

# Patients attending antiretroviral clinics: when and why to refer

**Antiretroviral therapy can be provided outside a hospital setting, but you need to know when to refer.**

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The South African public sector antiretroviral (ART) roll-out commenced on 1 April 2004. To date more than 300 000 people have started ART at more than 300 public health facilities, with close to 100 000 receiving ART in the private sector. The use of ART results in reductions in opportunistic infections (OIs), better quality of life and improved survival for HIV-infected people. Models suggest that on average 15 - 40 years of life are added to an HIV-infected person's life by the availability of multiple regimens of ART. Like most medical therapies, the benefits of ART are accompanied by a range of risks. Many patients in South Africa start ART with very low CD4 counts with increased risk of OIs as well as the immune reconstitution inflammatory syndrome (IRIS) – discussed below.

Currently, the majority of patients in the public sector receive ART in hospital-based settings, which is unsustainable, especially should the anticipated escalation in ART initiations proceed as outlined in government planning. There is a drive to have ART delivered by a nurse-run service at primary care level so as to cope with the anticipated load of patients requiring ART in the decades to come. Health personnel limitations make this an imperative, much like other chronic disease provision, such as hypertension, diabetes and asthma. Primary care delivery of ART in communities also makes sense: the service is more accessible and integrated into people's lives.

While most patients on ART can be prepared for treatment, initiated and managed at primary care according to established guidelines, a significant minority (around 15% in a Cape Town study) require secondary or higher level referral at some point prior to or while on ART.

This article addresses common reasons requiring referral of adult patients from primary care ART clinics for specialist and/or secondary level consultation or admission. We have divided this paper into two sections: referrals during work-up to start ART and referral of patients on ART. Some of the issues discussed under work-up for ART will also apply to patients on ART.

These general guidelines have been written for 'ideal' settings where a referral hospital staffed by specialists is accessible to the primary care ART clinic. In rural and other under-resourced settings this is often not the case. Where specialist referral is not possible, telephonic specialist advice may need to be obtained.

## *During ART work-up*

Late diagnosis of HIV is a global problem, but is often worse in developing world settings. Many patients in South Africa first present at ART clinics with active OIs and other morbidities due to advanced immunosuppression. Some problems can be investigated and managed in the primary care clinic, but certain patients will need secondary referral for investigation before ART initiation. Some important examples are:

### **Investigation of TB suspects and patients deteriorating on TB therapy**

Patients with HIV frequently present with tuberculosis (TB) that is difficult to diagnose – HIV-associated TB is more frequently smear negative, has an atypical chest X-ray (CXR) appearance or is extrapulmonary. Delays in diagnosis result in substantial morbidity and mortality.

Typically HIV-associated TB presents with the symptoms and signs summarised in Table I. Initial investigation of TB suspects (with the exception of patients with suspected TB meningitis who need immediate referral) should always include at least two sputum specimens sent for staining for mycobacteria (day 1 one 'on the spot' specimen; day 2 one early-morning specimen and one 'on the spot' specimen). Sputum induction in an appropriately ventilated room using an ultrasonic nebuliser and hypertonic saline is an inexpensive and effective way to obtain good-quality specimens in a primary care setting.

In HIV-infected patients who have negative smears or non-productive cough but clinical symptoms of TB, non-response to an appropriate antibiotic and a suggestive CXR, initiation of TB

**Table I. HIV-associated TB symptoms and signs**

Symptoms	Signs
Weight loss >5% over preceding 4 weeks	Consolidation
Chronic cough with or without sputum production or haemoptysis	Pleural effusion
Drenching night sweats	Pericardial effusion
Fevers and chills	Lymph node enlargement
Dyspnoea	Ascites
Chest pain during coughing	Signs of meningitis (requires urgent referral)
Fatigue	
Asymmetrical lymph node swelling	
Abdominal swelling	
Headache	

treatment for 'smear-negative TB' should be considered. At least one TB culture should be sent from all smear-negative TB suspects. The initiation of TB therapy before a positive culture result is obtained is usually necessary, as delay in therapy is associated with a high mortality. However, the decision needs to be made by an experienced clinician, and close follow-up after initiation to monitor treatment response is essential.

In those TB suspects who do not have a CXR suggestive of TB and in those in whom further investigation is deemed necessary before starting TB treatment, secondary referral without delay is appropriate for further investigations. This may include abdominal and pericardial ultrasound scan, aspiration of pleural and ascitic fluid, and biopsy of lymph nodes. Early-morning urine samples sent in sputum jars, and inoculation of blood and exudates into liquid medium TB culture bottles have a reasonable yield

on TB culture in advanced HIV disease. Cerebrospinal fluid commonly has few bacilli, and as large a volume as possible should be sent to the laboratory for culture. The World Health Organization (WHO) has published detailed guidelines on the diagnosis of HIV-associated TB: ([http://www.who.int/tb/publications/who\\_html\\_tb\\_2004\\_329/en/index.html](http://www.who.int/tb/publications/who_html_tb_2004_329/en/index.html)). Fig. 1 shows a WHO investigational algorithm for HIV-associated TB. All patients too ill to receive outpatient TB treatment need to be admitted.

