Review Article

POLYNEUROPATHY INDUCED BY HIV AND ANTIRETROVIRAL THERAPY: AN OVERVIEW

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Abstract: The objective of the article is to explain the most common HIV induced neuropathy; distal symmetrical polyneuropathy (DSP), and neuropathy induced by antiretroviral treatments. The emphases are given specially on mechanism of both the neuropathies. In antiretroviral induced therapy the main focus is on mitochondrial function impaired by nucleoside reverse transcriptase inhibitors (NRTIs). Here the role of HIV viral envelope protein gp120 is discussed for better understanding the axonal damage and neuronal toxicities. Beside these, management of neuropathies by medication and nutrition are also discussed.

Keywords: Polyneuropathy, distal symmetrical polyneuropathy, antiretroviral therapy.

INTRODUCTION

Polyneuropathy (PN) is the most common side-effects of HIV and antiretroviral therapy. About 30% of people with HIV develop PN. Peripheral neuropathy is one of many neurological conditions that can affect people with HIV, and it is the most common peripheral nervous system complication associated antiretroviral treatment.[1] Neuropathy can be classified according to their occurrence in different stages of HIV. Viral coated proteins causes nerve fibre damage and hypernociception through direct and indirect mechanisms. Direct interaction between viral proteins and nerve fibres leads to axonal pathology. While somal pathology is dominated by indirect mechanisms after virus-mediated activation of glia and macrophage infiltration into the dorsal root ganglia. The treatment-induced neuropathy and resulting hypernociception occur due to drug-induced mitochondrial dysfunction, which leads to the nerve fibre damage.[2] Distal symmetrical polyneuropathy (DSP) is the most common type of HIV induced neuropathy. It occurs due to the damage to axons or loss of their protective myelin sheaths (demyelination), but HIV does not directly infect nerve cells. Instead, HIV infection leads to immune activation and production of inflammatory chemicals called cytokines that cause axon damage. In addition, the gp120 envelope protein of the virus causes neuron apoptosis.

TYPES OF NEUROPATHY

There are several discrete types of HIV-associated neuropathy, which can be classified according to the timing of their appearance during HIV infection, their etiology, and whether they are primarily axonal or demyelinating (Table 1).[3]

Table 1: Peripheral nervous system (PNS) involvement in HIV infection.

HIV-associated PNS disorder	CDC stage	Course	Clinical features	Mechanism
Distal sensory neuropathies				
Distal symmetrical polyneuropathy	AIDS, CDC C	Subacute or chronic	Distal sensory loss, neuropathic pain	Immune dysfunction, Macrophage-mediated axonal injury
Anti-retro viral toxic neuropathy	Any stage, CDC A-C	Subacute	Distal sensory loss, neuropathic pain	DRG neuronal mitochondrial dysfunction
Mononeuritis multiplex				
Vasculitic neuropathy	Symptomatic HIV disease, CDC B	Stepwise progression	Multiple, asymmetric mononeuropathies, usually painful	Dysimmune/vasculitic mechanisms

Mononeuritis multiplex due to opportunistic pathogens	AIDS, CDC C	Acute, subacute	Multiple, asymmetric mononeuropathies, usually painful	CMV infection, VZV infection, hepatitis B and C (especially with cryoglobulinemia)
Inflammatory demyelinating polyradiculoneuropathies				
Acute inflammatory demyelinating Polyradiculoneuropathy	Early, pre-AIDS	Acute	Motor to sensory signs, NCS reveal demyelinating features	Immune dysfunction: macrophage/complement mediated demyelinating neuropathy
Chronic inflammatory demyelinating neuropathy	Early, pre-AIDS	Subacute to chronic	Sensorimotor neuropathy, NCS show demyelinating features	Immune dysfunction
Progressive polyradiculopathy				
CMV polyradiculopathy	AIDS	Acute	Lumbosacral pain, saddle anesthesia, rapidly progressive flaccid paraparesis	CMV infection, necrotizing neuropathy
Herpes zoster radiculopathy or myeloradiculopath	AIDS	Acute	Lumbosacral pain, saddle anesthesia, rapidly progressive flaccid paraparesis	VZV infection: Schwann cell and endothelial cell infection
Other				
Diffuse infiltrative lymphocytosis syndrome	AIDS	Subacute	Sjogren's like, sensorimotor, painful, distal sensory neuropathy or multiple mononeuropathy	Intense, angiocentric CD8 lymphocytic infiltration in Peripheral nerves, associated with high plasma viral loads

CDC, Centers for Disease Control and Prevention; DRG, dorsal root ganglion; CMV, cytomegalovirus; VZV, varicella zoster virus; NCS, nerve conduction studies.

