CLINICAL OUTCOME OF HIV INFECTED PATIENTS ACCORDING TO IMMUNOLOGIC RESPONSE AFTER HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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Abstract - Current mainstay of treatment for human immunodeficiency virus (HIV)-infected patients is highly active antiretroviral therapy (HAART) but little is known about the long-term clinical outcome for HIV-infected patients who have received HAART. Determining factors associated with long-term survival in the course of treatment may allow modification to be made for patients who are at a greater risk of treatment failure. In this study patients who were under HAART from March 2002 to September 2003 were evaluated. They were visited from 2 to 5 times and clinical and lab findings and CD4 count on every visit were recorded. Rates of progression from the initiation of HAART to treatment failure, defined as constant decline of CD4 numbers, occurrence of AIDS criteria and death, were determined. Forty three patients, 31 male and 12 female, with an average age of 39.6 were selected. The most common finding on initiation of treatment in these patients was wasting syndrome (16.3%). Overall, treatment failure occurred in 37.2%. Mean time to treatment failure was 13.3 months. There was correlation between baseline CD4 and survival of patients with history of monotherapy ($P<0.05$). Initial CD4 as a prognostic factor was valuable only in patients with history of monotherapy, also low initial CD4 correlated to death. Initial CD4 may help clinician to predict patient's response to HAART. A multicentric long-term follow-up of patients treated with HAART is imperative. Drug resistance is the major factor in treatment failure. It is also correlated to lack of drug diversity and virologic lab tools.


Key words: Human immunodeficiency virus, clinical outcome, antiretroviral therapy

INTRODUCTION

Although many drugs are approved for the treatment of human immunodeficiency virus type I (HIV-I) infection, the cause of the acquired immunodeficiency syndrome (AIDS), they belong to just four different classes: nucleoside or nucleotide reverse-transcriptase inhibitors (nucleoside analogues), non-nucleoside reverse-transcriptase inhibitors, protease inhibitors and fusion inhibitors. Because cross-resistance within a class is common, the failure of the initial regimen used may compromise the success of future regimens. Indeed, the results of cohort studies suggest that a patient's first treatment regimen has the greatest chance of success.

Initiated four years ago, highly active antiretroviral therapy (HAART) uses a combination of powerful drugs, including protease inhibitors and reverse transcriptase inhibitors, to overpower HIV infection and give the body the chance to increase its supply of infection-fighting CD4+ T-cells that are destroyed by HIV. HAART regimens have greatly diminished the morbidity and mortality associated with HIV infection but despite the effectiveness of
antiretroviral drugs, HIV positive patients are still very vulnerable to opportunistic infections. There is only limited information on the impact of HAART on AIDS-related opportunistic infections because it is still a relatively new treatment approach.

The optimal time to initiate antiretroviral treatment is unknown. Survival rates observed among patients who start therapy at high or low CD4 cell counts cannot be attributed solely to initiating treatment early or late in disease because of confounding with patients' underlying disease stage, unless matched controls are available for comparison. Current recommendations for initiation of antiretroviral therapy in patients infected with HIV-I are based on CD4 T-lymphocyte cell counts and plasma HIV RNA levels. The relative prognostic value of each marker following initiation of therapy has not been fully characterized. There is increased risk of HIV disease progression if therapy is initiated when CD4 cell counts drop below 200 cells/mm$^3$, suggesting that 200 cells/mm$^3$ may approximate a biological threshold beyond which response to therapy is compromised. It is currently recommended that HAART should be initiated in asymptomatic persons when CD4 < 350, but it is unknown how much lower than 350 could the therapy be initiated and still effectively decrease disease progression. Early identification of patients who do not respond to HAART should help to minimize viral resistance caused by suboptimal regimens and better prevention of disease progression.

This Cohort study was established to determine if CD4 lymphocyte threshold for the initiation of HAART is associated with clinical response to therapy. We present longterm follow-up data from patients with HIV infection who had been taking HAART for longer than two years and identify some early predictors of later disease progression. We designed this cohort study, because of lack of longterm follow-up and survival analysis of treatment of HIV patients in Iran. We also decided to illustrate factors related to treatment failure in our patients and to describe rates of disease progression to death or AIDS among patients starting triple-drug antiretroviral therapy, stratified by baseline CD4 cell count.

**MATERIALS AND METHODS**

This prospective follow up of a cohort of 43 unselected patients with HIV treated with HAART was conducted in Imam Khomeini Hospital. We gathered patients epidemiologic, demographics, and clinical and lab data. Inclusion criteria were 1) initiation of HAART before March 2002 to allow at least 18 month of observation and 2) availability of CD4 T cell counts recorded during the period patients receiving HAART.

