

SPECIAL ISSUE HIV and CHRONIC PAIN (The Global Task Force for Chronic Pain in People with HIV (PWH): Developing a research agenda in an emerging field)

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The Global Task Force for Chronic Pain in People with HIV (PWH): Developing a research agenda in an emerging field

Chronic pain is a common comorbidity in people with HIV (PWH), with prevalence estimates ranging from 25-85%. Research in this area is growing, but significant gaps remain. A Global Task Force of HIV experts was organized to brainstorm a scientific agenda and identify measurement domains that will be critical to advancing research in this field. Hybrid quantitative and qualitative approach. Experts were identified through literature searches and snowball sampling. Two online questionnaires were developed by a group of Task Force members. Questionnaire 1 asked participants to identify the most important knowledge gaps in the field of HIV and chronic pain and identify the most important measurement domains in studies of chronic pain in PWH. Responses were ranked in order of importance in Questionnaire 2, which was followed by a group discussion. Twenty-nine of the 31 Task Force members who were contacted completed Questionnaire 1, 25 completed Questionnaire 2, and 21 participated in the group. Many important clinical and research priorities emerged, including the need to examine etiologies of chronic pain in PWH and how those etiologies compare to those of chronic pain in the general population. Pain-related measurement domains were discussed, with a primary focus on domains that could be assessed in a standardized manner across various cohorts that include PWH in different countries. We collaboratively identified clinical and research priorities, as well as gaps in standardization of measurement domains, that can be used by Task Force and other investigators to move the field forward.

Keywords: HIV, pain, opioid, global health

Introduction

Chronic pain is a common comorbidity that negatively affects the health-related quality of life of people with HIV (PWH) globally. Prevalence estimates of chronic pain in PWH range from 25%-85% depending on the cohort studied, which is higher than estimates in the general (i.e., non-HIV) population (Dahlhamer, 2016; Fayaz, Croft, et al., 2001; National Department of Health, 2019; Sharma, Hoover, et al., 2018; Sabin, Hardin, et al., 2018; Merlin, Long, et al., 2018; Merlin, Westfall, et al., 2018; Merlin, Cen, et al., 2012). Chronic pain in PWH is associated with greater odds of impairment in physical function, more mental health problems (Scott, Arkuter, et al., 2018), and in some patients, suboptimal adherence to antiretroviral therapy, poor retention in HIV care, lower likelihood of virologic suppression, depression, suicidal ideation, and disability (Merlin, Long, et al., 2018; Merlin, Westfall, et al., 2013, Kietrys, Myezwa, et al., 2019) including missed days of work/education (Scott, Arkuter, et al., 2018).

HIV clinical and research communities have increasingly recognized chronic pain as an important comorbidity. For example, the Infectious Diseases Society of America / HIV Medical Association released guidelines for the care of chronic pain in PWH in 2018, recommending universal screening for chronic pain in PWH, among other strategies for diagnosis and management. The most recent UK Standards of HIV Care co-produced by HIV health professionals and community members stipulate that routine pain assessment should be conducted (British HIV Association, 2018). Additionally, leaders in HIV have proposed a global focus on health-related quality of life. Building on the UNAIDS 90-90-90 campaign (90% of PWH diagnosed, on treatment, and virologically suppressed), Lazarus et al. have proposed a

“fourth 90” to address factors that heavily impact quality of life, explicitly including non-communicable diseases, mental health, and pain (Lazarus, Safreed-Harmon, et al., 2016; Fredericksen, Edwards, et al., 2015). Indeed, PWH have, themselves, identified pain as one of the priority outcomes to be measured and addressed in routine HIV care (Bristowe, Clift, et al., 2019).

There is currently an incomplete understanding of whether and why PWH are at higher risk of developing chronic pain than people without HIV. Further, the etiological mechanisms involved in pain generation and maintenance for PWH remain unclear. Pain is a biopsychosocial phenomenon (Merlin, Zinski, et al., 2014) and comparison of the pain experience of PWH in different social contexts globally may also provide unique insights into geographical and cultural influences on pain for PWH. Such global research efforts will also require renewed attention to the relevance and utility of pain assessment approaches in the different settings to be studied, which are likely to vary substantially in many ways, including participant literacy, language, culturally acceptable questions, interpretation of medical terms (e.g. depression) and access to PWH who are willing to participate in research activities (Bruce, Merlin, et al., 2017). Proper assessment of pain is arguably the cornerstone to providing effective pain management. Lack of contemporary understanding regarding the types of chronic pain that affect PWH, and how best to assess them, may have thus far impeded research focused on pain management best practices for PWH.

