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People living with HIV and the emerging field of chronic pain—what is known about epidemiology, etiology, and management

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Abstract

Purpose of Review—Chronic pain is common in people living with HIV (PLWH). It causes significant disability and poor HIV outcomes. Despite this, little is understood about its etiology and management.

Recent Findings—Recent studies suggest that chronic pain in PLWH is caused by inflammation that persists despite viral load suppression. This coupled with central sensitization and psychosocial factors leads to chronic pain that is difficult to manage. PLWH with chronic pain often feel that their pain is incompletely treated, and yet there are few evidence-based options for the management of chronic pain in PLWH. Recent studies suggest that an approach pairing pharmacotherapy and nonpharmacologic therapy may address the complex nature of chronic in PLWH.

Summary—Chronic pain in PLWH is common yet poorly understood. Further research is needed in order to better understand the etiology of chronic pain and its optimal management.

Keywords

HIV; Chronic pain; Pain; Biopsychosocial; Biopsychosocial model

Introduction

People living with HIV (PLWH) have a high burden of chronic pain. Estimates of the prevalence of chronic pain in PLWH range from 25 to 85% [1–10]; this is higher than estimates of prevalence of chronic pain in the general population [11]. Chronic pain is defined as pain that continues for longer than 3–6 consecutive months, beyond the typical period of normal tissue healing [12]. It may manifest in PLWH in different ways, including but not limited to chronic low back pain, headaches, peripheral neuropathy, and fibromyalgia [13]. Chronic pain severely impacts quality of life in PLWH, and is associated with functional impairment, poor retention in care, poor antiretroviral therapy (ART) adherence, and virologic failure [14–18]. PLWH list chronic pain as a major health priority [19, 20].

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With the development, advancement, and widespread distribution of ART, the focus of care for PLWH shifted from the management of acute illness to the management of chronic manifestations of HIV infection [21]. In this context, there is an increasing recognition of the importance of chronic pain in HIV from clinical and research communities [22, 23]. Despite this, knowledge of the etiology and optimal management of chronic pain in PLWH remains poorly understood [22]. In this article, we review existing literature on the epidemiology, etiology, and management of chronic pain in PLWH.

Epidemiology

Chronic pain in PLWH has traditionally been tied to neurotoxic ART prescribed broadly in the early era of ART [24]. However, despite advancements in ART and improved control of HIV overall, chronic pain has persisted as a prominent health concern for PLWH [25, 26]. Some studies have characterized the epidemiology of general pain [1, 5, 7, 27, 28], but few have examined *chronic* pain in PLWH. In those studying chronic pain, prevalence varies greatly depending upon the cohort [8, 9, 13, 29, 30]. For example, in one sample of homeless PLWH living in an urban setting, 90% endorsed chronic pain [8]. In contrast, in a cohort of PLWH in care in Lweza, Uganda, only 21.5% of participants reported chronic pain [9]. This large variability is likely due to differences in how chronic pain was measured and clinical differences between cohorts.

Chronic pain in PLWH is more common in older patients and with complex medical, psychiatric, and substance use comorbidities [7, 13, 31]. It is associated with substantially diminished health outcomes, including increased healthcare utilization and greater odds of functional impairment [13, 14]. PLWH with chronic pain are more likely to have poor retention in care and poor ARV adherence and are ultimately more likely to experience virologic failure when compared with their counterparts who do not have chronic pain [7, 17, 18, 32]. Most PLWH with chronic pain experience musculoskeletal pain and neuropathic pain and many have multisite pain, reporting a median of 2–5 sites of pain [8, 13, 33–35].

Types of Chronic Pain in PLWH

Chronic pain in PLWH commonly falls into one of two categories: neuropathic or non-neuropathic [30, 33, 36]. Non-neuropathic pain generally refers to musculoskeletal pain and can also include other etiologies like multi-site pain and headaches [23]. Neuropathic pain was the first chronic pain syndrome associated with HIV, caused by exposure to nucleoside analog reverse-transcriptase inhibitors (NRTIs), the earliest of life-saving ART available to PLWH [37]. NRTIs cause neuropathic pain through interference of mitochondrial DNA replication and subsequent mitochondrial depletion [38]. Some also cause mitochondrial toxicity through inhibition of mitochondrial membrane potential [38]. Ultimately, mitochondrial dysfunction causes loss of oxidative respiration of affected tissues, which then causes neurotoxicity [38]. Since the lifespan of PLWH has extended and ART has advanced to safer drugs with lower likelihood of mitochondrial toxicity and neuropathy, non-neuropathic pain has emerged as a cause of morbidity in this population [37].

