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Peripheral neuropathy in people with HIV in resource-limited settings

Reviewers

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Introduction

It may **start** with a slight tingling or numbness in the toes or ball of each foot— something so minor that you don't think anything of it.

Whether caused by HIV, the toxic effects of medications (like ddI or d4T), alcoholism, diabetes or other factors, damage to the peripheral nerves — peripheral neuropathy — can be insidious. In fact, people commonly attribute their own early symptoms to poor blood circulation, a poor night's sleep, being cold, or an injury from work or exercise.

Different people may experience different symptoms, ranging from a loss of sensitivity, to paraesthesias (pins and needles or burning sensations) and an extremely heightened sensitivity to touch. But as it worsens and moves up from the feet to the ankles and legs, the sensory changes become increasingly persistent. And yet, the most common reaction to the first subtle symptoms is to ignore them or perhaps to self-medicate, taking things like paracetamol, herbal remedies or an alcoholic beverage.

Peripheral neuropathy is the most frequent neurological complication in HIV infection. But all too commonly people don't seek out medical attention or tell their care provider until the condition starts to become debilitating and interferes with sleep and the ability to work. And since walking and balance may remain normal until the condition becomes severe, healthcare workers who don't routinely screen for it may not become aware that their patient has peripheral neuropathy until it become very difficult to manage, if not irreversible.

This can even happen to some of the best-informed people with HIV, possibly because their health is otherwise improving on antiretroviral therapy (ART). For instance, the following case study describes the experience of Zachie Achmat, of South Africa's Treatment Action Campaign.

"I felt so much better, my headaches and infections had cleared up, my energy was flooding back, my CD4 count was rising and my viral load was coming down. My treatment was working. Going into my fifth month I started to feel a tingling sensation in my feet. At first, I dismissed it, thinking I'd done something at the gym.

When I finally told the doctor about my symptoms my feet were so sensitive I could hardly walk. My friends and my doctor had warned me about taking d4T in my combination as I already had mild peripheral neuropathy before I started ARVs because of HIV...

*All that was required was for me to change a drug – from d4T to AZT. I didn't do that quickly and instead nearly incapacitated myself for two, three months and only now am I starting to come out of it."*¹

But at least Achmat's doctor warned him. In many clinical settings, it doesn't seem to be on the radar screen.

"We did some work on d4T toxicity, and the experience in Kinshasa is that most patients do not complain and that nurses are not well trained in recognising it," said Dr Annelies van Rie of the University of North Carolina.

"In general I don't think neuropathy is so much on the clinician's agenda - up till recently the focus has been on getting drugs to keep people alive," Professor Bruce Brew, Head of Neurology at the University of New South Wales in Australia told HATIP. "But now that these drugs are increasingly available there has to be a shift in mind-set. Additionally, neurological complications including neuropathy are paid little attention - it is a problem with any disease that spans several specialities."

But recent data suggest that as people with HIV age and spend a longer time on treatment, more and more people may develop peripheral neuropathies, despite effective ART. Although data are currently limited, the situation may prove worse in many resource-limited settings — where antiretroviral drug options are limited — and where people often have multiple risks factors for neuropathy including poor nutrition, diabetes, and the toxic effects of commonly used medications.

As increased vigilance for peripheral neuropathy seems more than warranted, especially since early detection and intervention could help avoid a lot of unnecessary pain and suffering. And at present, finding ways to avoid peripheral neuropathy may be the best way to manage it, because the available treatment options appear to be woefully inadequate.

Background on the spectrum of neuropathies seen in people with HIV or in resource-limited settings:

The peripheral nervous system (PNS) consists of the nerves connecting the central nervous system to the rest of the body. In a general sense, peripheral neuropathy refers to a dysfunction or damage of one or more peripheral nerves.

In HIV disease, when people say peripheral neuropathy, they are usually referring either to:

- **distal symmetrical sensory polyneuropathy (DSPN)**, sensory neuropathies starting in the extremities (spreading up from the toes, and rarely, from the fingers) more or less on both sides of the body equally and/or

- **antiretroviral toxic neuropathy (ATN)**, which is clinically indistinguishable.

But a host of things can go wrong with the peripheral nervous system ranging from minor transient neuropathies (such as one's foot falling asleep) to neurological emergencies that can lead to paralysis, loss of essential bodily functions and then death.

The most common conditions are focal or mononeuropathies (disorders of a single nerve or nerve group) and radiculopathies (disorders affecting the roots of the spinal nerve) that may cause sensory disturbances and/or weakness in one part or on one side of the body, including injury-related mononeuropathies such as carpal tunnel syndrome (compression of the median nerve in the wrist).

In people with HIV, a number of PNS disorders seem to be either caused by the virus, opportunistic infections or neoplasms, by commonly used medications, or by the immune system's reaction to infection. These can be roughly distinguished by how the condition is localised (whether the disorder is focal or multifocal, and whether or not it is symmetrical), and whether it is primarily sensory (like DSPN or ATN) versus whether it also causes weakness and loss of motor/autonomic functions — though there can be some overlap in some situations. [This review will not address spinal cord problems, myelopathies or myopathies.]

What do all those initials stand for? A neuropathy glossary

AIDP	: acute inflammatory demyelinating polyneuropathies
ATN	: antiretroviral toxic neuropathy
BMI:	body mass index
CIDP	: chronic inflammatory demyelinating polyneuropathies
CMV	: cytomegalovirus
CROI	: Conference on Retroviruses and Opportunistic Infections
ddI	: didanosine
d4T	: stavudine
DSPN	: distal symmetrical sensory polyneuropathy
EMG	: electromyography
GBS	: Guillain-Barré Syndrome
MM	: mononeuritis multiplex
mtDNA	: mitochondrial DNA
PN	: peripheral neuropathy
PNS:	peripheral nervous system
SPN:	symptomatic peripheral neuropathy

Focal/asymmetrical deficits

Focal neuropathies are those which focus on one nerve or one place in the body. People with HIV are more prone to develop **lymphomas**, which can compress nerves or directly involve the nerve roots, and cause different focal disorders depending upon the site of the

lymphoma.^{2, 3} Similarly, **tuberculosis** appears to cause focal neuropathies.^{4, 5, 6}

But the pathogen with the greatest predilection for the nervous system is **varicella zoster virus (VZV)**, which can cause postherpetic neuralgia and radiculopathies with lingering asymmetric pain and motor weakness and sometimes more extensive polyradiculopathies too.^{7, 8} However, VZV related conditions are generally recognisable because they tend to be associated with the characteristic painful shingles rash.

