Clinical Infectious Diseases

IDSA GUIDELINE

2017 HIVMA of IDSA Clinical Practice Guideline for the Management of Chronic Pain in Patients Living With HIV

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Pain has always been an important part of human immunodeficiency virus (HIV) disease and its experience for patients. In this guideline, we review the types of chronic pain commonly seen among persons living with HIV (PLWH) and review the limited evidence base for treatment of chronic noncancer pain in this population. We also review the management of chronic pain in special populations of PLWH, including persons with substance use and mental health disorders. Finally, a general review of possible pharmacokinetic interactions is included to assist the HIV clinician in the treatment of chronic pain in this population.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of American considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

EXECUTIVE SUMMARY

Summarized below are the recommendations made in the new guidelines for chronic pain in patients living with HIV (PLWH). The Panel followed a process used in the development of other IDSA guidelines that included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [1-5]. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guidelines.

RECOMMENDATIONS FOR MANAGEMENT AND TREATMENT OF PERSONS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS AND CHRONIC PAIN

I. What is the recommended approach to screening and initial assessment for chronic pain in persons living with human immunodeficiency virus?

Recommendations

1. All PLWH should receive, at minimum, the following standardized screening for chronic pain: How much bodily pain have you had during the last week? (none, very mild, mild, moderate, severe, very severe) and Do you have bodily pain that has lasted for more than 3 months? (strong, low). *Remark: A response of moderate pain or more during the last week combined with bodily pain for more than 3 months can be considered a positive screen result.*
2. For persons who screen positive for chronic pain, an initial assessment should take a biopsychosocial approach that includes an evaluation of the pain's onset and duration, intensity and character, exacerbating and alleviating factors, past and current treatments, underlying or co-occurring disorders and conditions, and the effect of pain on physical and psychological function. This should be followed by a physical examination, psychosocial evaluation, and diagnostic workup to determine the potential cause of the pain (strong, very low). *Remark: A multidimensional instrument such as the brief pain inventory (BPI) or the 3-item patient health questionnaire (PEG; used to assess average pain intensity [P], interference with enjoyment of life [E], and interference with general activity [G]) can be used for pain assessments.*
3. Medical providers should monitor the treatment of chronic pain in PLWH, with periodic assessment of progress on achieving functional goals and documentation of pain intensity, quality of life, adverse events, and adherent vs aberrant behaviors (strong, very low). *Remark: Reassessments should be conducted at regular intervals and after each change or initiation in therapy has had an adequate amount of time to take effect.*

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II. What is the recommended general approach to the management of persons living with human immunodeficiency virus and chronic pain?

Recommendations

4. HIV medical providers should develop and participate in interdisciplinary teams to care for patients with complex chronic pain and especially for patients with co-occurring substance use or psychiatric disorders (strong, very low).
5. For patients whose chronic pain is controlled, any new report of pain should be carefully investigated and may require added treatments or adjustments in the dose of pain medications while the new problem is being evaluated (strong, high). *Remark: Providers should clearly document the new symptom and consult, if possible, with a provider experienced with pain management in PLWH or with a pain specialist.*

III. What is the recommended therapeutic approach to chronic pain in persons with human immunodeficiency virus at the end of life?

Recommendations

6. As PLWH age, their pain experience may change as other age-related and HIV-related comorbidities develop. It is recommended that the clinician address these changes in pain experience in the context of this disease progression (strong, moderate).
7. Critical to maintaining pain control, it is recommended that medical providers and an integrated multidisciplinary team engage in frequent communication with the patient and the patient's support system (eg, family, caregiver) (strong, low). *Remark: Communications should occur at a health literacy level appropriate for the patient and patient's support system. It may be necessary to schedule longer appointment times to allow both patients and providers to establish and clarify the goals of care.*
8. Consultation with a palliative care specialist to assist with pain management and nonpain symptoms and to address goals of care is recommended (strong, low).
9. Patients with advanced illness require a support system beyond the clinic, and timely referrals for palliative or hospice care are recommended. The primary care provider must remain in communication with the patient and family through the end of life to ensure accurate continuity and to preclude a sense of abandonment (strong, low).

IV. What are the recommended nonpharmacological treatments for chronic pain in persons living with human immunodeficiency virus?

Recommendations

10. Cognitive behavioral therapy (CBT) is recommended for chronic pain management (strong, moderate). *Remark: CBT promotes patient acceptance of responsibility for change and the development of adaptive behaviors (eg, exercise) while addressing maladaptive behaviors (eg, avoiding exercise due to fears of pain).*
11. Yoga is recommended for the treatment of chronic neck/back pain, headache, rheumatoid arthritis, and general musculoskeletal pain (strong, moderate).
12. Physical and occupational therapy are recommended for chronic pain (strong, low).
13. Hypnosis is recommended for neuropathic pain (strong, low).
14. Clinicians might consider a trial of acupuncture for chronic pain (weak, moderate). *Values and preferences: This recommendation places a relatively high value on the reduction of symptoms and few undesirable effects. Remark: Evidence to date is available only for acupuncture in the absence of amitriptyline and among PLWH with poorer health in the era before highly active antiretroviral therapy.*

V. What are the recommended pharmacological treatments for chronic neuropathic pain in persons living with human immunodeficiency virus?

Nonopioid Recommendations

15. Early initiation of antiretroviral therapy is recommended for the prevention and treatment of HIV-associated distal symmetric polyneuropathy (strong, low).
16. Gabapentin is recommended as a first-line oral pharmacological treatment of chronic HIV-associated neuropathic pain (strong, moderate). *Remark: A typical adult regimen will titrate to 2400 mg per day in divided doses. Evidence also supports that gabapentin improves sleep scores; somnolence was reported by 80% of patients who received gabapentin* (strong, low).
    a. If patients have an inadequate response to gabapentin, clinicians might consider a trial of serotonin-norepinephrine reuptake inhibitors based on their effectiveness in the general population (weak, moderate).
    b. If patients have an inadequate response to gabapentin, clinicians might consider a trial of tricyclic antidepressants (weak, moderate).
    c. If patients have an inadequate response to gabapentin, clinicians might consider a trial of pregabalin for patients with post-herpetic neuralgia (weak, moderate).
17. Capsaicin is recommended as a topical treatment for the management of chronic HIV-associated peripheral neuropathic pain (strong, high). *Remark: A single 30-minute application of an 8% dermal patch or cream administered at the site of pain can provide pain relief for at least 12 weeks. Erythema and pain are common side effects for which a 60-minute application of 4% lidocaine can be applied and wiped off before applying capsaicin* (strong, high).

18. Medical cannabis may be an effective treatment in appropriate patients (weak, moderate). *Values and preferences: This recommendation places a relatively high value on the reduction of symptoms and a relatively low value on the legal implication of medical cannabis possession. Remark: Current evidence suggests medical cannabis may be more effective for patients with a history of prior cannabis use; the potential benefits of a trial of cannabis need to be balanced with the potential risks of neuropsychiatric adverse effects at higher doses, the harmful effects of smoked forms of cannabis in patients with preexisting severe lung disease, and addiction risk to patients with cannabis use disorder.*
19. We recommend alpha lipoic acid (ALA) for the management of chronic HIV-associated peripheral neuropathic pain (strong, low). *Values and preferences: This recommendation places a high value on providing tolerable medications that may be of some benefit in patients with difficult-to-treat neuropathic pain. Remark: Studies in patients with HIV are lacking; however, there is a growing body of literature of the benefits of ALA in patients with diabetic neuropathy.*
20. We recommend against using lamotrigine to relieve HIV-associated neuropathic pain (strong, moderate). *Values and preferences: This recommendation places a relatively high value on the discontinuation of neurotoxic agents and on minimizing the incidence of lamotrigine-associated rash and places a relatively low value on the reduction in pain symptoms found in an earlier randomized controlled trial by the same authors. Remark: A benefit was only seen in patients currently receiving neurotoxic antiretroviral therapy (ART), and we recommend discontinuing all neurotoxic ART.*

Use of Opioids

21. For PLWH, opioid analgesics should not be prescribed as a first-line agent for the long-term management of chronic neuropathic pain (strong, moderate). *Values and preferences: This recommendation places a relatively high value on the potential risk of pronociception through the upregulation of specific chemokine receptors, cognitive impairment, respiratory depression, endocrine and immunological changes, and misuse and addiction.*
22. Clinicians may consider a time-limited trial of opioid analgesics for patients who do not respond to first-line therapies and who report moderate to severe pain. As a second- or third-line treatment for chronic neuropathic pain, a typical adult regimen should start with the smallest effective dose and combine short- and long-acting opioids (weak, low). *Remark: When opioids are appropriate, a combination regimen of morphine and gabapentin should be considered in patients with neuropathic pain for their possible additive effects and lower individual doses required of the 2 medications when combined.*

V. What are the recommended nonopioid pharmacologic treatments for chronic nonneuropathic pain in persons living with human immunodeficiency virus?

Recommendations

23. Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are recommended as first-line agents for the treatment of musculoskeletal pain (strong, high). *Remark: Acetaminophen has fewer side effects than NSAIDs. Studies typically used 4 g/day dosing of acetaminophen; lower dosing is recommended for patients with liver disease. Compared to traditional NSAIDs, COX-2 NSAIDs are associated with decreased risk of gastrointestinal side effects but increased cardiovascular risk.*

VI. What are the recommended opioid pharmacological treatments for chronic nonneuropathic pain in persons living with human immunodeficiency virus?

Recommendations

24. Patients who do not respond to first-line therapies and who report moderate to severe pain and functional impairment can be considered for a time-limited trial of opioid analgesics (weak, low). *Values and preferences: This recommendation places a relatively high value on safer opioid prescribing. The potential benefits of opioid analgesics need to be balanced with the potential risks of adverse events, misuse, diversion, and addiction. Remark: As a second- or third-line treatment for chronic nonneuropathic pain, a typical adult regimen should start with the smallest effective dose, combining short- and long-acting opioids.*
25. Tramadol taken for up to 3 months may decrease pain and improve stiffness, function, and overall well-being in patients with osteoarthritis (weak, moderate). *Remark: The range of tramadol dosing studied is 37.5 mg (combined with 325 mg of acetaminophen) once daily to 400 mg in divided doses.*

VII. What is the recommended approach for assessing the likelihood of developing the negative, unintended consequences of opioid treatment (eg, misuse, substance use disorder, or possible diversion) in persons living with human immunodeficiency virus?

Recommendations

26. Providers should assess all patients for the possible risk of developing the negative, unintended consequences of opioid treatment (eg, misuse, diversion, addiction) prior to prescribing opioid analgesics for the treatment of chronic pain (strong, low). *Remark: A trial of opioid analgesics for the treatment of moderate-to-severe chronic pain may be reasonable only when the potential benefits of chronic opioid therapy for pain severity, physical function, and quality of life outweigh its potential harms.*

VIII. What is the recommended approach to safeguard persons living with human immunodeficiency virus against harm while undergoing the treatment of chronic pain with opioid analgesics?

Recommendations

27. Routine monitoring of patients prescribed opioid analgesics for the management of chronic pain is recommended (strong, very low). *Remark: Opioid treatment agreements, urine drug testing (UDT), pill counts, and prescription drug monitoring programs are commonly used tools to safeguard against harms.*
28. An "opioid patient–provider agreement (PPA)" is recommended as a tool for shared decision making with all patients before receiving opioid analgesics for chronic pain (strong, low). *Remark: PPAs consist of 2 components: informed consent and a plan of care. When a patient's behavior is inconsistent with the PPA, the provider must carefully consider a broad differential diagnosis.*
29. The provider should understand the clinical uses and limitations of UDT, including test characteristics, indications for confirmatory testing, and the differential diagnosis of abnormal results (strong, low). *Remark: UDT results should never be used in isolation to discharge patients from care. Rather, results should be used in combination with other clinical data for periodic evaluation of the current treatment plan and to support a clinical decision to safely continue opioid therapy.*

IX. What are the recommended methods to minimize adverse effects from chronic opioid therapy in persons living with human immunodeficiency virus?

Recommendations

30. Controlled substances should be stored safely away from individuals at risk of misuse and/or overdose; family members should be educated on the medications and signs of overdose, and the poison control number should be readily visible (strong, low).
31. Clinicians should teach patients and their caregivers about opioid overdose and the use of naloxone to reverse overdose; a naloxone rescue kit should be readily available (strong, moderate).
32. Patient education is recommended to help patients avoid adverse events related to pharmacological interactions (strong, low).
33. Providers should be knowledgeable about common pharmacological interactions and be prepared to identify and manage those drug–drug interactions (strong, low). Providers should follow patients closely when interactions are likely (strong, low).

X. What is the recommended approach to prescribing controlled substances for the management of chronic pain to persons living with human immunodeficiency virus with a history of substance use disorder?

Recommendations

34. Persons with a history of a substance use disorder or addiction should be carefully evaluated and risk stratified in the same manner as all other PLWH with chronic pain (strong, low). *Values and preferences: This recommendation places a high value on clinical strategies that neutralize bias and reduce stigma in the care of all PLWH and the possibility of behavior change over time. Remark: A patient's history of addiction or substance use disorder is not an absolute contraindication to receiving controlled substances for the management of chronic pain. A risk–benefit framework that views controlled substances as medications with unique risks to every patient ("a universal precautions approach") should be applied uniformly to help providers make fair and informed clinical decisions about controlled substance prescribing.*
35. Persons with a history of addiction for whom the risks currently outweigh the benefits of a controlled substance prescription should have their chronic pain reasonably managed by other therapies and should receive emotional support, close monitoring and reassessment, and linkages to addiction treatment and mental health services as indicated (strong, low). *Values and preferences: This recommendation places a high value on access to pain management as a fundamental human right with an underlying principle that every person deserves to have his or her pain reasonably managed by adequately trained healthcare professionals and that every medical provider has a duty to listen to and reasonably respond to a patient's report of pain.*

XI. What are the recommended approaches to the pharmacological management of chronic pain in persons living with human immunodeficiency virus who are on methadone for the treatment of opioid use disorder?

Recommendations

36. A signed release for the exchange of health information between the provider and the opioid treatment program (OTP) is recommended prior to any controlled substance prescribing (strong, low). *Remark: Ongoing communication with the OPT is essential when there are 2 controlled substance prescribers. Sharing information about a patient's progress in recovery is an important component of the assessment and periodic monitoring of a pain treatment's risks and benefits, for example, whether to pursue a trial of or to continue or discontinue opioid analgesic therapy.*
37. Initial screening with electrocardiogram to identify heart rate corrected QT (QTc) prolongation for all patients on methadone is recommended, with interval follow-up with dose changes. This is especially helpful if the patient is also prescribed other medications that may additively prolong

the QTc (eg, certain psychotropics, fluconazole, macrolides, potassium-lowering agents) (strong, low).

38. The splitting of methadone into 6- to 8-hour doses is recommended in order to lengthen the active analgesic effects of methadone with the goal of continuous pain control (strong, low). *Remark: Some OTPs may be able to offer a split-dose methadone regimen for patients. Alternatively, the medical provider may need to prescribe the remaining daily doses: 5%–10% of the current methadone dose should be added, usually as an afternoon and evening dose for a total 10%–20% increase over the regular dose for the treatment of opioid use disorder (strong, very low).*
39. If prescribing additional methadone is not possible (eg, OTP policy, high baseline methadone dose, prolonged QTc intervals, high risk of diversion, the patient is new to or poorly adherent to the OTP), then an additional medication may be recommended for chronic pain management depending on the etiology of the pain (eg, gabapentin for neuropathic pain, nonsteroidal antiinflammatory drugs for musculoskeletal pain, or an additional opioid) (weak, low).
40. Acute exacerbations in pain or "breakthrough pain" should be treated with small amounts of short-acting opioid analgesics in patients at low risk for opioid misuse (strong, low). *Remark: Providers and patients should agree on the number of pills that will be dispensed for breakthrough pain, their frequency of use, and the expected duration of this treatment.*

XII. What are the recommended approaches to the pharmacological management of chronic pain in persons living with human immunodeficiency virus who are on buprenorphine for the treatment of opioid use disorders?

Recommendations

41. Clinicians should use adjuvant therapy appropriate to the pain syndrome for mild-to-moderate breakthrough pain (strong, moderate). *Remark: These adjuvants include, but are not limited to, nonpharmacologic treatments, steroids, nonopioid analgesics, and topical agents. (See section on "nonopioids" for treatment of chronic neuropathic and nonneuropathic pain.)*
42. Based on expert opinion, the clinician should increase the dosage of buprenorphine in divided does as an initial step in the management of chronic pain (strong, very low). *Remark: Dosing ranges of 4–16 mg divided into 8-hour doses have shown benefit in patients with chronic noncancer pain.*
43. Based on expert opinion, clinician's might switch from buprenorphine/naloxone to buprenorphine transdermal formulation alone (weak, very low).
44. We recommend that if a maximal dose of buprenorphine is reached, an additional long-acting potent opioid such as fentanyl, morphine, or hydromorphone should be tried (strong, low).
45. If usual doses of an additional opioid are ineffective for improving chronic pain, we recommend a closely monitored trial of higher doses of an additional opioid (strong, moderate). *Remark: Buprenorphine's high binding affinity for the μ-opioid receptor may prevent the lower doses of other opioids from accessing the μ-opioid receptor.*
46. For patients on buprenorphine maintenance with inadequate analgesia despite the above-mentioned strategies, we recommend transitioning the patient from buprenorphine to methadone maintenance (strong, very low).

XIII. What are the recommended instruments for screening common mental health disorders in persons living with human immunodeficiency virus with chronic pain?

