EVALUATING SUPERVISED HAART IN LATE-STAGE HIV AMONG DRUG USERS: A PRELIMINARY REPORT*

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ABSTRACT

Objective. To examine response to highly active antiretroviral therapy (HAART) among a sample of treatment-experienced patients in the late stage of human immunodeficiency virus (HIV) infection in residential health care facilities (RHCs) in New York City facilities designated for HIV/AIDS (acquired immunodeficiency syndrome) when access and adherence are maximized.

Methods. Medical record review of 111 patients.

Results. Demographics were mean age 42 years; 58% male; 60% African-American; 31% Hispanic; 57% injection drug users (IDUs); 23% with history of dementia; 52% hepatitis C virus (HCV) antibody seropositive; 80% on HAART, of whom 18% had lipodystrophy. Of 88 patients on HAART, 52% had a decreased viral load ($>1/2$ log) versus 13% of 23 not on HAART ($P < .05$); a $>1/2$ log viral load increase was seen in 8% and 35%, respectively ($P < .05$). Those with viral load increase were more likely than those with stable/decreased viral load to be IDUs (71% vs. 64%) and to have HCV seropositivity (86% vs. 53%), even with similar initial CD4⁺ cell count, viral load, and follow-up time.

Conclusion. In a predominantly minority IDU population who are treatment experienced, 50% of the patients successfully responded to treatment with supervised therapy. The RHCs in New York City provide a unique opportunity to examine further factors associ-

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ated with response to HAART in an environment in which medication administration and adherence are maximized and monitored carefully.

KEY WORDS Advanced HIV, HAART, Hepatitis C Seropositivity, IDUs, Residential Health Care Facilities, Substance Abuse, Viral Load.

INTRODUCTION

Standard therapeutic practice for human immunodeficiency virus (HIV) infection has evolved from monotherapy to a combination regimen that includes two nucleoside analogues and a protease inhibitor or non-nucleoside reverse transcriptase inhibitor, referred to as highly active antiretroviral therapy (HAART).¹ This advance has lengthened survival significantly.^{1,2} The goal of this potent therapy is substantial and lasting suppression of HIV viral replication; the full benefit of these complex regimens depends on strict adherence.³

Access and adherence to HAART for certain disenfranchised persons, such as injection drug users (IDUs), the homeless, and mentally compromised patients, for whom coordinated medical services are often difficult to achieve, is of considerable public health concern. Physicians may be less likely to prescribe combination antiretroviral therapy to these patients because of concerns about nonadherence and subsequent viral resurgence or the development of viral resistance.⁴

When issues of access and adherence are optimized, subsequent questions relate to the extent to which these therapies are tolerated and effective on a long-term basis. There is limited data on the response to HAART in a clinic setting in which medication access and adherence are maximized. In New York City, there is a constellation of residential health care facilities (RHCFs) with approximately 1,200 beds designated for HIV/AIDS acquired immunodeficiency syndrome. Originally established as hospice and terminal care centers, the advent of combination antiretroviral therapy has transformed these facilities to vital centers for supervised therapy for late-stage HIV-infected patients, the majority of whom are former or current drug users, and many have been homeless or in prison. The purpose of this preliminary report is to describe patients' demographic and clinical characteristics and to provide estimates of HAART response among late-stage HIV-infected IDUs and other marginalized patients when medication access and adherence have been maximized.

METHODS

STUDY SETTING AND PATIENT POPULATION

The AIDS residential health care facilities in New York City are not-for-profit, free-standing nursing facilities with revenue received primarily from public-

based insurance/entitlements. These nursing facilities include traditional skilled nursing facilities and health-related facilities and provide a wide range of medical care, including AIDS specialist medical services, on-site methadone maintenance and other substance abuse treatment, subacute care, palliative care, skilled nursing care, speech, occupational and physical therapy, and HIV-prevention services. Under the authority of the state legislature, the AIDS Institute of the New York State Department of Health has established clinical care guidelines and monitors HIV/AIDS care in these facilities.

