PALLIATIVE CARE FOR HIV DISEASE IN THE ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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BACKGROUND AND INTRODUCTION

Between 1981 and the end of 1998, there were 688,200 adult/adolescent cases of acquired immunodeficiency syndrome (AIDS) reported nationally.¹ Since 1996, there has been a nationwide increase in AIDS prevalence despite a decrease in AIDS incidence, reflecting improved survival.² These changes have been attributed to the introduction and increasing use of combination antiretroviral therapies (ARTs), including protease inhibitors.^{2,3} With advances in the understanding of the dynamics and pathogenesis of human immunodeficiency virus (HIV) and the advent of new classes of antiretroviral agents, the treatment and course of HIV infection has been modified dramatically.⁴

Standard therapeutic practice for HIV infection has evolved from monotherapy to a combination regimen that includes a minimum of two nucleoside analogues and a protease inhibitor or non-nucleoside reverse transcriptase inhibitor, referred to as highly active antiretroviral therapy (HAART). The advent of this therapeutic era recently culminated in 1997, when the US Public Health Service issued guide-

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lines for initiating HAART that include a protease inhibitor in combination with nucleoside and non-nucleoside reverse transcriptase inhibitors.^{4,5}

Prior to the introduction of HAART, treatment options for HIV had limited impact, and the primary clinical strategies used were palliative. These medications have had a dramatic and profound effect in reducing HIV viral load and improving the clinical and immunologic course of patients in randomized trials and clinical settings, even those patients with advanced HIV/AIDS.⁶⁻¹² Although these therapies do not constitute a cure, survival has been lengthened, as noted in clinical studies¹³⁻¹⁷ and in broad-based population analyses in New York City¹⁸ and the US overall.^{19,20}

These rapid and dramatic changes in HIV therapeutics have resulted in some persons living with HIV/AIDS being able to return to active, high-functioning lives for long periods of time. For others, decreased mortality rates have resulted in the emergence of a new, more prolonged chronic disease phase of the illness marked by progressive disability and significant comorbidities. This chronic disease phase—in effect, the conversion of death to disability—takes place over a potentially protracted time course, with exacerbations and remissions resembling other chronic diseases, unlike the more stereotypic and rapidly fatal course of HIV disease so familiar earlier in the epidemic prior to the advent of HAART. For such patients, the trends in improved survival will result in greater need for long-term care, including institutional care, with the likelihood that long-term care facilities will occupy an important and increasingly strategic role in the continuum of care services for AIDS patients. Such facilities will continue to be sites where patients with late-stage disease and disability will receive palliative, symptom-oriented care, as well as more disease-specific interventions as medical treatment for HIV continues to evolve.

In addition, while the cited changes in treatment have lengthened overall survival significantly, for some patients the treatment fails or is no longer effective due to factors such as development of viral resistance or nonadherence to treatment regimens as a result of toxicity or side effects. While there have been reports of substantial decreases in deaths, most likely due to HAART, recent observations in New York City of increasing deaths and nationwide decreases in mortality allude to a gradual reversal of this trend (M. A. Chiasson, personal communication, September 1999), suggesting further that these therapies are not curative, and that end-of-life issues remain salient. This review addresses some of the clinical issues now facing HIV caregivers in the new therapeutic era, specifically with respect to late-stage disease, long-term care, and palliative and end-of-life care.

PALLIATIVE CARE AND HIV

Although the care of HIV-infected patients has been revolutionized with the advent of HAART, many patients still die after a prolonged period of declining function and symptomatic disease, and chronic symptoms such as pain, fatigue, nausea/vomiting, and diarrhea have been well described in patients with AIDS.²¹⁻²⁴ While HIV/AIDS mortality has been reduced substantially, the prevalence and duration of the disease has increased,¹⁹ and quality-of-life (QOL) issues such as pain and symptom management, increasingly referred to as the discipline of palliative care, are becoming an increasingly important component of clinical management of advanced HIV/AIDS patients.²⁴⁻²⁶ (See ref. 26, the Institute of Medicine's 1997 report, *Approaching Death: Improving Care at the End of Life*, for further in-depth discussion of palliative care.) In addition, because the new treatments themselves can give rise to symptoms and side effects, the need for palliative care is increased further and may even facilitate patient tolerance of and successful adherence to these often-demanding regimens. The therapeutic capabilities afforded by HAART are not a substitution for the sometimes more difficult and necessary task of simply "being there" for patients.²⁴ The definition and practice of palliative care for HIV/AIDS patients will continue to evolve as AIDS shifts to a chronic, treatable, but ultimately fatal, illness. Attention to psychosocial issues, palliative care, and a focus on the patient are becoming and will continue to become increasingly important.²⁴

