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ARTIKEL JURNAL INTERNASIONAL SCOPUS Q4

Judul artikel: The prevalence of Tuberculosis among new diagnosed HIV/AIDS individual admitted in Gresik, Indonesia
Jurnal : Malaysian Journal of Medicine and Health Science, 16 (Supp 16)
Author : Fatimatuzzuhro; Sundari A. S; Indriati, D.W

No	Perihal	Tanggal
1	Bukti pengiriman artikel	03 Agustus 2020
2	Bukti hasil review I	07 September 2020
3	Bukti pengiriman revisi I	08 September 2020
4	Bukti hasil review II	11 September 2020
5	Bukti pengiriman revisi II	15 September 2020
6	Bukti penerimaan artikel	18 September 2020

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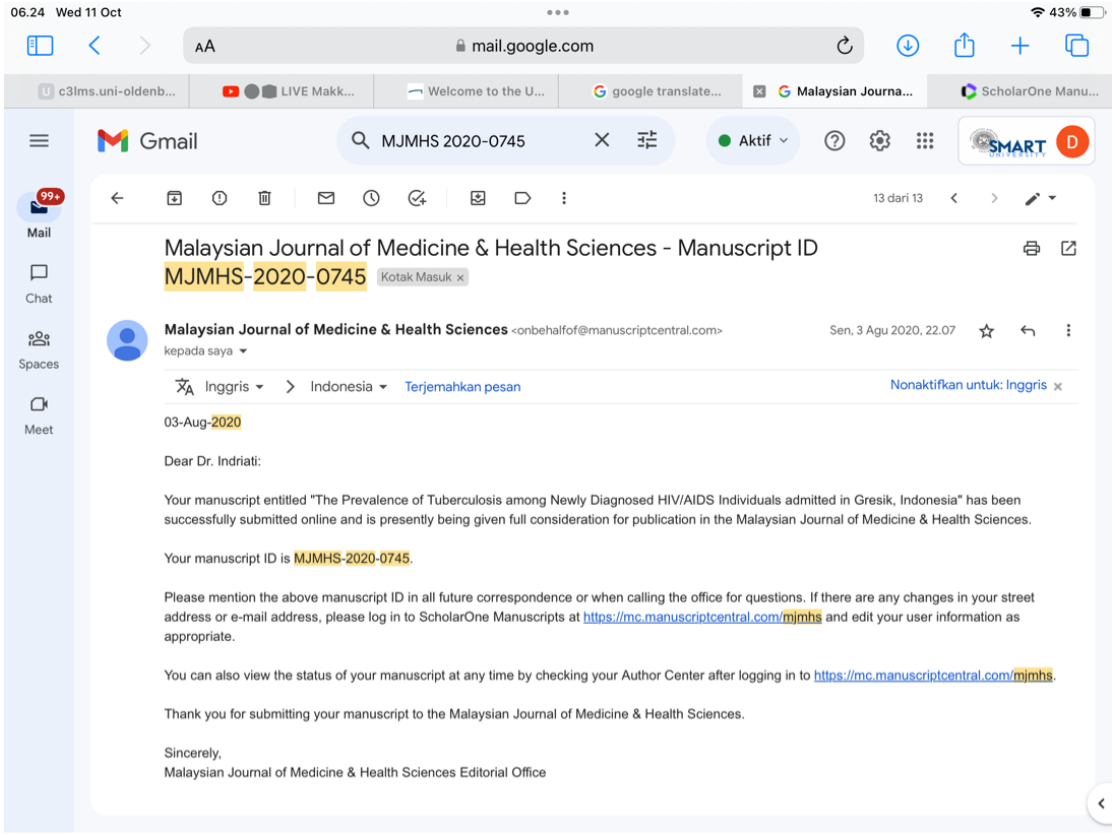
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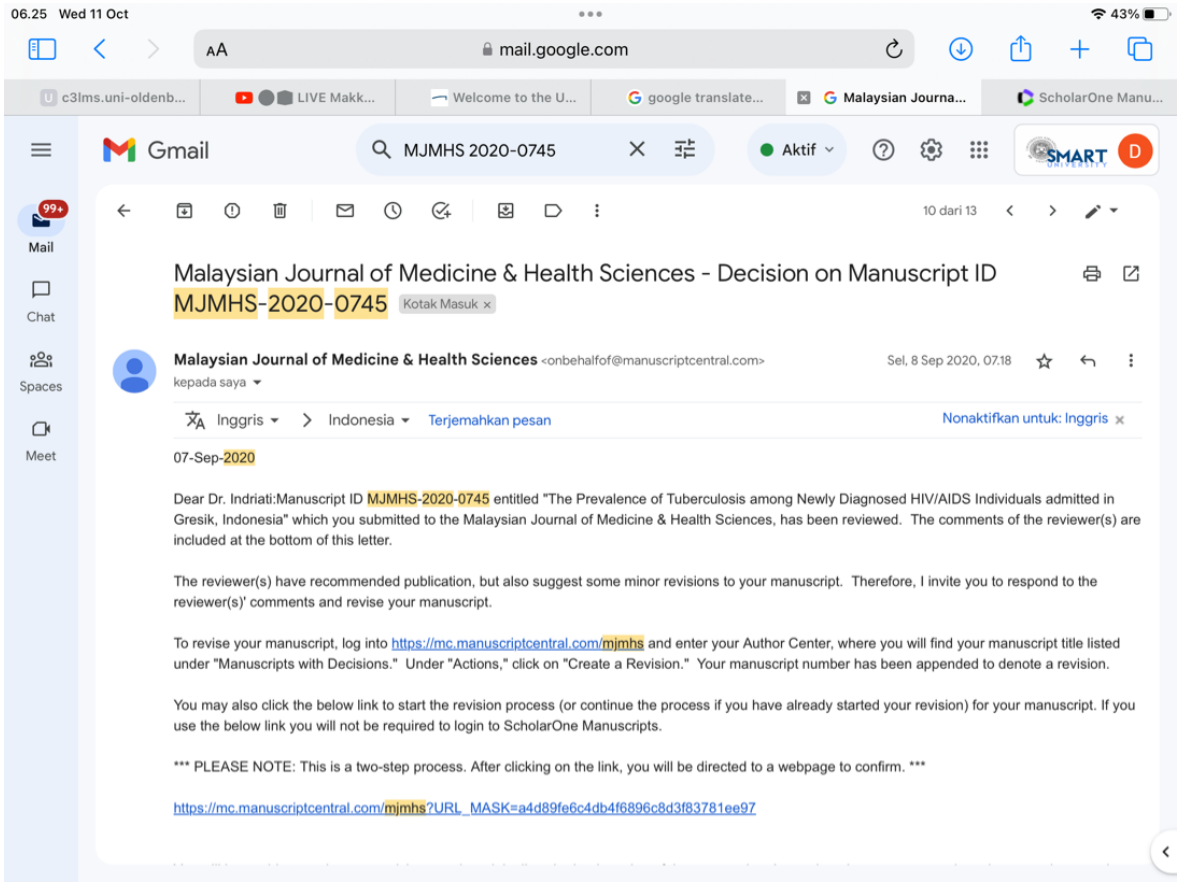
