

ABSTRACT # 121e
POSTER BOARD # 517-M



BASELINE CHARACTERISTICS ASSOCIATED WITH CD4 RESPONSE AFTER THREE CYCLES OF SUBCUTANEOUS rIL2 IN ESPRIT

A. Labriola¹, E. Denning², N. Klimas³, F. Gordin¹

The US Department of Veterans Affairs National Trial Coordinating Center
and the ESPRIT Study Group

¹Veterans Affairs Medical Center, Washington, DC

²University of Minnesota, Minneapolis, MN

³Veterans Affairs Medical Center, Miami, FL

ESPRIT IL-2 TRIAL



ABSTRACT #121e

Subject Category: 1. Therapy - Immune-Based Therapies

Title: Baseline Characteristics Associated with CD4 Response after Three Cycles of Subcutaneous (SC) Recombinant Human Interleukin-2 (IL2)

Key words: Immune Therapies, Interleukin 2, CD4 Response

Authors: A. Labriola^{1*}, E. Denning², N. Klimas³, F. Gordin¹ on behalf of the US Department of Veterans Affairs National Trial Coordinating Center and the ESPRIT Study Group.

¹Veterans Affairs Medical Center, Washington, DC. ²University of Minnesota, Minneapolis, MN. ³Veterans Affairs Medical Center, Miami, FL.

Background: ESPRIT is an open-label, randomized, controlled trial to determine if (SC) IL2 therapy + combination antiretroviral therapy (ART) vs ART alone reduces risk of AIDS or death in patients (pts) with baseline CD4 ≥ 300 c/ μ L. IL2 was given bid in three 5-day cycles q8 weeks, with more cycles if CD4 did not reach goal of ≥ 2 xbaseline or ≥ 1000 c/ μ L. We examined baseline characteristics of pts by CD4 change after 3 cycles of IL2.

Methods: So far, 396 patients have completed 3 cycles of IL2 therapy starting at 7.5 MIU bid and have month 8 CD4 data. Pts were grouped in tertiles based on month 8 CD4 change from baseline: < 212 c/ μ L increase (n=131); 212-426 increase (n=134); and > 426 increase (n=131). Demographics, injecting drug use history, co-infection with hepatitis B/C, nadir and baseline CD4, HIV RNA, HIV disease stage, body mass index, drug class exposure, and duration of ART (dual nucleosides or HAART) were compared across tertiles of CD4 change by analysis of variance. Multiple regression analysis with change in CD4 from baseline to month 8 as the outcome was performed using the above baseline factors.

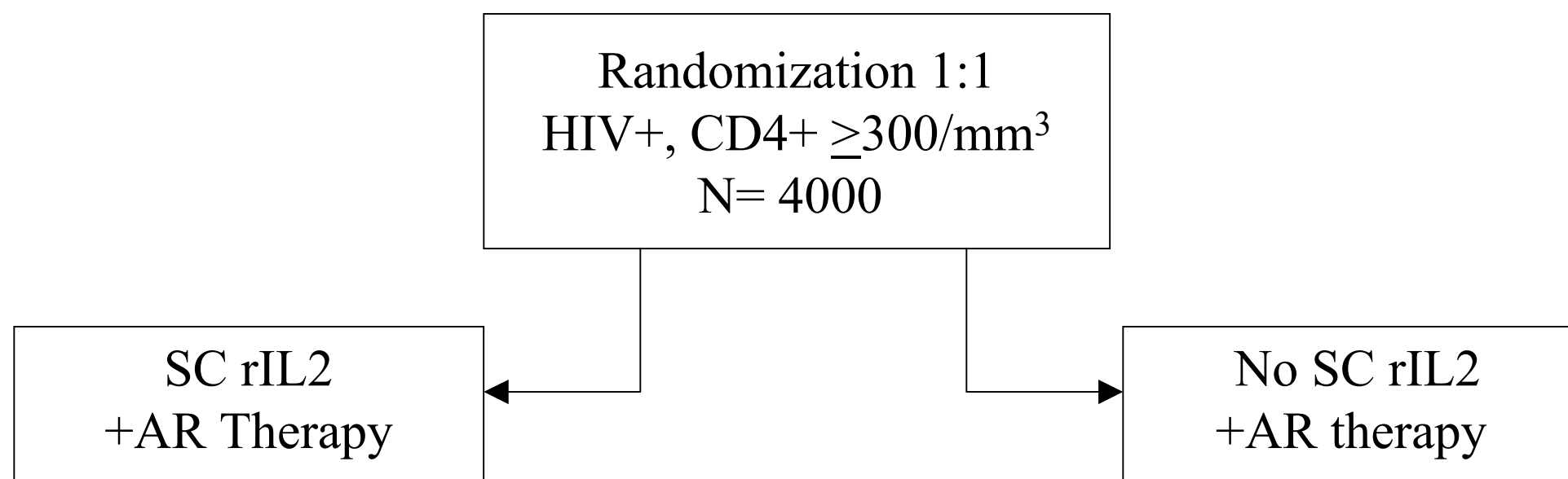
Results: In univariate analyses of baseline factors, baseline CD4 (p=0.0002), nadir CD4 (p<0.0001), age (p=0.02) and duration of ART (p<0.0001) varied significantly by tertile of CD4 change (534 vs 510 vs 596 for baseline CD4; 231 vs 255 vs 333 for nadir CD4; 41.7 vs 40.7 vs 39.9 years for age; 5.3 vs 5.0 vs 3.9 years for duration of ART). In multivariate analysis, nadir CD4 was significantly associated with CD4 change at month 8, with a 100 c/ μ L higher nadir having a 46 cell greater CD4 increase (p<0.0001); and a greater CD4 increase (112 c/ μ L more) was found among pts with < 1 year ART compared to other patients (p=0.051).

