Review

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Chronic Pain in HIV

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Abstract

The evolution of therapeutics for and management of human immunodeficiency virus-1 (HIV-1) infection has shifted it from predominately manifesting as a severe, acute disease with high mortality to a chronic, controlled infection with a near typical life expectancy. However, despite extensive use of highly active antiretroviral therapy, the prevalence of chronic widespread pain in people with HIV remains high even in those with a low viral load and high CD4 count. Chronic widespread pain is a common comorbidity of HIV infection and is associated with decreased quality of life and a high rate of disability. Chronic pain in people with HIV is multifactorial and influenced by HIV-induced peripheral neuropathy, drug-induced peripheral neuropathy, and chronic inflammation. The specific mechanisms underlying these three broad categories that contribute to chronic widespread pain are not well understood, hindering the development and application of pharmacological and nonpharmacological approaches to mitigate chronic widespread pain. The consequent insufficiencies in clinical approaches to alleviation of chronic pain in people with HIV contribute to an overreliance on opioids and alarming rise in active addiction and overdose. This article reviews the current understanding of the pathogenesis of chronic widespread pain in people with HIV and identifies potential biomarkers and therapeutic targets to mitigate it.

Keywords

HIV, chronic widespread pain, peripheral neuropathy, peripheral immune cells, inflammation, HIV-1 proteins

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Introduction

The prevalence estimates of chronic pain associated with human immunodeficiency virus-1 (HIV-1) infection vary widely, ranging from 25% to 90% of people with HIV (PWH) depending on the cohort.[1–3] The prevalence of pain associated with end-stage patients with acquired immunodeficiency syndrome (AIDS) is not unlike that of end-stage patients with cancer,[4] yet far fewer studies have focused on mechanisms of pain related to HIV and AIDS than cancer. The current review seeks to consolidate and review the existing body of literature regarding the etiology of chronic pain in PWH. The review is focused around three key mechanistic areas of current scientific interest: (1) host immune cells, (2) viral proteins, and (3) antiviral therapy.

Pain physiology

A conscious perception of pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[5] A common framework to facilitate our understanding of pain delineates four key events: sensory transduction, transmission, perception, and modulation. A noxious stimulus or tissue injury causes release of allogenic chemical mediators of pain and inflammation and neurotransmitters including interleukins (ILs), neuropeptides (substance P, calcitonin gene-related peptide), prostaglandins, histamine, bradykinin, glutamate, and norepinephrine.[6] These mediators stimulate first-order peripheral afferent neurons to generate an action potential in a process

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known as sensory *transduction*. Sensory information is then propagated and *transmitted* centrally via synaptic contact with second-order neurons within the dorsal horn of the spinal cord. Spinal projection neurons ascend via the spinothalamic tract to the thalamus, where third-order neurons then transmit information to limbic regions and somatosensory cortex where pain is consciously *perceived*. The spinal dorsal horn is a critical site of *modulation*, where incoming signals may be inhibited or excited via local (segmental or propriospinal) circuits or by descending input from supraspinal structures.

Acute pain serves a physiological purpose to alert the organism to imminent or ongoing tissue damage or injury and elicit a response for self-preservation. However, chronic pain can occur even in the absence of a noxious stimulus, such as tissue damage, and is characterized by changes in the way pain-related signals are processed and modulated. Peripheral injury and inflammation lead to local increases in chemical mediators that lower activation thresholds and increase responsiveness in peripheral nerves, where transduction occurs (peripheral sensitization). Intense or prolonged input to the central nervous system (CNS) as well as factors that influence pain modulation (e.g., stress) can further lead to amplification of nociceptive signaling within the spinal dorsal horn and brain (central sensitization). The consequences of these sensitization processes are the hyperalgesia and/or allodynia that are characteristic of chronic pain.

