Drug Safety 1998; Dec 19 (6): 481-494
0114-5916/98/0012-0481/$07.00/0

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Peripheral Neuropathy with Nucleoside Antiretrovirals

Risk Factors, Incidence and Management

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Contents

Abstract

Distal symmetrical peripheral neuropathy is a common adverse experience in persons with HIV infection. This condition, which presents as a pain, numbness, burning and/or dysaethesia initially in the feet, is often multi-factorial in its origin. Nucleoside analogue reverse transcriptase inhibitors represent an important contributor to peripheral neuropathy. Specifically, around 10% of patients receiving stavudine or zalcitabine and 1 to 2% of didanosine recipients may have to discontinue therapy with these agents due to neuropathy. Prompt withdrawal of these therapies enables gradual resolution of signs and symptoms in most patients, although a period of symptom intensification may occur shortly after withdrawal.

Risk factors for developing peripheral neuropathy during nucleoside analogue therapy include low CD4+ cell count (<100 cells/mm^3), a prior history of an AIDS defining illness or neoplasm, a history of peripheral neuropathy, use of other neurotoxic agents including high alcohol (ethanol) consumption and nutritional deficiencies such as low serum hydroxocobalamin levels. Thus, patients at increased risk of peripheral neuropathy should potentially avoid the use of the

neurotoxic nucleoside analogues or be more carefully monitored during therapy. Management of this problem includes patient education, prompt withdrawal of the likely causative agent (giving consideration not to leave the patient on a sub-optimal therapy regimen) and simple analgesia, with augmentation with tricyclic antidepressants or anticonvulsant agents when pain is severe. New agents that may assist in managing this condition include levacecarnine (acetyl-*L*-carnitine) and nerve growth factors such as recombinant human nerve growth factor.

1. Background

Maintaining future treatment options is critical to the long term management of individuals with HIV infection. Whilst resistance and cross-resistance are the most widely discussed mechanisms for loss of treatment options, drug toxicity from 1 antiretroviral agent may also limit the ability of an individual to tolerate, and hence benefit from, another agent.

Nucleoside analogue reverse transcriptase inhibitors provide proven clinical benefit in double and triple therapy regimens in individuals with HIV infection, relative to regimens consisting of fewer drugs.[1-5] Combined with a third agent from a second therapeutic class, they form the basis of what is widely called highly active antiretroviral therapy (HAART), the current standard of care.[4,5] Recommendations for second-line or salvage regimens include switching both nucleoside analogues and preferably including a new agent from a previously unused class.[4,5] Therefore, maintenance of nucleoside treatment options is critical to a planned therapeutic approach.

Treatment options with nucleoside analogues may be limited by cross-resistance between agents or by the development of a toxicity with 1 agent which overlaps with the potential toxicities of an alternative agent. Overlapping toxicities of nucleoside analogues, especially peripheral neuropathy, also limit the range of combination partners with these agents.

During the development of these agents in the late 1980s and 1990s, phase I/II dose-finding studies of several nucleoside analogues, including zalcitabine, didanosine and stavudine, unexpectedly revealed peripheral neuropathy to be the major dose-limiting adverse effect. Concern about peripheral neuropathy has remained an important factor in limiting the combination, or wider use, of these agents in the management of individuals with HIV infection.

This review discusses the incidence of, risk factors for, and management of nucleoside analogue–associated peripheral neuropathy during antiretroviral therapy.

2. Occurrence of Peripheral Neuropathy in Untreated HIV Patients

A predominantly sensory distal symmetrical polyneuropathy is the most common form of peripheral nervous system problem in individuals with HIV infection. Its incidence rises with falling CD4+ cell count. Prior to the availability of antiretroviral therapy, distal symmetrical polyneuropathy was reported in 30 to 35% of individuals with symptomatic HIV infection.[6-9] The annual incidence of peripheral neuropathy in untreated people with <100 CD4+ cells/μl is estimated at 8%.[10] Peripheral neuropathy commonly presents with distal paraesthesia, beginning in the toes and moving proximally. In 10 to 60% of patients it is associated with pain.[6,11,12]

HIV-associated distal symmetrical polyneuropathy is usually slowly progressive, but the arms are rarely affected and weakness is generally limited to the small muscles of the feet. Electrophysiological studies indicate a distal axonopathy affecting both sensory and motor fibres.[6,13] Histologically, there is prominent distal loss of unmyelinated fibres which often precedes the loss of larger myelinated fibres.[14,15] This correlates closely to the clinical findings of an early burning dysaesthesia in the feet and pin hyperalgesia followed by diminution of vibration sensation and ankle reflexes.[6-9,12,14]

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Speculation still surrounds the aetiology of HIV-associated distal symmetrical polyneuropathy. It has been proposed that distal symmetrical polyneuropathy is caused by HIV alone, as HIV-related mRNA has been found in macrophage-like cells in peripheral nerve endoneurium.[13] However, nutritional factors have also been implicated, as distal symmetrical polyneuropathy is more common in patients with wasting and co-infection, e.g. *Mycobacterium avium-intracellulare*.[16] Several reports have suggested that late onset painful distal symmetrical polyneuropathy may be caused or exacerbated by cytomegalovirus infection.[11]

