

# [Interactions of opioids and hiv infection in the pathogenesis of chronic pain](https://assignbuster.com/interactions-of-opioids-and-hiv-infection-in-the-pathogenesis-of-chronic-pain/)

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## Introduction

Pathological pain is a major neurological complication suffered by over 50% of HIV-1/AIDS patients ( [Hewitt et al., 1997](#B75) ; [Mirsattari et al., 1999](#B141) ; [Evers et al., 2000](#B50) ). Patients with HIV-associated pain syndromes may suffer headache, somatic pain, and visceral pain ( [Hewitt et al., 1997](#B75) ; [Mirsattari et al., 1999](#B141) ; [Evers et al., 2000](#B50) ; [Aouizerat et al., 2010](#B7) ). The pain is typically bilateral, of gradual onset and described as ‘ aching,’ ‘ painful numbness,’ or ‘ burnings’ ( [Cornblath and McArthur, 1988](#B37) ). However, the molecular and cellular processes by which HIV patients develop pain remain elusive. Pathologically, about 30% of HIV-1/AIDS patients with pain symptoms manifest clinically detectable peripheral neuropathy ( [Martin et al., 2003](#B127) ). Although highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality of HIV-1 infection ( [Mocroft et al., 2003](#B143) ), patients on HAART still develop symptoms of distally symmetric small-fiber retrograde axonal neuropathy and pain ( [Simpson, 2002](#B181) ; [Luciano et al., 2003](#B117) ; [Lopez et al., 2004](#B116) ; [Arenas-Pinto et al., 2008](#B8) ). Previous studies indicate that gp120 can induce cutaneous denervation in the transgenic mouse model ( [Keswani et al., 2006](#B101) ), intrathecal injection model ( [Milligan et al., 2001](#B139) ; [Yuan et al., 2014](#B236) ), and in the sciatic nerve exposure model ( [Wallace et al., 2007a](#B208) , [b](#B209) ). Gp120 can also cause axonal injury of sensory neurons in culture ( [Melli et al., 2006](#B132) ; [Hoke et al., 2009](#B76) ).

Controlling pain is a big challenge in HIV patient care. The clinical practice for pain management in HIV patients has been recommended to follow the WHO guideline ( [World Health Organization, 1996](#B230) ; [Basu et al., 2007](#B12) ). According to the guideline, opioids are the cornerstone medications for treating moderate to severe pain. Ironically, besides the powerful acute analgesic effect, emerging clinical data indicate that repeated use of opioid analgesics promotes chronic pain in HIV patients ( [Smith, 2011](#B184) ; [Onen et al., 2012](#B152) ). Studies on simian or simian-human immunodeficiency virus-infected monkey models suggest a role of opioids in HIV-related disease progression ( [Kumar et al., 2004](#B105) , [2006](#B104) ; [Rivera-Amill et al., 2010](#B171) ). HIV-1-infected opioid abusers also appear to show more severe neuropathology than HIV-1-infected non-drug users ( [Bell et al., 1998](#B17) , [2006](#B15) ; [Anthony et al., 2005](#B6) , [2008](#B5) ). Currently, the mechanisms by which opioid medicines exacerbate HIV- associated pain are unclear. Multiple molecular systems in neurons, including mu-opioid receptors, *N* -methyl-D-aspartate receptors, nitric oxide synthase, heme oxygenase, 5-hydroxytryptamine type 3 receptors, complement components, chemokines and the melanocortin system have been implicated in opiate-induced hyperalgesia ( [Basu et al., 2007](#B12) ), but whether (and how) they contribute to the exacerbation of HIV-associated pain is unclear. Opioids can also activate glial cells such as microglia and astrocytes ( [Tortorici et al., 1999](#B200) ; [Song and Zhao, 2001](#B187) ; [Raghavendra et al., 2002](#B165) ; [Mika, 2008](#B135) ; [Horvath and DeLeo, 2009](#B79) ; [Mika et al., 2009](#B136) ; [Lee et al., 2011](#B108) ), which may facilitate the expression of hyperalgesia by releasing various neural regulators such as cytokines, chemokines and brain-derived neurotrophic factor to induce sensitization of pain-processing neurons ( [Hao, 2013](#B67) ).

Although we have a significant understanding of the potential mechanisms by which HIV-1 infection (including antiretroviral therapy) and opioid use induce pain individually, little is known about how their interaction would contribute to pain pathogenesis. We will consider the potential pathogenic mechanisms from the perspective of neuron-glial crosstalk. In the following sections, we will first provide overviews of the detrimental effects of HIV-1 and opioids, separately or combinatorially, on neurons and glia. Based on these findings, we will discuss the possible pathogenic processes induced by HIV-1 and opioids that facilitate the development of HIV-associated pain. We regret that due to limited space we cannot cover all of the significant work in this field but are forced to focus on selected findings to illustrate our views. The purpose of this paper is not to provide a systematic review of current literature. Instead, we aim to provide mechanistic viewpoints on how HIV-1 infection might interact with opioids to promote pain pathologies.