To be eligible for admission to these facilities, a patient must meet the 1993 Centers for Disease Control definition for AIDS⁵ and one of the eligibility categories on the patient review instrument. This is completed by the referring agency and relates to level of dependency and reimbursement. The overall demographics for the entire population based on 1997 aggregate data compiled by the New York State AIDS Institute are as follows: 55% African-American, 30% Hispanic; 58% male; median age 42 years. For patients in the facilities at any time during the fourth quarter of 1997, the average number of days in the facility (calculated from admission date to discharge date or end of 1997) was 15 months (mean 463 days, interquartile range 126 days–653 days). Drug use is the principal mode of HIV transmission for more than half of the patient population, and in some facilities is the leading HIV risk behavior for as much as 90% of the patient population. The average daily census is consistently above 85%.

To obtain more detailed data, in the fall of 1998 a standardized data abstraction form was designed to estimate clinical, immunologic, and virologic parameters in a sample of patients in the residential health care facilities. The study population represents a convenience sample from 6 of the 12 residential facilities in New York City and was drawn from residents who were in the facility for at least 3 months.

Demographic and medical history data abstracted from a standardized form completed for all patients at the time of admission to the facility included gender, date of birth, education, racial/ethnic background, prior housing and ZIP code, income/public assistance, employment, incarceration history, source of referral to facility, and form of health insurance. Clinical data included medical history, illicit drug use/methadone maintenance history and current use, current antiretroviral medications, current HIV clinical manifestations, and evidence of physical lipodystrophy as recorded in the chart. Laboratory tests results of interest included CD4⁺ cell count, HIV viral load, complete blood count with differential, and clinical chemistry.

To maximize standardization, all laboratories performing blood tests for resi-

dential health care facilities use state-approved procedures and are required to participate in ongoing quality control programs. For measurement of T-cell subsets, heparinized whole blood is stained with monoclonal antibodies using a modified whole blood method,^{6,7} and percentages of CD3⁺, CD4⁺, and CD8⁺ cells are determined by flow cytometry at licensed local laboratories.⁸ Plasma HIV-RNA viral load quantification is performed routinely for each facility by the Amplicor HIV-1 Monitor reverse transcription polymerase chain reaction (RT-PCR) assay (Roche Diagnostics Systems, Indianapolis, IN), sensitive to 400 copies/ml.⁹ For HIV viral load and CD4⁺ cell counts, admission and most recent results were abstracted. For hepatitis B surface antigen, hepatitis C virus (HCV) seropositivity, and purified protein derivative (PPD) skin test admission results were recorded; for all other laboratory tests of interest, the most recent value was abstracted.

STATISTICAL ANALYSIS

Frequency distributions were generated for the demographic, virologic, immunologic, and treatment variables. For the viral load results, data were log transformed (base 10), and results were dichotomized initially as $>1/2$ log decrease between admission and subsequent measurement as the cutoff for treatment success and in a separate analysis were dichotomized as $>1/2$ log increase as the cutoff for treatment nonresponse (to reflect that nearly all patients were initiated on combination therapy prior to admission). Using dichotomized outcomes of change in viral load measurements from two time points, cross tabulations with other variables were examined using chi-square or Fisher exact test for categorical data and *t* tests for continuous data.

RESULTS

Of 169 patients surveyed who had baseline CD4⁺ cell counts and RT-PCR HIV viral load results available in their charts for at least two time points, 34% (*n* = 58) did not have detectable viral load on admission for a final sample size of 111 for this analysis. The demographic characteristics of the 111 patients in this sample were similar to those of the overall RHCF patient population. Table I presents the descriptive demographic data of the sample. An overwhelming majority of the population were African-American or Hispanic (91%), with a mean age at admission of 42 years, 58% were males, and almost all (94%) were on Medicaid. Most of the patients were admitted from an acute care setting (48%), private home or apartment (21%), or correctional facility (14%); 39% were homeless prior to admission. The major HIV risk factor was drug use (57%), followed by heterosexual contact (26%); only 8% reported male same-sex contact.

