CORRELATION BETWEEN INTERFERON GAMMA

by Nabil Salim Ambar

Submission date: 23-May-2023 11:07AM (UTC+0800)
Submission ID: 2099743330
File name: CORRELATION_BETWEEN_INTERFERON_GAMMA.pdf (5.63M)
Word count: 333
Character count: 1254

INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

PAGE 333
2019 July; 25(3): 333-339
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

CORRELATION BETWEEN INTERFERON GAMMA RELEASE ASSAY OF ELISPOT METHOD IN T.SPOT-TB AND CD4+ T LYMPHOCYTE CELL COUNT IN HIV POSITIVE PATIENTS

Nabil Salim Ambar[1], Aryati[1], Tutik Kusmiati[2], Erwin Astha Triyono[3]

[1] Department of Clinical Pathology, Faculty of Medicine, Airlangga University/Dr.Soetomo Hospital, Surabaya, Indonesia. E-mail: nbil_dr@yahoo.com
[2] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Airlangga University/Dr.Soetomo Hospital, Surabaya, Indonesia
[3] Department of Internal Medicine, Faculty of Medicine, Airlangga University/Dr.Soetomo Hospital, Surabaya, Indonesia

ABSTRACT

Human Immunodeficiency Virus (HIV) is a virus that causes Acquired Immunodeficiency Syndrome (AIDS), affecting the immune system and weakening the body function in fighting disease. The primary cells that HIV attacks are $CD4^+$T lymphocytes. Opportunistic Infections (OIs) are the largest risk factors of death in HIV patients and occur in $CD4^+$T cells <200 cells/µL lymphocytes. Tuberculosis (TB) is a disease with a high mortality rate in the world where Indonesia is a TB endemic country with the highest morbidity rates of TB in the world. The most common OI in people with HIV is TB. The number of limitations of the Tuberculin Skin Test (TST) is large, thus in-vitro T cells test with Interferon Gamma Release Assay (IGRA) is used in diagnosing latent TB. The aim of this study was to determine the correlation between IGRA ELISPOT method (T-SPOT.TB) and $CD4^+$T lymphocyte cell count in HIV positive patients. This was an observational analytical study with a cross-sectional design. The number of samples was 56 HIV positive patients who were treated at the Intermediate Treatment Unit of Infectious Disease (UPIPI) Clinic of the Dr. Soetomo Hospital Surabaya. The examination of $CD4^+$T lymphocyte count was performed by FACSCalibur and IGRA was examined with T-SPOT.TB. The results were analyzed using the Spearman correlation test. $CD4^+$ lymphocyte cell counts measured by FACSCalibur based on WHO groupings were as follows: > 500 cells/µL (33.93%), 200-349 cells/µL (25%), 350-499 cells/µL (25%) and <200 cells/µL (16.07%). IGRA examination results (T-SPOT.TB) showed 35.71% positive and 64.29% negative. The Spearman correlation test between $CD4^+$ T cell lymphocytes with IGRA in HIV positive patients showed r = 0.036 (p=0.794). There was no correlation between interferon-gamma release assay of ELISPOT method (T-SPOT.TB) and $CD4^+$ T lymphocyte cell count in HIV positive patients.

Key words: Human immunodeficiency virus, $CD4^+$T lymphocyte cell, latent TB, IGRA

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that causes Acquired Immunodeficiency Syndrome (AIDS), which can affect the immune system, interfere with and weaken the body's function to fight infections and diseases.[1] Primary cells that are attacked by HIV are $CD4^+$ T lymphocytes that help the immune function. In addition to the HIV virus as the leading cause of death in people with HIV/AIDS, the presence of Opportunistic Infections (OI) is the most significant risk factor of death in people with HIV. The occurrence of OI arises in T lymphocytes T $CD4^+$ <200 cells/µL.[2]

Tuberculosis (TB) is one of the oldest diseases with high mortality rates in the world. Indonesia is a TB endemic country with the highest rates of TB in the world.[2] People with HIV/AIDS are very easily infected by *Mycobacterium tuberculosis* (MTB) so that people with HIV have a greater risk of suffering from TB. The most common OI in people with HIV is TB. Human immunodeficiency virus infection and TB are a combination of deadly diseases because they are more destructive than when they occur singly in HIV or TB alone. Many people infected with HIV also suffer from TB in developing countries as early symptoms of AIDS. Human immunodeficiency virus and TB coinfection is estimated at around 11 million people worldwide, including patients receiving Highly Active Antiretroviral Therapy (HAART).[3]