## Neuronal Mechanisms

We postulate that neuronal damage is a major mechanism by which interaction of HIV-1 and opioids facilitates the development of hyperalgesia. Here, we will first discuss how nerve damage can lead to the expression of pathological pain and then how gp120 and opioids may cause neuronal damage.

Damage of peripheral or central pain transmission neurons, manifested by hyper-excitability and/or a lowered threshold of activation, directly contributes to neuropathic pain ( [Baron, 2000](#B10) ; [Treede et al., 2008](#B202) ). Pathological pain in HIV patients is frequently associated with peripheral sensory neuropathy, a form of the so-called ‘ dying-back’ degeneration of sensory neurons ( [Hao, 2013](#B67) ). Sensory neuropathy also develops in various animal models of HIV-associated pain, including rodents models generated by exposure of peripheral nerves or spinal cord to gp120 ( [Herzberg and Sagen, 2001](#B72) ), gp120 transgenic mice receiving antiretroviral drugs ( [Keswani et al., 2006](#B101) ) and SIV-infected monkeys ( [Hou et al., 2011](#B80) ). Thus, neuronal damage is intimately associated with the expression of HIV-associated pain. Many events such as neuronal hyper-excitation, inflammation and viral infection can cause nerve damage that leads to neuropathic pain ( [Woolf and Mannion, 1999](#B229) ). Neuropathic pain-related damage may lead to neuronal apoptosis via caspase-dependent and -independent pathways ( [Perl and Banki, 2000](#B155) ; [Oh et al., 2001](#B148) ; [Gougeon, 2003](#B58) ; [Silva et al., 2003](#B180) ). Using HIV-1 gp120 protein as an example, we will describe how HIV-1 infection may interact with opioids to promote these pathways in pain-processing neurons.

Damage of peripheral nerves may contribute to pain pathogenesis via various pathways. For instance, when peripheral nervesare damaged, sodium-channels may aggregate locally and/or in cell bodies, which may lead to hyper excitability ( [Lai et al., 2003](#B106) ; [Wood et al., 2004](#B228) ). Ectopic expression of specific calcium channels on DRG cells has also been observed following neuronal damage ( [Luo et al., 2001](#B119) ). The nerve-damage-induced changes of ion channel expression may be intimately linked to peripheral sensitization. In addition to ion channels, neuronal damage induces the ectopic expression of specific pain sensory receptors such as TRPV1, a vanilloid receptor for thermal sensation. TRPV1 is normally expressed on nociceptive afferent fibers. When nerve damage occurs, TRPV1 expression decreases on injured afferents and increases on undamaged Cfibers and Aδfibers ( [Hudson et al., 2001](#B84) ; [Hong and Wiley, 2005](#B78) ). Nerve-damage-induced increases of other pain-related factors, including acid-sensing ion channels (ASICs; [Price et al., 2001](#B163) ), adrenoceptors in neurons ( [Price et al., 1998](#B162) ; [Baron et al., 1999](#B11) ) and pro-inflammatory cytokines (e. g., TNF-α; [Marchand et al., 2005](#B126) ) in glial cells, have also been implicated in peripheral sensitization.

The sensitization of primary afferent nerves can facilitate the expression of central sensitization of CNS pain-processing neurons in the spinal cord dorsal horn and supraspinal regions ( [Price, 2000](#B161) ; [Zhuo, 2002](#B241) ). Peripheral nerve damage can lead to the activation of excitatory glutamate receptors such as NMDARs and AMPARs in spinal neurons ( [Miller et al., 2011](#B137) ). In addition, damage to peripheral nerves also causes reduced expression and uptake activity of both neuronal and glial glutamate transporters, which may contribute to increased neuronal excitability ( [Sung et al., 2003](#B192) ); these effects are mediated by the activation of PKC and MAPK signaling pathways ( [Malmberg et al., 1997](#B123) ; [Ji and Woolf, 2001](#B94) ). Furthermore, hyperactivation of Cfibers induces ectopic expression of sodium channels ( [Hains et al., 2004](#B64) ) and calcium channels ( [Luo et al., 2001](#B119) ) on dorsal horn neurons to facilitate pain transmission. Malfunction of inhibitory mechanisms may also facilitate central sensitization. Peripheral nerve damage can induce the apoptosis of GABA (γ-aminobutyricacid) inhibitory neurons in superficial layers of the dorsal horn ( [Moore et al., 2002](#B144) ; [Coull et al., 2003](#B39) ). Several studies suggest an association of neuronal apoptosis with neuropathic pain ( [Mao et al., 2002a](#B124) ; [Moore et al., 2002](#B144) ; [Campana and Myers, 2003](#B21) ; [Schmeichel et al., 2003](#B175) ), and inhibition of apoptosis decreases the pain behaviors ( [Joseph and Levine, 2004](#B96) ; [Scholz et al., 2005](#B176) ; [Sekiguchi et al., 2009](#B178) ).

