Original Article

The Use of Highly Active Antiretroviral Therapy (HAART) in Patients With Advanced HIV Infection: Impact on Medical, Palliative Care, and Quality of Life Outcomes

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Abstract
The effect of highly active antiretroviral therapy (HAART) in the treatment of HIV infection is usually measured by survival, CD4 lymphocyte counts, HIV-1 RNA viral load testing, and the occurrence of opportunistic infections. This pilot study sought to measure the impact of HAART treatments on a wide range of clinical outcomes and psychological variables in a sample of patients with advanced HIV infection. Seventy patients with advanced AIDS who were protease inhibitor naïve were started on HAART regimens. Patients were admitted to an AIDS inpatient unit of a long-term care facility that provides treatment and palliative care. All patients were diagnosed with AIDS, had CD4 cell counts below 300/cc\(^3\), and had a projected survival of greater than one month. Patients were started on triple-drug HAART regimens with daily medical supervision and observation. In addition to standard clinical and laboratory markers, a series of observer-rated and self-report instruments were used to measure various physical and psychological factors (e.g., pain and symptom distress, psychological well-being, depression). Data were collected at baseline and after 1 and 3 months of HAART therapy. As expected, the CD4 count increased and viral load levels decreased significantly over the 3-month study period. In addition, patients improved significantly in body weight, and serum albumin and ferritin levels. The only psychosocial measure that improved significantly with treatment was depression. Ratings of pain intensity, physical and psychological symptom distress, and overall quality of life did not change. Of the 70 patients studied, 84.3% were still alive after the 3-month study period. Of these, 6 (8.6%) were discharged to community. However, 17 surviving patients (24.3%) had HAART regimens discontinued due to drug intolerance and 11 patients (15.7%) expired during the study period. While these data are preliminary, HAART regimens appear to have positive effects on CD4 count, HIV viral load, and several other measures of physical well-being in patients with advanced AIDS. Despite these improvements, the benefits of treatment on pain and symptom distress, and psychological well-being were less clear. In addition, treatment failure (mortality

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and intolerance) were not uncommon in this sample (40%). Further research is clearly necessary to better understand the benefits of HAART therapy in patients with advanced HIV infection. J Pain Symptom Manage 2001;21:41–51. © U.S. Cancer Pain Relief Committee, 2001.

**Key Words**
AIDS, HAART, outcome, treatment, palliative care

**Introduction**

With the availability of protease inhibitor drugs, combination therapies incorporating nucleoside and non-nucleoside reverse transcriptase inhibitors have blossomed and guidelines for their use in the treatment of HIV-infected patients have evolved.1–5 These regimens have resulted in profound viral replication suppression, CD4 cell repletion, prolonged survival and decreased death rates.6–14 A decline in morbidity, usually measured as the occurrence of specific opportunistic infections, has also been demonstrated among patients with advanced HIV infection and is attributed to the use of these highly active antiretroviral therapy (HAART) regimens.14 Moreover, laboratory markers such as HIV-1 RNA viral loads and CD4+ lymphocytes have consistently been found to correlate with therapeutic success or failure; these markers are used to identify disease progression.15–19 Clinical studies measuring the effects of HAART in advanced HIV infection rarely have addressed its impact on palliative and quality of life variables at the same time as medical variables.

Previous reports have contributed to the current knowledge of outcomes in the pre- and post-HAART eras. Studies of pain have helped define the etiologies, prevalence, and management issues in the AIDS population.20–24 These observations have been made in ambulatory patients and preceded the HAART era. Symptom prevalence and palliative care needs have been described before and after the advent of HAART.25–30 However, these studies are not usually designed to weigh impact of HAART on symptom control.

There has been a surge in quality-of-life research that measures either quality of life in patients with AIDS or the effect of HAART on quality of life.31–34 These studies suggest a significant contribution by HAART to improved quality of life and maintenance of functioning and well being, at least during the study period. Likewise, some reports indicate that HAART benefits neuropsychological function and AIDS dementia complex.35,36 Finally, there are reports of the efficacies of triple regimens containing a protease inhibitor(s) for salvage therapy in patients having received extensive pre-HAART antiretroviral treatment or failing HAART.37–39 These reflect short-term virologic response rates of 20% to 54%, at best, due primarily to drug toxicity intolerance and resistance mutations.

