QUALITY OF LIFE AFFECTING IN HIV/AIDS PATIENTS: A REVIEW

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Abstract: The Acquired Immuno Deficiency Syndrome (AIDS) is a global pandemic causing the greatest public health concern. Its etiological agent, the Human Immunodeficiency Virus (HIV) is one of the commonest lethal infections worldwide. The physical and mental changes resulting from HIV infection and its treatment can affect a patient’s quality of life (QOL). Some of the most commonly reported symptoms affecting QOL in HIV-infected patients are fatigue, pain, and anxiety/depression and sleep disturbances. Fatigue often has a multifactorial etiology, including advanced HIV disease, opportunistic infections, poor nutrition, hormonal insufficiency, and anemia. Pain is one of the most overlooked factors by clinicians. Anxiety/depression and sleep disturbances are experienced by many HIV-infected individuals and are highly correlated with the perception and progression of disease. Although these common clinical symptoms impact QOL in HIV-positive patients, there are no established guidelines for treating them. As pain, anxiety/depression, and sleep disturbances can influence fatigue, as well as each other, the HIV care provider should monitor them closely because their severity reflects the clinical course of HIV as well as the overall well-being of the patient.

Key words: HIV infection, Quality of life

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS), is a fatal illness caused by a retrovirus known as the human immunodeficiency virus that breaks down the body’s immune system, that infects CD4+ cells initially and progressively leads to AIDS [1]. Recent estimates suggest that more than 30 million people are living with HIV infection worldwide [2]. There are 2.47 million persons in India living with HIV, equivalent to approximately 0.36 % of the adult population. The revised national estimate reflects the availability of improved data rather than a substantial decrease in actual HIV prevalence in India. The transmission route is still predominantly sexual (87.4%); other routes of transmission by order of proportion include prenatal (4.7%), unsafe blood and blood products (1.7%), infected needles and syringes (1.8%) and unspecified routes of transmission (4.1%). In 2005 more than 7600 people died daily from AIDS related causes, and about 38.6 million people worldwide are infected with HIV [3].

HIV infection and its treatment may result in numerous physical and mental changes that affect a patient’s quality of life (QOL). Highly active antiretroviral therapy (HAART) significantly prolongs life and has changed HIV infection from a terminal disease to a chronic disease. Thus, the focus of patient care has changed from a palliative care approach, with the intent to eliminate pain and provide end-of-life comfort measures, to one aimed at normalizing life as much as possible and addressing QOL. Cella et al. [4] showed that the most-reported symptoms in HIV-infected patients were fatigue, sleep disturbances, pain, anxiety, sadness and nausea (see Table 1).

Although HIV therapy has evolved since the time of that study, many of the clinical factors affecting QOL...
in the mid-1990s remain key QOL issues today. This article will therefore focus on the prevalence and etiology of four major QOL influencers: fatigue, pain, anxiety/depression and sleep disturbances. For a discussion of their clinical assessment and a review of strategies for intervention, please refer to the article by Anne Hughes in this supplement.

Fatigue: Fatigue is the seventh most common symptom seen in primary care [5]. Fatigue is a term used to describe feelings of exhaustion, sleepiness and a lack of energy. Fatigue may be a symptom of a disease or diseases or other problems that a person is experiencing and may be temporary or chronic. Fatigue is described as a lack of energy, sleepiness, tiredness, exhaustion, an inability to get enough rest, or weakness. Thus, fatigue causes changes in the quality of life of the person experiencing it.

Fatigue in HIV: From her review of the literature, Barroso, [6] estimated that the prevalence of fatigue among persons with HIV infection is 20% to 60%. Fatigue related to HIV infection has been shown to be a strong predictor of daily living limitations and days lost to disability [7,8]. Fatigue also significantly affects physical functioning [9]. Yet, fatigue is one of the most under treated concerns that people with HIV experience.