DISTAL SYMMETRICAL POLYNEUROPATHY (DSP)

DSP is characterized by distal degeneration of long axons.[4] This pattern is usually termed as 'dying back'; because it is observed that the distal regions of the fibers degenerate first, with centripetal progression. In DSP the density of small and large myelinated fibers, especially unmyelinated fibers are reduced.[5] In 'dying back' degeneration, the axon of a chronically injured neuron slowly degenerates from the distal end in a centripetal manner. The 'dying back' degeneration is a stereotyped response of axons,[6] which under some circumstances activate a self-destruct programme, similar to apoptosis in the cell bodies. Punch skin biopsies revealed that there is reduction in the density of intraepidermal nerve fiber, suggesting prominent involvement of small, unmyelinated fibers (Fig. 1).[7]
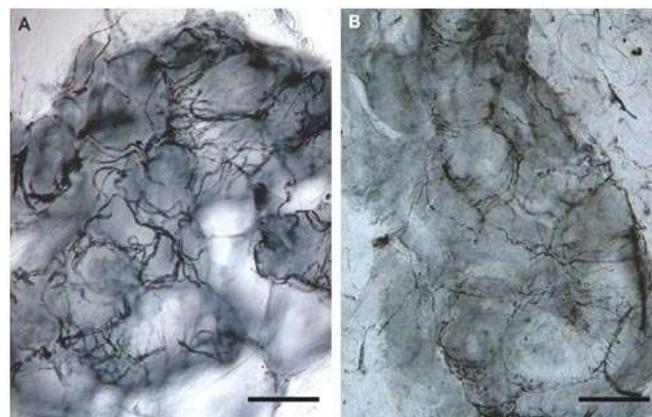

Figure 1: Skin biopsy from a normal control (a) and a HIV patient with DSP (b)

Role of gp120 virus envelope protein

The gp120 envelope protein of the virus causes neuron apoptosis. Firstly the axons are degenerated and then they are lost, starting with the nerve cells farthest from the CNS. In rodent dorsal root ganglia (DRG) cultures, HIV viral envelope protein gp120 results in neurotoxicity and axonal degeneration. The gp120 leads to neuronal apoptosis and axonal degeneration through two, independent and spatially separated mechanisms of action: (i) an indirect effect to cell bodies, requiring the presence of Schwann cells, results in neuronal apoptotic death and subsequent axonal degeneration; (ii) a direct, local toxicity exerted on axons through activation of mitochondrial caspase pathway. This local axonal toxicity is takes place due to the binding of gp120 to axonal chemokine receptors.[8] The gp120-induced axonal toxicity involves release of cytochrome c from mitochondria and activation of caspase pathway. The axonal activation of caspase pathway by gp120 may be responsible for the clinical observation in patients infected with HIV develop a distal axonopathy. Activation of chemokine receptors CXCR4 and/or CCR5 by gp120 causes membrane depolarisation, sensitisation of TRPV1 and bradykinin (BK) receptors, and release of substance P. Sustained exposure to gp120 leads to release of pro-hypernociceptive molecules CCL2 and TNF-α in the dorsal root ganglia (Fig. 2). Hyperactivity in the affected primary afferents leads to gliosis in the dorsal horn of the spinal cord, which maintenance the hypernociceptive state. Viral protein R (Vpr) may also lead to the development of hypernociception through membrane depolarization and release of interferon-γ in the dorsal root ganglion. However, the mechanisms behind these processes are largely unknown. The details of pathways shown with dashed lines are uncertain.
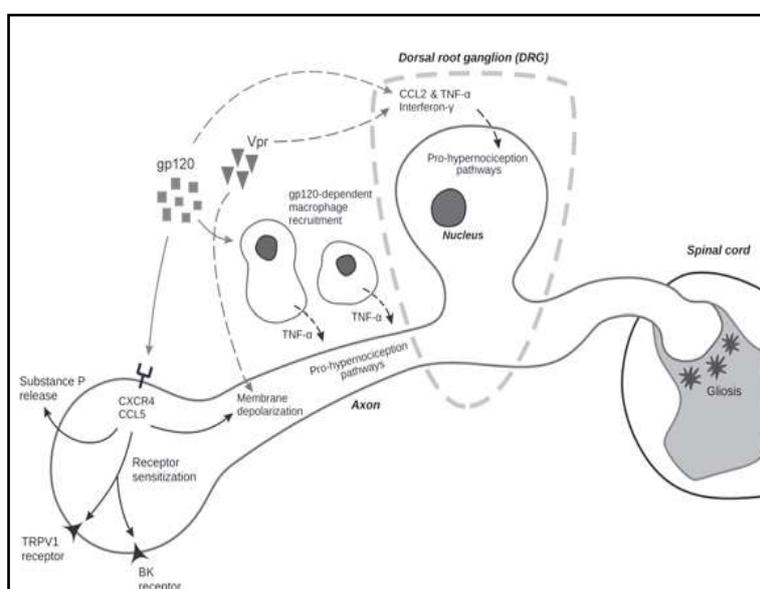

