

# Correlation Of Cd4, Cd8, And Cd4/Cd8 Ratio On Nuclear Factor Kappa Beta (Nf- $\kappa$ $\beta$ ) Expression In Condyloma Acuminata Patients With Hiv Infection

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## ABSTRACT

**Introduction:** Condyloma acuminata is the most common sexually transmitted infection that occur in immunodeficiency diseases such as HIV. NF- $\kappa$  $\beta$  signaling is a transcription factor that plays a role in the activation, differentiation, and function of T cell effectors, namely CD4 and CD8 cells. Level of CD4, CD8 and CD4/CD8 ratio are markers for immunological and progression of HIV-related diseases. Disruption of CD4 and CD8 cells increase NF- $\kappa$  $\beta$  expression in condyloma acuminata with HIV infection, potentially causing giant lesions, increasing recurrence and persistent infection. The purpose of this study was to determine the correlation between CD4, CD8 and CD4/CD8 to NF- $\kappa$  $\beta$  expression in condyloma acuminata with HIV infection.

**Method:** This study is an observational analytical study with a cross-sectional design conducted at the Dermatovenereology Outpatient Clinic of Dr. Moewardi Hospital Surakarta in March – May 2023. An immunohistochemical examination to assess NF- $\kappa$  $\beta$  expression was carried out at the Anatomical Pathology Laboratory of the Faculty of Medicine, Sebelas Maret University. Data on CD4, CD8, and CD4/CD8 levels were taken from medical record data.

**Results:** A total of 17 condyloma acuminata patients with HIV infection and all of them were male. The most common sexual orientation is homosexual with the location of the most lesions found in the anal region. The mean value of NF- $\kappa$  $\beta$  expression was 67.64 $\pm$ 13.67%. The mean CD4 level was 358.64 $\pm$ 247.29 cells/uL and CD8 level was 1467.77 $\pm$ 346.58 cells/uL with CD4/CD8 ratio was 0.25 $\pm$ 0.17 cells/uL. Analysis using the Spearman correlation test showed a  $p > 0.05$  value in CD4, CD8, and CD4/CD8 ratios to NF- $\kappa$  $\beta$  expression.

**Conclusions:** There was no association between CD4, CD8 and CD4/CD8 levels and NF- $\kappa$  $\beta$  expression in condyloma acuminata patients with HIV infection.

**Keywords:** CD4, CD8, HIV, condyloma acuminata, CD4/CD8 ratio,

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## I. INTRODUCTION

Condyloma acuminata (CA) is a sexually transmitted infection caused by *human papillomavirus* types 6 and 11.<sup>1</sup> The prevalence of CA in the general population is 1%, with 100-200 new cases annually.<sup>2,3</sup> Condyloma acuminata can affect different age groups, however the most common age peak is between the ages of 20-40 years.<sup>4</sup> Patients with compromised immune system, such as those with HIV infection, are more likely to have HPV infection and cell-mediated immunity plays a role in controlling HPV infection.<sup>5</sup> Reduced CD4 levels in HIV infection disrupt T cell function, thereby increasing susceptibility to HPV infection.<sup>6</sup>

*Nuclear factor kappa beta* (NF- $\kappa$  $\beta$ ) is an important signaling in regulating inflammation, activation, and cell survival as well as cytokine production. NF- $\kappa$  $\beta$  signaling plays a role in naïve T cell activation, differentiation and function of CD4 *helper* (Th) T cells such as Th1, Th2, Th17, Tfh, and regulatory T cells. The role of NF- $\kappa$  $\beta$  in memory T cell activation suggests that this signaling plays a role in the initial regulation of T cell activation and differentiation making it difficult to determine its unique role for memory T cells.<sup>7</sup>

A decrease in the CD4/CD8 lymphocyte T cell ratio inhibits HPV antigen presentation and subsequently lymphocyte T cell activation. Specific immunity to overcome HPV infection may not be induced. The correlation between HPV infection and weakened immune system remains unclear, making it difficult to investigate the pathological mechanisms and therapeutic strategies of HPV infection, especially those accompanied by HIV infection.<sup>8</sup>

CD4 T cells are a marker of HIV/AIDS progression and CD4 counts  $< 350$  cells/mm<sup>3</sup> reduce the risk of AIDS-related diseases and other opportunistic diseases. Although antiretroviral therapy can increase CD4 levels, the CD4/CD8 ratio usually cannot return to normal when treatment for a chronic disease is initiated. Impairment of T cell function in HIV infection causes CD4 depletion and CD8 expansion, resulting in an inverted CD4/CD8

ratio. A decrease in the CD4/CD8 ratio of ARVs is associated with persistently elevated markers of T cell activation, whereas in individuals not treated with ARVs is associated with exhaustion of T cells.<sup>9</sup>

## II. METHOD

This study is an observational analysis with a cross-sectional design on condyloma acuminata patients at the Dermatovenereology Outpatient Clinic of Dr. Moewardi Hospital Surakarta in March – May 2023. The inclusion criteria in this study are the age of  $\geq 18$  years who are diagnosed with condyloma acuminata with HIV positive status and predilection in genital or anogenital, while if the patient has malignancy, other viral diseases such as molluscum contagiosum and veruka vulgaris and incomplete medical record data will be excluded from this study. Immunohistochemical examination to assess NF-κβ expression using p-65 antibodies was carried out at the Anatomical Pathology Laboratory of FK UNS Surakarta and will be assessed using ImageJ software. Data on serum CD4, CD4/CD8, and CD8 levels are taken from patient medical record data. All data was collected and analyzed using SPSS software version 22.0.

