

## ORIGINAL ARTICLE

# The Prevalence of Candidiasis Oris, Tuberculosis, and Anemia in Hospitalized HIV Patients Admitted in Dr. Soetomo General Hospital, Surabaya, Indonesia

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## ABSTRACT

**Introduction:** HIV infection attacks the immune system, thus making a person vulnerable to various secondary diseases. Various secondary infections trigger systemic endothelium activation and lead to sepsis. Comorbid diseases cause high morbidity and mortality rates in HIV patients. This study aims to determine the prevalence of secondary diseases in HIV patients. **Methods:** Analytic and descriptive study with cross-sectional study design. Data were obtained from medical records of hospitalized patients at RSUD Dr. Soetomo Surabaya from August 2019 - February 2020. **Results:** Patients are dominated by the 30-39-year-old age group (48.8%) with male gender (69.4%), high school graduates (69.4%), private employees (44.7%), Muslim (90.3%), married (53.1%), CD4 <100 cells/ $\mu$ L (28.1%). From 392 patients, there were 46 2-time inpatients, seven 3-time inpatients times, and four 4-time inpatients, which brings a total of 320 HIV patients during the inclusion period. The highest prevalence of secondary disease was candidiasis oris (56.3%), tuberculosis (40.9%), and anemia (39.7%). There was association between age to complications ( $p=0.042$ ) and CD4 counts to complications ( $p=0.022$ ). **Conclusion:** HIV patients with CD4 counts of less than 200 cells /  $\mu$ L are very susceptible to various secondary diseases.

**Keywords:** HIV, AIDS, Secondary Disease

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## INTRODUCTION

HIV or Human Immunodeficiency is a virus that attacks and infects white blood cells, which causes a decrease in the human immune system. This virus infection is persistent because our body is unable to eliminate it despite renewable therapy (1). HIV replication will continuously attack the immune system of CD4 lymphocyte cells that promote the body's protection from various infections. If not appropriately treated, HIV will progressively decrease CD4 lymphocyte cells so the body will be susceptible to another disease. When CD4 lymphocyte cell counts <200 cells/microliters and the body no longer can fight various infections and diseases, this is called the AIDS (Acquired Immuno Deficiency Syndrome) phase (2).

According to data from the World Health Organization,

since the outbreak first became an epidemic, more than 70 million people were infected, and around 35 million people were reported dead. There are currently 36.9 million people with HIV, and around 0.8% (0.6-0.9%) in the 15-49 year age group (3). In Indonesia, reports development of HIV-AIDS Ministry of Health until December 2017, the number of people infected with HIV was reported to amount to as many as 280.623. The number of HIV cases found and reported is still far from the estimated ODHA (people with HIV-AIDS) in 2016, which amounted to 640.443. The HIV/AIDS case becomes a critical problem because the highest percentage of infections is in the productive age group (20 - 49 years), and not all of them get ARV therapy, so they are vulnerable to falling into the AIDS phase (4).

This study's purpose is to analyze the prevalence of comorbidities or secondary disease that are often found in HIV patients whether they are receiving ARV therapy or not because according to several journals it is stated that HIV patients experience abnormalities in almost all organs of their bodies thereby increasing their morbidity and mortality.

**MATERIALS AND METHODS**

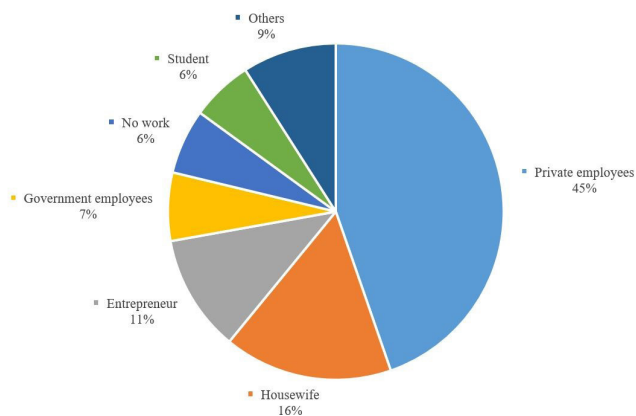
This is an analytic and descriptive research study with a cross-sectional study design using medical record data. Inclusion criteria were hospitalized HIV patients who were admitted to Dr. Soetomo General Hospital, Surabaya, Indonesia, in the period August 2019 - February 2020. HIV positive which was confirmed by 3 methods antibody/antigen test. All data were statistically analyzed using IBM SPSS version 17. Association analyses were performed using Chi-square Test. The study has been approved by the Health Research Ethics Committee of Dr. Soetomo General Hospital Surabaya with number 1306/KEPK/VII/2019.

