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Research Report

ANALYSIS ON SECONDARY INFECTION-TRIGGERING MICROORGANISMS IN HIV/AIDS PATIENTS AS A MODEL FOR POLICY CONTROL

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ABSTRACT

HIV infection is associated with immune-compromised and rising in opportunistic infection (secondary infection). Therefore, the number of mortality caused by HIV/AIDS is increasing. The use of ARV and development of HIV/AIDS management are expected to suppress the progress of HIV infection into AIDS and, therefore, the mortality can be diminished, while in fact most of the patients eventually suffer from AIDS due to secondary infection that commonly causes death. There should be a management by analysing microorganisms that trigger secondary infection. The method of this study was observational descriptive with cross sectional design. HIV infected blood samples were using ELISA Antibody (IgG and IgM) and Polymerase Chain Reaction (PCR) on laboratory test. The result showed correlation between HIV/AIDS severity and the amount and types of secondary infection. The most common secondary infections were toxoplasm (96.77%), hepatitis C (22.58%), tuberculosis (19.35%), and hepatitis B (3.22%). Other less frequent secondary infections, which were quite difficult to diagnose and not commonly found in Indonesia, were West Nile Virus (25.81%), Japanese Encephalitis Virus (3.22%), and Enterovirus (3.22%). Due to MDGs (Millenium Development Goals) target and the results above, researchers are highly demanded to contribute in decreasing mortality related to AIDS through early detection of secondary infection, including type of infection which have not been commonly found in Indonesia, such as West Nile Virus and Nipah Virus. The discovery of secondary infection in this study was not enough to suppress the occurrence of infection in HIV/AIDS patients. Antimicrobes and good nutrition are required. Moreover, there should be either a primary or secondary prophylaxis to prevent secondary infection that raises the number of mortality and morbidity of HIV/AIDS patients. The result of this study was to meet the target of MDGs by establishing new policies in handling HIV/AIDS infections and have potential as model for policy control in HIV/AIDS.

Key words: Microorganisms, secondary infection, HIV/AIDS, model, policy control

ABSTRAK

Infeksi HIV berkaitan dengan immune-compromised dan peningkatan infeksi oportunis (infeksi sekunder). Oleh karena itu angka kematian yang disebabkan HIV/AIDS semakin meningkat. Penggunaan ARV dan pengembangan penatalaksanaan HIV/AIDS diharapkan dapat menekan perkembangan HIV menjadi AIDS. Oleh karena itu tingkat kematian pun dapat berkurang, meskipun pada kenyataannya mayoritas pasien pada akhirnya mengidap AIDS karena infeksi sekunder yang umumnya mengakibatkan kematian. Diperlukan adanya sebuah penatalaksanaan dengan menganalisa mikroorganisme yang memicu terjadinya infeksi sekunder. Metode yang digunakan pada kajian ini merupakan pengamatan deskriptif dengan desain bagi silang. Sampel darah yang terinfeksi HIV dilakukan uji laboratorium menggunakan antibodi ELISA (IgG dan IgM) serta Polymerase Chain Reaction (PCR). *Hasil penelitian menunjukkan adanya korelasi antara tingkat keparahan HIV/AIDS dengan jumlah dan jenis infeksi sekunder. Infeksi sekunder yang paling umum terjadi ialah toksoplasma (96.77%), hepatitis C (22.58%), tuberkulosis (19.35%) dan hepatitis B (3.22%). Infeksi sekunder lainnya dengan frekuensi lebih rendah yang jarang ditemui di Indonesia saat ini adalah Virus West Nile (25.81%), Virus Japanese Encephalitis (3.22%) and Enterovirus (3.22%). Berdasarkan target Millenium Development Goals (MDG) dan hasil penelitian tersebut di atas, peneliti sangat*

