Basics of Pain Management and Special Considerations for HIV-infected Individuals

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Pharmacist Learning Objectives

• Differentiate between types of pain.
• Describe the mechanisms of action of various classes of medications used to treat pain.
• Develop a pain management strategy for an HIV-infected individual.

Technician Learning Objectives

• Differentiate between types of pain.
• Describe why opioids are not considered first line agents for many types of pain.
• Discuss what makes management of pain in HIV-infected individuals unique.
Pain

- It is estimated that >100 million persons in the United States live with chronic pain.
  - 56%-83% of individuals with AIDS have unrelieved or inadequately relieved pain
- Chronic pain results in
  - >550 million missed work days
  - >$50 billion in health care cost

Classification of Pain

- Classification of pain
  - Neuropathic mechanisms
  - Temporal aspects
  - Etiology
  - Region of the body affected

Neuropathic Classification

- Nociceptive
  - Pain caused by tissue injury.
  - Subdivided into somatic and visceral pain.
- Non-nociceptive
  - Results from injury to neural structures within the peripheral or central nervous system.
Nociceptive Pain

- Results from the activation or sensitization of nociceptors in the periphery.
- Impulses are transmitted to the spinal cord by peripheral neurons.
- Processed in the CNS.

Physiology of Nociceptive Pain

- Conduction: Generation of action potentials that are conducted along nerve fibers.
- Transduction: Stimulation of nociceptors causes release/activation of cytokines and chemokines.

Peripheral Neurons
Physiology of Nociceptive Pain

Transduction
- Stimulation of nociceptors causes release/activation of cytokines and chemokines.

Conduction
- Generation of action potentials that are conducted along nerve fibers.

Transmission
- Pain fibers stimulate the release of excitatory transmitters like glutamate and substance P in dorsal horn.

Perception
- Pain is a conscious experience.

Modulation
- The signal can also be attenuated/inhibited by descending pathways that consist of endogenous opioids (e.g., enkephalins, and β-endorphins) and γ-aminobutyric acid (GABA), norepinephrine, or serotonin.
- Blockade of N-methyl-D-aspartate (NMDA) receptors may increase the μ-receptors' responsiveness to opiates.

Nociceptive Pain

Somatic pain
- Stimulation of nociceptors in the periphery.
- Characterized as being well localized topographically, intermittent or constant, and is described as "aching, stabbing, gnawing, or throbbing.

Visceral Pain
- Diffuse and poorly localized.
- Referred pain
- Accompanied by motor and autonomic reflexes, such as the nausea, vomiting, and lower back muscle tension.
Non-nociceptive Pain

- Neuropathic pain
  - Three subsets: peripherally generated, centrally generated, and sympathetically maintained.
  - Sustained by aberrant somatosensory processing in the periphery or central nervous system.
  - Described as sharp or burning.
- Idiopathic pain

Temporal Classification

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic (Pathophysiologic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maybe directly related to tissue damage or trauma.</td>
<td>• Considered a disease state.</td>
</tr>
<tr>
<td>• Self-limiting.</td>
<td>• Outlasts the normal time of healing.</td>
</tr>
<tr>
<td>• Serves a useful biologic purpose.</td>
<td>• May arise from psychological states.</td>
</tr>
<tr>
<td>• Less than 3-6 months in duration.</td>
<td>• Lasts at least 6 months and has no recognizable endpoint.</td>
</tr>
<tr>
<td></td>
<td>• Serves no biologic purpose.</td>
</tr>
</tbody>
</table>

Assessment of Pain

- When did the pain begin?
- Did something trigger the pain?
- Describe the pain.
- What makes the pain better or worse?
- How does this pain compare with other pain you have experienced?
- Does the intensity of the pain change with time?
Assessment of Pain

Pain in HIV-Infected Individuals

- Typically nociceptive or neuropathic
- Multifactorial
- May result from:
  - HIV-related causes (30%)
    - Direct action of the virus on the nervous system
    - Immune suppression
    - Opportunistic infections
  - Side effects of anti-retrovirals (4%)
    - NRTIs: stavudine > didanosine or zalcitabine
  - Causes not related to HIV