Exclusion criteria from the study were 1) patients not receiving or had stopped receiving HAART, 2) lost to follow-up and 3) censored (event free). The excluded patients did not differ significantly from the included patients with regard to age, sex and CD4 T cell count at baseline.

A total of 43 patients were included in the study and were observed for at least 18 months. We analyzed data on 43 adult patients starting HAART with a combination of at least three drugs. Patients had regular follow up visits and had a high level of self-reported adherence. We observed their drug regimen in Imam Khomeini Hospital and also tabulated their referring time to hospital and called anyone who was assumed to be late for his visiting time. The patient was considered lost to follow up if he/she was not accessible. The baseline value was defined as the first visit values at start of study. CD4 T cell counts, which were assessed by means of flow cytometry, were determined on every visit.

We obtained informed consent from all patients. All adolescents enrolled in this study or treatment trials were eligible for enrollment. In first visit we recorded their demographics, route of transmission, time of starting HAART, past drug history (i.e., history of monotherapy with antiretroviral drugs) and all clinical symptoms and past history of other diseases, including TB and hepatitis.

All patients were receiving individualized treatment regimen, and all received HAART continuously for at least 18 month in our center. In Iran, drugs are available only in few governmental centers, and Imam Hospital is the oldest one. Until 2003, drugs were imported but since then lamivudine and zidovudine are produced locally. Most common regimen of HAART in Iran is a
combination of two reverse-transcriptase inhibitors and one protease inhibitor (nelfinavir). We have no drug diversity in Iran, because of governmental policy.

**Clinical end points**

Treatment failure was defined as progress to a combined endpoint of a new AIDS-defining disease or death. For patients who had an opportunistic infection diagnosed before the start of the HAART regimen, clinical failure was defined as relapse of the opportunistic infection or onset of a new AIDS-defining illness. Also, a constant decline in CD4 count was considered treatment failure.

**Statistical analysis**

For time-to-event analysis, we used the Kaplan-Meier method and the Cox proportional hazard model. Survival time was measured from the date of initiation of HAART to the occurrence of an AIDS-defining event or censoring time (i.e., end of study). Comparisons of survival rates across subgroups were performed by use of the log-rank test and the Cox proportional hazards model. Associations among subgroups were examined by use of Kaplan-Meier plots and proportional hazards models. Also proportional-hazards regression models were used to evaluate the association between the risk of death and other variables. All P values are 2-sided. Data were analyzed by use of SPSS software. Potential predictors of longterm clinical outcome included immunologic response (CD4 count of >200 cells/mm³ at month 8 of HAART), baseline CD4 count, CD4 as a continuous variable, stage of disease and pretreatment with antiretroviral agents prior to the commencement of HAART.

**RESULTS**

**Base-Line Characteristics**

We analyzed 43 patients in Imam Khomeini Hospital, Department of Infectious Diseases, who had received HAART for at least 18 months. Characteristics of patients at baseline are shown in table 1. Thirty one were male (72.1%) and 12 female (27.9%). Average age was 39.6 years. They were followed for 2 to 5 visits. All the patients were Iranian except one who was Korean.

The most common route of transmission among these patients was transfusion of coagulation factors in hemophilic patients. Other routes in decreasing order of frequency were unknown in 20.9%, intravenous drug use (IDU) in 18.6%, sexual contact in 11.6% and blood transfusion in 4.7%.

Mean duration of infection (time from diagnosis of HIV by ELISA and Western Blot to start of study) was 7.4 years. Median duration between becoming HIV positive and initiation of HAART was 4.53 years. The mean duration between start of HAART and start of study among patients was 2.8 years (1 month to 7 years). Thirteen patients (30.2%) had history of at least one period of stopping receiving HAART during course of therapy. Nine patients (20.9%) had history of monotherapy.

Mean CD4 count at the time of diagnosis of disease was 281 cell/mm³. In 8 patients (18.6%) the initial CD4 count was below 100, in 9 patients (20.9%) between 100 and 200 and in 26 patients (60.5%) above 200. Two patients were found to be HBs Ag positive, 3 were HBc Ab positive and 17 patients (39.5%) were HCV Ab positive.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=43)</th>
<th>Treatment failure (n=16)</th>
<th>No treatment failure (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>35.6±2.8</td>
<td>36.6±4.5</td>
<td>35.3±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>31/12</td>
<td>11/5</td>
<td>20/7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of follow up (month)</td>
<td>8.1±1.7</td>
<td>10.53±2.5</td>
<td>6.6±2</td>
<td>0.028</td>
</tr>
<tr>
<td>Duration of infection (year)</td>
<td>7.37±1.5</td>
<td>7.0±1.7</td>
<td>7.59±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of HAART treatment (year)</td>
<td>2.8±0.66</td>
<td>3.37±1.2</td>
<td>2.51±0.75</td>
<td>NS</td>
</tr>
<tr>
<td>Number of visits Mean</td>
<td>2.4±0.2</td>
<td>2.56±0.44</td>
<td>2.29±0.25</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NS, not significant.