dituntut untuk berkontribusi dalam menurunkan tingkat kematian yang berkaitan dengan AIDS melalui deteksi dini infeksi sekunder, termasuk jenis infeksi yang belum lazim ditemui di Indonesia seperti Virus West Nile dan Virus Nipah . Penelitian infeksi sekunder dalam kajian ini belum cukup untuk menekan terjadinya infeksi pada pasien HIV/AIDS. Antimikroba dan gizi yang baik sangat diperlukan. Selain itu diperlukan adanya profilaksi baik primer maupun sekunder untuk mencegah infeki sekunder yang dapat meningkatkan angka kematian dan morbiditas pasien HIV/AIDS. Hasil dari kajian ini adalah untuk memenuhi target MDGs dengan mengadakan kebijakan baru dalam penanganan infeksi HIV/AIDS dan berpotensi sebagai model untuk kebijakan kontrol pada HIV/AIDS.

Kata kunci: *Mikroorganisme, infeksi sekunder, HIV/AIDS, model, kebijakan kontrol*

INTRODUCTION

HIV infection is associated with decreased endurance and increased incidence of opportunistic infections that in a given period of time raises a set of disease called Acquired Immunodeficiency Syndrome (AIDS).[1] Human Immunodeficiency Virus (HIV) remains a global health problem, including in Indonesia. World Health Organization (WHO) reported that 2001 up to 58 million people worldwide have been infected with HIV, while in Indonesia until 2009 there were an estimated 186,000 HIV-positive people. The death rate from HIV/AIDS infection is reported quite high. Until 2000 it was reported that there were 22 million deaths related to HIV/AIDS.[2]

Indonesia was ranked first in the transmission of new cases of HIV and AIDS in Asia. Data from the Ministry of Health said there were 15,372 new HIV cases and 3541 new AIDS cases in January to September 2012. Majority of the patients were male in productive age. The highest transmission is through sexual contact, followed by needles and drug users, and it is reported that the number of patients is increasing sharply compared to ten years ago. Along with increased capacity for early detection, screening programs and increased public awareness of HIV disease, we will find more new cases. The area with the highest number of new cases is DKI Jakarta, followed by Papua and East Java.[3]

Currently, with the developing management of HIV/AIDS infection and increasingly widespread use of antiretroviral drugs, the progression of HIV infection to AIDS and death from AIDS should be reduced. In fact, most of the patients fell into AIDS as a result of the emergence of secondary infections (opportunistic infections) that often leads the patients to death.[1] In the decline of immune status, especially when the CD4 cells less than 200 cells/mL, a variety of microorganisms such as bacteria, viruses, protozoa and fungal infections also appear tend to be easy to grow and reproduce, causing secondary infections in the body of the people with HIV/AIDS.[4] The lower the CD4 cell count, the more types of microorganisms involved in secondary infection of HIV/AIDS. Fungal infections can occur simultaneously with bacterial infections, viruses and protozoa.[2,5] The main problem faced by people with HIV/AIDS is an opportunistic infection caused by a secondary infection.[6] The more advanced the severity of HIV/AIDS, the more increasing the potential incidence of secondary infections and death. Analysis of microorganisms triggering the secondary infection, as is often seen in people with HIV/AIDS and other viruses, is associated with CD4 count and viral load. Some secondary infections include CMV (Cytomegalovirus), Mycobacterium tuberculosis, West Nile virus, hepatitis B and C virus, and Candida sp.[7,8] It was not clear whether any people with HIV/AIDS will be infected by all these microorganisms.

Patients with infections are often followed by clinical conditions, such as malnutrition and wasting syndrome, which also will result in a decrease in CD4 T lymphocytes count. The condition results in a decrease of T lymphocytes count in patients susceptible to the incidence of secondary infections (opportunistic infections), such as hepatitis C, hepatitis B, hepatitis C, CMV, toxoplasmosis, Japanese encephalitis, West Nile virus, Nipah virus, all of which can be detected with CD4 and HIV RNA viral load. In HIV patients with secondary infections the increase of HIV progression is taking place. Therefore, HIV management policies is including promotion, prevention of secondary and tertiary infections, and complete therapy in accordance with the MDGs 2014, which comprises the absence of HIV-related deaths, the absence of new infections and the absence of discrimination.