## III. RESULT

The total subjects of this study was 17 male patients aged 18-60 years with a mean age of  $27.06 \pm 10.27$  years. Most of the subjects in this study were homosexual. The location of most lesions in this study was found in the anal region (**Table 1**).

**Table 1.** Characteristics of research subjects

Characteristic	Total	Percentage (%)
Mean age	27.06±10.27	
Gender		
Man	17	100%
Woman	0	0%
Sexual Orientation		
Homosexual	14	82,35%
Heterosexual	3	17,65%
Predilection		
Anus	10	58,83%
Genital	7	41,17%

Mean value of CD4, CD8 and CD4/CD8 ratio can be seen in **Table 2**. Analysis using the Spearman correlation test showed a p-value of  $>0.05$  in CD4, CD8, and CD4/CD8 ratios showing no correlation between these three parameters to NF-κβ expression (**Table 3**).

**Table 2.** Mean value of NF-κβ expression, CD4, CD8 and CD4/CD8 ratio

Variable	Mean value
Mean value of expression NF-κβ	67.64±13.67%
Mean CD4 cell count	358.64±247.29 cells/uL
Mean CD8 cell count	1467.77±346.58 cells/uL
CD4/CD8 ratio	0.25±0.17 cells/uL

**Table 3.** Relationship of CD4, CD8 and CD4/CD8 ratio to NF-κβ expression in condyloma acuminata patients

Variable	P-value	Correlation coefficient
CD4 Levels	0,815	0,061
CD8 Levels	0,881	0,039
CD4/CD8 ratio	0,764	0,079

## IV. DISCUSSION

Condyloma akuminata occurs most frequently during the productive age. Some studies reported different ages across countries, corresponding to age of first sexual intercourse, the number of sexual partners, and sexual behavior habits.<sup>10</sup> Some studies also reported a younger age in condyloma acuminata patients accompanied by HIV infection due to higher risk sexual behaviors such as multiple sexual partners.<sup>11</sup>

Condyloma acuminata affects both men and women with relatively similar incidence rates.<sup>12</sup> Some studies reported that more men experience condyloma acuminata accompanied by HIV infection than women.<sup>13</sup> Men tend to be more sexually active and have more sexual partners than women, making them more susceptible to sexually transmitted diseases such as condyloma acuminata and HIV.<sup>14</sup> All subjects in this study were men who had condyloma acuminata and were accompanied by HIV infection.

Sexual behavior and sexual orientation will also determine the location of the condyloma acuminata lesion.<sup>11</sup> Risky sexual behaviors such as genito-anal intercourse, especially in homosexual groups, will cause condyloma acuminata lesions to occur more frequently in anal region. This is also due to the transition zone on

the mucosa, which is more susceptible to microtrauma.<sup>2</sup> The most common sexual orientation in this study was homosexual and most lesion sites were found in the anal region.

CD4 cell levels are one of the strong markers of immunological improvement and progression of HIV/AIDS after antiretroviral therapy, and most HIV/AIDS-related deaths are due to CD4 cell levels of <350 cells/uL. CD4 cells have also known to be associated with the recurrence of condyloma acuminata in HIV patients, with low CD4 cell levels are associated with increased recurrence. Currently, CD8 T cell levels and CD4/CD8 ratios are widely considered as additional markers of clinical progression and immunological improvement. CD8 cell levels remain elevated in chronic infections such as HIV infection, but can also increase in response to acute infection. Elevated CD8 cell levels are associated with homeostasis reactions to low CD4 levels.<sup>16,17</sup>

Studies on NF-κβ expression in condyloma acuminata are limited. Weng *et al.* reported stronger NF-κβ expression in condyloma acuminata patients compared to veruka vulgaris and healthy skin.<sup>18</sup> Some viruses such as HPV and HIV can modulate NF-κβ signaling, which helps increase viral gene expression.<sup>19</sup> The presence of HPV and HIV infection can cause decrease CD4 cell levels which also affects T cell function.<sup>17</sup> NF-κβ signaling plays a role in T cell activation, differentiation, and effector function.<sup>20</sup> NF-κβ signaling also plays a role in the development of cells in the thymus gland that later differentiate into mature CD4 and CD8 cells, although the underlying mechanism is still not fully understood.<sup>21</sup>

Disruption of effector T cell function such as CD4 and CD8 due to HIV infection can lead to susceptibility to other infections such as HPV infection.<sup>6</sup> HIV infection will increase the expression of NF-κβ which will stimulate HPV protein E1 to increase viral replication.<sup>21</sup> Condyloma acuminata lesions accompanied by HIV infection will increase the risk of giant condyloma, increase recurrence and persistent infection.<sup>11</sup>

This study has limitations due to small number of subjects, so further studies with a larger number of subjects are required to establish further associations regarding CD4, CD8, and CD4/CD8 levels to NF-κβ expression in condyloma acuminata patients with HIV infection.

## V. CONCLUSION

There was no association between levels of CD4, CD8, and CD4/CD8 ratio to NF-κβ expression in condyloma acuminata patients with HIV infection.

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