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Viral and Host Factors are Related to the Progression of HIV Diseases in Mimika, Papua

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Abstract

BACKGROUND: Papua has a high cumulative number of HIV, which has expanded epidemic status with the most risk factors are heterosexuals.

AIM: This study aims to determine factors associated with HIV disease progression include host and viral factors.

METHODS: Eighty-four subjects recruited in Rumah Sakit Mitra Masyarakat (RSMM) VCT's laboratory, interviewed with questionnaires and also did laboratory examinations. HIV-1 subtypes were identified using RT-PCR, nested PCR and sequencing. Then, CD4+ data is checked using PIMA Analyzer. Demographic and clinical data obtained from the patient's medical record. After collected, data were analysed using Fisher's exact test.

RESULTS: The results showed two factors that influence the progression of HIV disease were HIV subtypes ($p = 0.002$) and Body Mass Index ($p = 0.033$). The HIV-1 subtype also correlated with CD4+ levels with a value of $p = 0.04$.

CONCLUSION: HIV-1 subtype correlates with HIV progression, so it is necessary to develop HIV/AIDS management strategies and clinical counselling.

Introduction

The report that provides by UNAIDS that the number of people living with HIV in the world reached 34 million people with 17 million (50%) are women, and 2.1 million are children less than 15 years [1]. In June 2018, Papua recorded with the cases of HIV were 14.315 inhabitants and 2.114 people are dead because of AIDS. Heterosexuals are the highest risk factors of HIV transmission in Papua with 13.888 cases, followed by mother to infant transmission by 208 cases [2].

Generally, it needs eight to ten years for HIV to develop into AIDS. Several factors were found to contribute to the progression of HIV infection is a factor immunological, virological, environmental and genetic factors hosts [3], [4], [5], [6]. Factors that may affect the host is the Human Leukocyte Antigen (HLA), CYP polymorphisms, gender, age, ethnicity, psychosocial and body mass index (BMI). Environmental factors that affect the progression of diseases such as transmission modes and socio-economic status [7]. Viral factors, including viral subtypes or mutations that destroy the virus [8].

A study in Thailand found that the subtypes of HIV-related manner and speed of transmission, where subtype B associated with the transmission of homosexuals and intravenous drug users (IDUs), while subtypes A, CRF01_AE, and C related to heterosexual transmission [9]. Studies conducted in Tanzania and Uganda found that subtype D correlated faster with a decrease in $CD4^+$ T cells and increased disease progression than other subtypes and recombinant forms [10], [11]. However, a retrospective cohort study conducted during 1996 and 2007 reveals that Africans infected with subtype B has the progression of HIV/AIDS faster than those infected with non-B subtypes [12].

Many studies in other countries have reported correlations between various factors with the

progression of HIV disease, but in Indonesia, the data is still limited or limited.

The purpose of this study is to determine what factors associated with the progression of HIV disease, including host factors, environmental and viral factors.

Material and Methods

Study and subject

The study was conducted for ten months, from January to October 2015. Blood sampling was taken at the VCT Laboratory of Rumah Sakit Mitra Masyarakat (RSMM) Mimika. Samples are HIV/AIDS patients were selected for continuous sampling and has received antiretroviral therapy who have met the inclusion criteria. Calculation of sample size for cross-sectional design uses the Lemeshow formula from the calculation results obtained eighty-four respondents. The results from interviews of demographic and clinical data with questionnaire collected for further processing. $CD4^+$ examination uses the PIMA Analyzer and haematology examination using Sysmex.

Subtyping HIV

The extraction process uses a standard kit from Qiagen with catalogue # 52906. Firstly RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) amplification using a specific primer. The primers used are obtained from the HXB2 reference journal access code Geneva K03455 (http://hiv.web.lanl.gov/NUM-HXB2.MAIN.html).
Second is electrophoresis, and this stage aims to see the results of amplification in the previous step. The PCR results were detected by electrophoresis of 5 ul PCR products plus 1 ul loading buffer on 2% agarose gel and 100 v voltage for 40 minutes. The PCR product was visualised by placing the gel on the doc-gel. DNA isolates which showed a band of 460 bp were affirmed to contain the target gene. The next stage is sequencing; Sequencing is done to find out the nucleotide sequence in several PCR gene envelope products. Sequencing using ABIPrism 3500 Genetic Analyzer (Applied Biosystem, USA). This sequencing process is carried out in 2 stages, namely, cycle sequencing reaction and purification of PCR products and sequencing. Sequencing results were analysed using Bioedit software. The last is BLAST (Basic Local Alignment Search Tool) process, the purpose of which is to get the HIV genotype and subtype. BLAST was conducted using the internet to two gene bank sites to confirm; the two sites are BLAST from NCBI (National Center for Biotechnology Information) at www.ncbi.nlm.nih.gov and the HIV sequence database at www.hiv.lanl.gov.

