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Cognitive impairment among HIV-infected adults on antiretroviral therapy in Indonesia

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Abstract

Introduction: Human immunodeficiency virus (HIV) infection and its related complications remain a health problem in developing countries. Cognitive impairment is a complication of HIV infection and is often undetected. Untreated cognitive impairment can lead to decreased quality of life. This study aimed to determine the prevalence of cognitive impairment among HIV-infected patients and its associated risk factors.

Material and methods: A cross-sectional study was conducted at Wahidin Sudirohusodo Hospital Makassar Indonesia, from October to December 2020. It involved 93 HIV outpatients aged 18-59 years. Cognitive impairment was determined by the Montreal cognitive assessment (MoCA) test. Blood samples were taken for CD4, anti-HCV, and routine blood tests. Nadir (lowest ever) CD4 and antiretroviral therapy (ART) information were obtained from patient medical records. Data were analysed using SPSS version 22. The statistical tests used were the chi-square test and multiple logistic regression.

Results: Cognitive impairment was found in 47.3% of subjects. Bivariate analysis found a significant relationship between age 41-59 years (p = 0.025), nadir CD4 count < 200 cells/µl (p = 0.001), and anaemia (p = 0.04) with cognitive impairment. Multivariate analysis showed that the most significant factors associated with cognitive impairment were nadir CD4 count < 200 cells/µl (OR 4.4; 95% CI: 1.75-11.17) and age 41-59 years (OR 3.0; 95% CI: 1.01-8.73).

Conclusions: The prevalence of cognitive impairment was found to be high in HIV-infected adults receiving ART. Low nadir CD4 count (40 years old) was identified as a risk factor associated with impaired cognitive function.

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Key words: HIV, AIDS, cognitive impairment, MoCA, HAND.

Introduction

The advent of effective combination antiretroviral therapy (CART) has revolutionized the treatment of human immunodeficiency virus (HIV) and led to dramatic reductions in the incidence and prevalence of acquired immune deficiency syndrome (AIDS)-related illnesses [1]. These advances have transformed HIV from a deadly disease into controlled infection with a near-normal life expectancy [2]. However, various health issues related to HIV are still prevalent in the CART era, one of which is cognitive impairment.

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The prevalence of cognitive impairment among people living with HIV was estimated at 20-50%, despite effective CART [3-7]. Cognitive impairment may lead to limitations in daily activities, increased unemployment, depression, social isolation, and eventually reduced the quality of life [1].

Two main processes are thought to cause neuronal injury that underlies HIV-associated neurocognitive disorder (HAND) pathogenesis: direct neurotoxicity by HIV and/or its viral proteins, and, more importantly, indirect neuronal damage through neuroinflammation, the so-called 'bystander effect' [8]. The damaged neurons may not fully recover, and leave a legacy effect [1]. Cognitive impairment in HIV patients was associated with various factors such as ageing [9], low education [3], nadir (lowest ever) CD4 cell count < 200 cells/µl [10], hypertension [11], hepatitis C co-infection [12], low central nervous system penetration effectiveness (CPE) of CART [13], and efavirenz use [14].

The assessment of cognitive function using standard neuropsychological test batteries is difficult to apply with limited resources. Meanwhile, Montreal Cognitive Assessment (MoCA) is a simple cognitive test that has been widely used in daily practice. Several studies have reported that MoCA has good sensitivity to detect cognitive impairment in HIV patients [15, 16]. Cognitive function tests have not been routinely performed at HIV clinics in Indonesia, so cognitive impairment often goes undetected. A study conducted at a national referral hospital in Jakarta reported that around 51% of Indonesia HIV-naive patients with low CD4 cells count (< 200 cells/µl) had HAND, where lower education was associated with lower neurocognitive performance [17]. A further observational study reported that cognitive improvement among Indonesia HIV patients after beginning ART was influenced by age, education, and CD4 cell count [18]. This study aimed to determine the prevalence and associated factors of cognitive impairment among HIV patients on ART in Makassar, an eastern region of Indonesia.

