

Abstract

Human immunodeficiency virus (HIV) is a controllable yet incurable virus associated with numerous age and pain-related conditions that remain not well understood. HIV patients are highly likely (up to 83%) to experience chronic pain while simultaneously being at risk of other pain-related conditions like peripheral neuropathy and migraines. This study analyzed the eligibility section of all HIV clinical trials available on ClinicalTrials.gov to identify the prevalence of cotreatment clinical trials focusing on HIV and pain-related conditions. The results indicated that HIV clinical trials were highly unlikely (<1%) to consider pain-related conditions in the eligibility section. Of those that did consider pain-related conditions, the majority (87.5%) of diseases were excluded. This effect was exacerbated for certain conditions such as peripheral neuropathy and migraines which elicited an exclusion rate in those groups, near 95%. This study exemplifies a need for the increased consideration of pain-related conditions in HIV clinical trials to continue improving symptom management of this incurable virus.

Background

Human immunodeficiency virus (HIV) is a controllable yet incurable virus that directly attacks the body's immune system. Though the virus has become more manageable, it's still responsible for notable age and pain-related symptoms that aren't fully understood. For example, up to 83% of people living with HIV or AIDS experience clinically significant chronic pain (Parker et al., 2014, 18719). Despite the high likelihood that those with HIV will experience chronic pain, few pharmacological options are available to manage these symptoms (Scott et al., 2018, 2461).

Beyond chronic pain, those with HIV may be at an increased risk of age-related chronic diseases including diabetes, hypertension, stroke, cancer, lung diseases, cardiovascular diseases, and cognitive impairment (Yang et al., 2019, 1-8). Age is also considered a risk factor for peripheral neuropathy and can sometimes prompt the discontinuation of some anti-retroviral therapies (Julian et al., 2021, 1420-1431). Additionally, those with HIV are more likely to experience headaches or migraines which were shown to exacerbate functional impairment in 55% of participants in one study (Sohail et al., 2019, 248-253). Ultimately, it's clear that HIV contributes to various sources of pain that can detract from patients' quality of life.

Methods

The primary focus of this study was to determine if HIV clinical trials had properly investigated the cotreatment of HIV and chronic pain and other age-related conditions like dementia. Researchers used ClinicalTrials.gov to investigate the eligibility criteria of HIV clinical trials (MeSHID D000015658) from 1990 to 2022. Researchers identified chronic pain and age-related search terms within the eligibility sections which were subsequently divided into inclusion and exclusion sections where the frequency of each respective search term was recorded. Data were organized using the tidyverse (1.3.2) suite of R (4.2.2) packages. Search term instances were counted once per study in either the inclusion or exclusion criteria. Clinical trials that lacked explicit inclusion and exclusion sections or mentioned the same search term in both

sections were flagged and manually inspected to determine the correct term assignment. Data were analyzed using the R Stats package ('aov' function) to establish any significant trends. Figure 1 and Table 1 were created using ggplot2 (3.4.0) in R representing all search terms.

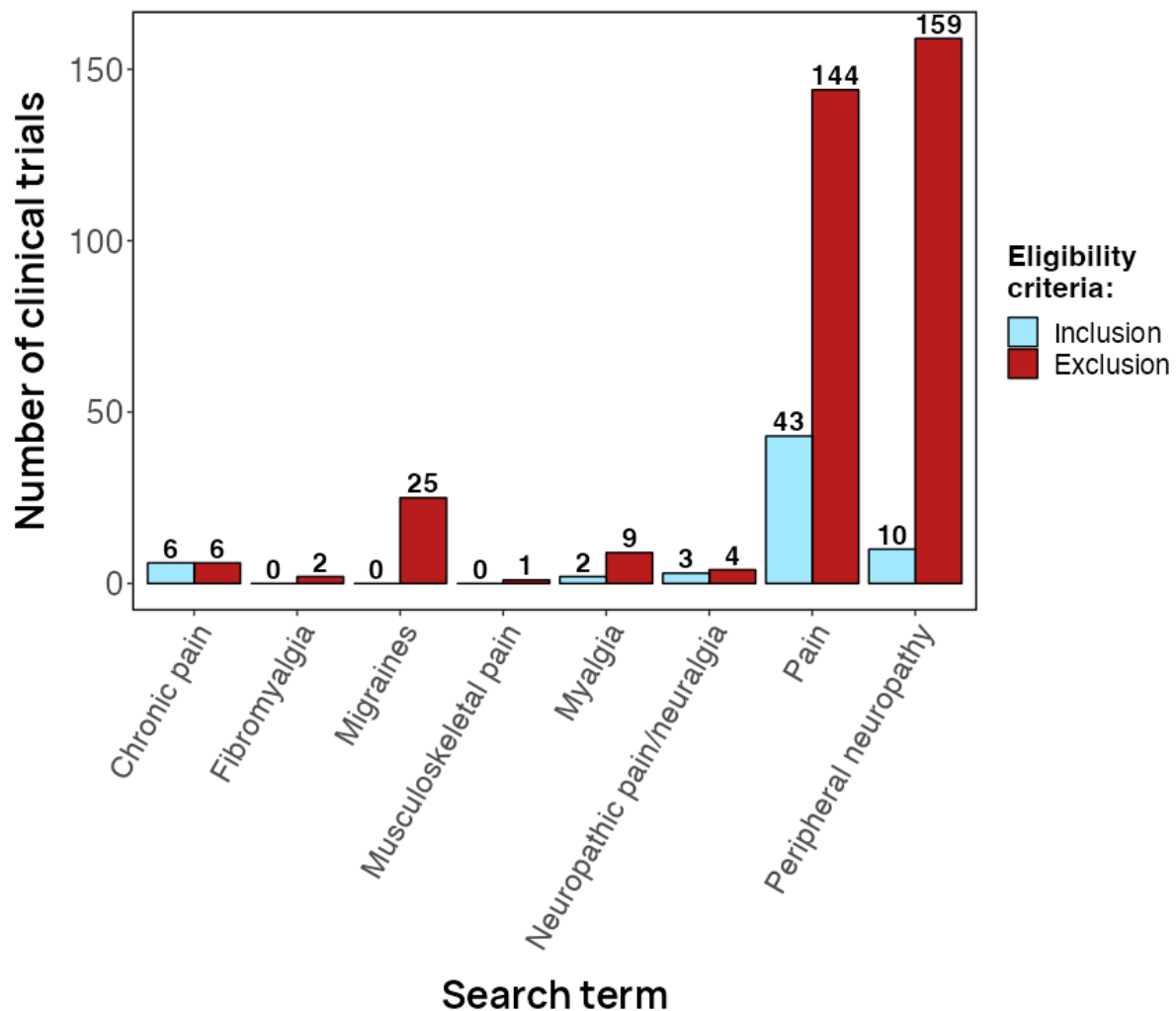
Table 1. Inclusion and exclusion frequencies of chronic pain and age-related search terms identified in HIV clinical trials.

