Predictors of Survival in Human Immunodeficiency Virus Type 1-Seropositive Intravenous Drug Users

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In an ongoing prospective study of street-recruited intravenous drug users (IDUs) in Miami, Fla., 116 human immunodeficiency virus type 1 (HIV-1)-infected IDUs were monitored for up to 7 years. This provided an opportunity to evaluate baseline immunological parameters as potential predictors of survival among HIV-1-infected IDUs. As expected, HIV-1-infected IDUs who had an advanced stage of the disease (Centers for Disease Control and Prevention classification III or IV); p24 antigenemia; human T-cell leukemia virus type 1/2 seropositivity; low CD4 counts (≤ 200); low hemoglobin (≤ 14), high serum immunoglobulin A (IgA) (> 500 mg/dl), or high serum IgG ($\geq 3,500$ mg/dl) levels; or low proliferative responses to pokeweed mitogen ($\leq 1,500$ cpm) and to phytohemagglutinin ($\leq 80,000$ cpm) at baseline had worse survival rates. Results from multivariate Cox's models of survival showed that the baseline serum IgG level, serum IgA level, and CD4 count independently predict survival in HIV-1-infected IDUs. Cross-validation procedures verified the above-mentioned findings. These findings support the routine consideration of serum immunoglobulin levels in addition to CD4 count, especially in early evaluation of disease stage, as these evaluations may modify application of prophylaxis and treatment for HIV-1-infected IDUs. We recommend consideration of use of serum IgG and IgA as immunological markers for long-range prediction of survival in HIV-1-infected IDUs. These determinations are less onerous and more appropriate for use in field studies and financially less favored settings.

According to the latest HIV/AIDS Surveillance Report from the Centers for Disease Control and Prevention (CDC), intravenous drug users (IDUs) account for about one-quarter of the cases of AIDS in the United States (3). Given the unique role of intravenous drug use in the AIDS epidemic, the identification of factors that are associated with the outcome of infection by human immunodeficiency virus (HIV) among IDUs is of great importance for our understanding of the pathogenesis and natural history of HIV infection. Use of illicit drugs has been implicated as an important immunomodulating cofactor in the progression to AIDS after HIV type 1 (HIV-1) infection (6). Although several reported studies of HIV infection among drug users have identified prognostic markers for the progression of HIV disease (1, 2, 5, 8, 9, 16, 23, 29, 31, 39), little is known about long-range prognostic markers for survival of IDUs infected with HIV (25). Among the markers seen as most useful for prognostication, CD4 counts, p24 antigenemia, immunoglobulin A (IgA), beta-2 microglobulin, and neopterin have all been proposed, but in most studies attempting to establish their importance in predicting clinical end points, patients have been monitored for a maximum of 36 months only (30). Furthermore, most studies have used first presentation of AIDS-defining disease, rather than death, as the end point. In the present study, a cohort of 116 seropositive IDUs has been monitored for up to 84 months.

To address the relationships among HIV infection, immunosuppression, drug use, and mortality, we have been conducting a prospective study of HIV infection among IDUs in Miami, Fla., for the last 7 years. This report describes the

identification and validation of prognostic markers for survival for those IDUs.

MATERIALS AND METHODS

Beginning in March 1987 and ending in April 1988, a team of field researchers recruited 230 current IDUs for participation in a longitudinal study of retroviral infections and associated factors in Miami and Dade County, Fla. (13). Networks of informal social relations among drug users led the researchers to make contact with prospective study participants. As in all studies of IDUs, the investigators can make no claims of representativeness for the recruited sample. The study aimed at recruiting people from street-based populations rather than institutional sources of IDUs, such as treatment and emergency centers. None of the participants had taken part in programs for treatment of drug abuse for at least 6 months before recruitment. In all but five cases, the HIV enzyme-linked immunosorbent assay (ELISA) and Western blot (immunoblot) tests at baseline were the first in which the participant received a result.