Figure 2: HIV-induced hypernociception.

The gp120 protein alone, in absence of the whole infective virus, is toxic to sensory axons and this toxicity involves chemokine receptors CXCR4 and CCR5. Activation of chemokine receptors on sensory neurons by gp120 is responsible for the neuronal excitation and pain.[9] Binding of natural ligands to chemokine receptors on hippocampal neurons have a pro-survival effect, whereas binding of HIV-1 to these receptors produces apoptosis.[10] SDF-1α, the natural ligand of CXCR4 (chemokine receptor), and gp120 activate different cellular pathways. Both are the potent activators of MAP kinases, but only SDF-1α stimulates Akt and anti-apoptotic factors.[11] Binding of gp120 to CXCR4, in the absence of CD4 signal, induce cytochrome c release and caspase activation.[12] Sensory neurons in humans express CXCR4 and CCR5 receptors and activation of these receptors can occur independently of association with CD4.[13-15] G120-induced apoptosis in cerebellar granular cells can be prevented by AMD3100, a CXCR4 inhibitor.[16] Similarly, in our system, the CXCR4 chemokine receptor can be blocked by monoclonal antibody which prevents the axonal toxicity induced by gp120.

The Pathogenesis of Pain in DSP

The pathogenesis of pain can be explained by the hypothesis explained below. The first, or 'peripheral' hypothesis is that the neuropathic pain associated with DSP is derived from spontaneous activity of uninjured C (nociceptive or pain) fibers after injury in neighbouring peripheral nerve fibers.[17] Wallerian degeneration also produces altered properties in adjacent intact nociceptive afferents.[18] The macrophage inflammation in DSP has suggested that the local release of proinflammatory cytokines sensitizes the nerves. Indeed, in animal models, endoneural injection of TNF-α into the sciatic nerve sensitizes the nociceptive fibers to produce neuropathic pain.[19] The second or 'central' hypothesis is the alterations in dorsal root ganglion (DRG) neuronal sodium and calcium channel expression and function result in abnormal

processing of pain after peripheral nerve injury.[20] Viral proteins such as gp120 induces allodynia when injected into rat paws, when delivered epineurally to the rat sciatic nerve,[21] and when administered intrathecally.[22]

Diagnosing DSP

DSP diagnosis is based on reports of symptoms, findings on physical exams, and ruling out other potential causes. If a patient reports symptoms such as pain, burning, numbness, or tingling in the feet, a neurological exam may help determine the cause of the symptoms. Inflammatory demyelinating polyneuropathy (known as Guillain-Barré syndrome in its acute form) is marked by progressive weakness of the extremities and poor reflexes at all sites.[23] Progressive polyradiculopathy (damage to nerve roots near the spine) can be caused by the opportunistic infection cytomegalo virus or herpes simplex virus; this mostly occurs in people with CD4 counts below 200 cells/mm³. Polyradiculopathy is characterized by weakness and numbness in the feet, bowel incontinence, bladder retention (difficulty passing urine), and saddle anaesthesia.[24]

