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Response of CD4 Lymphocytes and Clinical Consequences of Treatment Using ddI or ddC In Patients with Advanced HIV Infection

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Summary: The value of CD4 lymphocyte counts as a surrogate marker in persons with advanced human immunodeficiency virus infection during antiretroviral treatment was assessed using longitudinal models and data from the Terry Beirn Community Programs for Clinical Research on AIDS didanosine/zalcitabine trial of 467 HIV-infected patients. Patients with AIDS or two CD4 counts of ≤300 who fulfilled specific criteria for zidovudine intolerance or failure were randomized to receive either 500 mg didanosine (ddI) daily or 2.25 mg zalcitabine (ddC) per day. Absolute CD4 counts were recorded at study entry and at as many as four visits. Patients were followed for clinical disease progression and survival. At 2 months, the difference in mean CD4 count from baseline was +15.4 cells/mm^3 in the ddI group but −1.3 cells/mm^3 in the ddC group. Patients assigned to ddI had a greater chance of a CD4 response at 2 months than those on ddC, yet only those in the ddC group with a response showed significant improvement in progression of disease or survival compared with ddC nonresponders, ddI responders, and ddI nonresponders (p = 0.03). We conclude that a CD4 response does not necessarily correlate with improved outcome and is therefore not a useful surrogate marker in these patients. **Key Words:** Surrogate marker—Didanosine—Zalcitabine—ZDV failure—ZDV intolerance.

The absolute number of CD4 lymphocyte cells in the peripheral blood is used extensively as a prognostic factor and as a surrogate marker for progression of disease and for death in clinical studies of human immunodeficiency virus (HIV) infection. As a prognostic tool, the CD4 count is used to initiate and modify antiretroviral treatment, for initiation of primary prophylaxis against various opportunistic infections (1,2), and for selection and stratification of patients in clinical trials (3,4). The utility of a change in CD4 count related to antiretroviral drugs as a surrogate end point in efficacy trials has also been studied. The hope has been that an early evaluation of such changes can reliably predict their efficacy for preventing or delaying eventual clinical outcome, such as progression of disease or death (5). An effective surrogate marker could markedly

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reduce the amount of time and cost needed to complete pivotal drug trials and make policy decisions with regard to their efficacy.

As proposed by Prentice (6), in order for changes in CD4 to be an adequate surrogate, they must completely capture the effectiveness of the drug in delaying the time to the true end point. Yarchoan et al. (7) restated this definition in terms of the following three criteria: (a) the marker must be prognostic for the outcome, (b) the treatment(s) being studied must change the marker, and (c) the prognostic value of the marker must be independent of the treatment(s). Many investigators have shown that CD4 count is important for prognosis and also varies with antiretroviral treatment, thus fulfilling the first two criteria (7). Several recent articles have cast doubt on the fulfillment of the third criterion. Lin et al. (8) tested whether the hazard rate of the clinical end point at any follow-up time was independent of treatment, conditional on previous CD4 history. They concluded that CD4 count was not an adequate surrogate for first opportunistic infection in the Burroughs Wellcome 02 trial, nor for the development of the acquired immunodeficiency syndrome (AIDS) or death in AIDS Clinical Trials Group Protocol 016 (ACTG 016). Choi et al. (9) and Lagakos (10) also found CD4 count to be an incomplete surrogate marker for AIDS using results from the original ACTG 019 comparing progression to AIDS of asymptomatic patients for two dose groups of zidovudine (ZDV) and placebo.

Recent trials of other antiretroviral drugs in addition to or in place of ZDV in patients with advanced disease have also examined the relationship between CD4 counts and treatment. Before clinical endpoint data were available, surrogate marker data from ACTG 116B/117 on improvements in p24 antigen levels, CD4 counts, and weight led to Food and Drug Administration approval of didanosine (ddI, *Videx*) for patients intolerant of or failing ZDV (4). After 8 weeks on ddI, patients had a median change in CD4 count of +3 cells (750 mg daily) and +2 cells (500 mg daily) compared with a median change of −10 cells for those continuing on ZDV. Other ACTG studies have shown similarly small changes in CD4 counts associated with treatment, but no clear association with clinical outcome (11,12).