Epidemiology of chronic pain in HIV

Chronic pain, defined as lasting at least three months and not associated with ongoing tissue injury,[7] is a burdensome comorbidity of HIV infection. In PWH, chronic pain is associated with a high rate of disability and decreased quality of life.[8] In particular, the prevalence of chronic pains at more than one anatomical site (i.e., chronic widespread pain (CWP)) in PWH ranges from 25% to 90%.[2,3,9,10] As with other chronic pains, women are more likely to have chronic HIV-related pain and are at a higher risk for under treatment of their pain.[11] Chronic pain associated with HIV includes regional and widespread musculoskeletal pain[3] of neuropathic and inflammatory nature.[10,12,13] The primary sites of HIV-related CWP are the joints, head, legs, and back,[14,15] with 53.7% of PWH rating their pain as severe.[3] HIV-related CWP leads to serious health consequences, including up to 10× greater odds of functional impairment.[9] Disproportionately high rates of chronic pain in PWH have been attributed to virus- and drug-induced peripheral neuropathies[16,17] and chronic, non-neuropathic inflammation.[12] Despite an increase in awareness that pain is a significant problem for PWH, including the creation of an International Task Force on Pain and AIDS in 1994 to address this problem, the prevalence of HIV-related pain since the 1980s has not diminished. This underscores the fact that highly active antiretroviral therapy (HAART) and current pain management strategies are not sufficient to address the individual and socioeconomic burden of pain in PWH.

Opioid use in PWH with CWP

Despite a lack of evidence demonstrating their long-term efficacy,[18,19] prescription opioids remain an essential element of long-term pain management in PWH. Their use as a chronic therapy brings a complex set of issues and risks both in the general population and in PWH. In the general population, the epidemic of prescription opioid misuse has resulted in a transition to injectable forms of illicit opioids (e.g., heroin), with almost 80% of new heroin users reporting prior prescription opioid abuse.[20] Within the HIV patient population, those with a history of illicit substance abuse are statistically more likely to report pain.[21] Furthermore, comorbid illicit substance abuse increases pain symptoms in PWH[22] despite physician-prescribed pharmaceutical pain treatment, underscoring the inadequacy of current pain management strategies in this population.[23] PWH with a history of opioid dependence often need higher doses of opioids to treat acute bouts of pain due to the development of tolerance,[24,25] and long-term opioid use leads to depression and may paradoxically worsen chronic pain.[26] From a public health perspective, there is an increased chance of transmitting and acquiring hepatitis B and C due to opioid use-related engagement in high risk behaviors.[27] Therefore, there is an urgent need to develop novel, targeted therapeutic strategies and minimize the use of opioids in PWH.

Mechanisms of chronic pain in HIV

Peripheral immune cells

The peripheral immune system may play an important role in the development of HIV-associated hypersensitivity. The activation of pro-inflammatory pathways in peripheral immune cells in adaptive response to infection with the HIV-1 virus may come at the cost of changes in afferent nociceptive signaling that contribute to the development of hypersensitivity and pain-related syndromes. As is typical with viral infection or peripheral tissue injury, there is an early activation and proliferation of resident macrophages with concurrent recruitment and inflammatory specialization of infiltrative macrophages. Macrophages are the earliest and most prolific of the infiltrating cells observed with nerve injury and neuro-inflammation and, importantly, this

pattern is conserved across various preclinical models of neuropathy.[28] Injury leads to macrophage release of matrix metalloproteases that further contribute to recruitment and infiltration of immune cells to the initial site of damage.[29] This peripheral inflammatory milieu causes neuronal damage as well as direct stimulation of nociceptors with signal amplification leading to glial cell activation, thus provoking an innate, macrophage-driven immune response more proximally within dorsal root ganglia (DRG), where primary afferent somata are located.[29,30]

