From Viral Load to Pain Mode: Navigating Chronic Pain in HIV

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Learning Objectives

By the end of this presentation, the audience will be able to:

1. Explain what chronic pain is and its classification.
2. Describe foundational principles in chronic pain management, including the adapted biopsychosocial framework for chronic pain in HIV and adapted fear avoidance model for people with HIV and chronic pain.
3. Describe HIV associated neuropathic pain and its management.
4. Recognize the growing likelihood of encountering chronic pain associated with osteoarthritis in the HIV population and be familiar with recommended non-surgical management strategies.

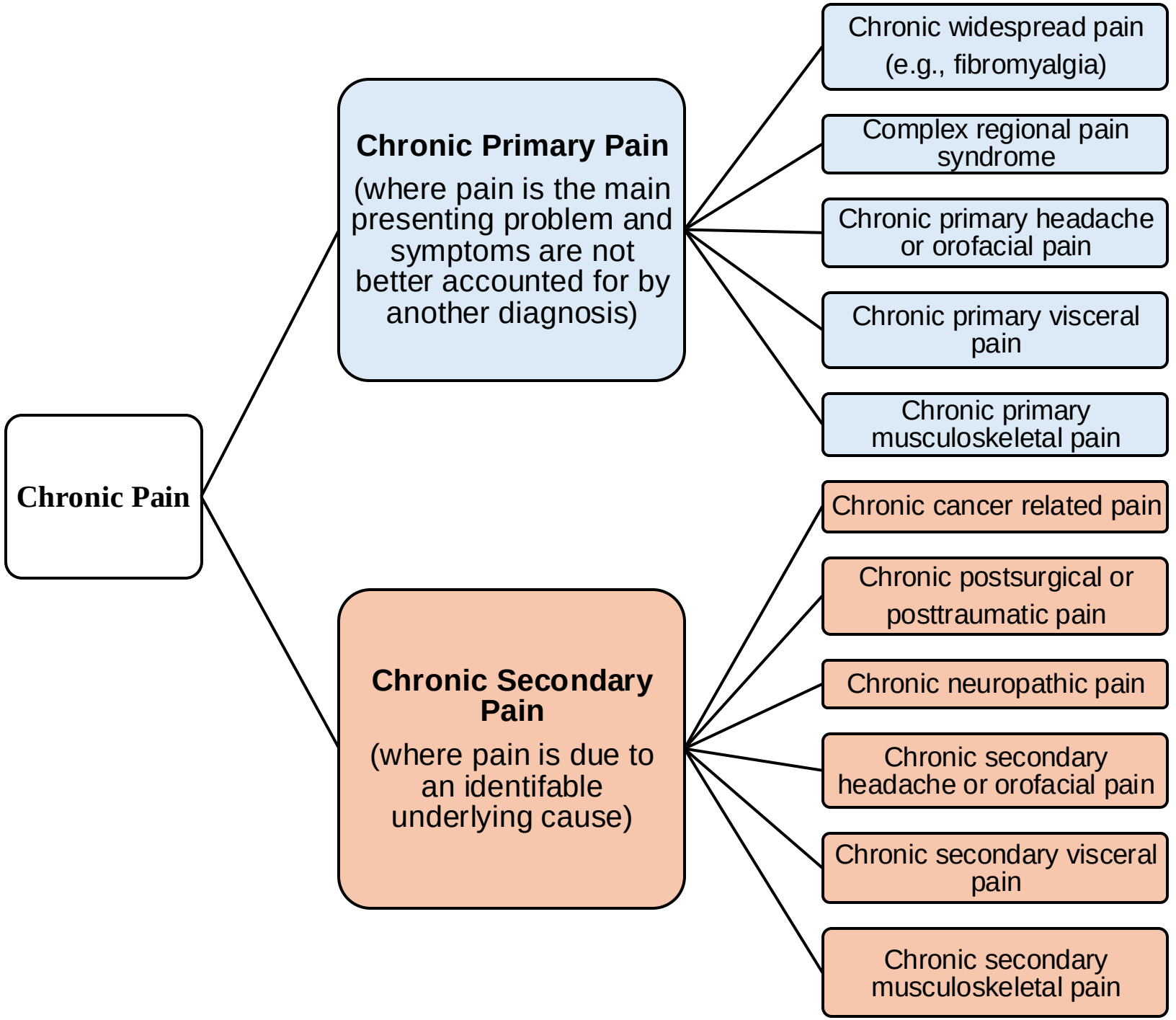
Intro to Pain

The International Association for the Study of Pain (IASP) defines pain as:
"an **unpleasant sensory and emotional experience**
associated with, or resembling that associated with,
actual or potential tissue damage.

Pain becomes chronic when it lasts or recurs for >3 months.

The WHO recognizes **chronic pain as a disease** in the ICD-11, **with a code for pain severity that accounts for: pain intensity**, **emotional distress,** and **interference with function**.

IASP Chronic Pain Classification



Source: data from Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. Jan 2019;160(1):19-27.

