Prognostic Indicators for AIDS and Infectious Disease Death in HIV-Infected Injection Drug Users

Plasma Viral Load and CD4+ Cell Count

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Context.—Plasma human immunodeficiency virus type 1 (HIV-1) viral load and CD4+ cell count are used to predict prognosis of persons infected with HIV. However, whether combining these markers improves prognostic accuracy and whether they predict progression for injection drug users (IDUs) and nonwhite persons infected with HIV has not been extensively investigated.

Objective.—To evaluate plasma viral load and CD4+ cell count as prognostic indicators for the acquired immunodeficiency syndrome (AIDS) and infectious disease deaths.

Design.—Cohort study initiated in 1988 and 1989 with follow-up for up to 7.9 years.

Participants.—Injection drug users infected with HIV recruited from the community in Baltimore, Md.

Main Outcome Measures.—Plasma HIV-1 RNA and CD4+ cell count measured at baseline compared with time to first clinical AIDS diagnosis and death due to an infectious disease.

Results.—Of 522 subjects, 96% were African American, 80% were male, 96% injected drugs within the past 6 months, and the median age was 33 years. A total of 146 cases of AIDS and 119 infectious disease deaths were seen during a median follow-up period of 6.4 years. Time-fixed baseline levels of viral load and CD4+ cell count were independent predictors of progression to AIDS and infectious disease deaths, but in proportional hazards models, viral load had better predictive value than CD4+ cell count. Kaplan-Meier analysis of time to AIDS and to infectious disease deaths by viral load (<500, 500-9999, 10 000-29 999, ≥30 000 copies/mL) at 3 levels of CD4+ cell count (<0.20, 0.20-0.49, and ≥0.50×10^9/L) was reduced to a 5-stage classification scheme using a backward stepwise regression procedure. The 5-year cumulative probabilities for AIDS and infectious disease deaths ranged from 0% and 0%, respectively, for group I (viral load, <500 copies/mL; CD4+ cell count, 0.50×10^9/L) to 81.2% and 76.1% respectively, for group V (viral load, ≥10 000 copies/mL; CD4+ cell count, 500×10^9/L).

Conclusions.—In this study, plasma HIV-1 viral load independently and in combination with CD4+ cell count measurements provides powerful prognostic information for progression to AIDS and death caused by infectious disease in a population of predominantly African American IDUs. Combining categories of both markers provided a simple method for prognostically staging HIV disease.

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CROSS-SECTIONAL STUDIES have shown that higher titers of human immunodeficiency virus type 1 (HIV-1) in peripheral blood mononuclear cells and plasma are associated with lower CD4+ cell counts.1-5 Prospective studies of viral burden in persons measured soon after HIV infection (ie, seroconversion) found higher viral load to be predictive of more rapid progression of HIV-1 disease.6,9 More relevant to the typical clinical setting, where date of onset of HIV-1 infection may be unknown to the physician, higher plasma viral load also predicts more rapid development of the acquired immunodeficiency syndrome (AIDS) and death in seropositive patients.10,11 Viral load reductions in response to antiretroviral therapies are predictive of subsequent clinical response.12-21 However, important questions remain unanswered regarding the relationship between CD4+ cell count and plasma HIV-1 viral load and the usefulness of these markers in combination as prognostic indicators for AIDS and death. First, most studies have reported data largely from white homosexual men and hemophilia patients.10,11,14 Whether interpretation of viral load from these studies can be extended directly to injection drug users (IDUs), women, and minorities needs to be clarified. Second, prior reports of prognostic accuracy were concentrated on showing that viral load measurements are useful independently of CD4+ cell counts.10 Attempts to combine these 2 measures to establish more powerful and useful prognostic classifications of HIV disease are sparse.11 Moreover, from a clinical standpoint, in the past decade and prior to availability of HIV-1 plasma viral load measurements, prognostic and therapeutic studies used CD4+ cell count cutoff values of 0.20 and 0.50×10^9/L (200 and 500/µL).15,16 The ability of plasma HIV-1 RNA levels...
METHODS

Study Population

The methods used for organization, recruitment, and data collection have been described. In brief, between February 1988 and March 1989, IDUs were enrolled in a longitudinal study of HIV-1 infection. Subjects were recruited by word of mouth from community sources, which included drug abuse treatment centers, city health department sexually transmitted disease clinics, emergency departments, state probation and parole offices, university hospital HIV/AIDS clinics, homeless shelters, and a street AIDS prevention outreach program. Study participants were also encouraged to refer eligible friends. Eligibility criteria included age of at least 18 years, injection drug use within the previous 11 years, and absence of AIDS-defining illness. Study and consent procedures were reviewed and approved by the Institutional Review Board of the Johns Hopkins School of Hygiene and Public Health.