Frequently identified causes of fatigue in HIV include lack of rest or exercise, or improper or inadequate diet; psychological stress including depression and anxiety; use of recreational substances such as alcohol, tobacco, and drugs; side effects from medications, both those used to treat HIV disease and those used to treat or prevent opportunistic infections; infections, such as infectious mononucleosis, hepatitis, endocarditis, urinary tract infections, tuberculosis, and those that are common in HIV-infected persons (opportunistic infections); abnormalities of the adrenal gland, thyroid gland, and gonads; sleep disturbances; fever; and anemia. Lee et al. [10] found that lower CD4 cell counts were related to more daytime sleep, higher evening fatigue, and higher morning fatigue in women infected with HIV.

The first instrument used to measure tiredness was developed in the 1920s, and the first major text on fatigue was published in 1947. Throughout the 1970s and 1980s, nurses and members of other disciplines to identify the causes and mechanisms of fatigue conducted many studies. In 1972, Hart [11] compared patients who had multiple sclerosis with healthy controls and found that patients with multiple sclerosis experienced more severe fatigue than healthy controls. There are tools available to assess fatigue, but unfortunately they only inform the clinician whether or not fatigue is present [6].

Fatigue is common among patients with HIV/AIDS and may contribute to impairment in physical function and disability [12,13]. The prevalence of fatigue reported in clinical samples is 2 to 27% in the early “asymptomatic” stages of HIV illness, and 30 to 54% in symptomatic HIV-infected and AIDS patients. Fatigue has been defined as a reactive state, following a period of mental or physical exertion, which is characterized by a lessened capacity for work [14]. However, HIV-related fatigue is often reported by patients to be independent of exertion. Fatigue may comprise a multitude of symptoms and descriptors, such as weakness, listlessness, sleepiness and low energy and may have physiological and psychological components, most frequently depression. Rating scales used to measure fatigue reflect this multidimensionality.

The most common hematologic abnormality in patients with HIV is anemia and it increases in frequency as the disease advances [6]. Approximately 10% to 20% of patients are anemic at initial presentation and 70% to 80% become anemic as HIV progresses [15]. Anemia thus may be a primary cause of fatigue in patients with AIDS [16]. The causes of anemia are multifactorial; anemia may be secondary to hypoproliferative bone marrow, neoplasia, opportunistic infections, chronic inflammation, marrow damage, or iron deficiencies (or other nutritional problems).

Anemia is defined as a hemoglobin level below 14 g/dL in men and below 12 g/dL in women. Some studies describe anemia in HIV-infected patients as a

Table 1: Symptoms Reported in HIV-Infected Patients. Source: Data from Cella, Mo, and Peterman [4].

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>73</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>71</td>
</tr>
<tr>
<td>Pain</td>
<td>60</td>
</tr>
<tr>
<td>Anxiety</td>
<td>59</td>
</tr>
<tr>
<td>Sadness</td>
<td>58</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
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hemoglobin level below 9.5 g/dL [17]. In a study examining HIV-positive patients with CD4 cell counts below 200 cells/mm$^3$, who were not directed to take antiretroviral therapy, the 1-year incidence of anemia was higher in women than in men (34.1% vs. 23.6%) and higher in Blacks (30.4%) than in Whites (23.6%) or Hispanics (18.8%) [18].

A recent retrospective analysis of 13,768 HIV-infected patients in more than 100 clinics in the United States found the prevalence of fatigue to be 37% [19]. Risk factors for fatigue were clinical AIDS, depression, and hemoglobin (Hb) < 12 g/dL. In a cross-sectional survey of ambulatory AIDS patients, fatigue was significantly associated with the number of AIDS-defining symptoms (p < 0.0001), current therapy for HIV-related comorbidities (p < 0.001), anemia (p <0.02), and pain (p <0.001), more likely to report fatigue than were men (p < .03; Bretibart et al [20]. In a study of HIV/AIDS outpatients, fatigue was present in 85% of the study population, and more than half of these patients reported that the fatigue caused distress in their daily routine [21].