This study aims to analyze how far the correlation between HIV/AIDS severity with the involvement of the type and number of secondary infections. The results are expected to be a new policy on HIV/AIDS, thereby supporting the achievement of the MDG targets in the field of infectious diseases of HIV/AIDS is zero new infections, zero discrimination, and zero AIDS-related deaths. From the laboratory results can be seen how far the relationship between the severity of HIV/AIDS with the involvement of the type and number of secondary infections. Based on the analysis of microorganisms triggers the secondary infection, according MDGs (Millennium Development Goals) in the field of infectious diseases HIV/AIDS, the results of this study are expected to contribute in lowering AIDS deaths through early detection of secondary infection, including an infection that has not been commonly detected in Indonesia, West Nile Virus Infection and Nipah virus. The results of this study are also expected to be a new policy on HIV/AIDS, thus supporting the achievement of the MDG targets, and can generate a new reference in the information and health sciences in the form of a journal.

METHODS

This study was a descriptive observational using cross-sectional design. Blood samples were taken from HIV-infected patients in Hospital Universitas Airlangga (RSUA), and Infectious Disease Intermediate Care Unit (*Unit Perawatan Intermediet Penyakit Infeksi*, UPIPI) Dr Soetomo Hospital, then we conducted laboratory tests to determine secondary infections experienced by the patients. From the laboratory results, we could see how far the relationship between the severity of HIV/AIDS with the involvement of the type and number of secondary infections.

The laboratory tests were carried out at the Institute of Tropical Diseases (ITD), Universitas Airlangga. The study was conducted for three months. The population in this study was HIV-positive patients who have received antiretroviral therapy, whereas the samples in this study were part of the whole object under study who met the inclusion criteria. Criteria for inclusion in this study were as follows: willingness to involve, HIV-positive, and has received antiretroviral therapy. To obtain accurate results, this research was conducted using Antibody (IgG and IgM) ELISA and PCR.

RESULTS & DISCUSION

The number of patients included in this study was 31 patients. The mean age of patients in this study was 35.06 ± 11.20 years, with the youngest two years old and the oldest 54 years of age. The highest number of the patients in age group of 31–45 years was 22 patients (70.96%), the least in the age group of < 16 years was 2 patients (6.46%), whereas the age group of 16-30 years was 3 patients (9.67%), and 46–60 years was 4 patients (12.91%) (Figure 1).

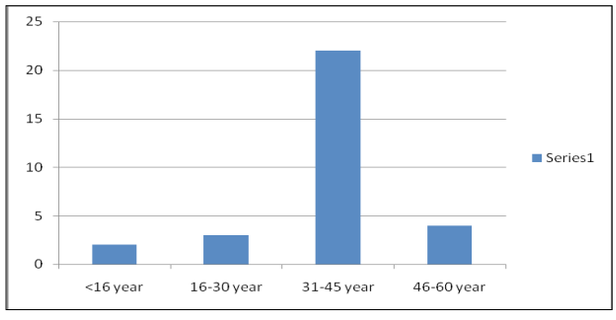

Figure 1. HIV patients distribution by age group.

Characteristics of the subjects by sex showed that the males were 15 patients (48.38%) and females 16 patients (51.62%). A total of 26 (83.87%) patients had married and 5 (16.13%) unmarried (Figure 2). Characteristics of study subjects based on tribes revealed Javanese of 27 (87.12%), Arabic 1 (3.22%), Chinese 1 (3.22%), Banjarese 1 (3.22%), and Tetungs 1 (3.22%).

