Chapter 27

MANAGEMENT OF HIV INFECTION IN ADULTS

THE LABORATORY DIAGNOSIS OF HIV

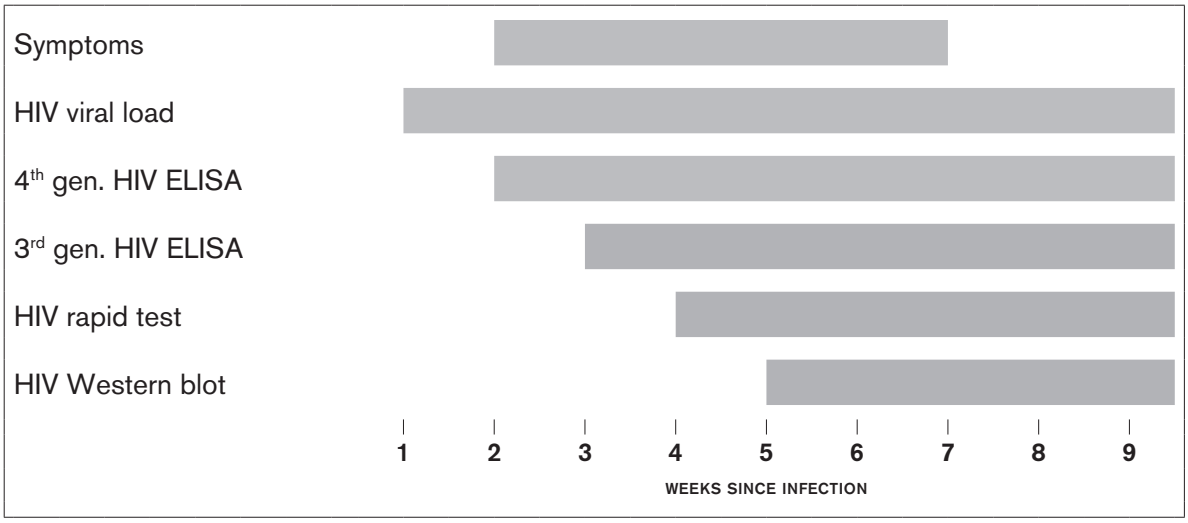
HIV LABORATORY TESTS AVAILABLE

SEROLOGY	DETECTS	INTENDED USE	PITFALLS
4th generation HIV 1/2 ELISA	HIV p24 antigen and HIV IgM and IgG antibodies	Screening test for HIV infection (highly sensitive)	False positive results hence need for confirmation
3rd generation HIV 1/2 ELISA	HIV IgM and IgG antibodies	Screening test for HIV infection	False positive results Longer window period than 4th generation tests
Rapid HIV 1/2 test	HIV IgM and/or IgG antibodies	Screening test for HIV infection	False positive results Longer window period than laboratory ELISA testing
HIV-1 Western blot	HIV IgG antibodies	Confirmatory test following a positive ELISA result (highly specific) To resolve indeterminate ELISA results	Long window period ~ 5 weeks Cross-reactivity with HIV-2 occurs

MOLECULAR	DETECTS	INTENDED USE	PITFALLS
HIV-1 viral load	HIV-1 RNA	HIV diagnosis • Confirmatory test following a positive ELISA result • To resolve indeterminate ELISA results • Diagnosis of acute HIV infection HIV monitoring • Baseline HIV-1 viral load prior to antiretroviral treatment • Monitoring of patients on antiretroviral treatment	True positive HIV ELISA with undetectable HIV-1 viral load in adults may be seen in: • HIV infection on ART • HIV elite controllers • HIV-2 infection
HIV-1 PCR	HIV-1 DNA and RNA	HIV diagnosis in exposed infants < 18 months of age	False negative results if performed too soon following exposure
HIV-2 PCR	HIV-2 DNA	HIV-2 diagnosis in children or adults	