A dying-back axonopathy is the most common histological finding in HIV-associated distal symmetrical polyneuropathy. However, this can be produced by a wide range of neurotoxins (including nucleoside analogues) and in itself may provide little additional information about the underlying cause of the nerve damage. Increased numbers of macrophages are seen in peripheral nerves and dorsal root ganglia of patients with distal symmetrical polyneuropathy.[15] Immunostaining indicates that these macrophages express major histocompatibility complex (MHC) class II molecules, interleukin (IL)-1, IL-6 and tumour necrosis factor-α (TNFα). In addition, TNFα mRNA levels are significantly higher in patients with distal symmetrical polyneuropathy compared to those without neuropathy.[17]

A multifactorial model for the aetiology of HIV-associated distal symmetrical polyneuropathy has been postulated. Macrophage activity increases late in the course of HIV infection owing to a reduction in macrophage-inhibitory T cell cytokines such as IL-10 and IL-4. This leads to the liberation of high levels of the neurotoxic cytokine TNFα, quinolinic acid and gp120 and subsequently to distal symmetrical polyneuropathy.[12,18,19] Any predisposition to neuropathy such as nutritional deficiencies, use of neurotoxic prescription or illegal drugs, or inherited or other acquired neuropathy accelerates the development of distal symmetrical polyneuropathy.[20]

3. Nucleoside Analogue–Associated Peripheral Neuropathy

The nucleoside analogue vidarabine was the first drug of this class found to cause peripheral neuropathy during clinical trials in individuals with hepatitis B.[21] Since then, zalcitabine, didanosine and stavudine have all been shown to be associated with dose- and treatment-limiting peripheral neurotoxicity in patients with HIV infection.[22-26]

The clinical presentation of nucleoside analogue-associated neuropathies is similar to that of HIV-associated distal symmetrical polyneuropathy. However, nucleoside analogue–associated distal symmetrical polyneuropathy is more likely to be painful, have an abrupt onset and rapid progression. The electrophysiological changes are similar to those seen in distal symmetrical polyneuropathy, suggesting axonopathy. The main diagnostic clue is the relationship of peripheral neuropathy to the start of nucleoside analogue therapy and stabilisation, or at least partial resolution, when therapy is interrupted.

Again, there are several theories for the mechanism of this toxicity. Nucleoside analogues are toxic to the main mammalian respiratory organelle, the mitochondria, through inhibition of mitochondrial DNA polymerase. Results of *in vitro* experiments on human lymphoblastoid cell lines have shown the relative potency of these compounds in reducing mitochondrial DNA to be: zalcitabine > stavudine > zidovudine > didanosine.[27] The apparent discrepancy that zidovudine inhibits mitochondrial DNA at a lower concentration than didanosine, and yet is not associated with neuropathy, may be explained by the dose-limiting cell growth inhibition observed with zidovudine *in vitro*.[27] Zidovudine inhibits cell growth more potently than it induces mitochondrial toxicity, and cell lines stop growing at concentrations of zidovudine below that necessary to deplete mitochondrial DNA.

In addition, *in vivo* tissue selectivity may influence the sites of prime toxicity, as there may be differential uptake or phosphorylation of nucleo-

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side analogues in different tissues.[28] In a neurotoxicity model, using PC12 cells, which differentiate into neuron-like cells on exposure to nerve growth factors, zalcitabine and didanosine have been shown to reduce mitochondrial DNA, leading to destruction of mitochondria and an increase in intracellular lactate levels.[28] Thus, cellular metabolism is substantially affected by nucleoside analogue–related inhibition of mitochondrial DNA polymerase. Nerve biopsies from patients with nucleoside analogue–associated neuropathy have demonstrated mitochondria with disrupted cristae, which resemble those seen in specimens from zalcitabine-treated rabbits.[29]

Mitochondrial toxicity may account for many of the long term features of nucleoside analogue–associated peripheral neuropathy, including the delayed onset (as mitochondrial DNA levels gradually decline) and the initial worsening of the neuropathic symptoms (sometimes called coasting) after stopping the drug (as restoration of mitochondrial DNA levels is gradual, abnormal signalling may occur during recovery).

A recent study has found depleted concentrations of levacecarnine (acetyl-*L*-carnitine) in patients with peripheral neuropathy taking zalcitabine, stavudine or didanosine therapy, compared with those taking the same drug without peripheral neuropathy.[29] The main functions of levacecarnine are mitochondrial β-oxidation of fatty acids and membrane energy balance.[16,30] It has also been found to have neuroprotective effects in studies using ischaemia, acidaemia, *N*-methyl-*D*-aspartate and amyloid protein to cause damage in cell culture, and in patients with Alzheimer's disease.[31-33]

Levacecarnine may increase the speed of peripheral nerve regeneration following injury by promoting nerve growth factor release.[34] In the short term, depletion of levacecarnine disrupts mitochondrial metabolism and causes a toxic accumulation of fatty acids.[30] This provides a further mechanism for nucleoside analogue neurotoxicity which, combined with other risk factors, may lead to clinically significant peripheral neuropathy in a given individual.

