

# ANTIRETROVIRAL ADVERSE DRUG REACTIONS AND THEIR MANAGEMENT

*How to recognise, manage and avoid adverse effects of antiretrovirals.*

**CATHERINE ORRELL, MB CHB, MMed, MSc, DCh, Dip HIV Man**

*Project Leader, Treatment Division, Desmond Tutu HIV Centre, Faculty of Health Sciences, University of Cape Town*

*Catherine Orrell is a clinical pharmacologist and HIV clinician who has been working with HIV-infected patients since 1997. She has been involved in several of the first programmes to deliver antiretroviral therapy in South Africa. Her particular interests are in HIV pharmacology, adherence to ART and long-term retention in care.*

*Correspondence to: Catherine Orrell (catherine.orrell@hiv-research.org.za)*

The 2010 South African ART guidelines recommend the use of tenofovir (TDF) and lamivudine (3TC) with efavirenz (EFV) or nevirapine (NVP) as first-line therapy for treatment-naïve adults starting antiretroviral therapy.<sup>1</sup> Second-line therapy is determined by the NRTI choice in first line. Patients on a first-line regimen with TDF will be prescribed lopinavir/ritonavir (LPV/r), zidovudine (AZT) and 3TC while patients on a first-line regimen with AZT or d4t will receive lopinavir/ritonavir (LPV/r), tenofovir and 3TC. Other antiretrovirals commonly used in the private sector are abacavir (ABC), atazanavir/ritonavir (ATV/r) and the recently registered darunavir/ritonavir (DRV/r). Newer antiretrovirals, used for more treatment-experienced patients, are still in the registration process, such as the second-generation NNRTI etravirine (ETV) and the integrase inhibitor raltegravir (RLT). These drugs may be prescribed for patients with limited treatment options subject to MCC approval on a case by case basis.

***If ANY systemic features are noted the NNRTI should be stopped immediately and the patient treated supportively until the rash recovers.***

This article discusses the common and serious adverse effects (AEs) related to the above antiretrovirals and the steps to take to avoid and manage these events. Table I summarises these AEs.

## **Serious adverse reactions**

### **Drug hypersensitivity reactions**

Nevirapine and efavirenz (and etravirine) can cause a drug hypersensitivity rash in the first 12 - 18 weeks of therapy. A minor rash may occur in up to 18% of those commencing EFV and 24% of those on NVP. In the case of NVP, women, especially with a higher CD4 cell counts, are at increased risk of developing rash. Failure to use the lead-in dose of 200 mg per day for the first 2 weeks also increases the risk of rash.

- *Patients should be advised to present immediately if they note a rash.*

A typical rash will be maculo-papular and generalised, although it may be urticarial. The majority of rashes are mild and treatment can continue under close supervision (preferably with daily review until the rash is obviously resolving). Patients can be treated symptomatically with antihistamines and steroid cream.

At initial presentation, systemic symptoms should be noted, i.e. fever, tachycardia, fatigue, myalgia and any signs of mucosal involvement (conjunctival, oral or perineal). If ANY systemic features are noted the NNRTI should be stopped immediately and the patient treated supportively until the rash recovers. Blood should be drawn to check ALT or AST, and if these transaminases are outside of normal range, again the NNRTI should be stopped immediately. The risk of continuing NNRTI therapy in the face of systemic symptoms, blistering or mucosal involvement is the development of toxic epidermal

necrolysis or Stevens-Johnson syndrome (blistering of mucosae), both which have been fatal.

- *NNRTI treatment should be stopped immediately in anyone presenting with a rash and systemic symptoms.*

If a rash occurs during the lead-in phase of NVP dosing (200 mg daily for the first 2 weeks) the dose should not be escalated until the rash resolves. Rechallenge: If NVP is stopped for a severe rash or one with constitutional symptoms, it should never be given again. The patient may be rechallenged with EFV after a NVP rash, but only under close supervision (possibly in hospital) and if possible, preference should be given to a treatment regimen that does not contain a NNRTI. If the severe rash was due to EFV, neither NNRTI should be given again and a protease-inhibitor based regimen used instead.