It is common for the etiology of fatigue to be multifactorial [8]. Active/advanced HIV infection; opportunistic infections, poor nutrition, hormonal insufficiency, antiretroviral drugs, and/or anemia may play a role. Typically, as HIV disease progresses, fatigue becomes more prevalent [8]. Pneumonia, cytomegalovirus, and toxoplasmosis are opportunistic infections that induce fatigue, [8] and HIV disease itself, even without an acute infection, can also cause fatigue. Inadequate intake of vitamins and protein can result in fatigue; therefore, a thorough diet history should be obtained on routine visits [8]. In addition, patients should be evaluated for thyroid abnormalities and hypogonadism. Hyperthyroidism is common among both male and female patients, but typically more women than men suffer from it [8]. Fatigue is often associated with treatment for HIV infection. Duran et al. [22] showed that 62.5% of the HIV-positive patients on a protease inhibitor– containing HAART regimen reported month after initiating treatment, and 53% of all HIV-positive patients on a protease inhibitor containing HAART regimen reported fatigue 4 months after initiating treatment [22].

Anemia may have a dual etiology in HIV-infected patients, [8] resulting either from living with a chronic disease (anemia of chronic disease [ACD]), such as HIV/AIDS; from HIV therapies that suppress bone marrow production of red blood cells; or both. ACD is quite common in HIV-infected patients, [23] and it can be exacerbated by antiretroviral medications (e.g., zidovudine, lamivudine, didanosine, and stavudine) and drugs used to treat coinfections, such as ribavirin for hepatitis C virus coinfection [23,24]. In the HIV population, the effects of anemia on disease progression and QOL have been studied extensively. The prevalence of anemia increases with increasing disease severity. Anemia can range in prevalence from 28% in patients with HIV infection with no AIDS to 87% in patients with clinical AIDS [18]. Anemia is very common in both men and women, even in the early stages of HIV, when overt symptoms may not be present.

Anemia should be carefully monitored because it has been correlated with an increased rate of disease progression and decreased survival [25-27] Anemia has been shown to be a negative influence on QOL in HIV-infected patients, impairing physical activities involved with daily living and negatively affecting perceived health, psychological well-being, and social functioning [28]. As one component of fatigue, anemia can have an impact on multiple health outcomes. Thus, the chronicity of HIV disease does not warrant overlooking or minimizing consideration of fatigue; it is a legitimate, serious symptom that should be addressed and treated.

**Pain in HIV:** Pain, a common and pervasive symptom in HIV infected patients, [29] is also one of the most overlooked symptoms affecting QOL. Unless the care provider directly asks the patient, “Are you having any pain?” a patient’s pain may go unnoticed because the patient may believe that pain is to be expected and therefore must be endured. Patients who have a history of past or current substance use and/or abuse are at risk of not being adequately treated for pain because of provider judgment about substance users and pain.

Recently published results from a survey of 2,267 patients in the HIV Cost and Services Utilization Study showed that 67% of patients reported experiencing pain during the previous 4 weeks, [30] and the prevalence of pain typically increases with increasing severity of disease [31]. The HAART transformation of HIV from a terminal disease to a chronic disease, although a monumental achievement, also means that patients today are experiencing pain for longer periods of time [32]. Pain is difficult to
assess, and providers must use the subjective information from a patient regarding pain and effectiveness of pain medication to make decisions regarding its treatment. Similar to fatigue, pain can also have a diverse etiology.

Chest pain is encountered frequently in the rehabilitation phase of an HIV-infected patient. It typically has a broad differential diagnosis, including but not limited to coronary artery disease, gastroesophageal reflux, fungal esophagitis, musculoskeletal pain, and spontaneous pneumothorax. Spontaneous pneumothorax has become more common in HIV-infected patients in recent years and has been shown to occur 450 times more frequently than in the general population. Distal sensory neuropathy (DSP) is another clinical factor contributing to pain.