*Data are given as mean (±2SE) except for sex.
Predictors of clinical failure

During the 18 months of follow-up disease progressed in 16 patients (37.2%) to an AIDS-defining event or death (4.7%) due to an AIDS-related cause. Table 2 lists the frequencies of the clinical end points. The most common finding at the start of treatment in these patients was wasting syndrome (16.3%); 11.6% of patients had TB in beginning of the study. Two cases died during the study.

Overall, treatment failure occurred in 37.2% of patients. In bivariate analysis by Fisher's exact test and Mann-Whitney U test, variates including time from diagnosis, duration of HAART therapy, age, sex, history of stopping drug and history of monotherapy were not associated with mortality; only low initial CD4 count on diagnosis and low baseline CD4 count at the start of study remained statistically significant ($P < 0.05$).

In survival analysis using Kaplan-Meier Product Limit, the median time to treatment failure was 13.5 months (10.68-16.32, CI=95%). It means that after 13.5 months 50% of patients encountered treatment failure. There was no significant difference in time to treatment failure by age or sex or educational and job level. There was no significant statistical association between route of transmission and treatment failure ($P > 0.05$).

Mean duration time of treatment failure in patients with history of stopping HAART was 13.63 month and in patients without this history was 13.3 month. There was no significant difference between survival time and history of stopping HAART ($P = 0.54$). Also, there was no significant difference between survival time and history of monotherapy ($P = 0.72$; Power=20%). By using Multifactorial ANOVA to omit interaction of confounding variates on survivorship function, only “monotherapy with initial CD4” and “monotherapy with treatment stop” were statistically associated to survivorship function ($P <0.05$). The initial CD4 on diagnosis in subgroups: <100, 100-200 and >200 were not significantly associated to survival time ($P = 0.387$, Power = 20.5%). Only CD4 cell count remained statistically significant in the multivariate analysis. Patients with CD4 cell counts of less than 50/microL were 6.67 times (95% confidence interval (CI), 3.61-12.34) and those with counts of 50/microL to 199/microL were 3.41 times (95% CI, 1.93-6.03) more likely to die than those with counts of at least 200/microL.

In statistical analysis of association between quantitative variates and survival time by using Cox regression, there was no significant association between initial CD4, age, infection duration, treatment duration and weight with survival time in our study. In multivariant analysis to determine important predictors of treatment failure we used proportional hazard analysis or Cox regression. Three variates including HCV-Ab, HCV-Ab, HBs-Ag were variables during different visits, so we used time-dependent covariates method. Results of Cox regression analysis by using “Backward: Conditional” method were interpreted. There was no significant association between covariate of “CD4 and monotherapy” and survival time in our patients.

There was no significant association between other variates like sex, age, route of transmission, history of stopping treatment, history of monotherapy, initial CD4, HBsAg, HCV Ab, HBCaAb, weight, infection duration, HAART duration and survival time.

Correlation of low baseline CD4 and treatment failure were explored during this study. There was correlation between baseline CD4 and survival of patients with history of monotherapy ($P< 0.05$). HAART resulted in decreased disease progression among persons with fewer than, but not more than, $200 \times 10^6$ CD4 lymphocytes/L prior to treatment. In a Cox multivariate proportional hazards model that adjusted for age, sex, race, prior opportunistic infection, and CD4 T lymphocytes, $\leq 200 \times 10^6$ CD4 lymphocytes/L was the strongest predictor of disease progression.
Table 2. Frequencies of clinical end points

<table>
<thead>
<tr>
<th></th>
<th>1st visit</th>
<th>2nd visit</th>
<th>3rd visit</th>
<th>4th visit</th>
<th>5th visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>43 (100%)</td>
<td>43 (100%)</td>
<td>15 (34.9%)</td>
<td>3 (7%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>23.3%</td>
<td>9.3%</td>
<td>6.6%</td>
<td>33.3%</td>
<td>100%</td>
</tr>
<tr>
<td>CMV infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>33.3%</td>
<td>0</td>
</tr>
<tr>
<td>Cryptosporium infection</td>
<td>0</td>
<td>2.3%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Toxoplasma infection</td>
<td>2.3%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>16.3%</td>
<td>9.3%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Opportunistic Pneumonia</td>
<td>7%</td>
<td>7%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Opportunistic TB</td>
<td>11.6%</td>
<td>11.6%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Opportunistic Salmonellosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zona</td>
<td>7%</td>
<td>4.7%</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

DISCUSSION

The administration of HAART to HIV-infected patients has led to dramatically decreased rates of morbidity and mortality. However, the failure of HAART to eradicate HIV leaves the patient vulnerable to the emergence of viral replication. We conducted this study to assess the long-term survival, effects of HAART on survival of patients in Iran and factors that are associated with long-term HAART administered in our Hospitals in an outpatient setting.