In people with HIV, a number of things appear to cause **mononeuritis multiplex (MM)**, painful asymmetric sensory and motor peripheral neuropathies involving isolated damage to more than one independent nerve area, usually as the result of a lack of oxygen due to decreased blood flow or inflammation of blood vessels. For instance, this has been reported in people with hepatitis B and C in people with or without HIV.^{9, 10, 11}

HIV itself can also trigger MM; for instance, a number have been reported to develop a **brachial neuritis** (Parsonage-Turner Syndrome), characterised by the acute onset of shoulder pain followed by weakness of the related muscles, usually during primary infection.^{12, 13} Other forms of MM can occur later but as long as the CD4 cell count is above 200, the condition tends to be less severe and self-limiting.^{14, 15} Bell's palsy and other isolated cranial/facial nerve palsies have also been observed to occur in people with HIV in early and late stage disease.^{16, 17, 18}

However, in patients with less than 50 CD4 cells, CMV can cause a severe life-threatening form of MM affecting multiple nerves and muscles, often surrounding the pectoral/shoulder girdle.^{19, 20}

Also in very late stage HIV disease, CMV can infect and destroy nerve roots around the spinal cord causing **CMV polyradiculopathy**.^{21, 22, 23, 24, 25} This is a neurological emergency with rapid progression of symptoms ranging from loss of feeling and reflexes in the lower limbs and back pain to paralysis, urine retention, and loss of normal bowel function. CMV polyradiculopathy can be fatal within days or weeks of presentation unless it is promptly treated with empiric ganciclovir, which can also lead to partial recovery. The condition is usually observed in people with some concurrent CMV disease (such as retinitis, encephalopathy or gastroenteritis). However, there have also been reports of neurosyphilis, VZV, and lymphoma causing polyradiculopathies.^{26, 27, 28}

Symmetrical sensory and motor polyneuropathies

Other symmetrical neuropathies may also begin with tingling and numbness in the hands or feet, including **acuteinflammatory demyelinating polyneuropathies (AIDP)**, such as **Guillain-Barré Syndrome (GBS)**, and **chronic inflammatory demyelinating polyneuropathies (CIDP)** — but these soon progress with marked muscle weakness and then paralysis in the leg, arms, face, and even the respiratory system (this is rare, but represents another neurological emergency).^{29, 30}

GBS is an autoimmune reaction that typically occurs within a week or two of a gastrointestinal or respiratory infection — and it appears that HIV can trigger a similar reaction in susceptible people. With AIDP, progression occurs within hours, days or weeks but reaches a maximum within four weeks; with CIDP deterioration may continue over months. GBS can be triggered in people by relatively minor infections, but has been observed in people soon after infection with HIV, including one series from Zimbabwe.³¹

A similar syndrome of sensory neuropathies and muscular weakness, now being called HIV-associated neuromuscular

weakness syndrome, has also been associated with mitochondrial toxicity after taking nucleoside analogues, particularly d4T (stavudine) and is commonly a sign of lactic acidosis.^{32, 33} Of note, the antibiotic dapsone can also produce a sensory/motor neuropathy with marked muscular atrophy but with a delayed onset.^{34, 35, 36}

Distal sensory (axonal) polyneuropathies

It is usually possible to distinguish most of the above neuropathies from the more common **sensory bilateral neuropathies** such as DSPN or ATN (which both primarily affect the axon or ganglion) on the basis of clinical features.

If a neuropathy is asymmetric, or if there is a pronounced or rapid development of weakness and loss of motor or autonomic functions, then by definition, **it isn't a sensory neuropathy**. The stage of HIV disease at which the symptoms occur is also an important consideration.³⁷

HIV-related sensory neuropathies

(or HIV DSPN) can start to develop when CD4 cell counts are higher, but they are more commonly seen in people with CD4 cell counts below 200 (see more below).

The neuropathies tend to have a gradual onset, usually starting with numbness, a sensation of pins and needles or pain in the most distal part of the longest nerves, in other words, in the toes or anterior plantar surface (balls) of each foot, which then spreads up to the rest of each foot, to the ankles and beyond.³⁸ Similar sensations may start to develop in the fingertips and hands, at about the same time pain begins to reach the middle of the leg, so sensory neuropathies are said to have a stocking and glove distribution.³⁹

People with similar degrees of (measurable) sensory loss may have very different perceptions of the pain, anything from a prickling or tingling discomfort, to tightness and aching, burning sensations, sporadic shooting, stabbing pain or even electrical shocks.⁴⁰

The pain can be spontaneous or in response to touch. Some people with sensory neuropathy become so sensitive to touch that they cannot tolerate wearing shoes or socks or lying under bedclothes. Pain is often worse at night and can disrupt sleep. At the same time, ability to accurately sense heat and vibrations may also become impaired — which seems to support the hypothesis that the pain actually originates from uninjured nerve fibres after injury to neighbouring fibres.⁴¹

Motor function is preserved for the most part, and walking and balance can appear normal. If the gait is changed, it is usually as the result of an effort to avoid pain. Weakness is uncommon, though there can be somewhat reduced or absent deep tendon reflexes at ankle jerks.

walk because of his foot pain. He states that the pain keeps him awake at night.

On examination, his lower extremities appear normal. Dorsalis pedis and posterior tibial pulses are present bilaterally. Ankle jerk reflexes were diminished bilaterally.⁴²

The man in the case study above has ATN, which is clinically indistinguishable from HIV-related sensory neuropathy^{43, 44}. However, the onset may be more acute, and the pain somewhat more severe; for instance, there could be more reports of deep aching pain, particularly across the top of the foot.⁴⁵ The only real way to tell ATN apart from HIV sensory neuropathy is that it appears one week to six months after starting an ART regimen containing d4T or ddI (especially when used in combination) — and may resolve eventually in up to two-thirds of patients upon discontinuing the offending drug.⁴⁶ Again, the most notable clinical feature is pain — if instead, there is rapidly progressive weakness and high lactate the clinician should be alerted to HIV-associated neuromuscular weakness syndrome and lactic acidosis.

Other toxic sensory neuropathies

Many toxins, solvents, insecticides and medications can also cause peripheral neuropathies. Perhaps most importantly for people with HIV, this includes isoniazid when it is given without supplemental vitamin B6 (pyridoxine), but also ethambutol, ethionamide, vincristine, thalidomide, metronidazole, high-doses of vitamin B6 and other drugs. The Merck Manual Online has [a table listing the toxic causes of neuropathy](#), categorised by the types of neuropathy each drug causes. Most of the medications that may be used by people with HIV cause sensory neuropathies, though, as already mentioned, motor problems are a big part of the neuropathy on dapsone.

"Although [d4T and other d-drugs] are undoubtedly major players in the risk for PN there are other contributors," Dr John T Brooks, of the US Centers for Disease Control told HATIP. "Alcohol or solvent (e.g. glue sniffing) abuse are well known causes and these behaviours are not rarely encountered among HIV-infected persons. Indeed, persons seeking symptom relief for peripheral neuropathy might engage in these behaviours, which in turn might exacerbate their peripheral neuropathy."

Indeed, a history of alcohol overuse is associated with gradually progressive sensorimotor neuropathies, probably due to both toxic effects of ethanol and metabolites, and because of nutritional deficiencies that are often associated with alcoholism (in particular thiamine deficiency).^{47, 48} Malnutrition and nutritional deficiencies — either inadequate intake or an inability to absorb or properly utilise certain nutrients such as B vitamins, especially vitamin B12 — have also been linked with neuropathy.⁴⁹

In addition, many other things commonly cause, or could aggravate sensory neuropathy in resource-limited settings. For instance, **diabetes** (type I and II) is associated with many different types of neuropathy (mononeuropathies, diffuse neuropathies, loss of motor or autonomic functions, as well as distal sensory polyneuropathies, etc) that can lead to severe pain, foot injuries/ulcers (so severe as to require amputation), and death in cases of autonomic neuropathy.^{50, 51} Globally, about 10% of the

Case study (paraesthesias)

A 42-year-old man has been taking didanosine, stavudine and nevirapine for five months. He also takes cotrimoxazole 960 mg daily. He has gained weight and is pleased with his progress.

For several months, he has experienced tingling, numbness and pain in both his lower extremities, especially his toes. At first he took paracetamol, which offered little relief. At the last visit, a month ago, you added amitriptyline to his regimen. Today, he can hardly

population with diabetes have developed symptomatic neuropathy. Symptoms are more likely to occur in diabetics with poor glycaemic control, and there is often evidence of concurrent diabetic complications such as nephropathy, retinopathy etc. Although muscle weakness and loss of reflexes tend to be more common in people with diabetic neuropathy, many cases can be difficult to distinguish from HIV-related neuropathies.

