Clinical Evaluation of HIV/AIDS Patients on Antiretroviral Therapy using HIV Symptoms Index: A reliability and Applicability Evaluation using Indonesian Language

Khalid M. Shidiq[1], Erni J. Nelwan[2], Evy Yunihastuti[3], Kuntjoro Harimurti[4], Herdiman T. Pohan[2]

[1] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3] Allergy and Immunology Division, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4] Board of Fellow, Center for Clinical Epidemiology and Evidence-Based Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Author**:*
Erni J. Nelwan, MD, PhD. Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71, Jakarta 10430, Indonesia. email: ejnelwan@yahoo.com.

ABSTRAK

Latar belakang: *HIV/ AIDS merupakan penyakit kronis seumur hidup dengan spektrum klinis yang luas yang dapat menurunkan kualitas hidup. Pengukuran gejala obyektif penting karena berhubungan dengan kepatuhan pengobatan dan progresivitas penyakit. Saat ini, tidak ada alat klinis yang tersedia untuk mengevaluasi gejala infeksi HIV dan efek samping pengobatan untuk pengaturan rawat jalan. Penelitian ini bertujuan untuk menilai keandalan Indeks Gejala HIV versi Indonesia untuk mengukur gejala pasien HIV/ AIDS, dan menggunakannya untuk menilai profil gejala mereka.* ***Metode:*** *penelitian cross sectional pada pasien rawat jalan penderita HIV / AIDS (n = 87) yang direkrut di Poliklinik HIV RSUD Cipto Mangunkusumo periode September-November 2018. Indeks Gejala HIV terdiri dari 20 item evaluasi somatik, psikis, dan kombinasi keduanya. gejala, dan 'adaptasi bahasanya ke bahasa Indonesia dilakukan dengan metode Beaton dan Guillemin. Reliabilitas Indeks Gejala HIV versi Indonesia diuji dengan analisis koefisien alpha cronbach, dan validitas internal diuji dengan analisis multitrait scaling sebelum digunakan untuk profil pola gejala pasien HIV/ AIDS.* ***Hasil:*** *indeks gejala HIV versi Indonesia dapat diandalkan (cronbach alpha 0.76) dan valid (korelasi multitrait> 0.4) untuk mengukur gejala pasien HIV/ AIDS. Gejala yang paling umum adalah kelelahan (55,7%), diikuti insomnia (43,3%), pusing dan pusing (42,3%), masalah kulit (42,3%), dan nyeri, mati rasa, atau kesemutan pada tangan atau kaki (39,2%) .* ***Kesimpulan:*** *indeks Gejala HIV versi Indonesia dapat diandalkan dan valid untuk mengukur gejala penderita HIV / AIDS secara obyektif.*

Kata kunci*: gejala, HIV/AIDS, evaluasi klinis.*

ABSTRACT

Background: *HIV/AIDS is a chronic, lifelong disease with a wide clinical spectrum which could decrease the quality of life. Objective symptoms measurement is important because it is correlated to treatment adherence*

and progressivity of the disease. Currently, there is no clinical tool available to evaluate symptoms of HIV infection and the treatment's side effect for the outpatient setting. This study aimed is to assess the reliability of the Indonesian version of HIV Symptom Index for measuring symptoms of HIV/AIDS patients, and use it for assessment of their symptom profile. ***Methods:*** *this is a cross sectional study in outpatient HIV/AIDS subjects (n=87) recruited in Cipto Mangunkusumo Hospital's HIV clinic from September-November 2018. The HIV Symptom Index consisted of 20 items evaluating somatic, psychologic, and the combination of both symptoms, and its' language adaptation to Indonesian was done with Beaton and Guillemin method. Reliability of the Indonesian version of HIV Symptom Index was tested by alpha cronbach's a coefficient analysis, and the internal validity was tested with multitrait scaling analysis before being used to profile the symptom pattern of HIV/AIDS patients.* ***Results:*** *Indonesian version of HIV Symptom Index is reliable (cronbach alpha 0.76) and valid (multitrait correlation >0.4) for measuring symptoms of HIV/AIDS patients. The most common symptom is fatigue (55.7%), followed by insomnia (43.3%), dizziness and lightheadedness (42.3%), skin problems (42.3%), and pain, numbness, or tingling in the hands or feet (39.2%).* ***Conclusion:*** *Indonesian version of HIV symptom Index is reliable and valid to measure symptoms of HIV/AIDS patiens objectively.*

