AETC AIDS Education & Training Center Program Northeast/Caribbean

Chronic Pain & Effects on the Nervous System in People with HIV

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Disclosures

- **Scientific Advisory Board Member**
  - Neuropathix Inc
  - Immgenuity Inc
- **Consultant**
  - Eli-Lilly
  - Vertex
  - Lexicon
  - Tris Pharma
- **UpToDate (Royalties)**

Learning Objectives

- Explain how HIV interacts with the nervous system leading to neurologic disorders.
- List the neurologic disorders which are common in people with HIV.
- Describe the approach to evaluation and management of pain in people with HIV.

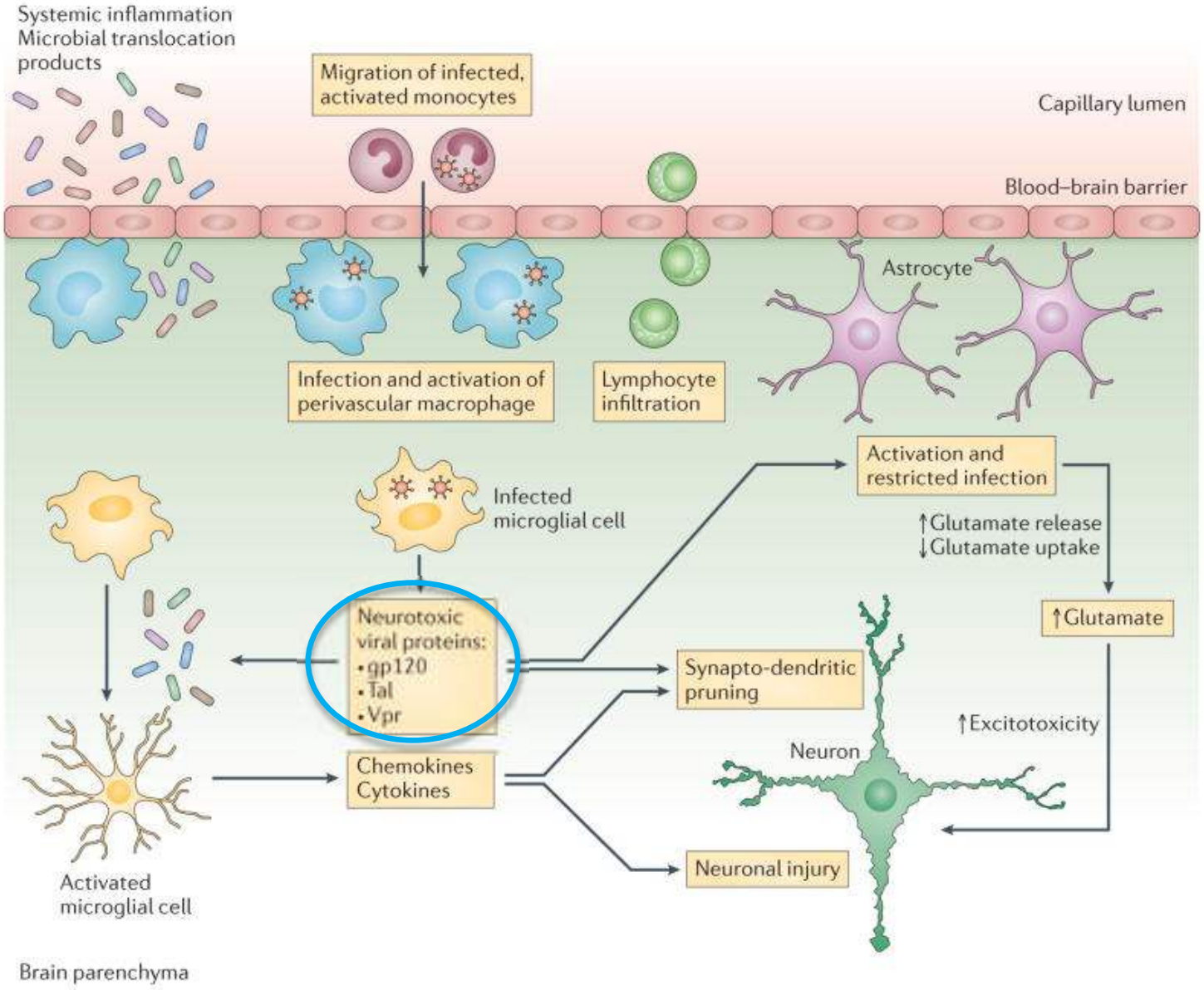
How does HIV interact with the nervous system?

HIV in the Brain

- **HIV-encephalitis**
- Primary infection of the brain with HIV

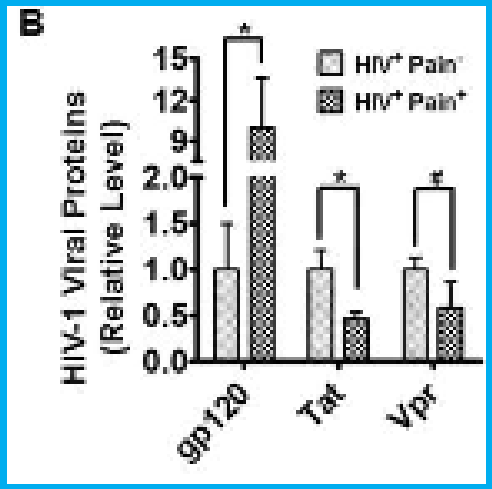
PLUS

- Inflammatory response
- Neurotoxic proteins can still be produced even when HIV is controlled

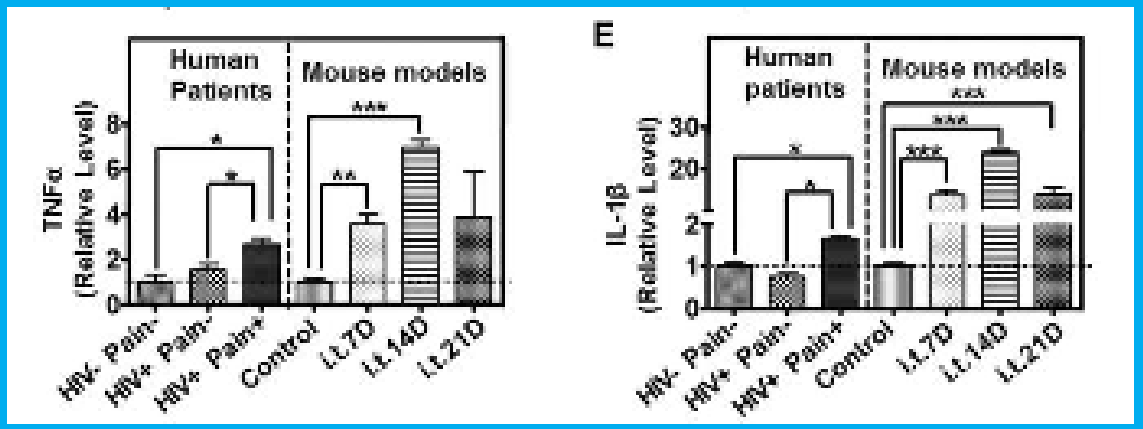


Saylor D et al. **HIV-associated neurocognitive disorder--pathogenesis and prospects for treatment.** ***Nat Rev Neurol 2016; 12(4):234-248.***

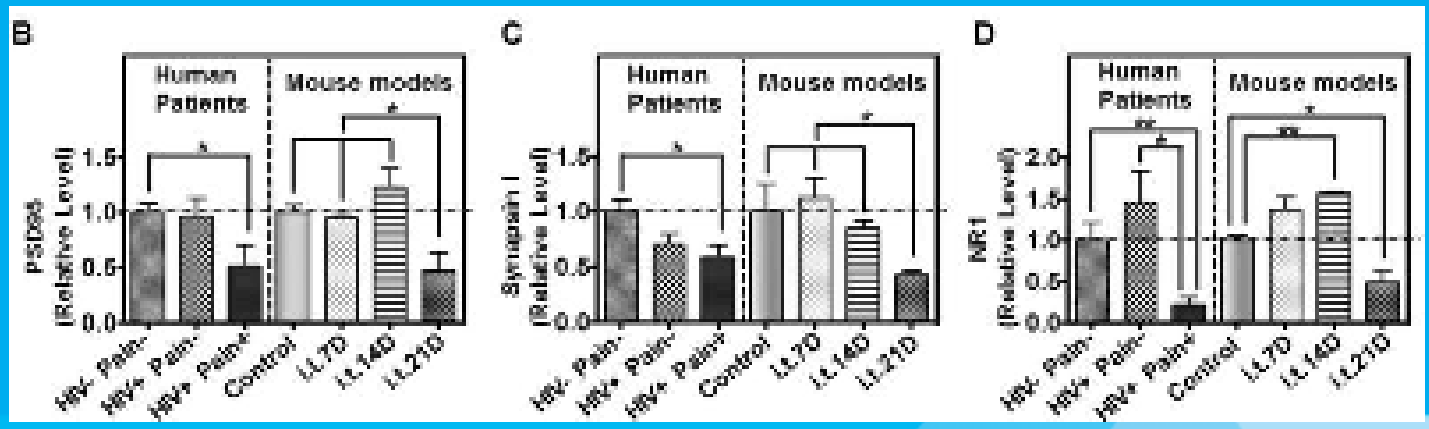
HIV in the spinal cord



- Classic syndrome of HIV-associated myelopathy (progressive spastic paraparesis) rarely seen today
- Post-mortem spinal dorsal horn (SDH) specimens from people with HIV and pain displayed:



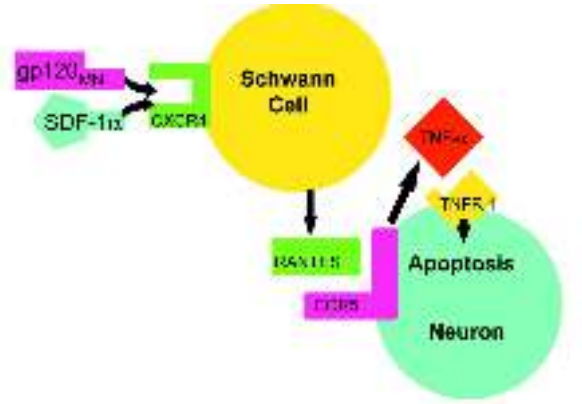
- Elevated gp120
- Neuroinflammation
- Synapse degeneration

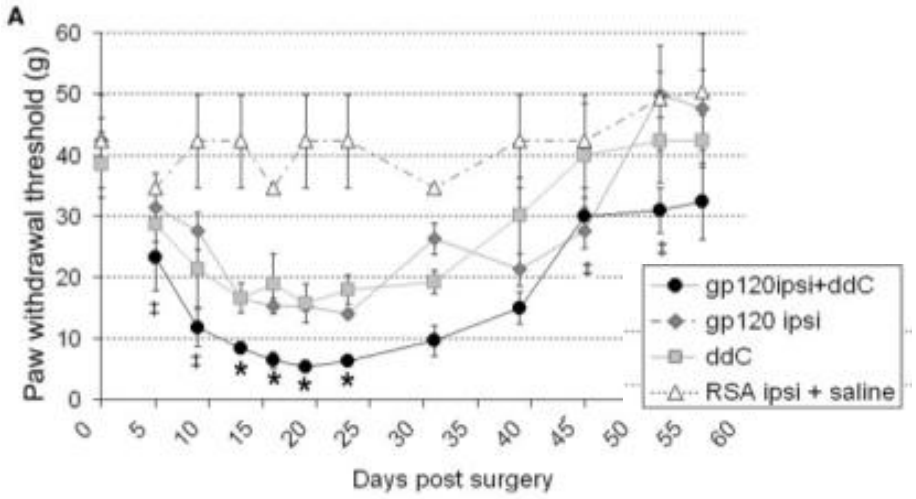


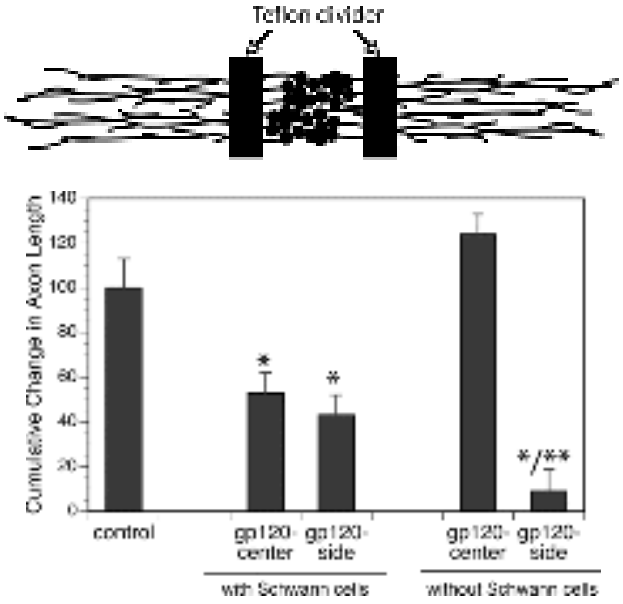
Yuan et al. Ann Neurol. 2014.

HIV and the PNS: gp120

- Early work focused on DRG culture system
- Later included work at the axonal level and showed an additional local axonal toxicity of gp120 via mitochondrial capsase pathway
- Animal models exposing rat sciatic nerve to gp120 recapitulated clinical features of neuropathy







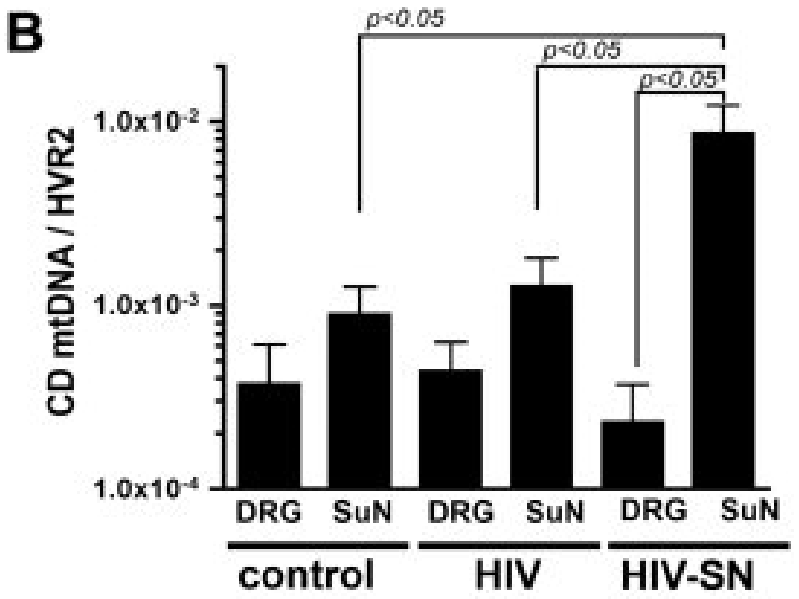
Keswani, S. C., et al. (2003). "Schwann cell chemokine receptors mediate HIV-1 gp120 toxicity to sensory neurons." Annals of Neurology 54(3): 287-296.