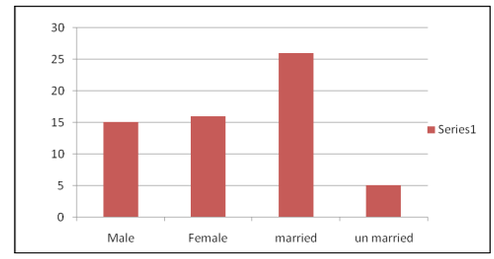

Figure 2. Distribution of HIV patients by sex and marital status.

In this study, HIV/AIDS transmission through sex was 21 patients (67.74%), through IDU (Intravenous Drug Users) was 8 (25.81%), and through vertical mother to child transmission (MTCT) was 2 patients (6.45%) (Figure 3).

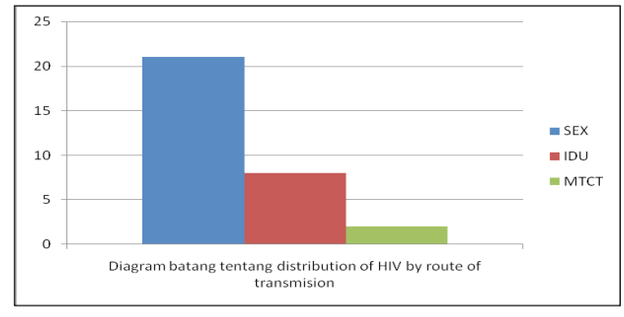

Figure 3. Distribution of HIV by Route of Transmission.

A total of 29 (93.54%) patients had received antiretroviral drug therapy and 2 (6.46%), while the rest had not received (Figure 4).

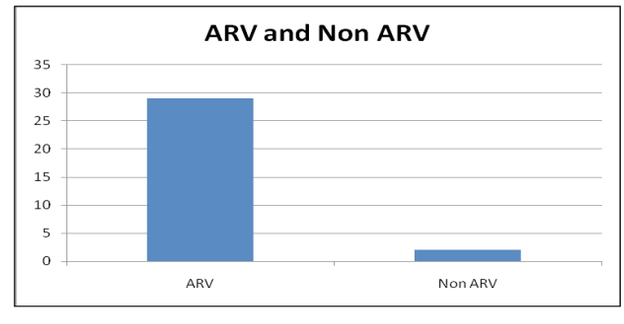

Figure 4. Distribution of HIV patients by antiretroviral therapy.

According to the length of antiretroviral therapy, 7 (24.14%) of the patients had received antiretroviral therapy for < 1 year, 11 (37.94%) patients for 1–3 years, 6 (20.68%) patients for 3–5 years and 5 (17.24%) patients for > 5 years (Figure 5).

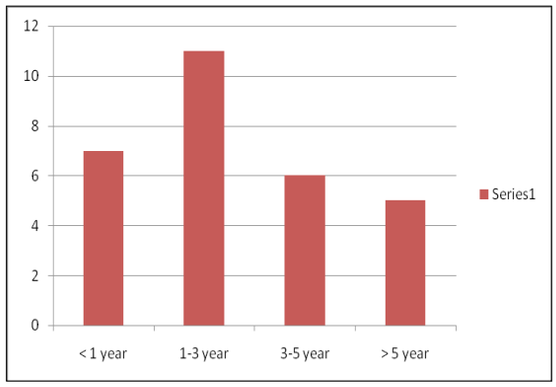

Figure 5. Distribution of HIV patients by the length of antiretroviral therapy.

Based on HIV/AIDS clinical stage according to WHO in 2010, this study found that 13 (41.94%) of the patients were at stage I, 11 (35.48%) patients at stage II, 7 (22.58%) patients at stage III and there were no patients at stage IV (Figure 6).