POLYNEUROPATHY CAUSED BY ANTIRETROVIRAL DRUGS

Polyneuropathy induced by antiretroviral therapy is thought to be due to impaired mitochondrial function. Mitochondria are structures within a cell that produce energy and are involved in other crucial cell functions. The US Food and Drug Administration (FDA) have approved 18 antiretroviral drugs for the treatment of HIV-1 infection including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, and fusion inhibitors.[25] Different nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) are associated with varying degrees of mitochondrial toxicity, with ddC (zalcitabine) causing the most damage, followed by d4T (stavudine), ddI (didanosine), and AZT (zidovudine; Retrovir). The remaining drugs in this class-3TC (lamivudine), emtricitabine (Emtriva), abacavir (Ziagen), and tenofovir (Viread) are less likely to interfere with mitochondrial function. Other types of antiretroviral drugs, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, and entry inhibitors, are less likely to cause mitochondrial toxicity. Nucleoside analogues inhibit human DNA polymerase g, produce mitochondrial toxicity.[26]

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs can inhibit mitochondrial DNA polymerase γ in-vitro which is the host enzyme responsible for mitochondrial DNA synthesis.[27, 28] Mitochondrial toxicity may result from mitochondrial DNA depletion.[29] There are now eight drugs in this group including 3'-azido-2',3'-dideoxythymidine (zidovudine; AZT),[30] 2',3'-dideoxyinosine (didanosine; ddI),[31] 2'3'-didehydro-2',3'-dideoxythymidine (stavudine; d4T), 2,3'-dideoxycytidine (zalcitabine; ddC),[32] (-)2'-deoxy-3'-thiacytidine (lamivudine; 3TC),[33] emtricitabine (FTC), abacavir (ABC) and tenofovir disoproxil (TVD). Inhibition of mitochondrial DNA polymerase γ leads to chain termination or nucleoside analogue incorporation into the elongating DNA. The triphosphate forms of NRTIs compete with endogenous nucleotides for HIV DNA synthesis in the presence of HIV enzyme, reverse transcriptase (RT), thus acting as chain terminators. NRTIs also act as substrates for mitochondrial DNA (mtDNA) polymerase γ which leads to interrupt replication even of mtDNA. NRTI can exert rapid cellular toxicity directly by inhibiting mitochondrial bioenergetic function in a tissue specific fashion.[34] Zidovudine-associated skeletal myopathy was observed early after the introduction of the drug in 1987, and some changes like ragged-red fibres and reduction of mtDNA content and some morphological changes in the mitochondria were demonstrated in skeletal muscle.[35, 36] Zidovudine (AZT) inhibits the NADH-linked respiration and NADH-cytochrome c reductase activity in isolated rat skeletal muscle, brain and liver mitochondria.[37] AZT also inhibits adenylate kinase and the ADP/ATP translocator in isolated liver mitochondria, resulting in early impairment of oxidative phosphorylation which means impairment in energy production.[38-40] In cultured human muscle cells, AZT also reduces the activity of SDH, a complex II protein that is encoded by nuclear rather than mitochondrial DNA.[41] Zalcitabine (ddC) induces cardiotoxicity rapidly in rats, and this disorder is associated with decreased activity of respiratory complexes, but not with mitochondrial DNA depletion.[42] There is no correlation between the ability of nucleoside analogue to increase lactate production and their potency in mitochondrial DNA depletion.[43]

Effects on DNA pol γ

The nuclear-encoded mitochondrial DNA pol γ is the only DNA polymerase found in mitochondria. It is crucial for mtDNA replication as well as for mtDNA repair capacity.[44, 45] Inhibition of mtDNA replication will leads to a reduction of mtDNA content, and thereby decreased synthesis of the mtDNA-encoded protein subunits of the oxidative phosphorylation (OXPHOS) system. It also reduced ATP production, and increase in the concentrations of reactive oxygen species.[46]

Effects on Thymidine Kinases (TKs)