Types of data gathered. After providing informed consent, the study participants responded to a standardized interview about their demographic information, drug use behaviors, sexual behaviors, medical history, any medication (including any antiviral therapy, if infected), and current clinical symptoms. A blood sample was obtained for the following laboratory tests: (i) determination of HIV-1 and human T-cell leukemia virus type 1/2 (HTLV-1/2) serostatus; (ii) CD4 and CD8 lymphocyte counts; (iii) levels of IgG, -A, and -M in serum; (iv) lymphocyte proliferative responses to phytohemagglutinin (PHA) and pokeweed mitogens (PWM) (18); and (v) levels of beta-2 microglobulin and HIV-1 p24 antigen in serum. Follow-up visits with repeat interviews on changes in risk behaviors, medication, and health status and laboratory testing were scheduled every 6 months. The presence of anti-HIV-1 and anti-HTLV antibodies was assessed by ELISAs (Abbott Laboratories, North Chicago, Ill.); reactive samples were assayed twice, and doubly positive samples were confirmed by a protein immunoblot (Hillcrest Biologics, Hillcrest, Calif.). HTLV-1/2 seropositivity was assessed in June 1988, after study participants had been actively recruited for 1 year. To confirm equivocal reactions, repeat tests of up to 3 dilutions were done.

Levels of immunologic markers were assessed as described previously by Klimas et al. (18). Surface marker phenotypic distributions in the lymphocyte populations were determined by two-color direct immunofluorescence by the whole-blood staining technique with the appropriate antibodies and a single-laser flow cytometer. Lymphocyte proliferation in response to stimulation with PHA and PWM was measured by using a whole-blood procedure (reference ranges, PHA, 32,140 to 264,340 cpm; PWM, 5,930 to 23,090 cpm). Levels of IgG, -A, and -M were determined by nephelometry by using an automated Kallestad

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instrument and reagents (reference ranges, IgG, 896 to 1,408 mg/dl; IgA, 126 to 308 mg/dl; IgM, 75 to 195 mg/dl).

Deaths of study participants were closely monitored. In addition to making regular visits to the project's assessment office at 6-month intervals, the participants and/or their associates and families were contacted by study staff on numerous informal occasions, including hospitalizations. All deaths were confirmed at least by a review of the death certificate. Among 43 deaths reported here, 32 occurred in hospital or hospice and 11 were at home or under street circumstances. Among the 230 study participants, 102 were HIV seropositive at baseline and an additional 14 who had been seronegative at baseline had seroconversions during the 6-year follow-up period (up to December 1993). Of 116 HIV-infected IDUs, 24 (20.7%) were found to be seropositive for HTLV at baseline. One seroconverted to HTLV positivity during the follow-up period. For the purpose of this report, only data from these 116 HIV-infected IDUs were used.

Statistical methods. (i) **Estimation of survivor function.** Time of entry was defined as the date of the first interview. For those who were HIV-1 positive at baseline, the survival time was calculated from the date of the baseline interview to the date of death or date of censoring (i.e., the last date for which we monitored survival in this analysis, either 31 December 1994 or the date the participant was last seen). For the 14 seroconverters, survival time was calculated from the date of seroconversion to the date of death or date of censoring. At the time of censoring, 43 participants had died, 38 of HIV-related disease and 5 of other causes, including a stab wound, complications from a perforated ulcer, a heart attack, and an auto accident. Of the 73 not known to be dead, 61 were known to be alive and 12 were lost to follow-up at various dates between 24 April 1987 and 31 December 1994. A Kaplan-Meier (the product limit) estimator was used to estimate the survivor functions (distribution of survival time), and a log-rank statistic was used to test equality of survivor functions.

(ii) **Transformation of variables.** Since the immunologic parameters were not normally distributed and the link between the immunological parameters and the distribution of survival can be very general, nonparametric additive models were first used to explore appropriate regression functions or transformations of immunological parameters (12). This process converts the raw numbers (counts, weight per unit of volume, counts per unit of time) into ranges that carry clinical meaning, in this case a relationship with death by AIDS. In order to categorize the immunological parameters robustly, each parameter was first divided by cut points at the 1st through 10th deciles and then risk ratio (estimation of the relationship between that specific range of values and death) was calculated for each decile, by using the first decile as a reference group, with Cox's proportional hazards model. On the basis of these results, the analyst divided the range of these parameters into two (dichotomization) or, if necessary, three (trichotomization) meaningful categories.