The didanosine/zalcitabine study conducted by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) provided additional data relevant to the issue of using CD4 as a surrogate marker. This study was a direct randomized comparison of ddI and zalcitabine (ddC) in patients intolerant of or failing ZDV therapy. The principal end points were progression of disease, death, and toxicity, but, in addition, absolute CD4 lymphocyte counts were measured at baseline and at specified intervals during follow-up. The main report of the study appears elsewhere (13); herein we analyze the associations among treatment, CD4 counts over time, and clinical outcome.

METHODS

Study Design

The ddI/ddC study was a multicenter randomized open-label clinical trial to compare the clinical efficacy and safety of ddI and ddC in patients with HIV infection who could not tolerate ZDV or who had experienced clinical disease progression while taking ZDV. It was conducted by the CPCRA, a consortium of 17 administrative units funded by the National Institute of Allergy and Infectious Diseases to conduct community-based clinical trials at >130 primary care clinical sites.

The details of the conduct and results of the ddI/ddC study are described by Abrams et al. (13); only a summary of the relevant points is given here. HIV-infected patients were eligible if they had two CD4 counts of ≤300 cells or AIDS, and if they fulfilled specific criteria for ZDV intolerance or ZDV failure. The randomization was to treatment groups of either 500 mg ddI per day or 2.25 mg zalcitabine ddC, stratified by clinical unit and by ZDV intolerance versus failure. These standard doses could be adjusted for patients with lower body weight or those experiencing toxicities.

The study opened December of 1990 and completed enrollment of 467 patients the following September. The study concluded as planned in September of 1992, with a minimum of 12 months of follow-up and an average of 15.6 months. Interim analyses and progress reports were reviewed by an independent data safety and monitoring board five times during the conduct of the study.

The main end points were progression of disease, including death (as defined for CPCRA studies); study drug intolerance (as defined by the protocol); and death from any cause. Clinical event reports were reviewed by a blinded committee. Absolute CD4 lymphocyte counts were measured at baseline and at the 2-, 6-, and 12-month visits (and a few at 18 months), but less frequently if the patient refused or was too ill for testing.

Modeling of Changes in Individual CD4 Counts over Time

As discussed in more detail in the Appendix, we used a hierarchal random effects model for modeling sequential CD4 counts (14). It is similar to a standard regression model but allows for variation between patients and correlation among values within a patient, as well as the incorporation of treatment group and prognostic variables as covariates. In order to examine the relationship between treatment and a possible "boost" in CD4 count 2 months after starting treatment, we estimated CD4 trajectories with possibly different slopes before and after this 2-month

change point. We also allowed these trajectories to depend on three important covariates: treatment group (either ddI or ddC), previous AIDS diagnosis (either yes or no), and baseline Karnofsky score. Our primary interest was whether CD4 trajectories differed for patients taking ddI compared with ddC and whether a CD4 response translated into a delay in progression of disease or improved survival and the association with treatment and baseline prognosis.

Numerical estimation of random effects models requires evaluation of complicated integrals. Fortunately, a recently developed method known as the Gibbs sampler (15) allows for the use of models of almost unlimited complexity. For example, Lange et al. (16) used this method to model sequential CD4 counts for a group of HIV-positive men in San Francisco.

Modeling the Probability of a CD4 Response at 2 Months

To determine whether either drug produced an increase in the CD4 count at 2 months, we classified each patient as a "responder" or "nonresponder," depending on whether or not the CD4 count increased from its baseline value. The probability that a patient was in the "responder" group was estimated using a probit regression model, again evaluated using the Gibbs sampler (17,18). Treatment group, previous AIDS diagnosis, and baseline Karnofsky score were potential covariates, as was a term for the possible interaction between treatment and previous AIDS diagnosis. This model allowed us to study the association between the covariates and CD4 response and also to estimate the probability of a CD4 response in subgroups of patients by treatment and baseline prognosis. More details are included in the Appendix.

Landmark Analysis of Clinical Outcome by CD4 Response

Landmark analysis was performed on a portion of the data to evaluate the clinical consequences of 2-month changes in the CD4 lymphocyte count associated with the study drugs. First, patients who died within 2 months of randomization (i.e., before the landmark) were disregarded. Similarly, any progression of disease that occurred within the first 2 months was ignored, and the next subsequent event became the qualifying end point. As before, patients were divided into CD4 responders and nonresponders according to whether the 2-month CD4 count had decreased from baseline. Analyses of time to event for progression of disease and for death by treatment group and by response group were then performed on the modified data, including Kaplan-Meier curves and proportional hazards models.