Despite the importance of this information, studies are needed that focus on patients with advanced AIDS, the efficacy of newer treatment modalities in this population, and the outcomes that relate to palliative and psychosocial variables in addition to those that are strictly medical. Relatively few studies have investigated the effects of HAART regimens on palliative care outcomes or psychological factors, such as quality of life or psychological distress, in patients with advanced disease.

In this pilot study, we attempted to address the impact of HAART on medical outcomes, pain and symptom distress, and psychological well-being in patients with advanced AIDS. Therefore, in addition to studying the effect of HAART regimens on clinical parameters such as HIV-1 RNA, CD4+ lymphocytes, and nutrition, we also studied the impact of treatment on several palliative care and psychological parameters that included depression and psychological distress. This study used a prospective, longitudinal design incorporating repeated measurements of clinical and psychological parameters to investigate the impact of therapy in this often-neglected population. The study made no attempt to draw conclusive evidence favoring one protease inhibitor drug regimen versus another, but, rather, was intended to be
Methods

Subjects
All subjects were admitted directly to the Terence Cardinal Cooke Health Care Center (TCCHCC), a large free-standing skilled nursing facility in New York City that contains a 156-bed AIDS Discrete Unit, from acute care facilities throughout New York City during a period from March 1997 through April 1998. All patients approached for study participation had either been protease inhibitor naïve at the time of transfer or only recently started on HAART regimens during the acute hospitalization. Because the latter population had the potential for lead-time bias, a statistical analysis was performed comparing it to the protease inhibitor naïve group. There were no significant differences ($P < .05$) in any variables measured at the time of study entry. (While the precise lead times of HAART for this group during hospitalization are unknown retrospectively, it is estimated that the median lead time was 7 to 10 days. It is unlikely HAART would have had substantial effect during that time frame). Thus, all data analyses included the entire sample of patients.

Patients who met study inclusion criteria were started (or continued) on a drug regimen containing a nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, and a protease inhibitor. Because the purpose of this study was not to compare specific drugs, selection of drugs from each class was based on clinical factors (i.e., treatment history, etc.). The proportionate use of protease inhibitors in this study were: nelfinavir (40%), indinavir (36%), saquinavir (19%), and ritonavir (5%). All subjects were diagnosed with AIDS according to the CDC’s 1993 Revised AIDS Definition System and had CD4 count less than 200 per cc$^3$ (one exception, CD4 = 265) at the time of transfer to TCCHCC. Patients with a life expectancy of less than 4 weeks were excluded from study participation. Patients manifesting evidence of severe dementia as defined by American Academy of Neurology criteria, scored less than 20 on a Mini Mental Status Examination, or had a history of psychotic mental disorders were also excluded from questionnaire participation; however, medical and laboratory outcome data were measured for this subset of patients. There were no control subjects since it was deemed unethical to withhold treatment or use presumably less effective regimens for study purposes. The study was approved by the TCCHCC Internal Review Board. All interviewed patients provided written informed consent.

Procedures
Within several days of admission to TCCHCC, all subjects (i.e., patients who met inclusion criteria and consented to participate in the study) were interviewed by at least one member of the research team in order to obtain baseline demographic data, as well as to complete a battery of self-report and clinician-rated instruments (described below). All self-report questionnaires were read to patients in order to minimize patient burden and fatigue. Patients who were still inpatients at follow-up, i.e., barring death or discharge, were re-evaluated, using the same battery of measures at one month and three months after this baseline evaluation. Medical outcome was also monitored, including termination of treatment due to failed adherence, drug intolerance, death, or discharge. Medical data included an HIV/AIDS medical checklist that identified past and on-going AIDS-defining conditions. Laboratory testing included a complete blood count and a chemistry profile that included serum albumin and ferritin (ferritin was measured as a marker for body iron stores and utilization plus its role as acute phase reactant.), CD4 lymphocyte count, and HIV-1 RNA viral load tested by branched DNA methodology. Medical therapy and supervision was provided by full-time AIDS Discrete Unit physicians.

Measures
Karnofsky Performance Rating Scale (KPRS). An observer-rated scale used to report a patient’s level of physical functioning ability. Patients are rated on a scale of 0–100, with 0 corresponding to no functioning ability (i.e., death) and 100 corresponding to complete, independent functioning.