HIV-RELATED SYMPTOMS

Throughout the course of HIV disease, patients experience multiple symptoms of varying intensities and frequencies. The principal symptom categories are gastrointestinal, respiratory, neurologic, constitutional and psychological.²¹⁻²³ While the majority of symptoms are often treatable, there are considerable challenges toward achieving effective treatment/control. The correct administration of drug therapies for symptom alleviation and control necessitates an accurate profile of symptoms at varying stages of the disease. With the increased survival associated with the new combination therapies, the constellation of symptoms during the end of life are becoming an increasingly important aspect for clinical management. For many patients, curative treatment must be replaced or coupled with palliative/supportive care during this phase of the illness as symptom effects have a great impact on QOL and sense of well-being, as well as on functional status.^{24,26}

During early HIV disease, common clinical manifestations include asthenia, anorexia, and pain,^{21,27} with increasing prevalence as the disease progresses.¹⁶ An

earlier (1991) report of symptoms occurring during late-stage HIV found 75% of patients presented with one or more symptoms, and over half reported pain.²⁷ Data suggest that the specific symptoms that predominate during the terminally ill phase may shift as the patient approaches death. Shortly before death (10 weeks), gastrointestinal and constitutional symptoms were the most frequent, and at the time of death, cough and breathlessness were the most common.²⁷ In a symptom profile study of terminally ill ambulatory and hospitalized AIDS patients who died before 1995, the most frequent symptoms 3 months prior to death were anorexia (63%), fatigue (60%), and pain (60%); at the time of death, the most frequent symptoms were fever (82%), fatigue (70%), and dyspnea (68%).²⁸

It is possible that, with many patients experiencing lengthened survival during the era of HAART, the predominant symptoms will be peripheral neuropathy, pain, and fatigue. With increasing use of medications and increased combination therapies, there is also likely to be a shift in the symptom profile, with a possible increase in toxic neuropathy²⁹ and gastrointestinal symptoms.

There are few systematic studies on the prevalence and characteristics of fatigue, despite the fact that is common during HIV disease. A recent study of fatigue in ambulatory AIDS patients reported a significant association of fatigue with the number of AIDS-related physical symptoms, current treatment for HIV-related medical disorders, anemia, and pain.²⁸ Patients with fatigue had poorer physical functioning ability, a greater degree of psychological distress, and lower QOL.²⁸ The reported prevalence of pain during HIV infection ranges between 30% and 80%, depending on the stage of disease, the mode of data collection, and the clinical care setting.^{23,30-35} Pain in HIV/AIDS patients can be due to HIV infection itself or consequences of HIV infection, such as tumors, or secondarily due to treatment medications.³⁶ In many cases, pain severity is underestimated by the clinician,³⁵ and in many instances, it may be treated inadequately.^{32,35,37} The presence and intensity of pain have also been associated with poorer psychological well-being and perceived QOL.³⁸ Fatigue and pain are likely to be increasingly important symptoms during the end stages of disease and to have a significant impact on the QOL.

Limited data suggest that the spectrum of symptoms may be distinct for men and women: Men report experiencing more neuropathic pain and visual loss, while women report experiencing more headache and musculoskeletal pain and lower respiratory tract symptoms, especially among injection drug users (IDUs).²² Fatigue has also been reported more frequently by women than men and more commonly reported among patients who reported heterosexual or injection drug use compared to those with homosexual high-risk transmission behavior.³⁹ An

updated, precise assessment of the symptomatic profile during the end-of-life phase among late-stage HIV-infected men and women is necessary to elucidate the evolving symptom profile to provide successful symptom management and palliative care.

CLINICAL MANAGEMENT OF PAIN

While pain management strategies are highly individualized, there are some general guidelines, and much has been written about the basics of pain management.^{40,41} The World Health Organization has established clear guidelines for cancer pain management⁴² that have been well validated.^{43–45} These same guidelines can be applied to pain in HIV disease.⁴² Although adequate control of pain often is achievable and desired, for AIDS patients, adequate control of pain may be hindered by lack of education about pain, difficulty assessing pain properly,³⁵ continued bias against the use of opioid analgesics, failure to use adjunctive medications and other modalities properly, and patient-related factors.^{36,37} With the longer survival now experienced by many HIV/AIDS patients, complicated symptoms associated with terminal illness and increased pain are common. The prevalence of pain often increases as the disease progresses,³⁶ and improvement in survival may also coincide with a longer period of symptomatic disease.