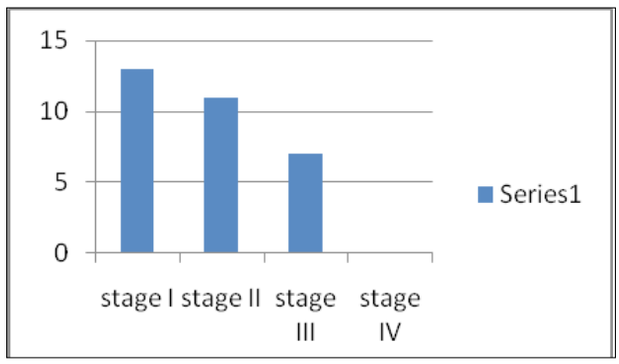

Figure 6. Distribution of patients based on WHO's clinical stage of HIV/AIDS.

In this study, most patients with undetected HIV viral load test results were 23 (74.19%) patients. Results of viral load < 4 × 102 copies/mL were in 2 (6.45%) patients and viral load > 4 × 102 copies/mL were in 5 (16.12%) patients (Figure 7).

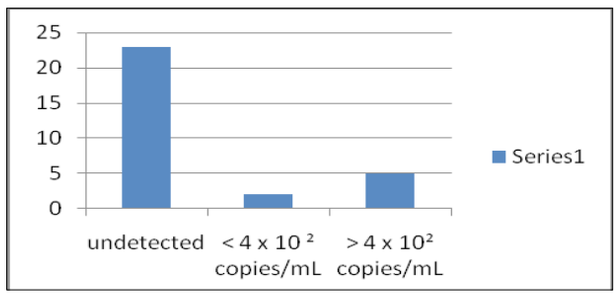

Figure 7. Patients distribution by HIV viral load.

Secondary Infection in Subjects Research

In this study we performed examination of secondary infections in people with HIV/AIDS. The results showed that 6 patients (19.35%) of the patients were with secondary infection of tuberculosis of 7 (22,58%) patients of the patients had secondary infection of hepatitis C, 1 (3.22%) of the patients had secondary infection of hepatitis B, 30 (96.77%) with secondary infections Toxoplasma, 8 (25.81%) with West Nile Virus, 1 (3.22%) patients with Japanese encephalitis virus, 2 (6.45%) patients with Enteroviruses, and 1 (3.22%) patients with secondary infections of dengue virus. There were no patients with secondary infection of cytomegalovirus (Figure 8).

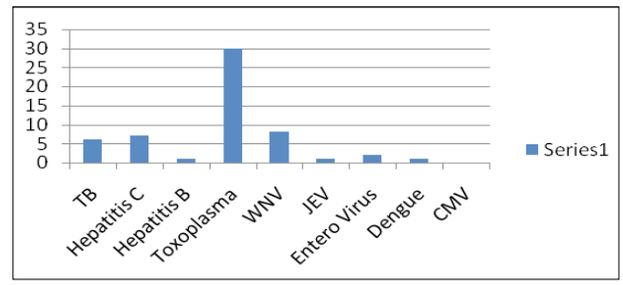

Figure 8. Distribution of secondary infection in the subjects.

Secondary Infection in the Subjects by HIV/AIDS Clinical Stage

In this study, we performed examination on secondary infections in people with HIV/AIDS. Based on the clinical stage according to the WHO in 2010 the secondary infections appeared on stage I was tuberculosis of 3 patients (23.07%), Hepatitis C of 4 patients (30.76%), West Nile Virus of 2 patients (15.38%), and Toxoplasma of 12 patients (92.31%). In stage II the secondary infections were Tuberculosis of 3 patients (27.27%), Hepatitis C of 1 patients (9.09%), Hepatitis B of 1 patients (9.09%), West Nile Virus of 6 patients (54.55%), Japanese encephalitis virus of 1 patients (9.09%), enterovirus of 1 patients (9.09%), dengue virus of 1 patients (9.09%) and Toxoplasma of 11 patients (100%). Whereas, stage II the secondary infections were Hepatitis C of 2 patients (28.57%), enterovirus of 1 patients (14.28%) and Toxoplasma of 7 patients (100%).[7]

