MAJOR ARTICLE

Initial Virological and Immunologic Response to Highly Active Antiretroviral Therapy Predicts Long-Term Clinical Outcome

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Little is known about the long-term clinical outcomes for human immunodeficiency virus (HIV)–infected patients who have received highly active antiretroviral therapy (HAART). Determining factors associated with long-term clinical outcomes early in the course of treatment may allow modifications to be made for patients who are at a greater risk of treatment failure. To evaluate these factors, we studied 213 HIV-infected patients who had received HAART for at least 115 weeks. In the univariate analysis, virological response, which was measured as the change in virus load from baseline at month 3 of treatment, was the single best predictor of clinical outcome (relative hazard, 0.722; $P = .001$), independent of virological suppression. In the multivariate analysis, virological response and immunologic response, which was measured as an increase in CD4 cell count of >200 cells/mm^3, resulted in better prediction of clinical outcomes than did use of either variable alone ($P = .02$). Our results indicate that changes in virus load and immunologic response together are good predictors of clinical outcome and can be assessed after the initiation of HAART, which would allow clinicians to identify patients early in the course of therapy who are at greater risk of negative outcome.

The use of highly active antiretroviral therapy (HAART) with combinations of reverse-transcriptase and protease inhibitors to manage HIV disease has led to dramatically reduced morbidity and prolonged life among HIV type 1 (HIV-1)–infected patients [1, 2]. The initiation of HAART rapidly and significantly reduces the levels of virus replication in the peripheral blood [3–5]. In the HIV-infected patient, higher baseline levels of HIV RNA and lower baseline levels of $CD4^+$ T lymphocyte cells in the peripheral blood are strongly predictive indicators of disease progression [6, 7]. However, these and other prognostic indices are poorly defined for patients who have received long-term HAART and for patients who receive salvage therapy.

In the clinical setting, virological treatment failure occurs for many patients, prompting the administration of salvage therapy with a different combination of drugs [8, 9]. Virological treatment failure may be due to nonadherence, toxicity, intolerance, or emergence of drug-resistant mutations [10–13]. Examination of clinical outcomes for patients who have received long-term HAART can yield insights into the predictive power of surrogate markers. Use of the markers can identify, early on, patients who are at higher risk of clinical failure. For patients deemed to be at higher risk, modification or intensification of therapy may be necessary.

The factors that have previously been associated with progression of HIV disease are baseline quantitative HIV-1 RNA levels, baseline CD4 T cell counts [6, 7, 14–20], virus load at the nadir [21, 22], CD4 T cell

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counts of >200 cells/mm^3 at month 3 after the initiation of HAART [23], and area under the curve (defined as the sum of the area underneath the virus load curve between 2 points; area under the curve can also be used to measure the change in virus load) [24]. Several studies have analyzed the effects of long-term HAART on virological and immunologic responses.

Deeks et al. [25] found that sustained CD4 T cell response was related to changes in HIV RNA levels to below pretreatment baseline levels, and that even transient or partial decreases in virus levels can have sustained effects on CD4 T cell counts. Mezzaroma et al. [26] described discordant immunologic and virological responses in patients who had undergone treatment with multiple drugs. They found a decreased risk of mortality and immunologic benefit for patients who were receiving HAART, even in the absence of sustained viral suppression. Our study examines virological response and immunologic response as predictors of clinical outcome for patients who have received long-term HAART. We relate immunologic and virological factors and their interaction, as well as disease stage and pretreatment with antiretroviral agents, to virological and clinical failure.

We found that changes in virus load to below baseline levels—not the level of virological suppression—was the most important factor in the determination of clinical outcome. We also found that virological response and immunologic response together are good predictors of clinical outcome and can be assessed early in the course of HAART, which allows for the early identification of patients who are at greater risk of negative clinical outcomes.

SUBJECTS AND METHODS

Study subjects. A 20% random sample was taken from the entire HIV-positive clinic population in an outpatient clinic in Los Angeles. The random sample was generated on the basis of the unique patient identification numbers that are used within the clinic. Inclusion criteria were the following: (1) initiation of HAART before June 1997 (to allow at least 115 weeks of observation) and (2) availability of HIV RNA levels and CD4 T cell counts that were recorded before the patients began receiving HAART.