Common Sources on Nociceptive Pain in Patients with HIV

<table>
<thead>
<tr>
<th>Cutaneous Causes</th>
<th>Visceral Causes</th>
<th>Deep Somatic Causes</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>Tumor</td>
<td>Rheumatologic</td>
<td>HIV-related (e.g., meningitis, encephalitis, seizures)</td>
</tr>
<tr>
<td>Oral cavity pain</td>
<td>Gastritis</td>
<td>Back pain</td>
<td>Non-HIV-related iatrogenic (e.g., medications)</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td>Myopathies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Arthralgias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biliary tract disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Common Pain Syndromes in Patients with HIV

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>26%</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>20-44%</td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
</tr>
<tr>
<td>HIV-related Headaches</td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>5-12%</td>
</tr>
<tr>
<td>Migraine</td>
<td>10%</td>
</tr>
<tr>
<td>AIDS-induced headache</td>
<td>10%</td>
</tr>
<tr>
<td>Couples</td>
<td>5%</td>
</tr>
<tr>
<td>Back pain</td>
<td>5%</td>
</tr>
</tbody>
</table>

Painful Neuropathies According to Stage of HIV

- Acute or seroconversion phase
  - Peripheral (e.g., mononeuritis multiplex)
  - Acute demyelinating polyneuropathy (e.g., Guillain-Barré syndrome)
- Latent (asymptomatic) phase (CD4+ >500/mm³)
  - Acute demyelinating polyneuropathy (e.g., Shikata-Barré syndrome)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Transition phase (CD4+ 200-500/mm³)
  - Shingles
  - Mononeuritis multiplex
- Late phase (CD4+ <200/mm³)
  - Secondary polyneuropathy
  - CMV
  - Mononeuritis multiplex (severe)
  - Drug toxicity
  - Other opportunistic infections

Pain in HIV-Infected Individuals

- 50 to >70% of people with HIV/AIDS report pain in the past 3 months.
  - Lower limbs, head, and neck are most commonly involved.
  - Most pain is moderate to severe in intensity.
- Associated with disease progression.
  - 25-35% of individuals with early-stage HIV
  - 50% of ambulatory patients with AIDS
  - 50-60% of hospitalized patients with AIDS
  - 60-70% of AIDS patients in hospice
- Pain less likely for individual on and adherent to HAART.
Pain in HIV-Infected Individuals

- Untreated pain is associated with lower rates of HAART adherence.
- Presence of pain in the past week associated with more anxiety and depression.
  - Depression, psychological distress, and lower levels of emotional control are associated with greater levels of pain.

WHO Pain Management Ladder

<table>
<thead>
<tr>
<th>Step 1 (Pain score 1-4)</th>
<th>Step 2 (Pain score 5-7)</th>
<th>Step 3 (Pain score 8-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid</td>
<td>Opioid for moderate pain</td>
<td>Opioid for moderate to severe pain</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Non-opioid</td>
<td>Non-opioid</td>
</tr>
</tbody>
</table>

Non-opioid: NSAID or acetaminophen
Adjuvants: Antidepressants, antiepileptics, topicals, muscle relaxants
Opioids: Codeine, hydrocodone, or oxycodone in combination with NSAID or acetaminophen or tramadol
Opioids: Morphine, hydromorphone, oxycodone, levorphanol, methadone, or fentanyl

Management of Pain

- Nonpharmacologic therapies should always be considered first-line for acute or chronic pain.
  - Physical manipulation, heat or cold, massage, biofeedback, cognitive behavioral therapy, relaxation, or acupuncture.
  - Multimodal and multidisciplinary approaches work best.
Examples of Behavioral Therapies

- Progressive Muscle Relaxation
- Cognitive Behavioral Therapy
- Neurofeedback
- Biofeedback

Non-Opioid Agents

- Acetaminophen
  Mechanism: Believed to inhibit prostaglandin by inhibiting cyclooxygenase (COX) synthesis in the CNS and block peripheral nerve impulse.
  - Does not have anti-inflammatory properties.
  - Does not inhibit platelet aggregation.
  Dose: 650mg every 4-6 hours (maximum daily dose 3,250 mg)
  Drug interactions: Minimal
  ADR: Primary concern is hepatotoxicity