WINDOW PERIODS OF DIFFERENT HIV LABORATORY TESTS USED FOR HIV DIAGNOSIS

TEST REACTIVITY DURING EARLY STAGES OF HIV INFECTION



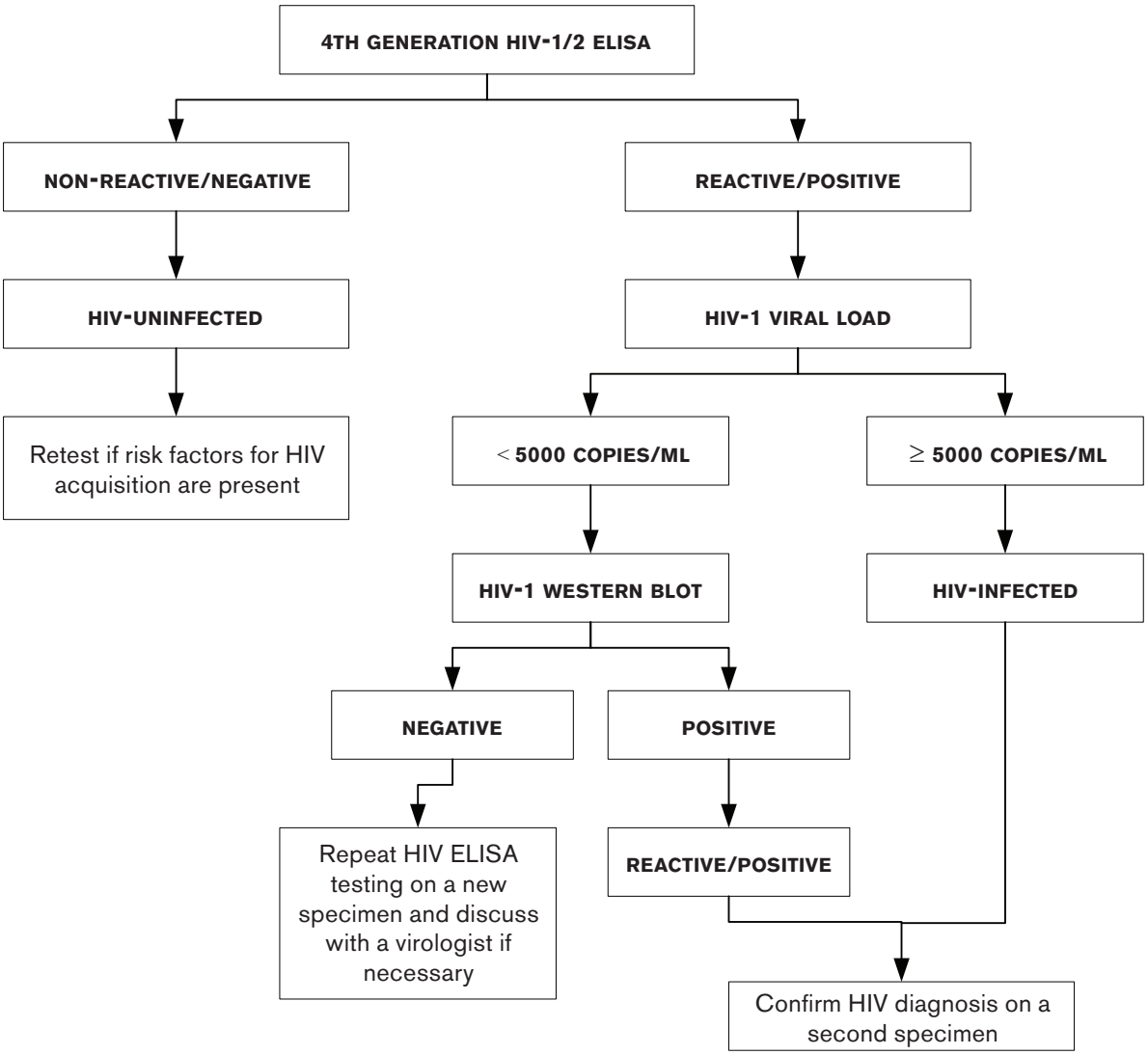
DIAGNOSTIC ALGORITHMS

There are a number of HIV diagnostic algorithms in use today. The choice of algorithm used depends on a number of factors including cost, seroprevalence of HIV in the population being tested, and access to specialised laboratory tests. Algorithms using only ELISA or rapid tests for HIV antibodies run the risk of false positive results.

Ampath laboratories use an algorithm starting with a screening fourth generation ELISA assay followed by an HIV-1 viral load assay to confirm reactive screening ELISA results. A viral load of > 5000 copies/mL* is regarded as confirmed HIV infection and where the viral load is < 5000 copies/mL or undetectable, further serological testing in the form of Western blot testing is performed to confirm seroreactivity. The cause of the low or undetectable viral load can subsequently be explored further should the Western blot be positive (elite or viremic controller, on antiretroviral therapy or HIV-2 infection). A positive HIV result on a single blood specimen should be confirmed by means of an ELISA on a follow-up specimen to guard against the unlikely risk of false positive results due to mislabelled specimens or laboratory error.

* M53-A Vol. 31(13). Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infections: Approved Guideline. Clinical and Laboratory Standards Institute.

FLOW DIAGRAM OF AMPATH'S HIV TESTING ALGORITHM



ANTIRETROVIRAL THERAPY

INTRODUCTION

Rather than acting as a detailed guideline, this chapter aims to provide general information with recommendations that will enable the clinician to understand the principles of antiretroviral therapy (ART) in adults.

For further reading we recommend the following detailed guidelines:

- Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults, 2014. Available at: www.sahivsoc.org.
- SA National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV and the management of HIV in children, adolescents and adults. 2015. Available at: www.sahivsoc.org.
- For up-to-date information on drug-drug interactions, please consult the University of Liverpool Drug Interactions Charts, available at: www.hiv-druginteractions.org.

GOALS OF ANTIRETROVIRAL THERAPY

The primary goals of antiretroviral therapy (ART) are to increase disease-free survival and quality of life through:

- Long-term suppression of viral replication (HIV viral load)
- Improving or restoring immunological function as indicated by the CD4 cell count and clinical response.
- Preventing HIV transmission

To achieve these goals, well-tolerated, appropriate regimens with excellent drug adherence is essential. Long-term cohorts have shown that if patients are started on ART early enough and adhere to treatment, they can expect to have a near-normal life expectancy.

INDICATIONS FOR ANTIRETROVIRAL THERAPY

SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

- All patients diagnosed with HIV infection should be advised that lifelong ART is indicated regardless of their clinical stage or CD4 count (TEMPRANO and START clinical trials).
- ART should be given to the HIV-infected partner in a serodiscordant relationship to prevent HIV transmission to the uninfected partner regardless of their clinical stage or CD4 count.
- The following patients should be given priority and start ART as soon as possible:
  - Pregnant women
  - Patients with CD4 counts < 350 cells/μL
- WHO clinical stage three and four

WHEN TO START ART IN PATIENTS WITH OPPORTUNISTIC INFECTIONS

- ART should be started as soon as possible in patients with other opportunistic infections, preferably within the first two weeks.
- Tuberculosis (TB)
  - CD4 count ≤ 50 cells/μL: ART should be started within two weeks of starting TB treatment.
  - CD4 count > 50 cells/μL: ART should be started within eight weeks of starting TB treatment.
  - TB meningitis: The optimal timing is not clear, but ART should be started four to eight weeks following the start of TB treatment.

