenatal and immediate post-partum period who present with clinical features suggestive of HIV:

- Screen with an HIV antibody test – if the screening is positive, perform an age appropriate further test. In infants younger than 24 months positive antibody tests must be confirmed with 2 positive viral nucleic acid tests. If screening test is negative but there is still concern for HIV consider a DNA/RNA PCR and screening the mother with an antibody test. Also consider additional HIV testing in the mother

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

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. Testing should be considered in children presenting with any severe clinical illness, poor growth, tuberculosis, developmental delay and recurrence of chronic illnesses.

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

- Parent with HIV
- 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 pneumonia 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

Resistance Testing Prior to Initiation of Therapy

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

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

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

The resistance test must be preapproved by AfA.

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

Classification

The clinical classification should be made with all available information including history, laboratory data and imaging, where appropriate. The baseline staging does not change regardless of the improvement on ART. As the clinical condition improves, staging can be reviewed, the new stage noted but baseline staging retained as well.

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

Clinical stage 2[i] (continued)

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 ($<0.50 \times 10^9/L^3$) or chronic thrombocytopaenia ($<0.50 \times 10^9/L^3$)

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

Clinical stage 4 [(i)] [(ii)] (continued)
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 while CD4 cell percentages remain 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 if available 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 next table.

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

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

* *The stage is based primarily on the CD4 count*

The Management of a Newly Diagnosed Child

HIV Infection is a Disease of the Family

ART should be initiated as soon as possible, provided the child is stable. Counselling on adherence must continue after therapy has been initiated.

Important points when counselling parents of HIV-infected children:

- Survival of infected and uninfected children is intimately linked with health of the parents. Every effort should be made to screen and counsel family members and refer for appropriate therapy. This includes mothers, fathers and siblings who may be untested or not on therapy
- 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
- Early ART is associated with excellent outcomes, comparable to children without HIV
- 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 consider the need for support and planning for the child if they are severely ill or have advanced disease
- **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
- Note feeding choices for neonates and infants
- Record all clinical events including ear and skin infections and upper respiratory tract infections like otitis media
- Actively ask about TB in close contacts
- Take a history for any new event
- Take full history for neurodevelopment and where appropriate school performance
- Check the perinatal details, including maternal syphilis results and previous weights in the health records and the “Road to Health” card. Also check mother’s Hepatitis B status
- Check the immunisation status on the “Road to Health” card

Clinical Assessment

- Record the child's weight, height and head circumference. All these values should be noted on the appropriate centile charts. In children >2 years, head circumference does not have to be recorded at every follow-up visit
- Check for generalised lymphadenopathy, hepatosplenomegaly, parotid enlargement, digital clubbing or oral thrush
- Check dental hygiene and refer to dentist if necessary
- Do a full clinical assessment and careful age appropriate neurodevelopmental and neurological assessment
- **The possibility of TB infection should be reassessed with ANY new TB source case and if disease is excluded, TB prevention therapy should be provided**

Baseline Investigations

- Hearing test if not previously performed AND in all children with poor school performance, neurodevelopmental delay or clear neurological abnormalities
- Hepatitis B serology, even if partially or fully immunised. If the surface antigen is positive, check the mother. If surface antibody negative and not fully immunised (6, 10, 14 weeks and 18 months), complete the series and then check antibody levels after 1 month. If fully vaccinated and antibody negative revaccinate and consider an increase in the dose
- Mantoux or IGRA
- Baseline chest radiograph – this is extremely valuable as many children develop chronic lung disease or TB
- Full blood count and differential
- ALT
- CD4 count
- Urinalysis (dipstick)
- Viral load should be done in all children to confirm diagnosis before starting treatment
- Consider retesting for syphilis – if mother's status during pregnancy is uncertain
- Stool for microscopy, culture and sensitivity, and parasites if diarrhoea is present
- Baseline electrolytes, urea and creatinine and non-fasting lipid profile (fasting profile only if non-fasting values abnormal)
- If a close contact has TB or if there are suggestive features, actively exclude TB. The child should be fully investigated for TB, with tests for infection (Mantoux or IGRA), chest x-ray, induced sputum or gastric washing/lavage. If negative, TB prevention therapy should be given. If positive, the child should be referred to a TB clinic for treatment. The Mantoux skin test is the preferred skin test in children living with HIV. Induration of ≥5 mm is considered positive. Interferon gamma release assays (IGRAs) provide similar information. Positive skin tests and IGRAs indicate TB infection not necessarily disease, and negative tests cannot exclude infection. Newly diagnosed children will all require TB preventive therapy

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 suggest that clinicians use vaccine specific antibody levels to guide actions; however, this is not practical. For Hepatitis B, measure HBV surface antibodies to confirm seroconversion and if absent or low, repeat vaccination. In general, all childhood vaccinations should be given. Revaccination is not universally recommended but there is increasing evidence that it should be considered. We recommend repeating the MMR in childhood e.g. >5 years of age. HPV vaccination is 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. Although BCG vaccination was contraindicated in the pre-ART era in children with confirmed HIV infection, with ART, BCG is safe and protective. In the past, most infants received this vaccine prior to the availability of test results and without complications.

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

Age of Child	South African EPI schedule	Private sector
At birth	OPV (0) BCG	OPV (0) BCG *see below regarding Hep B vaccine at birth
6 weeks	OPV (1) RV (1) PCV (1) DTaP-IPV-Hib—HBV (1)	OPV (1) RV (1) PCV (1) DTaP-IPV-Hib—HBV (1)
10 weeks	DTaP-IPV-Hib—HBV (2)	RV (2) PCV (2) DTaP-IPV-Hib—HBV (2)
14 weeks	RV (2) PCV (2) DTaP-IPV-Hib—HBV (3)	RV (3) PCV (3) DTaP-IPV-Hib—HBV (3)