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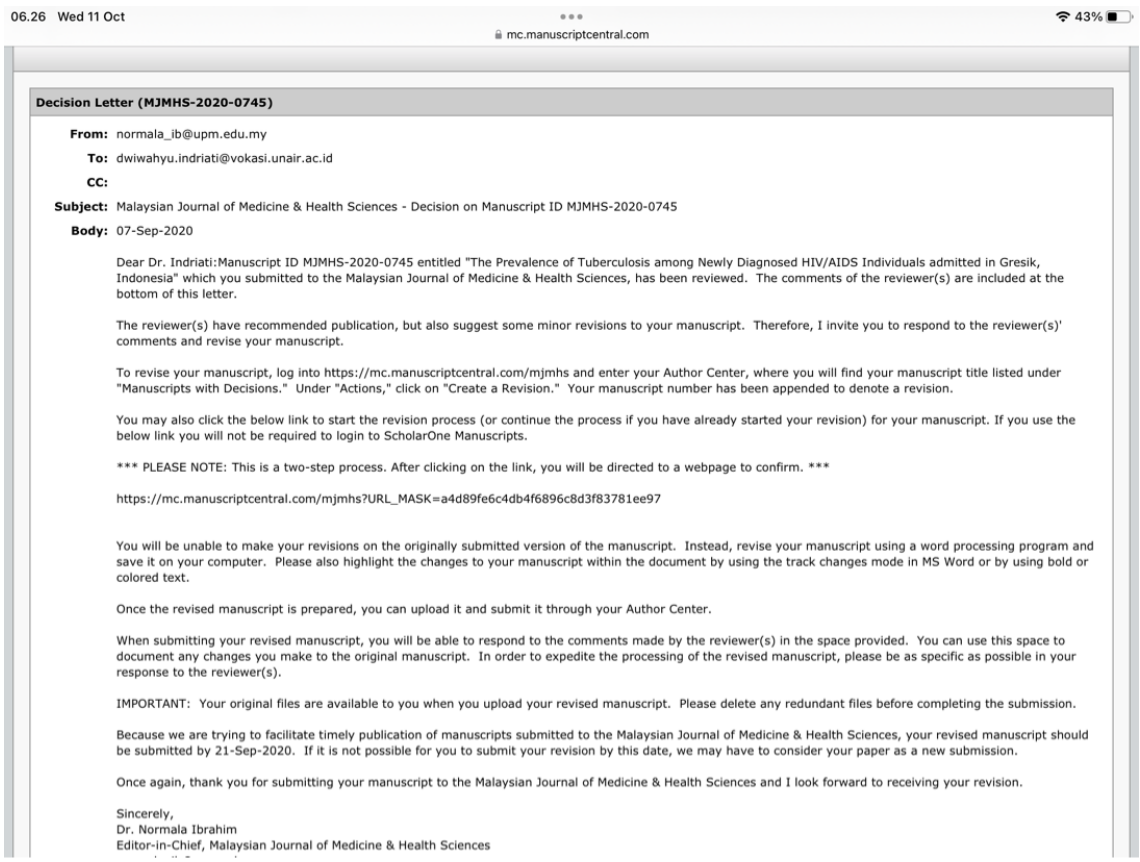
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P1 line 18-20 (Abstract; methods section)
It is stated that data was collected from patient with pulmonary TB. But the main purpose of the research is to define TB prevalence in newly diagnosed individuals. Please revise the sentence so it will not cause any confusion.

P2 line 53-55 and P3 line 3 (Introduction)
Data presented is hard to be understood. Kindly check the numbers and revise the sentence as need.

P12 Table 3
What classification was used for the CD4 count data? Why classify only into two categories? Please state the classification used in the CD4 count section of materials and methods (P4 line 12-24).