- Cryptococcal meningitis (CM)
  - The optimal timing is not clear and early treatment may be associated with increased mortality.
  - Current guidelines recommend starting ART around four to six weeks after antifungal treatment (amphotericin B-based) has been started.

SPECIFIC PATIENT GROUPS

Acute HIV Infection: Patients diagnosed with HIV during an acute infection should be started on ART. Treatment should be expedited as there is evidence that early treatment reduces the size of the HIV reservoir which may benefit the patient with respect to potential future therapy targeting the HIV reservoir. Once ART is started, treatment should be continued lifelong.

Pregnant and breastfeeding women: All pregnant and breastfeeding women should be started on ART without delay regardless of CD4 count to prevent transmission to their child. ART should be continued lifelong and not stopped after the pregnancy and weaning.

Elite controllers: These are patients who maintain an undetectable HIV viral load in the absence of ART due to effective immune control of viral replication. It is recommended that these patients start ART despite the fact they typically have CD4 counts in the normal range. Although there is no evidence from randomised controlled trials, elite controllers still have chronic immune activation and inflammation that drives non-infectious morbidities.

BASELINE EVALUATION OF PATIENTS

There are certain laboratory tests that should be performed with the initial evaluation of an HIV-infected patient. If need be, the HIV diagnosis should be confirmed on a new specimen and submitted to the laboratory for an HIV ELISA test. This is particularly important if the diagnosis has been made on the basis of HIV rapid tests. In addition to the clinical stage of HIV infection, the pre-therapy evaluation should address comorbidities, metabolic abnormalities, anaemia, and coinfection with hepatitis, tuberculosis and sexually transmitted diseases.

TESTS RECOMMENDED PRIOR TO COMMENCING ART INCLUDE

- HIV viral load (baseline)
- CD4 cell count (baseline)
- FBC
- Serum creatinine and calculated creatinine clearance
- ALT
- Fasting glucose
- Serum lipid profile
- Hepatitis B surface antigen, hepatitis B surface antibody and hepatitis B core antibody (immunise if not immune and not infected)
- Hepatitis C antibodies
- Syphilis serology
- Cervical PAP smear in women (and annually thereafter)
- Urine analysis for protein
- Cryptococcal antigen test on serum if CD4 count < 100 cells/μL

PRE-TREATMENT GENOTYPIC RESISTANCE TESTING

The current SA HIV Clinicians Society treatment guidelines in adults (unlike the IAS-USA and DHHS guidelines in USA) do not recommend that pre-treatment genotypic resistance testing should be routinely used to identify potential agents for all drug-naïve patients. This is an expensive test which we currently regard as a test to be used in patients who fail antiretroviral therapy in spite of adequate adherence. In the USA, transmitted drug resistance prevalence is high at six to 20% and under these circumstances baseline genotypic resistance testing is desirable. In South Africa, the transmitted resistance level is still low at < 5% and baseline resistance testing is not necessary at this stage.

Certain pre-therapy tests may indicate that a particular agent should not be considered at all. For instance, a high CD4-cell count (> 250 cells/μL in women and > 400 cells/μL in men) indicates that nevirapine should be used with great caution and only if other options are not appropriate as the risk of a hypersensitivity reaction to nevirapine is greatest in those with high CD4-cell counts prior to therapy.

ADHERENCE

Successful therapy depends on a high level of adherence to the treatment regimen and hence counselling and patient readiness to start therapy is paramount to ART success. Disclosure of HIV status to a partner or close family member is important for adherence and patient support. There are some for whom therapy might better be temporarily delayed depending on the urgency of starting ART. Prolonged delays in commencing ART must be avoided though.

- Depression is a condition that interferes with adherence to ART. Therefore, patients with significant depression might benefit from antidepressant therapy before starting ART.
- Alcohol or recreational drug abuse may similarly interfere with treatment adherence, so patients who are experiencing these problems should be encouraged to enter a treatment programme before they begin ART.
- There are other medical conditions which may necessitate a delay of ART, such as concomitant use of medications with significant drug interactions or overlapping toxicities with antiretroviral agents, e.g. antituberculous agents.

CARDIOVASCULAR RISK

Untreated HIV adversely affects cardiovascular disease risk including myocardial infarction, stroke and death. Cardiovascular risk should therefore be assessed when considering the initiation of ART. All ritonavir-boosted PIs (particularly lopinavir/ritonavir) elevate lipids, particularly total cholesterol and triglycerides, and to a lesser extent LDL-cholesterol and HDL-cholesterol. There is also an association between abacavir and an increased risk of myocardial infarction, although this was not confirmed in a recent meta-analysis. Nonetheless, abacavir should be used with caution if there is underlying ischaemic heart disease. Hence, if any cardiovascular risk factors exist, e.g. hypertension, pre-existing hyperlipidaemia, diabetes etc., then we recommend a NNRTI over a PI, and the use of an NRTI combination that does not include abacavir. Atazanavir affects lipid profiles less than the other PIs and may be useful in these patients, and raltegravir (an integrase inhibitor) can also be considered. If a statin is required to manage hypercholesterolaemia in a patient on a PI containing regimen, then fluvastatin or pravastatin are preferred as they can be used without dose adjustment.