Non-Opioid Agents

- Nonsteroidal Anti-inflammatory Drugs
  Mechanism: Act by decreasing central and peripheral production of prostaglandins by inhibiting cyclooxygenase (COX).
  - Reduces pain, swelling, and edema.
  More than 20 available agents
  - Use ketorolac with caution (Risk of bleeding and renal injury)
  - Trial of at least 1 month. May try a different agent.
  Drug interactions: Interaction with metabolic pathways varies among agents.
  - Typically because of anti-platelet effects and fluid retention
Metabolism of NSAIDs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celocoxib</td>
<td>CYP2C9, CYP3A4</td>
<td>CYP2C9, CYP2C8</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>CYP2C9, CYP2C19</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>CYP2C9, CYP2C19</td>
<td>CYP2C9, CYP2C19</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>CYP2C9, CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>CYP1A2, CYP2C9</td>
<td></td>
</tr>
</tbody>
</table>

Overall the risk if metabolic interaction is relatively low.

Non-Opioid Agents

- Nonsteroidal Anti-inflammatory Drugs
  - Mechanism: Act by decreasing central and peripheral production of prostaglandins by inhibiting cyclooxygenase (COX).
  - Reduces pain, swelling, and edema.
  - More than 20 available agents.
  - Drug interactions: Interaction with metabolic pathways varied among agents.
  - Typically because of anti-platelet effects and fluid retention
  - ADR: Gi bleed (lower with ibuprofen), renal failure, fluid retention, Gi

Risk of GI Bleed with NSAIDs

Risk of GI Bleed

400mg every 6 hours = 1,600mg daily
Nephrotoxicity with NSAIDs

- Normally the afferent arteriole is dilated because of prostaglandins.
- Inhibition of prostaglandin synthesis by NSAIDs reduces blood flow to the glomerulus leading to decreased pressure and GFR.

Non-Opioid Agents

Nonsteroidal Anti-inflammatory Drugs

- Pain relief is slightly improved (10%) by doubling dose.
  - Have a ceiling effect for pain (ibuprofen 400 mg)
  - Higher doses may improve anti-inflammatory effect.
- Start with a low dose and escalate to effect.
- Higher doses may increase the rate of side effects.

Opioids

- In 2014, 245 million prescriptions for opioids were filled in the United States.
  - 3%-4% of the adult population in on long-term opioid therapy.
  - 37% of drug-overdose deaths were attributable to prescription opioids.
Prescription Opioids in Michigan

- Counties with the highest prescribing rates

<table>
<thead>
<tr>
<th>County</th>
<th>Rate per 10,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bay</td>
<td>19,365</td>
</tr>
<tr>
<td>Iosco</td>
<td>17,975</td>
</tr>
<tr>
<td>Roscommon</td>
<td>17,617</td>
</tr>
<tr>
<td>Montmorency</td>
<td>17,495</td>
</tr>
<tr>
<td>Oscoda</td>
<td>16,917</td>
</tr>
<tr>
<td>Lake</td>
<td>16,778</td>
</tr>
<tr>
<td>Ogemaw</td>
<td>16,705</td>
</tr>
<tr>
<td>Arenac</td>
<td>16,498</td>
</tr>
<tr>
<td>Crawford</td>
<td>16,352</td>
</tr>
<tr>
<td>Gladwin</td>
<td>16,122</td>
</tr>
</tbody>
</table>

Source: MDHHS 2016
Prescription Opioids in Michigan

- Counties with the highest prescribing volumes

<table>
<thead>
<tr>
<th>County</th>
<th>Number of Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wayne</td>
<td>2,283,994</td>
</tr>
<tr>
<td>Oakland</td>
<td>1,126,356</td>
</tr>
<tr>
<td>Macomb</td>
<td>1,026,084</td>
</tr>
<tr>
<td>Genesee</td>
<td>608,868</td>
</tr>
<tr>
<td>Kent</td>
<td>563,320</td>
</tr>
<tr>
<td>Ingham</td>
<td>273,653</td>
</tr>
<tr>
<td>Muskegon</td>
<td>260,949</td>
</tr>
<tr>
<td>Kalamazoo</td>
<td>248,810</td>
</tr>
<tr>
<td>Saginaw</td>
<td>248,314</td>
</tr>
<tr>
<td>Washtenaw</td>
<td>243,936</td>
</tr>
</tbody>
</table>

Opioids

- Act by stimulating $\mu$-opioid receptors in the brain.
  - Modulates calcium and potassium ion channels to inhibit neuronal activity.
  - Accounts for analgesia, euphoria, and respiratory depression.