HIV-1 does not infect neurons ( [Lipton, 1998](#B114) ; [Michaels et al., 1988](#B134) ). However, HIV-1 infection of the nervous system, especially of microglia and astrocytes, can cause neuronal damage and apoptosis via toxic viral proteins that are secreted from infected cells. Glycoprotein 120 (gp120), the viral envelope protein that mediates HIV infection, is one of the secreted HIV-1 proteins that causes neuronal dysfunction ( [Michaels et al., 1988](#B134) ; [Nath, 2002](#B145) ). Our recent analysis on HIV patient tissues and mouse models suggests a crucial role of gp120 in the pathogenesis of HIV-associated pain ( [Yuan et al., 2014](#B236) ). Gp120 may induce neurotoxicity either by directly stimulating neurons (“ direct injury”) or indirectly by activating glial cells (“ bystander effect”; [Kaul et al., 2001](#B98) ). For instance, gp120 activates C-X-C chemokine receptor 4 (CXCR4), which is constitutively expressed on DRG and spinal cord neurons ( [Oh et al., 2001](#B148) ; [Miller et al., 2009](#B138) ), and up-regulates C-C chemokine receptor 2 (CCR2) in a calcium-dependent manner to produce neurotoxicity ( [Hesselgesser et al., 1997](#B73) ; [Jung and Miller, 2008](#B97) ). It has been suggested that gp120-induced neuronal CXCR4 activation may up-regulate pro-inflammatory cytokine IL-1β in a neuronal autocrine fashion, which then causes the neuronal excitotoxicity ( [Bagetta et al., 1999](#B9) ; [Corasaniti et al., 2001a](#B35) , [b](#B36) ). In addition, gp120 is known to stimulate CXCR4 on DRG satellite glia and induce the secretion of RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) chemokine (a. k. a. CCL5), which induces neuronal damage by activating CCR5 receptors on DRG neurons ( [Hesselgesser et al., 1997](#B73) ; [Oh et al., 2001](#B148) ). Glutamate receptors ( [Mattson et al., 2005](#B129) ), especially NMDA receptors ( [Lipton et al., 1991](#B115) ; [Lipton, 1992](#B113) ; [Bennett et al., 1995](#B18) ; [Lannuzel et al., 1995](#B107) ; [Meucci and Miller, 1996](#B133) ; [Chen et al., 2005](#B24) ), are targets of gp120, and their over-activation by gp120 can cause neurotoxicity.

There are three apoptotic pathways: caspase-dependent extrinsic (also known as death receptor approach) and intrinsic (known as mitochondrial approach) pathways ( [Sinkovics, 1991](#B183) ) as well as a caspase-independent pathway that is T cell-mediated and exhibits perforin-granzyme-dependent apoptosis ( [Elmore, 2007](#B49) ). Gp120 can induce neuronal apoptosis via the extrinsic and intrinsic pathways ( [Bagetta et al., 1999](#B9) ; [Chen et al., 2005](#B24) , [2011a](#B22) ; [Singh et al., 2005](#B182) ). In the extrinsic pathway, TNF-α secreted by gp120-activated glial cells can bind to TNF-α receptor 1 on neurons and induce neuronal apoptosis. Gp120 also can bind to CXCR4 on neurons to induce apoptosis by promotingcalcium influx and glutamate uptake ( [Hesselgesser et al., 1998](#B74) ). In the intrinsic pathway, gp120 is able to increase the expression and phosphorylation of p53 and subsequently induce the disruption of the mitochondrial membrane by activating BCL-2-associated X protein (Bax; [Gougeon, 2003](#B58) ). Interestingly, accumulation ofp53 has been observed in the neurons of AIDS patients ( [Silva et al., 2003](#B180) ). Gp120 also can activate phospholipase A2 and increase the release of arachidonic acid to disrupt glutamate metabolism in neurons via NMDA-receptor-mediated neurotoxicity, which can lead to cell dysfunction or death ( [Ushijima et al., 1995](#B206) ).