ANTIRETROVIRAL DRUGS

The major classes, dosage and side effects of antiretroviral drugs available in South Africa are listed below:

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

GENERIC NAME	TRADE NAME	USUAL DOSE	SEVERE, POTENTIALLY LIFE THREATENING SIDE EFFECTS	OTHER SIDE EFFECTS
Tenofovir (TDF)	Viread	300 mg daily	Nephrotoxicity, reduced bone mineral density, proximal renal tubular injury	GIT upset
Lamivudine (3TC)	3TC	150 mg 12 hourly OR 300 mg daily	Anaemia (pure red cell aplasia), hyperlactataemia (both rare)	Headaches, GIT upset
Emtricitabine (FTC)	Emtriva	200 mg daily	Hyperlactataemia (rare)	Headaches, GIT upset, rash
Abacavir (ABC)	Ziagen	300 mg 12 hourly OR 600 mg daily	Hypersensitivity reaction (HLA-B*5701 predicts increased risk in Caucasians)	Headache, GIT upset
Zidovudine (AZT)	Retrovir	300 mg 12 hourly	Anaemia, neutropaenia, hyperlactataemia (rare)	Headache, GIT upset, myopathy
Stavudine (D4T)	Zerit	30 mg 12 hourly	Hyperlactataemia (high risk), pancreatitis, peripheral neuropathy, lipoatrophy	Headache, GIT upset
Didanosine (ddI)	Videx	400 mg daily OR 250 mg daily if < 60 kg Take on empty stomach or use enteric formulation	Hyperlactataemia (high risk), pancreatitis, peripheral neuropathy	Headache, GIT upset, fever

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

GENERIC NAME	TRADE NAME	USUAL DOSE	SEVERE, POTENTIALLY LIFE THREATENING SIDE EFFECTS	OTHER SIDE EFFECTS
Efavirenz (EFV)	Stocrin	600 mg at night OR 400 mg if < 40 kg	Hepatitis, rash, neuropsychiatric symptoms	CNS side effects in 50% of patients (vivid dreams, dizziness, confusion)
Nevirapine (NVP)	Viramune	200 mg daily for 2 weeks then 200 mg 12 hourly.	Hepatitis, severe skin reactions	Rash

Rx	Etravirine (ETV)	Intelence	200 mg 12 hourly	Severe skin reactions, hepatitis (both rare)	Rash, nausea
	Rilpivirine (RPV)	Edurant	25 mg daily with food	Hepatitis, neuropsychiatric symptoms (rare)	Headache, rash, insomnia

Rx **PROTEASE INHIBITORS (PIs)**

GENERIC NAME	TRADE NAME	USUAL DOSE	SEVERE, POTENTIALLY LIFE THREATENING SIDE EFFECTS	OTHER SIDE EFFECTS
Atazanavir (ATV)	Reyataz	400 mg daily (ART-naive only) OR 300 mg with ritonavir 100 mg daily With TDF 300/100 mg daily With EFV 400/100 mg daily	Severe skin eruptions, hepatitis (rare)	Unconjugated hyperbilirubinaemia, dyslipidaemia, renal stones, GIT upset, headache
Lopinavir/ ritonavir (LPV/r)	Aluvia	400/100 12 hourly OR 800/200 daily (if PI- naive)	Hepatitis, severe skin eruptions (rare)	Dyslipidaemia, GIT upset
Darunavir (DRV)	Prezista	600 mg with 100 mg ritonavir 12 hourly OR 800/100 mg daily (if PI-naive)	Hepatitis, severe skin eruptions (rare). Use with caution in those with a sulpha allergy	GIT upset, headache, rash, dyslipidaemia
Saquinavir (SQV)	Invirase	1000 mg with 100 mg ritonavir 12 hourly OR 1600 mg with 100 mg ritonavir daily (if PI-naive). Take with a fatty meal	Heart block, hepatitis, severe skin eruptions (rare)	GIT upset, headache, dyslipidaemia
Indinavir (IDV)	Crixivan	800 mg with 100 mg ritonavir 12 hourly Maintain high fluid intake	Hepatitis (rare)	Renal stones, hyperbilirubinaemia,GIT upset, headache, dyslipidaemia

INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)

GENERIC NAME	TRADE NAME	USUAL DOSE	SEVERE, POTENTIALLY LIFE THREATENING SIDE EFFECTS	OTHER SIDE EFFECTS
Raltegravir (RAL)	Isentress	400 mg 12 hourly	Hepatitis, severe skin eruptions, rhabdomyolysis (rare)	GIT upset, headache
Dolutegravir (DTG)	Tivicay	50 mg daily	Hypersensitivity reactions, hepatitis (rare)	GIT upset, insomnia, headache

CCR5 CO-RECEPTOR ANTAGONIST

GENERIC NAME	TRADE NAME	USUAL DOSE	SEVERE, POTENTIALLY LIFE THREATENING SIDE EFFECTS	OTHER SIDE EFFECTS
Maraviroc (MVC)	Celsentri	300 mg 12 hourly. Dose adjust with depending on co-administered drugs	Hepatotoxicity, myocardial infarction, severe skin eruptions (rare)	GIT upset, insomnia, headache, cough, myalgia

ART REGIMENS FOR TREATMENT NAÏVE PATIENTS

For initial ART at least three drugs are used in combination to provide durable HIV viral load suppression and prevent the emergence of drug resistance.