In resource-limited settings, **leprosy** is still one of the most common causes of neuropathy with a range of clinical presentations.^{52, 53} Since symptoms of neuropathy can occur in the absence of skin lesions, it may take a nerve biopsy to be able to make a definitive diagnosis of leprosy.^{54, 55}

It must be noted that even when these other conditions cause primarily sensory neuropathies that are linked to axonal damage, they don't all cause the disorder in the same way. In fact, there are far more theories about how HIV and each of these illnesses might cause sensory neuropathies than there are ideas about how to treat them. It is safe to say that the pathogenesis of sensory neuropathies is multifactorial. Nevertheless, having any of these other conditions at the same time as HIV may increase the likelihood of developing HIV-related DSPN or ATN.⁵⁶

Epidemiology and risk factors for sensory neuropathies (DSPN and ATN)

It is difficult to pin down just how common HIV-related DSPN and ATN really are because of changes in the standard of care, differences in populations involved in the studies, and how neuropathy was measured in a study.

For instance, some studies look at easily measured clinical symptoms, others measure loss of vibration or heat sensation and reflexes the patient may not be aware of, and still others use electromyography (EMG), and nerve conduction studies that can detect subclinical nerve damage. One early review which included some autopsy studies found evidence of peripheral nerve damage in almost everyone with HIV – even though only 40% had symptoms.^{57, 58}

Based mostly on studies from the US, it is generally estimated that at least one-third of people with advanced HIV disease develop symptomatic HIV-related DSPN.⁵⁹ Another 15 to 30% of those who take ddI, d4T or ddC appear to develop ATN.^{60, 61} However, with the discontinuation of ddC (by far the most toxic nucleoside analogue) and recommendations against using ddI and d4T together, those figures could be lower.

In one early pre-ART report, clinical and EMG evidence of a distal symmetric polyneuropathy was found in 35% (13/37) of hospitalised patients without other risk factors for neuropathy. Most of the symptoms were mild, however.⁶² Another prospective study from the pre-ART era in people with less than 200 CD4 cells, reported that 36% developed symptomatic sensory neuropathy within the first year of follow-up, 52% within 24 months.⁶³ Soon after the introduction of ART, the yearly incidence of peripheral neuropathy was reported to fall to about 21%. It is not clear that the news remains as good for people on prolonged treatment however.

Recent evidence from two major studies from the US, presented this year at the Conference on Retroviruses and Opportunistic Infections (CROI) suggests the degree of immunosuppression at the time ART is commenced remains an important predictor for sensory neuropathies – while the current CD4 cell count and/or viral load is not.

At entry into the first study, called CHARTER, 57% of 1539 participants were reported to have at least one sign of DSPN

(and/or ATN).^{64, 65} Signs of DSPN included diminished ability to recognise vibration on bilateral great toes, reduced ability to reliably discriminate sharp from dull in the lower legs, feet and toes, and absent or weakened bilateral ankle reflexes compared to knees as assessed by a trained clinician using a standardised trial protocol. However, only 61% of these actually reported experiencing symptoms – in other words, a little over one-third of the entire cohort. Only 15% of those with at least one sign of DSPN reported moderate or severe pain, although reduced quality of life was reported in some subjects with only slight and mild pain (overall, 23% of those with signs of DSPN).

It is important to note that CHARTER had sought to enrol typical clinic attendees at six sites in the US. At baseline, the typical study participant was 43 years old. 77% were male; 49% were African American; 63% had already received an AIDS diagnosis, 37% had a history of previous (but not current) opportunistic infections. 26% were positive for hepatitis C. The baseline CD4 cell count was 420 (256-603), but the nadir CD4 (the lowest CD4 cell count before going onto ART) had been around 174 (49-300). The median plasma HIV RNA load was 2.3 log/mL (1.7-4.0), but 59% had detectable viral loads above 50 copies/mL. 71% were currently on ART.

In multivariate analysis, significant risk factors for DSPN (in order of importance) was older age, prior d-drug use (i.e., d4T, ddI or ddC), currently being on ART (generally a sign of having had more advanced disease), a history of opiate abuse or dependence, and having a very low CD4 cell count before starting ART.

Factors not significant in the multivariate regression were gender, CD4 recovery, plasma viral load, and history of alcohol abuse or dependence and, notably, current d-drug use (although it should be noted that the use of all the 'd' drugs, including d4T has fallen out of favour in the US and most of the industrialised world).

Nevertheless, it is worrisome that the effects of DSPN and ATN seem to be lingering, particularly in the older subjects who once had more advanced disease. While 20% of 20-29 year olds had at least one symptom of DSPN, this proportion climbed to 60% in 40-49 year olds and 75% in 50-59 year olds.

And what appears clear from an analysis of the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort is that DSPN and/or ATN is growing more common despite suppressed viral loads, higher CD4 cell counts on ART – and a decline in d-drug usage.⁶⁶

In one of the ALLRT substudies, trained non-neurologist staff administered the Brief Peripheral Neuropathy Screen (BPNS), which assesses signs (vibration sensation and ankle reflexes) and symptoms (pain, "pins and needles", and numbness) in the study participants every 48 weeks. PN was defined as at least mild loss of vibration sensation in both great toes bilaterally, or absent or hypoactive ankle reflexes bilaterally relative to knees. Symptomatic PN (SPN) was defined as PN plus bilateral symptoms.

At present, the study involves 2135 participants who were ART-naïve at study entry: 81% male, 44% white, 32% black, median age of 39 years, median viral load 4.9 log/ml and median CD4 count of 206 at ART initiation. Of note, the following analysis presented at CROI reported *only* on those participants with a good response to treatment (CD4 cell counts over 350 and viral loads below 400 copies/ml (undetectable for this study).

For instance, at week 48, 29.5% of those with undetectable viral load (n=1253) had PN, 10.1% had SPN (slightly less for those with CD4 cell counts over 350). But neuropathy was worse after each 48 week period of treatment. At week 384, follow-up data are available for 331 subjects with undetectable viral load: 44.4% have PN, 14.2% SPN.

Of note, d-drug use in the cohort peaked at week 144 (at 25%) dropping to 10.9% at week 384. Even so, PN appears to increase over time after initiation of ART. The study notes that most of this PN is not causing much pain (although around 15% of those with PN reported moderate to severe pain). However, it bears repeating, *these are just the people with good virologic responses to treatment.*

In multivariate analyses, age, d-drug use and viral load at baseline were significantly associated with both the likelihood of PN and SPN.

Neuropathies in non-white populations

Another finding from both CHARTER and the ALLRT studies, is that race did not seem to affect the likelihood of developing peripheral neuropathy.

This is in contrast to the findings from an earlier North American study, the HIV outpatient study (HOPS) where 490 (22.5%) out of 2178 people with HIV had peripheral neuropathy, and the data suggested that white race increased the risk of peripheral neuropathy (adjusted odds ratio (aOR) 1.26; 95% CI: 1.02-1.56; $p=0.033$).⁶⁷

However, other factors were much more strongly associated with peripheral neuropathy in HOPS, including (once again) age over 40 years, nadir CD4 cell count <50 cells/mm, nadir CD4 50-199 cells/mm, viral load >10,000 copies/ml (all $p<0.001$) and diabetes ($p=0.012$).