Of 2960 IDUs recruited, 704 were HIV seropositive at baseline. All HIV-1-seropositive persons were invited to enroll in the cohort for detailed clinical and laboratory follow-up. Consenting subjects (664 HIV-1-seropositive persons) agreed to return at 6-month intervals for interviews, physical examinations, and venipuncture and signed release forms for us to obtain medical records to confirm the diagnosis of AIDS. Annual rates of continued participation in the follow-up clinic consistently exceeded 91%.

Data Collection

A baseline interview obtained information on age, race, sex, injection drug use within 6 months prior to enrollment (“current” drug use), and presence or absence of several symptoms during the 6 months prior to interview. Those symptoms included fatigue, unintentional weight loss (>4.5 kg), oral thrush, shortness of breath, and chills or fever of 2 or more weeks’ duration. Given the near universal reports of lymphadenopathy, fever, and night sweats in pilot studies, which we considered related to illicit drug use, these were excluded from the final instrument. For analysis, at each follow-up visit we asked subjects about intercurrent illnesses, diagnoses, and utilization of health care services; positive responses were followed by a request for consent to obtain medical records. Medical records were abstracted using standard forms by trained nurses, and final diagnoses were established by a physician-led end points committee. The outcome variable, AIDS, was diagnosed according to clinical criteria used in the 1993 Centers for Disease Control and Prevention criteria based on review of medical records through January 1997. Mortality was ascertained through a National Death Index search and through retrieval of death certificates through January 1997.

Laboratory Studies

Antibodies to HIV-1 were detected by commercial enzyme-linked immunosorbent assay (ELISA; Genetic Systems, Seattle, Wash) with confirmation of repeatedly reactive ELISA tests by Western blot (DuPont, Wilmington, Del).

For measurement of T-cell subsets, heparinized whole blood was stained with monoclonal antibodies using a modified whole blood method, and percentages of CD3+, CD4+, and CD8+ T cells were determined by flow cytometry. Using these percentages along with automated complete blood cell count and differential, we determined absolute count of CD3+, CD4+, and CD8+ T-cell subsets.

Quantitation of HIV-1 RNA was performed using a second-generation branched-chain DNA signal amplification assay (Chiron Corp, Emeryville, Calif) with a quantification limit of 500 copies/mL and a linear dynamic range between 5.0×10³ and 1.5×10⁶ copies/mL. Heparinized plasma specimens for quantitation of viral load were processed within 4 to 6 hours of collection and stored at −70°C until testing. Assays were performed in duplicate using 1-mL aliquots; 97% of duplicate specimens had a coefficient of variation below 30%, which is the standard specified by the manufacturer. Baseline levels of CD4+ cell count and plasma HIV-1 RNA were used in this analysis.

Statistical Analyses

Analyses were performed using 2 progression end points: (1) first clinical AIDS diagnosis, and (2) death due to an infectious disease. While all-cause mortality in people diagnosed as having AIDS is a typical end point in studies involving other populations, HIV-1 immunosuppressed IDUs are more likely than other groups to develop non-AIDS-defining bacterial infections or to die of trauma or drug overdose. To increase the HIV-AIDS specificity of mortality in this cohort, we used only deaths due to infectious diseases (eg, an AIDS-defining diagnosis, nonrecurrent bacterial pneumonitis, bacterial sepsis, endocarditis, and pyogenic meningitis) for mortality.