Recommendations

47. Clinicians should fully review a patient's baseline mental health status for modifiable factors that can impact successful pain management (strong, low). *Remark: Potentially modifiable factors include self-esteem and coping skills; recent major loss or grief; unhealthy substance use; history of violence or lack of safety in the home; mood disorders; and history of serious mental illness or suicidal ideation.*
48. All patients should be screened for depression with the following 2 questions: During the past 2 weeks have you often been bothered by feeling down, depressed, or hopeless? During the past 2 weeks have you been bothered by little interest or pleasure in doing things? (strong, high). *Remark: If the patient answers in the affirmative to either question, a follow-up question regarding help should be asked: Is this something with which you would like help?*
49. The patient health questionnaire-9 (PHQ-9), which is in the public domain, is recommended as a screening tool in clinical settings without access to trained mental health professionals as it can be used to diagnose depression (strong, high). *Remark: Psychiatric follow-up for a result that is ≥10 (88% sensitivity and 88% specificity for major depression) is recommended, and the clinical site should have a policy for referrals for more in-depth evaluation of these issues.*
50. All patients should be screened for comorbid neurocognitive disorders prior to and during use of long-term opioid therapy (strong, low). *Remark: Questions administered to elicit cognitive complaints in the Swiss HIV Cohort study (eg, frequent memory loss; feeling slower when reasoning, planning activities, or solving problems; and difficulties paying attention) detected, but have not been tested as screening questions in the clinical setting.*
51. It is recommended that all patients with chronic pain have a full neuropsychiatric evaluation with history, physical, and use of the HIV dementia scale or an equivalent to document baseline capacity (strong, high).

INTRODUCTION

Epidemiology and Definitions

Chronic pain remains a significant problem in persons living with human immunodeficiency virus (PLWH) and is associated with psychological and functional morbidity, even in the absence of advanced disease complications. Depending on the study, current prevalence estimates of chronic pain in PLWH ranges from 39% to 85% [6–13]. Pain is the second most common symptom in ambulatory settings where HIV disease is treated. Nearly half of that pain is neuropathic due to injury to the central or peripheral nervous systems from direct viral infection, infection with secondary pathogens, or side effects of medications [6, 14]. Many other etiologies for neuropathic pain exist outside of HIV-related conditions (eg, syphilis, alcohol use disorders, nutritional deficiencies, diabetes mellitus, thyroid dysfunction, kidney disease, and multiple myeloma). Nonneuropathic pain, such as nociceptive pain, in PLWH is caused by tissue injury as a result of inflammation (eg, autoimmune responses), infection (eg, bacteria, other viruses, tuberculosis), or neoplasia (eg, lymphoma or sarcoma). Historically, pain among PLWH has been undertreated, particularly among women, persons with low socioeconomic status, and persons who inject drugs [15–17]. In this context, those who treat patients with HIV (ie, providers) must be familiar with the evaluation and management of chronic pain. Although chronic pain management is recognized as a specialty discipline within medicine, many patients lack access to specialized pain management services and must rely on their HIV clinical providers to initially evaluate and address their chronic pain needs. Just as with cancer patients, pain management is an essential component of overall disease management for PLWH [18].

Pain is comprised of sensory and affective components; that is, pain is a sensory experience that is emotionally distressing and aversive, and pain ranges from unpleasant to intolerable. Although some persons tolerate high levels of the sensory or nociceptive element of pain without emotional distress, others experience overwhelming distress to modest nociceptive stimulation. Pain is one of the great medical challenges, as it can profoundly interfere with function and disable the people who experience it.

Acute pain is caused by several neuronal mechanisms, including receptors that mechanically sense tissue disruption and heat as well as the local release of transmitters at the site of injury that stimulate receptors to transmit pain signals. These mechanisms have complex interactions and mutual regulatory signaling that make nociception one of the most integrated sensory experiences studied. The pain system synapses at the level of the dorsal root and in the spinal column, having recurrent connections that cross the midline. Pain signals converge on the thalamus and are then relayed to higher centers in the cortex where the conscious experience of pain is generated. This interpretation of the peripheral impulse within the larger physical and psychosocial context of the individual may result in pain of varying degrees and dimensions. In other words, pain is much more than a simple electrical impulse generated in the periphery that is transmitted to the brain with a known effect. The same signal in different individuals will produce different sensations of pain, because that signal must be interpreted within the larger context of the biopsychosocial factors that influence pain (see Foundational Principles of Chronic Pain Management regarding the biopsychosocial model of pain management).

With chronic pain, in distinction from acute pain, the immediate sensory and emotional response to injury gives way to a complex series of changes as stimulation continues (see the section on Types of Pain below). Nociception changes over time. Chronic pain may represent ongoing injury or an upregulation of the sensory system such that, in the absence of injury, the nociceptive signals continue. The patient cannot consciously tell the difference between these 2 states.

Although PLWH may experience novel types of injury due to HIV-related inflammation and infection, their pain does not essentially differ from acute pain due to other causes. Pain that is predominantly inflammatory will typically respond to inhibition of inflammation with steroids and nonsteroidal antiinflammatory medications. Other injuries respond to analgesic medications, such as acetaminophen, which ameliorate the central experience of pain, and to opioids, which diminish the affective response at lower doses and block the sensory elements of pain at higher doses (although both effects can occur at all doses).

Management discussed in these guidelines is directed at promoting well-being and engaging PLWH appropriately in the treatments and rehabilitation interventions, which are supported in the literature for chronic, noncancer pain. There are large limitations in the literature on the management of chronic pain, including few studies conducted in PLWH, heterogeneous diagnostic criteria, and high rates of placebo responses that potentially obscure beneficial treatments. Recommendations for the detailed treatment of acute pain are beyond the scope of this guideline but have been extensively reviewed in other guidelines [19, 20]. Persons living with HIV and malignant pain should be managed according to cancer pain guidelines.

Types of Pain

Chronic pain or pain that lasts longer than 3–6 months persists beyond the typical period of direct tissue injury and repair. The pathophysiology of chronic pain in most conditions is not well understood but is an area of active investigation. Many chronic pain syndromes are associated with substantial functional and structural changes, or plasticity, in the central nervous system, resulting from altered sensory and nerve function (eg, upregulation of nociception) at every level of the nervous system [21, 22]. Both afferent and efferent signals can be altered, including sympathetic nervous system activation, hormonal regulation,

and stress-axis signals [23]. Many forms of pain are the result of denervation rather than overstimulation. This deprivation of coherent sensory information can result in the production of pain that conveys incorrect messages. On functional imaging studies in persons with chronic pain, even with different pain locations and etiologies, a group of cortical and subcortical brain regions referred to as the "pain matrix" often show abnormalities, and changes in the motor and sensory homunculus also are seen [22]. In addition, disuse of painful body parts may result in pain upregulation, so that over time the pain prevents activity and the lack of activity increases the pain. Within the types of chronic pain syndromes, model subtypes of pain have been described and are receiving research attention. The 2 most common types of pain found in PLWH are neuropathic and nonneuropathic (most specifically, musculoskeletal) [24–26]. While all of the varied types of chronic pain that PLWH may experience cannot be covered in sufficient detail here, a brief description of some of them follows. The reader is referred to the evidence summaries below and the associated literature for a more in-depth review of the treatment for particular syndromes.

Musculoskeletal Pain

Musculoskeletal pain, especially osteoarthritis and nonspecific low back pain (ie, low back pain that cannot be linked to a specific etiology), is common among PLWH, [24]. However, few studies have addressed the treatment of musculoskeletal pain in PLWH. Until such studies are conducted, the recommended management of chronic musculoskeletal pain in PLWH is the same as for persons living without HIV. The reader is referred to the extensive reviews and guidelines that have been written by Chou and others on the evaluation and treatment of musculoskeletal pain in the general population for more detailed information [19, 27–32].

Neuropathic Pain

Neuropathic pain is common in patients with ongoing nerve injury from diabetes, inflammation, toxins, and infectious agents such as HIV [33, 34]. Peripheral sensory neuropathic pain is described as a "cold burning pain" (ie, dysesthetic pain) in a glove-and-stocking distribution that starts distally, with lower extremities more affected than upper extremities. Typically there is an increased painful response to light touch (ie, allodynia) that correlates with mostly small nerve fiber pathology.

HIV-associated neuropathic pain has a prevalence of between 13% and >50% and is comprised of at least 2 often coexisting and clinically indistinguishable distal sensory polyneuropathies associated with HIV disease itself and associated with antiretroviral treatment (ART) [35–38]. A significant association between plasma HIV-1 RNA levels and severity of HIV-associated distal symmetrical polyneuropathy has been observed in numerous cohort studies [39–41]. Neuropathic pain associated with the older nucleoside analogues, stavudine, didanosine, and zalcitabine, has been attributed to mitochondrial toxicity, although other mechanisms such as chemokine receptors also may be involved [42, 43]. Neuropathic pain in PLWH also can occur in the setting of alcohol use disorders, syphilis, isoniazid treatment, vitamin deficiencies (vitamin B6, B12, folate), thyroid dysfunction, multiple myeloma, and diabetes mellitus, which has been increasing in prevalence among PLWH. Post-herpetic neuralgia, a complication of varicella zoster infection, is another form of neuropathic pain frequently encountered in the HIV clinic. It can be incapacitating in patients with advanced HIV disease.

Denervation Pain

Phantom limb pain is a model for denervation pain in which the pain is experienced at a site localized to the missing body part. Interruption of nociceptors has been shown to result in chronic pain in some cases. This "pathological pain" occurs in the absence of ongoing injury. Although the mechanism is still unclear, new data suggest that phantom limb pain may result from exaggerated input from the dorsal root ganglia that used to innervate the limb [44].

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS), also called sympathetically maintained pain, causalgia, or reflex sympathetic dystrophy (RSD), usually follows an injury, often minor, and is described as excruciating and made worse by touch or stimulation. The pain gradually increases in intensity and size in the affected limb, sometimes spreading to the contralateral limb. Sympathetic dysregulation is proposed to play a role [45]. Little is known about its prevalence, but the condition has been reported in PLWH [46]. CRPS can be associated with hair loss, tissue changes, and skin discoloration at the site of the pain. Although some pain syndromes have noticeable placebo response rates, in a recent 2015 systematic review, CRPS did not have noticeable placebo analgesia except at very early time points (eg, 15 to 30 minutes) [47]. The reader is referred to a review by Freedman and colleagues for more information about this type of pain [48].

A variety of central pain syndromes, including those associated with direct spinal cord, thalamic, or cortical injury and/or interruption of pain pathways in the brain, are rarely seen in PLWH and are reviewed elsewhere [49, 50].

Fibromyalgia (Systemic Exertion Intolerance Disease, Myalgic Encephalopathy)

Fibromyalgia, or chronic fatigue syndrome, renamed myalgic encephalopathy (ME), and proposed renaming as "systemic exertion intolerance disease" by the Institute of Medicine (IOM) in 2015, is a serious, complex, multisystem disease; it is a controversial diagnosis that remains poorly described. ME has been reported as fibromyalgia in PLWH and can severely affect quality of life and function [51]. A multidisciplinary team with

a rehabilitative approach has been recommended for managing this condition; however, high placebo responses and lack of diagnostic clarity have made clear treatment recommendations for this condition difficult [52]. Many authors have included these syndromes under the rubric of chronic noncancer pain, but are not addressed in this guideline. The reader is referred to the 2015 IOM report for additional information about this type of pain [53].

Foundational Principles in Chronic Pain Management

At the outset of any discussion on chronic pain in PLWH, it is paramount to assert that the chronic pain be initially assessed in the same manner as chronic pain in persons without HIV.

Regardless of HIV status, the experience of unaddressed chronic pain is demoralizing, decreases quality of life and function, and disrupts treatment adherence for health conditions, such as HIV. At the conclusion of the 13th World Congress on Pain in 2010, the International Association for the Study of Pain adopted a declaration that access to pain management, which includes assessment and treatment, is a fundamental human right [54]. Underlying this declaration is the principle that every medical provider has a duty to listen to and reasonably respond to a patient's report of pain, and every person deserves to have his or her pain reasonably managed by adequately trained healthcare professionals [55]. In keeping with the international right to pain management, the World Health Organization's 19th List of Essential Medicines (those that satisfy the priority healthcare needs of the population) includes the following analgesics: aspirin, ibuprofen, acetaminophen, codeine, and morphine. Methadone and buprenorphine, which can be used for the treatment of opioid use disorders as well as chronic pain, are also listed.

Barriers to adequate pain management have been attributed to cultural, societal, religious, and political attitudes, including the acceptance of torture, as well as biomedical models of disease that focus on pathophysiology instead of quality of life [55].

The biopsychosocial model of medicine is an important conceptual framework for understanding, assessing, and effectively managing chronic pain [56]. This model emphasizes the multidimensional nature of chronic pain, which includes not only the structural pathophysiology of nociception but also the dynamic interplay of a patient's thoughts, emotions, behaviors, and sociocultural influences [57, 58]. Because chronic pain's relationship to affective distress states and functional limitations are key features, comprehensive interdisciplinary programs that use a biopsychosocial approach aim to increase self-management of pain, improve pain-coping resources, reduce pain-related disability, and reduce emotional stress. Clinically effective and cost-effective programs typically rely on teams that consist of primary care providers and nurses, physical and occupational therapists, psychologists, psychiatrists, and case managers [59]. Multimodal treatments combine analgesics, physical therapy, and behavioral and psychological therapy. Rather than seeking to eliminate the locus of pain, the interdisciplinary team addresses biological, behavioral, and social factors to achieve functional restoration [58].

Empathy and patient-centered communication skills are essential to the management of chronic problems in any patient population. At the individual provider level, a therapeutic relationship with the patient is a fundamental component of chronic pain management. A large body of literature stresses the importance of patient beliefs about the future successful control of the pain and the medical provider's role as a partner in addressing the pain. The medical provider can build a therapeutic partnership with the patient using behaviors that build trust and demonstrate acceptance, such as reflective listening, believing a patient's expression of pain, and regularly recording detailed historical information and the results of assessments for each pain described. Recognizing that pain is subjective, verbal acknowledgment of a patient's experiences is known to be helpful when patients encounter difficult problems. Understanding how pain impacts a patient's daily life is an important step toward being able to address the symptom. Summarizing and clarifying "next steps" also helps to reassure the patient that together you are actively addressing the issue.

Medical providers should clarify and document the presence of specific HIV-related pain syndromes to guide future pain management, discuss the full management strategy with the patient, manage expectations about the effectiveness of various pain management strategies, and document the discussion in the medical record.

Medical providers should understand the basic concepts of pain management, including when specific treatments should be recommended, their potential risks and benefits, and the adverse drug reactions and drug–drug interactions that can occur when pharmacotherapies are prescribed. Medical providers should maintain a nonjudgmental perspective and broad differential diagnosis when managing unexpected patient behaviors. For example, the phenomenon of "pseudo-addiction" (see evidence summary for recommendation 26 below) may explain the behavior of patients who appear to be hoarding their medications or requesting early refills.

Pain is exacerbated by other psychosocial variables such as stressful events that include, but are not limited to, depression, a history of sexual abuse, trauma, and post-traumatic stress disorder [60]. Appropriate screening and treatment for these factors are a requisite for the success of a comprehensive treatment plan for chronic pain. All chronic pain patients should be screened for unhealthy substance use. If identified, their pain management may require consultation with and concomitant treatment from an addiction specialist. Higher complexity and co-occurring disorders, however, should not delay the primary HIV provider's systematic evaluation and treatment of chronic pain symptoms. A systematic, general approach is described below in recommendations 1 and 2.

The presence of chronic pain is not a contraindication to the initiation of ART. Although poor ART adherence has been documented in patients with severe neuropathic pain [61], universal ART is the standard of care, and the treatment of chronic pain is critical to improvement of quality of life and medication adherence [55, 62–66]. Furthermore, ART may improve neuropathic pain as there is an association between plasma HIV-1 RNA concentration and the severity of neuropathic pain [67].

Drug–drug interactions of varying clinical significance exist between all ART classes and opioid analgesics, such as methadone, buprenorphine, meperidine, and fentanyl. Opioid analgesic requires closer monitoring in PLWH on ART [68].

Summarized below are the panel's recommendations for the evaluation and management of chronic, nonmalignant pain in PLWH.

METHODOLOGY

Practice Guidelines

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [69]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [69].

Panel Composition

The Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee (SPGC) collaborated with partner organizations to convene a panel of 10 experts in HIV, pain, pharmacology, psychiatry, palliative care, and addiction medicine with a goal of developing recommendations for clinical practice for this complex patient population. The panel represented diverse geographic areas, pediatric and adult healthcare providers, and several specialties and organizations including the HIV Medical Association (HIVMA), the American Society of Addiction Medicine (ASAM), the Association for Medical Education and Research on Substance Abuse (AMERSA), and the American Academy of Hospice Palliative Medicine (AAHPM).

Process Overview and Consensus Development Based on Evidence

Panel subgroups reviewed the initial literature search, selected references, evaluated evidence, drafted recommendations, and summarized the evidence for each section. The evidence evaluation process was based on the IDSA Handbook on Clinical Practice Guideline Development, which involves a systematic weighting of the quality of evidence and the grade of recommendation using the GRADE system (Figure 1) [1–4, 70, 71].

Drafts were circulated among panel members for commentary. The drafts were discussed on 10 occasions by teleconference or in-person meeting. Feedback from 3 external peer reviewers and endorsing organizations was obtained and used to modify the document. The guideline was reviewed and endorsed by representatives of the American Academy of Hospice Palliative Medicine (AAHPM) and the HIV Medical Association (HIVMA). The guideline was also reviewed and approved by the IDSA SPGC and the Board of Directors (BOD).