Statistical Analysis

Statistical analysis was performed using Fisher's exact test for categorical variables. Briefly, a 2 × 2 contingency table on the selected Data was constructed, and the two-tailed p-value. P values less than or equal to 0,05 were considered to be significant.

Results

Demographic Characteristics of Subjects

Demographic characteristics showed that HIV/AIDS patients in Rumah Sakit Mitra Masyarakat (RSMM) Mimika dominated by women as many as 61 people (72.6%), Papuans 60 people (71.4%), educated (81%), Working (83.3%), body mass index 18.5-25 kg/m2 69 people (82.1%), married 47 people (56%), heterosexual transmission routes 80 people (95.2%), $CD4^+$ levels as much as > 350 cells/mm^3 77 people (91.7%), and opportunistic infections of tuberculosis 69 people (82.1%).

The factors associated with the progression of HIV

A significant relationship between demographic variables clinical and clinical stage of HIV/AIDS is a subtype variable, BMI and Route transmission. The results of the analysis are shown in Table 1.

Table 1: Demographic Characteristic of study Subject

Characteristic	Clinical Stage (WHO)		∑	*p*
	I, II, III	IV		
Sex				
Male	17	6	23	0.356
Female	51	10	61	
Ethnic				
Papua	50	10	60	0.375
Non-papua	18	6	24	
Subtype				
CRF01_AE	30	8	38	0.002*
Non-CRF01_AE	20	26	46	
Opportunistic Infection				
TB	56	13	69	1.000
Non-TB	12	3	15	
Body Mass Index				
Other	9	6	15	0.033*
Normally	59	10	69	
$CD4^+$				
< 350 cell/mm3	6	1	7	1.000
> 350 cell/mm3	62	15	77	
Hemoglobin				
< 12 g/dl	22	14	36	0.826
12-15 g/dl	28	20	48	
Trombosit				
< 150.000 ul	5	6	11	0.340
150 – 400.000 ul	45	28	73	
CD4 Failure, < 50 cell/mm3/year				
Yes	37	7	44	0.580
No	31	9	40	

Table 2 shows the analysis of the relationship between the subtypes and clinical characteristics of the levels of $CD4^+$ HIV patients in Mimika. Results indicated exhibited significantly between subtypes of HIV-1 and $CD4^+$ cells of patients with p = 0:04 (α < 0,05). The results of the analysis are shown in table 2.

Table 2: The correlation between HIV-1 subtypes and the level of CD4

Characteristic	Cluster Differentiation-4		∑	*p*
	< 350	> 350		
Sex				
Male	2	21	23	0.62
Female	5	26	61	
Ethnic				
Papua	6	54	60	0.66
Non-papua	1	23	24	
Subtype				
CRF01_AE	6	33	39	0.04*
Non-CRF01_AE	1	44	45	
Opportunistic Infection				
TB	7	62	69	0.34
Non-TB	0	15	15	
Transmission Mode				0.70
Heterosexual	7	73	80	
Others	0	4	4	
Body Mass Index				
Other	3	12	15	0.10
Normally	4	65	69	
Hemoglobin				
< 12 g/dl	4	32	36	0.45
12-15 g/dl	3	45	48	

Discussion

Many factors affect the disease progression of HIV/AIDS, including host factors, environmental and viral factors [13]. Two factors that affect the progression in this study is a host factor is the body mass index and factor virus itself is a subtype of HIV-1. One element that has a relationship with the clinical stage is the body mass index (BMI). BMI is one of the WHO's clinical assessment parameters that weight loss in people with HIV/AIDS. However, the association of BMI with $CD4^+$ levels did not show significant results. In this study, the patients' BMI is normal for clinical stage I, II and III. A study in France showed that mortality was higher in patients with BMI between 16-18.4 kg/m^2 with HR 2.2 (CI: 1.6-3.0) and a BMI < 16 is 4.4 (CI: 3.1-6.3) and standard BMI 18.5 [14], [7]. These results are similar to studies in Surabaya which is one of the factors that affect the progression of HIV disease is the body mass index [7].