(iii) **Proportional hazards modeling.** The univariate Cox's proportional hazards model was then used to estimate the effect of each factor, including demographic variables, drug use variables, hematological parameter, and immunological parameters, on survival (4). Since zidovudine (AZT) use may affect survival, AZT use was treated as both a time-dependent covariate and a dichotomized variable in the univariate Cox's models to explore the effect of AZT treatment on survival. Our information on AZT involved length of time used by participants known to have taken the medication, rather than dosage, hence its use as a time-dependent covariate. Those variables that exhibited statistical significance ($P < 0.10$) in univariate proportional hazards models were jointly entered into a multivariate model and those that ceased to be significant were deleted, yielding the final model. Since our original data suggested that the study participants who were coinfectd with both HIV and HTLV may be different from those who were infected with HIV only with respect to the immunological predictor(s), the final models were also fitted by using HTLV seropositivity (13).

(iv) **Cross-validation.** In order to evaluate the predictive value of the Cox's proportional hazards model that resulted from the analyses described above, cross-validation was implemented by the use of the cross-validation likelihood (CVL) method. For a given Cox's model, the CVL measures how well survival for each study subject in the study population can be predicted by using data from other study subjects and thus serves as a measure of predictive value (36). Explained variation in survival was also measured to quantify the predictive power of factors identified in the Cox's models resulting from our analyses (19, 27). In order to describe effect modification, HTLV-1/2 seropositivity was also treated as a stratification variable and the Cox's models were fitted for HTLV-1/2 negatives and positives separately. Fourteen individuals who had been HIV negative at the time of the baseline evaluation seroconverted to HIV after entering this study. Statistical analysis was also implemented without them. Only results obtained from analyses with all subjects are presented because exclusion of seroconverters from the analyses did not affect the final results. All P values reported are two-sided.

RESULTS

Data for a total of 116 study participants are included in this report. Among 116 HIV-1-infected study participants, there were 108 (93.1%) African Americans, 3 (2.6%) white non-Hispanics, and 5 (4.3%) Hispanics. Eighty-four (72.4%) were

TABLE 1. Basic characteristics of HIV-infected IDUs

Characteristic	n (%)
Age (yr)	
≤30.....	12 (10.3)
30–40.....	80 (69.0)
40–50.....	20 (17.2)
>50.....	4 (3.4)
Sex	
Male.....	84 (72.4)
Female.....	32 (27.6)
Race or ethnicity	
White.....	3 (2.6)
Black.....	108 (93.1)
Hispanic.....	5 (4.3)
HTLV-1/2 status	
Negative.....	91 (78.4)
Positive.....	24 (20.7)
Seroconversion.....	1 (0.9)
HIV status	
Positive.....	102 (87.9)
Seroconversion.....	14 (12.1)
CD4 count at baseline	
≤200.....	14 (12.1)
>200.....	102 (87.9)
Alcohol consumption	
Less than every day.....	49 (42.2)
At least every day.....	67 (57.8)
Heroin use ^a	
Less than every day.....	68 (58.6)
At least every day.....	48 (41.4)
Cocaine use ^b	
Less than every day.....	31 (26.7)
At least every day.....	85 (73.3)
Speedball use ^a	
Less than every day.....	90 (77.6)
At least every day.....	26 (22.4)
AZT treatment	
No.....	102 (87.9)
Yes.....	14 (12.1)
Level (mg/dl) of:	
IgG	
≤3,500.....	101 (87.1)
>3,500.....	15 (12.9)
IgM	
≤350.....	89 (76.7)
>350.....	27 (23.3)
IgA	
≤500.....	100 (86.2)
>500.....	16 (13.8)
Response (cpm) to:	
PHA	
≤80,000.....	89 (77.4)
>80,000.....	26 (22.6)
Missing.....	1
PWM	
≤1,500.....	42 (36.8)
>1,500.....	72 (63.2)
Missing.....	2

^a Data reflect injection frequency.

^b Data reflect both injection and smoking frequency.

males. Table 1 shows the basic characteristics of the HIV-1-infected study participants. The mean age of these study participants at baseline was 34.5 years (standard deviation, 6.22; range, 23 to 60 years). Of the 116 study participants, 25 (21.6%) were HTLV-1/2 seropositive. At the baseline evaluation, 14 of 116 (12.1%) participants had CD4 counts of ≤200.