According to the World Health Organization (WHO) 2012, one-third of the 34 million people with HIV are infected with latent TB. Latent TB infection is marked by the absence of symptoms and signs of TB infection on normal chest radiographs, negative sputum direct staining (microscopically), negative

sputum culture and positive Tuberculin Skin Test (TST) or positive Interferon Gamma (IFN-γ) Release Assay (IGRA).[3]

Tuberculin skin tests have been used for the diagnosis of latent tuberculosis, but this test has limitations such as low sensitivity and specificity. Due to the many weaknesses of the TST test, the in-vitro T cell test with Interferon Gamma Release Assay (IGRA) after challenged with MTB antigen can minimize false-positive or false-negative results.[4] There are several IFN-γ checks on the market, namely: QuantiFERON-TB Gold in-Tube assay (QTF-GIT) with ELISA and T-SPOT.TB assay based on the ELISPOT method. Research by research and training in tropical disease (TDR) showed that T-SPOT had a sensitivity higher than QFT-GIT.[5]

Research on IGRA in developing countries is still very rare especially in HIV patients, thus encouraging researchers to know the correlation between interferon-gamma release assay of ELISPOT method (T-SPOT.TB) and the number of $CD4^+$ T lymphocyte cells in HIV positive patients.

The aim of this study was to determine the correlation between IGRA ELISPOT method (T-SPOT.TB) and $CD4^+$ T lymphocyte cell count in HIV positive patients.

METHODS

This research was an observational analytical research with a cross-sectional design. The diagnosis was based on history, chest X-Ray examination, and examination of GeneXpert sputum, followed by an examination of $CD4^+$Tcell lymphocyte count by FACSCalibur and IGRA examination with T-SPOT.TB. The sample collection started at the end of December 2017 until March 2018. The research location was the Intermediate Treatment Unit of Infectious Disease (UPIPI), Dr. Soetomo Hospital, Surabaya. The IGRA examination was conducted at a major private laboratory accredited in Surabaya (Parahita). Sampling was done by consecutive samples with the criteria of HIV patient on ARV therapy, age minimum of 21 years and not suffering from active TB. Patients with extrapulmonary TB were excluded from the study. The total sample size was 56 people.

Descriptive analysis was performed using statistical measures (mean, standard deviation, proportion, and frequency distribution table). A paired student t-test was used to compare the two groups, which was positive IGRA and negative IGRA. The correlation analysis between the ELISPOT IGRA method and $CD4^+$ T lymphocyte cell count in HIV positive patients was performed using the Spearman correlation test. Results were evaluated with a significance value of $p < 0.05$.

This research had passed the ethical feasibility test in Dr. Soetomo Hospital No: 739/ Panke.KKE/ XII/ 2017.

RESULTS AND DISCUSSION

The number of samples of HIV male patients was 36 (64.28%) and females 20 (35.71%). According to the Centers for Disease Control and Prevention (CDC) 2016, adult and adolescent HIV infections in the United States were predominantly male by 76%. In accordance with the Ministry of the Health Republic of Indonesia.[1] The ratio between HIV-infected males and females was 2.6: 1.

Cases of HIV in males are higher because of sexual behavior such as sex worker customers and drug abuse (Drugs, Psychotropics, and Additives), which also higher in males than females. The sexual act between males was also one of the causes.

The grouping of $CD4^+$ T lymphocyte cell count data in this study was conducted according to the WHO criteria.[6] The largest number of $CD4^+$ T cell lymphocyte cells was found in $CD4^+$ T cell lymphocyte count> 500 cells/µL of 33.92% and the lowest was found in the number of lymphocyte cells T $CD4^+$ <200 cells/µL of 16.07%. Mean $CD4^+$ T cell lymphocyte value of 440±257 cells/µL can be seen in Table 1.