RESULTS

Preliminary Descriptions

The ddI/ddC study enrolled 467 patients; 230 patients were randomized to receive ddI and 237 to ddC. After an average follow-up of 15.6 months, 309 (66%) patients had experienced progression of disease (including death), and 188 (40%) had died. A third of all patients (164, or 35%) became study drug intolerant, and 143 (57% of the 249 still living and followed) had been permanently discontinued from the original study drug. Vital status was unknown for only four patients (1%), and 31 patients (7%) were no longer participating in the study. We found no statistically significant differences between treatment groups for any of these factors except survival, which was found to be better in the ddC group (100 versus 88 deaths; $p = 0.003$) using a proportional hazards model with stratification by clinical unit and covariate adjusted for baseline CD4 count, Karnofsky score, and previous AIDS diagnosis. More details on the main results of the study were reported by Abrams et al. (13).

The average CD4 count rose during the first 2 months in the ddI group but fell in the ddC group (Table 1, mean CD4 at visit). After 2 months, the counts tended to fall in the ddI group but appeared to rise in the ddC group. The means of the changes in CD4 counts (follow-up visit—baseline) tell a different story, showing a slow decline over time in both treatment groups after the 2-month visit. The ddC group appeared to deteriorate more slowly, and the ddI group had lost the advantage of the initial boost ~12 months after randomization.

The increase in the number of missing CD4 counts with follow-up is of statistical concern, although the problem is unavoidable in long-term studies of late-stage HIV patients. Although only 31 patients dropped out of the study and all were enrolled ≥12 months before the close of the of the study, many patients had died and others refused or were sufficiently ill that CD4 testing was omitted. Those with missing CD4 counts at the 2-month visit had slightly lower baseline values, on average, than those with measurements, but differences were about the same in the two treatment groups (mean counts of 79 versus 65 for ddI, 74 versus 70 for ddC). At later visits, the baseline values for those missing CD4 counts were about the same as those with measurements in the ddI group but were markedly lower for those assigned ddC.

Not surprisingly, those patients who died during the study had much lower baseline counts, on average, than those who survived. The two treatment groups had approximately equivalent baseline CD4 counts, but more patients died in the ddI group.

Changes in Individual CD4 Counts over Time

A common method for summarizing the effect of treatment on levels of CD4 is to examine the average change in counts from baseline, as we did in Table 1. But our random effects model more effectively uses the available data by allowing the inclu-

TABLE 1. *Mean of available CD4 counts/mm³ at baseline and follow-up visits*

Visit and status	ddI N	ddI Baseline CD4 (mean)	ddI Fup visit CD4 (mean)	ddI Change in CD4 (Fup-BL) (mean)	ddC[a] N	ddC[a] Baseline CD4 (mean)	ddC[a] Fup visit CD4 (mean)	ddC[a] Change in CD4 (Fup-BL) (mean)
Baseline								
All CD4	230	75	75	N/A	236	71	71	N/A
Alive, study end	130	104			149	93		
Died during study	100	38			87	34		
At 2-month visit								
CD4 measured	182	79	91	+22	185	74	70	−4
CD4 missing, alive	38	65			41	70		
CD4 missing, dead	10	40			10	15		
At 6-month visit								
CD4 measured	153	80	74	−6	157	80	62	−12
CD4 missing, alive	40	95			48	70		
CD4 missing, dead	37	32			32	27		
At 12-month visit[b]								
CD4 measured	103	100	79	−21	123	98	74	−24
CD4 missing, alive	33	95			42	58		
CD4 missing, dead	64	27			56	30		
At 18-month visit[b]								
CD4 measured	22	96	52	−44	15	122	83	−39
CD4 missing, alive	8	80			10	29		
CD4 missing, dead	8	45			15	59		

Fup, follow-up visit; BL, baseline; N/A, not applicable.
[a] One patient in the ddC treatment group who died after 5 months was missing the baseline CD4 and is excluded from the table.
[b] Patients were excluded from all three CD4 categories, regardless of vital status, if the study closed before they could have their 12-month (n = 45) or 18-month (n = 389) visit, respectively.