**RESULTS**

The number of HIV/AIDS patients who were hospitalized was 392. Forty-six patients were hospitalized two times, seven patients were hospitalized three times, and four patients were hospitalized four times, so the HIV patients total during the inclusion period is 320.

**Sociodemographic Characteristic of HIV Patients**

The average patient was 38.6 (± 10.9) years old, the most age group was 30 - 39 years (38.8%), with the youngest patient being 19 years old and the oldest patient 82 years old. Patients are predominantly male (69.4%). The most education completed by patients is senior high school graduate (69.4%). The most common patient occupation is a private employee (44.7%) (Figure 1), and the religion most widely practiced by patients is Islam (90.3%) (Table I).



**Figure 1: Distribution of the patients' occupation**

**Immunity Characteristic of HIV Patients**

24.4% of HIV patients had sepsis, and 34.7% HIV patients died, with the highest CD4 cell count range being <100 cells/μL (28.1%) with an average of 124.1 cells/μL. The highest value was 917 cells/μL, and the lowest was 1 cells/μL (Table II).

**Prevalence of Secondary Disease in HIV Patients**

The most common secondary disease of HIV patients found in this study was candidiasis oris and lung

**Table I: Sociodemographic characteristic of HIV Patients**

Variable	n	%
<b>Age</b>		
< 20 years old	4	1.3
20 – 29 years old	62	19.4
30 – 39 years old	124	38.8
40 – 49 years old	67	20.9
50 – 59 years old	53	16.6
≥ 60 years old	10	3.1
<b>Sex</b>		
Male	222	69.4
Female	98	30.6
<b>Education</b>		
Not complete Primary school	13	4.1
Graduated Primary School	34	10.6
Graduated JHS	26	8.1
Graduated SHS	222	69.4
Graduated Bachelor	25	7.9
<b>Occupation</b>		
Private employees	143	44.7
Housewife	52	16.3
Entrepreneur	36	11.3
Government employees	21	6.6
No work	20	6.3
Student	19	5.9
others	17	5.3
Driver	3	0.9
Farmer	3	0.9
Fisherman	2	0.6
Salesman	2	0.6
Army	1	0.3
Teacher	1	0.3
<b>Religion</b>		
Islam	289	90.3
Christian	21	6.6
Catholic	8	2.5
Buddhist	2	0.6
<b>Marital status</b>		
Married	170	53.1
Single	103	32.2
Divorce	47	14.7

**Table II: Immunity Characteristic of HIV Patients**

Variable	n	%
<b>Sepsis</b>		
Yes	78	24.4
No	242	75.6
<b>Died</b>		
Septic Shock	47	14.7
Respiratory failure	56	17.5
Mixed	8	2.5
Survive	209	65.3
<b>CD4 (cells/μL)</b>		
> 500	8	2.5
200 - 499	18	5.6
100 - 199	23	7.2
< 100	90	28.1

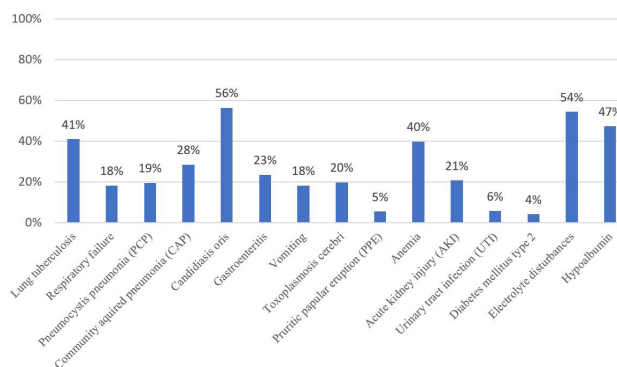
tuberculosis, but most of the patients also experienced electrolyte and hypoalbumin disorders (Table III, Figure 2).