Keywords: *symptom, HIV/AIDS, clinical evaluation.*

INTRODUCTION

HIV/AIDS infection is a global epidemic disease with increasing burden. Despite the decreasing mortality due to antiretroviral (ARV) therapy, HIV/AIDS is still a fifth leading cause of morbidity and disability.[1,2] HIV has a wide clinical spectrum, and since it's a chronic disease with no total cure yet possible, symptoms and quality of life are very important to attend to.[3,4]

ARV therapy has a big impact on the clinical presentation of HIV patients. Clinical improvement after ARV therapy may decrease patient's symptoms, but adverse effects of ARV may cause new symptoms.[4,5] These clinically stable patients could still deal with chronic, not severe symptoms on a daily basis either caused by the HIV related problems or side effects of the therapies. These symptoms in a long term might be causing disturbance in patient's life, since symptoms of HIV patients are correlated with adherence to therapy, depression, and possibly the quality of life.[1,5] It is important to detect symptoms accurately in such patients, and to monitor the progress objectively in a routine evaluation.[6-8] Thus a tool that is more sensitive and measurable than a routine anamnesis by a doctor is needed.[7,8] In this study we used HIV Symptom Index developed by Justice et al,[5] because it is a simple, self-reported questionnaire that was developed by comparing and improving several tools, and only took no longer than 5 minutes to finish.

METHODS

The Ethical Committee of the Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital has given their approval for this study (No. 0850/UN2.F1/ETIK/2018). This cross-sectional study used random sampling method from HIV clinic's enrollment sequence to include HIV/ AIDS patients aged 18 years and over who had received ARV therapy for at least 6 months who came to seek treatment at UPT HIV RSCM in August to September 2018. Patients who were not able to read or write, do not understand Indonesian, use anti-anxiety drugs, anti-depressants, and psychotropic drugs, and those whose medical history is incomplete are excluded from the study. A self-reported HIV Index symptoms consisted of 20 questions. Language adaptation from the original english version into Indonesian was done with Beaton and Guillemin method.

This research is broadly divided into pre-analysis and analysis stages. The pre-analysis stage includes the process of language and cultural adaptation and the final stage, namely the reliability test and validity of the HIV Symptom Index. Reliability was assessed by the test-retest test with a 14-day interval and internal consistency was analyzed using Cronbach's Alpha coefficient. Reliability is rated as adequate if it is > 0.70 and optimal if > 0.80. Construct validity was assessed by a multitrait scaling analysis that assessed

convergence and discrimination from validity. Convergence is said to be significant if> 0.40 and discrimination is said to be meaningful if the correlation coefficient between items and domains is higher than other domains. Next The tested questionnaire was given to a larger sample.[9,10] The results of filling out the HIV Symptom Index questionnaire were presented descriptively to obtain symptomatic profiles of HIV patients.

Data analysis was carried out using the SPSS program. Data on socio-demographic, clinical characteristics and health-related quality of life are described using descriptive statistical methods. Validity test for the HIV Symptom Index questionnaire was carried out using a multitrait scaling approach, whereas reliability testing with interclass correlation coefficient (ICC). We calculated the reliability of the questionnaire following the retest method by assessing the correlation coefficient of the first and eighth day HIV symptom index questionnaire. Further reliability analysis was done by calculating the internal consistency of the questionnaire by calculating the Cronbach α.[9,10]

Descriptions of symptoms of HIV patients are delivered in the form of frequency of symptoms (presentation of each symptom) and total score. The total score is calculated by summing the numbers of each symptom (0 = no symptoms, 1 = no disturbing symptoms, 2 = there are symptoms that are a little annoying, 3 = there are disturbing symptoms, 4 = there are very disturbing symptoms), with a minimum score of 0 and maximum 80.[5] HIV symptoms are compared between patients with male and female gender, CD4 above 350 and below 350, detectable and undetectable viral load , and line 1 and line 2 ARV therapy.