Table I. Diseases causing polyneuropathies in neurological practice[39]

Cause	% of patients developing polyneuropathies
Alcohol abuse	20-40
Diabetes mellitus	15-30
Guillain-Barré syndrome	6-13
Tick-borne radiculopathies	<10
Hereditary neuropathies	<5
Paraneoplastic neuropathies	<4
Parainfectious neuropathies	<3
Malabsorption of vitamins	<3
Toxic neuropathies	<3
Vasculitis	<2
Renal failure–related	<2
Multifactorial or unclassifiable	10-30

Thus, peripheral neuropathy in HIV patients on therapy is likely to have a multifactorial origin: drugs may themselves cause peripheral neuropathy but may also merely unmask a pre-existent subclinical distal symmetrical polyneuropathy. Hence, the likelihood of neuropathy, its severity and the degree to which the patient recovers following nucleoside analogue withdrawal, may depend more on pre-existing risk factors than the choice of nucleoside analogue itself.

4. Detection and Management of Risk Factors

Existing peripheral neuropathy or a prior history of peripheral neuropathy is associated with an increased risk of peripheral neuropathy development during nucleoside analogue therapy. Indeed, partially resolved zalcitabine-associated neuropathy has been reported to be exacerbated by subsequent therapy with didanosine or lamivudine.[35,36] Numerous studies have reported an association between lower CD4+ cell counts and increasing risk of peripheral neuropathy during therapy. In addition, patients with higher CD4+ cell counts may experience less severe neuropathy. One-third of AIDS patients develop distal symmetrical polyneuropathy in the absence of nucleoside analogue therapy, but subclinical neuropathy, de-

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tected by electrophysiological testing, occurs even more commonly.[37] It is difficult to identify susceptible patients prior to initiating therapy, as even pretreatment nerve conduction studies may not predict the development of peripheral neuropathy during nucleoside analogue treatment.[38]

Extensive investigations prior to starting nucleoside analogue therapy are not warranted in asymptomatic patients and are unlikely to be performed. Taking an adequate history and using direct questioning to elicit medical problems associated with peripheral neuropathy[39] (table I) and past and current drug use (table II) will identify most patients at increased risk.

Presence of low serum hydroxocobalamin (vitamin B12) levels and on-going heavy alcohol (ethanol) consumption appear to be useful in distinguishing patients at higher risk of nucleoside analogue–associated neuropathy.[40] An examination for signs of peripheral neuropathy, which probably needs only to involve the legs, unless upper limb symptoms are described, is prudent. One study found that 2 out of 38 patients with distal symmetrical polyneuropathy had clawing of the toes, which suggested that these patients had a long-standing or inherited neuropathy which was subclinical prior to nucleoside analogue therapy.[37] Such an examination will identify many patients at increased risk of peripheral neuropathy, or worsening of existing symptoms. The indication for a potentially neurotoxic nucleoside analogue should be re-examined in any such patients. If a trial of therapy with a potentially neurotoxic nucleoside analogue is still warranted, all correctable additional risk factors for neuropathy, such as vitamin deficiencies, poorly controlled diabetes mellitus, alcoholism, etc, need to be addressed before therapy starts.

Baseline nerve conduction studies may be useful in at-risk patients (or in patients with an equivocal clinical picture of peripheral neuropathy) before starting nucleoside analogue therapy. However, to avoid over-diagnosis of peripheral neuropathy, at-risk patients should be carefully re-examined if they complain of symptoms which may suggest peripheral neuropathy while on treatment. A re-evaluation of neuropathies reported in the AIDS Clinical Trials Group (ACTG) 175 trial using defined criteria for peripheral neuropathy (table III)[20] found that half of those reported did not meet the criteria for a drug-associated neuropathy.[2,41] It is important not to deny a patient the chance of effective treatment on the basis of an inadequate medical history.

Table II. Drugs used in HIV infection that are associated with peripheral neuropathy

Antibacterials
Metronidazole
Isoniazid
Streptomycin
Ethionamide
Anti-cancer agents
Vincristine
Vinblastine
Antiretrovirals
Didanosine
Zalcitabine
Stavudine
Antivirals
Cidofovir
Other agents
Corticosteroids
Thalidomide
Dapsone
Amphotericin B
Amitriptyline
Phenytoin

Table III. Criteria for the diagnosis of drug-associated peripheral neuropathy (PN) [after Simpson & Tagliati,[20] with permission]

Appropriate for PN	Inappropriate for PN
Pain, numbness, paraesthesias	Weakness
Lower extremities > upper extremities	Upper extremities > lower extremities
Bilateral, symmetrical	Unilateral, asymmetric
Distal	Proximal
No other causes	Other identifiable causes

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5. Nucleoside Analogue–Associated Neurotoxicity

Reporting of peripheral neuropathy in patients receiving nucleoside analogue therapy has varied between studies. Most trials have defined peripheral neuropathy as grades 1 to 4 (mild, moderate, severe, and potentially life-threatening) based on symptoms, signs and need for analgesia. In addition, the relationship of peripheral neuropathy to medication, as assessed by the investigators, has been included in some trials. Published reports have presented data ranging from a description of only those patients who withdrew from a trial because of peripheral neuropathy, to inclusion of all grades of neuropathy and all treatment relationships. Comparison of the incidence of peripheral neuropathy across studies is, therefore, difficult.