Seven patients were excluded from the study because they were not receiving or had stopped receiving HAART. The excluded patients did not differ significantly from the included patients with regard to age, sex, CD4 T cell count at baseline, virus load at baseline, or disease stage. A total of 213 patients were included in the study and were observed for at least 115 weeks (range, 115–153 weeks). Risk factors for transmission were homosexual contact (194 patients [91%]), heterosexual contact (17 patients [8%]), and injection drug use (2 patients [1%]). Patients had regular follow-up visits and had a high level of self-reported adherence. Consent was given under the condition that the anonymity of the patients be preserved.

The study population consisted of 195 men and 18 women. Table 1 lists the characteristics of the patients at baseline. The "baseline value" is defined as the average of 2 consecutive measurements taken before the start of the first HAART regimen. The median age at baseline was 41 years. Plasma HIV-1 RNA levels, which were measured by use of an ultrasensitive assay with a quantification limit of 20 copies/mL (Immune Diagnostic Laboratory), and CD4 T cell counts, which were assessed by means of flow cytometry (Becton Dickinson), were determined monthly. Median HIV-1 RNA level at baseline was 4.239 log copies/mL (range, 1–5.8 log copies/mL). The median baseline CD4 T cell count was 230 cells/mm^3 (range, 0–1011 cells/mm^3). Thirty-seven patients (17%) were antiretroviral naïve. Thirty-two patients (15%) had received ⩾3 reverse-transcriptase inhibitors before they started receiving HAART. Opportunistic infections were diagnosed in 41 patients before they began receiving HAART.

All patients were receiving individualized treatment regimens, and all received HAART continuously for at least 115 weeks. Table 2 lists the most common initial HAART regimens. For this study, HAART was defined as the administration of a

Table 1. Characteristics of the 213 HIV-infected patients at baseline.

Characteristic	No. (%) of patients[a] (n = 213)
Sex	
Male	195 (92)
Female	18 (8)
Age, median years (range)	41 (21–69)
Clinical stage	
Asymptomatic[b]	85 (40)
Symptomatic[c]	87 (41)
Clinical AIDS[d]	41 (19)
CD4$^+$ T cell count, cells/mm^3	
Median (range)	230 (0–1011)
0–99	43 (20)
100–199	45 (22)
200–399	80 (36)
>400	45 (22)
HIV RNA, median log copies/mL (range)	4.239 (1–5.8)
Experience with reverse-transcriptase inhibitors	
Antiretroviral naïve	37 (17)
"Moderate" or <3 drugs	144 (68)
"Heavy" or ⩾3 drugs	32 (15)

[a] Unless otherwise indicated.
[b] Centers for Disease Control and Prevention (CDC) stage A.
[c] CDC stage B.
[d] CDC stage C.

Table 2. Most common initial regimens of highly active antiretroviral therapy.

Regimen	No. of patients
Two RTIs and indinavir	69
Two RTIs, saquinavir, and ritonavir	47
Two RTIs and saquinavir	44
Two RTIs and nelfinavir	35
Two RTIs, nelfinavir, and saquinavir	12
One RTI, ritonavir, and saquinavir	6

NOTE. RTI, reverse-transcriptase inhibitor.

combination of ⩾3 antiretroviral agents, among which at least 1 antiretroviral agent was a protease inhibitor. For many patients (156 patients), it was necessary to administer a salvage regimen that consisted of different combinations of antiretroviral agents because of intolerance (in 43 patients) or increasing plasma HIV-1 RNA levels (in 113).

Clinical end points. "Virological suppression" was defined by a virus load measurement of <100 copies/mL. "Virological failure" was defined by 2 consecutive virus load measurements of >500 copies/mL. "Clinical failure" was defined by diagnosis of an AIDS-defining illness or death, regardless of CD4 T cell count. For patients who had an opportunistic infection diagnosed before the start of the HAART regimen (41 patients), "clinical failure" was defined as relapse of the opportunistic infection or onset of a new AIDS-defining illness.

