

# HATiP

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# How frequently are ARV side-effects being seen in resource-limited settings, and how are they dealt with?

By Keith Alcorn and Theo Smart

Now that antiretroviral therapy is beginning to become available on a large scale, and across a wide range of populations in Africa and Asia, evidence is beginning to emerge about the variations in side-effects and tolerability between different populations.

In particular, side-effects associated with nucleoside analogue treatment, and stavudine (d4T, *Zerit*) especially, attracted a lot of attention at the Thirteenth Conference on Retroviruses and Opportunistic Infections.

Unfortunately these side-effects have been seized upon in a misleading way by AIDS denialists in South Africa as part of a shameless and highly misleading campaign to derail the roll-out of antiretroviral therapy in a country desperately in need of wider treatment access. AIDS denialists claim that side-effects experienced by people on treatment are a sign that antiretrovirals are 'poisoning' South Africans.

"It is really shocking what damage [these] lunatics are doing to HIV care," said Dr Halima Dawood of King Edward's Hospital in Durban. "HIV is a disease that results in death and while the drugs have side effects, we are able to keep patients alive with the drugs."

Indeed, any rational, evidence-based approach to HIV treatment will reject such scare-mongering claims — unfortunately, these tactics do sometimes steer patients away from going on treatment. According to Chris Green, a treatment educator working with the Spiritia Foundation in Jakarta, Indonesia, "the word gets around. In our experience, a number of people who are probably inclined to avoid taking drugs when they feel well decide to delay starting ART because of these concerns."

It is also important to understand that drug toxicity is one of the major obstacles to good adherence, so careful observation of toxicity, education of patients and timely response to their concerns is a necessary part of HIV management.

## What toxicities are being commonly reported?

Toxicities most commonly reported in cohort studies from resource-limited settings presented at the Thirteenth Conference on Retroviruses and Opportunistic Infections included:

- Peripheral neuropathy (damage to the nerves in the feet and legs, caused by d4T, universally reported as the most common serious toxicity)
- Lactic acidosis (a build-up of lactate in the body)
- Rash (caused by nevirapine)
- Anaemia (caused by zidovudine (AZT))
- Lipoatrophy (loss of fat from the limbs and face, chiefly caused by d4T, more prominently a problem in reports from Rwanda and India than from Uganda, South Africa or Kenya)

## Peripheral neuropathy

In a Ugandan report on 1037 patients receiving d4T-based therapy through a home-based care programme for up to 18 months, 36% had developed peripheral neuropathy. In 10% of cases it was severe (grade 3 or 4), but the proportion of patients who switched treatment because of peripheral neuropathy was not specified.

A Kenyan study of 283 people receiving ARVs in the slum district of Kibera found that 23% of patients receiving a d4T-based combination had developed peripheral neuropathy after close to a year on treatment. Three per cent had developed severe neuropathy by this point. (Full report

<http://www.aidsmap.com/en/news/48A79438-B95F-49B9-90FB-B8D4A246C5DC.asp>)

In Khayelitsha, South Africa, a study of around 1700 patients treated for up to 36 months found that the rate of switching from d4T due to peripheral neuropathy was 17 cases per 1,000 years of patient follow-up. (Full report

<http://www.aidsmap.com/en/news/2AF3CBB2-4B24-407C-B905-6354C1E548B7.asp>)

These rates are similar to those seen in the developed world.

Peripheral neuropathy may be caused by HIV, but in the Ugandan study patients with neuropathy prior to treatment were excluded from the analysis. Peripheral neuropathy is also caused by d4T, and the risk is increased when the drug is used alongside ddI (didanosine).

Neuropathy may be more likely when d4T and isoniazid are used together — which is an argument for closer communication between the TB and HIV clinic, and also a cause for concern as more patients on ART are put on isoniazid preventative therapy for latent TB.

The major symptom of neuropathy is pain, which can range from tingling discomfort through to burning sensations and a super-sensitivity to touch. This extreme sensitivity can be so severe that just wearing shoes or socks or lying under bedclothes can be unbearable. These symptoms are usually symmetrical, affecting both sides of the body equally.