Conclusion: These preliminary data indicate that the CD4 increase after 3 cycles of IL-2 given with ART is substantial (median increase 326 cells/mm³) and consistent across demographic characteristics as well as HIV stage, and baseline levels of CD4 and HIV RNA. Duration of ART appears to be inversely associated with CD4 response, while nadir CD4 is directly related. Among these pts with baseline CD4 ≥ 300 c/ μ L, nadir CD4 was the strongest predictor of response in multivariate analyses.

Introduction

Evaluation of Subcutaneous (SC) Proleukin Interleukin-2 Trial (ESPRIT) is an open-label, randomized, controlled trial to determine if SC rIL2 therapy with combination antiretroviral therapy (ART) vs ART alone reduces risk of AIDS or death in patients with baseline CD4 cell count of $\geq 300/\text{mm}^3$. SC rIL2 was given bid in three 5-day cycles every 8 weeks, with additional cycles given if CD4 did not reach goal of twice the baseline or ≥ 1000 cells/ mm^3 .

ESPRIT Design and Sample Size



Several controlled trials such as those done by the Vanguard Study Group, CPCRA 059, and this ongoing ESPRIT trial have showed that intermittent administration of SC rIL-2 can result in a substantial increase in CD4 cell counts in patients with HIV disease. However, there is a variable response to rIL-2 therapy.

In the ESPRIT trial, the CD4 response at month 8 ranged from a decline of 500 cells/ mm^3 to an increase of 2,331 cells/ mm^3 , with a mean response of 370 cells/ mm^3 increase (median 326 cells/ mm^3). 43.4% of patients reached the goal of twice baseline or $\geq 1,000$ cells/ mm^3 by 8 months.

Objectives of this Analysis

To determine which baseline characteristics may be predictors of CD4 cell count response.

To examine the baseline characteristics and CD4 cell count changes in those patients who received three cycles of SC rIL2 therapy over an 8 month period.

To explore the interrelationships of nadir CD4, baseline CD4, and duration of ART with CD4 response.

Methods

Using the existing data base from the Vanguard Study Group trials, the CPCRA 059 study and the ESPRIT trial, we reviewed the data of patients who were initially randomized to 7.5 MIU of SC rIL2.

We selected an **analysis cohort** of those patients who received three cycles of SC rIL2 therapy over a 8 month period.

Patients were grouped in tertiles based on month 8 CD4 change from baseline CD4 (see Table 2).

Twelve baseline characteristics were compared across tertiles of CD4 change by analysis of variance. Multiple regression analysis with change in CD4 from baseline to month 8 as the outcome was performed using these baseline factors.

All analyses were done using SAS. Selected variables were divided into categories (either quantiles or clinically relevant) in order to better examine univariate and bivariate relationships. Univariate and multivariate associations with change in CD4 were studied using multiple regression analyses.

Summary of Results

2,560 patients were enrolled in ESPRIT at the time of these analyses. 1,307 were randomized to the rIL2 arm. Of those, 396 patients completed three cycles of rIL2 starting with 7.5 MIU bid and have month 8 data and were used as the analysis cohort. The results of the analyses are as follows:

Table 1: The analysis cohort was similar to the larger group of patients randomized to rIL2 with regard to all twelve baseline characteristics studied.

