

Global Prevalence of Chronic Pain in Women with HIV: A Systematic Review and Meta-analysis

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Chronic pain is common among people with human immunodeficiency virus (HIV) and detrimental to quality of life and overall health. It is often underdiagnosed, undertreated, and frankly dismissed in women with HIV, despite growing evidence that it is highly prevalent in this population. Thus, we conducted a systematic review and meta-analysis to estimate the global prevalence of chronic pain in women with HIV. The full protocol can be found on PROSPERO (identifier CRD42022301145). Of the 2984 references identified in our search, 36 were included in the systematic review and 35 in the meta-analysis. The prevalence of chronic pain was 31.2% (95% confidence interval [CI], 24.6%–38.7%; $I^2 = 98%$ [95% CI, 97%–99%]; $P < .0001$). In this global assessment, we found a high prevalence of chronic pain among women with HIV, underscoring the importance of understanding the etiology of chronic pain, identifying effective treatments, and conducting regular assessments in clinical practice.

Keywords. AIDS; chronic pain; HIV; neuropathy; women.

Chronic pain is a concerning comorbidity among people with human immunodeficiency virus (HIV) that can significantly affect medication adherence and retention in care [1], mobility [2], mental/emotional well-being [3], and quality of life [3]. According to the 2017 Infectious Diseases Society of America guidelines, the combination of moderate or higher pain intensity in the last week and bodily pain for >3 months indicates chronic pain syndrome based on the 2-item Brief Chronic Pain Questionnaire. These guidelines suggest that all people with HIV should receive standardized chronic pain screening [4]. Pain prevalence estimates differ depending on country and antiretroviral therapy (ART) era, ranging from 22% to 91% [1, 5–8]. Importantly, the Global Task Force for Chronic Pain in People With HIV

has identified “understanding the prevalence of pain” as a research priority [9].

The etiology of pain in people with HIV is likely multifactorial, including biological factors related to HIV, medication side effects, and psychosocial conditions [10]. Prior to the advent of ART, pain among people with HIV was often associated with malignancy, opportunistic infections, or HIV-mediated neuronal damage [11]. Viral proteins can directly damage neurons, resulting in increased pain sensitivity. Immune activation from chronic inflammation further contributes to neuropathy [12]. Opportunistic infections, including tuberculosis (musculoskeletal damage) [13], *Cryptococcus* (meningitis) [14], and herpes zoster (postherpetic neuralgia) [15], can also lead to persistent pain. With the introduction of first-generation ART, particularly the “d-drugs” (eg, didanosine, stavudine, and zalcitabine), the majority of research and clinical attention was focused on neuropathic pain [12]. While neuropathic pain is much less common with modern ART, the risk is not entirely eliminated [16]. In addition, differences in drug metabolism and body weight may expose women to higher drug concentrations and thus more adverse drug reactions [17], although this has not been specifically linked to chronic pain. More recent studies have focused on nonneuropathic pain subtypes, including headache, myalgia/fibromyalgia, and arthritis. Indeed, recent data suggest that people with HIV frequently experience pain in several body sites [3]. In addition to HIV and ART,

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psychosocial and behavioral factors likely contribute, including depression [6], posttraumatic stress disorder [18], substance use [19], and HIV-related stigma [20]; these disproportionately impact women with HIV [21–24].

Several reviews have described the prevalence of and risk factors for pain in people with HIV [3, 10, 12, 19, 25], but none to our knowledge has specifically focused on women, even though data suggest that women in the general population experience a higher prevalence of chronic pain than men [26]. This paucity of research is unsurprising given the general lack of women-centered clinical HIV research or study of comorbid disease among women with HIV [27]; nevertheless, it is a stark omission in the literature. Importantly, chronic pain reduces retention in care and medication adherence [1], which are often lower among women with HIV compared to men with HIV [28]. This suggests that understanding and treating chronic pain will be critical to reaching the final 95 (virological suppression) in the Joint United Nations Programme on HIV/AIDS 95-95-95 targets [29]. Furthermore, women with HIV have identified chronic pain as a priority area of research [9], emphasizing the importance of this review for members of the HIV community. Therefore, we assessed the global prevalence of chronic pain among women with HIV and identified gaps in the literature.

METHODS

Search Strategy and Selection Criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 checklist [30]. A research librarian with expertise in systematic reviews was consulted throughout the review process. The full study protocol can be accessed in the International Prospective Register of Systematic Reviews (PROSPERO) repository (ID: CRD42022301145).

Throughout this article, we use the term “women” to characterize persons who identify as women, including in studies that report pain prevalence by biological sex of “female” or gender identity of “woman.” We aimed to include both cisgender and transgender women in this analysis, as evidence suggests that cisgender and transgender women with HIV experience greater pain sensitivity compared to cisgender men [31].

Observational cross-sectional or cohort studies were eligible for inclusion as they are most appropriate for prevalence estimation. Case-control and randomized controlled trials were not included as these study designs intentionally select for participants with certain conditions and are thus not reflective of the general population of people with HIV [32]. Articles were included if they reported the prevalence of chronic pain in women with HIV ≥ 16 years old. We defined chronic pain as that lasting for at least 3 months in at least 1 anatomical site [4], or diagnosis of a chronic pain disorder (eg, arthritis, neuropathic pain, fibromyalgia, dyspareunia [pain with

intercourse]). In our initial search, we selected articles published from the time that HIV was discovered (1983) to 19 January 2022. We then repeated the search on 21 November 2022 to capture newly published articles. Both inpatient and outpatient settings were considered, and data were included from high-, middle-, and low-income countries. In addition, studies that did not include sex/gender-disaggregated prevalence, only assessed pain that was directly attributable to an opportunistic infection (eg, cytomegalovirus meningitis), included <30 women/female participants, or reported on histopathology without subjective symptom experience were also excluded.

Data sources included Medline (Ovid), Embase (Ovid), Evidence-Based Medicine Reviews (Ovid), Cumulative Index to Nursing and Allied Health Literature (EBSCO), and Web of Science Core Collection (see [Supplementary Material 1](#) for the Medline [Ovid] search strategy). We also searched “gray literature” (eg, conference proceedings, HIV/AIDS organization websites), as well as reference lists of relevant review articles. Articles of all languages were eligible for inclusion and translation was sought for those that were not published in English or French.