Kaplan-Meier estimates were obtained separately on clinical AIDS and infectious disease deaths by single baseline levels of CD4+ cell count (stratified by levels of <0.20, 0.20-0.49, and ≥0.50×10⁹/L and by single baseline HIV-1 RNA levels (<500, 500-9999, 10 000-29 999, ≥30 000 copies/mL). These strata of CD4+ cell count reflect the commonly used staging of HIV-1 disease by this measure. The categorization of HIV-1 RNA levels reflects several characteristics, namely, (1) a distinction between undetectable (<500 copies/mL) and low detectable levels, and (2) within the range of detectable values for this cohort the median and upper quartile were rounded to 10 000 and 30 000 copies/mL, respectively. The censoring time was the date of either the last semianual study visit, AIDS, or death if these occurred prior to January 1, 1996, or January 1, 1996, if these events occurred after that date. We also constructed Cox proportional hazards models separately for AIDS and infectious disease deaths using baseline CD4+ cell count and baseline HIV-1 RNA levels as continuous variables; we used increments directly comparable to a prior report. We created a 3×4 cross-classification table (to reflect the 3 CD4+ cell count and the 4 HIV-1 RNA levels) and separately fit Kaplan-Meier models of time to AIDS and infectious disease deaths in 11 of the strata. (No person fell into the strata with HIV-1 RNA level of <500 copies/mL and CD4+ cell count of <0.20×10⁹/L. Five-year probabilities for AIDS and for infectious disease deaths for each stratum are reported.

To achieve a simplified staging model based on the combined information of CD4+ cell count and HIV-1 RNA levels, cells within the matrix were merged into clusters with statistically similar survival functions. This was done using a systematic stepwise backward regression approach that collapsed cells with similar survival functions based on comparing log-likelihoods of 2 regression models via the likelihood ratio test. An initial model of time to AIDS was created using separate survival curves for each of the 11 strata. At each step of the procedure, the number of cells was reduced by 1 by combining the adjacent pair of cells which resulted in minimal change in log-likelihood. This continued until reduction in number of cells resulted in significant change in log-likelihood at P<.05. The model with the second model with fewer cells in favor of the model with more cells. This procedure reduced the original 11 cells to
The 522 remaining HIV-1 seropositive participants, most were male (80%), African American (96%), and currently active drug injectors (96%). Median baseline CD4+ cell count was 0.61 × 10^9/L (interquartile range, 0.35-0.71 × 10^9/L). The overall median HIV-1 RNA viral load was 7630 copies/mL (interquartile range, 1490-27 800 copies/mL). As 11% had less than 500 copies/mL, the median (and interquartile range) for plasma viral load in the detectable range was 10 120 copies/mL (2660-30 770 copies/mL), which was rounded to 10 000 copies/mL (2500-30 000 copies/mL) for analyses. Overall, 4.2% reported recent oral thrush at baseline. Six percent were taking azidovudine (AZT) at baseline and 49.6% reported some use of monotherapy with nucleoside analogues during the 7-year follow-up; use of protease inhibitors and nonnucleoside reverse transcriptase inhibitors were not reported during follow-up.

The 146 cases of clinical AIDS in the 522 seroprevalent subjects followed for a median of 6.4 years (range, 0.01-7.9 years) translates to a crude annual incidence of 4.4%. Some had more than 1 presenting condition at time of diagnosis and there were a total of 160 presenting illnesses. The 9 most frequently identified conditions included Pneumocystis carinii pneumonia (33), candidiasis (25 esophageal, 1 pulmonary), Mycobacterium avium infection (22), recurrent bacterial pneumonia (15), cryptococcosis (15), AIDS dementia (8), toxoplasmosis (3), esophageal herpes (3), and "other" atypical mycobacterium infections (5); 18 cases of AIDS-defining complications were identified at death, and the presenting illness for these 18 was not further specified. Overall, there were 182 deaths. Causes of the 119 infectious disease deaths included AIDS-defining complications (97), sepsis (12), bacterial pneumonia (6), endocarditis (3), and pyogenic meningitis (1). There were 63 noninfectious causes of death, including 26 due to drug overdose and 12 due to trauma; other noninfectious disease deaths included myocardial infarction, cerebrovascular accidents, cancer, and end-stage organ failure.