Causes of pain in HIV disease may include HIV-related cancers (e.g., Kaposi's sarcoma, lymphoma), viral infections (e.g., herpes, cytomegalovirus), osteomyelitis, drug-related etiologies (e.g., painful neuropathy associated with many antiretrovirals), loss of skin integrity, general debility secondary to cachexia and weakness, and other etiologies, some of which remain unknown.⁴⁶ The most common pain syndromes in HIV disease involve the gastrointestinal tract, especially oral pain, difficulty swallowing, and abdominal pain and discomfort.^{23,34,36,47}

As is true with cancer pain, opioids are the main analgesic, but adjuvant medications/therapies are often necessary.^{46,48,49} Adjuvant therapies include pharmacologic adjuvants, palliative radiotherapy, and complementary therapies (e.g., acupuncture, hypnosis, relaxation therapy, therapeutic massage).^{50,51}

A number of studies have reported undertreatment of pain in HIV/AIDS patients,^{30–32,35,36} and that opioid analgesics are rarely prescribed.^{32,36,37} In one study, only 6% of patients with severe pain were prescribed a strong opioid as World Health Organization (WHO) guidelines recommend,³⁷ and only 15% received adequate analgesic therapy. History of injection drug use is one of the more frequently identified predictors of undertreatment.^{30,37}

Injection drug use is a potential complicating factor in pain assessment and management among many HIV-infected patients. Concerns have been expressed

about the credibility of self-report of patients with a history of substance abuse,⁵² although there has been a high degree of concordance between HIV-infected substance users and their partners for self-reported drug and sexual behavior.⁵³

Factors that have an impact on pain management include patient reports of fear of addiction to analgesic medications^{28,54} and physician fears of contributing to substance use behavior.^{55,56} Data from a recent study indicated a high rate of pain-related concerns among ambulatory AIDS patients and concern about addiction potential of pain medications as one of the more important patient-related barriers of pain medication.²⁸ A recent report found that, while ambulatory HIV/AIDS IDUs were significantly more likely to receive inadequate analgesic therapy and to report lower levels of pain relief and a greater sense of psychological distress, there was no difference in the prevalence of pain, pain intensity, and pain-related functional interference among current and former IDUs and those without a history of substance use.³⁷ These data suggest that IDUs do not exaggerate pain, and undertreatment of pain may not be due to exaggerated symptom reports by IDUs.

Prior studies also indicate that women are significantly more likely to be undertreated,^{37,57} yet no differences were found between men and women for patient-related barriers, suggesting that physician biases may play an important role.²⁸

Elucidating pain management in late-stage HIV-infected patients and its relation to reported pain, perceived relief, and QOL during the end-of-life phase is crucial for patient care. In this study, we examine pain management during the end-of-life phase through a nested case-control study with attention to gender and substance use behavior. The existence of the WHO analgesic ladder has contributed greatly to the development and evaluation of standard care for pain management in palliative care.⁵⁸ Using this well-established reference standard, we review patients' charts to determine adequacy of medication administration for pain management in accordance with the WHO pain treatment ladder.⁵⁸

CLINICAL MANAGEMENT OF NAUSEA/VOMITING

Recent work on the pathophysiology of nausea and vomiting has yielded much information on the multiple mechanisms that may be involved, ranging from local effects on the stomach and gastrointestinal tract to central effects on the vestibular system, the chemoreceptor trigger zone, the brainstem-medullary vomiting center, and the cerebral cortex.^{59,60-62} Therapeutic advances have paralleled the increased understanding of the mechanisms of nausea and vomiting and now include four major classes of medications: (1) antidopaminergic agents (e.g.,

haloperidol, prochlorperazine), which may be beneficial in nausea and vomiting related to the chemoreceptor trigger zone); (2) antiserotonergic or prokinetic agents (e.g., metaclopramide, cisapride), which may facilitate gastric emptying and relieve gastrointestinal tract-related nausea and vomiting; (3) anticholinergic and/or antihistaminic agents (e.g., scopolamine, meclizine, diphenhydramine), which may help treat nausea and vomiting due to vestibular system disturbances; and (4) miscellaneous centrally acting agents (e.g., corticosteroids, lorazepam, dronabinol), which may exert global or more specific effects on higher cortical function, learned associations and behavior, and possibly increased intracranial pressure.^{60,63-67}

In patients with AIDS, a high prevalence of nausea and vomiting has always been observed.²²⁻³⁴ Traditionally, this has been due mostly to the effects of various opportunistic infections on the oroesophageal and lower gastrointestinal tract. More recently, the advent of HAART therapy has introduced a wide range of therapeutic agents that may also cause significant gastrointestinal symptoms, especially nausea/vomiting. The existence of multiple classes of antiemetic medications to assist patients in adherence to the increasingly complex HIV medication regimens helps to establish a standard of care that may help to both define and evaluate the effectiveness of interventions that treat nausea/vomiting in the patient population.