The online software Covidence (v.2893) [33] was used for reference screening, full-text review, and data extraction. All abstracts and full texts were screened by 2 authors (T. P. and S. A. S. for English-language references and S. L. A. L. and H. C. F. C. for French-language references). Conflicts were resolved either by consensus or by a third author (A. R. C.).

Data Extraction, Study Quality, and Data Synthesis

Data were extracted in duplicate by T. P. and S. A. S. for English references and S. L. A. L. and H. C. F. C. for French references. Any inconsistencies were resolved as described above. For the primary outcome (pooled prevalence of chronic pain in women with HIV), we extracted data on absolute number of women with chronic pain and total number of women in the study. Data were also extracted for a priori secondary outcomes, including type of pain and country where the study was conducted. Risk of bias was assessed in duplicate using the 9-item Joanna Briggs Institute Prevalence Critical Appraisal Tool ([Supplementary Material 2](#)) [34]. We considered studies rated 8–9, 5–7, and ≤ 4 as high, moderate, and low quality, respectively. Of note, a study may indeed be high quality for its intended objective but rated as low quality based on the risk of bias assessment for systematic reviews. Results of the critical appraisal are represented using GraphPad software (version 9.4.0 for Windows, GraphPad, San Diego, California; www.graphpad.com). Other extracted data included study title and date, design, setting, and sample characteristics (eg, size, inclusion/exclusion criteria, demographic characteristics, HIV medical history). We also extracted data concerning possible confounders or mediators of chronic pain, such as smoking, substance

use, diabetes, and exposure to neurotoxic ART or tuberculosis medications, all of which are known risk factors for peripheral neuropathy [35–38]. If 2 references were found to have duplicate data, we selected the one with the most complete and recent dataset.

Data Analysis

Our primary outcome of interest was the prevalence of chronic pain in women with HIV. Given the differences in study design and methodologies, we used a random-effects model. Analyses were performed in RStudio using the metafor package after logit transformation [39–41]. Heterogeneity between studies was calculated using the I^2 statistic [42], classifying $\leq 25\%$ as homogenous, 26%–50% as low heterogeneity, 51%–75% as moderate heterogeneity, and 76%–100% as high heterogeneity. We formally tested for outliers and influential studies using leave-one-out analyses, screening of studentized residuals, and diagnostic plots contained within the metafor package. For secondary outcomes, we assessed the pooled prevalence by pain subtype (peripheral neuropathy vs other pain type) and country of study (low-middle vs high-income countries, based on the World Bank classification) [43]. We used funnel plots to visually assess for publication bias and to examine whether sample size impacted the prevalence estimate. Egger regression test was used to assess funnel plot symmetry. All statistical analyses were completed in R version 4.2.1 software. Figures were made in GraphPad (version 9.4.0) and Servier Medical Art (<https://smart.servier.com>).

RESULTS

After removal of 1090 duplicates, our search yielded 2984 references, of which 36 were included in the systematic review (Table 1) and 35 in the meta-analysis (Figure 1). These studies provided data from 19 966 participants. One article was excluded from the meta-analysis as its chronic pain prevalence data was reported by CD4 count and ART subgroup [52], which we were unable to combine. The most common reason for article exclusion was lack of sex/gender-disaggregated data. The 36 studies included in the systematic review spanned 22 countries and 5 continents (Figure 2). Two references included data from multiple countries. Most articles (66.7%) were published in the last 10 years. The most commonly reported pain subtype was peripheral neuropathy ($n = 22$ articles), followed by widespread or other type of chronic pain ($n = 6$), fibromyalgia/myalgia ($n = 3$), headache ($n = 2$), combined chronic pain and peripheral neuropathy ($n = 2$), and dyspareunia ($n = 1$). More than half of the articles ($n = 25$) used validated tools to assess for chronic pain (Table 1). Eight references were rated as high quality, 25 as moderate quality, and 3 as low quality. Missing demographic data and a low number of women enrolled in a study were the most common reasons for lower quality (Supplementary Figure 1).

Participant demographics are presented in Supplementary Tables 2 and 3. Eight articles (22%) reported on substance use (Figure 3) and among them, the proportion of participants with a history of illicit substance use ranged from 8% to 77% (Supplementary Table 2). Nine articles (25%) reported on tobacco smoking status, with current or past smoking histories reported for 1%–38% of participants. Fifteen articles (42%) reported on history of alcohol use, with estimates ranging from 6% to 83%.

Included studies spanned the pre-ART era to newer ART; hence, percentage of participants with current ART use varied widely between studies, ranging from 0% to 100% (Supplementary Table 3). Use of neurotoxic HIV or tuberculosis medications was also highly variable. Most articles included data on CD4 counts and HIV plasma viral loads, but few described duration of ART use and/or HIV infection. Several articles either described the prevalence of diabetes among participants (8/35) or identified this as an exclusion criterion (9/35).

In the primary meta-analysis, the pooled prevalence of chronic pain across all studies was 31.2% (95% confidence interval [CI], 24.6%–38.7%) (Figure 4). The lowest prevalence was reported by Evans et al [55] at 4.0% (95% CI, 3.5%–4.5%) and the highest by Giani et al [73] at 84.1% (95% CI, 79.9%–87.8%). Formal tests for identifying outliers, as well as visual inspection of the leave-one-out plot (Supplementary Figure 2) and studentized residuals (Supplementary Table 1), indicated no truly influential outliers and thus all articles were retained in the final model. Visual inspection of the funnel plots revealed no bias by sample size (Supplementary Figures 3 and 4), and Egger regression test confirmed the absence of significant asymmetry ($P = .19$). However, the studies showed a high degree of heterogeneity, with an I^2 of 98% (95% CI, 97%–99%) ($P < .0001$), highlighting methodological and demographic differences of the studies analyzed.

In the subgroup analysis, the prevalence of peripheral neuropathy was compared to all other chronic pain subtypes (Figure 5). Twenty-two articles were included in the peripheral neuropathy subgroup, with a pooled prevalence estimate of 27.8% (95% CI: 19.7%–37.7%) and an I^2 of 99% (95% CI: 97%–99%) ($P < .001$). For all other pain subtypes, the pooled prevalence was 37.3% (95% CI: 24.2%–52.5%) and I^2 of 97% (95% CI: 94%–99%) ($P < .001$), which was not significantly different from the peripheral neuropathy subgroup ($P = .27$).

