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ORIGINAL ARTICLE

Clinical manifestations of treatment-naive patients with acquired immunodeficiency syndrome and responses to highly active antiretroviral therapy in the Taipei Veterans General Hospital: A 5-year prospective study

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KEYWORDS
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Background: Taipei Veterans General Hospital, one of the medical centers in Taiwan, has provided highly active antiretroviral therapy (HAART) to human immunodeficiency virus/AIDS patients for more than 10 years. Five years ago, we began a prospective follow-up of our patients' clinical manifestations and responses to HAART by collecting their clinical data. In this study, we analyzed the morbidity, mortality, and responses to HAART of treatment-naive AIDS patients. The purpose was to provide local data that may be valuable in Taiwan.
Methods: Study cases were enrolled from January 1, 2004, to February 28, 2009, with inclusion criteria of newly diagnosed AIDS during hospitalization and being naive to HAART. Antiretroviral therapy was initiated. To evaluate the clinical responses to HAART, we excluded patients who were pregnant, died within 1 month after confirmation of an AIDS diagnosis, failed to initiate HAART, or were lost to follow-up for more than 6 months. Plasma viral loads and $CD4^+$ counts were quantified by reverse-transcriptase polymerase chain reaction and flow cytometry, respectively. Statistical analysis was performed using SPSS statistical software.
Results: A total of 49 patients were enrolled and 45 patients fulfilled the inclusion criteria for evaluating the efficacy of HAART. At 3 months, 12 months, and 30 months after the initiation of HAART, 64.4% (29 of 45), 88.2% (30 of 34), and 93.8% (15 of 16) had undetectable plasma viral loads, respectively, and 37.8% (17 of 45), 73.5% (25 of 34), and 81.2% (13 of

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16) had $CD4^+$ counts of more than 200 cells/μL, respectively. Median $CD4^+$ counts increased from baseline at Month 3 by 171 cells/μL and at Month 30 by 375 cells/μL. The overall mortality was 22.4% (11 of 49).
Conclusion: The virologic and immunologic responses after initiating HAART in this study demonstrated our achievements in providing care and treatment for AIDS patients during this 5-year period, which provides a strong evidence of the efficacy of HAART.

Introduction

Since 1996, the widespread use of highly active antiretroviral therapy (HAART)—a combination of at least three drugs that typically includes either a protease inhibitor (PI) or a non-nucleoside-analog reverse-transcriptase inhibitor and two nucleoside-analog reverse-transcriptase inhibitors (NRTIs)—has substantially improved the prognosis of human immunodeficiency virus (HIV)-infected patients.[1–3] There are several predictors of mortality for patients on antiretroviral therapy: viral load, $CD4^+$ count, total lymphocytes, body mass index, and adherence. Randomized clinical trials have provided strong evidence that HAART is beneficial for patients with $CD4^+$ count less than 200 cells/μL[4,5] and is also recommended for those with $CD4^+$ counts of 200—350 cells/μL.[6] However, the optimum time to start antiretroviral therapy among symptom-free patients with $CD4^+$ counts above this threshold and low or intermediate viral loads is a matter of debate.[7,8]

According to the report of the Department of Health, ROC (Taiwan), in April 2010, the seroprevalence rate of HIV infection in Taiwan was 69.8 cases per 100,000 population, with a total of 16,146 cases, which has been increasing in recent years. The proportion of males to females was nearly 11:1, and most patients were 15—39 years old, a period of known sexual activity. The proportions of newly reported HIV cases by mode of transmission in 2008 were as follows: homosexuals and bisexuals, 42%; heterosexuals, 22.6%; and intravenous drug users, 33.7%;[9] a clinical spectrum similar to those in developed countries.[10–12] All HIV-infected patients were provided with free access to inpatient or outpatient care, and antiretroviral therapy was available at 42 designated hospitals around Taiwan.

The Taipei Veterans General Hospital (VGHTPE), one of the medical centers in Taiwan, has provided care for HIV-infected patients for two decades since the first native HIV-infected patient was diagnosed at the VGHTPE in 1986. However, until now, we have not presented our achievements in mortality reduction and improving the quality of life of HIV-infected patients. In this prospective study, we have characterized the clinical spectrum, morbidity, mortality, and responses to HAART of AIDS patients in the VGHTPE during the recent 5-year period.