Referral is also indicated for patients on TB therapy who are not clinically improving or are deteriorating. The differential diagnosis is fairly wide and is summarised in Table II.

### Neurological and psychiatric problems

Patients who present with neurological or psychiatric problems frequently need specialist referral prior to starting ART. It

is important to diagnose and treat where possible, as central nervous system (CNS) OIs may rapidly deteriorate on ART as a result of IRIS. The long-term prognosis of many of these patients, especially those with cryptococcal disease and toxoplasmosis if they survive the initial 3 months of ART, is very good, so every effort should be made to obtain a diagnosis. Untreated psychiatric disease, especially depression, which is underdiagnosed in HIV-infected patients, may compromise adherence.

In particular, all patients with new-onset headaches need urgent investigation before starting ART. Provided there is no contraindication, all these patients require a lumbar puncture to exclude cryptococcal meningitis (CM) and other causes of meningitis. CM frequently presents with headaches and fevers in the absence of neck stiffness. Missing the diagnosis and starting ART may lead to accelerated deterioration.

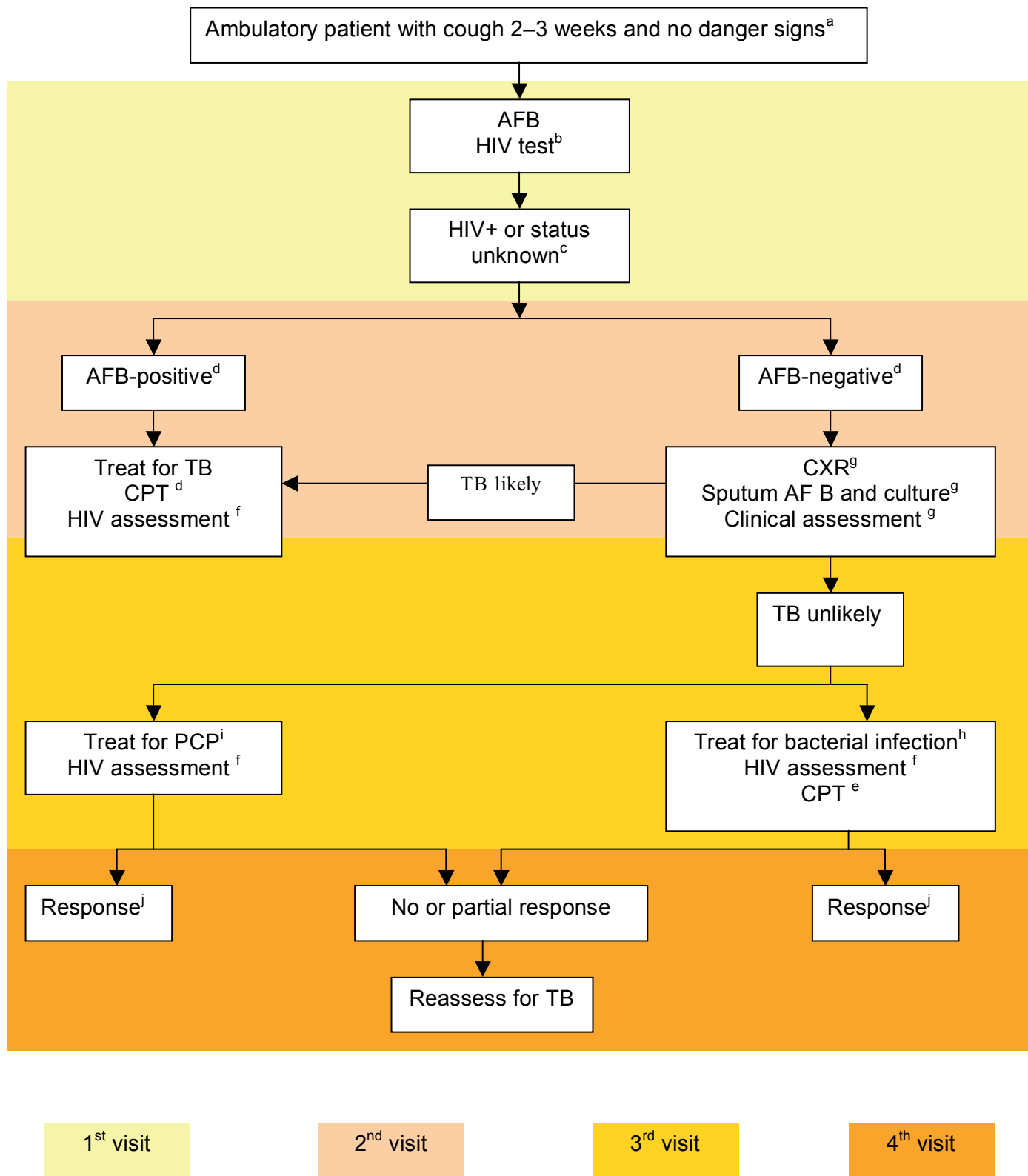
Patients with other CNS presentations (such as confusion, focal neurology and myelopathy) also frequently have CNS OIs and require specialist investigation before starting ART. Patients with focal neurology require a CT and appropriate neurological investigations. The common causes for this in HIV-infected patients in our setting are toxoplasmosis, tuberculomas and stroke. Patients who present with gradual-onset subcortical dementia (characterised by memory loss, poor attention and motor skills impairment) may have HIV encephalopathy, but this remains a diagnosis of exclusion after neurological investigations to exclude OIs.