QUALITY OF LIFE AND QUALITATIVE EXPERIENCE OF HIV INFECTION

HIV disease progression has been associated with a continued decline in patient functioning and well-being.⁶⁸⁻⁷⁰ While earlier studies with zidovudine did not show improved functional status and well-being,⁷¹⁻⁷³ data on the impact of saquinavir and zalcitabine on QOL are more encouraging.^{74,75} Most recently, in a randomized, placebo-controlled trial, patients with advanced HIV disease who received HAART with zalcitabine experienced statistically significant increases in measures of physical function, general health perceptions, social functioning, and energy level.⁶⁵ In one recent study, a worse QOL was associated with recent hospitalization and symptomatic status, and the presence of symptom distress was related to lower QOL, with women showing a lower QOL on all measured domains.⁷⁶ Population-based studies of the impact of HIV on QOL during the era of HAART are needed to further our knowledge about the balance between the adverse effects and health-related QOL improvements, an important factor when considering treatment options for HIV-infected patients.⁷⁵ The QOL and the qualitative experience of living with AIDS in the context of advanced HIV disease and the

emergence of new therapeutic drugs are phenomena largely unstudied to date.

Individuals living with HIV infection—the patient and his or her family and caregivers—face profound social and psychological challenges in addition to the demanding physical aspects of the disease. A number of qualitative studies have focused on these themes, including employment, accommodation, finances, relationships, willingness to comply with care, coping strategies, and existential issues.^{77–82} The social stigma of living with HIV infection generates guilt and blame over being a potential source of infection. Discrimination against individuals who have a history as drug users and/or sex workers is a painful consequence of the disease. Caregivers share “guilt by association” when they “go public” as AIDS family caregivers.^{83,84} With the advent of HAART, we anticipate different issues will arrive as patients and caregivers, who expected clinical decline with HIV infection, experience clinical stabilization or even improvement related to the new therapy. Whether this results in return to previous activity levels or simply draws out the time to death needs elaboration and clarification. The extent to which patients in an apparent remission experience the “Lazarus syndrome” (having already prepared for death, but receive a reprieve, and the attendant feelings of hope or dread) is unknown.⁸⁵

Women who are HIV-positive family caregivers face even more complicated challenges as they struggle under this dual burden.⁸⁶ Having the disease affects women in all the ways others are affected. It may also imply, in their social context, that they have failed in their roles as caregivers and nurturers.⁸³ Two divergent patterns have been documented; in the first, fear of the symptoms and implications of HIV infection influence women to avoid contact with the health care system,⁸⁷ in the second, some women use their experience of HIV as a vehicle for psychological and spiritual growth.⁸⁸ The experience of living with advanced AIDS in the context of progressive disease during the era of potent therapeutic drugs is an existing problem about which little is understood.

CAUSE-SPECIFIC MORTALITY

With the newer potent antiretroviral drug combinations, the clinical course of HIV infection has changed dramatically, with markedly decreased morbidity paralleled by significant decreases in mortality and more advanced immunosuppression at the time of death.⁸⁹ Trends in cause-specific mortality during the AIDS epidemic indicate shifts in the predominant causes of mortality from the early days of the epidemic. With the widespread use of treatment and prophylaxis for opportunistic infections, the advent and use of antiretrovirals in the mid-1980s, and the increased immunosuppression associated with prolonged survival

in the mid-1990s, the contribution of infections has decreased, while death due to noninfectious diseases has increased. Published reports of trends in mortality have generally been retrospective^{90,91} and of limited duration; cause of death has often been ascertained through death certificates, which have been shown to be inaccurate for both HIV-infected and uninfected persons.⁹²⁻⁹⁴ Medical chart review for cause of death during 1984-1995 revealed that mortality due to *Pneumocystis carinii* pneumonia (PCP) significantly decreased from 1984 to 1995, while death due to wasting syndrome significantly increased; death due to malignant neoplasms increased, as did death due to *Mycobacterium avium* complex, despite use of primary prophylaxis.⁹⁵ During the current era of HAART, several recent reports suggest that PCP prophylaxis may be discontinued as patients' CD4+ cell counts increase.⁹⁶⁻⁹⁹ Consequently, it can be expected that PCP will continue to decrease as a cause of death among HIV-infected persons, and it is reasonable to assume that mortality patterns may continue to change as potent antiretroviral combination therapies are used more widely and the impact is felt more widely. However, updated systematic documentation of cause-specific mortality in HIV-infected persons is lacking.