Recent studies have shown that during HIV-1 infection in humans and simian immune virus (SIV) infection in macaques, monocyte/macrophages traffic to the DRG and cause damage resulting in peripheral neuropathy.[31–34] Hahn et al. showed that the exposure of supernatant from macrophages infected with HIV-1 strains to dissociated, cultured human DRG neurons induced somata and axonal mitochondrial dysfunction and neurite retraction.[32] Treatment with antioxidants rescued the neuronal cell body but not the axon from the toxic mitochondrial effects of the culture supernatants.[32] Laast et al. demonstrated that the SIV-infected macaques had significantly lower C-fiber conduction velocity in sural nerves than uninfected animals, and the magnitude of decline correlated strongly with extent of DRG macrophage infiltration.[33] Lakritz et al. further demonstrated that the loss of intraepidermal nerve fiber density during SIV peripheral neuropathy is mediated by monocyte activation and elevated monocyte chemotactic proteins.[35]

Once activated, resident macrophages release damage-associated molecular patterns that serve to further activate and recruit immune cells, including T helper type 1 (Th1) cells. Th1 cells release the cytokine interferon-gamma capable of instigating the Janus kinase-signal transducer and activator of transcription-1 (JAK-STAT-1) signaling pathway and inducing activation of the pro-inflammatory macrophage phenotype.[28,36] Pro-inflammatory macrophages express inflammatory cytokines including IL-1β, IL-6, and tumor necrosis factor (TNF)-α, which enhance local neuro-inflammation, play a role in establishing a neuropathic pain state, and lead to peripheral and central sensitization (Figure 1).[28,30] Conversely, Th2 cells release IL-4 and IL-13 that promote the development of the pro-resolution, macrophage phenotype characterized by expression of the anti-inflammatory cytokine IL-10 (Figure 1). The ratio of pro-resolution to anti-inflammatory macrophages appears important in neuropathic pain, and pharmacologic attempts to modulate this balance have been reviewed recently.[28] In a recent study of PWH who self-reported chronic pain, plasma levels of IL-1β were significantly higher than in individuals without chronic pain.[12] Measurement of cytokines

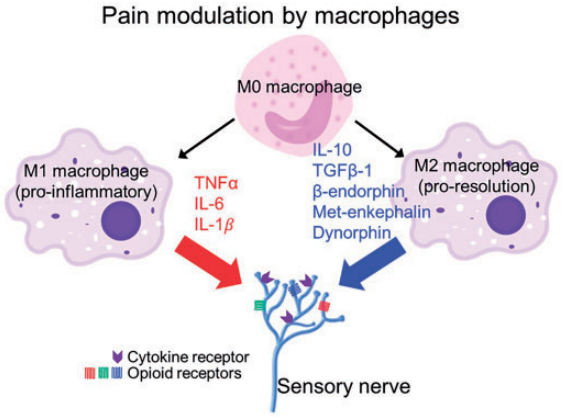

Figure 1. Pro-inflammatory M1 macrophages release pro-algetic cytokines, IL-1β, IL-6, and TNF-α. However, pro-resolution M2 macrophages release anti-inflammatory cytokines, IL-10, and anti-algetic endogenous opioid peptides Met-enkephalin, dynorphin A, and β-endorphin. IL: interleukin; TNF: tumor necrosis factor; TGF: transforming growth factor.

in PWH demonstrated that the ratios of pro- and anti-inflammatory cytokines (TNF-α/IL-4, IL-6/IL-4, and interferon-γ/IL-10) were higher in PWH with peripheral neuropathy.[37] Moreover, overexpressing IL-10 has been shown as a therapeutic strategy to decrease TNF-α and increase mechanical pain threshold in rats with neuropathic pain.[38]