**Association between sociodemographic and sepsis, death, complications in HIV patients**

We want to check whether the prevalence of sepsis, death, and complication in HIV patients was affected by differences in age, sex, marital status, occupation, education, and CD4 counts. Our result showed only

**Table III: Prevalence of Secondary Disease in HIV Patients**

Variable	n	%
<b>Respiratory</b>		
Lung Tuberculosis	131	40.9
Community aquired pneumonia (CAP)	91	28.4
Pneumocytis pneumonia (PCP)	62	19.4
Respiratory failure	58	18.1
Pneumonia	38	11.9
Pleura effusion	19	5.9
Lower respiratory tract infection	14	4.4
Dyspneu	7	2.2
Hospital-Acquired Pneumonia	6	1.9
Sputum Retention	5	1.6
<b>Gastroenterology</b>		
Candidiasis oris	180	56.3
Gastroenteritis	75	23.4
Vomiting	58	18.1
Transaminitis	38	11.9
Hepatitis	37	11.6
Dyspepsia	18	5.6
Candidiasis Orofaring	17	5.3
Melena	15	4.7
Hematemesis	14	4.4
Cirrhosis Hepatic	6	1.9
Ascites	5	1.6
Gastritis	5	1.6
Drug Induced Liver Injury	4	1.3
<b>Neurology and Psychology</b>		
Toxoplasmosis Cerebri	63	19.7
Loss of consciousness	20	6.3
Psychiatry disorder	17	5.3
Meningoensefalitis/Ensefalitis	12	3.8
Ensefalopati	10	3.1
Brain cancer	6	1.9
Headache	5	1.6
Hemiparese	3	0.9
Stroke	3	0.9
Seizure	3	0.9
Polineuropati	3	0.9
Hydrocephalus	3	0.9
<b>Dermatology</b>		
Pruritic Papular Eruption (PPE)	17	5.3
Pressure sores	4	1.3
Tineaasis	3	0.9
Dermatitis	3	0.9
<b>Hematology and Oncology</b>		
Anemia	127	39.7
Bisitopenia	29	9.1
Limfadenitis TB	19	5.9
Pancytopenia	10	3.1
Thrombocytopenia	6	1.9
Lymphoma Maligna	4	1.3
Leukopenia	3	0.9
CA Cervix	3	0.9
<b>Genitourinary</b>		
Acute Kidney Injury	66	20.6
Urinary Tract Infection	18	5.6
Chronic Kidney Disease	15	4.7
Hemorrhoid	6	1.9
Condyloma akuminata	3	0.9
<b>Endocrinology</b>		
Diabetes Mellitus Type 2	13	4.1
Diabetic Kidney disease	2	0.6
<b>Cardiology</b>		
Hypertension	10	3.1
Cardiomyopathy	3	0.9
<b>Others</b>		
Electrolyte disturbances	174	54.4
Hypoalbumin	151	47.2
Metabolic acidosis	26	8.1
Respiratory alkalosis	7	2.2



**Figure 2: Secondary Disease in HIV Patients at Dr. Soetomo General Hospital Surabaya**

age and CD4 counts contribute to the prevalence of complications ( $p < 0.05$ ) (Table IV).

## DISCUSSION

### Sociodemographic

In this study, most HIV/AIDS patients found were in the age group 30-39 years according to HIV/AIDS reports in Indonesia and the world (3,4). Young age is an age group with high impulsiveness sexual behavior that engages in unsafe sexual behavior, multiple sex partners, and uses narcotics (5). Age is also known to be a factor in the emergence of multi-complication, especially those over 50 years old (6).