Endogenous thymidine, cytidine, and thymidine analogues (zidovudine and stavudine) are phosphorylated to monophosphates by the nucleotide kinases TK1 (localized in the cellular cytoplasm) or TK2 (localized in the mitochondria). Zidovudine may even inhibit TK2, and cause reduced levels of endogenous nucleotides and thereby decreased synthesis of mtDNA.[47] Reduction of endogenous nucleotides could also be caused by favouring the transport of phosphorylated NRTIs into the mitochondria compared with endogenous nucleotides.[48]

Mitochondrial dysfunction by mechanisms other than inhibition of DNA pol γ

NRTI can also cause mitochondrial dysfunction by mechanisms other than inhibition of DNA pol γ like:

- By predisposing, pre-existing mutations.
- Accumulation of mtDNA mutations as a result of NRTIs.
- Decreased expression of mitochondrial genes.[49]

The spontaneous mutation rate is generally higher in mtDNA compared with nuclear DNA. Patients exposed to NRTI have mtDNA deletions in muscle tissue.[50] Another factor for reduced mitochondrial function is a decreased expression of mitochondrial genes, detected in adipocytes.[51-53]

Non-NRTIs and Mitochondrial Toxicity

Although non-NRTIs do not inhibit DNA pol γ, a recent study found that both efavirenz and nevirapine might reduce mitochondrial membrane potential ($\Delta\Psi_m$). Current treatment with nevirapine was also in fact associated with apoptosis of lymphocytes.[54] In keeping with this notion, efavirenz was associated with apoptosis in-vitro, induced by the intrinsic mitochondrial apoptotic pathway.[55]

MANAGEMENT OF NEUROPATHY

US Food and Drug Administration (FDA) have approved five medications for the treatment of NP, namely:

- Postherpetic neuralgia: lidocaine patch (5%), gabapentin, pregabalin.
- Painful diabetic polyneuropathy: pregabalin and duloxetine.
- Trigeminal neuralgia: carbamazepine.

Managing Peripheral Neuropathy with Medication

Simple analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs and coxibs) are ineffective in pure NP.[56]

First-line medications
Tricyclic antidepressants (TCAs)

Low doses of tricyclic anti-depressants are used to treat the moderate symptoms of Peripheral Neuropathy because they do not appear to cause mood changes and are especially indicated in neuropathy that causes difficulty in falling asleep. The most common drug of this class is amitryiptyline but other medications including nortriptyline and despiramine may also be used. It should be noted that these medications do have side-effects and interact with the protease inhibitor, ritonavir (Norvir).

Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)

Duloxetine is a SSNRI and has demonstrated significant pain relief compared with placebo in randomised controlled trials (RCTs). Duloxetine produces favourable side-effect profile in comparison with TCAs.[57]

Calcium channel α2-δ ligands

Both gabapentin and pregabalin have a unique mechanism of action that differs from other anticonvulsants. They bind to the α2-δ subunit of the voltage-gated calcium channels, which results in the inhibition of glutamate and substance P release in the spinal dorsal horn.[58] The α2-δ subunits of the voltage-gated calcium channels are widely distributed throughout the peripheral and central nervous system, and up regulation of the α2-δ subunits are thought to play an important role in the central sensitisation process after damage to the nervous system.[59]

5% Lidocaine patch

It has proven efficacy in patients with allodynia, and has been approved by FDA for this indication.[60]

Second-line medications

Opioid analgesics and tramadol have demonstrated efficacy in neuropathy patients in a recent meta-analysis. They may be used as second-line treatment, alone or in combination with first-line medication(s) in patients with an inadequate response to first-line pharmacotherapy. When prompt pain relief is required, opioid analgesics and tramadol can also be used as first-line medications. Three RCTs of tramadol for neuropathic pain have yielded significant evidence for its use in neuropathic pain with an overall number-needed-to-treat (NNT) of 3, 9.

Third-line medications

Anticonvulsants (carbamazepine, oxcarbazepine, valproic acid, phenytoin, lamotrigine): The neuronal hyperexcitability and molecular changes (abnormal expression of sodium channels, increased activity at glutamate receptor sites, and an alteration of calcium influx into cells) in neuropathic pain have many common features with the cellular changes in certain forms of epilepsy. This has led to the use of anticonvulsant drugs for the treatment of neuropathic pain. Carbamazepine is considered first-line therapy for trigeminal neuralgia with a NNT of 1, 7. It is also recommended for patients with other types of neuropathy who do not respond to gabapentin or pregabalin, It has yielded inconsistent results in RCTs of other neuropathy conditions. Lamotrigine, a new anticonvulsant, is effective in trigeminal neuralgia, painful peripheral neuropathy.