Kaplan-Meier analyses estimate that 36% of moderately-to-severely immune suppressed HIV-infected patients suffer from DSP. Furthermore, the severity of DSP has been correlated with increases in HIV-1 plasma viral load (p < 0.05). Posttraumatic stress disorder (PTSD) may also contribute to pain. Individuals with persistent pain have a heightened sensitivity to PTSD, and in one study, HIV diagnosis was rated as one of the more stressful traumas experienced. Smith showed that HIV infected patients with PTSD typically experience greater pain intensity and pain disability than do those without PTSD. The experience of physical pain can be influenced by stress-inducing psychosocial factors such as sexual or domestic violence and should be monitored carefully because multiple clinical factors may affect one another (please refer to the article by Barbara Aranda-Naranjo in this supplement for further details about psychosocial factors affecting the QOL of HIV-infected patients).

HIV-related pain in the new millennium: As HIV/AIDS becomes more of a chronic disease state than a progressive terminal illness, the prevailing paradigm for the pain management, based on the analgesic ladder concept, may no longer be the most appropriate. A multimodal approach to management, such as that advocated in the ‘pyramid-plus-ribbon’ model of contemporary cancer pain management, is likely to be more suited to HIV-related pain because it emphasizes the importance of disease-specific therapy, psychosocial interventions and physical modalities in addition to standard analgesic techniques (Fig.1).
Anxiety / Depression: Depression is one of the most common reasons for psychological evaluation and treatment of people living with HIV infection. HIV clinical care providers are increasingly confronted by co-morbid psychiatric illness among their patients. Prevalence rates of psychiatric disorders among HIV-infected patients approach 50% [38]. These conditions commonly manifest around the time of diagnosis [39], but many patients develop symptoms later in their course of illness [38]. Axis I disorders, including anxiety and depression, are particularly likely to occur at times of stress—such as divorce or loss of a loved one, and when facing a new disability. Anxiety and depression are among the most commonly diagnosed psychiatric conditions affecting HIV-infected patients [40,41]. These can complicate the treatment of HIV, presenting numerous diagnostic and interventional challenges for the clinician.

Adherence to highly active antiretroviral therapy (HAART) can be markedly reduced by co-morbid psychiatric disorders, but proper treatment of the psychiatric disorder can reverse this effect [42-45]. The appropriate evaluation and treatment of psychiatric symptoms can significantly affect a patient’s quality-of-life, as well as the risk of relapse into injection drug use and willingness to return for medical care [46]. Undiagnosed and untreated mental illness may lead to HIV risk behaviors and therefore contribute to the acquisition and spread of HIV [47,48].

The distress associated with a diagnosis of HIV infection can result in anxiety and depression about a range of issues, including treatment, mortality, stigma, and change in daily life. Accordingly, the prevalence of anxiety/depression in HIV-positive patients has been shown to be higher than that in HIV-negative patients. In that study, HIV-positive patients were more likely to use antipsychotics, antianxiety agents, and hypnotics than were HIV-negative patients [49].

One recent study of 422 HIV-infected patients found that 17% reported anxiety to be their most frequent troublesome symptom, with risk factors for anxiety being female gender, fewer years of education, and use of antiretroviral medications [50]. Estimates of the prevalence of major depression in HIV-infected individuals have been reported to be as high as 36% [51]. A meta-analysis showed that depression was twice as high in HIV-positive individuals compared with HIV-negative individuals. In a study of women, the rate of major depressive order was 4 times higher in HIV-positive (19.4%) than in HIV-negative (4.8%) women [52]. HIV-positive women had higher mean depressive symptom scores than did uninfected women, and substance abuse/dependence, albeit prevalent in this study cohort, did not affect this relationship [52]. As assessed by the Hospital Anxiety and Depression Scale, approximately 54% of the HIV-positive patients in an urban primary care setting experienced anxiety (70.3%) and depression (45.5%) and, as a consequence, distress [53]. Kalichman et al. [54] have shown that anxiety/depression is highly correlated with the perception of disease state. This finding is consistent with the findings of the Cohen et al. [53] study that higher viral loads were also associated with higher levels of distress (p < .0005). Even in an older age group of HIV-infected patients (> 50 years of age), depression is common. Although this age group comprises only approximately 10% of the U.S. HIV-infected population, it is a growing population, and at least 25% of an urban older age cohort that completed self-reported surveys experienced moderate-to-severe depression based on the Beck Depression Inventory [55]. Distinguishing underlying mental illness from that acquired after the onset of HIV infection is very difficult for the HIV care provider. The mental health needs of the HIV-infected population are very real, and mental illness is a complex co-morbid state for the care provider to assess and treat. Drug interactions between psychiatric medications and commonly prescribed HIV medications can also occur, and it is vital that providers are aware of all prescribed and over-the-counter medications that patients are taking.

