Brief Review

Pain syndromes in HIV infection

Jamie Penfold BSc MD, A.J.M. Clark MD FRCPC

Pain causes considerable disability and discomfort in HIV (Human Immunodeficiency Virus) infected individuals. A large number of patients infected with HIV suffer from one or more pain-related syndromes. Pain is under-reported and suboptimally managed in these patients. An outline of the different pain syndromes, including headache, oral cavity pain, chest pain, abdominal pain, anorectal pain, musculoskeletal pain and peripheral neuropathic pain, and their aetiologies are discussed. Current pain management modalities, including non-narcotic and narcotic analgesics, tricyclic antidepressants, anticonvulsants, physical therapy and psychological techniques, are outlined. Treatment should be based on the same principles applied to the management of cancer-related pain. A multidisciplinary, comprehensive approach to pain management will assist these individuals to achieve improved levels of comfort, function and quality of life in this ultimately terminal illness.

La douleur cause un inconfort et une incapacité considérable chez les individus infectés avec le virus HIV (Human Immunodeficiency Virus). Plusieurs patients infectés avec le virus HIV souffrent d'un ou de plusieurs syndrômes associés à de la douleur. On parle peu de cette douleur chez ces patients et elle est traitée de façon inadéquate. Nous décrivons les différents syndrômes douloureux suivants et discutons de leur étiologie : céphalée, douleur de la cavité orale, douleur thoracique, douleur abdominale, douleur anorectale, douleur musculosquelettique et douleur de neuropathie périphérique. Nous décrivons les

modalités thérapeutiques courantes incluant les analgésiques narcotiques et non narcotiques, les antidépresseurs tricycliques, les anticonvulsivants, la physiothérapie et les techniques psychologiques. Le traitement devrait être fondé sur les mêmes principes que ceux de la douleur reliée au cancer. Une approche compréhensive et multidisciplinaire face au traitement de la douleur aidera ces individus à obtenir un niveau amélioré de confort, de fonctionnement ainsi qu'une meilleure qualité de vie face à cette maladie terminale.

The clinical spectrum of human immunodeficiency virus (HIV) infection ranges from an acute mononucleosis-like illness, associated with seroconversion, to the immunocompromised state of acquired immunodeficiency syndrome (AIDS) with its life-threatening opportunistic infections. Between these two clinical manifestations are: (1) the asymptomatic state, (2) persistent generalized lymphadenopathy (PGL), (3) the condition previously known as the AIDS-related complex (ARC). Human immunodeficiency virus (HIV) infection can involve every organ system in the body and cause organ-specific symptoms as well as non-specific systemic symptoms.¹ One of the non-specific symptoms responsible for considerable disability, discomfort, and impaired quality of life is pain.

Recent studies by Lebovits and Schofferman in hospitalized and hospice/home care patients have indicated, based on chart reviews, that approximately 50% of patients infected with HIV admitted to hospital suffer from pain-related syndromes.^{2,3} Pain was the primary reason for admission to hospital in 30% of these patients.² Both authors expressed the opinion that the symptom of pain was under-reported and that the overall incidence of pain in this group of patients was probably higher than they reported.^{2,3}

The most frequently reported pain syndromes were chest pain, headache, abdominal pain, oesophageal and oral cavity pain, anorectal pain, pain related to peripheral neuropathies and musculoskeletal pain. Some patients suffered from more than one type of pain related to the HIV infection.^{2,3}

Key words

INFECTION: HIV, AIDS;

PAIN: chronic.

From the Department of Anaesthesia, Victoria General Hospital and Dalhousie University, Halifax, Nova Scotia.

Address correspondence to: Dr. A.J.M. Clark, Pain Management Unit Ambulatory Care Centre, 4th Floor Victoria General Hospital, 1278 Tower Road Halifax, Nova Scotia, Canada B3H 2Y9.

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Pain syndromes

Chest pain

The incidence of chest pain in HIV-infected persons has been reported to be as high as 41%² and reflects the high incidence of pneumonia.^{4,5} Chest pain related to *Pneumocystis carinii* pneumonia (PCP) is characterized by retrosternal burning on deep inspiration. Pneumothorax due to PCP may result in the acute onset of pleuritic chest pain. Other organisms responsible for pneumonia include mycobacterium tuberculosis, atypical mycobacteria, pyogenic bacteria, fungi and cytomegalovirus (CMV).^{4,5}

Chest discomfort may also arise from oesophageal pathology and is usually associated with the symptoms of odynophagia and dysphagia. Oesophageal candidiasis and its resultant ulcerations are responsible for more than 75% of the cases of odynophagia.^{5,6} Herpes simplex virus (HSV), CMV and HIV can also cause oesophageal ulcers.⁷ Other causes of dysphagia and chest pain include Kaposi's sarcoma and lymphomas.⁵ Reflux oesophagitis, oesophageal cancer and achalasia occur in this group of patients as they do in the immunocompetent patient.