Suggestion
1. Please include data regarding patients' HIV viral load if available. It will enrich the data presented in the manuscript.
2. Please include data about the prevalence of TB-HIV co-infection in East Java or Gresik, specifically in the introduction and discussion. This may show an interesting comparison between data in the present study with previous study.
3. If the manuscript has yet to be proofread, please kindly do so. Some sentences and phrases are hard to be understood.

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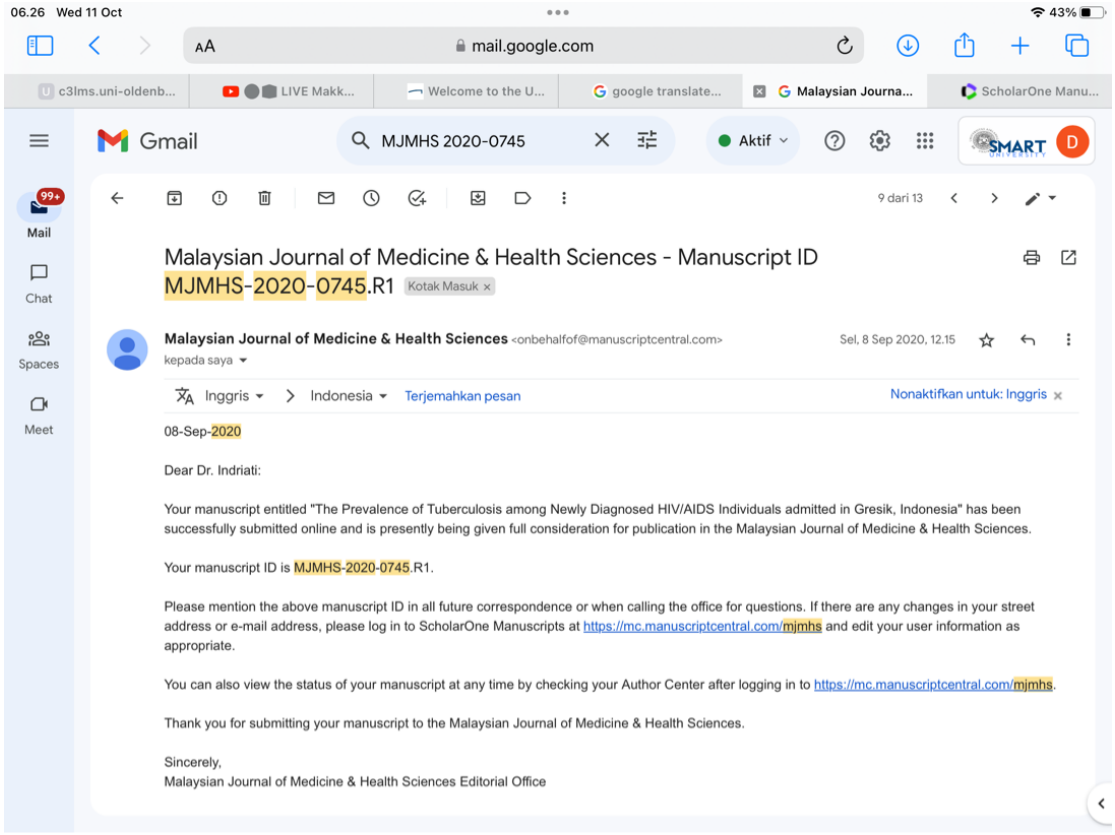
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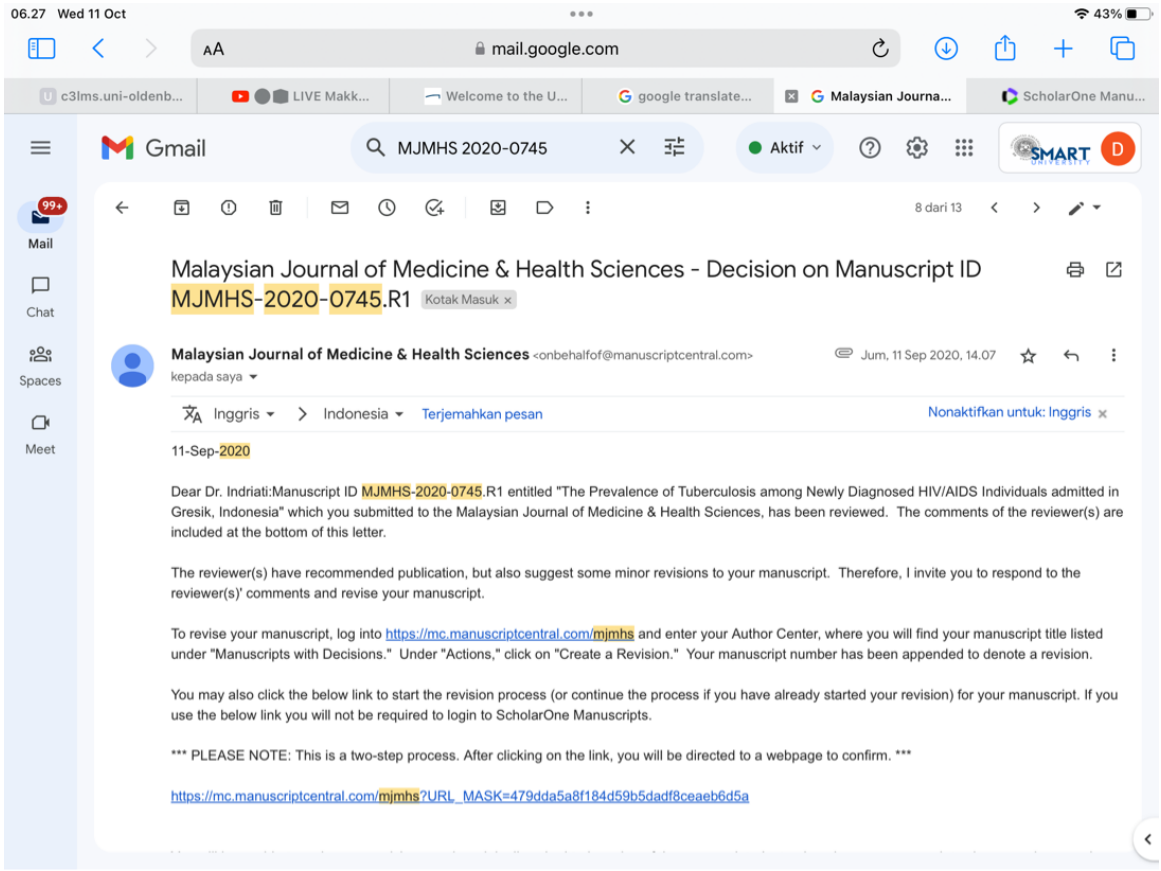
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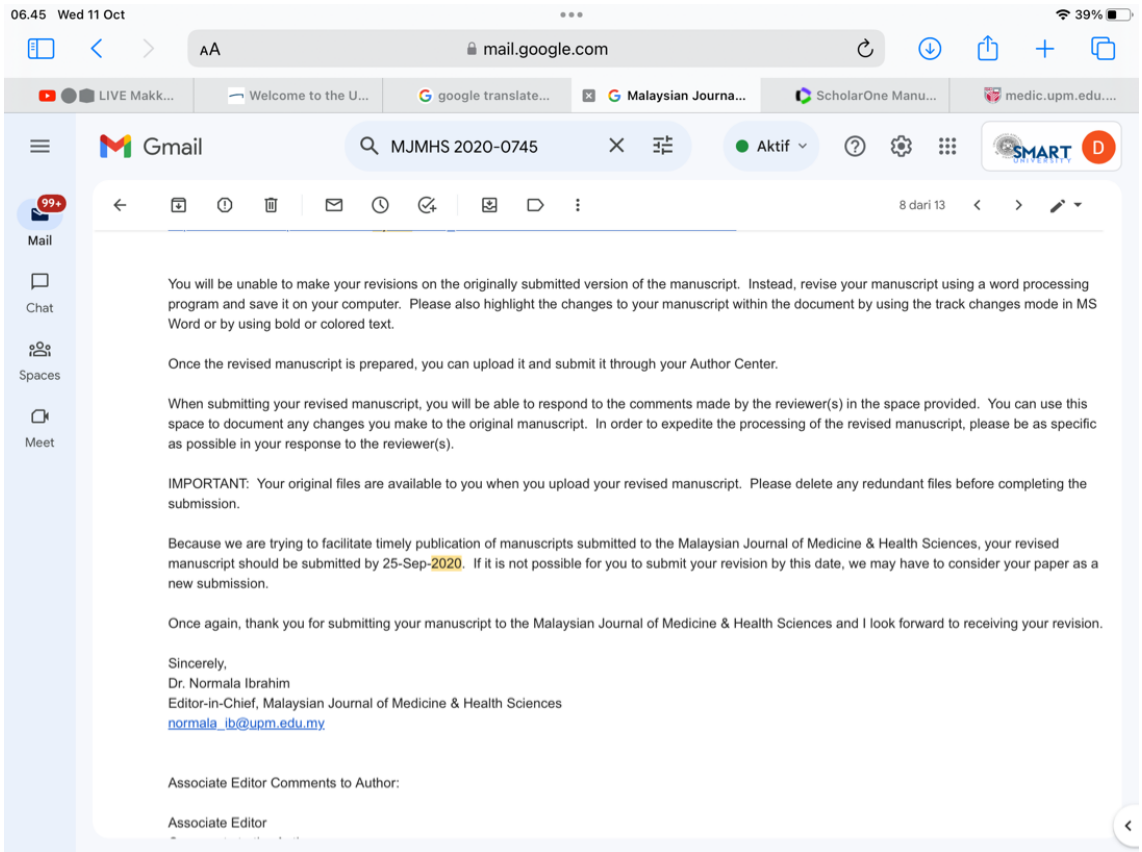
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The Prevalence of Tuberculosis among Newly Diagnosed HIV/AIDS Individuals admitted in Gresik, Indonesia