The high prevalence of HIV/AIDS cases in men due to male sexual desire is higher than women (7). Besides, the high incidence of male sex male in young men is also a key population in the transmission of HIV infection (8).

The education level of HIV patients found agrees with other studies, i.e., namely high school graduation/equivalent. In Indonesia, there is a compulsory education program from the government, which makes access to education straightforward (9). Research in India has also shown similar results, with secondary schools being the largest group (10). Other studies show that there is no significant relationship between education level and HIV transmission prevention measures because there has been a paradigm shift where the level of education is no longer directly proportional to the awareness of HIV infection (11).

In this study, most HIV patients have a job. The most common occupations were private employees and housewives following the Indonesia Ministry of Health data in 2017. The high level of education had a positive impact on getting a job, but stigma and discrimination also affected HIV patients (12). Other studies in India say housewives are very vulnerable to HIV infection because it is transmitted by their partners (13).

In this study, the patients are predominantly Muslim. This finding is different from studies in other countries, such as in Ethiopia where the majority of HIV patients are

**Table IV: Association between sociodemographic, CD4 counts to sepsis, death, complications**

Variable	Total (n= 320)		Sepsis (n= 78)		P	Death (n= 111)		P	Complication				P
									Mild (n= 122)		Serious (n= 198)		
	n	%	n	%		n	%		n	%	n	%	
Age					0.561			0.429					0.042
< 20 years old	4	1.3	2	2.6		3	2.7		4	0.0	4	2.0	
20 – 29 y.o.	62	19.4	14	17.9		21	18.9		32	26.2	30	15.2	
30 – 39 y.o.	124	38.8	32	41.0		47	42.3		40	32.8	84	42.4	
40 – 49 y.o.	67	20.9	19	24.4		21	18.9		23	18.9	44	22.2	
50 – 59 y.o.	53	16.6	9	11.5		17	15.3		21	17.2	32	16.2	
≥ 60 years old	10	3.1	2	2.6		2	1.8		6	4.9	4	2.0	
Sex					0.753			0.307					0.510
Male	222	69.4	53	67.9		73	65.8		82	67.2	140	70.7	
Female	98	30.6	25	32.1		38	34.2		40	32.8	58	29.3	
Marital Status					0.482			0.270					0.649
Married	170	53.1	37	47.4		53	47.7		66	54.1	104	52.5	
Single	103	32.2	29	37.2		42	37.8		36	29.5	67	33.8	
Divorce	47	14.7	12	15.4		16	14.4		20	16.4	27	13.6	
Occupation					0.743			0.817					0.053
Formal	166	51.9	42	53.8		56	50.5		55	45.1	111	56.1	
Informal	63	19.7	13	16.7		21	18.9		23	18.9	40	20.2	
Unemployed	91	28.4	23	29.5		34	30.6		44	36.1	47	23.7	
Education					0.572			0.376					0.366
Low	47	14.7	11	14.1		13	11.7		22	18.0	25	12.6	
Middle	248	77.5	63	80.8		91	82		92	75.4	156	78.8	
High	25	7.8	4	5.1		7	6.3		8	6.6	17	8.6	
CD4 (cells/μL)					0.145			0.432					0.022
< 100	90	28.1	23	29.3		31	27.9		29	23.7	61	30.8	
100 - 199	23	7.2	2	2.6		5	4.5		13	10.6	10	5.1	
200 - 499	18	5.6	4	5.1		6	5.4		11	9.0	7	3.5	
≥ 500	8	2.5	0	0.0		1	0.9		5	4.1	3	1.5	

Orthodox (14), in Nigeria where they are predominantly Muslim (15), and in China found where the majority of patients had no religion (16). This difference was based on the characteristics of religious adherents in the country where the study was conducted (17).

Marital status in this study is not much different from other studies. Research in Nigeria states that married women have a higher risk of becoming infected with HIV than unmarried (18). Marital status also has a significant relationship to mortality in HIV patients (19).