Statistical analysis. For time-to-event analysis, we used the Kaplan-Meier method and the Cox proportional hazards 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, including partial likelihood ratio χ^2 statistics. All P values are 2-sided.

Statistical and graphic testing showed that the proportional hazards assumption was not violated. Data were analyzed by use of SAS software, version 6.11 (SAS Institute).

Potential predictors of long-term clinical outcome included virological response (measured as change in virus load between baseline and month 3 of HAART), immunologic response (CD4 T cell count of >200 cells/mm^3 at month 3 of HAART), change in CD4 T cell count at month 3 of HAART, interaction between virological and immunologic parameters, virus load at the nadir, baseline virus load, baseline CD4 T cell count, virus load as a continuous variable, CD4 as a continuous variable, stage of disease, and pretreatment with antiretroviral agents prior to the commencement of HAART.

RESULTS

We analyzed 213 patients in an outpatient clinic who had received HAART for at least 115 weeks. The characteristics of the 213 subjects are listed in table 1.

Virological suppression. "Virological suppression" was defined as an HIV-1 RNA level of <100 copies/mL. "Virological rebound" was defined as 2 consecutive virus load measurements of >500 copies/mL that occurred after virological suppression. The virological suppression rate was 69% (147 of 213 patients). Of the 66 patients in whom virological suppression did not occur, 63 (95%) were pretreated and 3 (5%) were treatment naïve.

Of the 147 patients in whom virological suppression was achieved, 56 (38%) had a rebound in virus load by the end of the 115-week period. Of the 110 pretreated patients, 49 (45%) had a rebound in virus load, whereas only 7 (19%) of the 37 treatment-naïve patients had a viral rebound. Predictors of virological failure were baseline virus load, baseline CD4 T cell count, history of experience with antiretroviral agents, and history of opportunistic infection. Table 3 lists the relative hazards and 95% CIs of virological failure from the Cox proportional hazards model.

Predictors of clinical failure. During the 115 weeks of follow-up, 71 patients (33%) had conditions that progressed to an AIDS-defining event or death due to an AIDS-related cause. Table 4 lists the frequencies of the clinical end points that occurred. We tested whether the initial virological response was predictive of clinical failure. Virological response was measured as the change in HIV-1 RNA levels from baseline after 3 months of HAART. (Note that with 2 timepoints, this method yields the same information as area under the curve.) Subjects who had more dramatic virological responses (i.e., greater decreases in HIV RNA levels from baseline at month 3) had a lower risk of progression than did those who had a more modest response (relative hazard [RH], 0.722; 95% CI, 0.5931–0.8407; $P =$ .0001). Therefore, for each decrease in HIV-1 RNA level of 1.0 log copies/mL that occurred after the initiation of HAART, the hazard of clinical failure decreased by an estimated 27.8%.

To analyze this result more closely, patients were stratified according to initial virological response into the categories of "high," "moderate," and "low." High virological responders had

Table 3. Relative hazards (RHs) of virological failure and 95% CIs from the Cox proportional hazards model.

Model covariate	RH (95% CI)	P
Previous OI	5.334 (3.784–7.456)	.0001
Baseline virus load	1.591 (1.202–2.104	.0012
Baseline CD4 T cell count	0.938 (0.918–0.969)	.0182
Treatment naïve	0.625 (0.387–0.989)	.054

NOTE. OI, opportunistic infection.

Table 4. Frequencies of clinical end points.

Clinical end point	No. (%) of patients[a]
Wasting	17 (24)
Cytomegalovirus infection	10 (14)
Mycobacterium avium complex infection	8 (11)
Cryptosporidiosis	7 (10)
Kaposi's sarcoma	7 (10)
Death	7 (10)
Encephalopathy	4 (6)
Pneumocystis carinii pneumonia	2 (3)
Progressive multifocal leukoencephalopathy	2 (3)
Toxoplasmosis	2 (3)
AIDS dementia	2 (3)
Esophageal candidiasis	2 (3)
Recurrent pneumonia	1 (1)

[a] Some patients experienced >1 clinical end point.

a decrease in virus load of >1.0 log copies/mL by month 3 after the initiation of HAART. Moderate virological responders had a decrease in virus load of 0.5 log copies/mL to 1.0 log copies/mL. Low virological responders had a decrease in virus load of <0.5 log copies/mL after 3 months of HAART. Kaplan-Meier curves were constructed with use of these strata and are shown in figure 1. Differences in the strata were statistically significant, according to the log-rank test ($P = .0001$). Furthermore, baseline virus load was not significant as a predictor of clinical failure for recipients of long-term HAART ($P = .4280$).