According to Chris Green, a treatment educator working with the Spiritia Foundation in Jakarta Indonesia, "severe peripheral neuropathy can be incapacitating — and is frequently irreversible, with no effective treatment."

So it is crucial to promptly diagnose peripheral neuropathy, usually on the basis of the symptoms, especially abnormal sensations in the feet and reduced or absent ankle reflexes.

Peripheral neuropathy should be managed by switching from d4T to AZT. Peripheral neuropathy will continue to worsen if d4T treatment is maintained, although some clinicians say that providing the neuropathy has cleared up, d4T treatment can be resumed later, at a lower dose.

However, for patients paying for their own treatment, switching to AZT, which costs slightly more in some settings can be difficult. In fact, in an Indian study, peripheral neuropathy was the leading cause for people to switch off of d4T — but according to the authors "despite the high incidence of d4T-related toxicities, including... peripheral neuropathy, d4T continues to be widely used because of its low cost." (Full report

<http://www.aidsmap.com/en/news/DFE0AD54-F746-47B9-A490-B08190959082.asp>)

Neuropathy guide

<http://www.aidsmap.com/en/docs/DBECFD18-184C-410F-91BC-1E9703317188.asp>

## Lactic acidosis

Lactic acidosis is the condition caused by over-accumulation of lactate in the bloodstream and tissues, which the body is unable to clear.

Lactic acid and lactate are produced when glucose is broken down by the body's cells to produce energy. More lactate is produced when oxygen supply is limited, such as during exercise, or in certain types of cells, or when the mitochondria, organelles inside the cells that normally produce energy, are not functioning properly.

Elevated lactate is rather common in patients treated with nucleoside analogues (up to 25%) but there are usually no symptoms. However, in some cases there can be an abnormal accumulation of lactic acid in the blood, 'hyperlactataemia' or lactic acidaemia, that may be associated with symptoms such as fatigue, breathlessness, abdominal pain and weight loss.

If the condition worsens, the patient may develop lactic acidosis, which may occur in conjunction with severe hepatomegaly (enlarged liver). The patient may suffer respiratory failure and fall into a coma.

In patients on ART, lactic acidosis is attributed to nucleoside analogues, particularly d4T, ddI (especially the combination of d4T/ddI) and AZT, which all can cause damage the mitochondria. It primarily occurs in women, particularly pregnant women, who have been on ART for several months.

In resource-rich nations, lactic acidosis is a quite rare though a potentially fatal side effect.

However, in South Africa, "We see plenty!" said Dr. Francois Venter, Clinical Director, Esselen Street Project in Johannesburg, and currently president of South Africa's HIV Clinician's Society.

A South African study reported at the Thirteenth Conference on Retroviruses and Opportunistic Infections found that lactic acidosis is occurring at an unusually high frequency in patients receiving either d4T or AZT-based antiretroviral therapy.

The South African study found an incidence of 15 cases per 1000 years of patient follow-up (almost as high a frequency as that reported for peripheral neuropathy in the same study).

The risk of developing lactic acidosis seemed to be greater in women with a higher body weight – which, for cultural reasons, is much more common in South Africa than in most other settings.

Multivariate analysis found that women weighing 75kg or more had an adjusted hazard ratio of 25 for lactic acidosis when compared with males, while women weighing between 60 and 75kg had an AHR of 5.6 for lactic acidosis. Weight gain of 5kg or more by month 3 of treatment carried an AHR of 2.5 for lactic acidosis. (all  $p < 0.01$ )

Discussion following the presentation could not offer a biological explanation for this phenomenon, but questions from the floor revealed that a similar trend has been seen in the Botswana treatment programme.

(For further details see

<http://www.aidsmap.com/en/news/2AF3CBB2-4B24-407C-B905-6354C1E548B7.asp>)

As already noted, asymptomatic lactate elevations are fairly common and a number of studies have found that individual measurements of lactate in the blood are a poor predictor of the subsequent risk of developing lactic acidosis. Routinely screening lactate levels could therefore be misleading – and impractical in many settings (see below).