### **Abacavir hypersensitivity reaction (HSR)**

Four per cent of individuals using abacavir experience an abacavir HSR, which can be fatal. This most commonly presents as a rash and a fever, but may manifest as fatigue, flu-like symptoms or gastrointestinal upset. The reaction usually occurs in the first 6 weeks of treatment and continues to worsen unless ABC treatment is stopped. If the diagnosis is in doubt, it is better to stop ABC treatment. ABC should never be reintroduced after such a reaction is documented. Of note – this reaction may occur after an ABC treatment interruption in individuals who did not previously experience the hypersensitivity reaction.

This reaction has been found to be genetically linked to HLA-B57. There are a number of genetic variants of this protein and individuals with HLA-B\*5701 are at high risk of ABC hypersensitivity, while those with other variants are not. It is possible to screen for HLA-B57 type and this should be done for people belonging to high-risk populations such as South Africans of Tamil descent, where 10.2% have the B\*5701 variant.<sup>2</sup>

### **Drug-induced hepatitis**

Many of the antiretrovirals in common use have been shown to cause a drug-induced hepatitis, including the PIs lopinavir and darunavir, but the most severe reactions have been reported with the NNRTIs.

A number of people exposed to EFV (3%) may develop an increase in transaminases to more than 5 times the upper limit of normal. This is more frequent in individuals with hepatitis B or C. The benefit of continued use of EFV in this situation needs to be weighed against the possibility of severe hepatotoxicity.

***The risk of continuing NNRTI therapy in the face of systemic symptoms, blistering or mucosal involvement is the development of toxic epidermal necrolysis or Stevens-Johnson syndrome (blistering of mucosae), both which have been fatal.***

Table I. Class-related, serious and common adverse effects of frequently used antiretrovirals			
	Class AEs	Serious AEs	Common AEs
<b>Nucleos(t)ide reverse transcriptase inhibitors (NRTI)</b>			
Tenofovir (TDF)	Hyperlactataemia and lactic acidosis, with hepatic steatosis	Renal failure, Fanconi's syndrome	Mild dizziness, headache, diarrhoea and nausea
Lamivudine (3TC) and emtricitabine (FTC)	Lipodystrophic changes		
Zidovudine (AZT)		Anaemia, leuco- or neutropenia	Skin or nail pigmentation, nausea, myalgia, change in taste
Abacavir (ABC)		Drug hypersensitivity reaction	Headache, loss of appetite, nausea, diarrhoea
Stavudine(d4T)			Peripheral neuropathy
Didanosine (ddI)		Pancreatitis	Peripheral neuropathy
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTI)</b>			
Efavirenz (EFV)	Drug hypersensitivity rash (NVP 24%, EFV 18% ); Stevens-Johnson syndrome (NVP 0.3%, EFV 0.14%) Drug-induced hepatitis (transaminases > 5 times upper limit of normal: NVP 15%, EFV 8%)	Rare (0.2%) but severe neuro-psychiatric effects (depression, delusions). Possible first-trimester teratogenicity (neural tube defects)	Abnormal dreams, dizziness, drowsiness, nausea, headache, fatigue
Nevirapine (NVP)		Rash, hepatitis	
Etravirine (ETV)		Rash	Peripheral neuropathy
<b>Protease inhibitors (PI)</b>			
Lopinavir/r (LPV/r)	Lipodystrophic changes, metabolic syndrome (impaired glucose, tolerance hyperlipidaemia) GIT adverse effects including diarrhoea, nausea, vomiting, abdominal pain and flatulence	Rash (usually mild), hepatitis	
Atazanavir/r (ATV/r)		Rash (usually mild)	Unconjugated hyperbilirubinaemia (harmless)
Darunavir/r (DRV/r)	(ritonavir and lopinavir >> darunavir* (r)	Hepatitis	
<b>Integrase inhibitors</b>			
Raltegravir		Myopathy	Headache, diarrhoea, nausea

\* Only used as low dose, usually 100 mg per dose, to boost other PIs through inhibition of cytochrome p450 enzymes.  
REFER TO PACKAGE INSERTS FOR COMPLETE LIST OF ADVERSE EFFECTS OF THESE MEDICATIONS.