In a time-fixed proportional hazards model that used only baseline CD4+ cell count and plasma viral load (Table 1), the adjusted relative risks of AIDS and infectious disease death within 7 years were significant for both CD4+ cell count and viral load. Viral load was more significant in this respect than CD4+ cell count in these models as indicated by the Wald χ² of 54.4 for viral load vs 25.1 for CD4+ cell count in the proportional hazards model for AIDS, and 63.3 and 10.6 for infectious disease deaths, respectively. Neither CD4+ cell count nor HIV-1 RNA level was associated with noninfectious disease deaths in proportional hazards models.

Further analyses were restricted to the 3 categories of CD4+ cell count and the 4 categories of HIV-1 RNA levels as defined ("Methods"). Figure 1 shows the cumulative probability curves, derived from the Kaplan-Meier procedures, for the onset of AIDS or infectious disease deaths by the initial HIV-1 RNA level for the 3 categories of CD4+ cell count. For both outcomes, there was a significant trend toward faster progression as the "viral load level increased within the CD4+ categories of 0.20-0.49 × 10^9/L and less than 0.50 × 10^9/L (P<.001 for all comparisons) and within the less than 0.20 × 10^9/L CD4+ cell count category (P=.02 for AIDS and P=.003 for infectious disease death), where the sample size was small. Due to limited sample size within subgroups, further pairwise comparisons were not performed. However, descriptively, within the less than 0.20 × 10^9/L CD4+ cell count stratum, there were no persons with viral load less than 500 copies/mL; risk for AIDS and death appeared similar between persons in the 2 strata of the highest viral load categories and appeared higher than that of persons with viral load of 500 to 9999 copies/mL (Figure 1A). In the 0.20 to 0.49 × 10^9/L stratum of CD4+ cell count, risk of AIDS and infectious disease deaths appeared higher in those with viral load greater than 10 000 copies/mL than in those with lower viral load levels (Figure 1B). For the greater than or equal to 0.50 × 10^9/L CD4+ cell count stratum, the risks for AIDS and infectious disease deaths were similar for the middle categories of viral load and risks for the 2 outcomes appear highest in those with viral load levels of 30 000 copies/mL or more (Figure 1C).

Data from the Kaplan-Meier curves are summarized in Table 2 as 5-year cumulative probabilities.
there were significant linear trends by viral load in all strata of CD4+ cell count (P = .02 for AIDS within a CD4+ cell count, <500; P = .003 for infectious disease death within a CD4+ cell count <0.20 × 10^9/L; and P = .0001 for all other categories). (In A and D, there were no HIV-infected individuals with a CD4+ cell count of <0.20 × 10^9/L who had undetectable viral load [<500 copies/mL].)

Table 2.—Five-Year Cumulative Probabilities for AIDS and Deaths Due to Infectious Diseases by Strata of Plasma HIV-1 Viral Load and CD4+ Cell Count*

<table>
<thead>
<tr>
<th>CD4+ Cell Count</th>
<th>Viral Load</th>
<th>AIDS, %</th>
<th>Infectious Disease Deaths, % (n)</th>
<th>Staging Group</th>
<th>AIDS, %</th>
<th>Infectious Disease Deaths, % (n)</th>
<th>Staging Group</th>
<th>AIDS, %</th>
<th>Infectious Disease Deaths, % (n)</th>
<th>Staging Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, &lt;0.20 × 10^9/L</td>
<td>Undetectable, &lt;500 copies/mL</td>
<td>57.7</td>
<td>14.3 (10)</td>
<td>III</td>
<td>12.0</td>
<td>7.2 (96)</td>
<td>II</td>
<td>0.0</td>
<td>0.0 (42)</td>
<td>I</td>
</tr>
<tr>
<td>Moderate, 500-9999 copies/mL</td>
<td>75.0</td>
<td>75.6 (5)</td>
<td>V</td>
<td>4.2</td>
<td>32.3 (53)</td>
<td>IV</td>
<td>23.0</td>
<td>14.6 (52)</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>High, ≥30 000 copies/mL</td>
<td>83.3</td>
<td>76.4 (16)</td>
<td>V</td>
<td>42.4</td>
<td>32.3 (53)</td>
<td>IV</td>
<td>23.0</td>
<td>14.6 (52)</td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

* AIDS indicates acquired immunodeficiency syndrome; HIV-1, human immunodeficiency virus type 1; and ellipses, not applicable.