So diagnosis starts with the symptoms. Initial signs of high lactate levels include loss of weight, nausea and vomiting, lack of appetite and malaise, as well as fatigue and difficulty in breathing. Muscle pain and numbness or tingling sensations have also been reported. In lactic acidosis, the liver may become swollen and tender, and liver enzymes may be elevated. Symptoms of acute lactic acidosis include severe difficulty in breathing, hyperventilation and stupor.

A diagnostic algorithm has been developed by the South African HIV Clinicians Society, which just published "Guidelines for the prevention, diagnosis and management of nucleoside reverse transcriptase inhibitor-associated symptomatic hyperlactataemia and lactic acidosis" (the full guidelines are due to be published shortly at <http://www.sahivclinicianssociety.org/>)

Any patient presenting with signs of hyperlactataemia or lactic acidosis (see algorithm figure A) should have their lactate levels checked immediately as a delay in diagnosis can be life-threatening.

Measuring lactate requires specialised equipment which can be a challenge in settings without convenient access to a reference laboratory (specimens must be centrifuged and transported on ice). Point-of-care devices have been developed, however, which can be used at primary care and rural facilities (Accutrend lactate portable lactate analyser; Sports Resource Group, Inc., USA). These devices can reliably determine lactate levels within  $\pm 1$  mmol/l of the laboratory measurement. They are now being used to diagnose ART-related lactic acidosis in rural clinics across Haiti, according to a recent letter in AIDS (Ivers and Mukherjee).

If lactate levels are below 2.5mM, the diagnosis has been excluded and other causes should be investigated. However, when lactate levels are higher, action must be taken.

If lactate is not available, an alternative is standard bicarbonate ( $< 15$  suggests severe lactic acidosis). Venous or arterial pH also useful, but only becomes abnormal if severe lactic acidosis.

Even if no laboratory is available, and these tests cannot be performed, – the clinician should err on the side of making the diagnosis of lactic acidosis and treating sepsis, while investigating other causes.

The South African guidelines are based on expert experience rather than prospective clinical trials and may change as more evidence becomes available, and practice may vary somewhat by setting. Management for moderate or severe lactic acidosis (lactate  $> 5$  mM, with bicarbonate  $< 15-20$ ) typically consists of hospital admission, and maintaining adequate hydration and bicarbonate administration. Patients may also need respiratory support. All antiretrovirals should usually be discontinued until lactate levels have returned to normal (see algorithm figure B).

Lactate levels may take some months to return to normal levels, suggesting that abnormal lactate production by damaged mitochondria takes some time to correct.

Lactic acidosis guide

<http://www.aidsmap.com/en/docs/OBFBE157-F1FB-40C4-8540-D6692F734438.asp>

## Anaemia

Anaemia is a frequent condition in resource-limited settings and is a major risk factor for death in the first year of treatment. For further details see:

<http://www.aidsmap.com/en/news/52DCF142-EA42-430D-B1B3-C E93E63E1DBB.asp>

Anaemia can also be caused or worsened by AZT. This is a major reason for the avoidance of AZT in first-line therapy in resource-limited settings, and since all the cohorts reported at the Thirteenth Conference on Retroviruses and Opportunistic Infections used d4T-based regimens in the vast majority of patients, it is a little difficult to characterise the frequency of this side-effect, or highlight variations in its frequency between different regions.

However, the Khayelitsha cohort, in which AZT was used as the basis of a first-line regimen in the early years of treatment, found that 8.2% of AZT-treated patients had switched from the drug after 24 months of treatment, 82% of whom switched due to anaemia.

However, in some parts of the world, as doctors appear to be becoming more comfortable with AZT as first-line. According to Chris Green in Indonesia, "The national preferred regimen is AZT/3TC/NVP. Generally patients are only switched to d4T if they experience side effects (mainly anaemia) from the AZT. But I think that doctors are too quick to blame AZT, and rarely really look for all the causes. Recently, I heard from doctors in Thailand that they switch back to AZT after six months or so once haemoglobin is normal, to avoid the long term problems of d4T."