Opioids

- Repeated administration will result in tolerance and physical dependence.
  - Tolerance to analgesic effect and euphoric effects develops quickly.
  - Tolerance to respiratory depression occurs slowly.
  - No tolerance develops to constipation.
  - Physical dependence is not addiction.
    - Physiological adaptation.
    - Abrupt discontinuation results in withdrawal symptoms.
Opioids

- Addiction
  - Occurs slowly.
  - Risk factors
    - Higher doses (>100 morphine milligram equivalents)
    - Long-term use (>3 months)
    - Depression
    - Substance-use disorder (including alcohol)
    - Adolescence

<table>
<thead>
<tr>
<th>Opioid Conversion Factor</th>
<th>Codeine</th>
<th>Fentanyl transdermal</th>
<th>Hydrocodone</th>
<th>Hydromorphone</th>
<th>Morphine</th>
<th>Oxycodone</th>
<th>Oxymorphone</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.15</td>
<td>2.4</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1.5</td>
<td>4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

WHO Pain Management Ladder

Step 1 (Pain score 1-4)
- Non-opioid
- Adjuvant

Step 2 (Pain score 5-7)
- Opioid for moderate pain
- Non-opioid
- Adjuvant

Step 3 (Pain score 8-10)
- Opioid for moderate to severe pain
- Non-opioid
- Adjuvant

Opioid Use Guidelines

- Nonpharmacologic and nonopioid therapies are recommended for chronic pain.
  - No good data on long-term (>1 year) pain management.
  - If opioids are prescribed, reevaluate use every 3 months or less.
  - Risk associated with opioids for fibromyalgia outweigh benefits.
- Before starting opioids, establish goals for pain and function with patients.
  - Pain relief and improvement in function (e.g., emotional, social, and physical function).
- Discuss risks and realistic benefits of opioids.
**Pain, Enjoyment, General Activity (PEG) Score**

- Calculate score by adding scores and dividing by three.
- Track an individual's changes over time.

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**Opioid Use Guidelines**

- Start with immediate-release opioids.
  - Initiation with extended release or long-acting opioids is associated with increased risk of non-fatal overdose. Greatest risk within first 2 weeks.
- Use of opioids for low-risk surgery or injury-related low back pain is associated with a greater likelihood of long-term use.

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**Opioid Onset of Action**

<table>
<thead>
<tr>
<th>Opioid (Generic)</th>
<th>Other Names</th>
<th>Onset of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Tylenol with codeine</td>
<td>45-60 min</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>Duragesic</td>
<td>6 hours</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Norco, Vicodin</td>
<td>45-60 min</td>
</tr>
<tr>
<td>Hydroxyamphetamine</td>
<td>Dilaudid</td>
<td>30 min</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>30-45 min</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Opana</td>
<td>20-45 min</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Nucynta</td>
<td>30-45 min</td>
</tr>
</tbody>
</table>
Opioid Use Guidelines

- Start with low doses and escalate.
  - Reassess doses of >50 MME per day.
  - Dose around the clock as long as responsive stimulus is present.
- For acute pain, prescribe no greater quantity than needed for the expected duration of pain.
  - Three days or less is usually enough.
  - More than 7 days is rarely needed.
- Consider prescribing naloxone.
  - History of overdose, substance abuse, >50 MME/day, or concurrent benzodiazepine use.
  - Methadone is associated with a disproportionate number of overdose deaths.

Opioid Use Guidelines

- Review patient’s use of controlled substances when starting opioids and during use.
- Use urine drug testing to verify use.
- Avoid benzodiazepines.