As illustrated by the separate Kaplan-Meier curves of time to AIDS and infectious disease deaths (Figure 2) and the proportional hazards model in Table 3, the 5-group staging model provides strong discrimination for both AIDS and infectious disease death in this population. There is not only a trend toward less AIDS-free time (P < .001) and worse survival (P < .001) as we shift to a higher group, but each group is also statistically distinct from the comparison group II (ie,
Table 3.—Five-Year Cumulative Probabilities and Relative Hazards for AIDS and Deaths Due to Infectious Disease by HIV-1 Staging System

<table>
<thead>
<tr>
<th>Staging Group†</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year probabilities, %</td>
<td>0</td>
<td>10.4</td>
<td>31.0</td>
<td>42.4</td>
<td>81.2</td>
</tr>
<tr>
<td>AIDS</td>
<td>0</td>
<td>5.5</td>
<td>15.0</td>
<td>32.3</td>
<td>76.1</td>
</tr>
<tr>
<td>Infectious disease deaths</td>
<td>0.14 (0.02-0.96)</td>
<td>1.00 (Referent)</td>
<td>2.81 (1.89-4.16)</td>
<td>4.79 (3.03-7.59)</td>
<td>17.43 (9.83-30.94)</td>
</tr>
<tr>
<td>Relative hazards (95% CI)</td>
<td>0.44 (0.11-1.82)</td>
<td>1.00 (Referent)</td>
<td>3.51 (2.24-5.52)</td>
<td>5.99 (3.58-10.03)</td>
<td>21.72 (11.83-39.86)</td>
</tr>
</tbody>
</table>

*AIDS indicates acquired immunodeficiency syndrome; HIV-1, human immunodeficiency virus type 1; and CI, confidence interval.
†Staging groups are defined by a combination of plasma viral load and CD4+ cell count categories from Table 2 as described (“Methods”).

Figure 2.—Kaplan-Meier curves of cumulative probabilities for the acquired immunodeficiency syndrome (AIDS) and for deaths due to infectious disease by 5 stages (I-V) based on combination of plasma human immunodeficiency virus type 1 RNA and CD4+ T-lymphocyte measurements obtained at baseline visit, the AIDS Link to Intravenous Experiences (ALIVE) study, Baltimore, Md, 1988-1996. There was a significant linear trend by disease stage for both AIDS (P<.001) and infectious disease death (P<.001).

95% confidence interval [CI] excludes unity. Addition of CD4+ cell count and viral load as continuous variables to the proportional hazards model using the 5 staging categories was not significant (χ²=5.90, df=2, P=.05). The 5-year cumulative probabilities for AIDS and infectious disease death in the 5 categories are shown at the top of Table 3 and ranged from 0% for AIDS and infectious disease deaths in group I to 81.2% for AIDS in group V.

Building on this classification scheme, which was based on CD4+ cell count and HIV viral load, we examined the potential contributions of demographic information and presence or absence of clinical symptoms at baseline. In bivariate proportional hazard models performed separately for each of the variables in combination with the 5-stage CD4+ cell count and viral load variable, oral thrush contributed prognostic information for the development of AIDS (relative hazard, 2.45; 95% CI, 1.30-4.62). Race, current drug use, and number of clinical symptoms were not statistically significantly associated with AIDS or infectious disease death after controlling for the 5-stage CD4+ cell count and viral load variable.

COMMENT

The major finding of this study was that plasma HIV viral load independently and in combination with CD4+ cell count provided a powerful predictor for progression to AIDS, and for death caused by infectious disease, in our study population. This study is unique because in contrast to prior studies of this type, largely involving white homosexual men, this study includes mostly African American men and women as well as large numbers of active IDUs. Some earlier cross-sectional data on p24 antigenemia hinted that racial or ethnic differences might be expected.24 Thus, an important finding is that the same basic relationship between virologic and immunologic factors applies in African American IDUs as in nonminority persons from other risk groups. These results support the conclusion that the same level of aggressive therapy should be offered irrespective of demographic or risk group.