Brief Pain Inventory (BPI). A self-report measure of pain intensity and pain-related interference that has been validated in both can-
cer and AIDS populations. The BPI asks patients to rate their pain intensity during the past week using a series of 11-point (0–10) numerical rating scales corresponding to current pain, pain “at its worst”, pain “at its least” and pain “on average.” Patients are also asked to rate, using a similar format, the extent to which their pain interferes with seven aspects of their functioning (general activity, mood, walking ability, sleep, relations with others, and enjoyment of life). The latter scales are summed to form an overall index of pain-related functional interference.

Memorial Symptom Assessment Scale (MSAS). A symptom checklist that elicits information about the intensity, frequency, and distress associated with 32 physical and psychological symptoms.\cite{25,29} It has been validated for use in cancer and AIDS patients and generates an index of overall symptom distress (the Global Distress Index, or GDI), as well as two subscales that correspond to physical symptom distress and psychological symptom distress.

Hamilton Depression Rating Scale (HDRS). A 21-item clinician-rated measure of depressive symptoms.\cite{46} Subjects are rated using a 0–4 scale for most items and a 0–2 scale for others. Items are anchored with descriptive statements for each level of symptom severity. This instrument has been widely used in both medically ill as well as non-medically ill populations and provides an accurate index of the severity of depressive symptoms.

Edmonton Functional Assessment Tool (EFAT). A brief, clinician-rated measure of quality of life based primarily on physical functioning abilities.\cite{47} This relatively new measure was designed for use in hospitalized, palliative care populations and has demonstrated reliability and validity as a measure of quality of life.

Statistical Analyses
Repeted measurements of medical outcome, and symptomatic and psychosocial data were primarily analyzed using change scores derived from both follow-up assessment points.\cite{48} Change scores were calculated by subtracting baseline data from data obtained at follow-up such that positive values corresponded to an increase in the variable (i.e., gain) and negative values corresponded to a reduction (i.e., decrease). These change scores were then analyzed using matched t-tests to assess whether or not the changes were statistically significant ($P < .05$) after one month and three months of HAART therapy. Because some variables were highly skewed (i.e., CD4 lymphocyte count, HIV-1 RNA viral load), these data were transformed using a log-transformation prior to analyses (although data are reported using the original scale to ease interpretation). Categorical variables (i.e., pain presence) were analyzed using frequency analyses (Chi-square tests of association). We initially planned to compare subjects who were started on HAART regimens after their admission to TCCHCC versus those who had been started on this regimen during the preceding hospitalization. Because this analysis failed to reveal any significant differences ($P < .05$), all subsequent data analyses included the entire sample of patients.

Results

Subject Characteristics
There were a total of 70 patients enrolled in the study, 49 (70%) of whom entered TCCHCC protease inhibitor-naïve and 21 (30%) who had been started on HAART regimens recently during the antecedent acute hospitalization. The majority of the study patients were male (77%). The racial composition of the sample was 44% African-American, 23% Hispanic, 9% Caucasian, and 24% unknown or mixed. The average age was 34 years with a range of 25–78 years. Reported risk factors for HIV infection were intravenous drug use (40.4%), heterosexual contact (31.6%), homosexual contact (19.3%), transfusion (1.8%), and unknown (5.3%). While all subjects were classified as having AIDS, 9% had no history of an AIDS-defining condition (i.e., were classified as having AIDS based on CD4 cell count), and 91% had both low CD4 cell counts and history of opportunistic infections. Admission CD4 lymphocyte counts ranged from 0–265 per cc$^3$, with a mean of 66 (median 35) per cc$^3$. Admission HIV-1 RNA viral load testing demonstrated a range of less than 500 copies per cc$^3$ to 8,600,000 copies per cc$^3$, with a mean of 286,116 (median 40,450) copies per cc$^3$. Other medical data are summarized in Table 1.