Treatment is often on an empiric basis, initially with an oral antifungal agent; further investigations are undertaken only if there is no response to this therapy. Candidiasis is treated with ketoconazole, fluconazole, and occasionally amphotericin B. Herpes simplex virus is treated with a course of acyclovir and CMV is usually treated with ganciclovir.^{5,6} Pneumonia-related chest pain is treated with non-steroidal anti-inflammatory drugs (NSAID's) and transcutaneous electrical nerve stimulation (TENS) in addition to antimicrobial therapy.⁴

Herpes zoster radiculitis causes chest pain in 2% of HIV infected individuals.² Treatment may include NSAID's, sympathetic blocks and/or acyclovir. Some patients will develop post-herpetic neuralgia which is treated with topical capsaicin, low dose tricyclic antidepressants and/or anticonvulsants.^{8,9}

Oral cavity pain

Oral cavity pain is experienced by 28% of HIV-infected individuals.² The most common cause for this discomfort is oral candidiasis ("Thrush"). Herpes simplex virus stomatitis, herpes zoster radiculitis, recurrent aphthous ulcers, and Kaposi's sarcoma also cause oral pain. Treatment includes antimicrobial therapy as indicated previously, in conjunction with local anaesthetic oral solutions (e.g., viscous xylocaine or Tantum[®]). Steroids and sucralfate emulsion have also been employed as therapeutic agents for aphthous ulcers. Kaposi's sarcoma can be treated with intralesional vinblastine, radiotherapy

and/or laser. Steroids may be employed to reduce soft tissue swelling and provide symptomatic relief. Maintenance therapy with ketoconazole can be used to control recurrent candidal infections.⁶

Headache

Headache may signal HIV-related involvement of the central nervous system (CNS). Aseptic meningitis associated with acute HIV infection is characterized by fever, headache and meningism. Other causes of headache include primary CNS lymphoma and metastatic Kaposi's sarcoma, toxoplasmosis, HSV, papovavirus, and HIV.^{4,10,11}

Other causes of headache, which are frequently seen in the general population, include tension headache, vascular headache and sinus infections. Nearly 50% of patients on zidovudine (azidothymidine) therapy develop headache as a side effect of this therapy which resolves with discontinuation of the drug.⁴

Treatment of headache is directed at correcting the underlying process with antimicrobial agents, antineoplastic agents or radiotherapy. Non-steroidal anti-inflammatory drugs and acetaminophen are employed for symptomatic relief as well. Low-dose tricyclic antidepressants are frequently helpful. Psychological interventions, such as biofeedback and stress management, are adjuncts to treatment.⁴

Peripheral nervous system

Abnormalities of peripheral nerves occur in 10–50% of HIV-infected individuals.^{10–12} Painful peripheral neuropathy is characterized by dysaesthesiae, stocking-glove sensory loss, diminished reflexes, distal weakness and atrophy.^{2,4,12}

The pathogenesis of these peripheral neuropathies remains unclear; however, it may be related to the loss of myelinated fibres with disproportionately greater loss of large myelinated fibres.¹³

Toxic effects, secondary to administration of the anti-retroviral agents ddI (dideoxyinosine) and ddC (dideoxycytosine) and metabolic abnormalities, such as vitamin B and vitamin E deficiencies, can result in painful peripheral neuropathies.^{4,11,12} Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), herpes zoster radiculitis, CMV and neuropathies related to direct infiltration of the nerves with lymphoma, can also cause neuropathic pain.^{4,12}

Treatment involves treating the underlying infections or neoplasms and use of tricyclic antidepressants, anticonvulsants, topical capsaicin, retroviral therapy (zidovudine) and/or mexilitene. Dejgard *et al.* found that mexilitene provided considerable improvement in the

treatment of the pain, paraesthesiae and dysaesthesiae of diabetic peripheral neuropathy.¹⁴ Mexilitene has been applied to the treatment of HIV-related neuropathic pain with similar results in our own experience (three patients).