Antidepressants (paroxetine, citalopram, bupropion): Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and citalopram are not as effective as SSNRIs and TCAs. They have a NNT 6, 7. Paroxetine and citalopram have demonstrated modest efficacy in the management of neuropathic pain. Bupropion, which is a noradrenaline and dopamine uptake inhibitor, indicated a surprisingly high efficacy in peripheral neuropathic pain.

NMDA receptor antagonists (ketamine): NMDA-receptor antagonists with affinity at the phencyclidine site have been shown to modulate pain and hyperalgesia but are limited by dose-limiting side effects. Thus, provided their therapeutic ratio is favourable.

Capsaicin: Capsaicin inhibits the release of substance-P from nerve endings, with a gradual analgesic effect, which may take effect only after 2-4 weeks with consistent application.

Managing peripheral neuropathy with nutrition

Although there has been no research to date on the effect of nutrition on HIV-related peripheral neuropathy, but there has been a lot of research on diabetic neuropathy. Because of the similar processes of these two diseases, this is believed that this research will also be applicable to HIV induced neuropathy.

B Vitamins: Several B vitamins help in rebuilding the myelin sheath around the nerves and also help to repair the nerve functioning. Vitamin B12 deficiency is a known cause of neuropathy specific to foot and leg pains.

Acetyl-L-Carnitine: Acetyl-L-Carnitine is a version of L-carnitine which is an amino acid that plays a role in the conversion of triglycerides in the mitochondria. It is also an essential co-factor in the metabolism of fatty acids. This nutrient can protect nerves from oxidization and consequently from free radical damage. There have been two studies of HIV-positive people. One study showed that HIV-positive individuals with Peripheral Neuropathy showed a deficiency of L-Carnitine.

Alpha Lipoic Acid (ALA): ALA is an anti-oxidant that helps to protect the cells against damage from free radicals. Since it is a small molecule that can move easily between cell membranes, it captures free radicals and can even remove them. Its anti-oxidant properties are thought to protect the nerves from inflammation and the oxidative damage that HIV induces.

Gamma Linolenic Acid (GLA): It has been shown to be successful in reversing nerve damage in diabetics suffering from peripheral neuropathy. It is thought that GLA may help to rebuild the myelin sheath around the nerves and restore proper nerve conduction.

Other vitamins: Magnesium is one of the nutrients that are found deficient in HIV-positive people and is known to cause Peripheral Neuropathy symptoms. It helps in nerve conduction. It can also ease muscle problems, especially muscle cramping.

OVERVIEW AND CONCLUSION

The main objective of this article is to highlight the mechanism and management of polyneuropathy induced by HIV and antiretroviral therapy. From the above discussion it has been concluded that neuropathies are of many types based on their timing of occurrence at the different stages of HIV. Symptoms of DSP are pain, burning, numbness, or tingling in the feet, hypernociception, allodynia etc. The main characteristic of DSP is distal degeneration of long axons (dying back) means the distal regions of the fibers degenerate first in a centripetal manner. Skin biopsies during DSP revealed that there is reduction in the density of intraepidermal nerve fiber. DSPN occurs due to the damage to axons or demyelination. Damage to axons or neurotoxicity is caused by HIV viral envelope protein gp120 by direct (presence of Schwann cells) or indirect mechanism (activation of mitochondrial caspase pathway). Activation of chemokine receptors (CXCR4 and CCR5) on sensory neurons by gp120 is responsible for the neuronal excitation and pain. Polyneuropathy induced by antiretroviral therapy is thought to be due to impaired mitochondrial function. NRTIs have been shown in-vitro to inhibit mitochondrial DNA polymerase γ. Due to inhibition of DNA polymerase γ, synthesis mitochondrial DNA is also inhibited. They also inhibit the NADH-linked respiration, NADH-cytochrome c reductase, adenylate kinase and the ADP/ATP translocator. Non-NRTIs do not inhibit DNA pol γ but they might reduce

mitochondrial membrane potential ($\Delta\Psi_m$). Neuropathies can be managed by both medication and nutrition.

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