Mounting evidence indicates that chronic opiate use exacerbates the neuronal damage induced by HIV proteins gp120 and tat through synergy of neuronal apoptosis ( [Gurwell et al., 2001](#B63) ; [Hu et al., 2005](#B81) ) and alteration of dendritic spines and dendrites ( [Fitting et al., 2010](#B51) ). Ion channels have been implicated in the synergic neurotoxic effects of opioids and gp120. Gp120 can induce K + eﬄux by activating K channels when it binds to CXCR4 ( [Chen et al., 2011a](#B22) ). Chronic administration of opioids can reduce K + inflow by down-regulating MOR ( [Christie, 2008](#B29) ). Thus, dysfunction of K + channels may contribute to neurotoxicity and may be a point of convergence for gp120-opioid synergism of chronic pain ( [Podhaizer et al., 2012](#B159) ). In addition, chemokine receptors can dimerize with MOR, implying a functional interaction between these receptors ( [Toth et al., 2004](#B201) ). In this context, CXCR4 and CCR5 are particularly interesting because they not only are co-receptors of gp120 but are also co-expressed with MOR on neurons ( [Sengupta et al., 2009](#B179) ; [Heinisch et al., 2011](#B71) ). Besides synergism in neurons, gp120 and opioids may also functionally interact in glia to indirectly facilitate neuronal damage by regulating chemokines ( [Mahajan et al., 2005](#B122) ) and glutamate uptake ( [Podhaizer et al., 2012](#B159) ), which is the focus of a later section.

When gp120 and/or chronic opioids cause damage to pain-processing neurons, they may induce neuropathic pain. Gp120 not only directly excites rat DRG neurons and induces allodynia by activating their chemokine receptors ( [Oh et al., 2001](#B148) ) but also mediates local axonal degeneration of cultured rodent DRG neurons, which is dependent on activation of the caspase pathways ( [Melli et al., 2006](#B132) ). By a similar mechanism, exposure to gp120 also leads to up-regulation of MCP-1 and CCR2 on DRG neurons and upregulation of their activation, which is expected to contribute to neuropathic pain ( [Miller et al., 2009](#B138) ). We have generated a gp120 neuropathic pain model that develops similar neuropathologies as human HIV patients, including peripheral neuropathy and synapse degeneration ( [Yuan et al., 2014](#B236) ).

Accumulating data indicate that glial-neuronal cross-talk plays an important role in opioid-abuse-induced paradoxical pain ( [Raghavendra et al., 2003](#B166) ; [Hutchinson et al., 2008a](#B87) ; [Zhao et al., 2012](#B240) ; [Sun et al., 2014](#B191) ). The underlying mechanism remains obscure. Application of exogenous CXCL12 ( [Heinisch et al., 2011](#B71) ) and gp120 ( [Chen et al., 2011b](#B23) ), both of which are ligands of CXCR4 receptor, significantly attenuate morphine-mediated hyperpolarization in rodent periaqueductal grey (PAG) neurons. [Wilson et al. (2011)](#B227) also suggested that sensory neurons sensitized by the CXCL12-CXCR4 axis (or the gp120-CXCR4 axis) may facilitate the hyperalgesia induced by opioids. Moreover, morphine induces CXCR4-mediated activation of extracellular signal-regulated kinase (ERK) in rat neurons, a crucial regulator of peripheral and central sensitization. This may be one mechanism of gp120/opioid synergism in neuropathic pain ( [Ji, 2004](#B90) ; [Patel et al., 2006](#B154) ; [Sengupta et al., 2009](#B179) ).

## Glial Mechanisms

Converging evidence indicates a key role for glia and neuron-glia interactions in the development and maintenance of neuropathic pain ( [Jin et al., 2003](#B95) ; [Hansen and Malcangio, 2013](#B66) ; [Ji et al., 2013](#B91) ; [Walters, 2014](#B210) ). Glia mediate many of the neurotoxic effects of HIV-1 and co-exposure of glia to opioids and HIV-1 appears to exacerbate proinflammatory and excitotoxic events that lead to neuron dysfunction. Because of these observations, we are investigating the potential that glia-mediated mechanisms may contribute to the pathogenesis of neuropathic pain that is caused by HIV-1 and chronic opioid use.