The primary risk of HIV infection for most participants was intravenous drug use, although 71 (61.2%) had some experi-

FIG. 1. Estimated distribution of survival for all study participants according to HTLV-1/2 seropositivity.

ence of exchanging sex for money or drugs, including 45 men. Self-injection experience ranged from a few shots in the weeks prior to recruitment to an estimated 60 shots per week. Median injection experience was approximately four or five shots per week prior to the baseline interview.

As of December 1994, a total of 43 deaths attributed to HIV-related diseases in the cohort of 116 HIV-infected IDUs occurred over more than 7 years of follow-up. An additional four deaths not attributed to HIV occurred during the follow-up period. Since the end point in this study was HIV-related death, these four deaths were censored at the time of death.

Among the 116 participants, there were 14 (12.1%) who were ever treated with AZT. Among these 14, 5 have died and 9 are still alive. Ongoing contact with the participants has made possible this assessment, but we have only begun to measure blood AZT levels in more recent studies. Although we have no consistent information on prophylaxes for specific infections such as *Pneumocystis carinii* pneumonia and toxoplasmosis, we have observed that most of the participants who have taken trimethoprim-sulfamethoxazole (Bactrim) or other prophylaxes have died. We know of only three participants who are still alive who have ever taken any of these medications. Furthermore, first doses of these have tended to be administered

after first onset of the infection as a secondary preventive strategy.

Figure 1 presents the Kaplan-Meier estimated survival curves for those participants who were HTLV-1/2 seropositive and those who were HTLV-1/2 seronegative. Those who were HTLV-1/2 seropositive, with a median survival time of 82.4 months, had worse survival than did those who were HTLV negative, whose median survival time could not be calculated because more than one-half survived the entire censoring period (Fig. 1; lower boundary of 95% percent confidence interval, 77.6 months; $P = 0.088$). Figure 2 shows the Kaplan-Meier estimated survival curves for those participants who had high serum IgG levels ($>3,500$ mg/dl) at baseline and those who had IgG levels less than 3,500 mg/dl. Those who had high serum IgG levels at baseline, with a median survival time of 46.1 months, had significantly worse survival than did those who had relatively low levels of IgG, with a median survival time of 82.4 months ($P < 0.009$). Figure 3 shows the Kaplan-Meier estimated survival curves for those who had high serum IgA levels (>500 mg/dl) at baseline and those who had IgA levels less than 500 mg/dl. Those who had high serum IgA levels at baseline, with a median survival time of 30.3 months, had significantly worse survival than did those who had relatively low levels of IgA, with a median survival time of 82.4 months

FIG. 2. Estimated distribution of survival for all study participants according to baseline serum IgG levels.

($P < 0.0016$). Figure 4 shows the Kaplan-Meier estimated survival curves for those who had low CD4 counts (≤ 200) at baseline and those who had CD4 counts of higher than 200. Those who had low CD4 counts at baseline, with a median survival time of 45.2 months, had significantly worse survival than did those who had CD4 counts of above 200, with a median survival time of 82.4 months ($P = 0.002$).

Table 2 shows the results of the univariate proportional hazards models. On the basis of univariate analyses, age, ethnicity, alcohol consumption, heroin use, cocaine use, speedball use, AZT treatment, and beta-2 microglobulin were not significantly associated with survival ($P > 0.10$), while sex; HTLV-1/2 seropositivity; a higher disease stage (CDC classification III or higher); a positive p24 antigen test result; high IgG ($> 3,500$ mg/dl), high IgA (> 500 mg/dl), and high hemoglobin (> 14) levels; a low response to PWM ($\leq 1,500$ cpm); a high response to PHA ($> 80,000$ cpm); and a low CD4 count (≤ 200) were at least marginally associated with survival ($P < 0.10$). In order to develop a parsimonious initial model that identified a factor(s) independently associated with survival, a multivariate proportional hazards model that incorporated variables showing significant association with P values below 0.10 was constructed. The univariate Cox's model showed that AZT use, when treated as either a dichotomized or a time-dependent covari-

ate, did not significantly affect survival. Therefore, only HTLV-1/2 seropositivity, disease stage (CDC classification), hemoglobin level, presence of p24 antigen, CD4 count, IgA and IgG levels, and responses to PHA and PWM were included in the multivariate model.