RESULTS

Of the 155 randomized subjects, 48 subjects did not meet the inclusion / exclusion criteria. The remaining 107 patients were subjected to a pre-analysis of 20 patients and subjects analyzed by 87 patients.

A valid and reliable questionnaire was used to assess symptoms in 87 HIV patients with characteristics as in **Table 1**.

Table 1. Characterictics of Study Subjects.

Variables, n (%)	Frequency (n = 87)
Gender	
Man	64 (73,6)
Woman	23 (26.4)
Age, average (SD)	38.91 (8.63)
Education	
Low	10 (11.5)
Middle class	40 (46.0)
High	37 (42.5)
Income	
< Regional Minimum Wage	30 (345)
> Regional Minimum Wage	57 (65.5)
Marital status	
Married	45 (51.7)
Unmarried	42 (48.3)
CD4 , mean (SD)	464.80 (320.23)
Hospitalization in 3 months	
Yes	5 (5.7)
No	82 (94.3)
Viral load	
Detected	18 (20.68)
Undetected	40 (45.97)
no data	29 (33.33)
ARV therapy	
1st line	77 (88.5)
2nd line(with a protease inhibitor)	10 (11.5)
Risk factors for transmission	
Syringes	34 (39.1)
Homosexual	17 (19.5)
Free sex (Heterosexual)	31 (35.6)
Do not know	2 (2.3)
No answer	3 (3.4)

Language and Culture Adaptation

In the pre analysis of language and culture adaptation, the final language and cultural adaptation of the HIV Index Symptoms questionnaire into Indonesian. (**Table 2**)

Tests for the reliability and validity of the HIV Symptom Index questionnaire was done on 20 subjects with good results (cronbach alpha > 0.7). Results can be seen in **Table 3**.

Test the Reliability and Validity of the HIV Symptom Index

The internal validity test of the HIV Symptom Index shows a good correlation (r> 0.4) between each item with a domain score, and an optimal correlation (r> 0.8) between domain scores and total scores. Results can be seen in **Table 4**.

Table 2. Indonesian version of HIV Symptom Index.

Indeks Simtom HIV	
Nama Pasien	*Usia*
Nomer Rekam Medis	*Tanggal*
Nomer Protokol	*Kode*

Instruksi : Jawablah pertanyaan berikut dengan membubuhkan tanda centrang (√) pada jawaban yang dianggap paling tepat.

A. Pertanyaan-pertanyaan di bawah ini berkaitan dengan simtom/keluhan-keluhan yang pernah saudara alami dalam 4 minggu terakhir. Mohon berikan tanda centang (√) pada lingkaran yang paling sesuai selama saudara mengalami masing-masing keluhan tersebut.

(pilih salah satu √)		***SAYA TIDAK MEMILIKI KELUHAN INI***	***SAYA MEMILIKI KELUHAN INI DAN KELUHAN INI***			
			tidak mengganggu saya	***Sedikit mengganggu saya***	***Mengganggu saya***	***Sangat mengganggu saya***
1	*Kelelahan atau kurang energi?*	□	□	□	□	□
		0	1	2	3	4
2	*Demam, menggigil, atau berkeringat?*	□	□	□	□	□
		0	1	2	3	4
3	*Pusing atau kliyengan?*	□	□	□	□	□
		0	1	2	3	4
4	*Nyeri, mati rasa, atau kesemutan di tangan atau kaki?*	□	□	□	□	□
		0	1	2	3	4
5	*Kesulitan mengingat?*	□	□	□	□	□
		0	1	2	3	4
6	*Mual atau muntah?*	□	□	□	□	□
		0	1	2	3	4
7	*Diare atau sulit buang air besar?*	□	□	□	□	□
		0	1	2	3	4
8	*Merasa sedih, putus asa, atau depresi?*	□	□	□	□	□
		0	1	2	3	4
9	*Merasa cemas atau gelisah?*	□	□	□	□	□
		0	1	2	3	4
10	*Tidak bisa tidur atau mudah terbangun?*	□	□	□	□	□
		0	1	2	3	4
11	*Masalah pada kulit, seperti kemerahan, kering, atau gatal-gatal?*	□	□	□	□	□
		0	1	2	3	4
12	*Batuk-batuk atau sulit bernafas?*	□	□	□	□	□
		0	1	2	3	4
13	*Sakit kepala?*	□	□	□	□	□
		0	1	2	3	4
14	*Hilang nafsu makkan atau perubahan cita rasa makanan yang dikonsumsi?*	□	□	□	□	□
		0	1	2	3	4