sion of prognostic information and compensating for temporal variability. We obtained an estimate of the sequence of CD4 counts for subgroups of patients with a given set of prognostic factor values. For example, the upper set of curves in Fig. 1 compares the fitted CD4 trajectories in the two drug groups of typical patients with a better prognosis (Karnofsky score of 100 and no previous diagnosis of AIDS). The fitted CD4 response is modest for those in the ddI group and even smaller for ddC recipients. The lower curves repeat these calculations for a typical patient with a poor prognosis (baseline Karnofsky score of only 70 and previous AIDS). The fitted CD4 counts start out nearly 100 units lower, with a barely perceptible boost in the ddI group and a constant decay in the ddC group. After the initial 2 months, the fitted trajectories decay in all the subgroups at rates that are almost identical for the two treatments, thus negating the treatment differences hinted at in Table 1.

CD4 Response to Treatment at 2 Months

The probability of a 2-month CD4 response was estimated using our probit model. Karnofsky score was eliminated from the model because it did not contribute. The estimates and 95% confidence intervals for the weights associated with the remaining covariates are shown in Table 2. The negative weight for AIDS indicates that patients without a previous AIDS diagnosis were more likely to experience a CD4 response. This was the only one of the four confidence intervals to exclude zero, indicating that previous AIDS diagnosis is the only statistically significant predictor of a change in CD4, at the 0.05 level.

Converting these results to estimates of the probability of response for different subgroups, we again compared the "poor prognosis" and "better prognosis" patients, defined solely by whether they had a previous diagnosis of AIDS. Table 3 reflects the minor treatment effect, modest prognosis-treatment interaction, and substantial difference by prognosis. Patients without previous AIDS diagnosis had the greatest chance of a response (60% for the ddI group and 58% for ddC), while for those with a poor prognosis the estimated probabilities were 52 and 39%, respectively. Notice that even for the group with the best chance of response (good prognosis patients assigned to ddI), a substantial proportion of patients were not expected to respond, in agreement with the weak evidence in favor of a rise in

TABLE 4. *Effect of CD4 response and treatment group on survival*

CD4 group	ddI N	ddI No. deaths	ddI Rate (median)[c]	ddC N	ddC No. deaths	ddC Rate (median)[c]	Compared RR[d]	Compared p value[d]
All patients	230	100	42.8 (19)	237	88	35.1 (24)	0.63	0.003
Landmark (after 2 months)[a]	221	92	47.0 (20)	228	80	37.8 (24)	0.62	0.004
CD4 change unk[a]	39	27	108.5 (10)	42	20	62.4 (15)	0.58	0.17
CD4 change < 0[a]	81	30	39.8 (23)	101	40	42.5 (22)	1.02	0.93
CD4 change ≥ 0[a]	101	35	36.6 (25)	85	20	23.4 (36)	0.49	0.03
Comparison RR (p value)[b]			0.78 (0.35)			0.50 (0.03)		

[a] Patients who died within 61 days and progression of disease events that occurred within 61 days of randomization have been excluded from the analysis.
[b] RR = relative risk (CD4 response/nonresponse) from proportional hazards model with stratification by unit and covariate adjusted for baseline CD4 count, Karnofsky score, and previous AIDS diagnosis.
[c] Events per 100 person years starting 2 months after randomization; estimated median months to event: median = 2 + 12 × ln 2/rate.
[d] RR = relative risk (ddC/ddI) from proportional hazards model with stratification by unit and covariate adjusted for baseline CD4 count, Karnofsky score, and previous AIDS diagnosis.

analysis was done by subgroups of the 2-month response in CD4 count. The subgroup of responders among patients assigned to ddC stands out using death as the outcome variable (Fig. 2). This group was significantly different when compared with the nonresponders also taking ddC ($p = 0.033$) and when compared with the response subgroups taking ddI (both $p = 0.03$). In the ddI treatment group, CD4 responders and nonresponders had almost the same outcomes. Results for progression of disease as an end point were similar.

DISCUSSION

There is little doubt that the CD4 lymphocyte count is a valuable prognostic indicator for opportunistic disease or death and therefore continues to guide treatment and is an important covariate in the design and analysis of clinical trials. The CD4 count thus fulfills the first Prentice criterion for an effective surrogate marker of clinical outcome. However, data from the ddI/ddC study of the CPCRA are contradictory with respect to the second and third criteria, as defined in the Introduction, and the type and extent of missing data present a serious, unsolvable problem.