Age of Child (continued)	South African EPI schedule	Private sector
6 months	Measles# (1)	Influenza Measles# (1)
9 months	PCV (3)	MCV (1) PCV (4)
12 - 15 months	Measles# (2) at 12 months	MMR (1) at 12 months HAV (1) at 12 months Varicella (1) MCV (2)
18 months	DTaP-IPV-Hib—HBV (4)	DTaP-IPV-Hib—HBV (4) HAV (2)
5 - 6 years	Td vaccine (6 years)	Dtap-IPV or Tdap-IPV MMR (2) Varicella (2)
9 years	HPV	HPV
12 years	Td vaccine SARS-CoV-2	Tdap-IPV or Tdap SARS-CoV-2

* *Vaccine given at birth to babies born to mothers who test positive for hepatitis B*

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

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, cardiac disease or other significant end organ disease may require additional nutrition
- Iron should be given only if iron deficiency is confirmed
- Dietetic advice must be sought for children with a high BMI and hypercholesterolaemia

Follow-Up

All children with HIV should be rapidly initiated on ART. Thereafter a follow-up at 2-4 weeks is needed to review any medication difficulties. Monthly follow-ups are recommended initially with 3-6 monthly review once stable on ART and suppressed.

Monitoring

Clinical Monitoring, Height, Weight and Head Circumference

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

Growth: The "Road to Health" card is a valuable tool for monitoring wellbeing. Failure to gain weight is common among untreated children living with HIV 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 children living with HIV 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 and referral to a dietician may be needed.

Neurocognitive: The neurotropic nature of HIV makes assessment of these children essential. 50% of untreated infants will experience developmental delay if HIV was diagnosed late. Older children may experience school failure, ADD/ADHD and poorer cognitive outcomes. 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 for developmental assessment may change the outcomes of these children. Interventions include cognitive and hearing assessment, assessment for ADD/ADHD, encephalopathy and mobility support. The help of a developmental paediatrician should be routinely sought.

Head circumference: This should be measured and plotted on a growth chart in the first 2 years of life as it reflects brain growth. Flattening of the curve is highly suggestive of encephalopathy.

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

Psychiatric illness: With use of ART the general health of children living with HIV has 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, adaptation and coping skills may be poor. Clinicians should look for these problems and intervene early.

CD4 Lymphocytes

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

Viral Load

Viral loads in infants are 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 untreated infants have viral loads above 100 000. Viral loads >299 000 correlate with rapid disease progression and death in infants below one year of age. Viral loads are most useful to monitor response to ART.

Summary of suggested routine monitoring of a child on ART

Every visit	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)

Initiation Criteria for ART

ALL children living with HIV should be on ART. Carers require adequate counselling to support lifelong ART with optimal adherence for their children. Disclosure of HIV status to a child should be planned from the outset and is a process rather than a single event.

Viral load for monitoring ART

Although clinical and immunological responses are seen in the absence of fully suppressed viral loads, these infants and children will accumulate resistance mutations. Initial virological response may be slower than in adults, especially in young infants or if the baseline viral load is very high.

The overall aim of treatment is to reduce the viral load to levels below the limit of detection rapidly and to maintain undetectable levels throughout life. Large cohort observational studies report suppression to an undetectable viral load in 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

New data supports dolutegravir (DTG) in first-line ART instead of boosted PIs or NNRTIs. DTG is given once daily and has a higher genetic barrier to resistance than raltegravir (RAL), which should no longer be used as resistance develops rapidly and compromises the activity of DTG. The DTG 10mg dispersible tablet can be used in children from 1 month and 3 kg and the 50 mg tablet from 20 kg.

Boosted protease inhibitors (PIs) are superior in infants. For older children one randomised study showed no difference between NNRTIs and boosted PIs. Boosted lopinavir (LPV/r) can

be used from 42 weeks gestation and boosted atazanavir (ATV/r) from 10 kg. ATV/r allows for once daily dosing but cannot be used with rifampicin. Boosted darunavir (DRV/r) is usually reserved for third-line regimens and can also not be used with rifampicin.

The NRTI combination of ABC and 3TC has a favourable toxicity profile and in one study was superior to AZT and 3TC. 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 low. TDF can be used in children from 10 years of age and weighing 30 kg or more provided their renal function is normal. TAF can be used in children from 2 years of age and weighing 25 kg. ABC, TDF, TAF, 3TC and FTC can all be used once a day. There are a number of fixed-dose combination products available which can be used in children.

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 daily frequency. It is good practice to show the family the medication. 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 dosing adequately readjusted as the child enters a new weight band. For young infants, initiate ART early, preferably immediately after confirmation of diagnosis and continue educating about the medication over the next few weeks.

Summary of Recommendations on Which ART to Start

Neonates				
Gestation	**Chronological age**	**NRTI**	**3rd agent**	**At 4 weeks and >3 kg**
Term	<4 weeks	AZT/3TC	NVP	Switch to ABC/3TC and DTG
Preterm		*AZT/3TC	NVP	Seek advice from AfA

* *Consult AfA if infant anaemic*

Weight	Age	Preferred Regimen	Alternate Regimen
3 kg to <25 kg	All	ABC/3TC + DTG[1]	
25 kg to <30 kg		ABC/3TC/DTG[1]	TAF/3TC/DTG[1] TAF/FTC/DTG[1] (> 2 years)
≥30 kg	<10 years	ABC/3TC/DTG[1]	TAF/3TC/DTG[1] TAF/FTC/DTG[1]
	≥10 years	TDF[2]/3TC/DTG[1]	ABC/3TC/DTG[1] TAF/3TC/DTG[1] TAF/FTC/DTG[1]

[1] *Important drug interactions between DTG with rifampicin, polyvalent cations, metformin and some antiepileptics*

[2] *If <16 years: use Counahan Barratt formula:*

$$eGFR\ (mL/min/1.73\ m^2) = \frac{height\ [cm] \times 40}{serum\ creatinine\ [\mu mol/L]}$$

If ≥16 years: use adult formula (modified Cockroft Gault)

Fixed-dose combination tablets are always preferred. Use individual components only if fixed-dose combinations not tolerated

Alternate 3rd drug options if DTG is contraindicated or not tolerated: ATV/r, LPV/r, RPV or EFV

In infants with baseline resistance to any drugs apart from NNRTIs seek advice from an expert. In children on anti-tuberculosis regimens that contain rifampicin, ART should be adjusted accordingly.