Table 1 – Baseline Characteristics for Analysis Cohort and All Patients Assigned to IL-2

Characteristics	Randomized to IL-2, followed ≥8 months	Randomized to IL-2 7.5 MIU, followed ≥8 months	Analysis cohort: Randomized to IL-2 7.5 MIU, followed ≥8 months, started ≥3 cycles
	(N=848)	(N=669)	(N=396)
CD4 (mean cells/mm ³)	543.5	539.2	547.0
Nadir CD4 (mean cells/mm ³)	268.6	253.3	274.0
Age (mean years)	40.4	40.8	40.7
Gender (% female)	18.3	17.2	17.7
Race (% nonwhite)	28.1	25.5	26.8
Duration of AR tx (mean years)	4.2	4.6	4.7
Exposed to PI, NNRTI, nuc (%)	7.9	8.4	8.8
Progression of HIV disease (%)	7.3	9.3	6.3
HIV RNA < 500 copies (%)	71.3	74.7	71.6
Hepatitis B or C (% co-infected)	15.1	15.0	13.7
BMI (mean kg/m ²)	24.6	24.6	24.7
Injection drug use (%)	10.3	9.7	9.8
IL-2 taken over 3 cycles (mean MIU)*	182.6	204.0	204.0

* Maximum possible dose 225 MIU over 3 cycles

Table 2: CD4 change was divided into tertiles and compared to baseline characteristics in univariate and multivariate analysis. Baseline CD4 count ($p=0.0002$), nadir CD4 count ($p<0.0001$), age (0.02) and duration of AR therapy in years ($p<0.0001$) were significant predictors of CD4 response in univariate analysis. Nadir CD4 ($p<0.001$) and duration of AR therapy remained predictors of response in multivariate analysis.

Characteristics	CD4 Change Tertiles			p-value*	p-value**
	I (<212)	II (212-426)	III (>426)		
CD4 (cells/mm ³)	534.1	510.4	595.8	0.0002	0.11
Nadir CD4 (cells/mm ³)	231.4	255.2	333.2	<0.0001	<0.001
Age (years)	41.7	40.7	39.9	0.02	0.72
Gender (% female)	16.0	20.2	16.8	0.83	0.47
Race (% nonwhite)	25.4	24.6	31.3	0.25	0.79
Duration of AR rx (years)	5.3	5.0	3.9	<0.0001	0.09
Exposed to PI, NNRTI, nuc (%)	9.9	9.0	7.6	0.40	0.98
Previous AIDS (%)	5.3	9.7	3.8	0.92	0.11
HIV RNA < 500 copies (%)	68.2	72.5	74.0	0.47	0.25
Hepatitis B or C (% co-infected)	16.7	14.3	10.9	0.48	0.69
BMI (kg/m ²)	24.7	24.7	24.6	0.19	0.15
Injection drug use (%)	13.8	9.0	7.6	0.34	0.66
* p-value from univariate regression of change in CD4 (as a continuous variable) on characteristic					
** p-value from regression of change in CD4 (as a continuous variable) on characteristic, adjusted for all other covariates listed					

Graph 1: This graph shows that patients in each tertile received a similar dose of SC rIL2 per-cycle and had similar decreases in the per-cycle dose over the course of the first three cycles.