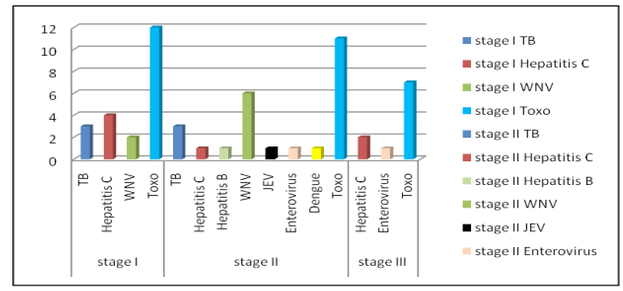

Figure 9. Distribution of secondary infection by HIV/AIDS Clinical Stage.

Secondary Infection in the Subjects by HIV Viral Load

We carried out examination of secondary infections in people with HIV/AIDS. Based on HIV viral load, the secondary infections in patients with HIV viral load < 4 × 102 copies/mL was toxoplasma of 2 (100%). Patients with HIV viral load > 4 × 102 copies/mL the secondary infections were tuberculosis in 2 (40.0%), hepatitis C 2 (40.0 patients, West Nile Virus of 1 patients (20.0%), Japanese encephalitis virus of 1 patients (20.0%), and enterovirus by 1 patients (20.0%), and Toxoplasma of 4 patients (80.0%). Whereas, in patients with undetectable HIV viral load, the secondary infections were tuberculosis in 4 (17.39%) patients, hepatitis C 5 (21.73%), hepatitis B 1 (4.34%), West Nile Virus 7 (30.43%), enterovirus 1 (4.34%), Dengue virus 1 (4.34%) and toxoplasma in 3 (100%) (Figure 10).

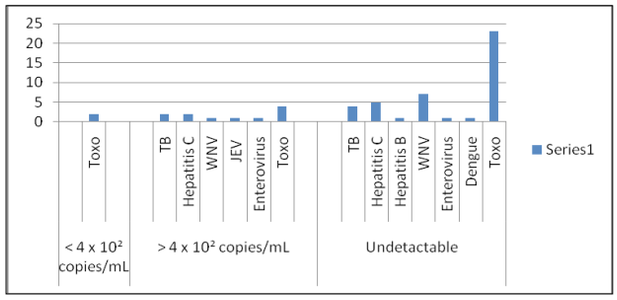

Figure 10. Distribution of secondary infection by HIV viral load.

Characteristics of the study population

In this study, the subjects were patients with HIV/AIDS of 31 patients. The mean age of the patients was 35.06 ± 11.20 years, with the youngest 2 years old and the oldest 54 years of age. The age distribution of the patients showed those of < 16 years were 6.46%, 16–30 years were 9.67%, 31–45 years were 70.96%, and aged 46–60 years were 12.91%. The proportion of males was 48.38% and females 51.52%, mostly (83.87%) were married and 16.13% unmarried. This figure showed that the incidence of HIV/AIDS infections is more common in reproductive age, which is along with the data from the Ministry of Health of Indonesia in 2011 that the highest percentage of HIV/AIDS was at the age of 20–29 years with a ratio of men and women 3:1.

Indonesia ranked first in the transmission of new HIV and AIDS cases in Asia. Data report of the Directorate General of PP & PL, the Ministry of Health, mentioned that there were 15,372 new cases and 3541 new cases of AIDS in January to September 2012. The majority of sufferers were of childbearing age and men. Highest transmission was through sexual contact followed through needles of drug users. The number increased significantly when compared to ten years ago, along with an increase in the ability of the government to detect, to carry out screening programs and increase public awareness of HIV disease, then there will be more new cases to be found. Areas with highest number of new cases are Jakarta, followed by Papua and East Java. Since 1999 a new phenomenon in HIV/AIDS dispersion occurred, that was the predisposition of transmission through blood contact, especially among Intravenous Drug Users (IDUs). Transmission in IDUs occurs rapidly due to the use of shared needles. In 2000 there was a significant increase in the spread of HIV pandemic among sex workers in Indonesia (Indonesian Ministry of Health, 2011). In this study, sexual transmission of HIV/AIDS was 67.74%, through IDU (Intravenous Drug Users) was 25.81%, and through mother-to-child vertical transmission or MTCT (Mother to Child Transmission) was 6.45%. This indicates that the highest incidence rates of HIV/AIDS transmission was through unhealthy sexual relationships.