Psychiatric presentations in HIV-infected patients may be functional disorders (e.g. depression) or may be manifestations of HIV encephalopathy (this may present as dementia or psychosis) or OIs. Many cases of depression can be managed in primary care, but patients with severe psychiatric illness should have psychiatric referral for stabilisation prior to starting ART.

In patients with typical HIV or INH-induced sensory peripheral neuropathy specialist referral is not required and patients can be treated with amitriptyline and other analgesia in primary care. In such patients d4T is preferably avoided. If INH is suspected as contributing, pyridoxine should be given. If atypical features (e.g. rapid progression over weeks) are present specialist referral is advised. OIs such as CMV can result in certain forms of neuropathy (CMV lumbosacral radiculopathy).

**Table II. Diagnostic considerations in TB patients deteriorating on TB therapy**

Possible diagnosis	Action
Non-adherence to TB therapy	Check TB clinic card and contact TB clinic
Secondary infection, either focal (e.g. pulmonary) or systemic (e.g. non-typhoid salmonellosis)	Treat for bacterial pneumonia or pneumocystis as appropriate, and consider admission for intravenous third-generation antibiotics (avoid quinolones)
Multidrug-resistant TB (MDR TB)	Send off good clinical specimens for TB culture and drug susceptibility testing
Fungal infections	Look for skin lesions to biopsy, send away blood for cryptococcal agglutination test and consider lumbar puncture, bone marrow biopsy and liver biopsy
Kaposi's sarcoma and lymphoma	Look for skin lesions, enlarging lymph nodes (including in the chest and abdomen) and hepatosplenomegaly; refer for biopsy



- a. The danger signs include any one of: respiratory rate > 30/minute, fever > 39 °C, pulse rate > 120/min and unable to walk unaided. Patients with danger signs should be referred for admission immediately.
- b. For countries with adult HIV prevalence rate ≥ 1% or prevalence rate of HIV among tuberculosis patients ≥ 5%.
- c. In the absence of HIV testing, classifying HIV status unknown as HIV-positive depends on clinical assessment or national and/or local policy.
- d. AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.
- e. CPT = Co-trimoxazole preventive therapy.
- f. HIV assessment includes HIV clinical staging, determination of CD4 count if available and referral for HIV care.
- g. The investigations within the box should be done at the same time wherever possible in order to decrease the number of visits and speed up the diagnosis.
- h. Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.
- i. PCP: *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia.
- j. Advise to return for reassessment if symptoms recur.

Fig.1. Algorithm for the diagnosis of tuberculosis in ambulatory HIV-positive patients.

## Liver pathology

All patients entering ART programmes should have an alanine transaminase (ALT) and hepatitis B surface antigen assessment, if possible. Patients with elevated ALT should then have full liver function tests (LFTs) performed. The list of conditions resulting in liver disease in HIV-infected patients is shown in Table III. It is important to take a thorough history, in particular regarding all medications, traditional or homeopathic remedies and alcohol intake.

Before starting patients on potential hepatotoxic ART, probably the most important issue to address is a drug-

induced hepatitis due to drugs such as those used in TB treatment, fluconazole or co-trimoxazole (the latter typically causes a cholestatic hepatitis). Cholangiopathies are also common in HIV-infected people, and pose complex management issues. Any patient with significant LFT derangement should be referred for specialist assessment or discussed telephonically. Investigations may involve viral hepatitis screen, ultrasound, liver biopsy and more advanced imaging. Management may involve interrupting potentially hepatotoxic drugs and observing LFT responses and, if drugs are implicated, doing a drug rechallenge and/or using safer alternatives.

**Table III. Common causes of liver abnormalities in HIV-infected patients**

### Patients not on ART

- Drugs: TB medications (rifampicin, INH, PZA), co-trimoxazole, fluconazole, antibiotics and others.
- Acute and chronic hepatitis B and C
- TB: granulomatous hepatitis, lymph nodes at porta hepatis causing obstruction
- Fatty liver
- HIV cholangiopathy
- Lymphoma
- Toxins: alcohol, alternative therapies
- Bacterial sepsis

### Patients on ART

- All of the above
- HAART: NRTIs cause fatty liver/steatohepatitis; NNRTIs (nevirapine > efavirenz) cause immune-mediated hepatitis; PIs may also cause drug-induced hepatitis
- Immune reconstitution inflammatory syndrome: TB, hepatitis B or C
- Hepatitis B flares on stopping 3TC or tenofovir

**Table IV. Causes of diarrhoea in HIV-infected patients**

### Acute (<2 weeks)

- Viral
- Bacterial (*Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, *Clostridium difficile*)
- Early phase of chronic causes

### Chronic (>2 weeks)

- *Isospora*
- *Cryptosporidium*
- *Microsporidium*
- Amoebiasis
- *Giardia*
- CMV
- *Mycobacterium avium* complex (MAC)
- TB
- Kaposi's sarcoma
- Intestinal atrophy
- HIV itself