Important aspects of any regimen to consider include:

- Pill number: fixed dose combinations should be used where available for ease of use and improved patient compliance
- Dosing frequency: once daily dosing is preferred for better patient compliance
- Food requirements
- Known adverse effects
- Drug interactions
- Storage conditions for the prescribed regimen

RECOMMENDED FIRST-LINE REGIMENS

Two NRTIs combined with a NNRTI	Any of the following two NRTIs can be combined with an NNRTI: • Tenofovir **AND** emtricitabine • Tenofovir **AND** lamivudine • Abacavir **AND** lamivudine Efavirenz is the preferred NNRTI with rilpivirine and nevirapine as alternative initial NNRTIs. The fixed dose combination of tenofovir **AND** emtricitabine **AND** efavirenz is the preferred initial regimen and allows once daily dosing.
OR	

Rx	Two NRTIs combined with an integrase inhibitor	Use only if there is intolerance or contraindications to NNRTIs in order to harmonise with the public sector
	Not recommended	PIs are not recommended for first line therapy and should be reserved for subsequent regimens.

NOTE

DRUG	SIDE EFFECTS OR CONTRAINDICATIONS	ACTION
Tenofovir	Contraindicated if CrCl < 50 mL/min (nephrotoxic)	Rather use abacavir
Abacavir	Ischemic heart disease High baseline viral load of > 100 000 copies/mL associated with virological failure	Use an alternate NRTI
AZT	Anaemia and neutropaenia	Use only if tenofovir and abacavir are contraindicated
Stavudine	High risk of severe side effects	Should not be used
Efavirenz	Neuropsychiatric side effects thus contraindicated in night shift workers, drivers of heavy duty and industrial vehicles	Use an alternate NNRTI or an integrase inhibitor
Nevirapine	Contraindicated in women with a baseline CD4 > 250 cells/μL and men with a baseline CD4 count > 400 cells/μL due to risk of hepatotoxicity and rash	Use an alternate NNRTI or an integrase inhibitor
Rilpivirine	High baseline viral load of > 100 000 copies/mL associated with virological failure	Use an alternate NNRTI or an integrase inhibitor

MONITORING PATIENTS ON ANTIRETROVIRAL THERAPY

Patients taking antiretroviral therapy require close monitoring of the following:

CLINICAL STATUS AND TREATMENT ADHERENCE

These should be initially assessed four to eight weeks after starting therapy, and then every three to six months once stable.

EFFICACY OF ANTIRETROVIRAL THERAPY

A baseline (pre-ART) HIV viral load should be performed and then repeated three months after starting therapy. At three months the HIV viral load should have dropped by at least two $\log_{10}$ from baseline. A detectable viral load may indicate adherence problems and should trigger additional adherence counselling. The HIV viral load should be repeated at six months and then six monthly thereafter in patients with undetectable viral loads.

The CD4 count should be checked six months after initiating ART. This rises rapidly within four weeks of starting ART and then more gradually. The average rise seen is ~150 cells/μL in the first year and about ~80 cells/μL per year thereafter, but this is extremely variable. In some patients (about 10–20%), the CD4 count fails to rise despite a suppressed viral load – there is no point in changing the ART regimen in such patients. This discordant response is more frequently seen in patients who start ART with low CD4 counts (< 200 cells/μL). There is no 'switch' data that

supports a change from one regimen to another in these patients, although the combination of tenofovir and didanosine should be avoided and there may be potential benefit of a non-AZT containing regimen. Once the CD4 count has increased beyond 200 cells/μL, there is little point in monitoring it further unless there is virological failure or clinical evidence of deterioration as cotrimoxazole prophylaxis may be required if the CD4 count drops below 200 cells/μL.

TOXICITY OF ANTIRETROVIRAL THERAPY

Full blood count: The FBC is useful as anaemia, leucopaenia and thrombocytopaenia are common due to HIV per se or due to medications. This should be performed at baseline, three months and six months. In patients on AZT perform a baseline FBC, then monthly for three months, then at six months. Thereafter, only as clinically indicated. Other drugs which are also commonly used in people with HIV such as cotrimoxazole can also cause a neutropenia (usually at therapeutic doses rather than prophylactic). Exercise caution when using combinations of drugs that can cause bone marrow toxicity and monitor neutrophil counts when doing so.

Liver function tests: All ARV drugs can cause hepatotoxicity, but this is more frequently encountered in patients receiving nevirapine. ALT should be performed at baseline, and then at two, four, eight and twelve weeks after initiation of NVP. While ALT is the most sensitive indicator of liver injury, the full LFT should be requested if hepatitis develops. Any elevation in ALT > 5 x ULN is significant and the offending drug should be stopped. In other patients an ALT should be performed if there is clinical suspicion of liver dysfunction. Nevirapine should be avoided in patients with a baseline ALT > 100 U/L. If a hepatitis develops with rash, fever or any other systemic involvement, the drug should be discontinued and challenging the patient again with that drug should not be attempted. This is particularly true of NVP, ABC and cotrimoxazole.

There have been case reports of efavirenz drug-induced liver injury in the literature. There is however insufficient evidence to justify routine liver function monitoring based on these findings. There is also insufficient evidence to indicate that EFV should not be used at a high CD4 count or in cases of hepatitis B infection without cirrhosis. Patients on EFV treatment should be monitored clinically for new upper gastrointestinal symptoms, malaise/fatigue or jaundice and an LFT requested if indicated.