Of the original 70 study patients, 20 demon-
strated sufficient cognitive impairment to preclude meaningful data collection and were not administered the self-report or observer-rated instruments. They were followed for medical parameters and outcomes, however. Data regarding the psychological and symptom characteristics of this sample were based on the subset of 50 subjects who completed study questionnaires and were evaluated using clinician-rated instruments. Of these 50 patients, 31 (62%) reported having experienced pain in the preceding 2 weeks and were administered the Brief Pain Inventory. Of the 31 patients reporting pain, the average level of pain reported (i.e., mean score) was 5.46 (SD 2.52), corresponding to a moderate level of pain. The mean level of pain-interference (based on the seven pain-interference items) was 4.78 (SD 3.38). Patients endorsed an average of 27.67 different physical and psychological symptoms on the MSAS (SD 4.89), with a mean Global Distress Index score of 1.38 (SD 0.54), corresponding to a moderate level of symptom distress. Examination of patient’s Hamilton Depression Rating Scale scores revealed a modest level of depressive symptoms, with an average HDRS score of 14.56 (SD 9.67).

**Improvement After One Month of HAART Therapy**

After one month of therapy, study patients demonstrated significant improvement in a number of clinical parameters (see Table 1). These parameters included CD lymphocyte counts, which rose by an average of 23.3 per cc$^3$ (a 35% increase) and HIV-1 RNA viral load, which decreased by an average of 65,596 copies per cc$^3$ (a 23% decrease). In addition, study patients demonstrated a significant weight gain over the one month period (8.3 lbs) and serum albumin levels rose an average of 0.17 g/dl ($P = .027$). There was no significant change in average hematocrit, hemoglobin, white blood counts, or ferritin levels.

Among the various psychological and symptom distress measures, only depression ratings (based on the Hamilton Depression Rating Scale) decreased significantly after one month of treatment. The average declined from 14.56 to 10.54 ($P < .0026$). There were no significant changes in any other symptom distress measures (see Table 2). Likewise, there was no significant decrease in the number of symptoms endorsed on the MSAS, ratings of patients’ overall physical functioning (KPRS scores), or quality of life as measured by the EFAT. Among patients who reported pain at both time points, there was no significant change in the level of pain intensity or pain-related functioning interference.

**Improvement After Three Months of HAART Therapy**

At the second follow-up assessment, three months after the initial baseline evaluation, the remaining patients demonstrated an even larger degree of improvement on a wider range of clinical and psychological variables (see Tables 1 and 2). At that assessment, CD4 lymphocyte counts had risen by a mean of 65.7 cells per cc$^3$ (a 100% increase) compared to baseline CD4 values ($P = .0001$) and HIV-1 RNA viral load levels had decreased by 119,069 copies per cc$^3$ ($P = .0439$), or 42% decrease. Patients also demonstrated an average weight gain of 24.9 pounds ($P = .0003$). The mean serum albumin

<table>
<thead>
<tr>
<th>Measures</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Month 3</th>
<th>$P^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count (per cc$^3$)</td>
<td>66</td>
<td>83</td>
<td>132</td>
<td>0.0001</td>
</tr>
<tr>
<td>Viral load (copies per cc$^3$)</td>
<td>286,116</td>
<td>220,520</td>
<td>167,047</td>
<td>0.0439</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>30.4</td>
<td>31.4</td>
<td>33.3</td>
<td>0.0656</td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
<td>10.5</td>
<td>10.9</td>
<td>11.4</td>
<td>0.0116</td>
</tr>
<tr>
<td>WBC (per cc$^3$)</td>
<td>4,882</td>
<td>4,771</td>
<td>6,500</td>
<td>0.8059</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.34</td>
<td>3.50</td>
<td>3.56</td>
<td>0.0008</td>
</tr>
<tr>
<td>Ferritin (ng/dl)</td>
<td>934.7</td>
<td>585.7</td>
<td>556.7</td>
<td>0.0475</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>129.9</td>
<td>139.6</td>
<td>154.9</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*a n varies slightly due to occasional missing laboratory results.

$^b$P-value changes between baseline and month 3.
rose by 0.22 gm/dl ($P = .0008$) and ferritin levels dropped by 378 ng/dl ($P = .0475$). Hemo-
globin levels also rose significantly ($P = .0016$). There was no significant change in hemato-
crit levels or white blood counts (see Table 1).

Despite these significant improvements in clinical variables, however, there were few sig-
ificant changes in any of the psychological or symptom distress variables after three months
of treatment (see Table 2). Consistent with the results obtained after one month of therapy,
only depression ratings decreased significantly ($P = .0038$) and the decrease in overall num-
ber of physical symptoms (based on the MSAS) approached statistical significance ($P = .0817$).