## Chronic diarrhoea

Chronic diarrhoea (duration >2 weeks) is a frequent complaint in patients with advanced HIV. In patients who present with significant dehydration or those who are systemically toxic, acute referral is indicated. In other cases patients should initially be investigated in primary care by sending a stool for microscopy, culture and sensitivity. In addition, specific stains for *Isospora*, *Cryptosporidium* and *Microsporidium* should be requested as these organisms are not visualised on the usual wet preparation. The treatment of isosporiasis is co-trimoxazole, certain microspora species respond to albendazole and cryptosporidiosis responds poorly to antimicrobial therapy. If patients have negative investigations in primary care it is appropriate to refer them for gastroscopy and duodenal biopsy and/or sigmoidoscopy before starting ART. Patients may find it difficult to take ART if they have untreated gastroenteritis, particularly if there is accompanying vomiting, and there is a risk of malabsorption of therapy. However, there are settings where scope facilities are unavailable or where the waiting list is too long, and here ART should not be deferred because of diarrhoea. Indeed, for most causes of chronic diarrhoea ART initiation leads to improvement even in the absence of specific antimicrobial therapy.

A list of causes of diarrhoea in HIV-infected patients and an algorithm for the investigation and management of this are shown in Table IV and Fig. 2.

## Kaposi's sarcoma

Patients presenting to an ART clinic should be thoroughly examined for Kaposi's sarcoma (KS). This includes examination of the skin and oral cavity. In many patients the lesions of KS are characteristic, but if lesions are atypical or if there is diagnostic uncertainty patients should be referred for a diagnostic biopsy. Conditions such as bacillary angiomatosis may mimic KS, but are rare. Patients with KS should always have a chest radiograph performed to look for features of pulmonary KS.

The cornerstone of KS management is ART – this should never be delayed while awaiting oncology review. Once started on ART, patients with KS may experience partial and sometimes complete resolution of lesions. Thus if patients have only a few small skin lesions it may be possible to initiate ART in primary care and monitor response. However, most patients with KS do require referral to an oncologist. This includes all patients with multiple lesions, symptomatic lesions, any visceral involvement or any systemic

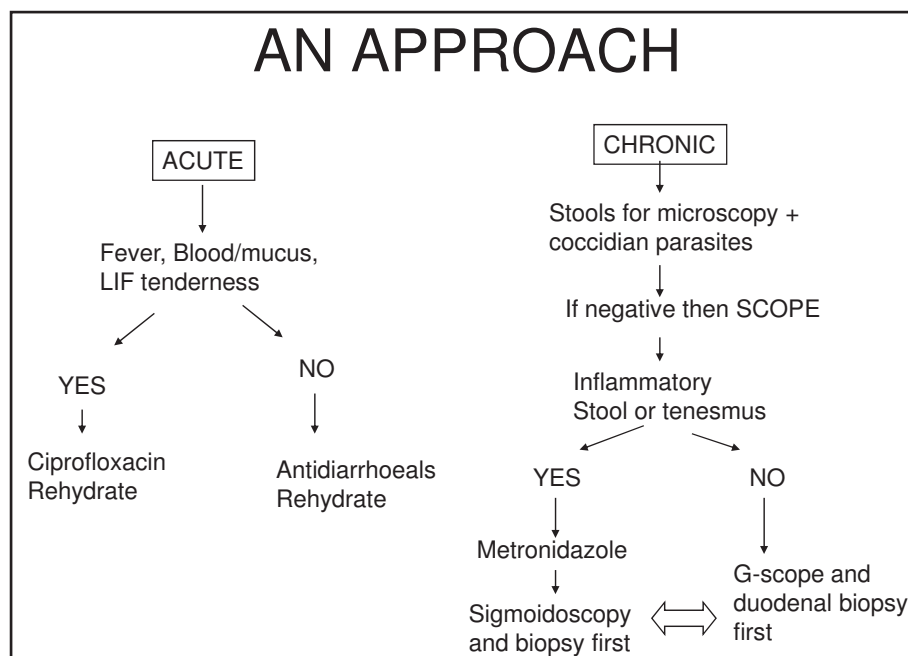


Fig. 2. Algorithm for investigation of diarrhoea.

symptoms. Oral lesions are correlated with pulmonary involvement, and these patients should be referred for assessment. Any patient with limited disease that does not respond to ART within 3 months also requires referral. Occasionally, patients may even experience IRIS symptoms, with swelling of the lesions. Patients with KS referred to an oncologist will be treated with chemotherapy or radiotherapy or a decision may be taken to defer therapy and first assess response to ART. AZT should be avoided in the patient's ART regimen because of its potential for myelosuppression; these patients may require chemotherapy which is also myelosuppressive.