In contrast to the research of Mrudula *et al.* the average $CD4^+$ T lymphocyte cell in HIV positive patients who had been receiving antiretroviral

Table 1. Examination results of $CD4^+$ T-cell lymphocytes

$CD4^+$ T lymphocyte cell	Total patients	Total (%)	Average ± SD
< 200 cell/µL	9	16.07	104 ± 73
200 – 349 cell/µL	14	25	299 ± 44
350 – 499 cell/µL	14	25	421 ± 32
> 500 cell/µL	19	33.93	716 ± 211
Total	56	100	440 ± 257

therapy for six months was 306±178 cells/μL.[7] The average difference in $CD4^+$ T lymphocyte cell values with the investigators could be due to the fact that the researchers did not take into account the duration of antiretroviral therapy in the study subjects.

Provision of ARVs in the study subjects started when the T cell lymphocyte T cell count was <350 cells/μL according to the protocol of the Dr. Soetomo Hospital Surabaya, while in the study by Mrudula *et al.*, antiretroviral drugs were administered when $CD4^+$ T cell lymphocyte count was <250 cells/μL.[8] Patients who received ARV treatment for more than 6 months, will have an increase in the number of $CD4^+$ T lymphocyte cells on an average between 104-174 cells/μL. According to Mocroft *et al.*, HIV-infected patients receiving antiretroviral treatment will experience the largest increase in T-cell count of $CD4^+$ T lymphocytes >100 cells/μL in the first year after ARV consumption.[9]

Mandal stated that people with HIV were able to survive longer when taking antiretrovirals on a regular basis. ARVs were able to suppress the development of the HIV virus so it is likely that the survival of their lives is similar to that of individuals not infected by HIV.[10] According to the WHO, consumption of antiretrovirals also had an effect on the increase of $CD4^+$ T lymphocyte cells so that it could improve the immune system and avoid opportunistic infections.[7]

There are several IFN-γ checks on the market, including QuantiFERON-TB Gold in-Tube assay by Cellestis Ltd, Australia (currently there is a new product called Quantiferon Gold Plus) and T-SPOT.TB assay (Oxford Immunotec, UK).

T-SPOT.TB was used in this study because the research subjects were HIV positive patients who were patients with a low immune system. According to Oni *et al.*, IGRA T-SPOT.TB had more positive results compared with Quantiferon Gold in Tube in HIV-infected patients.[11] In accordance with the research of Ramos *et al.*, i.e., T-SPOT.TB was less affected by the state of advanced-stage immunosuppression.[12] Rangaka *et al.* also suggested the use of T-SPOT.TB in TB endemic areas and patients with advanced immunosuppression.[13,14]

Examination of Interferon-Gamma Release Assay (IGRA) obtained positive results as much as 35.71% and negative results as much as 64.29%.

Individuals infected with HIV have a relatively low accuracy of IGRA, both to ascertain and exclude the diagnosis of active TB.[15] Many studies of T-SPOT.TB to detect TB in HIV-infected patients exist, but research on HIV-infected patients is still limited. Several studies have concluded that the sensitivity and specificity of T-SPOT.TB was 65% and 70%.[5]

IGRA T-SPOT.TB examination in this study obtained positive results as much as 35.71% and negative results as much as 64.29%. This was in accordance with the research of Sinaga, who obtained positive results IGRA of 29.54% and negative as much as 70.46%.[16] In contrast to the study in Italy, IGRA positive results showed as much as 11.54%, negative as much as 75.96% and indeterminate as much as 12.5%.[3]

According to Elzi, latent TB detection in HIV patients was more difficult than non-HIV patients because of immune system destruction, so the sensitivity of IGRA became low.[17] Data from this study of the length of time infected HIV with IGRA in HIV positive patients underwent statistical analysis using the Spearman correlation test. Results of analysis in HIV positive patients showed no correlation between the time of subjects infected by HIV with IGRA that was r = 0.095 (p=0.487). Results of IGRA according to the duration of HIV can be seen in Table 2.

Research data on the duration receiving ARV with IGRA in HIV positive patients, then underwent statistical analysis using the Spearman correlation test. Results of study in HIV positive patients showed no correlation between the duration of receiving ARV with IGRA that was r = 0.070 (p = 0.606). The results of IGRA according to the length of antiretroviral treatment can be seen in Table 3.