But it would be premature to conclude that the risk of sensory neuropathy will be the same across the world, without significant differences between populations. There are a number of inherited characteristics that affect susceptibility to disease, drug metabolism and toxicity. For instance, several recent studies have been exploring whether inherited differences in the haemochromatosis gene, involved in iron absorption and regulation in the body, and genetic polymorphisms (mutations) affecting the production of inflammatory cytokines such as TNF-alpha or interleukin-12B might be involved in susceptibility to neuropathy.^{68, 69, 70}

Researchers have also proposed that inherited differences in mitochondrial DNA (mtDNA, the maternally inherited DNA inside of mitochondria, organelles that are involved in cellular energy production (ATP synthesis), managing oxidant stress and apoptosis) may also play a role in susceptibility to d-drug related mitochondrial toxicity and thus, possibly, peripheral neuropathy.⁷¹

At CROI this year Dr Todd Hulgan of Vanderbilt University presented the first data from African-Americans with HIV suggesting that people from one subgroup of mtDNA (L1c) could be three times more like than other African-Americans to develop peripheral neuropathy when taking a d-drug containing regimen.⁷² Dr Hulgan has [previously published data](#) suggesting that people with the mitochondrial haplogroup T (one of about a dozen mitochondrial haplogroups found in Europe), were almost five times as likely as other Caucasian participants in ACTG 384 to develop peripheral neuropathy when taking ART regimens containing ddI/d4T.⁷³

Dr Hulgan cautioned that the sample size is rather small, and that no clear mechanism has been identified that might explain increased susceptibility to peripheral neuropathy.

"Studies to replicate this association in other African-American and African populations, are warranted and also in other ART-associated toxicity phenotypes," he said.

Indeed, there is no replacement for doing studies within Africa. The handful of studies that have been done report a significant burden of DSPN and PN in Africa and most other resource-limited settings — but rates do vary a bit and it is difficult to make

comparisons between studies using different methods to assess neuropathy.

According to a pre-ART study from Zimbabwe 60% of people with HIV had peripheral neuropathies, 37% were symptomatic, but these included some neuropathies other than DSPN (such as AIDP).^{74, 75} In a more recent study in Uganda, 47% of people with HIV were reported to have signs of peripheral neuropathy, though only 9% were symptomatic.⁷⁶ In a more recent report from the same cohort, symptoms of neuropathy developed in 38% of previously asymptomatic HIV+ patients after initiation of d4T-containing ART.⁷⁷

Also in Uganda, Forna et al reported that peripheral neuropathy was by far the most commonly reported toxicity among 1029 subjects receiving home-based ART in Tororo district, with 36% developing ATN, 9% severe.⁷⁸ Severe neuropathy was defined as having pain, moderate weakness in the feet, mild weakness in the hands, or severe sensory loss in the extremities, causing moderate interference with ambulation. Note, this analysis excluded 135 patients (13.1%) who had DSPN before going onto ART. In a multivariate analysis, age >35 years was associated with increased hazard of any peripheral neuropathy. Age >35 years and tuberculosis treatment at baseline were associated with increased hazard of severe peripheral neuropathy. Note TB treatment was given with pyridoxine.

"We believe that clinicians should pay increased attention to neuropathy, especially in persons older than 35 years and in those receiving treatment for tuberculosis," Forna et al wrote.

In Zambia, 32.2% of the HIV-positive clinic patients self-reported experiencing peripheral neuropathy symptoms (of tingling, burning, or numbness in their feet or hands) *before* going onto ART according to a report from Dr Gretchen Birbeck, of the Chikankata Epilepsy Care Team, Mazabuka, Zambia.⁷⁹ 17.3% more reported developing new symptoms after going onto ART (*Triomune*).

HATIP asked Dr Birbeck why these rates of symptomatic neuropathy seem so much higher than reported elsewhere in Africa.

"Standard *Triomune* is used here without any [d4T dose] adjustments, though the BMI of our patient population is quite small relative to the US. There are no population-based data at all out there that I know of regarding [the prevalence of] malnutrition here. We published a hospital-based period prevalence study of neurologic conditions here and have a similar one almost ready for submission from the University Teaching Hospital in Lusaka where 24.1% of outpatient visits to neurology were for neuropathies - the most common single reason for neurology consultation.

"The key issue is that neuropathies are common, but folks often have multiple reasons for neuropathies so aetiology is hard to sort out without punch biopsies. For example, people might have poor nutritional status but have also been on isoniazid (INH) without vitamin B 6 (pyridoxine) — which isn't routinely available for the TB cases on long-term INH who are already nutritionally marginalised. Diabetes isn't that uncommon here. Leprosy is still a problem too."

She noted that a new EMG/NCV machine is now available in neighbouring Malawi, and that she would like to do "some decent work on this issue in the future."

In South Africa, there are surprisingly few data. One study reported that 6% of patients put onto a d4T-based regimen switched due to peripheral neuropathy.⁸⁰ In a recent study at Kalafong Hospital HIV Clinic in Pretoria, a questionnaire was administered to 354 patients, 20.9% of whom reported having neuropathic pain prior to starting ART.⁸¹ This pain was significantly more frequent in patients who were male, had lower CD4 counts or higher viral load levels, and those on TB treatment. 80% of these reported significant pain. Note this was assessed by a questionnaire and was not a

diagnosis of DSPN, since postherpetic neuralgia and other conditions can also cause neuropathic pain. However, the pain was localised in the lower limbs in 84% and thus more likely to be peripheral neuropathy.

Patients with lower CD4+ counts ($p=0.009$) and those with higher viral load values ($p=0.006$) showed a significantly higher prevalence of neuropathic pain, as did patients with a history of recent or current treatment for tuberculosis ($p<0.001$). The authors concluded that the prevalence of neuropathic pain, “20.9% is lower than expected in comparison with previous studies in Africa and the USA.” Even so, 20% with pain before going onto ART is nothing to sneeze at. Furthermore, it is hard to compare cohorts directly. For instance, simply having a younger cohort could result in finding less symptomatic pain.

Indeed, Professor Gabriel Anabwani of Baylor College of Medicine and Director of the Botswana-Baylor Children's Clinical Center of Excellence told HATIP: “We have about 600 children who have been treated with a d4T-containing regimen for up to six years in an ongoing RCT. Only a small number have had lipodystrophy and probably none has experienced peripheral neuropathy.”

Furthermore, an analysis of the toxicity of dual nucleoside analogues in over 2233 children with HIV under 13 years of age in the US study, AIDS Clinical Trials Group 219C, reported that less than 1% developed peripheral neuropathy — even on ddI/d4T.⁸² The question is, whether they will start to develop neuropathies if they remain on the same regimens when they are older.

But there do appear to be some significant differences by population.

Associate Professor Somnuek Sungkanuparph of Mahidol University, in Bangkok told HATIP:

“I always had a belief, but no time to prove, that ethnicity has a big influence on peripheral neuropathy. I have cared for HIV-infected patients for more than eight years and now we have a big HIV cohort in my hospital [>2000 patients]. We find that the rate of peripheral neuropathy is very low (2-3%), compared to that reported in whites and Africans, although we always look for it. Most of the cases with peripheral neuropathy also had diabetes mellitus (fair to poorly controlled) and older age (40+).”

He notes that they had slightly higher rates, 5-8%, when they used ddI/d4T, which they no longer do.

Published studies from Thailand do show somewhat lower rates of peripheral neuropathy.⁸³ For instance, a study from Bangkok reported an overall frequency of probable HIV DSPN of 10% (symptomatic) and that of possible DSPN at 28% among HIV-infected subjects attending an outpatient ID clinic in Bangkok, Thailand.