(pilih salah satu √)		*SAYA TIDAK MEMILIKI KELUHAN INI*	*SAYA MEMILIKI KELUHAN INI DAN KELUHAN INI*			
			tidak mengganggu saya	*Sedikit mengganggu saya*	*Mengganggu saya*	*Sangat mengganggu saya*
15	*Perut kembung, nyeri perut, atau gas dalam lambung?*	□	□	□	□	□
		0	1	2	3	4
16	*Nyeri pada otot atau tulang/sendi?*	□	□	□	□	□
		0	1	2	3	4
17	*Masalah seksual, seperti kehilangan hasrat, impoten, atau sulit mencapai kepuasan seksual*	□	□	□	□	□
		0	1	2	3	4
18	*Perubahan bentuk tubuh seperti penumpukan lemak atau bertambah berat badan?*	□	□	□	□	□
		0	1	2	3	4
19	*Berat badan menurun atau menjadi kurus?*	□	□	□	□	□
		0	1	2	3	4
20	*Rambut rontok atau kusam?*	□	□	□	□	□
		0	1	2	3	4

Table 3. Reliability Test Results with Cronbach Alpha.

	Cronbach alpha
Mental domains	0.842
Physical domains	0.878
Mental domain / physical-total score	0.760

Table 4. Internal Validity Test Results.

	Internal Validity Test	
	Correlation coefficient	p
Mental Domain - total score	0.871	<0.001
Physical Domain - total score	0.865	<0.001

Profile of Symptoms of HIV Patients

Symptoms of HIV Patients as measured by the HIV Symptom Index can be seen in **Table 5**.

The five symptoms most experienced by subjects were fatigue (55.7%), dizziness / keliyengan (43.3%), sleep disorders (43.3%), skin problems (42.3%), and pain, numbness , or tingling in the hands and feet (39.2%). The most moderate-to-severe symptoms (score 3-4) were the skin disorders (13.4%), dizziness (10.3%) and headaches (10.3%). The most disturbing symptoms with the most intensity are hair loss or dullness (6.2%), headache (5.2%) and skin problems (5.2%).

DISCUSSION

Average of subject's ages is 38.78 years, and male sex proportion is 72,9%. These findings are comparable to data from the Republic of Indonesia Ministry of Health in 2018, where the highest presentation of HIV infection was at the age of 25-49 years at 70.2%, and proportion of male to female HIV sufferers are 2: 1.[11]

Interesting data can be seen in the patient's income and education status. 67.1% of the subjects had income above the regional minimum wage, and 88.3% of the subjects had a secondary education level. This is quite different from other studies which show that patients with low education levels tend to have a higher risk of experiencing HIV. Even the research by Nokes et al illustrates that 75% of HIV sufferers in their study did not have jobs.[12,13]

Most risk factors for HIV transmission are through needles (39.1%), followed by heterosexual (35.6%) and homosexuals (19.5%). This finding is in contrast with the

Table 5. Symptoms of Subjects Based on HIV Symptom Index.