As zidovudine, lamivudine and abacavir have not been associated with peripheral neuropathy they have not been included in this discussion. Moreover, the initial studies of zalcitabine, didanosine and stavudine used dosage schedules that are not currently recommended. The currently approved oral dosages and their equivalent intravenous dosages are as follows: oral zalcitabine 0.75mg 3 times daily and intravenous zalcitabine 0.01 mg/kg 8-hourly; oral didanosine 200mg twice daily and intravenous didanosine 2.5 mg/kg 12-hourly; and oral stavudine 40mg twice daily and intravenous stavudine 0.6 mg/kg 12-hourly.

6. Zalcitabine

6.1 Monotherapy and Dose-Finding Studies

Phase I/II studies established peripheral neuropathy as the major dose-limiting toxicity of zalcitabine. Merigan et al.[42] observed peripheral neuropathy in all 29 recipients of zalcitabine at dosages of 0.03 mg/kg and 0.06 mg/kg 4-hourly with onset of symptoms as early as 2 weeks after the start of therapy. Tolerability was better at dosages <0.03 mg/kg 4-hourly; 25% of patients receiving such dosages had not developed peripheral neuropathy after >9 months of therapy. At the current recommended total daily dosage (but given as 0.005 mg/kg 4-hourly) no neuropathy was observed in 6 out of 8 patients.

In the ACTG 106 trial,[43] zalcitabine at dosages of 0.005 mg/kg and 0.01 mg/kg 8-hourly in combination with zidovudine resulted in a much lower incidence of peripheral neuropathy than reported at the higher dosages used in early studies. Over a 40-week follow-up period only 2 out of 47 patients (1 in each dose group) developed severe peripheral neuropathy (grade 3 or worse), with a further 4 patients experiencing mild symptoms which did not require interruption of zalcitabine therapy. The improved safety and greater antiviral activity observed in this phase I/II study, was the basis for further development of zalcitabine as a combination therapy agent, initially in regimens with zidovudine.

The mean time of onset to quantitative sensory abnormalities in these phase I/II studies was 7.3 weeks.[23,24,42-45] Nerve conduction studies performed on 20% of patients gave results typical of axonal dysfunction, with reductions in sural sensory potential amplitudes and prolongation of peroneal F response latencies. Electrophysiological abnormalities appeared later than overt symptoms and were frequently only mildly abnormal despite severe symptoms. At the zalcitabine dosage of 0.01 mg/kg 4-hourly, twice the current recommended dose, neuropathy was milder and delayed, with a mean onset of 9.3 weeks.[23,24]

In addition to peripheral neuropathy, case reports have suggested that neuropathy may also rarely involve the cranial nerves; progressive hearing loss has been reported in 2 patients receiving zalcitabine which resolved after withdrawal of the drug.[46,47] The incidence of peripheral neuropathy with zalcitabine may be reduced by alternating zalcitabine therapy with zidovudine, but with current treatment approaches this is not a feasible management strategy.[44]

After stopping zalcitabine therapy, some patients with peripheral neuropathy experience a period of symptom intensification (sometimes called coasting), lasting for several weeks to months. In a study of 52 patients by Berger et al.[23] recovery to

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mild symptoms or no symptoms had occurred in 83% of patients by 19 weeks (after 0.06 mg/kg 4-hourly), 15 weeks (0.03 mg/kg 4-hourly) and 11 weeks (0.01 mg/kg 4-hourly). Patients in whom peripheral neuropathy has resolved may be able to tolerate re-challenge with zalcitabine at a reduced dosage.

A strong relationship exists between the likelihood of zalcitabine-associated peripheral neuropathy and low CD4+ cell counts at the start of therapy. In a study of 59 patients, 5 out of 19 (26%) patients with a CD4+ cell count of <50/μl developed peripheral neuropathy compared with only 6 out of 40 (15%) patients with a CD4+ cell count 50/μl.[20] Similar observations were reported from ACTG 119[41] and from an international study of zidovudine and zalcitabine in combination in which a CD4+ cell count of 100/μl was used as a discriminator.[48]

A relationship was reported between a prior history of an AIDS–defining event and an increased incidence of peripheral neuropathy in the European expanded access programme (fig. 1).[49] However, in the ACTG 155 trial there was no significant difference between the incidence of grade 3 or 4 neuropathy in zalcitabine- and zidovudine-treated groups at CD4+ counts below 50/μl.[41]

These data suggest that at very low CD4+ cell counts the contribution of a nucleoside analogue to the development of peripheral neuropathy may be difficult to quantify. Moreover, peripheral neuropathy is more likely to persist in these patients when the nucleoside analogue is stopped.[23,50] Table IV shows the incidence of peripheral neuropathy of all grades and risk factors in several studies.[41,48,49]

Table V shows the incidence of peripheral neuropathy reported in large studies of zalcitabine monotherapy at the approved dosage of 0.75mg 3 times daily orally.[41,49,51] Where available, the incidence of peripheral neuropathy in comparator arms of similar size and with similar baseline characteristics is shown. These data indicate that although peripheral neuropathy (all severity grades) is reported in approximately 25% of patients when zalcitabine is taken over prolonged periods (>9 months), severe peripheral neuropathy, or peripheral neuropathy necessitating cessation of therapy, occurs in 10% of patients.