Journal:	*Malaysian Journal of Medicine & Health Sciences*
Manuscript ID	MJMHS-2020-0745.R1
Manuscript Type:	Supp: Applied Health Study
Keywords:	HIV, Tuberculosis, CD4 level, Xpert MTB/RIF

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ABSTRACT

Introduction: HIV is a major problem that threatens Indonesia and across the world. Since HIV attack the immune system, people with HIV are susceptible to opportunistic infection due to low immunity such as tuberculosis. This study wants to address the prevalence of pulmonary tuberculosis in HIV/AIDS patients, and its risk factors contributing to TB infection in HIV/AIDS patients admitted in Ibnu Sina Gresik hospital in 2018-2019 ~~period.~~ **Methods:** This research uses the Observational Analytical, Cross-Sectional method. We collected data from newly diagnosed HIV patients with pulmonary tuberculosis. HIV diagnosis was obtained with a rapid test method and CD4 levels. At the same time, pulmonary tuberculosis diagnosis was obtained with Xpert MTB/RIF. **Results:** We found that 58 individuals were HIV positive, and eight among them were also positive for TB (13.79%). The majority of individuals were male (68.97%), in the age group of 26-45 years (70.69%). The majority of those positive with HIV-TB had CD4 number < 200 cell/µL. No significant difference in the prevalence of TB among HIV patients based on gender, age and number of CD4. **Conclusions:** We found TB co-infection among newly diagnosed HIV individuals with a low level of CD4. Initial screening of individuals at risk of HIV infection is important to avoid co-infection with other diseases that can worsen the individual's condition. So, in the end, the severity and mortality rate in HIV patients can be reduced.

