

# 08. Correlation between Serum Cortisol Levels and Cd4 08. Counts in Treatment-Naïve Patients with HIV AIDS Infection at Tertiary Hospital

*by Maria S Ganggur*

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## Correlation between Serum Cortisol Levels and Cd4 Counts in Treatment-Naïve Patients with HIV/AIDS Infection at Tertiary Hospital

Maria S Gangur<sup>1</sup>, Sony Wibisono<sup>2\*</sup>, Musofa Rusli<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

<sup>2</sup>Endocrine and Metabolic Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

<sup>3</sup>Tropical Disease and Infection Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia.

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### ABSTRACT

The increased cortisol is significantly correlated with HIV mortality. The objective of this study was to analyze the correlation between serum cortisol levels and CD4 counts in treatment-naïve patients with HIV/AIDS infection. This was an analytical cross-sectional study. Total serum cortisol levels were measured by ADVIA Centaur® using chemiluminescence immunoassay and CD4 counts were measured by flow cytometry technique using BD FACS Count CD4 reagents®. Among 56 samples of treatment-naïve patients with HIV/AIDS infection, the mean age was 34.3 ± 9 years and they were predominantly male. Mean total cortisol levels was 18.88 ± 9.90 µg/dL, and 32.1% of samples had total cortisol levels of >22.4 µg/dL. As much as 67.9% of the samples presented CD4 counts lower than 200 cells/mm<sup>3</sup>. There was a significant moderate negative

correlation between total cortisol levels and CD4 counts ( $r = -0.467$ ,  $p < 0.001$ ). Total cortisol levels were negatively correlated with CD4 counts. The higher the total cortisol levels of HIV/AIDS-positive patients, the lower the CD4 counts.

**Keywords:** cortisol, CD4, HIV/AIDS

### Correspondance:

Sony Wibisono  
Endocrine and Metabolic Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia  
E-mail: [sonywibisono@yahoo.com](mailto:sonywibisono@yahoo.com)  
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### INTRODUCTION

Human immunodeficiency virus (HIV) causes a serious health problem and has a big impact on Indonesian economics. Besides, HIV is rapidly growing, chronic, progressive and serious illness compared with other diseases.(1,2) HIV is a pandemic that has affected 36.7 million people worldwide in 2015. According to the Ministry of Health, in Indonesia between 1985 and 2016 there were 55,799 Indonesians who were infected with HIV and fell in AIDS conditions with high mortality rates and it became the number four cause of death in the world.(3,4) According to the Directorate General of Disease Prevention and Control, Ministry of Health, the mortality rate of HIV/AIDS patients in Indonesia as of March 2017 was reported as many as 14,754.(5) This created a complicated clinical problem so HIV prevention is very important and necessary.(6)

HIV infection is characterized by the suppression of cellular immunity that will affect many organ systems, including neuroendocrine.(7,8) CD4 cell count is also a major clue in asymptomatic patients.(9) Increased T cell activation is recognized as one of the main pathogenic characteristics of HIV infection and causes CD4 decline.(10) Factors affecting T cell activation have not been fully identified. Glucocorticoids, which are the final secretions of the HPA axis, are thought to affect T cell activation. Cortisol levels in patients with positive HIV infection are higher than cortisol levels in HIV negative patients.(11,11,12) The presence of hypercortisolism conditions will accelerate the progression of HIV disease and increase mortality.(13–16) Several studies have shown that an increase in cortisol is associated with a faster progression of HIV infection to AIDS and a predictor of mortality. Increased cortisol is significantly correlated with HIV mortality.(16) The results of that study were supported by Leserman's research that an

increase in cortisol in HIV patients was associated with three markers of disease progression, ie. AIDS, clinical conditions of AIDS and mortality. This study found that at each increase of 3 µg/dL in the cumulative mean of serum cortisol, there was an increased risk of AIDS by 40% and an increased risk of about 2.5 times of developing AIDS clinical symptoms or mortality.(13)