### New-onset visual problems

Any patient with new-onset visual symptoms presenting to an ART clinic requires an ophthalmology assessment prior to ART initiation. By far the commonest cause of painless loss of vision is CMV retinitis. This condition occurs mainly in patients with CD4 counts less

than 50 cells/mm<sup>3</sup> and presents with visual blurring, floaters or other visual impairment. Symptoms are usually unilateral at first, but may evolve to bilateral involvement. Patients should have fundoscopy performed at primary care, but even if no abnormalities are seen formal ophthalmology assessment is advisable. The treatment of cytomegalovirus (CMV) retinitis is with either IVI or intravitreal gancyclovir. Other ophthalmic infections that occur in patients with advanced immunosuppression are herpes simplex virus (HSV), herpes zoster virus (HZV), toxoplasmosis and *Candida*. Cryptococcal meningitis may occasionally present with sudden-onset blindness.

### Other reasons

There are a number of reasons to consider starting ART in patients that fall outside the commonly cited criteria (Table V). These conditions need assessment by a specialist before ART is started.

In general, patients with HIV renal disease (which tends to be progressive

and has significant implications for nucleoside-related toxicity, with the need for dose adjustments), significant hepatic compromise, cardiac failure, severe bronchiectasis, or any other condition that may worsen with initiation of ART should preferably be started in a more specialised setting. Patients with complex co-pathologies, such as transplants, or with multiple systemic diseases, should be monitored at the central site where they are receiving care for these pathologies. Pregnant patients with severe or multiple HIV-related complications should be initiated at a specialist site if possible. In all these cases, referral should be rapid. If referral means a wait of several weeks to access ART, this may mean exposure to an unnecessary morbidity and mortality risk.

## Patients on ART

### Drug toxicities

Most ART side-effects and toxicities can be adequately managed in primary care according to published guidelines (e.g. SA Department of Health and Southern African HIV Clinicians Society guidelines). However, certain toxicities, particularly when they are more severe, require secondary level/specialist referral. Table VI summarises reasons to refer for ART drug toxicities.

### Hepatotoxicity

Of the ART drugs, nevirapine is most likely to result in hepatotoxicity. Occasionally, efavirenz can produce a similar clinical picture. This is typically an immune-mediated drug-induced hepatitis with predominantly an elevation of transaminases that occurs within the first 3 months of starting the drug. There may be associated jaundice, fever and rash. It is suggested that the ALT is monitored when starting nevirapine (at baseline, 2, 4, 8, 12 weeks) to detect this side-effect early, although hepatitis may occur rapidly between these time periods. Patients who have elevations of ALT > 200 or those with lesser elevations who are symptomatic should have ART stopped and restart an efavirenz-containing regimen once the hepatitis has resolved. There are other antiretrovirals and medications used in HIV medicine that may result in drug-induced hepatitis (DIH) (see Table III) and management principles are the same.

All patients who develop significant hepatitis should be referred urgently. It is important to assess for mental changes and metabolic flap in any patient presenting with DIH, as this suggests liver failure and the need for urgent admission. These patients require specialist management

Table V. Other reasons to consider ART initiation

- Immune thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP)
- Autoimmune haemolytic anaemia (AIHA)
- Multidrug-resistant TB
- Severe HIV neuropathy or HIV myelopathy (although CD4 invariably <200)
- Refractory aphthous ulceration
- All malignancies (unless early malignancy that is surgically resected with low relapse risk)
- Diffuse infiltrative lymphocytosis syndrome (DILS) with severe symptoms
- HIV vasculopathy
- Guillain Barré syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP) non-responsive to immunomodulatory therapy

**Table VI. ART toxicities and reasons for specialist referral**

Toxicity	Main causative drug(s)	When to refer
Hyperlactataemia/lactic acidosis	d4T>ddI>AZT	All suspected cases (see Fig. 3)
Hepatotoxicity	NVP>EFZ>others (TB medication also an important cause)	Severe symptoms of hepatitis (such as jaundice and vomiting), signs of liver failure (flap, confusion, drowsiness) and patients on multiple drugs that could be causing hepatitis
Drug rash	NVP>EFZ>others	Severe rash – extensive involvement, mucosal involvement, blistering, desquamation or significant systemic symptoms
Myelosuppression (anaemia and neutropenia)	AZT	Symptomatic anaemia Neutropenia (neutrophil count <1) with fever
Neuropathy	d4T >ddI	Atypical and rapidly progressive presentations
Pancreatitis	ddI>d4T (also protease inhibitors via hypertriglyceridaemia)	All cases and suspected cases
Metabolic complications	Protease inhibitors (D4T can also cause impaired glucose tolerance and diabetes mellitus)	Hypertriglyceridaemia >15

which may include stopping all culprit medications, a liver biopsy in some cases and staggered re-introduction of medications following this general order, while monitoring ALT closely:

- rechallenge treatments of active OIs (e.g. TB drug rechallenge according to local guidelines)
- re-introduction of safer ART regimen (e.g. substituting nevirapine with efavirenz if nevirapine was in the ART regimen when hepatitis occurred)
- rechallenge prophylactic medication (e.g. co-trimoxazole).

Patients on NRTIs (especially d4T) may develop fatty liver, usually in association with hyperlactataemia due to the mitochondrial toxicity caused by this drug. Patients present with the symptoms of hyperlactataemia and right upper quadrant pain or discomfort, firm hepatomegaly and LFT derangement. Definitive diagnosis is by means of liver biopsy. Lactate should be checked in all these patients. Management involves interrupting ART or, if less severe, switching d4T to an alternative agent.