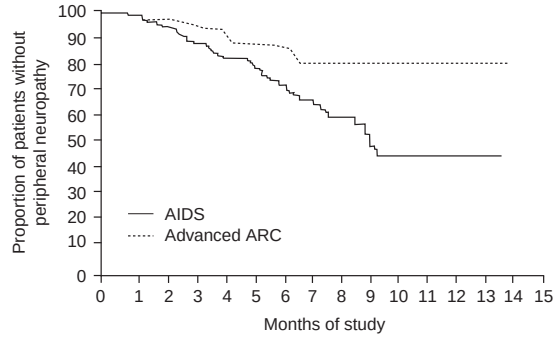

Fig. 1. Time to peripheral neuropathy in patients with AIDS and AIDS–related complex (ARC) taking zalcitabine 0.75mg 3 times daily in the European Expanded Access Programme (reproduced from Moyle et al.,[49] with permission).

6.2 Zalcitabine in Combination with Zidovudine

Table VI shows the incidence of peripheral neuropathy reported in large studies of zalcitabine, at the current recommended dosage of 0.75mg 3 times daily, in combination with zidovudine.[1,2,41,48,52,53] In the 3 largest studies, DELTA,[1] ACTG 175,[2,41] and Community Programs for Clinical Research on AIDS (CPCRA) 007,[53] although more peripheral neuropathy was reported in those patients in zalcitabine-containing groups, the overall incidence of adverse events was similar for zalcitabine, zidovudine alone, and zidovudine + didanosine. In addition, in studies of patients with well-preserved CD4+ cell counts such as the ACTG 175[2,41] and M50003[52] trials, the incidence of peripheral neuropathy appeared to be very low, particularly for severe or treatment-limiting peripheral neuropathy.

6.3 Zalcitabine in Combination with Protease Inhibitors

The combination of zalcitabine and the protease inhibitor saquinavir does not appear to increase the

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likelihood of patients developing peripheral neuropathy and may even decrease it. NV14256[54] was a randomised, double-blind controlled multicentre study comparing zalcitabine 0.75mg 3 times daily, saquinavir 600mg 3 times daily and a combination of the 2 drugs in zidovudine-pretreated patients. In this study, peripheral neuropathy tended to be less common in the combination therapy group (9%) than in the zalcitabine (25%). Patients treated with saquinavir monotherapy groups (3%) over approximately 18 months of follow-up.[54]

The Pisces study (SV 14604)[55] was a randomised, double-blind study, in which 3500 previously untreated or minimally pretreated patients with HIV infection, with CD4+ cell counts between 50 and 350 cells/μl, received zidovudine plus zalcitabine, zidovudine plus saquinavir or zidovudine plus zalcitabine plus saquinavir. In this study the incidence of peripheral neuropathy was low (ranging between 1.9 and 2.6%), with no observed difference in incidence of peripheral neuropathy between treatment groups.[41]

Whilst a protease inhibitor is unlikely to have a direct protective effect against peripheral neuropathy, the greater reductions in viral load, increases in CD4+ cell counts and reduced incidence of opportunistic disease observed with protease inhibitor-containing regimens, may reduce the number of risk factors/co-factors that usually contribute to nucleoside analogue-associated peripheral neuropathy.

7. Didanosine

Neuropathy has been reported to occur during didanosine therapy, however the incidence of neuropathy with the currently recommended dosage of didanosine, 400 mg/day, is similar to that occurring with zidovudine, a drug not considered to be neurotoxic.[1,2,56]

7.1 Monotherapy and Dose-Finding Studies

Dose escalation studies of didanosine established peripheral neuropathy and pancreatitis as dose-limiting toxicities of this drug. Initial studies used a sachet formulation of didanosine with a lower bioavailability than chewable didanosine; 500 mg/day of this form is equivalent to 400 mg/day of the currently available chewable tablets.