The subgroup analysis comparing countries indicated that the prevalence of chronic pain in high-income countries of 34.5% (95% CI: 25.4%–44.9%) was similar to that in low- and middle-income countries 28.9% (95% CI: 18.9%–41.4%) ($P = .5$; Figure 6). Again, there was significant heterogeneity in both the high-income and middle/low-income subgroups, with I^2 values of 96% (95% CI: 92%–98%) ($P < .001$) and 99% (95% CI: 98%–99%) ($P < .001$), respectively.

Table 1. Characteristics of Selected Studies

First Author (Year)	Study Type	Study Setting, Recruitment Dates	Inclusion/Exclusion Criteria	Sample Size (Females), No.	Definition of Chronic Pain	Pain Type	Pain Prevalence (%)
Evers (2000) [44]	Cross-sectional	Germany, dates NR	Inclusion: age ≥ 18 y Exclusion: prophylactic drugs for headaches, signs of central neurological manifestations of HIV infection	131 (30 F)	Headache Classification Committee criteria (migraine headaches)	Other (headache)	33
Liebschutz (2000) [45]	Cross-sectional	US, Feb 1994–Apr 1996	Inclusion: adult women seeking primary care for HIV for the first time; fluent in English, Spanish, or Haitian Creole Exclusion: prior medical care for HIV	50 (50 F)	Abdominal pain, headaches, low back pain, musculoskeletal pain, arthritis, pelvic pain, peripheral neuropathy on review of medical records	Chronic pain	62
Schiffitto (2005) [46]	Prospective cohort	US, dates NR	Inclusion: CD4 count < 200 cells/ μ L with or without cognitive impairment, CD4 count 200–300 cells/ μ L and evidence of cognitive impairment or neuropsychological testing Exclusion: past or current infection or neoplastic CNS diseases, non-HIV-related neurodegenerative disorders	376 (111 F)	Neurological examination created for the AIDS Clinical Trial Group, Neuropathic Pain Scale, Part III of the Unified Parkinson's Disease Rating Scale	Peripheral neuropathy	37
Onwuegbuzie (2009) [47]	Cross-sectional	Nigeria, Jun–Dec 2004	Inclusion: ART naive	100 (58 F)	Standardized Clinical Screening Tool for Sensory Neuropathy	Peripheral neuropathy	38
Cherry (2009) [48]	Cross-sectional	Australia, Malaysia, Indonesia, 2006	NR	294 (39 F)	BPNS	Peripheral neuropathy	18
Richardson (2009) [49]	Prospective cohort	US, 1996–1998	Inclusion: adult, CD4 count < 200 cells/ μ L between first and seventh WIHS visit	339 (339 F)	WIHS structured interview: estimate of frequency and severity of pain over the last 6 mo	Chronic pain	56
Ellis (2010) [50]	Cross-sectional	US, Sep 2003–Aug 2007	Exclusion: active opportunistic infection, uncontrolled major psychiatric disorder, inability to cooperate with full day clinical evaluation	1539 (362 F)	Structured interview to assessed self-reported neuropathic pain	Peripheral neuropathy	23
Wadley (2011) [51]	Cross-sectional	South Africa, Jul 2008–Apr 2009	Inclusion: adults, had used d4T for at least 6 mo	395 (295 F)	BPNS	Peripheral neuropathy	57
Mullin (2011) [52]	Cross-sectional	Tanzania, Nov 2007–Feb 2008	Inclusion: ART naive or at least 6 mo on ART Exclusion: random blood sugar > 11 mmol/L; current treatment with isoniazid, phenytoin, nitrofurantoin, thalidomide, or metronidazole; a history of high alcohol intake and any other neurological diagnosis other than DSP	326 (225 F)	BPNS	Peripheral neuropathy	ART/CD4 < 200 cells/ μ L: 39; ART/CD4 > 200 cells/ μ L: 39; no ART/CD4 < 200 cells/ μ L: 26; no ART/CD4 > 200 cells/ μ L: 14

Table 1. Continued

First Author (Year)	Study Type	Study Setting, Recruitment Dates	Inclusion/Exclusion Criteria	Sample Size (Females), No.	Definition of Chronic Pain	Pain Type	Pain Prevalence (%)
Menezes (2011) [53]	Prospective cohort	South Africa, Apr 2004–Dec 2007	Inclusion: attending HIV clinic, initiating ART with CD4 count \leq 200 cells/ μ L or WHO stage 4 AIDS- defining illness	9040 (5962 F)	Numbness/dysesthesia after the initiation of ART once other causes were excluded	Peripheral neuropathy	17
Luma (2012) [54]	Cross-sectional	Cameroon, Jul–Oct 2011	Inclusion: age $>$ 18 y, followed at tertiary hospital	295 (206 F)	BPNS	Peripheral neuropathy	18
Evans (2012) [55]	Prospective cohort	South Africa, Jun 2004–May 2010	Inclusion: age \geq 18 y, CD4 count at ART initiation of $<$ 200 cells/ μ L, initiated on standard first-line regimen Exclusion: diabetes, hypertriglyceridemia, hepatitis C	9399 (5824 F)	Symptom review by a clinician (numbness, dysesthesia, burning/stabbing pain)	Peripheral neuropathy	4
Robbins (2013) [56]	Cross-sectional	Thailand, Mar–May 2011	Inclusion: age \geq 18 y, ability to speak Thai	254 (141 F)	“Have you had this pain for more than 3 mo?”, Brief Pain Inventory–Short Form, Thai version of the Self-Administered Leeds Assessment of Neuropathic Symptoms and Sign	Peripheral neuropathy, chronic pain	27
Valadares (2014) [57]	Cross-sectional	Brazil, dates NR	Inclusion: age 40–60 y, vaginal intercourse in the past month Exclusion: nursing, bilateral oophorectomy, unable to answer questionnaire	128 (128 F)	Short Personal Experiences Questionnaire	Other (dyspareunia)	41
Turnusiime (2014) [58]	Cross-sectional	Rwanda, Mar–Jul 2012	Inclusion: on ART, age 18–60 y Exclusion: active opportunistic infections, CNS disorders, diabetes, vitamin B12 deficiency, renal failure, hypothyroidism, and other pathologies	507 (366 F)	BPNS	Peripheral neuropathy	57
Turnusiime (2014) [59]	Cross-sectional	Rwanda, 2005	Inclusion: $>$ 25 y, willing to undergo voluntary counseling and testing for HIV, present in Rwanda since 1994, willing to return for follow-up, ART naive	704 (704 F)	“In the past 6 mo, have you experienced numbness, tingling, or burning sensations in your arms, legs, hands, or feet that lasted for more than 2 wk?”	Peripheral neuropathy	52
Uebelacker (2015) [60]	Cross-sectional	US, Oct 2012–Dec 2013	Inclusion: age \geq 18 y, ability to speak English	238 (89 F)	“Have you had chronic pain for at least the past 6 mo?”	Chronic pain	62
Sharma (2016) [61]	Prospective cohort	US, 1994–2015	Not reported	1412 (1412 F)	Self-report of numbness, tingling, or burning sensations in arms, legs, hands, or feet	Peripheral neuropathy	21
Jiao (2016) [62]	Chart review	US, Nov 2013–Oct 2014	Inclusion: age 18–65 y, had at least 3 visits to primary care during study period, had at least 2 prescriptions for ART Exclusion: participants who died during the study period	638 (274 F)	ICD-9 codes that correspond to chronic pain disorders listed by the International Association for the Study of Pain codes	Chronic pain	46