Despite the large clinical need in this area, evidence-based guidance for how to optimally manage chronic pain in PWH has been slow to emerge. For example, a recent systematic review

found only 11 mostly low and very low-quality studies that addressed the key issue of chronic pain management in PWH. At present, pharmacologic pain treatment options, including opioid medications, appear to have limited efficacy for managing the chronic pain of many PWH (Merlin, Westfall, et al., 2018). Psychological approaches to chronic pain management in PWH have demonstrated initial promise (Hsieh, Shannon, 2016); however, the full potential of this treatment modality to yield positive outcomes remains unclear. There is emerging evidence to suggest that physical therapy and self-management interventions delivered online, face-to-face, or in group-based formats may be effective for improving pain and physical symptoms in PWH (Kietrys, Galantino, 2018). There remains a significant clinical need, however, for additional high-quality clinical trials addressing pain management techniques for chronic neuropathic and non-neuropathic pain in PWH.

To address the gap between clinical need and evidence, we organized a Global Task Force on Chronic Pain in PWH. The Task Force's aim is systematically to advance clinical care and science of this field through multinational, interdisciplinary collaboration and fostering community partnerships. To accomplish this, our objectives are to 1) Develop a scientific agenda that identifies the important gaps in knowledge in the field, including basic, translational, clinical and health services research; 2) Identify core measures that should be used across cohorts and countries to provide standardization in the field; 3) Using 1 and 2, promote research on chronic pain within existing, established HIV cohorts and clinical trials; 4) Initiate collaborations to answer research questions in this field that are ideally accomplished by recruiting from geographically diverse sites, and 5) Promote clinical care that is grounded in this emerging body of research and existing literature on chronic pain in other populations.

Here, we describe how our Task Force has addressed the first and second steps, developing a scientific agenda and identifying measurement domains. Our aim was to approach these steps in a systematic way, and in a way that would serve as a foundation for our future work (including steps 3-5).

Methods

Participant recruitment

We identified Task Force members through snowball sampling from an initial group of investigators (JSM, BRG, RP, AW, HK, WS) and literature searches. The target population was experts in HIV and chronic pain globally, based on active clinical work, research, leadership, or community engagement in the field. All Task Force members were eligible to complete the questionnaires and participate in the group discussion, and were permitted to complete any number of these tasks. Two Task Force members were added after the online questionnaires had been completed, and therefore, were only eligible to complete the group discussion.

Study design

Questionnaires were conducted online in June – July 2019 using Qualtrics (Provo, UT).

Questionnaires were conducted anonymously to minimize social desirability bias. Questionnaire 1 was an open-ended brainstorming task in which participants were asked to 1) identify the most important knowledge gaps in the field of HIV and chronic pain and 2) identify the most important domains to measure in studies of chronic pain in PWH, which could include pain, or related domains that are important to consider in PWH who have pain. Based on these results, Questionnaire 2 asked participants to 1) rank the knowledge gaps in terms of improving care and

advancing the science, and 2) select the 10 most and 10 least important domains, acknowledging that some would be more important for baseline measurement and some would be more important for outcome measurement (see Supplemental Content for full questionnaires).

To further investigate and clarify findings from the questionnaires, a group discussion was held at the in-person Task Force meeting held at the AIDSImpact conference in London, United Kingdom, on July 31, 2019. The discussion was facilitated by an experienced qualitative researcher (F.C.). Participants were allowed to join the group discussion in person or by phone, and were not required to stay for the entire session, which was scheduled for a 5-hour block during the conference and took 3½ hours to complete. The group discussed important topics and outcome domains to be studied such as prevalence and etiologies of chronic pain, psychosocial factors that impact chronic pain, and clinical treatment and management of chronic pain. Relevant research methods as well as approaches to operationalize research questions were also discussed.

The group discussion was confidential but not anonymous, as it was conducted in person and by phone. This also provided the opportunity to collect basic demographic information: degree, country, role (e.g., researcher). Due to the collaborative nature of this work, participants in the Task Force are included as co-authors. In an attempt to protect confidentiality in this context, all questionnaire and group discussion results presented below are presented without any accompanying demographic information.