Chronic Pain and HIV

- Chronic pain is the **second most common symptom** in ambulatory settings where HIV is treated

- Estimated **54-83%** of people with HIV experience chronic pain throughout their lifetimes, with prevalence increasing as they age

- More severe chronic pain outcomes and/or heightened pain medication use in people with HIV have been associated with presence of:
  - depression
  - psychological distress
  - post-traumatic stress
  - drug abuse
  - sleep disturbances
  - internalized HIV stigma
  - multi-morbidity
  - reduced antiretroviral adherence
  - missed HIV clinic visits, and
  - lower income/unemployment

- Pain in the HIV population is independently associated with greater odds of physical function impairment

- Individuals with HIV who have chronic pain are **twice as likely to consider suicide** as their pain-free peers

Pain Conditions in the HIV Population

Conceptualized as two general categories:

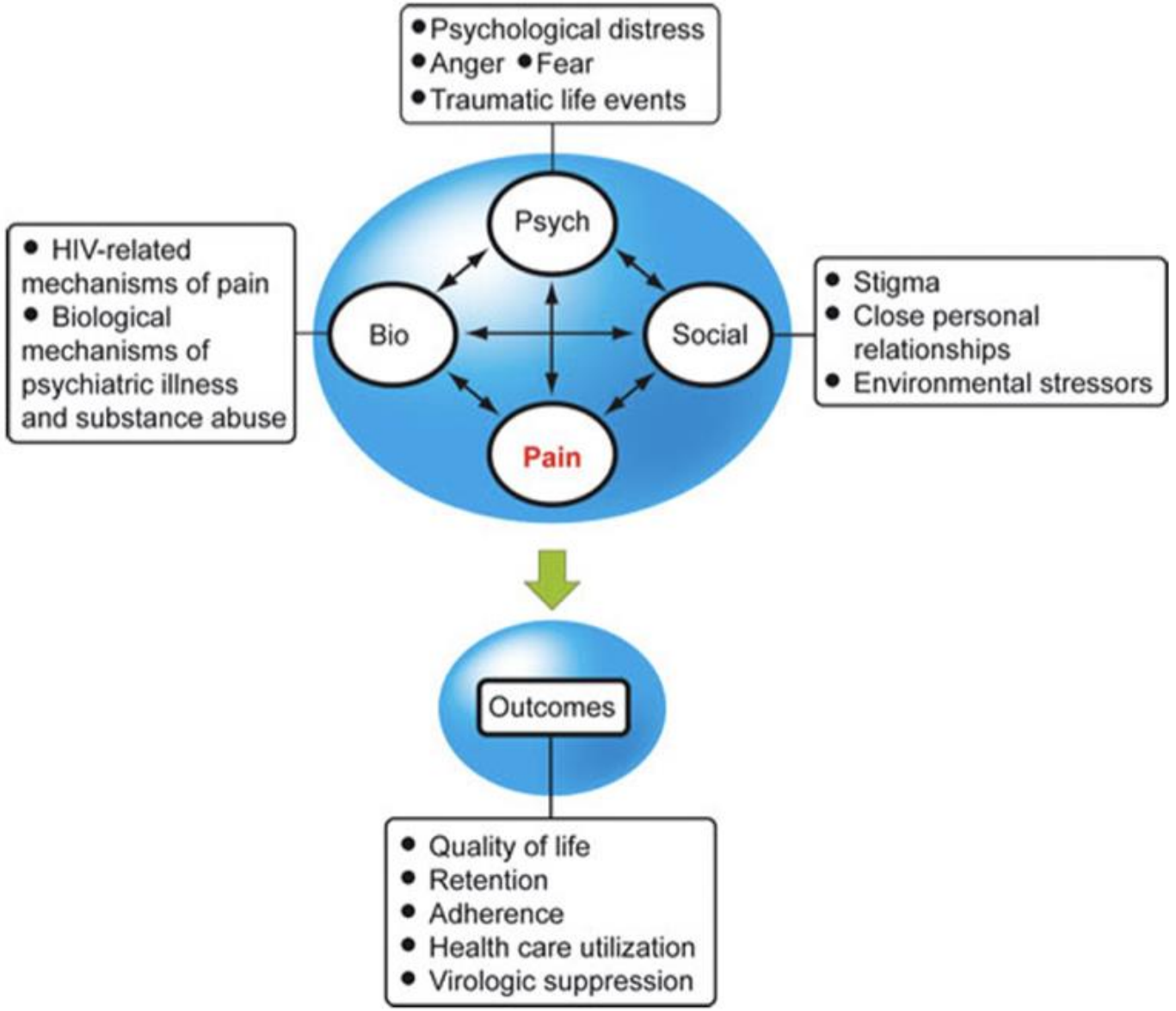
Pain **directly related to HIV**
infection or treatment

Pain **unrelated to HIV**
(e.g., musculoskeletal or rheumatic in nature or related to non-HIV infection)

Foundational Principles in Chronic Pain Management

1. **Comprehensive Pain Assessment**
2. Catastrophizing
3. Kinesiophobia/Fear Avoidance
4. Trauma Exposure and the Concept of Trauma Informed Care
5. Self-Management and Pacing
6. Psychological Therapies

An Adapted Biopsychosocial Framework for Chronic Pain in HIV



Merlin et al. Pain Pract. 2014 Mar;14(3):207-16.