Table 1. Continued

First Author (Year)	Study Type	Study Setting, Recruitment Dates	Inclusion/Exclusion Criteria	Sample Size (Females), No.	Definition of Chronic Pain	Pain Type	Pain Prevalence (%)
Benevides (2017) [35]	Cross-sectional	Brazil, Jan–May 2016	Inclusion: age 18–70 y Exclusion: cognitive disorder, admitted to the ICU	147 (60 F)	BPNS	Peripheral neuropathy	27
Adoukonou (2017) [63]	Cross-sectional	Benin, Apr–July 2011	Inclusion: people with HIV receiving care at the Parakou University Hospital	262 (202 F)	Modified BPNS (translated in French)	Peripheral neuropathy	44
Centner (2017) [64]	Prospective cohort	South Africa, dates NR	Inclusion: age ≥18 y, met criteria for ART initiation Exclusion: diabetes mellitus, serious systemic illness, severe diarrhea, comorbid neurological disease, TB treatment in the last 2 mo, exposure to glucocorticoids within the last 6 mo, pregnancy	Baseline: 184 (130 F) Follow-up: 102 (72 F)	BPNS and Total Neuropathy Score	Peripheral neuropathy	Baseline: 15 Follow-up: 15
Navis (2018) [65]	Cross-sectional	US, 2003–2008	Inclusion: age 18–65 y, at least 3 visits to HIV clinic in last 12 mo	638 (274 F)	ICD-9/10 codes according to the International Association for the Study of Pain classification of chronic pain	Peripheral neuropathy, chronic pain	10
Octaviana (2019) [66]	Cross-sectional	Indonesia	Inclusion: adults receiving ART for at least 12 mo (without d4T) Exclusion: history of other conditions linked to neuropathy	197 (57 F)	The Douleur Neuropathique 4 questionnaire	Peripheral neuropathy	7
Adem (2019) [67]	Cross-sectional	Ethiopia, Feb–Jun 2017	Inclusion: aged ≥18 y, attending HIV care clinic Exclusion: TB, cognitive disorders, peripheral nerve injury, chronic renal conditions, active opportunistic infection, leprosy, vitamin B12 deficiency, severe communication impairments	359 (234 F)	BPNS, neurological exam	Peripheral neuropathy	25
Demirdal (2019) [68]	Cross-sectional	Turkey, Jun 2018–Jun 2019	Inclusion: age ≥18 y Exclusion: other severe chronic systemic disease, severe psychiatric disorder, endocrinopathy, uncontrolled hypothyroidism or diabetes mellitus, known history of rheumatic disease, use of antidepressants, use of drugs for treatment of fibromyalgia, recent joint and/or muscle trauma, hepatitis B/C/D infection, malignancy	225 (33 F)	2016 American College of Rheumatology Fibromyalgia criteria	Fibromyalgia/myalgia	27
Sabin (2020) [69]	Cross-sectional	United Kingdom and Ireland, Apr 2013–Feb 2016	Inclusion: HIV acquisition through sexual transmission, cisgender, White or Black African ethnicity Exclusion: acquiring HIV through other routes	944 (128 F)	2019 American College of Rheumatology Fibromyalgia criteria	Fibromyalgia/myalgia	...
Ellis (2020) [70]	Prospective cohort	US, 2003–2019	Not reported	253 (54 F)	Self-reported neuropathic pain	Peripheral neuropathy	35

Table 1. Continued

First Author (Year)	Study Type	Study Setting, Recruitment Dates	Inclusion/Exclusion Criteria	Sample Size (Females), No.	Definition of Chronic Pain	Pain Type	Pain Prevalence (%)
Mukoma (2020) [71]	Cross-sectional	Kenya, Mar–Apr 2019	Inclusion: age 20–68 y, on ART	289 (222 F)	Clinical HIV Associated Neuropathy Tool	Peripheral neuropathy	55
Safri (2020) [72]	Cross-sectional	Indonesia, dates NR	Inclusion: adults on ART for at least 12 mo Exclusion: exposure to d4T, diabetes, stroke, schizoprenia, vasculitis, deafness, blindness, hyperthyroidism, systemic lupus erythematosus, cytomegalovirus radiculopathy, cancer chemotherapy	185 (67 F)	BPNS	Peripheral neuropathy	16
Giani (2020) [73]	Cross-sectional	Malawi, dates NR	Inclusion: age 18–65 y	498 (359 F)	Structured interview (authors report 1-y prevalence of headache)	Headache	84
Emorinken (2021) [74]	Cross-sectional	Nigeria, Jun 2016–May 2017	Inclusion: age ≥18 y, ART naive Exclusion: traumatic musculoskeletal disorders, rheumatic or connective tissue disease, psychological disorders, hypothyroidism, chronic viral infections, pregnancy, using medications to treat fibromyalgia	160 (110 F)	2011 modification of the 2010 American College of Rheumatology preliminary diagnostic criteria for fibromyalgia	Fibromyalgia/myalgia	12
Kowalski (2021) [75]	Cross-sectional	Poland, Feb 2014–Dec 2016	Inclusion: age ≥18 y Exclusion: any mental condition	196 (34 F)	Pain lasting ≥6 mo, Brief Pain Inventory–Short Form, physical exam	Chronic pain	38
Tu (2021) [76]	Cross-sectional	Canada, 2013–2019	Inclusion: HIV-1–seropositive adults Exclusion: nonfluency in English, age <18 y, less than grade 9 education, severe psychiatric or neurological disorders, history of brain damage/traumatic brain injury with loss of consciousness, uncorrected vision, or hearing impairments	519 (75 F)	Review of symptoms, laboratory results, and physical examination	Peripheral neuropathy	28
Nikolaïdis (2022) [77]	Cross-sectional	Greece, dates NR	Inclusion: adults on ART Exclusion: other types of peripheral neuropathy, diabetes, cytomegalovirus, herpes, autoimmune diseases, vitamin B12 deficiency, renal failure, hypothyroidism	420 (74 F)	BPNS	Peripheral neuropathy	47
Yitbarek (2022) [78]	Cross-sectional	Ethiopia, Nov–Dec 2020	Inclusion: receiving care at ART clinic Exclusion: current opportunistic infection, neurological problems, renal failure, hypothyroidism	555 (297 F)	BPNS	Peripheral neuropathy	29