Table 3 presents three final models: a model for all study subjects, a model for HTLV-seronegative subjects, and a model for HTLV-seropositive subjects. The first model shows estimated relative hazards from the final model, which includes serum IgG and IgA levels and CD4 count. According to this model, the relative hazard of death for individuals with baseline serum IgG levels of $> 3,500$ with respect to IgG levels of $\leq 3,500$ was 3.55, controlling for serum IgA and CD4 count. The relative hazard of death for individuals with baseline serum IgA levels > 500 with respect to IgA levels of ≤ 500 was 2.83, controlling for serum IgG and CD4 count. A low CD4 count was also significantly associated with worse survival (adjusted risk ratio, 2.67). This suggests that serum IgG and IgA levels and CD4 count are independently associated with survival among HIV-1-infected IDUs. Interactions among IgG and IgA levels and CD4 count were added to the final model. Neither the interaction between CD4 count and IgA level nor the interaction between IgG and IgA levels was significant. The interaction between IgG level and CD4 count, however, was

FIG. 3. Estimated distribution of survival for all study participants according to baseline serum IgA levels.

significant ($P = 0.045$), suggesting that those IDUs with high IgG and low CD4 counts may have much worse survival.

The second model in Table 3 was the final model for HTLV-1/2-seronegative individuals. This model indicates that although a low CD4 count (≤ 200) was significantly associated with worse survival (risk ratio, 2.43; $P = 0.05$) in the univariate analysis, CD4 count was not an independent predictor, after adjustment for serum IgG and IgA. Because of multicollinearity, interaction between IgA and IgG levels was not estimable. In order to investigate why CD4 count is not a predictor among HTLV-negative individuals, a logistic regression model with a dependent variable for CD4 (≤ 200 versus > 200) and independent variables for IgG ($\leq 3,500$ versus $> 3,500$ mg/dl) and IgA (≤ 500 versus > 500 mg/dl) was fitted. The result shows that in this bivariate model, CD4 count was highly associated with IgA level (adjusted odds ratio, 8.55; 95% confidence intervals [CI], 1.85 and 39.43; $P = 0.006$), while CD4 count was not associated with IgG level (adjusted odds ratio, 0.64; 95% CI, 0.07 and 6.09; $P = 0.70$), after IgA levels had been controlled for in the model. This may suggest that IgA level is a more independent predictor than CD4 count among HTLV-negative IDUs infected with HIV.

The third model in Table 3 was the final model for HTLV-1/2-positive individuals. This model suggests that CD4 count is

the only independent predictor of survival among HTLV-1/2-positive IDUs.

The results of both unadjusted and adjusted analyses for evaluating the relative importance of predictors identified by our models are shown in Table 4. In an unadjusted effect analysis, the relative importance was measured by the proportion of variation explained by a factor of interest in a univariate model, while in an adjusted effect model, the relative importance was measured by the proportion of variation explained by a factor of interest, with adjustment for other factors in a multivariate model. The analysis for all study subjects suggested that CD4 count and serum IgG and IgA levels were equally important in explaining the variation in survival. The analysis for HTLV-1/2-seronegative individuals indicated that serum IgA and IgG levels explained higher proportions of variation in survival than CD4 count did, while the analysis for HTLV-1/2-seropositive individuals implied that the most important predictor was CD4 count.

Table 5 shows the results of measuring the predictive value of the final models identified by methods for estimating cross-validation likelihood. The model with the largest change in cross-validation likelihood has the best predictive value for future data. The results suggested that serum IgG and IgA levels and CD4 count were the best combination for all study

FIG. 4. Estimated distribution of survival for all study participants according to baseline CD4 counts.

subjects, serum IgG and IgA levels were the best for HTLV-1/2-seronegative individuals, and serum IgG level and CD4 count were the best for HTLV-1/2-seropositive individuals.

DISCUSSION

This study had as its primary purpose the identification of baseline immunological parameters as potential markers to predict long-term survival among predominantly asymptomatic HIV-1-seropositive IDUs. Since one-quarter of the cases of AIDS reported to the CDC occur in IDUs and no prior studies have identified immunological markers for survival in IDUs, our study may provide some new information in this respect.

Major findings of this study are that CD4 count and elevated IgA and IgG levels were significant predictors of survival. Although the CD4 count is widely used to monitor the progression of disease, studies have shown that CD4 count itself may not be a perfect marker for predicting survival in HIV-1-infected individuals (11, 35). Among 14 participants who had low baseline CD4 counts (<200), 9 (64.3%) died during the follow-up period. Of these nine, however, one (11.1%) had high IgG levels and four (44.4%) had high IgA levels at baseline. Among 15 participants who had high baseline IgG levels (>3,500 mg/dl), 10 (66.6%) died during the follow-up period.