Screening Tool	Measure	Score
Brief Pain Inventory (BPI)	Severity of pain and daily functioning	Pain Score 0-10 (worst, least, average, right now); Function Interference Score 0-10 (7 categories total max 70)
36-Item Short Form Survey (SF-36)	Quality of life (QOL)	Scores in each domain are converted and tallied using a scoring key, for a total score indicating a range of low to high QOL (0-100)
Douleur Neuropathique 4 (DN4)	Neuropathic pain	Scores of 4/10 or more indicates neuropathic pain component
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	Neuropathic pain	Scores of 12/24 or more indicates neuropathic pain component
Tampa Scale of Kinesiophobia (TSK)	Kinesiophobia	Scores above 37/68 indicate component of kinesiophobia
Pain Catastrophizing Scale (PCS)	Pain-related catastrophizing	Scores 30/52 and above indicate a clinically relevant level of catastrophizing
Patient Health Questionnaire (PHQ-9)	Depression	None-minimal 0-4 Mild 5-9 Moderate 10-14 Moderately Severe 15-19 Severe 20-27
General Anxiety Disorder (GAD-7)	Anxiety	Minimal 0-4 Mild 5-9 Moderate 10-14 Severe 15 or above
PTSD Checklist for DSM 5 (PCL-5)	PTSD	Scores 31-33/80 or above provide provisional diagnosis

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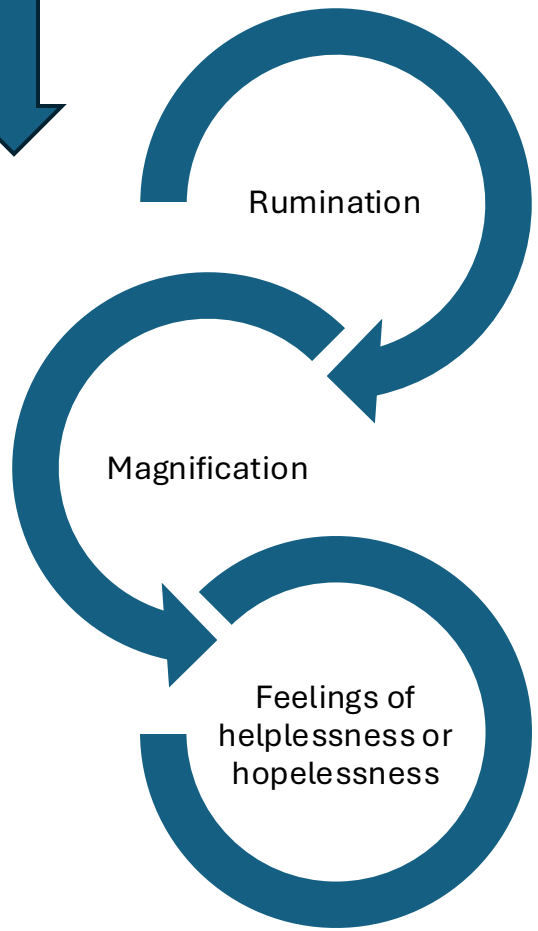
Catastrophizing



Select Interventions to Mitigate the Effects of Pain Catastrophizing

- Education about chronic pain is linked to improved outcomes and reduced catastrophizing.
- Therapy focuses on developing more adaptive responses to stress, thus lessening the negative effects of catastrophic thinking.

A 2019 study found that greater pain-specific resilience in people with HIV and chronic pain is associated with less pain catastrophizing.

Gonzalez CE et al. *Front Psychol*. 2019;10:2046.

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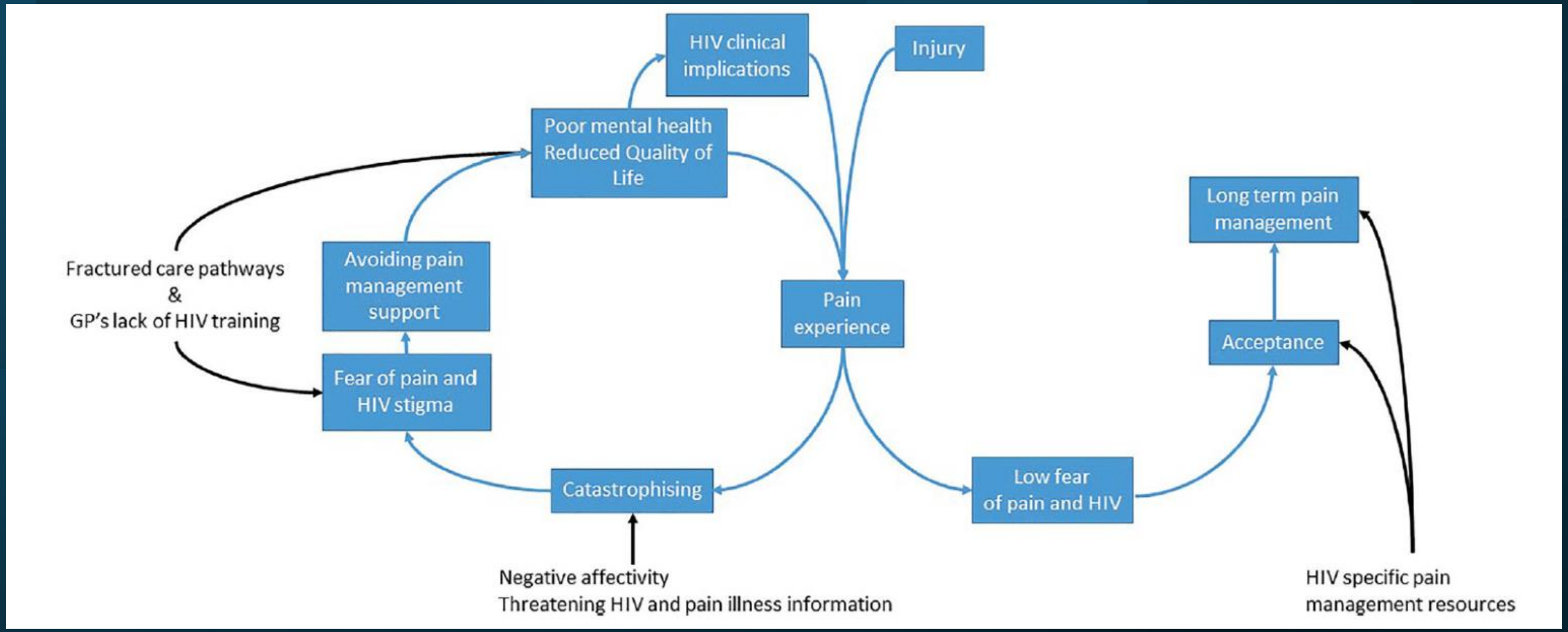
The Adapted Fear Avoidance Model for People with HIV and Chronic Pain