Abbreviations: ART, antiretroviral therapy; BPNS, Brief Peripheral Neuropathy Screen; CNS, central nervous system; d4T, stavudine; DSP, distal sensory polyneuropathy; HIV, human immunodeficiency virus; ICD, *International Classification of Diseases*; ICU, intensive care unit; NR, not reported; TB, tuberculosis; US, United States; WIHS, Women's Interagency HIV Study; WHO, World Health Organization.

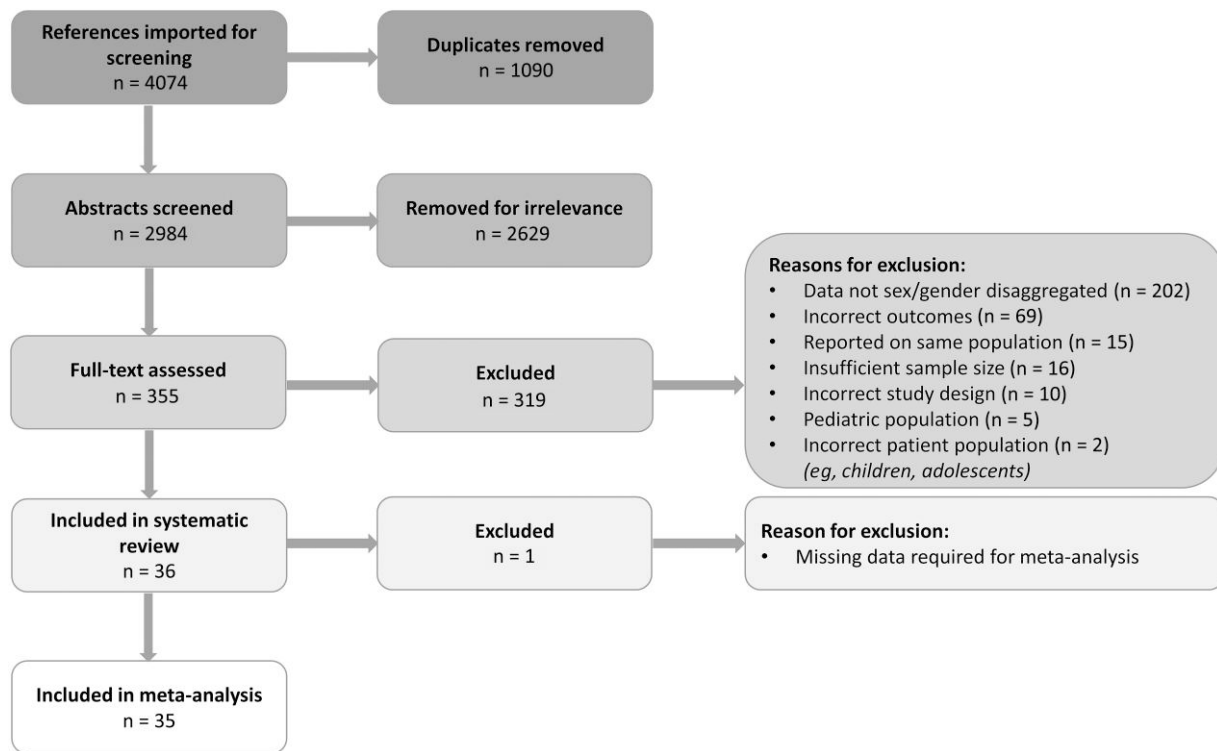


Figure 1. Study selection.

Three studies compared the prevalence of chronic pain between persons with HIV and HIV-negative controls. Sharma et al [61] reported on peripheral neuropathy among middle-aged women and reported a higher prevalence in women with HIV compared to HIV-negative controls (20.6% vs 14.0%; $P = .0003$). Similarly, Tumusiime et al [59] found that 52% of women with HIV experienced neuropathic pain symptoms, compared with 44% of HIV-negative women, although this difference was not statistically significant ($P = .06$). Finally, Valadares et al [57] examined the prevalence of dyspareunia and reported no difference between these 2 groups (41.4% in women with HIV vs 34.8% in HIV-negative women; $P = .24$).

Only 1 study reported on the severity of chronic pain among women with HIV and various pain subtypes, where the majority (65%) of participants had AIDS-defining illnesses [49]. Half of the women (50.0%) reported high levels of pain, including 34.5% with extreme pain.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to describe the prevalence of chronic pain among women with HIV. In our global assessment across 22 countries and 19 966 participants, we identified that at least one-third of women with HIV experience chronic pain, underscoring its

pervasiveness and signaling the importance of regularly assessing for pain. This is similar to the global prevalence of chronic pain among HIV-negative persons in middle- and low-income countries at 33%, but higher than the prevalence in the United States at 20.4% [79, 80]. However, few studies have directly compared the prevalence of chronic pain in women with and without HIV. Our results indicate that, although most research attention has been focused on peripheral neuropathy, women commonly experience other pain subtypes. Hence, further research is needed to holistically understand these pain experiences. Our analysis did not detect any difference between pain subtypes or country of study. To our knowledge, no previous meta-analyses have estimated the prevalence of chronic pain in people with HIV, although 1 meta-analysis exists including both acute and chronic pain [25]. That meta-analysis reported a pooled prevalence of 54%, which is higher than what we report here, but expected for data collected on both acute and chronic pain types. A scoping review of chronic pain in people with HIV suggested that the prevalence ranges from 25% to 90% [12], whereas we observed a range of 4.0% to 84.1%. This wider range is likely related to differences in search methodology and inclusion/exclusion criteria used by Addis et al [12], the details of which are difficult to ascertain.