Literature Review and Analysis

The authors of this guideline performed a review of the literature by examining the treatment of chronic noncancer pain in patients with HIV. The search, for the period from 1966 to 2016, included Ovid, PubMed, Medline, and Google Scholar for articles that contained HIV and 1 or more of the following terms: neuropathic pain, chronic pain, substance use, urine toxicology, substance use disorder, mental illness, depression, and pain treatment.

Guideline and Conflict of Interest

All panel members complied with IDSA policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. They were provided IDSA's conflict of interest disclosure statement and asked to identify ties to companies that develop products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel decided on a case-by-case basis whether a conflict should limit member participation. Potential conflicts are listed in the Acknowledgments section.

Revision Dates

At annual intervals, the panel chair, SPGC liaison advisor, and SPGC chair will determine the need for guideline revisions by reviewing current literature. If necessary, the entire panel will be reconvened. When appropriate, the panel will recommend revisions to the IDSA SPGC, board, and other collaborating organizations for review and approval.

RECOMMENDATIONS FOR MANAGEMENT AND TREATMENT OF PERSONS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS AND CHRONIC PAIN

I. What is the recommended approach to screening and initial assessment for chronic pain in persons living with human immunodeficiency virus?

Recommendations

1. All PLWH should receive, at minimum, the following standardized screening for chronic pain: How much bodily pain have you had during the last week? (none, very mild, mild, moderate, severe, very severe) and Do you have bodily pain that has lasted for more than

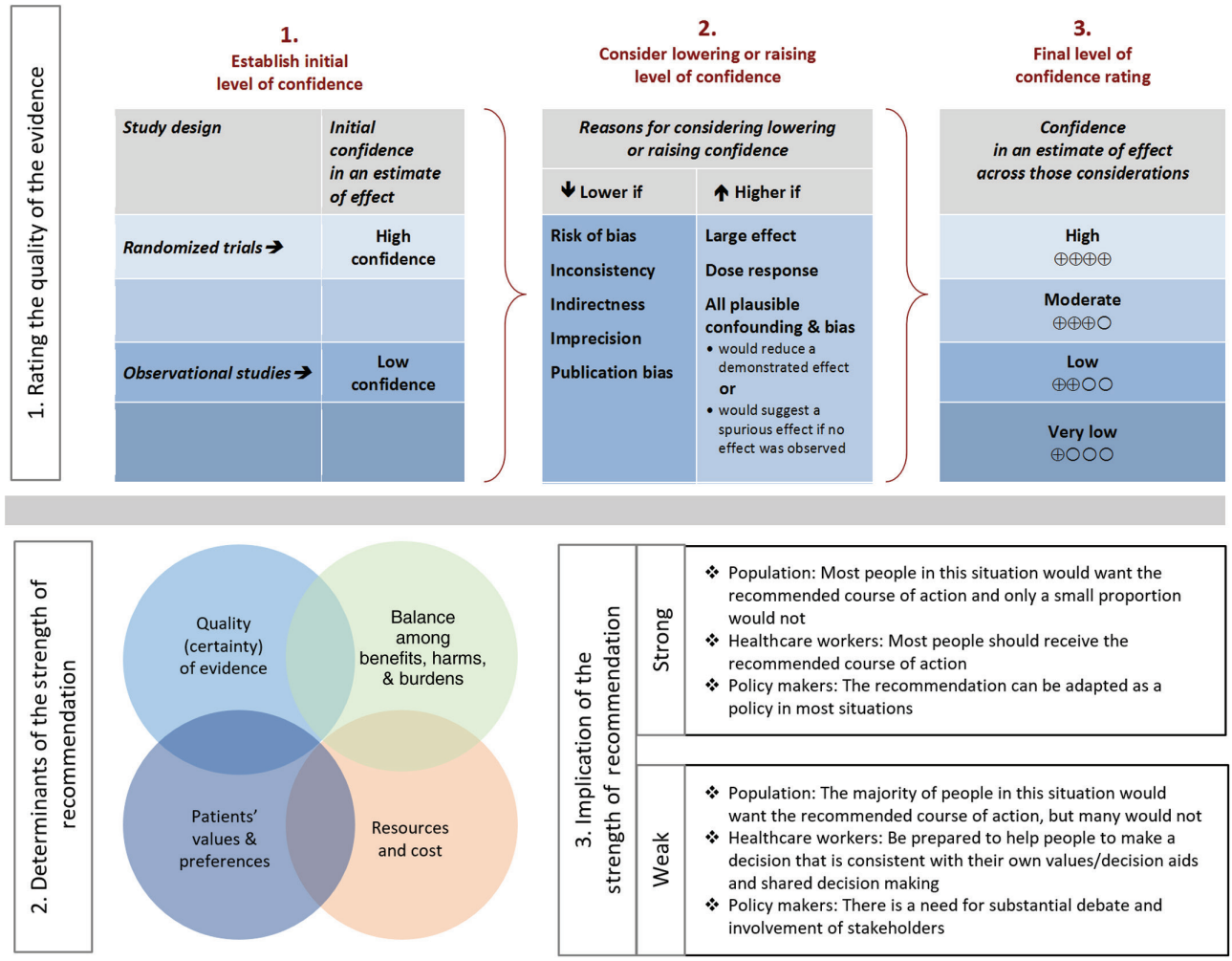

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE (*g*rading of *r*ecommendations *a*ssessment, *d*evelopment, and *e*valuation) methodology (unrestricted use of the figure granted by the US GRADE Network).

3 months? (strong, low). *Remark: A response of moderate pain or more during the last week combined with bodily pain for more than 3 months can be considered a positive screen result.*

2. For persons who screen positive for chronic pain, an initial assessment should take a biopsychosocial approach that includes an evaluation of the pain's onset and duration, intensity and character, exacerbating and alleviating factors, past and current treatments, underlying or co-occurring disorders and conditions, and the effect of pain on physical and psychological function. This should be followed by a physical examination, psychosocial evaluation, and diagnostic workup to determine the potential cause of the pain (strong, very low). *Remark: A multidimensional instrument such as the brief pain inventory (BPI) or the 3-item patient health questionnaire (PEG; used to assess average pain intensity [P], interference with enjoyment of life [E], and interference with general activity [G]) can be used for pain assessments.*
3. Medical providers should monitor the treatment of chronic pain in PLWH, with periodic assessment of progress on achieving functional goals and documentation of pain intensity, quality of life, adverse events, and adherent vs aberrant behaviors (strong, very low). *Remark: Reassessments should be conducted at regular intervals and after each change or initiation in therapy has had an adequate amount of time to take effect.*

Evidence Summary

Screening all patients for pain in a systematic fashion is recommended. Although a specific screening measure in HIV clinical settings has not been validated, Landmark and colleagues evaluated 2 screening questions (see Recommendation 1) in 6419 patients in the general population of which 3364 (52%) completed all assessments. Those 2 questions had a sensitivity of 80% and specificity of 90% to establish chronic pain when patients report at least moderate pain in the last week and report they have had pain lasting more than 6 months [72].

When a patient screens positive for chronic pain, the initial evaluation should focus not only on ascertaining the etiology and collecting a detailed history of the intensity and character of the pain, with intensity measured using a pain scale or a visual analog scale, but also on pain-related interference with function [73]. Since pain is subjective, it is important to listen to and accept the patient-described symptoms and to ask about other symptoms or unpleasant experiences associated with the pain (eg, fatigue, nausea, anxiety, depression). The pain's impact on physical and emotional function, such as activities of daily living (eg, an inability to walk a block due to leg pain), or mood may affect a patient's quality of life more than the pain's severity [74]. In addition, PLWH often have multiple types and locations of pain, each of which should be addressed. Because persons with advanced HIV disease may have many different symptoms of pain, this comprehensive history is particularly important, as the symptom may be the key to diagnosing the etiology.

The BPI is a multidimensional pain assessment tool that is widely used in part or as a whole at pain specialty clinics and in HIV research [16, 75, 76]. Another commonly used pain assessment tool is the McGill pain questionnaire. Both tools, however, are time consuming and may be impractical for assessing pain in busy HIV clinical settings [77, 78]. The ultra-brief, 3-item PEG is used to assess average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) in the past week using 3 visual analog scales [79]. The PEG was comparable to the BPI in initial validation studies conducted with veterans and primary care patients with chronic pain. Due to its brevity, the PEG may be easier to implement in a busy HIV clinical practice.

As in the evaluation of any clinical problem, chronic pain requires focused physical and psychosocial examinations and diagnostic testing as indicated. Only after the initial pain assessment is conducted, can a treatment plan be developed in collaboration with the patient. Reassessments should be conducted at regular intervals and after an adequate period of time for each change or initiation in therapy to take effect.

II. What is the recommended general approach to the management of persons living with human immunodeficiency virus and chronic pain?

Recommendations

4. HIV medical providers should develop and participate in interdisciplinary teams to care for patients with complex chronic pain and especially for patients with co-occurring substance use or psychiatric disorders (strong, very low).
5. For patients whose chronic pain is controlled, any new report of pain should be carefully investigated and may require added treatments or adjustments in the dose of pain medications while the new problem is being evaluated (strong, high). *Remark: Providers should clearly document the new symptom and consult, if possible, with a provider experienced with pain management in PLWH or with a pain specialist.*

Evidence Summary

As with other chronic diseases, chronic pain management requires repeated evaluations over time. A holistic, multimodal approach that involves a comprehensive interdisciplinary team is recommended for all persons with chronic pain. This approach may include patient education on the neurophysiology of pain, physical therapy, occupational therapy, and behavioral therapy [80]. While physical therapy is often prescribed for individuals with pain, the multifactorial nature of many pain syndromes complicates referral to physical therapy and its outcomes.

The goal of treatment is to restore function. When patients understand the pathophysiology of their pain, they are better able to manage their pain and to understand the goals of pain management. In a small randomized, controlled trial, Moseley and colleagues found that education on pain neurophysiology improved physical performance and pain cognitions in patients with chronic low back pain and suggested that this kind of patient education be included in a wider pain management approach. However, the sample size was small and the patients were not identified as having HIV [81].

Pain assessments should focus on achieving functional goals, decreasing pain severity, improving quality of life, and identifying and addressing any treatment-related adverse events or behaviors (eg, adherent vs aberrant) that alter the risk–benefit of the treatment.

A new report of pain by a patient being treated for chronic pain must be reevaluated. Common misconceptions by providers are that an existing chronic pain treatment is sufficient to ameliorate a new pain symptom or that addition of an opioid analgesic to an existing regimen will cause respiratory depression. For the patient whose pain was previously controlled with an opioid, a new pain may raise fears that a patient has developed an opioid addiction [82]. Healthcare providers should determine whether a new painful symptom is related to worsening of current pathology or the development of new pathology (eg, new opportunistic infection, an adverse event related to other medications, or another comorbid condition) [83]; is related to failure of a current analgesic, such as "end-of-dose failure" or when a patient develops tolerance to an opioid and requires an increase in overall dose; the new pain is not responsive to the current treatment and the patient requires management with a more effective approach; or whether an intercurrent event in the patient's life has interfered with the patient's usual ability to self-manage pain. In this latter case, it may be helpful to have the patient discuss the life event further with a behavioral health specialist (eg, social worker) or a nurse to review both the event and its impact on the pain [82].

III. What is the recommended therapeutic approach to chronic pain in persons with human immunodeficiency virus at the end of life?

Recommendations

6. As PLWH age, their pain experience may change as other age-related and HIV-related comorbidities develop. It is recommended that the clinician address these changes in pain experience in the context of this disease progression (strong, moderate).
7. Critical to maintaining pain control, it is recommended that medical providers and an integrated multidisciplinary team engage in frequent communication with the patient and the patient's support system (eg, family, caregiver) (strong, low). *Remark: Communications should occur at a health literacy level appropriate for the patient and patient's support system. It may be necessary to schedule longer appointment times to allow both patients and providers to establish and clarify the goals of care.*
8. Consultation with a palliative care specialist to assist with pain management and nonpain symptoms and to address goals of care is recommended (strong, low).
9. Patients with advanced illness require a support system beyond the clinic, and timely referrals for palliative or hospice care are recommended. The primary care provider must remain in communication with the patient and family through the end of life to ensure accurate continuity and to preclude a sense of abandonment (strong, low).

Evidence Summary

While HIV mortality has decreased dramatically with effective antiretroviral therapy, other serious comorbidities such as cancers, end-stage liver disease (often due to untreated chronic viral hepatitis), and tuberculosis still claim the lives of PLWH in many countries [84]. Patients with advanced disease are likely to be aware of their own deteriorating status and look to the primary HIV team for overall direction of care and clarification regarding changes in prognosis. Pain control is often impacted by psychosocial and spiritual concerns of the patient and his/her support system. When patients exhibit signs of clinical deterioration, regardless of the etiology, it is useful to review the expected goals and outcomes of ongoing care with the patient [85]. This is an ideal time for a family meeting that involves other members of the clinical team such as nurses and social workers to ensure uniformity of the goals of care [86]. This is also the time to review health power of attorney for the patient, update physician orders for life-sustaining treatment, and document these clearly in the patient's medical record. Consider referring the patient for social work or legal assistance in making an advance directive. Provider support throughout the course of the disease is meaningful for both the patient and his/her support system, and effective communication can prevent unnecessary hospital admissions.

Patients with chronic pain and a deteriorating clinical status may have specific needs such as changing transportation modes and increased frequency of medical visits. If the patient's disease process and/or pain are no longer controllable, it may be prudent to involve a palliative care team. Factors that impact effective referral include planning and timing of referrals, interprofessional variations in perceptions and reasons for delayed or difficult referrals, and cross-disciplinary communication [87]. The patient and family may benefit from alternative therapies such as music therapy, massage, or hypnosis that can be applied in the home [88, 89]. If there is a history of past addiction, staff should be educated about appropriate pain treatment in the context of addiction in order to prevent the undertreatment of pain, which may be caused by a fear of fueling or rekindling addictive behaviors [90].

Pain management guidelines should be followed regardless of the patient's prognosis [91]. If the primary physician has cared for the patient over time, the patient and family will be reassured if that provider remains involved. Recognition of the provider's need to have positive closure with the patient is also important. Such communication might include an appreciation for the opportunity to care for the patient, which can be shared by recalling an event or interaction that allows the patient to know that she or he has made an impact on the provider's practice. Unexamined emotions can lead to provider burnout and depression that, if unaddressed, could compromise patient care [92–94]. Additionally, other staff members should be encouraged to share a story about the patient during a staff meeting. This will assist staff in coping with a sense of loss when the patient is no longer attending appointments regularly.

IV. What are the recommended nonpharmacological treatments for chronic pain in persons living with human immunodeficiency virus?

Recommendations

10. Cognitive behavioral therapy (CBT) is recommended for chronic pain management (strong, moderate). *Remark: CBT promotes patient acceptance of responsibility for change and the development of adaptive behaviors (eg, exercise) while addressing maladaptive behaviors (eg, avoiding exercise due to fears of pain).*
11. Yoga is recommended for the treatment of chronic neck/back pain, headache, rheumatoid arthritis, and general musculoskeletal pain (strong, moderate).
12. Physical and occupational therapy are recommended for chronic pain (strong, low).
13. Hypnosis is recommended for neuropathic pain (strong, low).
14. Clinicians might consider a trial of acupuncture for chronic pain (weak, moderate). *Values and preferences: This recommendation places a relatively high value on the reduction of*

symptoms and few undesirable effects. Remark: Evidence to date is available only for acupuncture in the absence of amitriptyline and among PLWH with poorer health in the era before highly active antiretroviral therapy.

Evidence Summary

Many nonpharmacological treatments that address different types of chronic pain have been examined, although most studies were conducted in persons without HIV. We discuss treatments for which an evidence base has been established in the general population.

CBT is a form of psychotherapy that helps individuals to consider the accuracy and usefulness of their thoughts in order to change behaviors. This is done by identifying and correcting maladaptive thoughts and cognitive distortions [95]. CBT for chronic pain promotes an individual's acceptance of responsibility for change and the development of adaptive behaviors (eg, engagement in physical activity), while addressing their maladaptive counterparts (eg, avoiding physical activity due to fear of pain or reinjury) [96, 97]. Additionally, CBT can be used to develop coping strategies for anxiety related to current pain and/or the development of new or exacerbated pain over time.

Pain self-management (PSM) programs are CBT-based interventions that foster the development of behaviors that focus on the self-management of pain rather than its cognitive and behavioral components. PSM interventions have been developed for specific chronic pain syndromes, including low back pain, arthritis, and fibromyalgia. Despite the diversity of these pain conditions, protocols are often similar and address behaviors that are important in all chronic pain conditions. Numerous randomized, controlled trials (RCTs) and metaanalyses of effective PSM interventions in HIV-negative populations have been published [98–101].

Chronic pain psycho-education is a common component of PSM interventions. It is widely accepted as an important aspect of early patient-centered chronic pain discussions [102]. The Substance Abuse and Mental Health Services Administration recommends that the following information be included in such discussions: the nature of chronic pain as a chronic disease, which may have periods of improvement and periods of worsening; reasonable treatment expectations; discussion of the importance of both pharmacologic and nonpharmacologic treatment components; risks and benefits of any treatments prescribed; and how to safely take medications when they are prescribed.

There have been 2 small CBT-based chronic pain intervention studies in individuals with HIV. One consisted of a single-arm psychologist-administered CBT intervention in HIV-infected individuals with any chronic pain diagnosis; the study demonstrated modest effects on pain and functional outcomes [103]. An earlier randomized trial that was focused on peripheral neuropathy showed greater improvement in individuals who received CBT than in those who received supportive psychotherapy [104]. Although both studies were conducted in PLWH, neither was tailored to PLWH and both studies suffered from poor adherence. Neither intervention has undergone further investigation.

