

## CHAPTER 1

# Epidemiology of chronic pain in HIV-infected individuals

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### Introduction

Chronic pain is increasingly recognized as an important comorbidity of HIV-infected patients. In the current treatment era, HIV-infected patients who adhere to highly active antiretroviral therapy (HAART) and are engaged and retained in HIV primary care can achieve near-normal life expectancy [1]. Although patients with HIV can lead long lives, they often suffer from high rates of medical and psychiatric comorbidities. Due to a myriad of factors, chronic pain has also emerged as an important chronic condition in HIV-infected patients. This chapter focuses on the prevalence, etiology, and impact of comorbid chronic pain in HIV-infected individuals.

### A changing HIV epidemic

Early in the epidemic, HIV infection inevitably progressed to AIDS, often shortly after diagnosis. Pain and other physical symptoms were largely related to sequelae or opportunistic infections, uncontrolled HIV replication [2], and early antiretroviral therapies such as the “d-drugs,” which cause peripheral neuropathy [3]. Although there is no data on the prevalence of chronic pain in this early era, given the relatively rapid progression of disease, much of the pain experienced was acute. Like other forms of acute pain, it was managed by

treating the underlying cause when possible, and symptomatically using opioids [4].

In 1996, the discovery of effective, well-tolerated antiretroviral therapy changed HIV infection from an inevitably fatal disease to a complex, chronic infection. The key steps in maintaining HIV as a chronic infection involve timely HIV diagnosis, linkage to care, adherence to treatment, and ultimately viral suppression. These steps are otherwise known as the “HIV treatment cascade” and navigation through the cascade is key to successful treatment [5]. As HIV becomes a chronic infection, studies have found that life expectancy of infected patients has increased. A study of US national HIV surveillance data from 25 states including 220,646 people from 1996 to 2005 found that life expectancy at diagnosis had increased from 10.5 to 22.5 years [6]. This increase in life expectancy has contributed to a surge in the number of people living with HIV and to shift the age distribution of the epidemic. By 2015, half of the HIV-infected population in the United States will be older than 50 [7]. The interaction of HIV disease with the aging process can cause accentuated aging and earlier development of comorbid conditions frequently seen in older adults [7].

With decreasing mortality, increased life expectancy, and consequent increasing comorbid illnesses, pain syndromes have emerged as a chronic condition with HIV infection. Chronic pain is defined as pain lasting longer than 3–6 months, beyond the period of normal

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healing [8]. Chronic pain is a major health problem in the United States, affecting about 100 million adults [9]. Pain is the most common symptom for which patients seek care [10], and costs the nation up to \$635 billion each year in medical treatment and lost productivity [9]. A recent cross-sectional Internet-based survey in the United States found that about a third of adults experienced chronic pain, most commonly lower back pain and osteoarthritis pain [11].

## **Chronic pain in the HAART era**

Though there are no studies designed to directly compare the prevalence of chronic pain in HIV-infected patients versus the general population, the range of chronic pain observed in HIV-infected patients tends to be higher than that in the general population. Studies from the HIV treatment era document high levels of pain in HIV-infected patients with prevalence estimates of anywhere from 39% to as high as 85% [12–20]. Studies also show that patients' pain is often underdiagnosed and inadequately treated. A study of 34 HIV treatment facilities found that 30% of outpatients and 62% of inpatients reported pain due to HIV disease and the pain severity significantly decreased patients' quality of life. They also found that doctors underestimated pain severity in 52% of patients. Of the patients reported moderate-to-severe pain, 57% did not receive any treatment and 22% received weak opioids. Doctors were more likely to give an opiate prescription if they estimated the pain to be severe or if they thought the patients were sicker [2].

Compounding this underdiagnoses suboptimal treatment of chronic pain are the racial disparities associated with the domestic HIV epidemic. HIV infection disproportionately affects vulnerable populations such as racial/ethnic minorities, women, and people of low socioeconomic status [21]. In 2009, the rate of new HIV infections was eight times higher for blacks and three times higher for Hispanics than whites. In addition to this, HIV/AIDS mortality was nine times higher for blacks than whites. Also, in 2009, 280,000 women were estimated

to be living with HIV in the United States, with 15 times higher rates of new infections in black women and three times higher rates in Hispanic women [22]. Studies suggest that these vulnerable groups have higher rates of pain and more likely to be undertreated for their pain [23–26]. A recent telephone survey found that race, ethnicity, and socioeconomic factors influenced access to care for chronic pain [27]. Studies have also suggested in other chronic disease states that opioids were less likely to be prescribed for Black and Hispanic patients than White patients [28,29]. A recent study looking at the indigent HIV-infected population found chronic pain prevalence as high as 90% and 92% of these patients were found to have moderate-to-severe pain [20].

Pain is seen with increasing frequency in HIV-infected patients who have comorbid substance use and psychological disorders [30]. A recent study of 156 ambulatory HIV-infected patients in the United States found that 48.7% reported pain, of whom 51.3% had moderate-to-severe pain intensity and 57.3% of participants felt that their pain caused moderate-to-severe interference with their lives. This study further found that patients with psychiatric illness were 40% more likely to have pain and patients with a history of IV drug use who had pain were more likely to have severe or moderate pain than patients without a history of IV drug use. The authors suggested that comorbid IV drug use and psychiatric illness need to be addressed when treating pain and symptoms [12]. In fact, studies suggest that psychiatric illness can be more difficult to treat without concurrent pain treatment [31].