### Glial Activation and Pain

Glial cells, including astrocytes, microglia, and oligodendrocytes, play important roles in supporting and regulating neuronal functions ( [Watkins et al., 2005](#B215) ). The involvement of glia in neuropathic pain was first suggested in the mid-1990s ( [Colburn et al., 1997](#B31) ). Numerous studies have since suggested critical roles of both microglia ( [Raghavendra et al., 2003](#B166) ; [Tsuda et al., 2003](#B203) ; [Coull et al., 2005](#B38) ; [Ji and Suter, 2007](#B93) ) and astrocytes ( [Meller et al., 1994](#B131) ; [Watkins et al., 1997](#B217) ; [Ji et al., 2006](#B92) ; [Chiang et al., 2007](#B28) , [2012](#B27) ; [Guo et al., 2007](#B61) ; [Okada-Ogawa et al., 2009](#B151) ; [Gao and Ji, 2010b](#B53) ; [Ren and Dubner, 2010](#B169) ) in the pathogenesis of pathological pain. Activation of astrocytes and microglia can cause neuroanatomical and neurochemical transformations in the CNS that contribute to neuropathic pain ( [Colburn et al., 1999](#B32) ; [Woolf and Mannion, 1999](#B229) ). Malfunctioning astrocytes and microglia may dysregulate synaptic function and neuronal excitability by various mechanisms ( [Halassa et al., 2007](#B65) ; [Pocock and Kettenmann, 2007](#B158) ).

Reactive glia secret proinflammatorycytokines such as tumor necrosis factor-α(TNF-α), IL-1β, and IL-6 that facilitate the expression of central sensitization ( [Seifert and Maihofner, 2011](#B177) ). Inhibition of the cytokines can effectively reduce neuropathic pain ( [Moalem and Tracey, 2006](#B142) ). Cytokines are up-regulated in the spinal cord after nerve injury, inflammation, bone cancer, and chronic opioid exposure, and they contribute to the development and maintenance of various types of chronic pain ( [DeLeo and Yezierski, 2001](#B42) ; [Sommer et al., 2001](#B186) ; [Watkins et al., 2001](#B218) ; [Svensson et al., 2005](#B194) ). For instance, peripheral nerve injury causes the up-regulation of TNF-α and TNFR1 in DRG and the spinal dorsal horn ( [Schafers et al., 2003](#B174) ; [Ohtori et al., 2004](#B149) ; [Xu et al., 2006](#B232) ), which facilitates the development of neuropathic pain ( [Sommer and Kress, 2004](#B185) ; [Wieseler-Frank et al., 2005](#B226) ). Inhibition of TNF-α inhibits the pain pathogenesis ( [George et al., 2000](#B56) ; [Ribeiro et al., 2000](#B170) ). IL-1β is induced in the spinal cord in animal models of bone cancer pain, inflammatory pain, and nerve injury pain ( [Zhang et al., 2005](#B239) ; [Guo et al., 2007](#B61) ; [Wei et al., 2008](#B219) ; [Weyerbacher et al., 2010](#B223) ). Inhibition of spinal IL-1β signaling with IL-1 receptor antagonist (IL-1ra) or neutralizing antibody alleviatespain behaviors ( [Milligan et al., 2001](#B139) , [2003](#B140) ; [Sweitzer et al., 2001](#B195) ; [Guo et al., 2007](#B61) ; [Kawasaki et al., 2008b](#B100) ; [Wei et al., 2008](#B219) ; [Zhang et al., 2008](#B238) ). Conversely, intrathecal injection of IL-1βinduces hyperalgesia ( [Tadano et al., 1999](#B196) ; [Reeve et al., 2000](#B168) ; [Ji et al., 2002](#B89) ; [Sung et al., 2004](#B193) ; [Kawasaki et al., 2008a](#B99) ). Persistent IL-6 increase after spinal cord injury (SCI) appears to correlate with the development of chronic pain both in SCI patients ( [Davies et al., 2007](#B40) ) and in an animal model of SCI ( [Detloff et al., 2008](#B43) ). Furthermore, injection of IL-6 in rats causes hypersensitivity to thermal and mechanical stimuli ( [Oka et al., 1995](#B150) ; [Poole et al., 1995](#B160) ; [DeLeo et al., 1996](#B41) ; [Brenn et al., 2007](#B19) ). Pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) have been shown to induce the trafficking and surface expression of AMPA receptors in hippocampal neurons ( [Beattie et al., 2002](#B14) ; [Stellwagen et al., 2005](#B188) ), enhance NMDA currents of spinal lamina II neurons ( [Kawasaki et al., 2008b](#B100) ; [Gao et al., 2009](#B55) ), and increase the frequency and amplitude of spontaneous postsynaptic currents (sEPSCs) in dorsal horn neurons ( [Kawasaki et al., 2008b](#B100) ). These neuronal effects of cytokines may directly contribute to the expression of pathological pain.