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

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

Indications for Co-trimoxazole Prophylaxis

	Start	Stop
HIV positive infant <12 months		Provide regardless of CD4
HIV positive child 1 – 5 yrs	Clinical stage II/III/IV CD4 ≤25%	Discontinue if CD4 count >25%
HIV positive child 1 – 5 yrs who had PCP	As soon as therapy doses complete	Discontinue if > 5 years AND CD4 count >200
HIV positive child >5 yrs	Clinical stage II/III/IV CD4 ≤200	Discontinue if CD4 count >200

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)
3 to 5.9 kg	2,5 ml	¼ tablet, possibly mixed with feeding	-
6 to 13.9 kg	5 ml	½ tablet	-
14 to 24.9 kg	10 ml	1 tablet	½ tablet
≥25 kg		2 tablets	1 tablet

Commence an appropriate multivitamin preparation daily.

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)

- **Co-trimoxazole for PCP prophylaxis: see table for indications, doses, and when to stop**

Dapsone can be considered in children with low CD4% with serious co-trimoxazole adverse events, but it is inferior to co-trimoxazole. The dose is 2 mg/kg daily. Co-trimoxazole may benefit children with recurrent bacterial infections.

ART failure and resistance

ART failure is usually first virological, followed by immunological and clinical failure. Clinical failure includes the recurrence or non-disappearance of stage 3 or 4 disease. There are exceptions: for example, pneumonia can recur in children with underlying bronchiectasis. Immunological failure is the reappearance of low CD4 percentage (generally 20%, but could be lower in older children, or CD4 count when over 5 years of age). Intercurrent elevations with low viral loads (called "blips") can be triggered by intercurrent illness or vaccinations. These viral loads are usually <1000 copies and resuppression occurs rapidly.

The most common cause of treatment failure is poor adherence. Occasionally, inadequate drug levels or inadequate potency of the drugs chosen can contribute. 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 drugs with a high genetic barrier to resistance, like DTG and boosted PIs. Regrettably, first generation NNRTIs and RAL have a low genetic barrier to resistance, which can result in the selection of mutations conferring resistance within only a few days of viral replication.

Not managing drug interactions in patients on rifampicin is an important cause for antiretroviral resistance in adherent patients on boosted PIs. We do not have similar data for children on DTG as yet, but careful attention to co-management with TB is imperative.

The definition of virological failure is any persistently detectable viral load after 6-9 months on therapy OR new viraemia (viral load >50 copies) after initial suppression. All these children require assessment and adherence support. Children failing DTG or boosted PIs in the first 6-12 months will not immediately be switched because it is not yet clear at which level to change therapy and the intervention may depend on the age as well as the line of therapy.

Children on NNRTIs with unsuppressed viral loads should be switched to a DTG-based regimen. Children on a boosted PI or a DTG-based regimen for at least 2 years with viral loads ≥ 1000 copies or with signs of immunological or clinical failure (i.e. declining CD4 and/or opportunistic infections) should have resistance testing performed prior to a switch.

Recommended Second-line Combinations

The choice of treatment should be based on careful analysis of the cause of failure, previous regimens and results of resistance testing, if performed.

Failing Regimen	VL	Resistance Testing (RT)	New Regimen
NNRTI-based regimen	Any VL	RT can be done on request provided the VL is >1000 and scheme option allows	2 NRTIs + DTG (preferred) 2 NRTIs + boosted PI
PI-based regimen for >2 years*	VL >1000	Yes (provided adherence is confirmed)	Mutations detected – discuss with AfA No mutations detected - continue on current regimen and address adherence. Could consider switching to a DTG-based regimen (discuss with AfA)
InSTI-based regimen for >2 years*	VL >1000	Yes (provided adherence is confirmed)	Mutations detected – discuss with AfA No mutations detected - continue on current regimen and address adherence

* *In some cases, a RT may be considered before 2 years e.g. where DTG or LPV/r was not dose-adjusted with rifampicin containing TB-treatment (discuss with AfA).*

Switching Patients from a Boosted PI Regimen to DTG

Regimen	VL	Alternate regimen option
PI-based regimen	VL <1000	Can change to a DTG-based regimen as assume patient would not have developed PI resistance
PI-based regimen for <2 years	Any VL	Can change to a DTG-based regimen as assume patient would not have developed PI resistance

Resistance Assays

Genotypic resistance assays should be performed in all children living with HIV (less than two years) exposed to any ART during pregnancy. It is important to interpret the resistance test together with a history of antiretroviral exposure during pregnancy, breastfeeding and postpartum.

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

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

The resistance test must be preapproved by AfA.

Adherence

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

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.

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 often 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 IRIS. The infant develops painful, right axillary suppurative lymphadenopathy, usually after two to three weeks of ART. This can usually be managed symptomatically. Repeated aspiration is helpful for pus formation. Anti-mycobacterial drugs are only indicated if disseminated BCG is suspected. Paradoxical deterioration in tuberculosis and skin and mucosal lesions are commonly noted IRIS phenomena.

Toxicity

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

Weight gain

In adults excessive weight gain has been associated with the use of all InSTIs especially with TAF and DTG. Similar changes in BMI have not been reported in large cohorts of children on DTG. Although there is an increase in BMI as they gain weight and height and this is more than in children on previous regimens most of the data suggests that the changes are a return to health phenomenon as weight is generally still within normal limits. BMI should always be monitored and a healthy diet and exercise should be encouraged.

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 gender, advanced disease and duration of time on ART. The risk of fat redistribution was highest in children on d4T and ddI, which are no longer used, but also occurs with AZT.

A single drug switch away from the probable offending drug can be made provided that the child is virologically suppressed. This usually involves a switch from AZT to ABC or TDF. In children with previous treatment failure, the full ART history should be taken into consideration and advice may need to 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 should have non-fasting blood lipids measured at least annually. Request a fasting lipogram if any abnormality detected. Consider switching LPV/r to DTG, ATV/r or an NNRTI depending on the age, weight and previous treatment history. Confirm suppression prior to switching therapy. There is very limited experience of statins in children but referral to a paediatrician with experience in this field may be needed. Refer to a dietician and encourage physical exercise.