Melli, G., et al. (2006). "Spatially distinct and functionally independent mechanisms of axonal degeneration in a model of HIV-associated sensory neuropathy." Brain 129(5): 1330-1338.

Wallace, V. C. J., et al. (2007). "Characterization of rodent models of HIV-gp120 and anti-retroviral-associated neuropathic pain." Brain 130(10): 2688-2702.

HIV and the PNS: Mitochondrial mechanisms

- No evidence of direct infection of nerve by HIV
- Mitochondrial and immune mediated mechanisms
- **Mitochondrial:** Increased levels of mtDNA mutations identified in postmortem sural nerves of patients with HIV-DSP as compared to control patients or HIV patients without DSP. Mutations also more prevalent in distal sural nerves compared to dorsal root ganglia.



Annals of Neurology
Volume 69, Issue 1, pages 100-110, 8 NOV 2010 DOI: 10.1002/ana.22150
http://onlinelibrary.wiley.com/doi/10.1002/ana.22150/full#fig2

Clinical disorders

Common Neurologic Disorders in PWH

Can be directly HIV-related, related to immune suppression, or indirectly/not-clearly HIV related

CNS

- HIV-associated neurocognitive disorder (HAND)
- CNS opportunistic infections (now rare)
- Cerebrovascular disease

PNS

- HIV-associated neuropathies
- PNS opportunistic infections (very rare, historically mostly CMV related)

CNS

International HIV-Cognition Working Group 2023

Nature Reviews Neurology | Volume 19 | July 2023 | 424–433

Box 1

Summary of recommendations from the International HIV-Cognition Working Group

Recommendation 1
HIV-associated brain injury (HABI) should be considered as one cause of cognitive impairment alongside other potential causes of brain injury occurring in people living with HIV.

Recommendation 2
HABI should be differentiated on the basis of HIV RNA suppression and the activity of pathology.

Recommendation 3
Low performance on cognitive tests should not be labelled as cognitive impairment without clinical context.

Recommendation 4
When interpreting cognitive data, the false-classification rate should be considered.

Recommendation 5
A research classification of cognitive impairment in people living with HIV should consider a combination of cognitive symptoms, low performance on cognitive testing, and abnormality on neurological investigations.

Recommendation 6
Cognitive symptoms should refer to any change in cognition that has been noticed by the individual or an observer, whether or not this change has an impact on daily functioning.

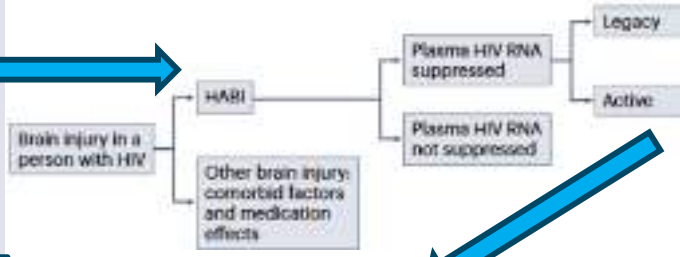
Box 2

Potential causes of brain injury in people living with HIV

This is not an exhaustive list, as any neuropathological process can potentially affect people living with HIV.

HIV-associated brain injury (HABI) (Fig. 1)
- Legacy HABI: inactive brain injury from pretreatment damage
- Active HABI: ongoing brain injury leading to clinical or radiological progression

Other causes of brain injury
- Previous or ongoing CNS infections (for example, neurosyphilis, CNS tuberculosis, CNS toxoplasmosis, CNS cryptococcosis and progressive multifocal leukoencephalopathy)
- Cerebrovascular disease
- Traumatic brain injury
- Neurodegenerative disorders such as Alzheimer disease
- Other non-HIV-related neurological condition (for example, multiple sclerosis or uncontrolled epilepsy)
- Developmental disability
- Nutritional deficiencies (for example, vitamin B_{12} or niacin deficiency)
- Coinfections (for example, syphilis or hepatitis C)
- Hazardous alcohol use
- Substance misuse
- Antiretroviral CNS neurotoxicity

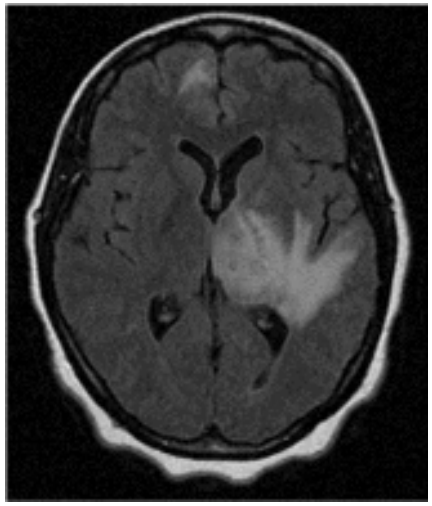


- Unsuppressed HIV
- CNS escape
- CD8 encephalitis
- IRIS

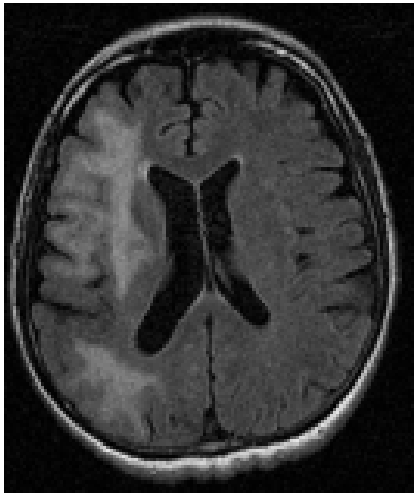
- Disparities in educational quality and literacy
- Culturally appropriate normal-values for neurocognitive tests
- Sociocultural factors

CNS Conditions in People with HIV (mostly untreated)

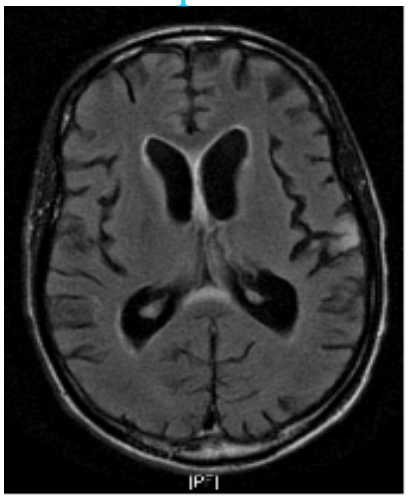
Toxo



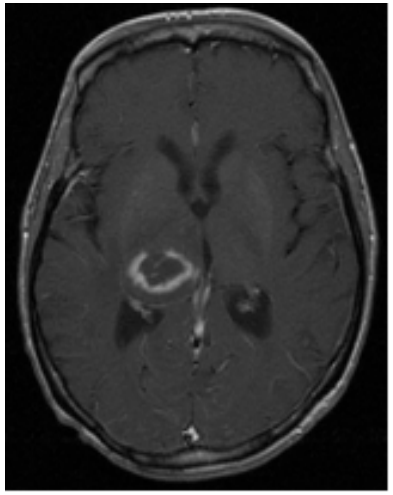
PML

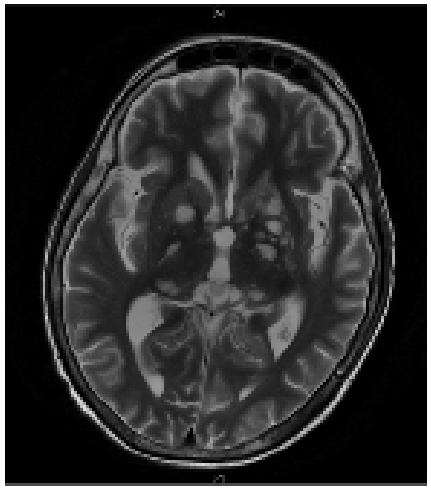


CMV encephalitis

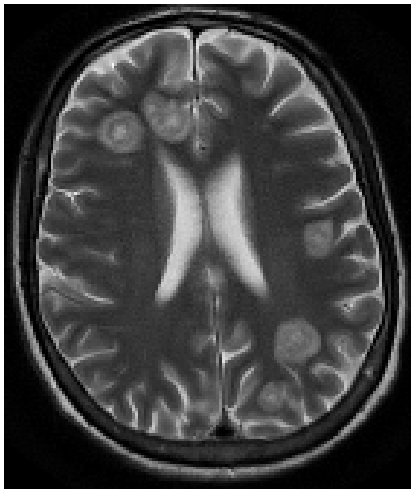


PCNSL

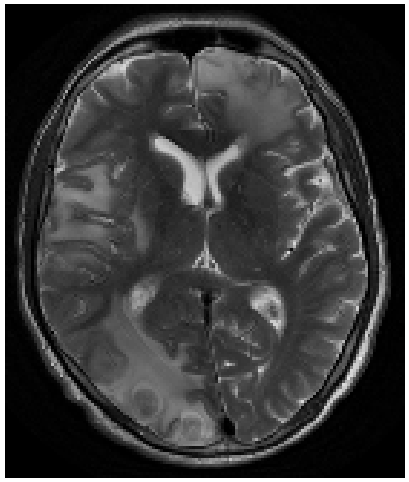




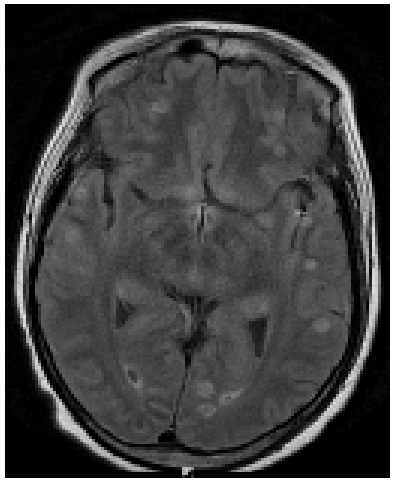
Cryptococcus



Aspergillus



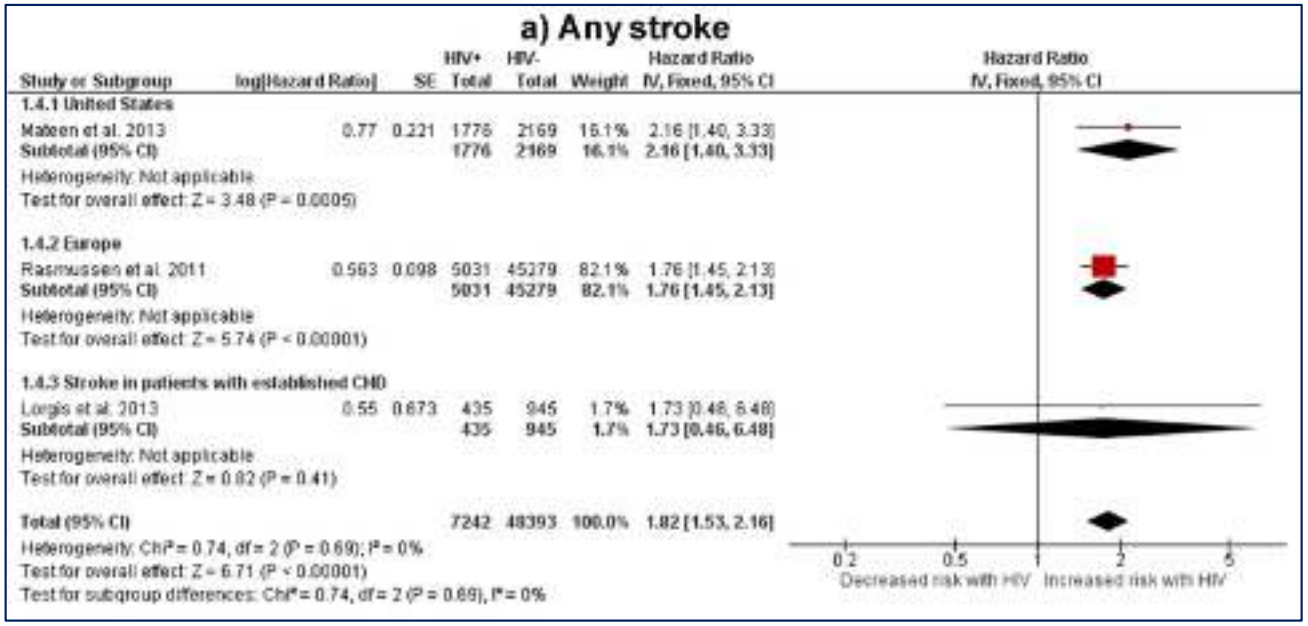
Nocardia

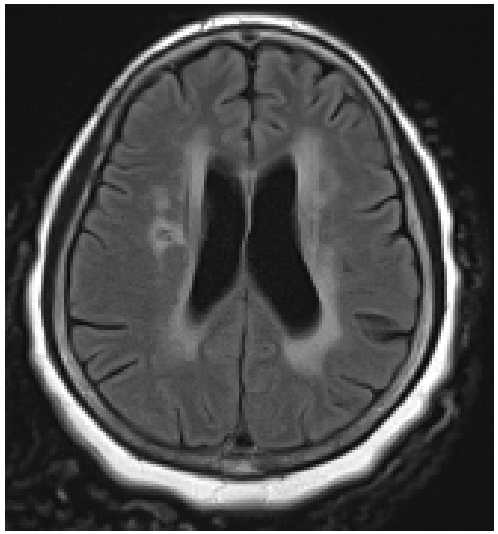


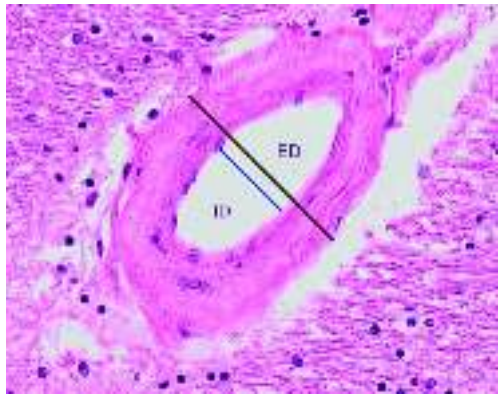
Bacterial (septic emboli)

Co-morbid cerebrovascular disease

- People with HIV have a high burden of traditional vascular risk factors
- HIV itself is also a risk factor for cerebrovascular disease







Gutierrez J, Albuquerque ALA, Falzon L. HIV infection as vascular risk: A systematic review of the literature and meta-analysis. *PLOS ONE 2017; 12(5):e0176686.*

Morgello S, Murray J, Van Der Elst S, Byrd D. HCV, but not HIV, is a risk factor for cerebral small vessel disease. Neurol Neuroimmunol Neuroinflamm 2014; 1(3):e27.