Chemokines are a group of cytokines that induce cell migration ( [Walz et al., 1987](#B211) ; [Yoshimura et al., 1987](#B235) ). Recent evidence suggests that chemokine signaling contributes to the pathogenesis of chronic pain by regulating glial activation and neural plasticity ( [White et al., 2007](#B225) ; [Abbadie et al., 2009](#B2) ; [Gao and Ji, 2010a](#B52) ; [Clark et al., 2011](#B30) ). Among them, CCL2 (MCP-1) is one of the best studied chemokines in pain modulation. It is highly expressed in astrocytes after spinal nerve ligation ( [Gao et al., 2009](#B55) ) and spinal cord contusion injuries ( [Knerlich-Lukoschus et al., 2008](#B102) ). Spinal injection of TNF-α-activated astrocytes results in persistent mechanical allodynia by releasing CCL2 ( [Gao et al., 2010](#B54) ). Chemokines may regulate pain transmission by stimulating specific chemokine receptors such as CCR2, CCR5, CXCR4, and CX3CR1 that are expressed in primary afferent neurons or secondary neurons in the spinal dorsal horn ( [Abbadie et al., 2003](#B3) ). In spinal cord slices, chemokines were shown to evoke excitatory postsynaptic currents (EPSCs) from lamina II neurons ( [Yoshimura and Jessell, 1989](#B234) ). Addition of CCL2 to cultured DRG neurons elicits release of calcitonin gene-related peptide (CGRP), a nociceptor neurotransmitter ( [White et al., 2009](#B224) ).

Glia may also regulate pain pathogenesis by modulating the level of extracellular glutamate, the major excitatory neurotransmitter. Glial glutamate transporter 1 (GLT-1) is abundantly expressed in astrocytes ( [Beart and O’Shea, 2007](#B13) ). It plays a critical role in clearing extracellular glutamate from synaptic clefts ( [Huang and Bergles, 2004](#B82) ; [Tawfik et al., 2006](#B197) ) and hence modulates glutamatergic transmission and neuronal plasticity ( [Rothstein et al., 1994](#B173) , [1996](#B172) ). Inhibition of glutamate transporters results in elevation of spinal extracellular glutamate and spontaneous pain ( [Liaw et al., 2005](#B111) ; [Weng et al., 2006](#B221) ). Spinal nerve injury induces an initial increase ( [Sung et al., 2003](#B192) ; [Wang et al., 2008](#B213) ) followed by a persistent decrease of GLT1 in the spinal cord astrocytes ( [Tawfik et al., 2008](#B198) ; [Xin et al., 2009](#B231) ). GLT-1 gene delivery to the spinal cord attenuates inflammatory and neuropathic pain ( [Maeda et al., 2008](#B121) ), supporting a critical contribution of glutamate transporter down-regulation to pain pathogenesis ( [Sung et al., 2003](#B192) ; [Weng et al., 2005](#B220) ).

The evidence outlined above illustrates that activated glia may promote pain pathogenesisthrough diverse mechanisms, including releasing pro-inflammatory cytokines and chemokines and down-regulating glutamate transporters. Interestingly, as we will discuss in the next sections, emerging evidence indicates that HIV-1 infection and chronic opioid use also dysregulate these pain pathogenic processes.

### HIV-1 and Opioids in Glial Activation

Opiate drug abuse and HIV-1 are interlinked epidemics ( [Bell et al., 1998](#B17) ; [Anthony et al., 2008](#B5) ), and opioids can exacerbate the neuropathogenesis of HIV-1 ( [Hauser et al., 2012](#B69) ). In human HIV-1 patients, opiate drug abuse was reported to increases glial reactivity in the CNS with specific alterations in the number and morphology of reactive microglia ( [Bell et al., 2002](#B16) ). Similarly, morphine rapidly and significantly increases the activation of microglia in the brains of Tat transgenic mice. Additionally, both HIV-1 proteins (e. g., gp120 and Tat) and opioids can activate astrocytes in the SDH ( [Milligan et al., 2001](#B139) ; [Huang et al., 2012](#B83) ).

Emerging evidence supports a role for the interaction of opioids and HIV viral proteins in glial activation, although the underlying mechanisms remain unclear. The interaction depends on mu-opioid receptors ( [Zou et al., 2011](#B242) ), which are widely expressed in astrocytes ( [Stiene-Martin et al., 1998](#B190) , [2001](#B189) ) and microglia ( [Tomassini et al., 2004](#B199) ). While opioids can directly cause glial activation ( [El-Hage et al., 2005](#B47) , [2006](#B48) , [2008a](#B45) , [b](#B46) ; [Bruce-Keller et al., 2008](#B20) ; [Turchan-Cholewo et al., 2008](#B204) , [2009](#B205) ; [Gupta et al., 2010](#B62) ), intrastriatal Tat infusion enhanced the activation of glia *in vivo* ( [El-Hage et al., 2006](#B48) ). Morphine analgesics can activate both classical opioid receptors andthe non-classical receptor Toll-like receptor 4 (TLR4; [Hutchinson et al., 2010b](#B86) ), which is expressed in glia that are implicated in various chronic pain syndromes ( [Hutchinson et al., 2008b](#B88) , [2010a](#B85) ; [Lewis et al., 2010](#B109) , [2012](#B110) ). Additional evidence indicates that TLR4 activation opposes the analgesic effect of morphine ( [Watkins et al., 2009](#B216) ; [Hutchinson et al., 2010b](#B86) ). The type of opioid receptor that is involved in the opioid/HIV-1 interaction for pain-related synergistic activation of glia is unknown.