The most common route of HIV transmission among our patients was infected blood products (hemophilic patients). According to the most up-to-date statistics of Ministry of Health, the most common route is IDU (62.8%) in Iran. This statistical difference is predicated on the basis that IDU patients do not still have compliance to get the HAART regimen.

Follow up time in our patients was 18 months which were 24, 19 and 36 in other studies (4-9). Long term studies are recommended to discern related factors to treatment failure. The most common AIDS defining illness in our patients was wasting syndrome; a finding which is not the same as other studies (8, 9).

Mean mortality rate in our patients was 4.7%. There was a considerable discrepancy between our results and other studies (3, 4, 6, 10). In other studies significant decline in mortality rate was ensued after HAART. Overall, 37.2% of our patients had treatment failure. The results admonished a higher number of treatment failure in comparison to other studies after nearly similar follow up time (4, 11, 5). This high number of treatment failure led us to peruse in our results, and more explicit observation during follow up and visits and determining factors associated to treatment failure. The mean duration from becoming HIV positive to initiation of HAART among our patients were 4.3 years. It is a much longer time in comparison with other studies (4). In our study, higher rate of treatment failure is attributed to procrastination of HAART. No differences in response to HAART were seen between different ethnic groups in our study but it is still controversial and needs more studies to be held (4).

Noncompliance has a critical effect on outcome of long-term treatment in an outpatient clinic. Patients who were not fully compliant, as defined by self reported adherence, were not dropped from the study. The result of this study should be considered in light of this finding.

Opportunistic infections were diagnosed in 51% of patients before the start of their first HAART regimen. These patients also had low CD4 T cell counts and were more likely to have been pretreated with reverse-transcriptase inhibitors (monotherapy). In this study none of variants including duration of infection, duration of HAART, age, sex, and history of monotherapy and history of stoppage of treatment had association to death, although, in other studies there was a correlation between some of those factors and treatment failure. In our study only low initial CD4 and basal CD4 in start of study were associated
to death. Longterm follow up in our patients seems necessary.

Mean duration to treatment failure in patients with history of antiretroviral therapy (monotherapy or HAART) before the start of study was 13.6 months and in patients without this history was 13.3, thus there was no significant difference between them.

In survivorship function variants including history of stopping treatment, history of monotherapy and initial CD4 were analyzed and only “monotherapy with initial CD4” and “monotherapy with treatment stop” were statistically associated to survivorship function ($P < 0.05$). It was conspicuous that only in patients with history of monotherapy the initial CD4 was a predictive factor to survival of the patients. It was predicated that longer follow up in those patients is necessary. The initial CD4 was not statistically associated with survival of our patients; these findings are not similar to other studies in which initial CD4 is of predictive value, although viral load is of greater value to survival of the patients (3-6,10-12).

Our findings have important implications for clinical management of HIV infected patients in Iran and should be taken into account in future treatment guidelines. Our data did not demonstrate uniformly low rates of disease progression to death or AIDS among patients starting antiretroviral therapy with CD4 cell counts of at least 200/microL. In our study, disease progression to death and AIDS or death was not clustered among patients starting therapy with CD4 cell counts less than 200/µL. Also, our data suggest that current guidelines for initiating HAART should place greater emphasis on HIV-1 RNA level than CD4 lymphocyte for both men and women and this technology is highly recommended. Further longitudinal follow-up will be necessary to better ascertain whether HAART initiated at > 200 x 10(6) CD4 lymphocytes/L is effective in slowing disease progression in Iran.

The impact of adherence on survival was substantial even amongst severely immuno-compromised patients. Although survival was not compromised by baseline CD4, persons with < 200 CD4 cells at baseline remained at increased risk of death despite adjustments for adherence.

On the other hand lack of drug diversity in Iran HAART regimen is a predicament and clinicians could not change the drugs in regimen as they encounter treatment failure in their patients, so it requires more attention of Ministry of Health to import different type of drugs particularly protease inhibitors to be available for clinicians. Henceforth, we need to evaluate drug resistance among our patients to decrease treatment failure and increase cost beneficiary regimens of HAART.

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