TBI Among People with HIV

- High prevalence of at least mild TBI, one study reporting 23.4% of their sample had been assaulted and 14.8% had been exposed to domestic violence.
- People with HIV and TBI have, compared to HIV+/TBI- (Lin et al 2011):
  - Decreased NAA in frontal lobes on MR spectroscopy indicating neuronal damage
  - Are more impaired on cognitive testing (working memory, learning)

Gupta et al. 2025. Traumatic brain injury: An emerging threat for HIV-associated neurocognitive disorder. In: Neuropsychiatric Complications of HIV.

Co-morbid neurodegenerative disease

- The great majority of people with HIV are still below the age in which neurodegenerative disorders like Alzheimer's become common
- But this is changing

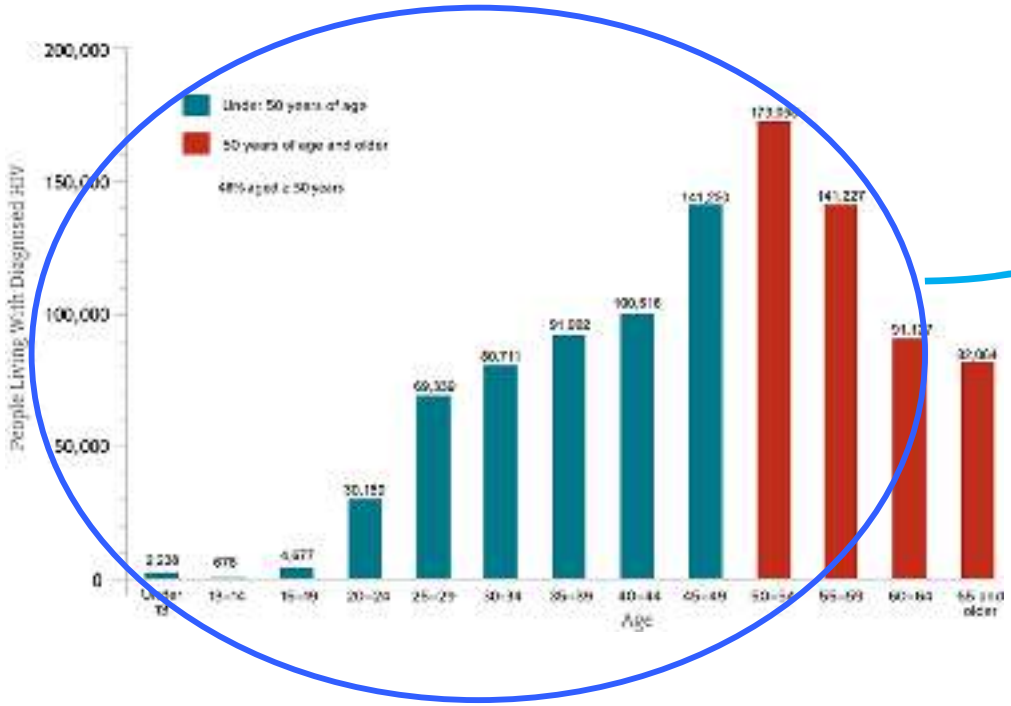
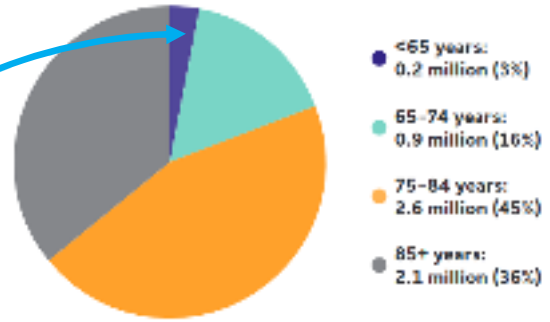
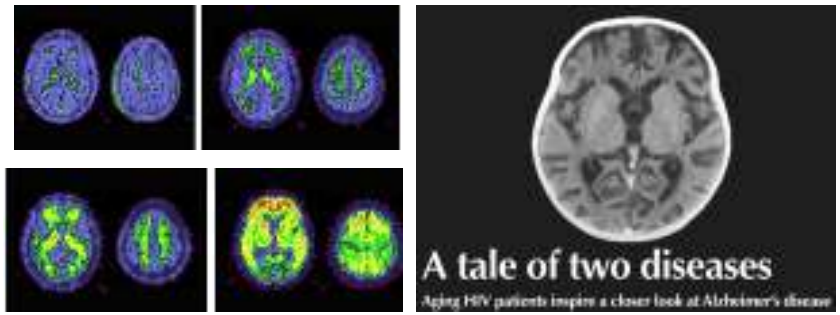


FIGURE 1

Ages of People with Alzheimer's Dementia, 2019



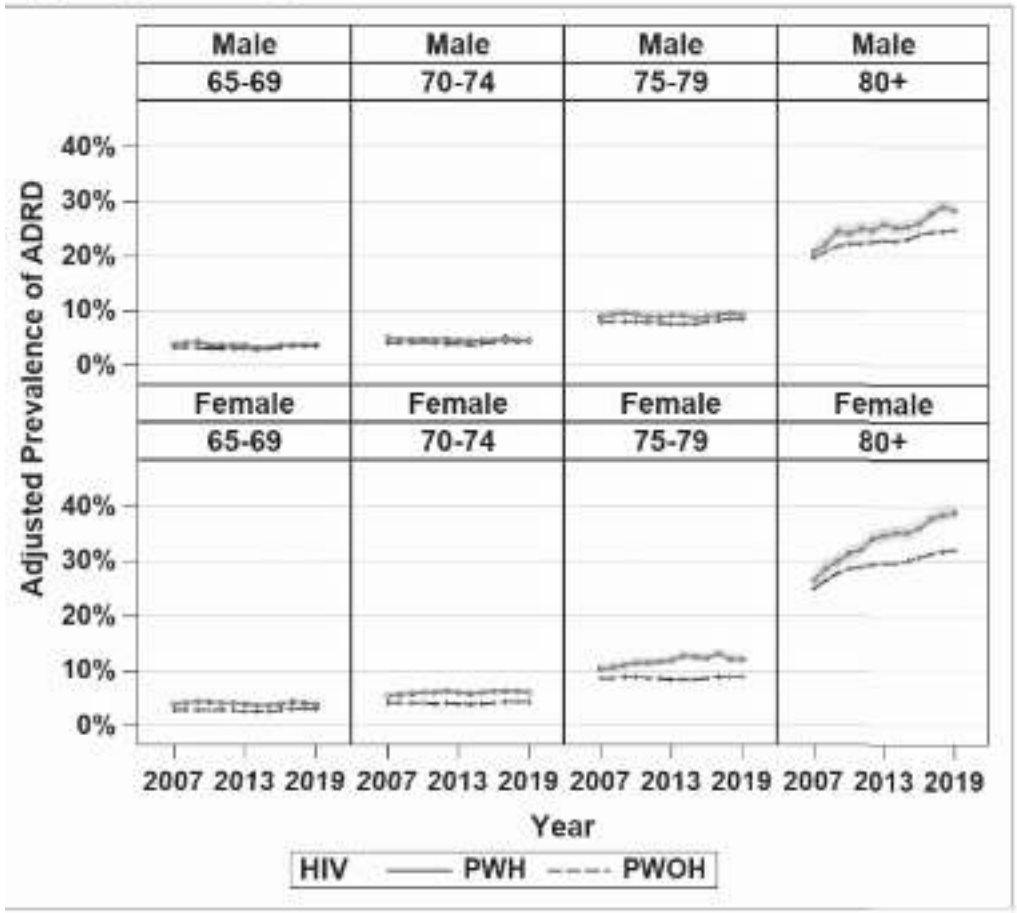


https://www.cdc.gov/hiv/group/age/olderamericans/index.htmaging
https://www.alz.org/media/documents/alzheimers-facts-and-figures-2019-r.pdf

Chakradhar S. A tale of two diseases: Aging HIV patients inspire a closer look at Alzheimer's disease. *NatMed 2018; 24(4):376-377.*
Canet G, Dias C, Gabelle A, Simonin Y, Gosselet F, Marchi N, et al. HIV Neuroinfection and Alzheimer's Disease: Similarities and Potential Links? Frontiers in Cellular Neuroscience 2018; 12(307).

Dementias Among Older Males and Females in the U.S. Medicare System With and Without HIV

Xiaoying Yu, MD, PhD,[a,b] Yong-Fang Kuo, PhD,[a,b] Mukaila A. Raji, MD,[c] Abbey B. Berenson, MD, PhD,[b,d] Jacques Baillargeon, PhD,[e] and Thomas P. Giordano, MD, MPH[f,g]



- Medicare data from all beneficiaries with HIV (~27,000) and a 5% sample of people without HIV
- Diagnoses included: AD, vascular, frontotemporal, and unspecified dementia
- Limitation is that these are chart derived diagnoses (so cannot exclude that some of these people have HAND)
- Alzheimer's can be more definitively diagnosed with biomarkers (amyloid PET, CSF amyloid/p-tau), but these are limited by insurance and availability

Sex	Age	p-value
Male	65-69	0.003
Male	70-74	0.02
Male	75-79	0.62
Male	80+	0.02
Female	65-69	0.59
Female	70-74	0.79
Female	75-79	0.01
Female	80+	0.002

J Acquir Immune Defic Syndr • Volume 93, Number 2, June 1, 2023

Practical Points: Clinical Evaluation of HAND

- Comprehensive medical history:
  - Current age
  - HIV-relevant history (disease duration, nadir, h/o CNS OIs)
  - Comorbidities especially cardio/cerebrovascular
  - Head trauma
  - Family history of dementia
  - Pre-morbid function
- Neurologic exam (looking for focality, motor abnormalities)
- MRI brain (r/o mass lesions, cerebrovascular disease)
- Assess for reversible causes of dementia (syphilis testing, TSH, B12)
- Neurocognitive testing (when available)
- Treatment?

Practical Points: Counseling

You are doing a great job taking your HIV meds and staying undetectable. It's the most important thing you can do for your brain.

You can promote brain health generally with exercise, a healthy diet, staying active and engaged, and avoiding drugs, alcohol and smoking.

This is not like Alzheimer's disease. Most people don't get worse and some even get better.

How's your sleep?

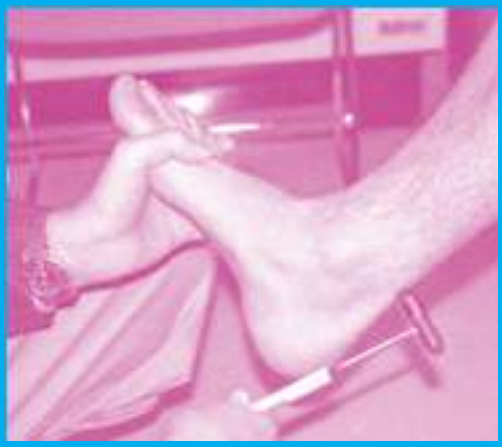
Mental health is so important for optimizing your cognitive function. How has your mood been?

If it's good for your heart it's probably good for your brain. Let's check your blood pressure and cholesterol.

Your memory tests did show some weaknesses but there are also areas where you did well. Let's think of strategies to put those strengths to work.

PNS

HIV-associated distal symmetric polyneuropathy (HIV-DSP)



- Symptoms: burning, tingling, numbness in the feet.
- Signs: decreased reflexes and sensation in the feet; may have mild distal weakness/atrophy.
- >50% of patients with longstanding HIV have signs of neuropathy; about half are symptomatic.
- Older antiretrovirals have neurotoxicity (stavudine/d4T, didanosine/ddI, zalcitabine/ddC).
- Current regimens unlikely to be significantly neurotoxic.
- None of the current single pill regimens list neuropathy as a side effect
- Non-HIV factors increasingly important: multi-morbidity, aging, increasing prevalence of obesity and diabetes, poor nutrition, substance use.