In 37 patients treated at different dosage levels for a mean of 17 weeks, peripheral neuropathy was reported in 1 out of 6 patients receiving didanosine 12 or 20.4 mg/kg/day, in 2 out of 6 patients receiving 30.4 mg/kg/day, and in 4 out of 4 patients receiving 45.6 mg/kg/day. Peripheral neuropathy was not observed in individuals receiving dosages ≤7 mg/kg/day.[57]

In a similar 12-week phase I/II study, peripheral neuropathy was observed in 5 out of 15 (33%) of patients receiving didanosine 1500 mg/day but in none of the 15 participants administered didanos-

Table IV. Risk factors for zalcitabine-related peripheral neuropathy identified in clinical studies

Trial	Risk category	Incidence(%)
ACTG 119[41]	CD4+ cell count < 50mm^3	26
	CD4+ cell count > 50mm^3	15
	CrCl < 110 ml/min	23
	CrCl > 110 ml/min	9.1
M50002[48]	CD4+ cell count < 100mm^3	16.1
	CD4+ cell count > 100mm^3	8.9
European EAP[49]	CD4+ cell count < 50mm^3	13.7
	CD4+ cell count > 50mm^3	11.1
	AIDS	16.7
	ARC	7.8
ACTG 155[41]	CD4+ cell count < 150mm^3	27-28
	CD4+ > cell count 150mm^3	16

ACTG = AIDS Clinical Trials Group; **ARC** = AIDS-related complex; **CrCl** = creatinine clearance; **EAP** = Expanded Access Programme.

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Table V. Incidence of peripheral neuropathy (PN) in patients receiving monotherapy with oral zalcitabine 0.75mg 3 times daily

Trial	Follow-up (median)	No. of patients	Mean baseline CD4+ cell count (cells/mm^3)	Incidence of PN with zalcitabine monotherapy (%)	Comparator drug	Incidence of PN with comparator drug (%)
US EAP[41]a	21.7 wks	1965	<201	11.4[b], 14.9[c]	Zalcitabine 0.375mg 3 times daily	7.7[b], 10.8[c]
CPCRA 002[50]a	16 mos	237	73	45.1[d]	Didanosine	22.1[d]
ACTG 119[41]a	279 days (zalcitabine arm)	52	84.3	10[b], 25[c]	Zidovudine	Not reported
ACTG 155[41]a	17.8 mos (12.2 mos on therapy)	285	117	6[e] 23[f]	Zidovudine Zidovudine + zalcitabine	4[e], 13[g], 6[e], 22[g]
European EAP[49]a	Maximum 429 days	517	51.8	2.3[b], 12.2[c]	No comparator	
ACTG 114[41]	Mean 309 days on therapy	320	98.7	14.4[e], 30.9[f], 50.3[c]	Zidovudine	2.8[e], 11.6[f], 33.3[c]

a All patients were zidovudine-experienced prior to study entry.
Where available all assigned relationships to study drug have been used, i.e. worst case:

b Withdrawals.

c All grades of severity.

d All grades/100 person-years.

e Severe.

f Moderate or worse.

g Moderate.

ACTG = AIDS Clinical Trials Group; **CPCRA** = Community Programs for Clinical Research on AIDS; **EPA** = Expanded Access Programme.

ine 750 mg/day.[58] In another study, 12 out of 151 (7.9%) zidovudine-experienced patients treated for a minimum of 1 year with didanosine 750 mg/day (12.5 mg/kg/day) developed grade 3 or 4 peripheral neuropathy at a median of 27.3 weeks (range 13 to 42 weeks).[50]

A dosage comparison study of didanosine 750mg and 200 mg/day involving 1775 participants treated for a mean of 12.4 months, found that neuropathy leading to treatment discontinuation occurred in 7.8 *vs* 5.9% of patients. Time to stopping didanosine therapy at a dosage of 750 and 500 mg/day was because of peripheral neuropathy was significantly shorter ($p = 0.03$ by log rank) in the higher dosage group.[59]

In ACTG 116b/117, didanosine at a dosage of 750 and 500 mg/day was compared with zidovudine monotherapy in zidovudine-experienced patients with a median CD4+ cell count of 95/μl. No significant differences in annualised incidence of grade 2 or worse peripheral neuropathy were reported with incidences of 13, 14 and 14% in the didanosine 750 mg/day, didanosine 500 mg/day and zidovudine groups, respectively.[60]

7.2 Combination with Zidovudine

The incidence of peripheral neuropathy in patients receiving didanosine, at the currently recommended dosage of 400 mg/day, in combination with zidovudine was similar to those for zidovudine alone in the DELTA[1] and ACTG 175 trials.[2] In DELTA,[1] peripheral neuropathy requiring cessation of therapy occurred in 2.4% of patients receiving zidovudine monotherapy, 1.1% of patients receiving zidovudine/didanosine and 1.6% of patients receiving zidovudine/zalcitabine. However, peripheral neuropathy reported as a serious ad-

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Table VI. Incidence of peripheral neuropathy (PN) in clinical studies of the combination of zalcitabine 0.75mg 3 times daily and zidovudine