Our analysis identified key gaps in the literature. First, more research is needed to understand nonneuropathic chronic pain

- ■ Setting of studies included in the review that spanned multiple sites
- ★ Setting of studies included in the review with a single site



Figure 2. Map of countries where studies included in the review took place. The majority of the studies (n = 34) spanned a single site, while only 2 studies spanned multiple sites.

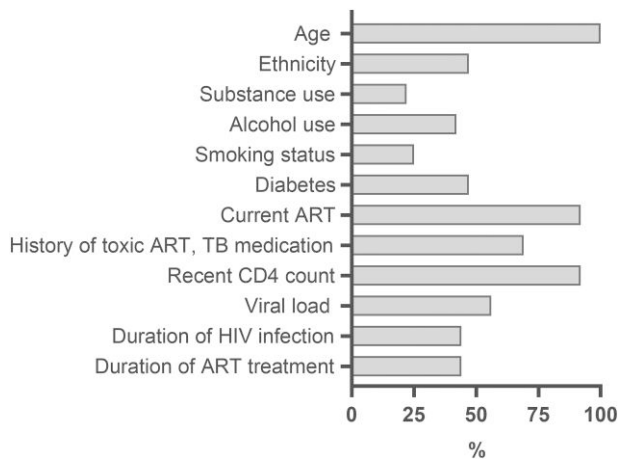


Figure 3. Proportion of studies that included data about selected demographic parameters of their study participants. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; TB, tuberculosis.

subtypes, especially those that are specific to women, such as breast, pelvic, vaginal, and menstrual pain. We identified only 1 article that assessed dyspareunia and none that evaluated other female-specific pain manifestations. Similarly, only 1 article discussed pain severity. This is a critical component of understanding the pain experience of women with HIV and its effect on quality of life. Furthermore, there was a paucity of studies discussing how chronic pain interferes with daily activities or contributes to stigma. Few studies included an HIV-negative control group, although we do acknowledge the difficulty of recruiting HIV-negative controls that share comparable psychosocial identities with women with HIV. We also note that although pain prevalence was reported across a diverse array of countries, some regions were missing, including South America, Asia, and Eastern Europe. Furthermore, we were unable to find any articles describing chronic pain among transgender women with HIV, which speaks to the importance of

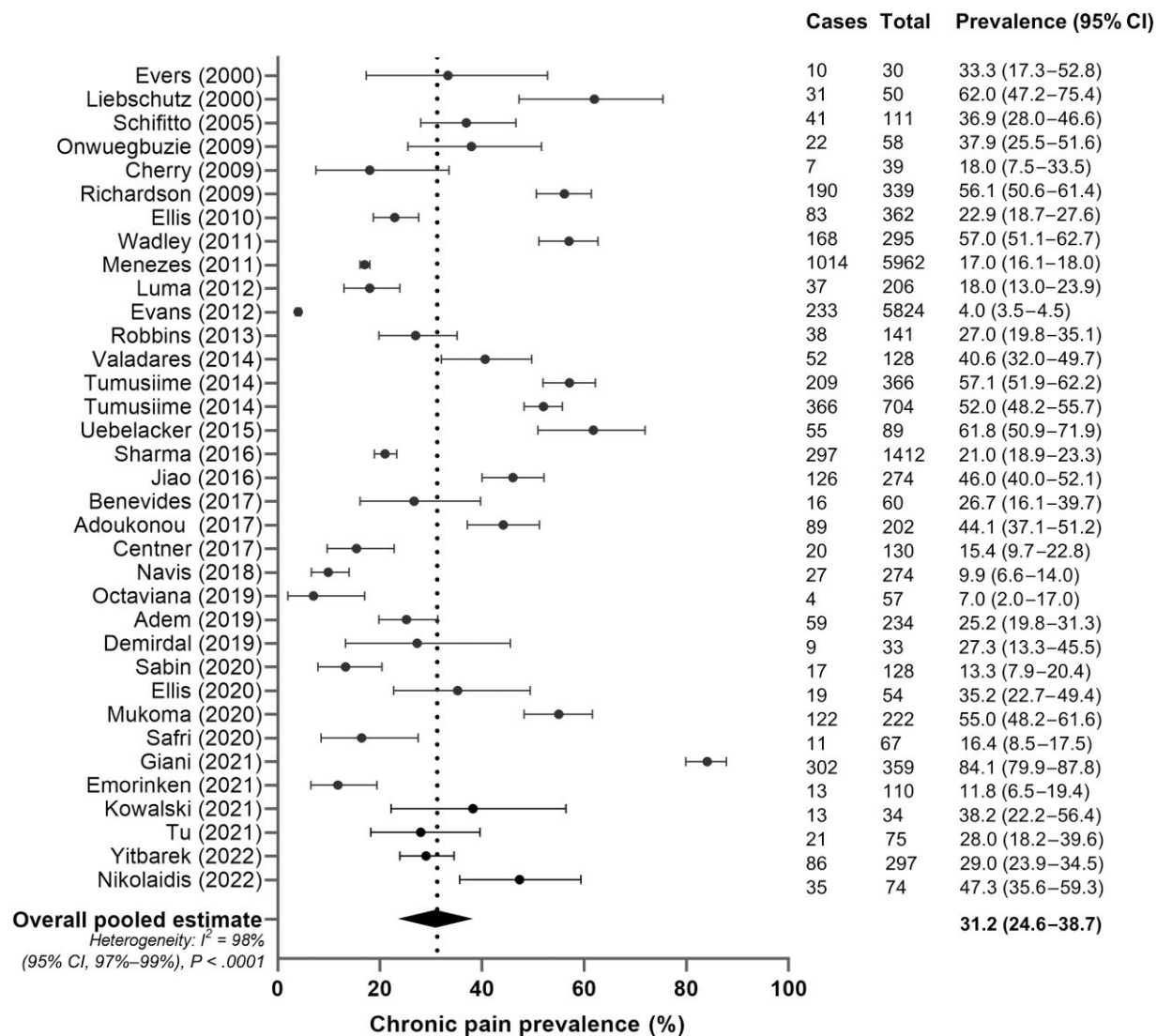


Figure 4. Pooled prevalence of chronic pain in women with human immunodeficiency virus. Cases: number of women with chronic pain in the study. Total: number of women enrolled in the study. Black circles indicate chronic pain prevalence in each study (with 95% confidence interval [CI]); diamond and vertical dashed line indicate the pooled estimate of chronic pain.

inclusion of this key population in research. This is especially concerning given that cisgender and transgender women with HIV have similar pain sensitivity, which is greater than that of cisgender men [31]. Also, much of the existing literature is in younger or middle-aged people, highlighting the need for more research into the chronic pain experience of older women. Last, we agree with Madden et al [3] that the literature lacks research into effective pain management, which should be noted as a critical area of further study.