Symptoms	Symptoms severity (n = 8 7) *				
	0	1	2	3	4
Fatigue or loss of energy, n (%)	43 (44.3)	22 (22,7)	22 (24,7)	6 (6.2)	2 (2,1)
Fever, chills, or sweating, n (%)	82 (84.5)	10 (10.3)	2 (2,1)	2 (2,1)	1 (1,0)
Dizziness or lightheadedness, n (%)	55 (56,7)	18 (18,6)	12 (12.4)	6 (6.2)	4 (4,1)
Pain, numbness or tingling, n (%)	59 (60.8)	17 (17,5)	12 (12.4)	7 (7.2)	2 (2,1)
Trouble remembering, n (%)	61 (62,9)	23 (23,7)	8 (8.2)	4 (4,1)	1 (1,0)
Nausea or vomiting, n (%)	77 (79.4)	12 (124)	3 (3,1)	3 (3,1)	2 (2,1)
Diarrhea or loose bowel movement, n (%)	76 (78.4)	17 (17,5)	4 (4,1)	0	0
Sad, down, or depressed, n (%)	73 (75.3)	13 (13.4)	8 (8.2)	1 (1,0)	2 (2,1)
Nervous or anxious, n (%)	66 (68.0)	13 (14.4)	12 (12.4)	2 (2,1)	3 (3,1)
Difficulty falling or staying asleep, n (%)	55 (56,7)	22 (22,7)	11 (11,3)	5 (5,2)	4 (4,1)
Skin problems, n (%)	56 (57.7)	17 (17,5)	11 (11,3)	8 (8.2)	5 (5,2)
Cough or difficulty breathing, n (%)	77 (79.4)	12 (12.4)	3 (3,1)	1 (1.0	4 (4,1)
Headache, n (%)	60 (61,9)	15 (15,5)	12 (12.4)	5 (5,2)	5 (5,2)
Loss of appetite, n (%)	74 (76.3)	13 (13.4)	4 (4,1)	3 (3,1)	3 (3,1)
Bloating, pain or gas in stomach n (%)	67 (69,1)	17 (17,5)	8 (8.2)	3 (3,1)	2 (2,1)
Muscle aches or joint pain, n (%)	63 (64,9)	16 (16,5)	12 (12.4)	3 (3,1)	3 (3,1)
Sexual problems, n (%)	69 (71,1)	10 (10.3)	14 (4,4)	4 (4,1)	0
Body shape changes, n (%)	64 (66.0)	20 (20,6)	7 (7.2)	4 (4,1)	2 (2,1)
Weight loss or wasting, n (%)	72 (74.2)	14 (14.4)	5 (5,2)	2 (2,1)	4 (4,1)
Hair loss or changes, n (%)	72 (74.2)	12 (12.4)	6 (6.2)	1 (1,0)	6 (6.2)

* the severity of symptoms is expressed on a scale:

0 = No symptoms
1 = Has symptoms but does not interfere
2 = Has symptoms and is a little annoying
3 = Having symptoms and disturbing
4 = Has symptoms and is very disturbing

report of the Indonesian Ministry of Health in 2018 where the use of non-sterile syringes was only 8.6% of the risk factors for HIV infection, and the majority were heterosexual (70.2%).[11]

This study was intended for outpatients who had received ARV therapy, the majority of the study subjects (71%) were at the WHO clinical stage 1. This was in accordance with the CD4 value where 74.7% of the study subjects had CD4 levels above 200. Most (79.32%) research subjects also had undetectable levels of viral load.

The HIV symptom index questionnaire detects more symptoms in patients than routine evaluation with history taking. By filling out the questionnaire 90.8% of patients had at least one complaint, albeit not disturbing. With history taking, only 20.6% of patients had complaints. This finding is in accordance with a previous study by Justice et al in 1999, where symptomatic surveys filled by patients were more sensitive than symptom surveys asked by health workers.[7,8] Several factors can explain these findings, the first routine evaluation by the doctor uses more open questions, while on the questionnaire every important symptom is asked in private.Second, during interviews with doctors, patients cannot remember and convey all the symptoms they experience, not only when they meet with a doctor but daily complaints that are felt at home, especially if the complaints felt by patients are relatively mild or do not interfere with daily activities. Third, doctors tend to ignore complaints that are not considered important, and some doctors still have a discriminatory feeling towards people with HIV who tend to underestimate some of the patient's complaints because they think the patient deserves the the symptoms and condition.[7,8,13,14]