The disturbed HPA axis in HIV infection is the effect of inflammatory cytokines such as TNF-α, IL-1, and IL-6 which are secreted together in response to infection.(17,18) This cytokine activates the HPA axis through CRH stimulation which results in the release of the hormone ACTH with cortisol as a final result.(19) In patients with HIV/AIDS, the activation of the HPA axis causes an increase in cortisol levels which has different effects on Th1 and Th2, resulting in a change of Th1/Th2 balance.(20,21) Cortisol inhibits Th1 cytokines: IL-1, IL-2, TNF-α, and IFN-γ, which are the main proinflammatory cytokines,(22) and suppress apoptosis. At Th2, cortisol stimulates the production of IL-4, IL-10, IL-13 and induces apoptosis.(23) In addition to cytokine stimulation, increased cortisol in HIV infection is also caused by the release of HIV toxin products such as GP 120 and vpr. Vpr also acts as a coactivator of glucocorticoid receptors, thereby increasing viral replication.(24) Hypercortisol conditions can accelerate the development of HIV disease by stimulating viral replication, modifying programmed cell death, changing the secretion pattern of cytokines and T helper suppression.(25,26) Some studies support the existence of a correlation between cortisol levels and CD4 counts. Several studies reported an increase in cortisol levels in HIV patients and showed a significant negative correlation with CD4 counts(11,27,28) Previous studies reported that cortisol levels at the start of a visit could predict a decrease in CD4 percentage on the

subsequent visits.(7) Other studies also report that an increase in initial serum cortisol can predict the length of stay and mortality.(14) Several other studies have shown inconsistent results.(16,29) This can be influenced by differences in the methods used in each study. Until now there have been no studies that identify the incidence of cortisol dysfunction in HIV/AIDS patients in Indonesia. The objective of this study was to analyze the correlation between serum cortisol levels and CD4 counts in treatment-naïve patients with HIV/AIDS infection.

## METHODOLOGY

This study was an observational analytic study with a cross-sectional analytic design. Fifty-six subjects were selected by consecutive sampling. Treatment naïve-patients with HIV/AIDS who were searching for treatment at HIV/AIDS Clinic at Dr. Soetomo Hospital, Surabaya, Indonesia were recruited by inclusion criteria, aged  $\geq 18$ -60 years, and willing to take part in the study by signing informed consent. Patients with a history of diabetes mellitus, chronic kidney disease, and liver cirrhosis, receiving corticosteroid therapy, had received antiretroviral therapy, had a history of alcohol use, pregnant, had fever and sepsis, were excluded from this study.

Research data were taken from the subjects by interview, physical examination, and blood sampling. Cortisol taken was morning cortisol between 7-9 am with a normal value of 4.3-22.4 ug/dL. CD4 count was determined by flow cytometry with BD FACSCount CD4 reagents\*. Blood specimens must be processed within 24 h after collection with a normal value of 500-1500 cells/mm<sup>3</sup>. HIV infection was proved using three methods of HIV testing, the HIV HIV SD, Intec, and Oncoprobe. Data were analyzed and presented in the form of frequency distribution tables and diagrams using SPSS version 22.0 software to determine the correlation of both variables. The interpretation of the results of the correlation test was based on the p-value, the strength of correlation and the correlation direction. A statistical test was regarded as significant if  $p < 0.05$ .

## RESULTS

The mean age of the subjects was  $34.3 \pm 9$  years, with the age of the youngest 19 years and the oldest 57 years. Most of the subjects were male (78.6%). The highest risk factor for the incidence of HIV infection is risky anal sex. Based on the stage, clinical stages 2 and 3 were not significantly different, i.e. 39.3% and 32%, while clinical stages 1 and 4 were 10.7% and 17.9% respectively. The mean BMI of the patients was  $21 \text{ kg/m}^2$  with the lowest BMI of  $15.22 \text{ kg/m}^2$  and the highest was  $32.74 \text{ kg/m}^2$ . As many as 50% of the subjects suffered from opportunistic infections with oral candidiasis as the most frequent, followed by chronic diarrhea (Table 1).

### Total serum cortisol levels in patients with HIV/AIDS

Mean total cortisol levels in 56 subjects were  $18.88 \pm 9.90$  ug/dL. Most subjects (62.50%) had normal total cortisol levels. Cortisol level as much as  $\geq 22.4$  ug/dL was obtained in 18 patients (32.1%) and the levels of  $< 4$  ug/dL were obtained in three patients. This study also assessed the mean total

cortisol levels at each stage of HIV (Table 2). Then, the post-hoc Bonferroni analysis was conducted to determine groups that had significant differences and a statistically significant difference in cortisol levels was obtained at stage 2 vs stage 3 and 4.