Measures of quality of life, physical functioning ability, and pain intensity did not change sig-
ificantly after three months of therapy.

### Clinical Events and Medical Outcomes

During the 3-month period, study patients were monitored for new-onset AIDS-defining
diagnoses or opportunistic infections. The illnesses that did arise in this group included
wasting syndrome ($n = 4$), AIDS dementia complex ($n = 1$), resistant esophageal candidi-
asis ($n = 1$), and acute herpes zoster ($n = 1$). In addition, there were a number of other infec-
tious medical events that occurred in this sample. Eight patients experienced gram-positive
infections, including *Staphylococcus* pneumonia or sepsis ($n = 2$), *Staphylococcus* soft tissue infec-
tions (cellulitis, axillary adenitis, and fasciitis, $n = 3$), methicillin-resistant *Staphylococcus aureus*
urinary tract infection ($n = 1$) and vascular catheter infection ($n = 1$), and vancomycin-resistant
*enterococcus* bacteremia ($n = 1$).

At the end of the 3-month study period, 36 of the initial 70 patients (51.4%) were still
alive, residing on the AIDS Discrete Unit of TCC/HC (see Table 3), and receiving HAART
regimens. These patients, along with 6 (8.6%) who were discharged to the community on
HAART and were alive at 3 months, reflected a 60% study completion rate in this sample of
advanced stage patients. Another 17 patients (24.3%), also alive on the Unit after 3 months,
had HAART regimens discontinued because of intolerance to side effects during that period.
There were 11 deaths (15.7%) during the study. This represents a 40% study non-com-
pletion rate. The overall survival rate was 84.3%. No patients demonstrated failed adher-
ence, i.e., willing noncompliance, which is likely reflective of the 24-hour medical and
nursing supervision at the study facility. The causes of death were progressive wasting ($n = 5$),
bacterial pneumonia ($n = 3$), disseminated Kaposi sarcoma ($n = 1$), non-Hodgkin lympho-
phoma ($n = 1$) and end-stage renal disease ($n = 1$). None of the 11 patients in the mortality
Group experienced drug intolerance and each received HAART regimens until near end-of-
life despite clinical decline. The mean study

### Table 2

**Symptom and Psychological Measures at Baseline and Study Intervals**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Baseline $n = 50$</th>
<th>Month 1 $n = 39$</th>
<th>Month 3 $n = 23$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported Pain (patients)</td>
<td>31 (62%)</td>
<td>22 (56%)</td>
<td>14 (61%)</td>
<td></td>
</tr>
<tr>
<td>Average Pain (BPI)$^b$</td>
<td>5.46</td>
<td>5.41</td>
<td>6.50</td>
<td>0.5495</td>
</tr>
<tr>
<td>Worst Pain (BPI)$^b$</td>
<td>7.67</td>
<td>7.95</td>
<td>8.72</td>
<td>0.1126</td>
</tr>
<tr>
<td>Pain Interference (BPI)$^b$</td>
<td>4.78</td>
<td>4.11</td>
<td>4.64</td>
<td>0.2565</td>
</tr>
<tr>
<td>No. of Symptoms (MSAS)</td>
<td>27.67</td>
<td>29.10</td>
<td>29.04</td>
<td>0.0817</td>
</tr>
<tr>
<td>Global Distress Index (MSAS)</td>
<td>1.38</td>
<td>1.26</td>
<td>1.44</td>
<td>0.3154</td>
</tr>
<tr>
<td>Physical Distress Index (MSAS)</td>
<td>1.19</td>
<td>1.23</td>
<td>1.30</td>
<td>0.1040</td>
</tr>
<tr>
<td>Psych. Distress Index (MSAS)</td>
<td>1.19</td>
<td>1.14</td>
<td>1.31</td>
<td>0.4377</td>
</tr>
<tr>
<td>Depression (HDRS)</td>
<td>14.56</td>
<td>10.54</td>
<td>8.82</td>
<td>0.0038</td>
</tr>
<tr>
<td>Quality of Life (EFAT)</td>
<td>6.37</td>
<td>4.22</td>
<td>3.80</td>
<td>0.8073</td>
</tr>
<tr>
<td>Physical Functioning (KPRS)</td>
<td>57.90</td>
<td>57.54</td>
<td>59.87</td>
<td>0.1229</td>
</tr>
</tbody>
</table>

$^a$Value changes from baseline to month 3.