Human immunodeficiency virus patients who started ART with high $CD4^+$ T lymphocyte cell counts tend to have a lower risk to suffer more opportunistic infections compared to when starting ARVs with low

Table 2. Results of IGRA examination on HIV duration

Result of IGRA Length of suffering HIV	Positive	Negative	P
0 – 5 years	17 (30.36%)	32 (57.14%)	
5.1 – 10 years	2 (3.57%)	4 (7.14%)	0.487
10.1 – 15 years	1 (1.79%)	-	
Total	20 (35.71%)	36 (64.29%)	

Table 3. IGRA examination results on duration of ARV

Result of IGRA Length of ARV therapy	Positive	Negative	P
0 – 4 years	14 (25%)	29 (51.79%)	
4.1 – 8 years	5 (8.93%)	6 (0.71%)	0.606
8.1 – 12 years	1 (1.79%)	1 (1.79%)	
Total	20 (35.71%)	36 (64.29%)	

Table 4. Number of T $CD4^+$ lymphocyte cells with positive and negative IGRA outcomes

Result of IGRA $CD4^+$ T lymphocyte cell	Positive	Negative	P
< 200 cell/µL	4 (7.14%)	5 (8.93%)	
200 – 349 cell/µL	3 (5.36%)	11 (19.64%)	0.794
350 – 499 cell/µL	6 (10.71%)	8 (14.29%)	
> 500 cell/µL	7 (12.5%)	12 (21.43%)	
Total	20 (35.71%)	36 (64.29%)	

$CD4^+$ T cell lymphocytes. Research by Kaufmann suggested that antiretroviral treatment in low $CD4^+$ T lymphocyte cell counts was more difficult to increase $CD4^+$ T lymphocyte cell counts.[18] Mrudula, stated that delaying antiretroviral therapy in HIV patients up to the T cell lymphocyte count of $CD4^+$ <200 cells/µL may reduce short-term immune response.[8] Patients with $CD4^+$ T lymphocyte cell count less than 50 cells/µL had a four-fold risk of no increase in $CD4^+$ T lymphocyte cell counts greater than 200 cells/µL.[18]

People with HIV who were taking antiretroviral drugs for more than two years have a better quality of life than people who take antiretroviral drugs under two years; this was because the immune system had improved so that the number of $CD4^+$T lymphocytes had increased.[19]

According to Oni, the proportion result of T-SPOT.TB positive with $CD4^+$ T cell lymphocyte count <200 cells/µL in the non-tuberculosis group with HIV is lower (p=0.029) than the TB group. This study showed that the consumption of ARV in the first four years comprised as many as 43 subjects infected with HIV and IGRA test. The number of subjects who were taking antiretroviral drugs over four years is lower due to: refusal to follow this study, ask another person to get the medicines, stopped taking drugs, lost follow-up, or the patient died.[11]

The result of IGRA detection of $CD4^+$ T lymphocyte that has high cell counts was very good, so there were no false-negative results, borderline or indeterminate.[20]

Results of $CD4^+$ T lymphocyte cell counts, when grouped according to IGRA test results, for most positive IGRA results in the $CD4^+$ T lymphocyte cell count group> 500 cells/µL of 12.5% and the least in the T cell lymphocyte T-cell count group $CD4^+$ 200-349 cells/µL of 5.36%. The most negative IGRA results were mostly in the $CD4^+$ T lymphocyte count group> 500 cells/µL of 21.43% and the least in the $CD4^+$ T cell lymphocyte count group <200 cells/µL of 8.93%. The grouping of $CD4^+$ T lymphocyte cell numbers based on IGRA results could be seen in Table 4.

The data of the research on the number of $CD4^+$ T lymphocyte cells with IGRA in HIV positive patients, then underwent statistical analysis using Spearman correlation test

Spearman correlation test was performed to determine the correlation between $CD4^+$ T lymphocyte cells with IGRA in HIV positive patients and obtained a p-value of = 0.794, showing no correlation between the two.

Analysis results in HIV positive patients showed no correlation between T lymphocyte T cell $CD4^+$ with IGRA i.e., R = 0.036 (p=0.794). The correlated graph of IGRA results with $CD4^+$ T lymphocyte cells can be seen in Figure 1.

Elzi study, showed no relationship between $CD4^+$ T lymphocyte cell count and T-SPOT.TB.[17] In accordance with Chen *et al.* and Oni *et al.*, who stated that there was no significant correlation between T-SPOT.TB with $CD4^+$ T lymphocyte cell counts in HIV-infected subjects with active TB.[21,11] No significant correlation was likely due to the small number of research subjects who were divided into groups based on $CD4^+$ T lymphocyte cell counts.