### CD4 count in HIV/AIDS patients

CD4 counts in the subjects varied between 1 cell/mm<sup>3</sup> to 710 cells/mm<sup>3</sup> with a median of 102.5 cells/mm<sup>3</sup> and an mean of  $151.39 \pm 165.66$  cells/mm<sup>3</sup>. Thirty-eight patients (67.9%) had CD4 count of less than 200 cells/mm<sup>3</sup>, 11 patients (19.6%) with CD4 count of 200-349 cells/mm<sup>3</sup>, 4 patients (7.1%) had CD4 count of 350- 499 cells/mm<sup>3</sup> and 3 patients (5.4%) had CD4 counts  $\geq 500$  cells/mm<sup>3</sup> (Figure 1).

This study also calculated mean total cortisol levels in the CD4 groups (Table 3). The highest mean cortisol levels was 21.69 in  $< 200$  CD4 group with 38 samples. Then, we performed Bonferroni post-hoc analysis and obtained significant differences in cortisol levels in groups with CD4  $< 200$  and CD4 200-350.

### Correlation between total serum cortisol levels and CD4 count

To analyze the correlation between total cortisol levels and CD4 counts, we used Spearman's rank non-parametric correlation test and obtained a Spearman's r-value of -0.467 with a p-value  $< 0.001$ . This study also analyzed the correlation between serum cortisol levels and the CD4 group and obtained a Spearman's r value of -0.368 with  $p = 0.004$ . The results of this analysis indicated that there was a significant negative correlation between total cortisol levels and CD4 counts of the subjects. The correlation between total cortisol levels produced was negative or inverse as seen in Figure 2. This means that in HIV/AIDS patients, the higher the total cortisol level, the lower the CD4 count.

## DISCUSSION AND CONCLUSION

Among 56 subjects, this study showed a significant negative correlation between total cortisol level and CD4 count in the subjects. This means the higher the total cortisol level, the lower the CD4 count in HIV/AIDS patients. The predictive marker of mortality was increasing cortisol. This result was different from the previous studies. The difference was probably influenced by differences in research methods, some samples, inclusion and exclusion criteria and normal reference values used by each study. The subjects in those studies were HIV patients who had received antiretroviral drugs which affected the patient's CD4 count.(16) The number of patients was fewer and the examination method, as well as the cortisol normal reference value, were different.(29)

The examination of the total cortisol level in this study was carried out in the morning following the circadian rhythm. In normal individuals, the highest-circulating cortisol concentration is between 06.00 and 09.00 and lowest between 23.00 and 01.00.(30) Normal values of total serum cortisol level vary according to the method used. Immunoassays for cortisol can cross-react with other steroids, causing variability in measurable results.(31) In this study, most of the subjects having normal total cortisol

levels. This study was slightly different from other studies.(29) This was due to differences in the method of measuring total cortisol levels, ie radioimmunoassay using PC-RIA.MAS.STARTEC, and different cortisol cut-off values. This study used the chemiluminescence immunoassay method with the ADVIA Centaur® instrument with a normal value of 4.3-22.4 ug/dL and a smaller number of samples.

This study also assessed the mean total cortisol levels in each of the clinical stages of the patient. HIV in late-stage made more opportunistic infections, reflecting more inflammatory sources in the body.(32) Besides, the high percentage in clinical stages 3 and 4 was due to the lack of knowledge about HIV/AIDS and awareness of HIV testing so that the patients were diagnosed too late. The widespread stigma and discrimination also caused the patients to be embarrassed and afraid to take an HIV test or seek treatment.(33) Moreover, there were significant differences between stage 2 cortisol levels with stage 3 and 4 cortisol levels. Increased cortisol in several studies indicated an increase in cortisol levels in advanced HIV.(34) Other studies reported increased cortisol in 12.8% of asymptomatic HIV patients.(35) This increase in cortisol level is in response to an increase in the degree of disease due to HPA axis cytokine modulation, release or viral toxic products, the envelope protein gp120, and structural proteins Vpr and Tat, and changes in tissue sensitivity to glucocorticoids.(12,24,36,37) In this study, the cause of high total cortisol levels was the possibility of opportunistic infections and HIV infection itself. Half of the subjects suffered from opportunistic infections with the most common being oral candidiasis followed by chronic diarrhea. Globally, the most common opportunistic infections in HIV/AIDS patients are oral candidiasis, followed by unspecified tuberculosis, herpes zoster, pulmonary TB, and bacterial pneumonia.(38)