$^b$Based on subsets of patients reporting pain.
survival time was 58.9 days (range 20–91) for the mortality group.

**Discussion**

This pilot study reflects a systematic attempt to assess the impact of HAART regimens among patients with advanced AIDS. Patients demonstrated significant improvement over the three-month study period in a number of clinical markers of HIV-disease, including CD4 cell count, HIV-1 RNA viral load, and weight. In addition, albumin, ferritin, and hemoglobin levels improved significantly during the course of this study. However, it is not possible to determine the extent to which clinical improvement was due to the impact of HAART regimens because of other possible intervening factors, such as the improved, continuous care and nutrition patients received in this skilled nursing facility. Nevertheless, the observations of this limited study suggest a strong contributory role of HAART regimens.

The finding that roughly 10% of patients experienced a new-onset AIDS-related diagnosis or opportunistic infection is inconclusive relative to the impact of HAART on the frequency of these events because of the small study size and the brief observation period of 3 months after initiation of HAART, during which a marked impact would be unlikely. Likewise, that 11.4% developed gram-positive *Staphylococcus* and *Enterococcus* infections is only observational and reflective of infection control practices and nosocomial infections common to immunocompromised inpatients.

Indeed, although the 3-month study completion rate of 60%, and overall survival rate of 84%, might be considered encouraging, particularly given the advanced stage of disease at which patients were admitted, the fact that nearly one-fourth of subjects were unable to tolerate the HAART regimens is of concern. This concern is heightened by the fact that failed adherence was not a significant factor. Thus, while side effects were not systematically assessed, this finding certainly raises concerns regarding the projected applicability of HAART regimens among some patients with advanced HIV disease. The mortality rate of nearly 16% over 3 months is likewise of concern and no doubt reflects the finding that 91% of patients were in CDC Category C3, with advanced disease at the time of study entry. While no prognostic indicator for mortality has been identified, there would appear to be subpopulations of patients with advanced AIDS who would benefit more from focused palliative care rather than burdensome HAART regimens. Identification of such indicators warrants further study.

Interestingly, despite the overall improvement in medical variables, there was relatively little corresponding improvement in measures of psychological well-being or general symptom distress. The only psychosocial variable that changed significantly during the treatment period was ratings of depression. Moreover, it is certainly plausible that decreased levels of depression were in part incidental, given the nature of this disadvantaged patient population, for whom treatment in a 24-hour facility likely represented a considerable improvement over their home environment.

The failure to demonstrate similar improvement in quality of life ratings is at first view surprising. Others have reported a significant contribution of HAART on maintenance of functioning and well-being. Our findings, however, may reflect the limitations in the quality of life measure that we utilized. The EFAT, which was designed for patients in a palliative care facility, is based primarily on functional aspects of the patient’s life and may, therefore, be somewhat impervious to changes in the absence of dramatic improvements in health or physical well-being. A review of existing studies utilizing various quality-of-life instruments shows that scores do not always correlate with disease stage or health indices, and that symptoms have a significant impact on quality of life. Also, patients in this study may have experienced early positive perceptions of TCCHCC compared to previous home and hospital environments shortly after admission and prior to baseline testing. These reasons, along with the short study period, may help to explain our findings. Certainly, future research should incorporate more sensitive measures of quality of life better suited to palliative care populations with advanced HIV disease.

Another confound which we were unable to adequately control was potential for outside or situational influences which might offset the apparent benefits of improved physical well-being. For example, the fact that surviving pa-
patients were still inpatients after 3 months of medical treatment may exert a negative influence on mood and quality of life, which counterbalances (or even outweighs) any gains perceived by patients who experienced medical improvements. Unfortunately, little longitudinal research has addressed this issue. Future research on the factors that influence quality of life in advanced disease or palliative care patients might be useful in better understanding the role that physical well-being and medical symptoms exert.

The finding that 62% of subjects able to respond to questioning reported pain is consistent with previous reports that identify a range from 25–80%. Much has been previously reported regarding the etiologies and management of pain in AIDS patients. While some antiretroviral agents are known to cause neuropathic pain, i.e., didanosine, zalcitabine, and stavudine, one report indicates that patients not receiving antiretroviral agents (zidovudine, didanosine) reported pain more frequently than patients receiving therapy. Such studies were performed during the pre-HAART era, however. Our finding that while pain intensity and pain interference neither improved nor worsened over time suggests that protease inhibitors may not contribute directly to pain production.