This study was reviewed by the University of Pittsburgh Institutional Review Board and was granted exempt status.

Analysis

Questionnaire 1 free text responses were analyzed by the study's lead qualitative investigator (MH) using a conventional content analysis approach, in which the analyst sorts content into categories derived from the original text (O'Brien, Hanna, et al., 2019). We chose this approach because participants were asked to brainstorm knowledge gaps and measurement domains rather than provide open-ended commentary; because of the one-sided online format, we were unable to probe participants further about their responses. Therefore, we anticipated the results would take the form of straightforward content rather than higher-level themes. Questionnaire 1 results were grouped into common research topics and measurement domains.

In Questionnaire 2, participants were asked to rank topics and domains in terms of their importance. The rankings were then presented to group discussion participants. The group discussion was audio-recorded and audio-coded by two qualitative investigators (JSM, who was part of the group discussion, and FC, who led the group discussion) who listened to the audio recording, coded the audio in 10-minute segments with the assistance of Express Scribe, and analyzed it, also using a conventional content analysis approach (Hsieh, Shannon, 2016). Specifically, we identified codes that clarified or added to the questionnaire results, and new codes that arose. These codes are presented below.

Results

Twenty-nine of the 31 (94%) Task Force members who were contacted completed Questionnaire 1. Table 1 lists all knowledge gaps identified, and Table 2 lists all measurement domains.

Twenty-five of the 29 (86%) participants who completed Questionnaire 1 completed Questionnaire 2. Table 3 summarizes Questionnaire 2's ranking/selection results. For example, best practices in chronic pain management, etiologies of chronic pain in PWH and if they are different from those in the general population, and evaluation of the relevance of animal models of chronic pain in PWH were identified as knowledge gaps, but rankings of importance varied. The group discussion included 21 participants. Most participants (15) attended in person. Participants included the following categories (not mutually exclusive): physicians (6), researchers (19: 17 clinical only, 1 basic science only, 1 basic science and clinical), and a lay patient advocate who is an HIV organization advisory board member and also has both HIV and chronic pain. Participants were from the US, UK, South Africa, Canada, and Australia.

The group discussion was conducted in three sections, and results are presented by section: clinical priorities, research priorities, and measurement domains. Patient involvement, a recurrent theme throughout the group discussion, is discussed separately.

Clinical priorities

Screening

Participants noted that all priorities on the list were important, and that prioritizing was difficult. Some participants were surprised that encouraging clinicians to employ universal screening for chronic pain in PWH was ranked so low (6/10, see Table 2). Several reasons were given why screening should be a high priority, including Infectious Diseases Society of America guidelines that recommend universal pain screening in PWH, and widespread acceptance that pain is under-

recognized, making screening of particular importance. However, reasons were also given why universal screening may have been devalued. These include: 1) a perception that pain is a condition that patients will bring to attention to clinicians, obviating the need to screen; 2) HIV clinicians are under time pressure during brief appointments and consider pain to be a lower priority issue; 3) lack of clarity of who bears responsibility for screening for and treating pain (e.g., HIV specialists vs. general practitioners); and 4) a perception that screening tools including questions about pain severity are subjective and therefore not rigorous. To this final point, one participant said,

“It’s relatively straightforward to measure someone’s lipids, and then if they’re abnormal give a statin...If you’ve got a 10-minute slot with someone and there [are] quite a few priorities, probably the last thing you want to touch on is something...complicated and [for which] you don’t know what to do.”

Also, participants noted that screening may be underutilized because a diagnosis of chronic pain often does not lead to specific pain treatments, as there are few high-impact evidence-based treatments that are widely available. One participant offered the counterintuitive that sometimes screening and diagnosis themselves can be therapeutic, particularly if the clinician offers empathy and understanding of the challenges of a chronic pain diagnosis. As one participant put it,

“Offering empathy and understanding is not offering nothing.”

Delivering pain management across contexts

Since research on chronic pain in PWH, particularly regarding interventions, has been sparse, participants discussed the importance of relying on the general literature until more research is done. One participant suggested relying on general low back pain literature since

“we don’t have anything to suggest that it shouldn’t work in our patients with HIV.”