Yoga has also been shown to improve the quality of life in PLWH with pain [105]. In a randomized, controlled open-label study, 61 healthy PLWH performed Sudarshan Kriya yoga or received the standard of care. Individuals in the yoga arm performed yoga once a week for 12 weeks. The validated World Health Organization Quality of Life-HIV Brief tool was used to assess quality of life [105]. This tool examines 6 domains, including a physical domain that contains pain, physical botheration, daily energy, and sleep. The overall quality of life increased by 6% ($P = .016$) and the physical domain increased by 12% ($P = .004$). The researchers were unable to determine the proportion of improvement in the physical domain related to pain relief vs change in physical botheration, daily energy, or sleep [105].

Several studies, including 2 metaanalyses, have evaluated yoga's impact on pain in a variety of patient populations, including PLWH. One metaanalysis of 16 studies found that yoga interventions had a positive impact on pain control in people without HIV with a variety of disease states, including chronic low back pain, migraine, and neck pain, as well as associated pain, anxiety, depression, and functional disability [106]. Twelve of these studies were randomized. The visual analog scale (VAS) was the most common tool used to assess the outcome variable of interest. For all pertinent outcome data, a standardized mean difference (SMD) and standard errors (SEs) were used to demonstrate the effects of yoga. An SMD less than 0 indicated superiority of the intervention group, with SMD less than −0.5 as clinically relevant. The range of SMD among all studies was −0.20 to −1.34, with an estimated overall treatment effect at SMD = −0.74 ($P < .0001$). A subsection of the metaanalysis looked at studies that used the VAS as the primary outcome. This subsection had a weighted mean difference of 12 mm on a 100-mm scale ($P < .001$). Two additional RCTs were published in 2013 subsequent to the metaanalysis that also showed a benefit of yoga for neck pain [107, 108].

There is some preliminary evidence for the use of hypnosis in treating neuropathic pain in PLWH, as well as chronic widespread pain and chronic low back pain in persons without HIV [109–111]. Dorfman and colleagues studied hypnosis in 36 PLWH with distal sensory polyneuropathy (HIV-DSP) [109]. The patients were given instructions and CDs for performing self-hypnosis. They were allowed to continue their previously prescribed pain management regimens and were evaluated on proper technique, difficulties with the process, and meeting patient-specific goals from hypnosis. Patients were evaluated 3 times at 3-week intervals before and after hypnosis. They were administered the short-form McGill pain questionnaire. Scores decreased from 17.8 to 13.2 ($P < .001$). Seventy-two percent of

patients had improved pain scores (mean pain reduction was 44% in these patients). There was no difference in pain scores between patients who were taking pain medications and those who were not, and there was no improvement in pain in patients with anxiety. Study limitations included lack of a control group that received the standard of care without hypnosis and the fact that it was an unblinded study. Additionally, the long-term benefits of hypnosis are unclear after 7 weeks.

Five studies have examined acupuncture to improve pain control in PLWH. Shlay conducted a multisite RCT of structured acupuncture, amitriptyline, or both compared with placebo in the era before highly active antiretroviral therapy and found no effect of acupuncture in reducing pain from HIV-related peripheral neuropathy. However, the authors did not account for significant interactions between the 2 interventions. As a result, the raw data were reanalyzed by 1 of the original authors and reported in 2 publications. The first publication examined 125 patients randomized to standardized acupuncture vs control points, amitriptyline (75 mg/d) vs placebo pill, or both for 14 weeks and were crossed in a 2 × 2 factorial design [112]. The main outcomes for the analysis were pain intensity and global pain relief at 6 and 14 weeks, attrition during the study, and mortality within 2 years of study completion. This analysis revealed that acupuncture and amitriptyline worked independently to reduce pain. Acupuncture had a greater effect in the absence of amitriptyline. Adverse events may be associated with a combination of the 2 treatments, as evidenced by a 10% mortality rate in acupuncture alone and 52.9% in acupuncture combined with amitriptyline. However, the original study was conducted in the era before effective combination antiretroviral therapy (ART). The second publication examined 114 men with HIV-associated lower extremity peripheral neuropathy and showed that acupuncture had a moderate effect on improving pain relief when compared to sham acupuncture [113]. However, acupuncture was no more effective than sham acupuncture in reducing pain intensity over the 14-week treatment period for all patients, regardless of treatment condition. This lack of effect is likely due to large declines in pain intensity in both groups over the course of the study. Acupuncture, however, was associated with significantly lower attrition and mortality rates, the latter especially in patients with poorer health assessed using the Karnofsky scale.

Anastasi and colleagues randomized 50 PLWH with a moderate level of DSP pain to acupuncture with moxibustion (Acu/Moxa) or sham acupuncture with placebo moxibustion (control) in 12 sessions over 6 weeks in a participant-and-evaluator–blinded clinical trial [114]. The benefit of Acu/Moxa was superior to control at the first follow-up visit 3 weeks after the cessation of treatment ($P < .05$), and a trend toward superiority at the second and third follow-up visits was retained ($P < .10$).

Two small observational studies examined acupuncture in PLWH with neuropathy. The first study was a pre-/post-treatment case series of 21 PLWH who were enrolled for 10 acupuncture treatments over 5 weeks [113]. The authors reported improvements in subjective pain related to peripheral neuropathy. The second study was an uncontrolled, observational study in 11 PLWH with ART-induced neuropathy [115]. Noninvasive skin electrodes were placed on leg acupuncture points, and low-voltage current was passed for 20 minutes daily for 30 days. The authors reported significant improvements between pre- and post-intervention assessments in function by Medical Outcomes Study-HIV questionnaire and on tibial H-reflex measurements from the right calf muscle.

V. What are the recommended pharmacological treatments for chronic neuropathic pain in persons living with human immunodeficiency virus?

Nonopioid Recommendations

15. Early initiation of antiretroviral therapy is recommended for the prevention and treatment of HIV-associated distal symmetric polyneuropathy (strong, low).
16. Gabapentin is recommended as a first-line oral pharmacological treatment of chronic HIV-associated neuropathic pain (strong, moderate). *Remark: A typical adult regimen will titrate to 2400 mg per day in divided doses. Evidence also supports that gabapentin improves sleep scores; somnolence was reported by 80% of patients who received gabapentin* (strong, low).
    a. If patients have an inadequate response to gabapentin, clinicians might consider a trial of serotonin-noradrenaline reuptake inhibitors based on their effectiveness in the general population (weak, moderate).
    b. If patients have an inadequate response to gabapentin, clinicians might consider a trial of tricyclic antidepressants (weak, moderate).
    c. If patients have an inadequate response to gabapentin, clinicians might consider a trial of pregabalin for patients with post-herpetic neuralgia (weak, moderate).
17. Capsaicin is recommended as a topical treatment for the management of chronic HIV-associated peripheral neuropathic pain (strong, high). *Remark: A single 30-minute application of an 8% dermal patch or cream administered at the site of pain can provide pain relief for at least 12 weeks. Erythema and pain are common side effects for which a 60-minute application of 4% lidocaine can be applied and wiped off before applying capsaicin* (strong, high).
18. Medical cannabis may be an effective treatment in appropriate patients (weak, moderate). *Values and preferences: This recommendation places a relatively high value on the reduction of symptoms and a relatively low value on the legal implication of medical cannabis possession. Remark: Current evidence suggests medical cannabis may be more effective for patients with a history of prior cannabis use; the*

potential benefits of a trial of cannabis need to be balanced with the potential risks of neuropsychiatric adverse effects at higher doses, the harmful effects of smoked forms of cannabis in patients with preexisting severe lung disease, and addiction risk to patients with cannabis use disorder.

19. We recommend alpha lipoic acid (ALA) for the management of chronic HIV-associated peripheral neuropathic pain (strong, low). *Values and preferences: This recommendation places a high value on providing tolerable medications that may be of some benefit in patients with difficult-to-treat neuropathic pain. Remark: Studies in patients with HIV are lacking; however, there is a growing body of literature of the benefits of ALA in patients with diabetic neuropathy.*
20. We recommend against using lamotrigine to relieve HIV-associated neuropathic pain (strong, moderate). *Values and preferences: This recommendation places a relatively high value on the discontinuation of neurotoxic agents and on minimizing the incidence of lamotrigine-associated rash and places a relatively low value on the reduction in pain symptoms found in an earlier randomized controlled trial by the same authors. Remark: A benefit was only seen in patients currently receiving neurotoxic antiretroviral therapy (ART), and we recommend discontinuing all neurotoxic ART.*

Evidence Summary

In the era of less neurotoxic ART, early initiation of ART is recommended to decrease the risk of developing HIV-associated distal symmetric peripheral neuropathy (HIV-DSP). In longitudinal cohort studies conducted throughout the HIV epidemic, an association of HIV-DSP with more advanced HIV disease has been observed [40, 41], and the incidence of HIV-DSP has decreased since effective combination ART was introduced [35]. In the Multicenter AIDS Cohort Study, in which 1604 PLWH were followed over a 10-year period (1985–1995), individuals with HIV RNA >10 000 copies/mL had a 2.3-fold (P = .008) greater hazard of sensory neuropathy than those with <500 copies/mL [40]. In the HIV Outpatient Study, a retrospective, longitudinal cohort analysis of 2515 persons of which 329 (13.1%) received a diagnosis of HIV-DSP between 1992 and 2003, nonmedication-related risk factors for HIV-DSP were age >40 years (adjusted odds ratio [aOR], 1.17), diabetes mellitus (aOR, 1.79), white race (aOR, 1.33), nadir CD4(+) T lymphocyte count <50 cells/mm^3 (aOR, 1.64), CD4(+) T lymphocyte count 50–199 cells/mm^3 (aOR, 1.40), and initial viral load >10 000 copies/mL (aOR, 1.44). The authors concluded that although host factors and signs of increased disease severity were associated with an increased risk of developing HIV-DSP during the initial exposure to ART, immunity improved and the risk of HIV-DSP decreased with continued ART. Currently, the presence of sensory neuropathic symptoms in a patient with untreated HIV is highly suggestive of HIV-DSP [38].

Systematic reviews of pharmacotherapies for neuropathic pain provide a broad overview of potential treatments that might be used in PLWH. Limitations in the literature, however, include the modest efficacy of active medications, large placebo responses, heterogeneous diagnostic criteria for neuropathic pain, inadequate classification of patients in clinical trials, and controversial dichotomous outcome measures for clinically meaningful pain reduction or improvement that have not been validated for chronic neuropathic pain [116, 117]. With these limitations in mind, a 2010 systematic review of 44 studies in PLWH with associated sensory neuropathy found no superiority over placebo in the 14 included randomized, controlled trials (RCTs) that examined amitriptyline (100 mg/day), gabapentin (2.4 g/day), pregabalin (1200 mg/day), Prosaptide (16 mg/day), peptide-T (6 mg/day), acetyl-L-carnitine (1 g/day), mexiletine (600 mg/day), lamotrigine (600 mg/day), and topical capsaicin (0.075% 4 times per day). Evidence of efficacy was found only for topical capsaicin 8%, recombinant human nerve growth factor (which is clinically unavailable), and smoked cannabis [38].

Gabapentin. Gabapentin is recommended as a first-line oral pharmacological treatment of chronic HIV-associated neuropathic pain. Possibly through central allodynic effects and inhibition of ectopic discharge activity from injured nerves, the anticonvulsant may reduce HIV-associated sensory neuropathies. In a small, double-blind RCT by Hahn and colleagues, gabapentin was titrated to a maximum of 2400 mg/day over 4 weeks and found to improve visual analog scale measures of pain and median sleep scores [118]. Somnolence was reported by 80% of patients who received gabapentin. This study, however, had several limitations. Only 26 patients enrolled (15 gabapentin and 11 placebos) and the placebo group had a 29.8% reduction in pain on the visual analog scale, suggesting a high placebo response rate. Larger studies are needed in PLWH to improve the quality of evidence supporting this recommendation.

Antidepressants. If patients have an inadequate response to gabapentin, clinicians might consider a trial of serotonin-norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants, both of which have been studied for the treatment of neuropathic pain.

Duloxetine is a SNRI approved by the US Food and Drug Administration for major depressive disorders, urinary stress incontinence, and pain associated with diabetic peripheral neuropathy [119]. Harrison and colleagues compared the effectiveness of duloxetine, methadone, and the combination of duloxetine–methadone with placebo for the treatment of painful HIV-associated polyneuropathies in a phase 2, randomized, double-blind, placebo-controlled, 4-period crossover multicenter study (ACTG A5252) [120]. Only 15 patients enrolled with 8 completing the trial, making the study unsuccessful in answering this clinical question.

In 2007, Saarto and colleagues reviewed 60 RCTs in a Cochrane systematic review to examine the use of antidepressants in the treatment of neuropathic pain. While evidence supported the use of amitriptyline, a tricyclic antidepressant, and venlafaxine, another SNRI, for the treatment of neuropathic pain due to other etiologies (eg, diabetes), evidence was lacking for HIV-associated neuropathy [121].

Phillips et al conducted another systematic review and metaanalysis in 2010 that focused on the clinical effectiveness of pharmacological treatment of painful HIV-associated sensory neuropathy. Of 44 studies identified, 19 were RCTs and 2 examined amitriptyline [38]. These 2 RCTs enrolled 270 PLWH and demonstrated that amitriptyline is no better than placebo in reducing painful HIV-related neuropathy [122, 123]. As discussed earlier (see Acupuncture section), the study of amitriptyline and acupuncture by Shlay had serious methodologic flaws [122], as they did not account for significant interactions between the interventions. When the raw data were reanalyzed, amitriptyline was helpful through week 6, but by week 14, pain increased to the highest level of pain among the groups studied [123]. In the second study (ACTG 242) [112], 145 PLWH were randomized to a double-blind, 10-week trial of amitriptyline, mexiletine, or matching placebo. This study was terminated early after an interim review of results determined the study was unlikely to detect significant differences between arms even with further enrollment. Analysis at the termination of the study showed no difference among the treatment groups in pain intensity between baseline and final visits.

Pregabalin. There is a lack of evidence for the use of pregabalin in the treatment of neuropathic pain in PLWH, except for those with post-herpetic neuralgia (see below). A double-blind RCT of pregabalin in 302 patients over 12 weeks with a 3-month open-label extension demonstrated pregabalin was similar to placebo in reducing the pain intensity of HIV-associated DSP as measured using the numeric pain rating scale [124]. In the study, doses of pregabalin could be titrated up to 600 mg/day in twice daily dosing. In a subsequent investigation, 377 patients were randomized to flexible-dose pregabalin (150–600 mg/day) or placebo in a single-blind, placebo lead-in, randomized, double-blind, parallel-group, placebo-controlled multinational trial for 17 weeks with a 6-month open label extension study. The sponsor terminated both after a preplanned interim analysis indicated trial futility [125].

Capsaicin. Capsaicin is recommended as a topical treatment for the management of chronic HIV-associated peripheral neuropathic pain. Three RCTs have examined capsaicin in persons with HIV-associated peripheral neuropathy. The first study by Paice and colleagues demonstrated no benefit of low-dose capsaicin (0.075% cream) compared to placebo [126]. However, interest in capsaicin persisted, and 2 studies examined a higher-dose (8%) dermal patch (NGX-4010). The first study by Simpson and colleagues reported on 307 patients randomized to the high-dose patch or to a control, low-dose patch (0.04%) [127]. Capsaicin was applied for 30, 60, or 90 minutes. Since capsaicin application is painful, lidocaine 4% was applied for 60 minutes before capsaicin and was washed off prior to capsaicin application. Additionally, opioids were available at the onset of treatment, as needed, and patients could take hydrocodone with acetaminophen for up to 7 days post-capsaicin application. Patients were allowed to continue any chronic pain medications they were already taking; however, the specific medications allowed were not reported. Patients were followed for 12 weeks after the application of capsaicin to ascertain benefit. The primary outcome was a reduction in the mean numeric pain rating scale (NPRS) for the average pain level in the past 24 hours. Reduction in pain intensity was greater in the intervention arm throughout the 12-week study, with 31% of the active arm experiencing >30% mean reduction on the NPRS compared to 14% of the controls (P = .007). After this 12-week study, patients were allowed to roll over into a 40-week open-label portion of the study where they could receive up to three 60-minute treatments of NGX-4010. Of the 307 enrolled, 272 (89%) elected to continue in the open-label portion. Repeated treatments were tolerated with equivalent reductions in pain scores occurring regardless of the number of treatments received [39].

A second RCT was undertaken to confirm the previous study [128]. This study randomized 494 patients (332 to NGX-4010, 162 to placebo). Capsaicin was applied for 30 or 60 minutes. This study failed to demonstrate a significant reduction in pain at either time point. This may be the result of a large reduction in pain among the 60-minute control group (30% reduction) compared to the 30-minute control group (19% reduction). This difference prevented pooling of the control group data and reduced the study's power to detect a significant difference in effect.

A subsequent integrated analysis that combined the data from both phase 3 studies described above demonstrated that a single 30-minute application of NGX-4010 provides significant pain relief for a least 12 weeks in patients with HIV-associated distal sensory polyneuropathy [129]. More research is needed to ascertain the frequency of reapplication, different doses, and duration of effect. In addition, patients and providers must be advised of the practical issues regarding the application of capsaicin, which is a local irritant. Gloves should be worn when placing the patch, and patients should use care to avoid contact with their eyes and genitalia until they have thoroughly washed their hands.