Abdominal pain

The incidence of abdominal pain is as high as 12% in HIV-infected individuals.¹⁵ Diagnosis can be a challenge as these patients frequently experience pain from the more common causes seen in immunocompetent individuals.^{15,16}

Cholecystitis can occur secondary to CMV or coincidental gallstones, or from infection of the bile by candida sp. or campylobacter. Ascending cholangitis can result from cryptosporidiosis and/or CMV infection of the biliary tract. All can manifest as episodic exacerbations of fever and right upper quadrant pain. Mycobacterium avium intracellulare (MAIC) and Kaposi's sarcoma can produce abdominal pain due to extraphepatic biliary obstruction.^{15,16}

Appendicitis, enteritis and colitis can also produce abdominal pain. Appendicitis can be coincidental or can result from obstruction by HIV-related neoplasms. Perforation of the large or small bowel may occur secondary to tumour involvement or CMV infection.^{4,15,16}

Infective diarrhoea is associated with crampy abdominal pain and fever caused by shigella, salmonella, campylobacter, E. histolytica and cryptosporidium.¹⁶

Pancreatitis may occur as a result of the administration of pentamidine, an agent used in the treatment of PCP¹⁵ or the antiretroviral agent, ddI. Organomegaly from CMV hepatitis, tumour involvement of intraabdominal organs, MAIC infiltration of the liver and/or spleen causes abdominal pain.^{4,15,16} It is important to remember that HIV-infected patients can also develop illnesses not unique to AIDS and the immunosuppressed state, for example, peptic ulcer disease.

Barone *et al.* reported there was only one surgery-related complication in a series of 53 laparotomies performed on HIV-infected patients, in spite of their immunocompromised status. These patients are not necessarily at increased risk of abdominal wound complications. The majority (60%) of those patients explored for illnesses not known to be manifestations of AIDS survived for more than three months after surgery, whereas only 33% of individuals with AIDS-related illnesses survived for three months postoperatively.¹⁵

Treatment of abdominal pain is directed by its aetiology. Antimicrobial therapy, antispasmodic and/or anti-diarrhoeal agents may be used. Narcotic analgesics, on a fixed time and dosage schedule, are sometimes necessary.

Anorectal pain

Infections, anal and rectal cancers, lymphoma, Kaposi's sarcoma, trauma, fissures/fistulae/abscesses and hemorrhoids are common causes of anorectal pain.

In a predominantly male homosexual population of AIDS/ARC individuals, 34% had diseases of the anorectal area and 50% required surgical intervention. Healing is poor and a higher number of complications are noted in this group of patients. The intravenous drug abuse risk group demonstrates a lower incidence of anorectal disease than the male homosexual risk group.¹⁵

Patients with recurrent anorectal sexually transmissible diseases, colonic enteric infection, herpes zoster, oral candidiasis, weight loss, fever, night sweats, diarrhoea, fatigue, lymphadenopathy and leukopenia are at risk of delayed healing and should be treated by non-surgical means if possible. The rate of postoperative complications and mortality are high in surgically treated patients.¹⁵ Pain control can often be achieved with NSAID's.

Musculoskeletal pain

Musculoskeletal manifestations of HIV infection range from arthralgias and myalgias to full-blown arthritides. Acute HIV infection can result in diffuse arthralgias and myalgias. A reactive, severe, persistent oligoarthritis, that affects the large joints, may develop. A Reiter's syndrome may occur, with the triad of arthritis, uveitis, and balanitis. A seronegative HIV arthropathy has been described, with the duration of symptoms lasting from 1–24 wk.^{17,18}

Psoriasis and psoriatic arthritis may flare up or appear *de novo* at the onset of ARC or AIDS. Immunosuppressive treatment of the arthritic and dermatologic features with methotrexate or phototherapy can result in clinical deterioration in immune status.¹⁷

Sjogren's syndrome and necrotizing vasculitides have been implicated as causes of arthralgias. Septic arthritis resulting from systemic opportunistic infections (i.e., cryptococcus) and pyogenic organisms can occur, especially in haemophiliacs with HIV infection.^{17,18} Myalgias may be caused by polymyositis or dermatomyositis. Polymyositis is characterized by proximal muscle weakness, myalgias and limb wasting. Myositis may be caused by zidovudine therapy.⁴

Back pain may result from causes other than the usual mechanical derangements commonly seen in the general population. Epidural metastases of lymphoma, or rarely, Kaposi's sarcoma should be considered.⁴

Hyperalgesic pseudothrombophlebitis is an entity peculiar to HIV-infected individuals characterized by painful calf swelling, erythema, cutaneous hyperalgesia and fever. Treatment consists of NSAID's.⁴

Most patients with arthralgias, myalgias and reactive arthritides respond to conventional anti-rheumatic therapy consisting of NSAID's and non-narcotic analgesics. More potent narcotic analgesics may be required. Deterioration of immunodeficiency status and progression to development of Kaposi's sarcoma and AIDS may be seen following immunosuppressive therapy. Accordingly, Espinoza *et al.* recommend that lower than usual doses of immunosuppressive agents be employed.¹⁷ Local steroid injections may be of benefit. A combined regimen of oral steroids and zidovudine is the current approach to management of polymyositis not due to zidovudine.¹⁷ Radiation therapy, steroids, and surgical decompression may occasionally be indicated in metastatic disease to the spine and epidural space.⁴

Table I lists the common aetiologies of pain and Table II provides an outline of the different classes of drugs, with appropriate doses, useful in the management of pain.