Renal function tests: A serum creatinine and urinalysis for proteinuria should be performed at baseline. The dose of NRTIs needs to be adjusted for patients with renal failure. In patients where tenofovir is being considered, a baseline serum creatinine and eGFR or CrCl must be determined and tenofovir not used if this is < 50 mL/min. Whilst on tenofovir, serum creatinine should be assessed at three and six months and six monthly thereafter. Combinations of tenofovir with other nephrotoxic drugs should be avoided.

Fasting cholesterol, triglycerides and glucose: This should be performed at baseline, three months and thereafter every twelve months for patients receiving a PI or NNRTI. Indications for statin therapy in HIV-infected patients is the same for HIV-uninfected patients and according to the Framingham heart disease score. PIs can significantly raise statin drug levels with the exception of fluvastatin and pravastatin which are the preferred statins for patients receiving PIs. All ARV drugs can cause visceral fat gain which is associated with insulin resistance. Serial glucose testing should be performed in all patients on ARV therapy.

Cardiovascular risk factors – lifestyle factors (smoking, diet, and exercise) should be monitored and blood pressure and weight checked regularly.

RECOMMENDED ROUTINE LABORATORY MONITORING

LABORATORY TESTS	BASELINE	MONTHS						THEN
		2 WKS	1	2	3	6	12	
HIV viral load	X				X	X	X	6 monthly
CD4 cell count	X					X		If < 200: 6 monthly If > 200: if indicated
FBC (not on AZT)	X				X	X		If indicated
FBC (on AZT)	X		X	X	X	X		If indicated
Creatinine (on TDF)	X				X	X	X	6 monthly
Creatinine (not on TDF)	X							
Creatinine clearance (on TDF)	X							
Urine protein	X							
ALT (on NVP)	X	X	X	X	X			
Glucose (fasting)	X				X		X	Yearly
Lipid profile (cholesterol/TG)								
Pap smear	X						X	Yearly

ART USE IN SPECIAL PATIENT POPULATIONS

PATIENTS WITH ACTIVE TUBERCULOSIS

All patients with active TB should be started on ART. For the timing of ART, refer to the section on indications for ART at the beginning of this chapter. Rifampicin is a critical component of a TB treatment regimen, however as rifampicin is a potent inducer of cytochrome P450, it reduces the levels of many ARVs and dose adjustment or alternative ARV drug regimens may be needed for patients on a rifampicin-containing TB drug regimen.

Efavirenz is the preferred NNRTI to use with rifampicin and no dose adjustment is required. The plasma concentrations of all boosted PIs are reduced to sub-therapeutic levels when co-administered with rifampicin. Dose adjustment of PIs is required which carries a risk of more drug side effects and toxicity. The integrase inhibitor, raltegravir is an option to administer with rifampicin and no dose adjustment is required. It is however, not as robust as a PI in a second-line ART regimen.

ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR USE*

CLASS	ARV DRUG	INTERACTION	RECOMMENDATIONS FOR USE WITH RIFAMPICIN
NRTI	All NRTIs	No significant interactions	No dose adjustment needed
NNRTI	Efavirenz	Mild reduction in efavirenz level	No dose adjustment needed (use 600 mg nocte)
	Nevirapine	Moderate reduction in nevirapine levels. Increased risk of virological failure	Use standard dose and start at 200 mg 12 hourly (omit lead-in dosing)
	Etravirine	Significant reductions in levels	Do not use with rifampicin
	Rilpivirine	Significant reductions in levels	Do not use with rifampicin
PI	Lopinavir/ritonavir	Lopinavir levels are decreased	Double the dose to 800/200 mg 12 hourly. Alternatively add 300 mg ritonavir 12 hourly to standard lopinavir/ritonavir dose
	All other PIs	Levels are significantly decreased	Do not co-administer
InSTI	Raltegravir	Levels are reduced but standard dosing results in virological suppression	No dose adjustment needed (use 400 mg 12 hourly)

*Adapted from the *Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults*. 2014. Available at: www.sahivsoc.org.

An alternative approach is to replace rifampicin with rifabutin which is a much weaker enzyme inducer than rifampicin. Rifabutin is however metabolised by a cytochrome P450 enzyme (CYP3A) which is inhibited by ritonavir boosted protease inhibitors. The dose of rifabutin must be reduced from 300 mg daily to 150 mg daily when co- administered with a protease inhibitor. Careful monitoring for rifabutin toxicity (uveitis, neutropaenia and hepatitis) is required for patients receiving rifabutin and a protease inhibitor.

PATIENTS WITH HEPATITIS B

Hepatitis B (HBV) coinfection is common in HIV-infected patients in South Africa. All patients with HIV must be screened for HBV infection by means of HBsAg ELISA testing. A baseline HBV viral load and liver function tests must also be performed in chronically infected patients so that treatment responses can be monitored.

All HIV-infected patients with chronic hepatitis B must be started on ART. As tenofovir, lamivudine and emtricitabine have activity against both HIV and HBV, a backbone of tenofovir plus emtricitabine or tenofovir plus lamivudine must be used as part of a fully suppressive ART regimen. Lamivudine or emtricitabine must not be the only HBV active agent as resistance develops quickly and they must always be combined with other anti-HBV drugs such as tenofovir. Nevirapine must not be used in patients with chronic HBV.

Should the patient need to be switched to a second-line ART regimen then the combination of tenofovir/emtricitabine or tenofovir/lamivudine must be continued to suppress HBV replication. Discontinuing agents with anti-HBV activity may result in serious hepatocellular damage from HBV reactivation.