A previous study by d'Arminio Monforte et al. [23] found that CD4 T cell counts of >200 cells/mm^3 at month 3 of HAART were predictive of clinical outcome. In univariate analysis, CD4 T cell response, which was measured as a CD4 T cell count of >200 cells/mm^3 at month 3 of HAART, was significant at $P = .001$. However, in multivariate analysis, virological response was found to be a better predictor of clinical outcome (virological response: RH, 0.278; 95% CI, 0.1678–0.4598; $P = .0001$; CD4 T cell response: RH, 0.562; 95% CI, 0.3482–0.9061; $P = .0181$). Table 5 lists the relative hazards of clinical failure and the 95% CIs from the multivariate Cox proportional hazards model.

Although virological response was superior to immunologic response as a predictor of clinical outcome, we found that combining the virological and immunologic information in the same analysis yielded a better predictor than did use of either variable alone ($P = .02$, by use of the likelihood ratio test). Patients with both a virological and an immunologic response at month 3 of HAART had a hazard of failure that was only 39% of that for patients who had a discrepant response (RH, 0.3947; 95% CI, 0.3056–0.5157; $P = .0001$). To better illustrate this result, patients were stratified by their virological and CD4 T cell response as follows: patients with a virological response (decrease in virus load of >1.0 log copies/mL by month 3 of HAART) and CD4 T cell response (CD4 T cell count of >200 cells/mm^3 by month 3 of HAART), virological response only, CD4 T cell response only, and no response. The Kaplan-Meier curves are presented in figure 2.

In both univariate and multivariate analyses, baseline CD4 T cell count was an important predictor of disease progression for this patient group. Patients with higher baseline CD4 T cell counts had a decreased risk of progression (RH, 0.884; $P = .001$). Baseline CD4 T cell counts were then stratified into clinically useful categories (<100 cells/mm^3, 100–199 cells/mm^3, 200–400 cells/mm^3, and >400 cells/mm^3). A Cox proportional hazards model was used to estimate the relative hazard of progression on the basis of baseline CD4 T cell count. Subjects who had CD4 T cell counts of <100 cells/mm^3 at the time of initiation of HAART were nearly 10 times more likely to have progression to AIDS than were subjects whose CD4 T cell counts were >400 cells/mm^3 (RH, 9.992; $P = .0001$). Compared with subjects who had CD4 T cell counts of >400 cells/mm^3, subjects with CD4 T cell counts that were between 100 cells/mm^3 and 199 cells/mm^3 were >4 times more likely to have progression to AIDS (RH, 4.221; $P = .001$), and subjects with counts that were between 200 cells/mm^3 and 400 cells/mm^3 were 3 times more likely to have progression to AIDS (RH, 2.991; $P = .01$). The Kaplan-Meier curves are presented in figure 3.

Although baseline CD4 T cell count was significant, changes in CD4 T cell counts at month 3 and over the course of time were not statistically significant ($P > .05$). Other univariate pre-

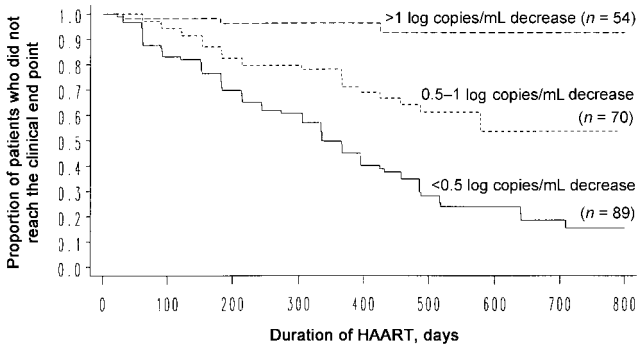

Figure 1. Kaplan-Meier estimates of the proportion of subjects who did not reach the primary clinical end point (i.e., clinical failure), among subjects stratified according to virological response. The *Y*-axis shows the proportion of patients left in the sample who did not have clinical failure. The solid line represents the survival curve for patients with a low initial response to highly active antiretroviral therapy (HAART). The short-dashed line represents the survival curve for patients with a moderate initial response to HAART. The long-dashed line shows the survival curve of patients with a high initial response to HAART ($P = .001$ for the comparison between subject groups).