Baker et al. AIDS Care. 2023 Aug;35(8):1164-1172.

Foundational Principles in Chronic Pain Management

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Trauma Informed Care

5 Principles:

Safety

Trustworthiness

Choice

Collaboration

Empowerment

Foundational Principles in Chronic Pain Management

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Foundational Principles in Chronic Pain Management

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6. **Psychological Therapies**

HIV-Associated Neuropathic Pain

Distal sensory polyneuropathy (DSP) related to HIV is one of the most common neurologic complications of HIV.

- Exact pathophysiology remains to be elucidated; thought to involve toxicity of the virus or indirect neurotoxicity through inflammation and viral proteins.
- Typically **distal, symmetric**, sensory phenomenon characterized by **decreased or absent ankle jerks** and **reduced sensation to pinpricks or vibration** in the distal lower extremities.
- Most individuals experience **numbness, tingling, or pain in a stocking distribution with minimal weakness**.
- Tends to be **relatively stable over time** without significant worsening.

HIV-Associated Neuropathic Pain

Neurotoxic effects associated with select older antiretroviral (ARV) agents can also contribute to HIV related neuropathy.

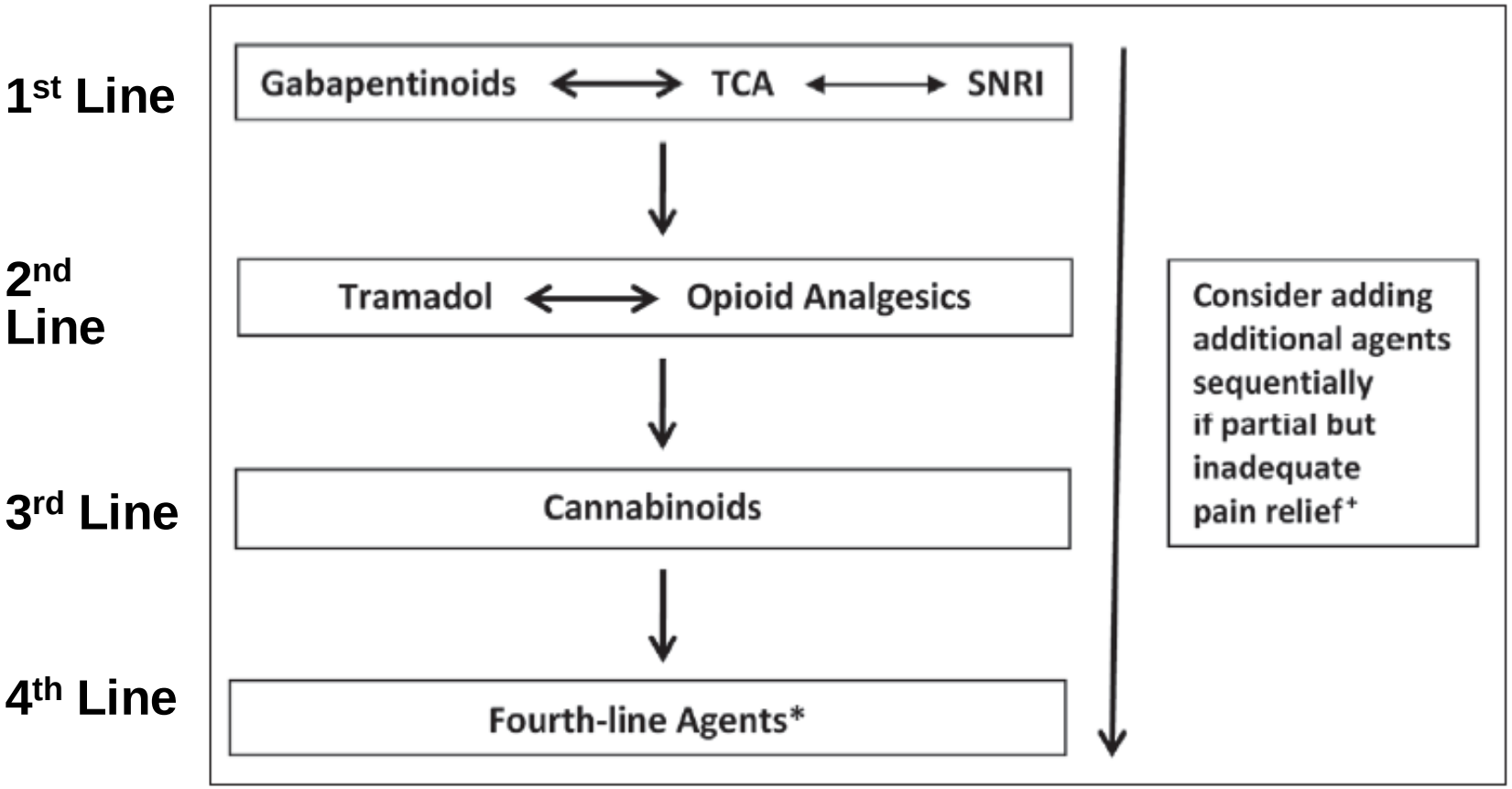
- Most implicated agents: the "**d-drugs**":
  - zalcitabine (ddC) - incidence of 30-100%
  - stavudine (d4T) – incidence of 31%
  - didanosine (ddI) - incidence of 23%

