Can Routine Clinical Markers Be Used Longitudinally to Monitor Antiretroviral Therapy Success in Resource-Limited Settings?

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(See the article by Calmy et al. on pages 128–34 and the editorial commentary by Schooley on pages 139–40)

Although routine clinical markers are used routinely to determine the stage of human immunodeficiency virus (HIV) disease, their use in monitoring response to antiretroviral therapy is poorly defined. Selected clinical markers were evaluated for their ability to predict first-line antiretroviral therapy success. No clinically meaningful variables were identified that predicted virologic or immunological success, implying that the CD4$^+$ cell count and HIV type 1 RNA level data are required for optimal management of antiretroviral therapy.

Infection with HIV has far exceeded pandemic dimensions, with >45 million people living with HIV infection globally. The World Health Organization (WHO) and many other agencies have joined efforts to expand access to antiretroviral therapy in resource-constrained nations [1], resulting in dramatic reductions in the cost of antiretroviral therapy. The standard of care in industrialized nations for determining treatment success or failure is to monitor changes in CD4$^+$ T cell counts and HIV RNA levels after the initiation of antiretroviral therapy. However, the cost of laboratory equipment and infrastructure required to monitor the efficacy of HAART by these methods remains a significant obstacle for many low-income countries [2]. Therefore, identification of low-cost methods of predicting response to antiretroviral therapy is a crucial priority for developing nations as therapies become more widely available. To address this issue, we undertook a retrospective, longitudinal study to evaluate potential clinical predictors of virologic and immunologic success other than determination of the HIV load or CD4$^+$ cell count among individuals attending the HIV Clinic at the University of Alabama at Birmingham.

Methods. The data for this study originated from an ongoing observational database developed in 1992. The University of Alabama at Birmingham Institutional Review Board approved the database protocol. For this study, a chart review was performed to retrieve clinical and laboratory data that were not present in the database, as well as to verify the dates on which the antiretroviral therapy regimen was initiated and discontinued.

Inclusion criteria for this analysis were as follows: subjects were at least 16 years of age, were antiretroviral therapy naive at the first clinic visit, received an index antiretroviral therapy regimen (defined as $\geq$3 antiretroviral drugs) for at least 3 months, had visited the clinic for care during the period from January 1995 through August 2004, and had follow-up data that included >1 CD4$^+$ cell count or HIV load measurement. Individuals who met these criteria were included in the analysis without considering adherence to antiretroviral therapy or medical care, to reflect conditions of actual HIV care and management in clinics. The outcomes analyzed were as follows: (1) virologic success, defined as an HIV load of either <50 or <400 copies/mL achieved at 12 months after therapy initiation (to account for "blips" in viral replication, values within a window of $\pm$3 months were considered for evaluation of virologic success); and (2) immunologic success, defined as an increase in the CD4$^+$ cell count of $\geq$50 cells/mm^3 at 6 months after the initiation of therapy.

Selected key clinical markers were chosen at month 3 of therapy and were evaluated in univariate logistic regression models for their ability to predict immunological success after 6 months and virologic success after 12 months of antiretroviral therapy. The predictor variables used for immunologic success were percentage change in the total lymphocyte count, hemoglobin level, platelet count, and weight during the first 3 months of antiretroviral therapy. Predictor variables used for virologic success included percentage change in the total lymphocyte count, hemoglobin level, platelet count, CD4$^+$ cell count, and weight during the first 3 months of antiretroviral therapy. Deaths were regarded as treatment failures. *P* values <.05 were considered to be statistically significant. No adjustments were made to account for the multiple tests performed.

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Table 1. ORs for a 10% change in clinical markers at 3 months on virologic and immunologic success of antiretroviral therapy.

	Estimated OR (95% CI)				
	Plasma viral load				
		Receiving initial HAART regimen			
Predictor variable[a]	<50 copies/mL	<50 copies/mL	<400 copies/mL	$CD4^+$ cell count ⩾50 cells/μL	$CD4^+$ cell count ⩾50 cells/μL and receiving initial HAART regimen
Total lymphocyte count	0.994 (0.977–1.011)	0.991 (0.974–1.008)	0.985 (0.963–1.007)	0.998 (0.978–1.018)	0.995 (0.975–1.015)
Hemoglobin level	1.019 (0.897–1.158)	1.019 (0.879–1.182)	0.910 (0.771–1.074)	0.913 (0.773–1.079)	0.889 (0.738–1.071)
Platelet count	1.003 (0.996–1.011)	1.003 (0.995–1.010)	1.003 (0.995–1.011)	1.030 (0.984–1.079)	1.026 (0.980–1.076)
$CD4^+$ cell count	0.997 (0.994–1.001)	0.997 (0.993–1.002)	0.996 (0.991–1.001)	…	…
Percentage weight change	0.782 (0.602–1.017)	0.732 (0.550–0.972)	0.723 (0.533–0.981)	0.844 (0.603–1.180)	0.841 (0.595–1.190)

[a] All variables were analyzed as continuous variables.

A retrospective power analysis was performed. Assuming a baseline probability of failure of 0.372 and a 2-sided alternative, a sample size of 244 observations achieves 80% power at a .05 significance level to detect an OR of 0.673. An adjustment was made to account for the observed R^2 of 0.114 between the independent variables in the model. Analyses were performed using SAS/STAT software, version 9.1 of the SAS System for Windows XP (SAS Institute).