The discovery of antiretroviral drugs (ARVs) in 1996 led to a revolution in the treatment of PLWHA (People Living with HIV and AIDS). Although antiretroviral therapy has not been able to cure the disease and the presence of major challenges in terms of side effects of drugs and the incidence of chronic resistance to antiretroviral drugs, such therapy can dramatically reduce mortality and morbidity, and improve the quality of life of people living with HIV. Currently HIV/AIDS has been accepted as a disease that can be controlled and no longer considered a dread disease.[2] In this study shown that antiretroviral therapy has been widely used in patients with HIV/AIDS in Indonesia, and with quite a number of study subjects who had received antiretroviral therapy for more than 5 years showed the role of ARVs in increasing the life expectancy of people with HIV/AIDS.

The findings in this research indicated that the majority of the study subjects were at an early stage (stage I and II) of HIV/AIDS infection. Undetectable viral load results indicated that the use of antiretroviral therapy in the majority of study subjects could control and suppress HIV/AIDS progress and improve the quality of life of the patients. This is in accordance with the policy on HIV/AIDS in Indonesia, which includes 4 pillars, all of which are aimed at bringing about a paradigm of zero new infection, zero AIDS-related death and zero discrimination:[9,10] (1) prevention: includes prevention of HIV transmission through sexual behavior and syringe, prevention in prisons and detention centers, prevention of mother-to-child transmission (PMTCT), prevention of transmission among sex workers and others, (2) Maintenance and support treatment (PDP): includes the strengthening and development of health services, prevention and treatment of opportunistic infections, ARV treatment, as well as support and education, training people living with HIV. PDP program is primarily intended to reduce morbidity and hospitalization, mortality related to HIV-AIDS and improve the quality of life of people living with HIV, (3) Mitigation of the impact of psychosocial and economic support, (4) creation of a conducive environment (creating the enabling environment) which includes institutional strengthening and management, program management and policy alignment.

With growing HIV/AIDS management infection and increasingly widespread use of antiretroviral drugs,

progression of HIV infection to AIDS and death from AIDS should have been suppressed. In fact, most of the patients fell into the emergence of AIDS as a result of secondary infections that often lead to death. Declining CD4 cell count to some extent (< 200 cells/mm^3) will open up opportunities for a secondary infection. The more advanced severity of HIV/AIDS, the more increase the potential incidence of secondary infection and death.[1] Based on Figure 8, there were no patients with secondary infection of cytomegalovirus. In this study, the encountered secondary infections were mostly Toxoplasma, as many as 96.77%. High toxoplasma infection in HIV/AIDS is related to the deterioration of the immune system.[11,12,13]

The parasite *Toxoplasma gondii* can reactivate again when CD4 lymphocyte count decreases to below 100 cells/mcl. The incidence of toxoplasma seroprevalence in a group of non-HIV individuals and groups of individuals with HIV/AIDS is almost the same, which is about 10–40%. In the United States, 67% of people with HIV/AIDS have positive Toxoplasma antibodies. However, the possibility of reactivation is 30% higher in people with HIV/AIDS.[11] Secondary infection of tuberculosis in this study was found to be 19.35%. This finding is in line with secondary tuberculosis infection data on HIV/AIDS. Tuberculosis is a secondary infection most often found in people with HIV and is the largest cause of morbidity and mortality in HIV infection in the world. More than 11 million HIV infections is accompanied with TB.[14,15,16] Thirty percent of is the cause of death in people with HIV is TB.[17] Data in UPIPI Dr. Soetomo Hospital showed that manifestations of AIDS due to secondary infection of pulmonary TB reaches 25–83%.[17]