Keywords: HIV/AIDS, Tuberculosis, CD4 level, Xpert MTB/RIF

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INTRODUCTION

Nowadays, a major problem that threatens Indonesia and other countries around the world are the Human Immunodeficiency Virus (HIV). HIV infection can progress for worse condition named Acquired Immune Deficiency Syndrome (AIDS). Around 36.9 million people in 2017 are living with HIV around the world. New HIV infections worldwide reached 1.8 million in 2017. While in Indonesia, from 2005 to March 2019, the number of HIV cases reaches 338,363 people. The case of AIDS in Indonesia since it was first reported from 1987 to December 2018, already reached 114.065 people. From January-March 2019, the documented HIV transmission reached 11,081 people, while the reported AIDS transmission reached 1,536 people(1).

Globally, although the number of cases of HIV decreases, many people are still susceptible to HIV infection, especially for populations with a high risk of HIV-infected or known as the key population of HIV. The key population of HIV is a population group that determines the success of preventive and treatment so that this group of ~~HIV key populations~~ needs to be actively involved in the prevention of HIV/AIDS for both themselves and others (2). The Ministry of Health has implemented a strategy ~~to reduce HIV transmission~~ ~~in key populations~~ by educating those in key populations ~~to be able~~ to reduce new HIV transmission rates, mortality rates ~~due to HIV/AIDS~~, ~~reduce~~ negative stigma and discrimination against people with HIV(3,4).

The final stage of HIV infection is marked by decreased immunity which further leads to AIDS. An individual living with HIV/AIDS (~~or ODHA in Indonesia~~) begins to reveal symptoms due to opportunistic infections. This opportunistic infection can be caused by microorganisms which in general may not cause serious illness in healthy people, but for ODHA it can jeopardize their life (5). At the beginning of the AIDS epidemic, the main target for various infections and tumors was the lung of people living with HIV (6). Opportunistic infections that arise in people living with HIV depend on the HIV stage, history of infection, virulence from infected organisms, and host-related factors. The infection can be observed in various body systems such as the digestive system, the central nervous system or peripheral systems, and various other organs that can be caused by bacteria, viruses, fungi, parasites or other metabolic diseases(5).

Approximately 10.4 million people were diagnosed with tuberculosis (TB) in 2015, this number also including 1.2 million people co-infected with HIV. Since almost 60% of TB-HIV co-

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infection was not detected, it led to 390.000 death related to TB in people living with HIV (32%). While in 2017, 10.0 million people were infected with TB and 900.000 among them were also infected with HIV. The number of deaths caused by TB-HIV was also reduced to 300.000 cases. Most TB cases occurring in Asia (60%) and in Africa (7% from Nigeria and South Africa) (7). The person living with HIV has a high risk for TB infection caused by reactivation of latent TB, and co-infection with TB could trigger to more rapid progression of the disease. In the initial phase, active pulmonary TB were observed non-symptomatic. At the same time, another type of TB (extrapulmonary) is commonly found. In those with immunosuppression (CD4 cells lower than 200cells mm-3, the clinical course can be vastly progressed and can lead to a high mortality rate(8).

Indonesia is known as the country with a high burden of TB. Currently, Indonesia placed the second rank in the world. In 2017, there were 420.994 TB reported cases, with 1.85% among them were also infected with HIV(9). Tuberculosis can be categorized as number two opportunistic infection observed in Indonesia, and it is also the highest cause of death in HIV patients (10). But early detection of TB infection in HIV patient can be helpful ineffective treatment; thus, it can prevent mortality rate in HIV patient caused by co-infection with TB.

In Indonesia, areas that have a high number of TB cases include West Java and East Java province (11). The number of new cases of tuberculosis by East Java province in 2018 reached 20.535 (9). It is a great of interest for us, to study the prevalence of TB in HIV infected patient in East Java province. Several reasons were accounted so that patients visit the healthcare centre once there were already developed opportunistic infections. One reason ~~is~~ that they are afraid to receive a negative stigma from their place while others did not realize that they already have HIV infections (12). Thus, in this study, we choose Gresik as one of the suburbs near Surabaya as the capital city of East Java province, especially for those newly diagnosed patients with HIV. Based on epidemiological results number of HIV cases in Gresik were increased by 29% in 2017 from 2015 data (13). So, early screening is favorable to controlled HIV transmission in Gresik area.

MATERIALS AND METHODS

A cross-sectional was conducted at RSUD Ibnu Sina, Gresik between January 2018 to December 2019. All patients were newly diagnosed as HIV positive. Inclusion criteria were set; patients

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with all gender and all age, positive TB which were confirmed by rapid diagnostic tests such as Xpert MTB/RIF only, and newly diagnosed HIV patient with known CD4 levels.

Xpert MTB/RIF assay

The Xpert MTB/RIF assay in this study referred to previous studies (13–15). In specimen (sputum) container, sample reagent was added with 3:1 ratio, then agitated gently twice in room temperature for 15 minutes incubation. Then 2 ml of these mixtures were placed on testing cartridge. Place the cartridge to Xpert MTB/Riff assay machine after closing its lid.