Discussion

Pain experienced by patients with HIV infection is often chronic and punctuated with acute exacerbations. The approach to treatment should model that used for chronic cancer-related pain.^{2,19}

Lebovits *et al.* noted that pain syndromes associated with HIV infection usually were not managed in this way. The dosing schedule of analgesics was p.r.n. rather than on a fixed time and dosage schedule. The most common analgesic used was acetaminophen alone or combined with codeine or oxycodone. No patient with pain was prescribed a tricyclic antidepressant, although these agents are frequently used in the treatment of chronic and cancer pain.²

The majority of HIV-infected patients are young people facing a terminal illness, who face severe psychosocial stresses associated with their disease. Tricyclic antidepressants would be of benefit in these cases as would psychological intervention and access to a hospice/palliative care programme.³

A recommended approach to pain management in HIV-infected patients consists of treating any correctable causes of pain with surgery, antiviral, antifungal or antibiotic agents as indicated by investigational results. During and following the initiation of definitive treatment, mild to moderate pain may be treated with a NSAID or acetaminophen on a fixed time and dosage schedule. If the pain is not adequately controlled, an opioid may be added to this regimen. Initially codeine in combination with acetaminophen should be used on a fixed schedule and *not prn*. Some patients will require a more potent narcotic analgesic (i.e., oral morphine sulphate). Additional doses of narcotic should be provided for break-

TABLE I Aetiology of pain syndromes.

<i>Chest pain</i>
Pneumonia
Pneumothorax
Oesophageal pathology
– candidiasis, HSV, CMV, HIV
– reflux oesophagitis
– oesophageal cancer
– achalasia
Herpes zoster radiculitis/post herpetic neuritis
<i>Oral cavity pain</i>
Oral candidiasis
HSV stomatitis
Herpes zoster radiculitis
Aphthous ulcers
<i>Headache</i>
Aseptic meningitis syndrome
Primary CNS lymphoma
Metastatic Kaposi's sarcoma
Toxoplasmosis
HSV encephalitis
HIV subacute encephalitis
Muscle tension
Vascular
Sinus infection
<i>Peripheral neuropathic pain</i>
Peripheral neuropathies
– toxic/metabolic causes
– Guillain-Barré
– CIDP
Herpes zoster radiculitis/post herpetic neuritis
CMV radiculitis
Infiltration of nerves with lymphoma
<i>Abdominal pain</i>
Cholecystitis
– acalculous/gallstones
Ascending cholangitis
– cryptosporidiosis ± CMV infection
Appendicitis
Enteritis/colitis
– infective
Perforated viscus
– tumour/CMV infection
Pancreatitis
– pentamidine/antiretroviral agents
Organomegaly
– tumour/infection
<i>Anorectal pain</i>
Infections
Anal/rectal cancers
Lymphoma
Kaposi's sarcoma
Fissures/fistulae/abscesses/haemorrhoids
<i>Musculoskeletal pain</i>
Arthralgias/myalgias
– acute HIV infection
Oligoarthritis
Psoriasis/psoriatic arthritis
Sjögren's syndrome
Necrotizing vasculitides
Septic arthritides
Polymyositis/dermatomyositis
<i>Back pain</i>
– mechanical
– epidural metastases
– Kaposi's sarcoma
– lymphoma
Hyperalgesic pseudothrombophlebitis

TABLE II Analgesics and adjuvant agents used in treatment of HIV-related pain syndromes