In addition to their direct effects on inflammation and sensitization, macrophages are important for the recruitment of other immune cells. Macrophages guide neutrophils and lymphocytes to the site of injury through chemokine signaling,[29] and together with Schwann cells synergistically contribute to a positive feedback loop of cellular recruitment and neuro-inflammation.[28] The infiltration of lymphocytes into DRG and spinal cord has been demonstrated in an LP-BM5, a murine retroviral isolate, infected murine AIDS (MAID) model.[39] Specifically, these immune cells released redox-active species into DRG neurons, resulting in oxidative damage and increased mechanosensitivity of the hindpaw.[39] The role of macrophages in neuropathic pain is further emphasized by demonstration of reduced mechanical hypersensitivity and Wallerian degeneration in rats after depletion of macrophages with dichloromethylene diphosphonate-containing liposomes.[40] Other animal models limiting macrophage recruitment have also demonstrated a corresponding reduction in neuronal degeneration and hyperalgesia.[41]

CWP has commonly been attributed to both diffuse inflammatory processes and to failed pain inhibitory systems.[42] Mechanisms of these endogenous inhibitory systems have included both central mechanisms and those involving peripheral actions of opioids, particularly in deep tissues.[43] Macrophages are a rich source of opioid

peptides[44–47] that inhibit inflammatory pain by binding peripheral opioid receptors.[48–50] Compared to pro-inflammatory (M1 phenotype) macrophages, pro-resolution (M2 phenotype) macrophages contain and release higher amounts of opioid peptides (met-enkephalin (ENK), dynorphin A (DYN), and β-endorphin (END)) and can therefore produce analgesia[51] (Figure 1). Preclinical adoptive transfer of M2 cells at the site of injury has been shown to reduce mechanical hypersensitivity and is reversed by the administration of naloxone methiodide,[51] a peripherally acting opioid receptor antagonist. Similarly, promoting the polarization of naive macrophages toward the M2 phenotype[52,53] has been shown to attenuate postoperative pain[54] and decrease tactile hypersensitivity.[55] Lakritz et al. demonstrated that the number of M1-like monocytes/macrophages correlated with more severe DRG histopathology and loss of intra-epidermal nerve fibers in SIV peripheral neuropathy.[56] In the context of HIV infection, it must be emphasized that macrophages play a crucial role as viral reservoirs, especially in the periphery. Polarization of macrophages to the M1 phenotype appears to help keep viral replication in check to some extent and to facilitate immune system clearance of infected cells.[57]

Envelope glycoprotein gp120

HIV-1 infection generates direct neuronal injury, instigates processes that result in inflammatory neuronal degeneration, and causes a generalized inflammatory milieu that contributes to pain independent of the concurrent cellular destruction. The viral envelop glycoprotein, gp120, plays a key role in viral entry and has attracted considerable attention for its role in contributing to neurotoxicity as well as establishing an inflammatory state. HIV gp120 facilitates viral entry through CD4-receptor binding and membrane fusion, with CCR5 and C-X-C chemokine receptor type 4 (CXCR4) functioning as coreceptors on the target cell. In many preclinical studies, HIV gp120 has been linked to mechanical hyperalgesia[58] and importantly can exert an effect on cells even in the absence of cellular viral infection[59,60] as direct neuronal infection is rare.

HIV gp120 binding to CCR5 has been linked to neurotoxicity and upregulation of pro-inflammatory gene expression in macrophages consistent with an M1 phenotypic state, demonstrating the potential role of viral immune modulation in the generation of pain.[61] HIV gp120 ligation of CXCR4 on Schwann cells leads to TNF-α/TNF receptor-1 (TNFR-1) neuronal apoptosis by initiating the release of Regulated on activation, normal T cell expressed and secreted (RANTES) and causing production of TNF-α within the DRG.[62] This effect was noted in the absence of macrophages detected in DRG cultures, demonstrating the ability of gp120 to potentially cause downstream neurotoxicity, axonal degeneration, and inflammatory mediator release independent of the host immune response. Zheng et al. further explored the interplay between gp120, TNF-α, and microglia in modulating mechanical allodynia. They found that in vivo application of gp120 to rat sciatic nerve caused mechanical allodynia, increased TNF-α mRNA expression in the lumbar spinal dorsal horn, and that colocalization implicated microglia in the release of TNF-α and increased TNF-α within the DRG of rats after gp120 application.[63] Importantly, these investigators were able to reverse the allodynia with a glial cytokine inhibitor, with a soluble TNF receptor, and by administering siRNA for TNF-α, drawing a direct linkage between the viral protein, glial cells, and a phenotype consistent with neuropathic pain.[63]