Results. The study population consisted of 466 eligible subjects. The median age ($\pm$SD) at baseline was 37.0 $\pm$ 9.3 years, and 352 patients (76%) were male. A total of 239 patients (51.3%) were black, 214 (46%) were non-Hispanic white, 4 (<1%) were Hispanic, and 9 (1.9%) were of other racial or ethnic background. Most of the subjects did not have injection drug use–related risk behavior (92% of patients were not injection drug users), and male-male sex risk behavior was well represented (47.4% of patients were men who have sex with men). Baseline laboratory characteristics were as follows: median $CD4^+$ cell count ($\pm$SD), 156 $\pm$ 207 cells/μL (range, 1.0–1211.0 cells/μL); median plasma HIV load ($\pm$SD), 71,285 $\pm$ 449,327 copies/mL (range, <50 to 6,352,941 copies/mL); median total lymphocyte count ($\pm$SD), 1150 $\pm$ 705 cells/mL (range, 52–3726 cells/mL); and median hemoglobin level ($\pm$SD), 12.5 $\pm$ 2.1 g/dL (range, 5.2–18.6 g/dL).

Some patients were excluded for reasons of missing data (109 patients for the virologic outcome and 185 patients for the immunologic outcome). There were no significant differences between patients in the study and those with missing data with regard to the numbers of individuals who continued to receive the initial HAART regimen after 1 year of therapy or with regard to the development of opportunistic infection. The significant differences between the study and missing data groups were as follows: (1) the immunological outcome study group had a higher proportion of white subjects than nonwhite subjects ($P = .014$), (2) the virological outcome study group had a higher proportion of men who have sex with men ($P = .001$), (3) the virological outcome study group had a lower rate of use of nonnucleoside reverse-transcriptase inhibitors ($P = .001$) and a greater rate of protease inhibitor use ($P = .021$), and (4) the virological outcome study group had a greater change of total lymphocyte count ($P = .022$) and platelet count ($P = .015$) after 3 months of therapy.

The only variable predictive of virologic success by either definition in the univariate analyses was percent change in weight, which was predictive of an HIV load <50 copies/mL ($P = .031$) and <400 copies/mL ($P = .037$) at 1 year for individuals who continued to receive their initial antiretroviral therapy regimen only (table 1). For the analyses predicting immunological success, no variables were found to be associated with this outcome in the univariate logistic regression models (table 1).

Discussion. In recent years, access to antiretroviral medications has dramatically expanded globally through numerous international initiatives. Owing to the tremendous need for therapy for so many infected persons worldwide, many programs have focused their resources on drug therapy, to the exclusion of virologic and immunologic monitoring. As such, there is a strong need to identify alternative methods of determining success of antiretroviral therapy in lieu of $CD4^+$ cell count and HIV load measurements. Although many studies have identified several clinical markers that correlate with HIV-related mortality, no such markers have been shown to predict virologic or immunological success after the initiation of therapy. In this study, we evaluated whether routinely collected clinical information could substitute for more-expensive markers of antiretroviral activity. With the exception of percentage change in weight, all variables evaluated showed no value as a potential substitute for virological or immunological measurements. Although changes in weight approached statistical significance, this variable is influenced by many other factors that

limit its precision and utility, especially in resource-poor settings; thus, the findings become clinically meaningless. We conclude, therefore, that no clinical marker or combination of markers can substitute for the use of $CD4^+$ cell count and HIV load data as indicators of successful antiretroviral therapy and that these metrics are required to accurately assess the effectiveness of antiretroviral therapy.

The WHO has recommended that monitoring the response to HAART be accomplished through a combination of clinical and basic laboratory tests, such as determination of total lymphocyte count and hemoglobin level, when $CD4^+$ cell count tests are not available [3]. Our data do not support these recommendations for longitudinal outcomes. Numerous studies in the literature have demonstrated the value of the total lymphocyte count [4–7] and other markers [8, 9] in determining the timing of antiretroviral therapy initiation. However, few studies have evaluated the use of changes in these markers for predicting treatment success or failure after the initiation of antiretroviral therapy [10, 11]. Some studies suggest correlation between changes in the total lymphocyte count and changes in the $CD4^+$ cell count, but no correlation was identified between changes in total lymphocyte count and changes in HIV load. Moreover, other readily available laboratory and clinical parameters have not been evaluated. Our study was, to our knowledge, the first to assess such a combination of variables in antiretroviral therapy–naive individuals, and none of the clinical variables analyzed in this study provided meaningful predictors of therapy outcomes.

There are several limitations to this study that may limit how it is interpreted. First, this was a retrospective analysis with a small sample size; therefore, we did not have the power to detect small effects of the individual predictor variables. However, our study had 80% power to detect clinically meaningful effects, and it is unlikely that any major significant correlations were missed. Second, the missing data in our study may have biased the study results towards a null finding, but this does not invalidate the study findings. Third, the data for this study population were from a clinical database in the United States. Conditions specific to resource-limited countries can influence the absolute values and the dynamics of $CD4^+$ cell count [12], and these may influence the interpretability and dynamics of the total lymphocyte count and other hematological parameters. Fourth, the specific antiretroviral medications used in this study population do not necessarily reflect first-line antiretroviral therapy regimens used in many resource-poor nations. However, studies of multiple regimens used in developed countries demonstrate that the responses to antiretroviral therapy are biological in nature and are not generally regimen specific. Finally, the list of potential markers examined in this study was limited to those identified in the literature and could be expanded in future studies.

In conclusion, our findings indicate that there is no set of readily identifiable clinical markers known at this time that can substitute for $CD4^+$ cell count and HIV load data in monitoring response to antiretroviral therapy. The findings reinforce the need to follow recommendations that advocate using both $CD4^+$ cell count and HIV-1 RNA testing for monitoring treatment response, because neither clinical features nor $CD4^+$ cell counts alone sufficiently predict virologic responses. Our study highlights the need for the development of novel, less expensive technologies that can measure $CD4^+$ cell counts and HIV load as delivery of antiretroviral therapy is expanded on a global scale.

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