Aidsmap.com overview of anaemia and its treatment:

<http://www.aidsmap.com/en/docs/4B95EF8B-A38A-4FFB-BD5B-4 D87339162B4.asp>

## Rash

Severe rash is a potential side-effect of nevirapine. It occurs during the first month of treatment in 16-20% of patients, but is usually mild and self-limiting, passing within a few weeks. Its frequency does not appear to be any greater in African populations than in developed world cohorts. In the Uganda home-based care study discussed above, 6% of patients reported rash (1000 of 1037 received nevirapine in this study). In 2% of cases rash was classed as severe. Four per cent of patients who received nevirapine (approximately half of those who developed nevirapine-related side effects such as rash, hypersensitivity or acute hepatitis) had to switch to efavirenz due to side-effects.

In the Kenyan study discussed above, 20% of patients experienced a rash, but only 1.4% (four patients) switched treatment. In the Khayelitsha cohort 8.9% of patients had switched from nevirapine after 24 months of treatment. Most switches from nevirapine occurred in the first six months of treatment.

However in an Indian cohort reported last year, 13% of patients switched from nevirapine due to side-effects, predominantly rash. However liver toxicity was also a prominent side-effect, occurring mainly in patients taking concomitant TB medication. (Full report see

<http://www.aidsmap.com/en/news/DFE0AD54-F746-47B9-A490-B 08190959082.asp>)

Management of nevirapine rash is discussed in the aidsmap.com overview of nevirapine:

<http://www.aidsmap.com/en/docs/5416032E-A9FB-4351-9863-5 D7F04ED8E07.asp>

## Lipoatrophy

However, even though it is not life-threatening, the side effect that, in seems to generate the most scare-mongering is lipoatrophy, the loss of fat on the arms, legs, buttocks and face (facial wasting).

"I have had women who have stopped their treatment because of it," said Dr Francesca Conradie of Helen Joseph Hospital in Johannesburg South Africa. "We have 4000 patients our programme and are enrolling two women for each one man. d4T is in our first line. With the program being 20 months old, we are seeing more and more lipoatrophy. It is disfiguring."

The causes of fat loss during antiretroviral treatment are still not fully understood, but analysis of clinical trials shows that two drugs, d4T (stavudine) and AZT (zidovudine) are strongly associated with the syndrome. These two drugs damage fat cells by inhibiting a component of the DNA of mitochondria, small bodies within human cells that generate energy for the cell's everyday processes. Other toxicities of the two drugs, such as peripheral neuropathy, are also due to mitochondrial damage.

However, not everyone who is treated with these drugs will experience fat loss or other mitochondrial toxicities. Other factors seem to increase the risk of fat loss when treated with AZT or d4T:

- High triglyceride or cholesterol levels before starting treatment
- Large increase in triglycerides within the first two months of treatment
- Older age (above 40)
- Hepatitis C coinfection
- AIDS diagnosis
- Use of AZT or d4T in combination with a protease inhibitor

However an analysis of one study, ACTG 384, presented last November at an international workshop on lipodystrophy (see <http://www.aidsmap.com/en/news/3B58DF3A-E1A1-447D-A18F-6 ADFD17C2B6A.asp>), found that drug effects were more important than any other previously identified risk factors, and that a low CD4 cell count before starting treatment did not increase the risk of fat loss.

How frequently does it occur?

Surprisingly few prospective studies have been able to come up with reliable observations on the proportion of people who develop lipodystrophy after exposure to specific drugs. Cross-sectional studies (studies which take a snapshot of people at one specific point in time) have come up with estimates as high as 30-40%, but the more reliable prospective studies, which follow people over a number of years show a lower prevalence.

A cross-sectional study in India, for example, showed that 26% of d4T-treated patients and 10% of AZT-treated patients had developed lipodystrophy after median of 18 months of treatment with triple therapy that also included nevirapine and 3TC (Pujari 2005) (see

<http://www.aidsmap.com/en/news/B15C0D05-95D8-42BF-ABEF-E 51EF79E10BE.asp>)

In the Gilead 903 study, which compared two backbones (d4T/3TC vs tenofovir/3TC) in combination with efavirenz, 12% of the d4T-treated group had developed some degree of fat loss after two years of treatment in the opinion of their doctor, compared with less than 1% of the tenofovir group.