Cannabinoids. Medical cannabis may be an effective treatment for chronic neuropathic pain in appropriate patients. A growing body of literature suggests that cannabinoids have a role in the modulation of pain [130]. Two RCTs have

examined cannabis for the treatment of HIV-associated neuropathic pain. Abrams and colleagues randomized patients to either 3.56% tetrahydrocannabinol or placebo cigarettes, both items were smoked 3 times daily for 5 days [131]. Patients in this study were allowed to continue other concomitant medications (15 patients on gabapentin and 14 on opioids). A total of 50 (91%) patients completed the study. The primary outcome measure was a reduction in pain intensity over the last 24 hours along a visual analog scale administered daily. Pain was reduced by 34% in the smoked cannabis group compared to 17% in the placebo group ($P = .03$). Of the 25 randomized to cannabis, 13 (52%) patients had greater than 30% reduction in pain from baseline to the end of treatment compared with 6 of 25 (24%) patients on placebo ($P = .04$). Despite this positive benefit, the study had 2 important limitations. First, all patients enrolled had prior cannabis exposure, and this may have created a selection bias toward individuals who benefited from cannabis treatment. Second, the requirement of prior use of cannabis likely limited the ability to blind the study participants [131].

Ellis et al conducted a double-blind, single-group, placebo-controlled crossover study to examine smoked cannabis (concentration 1%–8% tetrahydrocannabinol) in patients with HIV-associated neuropathic pain refractory to at least 2 previous analgesics [132]. Patients were allowed to continue other concomitant medications (18 opioids, 10 nonsteroidal antiinflammatory drugs, 8 tricyclic antidepressants, and 18 anticonvulsants) [132]. After a baseline series of assessments, patients were randomized to placebo or cannabis, 4 times a day for 5 days of dose titration. Patients had a 2-week washout phase and then repeated the 5-day dose titration with the alternative treatment. The primary outcome measure was the difference in the descriptor differential scale (DDS), a scale validated to measure pain intensity [133, 134]. Thirty-four patients were randomized, and 96% had prior exposure to cannabis. One patient without prior cannabis exposure developed an acute psychosis during the study and dropped out. Of the 28 patients who completed the study, the proportion with a pain reduction of >30% by the DDS was 0.46 among cannabis users vs 0.18 among placebo ($P = .043$). As in the Abrams study, patients' prior use of cannabis may have biased the study to those who had already perceived benefits from its use and limited the ability to blind patients to the intervention groups [132]. The evolving legal status of cannabis in the United States, the potential risk of neuropsychiatric adverse events in naive patients, and the risk of developing a cannabis use disorder are all considerations that patients and providers should discuss before pursuing a trial of this treatment.

Alpha-lipoic acid. ALA is a medium-chain fatty acid derived from linoleic acid. Twenty-seven RCTs have demonstrated some benefit in the symptoms of diabetic neuropathy. A recent metaanalysis found that oral ALA dosing of 600 mg once daily was equivalent to intravenous infusions.

Lamotrigine. We recommend not using lamotrigine to relieve HIV-associated neuropathic pain. Lamotrigine, another anticonvulsant, blocks voltage-sensitive sodium channels and inhibits the release of glutamate and aspartate. A small multicenter, randomized, double-blind, placebo-controlled study in patients with painful HIV-associated neuropathy titrated lamotrigine to 300 mg/day to evaluate possible improvements in average neuropathic pain at 14 weeks compared to baseline [135]. Of the 42 enrolled patients, 13 did not complete the study. Of the remaining 29 evaluable patients, 20 received placebo and 9 received lamotrigine. The reduction in average pain from baseline to week 14, however, was greater ($P = .03$) in the lamotrigine group (−0.55) than in the placebo group (−0.18), adjusting for baseline levels of pain. This finding prompted Simpson and colleagues to conduct a larger trial in which they randomized 227 HIV-infected patients in a 2:1 fashion to lamotrigine or placebo, stratifying for patients currently on neurotoxic HIV therapy [136]. In the stratum that received neurotoxic HIV ART, 62 were randomized to lamotrigine and 30 to placebo, while in the stratum not on neurotoxic HIV ART, 88 were assigned to lamotrigine and 47 to placebo. The primary outcome was a mean reduction in the Gracely pain intensity scale for the patient's average pain after a 7-week titration and a 4-week maintenance phase. The target dose was 400 mg/day (200 mg twice daily) for individuals who were not receiving enzyme-inducing medications (eg, medications that impact CYP450 isoenzymes such as efavirenz) and 600 mg/day for individuals who were receiving enzyme-inducing medications. Lamotrigine was not superior to placebo by the primary outcome. However, a secondary outcome, the visual analog scale for pain intensity, did show a significant reduction in the arm that received neurotoxic HIV ART and assigned to lamotrigine compared to placebo. Although lamotrigine may reduce neuropathic pain intensity in patients on neurotoxic HIV ART, we recommend that all neurotoxic ART be discontinued first. The findings from these 2 studies were included as the only data on PLWH in 2 larger Cochrane reviews, which found no convincing evidence that lamotrigine was effective in treating neuropathic pain and fibromyalgia at doses of 200 to 400 mg daily [137, 138].

Post-herpetic neuralgia

Post-herpetic neuralgia (PHN), a complication of acute herpes zoster infection that can occur in people with HIV, is distinct from painful distal symmetrical peripheral neuropathies associated with HIV. A 2005 systematic review of analgesic therapies for adults with more than 3 months of PHN and unspecified HIV status identified 31 placebo-controlled RCTs from 62 studies that were included in a metaanalysis [139]. Analgesic efficacy, defined

as a number needed to treat (NNT) of less than 5.00, was observed for tricyclic antidepressants (NNT = 2.64); certain opioids, including oxycodone, extended-release morphine, and methadone (NNT = 2.67); gabapentin (NNT = 4.39); tramadol (NNT = 4.76); and pregabalin (NNT = 4.93). Topically administered lidocaine patches (NNT = 2) and capsaicin 0.075% (NNT = 3.26) were associated with analgesic efficacy, but these studies were limited by low numbers of patient episodes. In addition, intrathecal therapy with lidocaine and methylprednisolone was associated with long-lasting analgesia (NNT = 1.13) [139]. The evidence summaries for specific pharmacological treatments are described below.

If patients have an inadequate response to gabapentin for post-herpetic neuralgia, clinicians might consider a trial of pregabalin. Pregabalin is a precursor to gabapentin. In 2 parallel-group placebo-controlled trials of pregabalin for HIV-negative persons with PHN, pregabalin was found to be superior over placebo [140]. However, 1 of these studies excluded patients who had failed to respond to previous treatment for PHN with gabapentin at doses ≥1200 mg/day [141]. Because of pregabalin's efficacy in treating PHN, 2 trials of pregabalin were conducted by Simpson and colleagues in PLWH, which was previously discussed.

Use of Opioids

21. For PLWH, opioid analgesics should not be prescribed as a first-line agent for the long-term management of chronic neuropathic pain (strong, moderate). *Values and preferences: This recommendation places a relatively high value on the potential risk of pronociception through the upregulation of specific chemokine receptors, cognitive impairment, respiratory depression, endocrine and immunological changes, and misuse and addiction.*
22. Clinicians may consider a time-limited trial of opioid analgesics for patients who do not respond to first-line therapies and who report moderate to severe pain. As a second- or third-line treatment for chronic neuropathic pain, a typical adult regimen should start with the smallest effective dose and combine short- and long-acting opioids (weak, low). *Remark: When opioids are appropriate, a combination regimen of morphine and gabapentin should be considered in patients with neuropathic pain for their possible additive effects and lower individual doses required of the 2 medications when combined.*

Evidence Summary

Opioid analgesics are an important class of medication used in the treatment of chronic pain. The effects of opioids beyond their interaction with the opioid receptor is a growing area of research. Although the data are limited, there are concerns that opioids could be pronociceptive when used to treat painful HIV-related neuropathy; this is in part due to the upregulation of specific chemokine receptors (eg, CXCR4) that are associated with promoting HIV-related pain [42]. Opioid use is further complicated by recent data that show that the HIV-1 envelope protein, gp120, impedes the ability of methadone and morphine (but not buprenorphine) to provide analgesia in a mouse model [142]. This is likely due to the higher binding affinity of buprenorphine compared to methadone and morphine [143]. The clinical implications are unclear, and further research is needed to determine if opioids with higher binding affinities, such as buprenorphine, may be preferable for pain control in patients with unsuppressed HIV viral loads. Finally, some data also suggest that exogenous opioids suppress the immune system (eg, reduce antibody production). However, the long-term impact of opioids and the clinical significance of any immunosuppression have not been evaluated [42, 144].

Studies that have examined opioid analgesics for the treatment of chronic neuropathic pain can be divided into short-term (less than 24 hours) and intermediate-term drug administration (1–8 weeks). In 2005, Eisenberg and colleagues conducted a systematic review of 8 blinded randomized, controlled trials in which full opioid agonists were administered orally over intermediate periods (between 8 and 56 days; median, 28 days) for the treatment of nonmalignant neuropathic pain. None of these studies included HIV-associated neuropathy [145]. The following 4 medications were tested: morphine (3 studies), oxycodone (3 studies), methadone (1 study), and levorphanol (1 study). All 8 studies reported improvements in neuropathic pain intensity or pain relief. Six of the trials (levorphanol and 1 morphine study were excluded) had data sufficient for pooling across studies, showing a 14-point reduction in the visual analog pain scale compared to the placebo group [145]. Medication-related nausea was the most common side effect, followed by constipation, drowsiness, vomiting, and dizziness. None of the observed side effects were life threatening. An updated Cochrane review in 2013 that included 14 intermediate-duration (lasting 12 weeks or less) trials provided data on 845 patients with neuropathic pain. Significant efficacy for opioid analgesics was shown when compared to placebo (at least one-third reduction in pain in 57% of patients who received opioids vs 34% who received placebo). Opioids, however, did not demonstrate significant improvements in physical or emotional functioning. Additionally, the authors concluded that there remains considerable uncertainty regarding the analgesic efficacy of opioids for chronic neuropathic pain since significant bias exists in the reported data "due to small size, short duration, and potentially inadequate handling of dropouts" [146]. A subsequent 2014 Cochrane review examined oxycodone for the treatment of neuropathic pain and fibromyalgia in adults. There were 3 studies with a total of 254 patients (204 with diabetic neuropathy and 50 with post-herpetic neuralgia), and oxycodone could not be recommended given the lack of unbiased evidence [147].

A more recent systematic review and metaanalysis was conducted in 2015 by the International Association for the Study of Pain's Special Interest Group on Neuropathic Pain (NeuPSIG) [116]. In this review, data from randomized, double-blind studies of neuropathic pain pharmacotherapy (oral and topical) were examined. Thirteen studies were identified in which full opioid agonists (oxycodone or morphine) were used, primarily for peripheral neuropathic pain. There was a moderate quality of evidence for the efficacy of opioid analgesics, with maximum effectiveness associated with 180 mg of morphine or equivalent. However, because of the increased risk for misuse, diversion, addiction, and adverse events (eg, overdose, cognitive impairment, immunologic and endocrine changes), the NeuPSIG authors designated opioid analgesics as a third-line treatment for neuropathic pain.

Additional clinical trials are needed to assess the effectiveness of the long-term use of opioids in neuropathic pain in PLWH. Although short-term use may provide some relief, these medications may be of limited success in chronic neuropathic pain. Due to these concerns, the European Federation of Neurological Societies (EFNS) Panel on Neuropathic Pain also recommends opioids as a third-line intervention for the treatment of painful peripheral neuropathies (eg, diabetes). Opioids are not currently recommended by the EFNS Panel for HIV-associated peripheral painful neuropathies due to the limited data on the use of opioids for the treatment of HIV peripheral neuropathy [148].

The additive or synergistic effects of combination therapy for chronic disease (as in the treatment of hypertension and diabetes) may be an important approach to improving neuropathic pain in PLWH. While the ACTG A5252 trial of duloxetine combined with methadone for the treatment of painful HIV-associated polyneuropathies could not enroll patients, Gilron and colleagues examined combination therapy in the treatment of neuropathic pain in patients without HIV [149]. In this study, an active placebo (lorazepam) preparation, gabapentin, sustained-release morphine, and a combination of morphine and gabapentin were compared. Pain intensity improved with all interventions, but the greatest improvement was with a combination of gabapentin and morphine. Moreover, combined gabapentin and morphine achieved better analgesia at lower doses than when used as single agents. Additional research is needed to validate the results from this small study and to determine which combination therapies, and in what doses, may be required to reduce neuropathic pain in PLWH.

V. What are the recommended nonopioid pharmacologic treatments for chronic nonneuropathic pain in persons living with human immunodeficiency virus?

Recommendations

23. Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are recommended as first-line agents for the treatment of musculoskeletal pain (strong, high). *Remark: Acetaminophen has fewer side effects than NSAIDs. Studies typically used 4 g/day dosing of acetaminophen; lower dosing is recommended for patients with liver disease. Compared to traditional NSAIDs, COX-2 NSAIDs are associated with decreased risk of gastrointestinal side effects but increased cardiovascular risk.*

Evidence Summary

There are limitations in the literature on the efficacy of nonopioid pharmacological treatments for chronic nonneuropathic pain, including a paucity of trials performed with PLWH. In 2008, Roelofs and colleagues conducted an updated systematic review of more than 11 000 patients enrolled in 65 trials of NSAIDs for the treatment of nonspecific acute and chronic low back pain [150]. Data from this review (42% of trials considered high quality) suggested that, compared to placebo, NSAIDs are effective for short-term symptomatic relief in patients with chronic low back pain without sciatica but at the risk of significantly more gastrointestinal and renovascular side effects [151]. It is important to note that effect sizes were small. An additional review for the American Pain Society and American College of Physicians also supports the use of NSAIDs for short-term symptomatic relief of low back pain [27].

For knee and hip osteoarthritis, the American College of Rheumatology continues to recommend the use of NSAIDS and acetaminophen [152]. Chou and colleagues conducted an extensive comparative effectiveness review of analgesics for osteoarthritis for the Agency for Healthcare Research and Quality in 2011 [153]. They found that one medication was not superior to others, largely due to the complex need to balance the varied risks and benefits of the medications. For example, the chronic administration of NSAIDs is linked to gastrointestinal (eg, bleeding), renal, and other systemic side effects that among PLWH could be exacerbated by other medication interactions (eg, tenofovir) and so require continual monitoring. Coprescribing of proton pump inhibitors or H2-antagonists reduced the risk of endoscopically detected gastroduodenal ulcers compared to placebo; and certain HIV antiretroviral therapy medications (eg, atazanavir) require an acid environment for absorption.

Studies with acetaminophen typically used 4 g/day, but acetaminophen prescription requires closer hepatotoxicity monitoring in populations with a higher prevalence of advanced liver disease, including persons with chronic viral hepatitis and alcohol use disorders. In the Veterans Aging Cohort, 31% of 14 885 patients with HIV disease received at least 1 prescription for acetaminophen of more than 2 g/day. Use of acetaminophen was common in both HIV (31%) and HIV/hepatitis C virus coinfected (32%) patients [154]. Current recommendations limit the dose of acetaminophen to no more than 2 g/day in patients with liver disease [155].

VI. What are the recommended opioid pharmacological treatments for chronic nonneuropathic pain in persons living with human immunodeficiency virus?

Recommendations

24. Patients who do not respond to first-line therapies and who report moderate to severe pain and functional impairment can be considered for a time-limited trial of opioid analgesics (weak, low). *Values and preferences: This recommendation places a relatively high value on safer opioid prescribing. The potential benefits of opioid analgesics need to be balanced with the potential risks of adverse events, misuse, diversion, and addiction. Remark: As a second- or third-line treatment for chronic nonneuropathic pain, a typical adult regimen should start with the smallest effective dose, combining short- and long-acting opioids.*
25. Tramadol taken for up to 3 months may decrease pain and improve stiffness, function, and overall well-being in patients with osteoarthritis (weak, moderate). *Remark: The range of tramadol dosing studied is 37.5 mg (combined with 325 mg of acetaminophen) once daily to 400 mg in divided doses.*

Evidence Summary

Short-acting opioids such as morphine, hydromorphone, oxycodone, and codeine are commonly used for effective pain management. Typically, they are initiated for acute pain that becomes chronic or used in the initial management of chronic pain to determine the patient's actual analgesic requirements (dosage titration). Frequent administration at short time intervals that reflect the specific medication's half-life may be necessary to achieve optimal control. Prescription of an opioid for chronic nonneuropathic pain raises concern among some healthcare providers about the risks of misuse, addiction, diversion, and overdose. There is a paucity of prospective data comparing specific opioids or formulations (eg, patch vs tablet) in PLWH; however, opioids do play a role in the treatment of chronic noncancer pain.

In a 2006 systematic review, Cepeda and colleagues examined 1019 persons on tramadol or tramadol/paracetamol (acetaminophen) and 920 patients assigned to placebo or an active control for the management of osteoarthritis. The range of tramadol dosing was 37.5 mg (combined with 325 mg of acetaminophen) once daily to 400 mg in divided doses, with the mean dose of 201.4 mg ± 50.15 mg. The average length of follow-up was 35 days (range, 7–91 days). Patients on tramadol demonstrated a decrease in pain, improvement in stiffness, and improvement in function and overall well-being [156]. However, these benefits remain small; there was a 12% relative decrease in pain intensity and a 37% increase in those reporting moderate improvement [156].

With the introduction of longer-acting formulations of opioid analgesics, patients may require less frequent administration of immediate-release opioids [83]. Scheduled administration of long-acting agents maintains plasma concentrations in a therapeutic range, minimizing the frequency of end-of-dose failures or withdrawal symptoms. Surveys of patients of unknown HIV status with chronic, noncancer pain have shown that around-the-clock pain relief with transdermal fentanyl and extended-release morphine resulted in a better quality of life [157]. In a systematic review published in 2015, Santos and colleagues examined the use of tapentadol compared to oxycodone for the treatment of chronic musculoskeletal pain in 4 randomized, controlled trials with a total of 4094 patients [158]. While the authors found that extended-release tapentadol reduced pain more than placebo and controlled-released oxycodone, the clinical significance was uncertain because of high dropout rates, lack of data for the primary outcome in some studies, and use of baseline-observation-carried-forward for imputed data analysis.