In patients with renal impairment and chronic HBV, tenofovir may be used with the dosing adjusted according to the creatinine clearance. If the renal dysfunction is severe or deteriorates with tenofovir, then entecavir may be used in addition to a fully suppressive ART regimen. Lamivudine monotherapy or pegylated interferon alfa monotherapy may also be considered in these patients.

PREGNANT WOMEN

All HIV-infected pregnant women should be started on ART, irrespective of CD4 count, viral load or clinical stage. ART is required for their own health, to reduce the risk of transmission to uninfected partners and to prevent transmission to their foetus and newborn.

ART should be started within two weeks of their first visit. When selecting an ART regimen, clinicians should consider the safety, efficacy and pharmacokinetic data during pregnancy for each agent. If a woman presents in the third trimester then ART initiation should be accelerated. Current SA and WHO guidelines recommend that efavirenz can be used in pregnancy and in women who intend to fall pregnant. Efavirenz is a category D drug and has been shown to be teratogenic in primates however there is no evidence to show teratogenicity in humans. The risk should be discussed with all pregnant patients and women who are planning on falling pregnant as an ART regimen excluding efavirenz may be preferred. For women on a suppressive regimen containing efavirenz who are pregnant and present in their first trimester, it is recommended that they continue with the efavirenz containing regimen thought the pregnancy.

HIV viral load testing should be performed at the initial visit, four weeks after initiating ART, and then monthly until the viral load is undetectable. After that the HIV viral load should be performed every three months during pregnancy, provided it remains undetectable. An HIV viral load also should be performed again at approximately 34–36 weeks gestation to inform decisions about the mode of delivery.

After delivery, it is recommended that ART be continued lifelong and not stopped. For women who elect to breastfeed, ART must be continued until weaning has occurred should there be a reason for wanting to stop treatment post-delivery.

PATIENTS WITH RENAL FAILURE

Patients with HIV may develop end-stage renal disease due to HIV itself (HIV nephropathy) or a cause unrelated to HIV. For patients who are receiving dialysis, adjustments to ART regimens is required. NRTI drugs are eliminated by the kidneys and doses need to be adjusted with the exception of abacavir. AZT should be avoided due to the anaemia seen in patients with chronic renal failure. Doses of NNRTIs, PIs and InSTIs generally do not need to be adjusted.

FIRST-LINE ART REGIMEN FOR PATIENTS ON CHRONIC HAEMODIALYSIS

Abacavir 600 mg daily

AND

Lamivudine 50 mg first dose then 25 mg daily (after dialysis)

AND

Efavirenz 600 mg nocte

NOTE

Renal function is estimated by either the modified Cockgraft-Gault equation or the modification of diet in renal diseases method (MDRD), reported as eGFR

THE MODIFIED COCKGRAFT-GAULT EQUATION

Creatinine clearance (CrCl)* = (140 – age × ideal weight) ÷ serum creatinine

*For women, multiply the total by 0.85

It is recommended that all patients with chronic renal failure on ART are reviewed every six months by an experienced HIV clinician.

For further reading and more detailed guidelines refer to "Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV". 2014. Update. *Clinical Infectious Diseases* 59(9):e96-e138.

ELDERLY PATIENTS

ART is important for elderly patients as they have higher rates of non-AIDS complications as well as a blunted immunologic response to ART. Adverse drug reactions from ART are also more common, and as polypharmacy is common in the elderly, the risk of drug-drug interactions is higher. Age-related comorbid illnesses may complicate the management of elderly patients and careful attention to the bone, cardiovascular, liver, mental and metabolic health of the elderly patient with HIV is essential.

INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY

TREATMENT FAILURE

Treatment success is defined as a decline in HIV viral load to < 50 copies/mL within six months of commencing ART and that is sustained thereafter. Treatment failure is defined as a viral load > 50 copies/mL confirmed in two specimens collected two to three months apart following intensive adherence counselling. Treatment failure is due to either:

- Drug resistance, or
- Failure of the drug to reach the target sites and is usually due to poor adherence, drug interactions, or altered pharmacology.

The standard approach to virological failure is to evaluate adherence, potential interactions with other drugs, drug absorption and to perform resistance testing if resources permit.

Ideally ART should only be changed in consultation with a clinician experienced in HIV management. Drugs used in second-line regimens may be problematic since not all the drug classes and agents are readily available to all clinicians in South Africa. They are also not as well tolerated and are more expensive than first-line agents.

TOXICITY

Adverse drug reactions are typically mild and occur within the first few weeks of therapy. If persistent or severe then the offending drug should be substituted for another drug. When substituting a single drug the HIV load should be undetectable before the substitution. If substituting a drug in the first few months of initiating therapy, it is acceptable to substitute a drug without a suppressed viral load as this may take up to six months to be suppressed. It is rarely necessary to stop the entire drug regimen, however, when severe life threatening complications such as hepatic necrosis with liver failure or severe lactic acidosis occur, then it may be necessary to stop the all ARVs until the patient is clinically well enough to start a new regimen.

SECOND-LINE ART REGIMENS

Ideally, a second-line regimen should be guided by the results obtained from a genotypic drug resistance test performed whilst the patient is on the failing regimen. This can differentiate non-adherence (no drug resistance found) from failure due to drug resistance and assist with the drug choices for a second-line regimen. A drug resistance test is particular useful if the patient is failing a first-line combination of a PI and two NRTIs as a 'best guess' second-line regimen is difficult and best guided by the resistance mutations present.