Sleep Disturbances: Human immunodeficiency virus (HIV) infection is often accompanied by a number of physical symptoms, including sleep disruption. A recent study classified 73% of 115 HIV-positive patients as having a sleep disturbance, based upon elevated scores on the Pittsburgh Sleep Quality Index (PSQI). Sleep disturbances seem to develop soon after initial infection and continue across the disease course [56].

Sleep disturbances are common in HIV-infected individuals. In a multicultural study of HIV-infected patients, difficulty sleeping was the second-highest reported symptom (71%); only fatigue was higher,
at 75%. In a sample of 100 HIV infected women, the average sleep duration was 6.5 hours, and daytime napping was reported by 45% [57]. There was no correlation between sleep measures and CD4+ cell counts [57]. In another study in which the average person in the sample was infected for 8.5 years, was 46 years of age, was not working, and was a person of color, both length of time living with HIV and use of antiretroviral medications were correlated with poor sleep quality (p = .02, p < 0.0001, respectively). In addition, depressive symptoms (p < 0.0001), state of anxiety (p = 0.001), disease symptom severity (p = .002), daytime sleepiness (p = 0.004), and functional status (p = 0.03) were all associated with poor sleep quality [58].

Sleep disturbances have been closely correlated with fatigue in HIV-infected patients. In a study of HIV-infected women, patients demonstrated increased difficulty in falling asleep and increased awakenings from nighttime sleep [57]. Similar to the study by Nokes and Kendrew [58], poorer daytime functioning and depression were associated with sleep disturbances [57]. Using the Impact of Events Scale and the Pittsburgh Sleep Quality Index, Cruess [59], found that greater psychological distress was associated with greater sleep disruption in HIV infected patients receiving combination antiretroviral therapy. Furthermore, greater sleep disturbances in that study were significantly related to lower CD3+/CD8+ cell counts. Certain antiretroviral medications may also contribute to sleep disturbances. In patients receiving efavirenz, increased plasma levels of efavirenz were associated with insomnia [60]. One study of 174 patients who had been receiving efavirenz for at least 3 months categorized the types of sleep disorders that occurred and found the following: abnormal dreams in 24.7%, nocturnal waking in 19.6%, and trouble falling asleep in 17.8% [61]. Preclinical evidence also suggests that HIV infection itself may affect the neural processing related to the sleep cycle; HIV-1 envelope glycoproteins were shown to bind beta (CC) chemokine receptors, which are mediators of the sleep cycle [62].

CONCLUSION

Fatigue, pain, anxiety/depression, and sleep disturbances affect QOL in the HIV-infected patient. Fatigue is one of the most common clinical symptoms affecting QOL in HIV-positive patients; however, there are no established guidelines for assessing or treating it. Because the prevalence of these clinical sequelae increases with increasing disease severity, the care provider can monitor a patient’s overall well being by asking if the patient feels tired, is experiencing any pain, feels depressed, or has trouble sleeping. The clinician should not wait for the patient to report such symptoms or assume that if the patient does not report them, they are not a problem. Creative approaches to assessing these symptoms, such as symptom checklists and severity scales, may be useful for providers and should continue to be created and validated. Many of these symptoms can be treated, thus alleviating discomfort or distress and improving QOL and, perhaps, health outcomes. For more information regarding the assessment and management of these clinical symptoms, please refer to the article by Anne Hughes in this supplement.

REFERENCES