Portenoy and colleagues conducted a prospective cohort study of 233 patients of unspecified HIV status with noncancer pain who were treated with controlled-release oxycodone and followed for up to 3 years [159]. Only 39 patients (17%) were retained for 3 years, but this subgroup had prolonged relief. It is unknown if those who discontinued treatment did so due to a lack of benefit, intolerable side effects, or improvement in their condition.

The potentially serious side effects of chronic opioid therapy make opioid analgesics second- or third-line agents for the management of chronic nonneuropathic pain. With all currently available opioids, constipation is an expected side effect that requires use of a stool softener or laxative and fluids, particularly in bed-ridden patients or during warm weather when patients are at higher risk for volume depletion. Unaddressed, opioid-related constipation can lead to ileus and gastrointestinal obstruction. Nausea or vomiting is another common medication side effect that may occur in the first week of opioid treatment but generally resolves as the patient develops tolerance. Recurrent or persistent nausea and vomiting should trigger a second evaluation of the patient for other causes. Opioid-induced hypogonadism (potentially worsened in untreated HIV) is another adverse effect, and there are no standardized time schedules for screening or monitoring. Individuals who are symptomatic (eg, sexual dysfunction, depression, osteoporosis) should be evaluated [160]. Women of child-bearing age who are considering opioid analgesic therapy must be informed of the risk of fetal physical dependence and neonatal abstinence syndrome.

Central respiratory depression, which can lead to stupor, apnea, and death, is typically associated with rapid opioid dose escalations, lowered opioid tolerance, drug–drug interactions, and/or underlying pulmonary disease. In a large cohort study in Denmark, those on chronic opioid therapy (COT) were found to have higher all-cause mortality than the background population. While there was no association between COT and a specific

etiology of death, individuals on COT had higher rates of injury and toxicity/poisoning that resulted in hospital admission [161]. Higher doses of opioids have been associated with overdose and death in several studies [162–164]. It is advisable for patients to avoid medications or other substances that could alter the pharmacology of the opioid analgesic and/or increase the risk of respiratory depression. This is especially true for alcohol and sedative hypnotics (benzodiazepines), which have been associated with increased risk of emergency department visits and overdose [165].

VII. What is the recommended approach for assessing the likelihood of developing the negative, unintended consequences of opioid treatment (eg, misuse, substance use disorder, or possible diversion) in persons living with human immunodeficiency virus?

Recommendations

26. Providers should assess all patients for the possible risk of developing the negative, unintended consequences of opioid treatment (eg, misuse, diversion, addiction) prior to prescribing opioid analgesics for the treatment of chronic pain (strong, low). *Remark: A trial of opioid analgesics for the treatment of moderate-to-severe chronic pain may be reasonable only when the potential benefits of chronic opioid therapy for pain severity, physical function, and quality of life outweigh its potential harms.*

Evidence Summary

Patients who receive opioid therapy for chronic pain are susceptible to both beneficial and adverse effects. Potential negative, unintended consequences include pharmacodynamic effects (eg, sedation, respiratory depression, nausea, constipation, tolerance, and physiologic dependence), as well as the development of concerning (sometimes called "aberrant") behaviors that may indicate misuse, addiction, or possible diversion.

A significant limitation in the literature on this topic is inconsistent terminology, including definitions for "aberrant drug-related behaviors" that are not standardized across studies and not uniformly stratified by severity. With these limitations in mind, "aberrant opioid-related behaviors" may be defined here as patient behavior patterns that should alert the provider to reassess the risk–benefit ratio of the treatment and possibly modify the treatment plan. Such patient behaviors include requests for early refills or escalating dosages, taking more medication than prescribed, an unremitting focus during clinic encounters on obtaining controlled substance prescriptions or certain brand-name formulations, repeated lost or stolen medications, having multiple prescribers, prescription forgery, and the sale or diversion of secure prescriptions [166–168]. Some "drug-seeking" behaviors, such as using or requesting more medication than prescribed, may simply be manifestations of the expected physical dependence and tolerance that patients will develop on chronic opioid therapy or, in some cases, are due to undertreated pain. These behaviors, when due to undertreated pain, have been coined "pseudo-addiction" and should be included in the differential diagnosis for patients who demonstrate concerning behaviors. Whereas the 4 principle features of addiction are impaired control over drug use, compulsive use, continued use despite harm, and craving, pseudo-addiction is characterized by the resolution of the behavior with effective pain treatment [169, 170].

The prevalence of "aberrant analgesic use behaviors" among PLWH in the published literature ranges from 9% in persons without a substance use history to 73% lifetime prevalence in urban indigent adults [166, 171]. In a cross-sectional study of 296 marginally housed or homeless adult PLWH in San Francisco, where 91% of respondents reported pain in the prior week, 54% met criteria for a lifetime history of cocaine, amphetamine, or heroin/opioid use disorder as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition), Washington, DC: American Psychiatric Association, 1994, and 73% reported a lifetime history of at least 1 of 20 concerning behaviors provided on an inventory. Additionally, 37% reported any "aberrant opioid behavior" within the prior 90 days, and 19% reported major aberrant behaviors, which were defined as "behaviors that posed imminent risk to the patient or others for overdose or legal consequences (eg, using opioid analgesics to 'get high' or snorting, crushing, injecting, or smoking opioid analgesics)" [166].

Passik et al compared a small sample of 73 PLWH with a history of substance use disorders to 100 cancer patients without a history of substance use disorders. In addition to experiencing higher global distress, greater pain-related interference in daily functioning, and less relief from their pain medications, the PLWH reported more than twice as many aberrant analgesic use behaviors than the cancer group [172]. Subsequently, Tsao and colleagues conducted a more rigorous examination of a nationally representative longitudinal sample of 2267 PLWH [171]. The investigators used structured equation modeling to test the predictive and concurrent associations between pain, aberrant use of opioids, and problem drug use history. Patients were considered to have a history of problematic drug use if they responded "yes" to both of the following conditions: they ever had to use much larger amounts of illicit drugs than usual to get the same effect or that the same amount had less effect on them than before or that they ever had any emotional or psychological problems from using drugs, such as feeling uninterested in things, feeling depressed, being suspicious of people, feeling paranoid, or having strange ideas. Compared to patients without a history of problematic drug use, patients with problematic drug use reported more pain, were more likely to report aberrant use of prescription analgesics, and were more likely to use such analgesics specifically for pain over time [171].

Routine screening for unhealthy substance use is recommended for all patients being considered for a trial of chronic

opioid treatment regardless of HIV status [32]. In addition to a prior history of a substance use disorder (including alcohol and tobacco), other factors associated with increased risk of opioid misuse that should be assessed include younger age, family history of substance use disorders, childhood trauma (including sexual abuse), personal/family psychiatric history, and history of motor vehicle collisions (possibly a marker for driving under the influence of substances) [97, 166, 173–179]. Validated screening tools for unhealthy alcohol, tobacco, or other drug use and for mental health problems are widely available, and several risk prediction instruments have been developed to aid in safer opioid prescribing. The results of these assessments should be discussed openly and nonjudgmentally with patients as a safety issue when developing a pain care plan.

Screening for unhealthy alcohol and drug use is feasible, particularly if conducted routinely as a clinic-wide practice with all new patients and annually in established patients. Validated tools have been developed to facilitate screening and assessment in primary care settings, and these are reviewed elsewhere [180, 181]. Suggested tools include the World Health Organization's alcohol, smoking, and substance involvement screening test (ASSIST), the alcohol use disorders identification test for alcohol (AUDIT), and the drug abuse screening test (DAST) or CAGE-AID for drug use [182–185]. At healthcare sites where a clinic-wide procedure cannot be operationalized, a single-question screener has been developed and validated for detecting unhealthy alcohol and drug use. The questions are: How many times in the past year have you had more than 5 (4 for women) standard drinks in 1 day? and How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons? [186, 187]. Responses of 1 or more are positive screens for unhealthy alcohol and/or drug use. The single-question alcohol screen was tested on 286 patients and found to have 81.8% sensitivity and 79.3% specificity for the detection of unhealthy alcohol use. The single-question drug screen was tested on 286 patients and was found to have 100% sensitivity and 73.5% specificity for the detection of unhealthy drug use.

Opioid risk prediction tools offer another approach to assessing a patient's likelihood of developing the negative, unintended consequences of opioid analgesic treatment. The American Pain Society and the American Academy of Pain Medicine recommend these tools for all patients with chronic pain who are being considered for initiation of chronic opioid therapy. Chou et al published a 2009 systematic review of methods to predict the risk of aberrant drug-related behaviors before initiation of opioids for chronic noncancer pain [188]. Several instruments exist for this purpose, including the screener and opioid assessment for patients with pain (SOAPP and the revised SOAPP-R), the opioid risk tool (ORT), the pain medication questionnaire (which is self-administered), and the diagnosis, intractability, risk, efficacy (DIRE) instrument. Risk prediction tools with good content and construct validity are the SOAPP, SOAPP-R, and ORT [189–193]. Since the 2009 review, 1 small study compared the SOAPP, ORT, and DIRE and found that the SOAPP best predicted concerning behaviors in patients for whom opioids were ultimately discontinued [194]. Another review by Solanki et al in 2011 could not identify any other studies that compared these instruments [195]. None have been evaluated in PLWH. To date, studies have not demonstrated whether pretreatment risk prediction tools assist HIV clinicians in making decisions that improve the clinical outcomes of their patients with chronic pain.

Based on risk stratification and other available clinical and laboratory information, providers should weigh and discuss the potential harms and potential benefits of chronic opioid therapy with each patient. In all cases, providers should use a risk–benefit framework to discuss safety with their patients and to set a level of patient monitoring and support that is appropriate to their risk of opioid analgesic misuse and harm. The decision to treat chronic pain with opioid analgesics is never a risk-free situation. One risk is a failure to provide needed treatment for suffering. The treatment of pain is a human right, and undertreating pain has resulted in legal judgments against physicians by state medical boards [73]. In patients for whom the potential benefits of opioid therapy in terms of analgesia, function, and quality of life outweigh its potential harms, a trial of opioid analgesics as a second- or third-line treatment for moderate-to-severe chronic pain may be appropriate. Patients with risk factors for opioid-related harms may require more frequent and intensive monitoring during a trial of opioid analgesic therapy (see recommendations on monitoring below). For some patients, the potential harms of opioid treatment may outweigh the benefits, and opioid analgesics should not be prescribed.

VIII. What is the recommended approach to safeguard persons living with human immunodeficiency virus against harm while undergoing the treatment of chronic pain with opioid analgesics?

Recommendations

27. Routine monitoring of patients prescribed opioid analgesics for the management of chronic pain is recommended (strong, very low). *Remark: Opioid treatment agreements, urine drug testing (UDT), pill counts, and prescription drug monitoring programs are commonly used tools to safeguard against harms.*
28. An "opioid patient–provider agreement (PPA)" is recommended as a tool for shared decision making with all patients before receiving opioid analgesics for chronic pain (strong, low). *Remark: PPAs consist of 2 components: informed consent and a plan of care. When a patient's behavior is inconsistent with the PPA, the provider must carefully consider a broad differential diagnosis.*
29. The provider should understand the clinical uses and limitations of UDT, including test characteristics, indications for confirmatory testing, and the differential diagnosis of

abnormal results (strong, low). *Remark: UDT results should never be used in isolation to discharge patients from care. Rather, results should be used in combination with other clinical data for periodic evaluation of the current treatment plan and to support a clinical decision to safely continue opioid therapy.*

Evidence Summary

In a 2008 systematic review, the prevalence of opioid misuse in the general populations of patients with chronic pain was between 27% and 42% [188]. Compared to the general public, PLWH are overrepresented among those with opioid use disorders and chronic pain; this increases their risk of prescription opioid-related harm [188]. In an anonymous waiting room survey of 262 PLWH in a San Francisco HIV clinic, 232 (89%) of respondents had ever received prescription opioids for pain; one-third reported taking them for reasons other than pain, including to sleep better, calm down when worried or anxious, prevent opioid withdrawal, come down off speed or crack, and keep from feeling sad [196].

Healthcare providers are often neither trained nor confident in identifying patients with or at risk of problematic drug use [197–199]. Lum and colleagues conducted an anonymous on-line survey of a national sample of 100 HIV clinicians who prescribed opioids to their patients with chronic pain [198]. The providers reported only limited confidence (6/10 on a visual analog scale) in their "ability to recognize abuse of prescription pain medications"; however, confidence was higher among clinicians who reported they discussed substance use issues and conducted UDT with their chronic pain patients [198]. In another study of 105 HIV-infected indigent adults and their primary care providers in San Francisco [199], providers' perceptions were discordant with their patients' self-reports of opioid analgesic misuse, defined as "getting high, altering the route, selling, stealing, forging prescriptions, trading street drugs for opioids, and exchanging opioids for sex in the past 90 days." Although previous data have suggested younger age is associated with prescription opioid misuse, the primary care providers in this study incorrectly assigned younger age and African American race but correctly used past year estimates of illicit substance use (cocaine, methamphetamine, and heroin) as predictors of opioid analgesic misuse in this high-risk cohort.

Given the high prevalence of both opioid use disorders and chronic noncancer pain among persons living with HIV in the United States and the difficulty that HIV providers report identifying individuals who struggle with one or both, prescribers should implement an appropriate level of treatment monitoring when prescribing opioid analgesics for chronic pain. Currently, there is no evidence to support the specific frequency with which patient monitoring should occur in any patient population. Intuitively, however, more frequent and intensive monitoring (eg, pill counts, random UDT) should be considered for higher-risk patients, which would permit earlier identification, intervention, referral, and support for patients in need. Some authors have suggested every 3–6 months for stable patients and monthly or even weekly monitoring for high-risk patients such as those with recent histories of substance use (last use <6 months) and active mental health disorders [83, 188]. Progress note templates such as the pain assessment and documentation tool are available to assist clinicians as they document these periodic assessments over time; however, studies are needed to ascertain the affect this tool has on clinical outcomes [188, 200]. The current opioid misuse measure (COMM) is a 17-item, patient-administered instrument to assess aberrant behavior during chronic opioid therapy and to also assist clinicians in documenting decisions about the level of monitoring planned or justification for a specialty referral [201]. Although not validated in HIV clinical settings, the reliability and predictive validity of the COMM was high in 226 patients with chronic noncancer pain recruited from 5 pain management centers in the United States [202].

Other tools that may help safeguard against the harms of chronic opioid therapy include opioid treatment agreements, UDT, pill counts, and PDMPs that provide statewide data on all controlled substance prescriptions filled by a patient in a specified period of time.

Patient–provider agreements. PPAs, sometimes referred to as "opioid treatment agreements" or "pain contracts," are recommended by professional pain societies and the Federation of State Medical Boards when patients with chronic pain are prescribed opioid analgesics. We prefer the term "agreement," as it reinforces the shared decision making valued in a therapeutic patient–provider relationship rather than the criminal justice or legal connotations implied in a "contract" [203, 204]. A model PPA consists of 2 components: informed consent and a plan of care. The purpose of informed consent is to openly acknowledge the intended benefits or targeted goals of the planned treatment (eg, decreased pain severity, increased physical function, and improved mood) and to educate the patient about the potential risks or adverse effects of the treatment plan. Opioid-related adverse effects that should be discussed during informed consent include constipation, nausea, urinary retention, hypogonadism, physical dependence, sedation, respiratory depression, and death. Other possible risks such as medication misuse, diversion, and addiction also should be discussed. A consensus statement from the Center for Practical Bioethics stresses the critical importance of informed consent as a component of the treatment agreement [204].

The second component of the PPA, the plan of care, describes the specific therapies or medications to be tried, how their effectiveness will be evaluated, what safety monitoring procedures will be followed, and the circumstances under which the treatment will be modified or discontinued.

Table 1. Basic Content of Any Pain Treatment Agreement

Pain Treatment Policy	Pain Treatment Agreement
The provider should inform the patient of the specific medications prescribed and the possible side effects of those medications	Should include the specific medications
The specific policy on how the medical team will handle requests for early refills (eg, not allowable or allowable under certain conditions)	Agreement should inform the patient of the policy on early refill requests
Specific policy on discontinuation of opioids when deemed ineffective	Opioids are being prescribed as a time-limited trial and may be discontinued if their prescription is no longer appropriate
Frequency of reevaluation should be standardized to avoid seeming bias where one patient is reevaluated frequently while others are not	Inform the patient that treatment will be continually reevaluated
A listing of other treatment options should be standardized across the agency	A listing of other treatment options (eg, physical therapy)
The content of the treatment goals (plan of care) should be standardized	Treatment goals (eg, improvement in walking upstairs)
The manner in which discontinuation of opioids occurs in the setting of illicit drug use should be specifically delineated	Conditions under which the risks of opioids might exceed the benefits (eg, use of illicit substances concurrently with opioids)
The role of patient and provider should be defined clearly	The responsibilities of both the patient and provider

Successfully met functional goals support the continuation of the treatment plan. Failure to meet these goals necessitates reevaluation and a possible change. Monitoring procedures may include UDT, pill counts, and use of a PDMP. If opioids will be prescribed, then the plan of care should explicitly state the clinic's prescription refill or renewal policies, how concerning behaviors or unexpected safety monitoring results will be addressed, and under what conditions the risk of ongoing opioid prescription might exceed the benefit (eg, an injury due to oversedation) (Table 1). Restructuring of the treatment plan may include more intensive monitoring, more education, resetting functional goals, increasing or reducing medication dosages or frequency, or discontinuing medications that are not providing any benefit [73].