Search Term	Inclusion criteria	Exclusion criteria
Chronic pain	6	6
Fibromyalgia	0	2
Migraines	0	25
Musculoskeletal pain	0	1
Myalgia	2	9
Neuropathic pain/neuralgia	3	4
Pain	43	144
Peripheral neuropathy	10	159
TOTAL:	64 (15.5%)	350 (84.5%)

Figure 1. Comparison of inclusion and exclusion frequencies and proportions of pain and age-related search terms in HIV clinical trials.

Search Terms in HIV/AIDS Clinical Trial Eligibility Criteria:

(Based on interventional trials initiated between 1990 and 2022.)



(Source: www.clinicaltrials.gov)

Results and Discussion

This study searched 5197 HIV clinical trial studies and identified a total of eight unique search terms found within 43 studies. HIV clinical trials included pain-related search terms in the eligibility criteria less than one percent of the time (0.83%). The eight unique search terms were identified a total of 343 times. Of these instances, 300 (87.5%) were found within the exclusion section compared to 43 (12.5%) in the inclusion section of HIV clinical trials.

Of all terms, "Peripheral Neuropathy" yielded the most significant overall volume with a total frequency of 169. Peripheral neuropathy was commonly excluded from HIV clinical trials, establishing a 94.1% exclusion rate. "Pain" and "Migraines" also established notable trends in

which “Pain” recorded the highest total frequency yet with a more proportionate inclusion while “Migraines” established the most pronounced exclusion rate (100%, 25 instances). Despite the notable exclusion rates, pain-related term rates between inclusion and exclusion criteria were not deemed statistically significant via ANOVA ($p = 0.163$). This could be partially explained due to the small sample size of some terms that acted as outliers.

The results of the present study identified numerous concerns regarding the inclusion of pain-related terms in HIV clinical studies. Less than one percent of HIV clinical trials considered pain within the eligibility section despite established trends of pain amongst HIV patients. General pain was noted the most frequently, however, migraines and peripheral neuropathy were excluded from HIV clinical trials nearly 95% of the time collectively. As identified by Julian et al. (2021, 1420-1431), such conditions could have implications on HIV treatment modalities, thus warranting further investigation. Overall, more HIV clinical trials should consider the cotreatment of pain-related conditions to improve the long-term quality of life among those with HIV.

References

- Julian, Thomas, Martina Rekatsina, Faiza Shafique, and Panagiotis Zis. "Human immunodeficiency virus–related peripheral neuropathy: A systematic review and meta-analysis." *European Journal of Neurology* 28, no. 4 (2021): 1420-1431.
- Parker, Romy, Dan J. Stein, and Jennifer Jelsma. "Pain in people living with HIV/AIDS: a systematic review." *Journal of the International AIDS Society* 17, no. 1 (2014): 18719.
- Scott, Whitney, Chinar Arkuter, Kitty Kioskli, Harriet Kemp, Lance M. McCracken, Andrew SC Rice, and Amanda C. de C. Williams. "Psychosocial factors associated with persistent pain in people with HIV: a systematic review with meta-analysis." *Pain* 159, no. 12 (2018): 2461.
- Sohail, Sachal, Gertrude Nakigozi, Aggrey Anok, James Batte, Alice Kisakye, Richard Mayanja, Noeline Nakasujja et al. "Headache prevalence and its functional impact among HIV-infected adults in rural Rakai District, Uganda." *Journal of neurovirology* 25, no. 2 (2019): 248-253.
- Yang, Hsin-Yun, Matthew R. Beymer, and Sze-chuan Suen. "Chronic disease onset among people living with HIV and AIDS in a large private insurance claims dataset." *Scientific reports* 9, no. 1 (2019): 1-8.