

Not so happy feet

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Peripheral neuropathy is a painful condition which affects about a quarter of people living with HIV in Australia. DAVID MENADUE looks at the condition and explores some treatment options.

About 25 percent of HIV patients experience HIV-associated neuropathy (HIV-AN), a condition characterised by burning, numbness and pain in the extremities, most commonly the feet but sometimes also the hands. In some cases, the pain is so severe the individual can no longer walk.

The condition occurs when small nerves at the edges of the body are damaged by [antiretroviral](#) [1]A medication or other substance which is active against retroviruses such as HIV. drug toxicity or by HIV itself. It can start with a tingling in the toes but over time people can experience burning, numbness, loss of reflexes, loss of heat and cold sensitivity in the feet and – worst of all – pain.

Dr Kate Cherry, who studied peripheral neuropathy in HIV patients as a part of her doctoral thesis, and is now continuing her work at the Burnet Institute in Melbourne, explains: “In the case of neuropathy due to some antiretroviral drugs, we believe drug toxicity prevents the transport of nutrients along the nerves, which is why it generally starts at the extremities, in the feet and, as it gets worse, creeps up the legs and also affects the hands,” she said.

Treatments for this condition are mostly focused around pain relief, but an Australian [clinical trial](#) [2]A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed. is now aiming to enrol 480 people who are experiencing pain related to HIV-associated neuropathy, to determine the [effectiveness](#) [3](Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. of a skin patch containing capsaicin, a compound extracted from hot chilli peppers. Two groups of patients will test two different concentrations of the patch, applied to the feet for either 30 or 60 minutes at an initial consultation. They will then be followed up for 14 weeks.

Capsaicin acts by depleting nerve cells of the neurotransmitters that convey the pain message. Capsaicin creams have been used with some success in the past to treat HIV-AN, but trials have failed to show a clear benefit, with high drop-out rates due to the burning sensation on the skin.

The Australian trial is using a patch formulation which has been better tolerated than capsaicin creams in studies overseas. The treatment lasts about six months so only one or two applications a year may be needed if it proves effective.

Not treated seriously

Cherry believes that some clinicians don't take the condition seriously enough until it becomes severe. “They think that HIV is fairly manageable as a medical condition these days and that a bit of numbness or tingling in the feet occasionally should be bearable. But some of my patients experience real pain and discomfort associated with neuropathy and they want their doctors to validate their pain, to try to do something about it. I explain to those who doubt the importance of neuropathy pain, ‘Imagine your foot goes to sleep on you one night – but it stays like that for the rest of your life.’ For some people that's the sensation involved with HIV-AN, and pain management of the condition can be very difficult.”

Cherry was involved in treating patients with HIV in the early 1990s at Fairfield Hospital in Melbourne. “Then, with few treatments, we knew that HIV itself was the cause of the nerve damage in peripheral neuropathy. It was not

uncommon for patients to come in with their first bout of PCP [Pneumocystis carinii [pneumonia](#) [4]An inflammation of the lung, usually caused by infection with bacteria or other microorganisms, in which the air sacs of the lung become filled with inflammatory cells which solidify and inhibit breathing.] and have a rapid onset of HIV-AN. Within a week or so they may require bed cradles to keep sheets off their feet, such was the pain associated with the condition. In the worst cases you had people who couldn't walk at all because of the nerve damage to the feet. On top of pain, the numbness would mean they lost the input to the brain on where the ground was and they could fall over."

The dreaded 'D' drugs

The so-called 'D' drugs – ddI (didanosine/Videx), ddC (zalcitabine/Hivid) and d4T (stavudine/Zerit) have long been strongly associated with the development of peripheral neuropathy. While the use of these drugs has largely fallen out of favour (and one, ddC, has been withdrawn altogether) some people who took them in the past continue to experience problems.

"It was not long into the use of d4T, in particular, that we realised that some people developed HIV-AN with its use," explained Cherry. People who had been positive for some time found that the added nerve damage caused by the drugs caused the onset of neuropathy or an increase in pain. "When I started to do my research on HIV-AN in 2001, testing people's legs and feet using various techniques, I discovered some 42 percent of the outpatients from an Alfred Hospital sample of 140 patients had peripheral neuropathy. Quite a number did not realise they had the problem despite having significant nerve damage."

In fact, when these findings were compared with earlier research done in Melbourne, they showed a marked increase in the prevalence of HIV-AN, from 13 percent in 1993 to 44 percent in 2001. A 2006 screening of 100 patients who attended the Alfred clinic found 42 percent had signs of HIV-AN. Many of these patients have been living with HIV for a long time, Cherry explained, often having had HIV-AN for more than ten years, although some are more recently diagnosed than this.

