Analysis cluster of differentiation 4 number and c-reactive protein concentration in patient with human immunodeficiency virus with or without lung tuberculosis

M J Nur\textsuperscript{1}, F Kuhuwael\textsuperscript{2}, S Katu\textsuperscript{2}, H Mubin\textsuperscript{2} and R Halim\textsuperscript{2}

\textsuperscript{1}Tropical Infection Division, Medical Faculty of Hasanuddin University, Makassar, Indonesia
\textsuperscript{2}Internal Medicine Department, Medical Faculty of Hasanuddin University, Makassar, Indonesia
\textsuperscript{*}Corresponding author: Jabalhanani@gmail.com

Abstract. HIV infected patients characterized by decrease CD4 cell count, where lower CD4 count, has higher infection risk. In HIV patients with Lung, Tuberculosis co-infection showed increase CRP level concomitant with disease severity. This study attempts to analyze TB incidence in HIV cases by looking at CD4 cell count and CRP levels in HIV-infected subjects. For analyzing the CD4 cell count and CRP levels in HIV patient with and without Lung Tuberculosis co-infection in Wahidin Sudirohusodo Hospital. Conducted observational study with cross-sectional design on HIV subjects with and without Lung Tuberculosis co-infection in Wahidin Sudirohusodo Hospital from September 2016 to June 2017. Patients divided into HIV group without TB co-infection, and with TB co-infection. Each group will be assessed CRP levels, which considered low <5 mg/L and high >5 mg/L, whereas CD4 cell count, considered low <200 cell/mm\textsuperscript{3} and normal >200 cell/mm\textsuperscript{3}. Results are considered significant if p-value<0.05. There were a significantly higher CRP levels (p<0.02) and lower CD4 counts (p<0.02) in HIV with TB co-infection and no significant relationship between CRP levels with aCD4 count in both groups.

1. Introduction
Patients with HIV infection had a 29-fold risk of TB occurrence than patients without HIV. The leading cause of death among patients with HIV is tuberculosis and one in five HIV related death globally.[1] CD4+ lymphocytes function is to coordinate some important immunological functions. This loss of function leads to progressive immune response disorders.[2] Various factors play a role in decreasing number of CD4+ lymphocyte cells. These factors are the direct cytopathic effects of HIV on CD4+ lymphocyte cells and their progenitors, induction of apoptosis through immune activation, stem cell destruction and bone marrow stromal cells, cytokine cytotoxicity, lymphoid tissue destruction including the thymus gland so that new cell production does not occur. Besides, also plays the role of anti-CD4 Cytotoxic cell factors (CD4+, CD8+, and NK cells), and CD4+ cell autoantibody.[3]

An acute phase protein is aC-reactive protein (CRP) synthesized in hepatocytes; its levels increased with infection and inflammation. This protein is synthesized in the liver which under normal circumstances its serum level is less than 6 mg/dL.[4] CRP is a component of the nonspecific immune system, particularly in response to Interleukin-6 (IL-6) and other cytokines. A study by Shaikh et al. showed an increase in CRP levels in patients with pulmonary tuberculosis, whose levels increased
concomitant with the degree of disease.[4] Lawn et al. showed symptomatic HIV patients showed a negative test for CRP <6 mg/L and increased in patients with Lung Tuberculosis co-infection.[5]

2. Methods
The research design used was an observational study with cross-sectional design to assess the relationship between CD4 and CRP values in HIV patients with or without co-infection of Lung Tuberculosis.

The study subjects were all HIV patients in Inpatient and Outpatient Department of Wahidin Sudirohusodo Hospital, Makassar starting from September 2016. Research path is the population of HIV patient and meets the inclusion criteria, are people diagnosed with HIV, people diagnosed with HIV with Lung tuberculosis co-infection. CD4 and CRP were examined in both groups of patients. Research data is processed using SPSS program 22nd version with research result shown in table form. Statistical methods used are the calculation of mean (mean), standard deviation (SD), frequency distribution and statistical test. Data from research results processed and presented in the form of table, graphics, and narration.

3. Result
In this study, subjects studied were 90 subjects, subjects aged 16 to 48 years old, with a mean age of 30-39 years, consisting of 70 male subjects and 20 female subjects. Characteristics of research subjects are shown in Table 1.

| Variable | Categories | N  | %   |
|----------|------------|----|-----|
| Gender   | Male       | 70 | 77.8|
|          | Female     | 20 | 22.2|
| Age      | <30 years old | 21 | 23.3|
|          | 30-39 years old | 45 | 50.0|
|          | >=40 years old | 24 | 26.7|
| CRP level| <5 mg/L    | 11 | 12.2|
|          | >=5 mg/L   | 79 | 87.8|
| CD4 count| <200       | 79 | 87.8|
|          | >=200      | 11 | 12.2|
| Groups   | HIV+TB     | 41 | 45.6|
|          | HIV        | 49 | 54.4|

The analysis of the relationship between CD4 cell count and CRP levels between HIV/TB and HIV without TB patients.