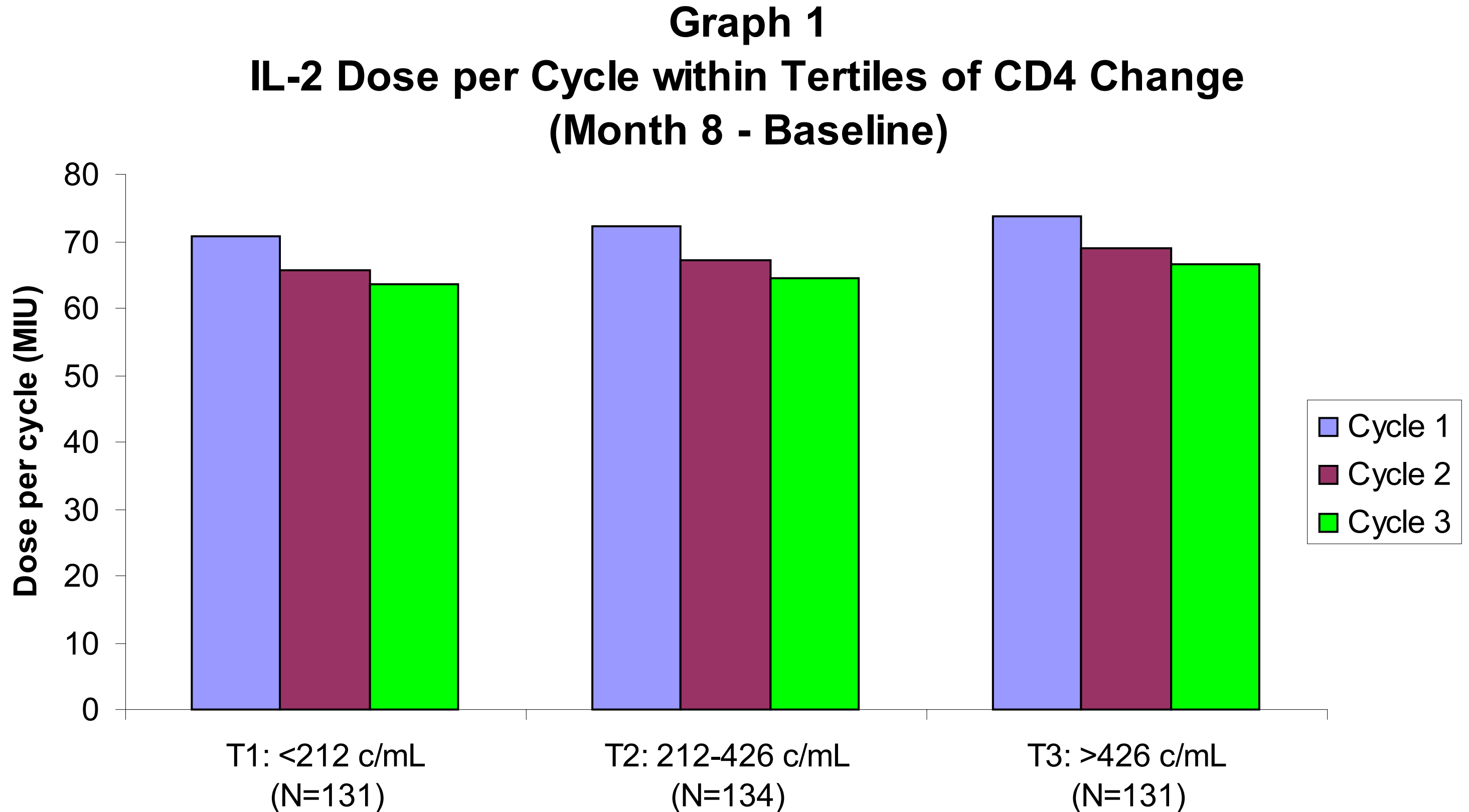


Table 3: This table shows that patients with the lowest nadir CD4 also had the lowest baseline CD4 and the longest exposure to AR therapy. These patients also had the smallest CD4 change from baseline to month 8.

Table 3 – CD4 Measures & Duration of AR Therapy at Baseline by Distribution of Nadir CD4

Nadir CD4 (cells/mm ³)	Baseline CD4 (cells/mm ³)	Duration of AR therapy (yrs)	% exposed to PI & NNRTI & nuc	CD4 change (M8 – BL, cells/mm ³)
< 100 (n=54)	439.3	6.7	24.1	256.4
100-199 (n=74)	472.2	5.8	5.4	290.1
200-299 (n=114)	537.4	4.6	5.3	321.6
300-399 (n=84)	563.3	4.3	8.3	474.0
400 + (n=69)	707.5	2.7	7.3	501.9

Table 3a: However, even in those patients with a nadir CD4 <100 cells/mm³, the mean CD4 increase was substantial.