Materials and methods

The study cases were enrolled from January 1, 2004, to February 28, 2009. The inclusion criteria were patients newly diagnosed with AIDS during hospitalization and patients naive to HAART. Antiretroviral therapy was prescribed during hospitalization or soon after discharge on an outpatient basis. For follow-up to evaluate their clinical spectrum, morbidity, mortality, and responses to HAART, a standardized data collection form was used to record the results of all histopathological and laboratory examinations, complications associated with HIV infection, numbers and durations of hospitalizations, regimens of prophylaxis, and the antiretroviral therapy that was administered.

To evaluate the clinical responses to HAART of treatment-naive patients, cases who were pregnant, died within 1 month after confirmation of AIDS diagnosis, failed to initiate HAART, or were lost to follow-up for more than 6 months, were excluded. The HAART regimen administered and a switch of the regimen in the presence of adverse effects were according to the recommendations of the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, developed by the panel of the Department of Health and Human Services, USA,[6] and the Guidelines for AIDS surveillance and treatment published by the Center for Disease Control in Taiwan. Plasma viral loads (PVLs) and $CD4^+$ counts were checked before HAART and at 1 month and 3 months after initiating ART. If the virologic, immunologic, and clinical responses were satisfactory, PVLs and $CD4^+$ counts were followed up every 6 months thereafter. Outcome measures were the proportions of patients with undetectable PVLs (<50 copies/mL) and changes of $CD4^+$ counts, calculated according to the data checked at Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60, after initiating HAART.

PVLs were quantified using reverse-transcription polymerase chain reaction with a Roche COBAS TaqMan 48 real-time PCR analyzer (F. Hoffman-La Roche, Basel, Switzerland). $CD4^+$ counts were evaluated by flow cytometry (FACS Calibur; Becton-Dickinson Diagnostic Instrument System, Sparks, MD, USA). Hemograms and blood biochemistries were also determined with the same blood sampling scheduled for quantifying PVL and the $CD4^+$ count.

Categorical variables were compared using a Pearson Chi-square test in terms of the virologic efficacy of HAART between patients with baseline PVL of higher and lower than 5 $\log_{10}$ copies/mL and baseline $CD4^+$ counts of higher and lower than 50 cells/μL. Cox proportional-hazards regression was used to estimate the influence of the baseline PVL and $CD4^+$ count on the immunologic response of the $CD4^+$ count after initiating HAART. We used Kaplan—Meier survival analysis to estimate any correlation between patients' mortality with baseline PVL and $CD4^+$ counts. Statistical analysis used SPSS statistical software (Version 17.0; SPSS Inc. Chicago, IL, USA). A p value less than 0.05 was considered to be statistically significant.

Results

From January 1, 2004, to February 28, 2009, 49 antiretroviral-naive patients were enrolled into this study. Three patients (3 of 49) expired within 1 month after AIDS diagnosis without receiving ART and one patient (1 of 49) was lost to follow-up for more than 6 months. Only 45 (45 of 49) patients were eligible for evaluating the efficacy of HAART. The baseline characteristics of these 49 newly diagnosed AIDS patients are shown in Table 1.

Except for the lost baseline PVL data of one patient and the baseline CD4$^+$ count of one other patient, the average baseline CD4$^+$ count was 59.1 cells/μL (range: 1.5—185 cells/μL), and the average baseline PVL was 5.28 $\log_{10}$ copies/mL (1.29 to >7 $\log_{10}$ copies/mL). Among these patients, 25 (25 of 49; 51%) had CD4$^+$ counts of ≤50 cells/μL; 38 (38 of 49; 77.6%) had PVLs > 5 $\log_{10}$ copies/mL; and 19 (19 of 49; 38.8%) had both of these.

There were four patients (4 of 49) with hepatitis B infections, one (1 of 49) with hepatitis C infection, and one (1 of 49) with both hepatitis B and C infections. Among these patients, 38 (38 of 49) had active AIDS-defining illnesses at enrollment, which included pneumocystis jiroveci pneumonia (PJP) (19), cytomegalovirus infection (6), tuberculosis (4), cryptococcosis (3), non-Hodgkin's lymphoma (2), Kaposi sarcoma (2), nontuberculosis mycobacterium infection (3), and toxoplasmosis (2). Only one patient each was noted for the following opportunistic illnesses: amebiasis, esophageal candidiasis, herpes simplex infection, herpes zoster, lymphoma of the central nervous system, and salmonella septicemia.