Material and methods

Study design

This was a cross-sectional study conducted at the HIV outpatient clinic of Wahidin Sudirohusodo Hospital, Makassar, Indonesia, the regional referral hospital in eastern Indonesia, from October to December 2020.

Participants

Participants were recruited by a consecutive sampling method from HIV outpatients. The inclusion criteria were HIV-infected adults aged 18-59 years, who had received ART for at least 6 months, and signed research informed consent form. The exclusion criteria were participants who had a history of the following medical conditions: stroke, severe central nervous system infection, severe head injury, brain tumours, and psychiatric disorders.

The study protocol was approved by the Health Research Ethics Commission of Hasanuddin University, Medical Faculty, following the ethical recommendations with approval letter number 679/UN4.6.4.5.31/PP36/2020.

Data collection

Cognitive assessment was performed by a single physician (corresponding author) using the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina) supervised by a psychiatrist involved in this study. The assessment steps strictly followed the MoCA test administration and scoring instructions. Participants were considered to have cognitive impairment if the total MoCA score was < 26. Demographic data (age, sex, education level) were obtained from interviews. The level of education was divided into 2 groups: those with formal education < 12 years (senior high school graduates and below) and those with > 12 years (diploma or university graduates). All participants were asked about a history of hypertension and underwent blood pressure measurements. Blood samples were taken for CD4, anti-HCV, and routine blood tests. Nadir (lowest ever) CD4 and antiretroviral therapy (ART) information were obtained from patient medical records. Anaemia was confirmed when haemoglobin (Hb) < 13 g/dl in males and < 12 g/dl in females. The CPE scoring of CART refers to the revised CPE ranking by Letendre *et al.* [19]. A regimen with a total score of < 7 is considered to have low penetration in the central nervous system, while a score of > 7 is considered to be highly penetrant [20].

Data analysis

Data analysis was performed using SPSS version 22. The statistical tests used were the $\chi 2$ test and multiple logistic regression. The results were considered significant if the p-value was < 0.05.

Results

This study included 93 HIV outpatients who met the study criteria. Baseline characteristics are shown in Table 1. Most of the participants were male (74.2%), aged 18-40 years (76.3%), and had formal education < 12 years (57%). A total of 59.1% of participants had nadir CD4 count < 200 cells/µl. Nearly all participants (95.7%) had current CD4 count ≥ 200 cells/µl. Hypertension, hepatitis C, and anaemia were found in 3.2%, 4.3%, and 12.9% of participants, respectively. The antiretroviral consumed by the majority of the participants had a CPE score < 7 (92.5%) and contained efavirenz (86%). Cognitive impairment was found in 44 (47.3%) participants. Bivariate analysis (Table 2) found a significant relationship between age 41-59 years (p = 0.025), nadir CD4 count < 200 cells/µl (p = 0.001), and anaemia (p = 0.04) with cognitive impairment. Multivariate analysis (Table 3) showed that the most significant factors associated with

Table 1. Baseline characteristics

Variable	*n* (%)
Sex	
Male	69 (74.2)
Female	24 (25.8)
Age (years)	
18-40	71 (76.3)
41-59	22 (23.7)
Education (years)	
> 12	40 (43.0)
≤ 12	53 (57.3)
Nadir CD4 (cells/µl)	
< 200	55 (59.1)
≥ 200	38 (40.9)
Current CD4 (cells/µl)	
< 200	4 (4.3)
≥ 200	89 (95.7)
Hepatitis C	
No	89 (95.7)
Yes	4 (4.3)
Anaemia	
No	81 (87.1)
Yes	12 (12.9)
Hypertension	
No	90 (96.8)
Yes	3 (3.2)
CPE score	
High (> 7)	7 (7.5)
Low (≤ 7)	86 (92.5)
Efavirenz use	
No	13 (14.0)
Yes	80 (86.0)
Cognitive function (MoCa score)	
Normal (≥ 26)	49 (52.7)
Impaired (< 26)	44 (47.3)

