Original Article

Patterns of Change in Symptom Clusters with HIV Disease Progression

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Abstract

Context. With better antiretroviral treatments (ARTs), persons living with HIV (PLWH) are living longer, healthier lives. Therefore, they also experience more medical comorbidities that come with normal aging, as well as side effects of multiple treatments and long-term sequelae of HIV. It can be hard to know whether symptoms reported by PLWH are related to comorbidities or are signs of HIV disease progression and possible treatment failure.

Objectives. The current study was designed to disentangle these issues by examining within-person symptom changes in data collected from a cohort of PLWH before the advent of highly efficacious ART.

Methods. This study was a secondary analysis of symptom reports in longitudinal data collected from 246 PLWH in 1992–1994. Multilevel modeling was used to test for changes over time in HIV-related symptom clusters. Analyses also tested the effects of person-level demographic covariates and co-occurring mental health symptoms on HIV symptoms and examined the magnitude of within-person versus between-person variations in reported symptom severity.

Results. Two of six HIV-related symptom clusters, *malaise/fatigue* and *nausea/vomiting*, increased over time in the context of HIV disease progression, but the other four did not. Changes were independent of baseline disease severity or psychological covariates. There was substantial within-person variability in absolute symptom severity.

Conclusion. Relatively small but consistent changes in symptoms related to nausea or fatigue may suggest HIV disease progression, but changes in other HIV symptom clusters may instead be related to comorbidities or normal aging. Further research is recommended on symptom progression in PLWH. J Pain Symptom Manage 2011;42:12–23. © *2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Aging, fatigue, HIV, nausea, symptom clusters

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Introduction

With improvements in antiretroviral treatment (ART), the expected course of HIV has substantially changed since 1997. On one hand, persons living with HIV (PLWH) may now enjoy a life expectancy similar to their noninfected peers; on the other hand, they now face a range of chronic disorders associated with aging, which are further complicated by HIV disease processes, treatment side effects, and drug interactions.[1,2] HIV treatment is, therefore, moving to a chronic care model that requires expertise in primary care, disease management, and health behavior in addition to knowledge of HIV.[3] Persons who have been infected with HIV for 20 years or more may have exceptionally complex clinical presentations. It can be difficult for practitioners to know whether patients' reported symptoms are related to HIV infection, comorbid illnesses, or the side effects of ART or other treatments.

One potential source of evidence to help practitioners disentangle the effects of HIV infection from other symptoms comes from data on the course of HIV in the absence of highly effective treatment. Such data are available in the AIDS Time-Oriented Health Outcome Study Databank (ATHOS), a large data set with HIV symptom data collected before the advent of highly effective ART in the late 1990s. The ATHOS data set is a longitudinal observational database of PLWH who received care from community-based providers. Data were collected from medical records and patient questionnaires at three private practices in the San Francisco Bay area, two private practices in Los Angeles, and five community clinics in San Diego. PLWH who provided information for this data set experienced HIV disease that was minimally treated by today's standards because the available drug therapy at the time (zidovudine) did not have a strong effect on disease progression or survival.[4] Using the ATHOS data set, the current study was designed to describe symptom changes in the context of HIV disease progression.

Symptoms in HIV May Have Multiple Etiologies

Symptoms are subjective health-related experiences that may be described in terms of their intensity, duration, interference with daily activities, or degree of change over time.[5] Although HIV can produce flu-like symptoms of fever, sore throat, weakness, or rash, these usually appear only two to six weeks after infection with the virus and tend to resolve in one to two weeks once the body begins producing antibodies to HIV. After this period of "primary HIV infection," the virus remains in the body but is largely asymptomatic.[6]

Later, if HIV is not effectively treated, symptoms result from disease progression as the amount of HIV in the bloodstream (viral load) increases and the number of $CD4^+$ cells in the bloodstream decreases, indicating diminished immune system functioning. As the immune system progressively weakens, PLWH become more vulnerable to opportunistic infections (OIs) that do not usually cause illness in nonimmunocompromised individuals. OIs can cause disease and illness in most major body systems, resulting in diverse symptoms such as mouth pain or sensitivity, genital pain or discomfort, digestion problems, neuropathic pain, muscle pain, breathing problems, vision problems, or cognitive disturbance. Further complicating the clinical picture is the fact that a given OI can produce multiple symptoms. For instance, cytomegalovirus is a common virus that is held in check by the immune systems of most healthy individuals but can lead to retinal damage, breathing problems, and/or colitis in immunocompromised persons. Untreated HIV itself can cause a wasting syndrome as immune functioning decreases and viral load increases; this can include weight loss, weakness, fever, nutritional problems, and diarrhea.[6] The advanced stage of HIV infection, also referred to as acquired immune deficiency syndrome (AIDS), is defined by a $CD4^+$ cell count below a certain level (<200 cells/mm^3 based on the current treatment guidelines but other values in past definitions) or by the presence of one or more OIs.[7]

Progression to AIDS is much less likely with current ART medications. Other sources of symptoms in PLWH may be related to normal aging. Dementia, physical wasting, and serious illnesses are more common overall in older individuals. However, HIV disease progression also occurs more quickly among older than younger PLWH, so causality can be difficult to determine. In addition, older PLWH have more comorbid illnesses that may produce