

# Determinants of Suboptimal Immunological Response After ART Initiation in Acute HIV

Ryan Handoko<sup>1</sup>, Donn Colby<sup>2</sup>, Eugene Kroon<sup>2</sup>, Mark de Souza<sup>2</sup>, Suteeraporn Pinyakorn<sup>2-4</sup>, Peeriya Prueksakaew<sup>2</sup>, Jennifer Chiarella<sup>1</sup>, Shelly Krebs<sup>3,4</sup>, Irini Sereti<sup>5</sup>, Victor Valcour<sup>6</sup>, Nelson Michael<sup>3</sup>, Nittaya Phanuphak<sup>2</sup>, Jintanat Ananworanich<sup>2-4</sup>, Serena Spudich<sup>1</sup>, on behalf of the RV254/SEARCH 010 Study Team.

<sup>1</sup>Yale School of Medicine, New Haven, CT, USA. <sup>2</sup>SEARCH, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand. <sup>3</sup>United States Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA. <sup>4</sup>The Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA. <sup>5</sup>Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. <sup>6</sup>Department of Neurology, University of California San Francisco Memory and Aging Center, Sandler Neurosciences Center, San Francisco, CA, USA



## Background

- Up to 30% of ART-treated individuals with suppressed chronic HIV infection fail to recover CD4+ T cell counts to a normal level (>500 cells/ $\mu$ L).
- The period of acute HIV infection (AHI) generally spans the first month of infection, is characterized by detectable HIV RNA but undetectable HIV IgG, and is further subcategorized into Fiebig stages 1-5.
- We investigated if suboptimal immunological response (SR) also occurs when ART is started during acute HIV infection (AHI), and identified clinical/laboratory factors associated with SR.