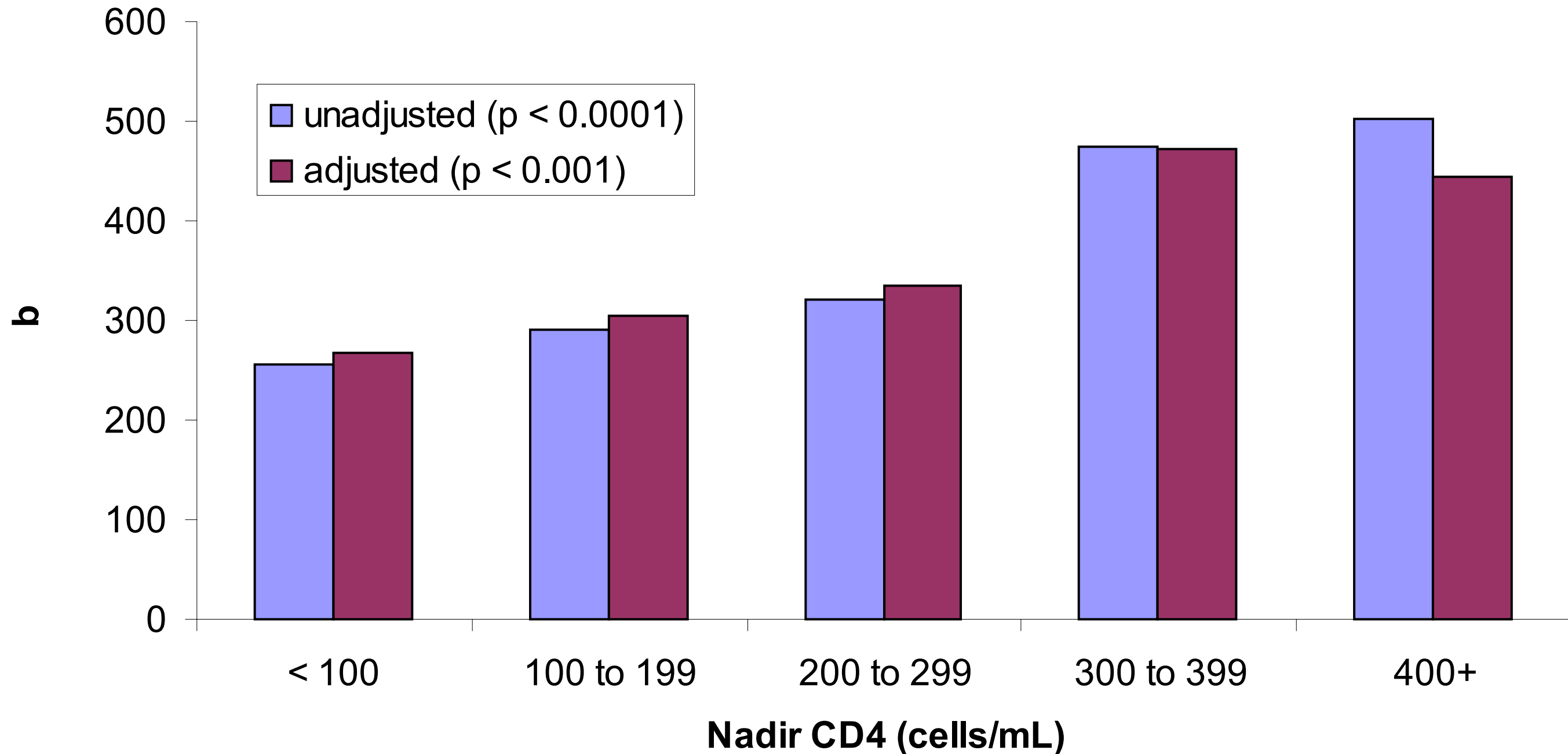
Table 3a – CD4 Change (Month 8 – Baseline) by Distribution of Nadir CD4, unadjusted and adjusted for all covariates

Nadir CD4 (cells/mm ³)	Unadjusted CD4 change (M8 – BL, mean cells/mL)	Adjusted CD4 change (M8 – BL, mean cells/mL)
< 100 (n=54)	256.4	268.2
100-199 (n=74)	290.1	305.5
200-299 (n=114)	321.6	335.7
300-399 (n=84)	474.0	471.5
400 + (n=69)	501.9	443.5

Graph 2: This graph shows that the nadir CD4 is a strong predictor of CD4 response. The greatest CD4 change is seen with a higher nadir CD4 count, unadjusted and adjusted for all covariates.

Graph 2

CD4 change by nadir CD4 unadjusted & adjusted for all covariates



Graph 3: This graph demonstrates the effect of baseline CD4 and nadir CD4 on CD4 change at month 8. At all levels of baseline CD4, patients with higher nadir CD4 count had larger increases in CD4 at 8 months.