**Immunity**

In this study, the prevalence of HIV patients suffering from sepsis is 24.4%. This result is not much different when compared with other studies in Brazil, Taiwan, and Uganda (20-22). Another study explained that HIV infection affects many components of the immune system, making patients vulnerable to secondary infections and also triggering the dysregulation of the immune response to sepsis (23).

Sepsis in its pathway can cause respiratory failure through endothelial damage and changes in microvascular flow in the lungs, which causes increased capillary permeability and becomes pulmonary edema. Pulmonary edema causes ventilation-perfusion imbalance and hypoxemia. The condition can trigger acute respiratory distress syndrome (24). Poor prognosis is associated with HIV patients with sepsis. The study estimated the danger of death in the first 28 days for HIV patients with sepsis four times greater than non-sepsis (20). The condition of sepsis is strongly associated with low CD4 cell counts even though patients are receiving ARV therapy, with a 7-fold higher incidence in patients with CD4 counts <200 cells / μL compared with CD4 patients > 500 cells / μL or more (22).

The average CD4 count of patients found in this study was meager at <100 cells/μL with the clinical conditions of patients found to be accompanied by various comorbid diseases, according to other studies conducted in India (25). This is because most patients will seek treatment if they feel sick, while low CD4 cell counts will increase

the risk of various diseases or complications, especially opportunistic infections and malignancies (11,26).

### Secondary Disease in HIV Patients

In this study, the prevalence of secondary disease most commonly found in HIV patients was candidiasis oris 56.3% and tuberculosis 40.9%. This study result is not much different when compared to studies in India, where it is dominated by tuberculosis and candidiasis oris (25).

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*, which usually attacks the lungs but can also attack other body organs such as bones, brain, and others. HIV/AIDS patients have a ten times greater risk of experiencing tuberculosis infection than in healthy people (27). The risk of tuberculosis in HIV patients also affected by CD4: the lower the CD4 count of patients, the risk of tuberculosis also increases (28).

In addition to tuberculosis infections, respiratory tract infections often also found are PCP/Pneumocystis carinii pneumonia. This infection is caused by the fungus *P. jirovecii/carinii*, which can cause pneumonia, especially in immunocompromised patients. This infection is usually hidden, progressive, and causes shortness of breath with dry cough and discomfort (29). Another pneumonia that is also often found in HIV patients is bacterial pneumonia. HIV patients who did not receive antiretroviral therapy properly have 5-25 times greater risk of suffering from bacterial pneumonia (30).

Candidiasis oris is the most common manifestation of opportunistic infections in patients with HIV/AIDS. This infection is generally caused by the fungus *Candida albicans*, which is a commensal organism in the skin, mouth, digestive tract, and reproductive organs, but *Candida albicans* can turn into pathogens because of changes in the host microenvironment. This change is also very dependent on the virulence agent factors, namely cell surface adhesins, proteolytic enzymes, morphologic switching, and the development of drug resistance (31). Just like tuberculosis infection, the incidence of candidiasis is also influenced by low CD4 of the patient, and its a sign occurrence of immunosuppression in patients (32). In addition to *Candida albicans*, other fungal infections that also often occur in HIV patients are *Candida parapsillosis*, *Candida dubliniensis*, *Aspergillus spp.* and *Penicillium spp.* (33).

Toxoplasmosis becomes an opportunistic infection in the central nervous system, which is quite common in HIV patients (19.7%). This prevalence is quite different from studies in India, which showed lower results were only 1.8% of HIV patients with toxoplasmosis (25). In another study that collected data from 37 countries around the world showed 26.22% found infections by the molecular method / PCR; however, there is only 3.24%

with reactive anti-Toxoplasmosis IgM. This infection is caused by the parasite *Toxoplasmosis gondii*, which often causes a focal lesion in the brain. This infection is usually chronic persistent and asymptomatic, where reactivation is the dominant route, especially in patients with a CD4 cell count below 200 cells/ $\mu$ L and carries a fatal risk if left untreated (34).