- **Dideoxynucleoside analogue induced neuropathy has been associated with mitochondrial toxicity** via competitive inhibition of mitochondrial g-DNA polymerase.
  - *In vitro* studies detected a hierarchy of mitochondrial g-DNA polymerase inhibition by NRTIs with zalcitabine > didanosine > stavudine > zidovudine > lamivudine = abacavir = tenofovir disoproxil fumarate.
  - This hierarchy aligns rather closely with the peripheral neuropathy incidence rates once encountered in practice for the NRTI class.

Uncommon to encounter new neuropathy cases related to ARVs nowadays given all the "d-drugs" have been removed from the Canadian market:
zalcitabine - July 2003
didanosine - May 2007
stavudine - March 2020

2014 Canadian Neuropathic Pain Guidelines

For Context



Moulin et al. Pain Res Manag 2014;19(6):328-335.

HIV-Associated Neuropathic Pain Management

Drug Class/Drug		Recommendation from the 2017 IDSA/HIVMA Clinical Practice Guideline for the Management of Chronic Pain in Patients Living with HIV	Evidence Summary
Gabapentinoids	Gabapentin	**Strongly recommended for 1st-line** treatment of chronic HIV-associated neuropathic pain.	An initial case report in 1998 noted successful treatment of HIV-related neuropathy with gabapentin in 3 patients. A case series from 2001 involving 19 patients with a mean gabapentin dose of 1480 mg/day found substantial benefit in 18 patients for both pain and sleep scores. A 2004 multicentered, DB-PC-RCT evaluating gabapentin in the treatment of painful HIV-sensory neuropathy found gabapentin (at doses starting at 400 mg/day and titrated up over 4 weeks to a maximum of 2,400 mg/day) resulted in significant improvement in median pain score and sleep score when compared with placebo. Small sample size (n = 15 in gabapentin arm; n = 11 in placebo arm) with high placebo pain score response rate.
	Pregabalin	**Shown to lack value** in the treatment of HIV-related neuropathic pain.	A 2010 double-blind RCT (n = 302) found pregabalin 150–600 mg/day to be no more effective than placebo for control of painful HIV-associated neuropathy. A subsequent double-blind, placebo-controlled RCT (n = 377) aimed to evaluate efficacy and safety of pregabalin for treatment of HIV-related neuropathic pain was terminated by the sponsor after a preplanned interim analysis revealed trial futility.
Tricyclic Antidepressants (TCAs)		**Weak recommendation** for a TCA trial if inadequate response to gabapentin.	3 studies evaluating efficacy of amitriptyline found no statistically significant improvement in pain scores vs. placebo, although one of the studies reported a trend toward improvement with amitriptyline (dose range 25–100 mg/day).
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)		**Weak recommendation** for a SNRI trial if inadequate response to gabapentin.	A study with a very small sample size evaluating the efficacy of duloxetine failed to find a significant reduction in pain.

HIV-Associated Neuropathic Pain Management

Drug Class/Drug	Recommendation from the 2017 IDSA/HIVMA Clinical Practice Guideline for the Management of Chronic Pain in Patients Living with HIV[5]	Evidence Summary
Capsaicin	**Strong recommendation for use of the topical capsaicin 8% patch** in the management of chronic HIV-associated peripheral neuropathic pain. The 8% capsaicin patch is ***not available in Canada.***	A DB-RCT of a single application of high dose (8%) capsaicin patch vs. a low-dose capsaicin (0.04%) control patch in the setting of HIV-associated DSP showed greater reduction in pain on the numeric pain scale in the high-dose group than in the low-dose group (mean reduction 22.8% vs. 10.7% between weeks 2 and 12). A 40-week open-label extension phase of the 12-week high-dose capsaicin patch trial permitted patients to receive up to 3 additional treatments with the high-dose capsaicin patch and found repeated treatments were generally well tolerated and produced consistent reductions in HIV-DSP-associated pain as well as improvement in patient-reported outcomes.
Alpha Lipoic Acid (ALA)	Recommended ALA for the management of chronic HIV-associated peripheral neuropathic pain based on evolving reports of ALA use in the management of diabetes related peripheral neuropathy. Acknowledged ALA studies in the HIV population were lacking; recommendation placed high value on providing a tolerable medication that may be of some benefit in patients with difficult-to-treat neuropathic pain.	No studies have been published on ALA for HIV related neuropathy to date.