Table 5. Relative hazards (RHs) of clinical failure and 95% CIs from the multivariate Cox proportional hazards model.

Model covariate	RH (95% CI)	*P*
Virological response	0.278 (0.1678–0.4598)	.0001
Immunologic response	0.562 (0.3482–0.9061)	.0181
Previous OI	3.326 (2.440–4.525)	.051
Treatment naïve	0.874 (0.447–1.7083)	.593
Nadir virus load	0.921 (0.823–1.464)	.351

NOTE. OI, opportunistic infection.

dictors of clinical outcome were virus load at the nadir (RH, 1.348; $P = .002$), history of opportunistic infection (RH, 5.415; $P = .001$), and no history of antiretroviral treatment (RH, 0.417; $P = .039$). However, none of these variables predicted long-term clinical outcome as well as did virological response and immunologic response combined.

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 [27, 28] leaves the patient vulnerable to the emergence of drug-resistant strains of the virus and resurgence of viral replication [29]. Wong et al. [29] found that the persistence of even low levels of detectable virus in the peripheral blood as a result of incomplete viral suppression reflects ongoing replication in the lymphoid system and the emergence of drug resistance.

We conducted this study to assess the factors that are associated with long-term HAART administered in an outpatient setting. We found that HAART was initially able to suppress viral replication in the majority of patients, more so for patients who were treatment naïve. However, we found that viral suppression was not sustained in 56 (38%) of the patients. The resulting viral rebound led to modification of the therapy regimens. This pattern of incomplete and transient virus suppression has been reported after several studies of clinical populations [10, 25, 26].

Almost all of the patients (156 of 213) had a rebound in virus load during administration of HAART, at which time salvage therapy regimens were instituted. In many instances, salvage therapy was not sufficient to suppress virus levels. This was most likely the result of the emergence of drug-resistant strains of the virus and, in some instances, because of the patient's failure to adhere to treatment regimens.

Noncompliance has a critical effect on the 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. Thirty percent of the patients acknowledged some noncompliance when questioned by the physician. The results of this study should be considered in light of this finding.

Opportunistic infections were diagnosed in 41 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. Fifteen patients (37%) were treated with ⩾3 nucleoside reverse-transcriptase inhibitors before the commencement of HAART. These patients accounted for the majority of cases of clinical treatment failure.

Predictors of virological suppression were baseline virus load, baseline CD4 T cell count, previous experience with antiretroviral agents, and history of opportunistic infection. These findings are similar to those of other studies [1, 6, 7, 10–19, 23, 24]. We found that one of the most important predictors of clinical progression in patients who were receiving long-term HAART was the initial virological response to HAART. Patients who have a decrease in virus load of ⩾0.5 log copies/mL (from baseline) at month 3 of HAART have a decreased risk of clinical failure. These results suggest that patients with high baseline virus loads or low CD4 T cell counts may have favorable clinical outcomes if they have a good virological response to HAART by month 3 of treatment.

Immunologic response was also an important predictor of long-term clinical outcome. We looked at CD4 T cell response in many different ways. CD4 T cell count, both as a continuous variable and in terms of the change from baseline level, was not statistically significant. In comparison with changes in virus load, changes in CD4 T cell count were not dramatic enough to have great statistical power. By defining "CD4 T cell response" as a count of >200 cells/mm^3, we were able to achieve significance. A CD4 T cell count of 200 cells/mm^3 is an im-