Yi et al. further elucidated the mechanisms downstream of TNF-α involved in gp120-induced neuropathic pain.[64] Again using HIV gp120 application onto the rat sciatic nerve, they demonstrated that gp120 increased TNF-α, TNFR-1, mitochondrial superoxide, phosphorylation of cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), and levels of phosphorylated cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein-β (pC/EBPβ) in the ipsilateral spinal dorsal horn.[64]By sequential inhibition of the above-mentioned individual components, the authors demonstrated that the gp120-induced neuropathic pain was mediated by the following pathway: TNF-α/TNFR-1—mitochondrial superoxide—pCREB—pC/EBPβ.[64] Other studies have also shown that C/EBPβ in DRG is involved in neuropathic pain and is a potential target for ameliorating neuropathic pain.[65] Similarly, increase in phospho-CREB levels have been reported in pain-positive HIV patients.[66] The gp120-induced mitochondrial superoxide production has been shown to be mediated by an increase in mitochondrial fission protein, dynamin-related protein-1 (Drp-1).[67] The inhibition of Drp-1 reduced mitochondrial reactive species production and gp120-related neuropathic pain in rats.[67] Moreover, gp120 has been shown to directly disrupt microtubule transport of mitochondria within the neuron, providing yet another mechanism by which cellular function is disrupted and intracellular energy deficits could result in axonal degeneration and a consequent neuropathic phenotype.[68]

Adenosine triphosphate (ATP) plays a critical role in acute pain signaling in the DRG as well as in the development and maintenance of chronic pain.[69,70] ATP activates purinergic P2 receptors, classified into (1) P2X receptors, which are ionotropic ligand-gated ion channels, and (2) P2Y receptors, which are metabotropic G-protein-coupled receptors. Seven P2X receptors (P2X1-7) and eight P2Y receptors (P2Y1, P2Y2, P2Y4,

P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14) have currently been recognized.[71,72] Several P2 receptors have been implicated in gp120-induced hypersensitivity. In two recent studies, Yi and colleagues studied the role of P2Y12 in a rat model of neuropathic pain induced by gp120 combined with the antiretro viral drug, ddC (2′,3′-dideoxycytidine). They found that gp120 + ddC treatment increased the expression of P2Y12 receptor in DRG. In contrast, genetically reducing P2Y12 receptor expression in DRG reduced the release of pro-inflammatory cytokines and relieved mechanical and thermal hyperalgesia in gp120 + ddC-treated rats.[73] Another study demonstrated elevated expression of P2X3 protein in DRG in gp120-treated rats that correlated with neuropathic hypersensitivity sensitive to pharmacological antagonism of P2X3.[74,75] Upregulation of DRG expression of P2X7 has also been demonstrated following gp120 treatment. Subsequent treatment with the P2X7 antagonist, brilliant blue G, decreased hyperalgesia and P2X7 expression, and also decreased IL-1β and TNF-α receptor expression while increasing IL-10 in gp120-treated DRG.[76] Together, these provide compelling evidence that the activation and upregulation of P2 receptors in DRG mediate grp120-induced pain and are therefore targets for HIV-associated pain.