Intracellular calcium may be a critical mediator in astrocyte activation that is induced by HIV-1 protein and opioids. Tat or gp120 can evoke an increase in intracellular Ca 2+ ([Ca 2+ ]i) in astroglia ( [Haughey et al., 1999](#B68) ; [Holden et al., 1999](#B77) ). Similar effects are also observed after acute μ-opioid receptor activation ( [Hauser et al., 1998](#B70) ). Morphine and HIV-1 viral proteins synergistically induce Ca 2+ release from the endoplasmic reticulum (ER) and Ca 2+ influx from extracellular spaces of astrocytes, which enhance cytokine and chemokine release ( [El-Hage et al., 2008b](#B46) ). The increased [Ca 2+ ]i may contribute to the development of hyperalgesia by regulating synaptic transmission and activity of NMDA and AMPA receptors in the spinal cord ( [Meller et al., 1996](#B130) ; [Guo et al., 2007](#B61) ; [Chen et al., 2010b](#B26) ). Furthermore, increased intracellular Ca 2+ can also activate Ca 2+ -sensitive proteins such as protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase II (CaMK II; [Kuhl et al., 2000](#B103) ), both of which play crucial roles in central sensitization during the development of neuropathic and inflammatory pain ( [Malmberg et al., 1997](#B123) ; [Martin et al., 2001](#B128) ; [Chen et al., 2010a](#B25) ). CaMKIIα is required for the initiation and maintenance of opioid-induced hyperalgesia ( [Chen et al., 2010a](#B25) ). Together, these findings indicate that enhanced intracellular Ca 2+ might be vital for astrocyte activation during pain development. Opioids may synergize with HIV viral proteins in these processes in glial cells. As a result, normally neuroprotective glia ( [Kaul et al., 2001](#B98) ) and mononuclear phagocytes ( [Persidsky and Gendelman, 2003](#B156) ) are functionally transformed into deleterious states thatdisrupt CNS homeostasis and create pathophysiological conditions that induce in juries in pain-processing neurons.

### Interactions of Opioids and HIV-1 in Neuropathic Pain

Findings such as those summarized above indicate that the interactions of HIV-1 and opioids have a synergistic effect on glial activation. Since glial activation plays a key role in neuropathic pain development, we reason that HIV-1 infection and opioids interact to promote pain pathogenesis. Several pathogenic pathways can be envisioned to mediate the synergistic effect of opioids and HIV-1 proteins in this scenario.

One of the potential mechanisms is probably mediated by the enhanced pro-inflammatory cytokine release from activated glia. Glial cells are the major source of cytokines (e. g., TNF-α, IL-1β, and IL-6) in the HIV-1-infected CNS ( [Dong and Benveniste, 2001](#B44) ; [Luo et al., 2003](#B118) ). Opioids exacerbate the glial response to HIV-1by accelerating cytokine release ( [El-Hage et al., 2005](#B47) ). Additionally, HIV replication in microglia can be stimulated by opioids, which leads to the release of toxic viral proteins that then stimulate the release of inflammatory toxins ( [Glass et al., 1995](#B57) ; [Nath et al., 1999](#B146) ; [Yadav and Collman, 2009](#B233) ). Opioids may directly activate MOR on microglia ( [Bruce-Keller et al., 2008](#B20) ; [El-Hage et al., 2008a](#B45) ; [Turchan-Cholewo et al., 2008](#B204) , [2009](#B205) ; [Gupta et al., 2010](#B62) ) to evoke cytokine and reactive/oxidative responses to insults ( [Wetzel et al., 2000](#B222) ; [Rahim et al., 2003](#B167) ; [Qin et al., 2005](#B164) ; [Wang et al., 2005](#B212) ). NF-κB is involved in the induction of cytokines in glia ( [Zhai et al., 2004](#B237) ). HIV-1 Tat activates NF-κB ( [Conant et al., 1996](#B34) ; [El-Hage et al., 2008a](#B45) ) to cause the release of a large amount of cytokines by glia ( [Conant et al., 1998](#B33) ; [El-Hage et al., 2005](#B47) , [2006](#B48) , [2008a](#B45) ). Pro-inflammatory cytokines could facilitate the development of hyperalgesia by regulating the activity of synaptic receptors such as NMDARs and AMPARs ( [Meller et al., 1996](#B130) ; [Guo et al., 2007](#B61) ; [Chen et al., 2010b](#B26) ). For instance, IL-1β, IL-6, and TNF-α can enhance excitatory synaptic transmission and increased density and conductance of neuronal AMPA ( [Ogoshi et al., 2005](#B147) ; [Stellwagen et al., 2005](#B188) ) and NMDA ( [Viviani et al., 2003](#B207) ) receptors, and these cytokines can down-regulate neuronal GABA receptors ( [Stellwagen et al., 2005](#B188) ).