The advantage of a written PPA is that it can be printed and provided for patient education and as a reference document. Vague or undocumented verbal agreements risk future misunderstandings between the provider and patient regarding their roles and responsibilities to each other, treatment expectations, and the management of unintended consequences. PPAs should meet the literacy level of the patient and avoid coercive language or attempts to apply legalistic terms or conditions to what should be a therapeutic clinical relationship [205–207]. While a standardized PPA form has not yet been validated, a model PPA form is undergoing pilot testing in New York by the US Food and Drug Administration.

The efficacy of PPAs in reducing prescription opioid-related harm is not well established in the pain literature. A 2010 systematic review identified only 4 studies that evaluated the effects of opioid treatment agreements on opioid misuse/aberrant behavior that included a control group. These studies showed a decline in concerning behaviors after the implementation of opioid treatment agreements, but the studies used only historical controls [206, 208]. Despite the low quality of evidence supporting PPAs, professional pain societies recommend them [209]. The American Pain Society and American Academy of Pain Medicine's guidelines for the use of chronic opioids for noncancer pain recommend and contain a sample written treatment agreement [210]. There is no evidence of a negative effect of treatment agreements on patient outcomes, and there is some low-quality evidence that providers who use them may experience positive effects. Opioid treatment agreements may improve primary care providers' comfort with opioid prescribing, facilitate an open dialogue between the patient and provider about the risks and benefits of pursuing a trial of opioid analgesic therapy, put everyone on the "same page," and provide a mechanism for providers to establish expectations around monitoring for benefit and risk. Pain medication agreements were found to be useful by 90% of internal medicine residents surveyed at a Rhode Island hospital. Residents who reported greater use of agreements were significantly more likely to report a greater sense of preparation and greater sense of reward for managing chronic noncancer pain [211].

Urine drug testing. Universal UDT is recommended as a clinical tool for monitoring the course of chronic pain treatment in all persons who receive opioid analgesics. In a 2012 study of 173 PLWH who were prescribed opioids for chronic pain in New York, 62% were found to have problematic prescription opioid use, with the majority detected by UDT [212]. In a prospective cohort study of 500 consecutive pain clinic patients, Manchikanti and colleagues reported significant reductions in overall illicit drug use (marijuana, cocaine, methamphetamine) when adherence monitoring was combined with random UDT and compared to a historical control [213].

We recommend baseline UDT to establish the reliability of a new patient's reported substance use history, because both clinician predictions and patients' self-reported history have been found in a number of studies to be unreliable [214–218]. Appropriate baseline UDT does not rule out the potential for future concerning behavior, and there is insufficient evidence to recommend the frequency with which UDT should be performed [212, 215]. However, Christo and colleagues delineated a practical approach to UDT monitoring among stable chronic pain patients that may be reasonable. This approach

includes baseline UDT of all patients prior to the initiation of opioids for chronic pain; adherence monitoring within 1–3 months after baseline monitoring; and routine, random monitoring approximately every 6–12 months, with provisions for additional monitoring for unexpected results or concerning behavior patterns [216]. Whichever strategy is adopted, we recommend that the UDT monitoring policy be applied uniformly to all patients who receive opioid analgesics ("we do this for everyone"), so as to prevent bias and reduce further stigmatization of patients. Randomly scheduled UDT may be most appropriate when additional monitoring is required, since predictably scheduled UDT increases opportunities for tampering [213].

When monitoring the course of opioid treatment for chronic pain, the provider should understand the clinical uses and limitations of UDT, including urine drug test characteristics, indications for confirmatory testing, and the differential diagnosis of abnormal results. Forensic use of UDT is strongly discouraged and has no place in the patient–provider relationship. In addition, the use of UDT in isolation is insufficient to diagnose a substance use disorder and should not be attempted. Urine testing can create an environment of mistrust and further stigmatize the use of opioids for pain in a population of patients who, by virtue of their HIV and chronic pain diagnoses, are already stigmatized [206]. Requiring baseline UDT in all patients prior to opioid analgesic prescribing establishes a standard that all patients in the clinic are treated in the same fashion. This measure serves to reduce the stigma of both UDT and unhealthy substance use in an already heavily stigmatized patient population. A failure to institute universal UDT highlights the biased assumption that the provider can correctly guess and identify patients using illicit or nonprescribed substances [198, 214, 215, 219].

Many providers have inadequate training in the interpretation of UDT results, and the ramifications of incorrect interpretation can be severe [216, 220, 221]. UDT is imperfect, as the immunoassays used in most screening tests can be falsely positive due to cross-reactivity with other agents and can be falsely negative due to dilution or adulteration. In a 2008 systematic review, Turk and colleagues found that a positive test result was only a moderately positive predictor of prescription opioid misuse [97]. Gas chromatography/mass spectroscopy, which is performed for confirmatory testing, is used to differentiate these false positives. Because new toxicology assays and medications are always being created, healthcare providers are encouraged to establish a working relationship with their local toxicologist who conducts the assays and can consult on results interpretation.

In patients who exhibit aberrant opioid-related behaviors or who have a urinary drug test that contains illicit or nonprescribed substances, providers should carefully but promptly consider a broad differential diagnosis before taking action [216]. Aberrant opioid-related behaviors may be due to inadequate analgesia, substance use disorders, development of tolerance to opioids, opioid-induced hyperalgesia, or self-medication of psychiatric symptoms [83, 222]. For patients in whom the prescribed substance is absent from the urine, the differential diagnosis includes diversion, levels of drug below the screening threshold due to a delay between the last dose and the test itself (eg, increased pain and need to consume more opioids thereby running out early), or dilution of the urine (eg, in the context of uncontrolled diabetes mellitus). Presence of an illegally prescribed substance should be discussed promptly with the patient in order to address a potential substance use disorder, keeping in mind that it may represent a false-positive result.

Unexpected UDT results and concerning behaviors should not be used to discharge patients from the practice; this violates the principle of nonabandonment and undermines the therapeutic relationship [204]. Instead, these results should be used in combination with other clinical data to reevaluate the current treatment strategy, including the risk–benefit ratio of opioid therapy and the potential for other clinical services (eg, substance use treatment).

IX. What are the recommended methods to minimize adverse effects from chronic opioid therapy in persons living with human immunodeficiency virus?

Recommendations

30. Controlled substances should be stored safely away from individuals at risk of misuse and/or overdose; family members should be educated on the medications and signs of overdose, and the poison control number should be readily visible (strong, low).
31. Clinicians should teach patients and their caregivers about opioid overdose and the use of naloxone to reverse overdose; a naloxone rescue kit should be readily available (strong, moderate).
32. Patient education is recommended to help patients avoid adverse events related to pharmacological interactions (strong, low).
33. Providers should be knowledgeable about common pharmacological interactions and be prepared to identify and manage those drug–drug interactions (strong, low). Providers should follow patients closely when interactions are likely (strong, low).

Evidence Summary

Controlled substances should be stored safely away from individuals at risk of misuse and/or overdose. Family members should be educated on the medications, their risks, and the signs of overdose. The poison control number should be readily visible. Family members should be educated on safe storage devices (eg, lock boxes) and, if needed, on safe disposal options. There is, however, a paucity of data on effective methods to accomplish these tasks [223].

Furthermore, clinicians should teach their patients about opioid overdose and the use of naloxone to reverse overdose; a naloxone rescue kit should be prescribed [224]. The availability and use of naloxone reduces the risk of overdose death, which is the leading cause of morbidity and mortality among illicit opioid users [225–234]. Prescribing naloxone to someone at risk of overdose is legal in every state [235].

It is important to clarify that much of the research discussed here was conducted with patients at specialty pain clinics [213–215, 218, 219]. These findings may not be generalizable to patients seen in HIV primary care clinics, because they may have a higher prevalence of substance use and mental health disorders. Furthermore, definitions for aberrant drug-related behaviors are not standardized across studies and not stratified by severity. Table 2 provides basic guidance when considering the discontinuation of controlled substances in patients.

Patients and providers should be educated on important pharmacological interactions. Pharmacological interactions between opioids and HIV therapeutics are well documented (Table 3) [236]. Methadone has a wide interindividual variability in its clinical pharmacology, and individual titration of doses is critical to avoid adverse outcomes [237]. Methadone has several interactions of import; specifically, efavirenz and rifampin can result in opioid withdrawal, and fluconazole can increase the effects of methadone [238].

When prescribing methadone for chronic pain, healthcare providers should be aware of the clinical discourse over heart rate corrected QT (QTc) prolongation, torsade de pointes, and the extent to which methadone, other medications prescribed to PLWH (psychotropics, macrolides, certain fluoroquinolones and antimalarials, pentamidine, azole antifungals) [239], and specific clinical states (eg, hypokalemia,

Table 2. Discontinuation of Controlled Substances for Pain Management Therapy: Techniques to Use When Continuation of Controlled Substances Are no Longer Useful or Indicated

1. When there is lack of benefit: patient is not improving and may have opioid-resistant pain (Some patients experience improvement in function and pain control when chronic opioids are stopped.)
• Stress how much you believe/empathize with patient's pain severity and impact
• Express empathy re: lack of good pill to fix it
• Focus on patient's strengths
• Encourage therapies for "coping with" pain
• Show commitment to continue caring about patient and pain, even without opioid therapy
• Taper dose slowly to prevent opioid withdrawal symptoms
• Schedule close follow-ups during and after medication taper
2. When discussing the possibility of a substance use disorder
• Explain why observed (and documented) behavior raises your concern for possible addiction
• Benefits no longer outweigh risks: "I cannot responsibly continue prescribing opioids at this time, as I believe it would cause you more harm than good."
• Always offer referral to substance use treatment
• Stay 100% in "benefit–risk of medication" mindset
• Be clear that you will continue to work on pain management using non-controlled medications
• Taper dose slowly to prevent opioid withdrawal symptoms

Adapted from Dan Alford [82, 295].

Table 3. Drug Interactions Between Opioids and Human Immunodeficiency Virus Medications[a]

Medication	Recommendation
Nucleoside Reverse Transcriptase Inhibitor	
Abacavir (ABC)	No dose change required for METH; no study for BUP
Emtricitabine (FTC)	No studies with METH or BUP
Lamivudine (3TC)	AZT/3TC coformulation studied only with METH; no dose adjustments necessary in METH or BUP
Tenofovir (TDF)	No dose adjustments necessary in METH or BUP; tenofovir AF (TAF) not studied, but likely no dose adjustment necessary
Zidovudine (AZT)	Watch for AZT-related toxicity (symptoms and laboratory); dose reductions of AZT may be required in METH patients; no dose adjustments for BUP
Nonnucleoside Reverse Transcriptase Inhibitor	
Efavirenz (EFV)	Opioid withdrawal from METH common; METH dose increase likely necessary; no dosage adjustments necessary with BUP
Etravirine (ETV)	No dose adjustments necessary for METH; no study for BUP
Nevirapine (NVP)	Opioid withdrawal from METH common; METH dose increase likely necessary; no dose adjustments necessary for BUP
Rilpivirine (RPV)	Monitoring for symptoms of METH withdrawal is recommended; no study for BUP
Protease Inhibitor	
Atazanavir (ATV)	No dose adjustments necessary in METH; some individuals may experience oversedation with BUP; ATV should be boosted with ritonavir when coadministered with BUP
Darunavir (DRV)	No antitretroviral dose change when combined with METH or BUP; 4 of 16 patients in METH study reported mild opioid withdrawal, but no dose adjustments were needed
Fosamprenavir (FAMP)	No dose adjustments necessary for METH or BUP
Lopinavir/ritonavir (LPV/r)	METH dose increase may be necessary in some patients; no dose adjustments are necessary for BUP
Nelfinavir (NFV)	No dose adjustments necessary for METH; no study for BUP
Ritonavir (RTV)	No dosage adjustments necessary for METH or BUP; boosts oxycodone and dose reductions in oxycodone may be necessary
Tipranavir (TPV)	METH dose may need to be increased; no dose adjustments necessary for BUP; clinical significance in the changes in TPV pharmacokinetic parameters in the presence of BUP is unknown
Integrase Inhibitor	
Elvitegravir (with cobicistat)	No dosage adjustments necessary for METH or BUP; cobicistat has similar mechanism of action as ritonavir and may (though not studied) increase oxycodone levels as well
Raltegravir	No dosage adjustments necessary for METH or BUP
Dolutegravir	No dosage adjustment necessary for METH [294]; no published data on BUP

Only includes commonly prescribed medications.

Abbreviations: ATV, atazanavir; BUP, buprenorphine; METH, methadone; TPV, tipranavir; AZT, zidovudine.

[a]Used with permission [236].

hypomagnesemia) may impact the QTc interval [240]. QTc prolongation has been observed primarily in persons receiving moderate to high doses of methadone once daily for the maintenance treatment of opioid use disorders. QTc prolongation has been rarely studied in a controlled manner in persons administered methadone for chronic pain [241, 242], usually cancer patients [241, 242], and not at all in PLWH. In 2015, a small prospective pilot study examined the effect of low-dose (<60 mg/day) methadone at a chronic pain clinic and compared automated QTc calculations from 12-lead electrocardiograms (ECGs) conducted at baseline (pretreatment) and at 6 months. The comparison was made between 82 patients who received <60 mg/day of methadone and 102 patients who received nonmethadone opioid therapy for chronic pain [243]. The incidence of clinically significant QTc prolongation (>470 milliseconds or >60 milliseconds increase from baseline) in patients who received methadone was no different than in patients who received nonmethadone opioid therapy. Patients did demonstrate an increase in QTc in the first month after starting methadone compared to control patients (P = .073), but this difference was not statistically significant and disappeared in the third and sixth months.

A 2013 Cochrane systematic review found no evidence to support the effectiveness of ECG-based screening strategies for preventing cardiac morbidity and mortality in persons who receive methadone for the treatment of opioid use disorder [244]. However, 2014 clinical practice guidelines on methadone safety from the American Pain Society, College on Problems of Drug Dependence, and Heart Rhythm Society continue to recommend an initial ECG in all patients with increased risk of an arrhythmia (eg, patients with elevated QTc, history of palpitations, or syncope) and that an initial ECG be considered in all patients starting methadone. Follow-up ECGs should be conducted based on the initial recording, with higher QTc intervals requiring closer follow-up (as early as 2 to 4 weeks) and as late as when the patient reaches 100 mg/day of methadone. The reader is referred to the detailed recommendations for more specific information [245] and is cautioned that due to the limitations in current research, most of the recommendations in this guideline are based on a low quality of evidence.

Oxycodone drug levels have been shown to increase 2–3 fold in healthy volunteers in the presence of CYP3A-mediated inhibition by short-term administration of ritonavir, suggesting that downward dose adjustments may be needed when oxycodone is prescribed in patients initially taking ritonavir [246]. Although not studied to date, cobicistat, another pharamcoenhancer, is likely to cause a similar effect given it has a similar mechanism of action [247]. Buprenorphine, despite pharmacokinetic interactions, can be safely administered with all currently available HIV therapies with minimal risk of clinical opioid withdrawal [68, 248, 249].

X. What is the recommended approach to prescribing controlled substances for the management of chronic pain to persons living with human immunodeficiency virus with a history of substance use disorder?

Recommendations

34. Persons with a history of a substance use disorder or addiction should be carefully evaluated and risk stratified in the same manner as all other PLWH with chronic pain (strong, low). *Values and preferences: This recommendation places a high value on clinical strategies that neutralize bias and reduce stigma in the care of all PLWH and the possibility of behavior change over time. Remark: A patient's history of addiction or substance use disorder is not an absolute contraindication to receiving controlled substances for the management of chronic pain. A risk–benefit framework that views controlled substances as medications with unique risks to every patient ("a universal precautions approach") should be applied uniformly to help providers make fair and informed clinical decisions about controlled substance prescribing.*
35. Persons with a history of addiction for whom the risks currently outweigh the benefits of a controlled substance prescription should have their chronic pain reasonably managed by other therapies and should receive emotional support, close monitoring and reassessment, and linkages to addiction treatment and mental health services as indicated (strong, low). *Values and preferences: This recommendation places a high value on access to pain management as a fundamental human right with an underlying principle that every person deserves to have his or her pain reasonably managed by adequately trained healthcare professionals and that every medical provider has a duty to listen to and reasonably respond to a patient's report of pain.*

Evidence Summary

The prescription of opioid analgesics to persons with a history of addiction and/or mental illness can make providers feel uncomfortable [250, 251]. Persons with active or recent substance use are at higher risk for the development of harmful opioid-related behaviors, and medical providers report a lack confidence when prescribing opioids to patients with histories of addiction [198]. In accordance with recommendations from the American Pain Society and the American Academy of Pain Medicine, higher-risk patients who are prescribed opioids should undergo routine monitoring, with providers using opioid risk mitigation strategies [32]. In addition, linkage to addiction treatment and recovery resources and mental health services, when applicable, is essential [83]. A mechanism for providing these safeguards should be detailed in the treatment agreement and explicitly discussed between patient and provider prior to initiating opioid analgesics.

Although specific data for the prescription of benzodiazepines in patients with chronic pain is lacking, we recommend a judicious approach. Providers are reminded that in addition to the rapid development of tolerance and physical dependence, benzodiazepines and other sedative–hypnotics may contribute to the risk of opioid analgesic overdose and cause anterograde amnesia. Moreover, long-term benzodiazepine use has been associated with cognitive impairment and dementia in the general population, and this may negatively impact other evidenced-based treatments for pain, such as cognitive behavioral therapy [165, 252–254].

XI. What are the recommended approaches to the pharmacological management of chronic pain in persons living with human immunodeficiency virus who are on methadone for the treatment of opioid use disorder?