In addition to body mass index, HIV-1 subtype also has a significant relationship with clinical stage and $CD4^+$. Correlation between HIV-1 subtypes and the development of the disease is controversial. Several studies have reported a correlation between subtypes of HIV-1 and the progression of HIV/AIDS by relating the time needed by HIV to develop AIDS, the rate of change low $CD4^+$ counts, viral load high, and mortality associated with HIV/AIDS. CRF01_AE commonly identified in HIV/AIDS patients in Papua. This indicates that the recombinant form of the virus worldwide associated with faster disease progression, such as in Cuba and Brazil [15], [13].

This study shows that CRF01_AE associated with faster HIV/AIDS progression. Similarly, studies in China (Li, 2014; Ng, 2011). It found that CRF01_AE-infected seroconversion experienced a faster rate of decline in $CD4^+$ T cells, requiring earlier initiation of ART compared to non CRF01_AE patients [16].

The study held by Chu et al. reported that the level of low $CD4^+$ changes was related to the CRF01_AE subtype [3]. Research in Indonesia in 2013 reported that CRF01_AE subtype also has a higher prevalence than other subtypes and associated with the level of $CD4^+$ cell changes in patients who had received HAART [17]. Subtype connection with deaths related to HIV/AIDS is still contradictory. Subtype CRF01_AE estimated time of the death of people with an average of 7.8 (7.0 to 9.1) years [18].

It remains unclear why CRF01_AE associated with $CD4^+$ decline very quickly. However, several studies have shown that the high proportion of tropism X4 in the CRF01_AE subtype and also that X4 tropism is associated with an increased rate of $CD4^+$ decline and progression for advanced immunosuppression [19], [20], [21]. Also, a decrease in the immune system on the host after infection with HIV-1 can allow the virus to grow and replicate independently. It can explain the increase in the rate of disease progression in HIV-infected patients with subtype CRF01_AE [22].

Some literature suggests that the virus subtype may affect the pathogenesis and progression of the disease during HIV infection. Hu, has reported that in PWID (people with an injected drug) patients with subtype CRF01_AE have higher plasma viral load compared to patients with subtype B, but there was no difference in the number of $CD4^+$ T cells [23]. Recent research in Singapore reported a decline in $CD4^+$ T cells faster for a shorter time in patients with subtype CRF01_AE than other subtypes [16]. Besides, in Shanghai, it was also reported that HIV homosexual patients with the CRF01_AE subtype found that more patients had lower initial $CD4^+$ T cells. This subtype of HIV disease progression was faster to AIDS and CXCR4 tropism frequency greater than with other subtypes [24].

Direct comparison of HIV subtypes often complicated by uncertainty factors for instance: the way of transmission and timing of infection, host genetic diversity, effects of comorbid conditions, small sample size, identification methods that cannot distinguish between subtypes and recombinant strains. This analysis is limited to a relatively homogeneous population of incidences of cases with a clear infection time and a known mode of transmission (sexual exposure).

It should be noted that despite the historical existence of subepidemics separated by genotypes

and risk factors, CRF01_AE now appears to be dominant in all risk groups throughout Asia [25]. It remains to be determined whether this can be accounted for by genetic DRIFT, or if there are inherent differences between strains such as plasma viral load, transmission or other biological or epidemiological factors that might underlie this shift.

In conclusion, HIV-1 subtype CRF01_AE primarily associated with HIV disease progression, in this case, is a clinical-stage and $CD4^+$. Routine surveillance of the subtypes of HIV-1 and $CD4^+$ will be useful in monitoring the progression of HIV/AIDS and improving the management and clinical counselling. The further study combines subjects with different ethnic backgrounds, and functional evaluation can be used to examine the relationship between subtypes of HIV-1 and the progression of HIV/AIDS. The research may use more samples, and the factors involved include the use of viral load markers to monitor disease progression. Finally, the sequencing of the HIV genome as a whole is the ideal method for concluding the relationship of the subtype by conducting a co-receptor analysis.

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