Trial	Follow-up (median)	No. of patients	Mean baseline CD4+ cell count (cells/mm^3)	Incidence of PN with zalcitabine + zidovudine (%)	Comparator drug(s)	Incidence of PN with comparator drug (%)
ACTG 175[2]	143 wks (118 wks on therapy)	615	352	11[a]	Zidovudine	9[a], 1[b]
				1[b]	Zidovudine + didanosine	8[a]
					Didanosine	8[a]
DELTA[1]	30 mos (19 mos on therapy)	1072	205	5.9[c]	Zidovudine	2.4[c]
					Zidovudine + didanosine	1.1[c]
CPCRA 007[53]	35 mos (12 mos on therapy)	372	113.3	15.3[d]	Zidovudine	6.7[d]
					Zidovudine + didanosine	6.6[d]
ACTG 155[41]	17.7 mos (11.9 mos on therapy)	423	112	6[e]	Zidovudine	4[e], 13[f]
				22[a]	Zidovudine + didanosine	6[e], 23[f]
M50002[49]	Up to 12 mos	561	141.5	12.7[d]	No comparator	
M50003[52]	Up to 24 mos	256	399	10.1[d]	Zidovudine	3.1[d]

Where available all assigned relationships to study drug have been used, i.e. worst case:

a Moderate or worse.

b Severe or worse.

c Withdrawals.

d All grades of severity.

e Severe.

f Moderate.

ACTG = AIDS Clinical Trials Group; **CPCRA** = Community Programs for Clinical Research on AIDS; **EAP** = Expanded Access Programme.

verse event occurred in 1.8, 1.1 and 5% of patients in these groups, respectively.

In ACTG 175,[2,41] moderate or worse peripheral neuropathy was reported in 9, 8 and 8% of zidovudine, zidovudine plus didanosine and didanosine monotherapy recipients, respectively, over 143 weeks of follow-up, with no significant differences between groups. Similarly in CPCRA 007,[53] in much later stage patients, all grades of peripheral neuropathy were reported in 6.7 and 6.6% of zidovudine and zidovudine + didanosine recipients, respectively.[53] Details of peripheral neuropathy in these studies relative to comparator arms are shown in table VI.

Thus, whilst initial studies at higher dosages of didanosine reported an elevated incidence of peripheral neuropathy relative to zidovudine (or historical control), approved dosages of didanosine do not appear to increase the incidence of peripheral neuropathy relative to zidovudine monotherapy when either used alone or in combination with zidovudine. However caution should still be used when administering didanosine to individuals with pre-existent or resolved peripheral neuropathy as didanosine use may exacerbate an established neuropathy.[35]

8. Stavudine

8.1 Monotherapy and Dose-Finding Studies

Phase I/II studies of stavudine demonstrated that the development of peripheral neuropathy is dose-dependent. Dosages above 4 mg/kg/day were associated with an incidence of peripheral neuropathy of 64 to 73%;[61] the approved dosage of stavudine is 40mg twice daily and this is equivalent to about 1 mg/kg/day.

In a study involving patients with a median CD4+ cell count of 41 cells/mm^3 and who were intolerant of other antiretroviral drugs, the incidence of all grades of peripheral neuropathy was 21 and 15% in patients taking oral stavudine 40mg

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twice daily and 20mg twice daily, respectively.[20] In phase I trials, the incidence of peripheral neuropathy was 21 patients per 100 person-years of treatment for both 0.5 mg/kg/day and 1 mg/kg/day, and 66 patients per 100 person-years of treatment with 2 mg/kg/day. The incidence was lower in a phase II study: 17 patients per 100 person-years of treatment with 0.5 mg/kg/day and 41 patients per 100 person-years of treatment with 2 mg/kg/day.[61] Neuropathy resolved within 1 to 9 weeks in 15 of 27 patients, with a median time to resolution of 3 weeks in the 2 mg/kg/day group.[62]

In the BMS-019 trial,[63] 15% of stavudine recipients and 6% of zidovudine recipients required dose-modification because of peripheral neuropathy by 82 weeks' follow-up, giving a relative risk of peripheral neuropathy with stavudine compared with zidovudine of 2.14 ($p = 0.04$). Time to development of neuropathy was not significantly different between groups. After symptom resolution, 63% of patients resumed treatment with stavudine, mostly at a dosage of 20mg twice daily.

In the US parallel track study, the largest completed study of stavudine, the incidence of peripheral neuropathy (all grades) at 24 weeks was 17% for patients administered stavudine 20mg twice daily and 23% for patients administered stavudine 40mg twice daily ($p < 0.0001$). Only 11 and 13% respectively, of patients discontinued stavudine because of peripheral neuropathy; the remainder of patients with peripheral neuropathy were managed by dose modification.[64]

Factors found to increase the risk of peripheral neuropathy in stavudine-treated patients include a history of peripheral neuropathy, male gender, low CD4+ cell count, low haemoglobin level (<11 g/dl) and a Karnofsky score of <80.[61,62]

8.2 Combination of Stavudine with Didanosine

While the combination of stavudine and didanosine is being increasingly widely used in clinical practice, only limited published data are available on the safety of this regimen over prolonged follow-up. The initial dose-finding study involved 86 patients treated in 5 different dose-administration arms starting with stavudine 10mg twice daily plus didanosine 100mg twice daily and increasing up to the approved dosages of both drugs. In this study, only 2 individuals experienced a grade 3 or worse peripheral neuropathy requiring cessation of therapy after 1-year of follow-up.[65] Similarly, only 1 out of 19 patients experienced peripheral neuropathy after 16 weeks of follow-up after receiving stavudine and didanosine in combination with hydroxycarbamide (hydroxyurea).[66]

Insufficient data, and no long term follow-up are available from other studies to provide information regarding the risk of peripheral neuropathy in patients taking triple stavudine-based therapy regimens.