The usual method for describing the pattern of CD4 counts over time and the effect of treatment is by the average change in the count since baseline at each of the visits with CD4 measurements (Table 1). Our random effects model for sequential CD4 counts captures the correlations among the obser-

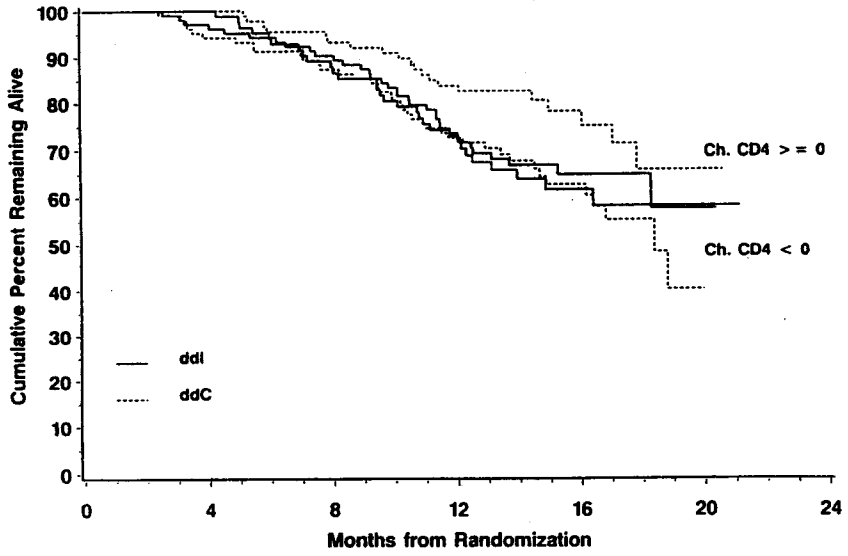

FIG. 2. Survival after 2 months by 2-month change in CD4 count and treatment group.

vations and accounts for individual variation better than this method of analysis but still cannot entirely overcome the problem of missing data. Little and Rubin (19) showed that missing data are "ignorable" if they are missing at random and if the probability of being missing is not correlated with their value or with treatment. Ignorable missing values do not bias estimates of mean counts, although their precision will be less than if they were based on all the patients. Since the type of missing values were different in the two treatment groups later in the study, they were obviously not ignorable in analysis of long-term effects. Even the random effects model will tend to inflate any effects of treatment on sustaining the CD4 level because data from patients who deteriorated early were simply not available for inclusion. Although the CPCRA trial possibly had more missing CD4 counts during follow-up than comparable ACTG trials, all studies of advanced HIV disease will increasingly have missing values for dead or very ill patients with low initial counts.

On the other hand, because they were nearly equivalent in the two treatment groups, missing values appear to have been only a minor problem during the first 2 months of the study. Consequently, our remaining analyses concentrated on the 2 month CD4 response associated with the two drug groups, the predictors of those who responded, and the clinical consequences. While we found evidence that, on average, patients assigned to ddI had a CD4 response but the ddC group did not, the boost was quite small. Figure 1 and Tables 2 and 3 show that baseline prognostic variables were better predictors of both the likelihood of a CD4 response and its magnitude than was treatment group. Finally, although more patients in the ddI group had a response, the landmark analysis surprisingly showed that only in the ddC group was a response associated with a better outcome. This association in the ddC group may merely be because a good prognosis at baseline (such as no previous AIDS diagnosis) was predictive of a CD4 response as well as of a delay in progression of disease or death without that association necessarily being causal.

Arguably, a treatment for HIV disease may not be deemed truly effective unless it has a dramatic effect on the number of CD4 cells in peripheral blood, but, certainly, none of the currently known drugs have this degree of efficacy. In the CPCRA study of ddI and ddC, as well as in ACTG studies of these antiretroviral drugs, the participating patients were much more immunocompromised than those in the initial ZDV studies, and their CD4 responses were much more modest. It may be that all of these treatments are only rarely effective in patients with advanced disease; hence there is little power for detecting small differences in CD4 response, and correlation with outcome may not be reliably estimated. In addition, our patients had been on ZDV for a considerable amount of time before randomization; the implications of switching to ddI or ddC and of the possibility of cross-resistance are not known. Nevertheless, our study, like others in the recent literature, calls into question the value of CD4 as a surrogate end point in efficacy studies of antiretroviral drugs.