Participants reflected on a desire among clinicians to offer some kind of treatment, even if it is not very effective and causes side effects. The lay patient advocate stated,

“I have heard 3 ... eminent people from a [notable organization] saying “well you’ve got to give them something...ok, it’s only 3% effective.” No you haven’t. You know? Because it’s something, it’s going to cause more problems and if you have pain, depression can set in because you’re trying everything, you’re being good as gold, you’re taking the maximum dose of [your medication], you can barely speak, but you don’t hurt!”

For interventions that were implemented, participants discussed the importance of knowing who provides front-line care in different settings. For example, in some parts of sub-Saharan Africa, HIV and related care is provided primarily by nurses, whereas in the UK, HIV specialist care is routinely provided by physicians or other clinical HIV specialists, with primary care-related complaints including pain referred back to the General Practitioner. A lack of pain specialists was noted in every setting.

Perception of pain within the medical community

Participants discussed the perception of chronic pain as compared to other medical conditions. Specifically, one participant described a “hierarchy of respectability of medical conditions” in which pain occupies a low spot. This hierarchy is

“reflected in the education of healthcare students...[and] in the knowledge of our colleagues.”

Another participant noted that clinicians may “actively avoid” addressing chronic pain because of a kind of “trauma,” caused in part by opioids, in which clinicians are caught between feeling helpless and guarding against being manipulated.

While there are chronic pain-specific guidelines that address PWH, chronic pain is noticeably absent from some HIV guidelines, something that participants felt the Task Force could help address.

Research Priorities

People generally agreed that the topics identified by the questionnaire (see Table 3) are the important research topics in the field. However, additional research priorities and further discussions arose in addition to what is presented in Table 3:

Characterizing pain etiology and mechanisms

- Whether seroconverter cohorts may be used to understand the etiology of chronic pain in PWH; specifically, whether there is something biological or physiological that happens around the time of acquiring HIV that causes pain.
- Whether pain in PWH is different in those who were diagnosed late and therefore not started on treatment until symptomatic, or in those who had low CD4 counts and then were exposed to antiretroviral therapy (ART) with painful side effects, compared to those who are diagnosed early and start ART immediately.

Novel therapeutic targets and pain management in complex populations

Participants agreed that future studies should investigate the role of cannabis in PWH and should be sure to include individuals with complex needs such as severe mental illness.

Implementation science

- For any of the research topics, participants repeatedly discussed the importance of related implementation science questions. They noted that implementation strategies must be tailored to front-line HIV health care workings and to the practitioner treating the pain; that, in regard to training opportunities, it may be better to offer training at conferences or on the ground, depending on one's ability to travel; and that, evidence-based non-pharmacologic therapies much continue to be investigated and disseminated, and may differ for different types of pain. Important implementation science challenge identified was the lack of access to evidence-based non-pharmacologic therapies such as physiotherapy/physical therapy and behavioral approaches. It was noted that the HIV field has had great success in implementing life-saving antiretroviral therapy globally and could leverage its expertise in implementation science to implement changes in chronic pain care.
- Participants also noted that, regardless of the type of clinician targeted, any change in the way pain care is delivered would need to involve a change in clinician behavior. This is a double-edged challenge, in that some clinicians may need to be taught how to treat pain, while others may need motivation and encouragement to overcome the “dread” that may accompany the difficult task of managing chronic pain.

Controversial research priorities

The following topics elicited considerable debate, particularly regarding their relative importance:

- Understanding the prevalence of pain in PWH, or whether it is common enough that it would be more important to understand differences in prevalence of chronic pain between people with and without HIV.
- Identifying strategies to prevent chronic pain from developing in PWH.
- Using “deep phenotyping” is avenue in understanding pain in PWH. This approach uses a combination of questionnaires about pain and its impact with physical measures such as Quantitative Sensory Testing (QST), in which pain is induced in laboratory settings and various responses such as sensitivity to pain are measured. It is anticipated that such phenotyping may identify underlying pain-generating mechanisms that could lead to more individualized therapy. Though participants acknowledged that projects in deep phenotyping in HIV sensory neuropathy are ongoing, several proposed that additional work for headache, “fibromyalgianess,” and chronic musculoskeletal pain in PWH should be undertaken. Establishing phenotypes within such broad, vague categories has important implications for accurate diagnosis and tailored therapies.
- There was general agreement that animal research could be important, but is most valuable when it is driven by observations in humans. There was also agreement that animal studies can help elucidate pain etiology and mechanisms, which was a highly rated priority, but this can also be accomplished in humans through approaches such as experimental approaches to measure pain in human subjects e.g., QST