Among the 45 patients who were eligible for the HAART efficacy analysis, 32 had initial HAART of two NRTIs plus efavirenz; 11 had two NRTIs plus a PI; and only two patients who were enrolled in 2004 received initial HAART of ritonavir, indinavir, and efavirenz. The initial NRTI regimens included lamivudine plus abacavir for 16 patients, lamivudine plus zidovudine for 20 patients, lamivudine plus stavudine for five patients, lamivudine plus didanosine for one patient, and abacavir plus stavudine for one patient.

The average observation duration for the responses to HAART was 33.1 months (4—60 months). The virologic data and immunologic responses are shown in Fig. 1. At 3 months, 12 months, and 30 months after the initiation of HAART, 64.4% (29 of 45), 88.2% (30 of 34), and 93.8% (15 of 16) had undetectable PVLs, respectively, and 37.8% (17 of 45), 73.5% (25 of 34), and 81.2% (13 of 16), respectively, had CD4$^+$ counts of ≥200 cells/μL. The average CD4$^+$ count increased from baseline at Month 3 by 171 cells/μL and at Month 30 by 375 cells/μL (Fig. 1). The average time was 7.6 months for the CD4$^+$ count to reach the target (≥200 cells/μL) and 6 months for the PVL to decline to the undetectable range.

There were no significant differences for the virologic responses between baseline PVL of more than and less than 5 $\log_{10}$ copies/mL and between CD4$^+$ counts of more than and less than 50 cells/μL ($p = 0.982$ and 0.887, respectively). The immunologic response based on CD4$^+$ counts was significantly different between baseline CD4$^+$ counts of more than and less than 50 cells/μL ($p = 0.004$, relative risk = 3.12, confidence interval = 1.44—6.76) (Table 2). Only one virologic failure was noted after 24 months for a patient treated with stavudine and lamivudine plus lopinavir/ritonavir; the regimen was shifted to lamivudine and atazanavir plus didanosine, and the viral load subsequently declined to the undetectable range. Two patients (2 of 34; 5.9%) had efavirenz-related hepatotoxicities, defined as elevations of the aminotransferase levels to greater than five times the upper normal limit. Allergic skin rashes attributed to drugs were noted in two patients, one because of efavirenz and the other because of combivir. Other side effects included zidovudine-related pancytopenia (1), stavudine-related peripheral neuropathy (1), and indinavir-related renal stones (1).

Table 1 Clinical characteristics of 49 AIDS, antiretroviral-naive Taiwan patients from January 1, 2004, to February 28, 2009

Characteristics on entry into study	Value
Age (yr)	
Median	45.5
Range	23—86
Gender, *n* (%)	
Male	47 (95.9)
Female	2 (4.1)
Routes of transmission, *n* (%)	
Heterosexual	10 (20.4)
MSM	24 (50)
Bisexual	2 (4.1)
IDU	1 (2)
Unknown	12 (24.5)
Baseline CD4$^+$ lymphocyte (cells/μL)	
Median	59.1
Range	1.5—185
Category of baseline CD4$^+$ lymphocyte, *n* (%)	
>200 cells/μL	0 (0)
100—199 cells/μL	12 (24.5)
50—99 cells/μL	11 (22.4)
<50 cells/μL	25 (51)
Lost data	1 (2)
Baseline PVL ($\log_{10}$ copies/mL), *n* (%)	
Median	5.28
Range	1.29 to >7[a]
>5 $\log_{10}$ copies/mL	38 (77.6)
Lost data	1 (2)
Baseline CD4$^+$ ≤50 cells/μL and PVL >5 $\log_{10}$ copies/mL, *n* (%)	19 (38.8)
Patients with AIDS-defining illness, *n* (%)	38 (77.6)
Time of enrollment, *n* (%)	
2004/1/1—2004/12/31	7 (14.3)
2005/1/1—2005/12/31	10 (20.4)
2006/1/1—2006/12/31	15 (30.6)
2007/1/1—2007/12/31	6 (12.2)
2008/1/1—2009/2/28	11 (22.4)

[a] One patient had PVL >7 $\log_{10}$ copies/mL, defined as 7 $\log_{10}$ copies/mL.
IDU = intravenous drug user; MSM = male who had sex with male; PVL = plasma viral load.