**Hyperlactataemia and lactic acidosis**

This is one of the most feared side-effects of ART, as it is commonly unrecognised until the advanced stages, when it carries

a high mortality, even with optimal management. d4T is the commonest culprit, but other nucleosides, especially ddI and AZT, may be implicated. The condition tends to occur after more than 2 - 3 months on treatment, and is usually insidious in nature, with fatigue, appetite loss, weight loss, nausea, abdominal pain and vomiting. The syndrome overlaps with other mitochondrial toxicity syndromes, such as peripheral neuropathy, lipoatrophy and fatty liver, and the presence of these should trigger investigation in the presence of any of the above symptoms.

A lactate test, done in the presence of symptoms (there is no place for routine monitoring in asymptomatic cases), can quickly exclude the diagnosis if normal, and investigations of the symptoms can be expanded. Point-of-care lactate measurement devices are increasingly available in peripheral sites, and can quickly and efficiently identify patients who may have the syndrome.

A management algorithm is shown in Fig. 3. All suspected cases should be immediately referred. Management involves stopping ART, identifying additional or other causes for the acidaemia, and general support measures. Once the lactate level has normalised, which takes months, a new regimen of less mitochondrial toxic drugs will need to be selected. In patients who have had life-threatening lactic acidosis

a combination of a boosted protease inhibitor with an NNRTI is preferable as there is no risk of recurrence with this combination.

**Drug rashes**

ART drugs (nevirapine > efavirenz > others) may result in drug rashes. This can range from a mild drug rash to a potentially fatal Stevens-Johnson syndrome. In all severe cases ART should be stopped immediately and the patient referred for admission. This includes patients with extensive involvement, mucosal involvement, blistering, desquamation or significant systemic symptoms, such as fever. The clinician should also consider that many other medications used in HIV medicine (especially co-trimoxazole and TB medication) may also result in skin reactions. Initiation of these drugs at the same time as ART should be avoided if possible. If there is doubt as to which agent may be causing the rash, all potential drugs causing it should be stopped and the patient's further management discussed with a specialist.

**Nucleoside-induced myelosuppression**

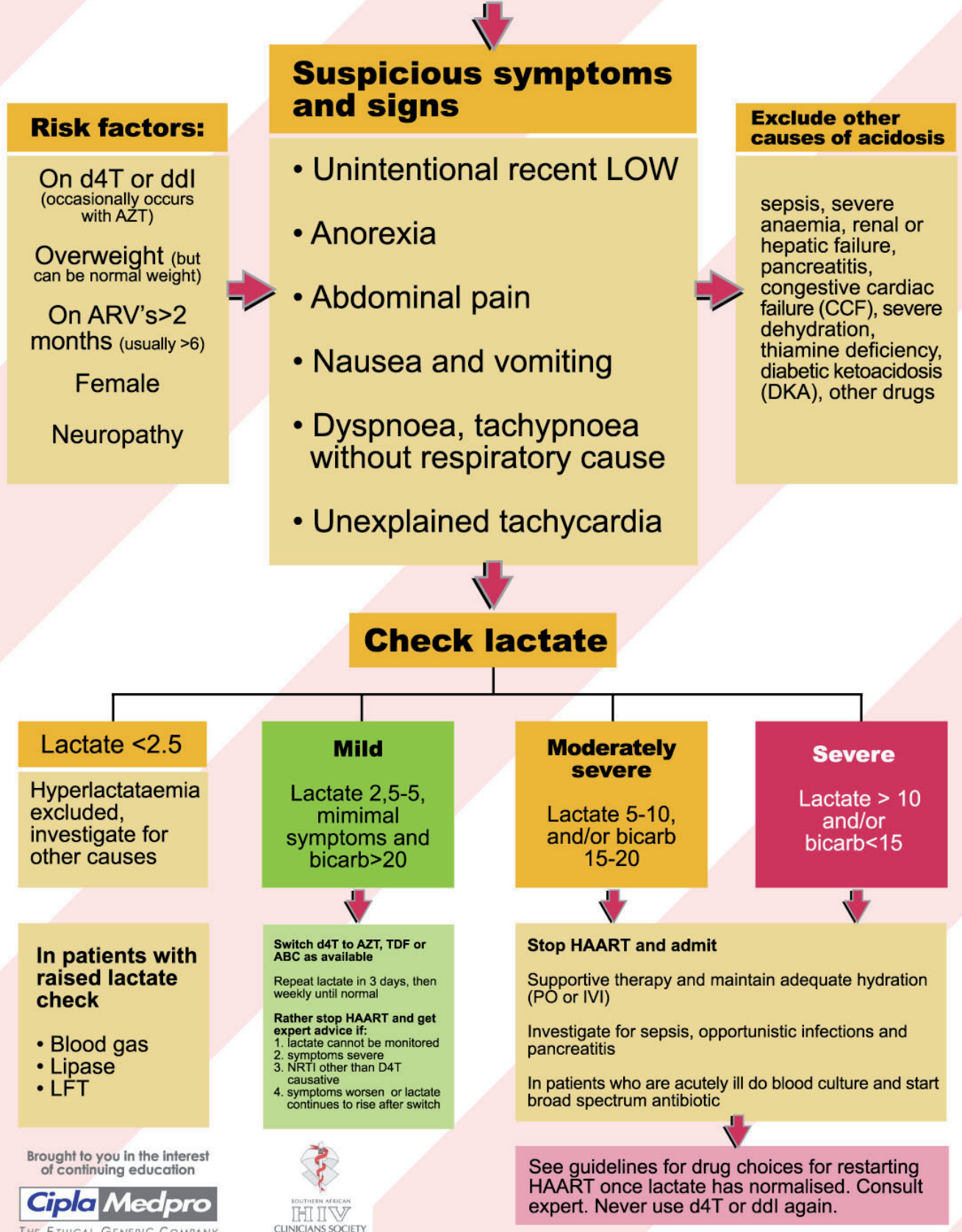
AZT may cause myelosuppression resulting in anaemia and neutropenia. Most patients who develop these complications can be managed in primary care and have their AZT switched to an alternative agent. However, patients with severe symptomatic anaemia may require referral for blood transfusion. Patients with neutropenia (neutrophils <1 × 10<sup>9</sup>/l) and fever require referral for investigation and management of neutropenic sepsis.