9. Management of Nucleoside-Related Peripheral Neuropathy

Patient education regarding the symptoms of peripheral neuropathy is essential to optimal management. Patients should be encouraged to report any neuropathic symptoms on each visit to the clinic and should have easy access to qualified personnel, e.g. a doctor or pharmacist, to discuss symptoms which have persisted for more than 48 hours.

In instances where withdrawing a drug is deemed prudent, options include stopping all antiretroviral drugs, to avoid the patient being left on sub-optimal therapy, or substitution with an agent likely to be of at least equivalent activity but with no chance of exacerbating the peripheral neuropathy. Zidovudine, lamivudine and abacavir are not generally associated with peripheral neuropathy, hence represent options in these circumstances.

Options for patients with no remaining nucleoside analogue options who do not wish to interrupt therapy include dual protease inhibitor combinations or protease inhibitor plus non-nucleoside therapy. In patients who interrupt therapy, reintroduction, generally at a reduced dosage (e.g. zalcitabine 0.375mg 3 times daily, stavudine 20mg twice daily), may be attempted once symptoms have resolved to mild.

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Once nucleoside analogue–associated peripheral neuropathy is suspected, the diagnosis should be confirmed by a history relating the onset of peripheral neuropathy to the commencement of nucleoside analogue therapy. The caveats outlined above need to be considered. A firm diagnosis of drug-related peripheral neuropathy can only be made if the neuropathy resolves after stopping the drug. Symptoms persisting beyond 2 months following drug withdrawal imply that other causes may be present.

Often symptoms predominate in the absence of objective signs of sensory loss. The patient should be warned about the coasting period, and reassured that recovery of sensory loss occurs in the majority of patients, although no clear time limits for recovery exist. It is probable that persistent deficits occur in those with pre-existing peripheral neuropathy, but it is not known whether these represent unmasking of the underlying peripheral neuropathy, new damage or both.

Pain is the main determinant of additional therapy. Nonsteroidal anti-inflammatory drugs and opioid analgesics may be of immediate benefit, and may be all that is required. However, as with other chronic painful neuropathies, tricyclic antidepressants, e.g. amitriptyline 25 to 75mg in the evening, may be of particular value for the more constant pain component, while agents such as carbamazepine or valproic acid (sodium valproate) may have a role in treating lancinating pains.[20]

Carbamazepine induces hepatic enzymes and this may affect the metabolism of some antiretrovirals, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors. The newer anticonvulsant, gabapentin, does not have this disadvantage and may be of value. Levacecarnine has been reported to have analgesic effects in painful peripheral neuropathy.[67] In view of the report of acetyl carnitine deficiency in HIV patients with nucleoside analogue therapy–induced neuropathy, it may be of particular benefit. A pilot study examining the role of this agent is currently in progress.

Although many patients may tolerate recommencement of the same nucleoside analogue at reduced dosage, reintroduction of a drug should only be done in the presence of careful clinical monitoring for toxicity and virological monitoring to ensure sufficient antiviral activity. Further nucleoside analogues, and other drugs with peripheral neurotoxic effects should be avoided, although this ideal may have to be modified if antiretroviral choice is limited for a particular patient.

10. Conclusion

The development of peripheral neuropathy is common in HIV patients and the incidence increases as CD4+ cell counts fall. The nucleoside analogues zalcitabine, didanosine and stavudine have all been associated with dose-limiting peripheral neuropathy in early, high dose studies. However, using the currently approved dosages peripheral neuropathy is much less likely to occur with didanosine in the absence of contributory factors. At the current recommended dosages of zalcitabine 2.25 mg/day and stavudine 80 mg/day the rate of neuropathy for both drugs is similar, causing approximately 10% of patients with symptomatic HIV infection to stop treatment; at the current recommended dosage for didanosine, approximately 1 to 2% of patients with symptomatic HIV infection to stop treatment because of neuropathy.

Pre-identifying and excluding patients at increased risk of peripheral neuropathy may reduce the incidence of this problem. The main risk factors for nucleoside analogue–related peripheral neuropathy are a low CD4+ cell count (<50/μl or <100/μl), prior opportunistic disease and pre-existing neuropathy. Additional risk factors include nutritional deficiencies and high alcohol consumption.

Management includes prompt withdrawal of the neurotoxic nucleoside and potentially the use of simple analgesics or, for more severe pain, tricyclic antidepressants or anticonvulsants. The use of levacecarnine and nerve growth factors is currently under investigation.

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Acknowledgements

The authors would like to thank Dr David Reddy and Dr Miklos Salgo of F. Hoffmann-La Roche for access to data on file for numerous studies of zalcitabine.

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