Are short people better off?

But perhaps the difference isn't genetic. Perhaps it is something much more basic, like height.

Another study presented at CROI reported that, along with age and increasing treatment exposure, being taller puts one at increased risk of developing ATN — whether you are from Australia, Indonesia or Malaysia (and time will tell whether this observation bears out in other settings such as Africa).⁸⁴

Dr Catherine Cherry of Monash University in Melbourne, Australia, presented findings from the study, which sought to identify risk factors associated with sensory neuropathy amongst HIV patients in the Asia-Pacific region — and to assess whether these risk factors could be used to predict sensory neuropathy in patients who were asymptomatic before d4T exposure. The idea

being that, if there is no choice but to use d4T in most patients, those who are most likely develop sensory neuropathy can be offered an alternative regimen — if they can be identified in advance.

So screening programmes for sensory neuropathy were set up in Melbourne (where d4T is very rarely used now and TB and therefore, isoniazid use is uncommon), Kuala Lumpur (where about half the patients use d4T, TB is a common opportunistic infection and therefore isoniazid is widely used), and Jakarta (routine d4T use and TB the most common opportunistic infection). The ACTG Brief Peripheral Neuropathy Screen (BPNS) was used to look for the presence of symptoms and signs of sensory neuropathy, and the participant's height, age, and weight were recorded along with demographic, laboratory, and treatment data obtained from the medical file. Close to 100 participants were enrolled at each site.

“What we found is that overall, neuropathy is highly prevalent throughout our region, ranging from a low of 19% in Kuala Lumpur up to 42% in Melbourne and 34% in Jakarta,” said Dr Cherry. In addition to treatment exposures, increasing age ($p = 0.002$) and height ($p = 0.001$) were independently associated with sensory neuropathy risk.

An analysis of the participant characteristics suggested “cut offs” of ≥ 170 cm height and age ≥ 40 years might be useful for predicting patients at risk of neuropathy. These were applied retrospectively to 181 d4T-exposed patients who were asymptomatic before starting d4T. Patients who were younger and shorter had a sensory neuropathy risk of 20%. A third of those who were younger but taller developed neuropathy, compared to 38% of older but shorter patients.

“But what I find really horrifying is that amongst patients who did not have neuropathy symptoms, but who are older than 40 and taller than 170 cm, fully two-thirds - 66% - developed neuropathy if given stavudine,” said Dr Cherry.

These observations were consistent across sites — neither weight nor ethnicity affected the risk.

“So the take home message that I get from this is that we could have used age and height to predict neuropathy risk, prior to stavudine use, in the countries where we were looking.”

Dr Cherry currently has a project underway in South Africa to investigate whether these observations hold true in African settings as well.

Key points

- **Neuropathy is a common symptom in people with HIV. It may be caused by antiretroviral drugs, by HIV disease, by an opportunistic infection, by isoniazid, or by the effects of concomitant conditions such as diabetes, alcoholism, leprosy.**
- **Neuropathy that develops fast, or which is focused in one place, is usually related to diabetes, to an infection such as CMV, to lymphoma, to an autoimmune reaction or an infectious cause.**
- **HIV or drug-related neuropathy tends to emerge more slowly, affecting both limbs (although diabetes or leprosy may also have this effect in some).**
- **Drug-related neuropathy is caused by d4T (stavudine) or ddI.**

- **HIV-related neuropathies occur more frequently in people with severe immune suppression, even after they start treatment and even if they do not take d4T**
- **The likelihood of developing peripheral neuropathy may vary by ethnic group, but more evidence is needed.**
- **There is evidence that older people are at higher risk of developing peripheral neuropathy, and taller people also have a higher risk. d4T appears to exacerbate this risk further in older, taller people. Age and height may prove to be useful screening tools for determining whether patients should avoid d4T altogether.**

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Peripheral neuropathy: diagnosis and treatment

Diagnosis of sensory neuropathies

Peripheral neuropathy remains under-diagnosed in people with HIV – partly because patients don't report milder signs of nerve damage, but more often because health care workers don't ask about it.

Early detection and diagnosis of peripheral neuropathy is important in those people not yet on ART who already have the condition because HIV-related DSPN may improve on treatment (provided it doesn't contain a d-drug - d4T or ddI). Furthermore, "early identification for ART-related peripheral neuropathy is important, since changing antiretrovirals early and assessing for treatable contributory conditions can halt progression of, and in some cases reverse, the signs and symptoms," Dr John Brooks of the US Centers for Disease Control told HATIP.

The good news for those working in resource-constrained settings is that skin punch biopsies, EMG, nerve conduction studies or other specialised investigations aren't usually needed to clinically diagnose DSPN or ATN (although if there are asymmetric neuropathies, marked motor problems, and situations where there is clear reason to suspect that some other factor is to blame for the symptoms, further investigations (or referral) for definitive diagnosis can be useful).¹

Diagnosis of HIV-related sensory neuropathy is based on clinically measurable signs and symptoms. One tool that may make this easier in resource-constrained settings is a simple questionnaire and brief examination called the brief peripheral neuropathy screening (BPNS) tool ([download here](#)).

The tool is straightforward. A trained healthcare worker asks the patient whether they have had any of the main symptoms of neuropathy (on both sides of the feet/legs), grades the severity of the symptoms, and then uses a reflex hammer to test ankle reflexes and a tuning fork to measure loss of sensitivity to vibrations in the great toe.

A clinical diagnosis of sensory neuropathy can be made when any of the bilateral neuropathic symptoms is present, plus either decreased ankle reflexes or vibration sense. The BPNS was developed and tested within US AIDS Clinical Trial Group studies and found to be nearly as specific (91%) for sensory neuropathy as a more extensive examination using a modified 'Total Neuropathy Score' administered by a neurologist, though it was not as sensitive (sensitivity of 46%).²

Subsequently, Dr Catherine Cherry and colleagues conducted a study in 80 people with HIV comparing a diagnosis using the BPNS to a diagnosis facilitated with computer-assisted sensory threshold testing and lower limb epidermal nerve fiber quantification of punch skin biopsies.³

The study excluded anyone with diabetes or any of the other common causes of neuropathy besides HIV and the d-drugs. 57 subjects reported symptoms of neuropathy, though only 40 had both symptoms and one of the two signs on the BPNS (and thus a clinical diagnosis). These 40 also had significantly decreased temperature or vibration sensitivity thresholds and lower nerve fibre densities than those without a sensory neuropathy diagnosis. However, no significant loss in nerve fibre density or changes in sensitivity thresholds could be found in the 17 with symptoms but no signs of neuropathy as defined by the BPNS.

Cherry et al concluded that the BPNS can accurately detect those HIV-infected individuals with the **greatest** degree of peripheral nerve dysfunction and pathology, and stressed that it is "is simple enough to be applicable in resource-limited settings."

However, from a patient advocate's perspective, one has to wonder about those 17 subjects who reported symptoms without loss of reflexes. In a clinical setting, Cherry et al wrote those with "isolated neuropathic symptoms require appropriate follow-up." Indeed, dismissing complaints of pain simply because there are no signs of neuropathy, may not be the best way to provide compassionate and palliative care, as other studies have noted that even mild pain and symptoms have a negative impact on a person's quality of life.