HIV-DSP Diagnosis (clinical setting)

- Can be a clinical diagnosis in patient with typical presentation (symmetric, distal, sensory predominant)
- Social history, medication review and limited laboratory testing to assess for exacerbating factors

Some of the drugs that may cause peripheral neuropathy include:

- Anti-alcohol drugs (Disulfiram)
- Anticonvulsants (Phenytoin)
- Cancer medications (Cisplatin)
- Vincristine
- Heart or blood pressure medications (Amiodarone)
- Hydralazine
- Perhexiline
- Infection fighting drugs (Metronidazole, Flagyl®, Fluoroquinolones: Cipro®, Levaquin®)
- Nitrofurantoin
- Thalidomide
- INH (Isoniazid)
- Skin condition treatment drugs (Dapsone)

https://www.foundationforpn.org/wp-content/uploads/2016/10/Medications-that-Can-Cause-Peripheral-Neuropathy.pdf


SPECIAL ARTICLE

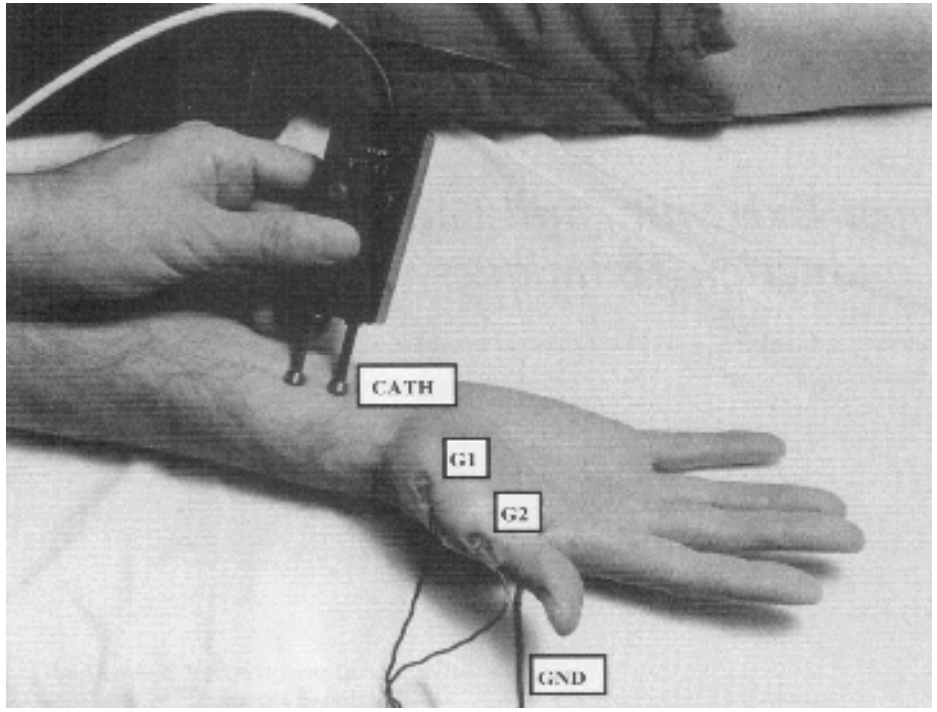
NEUROLOGY

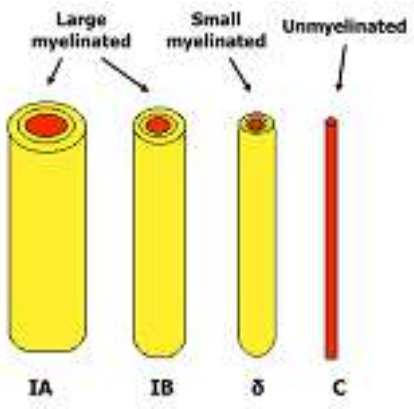
Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review)

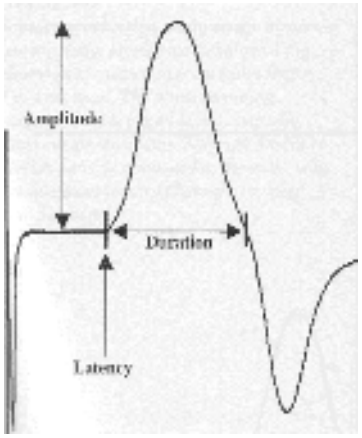
Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

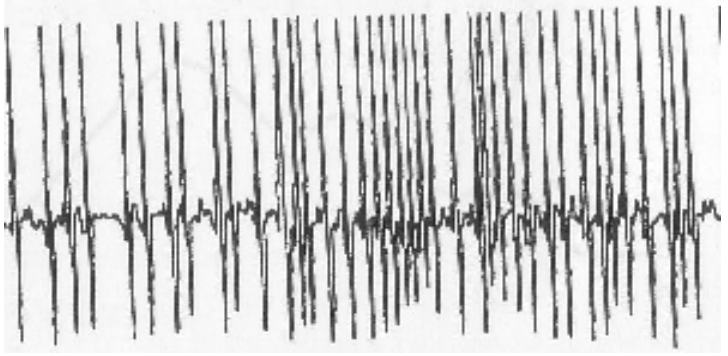
nostic (Class III).[10] The majority of studies indicated that screening laboratory tests comprised of a complete blood count, erythrocyte sedimentation rate, comprehensive metabolic panel (blood glucose, renal function, liver function), thyroid function tests, serum B12, and serum protein immunofixation electrophoresis are indicated for most patients with polyneuropathy.[4-13] Five

Diagnostic testing: Nerve Conduction Studies and EMG

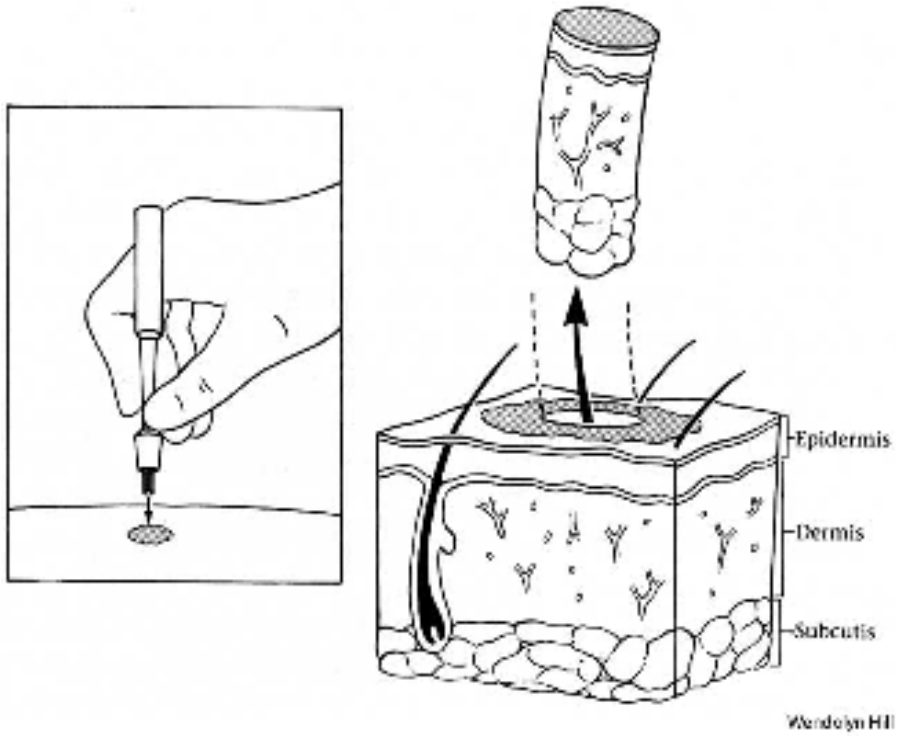


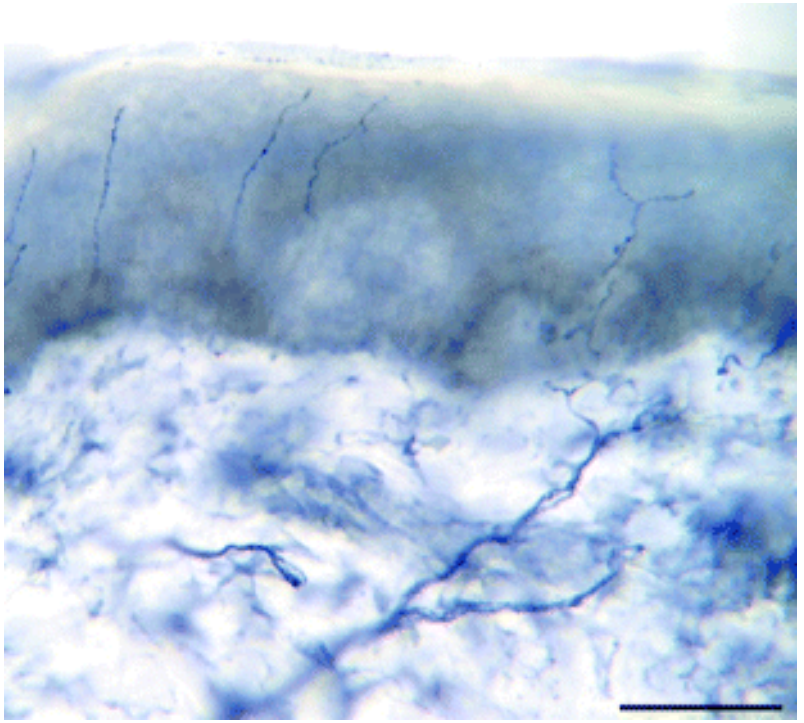






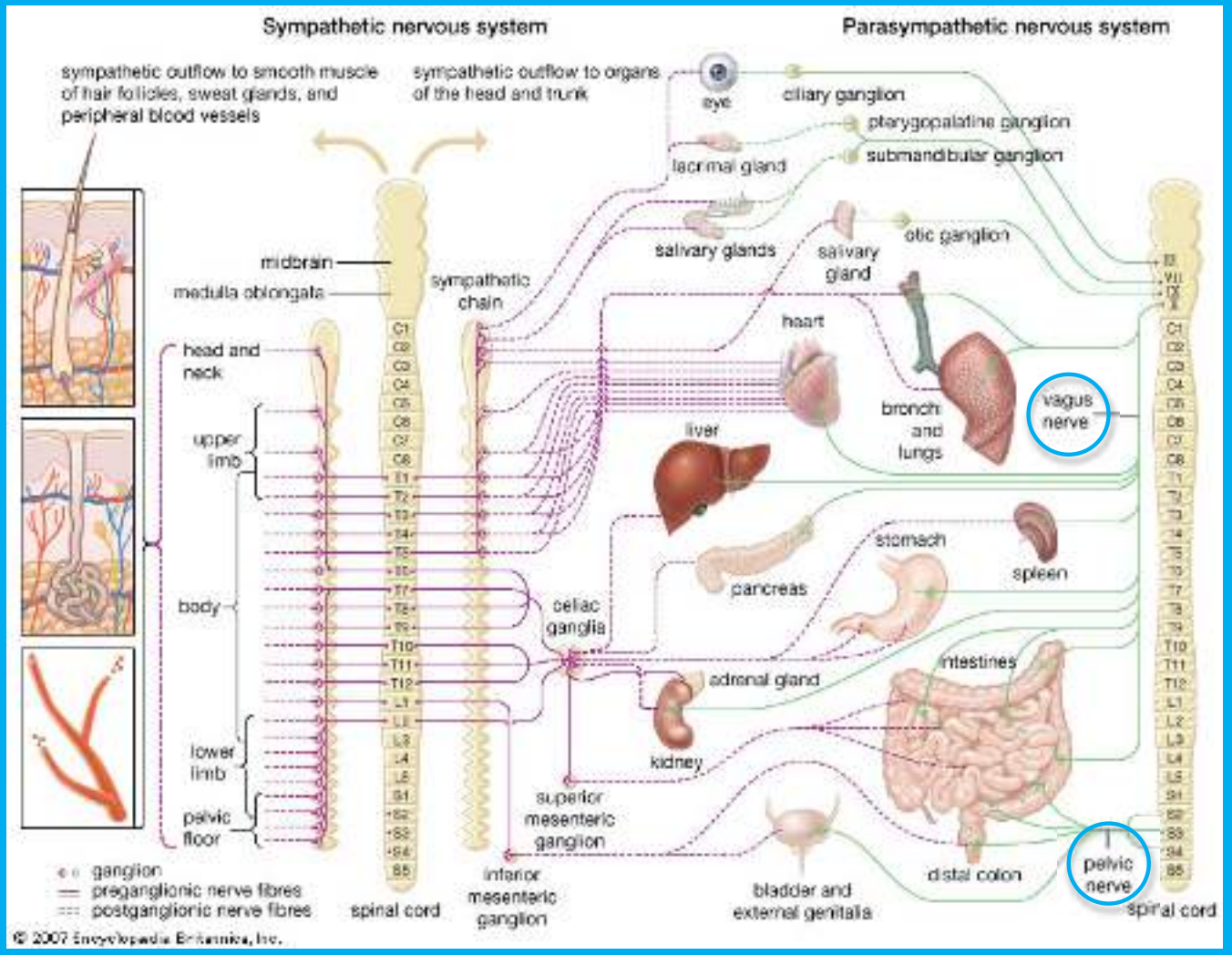
Diagnostic testing: Skin Biopsy





Autonomic neuropathy (AN)

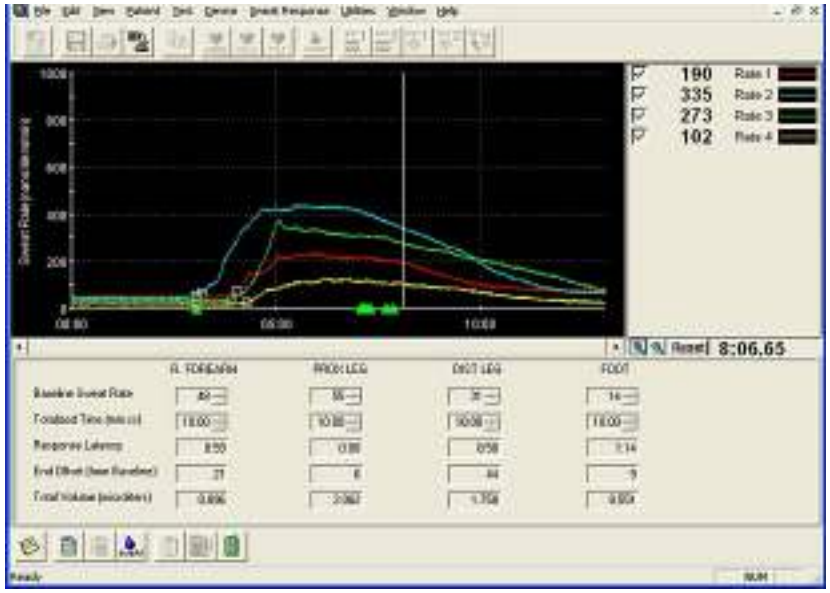
- Autonomic nerve fibers are structurally similar to the sensory fibers that are often affected in HIV-DSP, so likely vulnerable to the same insults that cause HIV-DSP.