In the ACTG 384 study which compared backbones of AZT/3TC or d4T/ddI combined with either nelfinavir or efavirenz, a 102 person substudy of patients evenly distributed between the two nucleoside backbones found that after 64 weeks on treatment, 44 of the d4T group had developed lipoatrophy, compared with 17 in the AZT group, a highly significant difference ( $P=0.006$ )

(see

<http://www.aidsmap.com/en/news/3B58DF3A-E1A1-447D-A18F-6ADFD17C2B6A.asp>)

Subsequent studies have tended to observe the development of lipodystrophy by measuring limb fat levels with a test called a DEXA scan, because this is a more objective measure, and plot the degree of fat loss in each treatment group rather than the proportion of patients who experience fat loss. This method is able to pick up more subtle differences and removes observer bias.

In the Gilead 934 study, which compared AZT/3TC with tenofovir/FTC, limb fat levels remained stable over 96 weeks of follow-up in those who received tenofovir, but fell significantly in those who received AZT (see

<http://www.aidsmap.com/en/news/CC754D1C-9F1C-4A59-B32C-8D6D450B7EAA.asp>).

Several members of HATIP advisory panel reported lipoatrophy in their patients, but it is difficult to say whether there are differences by region or ethnicity. According to Dr Gerald van Osch, who practices on the Caribbean island of St. Maarten, which has a mixed, multi-ethnic population, "Yes I'm seeing lipoatrophy rather frequently in a mix of black and white patients. I have no percentages available, but roughly 5 – 10 % seems a reasonable guess."

How quickly does it occur?

Some treatment programmes tell us that they are seeing very little lipoatrophy in patients yet. At present it's not clear whether there may be a genetic differences between Africans, Asians and Europeans, or even between one ethnic group and another within the same country, that means lipodystrophy will occur at different rates, or whether it's too early to tell. [Given that we don't know what genetic difference we are looking for, it seems rather premature to think in terms of races... however those are defined].

Several well-designed studies have found that people will typically gain body fat during the first six months of treatment, and thereafter lose fat from the limbs at a rate of around 13% of total limb fat per year (Mallon 2003; Lichtenstein 2002). However total body weight may remain relatively stable, because limb fat makes up a small proportion of the total body mass. Unfortunately the loss of limb fat and facial fat is highly noticeable, and creates an appearance that most people would identify as sick.

Fat can also accumulate in the abdomen, around the organs, leading to the appearance of a swollen belly. The accumulation of fat in the organs is not a redistribution of fat from the limbs; the processes of fat loss and fat gain in HIV lipodystrophy seem to occur by separate mechanisms (

<http://www.medscape.com/viewarticle/443352>).

How do the patients react?

Our advisory panel reported markedly different reactions to lipoatrophy among their patients — but then they serve very different populations. Some, such as the women at Dr Conradie's hospital in Johannesburg, are so distressed that they discontinue treatment, and this is similar to reports we've heard from Khayelitsha in the Western Cape.

Dr Dawood, however, practising in KwaZulu Natal says "it does not appear to worry the patients tremendously, especially after I explain that it is a side effect of the drugs and which drug causes it.

I also try and counsel the patients from early on, on what to expect." But she notes, "the main problem seems to be the comments from friends and people at work."

According to Dr van Osch, "Only a few in our clinic are actually bringing up the lipoatrophy problem themselves. Most don't mention it or even when I mention it to the patients they say it's not that much of a problem. Apparently there is less of a cosmetic pressure in our multi-cultural society (Caribbean, St. Maarten) compared to many Western countries."

"It is not an issue that prevents people to go on treatment. Patients in general are way too happy to be able to receive treatment. They hardly worry with side-effects. They see it as a task for the doctor to deal with."

Reactions clearly are different from one culture to another — and much of this may be amplified where there is a fear of Western medicine, or even the medical practice or pharmaceutical products. In Indonesia, Green noted, "Fear of side effects in general, including this, but more specifically Stevens Johnson Syndrome from nevirapine sometimes does impact people's willingness to go on or continue treatment, particularly (for unclear reasons) in Bali. I suspect lipoatrophy may impact more as the problem becomes more widespread in a year or two."