CD4 count

Then, HIV CD4 examination is carried out by PIMATM CD4 analyzer (Abbott, Illinois, USA) as it is described in another study (14). Twenty-five microliter (25 µl) blood venous sample was drawn from patients or sample obtained from a finger prick, then immediately placed to the cartridge. After the low and normal value control cartridge gave acceptable value, the sample then can be procced. Antibodies (anti CD4 and CD3) were added to samples. Visualization was done by observation of fluorescent omitted from labelled antibodies. The image of CD3 and CD4 then were presented as the number of cells/mm3 within 20 minutes incubation tim.

Statistical analysis

Age, gender and CD4 value were presented with n (%). Statistical analysis was calculated with Microsoft Excel for Mac version 16.25. Correlation analysis was performed with the Chi-Square test with $p < 0.005$.

RESULTS

The Occurrence of pulmonary TB and HIV co-infection.

Our results showed that there were 58 newly HIV-positive patients in the period 2018-2019. Among 58 HIV-positive patients, eight of them were also infected with TB (13.79%). All positive TB cases were pulmonary. Tuberculosis diagnosis was performed using Xpert MTB/RIFF with all TB positive were showing sensitivity toward rifampicin.

The majority of newly diagnosed HIV-patient were male (68.97) while those who were also positive with TB also majority male (6 patients from 8 HIV-TB patients, Table 1). The

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susceptibility of TB among HIV patient was not correlated with different gender ($\chi 2 = 0.16$; p=0.69).

While according to the Ministry of Health, Republic of Indonesia, we can categorize a range of age group to 12-25 years old (teenager), 26-45 years old (adult), 46-65 years old (adult). Majority of HIV patients were in a group of adults (70.69%). But the difference in a group of age also did not correlate with the susceptibility of TB infections among people living with HIV ($\chi 2 = 0.33$; p=0.85, Table 2).

HIV infection has damaged patient`s immune system

Later, we asked ~~whether~~ the number of CD4 were contributed to TB infection among individuals with HIV. Based on the CDC classification system for HIV infection, there were three categories. The first category for CD4 number below 200 cells/uL; second category for CD4 number between 200-499 cells/ul and third category for CD4 number above 500 cells/ul (17). These patients were admitted to the hospital with a low number of CD4 (below 200 cells/ uL, Table 3), and none of them has a CD4 number above 500 cells/uL. Due to several reasons, mostly to avoid negative stigma for being HIV-positive. Thus, they tend to visit healthcare center once their immune system is really bad or once opportunistic infection showing its symptoms. Since the majority of patients showing a low number of CD4, we could not conclude that a low number of CD4 can make these patients prone to TB infections. The correlation between the number of CD4 and the prevalence of TB infection in patients with HIV were not statistically significant ($\chi 2 = 0.18$; p=0.67, Table 3).

DISCUSSION

The occurrence of TB among newly diagnosed HIV-patients was 13.79%. Since almost all patients (97.87%) were showed a low level of CD4, it means that they already developed to AIDS. The manifestation of immunosuppression in AIDS patients reduced the number of CD4+ T cells which can contribute to increased risk of developing active TB (15). Even before the reduce the number of CD4+, it is known that individual with HIV infection can be susceptible to TB infection (16).

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Since the number of male patient's positive HIV was larger than the number of female patients, the comparison from which gender is prone to TB infection could not be answered in this study. Previous studies observed that males have two times the risk of developing HIV-TB (11). While other studies showed that though responses to tuberculosis could be the difference between male and female but the outcomes after tuberculosis treatment were similar (17). Thus, differences in gender could not lead to a difference in the prevalence of TB among individuals with HIV-positive. And this question should be addressed in a future study with more data of HIV-TB (greater area than Gresik) to give a definite conclusion.

Our result showed that the majority of HIV positive cases were in adult age (12-25) with the prevalence of TB in HIV patients were also high in this range of age (8.62%). Although the majority of individuals with HIV are in the productive age range, this does not affect the incidence of TB co-infection (18). While other study suggested that this phenomenon related to socio-economic issues and responsibility for individuals and families (19).

Several studies suggested that patients with lower CD cell count were prone to a higher risk of TB infection (20,21). But TB infection can also lower CD4 count. Since all HIV-TB patient in this study was visiting healthcare centre after TB symptoms appear, it is not clear whether reduce the number of CD4 were caused by HIV infection only, or it is already because of HIV-TB co-infection (22–24).

Finally, altogether our results showed that it is necessary to screen HIV infected individuals, especially in those areas which have a high risk of HIV transmission (among a key population of HIV). With early detection of HIV, we can reduce the occurrence of opportunistic infections. It has been mandatory from Ministry Health to educate people about HIV infection and transmission to reduce negative stigma and improve the quality of life of people with HIV. But we still observed that people are still reluctant to check their risk for HIV infection, especially those living with a key population group.

CONCLUSION

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We can conclude that the prevalence of TB in HIV positive patients admitted Ibn Sina Gresik Hospital from 2018-2019 was 13.79%. We did not observe significant difference in gender, age and number of CD4 that makes HIV patients easily infected with TB in this study.