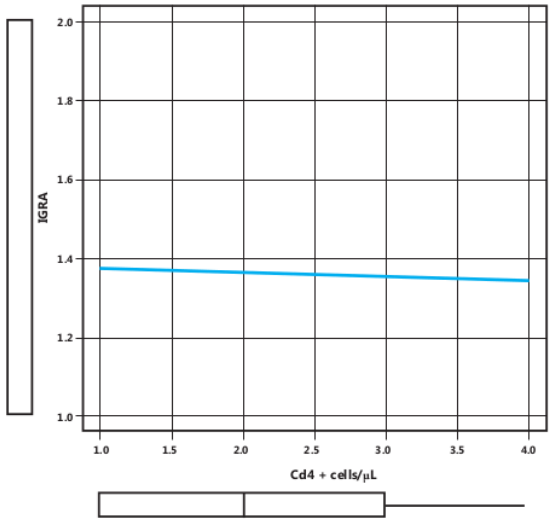

Figure 1. Correlation of IGRA results with CD4$^+$ T lymphocyte cell count from fifty-six patients. Description: IGRA results, 1 = negative; 2 = positive. Number of T lymphocytes CD4 $^+$ cells, 1 => 500 cells/µL; 2 = 350 - 499 cells/µL; 3 = 200 - 349 cells/µL; 4 = <200 cells/µL. Number of T lymphocytes CD4$^+$ cells from each of the research subject are close together, make it appear as a green line

A study by Cai *et al.* in HIV-infected patients with active TB, who divided the study groups into two categories.[15] The first category was divided into four groups with CD4$^+$ T lymphocyte cell counts: 1 - 10 cells/µL, 11 - 50 cells/µL, 51 - 100 cells/µL and 101 - 536 cells/µL. The two categories were divided into two groups of CD4$^+$ T lymphocyte cell counts: 1 - 50 cells/µL and 51 -536 cells/µL. There was no difference in outcome on positive T-SPOT.TB with various T CD4$^+$ lymphocyte values. The first category obtained value p=0.287 and category two p-value = 0.082, so it was concluded that there was no correlation between the number of T CD4$^+$ lymphocytes with T-SPOT.TB.

Different results obtained by Salvaggio *et al.* suggested that the number of CD4$^+$ T lymphocyte cells in HIV-infected patients was positively correlated with gamma interferon.[17] In accordance with Sultan *et al.* there was a correlation between median values of CD4$^+$ lymphocyte T cells and IGRA results r = 0.92 (p=0.02).[18]

Programmed Cell Death (PCD) was one of the mechanisms of CD4$^+$ T lymphocytic destruction in HIV infection. Intra-stimulated mitogen-stimulated PCD affected CD4$^+$ T lymphocytes, CD8$^+$T lymphocytes, and non-T lymphocytes, whereas antigen-stimulated PCD was selective for CD4$^+$ T lymphocytes.[22]

The investigators conducted a grouping of CD4$^+$ T lymphocyte cell counts based on the WHO classification in 2009 with the lowest limit of fewer than 200 cells/µL. Borderline or indeterminate results were not obtained in this study, but false-negative results could be obtained because immune disorders in HIV-infected cells had insufficient cytokine production, alternatively because of the energy condition of sensitized T cells against specific antigens or the accumulation of T cells at the site of infection.[23]

This study was a cross-sectional study, with limitations i.e. before patients received ARV treatment, CD4$^+$ T lymphocyte cells were unknown. Levels of gamma interferon in addition to CD4$^+$ T lymphocyte cells were also influenced by CD8$^+$ T lymphocytes, but in this study, there was no examination of CD8$^+$ T lymphocyte cells, so it was not known how large the T CD8$^+$ lymphocyte cell effect was on gamma interferon. Researchers did not perform TST in the study subjects due to the existence of tuberculin reagents nationally, whereas TST was one of the long-used examinations to confirm the diagnosis of latent TB.