Graph 3
Change in CD4 (Month 8-baseline)
by baseline & nadir CD4

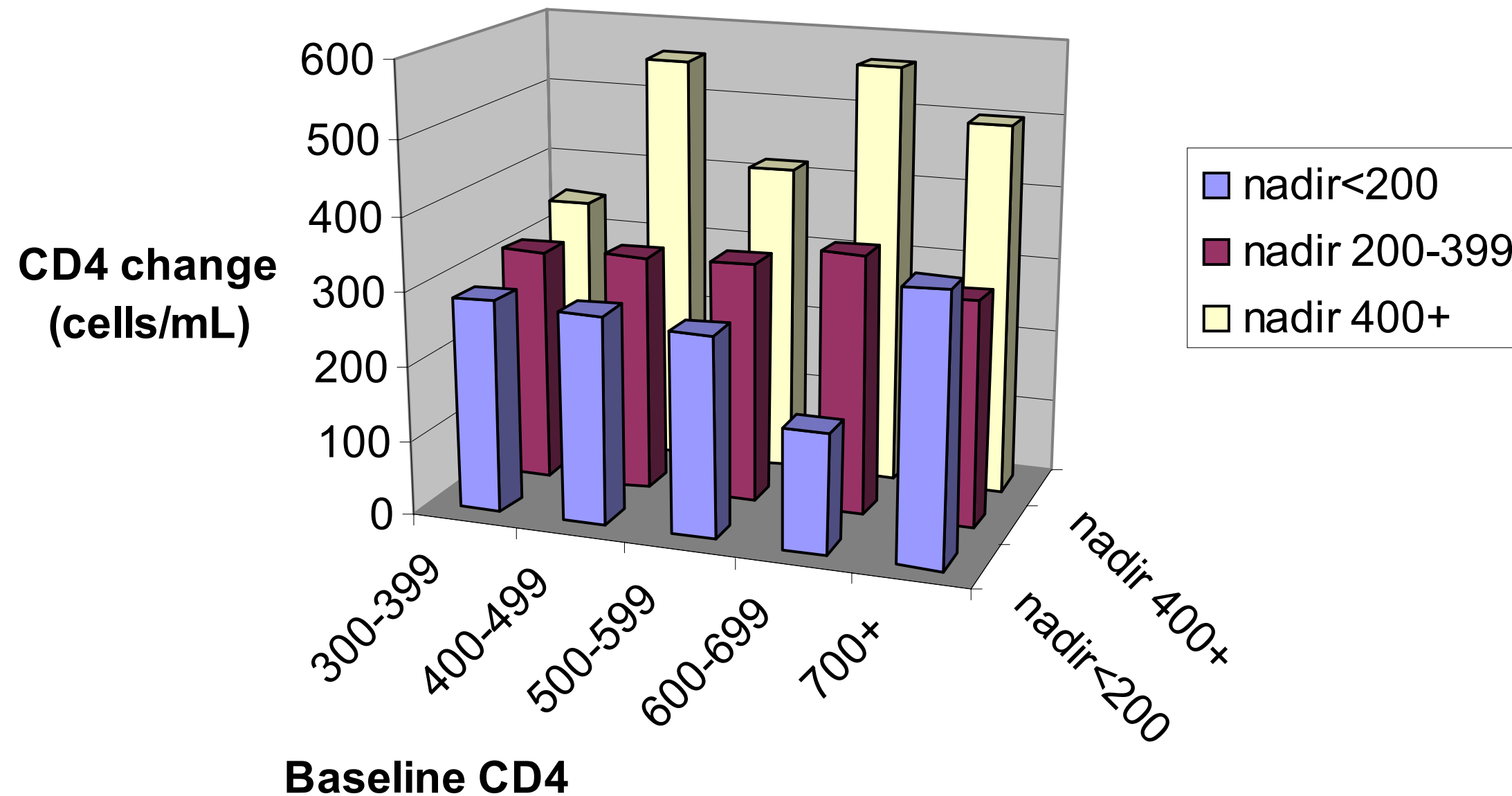


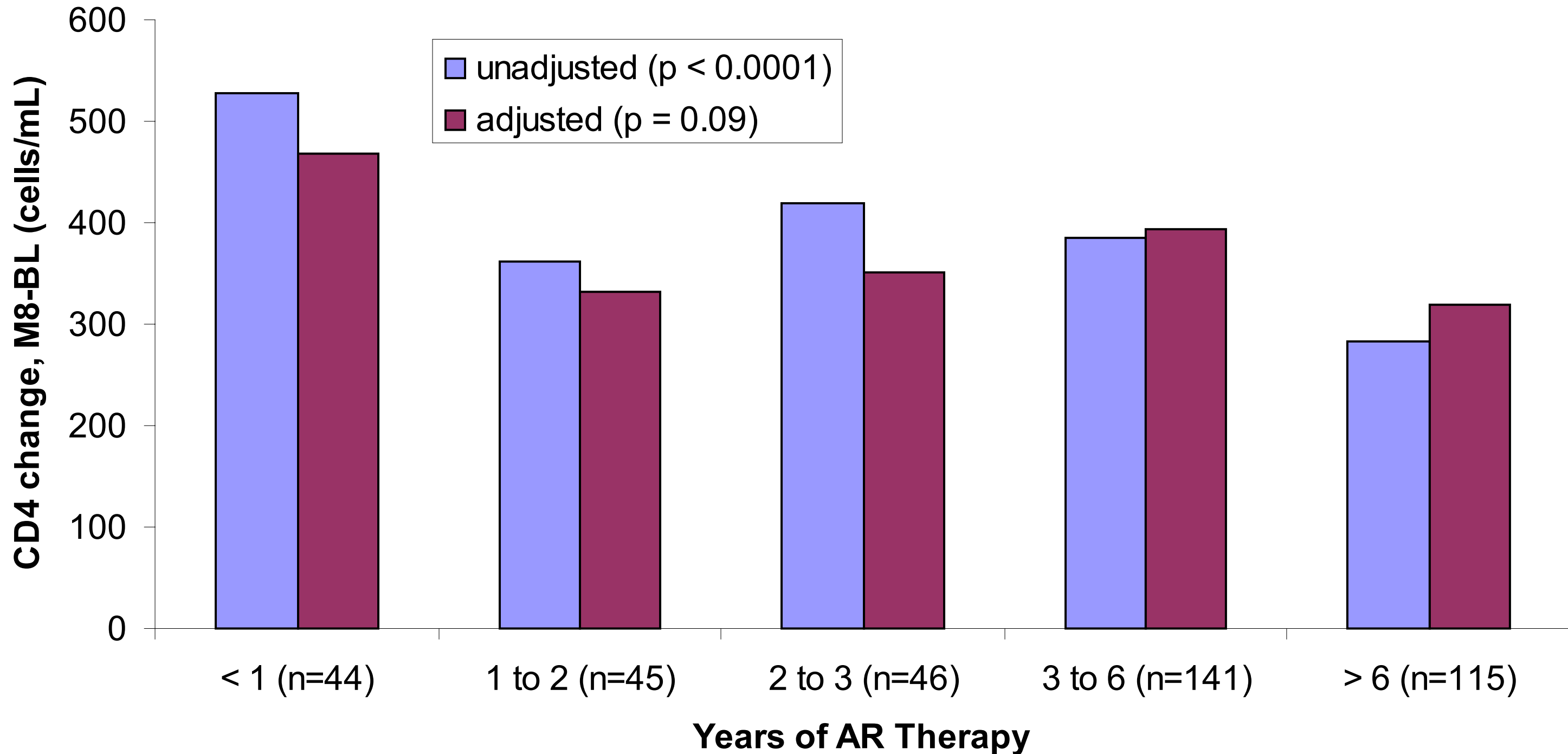
Table 4: This table shows the duration of AR therapy in years and the drug classes that the patients were exposed to, compared to baseline CD4, nadir CD4, and CD4 change, from baseline to month 8.