Category	Agent	Dosage	Comments	Alternatives
Non-narcotic	Acetaminophen	650 mg <i>po</i> Q4hr	<ul style="list-style-type: none"> – for mild intensity pain – NSAID's helpful in bony pain/arthritis/myalgia – consider cytoprotection of GI tract if NSAID's used (i.e., H₂ blockers, cytoprotective agents) – often used in combination with codeine for more intense pain (see below) 	ASA (acetylsalicylic acid) Other NSAID's e.g., Ibuprofen Naproxen Diclofenac
Narcotic agonists	(i) Codeine	30–60 mg <i>po</i> Q4–6hr	<ul style="list-style-type: none"> – for moderate pain – often used in combination with acetaminophen 	Oxycodone
	(ii) Morphine	20–30 mg <i>po</i> Q4hr – increase initial doses by 50–100% if no relief – provide doses for breakthrough pain	Exists in many forms: <ul style="list-style-type: none"> – syrup – tablets – slow release BID dosage Other methods of administration: <ul style="list-style-type: none"> – <i>iv</i>, <i>im</i>, <i>sc</i>, rectal – PCA Narcotic side effects need treating: <ul style="list-style-type: none"> – constipation – nausea/vomiting – drowsiness – confusion – urinary retention 	Dihydromorphone Methadone Dihydromorphone useful for PCA/SC administration
Adjuvants: (a) Topical	Capsaicin	<ul style="list-style-type: none"> – external use only 0.025%–0.05% cream – apply TID–QID to affected areas 	<ul style="list-style-type: none"> – neuralgia therapy – works by depleting and preventing reaccumulation of substance P in sensory neurons 	
	Viscous xylocaine	4% solution 10 ml QID or 5% ointment	<ul style="list-style-type: none"> – as oral rinse or gargle for oropharyngeal ulcers 	Benzydamine 15 ml TID–QID
(b) Tricyclic antidepressants	Amitriptyline	10–50 mg <i>po</i> qhs	Frequent use as adjunct for: <ul style="list-style-type: none"> – dysaesthesias – mood disturbances – sleep enhancement Side effects: <ul style="list-style-type: none"> – glaucoma – dry mouth – drowsiness/confusion – orthostatic hypotension 	Doxepin Imipramine
(c) Anticonvulsants	Carbamazepine	100–200 mg <i>po</i> BID–TID	<ul style="list-style-type: none"> – for neuropathic pain – monitor liver function with prolonged use – hematologic changes i.e., aplastic anemia 	
(d) Antiarrhythmics	Mexilitene	100–300 mg BID–TID	<ul style="list-style-type: none"> – oral analogue of lidocaine – originally used in treatment of diabetic neuropathies 	
(e) Steroids	Predisone	30–60 mg daily	<ul style="list-style-type: none"> – 30–60 mg – polymyositis – tumor/nerve edema – smaller doses used to relieve swelling related to oral aphthous ulcers 	

through pain. Stepwise increases in dosage may be used in a manner similar to those provided to patients with cancer pain. An appropriate bowel regimen, consisting of stool softeners and laxatives, should be instituted when narcotics are prescribed.¹⁹

Neurological impairment with cognitive abnormalities is present in up to 65% of HIV-infected patients.^{3,11} There is concern that narcotic analgesics may impair cognitive function, but this should not be a problem if the narcotic is administered carefully.² Non-steroidal antiinflammatory drugs should be used prior to the administration of narcotics in patients with neurological impairment, particularly in those with dementia.

Tricyclic antidepressants are an effective therapeutic adjunct in HIV-infected patients. Use of low doses of tricyclic antidepressants (10–50 mg amitriptyline or doxepin) at bedtime may assist in providing analgesia, improved sleep and mood.²

Other interventions such as epidural steroid injections, sympathetic and somatic nerve blocks, trigger point injections, splints and TENS units may be employed with success in certain selected cases. Psychological intervention involving biofeedback, relaxation training, hypnosis and group therapy is an important beneficial adjunct to therapy and provides a comprehensive approach to pain management in these individuals.² Additionally, access to hospice/palliative care services should be available.²⁰

Pain management potentially may be difficult in the intravenous drug abuse risk group. With their physical and psychological dependencies, concerns arise regarding adherence to treatment regimens. Specific pain control protocols (i.e., contracting) should be established in this group to circumvent these difficulties. It is interesting to note that, so far, this group has not demonstrated an increased requirement for analgesics as compared to the other risk groups.²

A final concern in the pain management of HIV infected individuals is the attitude of health care providers towards this patient population. Unwarranted fears and social isolation of HIV-infected individuals distances health care providers from the patient and impairs appropriate comprehensive care and management. Steps need to be taken to ensure this does not occur.

Conclusion

Patients infected with HIV experience a wide number of different pain syndromes affecting almost every organ. These syndromes are underreported and suboptimally managed. A comprehensive, multidisciplinary, approach to management can be instituted and modelled on the principles used in managing cancer-related pain. Consultation and periodic follow-up visits with personnel in a

multidisciplinary pain/palliative care/hospice clinic setting may be desirable. Health professionals should assist HIV-infected individuals in attaining the goals of improved levels of comfort and function, resulting in subsequent improvement in quality of life in this devastating terminal illness.

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