We identified several important characteristics that were inconsistently reported across studies, limiting meaningful interpretation of the results and likely contributing to the high I^2 values. For instance, several studies omitted data on ethnicity, substance use, alcohol, smoking, diabetes, HIV viral loads, duration of HIV infection, and duration of ART use (Figure 3).

We also noted that articles used a diverse array of tools or questions to assess chronic pain (Table 1), which further limits comparability. This emphasizes the need for consistent and validated tools to assess chronic pain in both clinical and research settings.

Our study should be interpreted in light of its limitations. First, there was a very high level of heterogeneity between articles, which likely reflects the differences in how chronic pain is defined and measured, diversity in the study samples, type of ART exposure, and time or location of data collection. This high heterogeneity was not explained by subgroup analyses. This suggests that careful consideration of geographic and individual-level factors are important when considering the risk for chronic pain in a patient population. However, Migliavaca et al [81] emphasize that a high I^2 is not unexpected

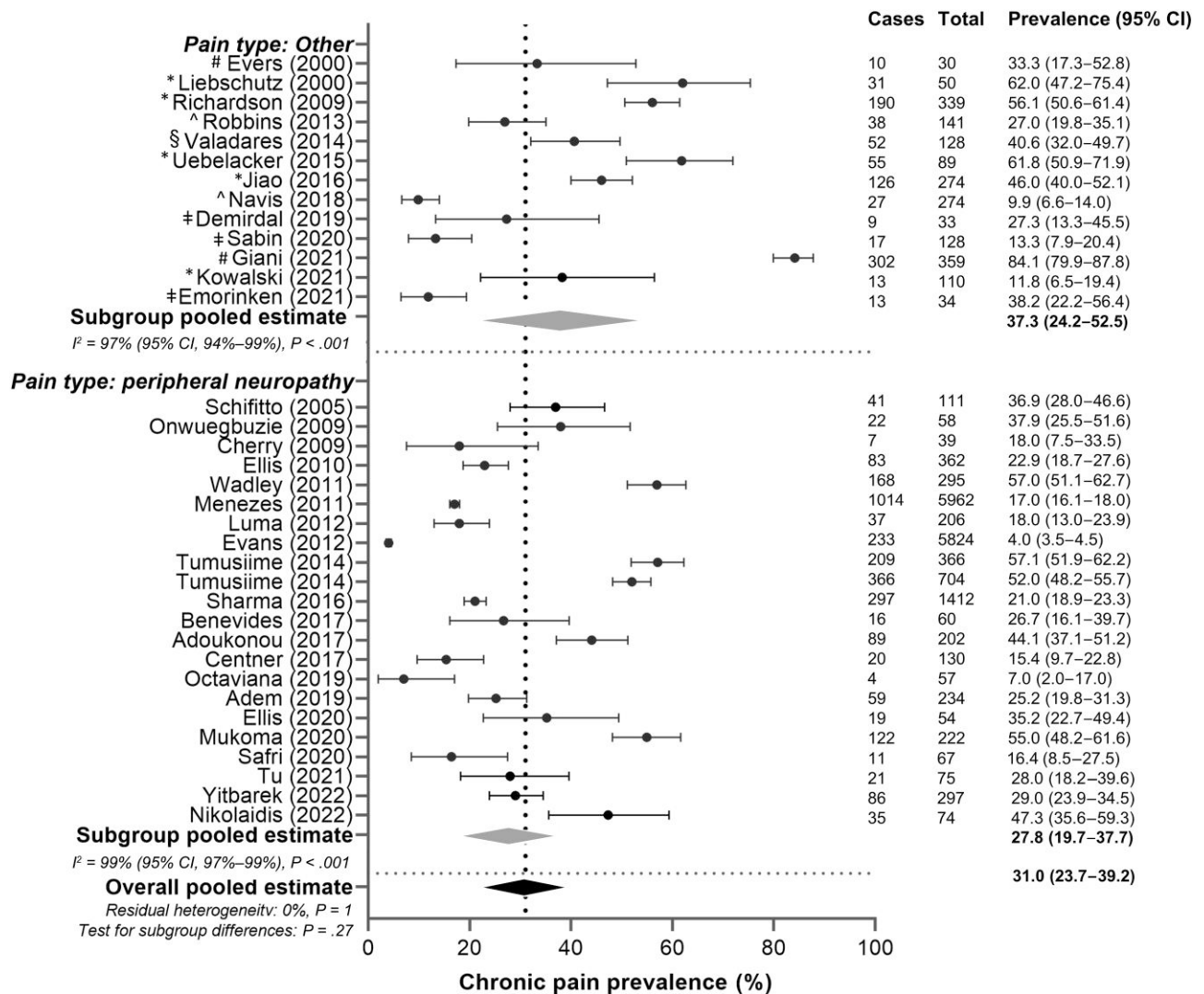


Figure 5. Subgroup analysis of chronic pain prevalence in women with human immunodeficiency virus based on chronic pain type (peripheral neuropathy vs other). Cases: number of women with chronic pain in the study. Total: number of women enrolled in the study. Black circles indicate chronic pain prevalence in each study (with 95% confidence interval [CI]); gray diamonds indicate pooled prevalence of chronic pain within the subgroups; black diamond and vertical dashed line indicate pooled estimate of chronic pain. #Headache. *Chronic pain. ^Chronic pain and peripheral neuropathy. §Dyspareunia. ‡Fibromyalgia/myalgia.

for this study type, as they found a median I^2 of 96.9% (interquartile range, 90.5%–98.7%) among 235 systematic reviews of prevalence. Given the sample size, we were unable to perform a meta-regression to account for important confounders, including age, use of neurotoxic medications, years with HIV, comorbid diabetes, or psychosocial conditions. Additionally, we were not able to conduct some important subgroup analyses, such as stratifying studies based on history of AIDS or opportunistic infections, duration of HIV/ART, or exposure to newer versus older ART regimens due to heterogeneity in data reporting and/or missing data. Finally, it should be acknowledged that most articles in this analysis were of moderate quality based on the risk of bias assessment, highlighting the need for more high-quality research in this area.