The WHO definition of palliative care stresses the "early identification and impeccable assessment and treatment of pain." Consequently, a variety of other tools have been developed to quantify the type and severity of pain that patients are experiencing. Notably, a study conducted in South Africa by Hitchcock, Meyer and Gwyther used the Neuropathic Pain Diagnostic Questionnaire (DN4) ([download 824kb pdf version here](#)) and adapted a scoring system called the Brief Pain Inventory (BPI) ([download pdf version here](#)) to gauge how much pain interfered with daily functioning.^{4, 5}

Talking about pain

With training and support, nurses and other clinicians should be able to administer these simple tools for diagnosis and for characterising pain — without expensive equipment.

"That being said, why is it that we seem to come to the diagnosis so late too often? I would posit at least two reasons: patients may have a high threshold for reporting signs/symptoms and we do a poor job at *routinely* assessing, screening and monitoring for peripheral neuropathy," said Dr John Brooks.

"I have been talking with the clinical officers (COs) here [in western Kenya] about the same issue, sadly all too common," Dr Ana-Claire Meyer of the University of California San Francisco and Kemri told HATIP. "I personally think the problem is that the COs do not do a sensory exam, ignore the pain, and base their staging of neuropathy on the motor aspects which generally come later in the progression of the disorder... one thing I was thinking was to convince COs to start using their tuning forks."

This may be a harder sell than she thinks. This writer knows dedicated HIV doctors in South Africa who would be hard-pressed to find their tuning forks.

But the key problem may be something much simpler. As Dr Julia Downing of the African Palliative Care Association (APCA) said in an earlier [HATIP clinical review](#), healthcare workers may be very good at providing supportive care, but they are often uncomfortable coming out and asking about pain.

"The challenge in Africa is that many clinicians do not look at pain as something they need to look out for from their patients. It is not routine that clinicians will ask about the presence of pain during the clinical assessment and because of this, they do not identify the pain," Dr Henry Ddungu, also of APCA, recently told HATIP.

This isn't unique to Africa. In one multicentre study in France, doctors underestimated the severity of pain in 52% of 135 patients with HIV reporting pain — especially when it was moderate or severe or when the source of the pain could not be identified.⁶ 85% were under-medicated according to the WHO guidelines.

Nor is this limited to the world of HIV. The following comes from an article on peripheral neuropathy in the journal *Diabetes & Metabolism*.⁷

"Listening to the patient... is an essential but sometimes neglected aspect. In fact, in the first stages of neuropathy, complaints are moderate, since the symptoms quite often emerge progressively, and are either ignored or initially incorporated by the patient into his/her everyday life. The patient does not complain much and the doctor listens distractedly."

So the first hurdle is simply getting healthcare workers to routinely ask about/or screen for pain. But although it's brief, it may be difficult to convince nurses working in packed clinics to routinely administer the BPNS to every patient with HIV. However, it should be possible to start including at least one targeted question about the symptoms of peripheral neuropathy into the examination.

Of note, Dr Gretchen Birbeck performed a validation study in 77 people with AIDS using a single question on peripheral neuropathy symptoms ("do you have symptoms of tingling, burning, or numbness in the feet or hands?") and found that even though the question cannot assess for important signs of neuropathy, its findings correlated pretty well with the BPNS.⁸ The single question neuropathy screen (SQNS) was 95.7% sensitive, 80% specific, with 88.2% positive and 92.3% negative predictive value.

One of the strengths of a single question screen is that it can be incorporated into a team approach that addresses the needs of patients and their families. Given the need to respond rapidly to the development of peripheral neuropathy, it might [in fact] be better to have adherence counsellors, peer supporter, or pharmacists who see the patient more often to routinely ask this question — especially soon after people start on d-drug containing ART — and refer those with positive responses for diagnosis with the BPNS by someone who's good with a tuning fork.

A key benefit of engaging the adherence counsellor or peer supporter, or community caregivers is that they can act as an advocate for the patient in pain — making sure the need for further assessment comes to the attention of the healthcare worker.

Treating HIV-related sensory neuropathy

The first step in treating sensory neuropathy is to treat or remove its cause or causes.

Start or optimise ART:

For those with DSPN (not yet on ART or failing on their first line regimen), this means starting effective antiretroviral therapy, which has been shown to reduce symptoms and reverse pathology for at least a while, in at least some cases (though clearly not all).

Manage other causes:

The initial assessment should have included a complete history and assessments for co-morbidities and other possible causes of neuropathy such as diabetes and alcoholism and known nutritional deficiencies. If any of these exist, they must be addressed. Of note, a Cochrane meta-analysis of available studies suggests that data supporting the use of B vitamins to treat neuropathy are mostly lacking, except in cases where there is a clear nutritional deficiency, such as thiamine deficiency which is common in alcoholics.⁹

In addition, 50 mg daily pyridoxine (vitamin B6) must be given to people on TB treatment or preventive therapy to prevent isoniazid-induced neuropathy, and the pyridoxine dose should be increased to 100 mg if neuropathies develop at a lower dose. But even though coadministration of pyridoxine is consistently recommended in guidelines whenever isoniazid is used, pyridoxine stock-outs seem surprisingly common.

"Why on earth is pyridoxine so hard to find in resource-poor settings?" asked Dr Liz Corbett of the London School of Hygiene and Tropical Medicine, who is based in Harare, Zimbabwe. "It should be dirt cheap and given with TB treatment as standard practice in HIV prevalent settings, but somehow peripheral neuropathy doesn't seem to make it high enough up the list to hit the radar screen."

Consider alternative medications for d-drug related ATN:

Acute ATN may reverse with discontinuation of the causative drug. However, there can be a 'coasting effect,' where symptoms may even get worse for 4-8 weeks after stopping the drug.¹⁰

"We keep a close eye on potential neuropathy by asking patients about it, and we change them off stavudine if they do. In the majority of people the neuropathy goes away or stabilises, though for a small percentage it gets worse," said Dr Jonathan Mermin, of the CDC in Kenya.

Dr Ana-Claire Meyer, who is also in Kenya, told HATIP that this is indeed what some of the most expert clinicians do, and what the national guidelines recommend. But giving up d4T is something many clinicians do not want to do.

"What I have found through chatting and anecdotal observation is that no one wants to change therapy for mild peripheral neuropathy, which makes sense when you have limited alternatives and it is [occurring in] nearly half of your population. But they often miss switching their patients for moderate neuropathy and don't really notice a problem until they end up with someone with severe neuropathy that they can't do much about."

"One of my missions while I am here is to come up with a way to identify those people who have a progressing neuropathy before it gets so severe that they cannot walk and are functionally impaired, [to develop] a simple way to test when we should change therapy. [If we could] convince COs to start using their tuning forks: once there is no vibratory sensation at the toes, you have tried one month of multivitamins (B6 and B12 if you have it), and checked a fasting

glucose, add in a pain/functional assessment scale... then switch therapy to be off d4T."

While this is an interesting algorithm to evaluate in a clinical study, clinicians and patient advocates should also remember that sensory neuropathy can be irreversible if left for too long. In many settings, the only real alternative is to switch to AZT, as tenofovir and abacavir are still considered to be too expensive for more widespread use.

"In Malawi we have a protocol to deal with the problem that includes dose reduction of stavudine (now obsolete as all patients now receive 30mg twice daily), amitriptyline and NSAIDs," said Dr Anthony Harries, who is now with the International Union Against Tuberculosis and Lung Disease. "If very severe, we then have the option of changing to AZT. Stavudine is the culprit, but at the moment in Malawi we have no real alternative for our first line regimen."

This is one of the most glaring disparities between the standard of HIV care in industrialised world, which has largely abandoned d4T, and what is given to those who can afford little else.