In this study, patients with a psychiatric disorder were also found, although not too large in prevalence. However, research in India revealed a clear relationship between HIV and psychiatric disorders, such as depression, psychosis, mania, anxiety, and suicidal ideas are typical (35). Psychiatric disorders are often found, especially depression, and significantly affect the quality of life in HIV patients (36). Psychiatric disorders that arise are mentioned due to the negative stigma from family and environment (37).

In this study, it was found that most patients had anemia. This condition is higher than research conducted in Ethiopia, which found that only 26.2% of HIV patients with anemia (38). This is significantly different from patients in India, which found 77.5% of HIV patients with anemia (39). The leading cause of this condition is drug-induced anemia, especially Zidovudine drugs that can reduce hemoglobin levels in 34% of research subjects, and the presence of infiltration or bone marrow suppression due to infection also contributed to it (40). Kidney dysfunction can cause chronic anemia and mentioned that anemia with thrombocytopenia should be a serious concern because of the high morbidity and mortality (41).

The gastrointestinal system complaints that often arise are transaminitis, gastroenteritis, diarrhea, vomiting, dyspepsia, and others. This occurs because of the side effects of the use of ARV drugs and the presence of pathogenic bacterial infections. Also, ARV drugs (HAART) can cause an increase in ALT serum more than 5x from the standard limit in 14% of patients (41). In gastrointestinal endoscopic studies of HIV patients, the esophagus consisted of candidiasis 28%, esophagitis 22%, ulcers 16%, gastritis 20%, congestive gastropathy 4%, the duodenum consisted of duodenitis 14% and only 18% with normal mucosa (42). In addition to experiencing histological changes in HIV patients treated and not, there are specific changes in the composition of the intestinal microbiome, namely Proteobacteria, Bacteroidetes, Firmicutes. At the genus level, there is a change from Bacteroides to Prevotella. Changes in these microbiome changes disrupt gastric mucosal permeability and loss of immune regulation and probiotic activity (43).

Metabolic disorders, i.e., diabetes mellitus, were also found in HIV patients in this study. This is interesting because diabetes is one of the non-communicable diseases which has high prevalence throughout the

world. Butt et al. in 2009 study said HIV infection had no correlation with an increased risk of diabetes, but increased age, coinfection of HCV, and BMI was a significant risk factor of diabetes in HIV patients (44). However, this is contradicted by Karla et al. in 2011 said that the high prevalence of diabetes in the general population also applies to HIV patients. According to him, in addition to being caused by sociodemographic factors and low CD4 cell counts, several mechanisms cause a high risk of diabetes that impaired glucose tolerance, insulin resistance, growth hormone deficiency, increased proinflammatory cytokines, and side effects of antiretroviral drugs (45). The same thing was also found in the study of Bourgi et al. In 2018, which explained the metabolic complications in HIV patients due to chronic inflammation at many tissue sites, which caused dysregulation transport, use, and storage of glucose and lipid (46).

In addition to metabolic disorders, this study also obtained HIV patients with electrolyte disturbances. This is due to increased excretion, decreased intake, or disruption in absorption and metabolism, for example, diarrhea, vomiting, and others (47). Other studies also reveal that kidney function is very influential in this condition wherein HIV patients with normal kidney function do not get significant differences in electrolyte levels compared to healthy people. However, the study also revealed that the conditions of infection, inflammation, endocrine, oncology could be a cause of electrolyte disorders and usually appear clinically only at an advanced stage (48).

HIV patients with hypoalbumin were also found in this study. According to the study of Dao et al. in 2011, it is a multifactorial problem and can be an indication of malnutrition, chronic inflammation, wasting syndrome, enteropathy, or liver problems (49).

## CONCLUSION

HIV patients with CD4 counts less than 200 cells/ $\mu$ L are very susceptible to various secondary diseases. Routine monitoring of the prevalence of secondary disease needs to be done to reduce morbidity and mortality in HIV patients.

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