Opioid Use Guidelines

- Use caution in patients:
  - With renal or hepatic dysfunction
  - Older than 65 years of age
  - With anxiety or depression
Opioid Use in HIV-Infected Individuals

- High potential for addiction.
  - Alcohol and intravenous drug use
  - Long-term opioid use is higher than general population
- Treat underlying psychosocial conditions
- Watch out for drug-drug interactions.
  - Many opioids are metabolized by CYP2D6 and CYP3A4
    - Opioids derived from opium poppies (e.g., heroin, morphine and codeine) are unlikely to cause changes in antiretroviral levels.
    - Several interact with various protease inhibitors

Opioid Drug Interactions

<table>
<thead>
<tr>
<th>Opioid (Generic)</th>
<th>Phase I Metabolism</th>
<th>Clinical Relevance</th>
<th>Interacting Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>CYP2D6, CYP3A4</td>
<td>Decreased analgesic effect when administered with CYP2D6 inhibitors</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A4</td>
<td>Increased opioid effects when administered with CYP3A4 inhibitors (Black Box Warning)</td>
<td>Protease inhibitors, Azole antifungals</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>CYP2D6, CYP3A4</td>
<td>May precipitate withdrawal</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP3A4, CYP2D6, CYP3A, CYP2C19</td>
<td>May precipitate withdrawal</td>
<td>Protease inhibitors, Azole antifungals</td>
</tr>
<tr>
<td>Morphine</td>
<td>CYP3A4</td>
<td>May precipitate withdrawal</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP2D6, CYP3A4</td>
<td>Increased opioid effects when administered with CYP3A4 inhibitors (Black Box Warning)</td>
<td>Protease inhibitors, Azole antifungals</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6, CYP3A4</td>
<td>Moderate (Less effective when used with ritonavir)</td>
<td>Protease inhibitors, Azole antifungals</td>
</tr>
</tbody>
</table>

Non-opioid Drug Interactions

<table>
<thead>
<tr>
<th>Agent (Generic)</th>
<th>Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Tenofovir</td>
<td>May increase risk of renal injury with tenofovir</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Efavirenz</td>
<td>May increase efavirenz levels</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Ritonavir</td>
<td>Levels of amitriptyline increased, decrease amitriptyline dose</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lopinavir, ritonavir</td>
<td>May decrease lamotrigine levels</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Didanosine</td>
<td>Antacid in didanosine may decrease gabapentin absorption. stagger doses.</td>
</tr>
</tbody>
</table>
Summary

• Not all pain is the same.
• Opioids are typically not first line for pain.
• HIV-infected individuals maybe at risk of overdose and drug-drug interactions with opioids.

Case

James is an HIV-infected client who presents to the pharmacy complaining of pain.

What questions would you ask James before making a recommendation?

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>When did the pain begin?</td>
<td>Awhile ago</td>
</tr>
<tr>
<td>Did something trigger the pain?</td>
<td>No</td>
</tr>
<tr>
<td>Can you describe the pain?</td>
<td>Pain in legs in tingling and burning Head is throbbing</td>
</tr>
<tr>
<td>What makes the pain better or worse?</td>
<td>Legs – Nothing</td>
</tr>
<tr>
<td>How does this pain compare with other pain you have experienced?</td>
<td>Legs – No Head – Really bad headache</td>
</tr>
<tr>
<td>Does the intensity of pain change with time?</td>
<td>Legs – No Head – Yes</td>
</tr>
<tr>
<td>Rate the severity of your pain?</td>
<td>6</td>
</tr>
</tbody>
</table>
Case

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>What medications are you currently taking?</td>
<td>Genvoya (Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) (\text{P}KR)</td>
</tr>
<tr>
<td>Do you know your CD4+ count?</td>
<td>&gt;1,000 cells/mm(^3)</td>
</tr>
<tr>
<td>Do you have any other medical conditions?</td>
<td>Depression</td>
</tr>
<tr>
<td>Do you use recreational drugs or alcohol?</td>
<td>Yes, marijuana and alcohol</td>
</tr>
</tbody>
</table>

---

**Case**

What do you think the etiology of James’ leg pain could be?

- Polyneuropathy caused by HIV-infection

What do you think the etiology of James’ head pain could be?

- Depression, stress, medications

---

**Case**

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head Pain</strong></td>
</tr>
<tr>
<td>Dry muscle relaxation techniques</td>
</tr>
<tr>
<td>Motrin 200-400 mg every 6 hours</td>
</tr>
<tr>
<td>Motrin 200-400 mg every 6 hours</td>
</tr>
<tr>
<td>Topical agents</td>
</tr>
<tr>
<td><em>New prescription if no relief</em></td>
</tr>
</tbody>
</table>
### Case

**Counseling points**
- Must practice relaxation techniques
- Set expectations for pain relief
  - Likely going to have some pain
  - Improve functionality
- Counsel on adherence to HAART
- Try for 2 weeks