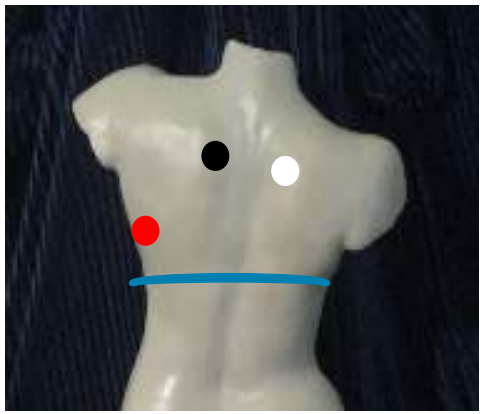
- Potential symptoms: orthostatic dizziness or fainting, nausea, vomiting, early satiety, bloating, diarrhea, constipation, urinary and sexual dysfunction, dry eyes and mouth, and changes in sweating.

Diagnosis of Autonomic Neuropathy: Autonomic Reflex Screen

Quantitative Sudomotor Axon Reflex Testing (QSART)



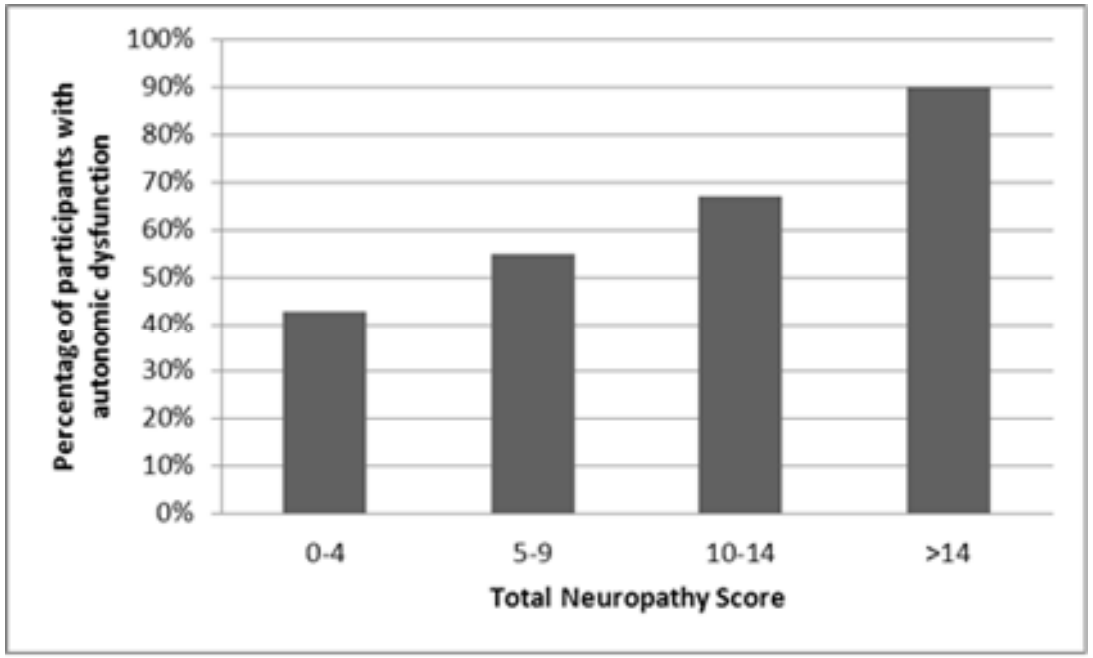
-Heart rate response to deep breathing (HRDB)
-Valslava maneuver (VM)
-Tilt



Data used to calculate the Composite Autonomic Severity Score (CASS)

Prevalence of AN in HIV

- 115 PLWH recruited from a primary care HIV clinic
- Autonomic reflex screen, neurologic exam, nerve conduction studies
- HIV-AN was prevalent: 61% (CASS ≥ 3) and a/w DSP severity (measured by Total Neuropathy Score)



Robinson-Papp and Sharma. AIDS Patient Care STDS, 2013.
Robinson-Papp et al. JNV 2013.

Long term outcomes

Kwon et al. Neurology Clinical Practice 2023.

- Almost 10 years of follow-up (used cut-off date just before COVID), review of EHR to determine if HIV-AN predicted morbidity and mortality in HIV
- One or more of: death from any cause, opportunistic infection, major cardiovascular, renal and hepatic disease (defined as myocardial infarction, stroke, coronary artery disease requiring surgery or interventional procedure, kidney failure, cirrhosis).

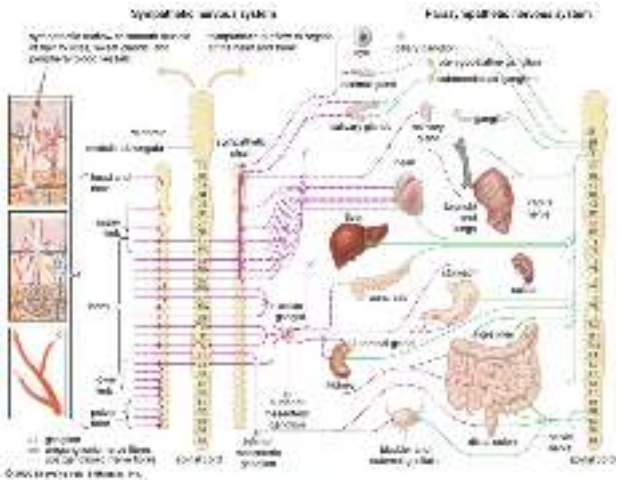
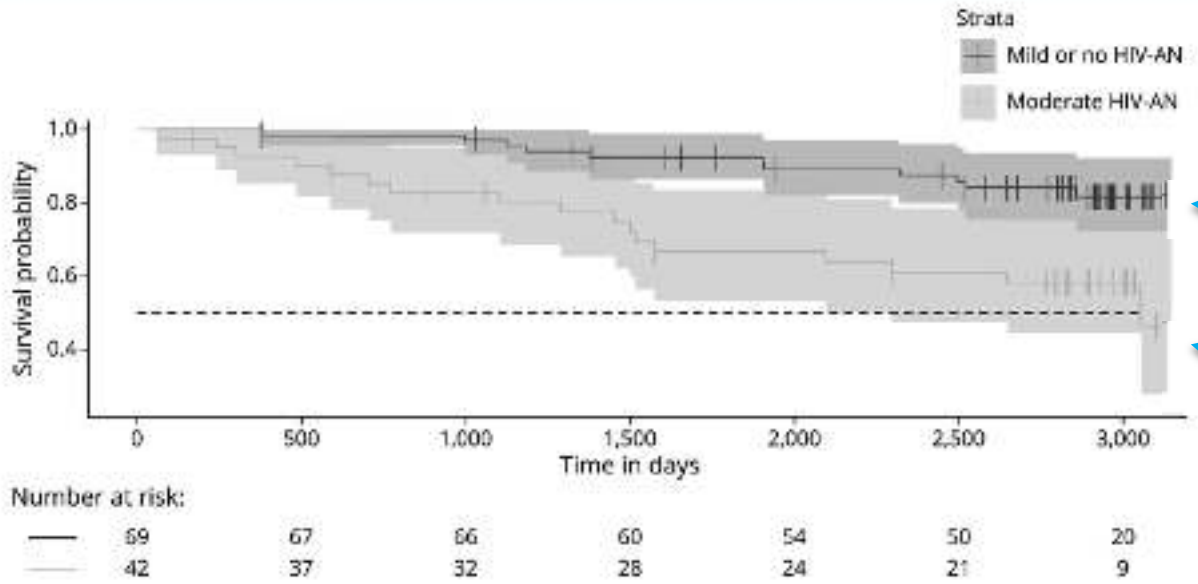


Figure Event-Free Survival in People With Moderate HIV-AN Compared With Mild or No HIV-AN



Kaplan Meier curves show the probability of our composite outcome in patients with mild or no HIV-AN (dark gray) and patients with moderate HIV-AN (lighter gray). HIV-AN = HIV associated autonomic neuropathy.

Adjusted HR 3.85, CI 1.61–9.20

11 total events (1 cardiac)

17 total events (6 cardiac)

Multi-system poor outcomes, not just cardiac. Inflammatory basis?

Chronic pain in People with HIV

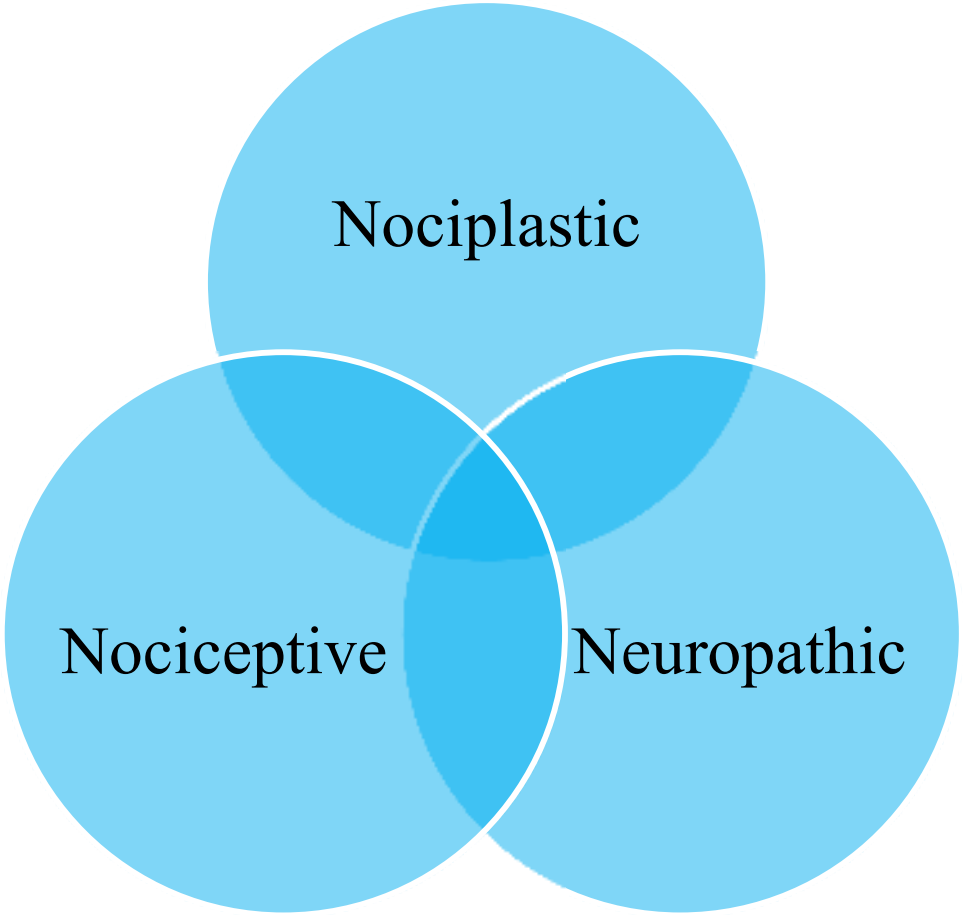
What is pain?

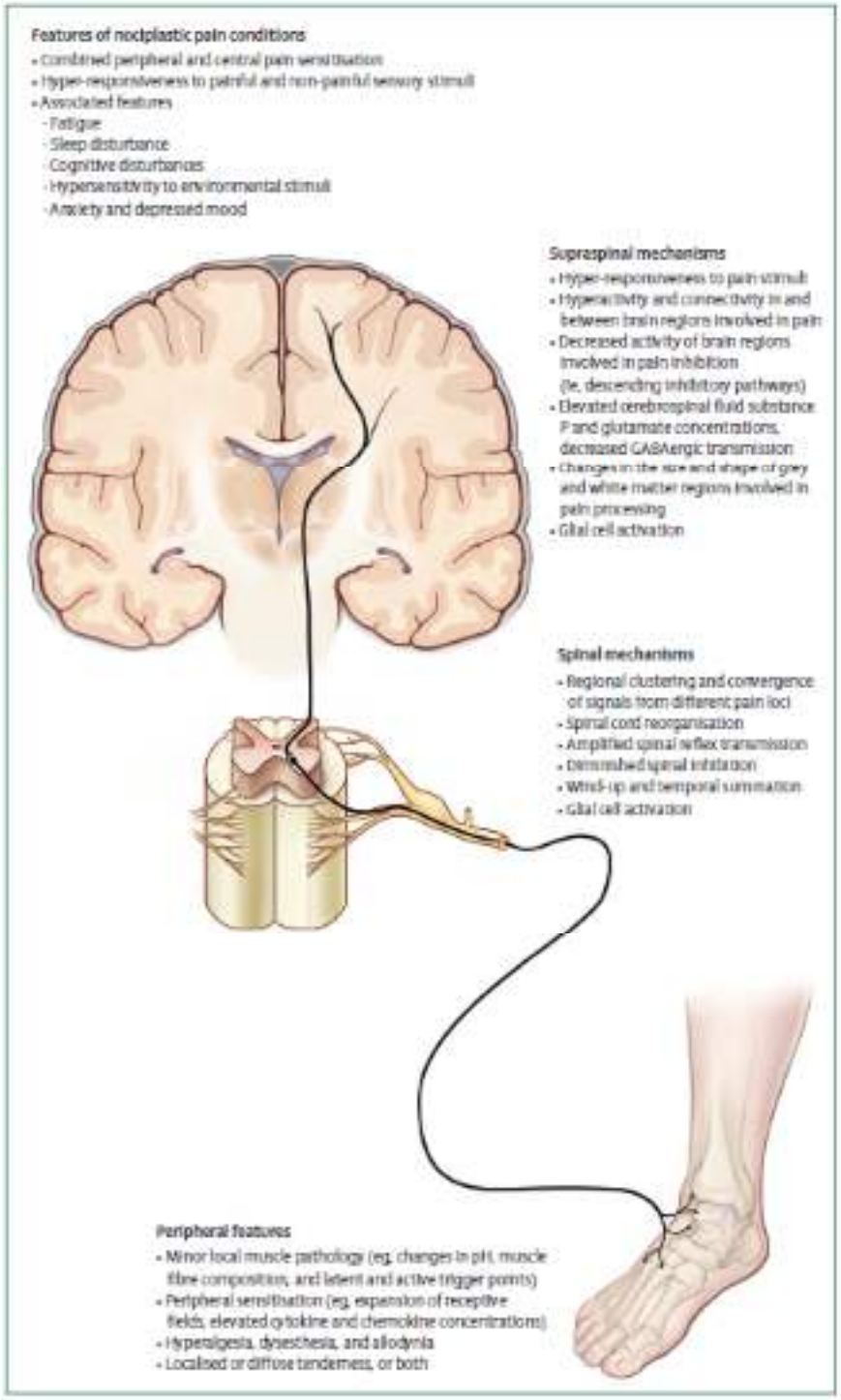
"An unpleasant **sensory and emotional experience** associated with, or resembling that associated with, actual or potential tissue damage."