Hepatitis is more frequent and often more severe with the use of nevirapine. The risk of NVP-induced hepatitis increases with higher starting CD4 counts, raised transaminases pre-ART and in individuals with concurrent hepatitis B and C infection (where the use of NVP should be avoided). NVP-induced hepatitis usually occurs within the first 6 weeks of therapy and transaminases should be monitored 2, 4, 8 and 12 weeks into therapy, then 3 - 6 monthly.

If raised transaminases (>5 times the upper limit of normal) are noted, or there are clinical symptoms of hepatitis, the offending agent should be stopped (see 'Interrupting

Treatment' below) and the patient monitored until the transaminitis is resolved.

- *Patients may be on more than one agent that can cause hepatitis, e.g. isoniazid, rifampicin or pyrazinamide.*

As with skin rashes, it may be possible to rechallenge cautiously with EFV after NVP-related toxicity, but it is unwise to ever rechallenge with NVP.

#### Hyperlactataemia and hepatic steatosis

Hyperlactataemia and lactic acidosis with or without hepatic steatosis can occur with the

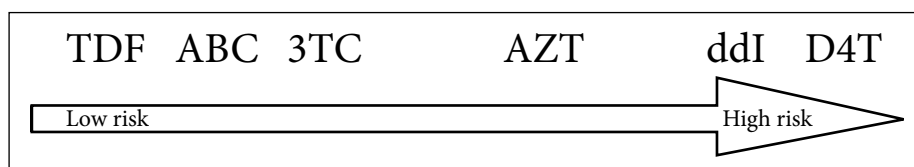


Fig. 1. Risk of hyperlactataemia by NRTI.

**Table II. Management of hyperlactataemia**

	Lactate <5 mmol/l	Lactate >5 mmol/l
Asymptomatic	Substitute high-risk NRTIs (d4T, ddI) with low-risk NRTIs and monitor weekly until raised lactate resolved	Stop all NRTIs and monitor closely until raised lactate resolved; recommence low-risk NRTIs only
Symptomatic or any evidence of acidosis*	Substitute high-risk NRTIs (d4T, ddI) with low-risk NRTIs and monitor weekly until raised lactate resolved	Stop all NRTIs and monitor closely (may need admission) until raised lactate resolved. Consider NRTI-sparing regimen or low-risk NRTIs with continued close monitoring

\* Seek specialist opinion for all cases of symptomatic hyperlactataemia.

use of any NRTI. It is most commonly seen in women with a body weight of >75 kg, or a high BMI (>28), who are using d4T. With the decreasing use of d4T and ddI due to the availability of tenofovir, lactate-related problems are becoming rarer, but clinical sensitivity to this possible fatal side-effect needs to remain high.

Hyperlactataemia is caused by the inhibitory effect of NRTIs on the human mitochondrial enzyme DNA polymerase. This effect varies between NRTIs. The more there is cross-inhibition, the greater the risk of hyperlactataemia (Fig. 1). Inhibition of DNA polymerase results in a decrease in production of mitochondria, responsible for oxidative metabolism. A lack of oxidative metabolism results in a build-up of lactate and fatty acids, causing hyperlactataemia and a fatty liver (hepatic steatosis).

Lactate should either be checked on a point-of-care fingerprick lactate meter or using venous blood (taken without a tourniquet) should be sent to the laboratory on ice. A normal lactate level is between 1 and 2 mmol/l. Many individuals on ART may have a slightly elevated level of lactate (<5 mmol/l), usually without symptoms (asymptomatic hyperlactataemia). Incidental finding of such a raised lactate should lead to a change from high-risk ART, to a less risky option (Table II). Lactate should be monitored weekly until it returns to normal.

Clinical symptoms of hyperlactataemia include nausea, fatigue, abdominal discomfort, loss of appetite and unintentional loss of weight. In more severe cases with acidosis, deep sighing breathing (often presenting as shortness of breath) may occur. Any symptoms associated with an increased serum lactate indicate potentially severe disease and NRTIs need to be substituted or stopped (Table II). The differential diagnosis for lactic acidosis includes septic illness or pancreatitis.