The most important biomarkers of disease stage and progression in patients with an HIV infection are the CD4 count.(39) The mean CD4 of this study is lower than that in other studies.(40,41) Difference in mean and median of CD4 in this study was because the majority of the subjects seeking treatment at an advanced stage and had CD4 count <200 cells/ $\mu$ L. There is a possibility that the subjects were late in knowing the diagnosis or seeking treatment. When there is a suspicion of HIV/AIDS or when an HIV/AIDS diagnosis has been established, the patients usually already have clinical manifestations, and there have already been opportunistic infections and advanced conditions. This is because a lack of knowledge about HIV/AIDS and/or infection or co-infection has been experienced, but asymptomatic (such as TB, hepatitis B, hepatitis C, toxoplasma, and cytomegalovirus),(42,43) which were not excluded from this study. Education regarding early screening of HIV for the public, especially groups at risk of HIV infection, is important to do because early HIV screening can improve quality of life and reduce morbidity and mortality. This study also compared the mean total cortisol in CD4 groups. Statistically significant differences in cortisol levels were found in the CD4 group <200 and 200-350. This result was different from that of other studies

which reported no significant difference between cortisol levels and CD4 groups.(27,29) This is because of the differences in reference values and selectivity of the subjects. Subjects in those studies did not distinguish patients who were hospitalized and outpatient either naive or those who had received treatment.

This study had several limitations. Total cortisol levels in the subjects can still be influenced by other factors, such as blood albumin levels, which were not measured in this study. Examination of free cortisol levels may provide better results, but requires greater costs and special preparation. This study could not control the confounding factors, such as opportunistic infections, and did not measure cytokines that affected the HPA axis, which would affect the mechanism of cortisol increase, and did not have normal reference value that applied universally to measure cortisol levels.

In conclusion, the total cortisol level was negatively correlated with CD4 counts in HIV/AIDS patients., The higher the total cortisol level, the lower the CD4 count.

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**Table 1.** General characteristics of patients with HIV/AIDS at at Infectious Disease Intermediate Care Clinic of Dr. Soetomo General Hospital, Surabaya, Indonesia

| Characteristics                      | Results (n=56) |
|--------------------------------------|----------------|
| Age (years)                          |                |
| Mean ± SD                            | 34.3 ± (9)     |
| Range (min. - max)                   | (19-57)        |
| Age groups (years)                   |                |
| <20 years, n (%)                     | 1 (1.8)        |
| 20-29 years, n (%)                   | 18 (32.1)      |
| 30-39 years, n (%)                   | 22 (39.3)      |
| 40-49 years, n (%)                   | 10 (17.9)      |
| ≥50 years, n (%)                     | 5 (8.95)       |
| Sex                                  |                |
| Male, n (%)                          | 44 (78.6)      |
| Female, n (%)                        | 12 (21.4)      |
| Risk factors                         |                |
| Risky anal sex, n (%)                | 29 (53.6)      |
| Risky vaginal sex, n (%)             | 22 (39.3)      |
| Injectable drugs, n (%)              | 5 (7.1)        |
| Clinical stage                       |                |
| Stage 1, n (%)                       | 6 (10.7)       |
| Stage 2, n (%)                       | 22 (39.3)      |
| Stage 3, n (%)                       | 18 (32.1)      |
| Stage 4, n (%)                       | 10 (17.90)     |
| Body Mass Index (kg/m <sup>2</sup> ) |                |
| Mean ± SD                            | 21.0 ± 4       |
| Range (min - max)                    | (15.22-32.74)  |
| Opportunistic infection              | 28 (50)        |
| Oral candidiasis, n (%)              | 13 (46.4)      |
| Chronic diarrhea, n (%)              | 7 (25)         |
| Pulmonary TB, n (%)                  | 4 (14.3)       |
| Extrapulmonary TB n (%)              | 2 (7.1)        |
| CMV, n (%)                           | 1 (3.6)        |
| PCP, n (%)                           | 1 (3.6)        |
| Without opportunistic infection      | 28 (50)        |