Neuropathic Pain

Neuropathic pain in PLWH is usually described as dysesthetic pain that is located in a stocking-and-glove distribution on distal extremities, and typically affects the feet more than the hands. It is associated with a painful response to light touch [39]. Neuropathic pain can be a complication of HIV infection, of other viral infections, such as postherpetic neuralgia following varicella zoster infection, and from other conditions such as diabetes mellitus, alcohol use disorder, and multiple myeloma.

The exact etiology of HIV-associated neuropathy is incompletely understood. In earlier years of the HIV pandemic, neuropathic pain was associated with the use of neurotoxic dideoxynucleoside reverse transcriptase inhibitors. In modern HIV care, we phased out this class of ART and replaced them with less toxic ART. It was also associated with opportunistic infections experienced by PLWH with end-stage disease [23]. Since then, with ART more widely available, fewer PLWH experience opportunistic infections as they did in earlier years of the AIDS epidemic [40]. Despite this, estimates of the prevalence of HIV-associated neuropathic pain range from 13 to 50% [41–43]. In a recent multi-national study following PLWH and people without HIV over 192 weeks, peripheral neuropathy was more common in PLWH than in HIV-uninfected individuals at baseline. As PLWH achieved HIV viral load suppression with ART, incidence of neuropathic pain decreased, suggesting that viremia is related to neuropathic pain [44]. These findings are preceded by studies in other cohorts of PLWH that found that severity of neuropathic pain was associated with HIV viremia [45–47].

There are reports of neuropathic pain persisting despite viral load suppression [24, 48]. Some hypothesize that chronic pain despite HIV viral load suppression is due to central sensitization in which the brain receives a strong signal of pain when there is no peripheral tissue injury present [12]. Some findings suggest that peripheral neurons experience inflammation indirectly through HIV-infected monocyte-macrophage lineage cells that excrete inflammatory cytokines [24, 49–51]. Inflammation persists in many, even with viral load suppression [52, 53]. This is a picture seen in other chronic pain illnesses such as fibromyalgia. Further research is needed to elucidate the relationship between HIV viremia, inflammation, other mediators, and neuropathic pain.

Non-neuropathic Pain

Non-neuropathic pain in PLWH can present in many different ways, including chronic low back pain, osteoarthritis, and multi-site pain [13, 54, 55]. In some cohorts, musculoskeletal pain is more common than neuropathic pain [13]. Non-neuropathic pain in PLWH is poorly studied. Musculoskeletal pain is common in multiple different cohorts of PLWH [13, 55, 56]. The etiologies of non-neuropathic pain in PLWH are disparate. Some are specific to HIV, such as avascular necrosis and osteoporosis with subsequent fracture [57], while others are less specific to HIV such as lumbosacral pain [13] and fibromyalgia [55]. In cohorts of patients with multi-site and non-neuropathic pain, elevated inflammatory cytokines were associated with increasing age and with worsening measures of chronic pain [52, 53]. Multi-site pain is associated with long duration of exposure to HIV, immuno-suppression, and exposure to many different ART [58]. Some hypothesize that much like neuropathic

pain, non-neuropathic chronic pain in PLWH is secondary to inflammation secondary to HIV-infection despite viral load suppression.

Other Factors That Contribute to Chronic Pain in PLWH

The Biopsychosocial (BPS) framework of chronic pain in PLWH is a conceptual framework to understand how chronic pain is related to a combination of factors, such as HIV viremia, inflammation, psychiatric diagnoses, substance use, stigma, and health behaviors (Fig. 1) [59]. One reason for why chronic pain is so poorly understood in PLWH is because its etiology is likely secondary to multiple factors that converge to cause chronic pain, and subsequently poor clinical outcomes, which in turn compound symptoms of chronic pain further. Some criticize this framework as being difficult to measure the weighted contribution of each construct; however, there is growing evidence of the bidirectional relationship between biopsychosocial factors and chronic pain in HIV [31, 60]. For example, increasing chronic pain severity is associated with worsening insomnia and depressive symptoms in PLWH [18, 31, 60]. This pattern is also seen with chronic pain severity and anxiety, post-traumatic stress disorder, opioid use disorder, and risky alcohol use in PLWH [60, 61]. Additionally, depression and anxiety are related to inflammation, much like pain is related to increased inflammation in PLWH [62].

Chronic pain, both neuropathic and non-neuropathic, in PLWH is also associated with poor adherence to ART and missed HIV clinic visits [7, 60, 63]. When considering the etiology of chronic pain and its clinical implications in PLWH, it is important to take into consideration the reciprocal relationship of chronic pain and biopsychosocial factors.