Finally, important interactions between gp120 and other mediators of chronic pain in HIV have been outlined. Using two neuropathic pain models to investigate the interplay between HAART neurotoxicity and gp120, the combined administration of both HAART and gp120 resulted in evidence of neuropathic pain greater than HAART alone, suggesting either an additive or synergistic effect.[77] In a more recent study, Takahashi et al. examined the interactions between HIV gp120 and opioid exposure. The group found that intrathecal administration of gp120 and morphine for five days induced greater persistent mechanical allodynia relative either gp120 or morphine alone.[78] Together, the above-mentioned studies show that gp120-initiated macrophage activation and inflammatory cytokine release in the DRG and peripheral nerves along with direct axonal damage and neuronal apoptosis are likely concurrently contributing to the effects seen in animal models and individuals with HIV sensory neuropathy (HIV-SN).[79,80]

Trans-activator of transcription (Tat)

Trans-activator or transcription (Tat) is the first protein produced and released by infected host cells after HIV infection. It continues to be expressed from reservoir host cells, despite HAART and persists within CNS tissues contributing to neuro-inflammation and consequent neurotoxicity.[81,82] Tat causes neurotoxicity through DNA double strand breaks[83] and via N-methyl-D-aspartate receptor-mediated alterations in intracellular calcium hemostasis[84–86] and glutamate excitotoxicity.[87] Its expression is associated with microglial priming and IL-1β release[88] and it activates nuclear factor-kB,[89] factors that lead to increased expression of inflammatory cytokines including IL-6 and TNF-α. While much initial attention has focused on the role of Tat neurotoxicity within the CNS leading to neurocognitive dysfunction, it may also contribute to HIV-SN through similar mechanisms. Recently, Tat mRNA expression was noted in DRG and skin samples after induction of its expression in mice, with an associated reduction in nerve fiber density and concurrent progressive mechanical hypersensitivity without motor impairment.[90] This is consistent with the clinical syndrome of HIV-SN, providing evidence that Tat may be integral in HIV-SN pathogenesis. Moreover, Tat has been shown to induce marked hyperexcitability and apoptosis of primary DRG neurons.[91]

Again in consideration of interactions between HIV-relevant proteins and opioids, Tat has been implicated in modification of opioid tolerance and physical dependence. Fitting et al. demonstrated that the induction of Tat mRNA in mice corresponded to a significant loss of morphine-induced antinociception, as assessed by the tail-flick test.[92] In a second study by the same group, the induction of Tat in mice resulted in increased tolerance for morphine, based on nociceptive assays and locomotor activity.[93] Furthermore, the induction of Tat resulted in reduced physical dependence to chronic morphine exposure.[93] Importantly, chronic Tat expression is noted in immune cells despite pharmacological therapy and irrespective of viral load, providing a challenging but potentially promising target for future therapeutic interventions.

Viral protein R (Vpr)

Viral protein R (Vpr) is observed early after HIV infection. It initially helps mediate viral replication and then is synthesized and exported later in the viral life cycle where it facilitates viral infection of macrophages and monocytes. As a highly conserved gene with a crucial role in viral infection, replication, and spread, it is an enticing therapeutic target.[94] Detectable levels of Vpr increase in late stage disease in the blood and cerebrospinal fluid of PWH. As an extracellular protein, Vpr triggers apoptotic pathways, stimulates inflammatory cytokine release, and interferes with ATP production leading to accumulation of reactive oxygen species and increasing oxidative stress.[95] Similar to gp120, the role of Vpr in CNS symptoms and HIV-related neurocognitive changes is a common focus in the literature, but scarce prior work has delved into the potential of its neurotoxicity in the context of neuropathic pain. In exception, Acharjee et al.[96] sought to examine the presence of peripheral Vpr and the role it may play in

establishing neuropathic pain in PWH. They reported Vpr expression in DRG autopsy specimens from HIV-infected individuals. Furthermore, by establishing an HIV infection in human DRG cultures, they were able to demonstrate Vpr expression as well as evidence of neuronal damage and innate immune system activation.[96] Mechanistically, they found increased cytosolic calcium levels in human and rat DRG neurons exposed to Vpr with an increase in neuronal excitability. They further demonstrated in a transgenic model expressing the Vpr gene on an immune-deficient the presence of mechanical allodynia associated with inflammatory cytokine dysregulation. In sum, these findings effectively link Vpr to both direct and indirect mechanisms of neuronal toxicity.[96]