3TC has been associated, in rare instances, with red cell aplasia. This condition usually presents after several months on treatment, with a profound anaemia usually necessitating transfusion. Diagnosis involves bone marrow biopsy and exclusion of other causes of red cell aplasia, such as parvovirus. 3TC should be replaced with another agent, once the diagnosis is made.

**Pancreatitis**

D4T and ddI may cause pancreatitis. Any patient with suspected pancreatitis on these drugs needs lipase checked. If pancreatitis is diagnosed (lipase >4 × upper limit of normal) or if this test is only available at secondary level, urgent referral is required. The treatment involves stopping ART and supportive measures (including IVI fluids, keeping nil per mouth and analgesia). There may be associated hyperlactataemia. D4T and ddI should not be used again after an episode of pancreatitis. Severe

# SYMPTOMATIC HYPERLACTATAEMIA / LACTIC ACIDOSIS SUSPECTED



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Fig. 3. Management of hyperlactataemia/lactic acidosis (Southern African HIV Clinicians Society guideline)

## Patients with severe hypertriglyceridaemia (>15) are at high risk of pancreatitis and need referral to a lipid clinic if this service is available.

hypertriglyceridaemia caused by protease inhibitors may also result in pancreatitis.

### Neuropathy

Many patients (20 - 30%) started on d4T will develop peripheral neuropathy due to this drug. The risk is higher in those with current or previous exposure to INH, and those with very low CD4 counts. Nucleoside peripheral neuropathy may occur at any time during treatment. This typically presents initially with paraesthesia and pain in the feet which may progress to causing sensory deficit (numbness) and motor fall-out. Very mild cases can be managed symptomatically with analgesia and amitriptyline, but more severe or progressive symptoms should be managed by a switch to another nucleoside that does not cause peripheral neuropathy. dDI can also result in neuropathy. Only patients with atypical presentations require specialist assessment to exclude other causes. Patients with rapid progression to severe neuropathy should have a lactate measurement as such presentations may be associated with hyperlactataemia.

### Metabolic complications

Protease inhibitors may cause hyperlipidaemia and insulin resistance. Patients with severe hypertriglyceridaemia (>15) are at high risk of pancreatitis and need referral to a lipid clinic if this service is available. If not they require strict dietary advice regarding fat elimination from the diet and medical therapy with a fibrate. Most other metabolic complications can be managed in primary care according to published guidelines.

### Immune reconstitution inflammatory syndrome (IRIS)

Some patients started on ART will experience clinical deterioration due to inflammatory reactions that occur during immune reconstitution. These are termed IRIS and are thought to be due to the immune system reacting, often in a dysregulated manner, to infective antigens that are present. This may result

in the 'unmasking' of unrecognised and untreated infections or paradoxical clinical deterioration in patients already on appropriate treatment for an infection. These paradoxical reactions are thought to be caused by inflammatory reactions directed at dead or dying organisms.

Common forms of IRIS seen in SA are related to TB, cryptococcosis and dermatological conditions. In patients who present with 'unmasking' TB or cryptococcal IRIS management involves standard treatment for these conditions. Obviously those patients who develop meningitis need immediate secondary referral. Patients with 'unmasking' TB-IRIS may develop rapid onset of respiratory symptoms with a picture resembling bacterial pneumonia and sometimes respiratory failure, and should be referred immediately.

Paradoxical TB-IRIS usually manifests with return of symptoms and fever after starting ART and/or the development of new, worsening or recurrent lymphadenitis, pulmonary infiltrates on CXR or effusions in patients on TB treatment already. If patients develop mild TB-IRIS they can usually be managed supportively in primary care. It is important to consider and exclude conditions that may mimic TB-IRIS such as MDR TB, *Mycobacterium avium* complex and bacterial infections. Patients with severe TB-IRIS such as those with massive painful node enlargement, respiratory distress, airway compression or neurological manifestations require specialist assessment which involves the investigation for conditions which mimic IRIS and consideration of corticosteroid therapy for which there is anecdotal evidence.