Mitochondrial Toxicity

Mitochondrial toxicity may result from therapy with NRTIs especially AZT. 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-positive 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 testing 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.

Osteonecrosis and 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-positive children than in the general population.

The incidence of osteopaenia and osteoporosis is increased in adults treated with ART, particularly with the use of TDF. 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 treatment. Osteopaenia can be counteracted by regular exercise (including weight-bearing exercise such as running), and a diet with sufficient Vit D and calcium requirements. Currently there are no recommendations for regular DXA scans but it should be considered in children who have fractures or other risk factors such as chronic renal and lung disease.

Diabetes

Impaired glucose tolerance is infrequently reported in children and diabetes is very rare. The true prevalence of insulin resistance is difficult to assess in clinical practice, but assumes greater importance as children remain on ART for longer periods of time.

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 infants with HIV in the presence of delayed 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 especially if you suspect BCG or non-tuberculosis mycobacteria.

Treatment:

- Antimycobacterial drugs: for suspected or confirmed systemic disease
  - Isoniazid (INH) 15 mg/kg/day
  - Rifampicin (RIF) 20 mg/kg/day
  - Pyrazinamide (PZA) 30-40 mg/kg/day (BCG is resistant to PZA but if there is uncertainty as to the diagnosis or if TB is also a concern PZA should be given for 2 months)
  - 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 positive 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 initiated.

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 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. Nappy rash can usually be treated topically with nystatin cream twice daily and needs meticulous attention, as may be a nidus for bacterial superinfection.

Cryptococcosis

Uncommon in children.

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

Induction Treatment:

Preferred regimen: 1 week of amphotericin B 1 mg/kg/day and flucytosine 100 mg/kg/day.

If flucytosine is unavailable: 2 weeks of amphotericin B 1 mg/kg/day and fluconazole 12 mg/kg/day (up to 800mg per day). Flucytosine is not currently registered in South Africa and will need to be accessed via a Section 21 application. It can only be used in children from 20 kg due to the formulations currently available.

Patients with initial raised intracranial pressure should have daily lumbar puncture, removing sufficient CSF to lower pressure to <20 cm H_20. Refer to: Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-positive persons: 2019 update on the SA HIV Clinicians Society website **(http://www.sahivsoc.org)**.

Consolidation treatment: fluconazole 6 to 12 mg/kg/day (up to 800mg daily) for 8 weeks.

Maintenance treatment: fluconazole 6 mg/kg/day (up to 200mg per day) until CD4 count is >200 if more than 5 years of age and >25% if 2 to 5 years of age on ART (minimum of 12 months).

Cryptosporidiosis

Diagnosis: stool examination.

Treatment: no effective therapy available – loperamide and oral rehydration solution helpful. Usually responds 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. In the majority of these children infection is asymptomatic or present with a mononucleosis like illness. However, it can cause significant morbidity and mortality in immunocompromised children and if congenitally acquired. 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:

- PCR 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
- A positive qualitative CMV PCR in the blood confirms the presence of CMV infection but not active disease. It is thought to be higher in disease and can be used to monitor therapy. There may be inter-laboratory variation in the quantitative testing and using the same laboratory for all tests is preferable
- 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 should not be performed to diagnose infection in young infants or disease in any child. 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 is helpful but is rarely done

Pneumonitis

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

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

Treatment: see adult section.

Congenital CMV

Clinical: the spectrum of disease varies. Infants can be asymptomatic, or have features of congenital infection soon after birth. Children who are asymptomatic at birth can develop hearing loss and other poor cognitive outcomes.

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

Treatment: indications and duration of therapy remain somewhat controversial with ongoing studies, particularly for asymptomatic children.

Symptomatic congenital infections: valganciclovir (oral) 16 mg/kg 12 hourly for 6 months. Monitor FBC, ALT/AST. Hearing loss should be assessed at diagnosis and testing should be repeated at 6, 12 and 24 months. MRI of the brain should be considered in all 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: valganciclovir dose = 7 × BSA × CrCl twice daily for 14 -21 days (maximum is 900mg per dose).

Maintenance treatment: valganciclovir dose = 7 × BSA × CrCl daily until the CD4 count is >100. Maximum dose is 900mg daily (Requires pre-authorisation by AfA).

CMV GIT (colitis/oesophagitis)

Seldom diagnosed in infants.

Diagnosis: histology of biopsy of ulcer.

Treatment: valganciclovir dose = 7 × BSA × CrCl twice daily for 14 -21 days (maximum is 900mg per dose).

Maintenance treatment: not necessary.

Diarrhoea (non-specific)

May be persistent and associated with failure to thrive.

Investigations

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

HIV Encephalopathy

Signs and symptoms include:

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

Differential diagnosis

Tuberculosis, CNS lymphoma and toxoplasmosis should be excluded.

Investigations

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

Herpes Simplex Virus Ulcers (Including Stomatitis)

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

Treatment: two years and over: acyclovir 400 mg eight hourly for five days; under two years: acyclovir 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 associated with Human Herpes Virus-8 (HHV-8) also known as KS Herpes Virus (KSHV)
- KS may involve the skin, oral cavity, lymph nodes or viscera (lung, intestines and rarely other organs such as the liver and bone marrow). Lymphoedema is a potential complication. Skin lesions usually subcutaneous
- The typical CXR appearance of pulmonary KS is a reticulonodular appearance spreading from the hilar regions bilaterally. The diagnosis is confirmed by visualising endobronchial KS lesions on bronchoscopy (biopsy poses a high risk of haemorrhage). Pulmonary KS may be associated with intrathoracic adenopathy and/or pleural effusions which are typically bloody or serosanguinous
- CXR is a useful screen for pulmonary KS. Faecal occult blood is a useful screen for GIT involvement
- KS is a WHO stage 4 defining illness
- Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions, certain cases should have biopsy confirmation. Atypical skin lesions should be biopsied
- Lymph nodes >2 cm should be biopsied to exclude TB and lymphoma
- Atypical oral lesions should be biopsied to exclude other malignancies such as lymphoma, squamous carcinoma and salivary gland tumours

Treatment principles

- Refer to adult section
- 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
- All children MUST be referred to a 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 jirovecii* pneumonia (PJP), which is more common below one year of age. Median survival is five times longer for children with LIP than PJP.