HIV-Associated Neuropathic Pain Management

Drug Class/Drug	Recommendation from the 2017 IDSA/HIVMA Clinical Practice Guideline for the Management of Chronic Pain in Patients Living with HIV[5]	Evidence Summary	Comments
Opioids	**Strong recommendation against use of opioids as a first-line therapy for chronic neuropathic pain in HIV setting due to lack of data.** **Weak recommendation** that clinicians may consider a time-limited trial of opioids for **individuals who do not respond to first-line therapies and report moderate-to-severe pain.**		Data from the general population has shown opioids for chronic non-cancer pain are associated with only small improvements in pain and physical functioning.
Cannabinoids	**Weak recommendation** that medical cannabis may be an effective treatment in appropriate patients.	Smoked cannabis has demonstrated efficacy for HIV associated neuropathic pain in a couple of studies; marijuana may cause deleterious and unwanted complications.	Small to very small improvements in self-reported pain intensity, physical functioning, and sleep quality have been reported in the general chronic pain population when non-inhaled medical cannabis or cannabinoids are used.

Spinal cord stimulation

- Applies energy via implanted leads in the epidural space to modulate pain signals
- Patient selection is important – high levels of catastrophizing preclude this option
- Effective option for those who fail conventional therapies

Robinson-Papp et al. AIDS Care. 2024 Apr 8:1-11.

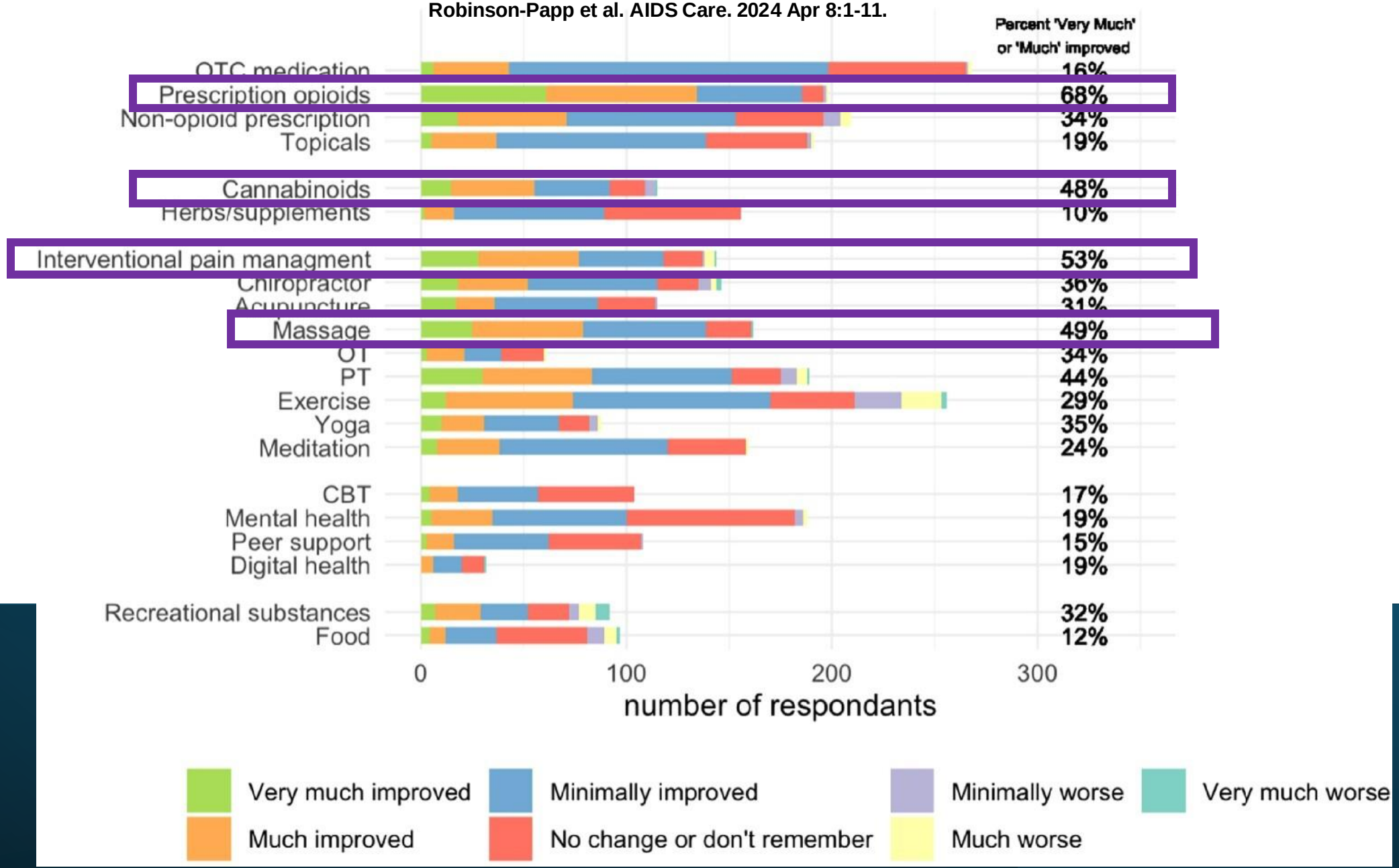
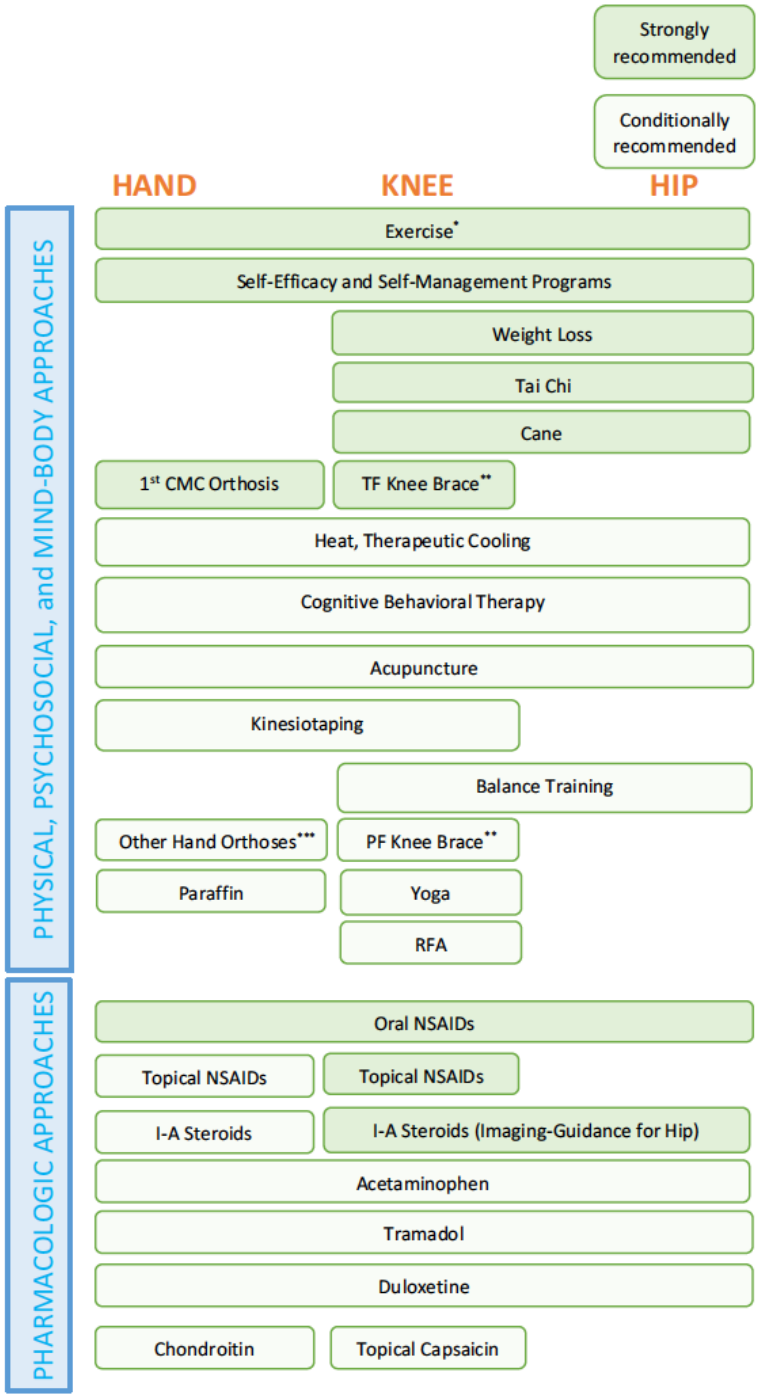