The World Health Organization has already attempted to limit the burden of toxicity associated with d4T by recommending that the dose be reduced to 30mg twice daily where no alternative to d4T is available, but some countries continue to use stocks of d4T-containing fixed dose combinations containing a 40mg dose of d4T.

"d4T toxicity is a critical aspect of ART scale up and even if countries continue to phase out its use - which seems to me will be a slow process in a majority of them, particularly in rural areas - the demand for peripheral neuropathy treatment will remain," Dr Marco Vitória of the World Health Organization told HATIP.

Symptomatic treatments

Perhaps the most contentious issue is whether any pharmacological treatment can help relieve painful symptoms of neuropathy.

The WHO [pain analgesic ladder](#) is a stepwise approach to pain management related to pain severity – beginning with simple analgesics (paracetamol or NSAIDs), then adding a weak opiate, such as codeine, moving onto stronger opiates if that doesn't work. But, these seem to be ineffective for neuropathic pain, at least when given on their own. This may even be true of the more potent opiates.

"In our experience morphine is not very good for neuropathic pain," said Dr Harries.

So many neurologists and palliative experts recommend adding a variety of adjuvants, including topical analgesics (lidocaine, low dose capsaicin cream, 0.075%, topical chloroform), but especially the tricyclic antidepressants (amitriptyline, desipramine, etc), and the anticonvulsant agents (including carbamazepine but especially the new drugs, gabapentin and lamotrigine). Some of these drugs have proven to be effective in treating other neuropathic pain, such as diabetic peripheral neuropathy, which has led to the development of [the Analgesic Ladder for Neuropathic Pain](#).

Unfortunately, clinical evidence in support of using these adjuvants in HIV disease is quite weak.

"This is one of the areas of HIV and treatment which abounds with myths and legends with regards to its treatment. And most of the commonly used treatments, in fact, work not at all," said Dr Steven Miller of the Innovir Institute in Johannesburg, South Africa, speaking about management of peripheral neuropathies at the International HIV Conference in Botswana in 2006.

Case in point: the tricyclic antidepressants, including desipramine, doxepin, imipramine, nortriptyline, but especially amitriptyline, are widely used for peripheral neuropathy with other causes. Doses usually start at around 25-75mg at night, and titrated up (if side-effects are tolerated) to a maximum dose of 300 mg/day.

But at least two randomised controlled studies show that amitriptyline is no better than placebo in people with HIV and sensory neuropathy.^{11, 12}

In the first study, Kiebert et al compared amitriptyline, mexiletine and placebo in 145 patients. The second study, by Shlay et al was also a three-way comparison between amitriptyline, acupuncture and control point (feigned acupuncture) in 250 people with HIV-associated peripheral neuropathy. All groups improved somewhat, but there were no significant differences between them. The authors speculated that the control point did have some beneficial effect and thus was not a true placebo. But there may have been other problems with these studies which render their conclusions suspect.

"The amitriptyline trials were not well designed: they were stopped early and underpowered," Professor Brew told HATIP. However, those studies took place over 10 years ago, and no one's bothered to re-examine the drug's usefulness for this indication.

Meanwhile, other drugs used for other causes of neuropathic pain, the anticonvulsants carbamazepine and phenytoin, cannot be given to patients who are taking antiretroviral therapy because they reduce blood concentrations of efavirenz/nevirapine, and protease inhibitors.¹³

When he was speaking in Botswana, the only symptomatic treatment that Dr Miller showed any hope for were the newer anticonvulsants. "Consistently in the clinic we see that the only compounds which consistently give relief are the newer anti-convulsants: lamotrigine, gabapentin, topiramate for some people," he said. He added that there are generic preparations of lamotrigine, making it more affordable.

Data on these drugs since that time have been rather mixed.

Early data were promising for lamotrigine (25 mg alternate days for two weeks then dose escalation over seven weeks to a target dose of 400 mg/day), though there was a very high drop-out rate in the study drug arm.¹⁴ A subsequent randomised study went up to 400 mg per day (600 mg if another medication which might lower lamotrigine concentrations was used, such as rifampicin), followed by a maintenance phase for HIV-associated painful sensory neuropathies.¹⁵ But it could find no clear benefit over placebo in pain scores at the end of the maintenance phase of the study. The authors did report a significant difference in some indicators, such as the slope of improvement for people with ATN and perception of improvement.

However, a recent Cochrane review of the performance of lamotrigine for neuropathic pain (from various causes) in a large number of studies concluded that the routine use of the drug "is unlikely to be of benefit in chronic pain conditions included in this review, or neuropathic pain (pain due to nerve damage)."¹⁶

Furthermore, the authors noted that the incidence of rash on the drug was "not trivial."

Gabapentin looked good in a small randomised, double-blind placebo-controlled study in 26 patients with HIV sensory neuropathy.¹⁷ Fifteen patients received gabapentin at 400mg per day before being increased to 1200mg per day over 2 weeks. This dose was maintained or increased to 2400mg per day if not beneficial. There was a significant decrease in pain score in the gabapentin group (-44%) but not the placebo group (n = 11; -30%) —

initially at least. It also helped people sleep, in fact, somnolence was reported in 80% of the gabapentin group. A review in 2003 concluded that the drug was effective for a number of types of neuropathic pain, though doses up to 3600 mg/d may be needed in some patients.¹⁸

Unfortunately, at the World AIDS Conference in Mexico City in 2008, Dr David Simpson of Mount Sinai Hospital in New York presented a large randomised, double-blind, placebo-controlled, multicentre trial of the very closely related pregabalin for HIV related peripheral neuropathy, which proved rather disappointing.¹⁹

151 subjects were randomised to each arm. Pregabalin doses were titrated from 150 mg to 600 mg/d BID over the course of two weeks, and then continued at their dose (average 385.7 mg/d) for 12 weeks. Surprisingly a large proportion of study participants in both arms felt better. 82.8% of pregabalin recipients rated themselves in one of 3 "improved" categories. So did 66.7% of placebo patients. This difference was not significant. Nor were there any difference in mean pain scores after the first couple of weeks on treatment.

With so much conflicting evidence, the experts don't always agree on what to recommend. This led to something of a debate on the [HATIP panel discussion blog site](#):

"I have found that amitriptyline does work; so does valproic acid. Opiates also work," said Professor Bruce Brew of the University of New South Wales.

"I think it is important to consider the principles of pain management, [and] that amitriptyline is an adjuvant drug in managing neuropathic pain. It is not in itself an analgesic. It should be combined with an analgesic to provide pain control, so morphine in severe pain plus amitriptyline in low dose is the combination that we use," said Dr Liz Gwyther of the Hospice Palliative Care Association of South Africa.

"We need to be very careful as the placebo effect is significant with pain treatments. Our anecdotal impressions that drugs work in individuals may be demonstration of placebo action not drug effect. I have stopped prescribing amitriptyline for HIV PN as it was demonstrated by two reasonable quality studies to be no more effective than placebo," Dr Sarah Cox, of London's Chelsea and Westminster Hospital told HATIP. "Opioids have not yet been trialled in HIV PN but do have an effect in neuropathic PN and are now my first line."

"The randomised clinical trials do say that nothing much seems to work for peripheral neuropathy in HIV (whether due to ARVs or HIV itself), but I personally find that it never hurts to try amitriptyline and a multivitamin (all we have here) and switch off offending meds if alternatives exist. Sometimes it works (whether [it's a] placebo or not)," said Dr Ana-Claire Meyer.