- Pain is always a **personal experience** that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=10475

Three general types of pain





Lancet, 2021

Pain disorders in people with HIV

Research Paper
PAIN

Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization

Jocelyn M. Jao, Eric So, Jebakaran Jebakumar, Mary Catherine George, David M. Simpson, Jessica Robinson-Papp*

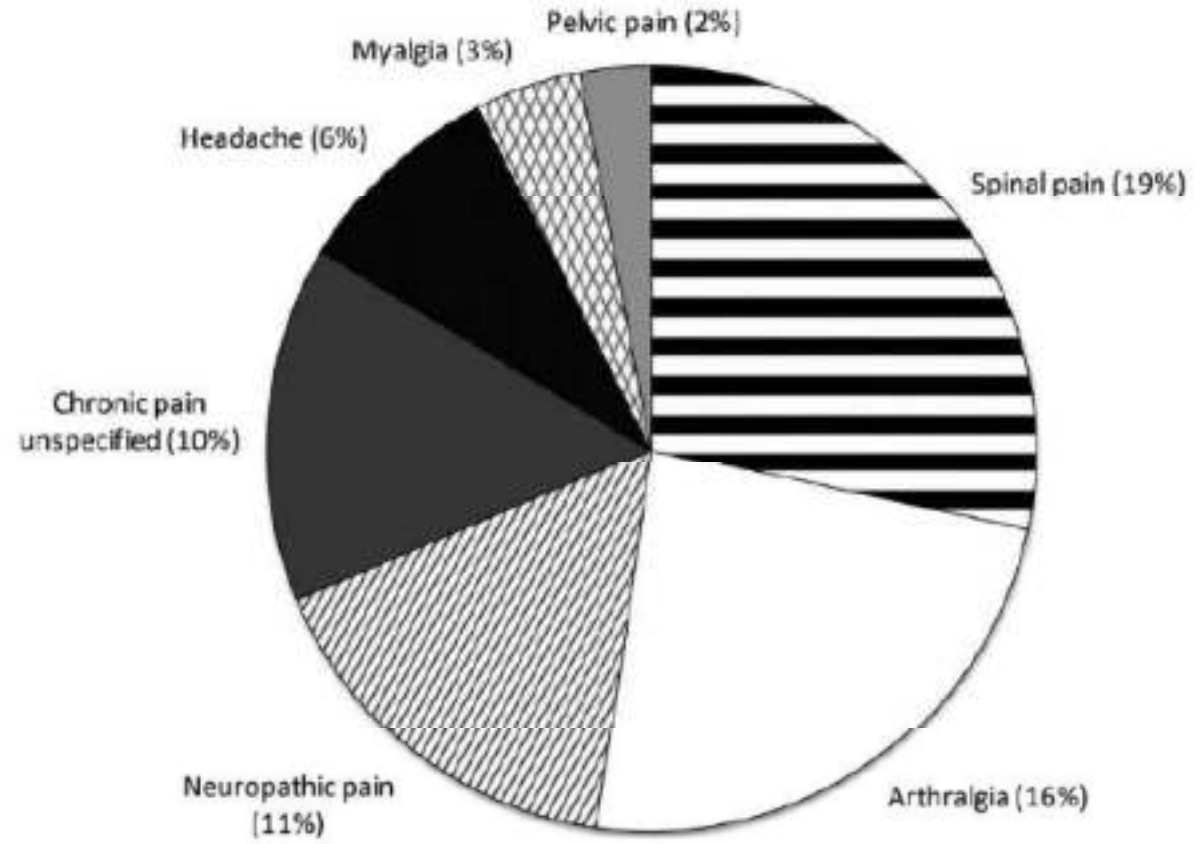


Figure 2. Common chronic painful diagnoses in treated HIV.

Most common types of pain:

Spinal pain
Joint pain
Neuropathic pain
Headache
Muscle pain
Pelvic pain

People living with HIV and chronic pain are complex

- Overlapping pain syndromes
- Multiple medical co-morbidities

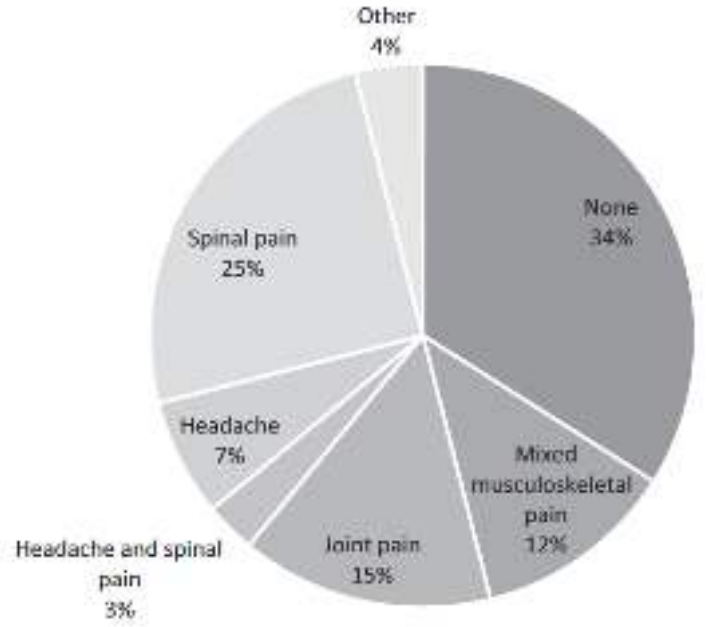


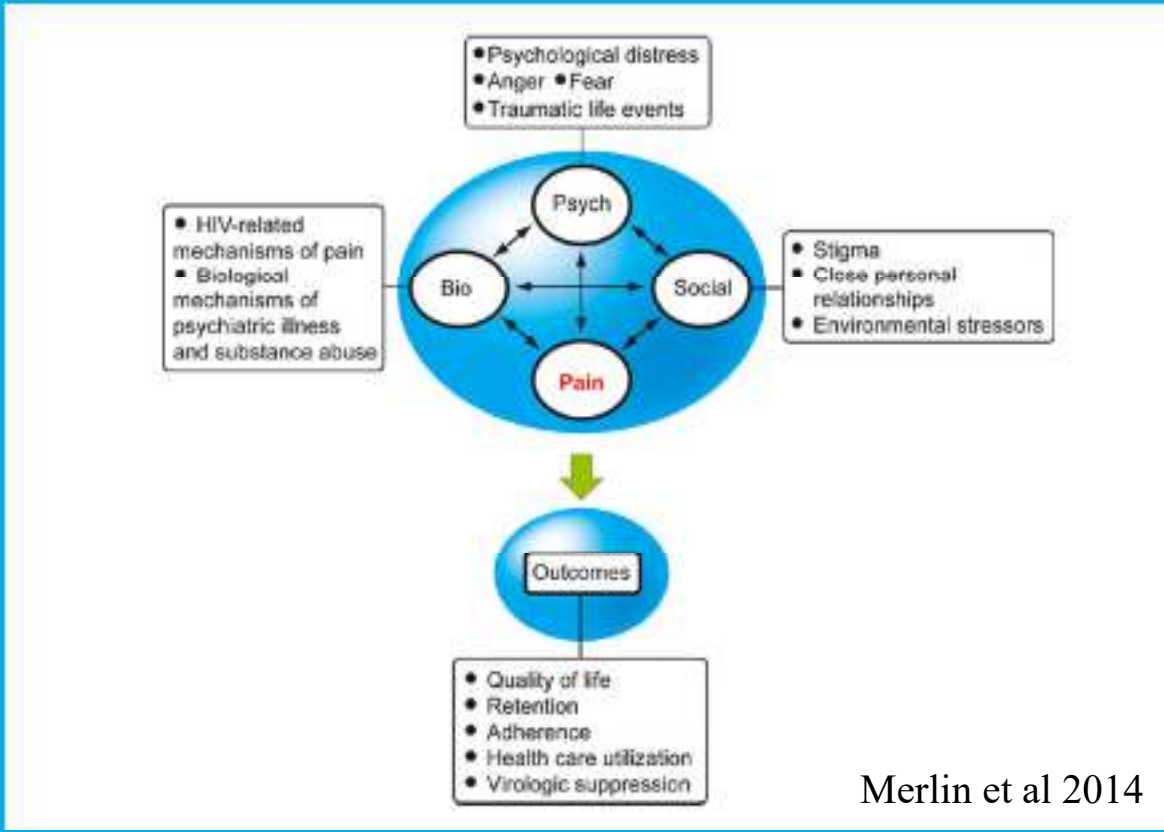
Figure 1 Breakdown of comorbid pain syndromes in HIV–peripheral neuropathy.

Table 1

Characteristics of HIV-infected patients with and without a chronic pain diagnosis*.

	All patients (n = 638)	Patients with a chronic pain diagnosis (n = 252)	Patients without a chronic pain diagnosis (n = 386)	*P*
VACS index	28 ± 21	30 ± 20	25 ± 21	<0.001
Mean numeric pain score rating (on a scale of 0–10)	2.1 ± 2.1	3.2 ± 2.1	1.4 ± 1.8	<0.001
Healthcare utilization				
Inpatient admissions	0.3 ± 1.0	0.5 ± 1.3	0.2 ± 0.70	0.001
Total days hospitalized	1.9 ± 7.3	2.4 ± 8.7	1.5 ± 6.2	0.001
ED visits	0.9 ± 2.1	1.4 ± 3.0	0.6 ± 1.2	<0.001
Radiological procedures	2.6 ± 4.8	3.7 ± 5.4	1.9 ± 4.2	<0.001
Surgical procedures	0.1 ± 0.4	0.2 ± 0.5	0.1 ± 0.4	0.001
Comorbid substance use diagnosis	32%	43%	25%	<0.001
Comorbid psychiatric diagnosis	48%	63%	39%	<0.001
Total number of psychiatric and substance use diagnoses	1.3 ± 1.6	1.9 ± 1.9	1.0 ± 1.3	<0.001

Biopsychosocial model of pain



Merlin et al 2014

"I have failed to separate my HIV from this pain": the challenge of managing chronic pain among people with HIV

V. Baker, K. Nkhoma, R. Trevelion, A. Roach, A. Winston, C. Sabin, K. Bristowe & R. Harding

thematic approach. Findings revealed that HIV stigma, fractured care pathways, and general practitioners' lack of HIV training are barriers to supported pain management. Unaddressed pain results in poorer mental health and reduced quality of life, which has important clinical implications for HIV treatment adherence. Creating HIV-specific pain resources, activating social

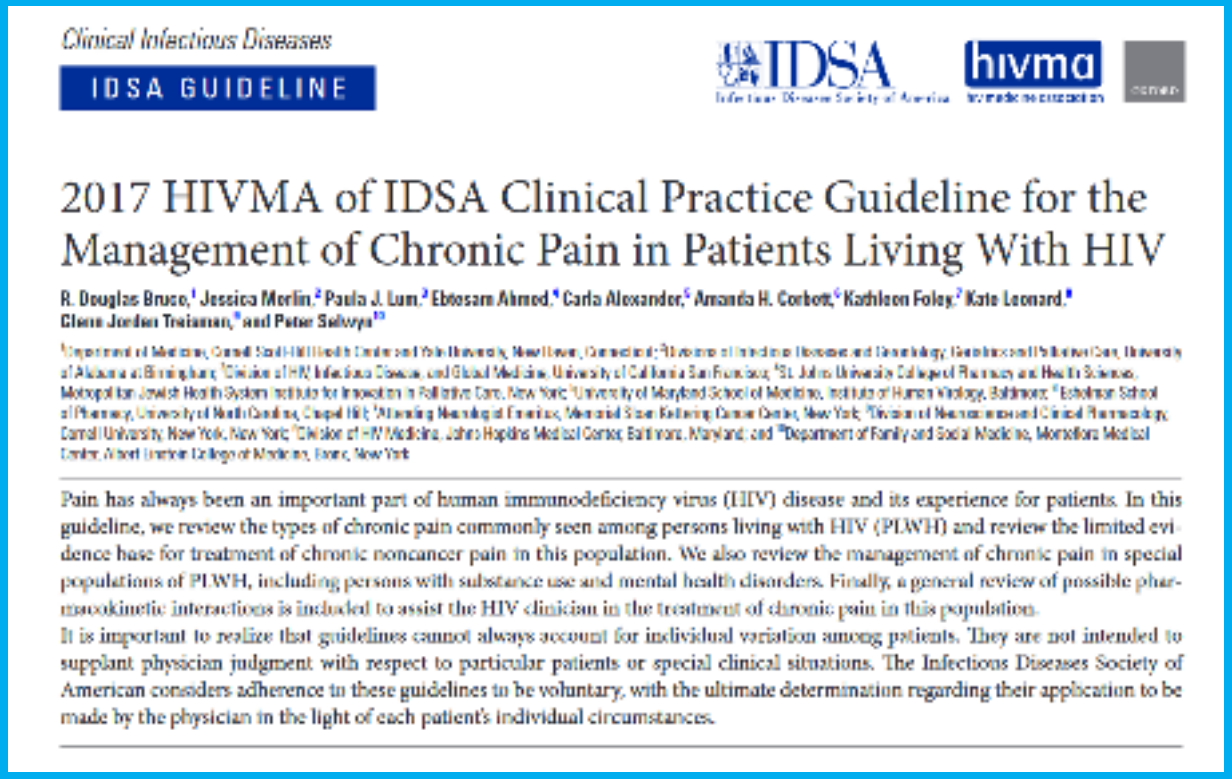
Pain Evaluation and Treatment

Principles of chronic pain evaluation

- Diagnostic evaluation for new pain conditions is warranted
- Once pain is chronic, additional diagnostic evaluation should be limited
- Expectation should be set that finding a specific “cause” of the pain in the painful area of the body may not be possible
- The idea of pain as a neurologic disorder can be introduced (this is tricky to explain well)
- Sometimes the diagnosis “fibromyalgia” can be very helpful

Treating pain in PLWH

- No FDA approved treatments specific for pain in PLWH
- There are some HIV-specific guidelines (HIVMA/IDSA) that are lengthy and recommend management strategies that are likely not accessible to most (e.g., interdisciplinary teams, behavioral interventions)
- Can also follow guidelines for general population and/or similar conditions (e.g., diabetic neuropathy for patients with HIV-associated neuropathic pain)
- Important to set reasonable goals. Pain freedom is unlikely.
- Two general categories:
  - Non-pharmacologic
  - Pharmacologic



Clinical Infectious Diseases

IDSA GUIDELINE

IDSA hivma

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

R. Douglas Bruce,[1] Jessica Merlin,[2] Paula J. Lum,[3] Ebtesam Ahmed,[4] Carla Alexander,[5] Amanda H. Corbett,[6] Kathleen Foley,[7] Kate Leonard,[8] Glenn Jordan Treisman,[9] and Peter Salwyn[10]

[1]Department of Medicine, Cornell Scott-Hill Health Center and Yale University, New Haven, Connecticut; [2]Division of Infectious Diseases and Geographic Medicine, University of Alabama at Birmingham; [3]Division of HIV, Infectious Diseases, and Global Medicine, University of California San Francisco; [4]St. John's University College of Pharmacy and Health Sciences, Metropolitan Jewish Health System Institute for Innovation in Palliative Care, New York; [5]University of Maryland School of Medicine, Institute of Human Virology, Baltimore; [6]Eshelman School of Pharmacy, University of North Carolina, Chapel Hill; [7]Weill Cornell Medicine of Cornell University, Memorial Sloan Kettering Cancer Center, New York; [8]Division of Neuroimmunology and Clinical Pharmacology, Cornell University, New York, New York; [9]Division of HIV Medicine, Johns Hopkins Medical Center, Baltimore, Maryland; and [10]Department of Family and Social Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

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.