Figure 3. T**reatments tried by respondents for pain and perceived efficacy.**
Abbreviations: OTC = over the counter, OT = occupational therapy, PT = physical therapy, CBT = cognitive behavioral therapy

Chronic Secondary MSK Pain Associated with Osteoarthritis (OA)

- May be spontaneous or movement-induced
- Related to structural changes of synovial joints, cartilage, and subchondral bone
- Prevalence increases with age
  - Given those with HIV are living long, it is likely OA will be encountered more frequently in the future for patients with HIV



Arthritis Care Res (Hoboken). 2020 Jan 6;72(2):149–162.

Think twice about those steroid injections!

- Pharmacokinetic (PK) enhancers, such as ritonavir and cobicistat, may interact with CYP 3A4 substrate corticosteroids administered via any route.
  - Result = ***elevation in systemic corticosteroid levels.***
  - HPA axis dysfunction, Cushing's syndrome, and adrenal insufficiency have been reported in up to 11% of patients with HIV receiving corticosteroid injections.

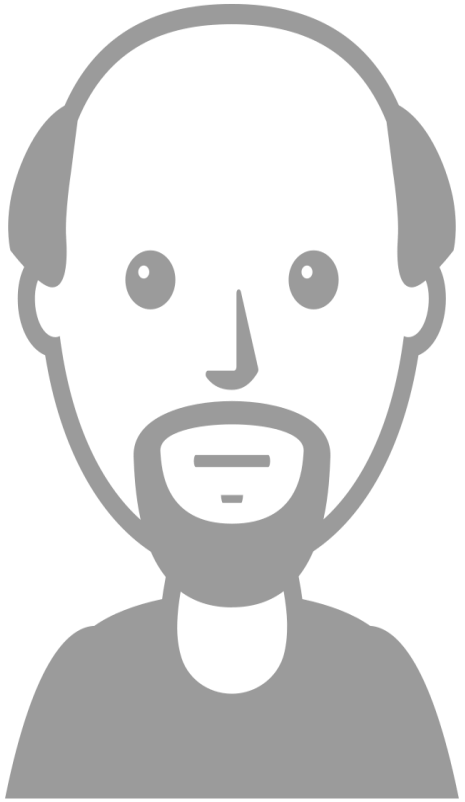
- While ARV regimen adjustments can be considered to remove the PK enhancer and mitigate interactions with steroids, it is prudent that indication and efficacy evidence for considering a steroid injection for pain management purposes be examined first.