Measurement domains

During the discussion, participants recommended additional measurement domains beyond those identified through the questionnaire (shown in Table 2). These included pain diagnosis, sleep, burden of medical illness, burden of adverse effects of treatment, and relatedly, polypharmacy. Participants agreed that all of these domains were important and should not be ranked. There was also agreement that the field of chronic pain in PWH needs a core set of domains that should, ideally, be measured in any studies with this population. Participants also expressed the importance of not “reinventing the wheel.” Many of the domains participants identified are also part of internationally recognized Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations. Therefore, the group recommended that a subgroup of the Task Force convene to map both sets of domains identified to IMMPACT, and to identify additional systematically identify overlapping or missing areas. Another measurement challenge that may occur more commonly in PWH is the episodic disability of chronic pain, which may not be adequately captured on standard pain measures. Finally, participants acknowledged that, once a key set of measurement domains for chronic pain in PWH is identified, it will need to be further adapted and tailored for geographic and cultural differences. Participants also mentioned that qualitative investigations are essential to understand nuanced patient experiences that may vary between types of care settings and geography.

Patient involvement

The importance of patient involvement in setting clinical and research priorities, as well as identifying key measurement domains, was a discussion that recurred throughout the group discussion. One participant referenced a patient speaker at a session earlier during the

AIDSImpact conference who said that it may not be that patients are hard to reach but rather that researchers hard to access. Participants brainstormed ways to involve patients from diverse geographical settings, discussed the need to overcome important barriers such as time zones and variable access to technology, and acknowledged that finding a truly representative group of patients is often extremely challenging. As the lay HIV organization advisory board member remarked, “patient representation is always minimal, always tokenistic, but always better than nothing.”

Discussion

This paper describes initial efforts identify a scientific agenda for pain in PWH. Many important research and clinical priorities emerged from the Task Force questionnaires and group discussion. For example, the etiologies of chronic pain in PWH emerged as a major knowledge gap, as did the question of how those etiologies compare with those of chronic pain in the general population. New empirical evidence addressing this knowledge gap could not only clarify why the prevalence of chronic pain in PWH appears to be consistently greater than in the general population, but could also suggest new potential therapeutic targets tailored to PWH. Similarly, many important pain-related measurement domains were identified and addressed, with a primary focus on domains that could be assessed in a standardized manner across various cohorts that include PWH in different countries. Certain measurement domains were considered to be fundamental but not specific to PWH (e.g., pain severity, pain interference, function), whereas other domains that are specific to PWH may be salient but not fundamental (e.g., stigma, viral suppression). Lastly, the Task Force agreed that ongoing efforts to establish a set of

standardized measurement domains for future clinical studies should be consistent with similar previous efforts such as IMMPACT.

Pain, including chronic pain in PWH, is influenced by biological and socio-cultural factors with vulnerability to pain differing by culture, genetics, environment and gender (Merlin, Zinski, et al., 2014). To date, the work on HIV-related pain has been conducted in discrete populations by independent groups of HIV clinical researchers. Future work on HIV-related chronic pain needs to be conducted in multiple diverse populations to provide insight into mechanistic commonalities and differences. While there are groups of HIV clinical researchers who have an interest in HIV-related pain, and whose existing data sets may provide further insight, these collaborations may be limited based on these present structures.

There is value in creating a globally representative group of investigators with a specific focus on chronic pain in PWH who collaborate on research questions using standardized outcome measures towards a common goal of understanding chronic pain in PWH and developing treatments to optimize quality of life (Bristowe, Clift, et al., 2019). This group would also have the potential to increase patient participation and improve diversity in representation. The HIV arena has a well-established history patient involvement in research. Active community groups, a tradition of prioritizing patients' voices at conferences, and patient representation on trial steering groups have led to a culture of patient-centered research in HIV. The tradition is also growing in pain research with the International Association for the Study of Pain increasing its support of patient involvement initiatives. In order to ensure that patient engagement is authentic and not tokenistic, it was decided that a key next step will be to survey international patient

opinion on research priorities using a significantly diverse group of patients, representing vastly different geographic locations, languages, and education levels. To accomplish this, we will leverage our Task Force's extensive connections to patient groups globally.