He also noted though that Indonesians as well, may not be as worried about physical appearance as some risk groups in Western countries are. "The aging process occurs rapidly in Indonesia," he said "usually starting around age 30, and maybe lipoatrophy will be seen as just another sign of this?" How can it be avoided?

Lipoatrophy is best avoided by using tenofovir or abacavir rather than stavudine or zidovudine. British and US treatment guidelines now recommend that stavudine and zidovudine should be avoided.

"I think that putting tenofovir in the first line would solve many of our problems," said Dr Conradie. Dr Dawood agrees, adding that "tenofovir should also be first line because of lactic acidosis."

However that's easier said than done in most resource-limited settings where AZT and d4T form the mainstay of cheap fixed dose combinations. Progress towards cheaper fixed dose combinations that include tenofovir or abacavir is slow.

Indeed tenofovir, manufactured by Gilead, is only registered in six countries, despite the fact that the drug is now being offered at \$357 and Truvada at \$296 to least-developed countries and most countries in Latin America and the Caribbean. In South Africa both products are licensed by Aspen Pharmacare, but neither product is yet registered in South Africa.

Despite a recent announcement by the Clinton Foundation of a reduced price for generic abacavir, the price ceiling has been set at \$440, which suggests that driving that price down will require massive increases in volume and further competition between manufacturers.

So moving towards the use of combinations that do not cause fat loss would more than double the cost of ART.

In the meantime the only treatment proven to reverse fat loss in a small preliminary study, a food supplement called Nucleomaxx, costs around 700 euros a month, considerably more than the cost of triple drug ART.

<http://www.aidsmap.com/en/news/104869B7-DFA8-4768-ADB5-D00A4DB77F3.asp>

How to manage patients in the meantime

Several of our panel members suggested changing treatments, "I agree with the dump d4T campaign," said Dr Conradie. Dr van Osch has the option of switching patients to tenofovir, but in South

Africa, the best Dr Conradie can do is “change them to AZT as soon as we see it.”

Everyone agreed on the importance of counselling. Dr Dawood describes the lipoatrophy upfront. “I tell them that the drugs may cause changes in body shape eg. the veins on the leg may start showing, the cheeks on the face may get thinner and the back of the neck may develop a fat pad.”

Chris Green told us: “We do refer to it in our briefings/trainings to peer educators, but try not to over-emphasise it. We note that while at this time there is no clear treatment for lipoatrophy, there is much research going on to determine the cause as well as identify solutions, which may become available before it becomes a problem for them.”

Meanwhile, Dr van Osch spreads his warnings out over time “Usually I only discuss the short term side-effects with them, depending on the combination prescribed – the side-effects they have to recognise and which we can treat or make more bearable. The long term side-effects I discuss later and bit by bit.”

“I think it’s important for persons to know what the obstacles are, but at the same time I don’t think it makes sense to delve them under a load of all the possible side-effects right at the beginning of the treatment. Patients in our region tend to take life and their disease day by day, and step by step, so I tend to go along with that approach as far as education concerned.”

It also depends on the relationship you have with each patient. The appropriate approach will of course vary by culture and by patient. For Dr van Osch, each patient typically comes from a different culture. “On our island we deal with many different cultures, races, literacy levels and socio-economic levels (last census count 105 different countries represented on our island), which makes it even more interesting but also sometimes challenging to deal with the different ways people deal with their infection/treatment.”

“Some are very interested in all the aspects of treatment and you discuss it broadly with them. Many are still stuck in a very dependent doctor-patient relationship and only slowly can you educate them on their own responsibilities for their health and treatment. Others are really not interested or due to education/literacy challenges just don’t always understand.

In HIV treatment when a person comes in with a CD4 of 3 – 10, an opportunistic infection and a viral load of over 300,000 you sometimes just don’t have the time to sit and discuss all the risks. This doesn’t mean you will never discuss these issues with them,

but rather discuss the most important issues first and take the rest as it comes.”

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## about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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