Original Article

Additive Effects of Numbness and Muscle Aches on Fatigue Occurrence in Individuals with HIV/AIDS Who Are Taking Antiretroviral Therapy

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Abstract

Context. Muscle aches, numbness in the feet/toes (neuropathy), and fatigue are often reported concurrently and are among the symptoms most frequently reported by individuals with HIV/AIDS, whether or not they are taking antiretroviral therapy (ART).

Objectives. This study used a longitudinal analytical methodology to analyze these symptoms together to determine whether symptom clusters are maintained over time and to determine whether there is a temporal relationship between fatigue and reports of neuropathic pain and muscle aches.

Methods. This was a secondary analysis of a subset of data from a six-month, longitudinal, randomized, controlled trial of 243 HIV-positive individuals taking ART. Self-reported symptom frequency and intensity were recorded using the Revised Sign and Symptom Checklist for Persons with HIV disease at baseline (Month 0), one, three, and six months. Multilevel, logistic regression models were used to analyze time-lagged effects of muscle aches, numbness of the feet/toes, and fatigue to estimate any predictive and interactive effects that the symptoms have upon one another.

Results. A significant relationship between muscle aches and fatigue intercepts was noted (odds ratio [OR] = 1.80, $P \leq 0.05$). Significant relationships between numbness and fatigue also were noted for the entire measurement period (OR = 2.70, $P \leq 0.05$). Time-lagged models showed persons reporting neuropathic-related numbness in one period were nearly twice as likely to report fatigue in subsequent periods (OR = 1.89, $P \leq 0.05$). The final model revealed that the addition of muscle aches and numbness explained 28% of the random

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variance in the occurrence of fatigue. Between-person descriptive variables including years living with HIV, age, having an AIDS diagnosis, ethnicity, and nucleoside reverse transcriptase inhibitor treatment regimens with stavudine, zalactabine, or didanosine did not significantly explain any additional model variation.

Conclusion. These findings are consistent with physiological research and provide evidence that analyzing multiple symptom change over time can provide a more accurate representation of an individual's symptom experience. When evaluating patients with muscle aches or numbness, particularly when both symptoms are present, an evaluation of fatigue should be considered. Similarly, if fatigue is reported, underlying physiological assessments for neuropathic symptoms and muscle aches may be considered. J Pain Symptom Manage 2011;41:469–477.

Key Words
Multilevel modeling, growth curve, symptom experience, HIV/AIDS, fatigue, neuropathy, muscle ache

Introduction

Symptoms associated with HIV illness and with the antiretroviral therapy (ART) regimens used to treat it have been associated with both decreased HIV medication adherence[1–5] and decreased quality of life.[6–9] In descriptive and cross-sectional studies, muscle aches, numbness in the feet/toes (neuropathy), and fatigue are commonly reported concurrently and are often among the symptoms most frequently reported by individuals with HIV/AIDS, both those taking or not taking antiretroviral medications (ARVs).

Fatigue in clinical conditions is generally assessed subjectively and is often described as a whole body feeling of muscle fatigue and loss of energy. Fatigue is frequently reported in individuals with HIV both taking and not taking ARVs. In addition to HIV, fatigue is documented as a frequently occurring symptom in several other chronic conditions, including fibromyalgia, osteoarthritis, and rheumatoid arthritis. As many as 76% of people with chronic widespread musculoskeletal pain report fatigue, and as many as 94% of people with chronic fatigue syndromes report muscle pain.[10] Recent animal studies in mice by Burnes et al.[10] suggest a biological link between testosterone and the pathways relating pain and fatigue in female and male mice that may help explain why more women than men are diagnosed with chronic pain and fatigue conditions such as fibromyalgia and chronic fatigue syndrome. The findings suggest that testosterone works in conjunction with a specific acid-sensing ion channel (ASIC3) involved in muscle pain to protect against muscle fatigue.

Mitochondrial Toxicity, Neuropathies, and Fatigue

Physiological research shows that in patients living with HIV/AIDS and receiving ARVs, acute fatigue is a lead indicator of cellular mitochondrial dysfunction and, as a result, acute fatigue onset and chronic fatigue may have differing physiological and psychological origins.[11] Sensory neuropathy occurring in the context of HIV/AIDS is also a frequently reported symptom, particularly in patients who received the nucleoside reverse transcriptase inhibitor (NRTI) antiretrovirals zalcitabine (ddC, Hivid®; Roche, Basal, Switzerland; discontinued manufacture in 2006), stavudine (d4T, Zerit®; Bristol Myers-Squibb, New York, NY, USA), and didanosine (ddI, Videx®; Bristol-Myers Squibb, New York, NY, USA) as part of their regimen. Although these NRTIs are recommended for cessation by the World Health Organization for use internationally, the long-term and irreversible neuropathic effects of stavudine are still likely. Only in April 2010 was stavudine removed from first-line treatment in current HIV treatment guidelines in South Africa.[12]