Of these 10, only 1 (10%) had a low CD4 count and 1 (10%) had a high IgA level at baseline. Among 16 participants who had high baseline IgA levels (>500 mg/dl), 10 (62.5%) died during the follow-up period. Of these 10, 4 (40%) had low CD4 counts and only 1 (10%) had a high IgG level at baseline. This also suggests that there is a close relationship between CD4 count and IgA level regarding the prediction of survival. On the other hand, of 43 deaths that occurred in our study, 34 (79.1%) were of participants with baseline CD4 counts of above 200. This implies that a low CD4 count (<200) had a low specificity for predicting death in HIV-1-infected IDUs. This finding is verified by the cross-validation results that suggest that CD4 count alone explained only about 6% of the variation in survival for all study subjects. Therefore, identifying additional immunological markers may be especially important for predicting survival in HIV-1-infected IDUs.

Our findings show that serum IgA and IgG levels are independent predictors of survival. Of 43 deaths, 19 (44.2%) occurred in participants who had elevated baseline serum IgG and/or IgA levels. Among these 19 participants, only 5 (26.3%) had low baseline CD4 counts (<200). On the basis of the cross-validation results, the proportion of variation in survival explained by CD4 count and serum IgG and IgA levels in combination was about 18%. Use of serum IgG and IgA levels

TABLE 2. Univariate proportional hazards model

Variable	Risk ratio	95% CI	P value
Age			
≤35	1.00	0.61, 2.18	0.18
>35	1.15		
Sex			
Male	1.00	0.85, 3.18	0.14
Female	1.64		
Race or ethnicity			
Non-black	1.00	0.33, 5.70	0.66
Black	1.37		
HTLV status			
Negative	1.00	1.06, 4.34	0.03
Positive	2.14		
CDC classification			
≤II	1.00	1.00, 4.12	0.049
>II	2.03		
Beta-2 microglobulin level			
≤4	1.00	0.70, 2.65	0.36
>4	1.36		
p24 antigen status			
Negative	1.00	1.51, 6.67	0.002
Positive	3.18		
Alcohol consumption			
Less than every day	1.00	0.65, 2.45	0.48
At least every day	1.27		
Heroin use			
Less than every day	1.00	0.40, 1.51	0.46
At least every day	0.78		
Cocaine use			
Less than every day	1.00	0.49, 2.08	0.97
At least every day	1.01		
Speedball use			
Less than every day	1.00	0.66, 2.80	0.40
At least every day	1.36		
AZT treatment			
No	1.00	0.15, 1.53	0.47
Yes	0.47		
Hemoglobin level			
≤14	1.00	0.20, 0.89	0.02
>14	0.42		
CD4 count			
>200	1.00	1.44, 6.39	0.003
≤200	3.03		
CD8 count			
≤1,000	1.00	0.49, 1.73	0.79
>1,000	0.92		
Response (cpm) to:			
PWM			
≤1,500	1.00	0.22, 0.76	0.005
>1,500	0.41		
PHA			
≤80,000	1.00	0.15, 0.96	0.04
>80,000	0.37		
Level (mg/dl) of:			
IgM			
≤350	1.00	0.48, 2.00	0.96
>350	0.98		
IgA			
≤500	1.00	1.46, 6.15	0.003
>500	3.00		
IgG			
≤3,500	1.00	1.22, 5.09	0.01
>3,500	2.50		

as predictors considerably improves the explanatory power of our survival model.