TABLE I Demographic Variables for Patients

	N (%)
Gender	
Male	64 (57.7)
Female	47 (42.3)
Race	
African-American	67 (60.4)
Hispanic	34 (30.6)
White	10 (9.0)
Education level	
Less than 8th grade	23 (20.7)
Grades 9th–12	66 (59.5)
Trade school/college	13 (11.7)
Not available	9 (8.1)
Medicaid	
Yes	104 (93.7)
No	6 (5.4)
Not available	1 (0.9)
Admitted from	
Private domicile	23 (20.7)
Assisted living/long-term care	12 (10.8)
Acute care hospital	53 (47.7)
Drug rehabilitation	2 (1.8)
Correctional facility	16 (14.4)
Psychiatric hospital	2 (1.8)
Other	3 (2.7)
HIV risk factor	
Injection drug use	63 (56.8)
Heterosexual contact	29 (26.1)
Male: same sex contact	9 (8.1)
Blood transfusion	3 (2.7)
Not available	7 (6.3)

Mean age at admission 42 years.

For this preliminary report, we did not review medical records for daily adherence.

Table II presents selected clinical variables. Admission median CD4⁺ cell count was 100 cells/mm³, and median log₁₀ viral load was 4.78. More than half (58%) of these patients reported a history of injection drug use. Of those who reported drug use, heroin use was the most common (77%), followed by cocaine use (68%). Of those who reported drug use, 40% were on methadone, and 15% reported current illicit drug use (prior 6 months) (see Table II).

The active AIDS-defining illnesses for which the patients were receiving treat-

TABLE II Selected Clinical Characteristics of the Patients
(Total N = 111)

Admission CD4 ⁺ cell count (median, IQR*)	100 (23, 189)/mm ³
Admission log ₁₀ HIV viral load (median, IQR)	4.78 (3.74, 5.33)
	(%)
Illicit drug use	
History of injection heroin use	54
History of injection cocaine use	58
History of crack use	51
Current drug use (prior 6 months)	
Injection of heroin	21
Injection of cocaine	24
Crack	27
Current use of psychotropic medications	
Neuroleptics	20
Mood stabilizers	8
Antidepressants	33
Selected active AIDS-defining illnesses	
Pulmonary tuberculosis	6
<i>Mycobacterium avium</i> complex	10
<i>Pneumocystis carinii</i> pneumonia	16
Cryptococcal meningitis	3
Cytomegalovirus retinitis	1
Kaposi's sarcoma	4
Esophageal candidiasis	10
Wasting	14
Selected comorbidities	
Mucosal candidiasis	31
Herpes simplex	13
Human papillomavirus	10
Anemia	34
History of dementia	23
PPD positive	25
Hepatitis B surface antigen positive	22
Hepatitis C seropositive	52

*IQR = interquartile range.

ment at the time of the study included pulmonary tuberculosis, *Mycobacterium avium* complex, *Pneumocystis carinii* pneumonia (PCP), cryptococcal meningitis, cytomegalovirus retinitis, Kaposi's sarcoma, esophageal candidiasis, cervical carcinoma, and HIV wasting. PCP was the most common AIDS-defining illness of those specified (16%), and 20% of the patients had two or more of the specified AIDS-defining conditions (Table II). Other comorbidities included anemia, herpes simplex, mucosal candidiasis, human papillomavirus, HCV seropositivity, hepa-

titis B surface antigenemia, and HIV-associated dementia. A notable percentage of the patients were coinfectd with HCV (52%) or hepatitis B (22%); a substantial proportion of the IDUs (81%) were HCV seropositive. A substantial proportion had evidence of mental illness; 23% had a history of dementia at the time of admission, and 46% were on a psychotropic medication.

Table III shows the percentage of patients on specific antiretroviral medications; 80% of the patients were on HAART. The most commonly prescribed protease inhibitor was nelfinavir (44%), and of those patients on at least one protease inhibitor, 22% were on two protease inhibitors. The majority of patients who were on ritonavir (80%) were also on another protease inhibitor. Of the 88 patients on HAART, 18% had physical evidence of lipodystrophy recorded in the medical chart based on clinical evidence of any of the following: HAART humps (excess cervical fat pads or "buffalo humps"), increased abdominal girth, thin face and limbs, narrowing of thighs, or breast enlargement in women. Univariate analysis revealed no significant association for the presence of lipodystrophy and gender, race/ethnicity, HIV risk group, methadone maintenance, current CD4⁺ cell count, current HIV viral load, current triglyceride level, current cholesterol level, and weight/height² (data not shown).