Antiretroviral drugs

The development of pharmacologic agents to treat HIV infection and the widespread implementation of HAART has significantly reduced HIV-related mortality, thereby changing the dynamic of the disease process and reframing HIV as a chronic entity no longer merely confined to an acute, severe condition. The long-term requirement for viral suppression by antiretroviral agents (ARVs) exposes PWH to both acute and chronic side effect profiles of ARVs. One common side effect of ARV is peripheral neuropathic pain. The determination whether viral proteins or ARV therapy are responsible for pathological basis of HIV-SN is often based upon the timing of ARV institution, as the etiology of the neuropathy is generally indistinguishable based on clinical symptoms.[97] ARV toxic neuropathy is also characterized by axonal loss and axonopathy as has been demonstrated in models developed in an attempt to isolate the toxic effects of these agents from the confounding neurotoxicity of the HIV viral proteins described above.[79]

The nucleoside reverse transcriptase inhibitors (NRTIs, including stavudine, zalcitabine, zidovudine, and didanosine) are particularly associated with the development of HIV-SN. Zalcitabine, although rarely used clinically today, has proven particularly useful in the model development for the study of neurotoxicity in vitro and in vivo.[79] The preponderance of evidence in both animal and human studies seems to implicate NRTI-induced mitochondrial dysfunction as a pivotal step leading to disruptions in calcium homeostasis and a pro-apoptotic state.[79] In a model of NRTI-induced neuropathy, Ferrari and Levine[98] found that inhibitors of the electron transport chain, oxidative stress, and caspase signaling were able to antagonize the mechanical hyperalgesia that occurred after NRTI exposures. Furthermore, they found that the combination of alcohol consumption (a known comorbid risk factor for HIV-SN development) and NRTI exposure was capable of producing mechanical hyperalgesia at respective dosages that do not independently affect nociception. This affect was attenuated by electron transport train and oxidative stress antagonism (but interestingly, not caspase inhibition), providing additional evidence as to the role mitochondria may play in HIV-SN.[98]

There is concurrent evidence of inflammatory dysregulation with macrophage infiltration and expression of inflammatory and nociceptive chemokines and cytokines.Specifically, exposure to zalcitabine induced macrophage infiltration and increased chemokine (C-C motif) ligand 2 (CCL2) and TNF-α expression in the DRG.[77,79,80] Similar to viral neurotoxicity, Schwann cells also appear instrumental in the pathogenesis of ARV-related neuropathy. Schwann cell exposure to recombinant gp120 leads to expression of C-X-C motif chemokine ligand 12 (CXCL12), which in turn interacts with CXCR4 and likely causes hyperalgesia through a similar mechanism as seen in in vivo gp120 toxicity.[62,79]

While significant focus has revolved around the more profoundly neurotoxic NRTIs, there is recent evidence that protease inhibitors may be able to independently elicit neuropathic changes as well as potentiate the neuropathic actions of NRTI therapy. In one observational study, the addition of a protease inhibitor to ARV therapy with stavudine, didanosin, or zalcitabine was associated with a higher incidence of development of both asymptomatic and symptomatic peripheral neuropathy.[99] Huang et al.[100] demonstrated mechanical hypersensitivity in rats treated with the protease inhibitor indinavir independent of HIV infection. They additionally demonstrated a reduction in intraepidermal nerve fibers on immunostaining of the hind paw after indinavir treatment, thus linking the altered response to