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

Clinical

Symptoms include: slowly progressive tachypnoea, cough and wheezing.

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

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

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

Management

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

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

Microsporidiosis

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

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

Maintenance treatment: none.

Mycobacterium Avium Complex (MAC Infection Disseminated)

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

Treatment: The treatment should be discussed with an infectious disease specialist. The basic therapy should consist of at least a macrolide (clarithromycin 15 mg/kg/day in two divided doses or azithromycin 10 - 12 mg/kg/day) plus ethambutol (15 - 20 mg/kg/day). In severe disease, the addition of a rifamycin (preferably rifabutin: 10 - 20 mg/kg with a maximum of 300 mg/day) may be considered. Dosing of rifabutin is complex and all cases should be discussed with AfA. Monitor closely for neutropaenia, uveitis and hepatitis.

There are drug interactions between some antiretrovirals and both macrolides and rifamycins. When EFV and clarithromycin are used together, the clarithromycin levels are decreased; therefore azithromycin should be used. Initiate ART. Minumum duration of MAC treatment is 12 months and can be stopped if CD4% >15.

Maintenance treatment: see above. Co-trimoxazole.

Mycobacterium tuberculosis

Diagnosis:

History: In children with HIV, pulmonary TB 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 TB. 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: respiratory and other specimens can be sent for microscopy - acid fast bacilli on Ziehl-Neelsen or Auramine, molecular test i.e. Xpert Ultra and culture. Culture should always be performed even if Xpert is positive. For positive cultures, a line probe assay for resistance should be performed, if needed.

Management: the source/index case should be identified and treated. All contacts should be screened for TB 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 using fixed-drug combinations is recommended to avoid drug resistance. Treatment should be given every day of the week in both the intensive and the continuation phases.

HIV-positive children with TB should be treated as per standard treatment protocols. Fixed-drug combinations should be used wherever possible and doses adjusted according to weight gain.

All children with HIV should receive four 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-positive children of any age in contact with an adult who has TB should be screened. If negative, the child should receive chemoprophylaxis.

Tuberculosis in the infant younger than 3 months

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

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

Treatment: neonates born to mothers with active TB who do not have signs of disease: INH for 6 months. In HIV-negative infants the BCG can be given after completion of chemoprophylaxis. If the child has symptoms at any stage, a full screen should be performed, including relevant cultures and therapy initiated if TB confirmed.

Pneumonia

Bacterial

Diagnosis: as for community-acquired pneumonia in HIV-negative children.

Treatment: similar to therapy in children without HIV, but opportunistic and gram negative infections should be considered.

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

Pneumocystis pneumonia

PJP occurs most commonly in infants younger than one year with a peak from three to six months. However, clinicians should maintain a high index of suspicion in all HIV-exposed and positive infants, particularly if they are not on ART and/or preventative therapy. In young infants the disease is particularly seen where HIV risk was not identified antenatally and where co-trimoxazole prophylaxis was not given. Unlike adults, onset of illness is often abrupt, but may be insidious. In HIV-positive children with pneumonia, four clinical variables independently associated with PJP are: age <6 months, respiratory rate >59 breaths per minute, arterial percentage haemoglobin saturation ≤92%, and the absence of vomiting.

Diagnosis: CXR shows bilateral interstitial (“ground glass”) infiltrates. Special stains of broncho-alveolar lavage or induced sputum (following nebulisation of hypertonic saline).

Treatment: co-trimoxazole 20 mg/kg/day in two to four divided doses. Initial intravenous therapy can be changed to oral therapy once the infant is stable. Treatment is for 21 days.

Adjuvant therapy includes prednisone 2 mg/kg/day for seven days.

There are limited options available in South Africa for patients with co-trimoxazole intolerance – rechallenge should be attempted. Rechallenge or desensitise rapidly with co-trimoxazole under antihistamine cover. This option is risky if the original co-trimoxazole hypersensitivity was life-threatening.

Maintenance treatment: co-trimoxazole 6 mg/kg/day until - one to five years of age: CD4% >25 and if > five years of age: CD4 >200 if 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 IRIS.

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: see adult section.

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 IRIS. This may not be possible in young infants – ask for advice when in doubt.

Specific Issues for Adolescents

What About Adolescents?

There is increasing expertise in treating adolescents in South Africa. They are at high risk for acquiring HIV and most vertically infected children are now surviving to this age. In these children the following is key:

- Disclosure should be done age appropriately but prior to sexual debut
- Caregivers should continue to support adherence as adolescents with chronic disease are often non-compliant which can cause significant harm
- Supporting transition to adulthood is necessary
- Early recognition of mental health concerns and referral for psychosocial support
- Females should be supported in their birth control choice
- Teaching how to use male and female condoms
- HIV-negative youth should be considered for PrEP

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 CHART FOR CHILDREN 2022

Compiled by Child AND Adolescent Committee of SA HIV Clinicians Society in collaboration with the Department of Health