ACKNOWLEDGEMENTS

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Table 1 Distribution of HIV-TB and HIV cases as regards gender

Gender	HIV (n %)	HIV (n %)	Total (n %)	Chi Square	#p
Female	2 (3.45)	16 (27.59)	18 (31.03)	0.16	0.69
Male	6 (10.34)	34 (58.62)	40 (68.97)		
Total	8 (13.79)	50 (86.21)	58 (100)		

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Table 2 Distribution of HIV-TB and HIV cases as regards age

Age	HIV-TB (n %)	HIV (n %)	Total (n %)	Chi Square	#p
12-25	1 (1.72)	4 (6.89)	5 (8.62)	0.33	0.85
26-45	5 (8.62)	36 (62.07)	41 (70.69)		
46-65	2 (3.45)	10 (17.24)	12 (20.69)		
Total	8 (13.79)	50 (86.21)	58 (100)		

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Table 3 Distribution of HIV-TB and HIV cases as regards CD4 number

CD4 count	HIV-TB (n %)	HIV (n %)	Total (n %)	Chi Square	#p
<200	7 (14.89)	39 (82.98)	46 (97.87)	0.18	0.67
>200	0 (0)	1 (2.13)	1 (2.13)		
Total	7 (14.89)	40 (85.11)	47(100)		

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ARTIKEL JURNAL INTERNASIONAL SCOPUS Q4

Judul artikel: The prevalence of Tuberculosis among new diagnosed HIV/AIDS individual admitted in Gresik, Indonesia
Jurnal : Malaysian Journal of Medicine and Health Science, 16 (Supp 16)
Author : Fatimatuzzuhro; Sundari A. S; Indriati, D.W

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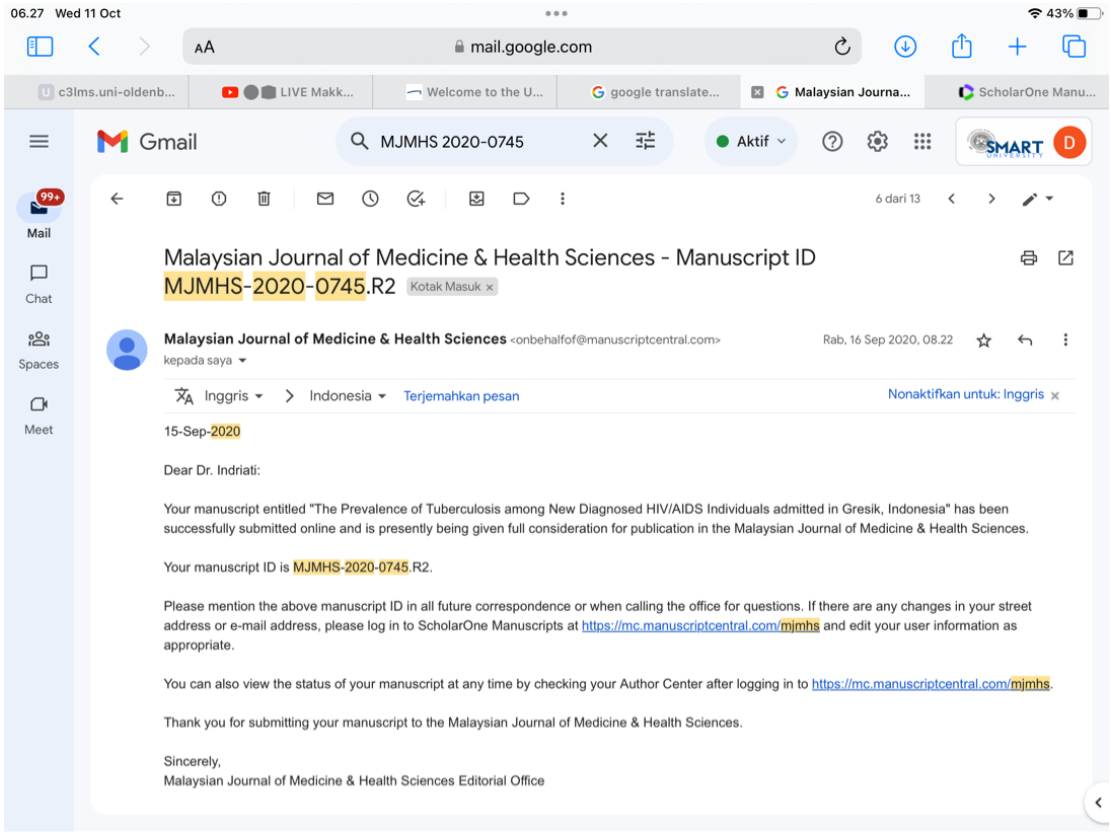
5	Bukti pengiriman revisi II	15 September 2020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Your manuscript entitled "The Prevalence of Tuberculosis among New Diagnosed HIV/AIDS Individuals admitted in Gresik, Indonesia" has been successfully submitted online and is presently being given full consideration for publication in the Malaysian Journal of Medicine & Health Sciences.
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Jurnal : Malaysian Journal of Medicine and Health Science, 16 (Supp 16)
Author : Fatimatuzzuhro; Sundari A. S; Indriati, D.W