Based on clinical symptoms obtained from the Indonesian version of HIV Symptom Index, 5

most common symptoms were fatigue (55.7%), sleep disturbances (43.3%), dizziness (42.3%), skin problems (42.3%), and pain, numbness or tingling in the hands or feet (39.2%). Among these symptoms the most disturbing intensity was skin problems (13.4%), dizziness (10.3%), and headache (10.3%). These complaints can be caused by various mechanisms. Fatigue can be caused by direct HIV infection, opportunistic infections, malnutrition, depression, or side effects of ARV drugs. Dizziness can be caused by encephalitis, HIV infection, or ARV side effects. Sleep disorders can be caused by depression, anxiety, encephalopathy, or ARV side effects. Skin problems can be caused by HIV infection, opportunistic infections, malnutrition, or sexually transmitted diseases. Pain, numbness, tingling can be caused by HIV infection, ARV side effects or TB treatment, diabetes mellitus, aging, alcohol consumption.[15-18] If further analyzed, opportunistic infections were only experienced by 11.34% of patients, mostly only candidiasis, and all patients had received appropriate therapy. Patients with TB treatment were only 9%, and had received vitamin B6 supplements. Encephalitis is only experienced by 3.4% of patients. HIV infection in more than 70% of patients has improved, CD4 values of less than 200 are only found in 25.3% of patients, and viral load is still detected in only 20.58% of patients. Sad/depressed complaints were only experienced by 24.7% of patients, anxiety was only experienced by 32% of patients and 14.4% did not interfere. Based on these data, it is likely that these complaints were caused by side effects of ARV drugs.[17] Fatigue can be caused by the use of zidovudine and efavirenz, sleep disturbances and dizziness can be caused by efavirenz, emtricitabine, indinavir, dolutegavir.[17,18] Pain, numbness and tingling can be caused by the use of zidovudine and lamivudine.[17] The few complaints that the patients complained were fever (15.5%), cough (20.6%), nausea (21.6%), diarrhea (21.6%). Symptoms of fever, cough, and diarrhea are most often caused by opportunistic infections, because the subjects in this study had received ARV therapy and therapy for opportunistic diseases, those complaints appeared less. This has similarities with the first study using HIV Symptom Index by Justice et al, in which the most common symptoms and the most disturbing are fatigue, pain, and muscle pain.[5]

In this study there were several symptoms that showed a large enough difference between men and women. In men there are more complaints of fever, cough, and diarrhea. These symptoms are mostly caused by opportunistic infections. In addition, in men also more complaints of weight loss and loss of appetite, which may be caused by HIV-related symptoms. The cause of these findings is the difference in pathogenesis and immunological response to HIV infection between men and women. In women, activation of CD8 + T lymphocyte cells is higher than that of men, besides that the expression of interferon is also higher in women. Women tend to have lower levels of HIV viral load in the early phase of infection.[19] Women are more likely to have viral control phenotypes than men.[19] A meta-analysis by Hongbo Jiang et al.[20] also showed that women were less likely to experience advance case of HIV infection and late presentation than men. Responses to ARV therapy differ between sexes, where women tend to experience better CD4 cell gains.[20]In addition, more men smoke cigarettes, which may increase coughing complaints. In women there are more complaints of disorders of the hair, skin problems, body shape disorders. These complaints are more experienced by women, perhaps because psychologically women are more concerned with their appearance.[19] In addition, women also complain more about dizziness, headache, and joint pain. One that might cause this is the pain threshold in women is lower than that of men. The difference was not due to differences in clinical stage, CD4 level, viral load, or ARV therapy, in the two groups there was no significant difference ($p > 0.05$).

CONCLUSION

Patients with detectable viral load had a higher percentage of complaints on all symptoms compared to the group of patients with an undetectable viral load. This is consistent with the pathophysiology of HIV/ AIDS where viral load usually becomes undetectable as the treatment progresses and the patient's CD4

increases. Similar results were obtained by the studies of Justice et al and Muhammad et al who showed symptoms and patients' quality of life was worse in patients who had a detectable viral load.[9,10] Indonesian version of HIV symptom Index is reliable and valid to measure symptoms of HIV/AIDS patients. Most frequent symptoms are fatigue or weakness, dizziness or lightheadedness, insomnia, skin problems, and pain, numbness, or tingling in the hands or feet. Further investigation should provide better solution for those symptoms in terms of causality.