Table 2. Bivariate analysis

Variable	Cognitive function		Total (*N* = 93)	*p*-value
	Impaired, *n* = 44 (47.3%)	Normal, *n* = 49 (52.7%)		
Sex, *n* (%)				
Male	32 (46.4)	37 (53.6)	69 (74.2)	0.759
Female	12 (50.0)	12 (50.0)	24 (25.8)	
Age (years), *n* (%)				
18-40	29 (40.8)	42 (59.2)	71 (76.3)	**0.025**
41-59	15 (68.2)	7 (31.8)	22 (23.7)	
Education (years), *n* (%)				
> 12	16 (40.0)	24 (60.0)	40 (43.0)	0.220
≤ 12	28 (52.8)	25 (47.2)	53 (57.3)	
Nadir CD4 (cells/µl), *n* (%)				
< 200	34 (61.8)	21 (38.2)	55 (59.1)	**0.001**
≥ 200	10 (26.3)	28 (73.7)	38 (40.9)	
Current CD4 (cells/µl), *n* (%)				
< 200	3 (75.0)	1 (25.0)	4 (4.3)	0.257
≥ 200	41 (46.1)	48 (53.9)	89 (95.7	
Hepatitis C, *n* (%)				
No	43 (48.3)	46 (51.7)	89 (95.7)	0.361
Yes	1 (25.0)	3 (75.0)	4 (4.3)	
Anaemia, *n* (%)				
No	35 (43.2)	46 (56.8)	81 (87.1)	**0.040**
Yes	9 (75.0)	3 (25.0)	12 (12.9)	
Hypertension, *n* (%)				
No	43 (47.8)	47 (52.2)	90 (96.8)	0.622
Yes	1 (33.1)	2 (66.7)	3 (3.2)	
CPE score, *n* (%)				
High (> 7)	3 (42.9)	4 (57.1)	7 (7.5)	0.806
Low (≤ 7)	41 (47.7)	45 (52.3)	86 (92.5)	
Efavirenz use, *n* (%)				
No	3 (23.1)	10 (76.9)	13 (14.0)	0.059
Yes	41 (51.2)	39 (48.8)	80 (86.0)	

Table 3. Multivariate analysis

Step	Variable	B	S.E.	Wald	*p*	OR	95% CI for OR	
							Lower	Upper
1	Age 41-59	1.133	0.558	4.121	0.042	3.1	1.04	9.27
	Nadir CD4 < 200	1.381	0.479	8.304	0.004	4.0	1.56	10.17
	Anaemia	1.156	0.754	2.353	0.125	3.2	0.73	13.93
	Constant	–5.991	1.906	9.875	0.002	0.0		
2	Age 41-59	1.089	0.550	3.929	**0.047**	**3.0**	1.01	8.73
	Nadir CD4 < 200	1.487	0.472	9.914	**0.002**	**4.4**	1.75	11.17
	Constant	–3.886	1.220	10.146	0.001	0.0		

B – coefficient, S.E. – standard error of the coefficient. Wald – [B/S.E.]², OR – odds ratio, CI – confidence interval

cognitive impairment were nadir CD4 count < 200 cells/µl (OR 4.4; 95% CI: 1.75-11.17) and age 41-59 years (OR 3.0; 95% CI: 1.01-8.73).