In many situations, the use of injectable steroids for pain management may be a low-value strategy and a comprehensive review of the patient's pain situation may reveal more appropriate, effective, and safer alternatives.

Knowledge Application Time!

Case #1: Henry

- 58-year-old man originally diagnosed with HIV in 1991.
- Presents with bothersome distal sensory polyneuropathy; described as numbness, most noticeable in his feet in the areas covered by his socks; causes difficulty walking.
- Has severe lipodystrophy from his previous use of AZT (zidovudine), DDC (zalcitabine), and DDI (didanosine).
- Takes both a statin and fenofibrate for significant hyperlipidemia.
- Undetectable HIV viral load since 2005. Taken dolutegravir 50mg/rilpivirine 25mg PO once daily since 2022.
- Henry’s goal: improve ability to ambulate with less pain.
- Henry’s family physician is willing to prescribe a medication to assist with neuropathic pain control but is unsure which medication to select and has consulted you for advice.



Knowledge Check Question #1

Which of the following are screening questionnaires specific for neuropathic pain?

a) Brief Pain Inventory (BPI)

b) Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and Douleur Neuropathique 4 (DN4)

c) 36-Item Short Form Survey (SF-36)

d) Patient Health Questionnaire (PHQ-9)

Knowledge Check Question #2

Which of the following medications have resulted in statistically significant improvement with respect to HIV-related neuropathic pain?

a. Gabapentin

b. Pregabalin

c. Amitriptyline

d. Duloxetine

Knowledge Check Question #3

All the following are potential causes of neuropathy in people with HIV except for:

a) Longstanding HIV infection

b) Use of dideoxynucleoside analogue reverse transcription inhibitors (“d-drugs")

c) A prior shingles episode

d) Cannabis

Case #2: Jean

- 55-year-old woman with HIV (VL undetectable for past 5 years since starting daily BIC/TAF/FTC) who has developed polyarticular arthritis impacting her hands and ankles.
- Off work for 5 months from her job at a packing and shipping company due to the severity of her pain.
- X-rays reveal mild to moderate degenerative changes.
- Pain has severely restricted her ability to perform daily activities, leading to a predominantly sedentary lifestyle.
- Jean has had negative experiences with physical therapy as she reports the sessions often leave her in more pain than when she started. This has solidified her belief that physical activity exacerbates her condition. Despite being provided with an exercise program tailored to her pain tolerance by her therapists, Jean has chosen not to follow it, fearing that any movement will accelerate the deterioration of her joints.
- In terms of medication, Jean is seeking what she considers a ‘non-addictive’ solution to get her back to work so she can earn an income. She is particularly wary of opioids, stemming from a fear of addiction influenced by her childhood experiences. Her father, who suffered from chronic back pain, used alcohol as a coping mechanism, which often led to unpredictable and physically abusive behavior towards Jean and her siblings. This traumatic past makes Jean apprehensive about potentially losing control over her pain management.

Knowledge Check Question #1

What concept describes an excessive and irrational fear of movement?

a) Catastrophizing

b) Pacing

c) Mindfulness

d) Kinesiophobia

Knowledge Check Question #2

True or False?

An adapted model of fear avoidance has been developed for people with HIV and chronic pain because the avoidance can be driven by the fear of HIV disclosure and the stigma associated with it.

a. True

b. False

Knowledge Check Question #3

How should a clinician approach Jean's care to align with trauma-informed principles?

a) By solely focusing on physical symptoms and prescribing pain medication.

b) By recognizing Jean's traumatic experiences and adapting care to include psychological support.

c) By disregarding Jean's concerns about addiction due to their irrelevance to her current condition.

d) By insisting on the importance of physical therapy without addressing Jean's psychological barriers.

Take Home Points

Chronic pain is the second most common symptom for patients with HIV; 54-83% will experience it throughout their life.

Routine screening for chronic pain is recommended in patients with HIV.

Comprehensive pain assessments should incorporate screening tools.

Consider biopsychosocial factors such as catastrophizing, kinesiophobia/ fear avoidance, and trauma when devising management plans.

Neuropathic pain is prevalent and can be related to HIV directly and/or select antiretroviral agents.

The most common presentation involves distal, symmetric, sensory polyneuropathy.

<u>Management:</u>

Gabapentin 1st line,

may consider TCA or SNRI thereafter with low expectation of benefit. Cautious trials of opioids and cannabinoids. Spinal cord stimulator for those not responding to drugs.

Chronic secondary MSK pain, such as OA, is increasingly common in people living with HIV. When considering steroid injections, caution is advised in those on CYP 3A4 inhibitor ART regimens due to potential drug interactions.

Management of chronic pain should include patient self-management strategies and involve an interdisciplinary team to facilitate evidence-based care.