Other reports have tended to compare the relative prognostic value for these 2 measures of HIV-1 disease stage and have established that plasma viral load is a better predictor for subsequent AIDS than CD4+ cell count in homosexual men.9-11 Since clinicians now have at their disposal 2 laboratory measures, each reflecting different parameters of HIV infection, our objective was to examine the combined utility of these 2 measures in predicting AIDS morbidity and mortality in IDUs. Our data suggest that a single measure of a nondetectable plasma viral load (ie, <500 copies/mL) with a CD4+ cell count above 0.50×10³/L was associated with the longest survival; conversely, persons with an HIV RNA load of 30,000 or more copies/mL and a CD4+ cell count of <0.20×10³/L had the highest probabilities of AIDS and infectious disease death in the next 5 years. At each level of CD4+ cell count, viral load provided prognostic information about probabilities of future AIDS and infectious disease death. More important, data presented here are confirmatory of recent analyses conducted in the Multicenter AIDS Cohort Study (MACS), which comprises mostly upper-middle-class white homosexual men.5,11

After accounting for both CD4+ cell count and viral load, we examined whether demographic characteristics and clinical symptoms provided additional prognostic information. In other studies, which did not include measurement of HIV viral load, serum immune activation measures, such as β₂-microglobulin levels, have provided prognostic information independent of CD4+ cell count;25,26 however, we did not study these markers because they have not been adopted in clinical practice. Clinical symptoms such as oral thrush have also provided independent prognostic information for the subsequent development of AIDS26 as in our analysis. Age did not differentiate prognosis as has been found elsewhere.24 Although about half of the cohort reported use of nucleoside analogue monotherapy, because prescribed use is more common in symptomatic patients27 and the effects are modest considering duration of follow-up in this study,28 we did not include their use as a factor in our analysis. Effect of therapy in this study probably results in more conservative estimates of association between baseline measures and clinical outcomes.

Several caveats bear mentioning. Plasma levels of HIV-1 RNA were mea-
sured using the bDNA assay on heparinized plasma specimens stored at −70°C. While similar procedures were followed in the MACS, which facilitates comparison of results between the MACS and the AIDS Link to Intravenous Experiences (ALIVE) studies, higher levels of HIV-1 RNA degradation occur when using heparin rather than ethylenediaminetetraacetic acid (EDTA) as an anticoagulant and when the processing time is longer than 4 hours between specimen collection and storage.29 Studies that compared blood specimens collected in EDTA vs heparin over a range of processing times suggest that plasma HIV-1 RNA levels reported here are probably about half what they were for specimens that had been collected in EDTA and processed within 4 hours.29 Other assays to measure plasma HIV-1 RNA are available, including reverse transcriptase polymerase chain reaction (RT-PCR) and nucleic acid sequence based amplification. Recently, studies that compared results of bDNA and RT-PCR testing on the same MACS specimens showed high correlation (r=0.93) between the 2 assays, but the RT-PCR results were about 2 times higher than those from the bDNA assay.30 This needs to be considered when interpreting our study results for clinical practice. While newer assays may lower the limit of detectable HIV-1 RNA below the 500 copies/mL of the assay used in this study, the sensitivity of the bDNA assay used here was adequate to provide important prognostic information in this population. However, more sensitive HIV-1 RNA assays might be useful to the clinician to gauge the effect of antiretroviral therapy, since HIV-1 RNA levels below the 500 copies/mL cutoff may be associated with an even better long-term prognosis.

In conclusion, our analyses were focused on the combination of plasma HIV-1 RNA levels and CD4+ T-lymphocyte counts as prognostic indicators for AIDS and death in an IDU population prior to the initiation of combination antiretroviral therapies. Even at a time when combination therapies are available, a prognostic indicator model developed using a cohort of IDUs, most of whom were initially untreated and only half of whom received antiretroviral therapy, may be relevant. Large numbers of HIV-infected IDUs remain untreated because of a variety of factors, including limited access to and utilization of health services. In our population, despite aggressive referrals to HIV clinics, only 6% reported use of antiretroviral combination therapies in early 1997. Given appropriate encouragement, IDUs have shown interest in their health and compliance with complex regimens.31 The prognostic indicator model presented here provides clinicians with a simple tool to help educate HIV-1 infected individuals about virally load and CD4+ cell count measurements and make decisions regarding initiation of therapy.

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References