Discussion

We found that nearly half (47.3%) of participants had cognitive impairment based on the MoCA test. Several studies have also reported a high prevalence of cognitive impairment in HIV patients, ranging from 20 to 50% [3-7]. We found a significant relationship between age and cognitive function, where participants aged > 40 years had a 3 times greater risk of experiencing cognitive impairment than participants aged < 40 years. The relationship between age and cognitive decline in HIV patients has been previously reported. Yitbarek *et al.* in Ethiopia reported that age > 40 years was significantly associated with cognitive impairment in HIV patients [9]. Chan *et al.* in Singapore also reported an association between age and cognitive impairment in HIV patients. The cognitively impaired group was significantly older (mean age 54.4 years) than those without cognitive impairment (mean age 43.45 years) [21]. Aging has been recognized as a risk factor for cognitive decline in the general population, but in HIV patients this decline occurs earlier, which raises the suspicion of premature cognitive aging in HIV patients. A study with a community sample of well-treated HIV-positive participants with low historical AIDS vs. comparable HIV-negative controls has demonstrated evidence of premature cognitive aging in HIV patients. That study reported that neurocognitive performance deteriorated with increasing age at a significantly higher rate among HIV-positive than among HIV-negative participants. A potential explanation for premature cognitive aging in HIV includes chronic immune activation and immune senescence. There is evidence of chronic neuroimmune activation and associated neuroinflammation despite successful CART and viral suppression. Altogether, aging and HIV may lead to brain damage via excitotoxicity, mitochondrial dysfunction, and oxidative stress [22].

This study also found a significant relationship between low nadir CD4 and cognitive impairment. Two studies have previously reported that in the CART era, cognitive impairment was associated with low nadir CD4 cell counts [10, 23]. A severe immunodeficiency is associated with high viral load in cerebrospinal fluid and severe neuronal injury [24]. The legacy effects from the previous neuronal damage may explain why cognitive impairment is still prevalent in HIV patients who have a history of severe immunodeficiency, despite their infection status being currently under control with ART [1].

Although the bivariate analysis found anaemia as a factor associated with cognitive impairment, the multivariate analysis showed that it was not a significant factor. Several studies have found anaemia as an independent risk factor for cognitive impairment in HIV patients [6, 25]. Cognitive impairment in anaemia is associated with impaired neuronal function due to a decrease in the number of erythrocytes and their oxygen-carrying capacity [26].

This study did not find a significant relationship between hypertension and cognitive impairment. In the era of CART, cardiovascular risk factors have been associated with cognitive impairment in HIV patients [11]. The prevalence of hypertension in this study was quite small because the majority of participants were still young (< 40 years), while as we know hypertension is more common in older age. Hepatitis C co-infection has been reported to be associated with an increased risk of cognitive impairment in HIV patients [12, 27]. This study did not find a significant relationship between hepatitis C co-infection and cognitive impairment. This result was following Almeida *et al.*, who reported that there was no significant difference in the occurrence of cognitive impairment between HIV mono-infected and HIV-HCV co-infected patients [28]. Meanwhile, the number of participants with hepatitis C and hypertension in this study were relatively small. Further studies with a larger number of participants and different designs may be needed to determine the effects of hypertension and hepatitis C on cognitive function in HIV patients.

Use of CART with low CPE scores (< 7) and those containing efavirenz was not associated with cognitive impairment in this study. Most of the participants were taking ART consisting of tenofovir, lamivudine, and efavirenz (total CPE score = 6), as these first-line drugs are administered in fixed-dose combination tablets. Several studies reported conflicting results regarding the association between the CPE score of ART and cognitive function. Smurzynski *et al.* reported that ART with a high CPE score was associated with better cognitive function in HIV patients [13]. Cross *et al.* reported that ART improved cognitive function in HIV patients, and there was no significant difference between low and high CPE score groups [20]. Kahouadji *et al.* instead reported that ART with a high CPE score was associated with poorer executive functioning [29]. Long-term use of efavirenz has been associated with risk of cognitive impairment [14, 30]. However, this is still controversial because other studies have reported that long-term use of efavirenz was not associated with neurocognitive impairment [5, 31]. Our study supports the use of a regimen containing efavirenz as first-line ART in Indonesia.

Conclusions

The prevalence of cognitive impairment was found to be high in HIV-infected adults receiving ART. Low nadir (lowest ever) CD4 count (< 200 cells/µl) and older age (> 40 years old) were identified as risk factors associated with impaired cognitive function. Cognitive function tests should be performed routinely in HIV-infected patients, and those with cognitive impairments should receive early intervention to prevent further deterioration.

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Conflict of interest

The authors declare no conflict of interest.

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