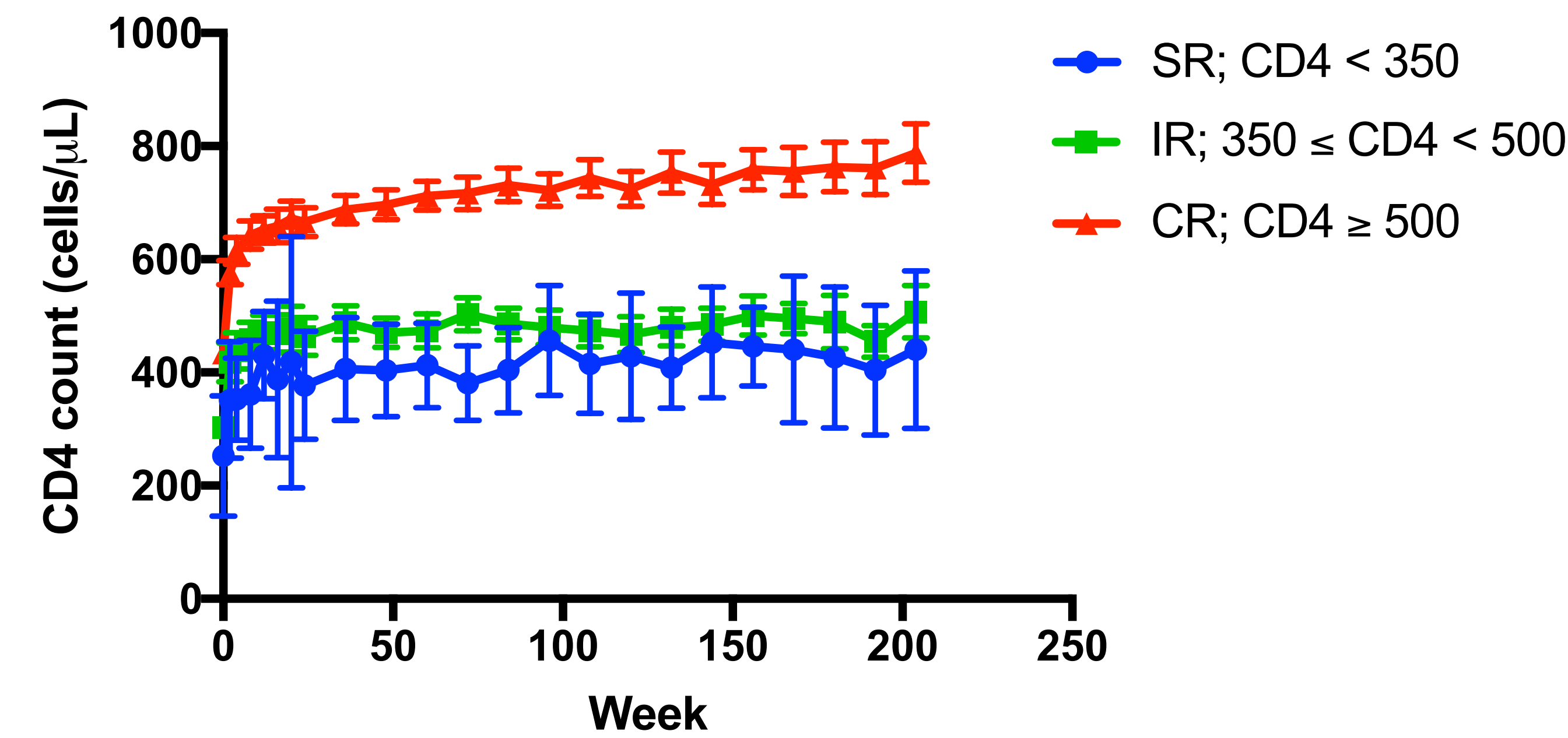
## Methods

Thai AHI participants (positive HIV RNA, non-reactive HIV IgG; n=304) underwent blood and optional cerebrospinal fluid (CSF; n=79) sampling followed by immediate ART and subsequent longitudinal follow-up in the RV254/SEARCH 010 study. Those with  $\geq 48$  weeks of documented HIV-RNA <50 copies/mL were stratified by latest CD4+ T cell count:

- Suboptimal response (SR; CD4 < 350 cells/ $\mu$ L)**
- Intermediate response (IR; 350  $\leq$  CD4 < 500)**
- Complete response (CR; CD4  $\geq$  500)**

- Clinical and laboratory parameters were assessed at baseline and latest study visit.
- CSF markers of immune activation, neuropsychological (NP) testing, and mood assessments were examined at baseline and at 96 weeks.
- Participants completed validated Thai versions of the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire (PHQ). NP testing comprised of the Grooved Pegboard test in nondominant hand (fine motor function), Color Trails 1 and Trail Making A (psychomotor speed), and Color Trails 2 (executive functioning/set-shifting). To calculate an overall measure of cognitive function based on a mean of z-scores (NPZ-4), raw NP testing results were standardized to healthy Thai control data.
- Mann-Whitney test was used for cross-sectional analyses between groups.