- Total of 51 recommendations on: screening for pain and comorbid psychiatric disorders, pharmacologic and non-pharmacologic treatments.
- Most had low to moderate evidence

Recommended non-pharmacologic treatments

- CBT, yoga for MSK pain, PT/OT, hypnosis for neuropathy pain, acupuncture

Recommended pharmacologic treatments

- For neuropathy: gabapentin, capsaicin patch, cannabis, alpha-lipoic acid

On opioids

- Similar to CDC guidelines

Clinical Infectious Diseases® 2017;65(10):e1–37

DOI: 10.1093/cid/cix636

Non-pharmacologic treatments

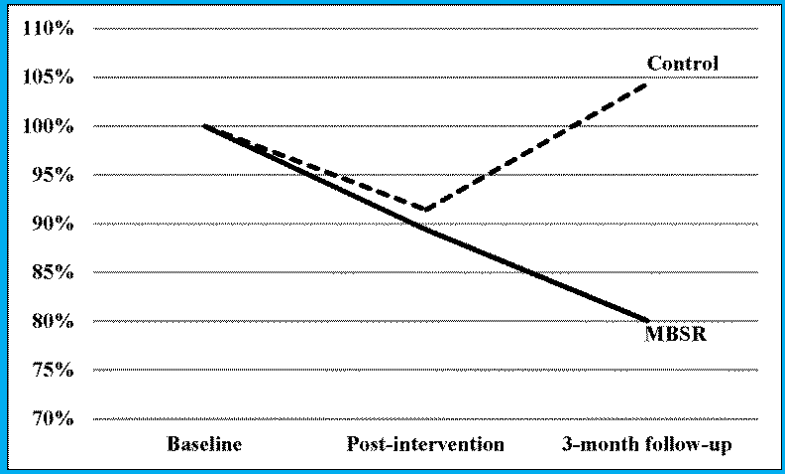
	Mainstream ⟷ Complementary/Alternative		
Active ↕ Passive	• Physical therapy • Exercise • CBT (and other behavioral interventions)	• Mindfulness based stress reduction • Biofeedback • Progressive Muscle Relaxation/Motor control	• Tai chi • Yoga • Meditation • Alexander technique
	• Therapeutic ultrasound • TENS	• Myofascial release • Music therapy	• Hypnosis
	• Interventional pain management • Trigger point injections	• Massage • Chiropractic and osteopathic manipulation	• Acupuncture, acupressure • Low level laser therapy • Reflexology • Craniosacral therapy • Feldenkrais • Rolfing • Reiki • Aromatherapy • Magnets • Natural products

Common threads among active non-pharmacologic treatments (mainstream and CAM)

- Often combine psychological and physical components
- Psychological:
  - Re-framing
  - Self-efficacy
  - Coping
- Physical:
  - Strength
  - Flexibility
  - Cardiovascular fitness
- Body awareness
- Teach techniques for pain self-management

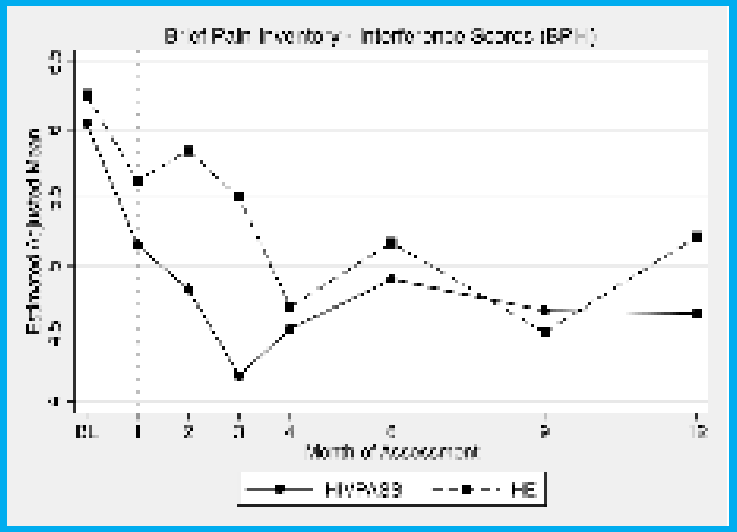
Non-pharmacologic therapies for Chronic Pain in HIV

- Mixed-methods feasibility study of MBSR versus health education control (N=32).
- Post-intervention primary outcome not met, but intervention group was better at 3-month follow-up



George et al. Behavioral Medicine. 2015.

- HIV-PASS study: a) psychoeducation about pain and depression; b) supportive coaching; c) education pacing; and d) behavioral activation to increase engagement in pleasant and meaningful activities



- Physical therapy-based interventions

An Innovative Physical Therapy Intervention for Chronic Pain Management and Opioid Reduction Among People Living with HIV

Sara D. Pullen,[1,*] Carlos del Río,[2,3] Daniel Brandon,[1] Ann Colonna,[1] Meredith Denton,[1] Matthew Ing,[1] Grace Lancaster,[1] Anne-Grace Schmidtke,[1] and Vincent C. Marconi[2,3]

BioResearch Open Access
Volume 9.1, 2020
DOI: 10.1089/biores.2020.0006

- STOMP (Skills to Manage Pain) Intervention

AIDS and Behavior (2018) 22:2733–2742
https://doi.org/10.1007/s10461-018-2028-2

ORIGINAL PAPER

A Randomized Pilot Trial of a Novel Behavioral Intervention for Chronic Pain Tailored to Individuals with HIV

Jessica S. Merlin[1] · Andrew O. Westfall[2,3] · Dustin Long[2,3] · Susan Davies[4] · Michael Saag[2] · William Demonte[2] · Sarah Young[2,16] · Robert D. Kerns[5,6] · Matthew J. Bair[7,8,9] · Stefan Kertesz[10,11] · Janet M. Turan[12] · Meredith Kilgore[12] · Olivio J. Clay[13] · Joanna Starrels[14] · Dorothy Pekmezi[4] · Mallory O. Johnson[15]

Pain treatments: Pharmacological

Pharmacologic treatment options

- Try to keep regimens simple when possible but may require agents from different classes

- NSAIDs/acetaminophen
- Gabapentinoids
- SNRIs
- Tricyclics
- Muscle relaxants
- Topicals

- CGRP-based therapies (migraine specific)
- Cannabinoids
- Opioids

Gabapentinoids

- Gabapentin
  - Very safe overall, few drug interactions
  - Mostly for neuropathic pain but also used more broadly
  - Inexpensive
  - Can cause sedation, weight gain, more rarely lower extremity edema
  - Wide dosing range: 100 tid to ~800 tid
- Pregabalin
  - Similar to gabapentin, twice daily dosing
  - Common dose range: 75 bid to max 300 bid

SNRIs

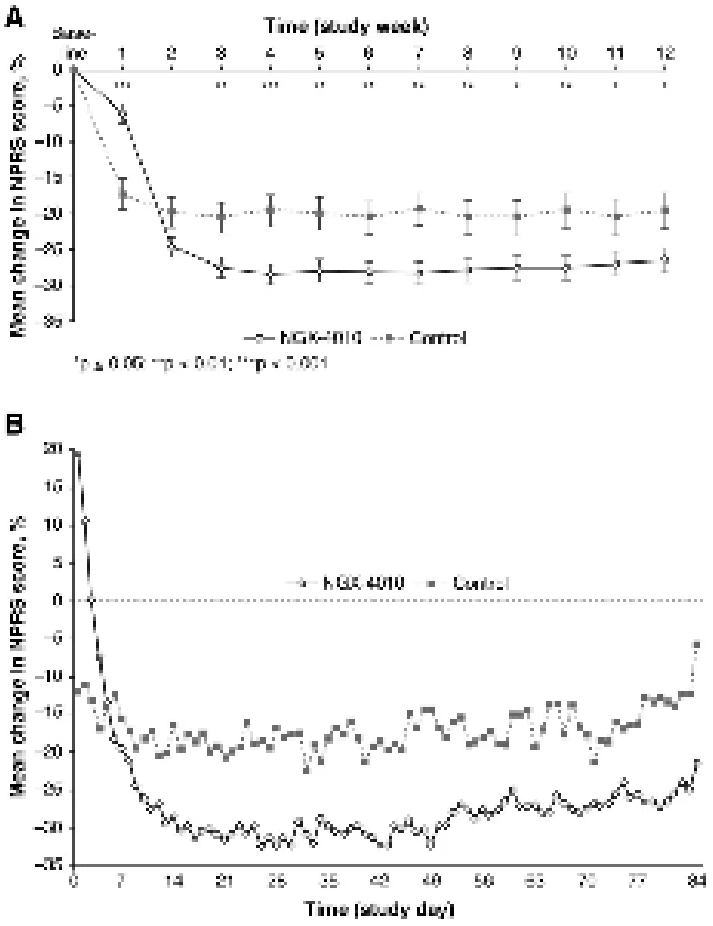
- Venlafaxine, **Duloxetine**, Milnacipran
- Can be helpful for multiple types of pain: musculoskeletal, nociplastic (e.g., fibromyalgia), neuropathic.
- Good choice in patients with co-morbid depression/anxiety.
- Nausea is common side effect, usually goes away within one week. Usually given in AM to avoid insomnia.
- Duloxetine start 20-30 qd, increase to 60 daily.

Tricyclics and muscle relaxants

- Tricyclic antidepressants: amitriptyline and nortriptyline
- Old drugs with lots of off target effects
- Avoid (or use with great caution) in elderly or medically frail
- May be helpful in more robust patients particularly when pain is worse at night and associated with insomnia (since these are sedating)
- Can give in a single evening dose usually 25mg, range 10 to ~50mg.

- Muscle relaxants mostly for musculoskeletal pain.
- Many different ones, common ones include: cyclobenzaprine and tizanidine.

Topicals: High dose concentration capsaicin patch



	NGX-4010		
	Total (n = 482)	30 minutes (n = 239)	60 minutes (n = 243)
LS mean change (SE) in NPRS score from baseline to Weeks 2–12	−27.4 (1.4)	−26.9 (2.1)	−27.9 (2.0)
95% CI of LS mean	−30.1, −24.7	−30.8, −23.0	−31.7, −24.0
p value[1]	0.0034	0.0024	0.2935
Patients with ≥30% reduction in NPRS score from baseline to Weeks 2–12, n (%)	193 (40)	95 (40)	98 (40)
OR	1.65	2.21	1.22
95% CI of OR	1.18, 2.30	1.29, 3.79	0.77, 1.95
p value[1]	0.0062	0.0040	0.3949
PGIC at Week 12	n = 439	n = 220	n = 219
Very much/much/slightly improved, n (%)	294 (67)	148 (68)	151 (69)
p value[1]	<0.0001	0.0001	0.0003

Other topicals include: topical diclofenac, low dose capsaicin products, menthol products. Mostly low risk, little systemic absorption.

Brown, S., et al. (2013). "NGX-4010, a capsaicin 8% patch, for the treatment of painful HIV-associated distal sensory polyneuropathy: integrated analysis of two phase III, randomized, controlled trials." 10(1): 5.

Cannabis HIV-neuropathy studies

- Abrams 2007
  - 50 participants with painful neuropathy randomized to cannabis vs. placebo cigarettes, TID x 5 days
  - Smoked cannabis reduced daily pain by 34% (median reduction; IQR = -71, -16) vs 17% (IQR = -29, 8) with placebo ($p = 0.03$).
  - Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$).
  - The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$).
  - No serious adverse events.

- Ellis 2009
  - Randomized, double-blind cross-over with 28 completed participants with painful neuropathy
  - Smoked cannabis or placebo 4 times daily for 5 days
  - Participants achieving at least 30% pain relief: 46% with cannabis versus 18% with placebo

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 71 / No. 3
November 4, 2022

CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A; evidence type: 2).

Prescription opioids in people living with chronic pain and HIV

- Starting opioids for chronic pain is generally not recommended given risk (although some evidence for efficacy).
- Long term opioid prescribing is common in people with HIV, originates in the early epidemic when care followed a palliative model.