	Abacavir + Lamivudine (ABC + 3TC)	Abacavir (ABC)	Lamivudine (3TC)	Zidovudine (AZT)	Dolutegravir (DTG)	Dolutegravir when on Rifampicin	Lopinavir/ritonavir (LPV/r)	Abacavir + Lamivudine + Lopinavir/ ritonavir	Lopinavir/ritonavir when on rifampicin (and for 2 weeks after stopping rifampicin)		# Atazanavir (ATV) + Ritonavir (RTV)	Efavirenz (EFV)	
Target dose	As for individual medicines **ONCE daily**	8 mg/kg/dose **TWICE daily** **OR** If ≥ 10kg: 16 mg/kg/dose **ONCE daily**	4 mg/kg/dose **TWICE daily** **OR** If ≥ 10kg: 8 mg/kg/dose **ONCE daily**	180-240 mg/m2/dose **TWICE daily**	By weight band **ONCE daily**	By weight band **TWICE DAILY**	300/75 mg/m2/dose LPV/r **TWICE daily**	By weight band **TWICE daily**	LPV/r std dose + super-boosting with ritonavir (RTV) powder **TWICE daily** (≥0.75xLPV dose bd)	**OR** Double-dose LPV/r tabs ONLY if able to swallow whole LPV/r tabs **TWICE daily**	By weight band **ONCE daily**	By weight band **ONCE daily**	**Target dose**
Available formulations	Dispersible tablet FDC: ABC/3TC 120/60 mg Tablets FDC: ABC/3TC 600/300 mg ABC/3TC/DTG 600/300/50 mg	Sol. 20 mg/ml Tabs 60 mg (scored, dispersible), 300 mg (not scored)	Sol. 10 mg/ml Tabs 150 mg (scored)	Sol. 10 mg/ml, Tabs 100, 300 mg (not scored), FDC: AZT/3TC 300/150 mg	Dispersible tabs (DT) 10 mg, Film coated (FC) tabs 50 mg, FDC: TLD 300/300/50 mg OR ABC/3TC/DTG 600/300/50 mg **DT AND FC TABLETS ARE NOT BIOEQUIVALENT**	Dispersible tabs (DT) 10 mg, Film coated (FC) tabs 50 mg, FDC: TLD 300/300/50 mg OR ABC/3TC/DTG 600/300/50 mg **DT AND FC TABLETS ARE NOT BIOEQUIVALENT**	Sol. 80/20 mg/ml Adult tabs 200/50 mg, Paed tabs 100/25 mg **TABLETS MUST BE SWALLOWED WHOLE** Pellets 40/10 mg per capsule **ONLY FOR USE IF NOT TOLERATING LPV/r SOLUTION. CAPSULES ARE NOT RECOMMENDED < 6 MONTHS OF AGE**	Caps 30/15/40/10 mg **IF PATIENT IS ON RIFAMPICIN TB TREATMENT, ADD RTV POWDER** (next column)	Oral powder 100 mg/packet	Adult tabs 200/50 mg, Paed tabs 100/25 mg	ATV caps 150, 200 mg; RTV tabs 100 mg; FDC: ATV/RTV 300/100 mg **RTV TABLETS AND ATV/r FDC TABLETS MUST BE SWALLOWED WHOLE**	Caps/tabs 50, 200, 600 mg; FDC: TEE 300/200/600 mg; **TABLETS MUST BE SWALLOWED WHOLE**	**Available formulations**
Wt. (kg)	Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3kg												**Wt. (kg)**
3 - 5.9	1 x 120/60 mg tab od	3 ml bd **OR** 1 x 60 mg tab bd	3 ml bd	6 ml bd	0.5 x 10 mg DT od	0.5 x 10 mg DT bd	* 1 ml bd **OR** 2 capsules bd	2 capsules bd	LPV/r std dose (see purple column) **+** oral RTV powder 100 mg (1 packet) bd	Do not use double-dose LPV/r tabs	Not recommended	Not recom-mended	**3 - 5.9**
6 - 9.9	1.5 x 120/60 mg tabs od	4 ml bd **OR** 1.5 x 60 mg tab bd	4 ml bd	9 ml bd	1.5 x 10 mg DT od	1.5 x 10 mg DT bd	* 1.5 ml bd **OR** 3 capsules bd	3 capsules bd					**6 - 9.9**
10 - 13.9	2 x 120/60 mg tabs od	**Once daily dosing > 10 kg** 4 x 60 mg tabs od **OR** 12 ml od	**Once daily dosing > 10 kg** 12 ml od	12 ml bd **OR** 1 x 100 mg tabs bd	2 x 10 mg DT od	2 x 10 mg DT bd	2 ml bd **OR** 4 capsules bd **OR** 2 x 100/25 mg **paed tabs** am **+** 1 x 100/25 mg **paed tab** pm	4 capsules bd	LPV/r std dose (see purple column) **+** oral RTV powder 200 mg (2 packets) bd	3 x 100/25 mg **paed tabs** bd	ATV 1 x 200 mg cap od **+** RTV 1 x 100 mg tab or 100 mg oral powder (1 packet) od	1 x 200 mg cap/tab nocte	**10 - 13.9**
14 - 19.9	2.5 x 120/60 mg tabs od	5 x 60 mg tabs od **OR** 1 x 300 mg tab od	1 x 150 mg tab od	2 x 100 mg tabs am **+** 1 x 100 mg tab pm **OR** 15 ml bd	2.5 x 10 mg DT od	2.5 x 10 mg DT bd	2.5 ml bd **OR** 5 capsules bd **OR** 2 x 100/25 mg paed tabs bd **OR** 1 x 200/50 mg adult tab bd	5 capsules bd		4 x 100/25 mg **paed tabs** bd **OR** 2 x 200/50 mg **adult tabs** bd		1 x 200 mg cap/tab **+** 2 x 50 mg caps/tabs nocte	**14 - 19.9**
20 - 24.9	3 x 120/60 mg tabs od	1 x 300 mg tab **+** 1 x 60 mg tab od **OR** 6 x 60 mg tabs od	2 x 150 mg tabs od	2 x 100 mg tabs bd **OR** 20 ml bd	3 x 10 mg DT od **OR** 1 x 50 mg FC tab od	3 x 10 mg DT bd **OR** 1 x 50 mg FC tab bd	3 ml bd **OR** 6 capsules bd **OR** 2 x 100/25 mg **paed tabs** bd **OR** 1 x 200/50 mg **adult tab** bd	6 capsules bd					**20 - 24.9**
25 - 29.9	1 x 600/300 mg tab od **OR** ABC/3TC/DTG FDC (600/300/50 mg) if eligible od	2 x 300 mg tabs od		1 x 300 mg tab bd **OR** 1 x AZT/3TC 300/150 mg tab bd	1 x 50 mg FC tab od **OR** FDC: ABC/3TC/DTG if eligible od	1 x 50 mg FC tab bd **OR** FDC: ABC/3TC/ DTG if eligible od **+** 50 mg DTG FC tab 12 hours later	3.5 ml bd **OR** 7 capsules bd **OR** 3 x 100/25 mg **paed tabs** bd **OR** 1 x 200/50 mg **adult tab** bd **+** 1 x 100/25 mg **paed tab** bd	Not recommended	LPV/r std dose (see purple column) **+** oral RTV powder 300 mg (3 packets) bd	6 x 100/25 mg **paed tabs** bd **OR** 3 x 200/50 mg **adult tabs** bd	1 x ATV/RTV 300/100mg FDC od **OR** ATV 2 x 150 mg caps od **+** RTV 1 x 100 mg tab or 100 mg oral powder (1 packet) od	2 x 200 mg caps/tabs nocte	**25 - 29.9**
30 - 39.9					1 x 50 mg FC tab od **OR** FDC: TLD if eligible od **OR** FDC: ABC/3TC/DTG if eligible od	1 x 50 mg FC tab bd **OR** FDC: TLD if eligible od **+** 50 mg DTG FC tab 12 hours later **OR** FDC: ABC/3TC/ DTG if eligible od **+** 50 mg DTG FC tab 12 hours later	5 ml bd **OR** 10 capsules bd **OR** 4x100/25 mg **paed tabs** bd **OR** 2x200/50 mg **adult tabs** bd			8 x 100/25 mg **paed tabs** bd **OR** 4 x 200/50 mg **adult tabs** bd			**30 - 39.9**
≥ 40												2 x 200 mg caps/tabs nocte **OR** FDC: TEE if eligible od	**≥ 40**