Cherry says the three main risk factors for the development of HIV-AN are having taken d4T in the past, increasing age (as getting older causes nerve damage anyway) and possibly the use of the protease inhibitor indinavir (Crixivan). She also believes that height is a factor, with taller patients more likely to report peripheral neuropathy – the likely explanation being that the longer the nerve in one's body, the easier it is to damage. She is involved in a study to see why some people are more prone to HIV-AN than others, looking at the possibility that some people are genetically pre-disposed to it.

Prevention

There are a number of steps that can be taken to reduce the risk of developing HIV-AN, according to Dr Cherry. "Getting adequate nutrition is important. It is important also to make sure people with HIV avoid medications that can cause nerve damage where possible, and that other medical conditions that cause neuropathy are treated. For example, Vitamin B-12 deficiency can be treated and can damage nerves. Your B-12 levels should be checked occasionally as a part of your full blood examination." Other things that can increase the risk of neuropathy include excessive use of alcohol and megadoses of some vitamins (such as B6).

"Avoiding the 'D' drugs, particularly d4T, is important although research has shown that if you are already on d4T and have had some nerve damage already it may not get worse with continued use of the drug. If you have [diabetes](#) [5][Diabetes mellitus] A disorder in which sugars in the diet cannot be metabolised into energy due to a lack of the enzyme insulin. Late-onset diabetes mellitus may be a long-term side effect of some anti-HIV drugs. then successfully managing this will help reduce the risk, given its association with neuropathy."

Treatment

Treatment for people who are already affected by neuropathy is mainly directed at symptom relief. The earliest signs of pain related to HIV-AN are treated with simple pain-killers such as paracetamol, often quite successfully. After this, pain modifiers (not pain-killers as such) are used which help your body reinterpret a pain message to the brain so that there is less distress felt. A low dose of some tricyclic antidepressants such as amitriptyline (Endep)

can help some people significantly; or anticonvulsant drugs (normally used for epilepsy) can be used. But the less expensive anticonvulsants that are available on the [PBS](#) [6][Pharmaceutical Benefits Scheme] The federal government program which subsidises medication costs in Australia. Anti-HIV drugs are part of a special part of the PBS called Section 100 (S100) which is used for expensive, highly specialised drugs. can interact with some HIV medications, while newer (and more expensive) drugs, which don't have an interaction with HIV [antivirals](#) [7]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals., are only funded for use in difficult cases of epilepsy. They can therefore be hard to obtain to treat neuropathy pain and sometimes will require a private script and significant expense for the patient.

When neuropathy pain remains severe despite these treatments, the next option to is a narcotic or morphine-related treatment. Doses have to be increased slowly to avoid too much sedative effect and these sorts of pain-killers can be very constipating. Many people are afraid to try morphine-related drugs for fear of becoming addicted but, used carefully, they can be a useful and safe addition to other neuropathy treatments. Even with this level of pain control Dr Cherry says she still has patients who experience significant pain. "The awful fact about peripheral neuropathy is that some patients will never get adequate relief from their pain and discomfort which is why we have to keep looking for better solutions."

Another measure which Dr Cherry says helps some people is foot massage. "Different things can work with it such as the Body Shop's peppermint foot cream (a favourite of a few), Voltaren ointment, and even moisturiser. If you have a partner who will massage your feet before going to bed at night it can help you sleep. Or there are foot massage machines that some people say help them."

Dr Cherry doesn't rule out acupuncture, Chinese herbs or anything that might work, providing it is affordable and clearly does no harm. She sees likely value in the use of some micronutrients such as Co-Enzyme Q-10, L-Acteyl Carnitine and uridine. These will need to have more research before they can be recommended, however, and they are expensive.

Uridine, in particular, looks promising in various types of neuropathy, including diabetic neuropathy, but it is very costly to purchase. Magnesium orotate, a compound which is metabolised to uridine in the body, appears to have worked for one of her patients and is much cheaper. While it's not possible to generalise about the effectiveness of any treatment from individual cases, Cherry says the results in this patient have been very encouraging. After taking magnesium orotate for three months, his results are so good that Cherry says "if I had peripheral neuropathy I would be trying it." (See Bernie's story).

Dr Cherry endorses the capsaicin patch trial, given the findings from a previous study presented at the Retrovirus Conference in 2006 that showed that people's pain scores generally went down soon after application. Improvements lasted at least three months after having the patch applied and most patients tolerated it well – better than the older cream-based formulations. If the patch is to go on to the PBS we need results of this study first so that the patch, if it works, can be affordable for patients.