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

Marco B Finnerup*, Nadine Attal*, Sören Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter Kalso, Kasper Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Pirkko Siddall, Bob H Smith, Mark Wallace

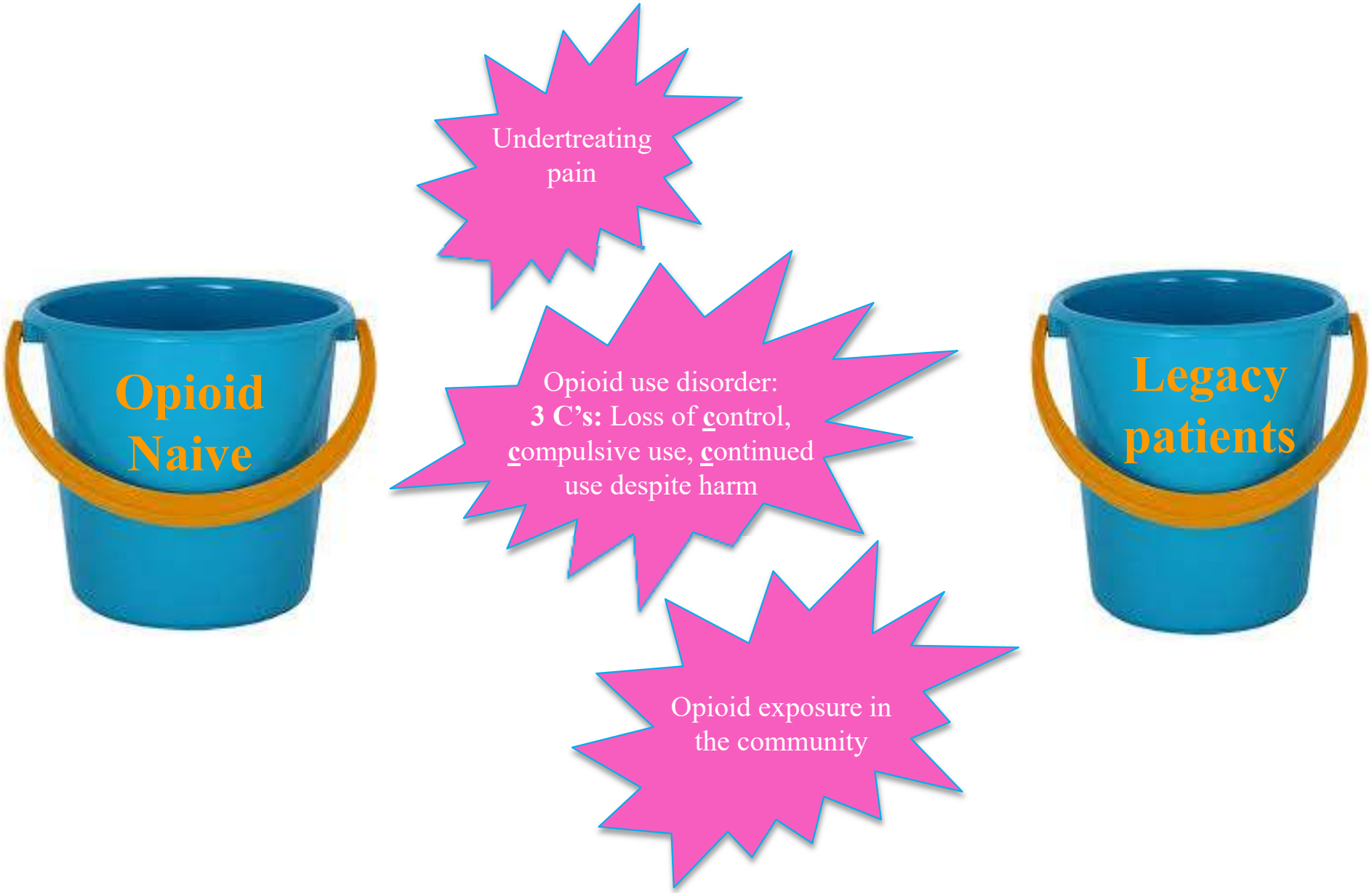
Lancet Neurol 2015; 162–73

We identified 13 trials of strong opioids, in which oxycodone (10–120 mg/day) and morphine (90–240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive: combined NNT was 4·3 (95% CI 3·4–5·8) and NNH was 11·7 (8·4–19·3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (no additional benefit for higher doses; appendix).

Clinical guidelines for neuropathic pain typically include tramadol as second line and strong opioids as third line

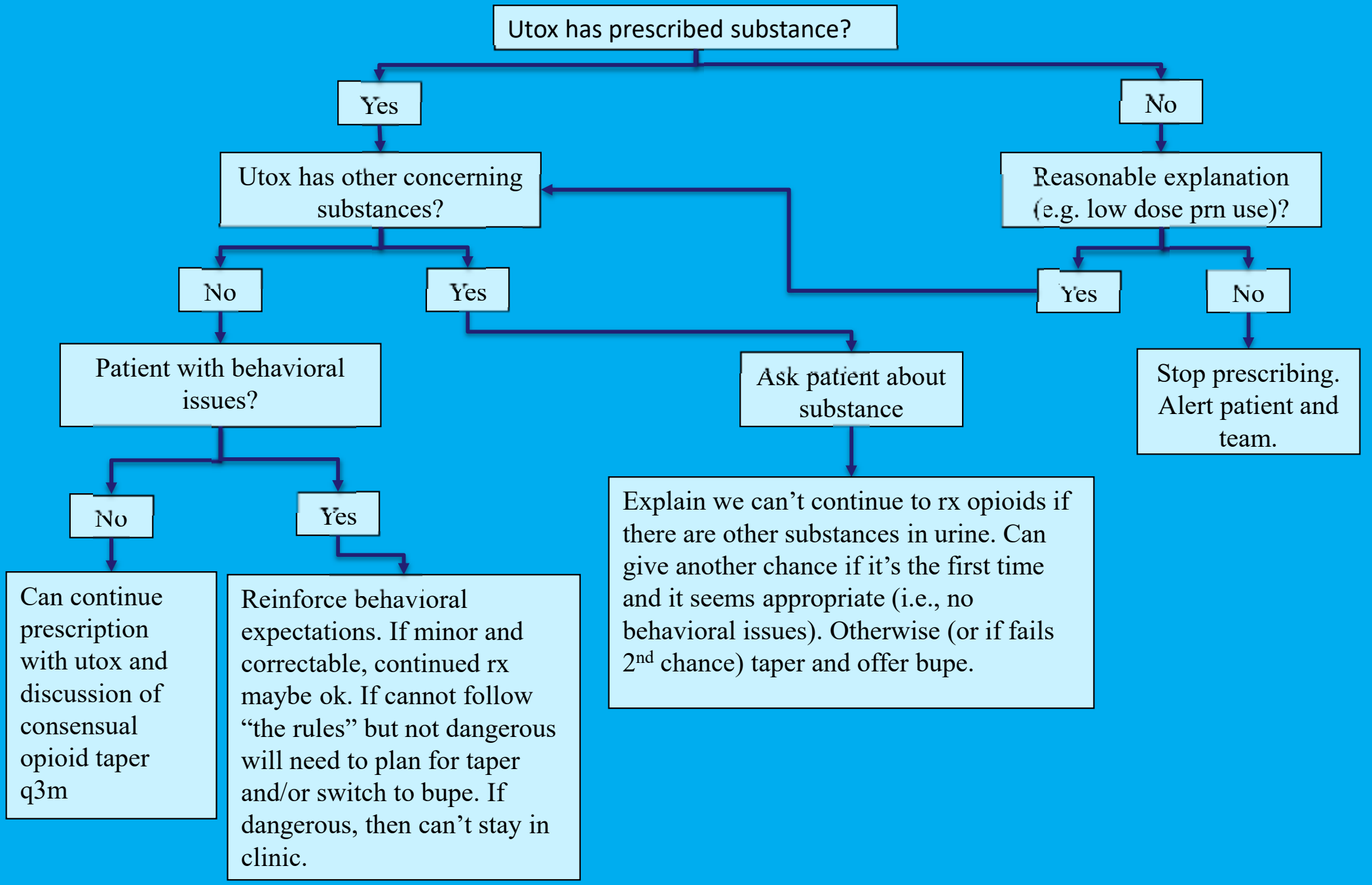
	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)	Susceptibility to bias‡
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)	1973
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)	1826
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)	2534
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)	1879
Tramadol	6	741	176/380	96/361	4·7 (3·6–6·7)	982
Strong opioids	7	838	211/426	108/412	4·3 (3·4–5·8)	1326
Capsaicin 8%	6	2073	466/1299	212/774	10·6 (7·4–18·8)	70¶
Botulinum toxin A	4	137	42/70	4/67	1·9 (1·5–2·4)	678

Two distinct groups of patients, One guiding principle



HARM REDUCTION… What am I most worried about and what do I think is the best way of avoiding it?

Opioid decision tree



Buprenorphine

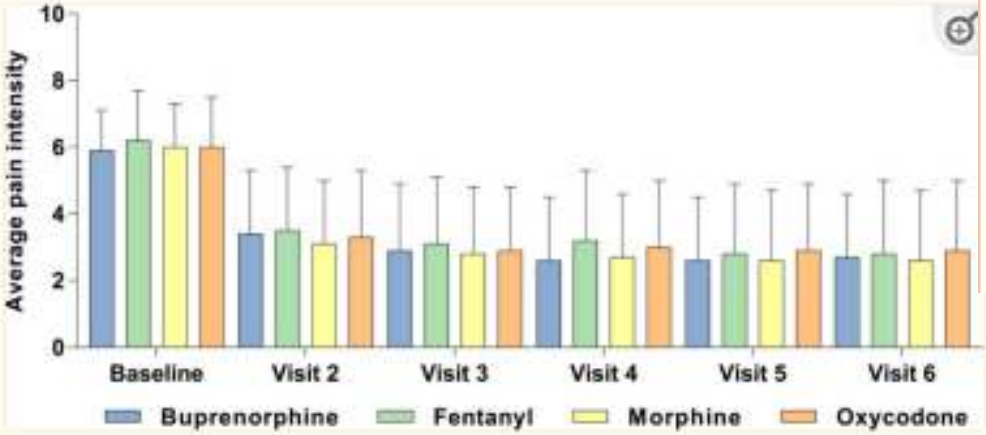


Figure 3

Efficacy of Transdermal Buprenorphine Compared With Conventional Opioids in Patients With Chronic Cancer Pain. Average pain intensity was measured on a numeric rating scale. Data are mean (SD). Data from Corli et al (2016).[53]

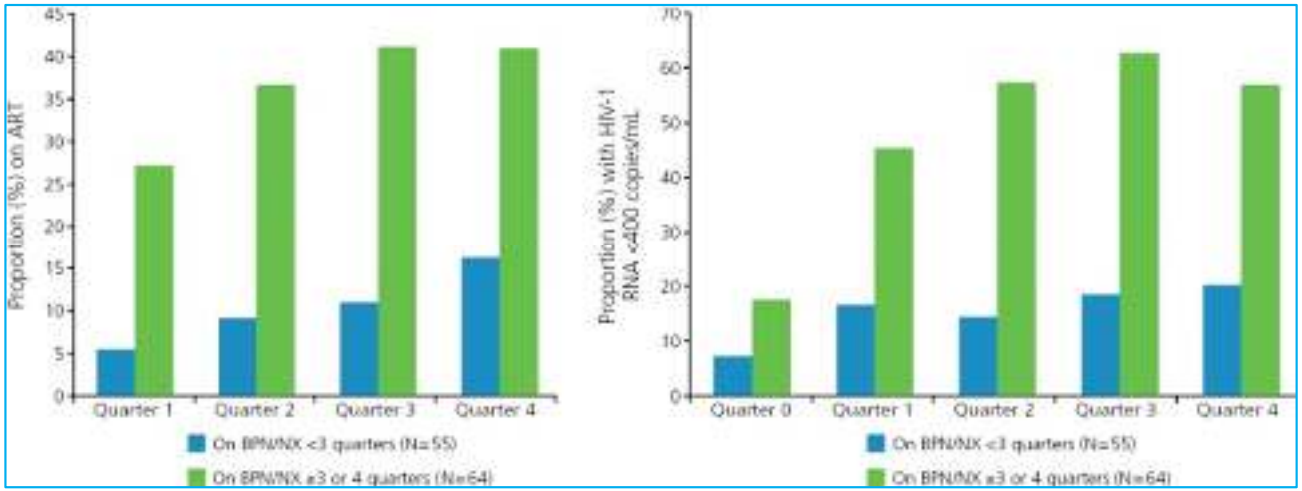
Table 1

Buprenorphine Products

FDA-Approved Indication	Pain Management			Addiction Medicine			
	Acute Pain	Chronic Pain		OUD		Opioid Dependence	
Trade name	Buprenex	Belbuca	Butrans	Brixadi®	Sublocade	Probuphine	Generic Sublutex
Route of administration	Injection	Buccal	Transdermal	Injection	Injection	Implant	Sublingual
Available dose range	300 µg/mL	75, 150, 300, 450, 600, 750, or 900 µg	5, 7.5, 10, 15, or 20 µg/h	8, 16, 24, or 32 mg weekly; 64, 96, or 128 mg monthly	100 and 300 mg/month	74.2 mg/6 months	2 or 8 mg
Bioavailability	100%	10%–65%	15%	100%	100%	N/A	15%–30%

Hale, Garofoli and Raffa 2021. Journal of Pain Research.

Buprenorphine treatment has positive outcomes in people living with HIV and chronic pain and may be useful for pain as well.



Cunningham 2018. PMID: 29689538

Conclusions

- HIV impacts the nervous system via neurotoxic viral proteins (especially gp120) and the inflammatory response to them
- Common neurologic disorders thought to be directly related to HIV are HAND and the peripheral neuropathies, but comorbidities can exacerbate both of these conditions
- Chronic pain is highly prevalent among people with HIV, may be in part due to central sensitization (aka nociplastic pain)
- Musculoskeletal pain, including spinal pain, is the most common, although it rarely occurs in isolation
- Multimodal treatment for pain is the goal but non-pharmacologic treatment choice may be limited by availability.
- Many people with HIV remain on opioids for chronic pain but this is largely a legacy effect. Probably best to avoid new prescriptions, unless benefit clearly outweighs risk, in which case buprenorphine is likely the safest option.