**Table 2.** Serum cortisol levels in each stage

| Stage             | Mean  | SD    | n (sample) |
|-------------------|-------|-------|------------|
| Stage 1           | 16.85 | 6.71  | 6          |
| Stage 2           | 13.51 | 6.58  | 22         |
| Stage 3           | 21.16 | 10.49 | 18         |
| Stage 4           | 27.83 | 9.62  | 10         |
| Total of Patients |       |       | 56         |

**Table 3.** Serum cortisol levels in the CD4 groups

| CD4      | Mean Cortisol | SD    | n  |
|----------|---------------|-------|----|
| >500     | 15.59         | 4.1   | 3  |
| >350-499 | 14.98         | 5.7   | 4  |
| 200-350  | 14.98         | 5.7   | 11 |
| <200     | 21.69         | 10.21 | 38 |
| Total    |               |       | 56 |

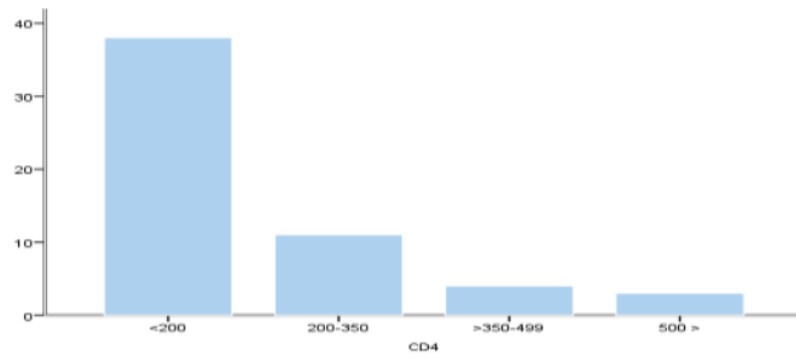


Figure 1. Distribution of CD4 counts

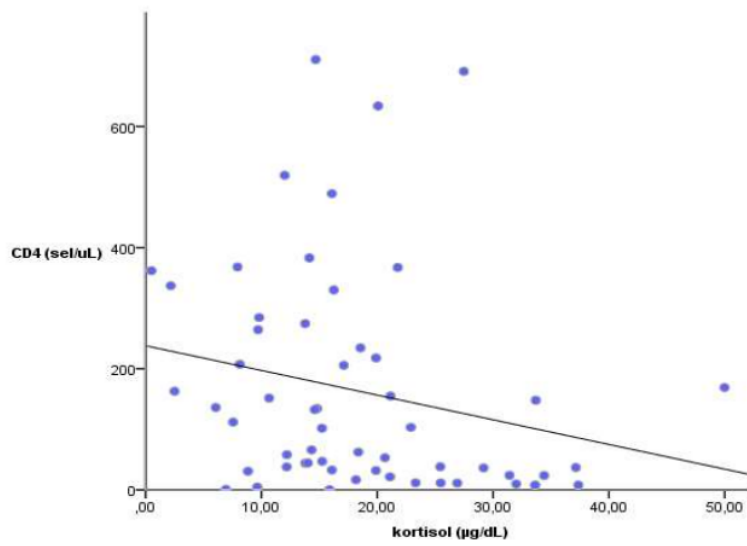


Figure 2. Correlation between total serum cortisol levels and CD4 count

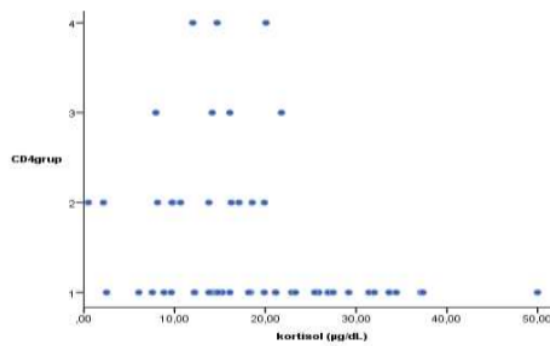


Figure 3. Correlation of total serum cortisol levels and CD4 group

Note: 1. CD4 <200; 2.CD4 200-350; 3. CD4 >350-499; 4. CD4> 500



# 08. Correlation between Serum Cortisol Levels and Cd4 Counts in Treatment-Naïve Patients with HIV AIDS Infection at Tertiary Hospital

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