The immune parameters analyzed in this study constitute a baseline view of the study participants whose survival was mon-

TABLE 3. Final multivariate proportional hazards model

Group (n) and variable ^a	Risk ratio	95% CI	P value
I. All subjects (116)			
CD4 count			
>200	1.00	1.16, 6.15	0.02
≤200	2.67		
IgG			
≤3,500	1.00	1.66, 7.61	0.001
>3,500	3.55		
IgA			
≤500	1.00	1.26, 6.38	0.01
>500	2.83		
II. HTLV-1/2 negative (91)			
CD4 count			
>200	1.00	0.62, 5.13	0.29
≤200	1.78		
IgG			
≤3,500	1.00	1.16, 6.84	0.02
>3,500	2.82		
IgA			
≤500	1.00	1.23, 10.33	0.019
>500	3.56		
III. HTLV-1/2 positive (25)			
CD4 count			
>200	1.00	2.50, 254.61	0.006
≤200	25.25		
IgG			
≤3,500	1.00	0.97, 20.34	0.055
>3,500	4.44		
IgA			
≤500	1.00	0.15, 6.06	0.95
>500	0.94		

^a Immunoglobulin levels are measured in milligrams per deciliter.

itored over time. This kind of predictive modeling offers valuable information about a variety of AIDS patients for whom clinicians may not have the opportunity to gather many datum points on these parameters. When they are first tested, HIV-infected IDUs may have deceptively high CD4 counts whereas they are in fact on the verge of serious illness. Longitudinal tracking of immune parameters, now under way with the same cohort but for which data are not yet ready for presentation, will offer information on immunosuppression and progression to AIDS, including relationships among parameters over time. At this time, however, the present results should be helpful to clinicians facing newly identified cases of HIV infection among IDUs.

Fahey et al. have demonstrated the importance of both immune deficits (as reflected by a decreased number of CD4 cells) and immune stimulation (reflected by IgA level) in predicting prognosis for HIV-1-infected homosexual men (7). The results of our studies corroborate other findings (23, 41) about the importance of IgA and IgG levels in assessing survival of HIV-seropositive IDUs.

Our findings highlight the importance of immune stimulation (as reflected by increased levels of serum IgG and IgA) in predicting survival. Because 34 of the 43 participants who died during the follow-up period did so despite having baseline CD4 counts of >200, which are outside the accepted range for beginning aggressive treatment and prophylaxis, it appears that elevated baseline IgG levels (in excess of 3,500 mg/dl) and/or elevated baseline IgA levels (above 500 mg/dl) may be additional indicators regarding treatment of HIV-1 infection in IDUs. Our data suggest that decisions about onset of prophyl-

TABLE 4. Relative importance of predictors^a

Group (total PVE ^b [%]) and factor	PVE ^b	
	Unadjusted effects	Adjusted effects
I. All subjects (17.6)		
CD4	0.061	0.041
IgG	0.049	0.069
IgA	0.071	0.054
II. HTLV-1/2 negative (14.7)		
CD4	0.039	0.023
IgG	0.040	0.050
IgA	0.077	0.062
III. HTLV-1/2 positive (38.8)		
CD4	0.256	0.225
IgG	0.074	0.088
IgA	0.066	0.039

^a The bootstrap sample size was 500.^b PVE, proportion of variation explained.

laxis for opportunistic infections and assessment of efficacy of antiretroviral therapeutic interventions should also take into account serum IgG and IgA levels in this population and not rely solely on the traditional CD4 cell count assessment. We cannot, on the basis of these data alone, determine the effect on survival prediction that additional consideration of IgG and IgA levels, and perhaps more-aggressive treatment based on those levels, could have for IDUs who have CD4 counts in excess of 200 but high IgG and/or IgA levels. Nevertheless, this question appears to be worth asking in future studies.

The findings presented here indicate a need for more investigations into the mechanisms by which a high serum immunoglobulin level is related to mortality. The relationship between use of illegal drugs and B-cell function may help to explain why serum IgG and IgA levels are prognostic markers in HIV-1-infected IDUs. If we can characterize this relationship adequately, we can use data on drug use to identify categories of HIV-1-infected IDUs whose B-cell function we can expect to become impaired.

Regarding the relevance of monitoring changes in B-cell function, AIDS patients do not present with a single defect due to loss of the CD4 cell population but frequently have many immunological defects, including myriad abnormalities associated with humoral immunity and B-cell function. These B-cell abnormalities include polyclonal activation (28, 38, 40) with circulating immune complexes (22), autoantibodies (32), elevated titers of Forssman-like antibodies (17), and elevated levels of IgA, -D, -E, -G, and -M (10). Elevated levels of immunoglobulin could in turn lead to formation of aggregates and inhibition of natural killer cell cytotoxic activity (13, 21, 24), for instance. Antibody-mediated enhancement of HIV-1 infection of both macrophages and T cells has also been documented (26) and shown to be blocked by heat-aggregated IgG (15, 34) and by soluble CD4 (33). Assessment of the nature of the idiosyncratic changes in B-cell function and its causes and mediators in HIV-1-infected IDUs is therefore of significant relevance.