* Avoid LPV/r solution in any full-term infant <14 days of age and any premature infant <42 weeks post conceptual age (corrected gestational age) or obtain expert advice.
◊ Children weighing 25-29.9 kg may also be dosed with LPV/r 200/50 mg adult tabs: 2 tabs am + 1 tab pm.
Atazanavir + ritonavir should not be used in children/adolescents on treatment with Rifampicin, obtain expert advice. No dosage adjustments are required for children receiving treatment with Efavirenz and Rifampicin.

od = once a day; nocte = at night; bd = twice a day; am = in the morning; pm = in the evening; std = standard; FDC = fixed dose combination; TLD = tenofovir/ lamivudine/dolutegravir; TEE = tenofovir/ emtricitabine/efavirenz

Weight (kg)	3 - 5.9	6 - 13.9	14 - 24.9	≥ 25
Cotrimoxazole Dose	2.5 ml od	5 ml or ½ tab	10 ml or 1 tab od	2 tabs od
Multivitamin Dose	2.5 ml od	2.5 ml od	5 ml od	10 ml od

ARV DOSING CHART FROM BIRTH TO 28 DAYS OF AGE[¥]

Birth weight ≥ 2 kg and gestational age ≥ 35 weeks[*]

	Lamivudine (3TC)		Zidovudine[**] (AZT)		Nevirapine (NVP)	
Target dose	2 mg/kg/dose TWICE daily (BD)		4 mg/kg/dose TWICE daily (BD)		6 mg/kg/dose TWICE daily (BD)	
Available formulation	10 mg/ml		10 mg/ml		10 mg/ml	
Weight (kg)	Dose in ml	Dose in mg	Dose in ml	Dose in mg	Dose in ml	Dose in mg
≥2 - <3	0.5 ml BD	5 mg BD	1 ml BD	10 mg BD	1.5 ml BD	15 mg BD
≥3 -<4	0.8 ml BD	8 mg BD	1.5 ml BD	15 mg BD	2 ml BD	20 mg BD
≥4 - <5	1 ml BD	10 mg BD	2 ml BD	20 mg BD	3 ml BD	30 mg BD

- Dosing is based on the birth weight of the child. It is not necessary to change the dose before 28 days of age if for example if the weight decreases in the first week or two of life.
- Caregivers administering ARV medication to the child must be supplied with a syringe (2 ml or 5 ml) for each of the 3 ARVs and shown how to prepare and administer the prescribed dose. If required, bottles and syringes should be colour coded with stickers and a sticker of the relevant colour used to mark the correct dose on the syringe.

[¥]Refer to the protocol for initiation of ART in HIV-infected neonates in the HIV guidelines which includes guidance on ARV management after 28 days of age
*Consult with a clinician experienced in paediatric ARV prescribing or the National HIV & TB Health Care Worker Hotline for neonates with birth weight < 2 kg or gestational age < 35 weeks
**If infant is found to have significant anaemia or neutropenia prior to or during treatment with AZT, discuss with a clinician experienced in paediatric ARV prescribing or any of the helplines listed below about switching to ABC