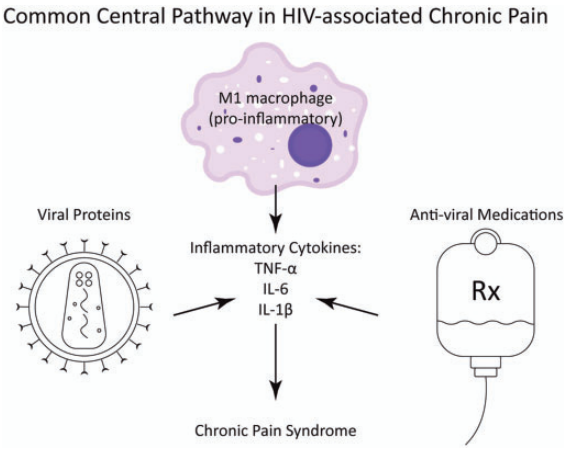

Figure 2. HIV-1 proteins, gp120, Tat, and Vpr along with the antiviral drugs increase the release of pro-inflammatory and pro-algetic cytokines, IL-1β, IL-6, and TNF-α from M1 macrophages, which contributes the development of chronic pain in HIV.
IL: interleukin; TNF: tumor necrosis factor.

Table 1. Key points to consider in clinical management of HIV-associated chronic pain.

• HIV infection can lead to chronic pain irrespective of viral load and/or CD4 count
• Pain in HIV may be debilitating and contributes to poor quality of life
• Pain may develop in the absence of antiviral therapy due to viral proteins and inflammation
• NRTIs are associated with development of sensory neuropathy in HIV
• Protease inhibitor therapy may lead to sensory neuropathy and may synergize with NRTIs to enhance pain
• Alcohol consumption enhances the hyperalgesia associated with NRTI therapy
Translational evidence suggests opioid agonism may enhance HIV-induced allodynia and therefore opioids should be avoided

HIV: human immunodeficiency virus; NRTI: nucleoside reverse transcriptase inhibitor.

mechanical stimuli to a potentially explanatory histological change consistent with findings characteristic of HIV-SN in humans.

Conclusion

Recent research into the pathogenesis of chronic pain associated with HIV infection indicates that its etiology is multifactorial and involves the host immune response, HIV-1 proteins, and antiretroviral medications (Figure 2). Intriguingly, each of the HIV-1 proteins seems to have a distinct downstream signaling pathway capable of inducing peripheral neuropathic changes and pain. It is also evident that, despite low viral count and nearly normal CD4 levels in PWH on HAART, the circulating or cellular levels of HIV-1 proteins including gp120, Tat, and Vpr remain high. Treatment strategies aimed at targeting a single particular molecule (protein or drug) yield promising results in animal models of peripheral neuropathy. Despite these encouraging findings, translation to the abrogation of chronic pain in humans, where a myriad of instigating factors are simultaneously present and potentially acting synergistically, poses a significant challenge. Moreover, currently, there are no known genetic manipulations or pharmaceutical drugs known to reduce the burden of HIV-1 proteins in humans. It is encouraging, however, that a common convergence becomes apparent in review of the current literature. It is evident from the studies mentioned in this review that most of the HIV-associated chronic pain pathways converge at the release of inflammatory cytokines, TNF-α, IL-1β, and IL-6 from peripheral immune cells. The inflammatory cells involved in the development and maintenance of chronic pain contain fewer endogenous opioids compared to their pro-resolution counterparts,[51] which may further contribute to increase pain in PWH. Therefore, pharmaceutical and nonpharmaceutical therapies along with lifestyle modifications aimed at lowering chronic inflammation may have a better chance in succeeding to alleviate chronic pain in PWH.

The multifactorial nature of HIV-associated chronic pain warrants a multimodal clinical approach to address a complex process. Direct acknowledgment of the complexity of HIV-associated chronic pain syndrome when communicating with patients may help in setting expectations and discussion options for treatment. We highlight some general clinical considerations related to HIV-associated chronic pain in Table 1 that reflect findings from the literature we have summarized. While research progresses to develop novel therapeutic approaches, physicians should recognize and validate the challenging nature and significance of HIV-associated chronic pain in the day-to-day life of their patients.

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