Hepatitis B and hepatitis C are blood-borne diseases, together with HIV transmission. Both are secondary infections commonly found in people living with HIV who are injecting drug users (IDUs). Coinfection of hepatitis C and HIV among injecting drug users were 40–90%, whereas coinfection of hepatitis B and HIV in sexual transmission was 77%.[18] In this study, secondary infection of 3.22% with hepatitis B and hepatitis C was 22.58%. This is because the transmission of HIV infection in the study was largely through sexual transmission (67.74%) and through injecting drug use (IDU) (25.81%).

Another finding in this study was the secondary infection that is rare and often undiagnosed in Indonesia, such as Japanese encephalitis virus, West Nile virus (WNV), enterovirus, and dengue viruses.[19] In this study, secondary infection of West Nile Virus was found to be 25.81%, which is quite a high figure for a rare viral infection and rarely diagnosed in Indonesia. WNV infection is a viral infection that is transmitted through mosquito bites, self-limited with mild symptoms such as flu-like syndrome that can occur more severe in HIV co-infection with neurological manifestations such as meningoencephalitis. There has been no report on the epidemiological data of WNV and HIV coinfection rate. Only in the United States some cases of WNV and HIV co-infection was reported with manifestations of severe encephalitis.[20]

As WNV, Japanese encephalitis virus (JEV) is also a coinfection virus that can be found in HIV. Often found in Asian countries including Indonesia, JEV is a flavivirus transmitted by mosquito bite with severe neurological manifestations of encephalitis and high mortality rate up to 60%.[21] In this study, a secondary infection of JEV was found to be 3.22%. Although the data on JEV findings is low, these findings need attention because of the limitations of the study that was only in Surabaya (which is a reference to Eastern Indonesia). Thus the molecular epidemiological studies are necessary to get the database on JEV infections that accompany HIV/AIDS so that the mortality rate of patients with HIV/AIDS can be prevented early. Enterovirus is a virus that is identified as one of the causes meningoencephalitis in patients with HIV. Neurological deficits often appear along with a decrease in CD4 cell counts. More common in children, enteroviruses are often associated with complaints of diarrhea in people with HIV.[22]

Dengue virus has been reported to coinfect with HIV. With the decline in immune status in HIV and high infection rates in dengue endemic areas, the incidence of co-infection becomes possible.[23] There have been no reports of dengue and HIV coinfection rate, but in this study, the rate was found to be 3.22%. The findings of secondary infection in this study showed ARVs alone is not sufficient to reduce the incidence of secondary infection in HIV/AIDS, so that it requires antimicrobial therapy and adequate nutritional support. There should also be a primary or secondary prophylactic measures to combat secondary infections that can increase mortality and morbidity of patients with HIV/AIDS. Primary prophylaxis is given to prevent an infection that has never been suffered, while secondary prophylaxis is a treatment given to prevent the repetition of an infection which never been suffered before. For primary prophylaxis we can give cotrimoxazole tablets of 960 mg/day single dose for 2 years, while for secondary prophylaxis the treatment was given in accordance with arising secondary infections.

CONCLUSION

Toxoplasma (96.77%) which is the most common secondary infection is higher than other infection. The benefits of this research to the patients is that they know the type and number of secondary infections associated with the severity of HIV/AIDS suffered, so they may immediately seek treatment in order to have better prognosis. By proving relationships between HIV/AIDS severity and the involvement of microorganisms in HIV/AIDS secondary infection, we can take strategic policy to reduce the transmission rate of secondary infections and related deaths.

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