Of comparable importance is updated information on predictors of mortality during the era of HAART. Specific studies that address prognostic indicators of mortality during the era of HAART are relatively few and show that viral load continues to be an important prognostic indicator of disease progression and death in patients receiving protease inhibitor treatment.¹⁰⁰ An earlier retrospective observational study of deaths among hospital-based patients treated with zidovudine found that the rate of CD4+ decline in the first year of therapy was predictive of survival rather than the initial CD4+ rise.¹⁰¹ Likewise, with HAART, it may be more important to look at the rate and duration of change in CD4+ cell count or RNA viral load levels rather than the magnitude of change as a predictor of survival. New predictors of mortality may also be emerging with the widespread use of HAART. Preliminary data from HIV/AIDS patients in a long-term care facility indicate that early mortality (<6 months) was predicted by the presence of impaired functional status in activities of daily living, as well as low CD4+ count and absence of a psychiatric history.^{102,103} This may be due to the fact that patients with psychiatric comorbidities are likely to be admitted into residential care facilities earlier in the course of their disease, occupying an increasing proportion of such beds over time. With continued prolonged survival associated with the newer antiretroviral therapies, identifying current predictors of mortality and survival is timely and important for health services planning for people with AIDS.

CONCLUSIONS

New potent combination antiretroviral therapies have created a renewed sense of hope for both clinicians and persons infected with HIV and have markedly extended life expectancy. However, for some patients, these changes have also resulted in the conversion of HIV disease into a chronic illness with exacerbations and remissions and a more prolonged period of disability and comorbidity. These trends have resulted in turn in the need for long-term care and new models of institutional care for the distinct subpopulation of patients with AIDS who continue to experience symptomatic illness and require more intensive medical and nursing services.

While clinicians now have more potent tools to manage the virus and the opportunity to affect the course of HIV disease, attention to palliative care and QOL issues have become increasingly important components of clinical care. Salient clinical problems include fatigue, pain, and gastrointestinal symptoms such as nausea and vomiting. Some of these symptoms (e.g., gastrointestinal symptoms) in themselves both may be made worse by antiretroviral medication regimens and may compromise the ability of patients to adhere to such regimens. With the changes in HIV disease trajectories during the era of HAART, the balance between curative and palliative care presents an ongoing challenge that will continue to unfold as HIV therapies continue to evolve. It is important for clinicians to be familiar and adept with the management of pain and other common symptoms that have always been noted in patients with AIDS. Likewise, it is critical to understand new or previously unrecognized symptoms and QOL issues that may emerge in patients with late-stage HIV who are now surviving longer. The special clinical needs of the subpopulation of patients who need long-term institutional care will require broad-based and specific expertise, as well as the necessary delivery systems to provide such care. These themes represent new challenges for health services planning for patients with AIDS and are, in effect, the consequences of success: The emergence of HIV as a chronic disease that requires long-term care is the direct result of the therapeutic advances that have reduced mortality and prolonged life.

Providing effective end-of-life and palliative care during this new therapeutic era necessitates an updated awareness of the current constellation of symptoms and other clinical problems experienced by patients with late-stage HIV disease. Protocols and guidelines for palliative care are as important as antiretroviral therapy algorithms for comprehensive clinical management of patients with HIV disease. Attention to QOL issues becomes increasingly important as the terrain of late-stage HIV disease is newly defined, especially within the context of long-

term institutional care. If not, we run the risk of narrowing the scope of HIV care to include only the technical elements of antiretroviral therapy, to the detriment of our patients and their caregivers. The clinical, psychosocial, and prognostic issues of late-stage disease continue to pose new challenges as the AIDS epidemic progresses; our new capabilities also engender new complexities. It is hoped that our clinical and programmatic responses will continue to keep pace with the changing expression of the disease and not ignore those domains that are perhaps more challenging than the increasingly medicalized model of HIV-specific therapy.

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