CONCLUSION AND SUGGESTION

The largest number of CD4$^+$ T lymphocyte cells in this study was > 500 cells/µL of 33.92% and the least in T cell lymphocyte counts of CD4$^+$ <200 cells/µL of 16.07%. IGRA T-SPOT.TB examination in this study obtained positive results as much as 35.18% and

negative results as much as 64.29%. Results of analysis in HIV positive patients in this study showed no correlation between $CD4^+$ T lymphocyte cells with IGRA T-SPOT.TB (p=0.794). Suggestions from this study, it should be further investigated with prospective studies to see the association of IGRA T-SPOT.TB with $CD4^+$ T lymphocyte cell counts, both before ARV and after ARV administration. A $CD8^+$ T lymphocyte count was needed to determine how much it affected the levels of gamma interferon. The addition of TST to the diagnosis of latent TB will further strengthen the evidence that the patient has latent TB.

ACKNOWLEDGMENT

The researchers would like to thank PT. Fokus Diagnostic Indonesia for providing T-SPOT.TB so that this research can be finished. Hopefully, this research can be useful and become the input for the parties in need.

REFERENCES

1. Kementrian Kesehatan RI. Situasi dan analisis HIV AIDS. Infodatin. Pusat data dan informasi kementrian kesehatan RI. Accessed August 1, 2017. Available at http://www.depkes.go.id/resources/download/pusdatin/infodatin/Infodatin%20AIDS.pdf.
2. Widiyanti M, Fitriana E, Iriani E. Karakteristik pasien koinfeksi TB-HIV di Rumah Sakit Mirna Masyarakat Mimika Papua. Jurnal Penelitian Kesehatan, 2016; 3(2): 49-55.
3. Badan Penelitian dan Pengembangan Kesehatan. Kementrian Kesehatan Republik Indonesia. Accessed August 9, 2017 Available at http://ejournal.litbang.depkes.go.id/index.php/sel/article/download/6382/4816.
4. Parrela R, Esposito V, Onofrio M, Parrella G, Viglietti R, *et al.* Interferon-gamma release assays and tuberculin skin test performance in different settings of HIV Immunodeficiency. In-Vivo Journal, 2015; 29: 137-140. Accessed July 18, 2017, Available at http://iv.iiarjournals.org/content/29/1/137.full.pdf+ html. 5.
5. World Health Organization. Global strategy and targets for tuberculosis prevention, care, and control after 2015. Accessed July 28, 2017, Available at http://www.who.int/tb/post_2015_tb_presentation.pdf.
6. Heri W, Antono S, Zahroh S. Faktor-faktor yang berhubungan dengan penggunaan jarum suntik bergantian diantara pengguna napza suntik di kota Semarang. Jurnal Promosi Kesehatan Indonesia, 2008; 3(2): 78. Accessed 1 August, 2017 Available at https://ejournal.undip.ac.id/index.php/jpki/article/view/2539/2249.
7. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Accessed September 19, 2017, Available at http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf
8. Mrudula ND, U Phute S, RK Khadse, Patil M, Kulkarni DS. Statistical analysis and evaluation of CD4 count after 6 months on ART. Indian J Community Med. 2012; 37(4): 266–267. Accessed September 19, 2017, Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3531025/
9. Mocroft A, Phillips AN, Gatell J, Ledergerber B, Fisher M, *et al.* Normalization of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: An observational cohort study. The LANCET Journal, 2007; 370(9585): 407–413. Accessed September 9, 2017, Available at http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(07)60948-9.pdf
10. Mandal BK. Penyakit Infeksi. Lecture notes. 6th Ed., Jakarta, Erlangga, 2008; 220–229.
11. Oni T, Patel J, Gideon HP, Seldon R, Wood K, *et al.* Enhanced diagnosis of HIV-1-associated tuberculosis by relating T-SPOT.TB and CD4 counts. Eur Respir J 2010; 36: 594–600. Accessed July 18, 2017. Available at http://erj.ersjournals.com/content/erj/36/3/594.full.pdf
12. Ramos JM, Robledano C, Masiá M, Belda S, Padilla S, *et al.* Contribution of interferon-gamma release assays testing to the diagnosis of latent tuberculosis infection in HIV- infected patients: A comparison of quantiferon-TB gold in tube,T-SPOT.TB and tuberculin skin test. BMC infectious diseases, 2012; 12: 169. Available at www.biomedcentral.com/1471-2334/12/169
13. Rangaka MX, Diwakar L, Seldon R, Cutsem GV, Meintjes GA, *et al.* Clinical, immunological, and epidemiological importance of antituberculosis T cell responses in HIV-infected Africans. Clin Infect Dis, 2007; 44: 1639-1646. Accessed July 18, 2017, Available at https://academic.oup.com/cid/article/44/12/1639/279999.
14. Rangaka MX, Wilkinson KA, Seldon R, Cutsem GV, Meintjes GA, *et al.* Effect of HIV-1 infection on T-cell-based and skin test detection of tuberculosis infection. Am J Respir Crit Care Med, 2007; 175: 514-520. Accessed July 18, 2017, Available at https://www.atsjournals.org/doi/full/10.1164/rccm.200610-1439OC.
15. Cai R, Chen J, Guan L, Sun M, Sun Y, *et al.* Relationship between T-SPOT.TB responses and numbers of circulating $CD4^+$ T-cells in HIV infected patients with active tuberculosis. BioScience Trends. 2014; 8(3):163-168. Accessed July 28, 2017. Available at https://www.jstage.jst.go.jp/article/bst/8/3/8_2014.01032/_pdf/-char/en
16. Sinaga Fransisca TY. Validitas dan reabilitas pemeriksaan TST dan T-SPOT TB dalam mendeteksi infeksi TB laten pada penderita infeksi HIV. Tesis