## **Etiology of chronic pain in HIV**

The etiology of chronic pain in the current treatment era is multifactorial and likely related to direct effects of HIV or HAART, opportunistic infections, increasing number of chronic comorbid conditions, the aging HIV-infected population, and other conditions unrelated to HIV [32]. HIV infection and HAART can cause pain by direct toxicity to the nervous system. Neuropathic pain is an important component of

HIV-infected patients' pain in the pre-HAART and current treatment era. Distal sensory polyneuropathy, the most common cause of neuropathic pain in HIV-infected patients, can be related to exposure to older ART regimens including stavudine, didanosine, and zalcitabine, or current protease inhibitor therapy and simple HIV infection [33] and prevalence estimates in the current treatment era range from 4.3% to 21.8% [34–36]. Headaches are also a common symptom of HIV-infected patients and in a recent cross-sectional study of 200 HIV-infected patients in an outpatient setting, 53.5% of patients reported headache symptoms, of which 85% met criteria for migraine and 14.5% met criteria for tension headaches. Severity of HIV was associated with headache severity, frequency, and disability [37]. In addition, as in the general population, low back pain is a common complaint in HIV-infected patients. In a recent study of 124 patients followed at an ambulatory palliative care clinic in the United States found that pain was the most common reason for referral and 21% of patients complained of low back pain [38] (see Chapter 4, Musculoskeletal pain in individuals with HIV and Chapter 2, Pathophysiology of chronic pain in individuals with HIV).

Medical comorbidities such as cardiovascular disease [39], metabolic bone disease [40], diabetes [40], non-AIDS defining malignancies [41], and frailty [7] occur with increasing prevalence in HIV-infected populations. There are many theories as to why these non-AIDS events are occurring in greater numbers and at an earlier age than a noninfected population. First, among the HIV-infected community, traditional modifiable risk factors such as smoking, alcohol abuse, and substance use are more prevalent than in the noninfected population [42]. Direct toxic effects of ART or metabolic changes related to exposure to ART have also been shown to increase the risk for non-AIDS events. Finally, there is a rapidly growing body of evidence that HIV infection itself is a proinflammatory state and can contribute to the early development of many of these non-AIDS events [43] (see Chapter 7, Common medical comorbid conditions and chronic pain in HIV).

It is likely that aging and high burden of medical comorbidities contribute to chronic

pain in HIV-infected patients. A recent telephone survey of HIV-infected patients older than 50 years assessing quality of life and chronic illness burden found that pain-related syndromes were second only to hypertension and 45% of the participants noted chronic pain other than back pain and headache, 35% had arthritis, 33% had chronic back pain, and 17% had chronic headaches [44]. Lower health-related quality of life (HRQOL) [45] and faster decline of physical functioning [46] have been shown to be associated with older age in HIV-infected patients.

### **Impact of chronic pain on HIV health behavior**

Given recent recognition of comorbid chronic pain in HIV-infected patients, several studies have investigated the relationship between chronic pain and HIV health behaviors such as adherence to HAART and retention in care. One study of 70 HIV-infected outpatients on methadone maintenance found that 57% of participants reported pain and that participants with pain were 87% less likely to be adherent to ART compared to those without pain [47].

Another important indicator of successful management of HIV infection along the treatment cascade is retention in care, and a recent study of 2811 patients in the United States found that patients with greater than one missed visit in the first year following diagnosis had a 71% increased mortality risk [48]. Another study in the United States of 1521 HIV-infected patients found that the presence of pain increased the odds of a no-show visit in participants without substance abuse and pain conversely reduced the odds of a no-show visit in participants with substance abuse. The authors suggest that the presence of pain negatively affected retention in care because patients may have felt too sick to come to their office or they prioritized pain relief over HIV management. They also suggest that patients with substance abuse maybe have been more likely to attend their appointments because of increasing pain management needs. The authors conclude that further research is

necessary into evidence-based approaches to pain management in HIV-infected patients [13].

Chronic pain in HIV-infected patients can also impact physical function. Physical function is an important component of HRQOL and one of the most important clinical outcomes in chronic pain care (see Chapter 10, Pharmacologic and Nonpharmacologic Treatment of Chronic Pain). A recent study of 1903 HIV-infected outpatients found that 37% of patients had pain, 27% of patients had mood disorders, and 8% were substance abusers. Pain was independently associated with up to 10 times greater odds of impaired physical function [49]. The authors suggest that appropriate management of pain is paramount to HIV disease management given that impaired physical function has been linked to increased mortality in HIV-infected patients [50].

Pain is also associated with increased healthcare utilization in the general population. A recent study at a large US academic health center, evaluating healthcare utilization, compared HIV-infected patients with chronic pain on opiates versus similar patients not on opiates. They used emergency room visits and hospitalizations as a measure of utilization and found that there was trend to increased emergency room visits and hospitalization in patients on opiates [51].

## Conclusion

Here one can start to see the framework of how chronic pain has emerged as a frequent and important chronic condition in HIV-infected patients in the current treatment era. Unique to our HIV patients suffering from chronic pain, pain can negatively impact adherence to lifesaving medications and decrease retention in care—both vital components of the HIV treatment cascade. Treating pain while taking into account comorbid psychiatric disease and substance abuse is of utmost importance to successfully caring for our HIV-infected community. The rest of the book will delve deeper into mechanisms of chronic pain, specific and common pain syndromes, comorbid conditions additive effect to chronic pain,

special populations of HIV-infected patients with concurrent substance abuse or psychiatric disorders, and finally pharmacologic and nonpharmacologic treatment of chronic pain. In addition, the book will touch on opioid risk mitigation strategies, approaches to “difficult” patients and further tools for educating providers about chronic pain.

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