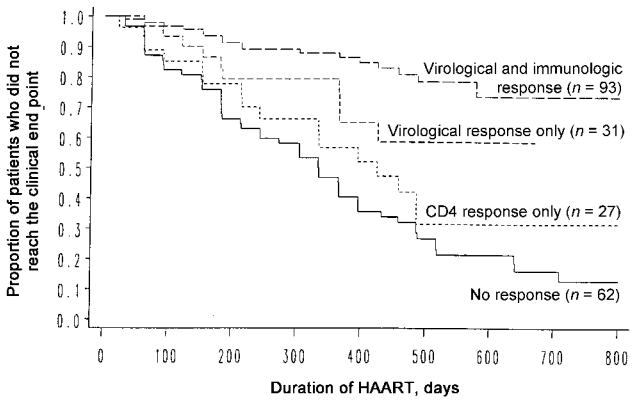

Figure 2. Kaplan-Meier estimates of the proportion of subjects who did not reach the primary clinical end point (i.e., clinical failure), among subjects stratified according to the following immunovirological responses: virological and immunologic response, virological response alone, immunologic (CD4 T cell) response alone, and no response. The *Y*-axis shows the proportion of patients left in the sample who did not experience clinical failure. HAART, highly active antiretroviral therapy.

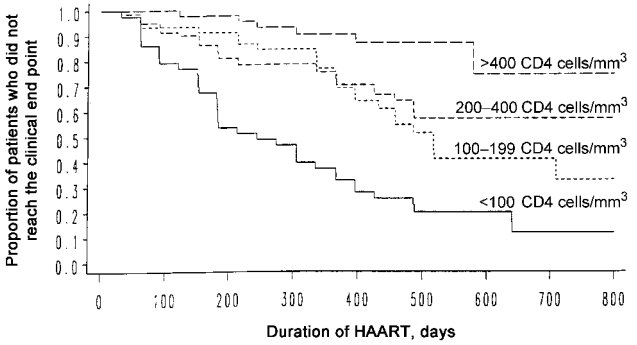

Figure 3. Kaplan-Meier estimates of the proportion of subjects who did not reach the primary clinical end point (i.e., clinical failure), among subjects stratified according to baseline CD4 T cell count. The *Y*-axis shows the proportion of patients left in the sample who did not experience clinical failure. The survival curves are based on CD4 T cell counts at baseline, before the start of highly active antiretroviral therapy (HAART; $P = .01$ for the comparison between subject groups).

portant threshold. Below that mark, patients are at increased risk of development of opportunistic infections and death. This result is confirmed by the Kaplan-Meier curves for baseline CD4 T cell count. The variable of immunologic response, as it was constructed, incorporated this threshold and offered greater statistical significance in both univariate and multivariate analyses.

Virological response was a better univariate predictor of long-term clinical outcome than was immunologic response. However, the combination of virological and immunologic response was a superior predictor of long-term clinical outcome than was virological response alone. Because both factors together offer better predictive power than does either variable alone, both measurements should be considered in the evaluation of a patient. Although the result may seem to be contrary to the findings of d'Arminio Monforte et al. [11], the discrepancy is due to the fact that we defined virological response as the change from baseline to month 3 instead of as the mean level of viremia. Because changes in virus load incorporated information about baseline levels and virus load trajectory, they have more predictive power than do absolute levels of HIV RNA, such as mean viremia or baseline virus load.

As documented by CD4 T cell response and virological response, 94 (44%) of the subjects had a good immunovirological response to HAART and 62 (29%) had a poor immunovirological response. Therefore, 57 (27%) of the patients had a discordant immunologic or virological response—the so-called "disconnect." Thirty-one patients had a good virological response, but their CD4 T cell counts did not have a subsequent increase. Twenty-seven patients had CD4 T cell counts that increased to >200 cells/mm^3, but their virus loads did not decrease to $\geq$0.5 log copies/mL from baseline. The Kaplan-Meier curves in figure 3 show the striking result of the immunovirological response and how it was predictive of clinical outcome. It also shows an ordering of clinical outcomes according to response to treatment.

Patients who had a virological response but did not have an immunologic response were less likely to experience clinical treatment failure than were patients who had high CD4 T cell counts and high levels of viremia. This suggests that, although physicians should look at both virological and immunologic factors when evaluating patients, the virological response should weigh more heavily in the decision to modify therapy.

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