In sum, this study was a first step toward establishing important areas for future research and identifying key measurement domains. Combining priorities presented here with those identified during the upcoming patient survey will ensure adequate stakeholder representation. Our new Task Force provides an important platform for future collaborations and has great potential to shape the future of global research in HIV and pain.

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Declaration of interest statement:

Dr. Uebelacker's spouse is employed by Abbvie Pharmaceuticals. Otherwise, the authors have no conflicts of interest to disclose.

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Table 1. Knowledge gaps (n=29)

What are the etiologies of chronic pain in people living with HIV (PWH)? Are those etiologies similar to or different from the etiologies of pain in the general population?

How do psychosocial factors impact the experience and management of chronic pain in PWH?

How prevalent is chronic pain in PWH?

How can chronic pain in PWH best be managed, including non-opioid and non-pharmaceutical forms of pain management?

How can chronic pain management be tailored for individuals, including personalized pain management and the integration of treatment for chronic pain and addiction in PWH?

How does lack of knowledge of HIV and chronic pain among general practitioners affect patients?

How can chronic pain in PWH be prevented?

How can clinicians be encouraged to universally screen PWH for chronic pain?

How should we evaluate the relevance of animal models of chronic pain in PWH?

What are cost-effective approaches to chronic pain management in PWH?

Table 2. Measurement domains from Questionnaire 2

Addiction

Anxiety

ART Adherence

Burden of Pain

Contribution of Therapies to Pain Management

Depression

Disability

Efficacy of Pain Management

Function (including pain interference, both physical and psychological)

Pain Interference

Pain-related cognition

Pain-related coping

Pain-related fear

Pain Severity

Psychological Well-Being

PTSD

Resilience

Self-Management of Pain

Site of Pain

Social Support

Stigma

Subjective Wellbeing

Trauma (e.g., measure of traumatic life events)

Treatment expectancies

Viral Suppression

Retention in Care

Table 3. Knowledge gap importance rankings for improving care (n=25)

Question	Number of participants who ranked question 1, 2, or 3 (out of 10)	Number of participants who ranked question 8, 9, or 10 (out of 10)
How can chronic pain in PWH best be managed, including non-opioid and non-pharmaceutical forms of pain management?	9	0
What are the etiologies of chronic pain in people living with HIV (PWH)? Are those etiologies similar to or different from the etiologies of pain in the general population?	6	3
How can chronic pain management be tailored for individuals, including personalized pain management and the integration of treatment for chronic pain and addiction in PWH?	6	1
What are cost-effective approaches to chronic pain management in PWH?	6	3
How can chronic pain in PWH be prevented?	5	4
How can clinicians be encouraged to universally screen PWH for chronic pain?	4	5
How do psychosocial factors impact the experience and management of chronic pain in PWH?	3	2

How prevalent is chronic pain in PWH?	3	9
How does lack of knowledge of HIV and chronic pain among general practitioners affect patients?	3	5
How should we evaluate the relevance of animal models of chronic pain in PWH?	0	13

Table 3. Knowledge gap importance rankings for advancing the science

Question	Number of participants who ranked question 1, 2, or 3 (out of 10)	Number of participants who ranked question 8, 9, or 10 (out of 10)
What are the etiologies of chronic pain in people living with HIV (PWH)? Are those etiologies similar to or different from the etiologies of pain in the general population?	11	1
How do psychosocial factors impact the experience and management of chronic pain in PWH?	7	2
How prevalent is chronic pain in PWH?	6	3
How can chronic pain in PWH best be managed, including non-opioid and non-pharmaceutical forms of pain management?	6	1
How can chronic pain management be tailored for individuals, including personalized pain management and the integration of treatment for chronic pain and addiction in PWH?	5	3
How should we evaluate the relevance of animal models of chronic pain in PWH?	4	7
How can chronic pain in PWH be prevented?	2	1

How can clinicians be encouraged to universally screen PWH for chronic pain?	2	9
What are cost-effective approaches to chronic pain management in PWH?	2	9
How does lack of knowledge of HIV and chronic pain among general practitioners affect patients?	0	9