A ritonavir-boosted PI and two NRTIs is the usual recommended second-line regimen. Protease inhibitors are robust drugs and viral suppression is likely to occur with good adherence even if the two NRTIs in the second-line regimen are partially compromised. NRTI combinations advised for second-line regimens include zidovudine **AND** lamivudine, OR tenofovir **AND** lamivudine (or emtricitabine) OR abacavir **AND** lamivudine. If lamivudine or emtricitabine was used in the first-line regimen and selected for the M184V mutation, it is recommended that the drug be continued in a second-line regimen as this mutation reduces the replicative capacity of the virus and re-sensitises the virus to zidovudine and tenofovir. PI options in a second-line regimen are ritonavir-boosted lopinavir, atazanavir or darunavir. Atazanavir is dosed daily and has a more favourable side-effect profile. It is, however, not co-formulated with ritonavir and additional ritonavir needs to be given (usual dose is 300 mg atazanavir plus 100 mg ritonavir once daily with food).

THIRD-LINE (SALVAGE) THERAPY

Third-line ART is used in a treatment experience patient who has been on NRTI, NNRTI and PI drugs and who has documented PI resistance. Before considering a salvage regimen, adherence counselling and interventions to ensure adherence should be performed. Only if the patient does not suppress after this should a genotypic drug resistance test be performed to guide drug choices for a third–line regimen. The HIV-resistance test will provide information as to the mutations present in the circulating population of HIV and not mutations present and archived from previous regimens. Interpretation of the drug resistance test must be performed by an expert together with the complete ART history and previous drug resistance test results. A number of drugs are available for third-line regimes including new NNRTIs such as etravirine and rilpivirine, PIs such as darunavir which has a very broad resistance profile, and integrase inhibitors such as raltegravir and dolutegravir. Maraviroc, a CCR5-receptor antagonist, is also a consideration for salvage therapy but requires a tropism test to ensure that the circulating virus only uses the CCR5 co-receptor.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune reconstitution inflammatory syndrome (IRIS) is an aberrant manifestation of ART due to disease- or pathogen-specific inflammatory responses in HIV-infected patients seen in the first few months of starting ART due to immune reconstitution.

There are two forms of IRIS, unmasking IRIS and paradoxical IRIS. Unmasking IRIS is when an unrecognised opportunistic infection present is 'unmasked' after starting ART. Paradoxical IRIS is when a known opportunistic infection which is being treated worsens after starting ART. A variety of IRIS conditions have been described with TB-IRIS being the most common in South Africa. There is no specific test to diagnose IRIS, thus it requires recognition of the common clinical presentations and exclusion of other causes for the deterioration, such as TB drug resistance.

For severe TB or fungal forms of IRIS, corticosteroids can be used to improve symptoms. The usual dose of prednisone used is 1.5 mg/kg/day and then weaned over a four-week period.

PROPHYLAXIS FOR PATIENTS RECEIVING ART

ISONIAZID THERAPY

Isoniazid preventive therapy (IPT) has been shown to significantly reduce incident TB rates in patients receiving ART and should be given to all patients on ART, provided that there are no contraindications to isoniazid and active TB is not suspected. A simple symptom screen for active TB can be used and TB investigations performed if any of the following symptoms are present: current cough for more than 24 hours, fever, night sweats and weight loss. The dose of isoniazid is 5 mg/kg/day (max. 300 mg/day) given for twelve months. Vitamin B6 (pyridoxine) 25 mg per day should be given concomitantly with isoniazid to prevent the occurrence of peripheral neuropathy.

COTRIMOXAZOLE PROPHYLAXIS

Cotrimoxazole prophylaxis is used to prevent infections such as *Pneumocystis jirovecii*, toxoplasmosis, malaria and other bacterial infections in HIV-infected patients. Cotrimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count of $\leq$ 350 cells/μL. Cotrimoxazole should also be given to all adults with active TB regardless of CD4 count. The dose is two single strength tablets or one double strength tablet daily. Prophylaxis can be stopped when patients are on ART with a CD4 count $>$ 350 cells/μL. Cotrimoxazole may cause a maculopapular rash and prophylaxis can be continued if the rash is mild. If the patient develops erythema multiforme or Stevens-Johnson syndrome then the cotrimoxazole must be stopped.

CRYPTOCOCCUS SCREENING AND TREATMENT

HIV-infected patients with a CD4 count of $<$ 100 cells/μL should be screened for cryptococcal disease before ART is started. A serum cryptococcal antigen assay (CrAg) should be requested and if positive, is indicative of disseminated cryptococcal disease requiring evaluation for symptoms of meningitis and appropriate treatment. CrAg positive patients without symptoms of meningitis and those with a negative CSF cryptococcal test regardless of symptoms, should be treated with oral fluconazole 800 mg daily for two weeks, followed by 400 mg daily for two months and then 200 mg daily for a minimum of one year. ART should be started after two weeks of antifungal therapy. Symptomatic patients should be started on fluconazole 1200 mg daily and require an urgent lumbar puncture. If their CSF cryptococcal test is positive then they require IV amphotericin B plus oral fluconazole 800 mg for two weeks in hospital followed by standard consolidation and maintenance therapy with oral fluconazole. ART should be started four to six weeks after antifungal treatment. Fluconazole maintenance can be stopped once the patients CD4 count is $>$ 200 cells/μL (two measurements taken six months apart).