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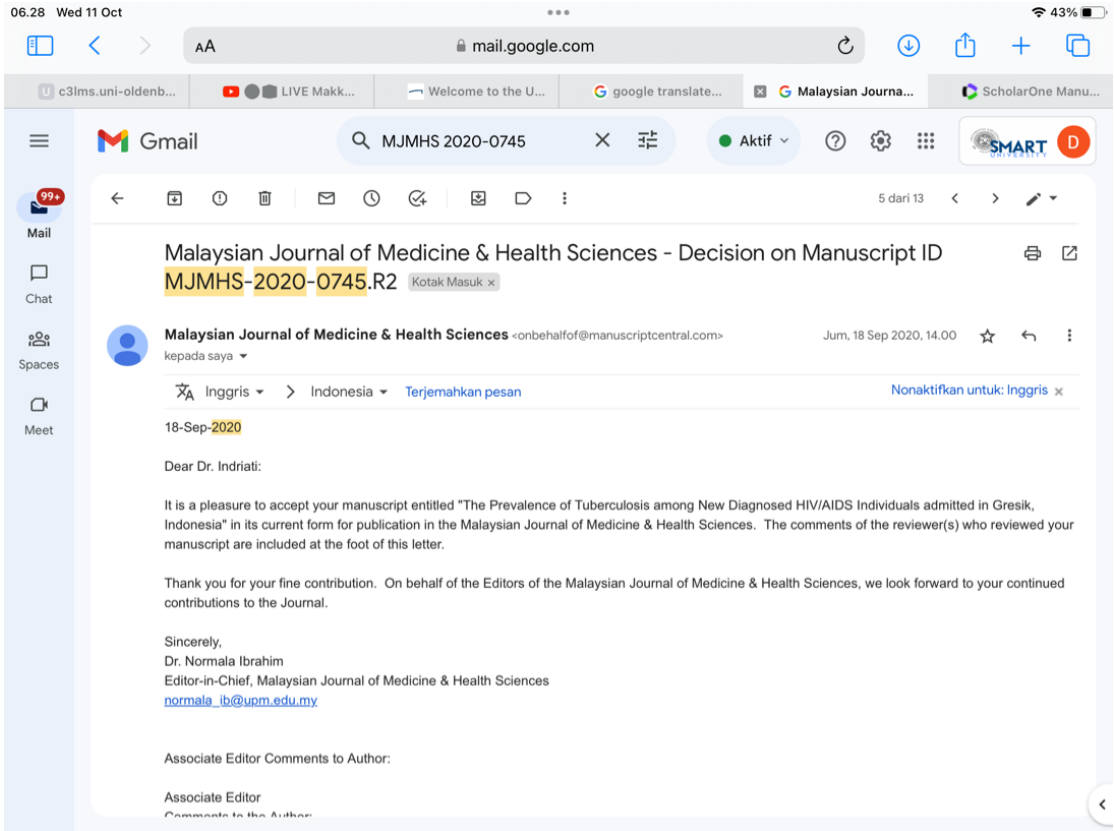
6	Bukti penerimaan artikel (*acceptance*)	18 September 2020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Thank you for your fine contribution. On behalf of the Editors of the Malaysian Journal of Medicine & Health Sciences, we look forward to your continued contributions to the Journal.
Sincerely,
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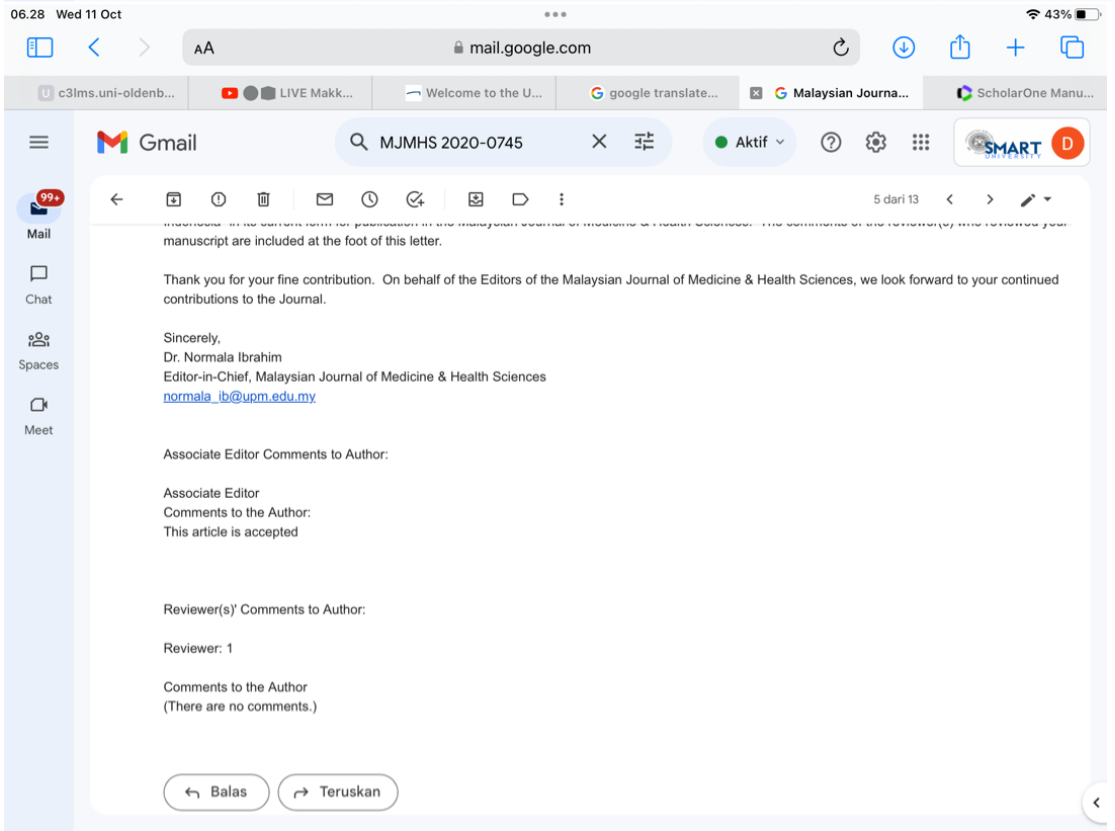
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