Hepatic steatosis results in a slight elevation of transaminases together with an increase in obstructive liver enzymes (GGT and alkaline phosphatase). A fatty liver would be noted on biopsy. Hepatic steatosis does not often require management in itself (though a specialist opinion should be requested with liver enzymes >5 times the upper limit

of normal), but this pattern of liver enzyme elevation should prompt screening for hyperlactataemia.

### *Hepatitis is more frequent and often more severe with the use of nevirapine.*

Table II outlines an approach to management of hyperlactataemia. Levels of lactate >5 mmol/l are potentially fatal and NRTIs should be withheld until hyperlactataemia has resolved (this may take some weeks to months). Thereafter only low-risk NRTIs should be considered. Severely symptomatic individuals with acidosis should avoid NRTI therapy entirely and opt for an NRTI-sparing regimen.

Symptomatic individuals with lower serum lactate (<5 mmol/l) may be maintained on ART, with a substitution of high-risk for low-risk ART. If the patient is already on low-risk ART then an NRTI-sparing regimen will have to be considered.

#### **Renal failure**

Tenofovir (TDF) is primarily eliminated by the kidney, both by glomerular filtration and through excretion at the renal tubule. Renal damage through TDF use might present with a picture of acute renal failure (decreasing glomerular filtration rate (GFR)) and a Fanconi's syndrome (tubular loss of phosphate, amino acids and glucose).

Due to the potential for renal injury, the estimated GFR (eGFR) should be calculated pre-treatment with TDF and regularly while on TDF. TDF should not be offered to individuals with an eGFR of <50 ml/min. The eGFR can be calculated using the serum creatinine and the patient's body weight using the modified Cockcroft and Gault formula:<sup>3</sup>

$$eGFR^* \text{ (ml/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kilograms})}{\text{serum creatinine in } \mu\text{mol/l}}$$

\*For women, the result should be multiplied by 0.85.

A rule of thumb, as given by the South African National ART guidelines, is that the eGFR must be calculated for any individual weighing <50 kg, who is older than 50 years or whose serum creatinine is >100  $\mu\text{mol/l}$ .<sup>1</sup>

TDF should not be given with any other nephrotoxic medications, such as aminoglycosides, including streptomycin (currently part of the re-treatment protocol for tuberculosis in South Africa).

If a decrease in eGFR is noted, tenofovir should be withdrawn and replaced with another NRTI. The eGFR should be monitored until it returns to normal. Specialist opinion should be obtained if no improvement is noted 1 month after withdrawal.

#### **Other common adverse reactions**

##### **Anaemia**

The use of AZT can cause bone marrow suppression which may present as anaemia or neutropenia. This anaemia is more common in late-stage HIV disease.

A full blood count or haemoglobin (Hb) should be checked prior to commencing AZT and AZT should be avoided in people with a low haemoglobin (<7.5 g/dl) or neutropenia (<0.75  $\times 10^9/l$ ). Hb should be monitored for the first few months on AZT and then checked every 6 months.

If anaemia is noted on AZT, usually within the first 6 weeks of therapy, the dose of AZT may be reduced from 300 mg twice daily to 250 mg twice daily, or the AZT may be replaced with another NRTI.

### Lipodystrophy

Antiretroviral therapy is associated with redistribution of body fat, termed lipodystrophy. Lipoatrophy, lipohypertrophy, or a combination of the two may occur. Lipoatrophy, which manifests as wasting of the buttocks, limbs and facial fat pads is caused by the NRTIs, particularly d4t, ddI and AZT. Lipoatrophy is only partially reversible if the causative drug is not stopped early. Lipohypertrophy, which consists of central obesity, a buffalo hump, and enlarged breasts, is less clearly associated with a particular drug or drug class.

Lipodystrophy is more commonly seen with longstanding use of the older PIs (e.g. indinavir, saquinavir, lopinavir) and NRTIs (d4T, ddI and AZT). It may be associated with metabolic changes, including impaired glucose tolerance and hyperlipidaemia (raised triglycerides and total and LDL cholesterol).