Initial analyses dichotomized patients based on whether they experienced more than ½ log decline in RT-PCR measurements from admission to current

TABLE III Current Antiretroviral Medication Use (Total N = 111)

	(%)
Reverse transcriptase inhibitors: nucleoside analogs	
Didanosine	27
Lamivudine	48
Stavudine	57
Zalcitabine	0
Zidovudine	12
Lamivudine + zidovudine	5
Reverse transcriptase inhibitors: non-nucleoside analogs	
Delvaridine	3
Nevirapine	8
Protease Inhibitors	
Indinavir	23
Nelfinavir	44
Ritonavir	14
Sequinavir	16
Other	
Expanded access protocols	10

levels cross tabulated by use of HAART; in the sample, the median time interval between admission and current viral load was 6 months. As Table IV shows, 52% of those on HAART versus 13% of those not on HAART demonstrated a greater than $\frac{1}{2}$ log decline in HIV viral load even though initial viral load, CD4⁺ cell count, and duration of follow-up were similar. Because many patients in these facilities are transfers from acute care facilities or outpatient clinics in which therapy had already been initiated, we conducted another analysis that considered a stable viral load over 6 months as possibly representing treatment responsiveness; in this analysis, we dichotomized the outcome as greater than $\frac{1}{2}$ log viral load increase (to represent possible treatment unresponsiveness) versus no increase/decrease (to represent responsiveness). Overall, increase in viral load in patients on HAART (8%) was significantly less common than for patients not on HAART (35%, $P < .05$), even though initial viral load, CD4⁺ cell count, and duration of follow-up were similar statistically by use of HAART. Viral load decreased a median of 0.89 log₁₀ copies/ml and CD4⁺ cell count increased a median of 44 cells/mm³ for patients on HAART compared to no change in viral load and a median decrease in CD4⁺ cell count of 16 cells/mm³ for the patients not on HAART. Among the patients on HAART, 33 (29%) reached undetectable levels of viral load compared to 2 (9%) of those not on HAART.

For more detailed analysis of HAART therapy responsiveness based on increase versus no increase (to represent unresponsive versus responsive) in viral load among the 88 patients on HAART, we examined potential factors associated with viral load increase among these patients (Table IV). Those with viral load increase were more likely than those with stable or decreased viral load to have a history of injection drug use (71% versus 64%), to be current (prior 6 months) IDUs (43% versus 36%), to be HCV seropositive (86% versus 53%, $P = .10$), and to have a positive PPD skin test (43% versus 30%), even though the initial CD4⁺ cell count, viral load levels, and duration of follow-up were similar.

TABLE IV Univariate Analysis: Viral Load Change from Admission to Survey Date by Highly Active Antiretroviral Therapy (HAART)*

Therapy	Viral Load Decrease > $\frac{1}{2}$ Log, n (%)	Viral Load Decrease < $\frac{1}{2}$ Log, No Change, or Increase, n (%)
HAART	46/88 (52.3)	42/88 (47.7)
No HAART	3/23 (13.0)	20/23 (87.0)

* $p < .05$.

TABLE V Univariate Analysis: Factors Associated with a $>1/2$ Log Viral Load Increase from Admission to Survey Date for the Patients on HAART (N = 88)

Variable*	Viral Load Increase (n = 7)	No Viral Load Increase (n = 81)
Male	(71%)	(59%)
History injection drug use	(71%)	(64%)
Injection drug use prior 6 months	(43%)	(36%)
Methadone maintenance	(0%)	(1%)
PPD positivity	(43%)	(30%)
Hepatitis C positivity	(86%)	(53%)
Lipodystrophy	(14%)	(19%)
Initial CD4 ⁺ cells/mm ³ : median/(IQR)†	150 (36,250)	96 (22,202)
Initial log ₁₀ viral load: median/(IQR)	4.36 (2.79,4.38)	4.41 (3.35, 5.33)

*All *p* values were not significant; *p* value for hepatitis C seropositivity was 0.099.

†IQR = interquartile range.

No further analysis was performed, given the small number of nonresponders in our sample.