Glia are also a major source of chemokines (e. g., CCL2/MCP-1, CCL5/RANTES, and CCL3/MIP-1a) in the HIV-1-infected CNS ( [Dong and Benveniste, 2001](#B44) ; [Luo et al., 2003](#B118) ). The contribution of chemokines to pain pathogenesis is well established ( [Liou et al., 2013](#B112) ). Opioids exacerbate the astroglial response to HIV-1and stimulate release of chemokines ( [El-Hage et al., 2005](#B47) ). NF-κB signaling is also implicated in chemokine induction in astrocytes ( [Zhai et al., 2004](#B237) ). HIV-1Tat activates NF-κB ( [Conant et al., 1996](#B34) ; [El-Hage et al., 2008a](#B45) ) to elicit release of many chemokines from astroglia ( [Conant et al., 1998](#B33) ; [El-Hage et al., 2005](#B47) , [2006](#B48) , [2008a](#B45) ). Previous studies observed synergistic effects of HIV-1 viral proteins and opiate agonists on chemokine release from glia ( [El-Hage et al., 2006](#B48) ). Similar to the cytokines discussed above, chemokines may also promote the development of hyperalgesia by regulating synaptic transmission and activity of NMDA and AMPA receptors ( [Meller et al., 1996](#B130) ; [Guo et al., 2007](#B61) ; [Chen et al., 2010b](#B26) ). Since specific chemokine receptors such as CCR2, CCR5, CXCR4, and CX3CR1 are expressed in primary afferents and/or secondary neurons in the spinal dorsal horn ( [Oh et al., 2001](#B148) ; [Abbadie, 2005](#B1) ), chemokines may modulate pain signal transmission.

Another potential mechanism by which opioids and HIV-1 may cooperate to dysregulate pain-related glial function is to down-regulate their glutamate re-uptake activity. Under normal physiologic conditions, extracellular glutamate is rapidly cleaned by re-uptake processes mediated by glutamate transporters EAAT1 (a. k. a. GLAST) and EAAT2 (a. k. a. GLT-1). EAAT1 and EAAT2 are predominantly expressed by astroglia (but only have low expression in microglia; [Gras et al., 2006](#B59) , [2012](#B60) ). Chronic morphine administration induces down-regulation of spinal glutamate transporters ( [Ozawa et al., 2001](#B153) ; [Mao et al., 2002b](#B125) ). Interestingly, a decrease of EAAT2 expression was also observed in human astrocytes exposed to gp120 or HIV-1 ( [Wang et al., 2003](#B214) ). Exposure to morphine and HIV-1 Tat boosts extracellular glutamate accumulation at the synapse ( [Madl and Burgesser, 1993](#B120) ; [Phillis et al., 2000](#B157) ), which is expected to cause excitotoxicity ( [Albrecht et al., 2010](#B4) ).

The above findings indicate that opioids and HIV-1 interact to activate glia, leading to enhanced cytokine and chemokine expression ( [Mahajan et al., 2005](#B122) ) and down-regulation of glutamate uptake ( [Zou et al., 2011](#B242) ). These biological effects are detrimental to neurons and may directly contribute to the development of hyperalgesia.

## Summary

Opioid abuse and HIV-1 have been described as interrelated epidemics, and they can exacerbate the neuropathogenesis of neuroAIDS ( [Hauser et al., 2012](#B69) ). Here, we have mainly considered the potential mechanisms by which the interaction of opioids and HIV-1 facilitates the development of hyperalgesia. Because mounting evidence suggests that they have synergistic effects on neurons and glia, we are working to understand the pathogenic processes from the perspectives of these cell types and their interactions. Based on the previously findings discussed earlier, we suggest that HIV-1 and opioids dysregulate the function of neurons and glia in the pain-processing neural pathway. The ongoing reactive cross-talk between opiate drugs and HIV-1 may not only directly injure pain-transmission neurons but also indirectly contribute to the injuries by activating glia, especially microglia and astrocytes.

## Author Contributions

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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