Results obtained from our statistical models have been cross-validated in order to evaluate the predictive values of our statistical models. This involves computer simulation of additional data sets and retesting of analyses with these simulated sets. Cross-validation is especially important in reviewing analyses of nonnormally distributed data gathered from nonran-

TABLE 5. Cross-validation for the proportional hazards models

Group and covariate	CVL	Change in CVL
I. All subjects		
No covariate	-223.94	0.00
IgG	-222.28	1.66
IgA	-221.54	2.40
CD4	-221.65	2.29
IgG, IgA	-218.68	5.26
IgG, CD4	-218.93	5.01
IgA, CD4	-221.38	2.56
IgG, IgA, CD4	-218.15 ^a	5.79
II. HTLV-1/2 negative		
No covariate	-158.53	0.00
IgG	-158.23	0.30
IgA	-156.64	1.89
CD4	-158.05	0.48
IgG, IgA	-155.73 ^a	2.80
IgG, CD4	-157.27	1.26
IgA, CD4	-158.22	0.31
IgG, IgA, CD4	-157.31	1.22
III. HTLV-1/2 positive		
No covariate	-42.07	0.00
IgG	-41.50	0.57
IgA	-43.11	-1.04
CD4	-38.55	3.52
IgG, IgA	-42.17	-0.10
IgG, CD4	-37.44 ^a	4.63
IgA, CD4	-40.53	1.54
IgG, IgA, CD4	-39.92	2.15

^a Best predictive value according to the CVL.

dom samples. The results of the cross-validation show that CD4 count and serum IgG and IgA levels also are good predictors for additional sets of similar computer-generated data.

The predictive power of a set of prognostic variables in a survival model is a concept distinct from the statistical significance of the variable or the adequacy of the model fit (36). Analysis of the relative importance of prognostic variables as shown in Table 4's presentation of proportion of variance explained is informative for survival analysis. The proportion of variance explained may reveal certain properties of a data set not adequately expressible by the use of the conventional methods to estimate relative risks or *P* values, since the predictive power of prognostic variables has often been overestimated by the conventional methods. This overestimation may discourage the search for better prognostic markers, and it may encourage the use of new diagnostic assessments of little practical value (18, 19).

Since coinfection with HIV-1 and HTLV-1/2 may adversely affect survival in IDUs (25), stratified analyses (by HTLV-1/2 seropositivity) were also performed. Current research is attempting to define the mechanism whereby coinfection may affect survival, and the results presented here suggest that the survival predictor(s) for coinfecting IDUs may be different.

Our study had at least two limitations that should be considered in the interpretation of the results. First, our study cohort did not represent a random sample of all HIV-1-infected IDUs. We recruited the study participants through network tracing. To the extent that those who did and those who did not participate may differ with regard to some exposure variables, our results may be biased. Nevertheless, associations between immunological markers and survival that we found make it unlikely that this potential bias could alter in any

important way the interpretation of our results. Furthermore, recent virological studies by Wei et al. (37) and Ho et al. (14) imply that strains of virus that may have infected specific drug-using networks may make little difference in ultimate survival. Second, since more than 90% of study participants are African Americans, our findings may be confounded by some as-yet-undefined factors linked to race or ethnicity and/or socioeconomic status. Lucey et al. (20) have found that African Americans have significantly higher IgG and IgA levels than do white non-Hispanics.

In spite of these limitations, our preliminary data provide new knowledge about survival and immunologic parameters. Definition of these markers is extremely important, not only in the understanding of the natural history and pathogenesis of HIV-1 infection among IDUs but also in classifying disease stage and in improving the timeliness of prophylaxis and other treatment in IDUs. The current structure of both the World Health Organization and CDC staging of HIV disease recognizes that some individuals with relatively high CD4 cell counts may show symptoms indicating advanced stages of disease. The findings presented here point to strategies for predicting in which patients this condition might occur. Routine use of levels of serum IgG and IgA to accompany CD4 count appears helpful in evaluation of disease stage and may improve application of prophylaxis and treatment for HIV-1-infected IDUs.

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