## Results

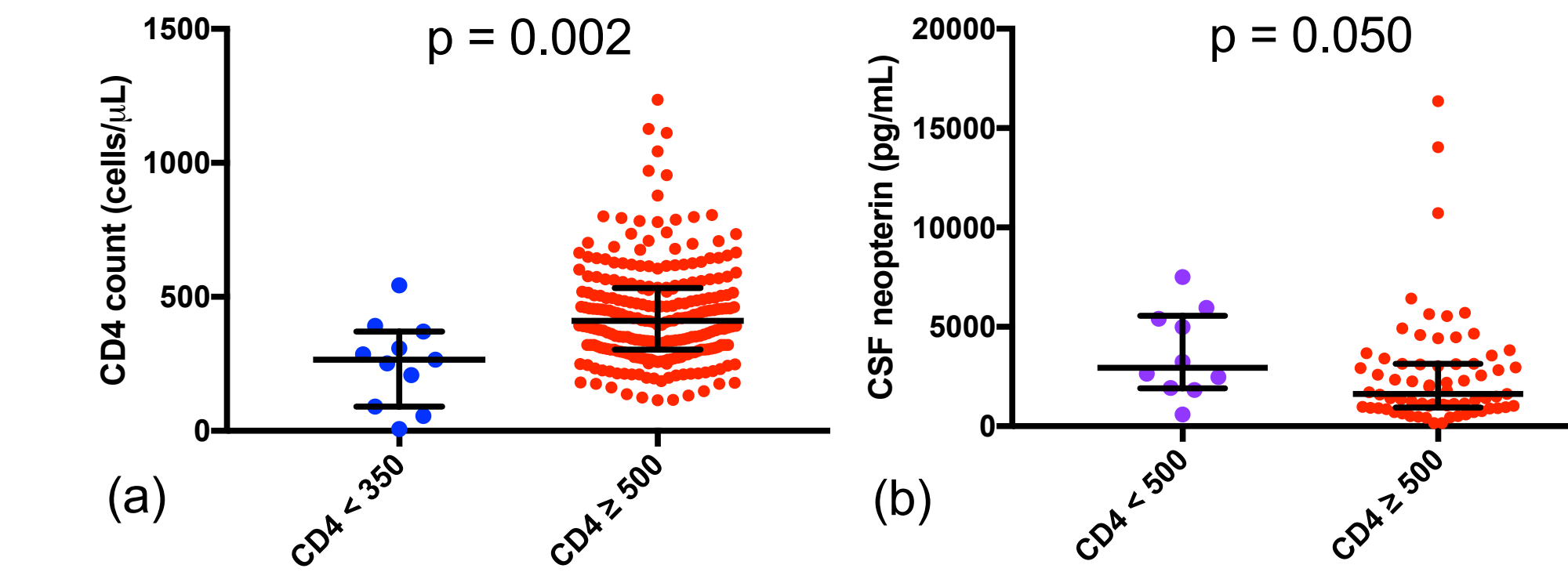


**Figure 1.** Mean CD4 trajectories over time by latest CD4 after ART. The degree of immunological response occurred early after ART in AHI and appeared to persist over time. Error bars are 95% confidence intervals.

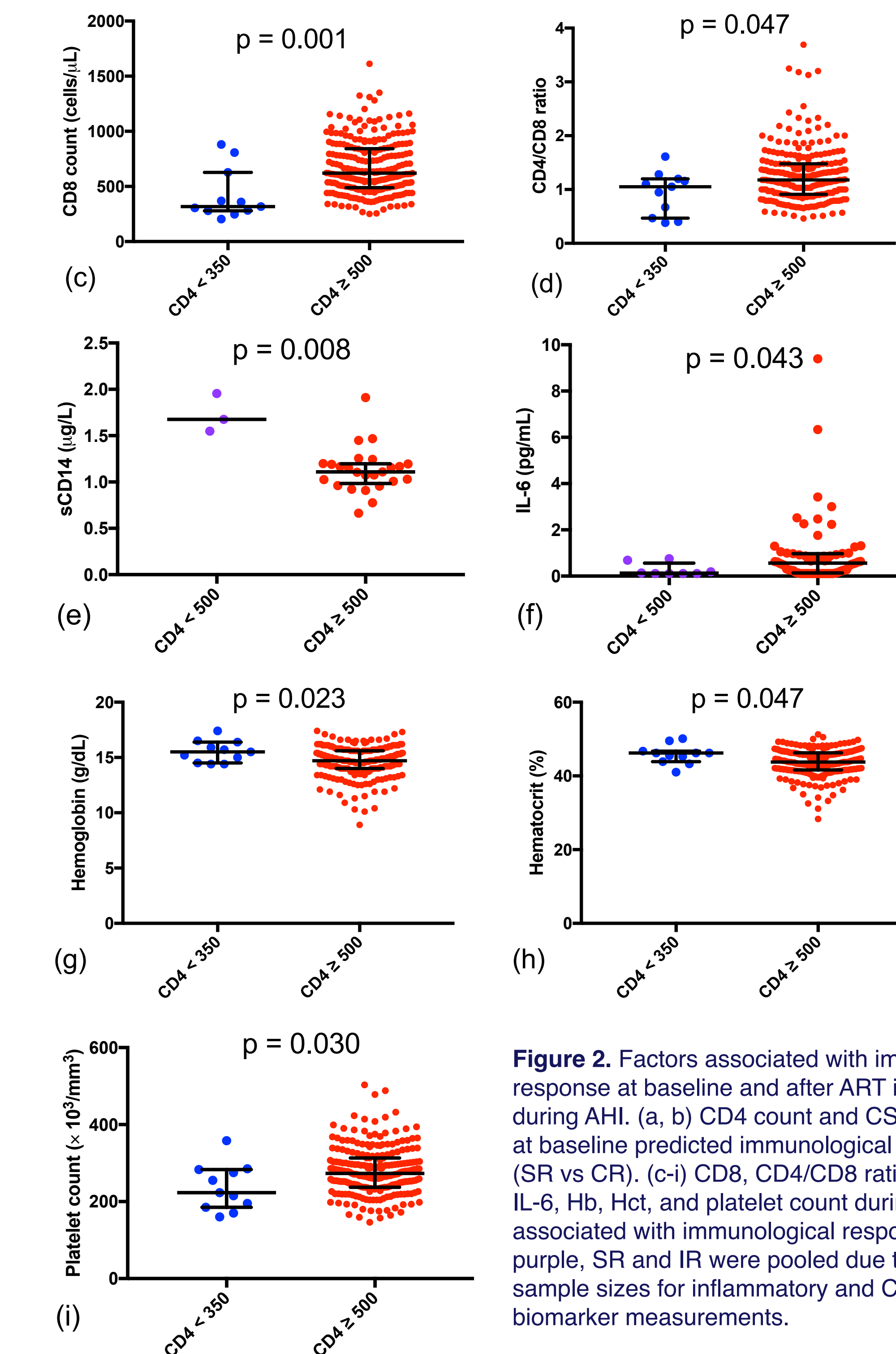
Characteristics	SR (n=11)	IR (n=44)	CR (n=249)	p-value
Age (years)	23 (20-30)	26 (23-30)	26 (23-33)	0.30
Gender male:female, n	11:0	44:0	237:12	0.25
Risk behavior, n (%)				
FSM	0 (0)	0 (0)	12 (5)	0.38
MSF	1 (9)	3 (7)	9 (4)	
MSM	10 (91)	41 (93)	228 (92)	
Thai ethnicity, n (%)	11 (100)	43 (98)	244 (98)	0.89
Drug use during HIV exposure, n (%)	2 (18)	13 (30)	51 (21)	0.39
Alcohol use during HIV exposure, n (%)	1 (9)	12 (27)	58 (23)	0.44
Infection duration (days), median (IQR)	20 (14-23)	21 (15-28)	19 (15-26)	0.64
1 <sup>st</sup> week of viral suppression, median (IQR)	16 (8-24)	12 (8-24)	12 (8-24)	0.96
Week of latest study visit, median (IQR)	156 (84-180)	120 (84-192)	156 (108-216)	0.03
Fiebig stage at baseline, n (%)				
Stage 1	2 (18)	5 (11)	44 (18)	0.24
Stage 2	4 (36)	9 (21)	71 (29)	
Stage 3	5 (45)	22 (50)	90 (36)	
Stage 4	0 (0)	6 (14)	26 (10)	
Stage 5	0 (0)	2 (5)	18 (7)	