Pascasarjana Universitas Sebelas Maret. Accessed July 11, 2017, Available at https://eprints.uns.ac.id/36656/1/S601208004_pendahuluan.pdf.

17. Elzi L. Improved sensitivity of an interferon-gamma release assay (T-SPOT.TB™) in combination with tuberculin skin test for the diagnosis of latent tuberculosis in the presence of HIV co-Infection. BMC Infect Dis, 2011; 11: 319. Published online 2011 Nov 15. Accessed December 20, 2016. Available at https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC3226666/.
18. Salvaggio A. CD4 count in HIV infection is positively correlated to interferon-γ and negatively correlated to interleukin-10 in-vitro production. AIDS Journal, 1996; 10(4): 449-450. Accessed August 18, 2017, Available at https://journals.lww.com/aidsonline/citation/1996/04000/cd4_count_in_hiv_infection_is_positively.20.aspx
19. Sultan B, Benn P, Mahungu T, Young M, Mercey D, *et al*. Comparison of two interferon-gamma release assays (quantiferon-TB gold in-tube and T-SPOT.TB) in testing for latent tuberculosis infection among HIV-infected adults. International Journal of STD & AIDS, 2013; 24(10) 775–779. Accessed July 18, 2017, Downloaded at https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC4107858/pdf/10.1177-0956462413486459.pdf
20. Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, *et al*. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis, 2005; 41(3): 361-72. Accessed July 17, 2017, Available at https://www.ncbi.nlm.nih.gov/pubmed/16007534.
21. Boris J, Danielle P, Musie G, Carmen C, Marcus A, *et al*. Factors predicting discordant virological and immunological responses to antiretroviral therapy in HIV-1 clade C infected Zulu/Xhosa in South Africa. Plos One. Accessed July 15, 2017, Available at http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0031161.
22. Handayani F, Fatwa STD. Faktor yang mempengaruhi kualitas hidup orang dengan HIV/ AIDS (ODHA) di kota Kupang. BKM Journal of Community Medicine and Public Health. Berita Kedokteran. 2017; 33(11): 509-514.
23. Chen J, Sun J, Zhang R, Liu L, Zheng Y, *et al*. T-SPOT.TB in the diagnosis of active tuberculosis among HIV-infected patients with advanced immunodeficiency. AIDS Res Hum Retroviruses, 2011; 27(3): 289-94. Accessed July 18, 2017, Available at https://www.ncbi.nlm.nih.gov/pubmed/20977360.

CORRELATION BETWEEN INTERFERON GAMMA

ORIGINALITY REPORT

10%	7%	6%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	epdf.pub Internet Source	3%
2	www.coursehero.com Internet Source	3%
3	Bowers, . "Setting Out your Findings", Getting Started in Health Research Bowers/Getting Started in Health Research, 2011. Publication	3%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

CORRELATION BETWEEN INTERFERON GAMMA

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7