DISCUSSION

In the present study, 52% of the patients receiving HAART experienced a greater than $1/2$ log decrease in HIV viral load over an average period of 6 months. This is considerably less than results from the original clinical trials with non-nucleoside reverse transcriptase inhibitors and protease inhibitors,^{3,10-13} but is consistent with more recent longer term follow-up studies in clinical settings.^{12,14-16} Given that the patient population of the RHCs is comprised of patients with late-stage HIV, they are likely to have been treated previously. Therefore, some benefit is likely to have been afforded, and stabilization of viral load (or maintenance of viral suppression) is a possible expected observation. Unfortunately, we did not have pharmacy records from the acute care setting prior to admission to our facilities and cannot describe this further. As these patients were treatment-experienced on admission, we considered response or nonresponse to therapy on the basis of increasing viral load inasmuch as therapy might be expected to produce a decrease, then stabilization, of viral load, but not an increase. Observing an increase in viral load in a proportion of patients (8%) receiving HAART, we further examined factors that might be associated with an increase in viral load.

Although adherence to therapy explains much of the magnitude and durability

of therapeutic response,^{3,5,14-18} other factors in addition to adherence may have an impact on HAART. We might expect that those failing therapy (i.e., having a viral load increase) might be IDUs who are less adherent despite nursing supervision, or the failures possibly might be due to some interaction with the drugs of abuse. However, drug abuse itself was not associated significantly with viral load response. Among IDUs, the potential interaction of methadone and antiretroviral therapy, as well as the influence of hepatitis and chronic liver disease, is of additional concern.

In the present study, we also considered the effects of opiate substitution treatment on viral load response. Data addressing the ongoing concern about the potential pharmacokinetic interactions of methadone and antiretroviral medications have focused on zidovudine and indicate that methadone impairs metabolism of zidovudine and results in increased bioavailability and decreased clearance.¹⁹⁻²¹ The resulting 21-45% decrease of zidovudine clearance may predispose patients to increased drug toxicity and decreased compliance with medication regimens.^{22,23} However, specific pharmacokinetic data on methadone and protease inhibitors are lacking. The available efficacy studies suggest no short-term effect of methadone/opiate substitution on HAART efficacy.^{22,24,25} Similar to these reports, in the present study, we found no effect of methadone/opiate substitution on changes in viral load; none of the patients who received methadone versus 1% of the patients who did not receive methadone experienced a viral load increase.

Finally, we noted that HCV seropositivity at the time of admission tended toward a significant association with viral load increase; 86% of patients with viral load increase were HCV seropositive compared to 53% without viral load increase. Although the sample size is small, these data suggest that HCV may exert some effect on response to antiretroviral therapy in illicit drug users and support previous findings that hepatic toxicity and subsequent intolerance to HAART are greater in patients coinfecting with HCV compared to patients negative for HCV.²⁶ These findings are relevant particularly for clinical management of HIV when therapy includes drugs that are metabolized by the liver, as are many of the antiretroviral medications, including protease inhibitors.^{23,27-29} Hepatic toxicity can develop with a number of antiretrovirals and occurs with greater frequency in patients with chronic hepatitis B³⁰ and C,^{31,32} especially with combination regimens containing indinavir^{33,34} or ritonavir.³⁵ Although we did not measure the proportion of the sample patients with hepatic toxicity, HCV seropositivity is often a marker for chronic hepatitis.³⁶ Among IDUs, HCV is the most common cause of chronic viral hepatitis³⁶ and may have an impact on the

therapeutic benefits of HAART through the emergence of chronic liver disease. The stronger association of viral load increase with HCV seropositivity suggests that the sequelae of hepatitis may have importance for clinical management of patients on HAART. As we did not monitor liver function tests, it is also possible that hepatitis seropositivity may be a marker for other influential events.

These preliminary data suggest that, when access and adherence to HAART are maximized in IDUs, treatment response is similar to other clinic populations. Despite the optimal treatment environment, 8% of the patients on HAART experienced treatment nonresponse (a greater than $\frac{1}{2}$ log increase in viral load), and another 31% experienced no change in viral load or less than a $\frac{1}{2}$ log decrease. These data support the view that other factors in addition to adherence are likely to have an impact on HAART response. The RHCs in New York City provide a unique opportunity to examine further factors associated with HAART response when medication access and adherence are maximized, particularly in populations with other contributory factors, such as chronic liver disease, treatment for drug abuse, and prior exposure to mono- or combination nucleoside analogues.

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