**Table 1.** Study population characteristics. ART was started at a median 19 days post-infection and median latest follow-up visit was at 144 weeks. 3.6% (11/304) and 14.5% (44/304) had SR or IR, respectively. Groups were compared using a  $\chi^2$  or Kruskal-Wallis test, as appropriate. Week of latest study visit was found to be different across SR, IR, and CR groups ( $p = 0.03$ ), but was not different between SR and CR using a Mann-Whitney test ( $p = 0.527$ ).

## Pre-ART Baseline Predictors for Immunological Response



## Post-ART Factors Associated with Immunological Response



**Figure 2.** Factors associated with immunological response at baseline and after ART initiation during AHI. (a, b) CD4 count and CSF neopterin at baseline predicted immunological response (SR vs CR). (c-i) CD8, CD4/CD8 ratio, sCD14, IL-6, Hb, Hct, and platelet count during ART are associated with immunological response. In purple, SR and IR were pooled due to small sample sizes for inflammatory and CSF biomarker measurements.

NP Testing and Psychiatric Indices	SR & IR (n=51)	CR (n=227)	p-value
NPZ-4	-0.002 (-0.472, 0.416)	-0.022 (-0.556, 0.614)	0.84
Hospital Anxiety and Depression Scale Anxiety subscore	15 (9, 21)	15 (9, 21)	0.77
Patient Health Questionnaire	12 (7, 15)	9 (6, 14)	0.09

**Table 2.** Neuropsychological testing and psychiatric indices not found to be associated with immunological response at baseline during AHI. SR and IR were pooled due to small sample sizes. Median (interquartile range).

## Conclusions

- Suboptimal immunological response (SR) occurs in a small subset of individuals despite treatment in the earliest stages of infection.
- SR is associated with low CD4+ T cell count at baseline and persistent low CD8+ T cell count during treatment.
- Poor response is associated with neuroinflammation at baseline (CSF neopterin) and systemic inflammation during treatment (blood sCD14 and CD4/CD8 ratio).
- SR is associated with elevated hemoglobin & hematocrit and lower platelet count during treatment.
- Neurocognitive deficits, anxiety, and depression at baseline not found to be associated with poor immunological response.
- Strategies in addition to early ART may be necessary to optimize CD4+ T cell recovery in acute HIV infection (AHI).

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## Disclaimers

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, or the National Institutes of Health.