Overall, our results suggest that chronic pain is highly prevalent among women with HIV and warrants regular assessment at healthcare visits. Several clinical tools exist to assess for the presence of chronic pain, as well as severity and subjective experiences, and should be used frequently [82–84]. We concur with recommendations from the Global Task Force for Chronic Pain in People With HIV [9], including the need for further research into effective methods of pain management, etiologies of chronic pain, and chronic pain prevention. Our results highlight that it is especially important to consider these factors from a women-centered lens [85]. Of note, this research was motivated by discussions with women with HIV and their interest in this topic. We therefore wish to emphasize the importance of sharing research results about

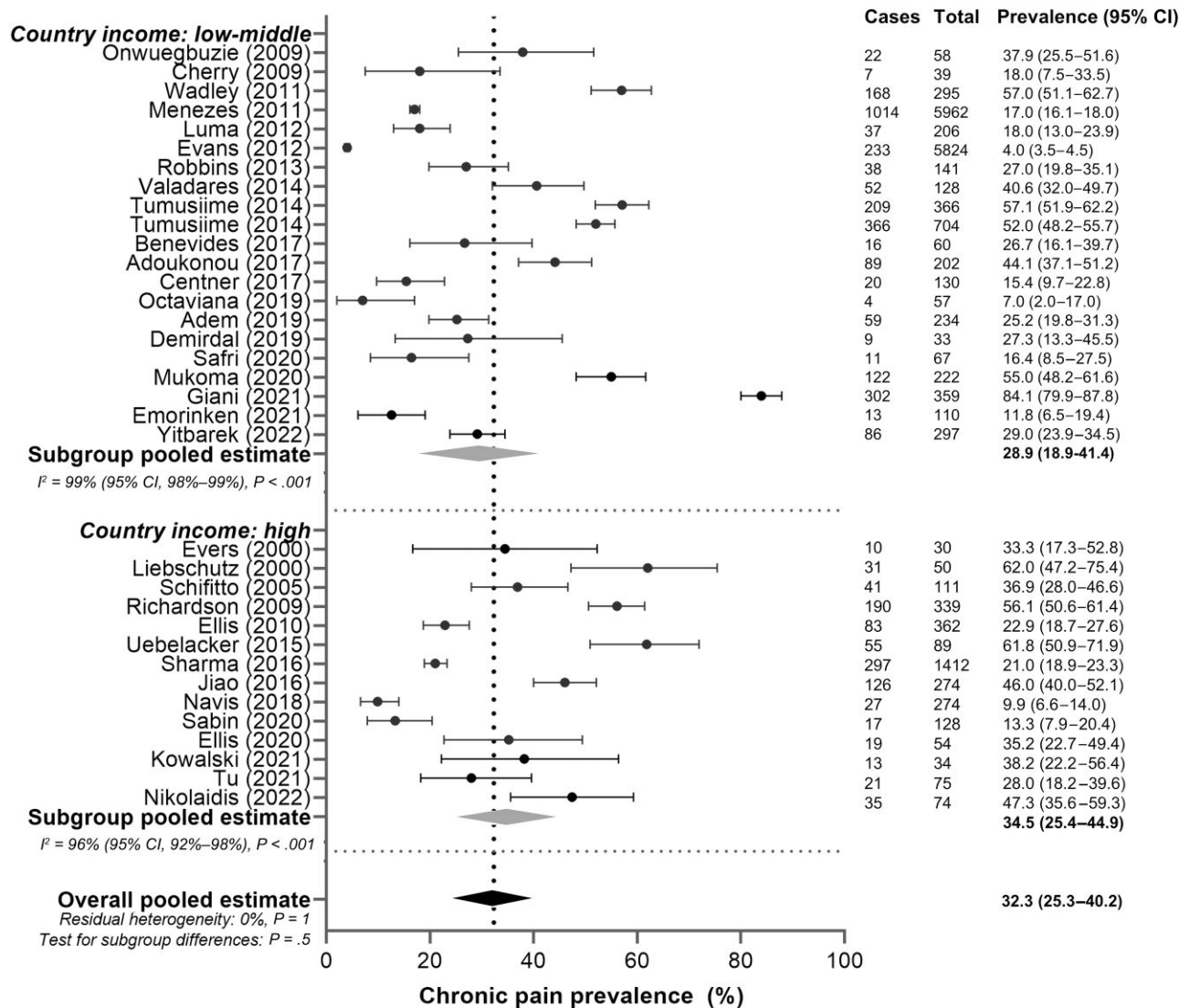


Figure 6. Subgroup analysis of chronic pain prevalence in women with human immunodeficiency virus based on country where the study was conducted (low-middle vs high income). Cases: number of women with chronic pain in the study. Total: number of women enrolled in the study. Black circles indicate chronic pain prevalence in each study (with 95% confidence interval [CI]); gray diamonds indicate pooled prevalence of chronic pain within the subgroups; black diamond and a vertical dashed line indicate pooled estimate of chronic pain.

chronic pain with women with HIV to validate their experiences, increase opportunities for meaningful dialogue, identify knowledge gaps, and encourage co-learning between clinical, academic, and community partners.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. S. A. S. and T. P. led the conceptualization of the research aims. S. A. S., with input from T. P., S. L. A. L., A. R. C., M. C.,

M. D., C. P., P. G., M. C. M. M., and H. C. F. C., created the study protocol. S. A. S. developed and executed the search strategy. S. A. S. and T. P., with input from S. L. A. L., A. R. C., and H. C. F. C., led article selection. S. A. S. and T. P. conducted the data extraction. T. P. led the data analysis and figure preparation. S. A. S. wrote the manuscript. T. P., S. L. A. L., A. R. C., M. C., M. D., C. P., P. G., M. C. M. M., and H. C. F. C. provided critical review of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing. Primary data were not collected for this study and thus are not available for sharing. The study protocol can be accessed on PROSPERO (ID number CRD42022301145).

Patient consent. This review utilized previously published summary-level data and therefore did not necessitate patient consent.

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