Management of Chronic Pain in PLWH

Chronic pain in PLWH has historically been undertreated and remains so [23, 56]. This is especially true in women, people with a history of substance use disorder, and those with low socioeconomic status [35, 64–66]. Both pain and HIV are heavily stigmatized conditions, and many PLWH with chronic pain feel a lack of validation of symptoms and dismissal by family members and healthcare providers [67]. Patients may even experience internalized stigma, which can lead to patients feeling devalued and inferior to their counterparts without chronic pain [66].

When approaching management of chronic pain in PLWH, it is important to take into account the BPS framework (Fig. 1) and understand that many different factors may be involved in the experience of pain. Management of chronic pain in PLWH can include both pharmacologic and non-pharmacologic treatments.

Pharmacologic Treatment

Pharmacologic treatments for the management of chronic pain in PLWH are poorly studied. Few if any studies focus on PLWH and the ones that do have small sample sizes or were inconclusive [23]. In this setting, for many years, chronic neuropathic pain and nonneuropathic pain were treated with chronic opioid therapy, with higher proportions of PLWH than people without HIV prescribed opioids in several cohorts [68]. Over the past decade, there has been a paradigm shift in the use of opioids for chronic pain in all

populations, including PLWH [69]. Due to the growing recognition of the risk of opioid use disorder and risk of opioid overdose, recommendations strongly advise against the use of opioids for the management of chronic pain and emphasize the use on nonopioid therapy [23, 69].

The remaining pharmacologic management of chronic pain relies on the use of medications with little evidence. Neuropathic pain is managed with anticonvulsants like gabapentin and antidepressants like serotonin-norepinephrine reuptake inhibitors (SNRIs) [23]. There is some evidence that capsaicin cream co-administered with lidocaine cream is effective for neuropathic pain in HIV [70].

Medical cannabis is a promising potential pharmacotherapeutic for the management of chronic pain in HIV. In studies of PLWH living in the USA and Canada, up to one-third of patients use cannabis—both medical and recreational [71–75]. In both qualitative and quantitative studies, PLWH describe using cannabis for the management of pain, alone and in conjunction with other pharmacotherapies [71, 76, 77]. Studies testing medical cannabis for pain in PLWH focus on neuropathic pain [78, 79] and found that medical cannabis reduces pain more than placebo. In other populations, multiple systematic reviews found that medical cannabis is an effective analgesic [80, 81]. Despite this, there remains significant gaps in our understanding of most appropriate use of medical cannabis, including dosing and frequency. As medical cannabis becomes increasingly available to patients through legislative action [82], there is increasing pressure to understand how to use medical cannabis safely and effectively in PLWH.

Non-pharmacologic Treatment

Non-pharmacologic treatments are important to be used in conjunction with pharmacologic treatment in PLWH with chronic pain [23]. It is particularly useful to address psychosocial aspects of chronic pain. One example is cognitive behavioral therapy (CBT) that can be useful to help identify behaviors that could be making pain worse (e.g., exercise avoidance) and develop coping strategies for anxiety related to pain [83]. Few studies examine CBT in PLWH, and those that did were not specifically tailored to the population [23, 84, 85]. Further research is needed to identify and test patient-centric nonpharmacological interventions in PLWH for the management of chronic pain.

Conclusions

Chronic pain is a major health complication in PLWH. Despite this, the etiology and management of chronic pain is incompletely understood. This paper provided a summary of the epidemiology, etiologies, and management of chronic pain in PLWH. With an aging population of PLWH [86], chronic symptoms and illnesses will continue to be the predominant health concern of PLWH. Given the many health consequences of chronic pain in PLWH, including poor HIV outcomes and engagement in care, it is essential that research in the etiology of chronic pain in PLWH is prioritized. With an improved understanding of the etiologies of chronic pain in PLWH, therapeutics can be targeted to maximize their efficacy and safety.

Future research should ensure that there is adequate representation of traditionally under-represented populations in research on chronic pain in PLWH including women and minorities and ensure that the BPS framework is considered to accurately capture the complexity of chronic pain in PLWH. A Global Task Force on Chronic Pain in PLWH recently published a scientific agenda to identify gaps in knowledge on chronic pain with the aim of advancing research in this field that can be implemented clinically [22]. Efforts such as these with adequate stakeholder engagement provide hope that future studies will fill gaps in our knowledge of chronic pain in PLWH and how to manage it.

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Fig. 1.

Adapted Biopsychosocial framework for chronic pain in HIV (Merlin, *Pain Practice* 2013)