| CRP  | HIV with TB | CD4 | < 200 | 1 | 38 | 0.02 |
|------|-------------|-----|------|---|----|------|
|      |             |     | >= 200 | 1 | 1 |      |
|      | HIV without TB | CD4 | < 200 | 6 | 34 | 0.199|
|      |             |     | >= 200 | 3 | 6 |      |

Table 2 above shows the relationship between CD4 cell counts to CRP levels in HIV patients with and without tuberculosis complications. Based on the table, can be seen that 97.4% of HIV patients with TB co-infection have CD4 count <200 cells/mm³ and CRP> 5 mg/L. Meanwhile, patients with CD4 count > 200 cells and CRP level <5 mg/L are 2.6%. In HIV-infected patients without TB co-infection,
85.0% of patients had CD4 <200 cells and CRP level > 5mg / L. While patients with CD4 levels > 200 cells and CRP level < 5 mg / L were 33.3%.

Also, statistical test results using chi-square method showed that there was a significant correlation between decreasing CD4 cell count to elevated CRP levels in patients with TB co-infection (p = 0.02). However, statistical testing of the relationship between CD4 cell counts to elevated CRP levels in patients without TB co-infection did not show any significant association (p = 0.199).

4. Discussion
Comparison of CRP levels and CD4 cell count between HIV / TB and HIV without TB patients found that CRP levels were significantly higher in HIV + TB than in HIV (p <0.002. Percentage of subjects with CRP> = 5 mg / L was higher in HIV with TB co-infection (95.1%) with an average of 116.6 mg / L compared to HIV (81.6%), although not statistically significant (p> 0.05). It is similar to that of Lawn et al. [5] and Wagdera et al. [8] which suggests a higher CRP level in HIV subjects with TB co-infection with mean values of 57.8 mg / L and 41 mg / L.

CD4 cell count was significantly lower in HIV + TB than in HIV (P <0.02). The percentage of subjects with a CD4 cell count <200 cells / mm$^3$ was more common in HIV + TB (95.1%) than in HIV (81.6%) with mean values of 53.7 and 110 cells / mm$^3$, although statistically insignificant (p> 0.05). This result is similar to that of Skogmar et al. [7] showing a lower CD4 cell count in HIV-infected subjects with TB co-infection with a mean value of 192 cells / mm$^3$.

In this study, an analysis of the relationship between CD4 cell count and CRP levels in HIV-infected patients with TB co-infection showed a significant association (p = 0.02). Whereas, in HIV-infected patients without TB co-infection, no significant association was found between CD4 cell counts and CRP levels (p = 0.119). ItAn acute phase protein is C-reactive protein (CRP) is in accordance with the study by Lawn et al. [6], showing an association between CD4 cell count <100 cells / mm$^3$ with CRP> 200 mg / L with poor prognosis, higher numbers of M. tuberculosis bacteria and a higher risk of death in TB co-infected HIV patients. Similar research result with Tahir et al. found a negative correlation between CRP levels and CD4 cell count. These different results were attributed to the number of samples that were lacking in our study, as well as some of our study subjects were in the treatment of ARVs and OATs that could affect the levels of CRP and CD4 cell counts.[8]

5. Conclusion
Our results show that CRP levels are higher, and CD4 cell counts are lower in HIV patients with TB co-infection compared with HIV without TB co-infection. There is no relationship between CRP levels and CD4 cell count in HIV patients with or without co-infection TB.

References
[1] World Health Organization 2011 Tuberculosis prevalence surveys: a handbook vol 11 (Geneva: World Health Organization) pp 160-4
[2] Merati T P 2014 Imunopatogenesis infeksi HIV Buku ajar ilmu penyakit dalam (Jakarta: Interna Publishing) pp 904-12
[3] Djoerban Z and Djauzi S 2014 HIV/AIDS di Indonesia Buku ajar ilmu penyakit dalam (Jakarta: Interna Publishing) pp 889-99
[4] Shaikh M K, Samo J A and Devrajani B R 2012 C- Reactive protein in patients with pulmonary tuberculosis World Appl. Sci. J. 17 140-4
[5] Lawn S D, Wiktor S, Coulibaly D, et al. 2001 Serum c-reactive protein and detection of tuberculosis in persons co-infected with the human immunodeficiency virus Trans. R. Soc. Trop. Med. Hyg. 95 41-2
[6] Wagdera N Y, Yadhav K and Nagaraja B 2012 C-reactive protein as an early marker of opportunistic infections in HIV Int. J. Pharm. Bio. Sci. 3 1194–203
[7] Skogmar S, Schön T, Balcha T T, et al. 2015 Plasma levels of neopterin and C-reactive protein (CRP) in tuberculosis (TB) with and without HIV coinfection in relation to CD4 cell count 

*PLoS ONE* **10** 1-12

[8] Tahir A, Yusuph H, Bakki B, et al. 2013 Correlation between c-reactive protein and CD4+ cell count in HIV-infected and HIV/PTB co-infected patients at the university of maiduguri teaching hospital, Maiduguri, Nigeria *Front. Immunol. Conference Abstract* (15th International Congress of Immunology)