PRACTICAL ADVICE ON ADMINISTRATION OF ARV DRUGS

ARV Drug	Formulations (as used in dosing chart)	Can tablets/capsules be split/crushed/opened if unable to swallow?	Comment
Abacavir (ABC)	Oral solution: 20 mg/ml Tablets: 60 mg, 300 mg FDC tablets: ABC/3TC 120/60 mg; ABC/3TC 600/300 mg; ABC/3TC/DTG 600/300/50 mg FDC capsules: ABC/3TC/LPV/r 30/15/40/10 mg	Tablets: **YES** FDC 120/60 mg tablet is a dispersible tablet. May be split/crushed. FDC capsules should be opened and contents added to a small amount of food or dispersed in a liquid.	Hypersensitivity reaction (fever, rash, GIT & respiratory symptoms) may occur during first 6 weeks of therapy, very uncommon in black African patients. Symptoms typically worsen in the hours immediately after the dose and after each subsequent dose. Caregivers or patients should discuss symptoms early with the clinician rather than stopping therapy. Stop ABC permanently if hypersensitivity reaction has occurred.
Lamivudine (3TC)	Oral solution: 10 mg/ml Tablets: 150 mg; FDC tablets: ABC/3TC 120/60 mg; ABC/3TC 600/300 mg, TLD 300/300/50 mg ABC/3TC/DTG 600/300/50 mg FDC capsules: ABC/3TC/LPV/r 30/15/40/10 mg		Well tolerated, adverse-effects uncommon. Pure red cell aplasia causing anaemia can occur but is very rare.
Zidovudine (AZT)	Oral solution: 10 mg/ml Tablets: 100 mg, 300 mg Capsules: 100 mg FDC tablet: AZT/3TC 300/150 mg	Tablets & FDC: **YES** Capsules: Can be opened and added to a small amount of soft food/liquid and ingest immediately.	Avoid or use with caution in neonates or children with anaemia (Hb <8 g/dl) due to potential to cause bone marrow suppression.
Tenofovir (TDF)	Tablets: 300 mg FDC tablets: TDF/FTC 300/200 mg, TEE 300/200/600 mg, TLD 300/300/50 mg	Tablet and FDC tablets: **YES**	TDF may be prescribed for adolescents ≥ 10 years of age AND ≥ 30 kg body weight after ensuring adequate renal function by checking eGFR/creatinine using the appropriate formula (refer to HIV guidelines). TDF is usually prescribed as part of an FDC tablet: TDF/FTC, TDF/FTC/EFV or TDF/3TC/DTG. To assess for TDF-induced nephrotoxicity, do creatinine and eGFR at months 3, 6 and 12 and thereafter repeat every 12 months.
Lopinavir/ ritonavir (LPV/r)	Oral solution: 80/20 mg/ml Capsules: Pellets 40/10 mg per capsule Tablets: 200/50 mg, 100/25 mg FDC capsules: ABC/3TC/LPV/r 30/15/40/10 mg	Tablets: **NO** **Must be swallowed whole and not divided, crushed or chewed.** Capsules: Can be opened and added to a small amount of soft food/liquid and ingest immediately.	Oral solution should be refrigerated/stored at room temperature (if <25°C) for up to 6 weeks. Preferably administer oral solution with food as increases absorption. Strategies to improve tolerance and palatability of oral solution: coat mouth with peanut butter, dull taste buds with ice, follow dose with sweet foods. Many drug-drug interactions.[#] LPV/r 40/10 mg **capsules should be opened**, and contents (pellets) of each capsule poured onto a spoon of soft food and fed to child. Don't try and dissolve pellets in food or water as they will develop a bad taste. ABC/3TC/LPV/r **capsules should be opened** and contents (granules) of each capsule poured onto a spoon of soft food or dissolved in water and fed to child. **Capsules should never be swallowed whole**. Discard capsule casing after contents have been emptied from it.
Ritonavir (RTV)	Oral powder: 100 mg/packet Tablets: 100 mg		Each 100 mg packet of RTV powder should be mixed with a small amount of water or soft food and immediately ingested. Many drug-drug interactions.[#]
Atazanavir (ATV)	Capsules: 150 mg, 200 mg FDC tablets: ATV/RTV 300/100 mg	Capsules: Can be opened and added to a small amount of soft/food/liquid and ingested immediately. FDC tablets: **NO** **Must be swallowed whole and not divided, crushed or chewed.**	ATV is used in combination with RTV. May cause unconjugated hyperbilirubinaemia resulting in jaundice but this does not indicate hepatic toxicity and not a reason to discontinue the drug unless it is worrying the patient. Consider drug-drug interactions.[#]
Dolutegravir (DTG)	Dispersible tablet (DT): 10 mg Film coated (FC) tablets: 50 mg FDC tablets: TLD 300/300/50 mg FDC tablets: ABC/3TC/DTG 600/300/50 mg	Dispersible tablets: **YES** Film coated tablets (including FDCs): **YES**	Iron supplements decrease DTG concentrations if taken together on an empty stomach. To prevent this, DTG and iron supplements can be taken at the same time if taken with food. May be helpful to administer as a morning dose rather than an evening dose if insomnia occurs with evening dosing. May raise creatinine levels by up to 15% without affecting renal function. Consider drug-drug interactions. [#] DTG DT and DTG FC tablets are not bioequivalent; 30 mg of DTG DT corresponds to 50 mg DTG FC tablets. DTG 50 mg FC tablets are preferred for children who have reached 20 kg (unless they cannot swallow tablets).
Efavirenz (EFV)	Capsules: 50 mg, 200 mg Tablets: 50 mg, 200 mg, 600 mg FDC tablets: TEE 300/200/600 mg	Tablets: **NO** **Must be swallowed whole and not divided, crushed or chewed.** Capsules: **YES.** Open and add to small amount of soft food and ingest immediately.	Best given at bedtime to reduce CNS side-effects, especially during first 2 weeks. Consider drug-drug interactions.[#]

FDC = fixed dose combination; eGFR = estimated glomerular filtration rate; GIT = gastrointestinal tract; TEE = Tenofovir/Emtricitabine/Efavirenz; TLD = Tenofovir/Lamivudine/Dolutegravir; #EML-Antiretroviral interactions table (http://www.mic.uct.ac.za) OR www.hiv-*druginteractions.org/checker* OR the Liverpool HIV iChart application for smart phones, or any of the helplines: **National HIV and TB Health Care Worker Hotline:** 0800 212 506 or **Right to Care Paediatric and Adolescent HIV Helpline:** 082 352 6642 and **KZN Paediatric Hotline:** 0800 006 603

NEED HELP?
Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline at 0800 212 506 / 021 406 6782
Alternatively "whatsapp" or send an SMS or "Please Call Me" to 071 840 1572

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE 0800 212 506

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

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General information

Contact information	
Medicines Information Centre	Toll-free National HIV & TB Healthcare Worker Hotline Tel: 021 406 6829 or 0800 212 506 Email: pha-mic@uct.ac.za
Clicks Direct Medicines	Tel: 0861 444 405
Pharmacy Direct	Tel: 0860 027 800 Email: care@pharmacydirect.co.za
Medipost	Tel: 012 426 4000 • Fax: 0866 488 446
Ampath	Tel: 012 678 0800
Neuberg Global	Tel: 031 904 0500
Lancet	Tel: 011 358 0800
Pathcare	Tel: 0860 410 3392
Vermaak & Partners	Tel: 012 404 2300

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