APPENDIX A

Random Effects Model

Our statistical model for sequential CD4 counts is similar to a standard regression model but allows for variation between patients and correlation among values within a patient. Let Y_{ij} denote the j^{th} CD4 measurement on the i^{th} patient. In our study, we had 467 patients and, at most, five observations for each patient. The model, first proposed by Laird and Ware (14), is $Y_{ij} = \alpha x_{ij} + \beta_i w_{ij} + \epsilon_{ij}$, where x_{ij} is a list of known covariate values (such as Karnofsky score, previous AIDS diagnosis, etc.) and α is a corresponding list of unknown regression coefficients (weights). The value w_{ij} is another, typically smaller list of known covariate values (here including only measurement time and a constant term), and β_i is a corresponding list of unknown subject-specific regression coefficients, which are assumed to be independently and normally distributed. That is, each patient has his or her own initial counts and decay slopes, but with an overall pattern or *prior distribution* assumed. The ϵ_{ij} are the residual errors.

In usual regression models the ϵ_{ij} are independent (uncorrelated) normally distributed random variables, all having the same mean, 0, and the same variance, σ^2. But the assumption of complete independence would be inappropriate here, since a single individual's CD4 counts measured over time are correlated with each other; that is, $\text{Corr}(Y_{ij}, Y_{ik}) = 0$. The desired nonzero correlations among observations within the same individual are induced by the randomness of the β_i, which are often referred to as *random effects*. This model can yield improved estimation of characteristics both within and between patients. Since we were primarily interested in seeing whether CD4 trajectories differed for patients taking ddI compared with ddC, the focus was on the coefficients corresponding to treatment group. The β_i coefficients were of secondary importance, since they describe the idiosyncrasies of CD4 counts for individual patients. Residual plots from the fitted model showed some evidence of skew toward positive values, suggesting that a

square root or log transformation of the data might be in order. An analysis on the square root scale was also done but was not presented, since it is more difficult to interpret and the fitted model was qualitatively very similar to Fig. 1.

In principle, models like ours can accommodate a far broader class of features than described herein. In practice, however, more complicated models cannot be analyzed using traditional statistical methods, since the resulting likelihood functions are extremely high dimensional and analytically intractable. For this reason, we adopted a *Bayesian* approach with a "noninformative" prior distribution for the β_i, since little reliable previous information was available. Numerical integration for evaluation of the posterior distribution was carried out using Monte Carlo integration and the Gibbs sampler (15,16).

Using our random effects model for CD4 counts over time, we obtained estimates of the posterior distribution for each coefficient. We then used the first equation to obtain an estimate of the sequence of CD4 counts for a typical study subject having a given set of prognostic factor values (Fig. 1). The adequacy of our model was checked by comparing it with several other candidates. Those with fewer parameters (e.g., the standard regression model, where $\beta_i = 0$ for all i) fit poorly, while those with more parameters (e.g., the heterogeneous variance model fitting a distinct error variance σ_i for each individual) led to poor convergence of the Gibbs algorithm.

Probit Model

We used probit regression, also evaluated with the Gibbs sampler method (17,18) to model the probability of a response or increase in the CD4 count. Defining p_i as the probability that patient i responded, let $p_i = \Phi(\gamma_0 + \gamma_1 r_i + \gamma_2 a_i + \gamma_3 r_i a_i)$, where Φ denotes the cumulative distribution function of a standard normal random variable and the covariates r_i and a_i describe treatment group and previous AIDS diagnosis, respectively. The γ values are unknown coefficients (or weights) multiplying the covariates, where γ_3 is the weight of the treatment-AIDS interaction term. In another model, baseline Karnofsky score was used as a third covariate, but the fitted coefficient was negligible. We used probit regression in place of the similar (but more common) logistic regression approach, since the former is more easily fit using the Gibbs sampler. The posterior distributions for each of the γ coefficients were used to derive point and interval estimates of the corresponding covariate effects (Table 2). In addition, given particular values of the covariates, the posterior distributions were used with the probit equation (above) to estimate the probability of a CD4 response in subgroups of patients by treatment and baseline prognosis (Table 3).

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