Table 4 – CD4 Measures by Duration & Exposure to Antiretroviral Therapy at Baseline			
Duration of AR therapy (Years)	Baseline CD4 (mean cells/mm³)	Nadir CD4 (mean cells/mm³)	CD4 change, M8 – BL (mean cells/mm³)
< 1 (n=44)	511.1	357.7	526.8
1-2 (n=45)	570.6	329.3	361.0
2-3 (n=46)	607.2	332.5	419.1
3-6 (n=141)	561.2	260.6	384.5
> 6 (n=115)	508.5	205.8	282.2
p-value*	0.04	<0.0001	<0.0001
Drug classes exposed to			
PI + NNRTI + nRTI (n=35)	517.4	227.2	322.6
PI + nRTI (n=186)	546.2	246.5	345.7
NNRTI + nRTI (n=99)	540.6	279.3	391.9
PI + NNRTI (n=7)	773.1	275.0	276.1
nRTI only (n=60)	550.6	361.8	469.7
p-value**	0.03	<0.0001	0.11
* p-value for regression of duration (as a continuous variable) on CD4 measurement			
** p-value for analysis of variance, 4 degrees of freedom			

Graph 4: This graph shows that CD4 change is inversely associated with the duration of AR therapy.

Graph 4

CD4 change (Month 8 - Baseline) by Duration of AR Therapy, Unadjusted & Adjusted for All Covariates



Graph 5: This graph demonstrates that there is a smaller CD4 change in those patients who have been on AR therapy a longer period of time and who have a low nadir CD4.