Recommendations

36. A signed release for the exchange of health information between the provider and the opioid treatment program (OTP) is recommended prior to any controlled substance prescribing (strong, low). *Remark: Ongoing communication with the OPT is essential when there are 2 controlled substance prescribers. Sharing information about a patient's progress in recovery is an important component of the assessment and periodic monitoring of a pain treatment's risks and benefits, for example, whether to pursue a trial of or to continue or discontinue opioid analgesic therapy.*
37. Initial screening with electrocardiogram to identify heart rate corrected QT (QTc) prolongation for all patients on methadone is recommended, with interval follow-up with dose changes. This is especially helpful if the patient is also prescribed other medications that may additively prolong the QTc (eg, certain psychotropics, fluconazole, macrolides, potassium-lowering agents) (strong, low).
38. The splitting of methadone into 6- to 8-hour doses is recommended in order to lengthen the active analgesic effects of methadone with the goal of continuous pain control (strong, low). *Remark: Some OTPs may be able to offer a split-dose methadone regimen for patients. Alternatively, the medical provider may need to prescribe the remaining daily doses: 5%–10% of the current methadone dose should be added, usually as an afternoon and evening dose for a total 10%–20% increase over the regular dose for the treatment of opioid use disorder (strong, very low).*
39. If prescribing additional methadone is not possible (eg, OTP policy, high baseline methadone dose, prolonged QTc intervals, high risk of diversion, the patient is new to or poorly adherent to the OTP), then the addition of an additional medication may be recommended for chronic pain management depending on the etiology of the pain (eg, gabapentin for neuropathic pain, nonsteroidal antiinflammatory drugs for musculoskeletal pain, or an additional opioid) (weak, low).
40. Acute exacerbations in pain or "breakthrough pain" should be treated with small amounts of short-acting opioid analgesics in patients at low risk for opioid misuse (strong, low). *Remark: Providers and patients should agree on the number of pills that will be dispensed for breakthrough pain, their frequency of use, and the expected duration of this treatment.*

Evidence Summary

Methadone, a strong full μ-opioid receptor agonist and N-methyl-D-aspartate antagonist, can provide effective analgesia when dosed carefully, especially for patients with severe pain that is not controlled by other opioids or for patients who poorly tolerate other opioids [255, 256]. Although methadone has a long half-life (30 hours) and is dosed once daily for the treatment of opioid use disorders, it has an analgesic effect of only 6 to 8 hours [257]. Patients with chronic pain who are on methadone maintenance for the treatment of opioid use disorder will have increased opioid tolerance but will not experience adequate analgesia with once daily dosing [82]. One option for some methadone-maintained patients is to split their once-daily dose of methadone into several daily doses. Methadone clinics have the capability of "split-dosing" methadone; that is, dispensing a morning dose of methadone and then providing take-home bottles of methadone for self-administration later in the day. This split-dosing is more traditionally reserved for "fast metabolizers" of methadone and for pregnant patients for whom once daily methadone may be inadequate [258]. Split-dosing is typically reserved for patients whose substance use disorder is in remission and who demonstrate good adherence to methadone treatment (ie, they have graduated to at least once weekly "pickups" or "take homes"). To begin split-dosing for the treatment of chronic pain, 5%–10% of the current methadone dose should be added, usually as an afternoon and evening dose for a 10%–20% increase over the regular dose. For example, 10% of a patient's 100-mg daily sdose is 10 mg that, when dosed at 10 mg in the afternoon and 10 mg in the evening, comes to a total of 120 mg daily. Methadone clinics have demonstrated an ability to successfully administer or dispense other treatments, including daily observed antiretroviral therapy or tuberculosis regimens, thereby supporting adherence [259–261]. The promotion of adherence to opioid tresatments for pain and/or addiction should be under the logical purview of the methadone clinic system. However, to date, no studies have examined the use of a methadone maintenance clinic's structure of dispensing methadone and splitting that dose for the treatment of chronic pain.

Methadone is known to prolong the heart rate QTc, and patients should be advised of the risk of arrhythmia when

prescribed methadone. Clinicians should ask patients about a prior history of structural heart disease, arrhythmia, or syncope. A pretreatment electrocardiogram (ECG) is recommended for all patients starting methadone for addiction to measure the baseline QTc, and a follow-up ECG should be performed within 30 days to determine changes impacted by methadone and/or additional medications [262]. Data are lacking on the pretreatment use of ECGs for patients prescribed methadone for the treatment of chronic pain. The reader is referred to additional literature on potential drug interactions that may impact QTc as well as recommendations on QTc management in methadone patients [240, 244, 262, 263].

XII. What are the recommended approaches to the pharmacological management of chronic pain in persons living with human immunodeficiency virus who are on buprenorphine for the treatment of opioid use disorders?

Recommendations

41. Clinicians should use adjuvant therapy appropriate to the pain syndrome for mild-to-moderate breakthrough pain (strong, moderate). *Remark: These adjuvants include, but are not limited to, nonpharmacologic treatments, steroids, nonopioid analgesics, and topical agents. (See section on "nonopioids" for treatment of chronic neuropathic and nonneuropathic pain.)*
42. Based on expert opinion, the clinician should increase the dosage of buprenorphine in divided does as an initial step in the management of chronic pain (strong, very low). *Remark: Dosing ranges of 4–16 mg divided into 8-hour doses have shown benefit in patients with chronic noncancer pain.*
43. Based on expert opinion, clinician's might switch from buprenorphine/naloxone to buprenorphine transdermal formulation alone (weak, very low).
44. We recommend that if a maximal dose of buprenorphine is reached, an additional long-acting potent opioid such as fentanyl, morphine, or hydromorphone should be tried (strong, low).
45. If usual doses of an additional opioid are ineffective for improving chronic pain, we recommend a closely monitored trial of higher doses of an additional opioid (strong, moderate). *Remark: Buprenorphine's high binding affinity for the μ-opioid receptor may prevent the lower doses of other opioids from accessing the μ-opioid receptor.*
46. For patients on buprenorphine maintenance with inadequate analgesia despite the above-mentioned strategies, we recommend transitioning the patient from buprenorphine to methadone maintenance (strong, very low).

Evidence Summary

Buprenorphine is a partial opioid agonist with a high binding affinity for the μ-opioid receptor [143]. This high affinity diminishes the ability of other more potent full agonist opioids to dislodge it from the receptor [264]. This blocking of other full opioid agonists is a beneficial property in the treatment of opioid use disorder [265]. This high affinity and slow dissociation are also beneficial in the treatment of chronic pain, providing analgesia over a long period of time [266, 267].

Buprenorphine is available as a sublingual tablet, sublingual film, and 6-month implant that are approved for the treatment of opioid use disorders; a transdermal patch is approved for the treatment of chronic pain. The tablet or film can be prescribed off label in split doses (ie, every 6–8 hours) for the treatment of pain; however, the buprenorphine patch cannot be prescribed off label for the treatment of opioid use disorder.

During acute episodes of pain, buprenorphine may pose a greater challenge than methadone in achieving analgesia [268]. The dose of buprenorphine can be increased to provide additional analgesia. Walsh and colleagues examined doses of buprenorphine up to 70 times the normal analgesic doses and verified the ceiling effect of buprenorphine on respiratory depression [269]. Rubenstein [270] argued that buprenorphine has not been studied for a ceiling effect on analgesia, and, given its potency and safety, buprenorphine may be beneficial at higher doses for treating pain. Malinoff and colleagues enrolled 95 individuals with chronic noncancer pain who were medically withdrawn from long-term opioid analgesic therapy and transferred to daily sublingual buprenorphine ranging from 4 to 16 mg (mean 8 mg) in divided doses. The mean duration of treatment was 8.8 months, and 86% of patients experienced moderate to substantial relief in pain with improved functioning and mood [271]. Additional buprenorphine side effects (eg, headache, constipation), however, may be more pronounced at higher doses.

For management of chronic pain in persons on buprenorphine for the treatment of opioid use disorder, clinicians might consider switching from buprenorphine/naloxone to buprenorphine transdermal alone. The sublingual formulation has a 90% first-pass hepatic metabolism. A transdermal patch bypasses hepatic metabolism and may provide better analgesia relative to the tablet or film formulation. Transdermal buprenorphine has proven efficacy and may be safer than full opioid agonists in the treatment of chronic pain. In a systematic review of buprenorphine vs transdermal fentanyl and morphine for chronic pain, it was found that buprenorphine provided comparable pain relief with fewer adverse events [272].

Because buprenorphine does not occupy all opioid receptors, other opioids can be given when pain is acute. High-potency opioids such as fentanyl or hydromorphone should be considered when the addition of nonpharmacologic treatments and nonopioid pharmacotherapies are ineffective [273]. If the maximum dose of transdermal buprenorphine is reached, consideration should be given to adding or replacing it with an additional long-acting potent opioid such as fentanyl, morphine, or hydromorphone.

As noted previously, patients on buprenorphine maintenance treatment for opioid use disorder who have inadequate

analgesia should be considered for methadone maintenance instead. Methadone is a full agonist and, when dosed appropriately, may provide greater analgesia. In addition, it can be prescribed with other opioid analgesics. Other agents such as long-acting morphine preparations can complicate substance use disorder treatment since heroin metabolizes to morphine, making it difficult to interpret urine drug testing results.

XIII. What are the recommended instruments for screening common mental health disorders in persons living with human immunodeficiency virus with chronic pain?

Recommendations

47. Clinicians should fully review a patient's baseline mental health status for modifiable factors that can impact successful pain management (strong, low). *Remark: Potentially modifiable factors include self-esteem and coping skills; recent major loss or grief; unhealthy substance use; history of violence or lack of safety in the home; mood disorders; and history of serious mental illness or suicidal ideation.*
48. All patients should be screened for depression with the following 2 questions: During the past 2 weeks have you often been bothered by feeling down, depressed, or hopeless? During the past 2 weeks have you been bothered by little interest or pleasure in doing things? (strong, high). *Remark: If the patient answers in the affirmative to either question, a follow-up question regarding help should be asked: Is this something with which you would like help?*
49. The patient health questionnaire-9 (PHQ-9), which is in the public domain, is recommended as a screening tool in clinical settings without access to trained mental health professionals as it can be used to diagnose depression (strong, high). *Remark: Psychiatric follow-up for a result that is ≥10 (88% sensitivity and 88% specificity for major depression) is recommended, and the clinical site should have a policy for referrals for more in-depth evaluation of these issues.*
50. All patients should be screened for comorbid neurocognitive disorders prior to and during use of long-term opioid therapy (strong, low). *Remark: Questions administered to elicit cognitive complaints in the Swiss HIV Cohort study (eg, frequent memory loss; feeling slower when reasoning, planning activities, or solving problems; and difficulties paying attention) detected, but have not been tested as screening questions in the clinical setting.*
51. It is recommended that all patients with chronic pain have a full neuropsychiatric evaluation with history, physical, and use of the HIV dementia scale or an equivalent to document baseline capacity (strong, high).

Evidence Summary

A patient's baseline self-esteem and coping skills play a significant role in controlling chronic pain. Depression, anxiety, and post-traumatic stress disorder (PTSD) are common in people living with HIV, as seen in a cohort of adults with severe mental illness where HIV was the third leading cause of death in one-third of the Medicaid recipients in 1 US state [274]. Mental illness in PLWH can in turn be impacted by dependency, disability, fear of pain, and fear of death. Patients with these diagnoses may have less-effective coping skills than those without a history of a mood disorder [275]. These diagnoses are known to result in recording of greater pain intensity and pain-related disability [10, 197, 276].

Full mental health management is beyond the scope of this guideline, but mental health disorders must be recognized as a potentially confounding problem for the successful management of chronic pain in PLWH since depression and pain frequently co-occur [17]. Effective screening tools for use in the clinical setting are available for many mental health syndromes. Some of the most common mental health syndromes experienced by individuals with chronic pain include self-esteem and coping skills used during previous difficult times in life; recent significant loss or grief; documentation of serious life events or traumas; mood disorders, especially those known to negatively impact adherence (eg, depression, PTSD); substance use disorders; or lack of safety in the home. Where possible, clinics should use standardized and validated instruments to screen for mental illness.

Screening for depression. The 2-question questionnaire referenced in recommendation 48 is simple to implement in even the busiest clinical practice. The screen has performed as well as other, longer screens in non-HIV clinical settings with a sensitivity of 96% and a specificity of 57% [277]. When a question was added inquiring if help is needed, the specificity increased to 94% [278]. In addition to this questionnaire, there is the PHQ-2 and the PHQ-9. The PHQ-2 lists responses on a Likert scale. The PHQ-2 and PHQ-9 have been validated in PLWH in Kenya [279, 280]. The PHQ-9 is a simple screen for depression that patients can self-administer prior to the provider seeing the patient [281, 282]. The site must have a policy to respond to positive screens for more in-depth evaluation. Current evidence demonstrates that screening programs with staff-assisted depression care (eg, case management, mental health specialist) are more likely to improve depression outcomes and that clinics should ascertain if they can either provide these services directly or through partnerships with other agencies [283].

Screening for neurocognitive disorders. HIV-associated dementia has declined dramatically with effective antiretroviral therapy (ART). However, HIV-associated neurocognitive disorder (HAND) remains underrecognized in the current HIV population and can complicate evaluation and management of the person with chronic pain. In a recent review of 364 patients in the Multicenter AIDS Cohort, the majority of PLWH on combination ART with virologic suppression were diagnosed with

HAND at the same rate, and it was not progressive over 4 years of follow-up [284]. Symptoms have been reported in 20%–50% of HIV-infected persons at all stages of illness regardless of viral suppression and ART use [285, 286]. Clinical signs include mental slowing, memory loss (seen in 20%–70%), and difficulty with complex function (executive function), plus motor disorders. Patients may demonstrate apathy, decreased spontaneity, or dampened emotional response. These signs must be distinguished from depression. Cognitive impairment may be subtle, making it useful to use a clinically tested screening tool such as the International HIV dementia scale (IHDS). This scale was designed to identify subcortical dementias, including HIV dementia, by assessing memory (registration and recall), attention, psychomotor speed, and timed construction [287]; however, the full instrument may require practice on the part of the administrator for efficient completion [286]. A modified HDS has been developed for nonneurologists but has been assessed only for HAND [288, 289].

In 2013, Hu et al conducted a metaanalysis and found that "IHDS and HDS may offer high diagnostic performance accuracy for the detection of HAND in primary health care and resource-limited settings" [290]. However, low accuracy of HDS and IHDS for the diagnosis of HAND and minor neurocognitive disorder (MND) was reported by Haddow et al [291]. The pooled diagnostic odds ratio for the HDS was 7.52 (95% confidence interval, 3.75–15.11); sensitivity and specificity for HAND were estimated at 68.1% and 77.9%; and sensitivity and specificity for MND were estimated at 42.0% and 91.2%. Zipursky et al published a systematic review of brief screening tools for neurocognitive impairment in PLWH and found that the HDS had poor pooled sensitivity (0.48) and that the IHDS had moderate pooled sensitivity (0.62) in detecting a range of cognitive impairments. Five newer screening tools had relatively good sensitivities (>0.70) [292]; however, none of the tools differentiated HAND conditions well enough to suggest broader use [292]. There were significant methodological shortcomings noted in most studies. These authors concluded that "HDS and IHDS perform well to screen for HAND but poorly for milder HAND conditions." Recently, a microRNA plasma biomarker has been developed to predict neurocognitive disorders in PLWH, but clinical screening will highlight the need for use of such a test [289].

The hallmark of HIV dementia is memory deficits with psychomotor retardation. Current outpatients with advanced HIV disease may develop minor cognitive motor disorders over months, with subtle neurological impairment in 20% of symptomatic adults regardless of degree of viral suppression. Clinical manifestations to watch for include cognitive, behavioral, and motor dysfunction such as gait disturbance or tremor [293]. Patients with these symptoms would benefit from a neurological consultation or formal neuropsychiatric testing.

In the Swiss Cohort, 80% of patients with long-standing HIV viral suppression demonstrated measurable cognitive deficits when screened with the following questions: Do you experience frequent memory loss? For example, forget the occurrence of special events or appointments; Do you feel you are slower when reasoning, planning activities, or solving problems?; and Do you have difficulties paying attention? For example, paying attention to a conversation, book, or movie. Answers included "yes," "no," or "definitely yes" [286]. Persons responding with "definitely yes" to any question should be formally evaluated for neurocognitive disorder [286].

Because of the impact controlled substances have on cognitive function, pain treatments should be managed as effectively as possible during the evaluation. Additionally, dosing should be stabilized at the time of testing to minimize confounding.

There is a significant continuum of mental health issues that represent serious comorbidities for PLWH who have chronic pain. These issues can complicate both evaluation and management of chronic pain and must be well documented in the patient record to allow for effective team-wide care planning. Each care delivery site must develop policies for screening, evaluation, and referrals related to mental health issues that will assist in streamlining pain management strategies. Patients and their support persons will appreciate overall coordination by the primary care provider to avoid potential difficulties encountered by many chronic pain patients.

Future Directions

Although chronic pain is common in PLWH, many questions remain unanswered. Findings from studies conducted in the general population are not always generalizable to PLWH, and interventions to reduce the negative unintended consequences of opioid treatment have not been rigorously tested. Additional studies are needed to ascertain the optimal nonpharmacological and pharmacologic treatment for HIV-associated neuropathic pain and nonneuropathic pain in PLWH. Additional research is needed to adapt behavioral interventions designed for relatively healthy general population to chronic pain in PLWH. Finally, work to understand the impact of chronic pain on outcomes in PLWH is needed.

Notes

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possible conflicts of interest is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader should be mindful of this when the list of disclosures is reviewed. A. C. has received research grants from the Centers for Disease Control and Prevention and National Institutes of Health. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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