Management may include a switch in ART to agents less likely to cause lipodystrophy, where this is possible. A healthy diet and regular exercise will reduce the fat accumulation and improve glucose and lipid abnormalities and should be encouraged. Metabolic abnormalities should be managed appropriately. Patients may need counselling support where no further options are available as severe lipodystrophy can be unsightly.

### Peripheral neuropathy

Peripheral neuropathy (PN) is a disease associated with HIV-infection itself, but may also be initiated or exaggerated by a number of medications used to treat HIV disease.

Peripheral neuropathy is a common adverse effect of stavudine use and may present with painful, hyperaesthetic soles or decreased sensation in the feet. ddI and AZT can also cause PN, as can isoniazid, used to treat TB. Use of more than one of these agents concurrently increases the risk of PN.

Vitamin deficiency can aggravate PN, and supplementation with vitamin B complex concurrently with d4T or ddI therapy may be advisable. Should a PN occur, the best management would be to remove the offending drug and substitute a safer drug such as tenofovir. Amitriptyline in a low dose (25 mg nocte) may assist with pain. Should discomfort continue after withdrawal of all agents linked with PN, a specialist opinion should be sought.

### Gynaecomastia (efavirenz)

Gynaecomastia, or an increase in breast tissue (with no other body changes), has been noted with the use of some antiretrovirals including efavirenz. It may be uni- or bilateral and there should be no lactation. Other causes of gynaecomastia should be excluded, such as hormonal abnormalities (pituitary abnormalities) and other medications (e.g. oestrogens) and hormonal causes.

A drug switch should be considered if the gynaecomastia causes distress, otherwise it usually resolves spontaneously over a year or two.

### Switching ART due to an adverse effect

A clinician may elect to change a medication causing an AE for another, usually in the same class. If an adverse effect occurs in the first few months of treatment, e.g. anaemia due to AZT, another NRTI such as tenofovir or d4T may be substituted for the AZT.

In the longer term, the clinician must be more cautious when swapping medication. Some side-effects have a negative impact on adherence and a few months on therapy without complete adherence may result in virological breakthrough and the development of HIV resistance. Replacing one drug in such failing regimen is not advised as resistance will develop rapidly to a medication that could otherwise be used as part of a completely new regimen.

- *Check the viral load is suppressed before making a swap of medication due to AEs.*

### Interrupting treatment

An adverse effect may also require a complete interruption in ART. Both doctor- and patient-initiated abrupt treatment interruptions may expose an individual to sub-therapeutic drug levels, particularly of NNRTIs due to their prolonged half-life compared with companion NRTIs. Such interruptions have been linked to virological failure.

In the event of stopping ART due to NNRTI toxicity the NRTI backbone should be continued for a week after the stop date in order to cover the NNRTI tail.

In the event of needing to stop NRTIs, the whole regimen should be stopped and the NNRTI tail covered by a week of lopinavir/r (standard dose).

In general, PI-based regimens with 2 NRTIs can be safely stopped without adjustment.

- *Cover the tail of NNRTIs when stopping an ART regimen.*

References available at [www.cmej.org.za](http://www.cmej.org.za)

## SINGLE SUTURE

### *Aloe bad for rats*

Aloe vera food supplements and drinks are supposed to help your gut stay healthy – or so herbalists claim. But now a warning flag has been raised by the US National Toxicology Program, which has found that some rats developed tumours after drinking water spiked with an extract of the plant.

The rodents were given relatively high doses of a whole-leaf extract of aloe vera over two years. In rats that had drunk water containing 1.5% by weight of the extract, 39% of females and 74% of males had malignant or benign tumours of the large intestine. None of these growths were seen in rats given pure drinking water.

The prime suspect for causing the tumours is aloin A, which together with other aloe extracts was removed from laxatives sold over the counter in US pharmacies in 2002 because manufacturers had not provided the US Food and Drug Administration (FDA) with sufficient safety information.

‘We’re looking at designing the next round of experiments,’ says Daniel Fabricant at the FDA. ‘We want to relate the results to the products that are out there.’

*New Scientist*, 16 April 2011, p. 7.