While it was not the intent of the study to identify patient characteristics that would predict HAART success or failure, post-hoc analyses revealed that those patients who died during the three month study period had substantially lower mean CD4 lymphocyte count (28.3 per cc³) and lower mean serum albumin (3.04 g/dl) than the overall study sample. Interestingly, however, the mean HIV-1 RNA viral load of the “mortality group” was actually lower at 45,840 copies per cc³ than that of the overall group. Of note, none of the mortalities was associated with non-adherence or intolerance to HAART therapy, as each patient remained on an active treatment regimen until near end-of-life, with an average survival of 58.9 days.

Despite these encouraging findings, a number of limitations must be acknowledged with regard to these data. Most importantly, our uncontrolled trial prevents any systematic comparison to untreated patients or those receiving alternative treatments. We initially planned to compare subjects started on HAART regimen after admission to TCCHCC versus those who had been started on this regimen during the antecedent hospitalization. However, there was no significant difference between these groups, likely because of the short treatment duration of the latter group prior to admission.

It is also impossible to disentangle treatment effects with expectancy effects (i.e., placebo effects) or the multitude of other potential benefits which might occur when a severely ill patient is transferred to an intensive treatment facility (e.g., improved nutrition and care, increased attention to existing and potential HIV-related conditions, changes in other medications, and more aggressive pain and symptom management). All of these factors might logically influence the overall health and mortality of our sample. However, many of our findings are somewhat counterintuitive, given this possible alternative explanation. Placebo effects or indirect benefits from improved medical care and nutrition would logically be expected to be most apparent in non-physiological measures (e.g., symptom distress ratings, quality of life, etc.), yet these measures were unimproved in our sample. On the other hand, physiological measures such as CD4 cell count and HIV viral load levels would likely be least influenced by non-physiologic influences, yet these variables showed the greatest improvement after treatment. Thus, while non-pharmacological influences can certainly not be ruled out, the pattern of findings supports our belief that HAART therapy resulted in statistically significant improvements in relevant measures of illness severity and physical well-being.

Another concern in these data which is difficult to fully address is an estimation of the magnitude of the effects obtained considering the brief 3-month study period. Nevertheless, consistent with current data, the subjects experienced statistically significant improvements in CD4 lymphocyte counts and HIV-1 RNA viral loads during the study period. Based on current knowledge, the significant improvement in nutritional measures (i.e., weight and serum albumin), and hematologic and inflammatory measures (i.e., Hgb and ferritin), during the same study period of 3 months correlate with the reversed directions of the HIV markers, especially HIV-1 RNA viral load. While it is tempting to anticipate a progressive in-
crease in clinical improvement and correction of laboratory measures over a longer time frame, presently long-term effect magnitude is unknown.

Finally, given the relatively small sample size, it was not possible to adequately analyze which, if any, variables might have predicted patient response to HAART therapy and which particular medication combinations are most effective in this population. Likewise, while we examined predictors of mortality in a simplistic manner, a thorough analysis of this outcome was precluded by our sample size. Future research, using a substantially larger sample size, along with more systematic comparisons of drug regimens, can be beneficial in addressing these questions.

Despite these limitations, our data suggest that HAART regimens can be beneficial in patients with advanced HIV illness. Most patients studied appeared to benefit from HAART regimens, as reflected by repletion of CD4 lymphocytes and decreased HIV viral load, improved nutritional status, and decreased levels of depression. However, we also observed that fully 40% of our sample could be classified as having “failed” HAART treatment due to poor drug tolerance or mortality despite treatment. Given the small sample, and lack of comparison group, it is unclear whether this failure rate is significantly greater than is typical of patients who do not receive HAART (although mortality would of course be lower in patients with less advanced disease). Although far from offering conclusive evidence, our findings suggest that very low CD4 lymphocyte counts and poor nutritional status, both of which are suggestive of more advanced disease (even among our sample of patients with advanced illness) might be factors that predict HAART therapy failure. Finally, the limited improvement observed in measures of psychological well-being highlights the importance of further research in palliative care populations in order to better understand not only the physical, but the psychological needs of this often overlooked population.

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