Paradoxical CM-IRIS occurs in patients who have a diagnosis of CM prior to starting ART and are typically improving on antifungal therapy. After starting ART they develop recurrent symptoms owing to an inflammatory response. The most common manifestation is recurrent meningitis that may be associated with raised intracranial

pressure, but other manifestations like enlarging cryptococcomas, encephalitis and lymphadenitis are described. Secondary level referral is important in all cases – a lumbar puncture to measure and if necessary reduce raised intracranial pressure and a CT scan of the head are required.

A range of skin conditions can occur, recur or worsen with IRIS. These include HSV-1 and 2, HZV, warts, molluscum contagiosum, papular pruritic eruption and acne. It is important to differentiate these forms of IRIS from a cutaneous drug reaction. In most instances these conditions can be managed with conventional therapy and specialist referral is not indicated.

### *Some general issues regarding primary and secondary care interaction*

Clear communication between facilities is essential. A summary letter, stating the background conditions, including prior OIs, dates of initiation of ART, lowest and latest CD4 count, last viral load, and reasons for any prior regimen changes, as well as listing other medications and comorbidities, in addition to the reason for the referral, is essential for all cases referred. Referral back to the ART initiation site should always be accompanied by a detailed letter of the course of treatment and management decisions.

From the secondary level, all patients eligible to start ART should be referred to an ART initiation clinic. Those HIV-infected patients who are not yet eligible need to be referred to a facility where they can get pre-ART care which includes CD4 monitoring.

If patients are started on ART as inpatients (this is done in exceptional circumstances, e.g. in patients with severe mental illness requiring institutionalisation, HIV dementia or advanced HIV-related malignancies), the secondary services must liaise with the primary care ART clinic and do their utmost to ensure smooth transition to outpatient care on discharge. Such patients are vulnerable to being lost to follow-up on discharge.

Finally, if patients taking ART are admitted to hospital it should be ensured that they do not have an interruption in their ART, particularly while waiting for a bed in casualty. Frequently patients arrive at the hospital without their ART and there is a 24-hour or longer delay before a supply is arranged. This interruption can result in the development of drug resistance, unnecessarily compromising future ART

## Referral back to the ART initiation site should always be accompanied by a detailed letter of the course of treatment and management decisions.



treatment choices. If possible the primary care clinic should ensure that patients are given a supply of ART when they are referred for admission.

If patients have their ART interrupted or switched while they are hospitalised because of drug toxicities this needs to be communicated to their primary care clinic, preferably telephonically, to ensure that the change is carried through when they next visit their clinic.

## Conclusion

The majority of patients commencing ART can be adequately managed in primary care. However, a significant minority require specialist referral either prior to or once started on ART. This mainly

applies to patients with low CD4 counts who enter programmes and whose course is complicated by OIs and IRIS and those who develop severe drug toxicities or have complex co-morbidities. In some areas where referral to a specialist is not possible, telephonic consultation may be required in its place.

### Further reading

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## Management of Type 2 Diabetes Mellitus, 2nd edition

### A Practical Guide

By **Steven Levene** and **Richard Donnelly**

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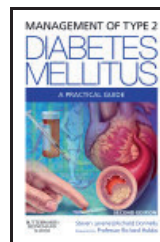
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In the 21st Century, the management of type 2 diabetes has become even more important both in the primary health care setting and in the government's health policy. With the publication of the National Service Framework and the allied National Clinical Guidelines, both patients and the government expect practices to deliver appropriate and effective care to a high standard. This book is aimed at all members of the primary health care team and concentrates on providing practical advice. Greater knowledge and skills will promote the delivery of high quality care to patients with type 2 diabetes in the community and, hopefully, reduce the impact of cardiovascular disease in this high risk group. This handbook addresses many concepts important in the day-to-day management of these patients. In addition to the discussion of specific medical management of type 2 diabetes (including the improvement of cardiovascular risk factors), the book explores the use of self-management techniques, the consultation process, and the use of psychological techniques to influence health-related behaviour. All aspects of the text are linked, when appropriate, to the GMS contract.

### Features

- The authors include a full time GP delivering diabetic care and an eminent Consultant/academic at the leading edge of diabetes research
- The text is completely up-to-date with numerous 2006 references, incorporating the latest guidance
- The span of the text is comprehensive, including clinical, organisational and psycho-social topics of importance in delivering high-quality diabetes care
- The text is cross-referenced to the relevant QOF indicators and NSF standards
- This book also covers the relevant aspects of diabetes in Curriculum Statement 15.6 prepared by the Royal College of General Practitioners, which forms the basis of the new membership examination and the competencies expected of General Practitioners.
- The management options include extensive balanced discussions about not just drugs, but also health education and appropriate referrals to specialists
- The approach is neither didactic nor promotional, and aims to provide sufficient practical information to help clinicians make optimal decisions that take full account of the latest authoritative guidance, but which can be tailored rationally to the individual patient's needs
- Many of the concepts covered - including reduction of cardiovascular risk, health education, audit and lifestyle - are extremely relevant to non-diabetes care
- The appendices include a detailed drug formulary and the relevant 2006-2008 QOF clinical indicators. Future trends and further reading are clearly set out, ensuring that the book will remain useful for the next few years.