There were 11 fatalities in this study, and three of them had expired within 1 month of the first hospitalization before initiating ART. Five patients died from malignancies, including visceral Kaposi's sarcoma (3), brain lymphoma (1), and hepatitis B virus (HBV)-related hepatocellular carcinoma (1). The six other deaths were consequences of opportunistic illnesses, including cryptococcal meningitis (2), recurrent pneumonia (2), disseminated cytomegalovirus infection (1), and PJP infection (1). Comparing the mortality rates among patients with baseline $CD4^+$ counts of higher and lower than 50 cells/μL, it was found that there was no significant correlation between survival and the baseline $CD4^+$ count ($p = 0.105$). However, the correlation was significant between baseline PVL of higher and lower than 5 $\log_{10}$ copies/mL and mortality ($p = 0.015$) (Table 2).

Discussion

HAART, which was introduced in Taiwan for AIDS patients in 1997, has demonstrated well its significant efficacy in reducing plasma viral burdens and in controlling disease progression in other studies conducted in Taiwan.[11,13–16] In this study, we found that our treatment-naive AIDS patients mostly had advanced disease both clinically and immunologically. Most of these patients were homosexual/bisexual male patients, followed by heterosexuals, and intravenous drug users were the minority, which was compatible with the epidemiology of sexually transmitted routes accounting for more than 90% of patients with high-risk behaviors before 2003.[10,12] The explanation for the aforementioned findings is that most of the patients acquired HIV infection before 2003 and developed to the AIDS stage after 2004. Their advanced disease was evidence of their ignorance in seeking medical consultation even with a high probability of acquiring HIV infection because of high-risk behaviors. In this era with evidence for the efficacy of HAART, more efforts should be made for the early diagnoses of these high-risk patients.

The regimens we chose appeared to be well tolerated in view of the advanced disease, which necessitated the concurrent use of multiple therapeutic or prophylactic antimicrobial agents for opportunistic infections in most of these patients, such as PJP and tuberculosis, for which a mere seven patients (7 of 45; 15.6%) reported significant adverse effects. Regarding the responses to HAART, the virologic and immunologic response rates were satisfactory before 36 months, but only a limited number of patients (11) had been followed up for more than 36 months, which resulted in decreased proportions of undetectable PVLs and $CD4^+$ counts of $\geq$200 cells/μL (Fig. 1).

The findings of our study indicated that the virologic outcome was not related to the baseline $CD4^+$ count or the PVL, which was consistent with the observations by Phillips et al.[17] However, the immunologic outcomes were significantly correlated with baseline $CD4^+$ counts in this study, which was comparable to a foreign study.[18] Nevertheless, the statistical analysis showed no differences in documented deaths between patients with baseline $CD4^+$ counts of more than and less than 50 cells/μL after initiating HAART, which was inconsistent with the results in a foreign study.[18] A reasonable explanation is the short-term follow-up and the limited numbers of cases in our study compared with the populations in studies conducted in Western countries. Also, the loss-to-follow-up rate was 2% (1 of 49) for those who had received ART but were not seen in the outpatient department for more than 1 year and had incomplete data for evaluation.

The mortality rate was 22.4% (11 of 49). Among these expired cases, seven patients died after receiving antiretroviral therapy, and four of these (4 of 7; 57.1%) had expired within 6 months after initiating therapy. This was assumed to be reasonable, as higher mortality rates and disease progression were shown to be clustered among