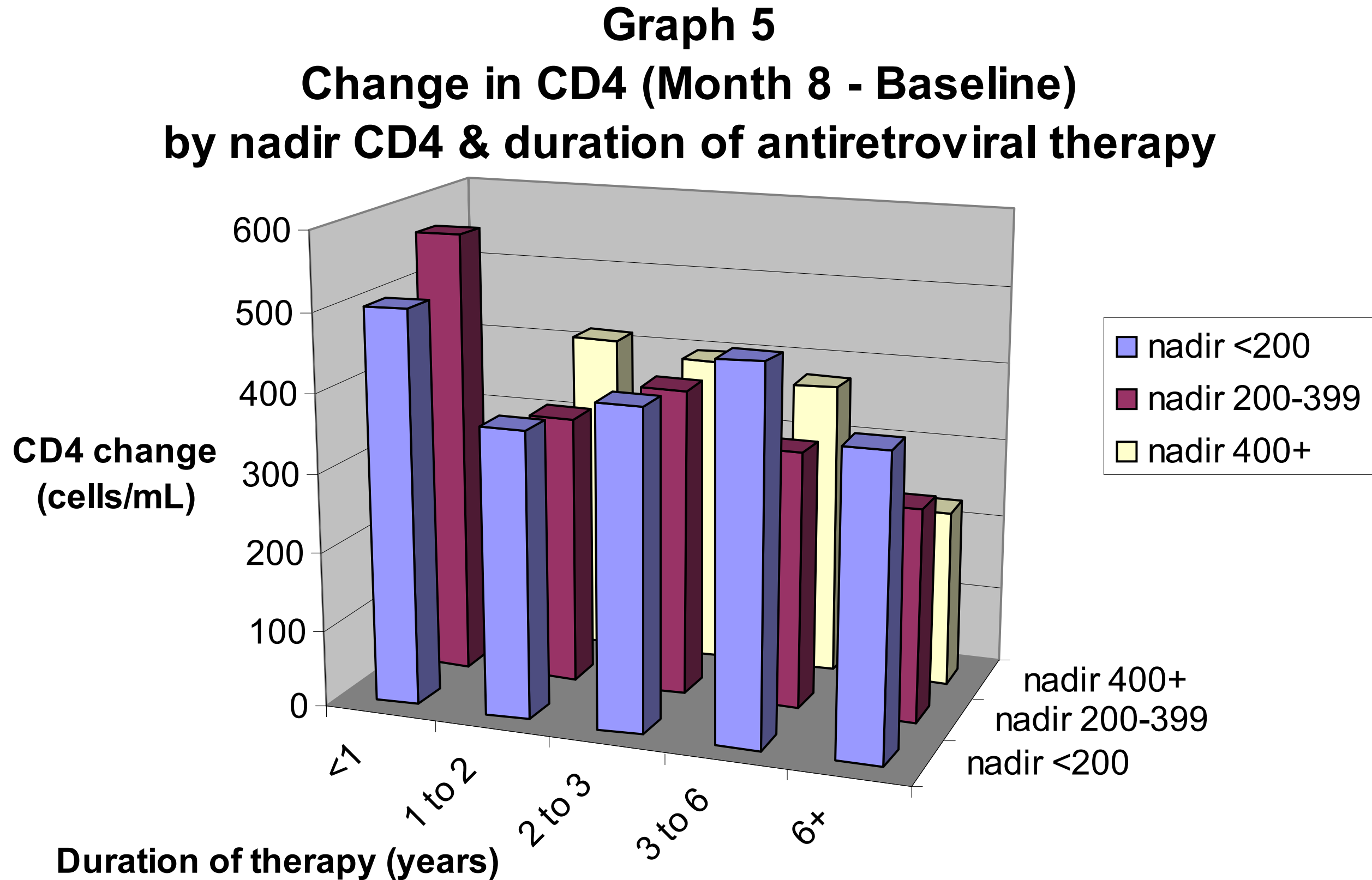


Table 5: This table shows that a substantially larger CD4 increase was found among patients with <1 year ART compared to all patients who had been on ART >1 year.

Table 5 – Change in CD4 by duration of therapy: unadjusted and adjusted for all covariates		
Duration of AR rx at BL (Years)	CD4 change, M8 – BL (mean cells/mm³)	
	<u>Unadjusted</u>	<u>Adjusted for all covariates*</u>
< 1	526.8	468.8
1-2	361.0	332.1
2-3	419.1	351.0
3-6	384.5	394.5
6+	282.2	319.7
p-value*	<0.0001	0.09

* p-value for regression of duration (as a continuous variable) on CD4 change

Conclusions

The increase in CD4 cell count after three cycles of SC rIL2 is substantial (mean increase 326 cells/mm³) and consistent across demographic characteristics. Even those patient with a nadir CD4 count <100 had significant CD4 increase (mean increase of 256 cells/mm³).

Nadir CD4 cell count was the strongest predictor of CD4 cell count response in multivariate analysis.

Duration of AR therapy was found to have a substantial inverse association with CD4 cell count response in multivariate analysis.

The ESPRIT study is ongoing and will follow 4,000 HIV-positive study subjects over 5 years to determine whether SC rIL2 induced increases in CD4 cell count translate into better health and increased survival.

Acknowledgments

ESPRIT Investigators/ Coordinators

ESPRIT Executive Committee

Minnesota Regional Coordinating Center - Jim Neaton, Judy Bebchuk

Patients who have enrolled in the ESPRIT study

ESPRIT is sponsored by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland, USA

Contacts

Ann Labriola MD
VA Medical Center
Division of Infectious Diseases 151B
50 Irving St., NW
Washington DC 20422
Phone: 202-745-8301
Fax: 202-745-8432/8694
E-mail: ann.labriola@med.va.gov

Nancy G. Klimas MD
Special Immunology Unit
VA Medical Center
1201 North West 16th Street Room 111-I
Miami FL 33125
Phone: 305-324-3267
Fax: 305-324-3139
E-mail: nancy.klimas@med.va.gov

Eileen Denning MPH
ESPRIT Minnesota Coordinating Centers
University of Minnesota School of Public Health
Division of Biostatistics
Coordinating Centers of Biometric Research
2221 University Ave., SE
Minneapolis MN 55414
Phone: 612-626-8049
Fax: 877-337-7748
E-Mail: eileen@ccbr.umn.edu

Fred M. Gordin MD
VA Medical Center
Division of Infectious Diseases 151B
50 Irving St., NW
Washington DC 20422
Phone: 202-745-8301
Fax: 202-745-8432/8694
E-mail: fred.gordin@med.va.gov