"My 2 cents is that whereas we must respect the evidence in clinical trials as the gold standard, we still must take care of patients and provide the best possible therapy, even if empirically driven. We are working hard on developing and testing better meds," Dr David Simpson told HATIP.

In fact, Dr Simpson has recently conducted a study that found positive results (a mean 22% reduction in pain scores) for 12 weeks from using a single very high dose capsaicin patch.²⁰ This uses doses much higher (8% capsaicin) than available in creams (0.025% to 0.075% capsaicin). The patch essentially works by desensitising the nerves. The patch itself initially causes pain and is put on following a one-hour application of a topical anaesthetic. This sounds as though it would be a bit difficult to administer in a busy clinic setting, and the patch isn't available yet.

A number of open label studies have reported subjective reductions in pain using the anti-oxidant acetyl carnitine (L-carnitine). For instance, in an open label study, Hart et al reported that LAC can reverse the loss of nerve fibres from the skin, and reduce mitochondrial toxicity and improve the symptoms of peripheral neuropathy after six months of treatment.²¹

However, in the most recently published study "changes were not observed in objective measures of IENF [nerve fiber] density or mtDNA levels, providing little objective support for use of ALC in this setting," wrote the authors.²² There were improvements in symptoms, but again, this was not a placebo controlled study.

A final approach which is often more readily available — though not legally — is medical marijuana. Several studies have reported positive results from using smoked cannabis for neuropathic pain.^{23, 24, 25, 26, 27} For instance, Abrams et al conducted a randomised clinical trial that found that smoked cannabis reduced daily pain by 34% (median reduction; IQR = -71, -16) vs a 17% reduction (IQR = -29, 8) on placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). "Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy," wrote the authors.

The approach has its proponents. "I just want to make the case for medical marijuana to sound stronger and clearer," Dr Zvi Bentwich, of Rosetta Genomics in Israel, told HATIP. "For the last 10 years I have been involved repeatedly with patients in whom this worked quite impressively! So much so that we succeeded in convincing the Ministry of Health, to adopt it as an official policy once each individual case was brought before a special committee that then decided whether to approve it or not."

But in settings where governments don't want to agree to make opiates available, despite their proven benefits for pain, suggesting marijuana is opening a can of worms, to put it mildly. The neurocognitive side-effects of the drug would also be a concern. Still it is hard to begrudge this approach to someone whose pain keeps them awake all night.

But more will need to be done for those patients who must live with pain.

"In contrast to pain management in general, neuropathic pain requires a more rigorous approach, involving a multidimensional bio-psycho-social approach that involves the use of appropriate pharmacological agents, exercise, behavioural therapy, attention to sleep quality, patient education and return to work if possible," wrote Hitchcock, Meyer and Gwyther in their assessment of neuropathic pain in South Africa.²⁶

In industrialised settings, people with peripheral neuropathy that won't heal are referred to physical and occupational therapists. Experts trained at offering people supportive care are rarely if ever available in resource-limited settings. But perhaps countries should begin training more of these cadres of healthcare workers, as it is evident that the demand for their services will be growing.

Prevention: avoiding the problem in the first place

Given the lack of adequate treatment options for sensory neuropathy, the best approach would be to simply try to avoid the problem altogether.

Both the CHARTER and the ALLRT studies presented at CROI concluded that **earlier antiretroviral treatment, at higher CD4 cell**

counts, would be the best strategy to prevent much of the sensory neuropathy directly related to HIV.

Avoiding drug-related neuropathy in resource-limited settings is more of a challenge given the few therapeutic options available. And yet some countries are doing this.

"We are lucky that the policy here in Indonesia now is to start with AZT, and only change to d4T in case of anaemia. However, once the change has been made, it can be difficult to get doctors to agree to changing back," Chris Green of the Spiritia Foundation told HATIP.

In settings where first line AZT is not an option, employing an algorithm such as the one suggested by Dr Cherry (age over 40, height over 1.70 cm should start with AZT) seems a prudent prevention approach (see part one). Perhaps advanced disease should be added to this algorithm given that several studies indicate a higher risk of neuropathy in those with lower CD4 cell counts and high viral loads.

"Ideally we should not be using d4T especially in people who have been treated before for TB, where incidence of peripheral neuropathy is huge," Dr Liz Corbett told HATIP.

Indeed, d4T should be avoided in anyone with major pre-existing comorbidities that may cause neuropathy (such as hepatitis C).

Clearly, there should be a work-up before going onto ART to detect DSPN and make certain that someone with sensory neuropathy is not put on a d-drug containing regimen.

Increasing patient awareness that they should report the first signs of neuropathy should also help. But this can cut both ways. Advocacy and treatment literacy groups could have perhaps done more to educate people to complain earlier, but as Zachie Achmat's case study in part one suggested, there may be a tendency not to want to scare already reluctant people away from life-saving treatment.

"I did not report my side effects for two reasons. Both of them were wrong. One, I did not want government or AIDS denialists to misuse my side effects. And, I did not want to believe that my medicines could go wrong," he said in the TAC report.

The TAC report clearly recommends that "because there is no cure for neuropathy yet, the best choice is to stop using d4T and change to another drug if this is possible.... If there are no other treatment choices, and you are otherwise doing well, it may be better to stop your treatment for a period until there are new treatment choices."

Although TAC recommended this should only be done following a consultation with a doctor, it is clear that if clinicians don't begin finding ways make certain that people at high risk of neuropathy aren't being put on d4T (or ddl), patients (and patient advocates) will increasingly make the decision to dump the drug — even when they may not be at much risk of neuropathy.

"We recommend anyone on d4T who experiences any 'pins and needles' to press for a change," said Green, who is a treatment educator. "And if they have been on d4T for more than six months, have a normal Hb and a CD4 count above 200, we encourage them to press for a change. If the doctor is unsupportive ('you're doing well on that regimen, don't change it') we suggest they report peripheral neuropathy (even if they haven't experienced it) *because the doctor can't tell...*"

Key points

- **Early detection and diagnosis is important – by the time peripheral neuropathy causes problems in walking, there is probably not a lot that can be done to reverse the condition.**
- **Patients should be routinely questioned about their experience of pain.**
- **There are a number of simple pain questionnaires that can be used, but a sensory exam using a tuning fork to measure sensitivity and a reflex hammer to measure ankle reflex should also be carried out.**
- **Antiretroviral therapy using AZT instead of d4T may reverse early symptoms in untreated people.**
- **If d4T is the cause, switch to AZT. If AZT is not available, the d4T dose should be no higher than 30mg bid.**
- **Evidence for other treatments is weak and experts have conflicting views about the best course of action. Medical marijuana is cheap and shows some evidence of efficacy, but like opioids, is difficult to use due to drug control policies.**
- **Prevention is the best policy: avoid d4T if at all possible, start treatment earlier, and raise awareness among patients and health care workers about the early signs of peripheral neuropathy and the need for early intervention.**

Resources

Where there is no neurologist:

[download book by following this link](#) (3.94mb pdf)

World Federation of Neurology:

<http://www.wfneurology.org/default.php>

WHO & WFN's Atlas of Country Resources for Neurological Disorders:

http://www.who.int/mental_health/neurology/epidemiology/en/

The Neuropathy Association

, an non-profit begun in NYC by people with neuropathy and their families with approximately 120 support groups throughout the US and abroad providing public awareness, patient support, education and advocacy.

<http://www.neuropathy.org>

The Neuropathy Trust

<http://www.neurocentre.com>

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about HATiP

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