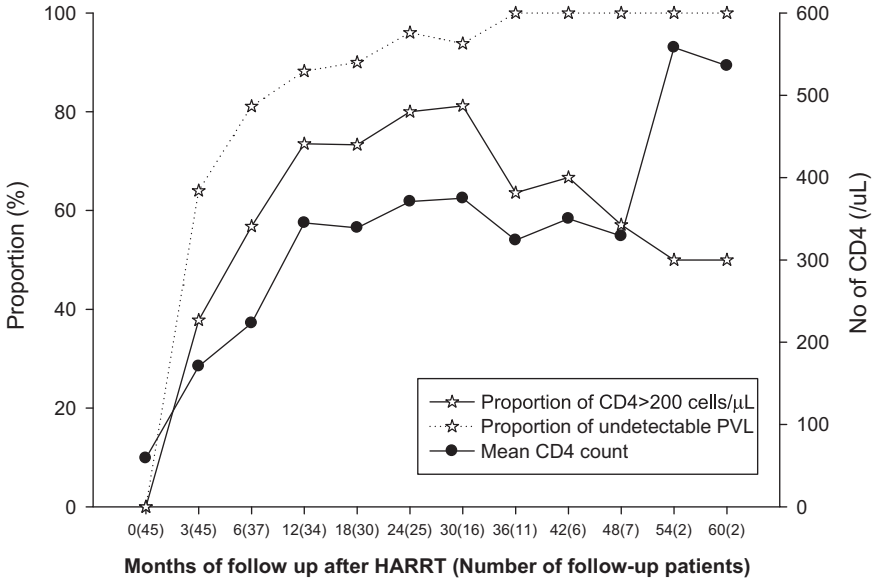

Figure 1. Proportion of patients with $CD4^+$ of $\geq$200 cells/μL and PVL less than 50 copies/mL (undetectable), and the $CD4^+$ count during follow-up after HAART treatment. HAART = highly active antiretroviral therapy; PVL = plasma viral loads.

Table 2 The correlation between baseline PVL/$CD4^+$ count and virologic/immunologic response and mortality

	n (%)[a]	Virologic response	Immunologic response	Mortality
		p	*p*	*p*
Baseline PVL		0.982	0.633	0.015[b]
≥5 $\log_{10}$ copies/mL	19/44 (43.2)			
<5 $\log_{10}$ copies/mL	25/44 (58.6)			
Baseline $CD4^+$ count		0.887	0.004[b]	0.105
≥50 cells/μL	38/44 (86.4)			
<50 cells/μL	6/44 (13.6)			

[a] One patient lost baseline PVL data and the other lost baseline $CD4^+$ count data.
[b] Statistically significant.
n = number.

people with depleted baseline $CD4^+$ counts.[19] In our study, it took an average of 6.8 months for the $CD4^+$ count to increase up to 200 cells/μL, and some of these patients died before immunity was built up by HAART.

The major cause of mortality was AIDS-defining illness (10 of 11; 90.9%), with only one death from HBV-related hepatocellular carcinoma (HCC). According to the surveillance done in Taiwan for 1994–2005,[11] AIDS-defining illness was the leading cause of mortality for HIV-infected patients (59.7%). Another study conducted in Taiwan[20] showed that most AIDS-related conditions associated with death (cryptococcosis and others) had decreased in frequency in recent years after the introduction of HAART, and that some AIDS-related conditions associated with death had remained stable or even increased, such as candidiasis, tuberculosis, and non-Hodgkin's lymphoma.

On the whole, the response rate to HAART of these treatment-naive patients was good, although antiretroviral resistance tests were not done, as has been recommended in the United States and Europe. Only one virologic failure was noted after two NRTI plus a PI were administered for 24 months. After adjusting the HAART regimen, this patient was followed up in our outpatient department with continued undetectable PVL and a $CD4^+$ count greater than 200. A surveillance study in Taiwan[21] found that the reported HAART resistance rate was 9.2%, which was higher than that in 2008 (2.4%). One study[22] suggested that genotypic antiretroviral resistance testing (GART) should be performed before initiating HAART when the resistance rate was higher than 15%. Another study[23] suggested that all AIDS patients should receive GART before HAART in those regions with a prevalence rate higher than 10%, if the economic situation permitted. In Taiwan, GART is not recommended for treatment-naive patients, and our results showed that the existing approach was feasible because of the low resistance rate.

In this prospective study, we have described the clinical spectrum, morbidity, mortality, and responses to HAART of treatment-naive AIDS patients in the VGHTPE for the recent 5-year period. The HAART resistance rate in Taiwan was lower than those in Western countries, and our study patients responded to HAART well, although GART was not performed initially. However, it has been noticed that the resistance rate has been increasing in recent years,[21] and the comprehensive implementation of GART for treatment-naive patients may be performed in the future.

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