REFERENCES

1. Ortblad KF, Lozano R, Murray CJL. The burden of HIV: Insights from the global burden of disease study 2010. AIDS. 2013;27(13):2003–17.
2. WHO 2014. WHO - The top 10 causes of death . Fact sheet N°310 (Updated May 2014). 2014. Available on: http://www.who.int/mediacentre/factsheets/ fs310/en/ pada 10 Oktober 2017.
3. World Health Organization. Prevalence of HIV among adults aged 15-49 (%). 2013. Available on: http://www.who.int/gho/hiv/epidemic_status/ prevalence/en/ pada 10 Oktober 2017.
4. UNAIDS. Global AIDS Update 2016. World Health Organization . 2016; March:422. Available on: http://www.unaids.org/sites/default/files/ media_asset/ UNAIDS_Gap_report_en.pdf pada 15 Oktober 2017
5. Justice AC, Holmes W, Gifford AL, et al. Development and validation of a self-completed HIV symptom index. J Clin Epidemiol. 2001;54-12.1.
6. Whalen CC, Antani M, Carey J, Landefeld CS. An index of symptoms for infection with human immunodeficiency virus: reliability and validity. J Clin Epidemiol. 1994;47(5):537–46.
7. Justice AC, Chang CH, Rabeneck L, Zackin R. Clinical importance of provider-reported HIV symptoms compared with patient-report. Med Care. 2001;39(4):397–408.
8. Justice AC, Rabeneck L, Hays RD, Wu AW, Bozzette SA, Group OC of the ACT. Sensitivity, specificity, reliability, and clinical validity of provider-reported symptoms: a comparison with self-reported symptoms. J Acquir Immune Defic Syndr. 1999;21: p. 126–33.
9. Sastroasmoro S, Ismael S. Dasar-dasar metodologi penelitian klinis. Jakarta: Sagung Seto; 2011. p. 25–32.
10. Muhammad NN, Shatri H, Djoerban Z, Abdullah M. Validity and reability test of indonesian version of world health the quality of life patients with HIV/AIDS Uji Kesahihan dan Keandalan Kuesioner World Health Organization Quality of Life-HIV Bref dalam Bahasa Indonesia untuk Mengukur Kualitas Hidup Pa. J Penyakit Dalam Indones. 2017;4(3):112–8.
11. Ditjen P2P Kementrian Kesehatan RI. Laporan situasi perkembangan HIV-AIDS dan PIMS di indonesia 2018. Jakarta: Dirjen P2P Kemenkes; 2018. p. 1.
12. Nokes KM, Kendrew J, Rappaport A, Jordan D, Rivera L. Development of an HIV educational needs assessment tool. J Assoc Nurses AIDS Care. 1997;8(6):46–51.
13. Murri R, Fantoni M, Borgo C Del, Visona R, Barracco A, Zambelli A. Determinants of health-related quality of life in HIV-infected patients. AIDS Care. 2010;15:4:581–90.
14. Kilbourne AM, Justice AC, Rollman BL, et al. Clinical importance of HIV and depressive symptoms among veterans with HIV infection. J Gen Intern Med. 2002;17(7):512–20.
15. Maartens G, Celum C, Lewin SR. HIV infection: Epidemiology, pathogenesis, treatment, and prevention. Lancet. 2014;384(9939):258–71.
16. Agustriadi O, Sutha IB. Aspek pulmonologis infeksi oportunistik pada infeksi HIV/AIDS. J Peny Dalam. 2008;9(3):233–44.
17. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet. 2000;356(9239):1423–30.
18. Ammassari A, Murri R, Pezzotti P, et al. Self-reported symptoms and medication side-effects influence adherence to highly active antiretroviral therary in persons with HIV infection. Vol. 28, JAIDS. 2001. 445–9.
19. Scully EP. Sex differences in HIV infection. Curr HIV/AIDS Rep. 2018;15(2):136-46.
20. Jiang H, Yin J, Fan J, Zhang Z, Liu L, Nie S. Gender difference in advance HIV disease and late presentation according to European consensus definition. Sci Rep. 2015: 5 (1453).