Dr Cherry is most enthusiastic about a novel pain-killing drug currently licensed as an over-the-counter drug in Europe. This drug appears safe and, when used with morphine-like drugs, has been reported to significantly improve control of nerve pain in other settings. It's currently unavailable in Australia, but a small Melbourne-based company is planning to study it as a possible treatment (in combination with morphine) for painful HIV-AIN. They hope to have a study ready to enrol patients before the end of 2007. If it is shown to improve pain from HIV-AIN they will work to have it licensed in Australia.

Dr Cherry is also involved with laboratory-based studies in Melbourne where nerve cells of rats are being used to see if micronutrients may prevent 'D' drug damage. Early results suggest a possible benefit from L-Acetyl-Carnitine in this model and ongoing work is investigating Co-Enzyme Q 10 and uridine.

Bernie's story

Bernie was diagnosed with HIV in 1995 with a T-cell count of 20. He tried a number of 'D' drugs as part of his treatment but was not on any of them when he developed peripheral neuropathy about five years down the track. HIV can cause HIV-AN without any treatment, and Bernie's [viral load](#) [8]A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood

plasma.(at 100,000) was not well-controlled at the time the problem manifested, so the virus itself may have been be a factor.

Things got bad for Bernie when he started falling over after getting out of bed in the morning: he had no feeling in the soles of his feet, tingling in his toes, pain and balance problems. His doctor wanted him to put a walking frame near the bed in the mornings but he felt lucky he had a four-poster bed that he could grab onto to get up in the mornings. The sensations would come back to his feet after a while and he could get around, but he foresaw a bleak future with a lack of mobility and independence and possibly the need for a wheelchair.

Bernie's luck changed when the treatments officer at PLWHA Victoria showed him a research article on the use of uridine and its possible benefits for people with peripheral neuropathy. He explored the idea but found it was only available overseas, was expensive, may have interactions with HIV drugs and there may be problems with customs if he tried to import it. He investigated the use of an alternative combination of supplements that is also known to increase uridine levels in the body.

Professor Frank Rosenfeldt from the Baker Institute of Heart Research at the Alfred. has been studying the use of Co-Enzyme Q-10 and magnesium orotate in heart patients and thought that this combination might be useful for HIV patients as the supplements together are thought to help reduce mitochondrial damage. Combining magnesium orotate with Co-Enzyme Q-10 increases uridine levels and, at the right dose, should not be toxic or have interactions with HIV drugs. After discussions with Professor Rosenfeldt and Dr Luis Vitetta from Epworth Hospital, Bernie started taking 100mg of Co-Enzyme-Q-10 and 800mg of magnesium orotate twice a day. Bernie emphasises that further research is required to see if these doses are the correct ones, and says the supplements cost him \$100 a month.

He started on the combination in March 2006 and within six weeks saw improvements in his balance. He no longer has tingling and burning in his feet, however there is still some occasional pain. When he went to Dr Cherry for diagnostic tests, his score for coldness had decreased by 5 (a decrease of 1 is seen as a significant improvement) and the vibrating fork test has shown a considerable improvement in the number of seconds he can feel it. In short there has been a considerable improvement and he feels confident his daily supplements have been the reason for this.

- There are seven sites [enrolling](#) [9]The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the informed consent process. for the capsaicin trial: St Vincent's Hospital (Professor Bruce Brew), Holdsworth House (Dr Mark Bloch), AIDS Research Initiative (Dr Cassy Workman), Taylor Square Clinic (Dr Neil Bodsworth) in Sydney, the Alfred Hospital (A/Professor Jennifer Hoy) and Carlton Clinic (Dr Jonathan Anderson) in Melbourne and the Sexual Health and AIDS Service (Dr Mark Kelly) in Brisbane.

This article includes information about [complementary therapies](#) [10]A broad range of healing philosophies, approaches, and therapies that Western (conventional) medicine does not commonly use to promote well-being or treat health conditions. Examples include acupuncture, herbs, Traditional Chinese Medicine, etc. which have not been the subject of rigorous [clinical](#) [11]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. trials. NAPWA cautions that before using these therapies, you should discuss the risks and benefits with your treating doctor.

- [peripheral neuropathy](#)

Links:

[1] <http://www.napwa.org.au/glossary/term/122>

[2] <http://www.napwa.org.au/glossary/term/89>

[3] <http://www.napwa.org.au/glossary/term/486>

[4] <http://www.napwa.org.au/glossary/term/351>

[5] <http://www.napwa.org.au/glossary/term/95>

[6] <http://www.napwa.org.au/glossary/term/121>

[7] <http://www.napwa.org.au/glossary/term/123>

[8] <http://www.napwa.org.au/glossary/term/416>

[9] <http://www.napwa.org.au/glossary/term/489>

[10] <http://www.napwa.org.au/glossary/term/478>

[11] <http://www.napwa.org.au/glossary/term/475>