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NEUROCOGNITIVE IMPAIRMENT IN HIV/AIDS: A CONCEPTUAL FRAMEWORK

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Abstract
HIV-associated with neurocognitive disorder (HAND) is a major interest issues worldwide, as results from introduction of Highly Active Antiretroviral Therapy (HAART) and increasing life expectancy. However, previous studies have been limited by lack of a guiding framework. The purpose of this review was to provide a conceptual framework to guide studies of neurocognitive impairment in patients with HIV/AIDS. A literature search was conducted of articles published from 1998 through December 2015 using the PubMed, Embase, Cochrane Library and Ebscohost databases on evaluating the problem of neurocognitive impairment in HIV. This search resulted in a total of 36 articles. Evidence has indicated that there are neurobiological changes and brain abnormalities among people living with HIV/AID, which may affect cognitive functioning. Being infected by HIV and increased age are independently factors on HAND. However, there is remaining unclear the effect of HAART, is protective factors or risk factors of HAND and its consequence on quality of life among patients with HIV/AIDS. Considering the major issues in above, patient with HIV/AIDS is vulnerable population for developing HAND that might have been resulted to under report. Future studies focus on exploring HAND is necessary especially from low income countries where the accessibility to HAART are limited.

Keywords: HIV; AIDS; neurocognitive impairment; review

INTRODUCTION

HIV/AIDS is global burden disease affected more than 36.9 million people worldwide in 2014 (UNAIDS, 2015). The number of people living with HIV/AIDS was increased from previous years since more people (>15 million) are receiving highly active antiretroviral therapy (HAART) (UNAIDS, 2015). The mortality in AIDS patients is declining from 2.3 million in 2005 to 1.2 million in 2014 (UNAIDS, 2015). Successful of HAART had impact on prolonged life expectancy from 36.1 to 49.4 years at age 20 years (Hogg, 2008).

With the prolong life expectancy, patients with HIV/AIDS reported higher proportion of mild neurocognitive impairment (MCI) ranged from 7% to 70% and predicted to be continue increased either in developing or developed country (Attonito, Devieux, Lerner, Hospital,

& Rosenberg, 2014; Cohen et al., 2010; Fazeli et al., 2014; Meade, Towe, Skalski, & Robertson, 2015; Nakku, Kinyanda, & Hoskins, 2013; Yusuf et al., 2014; T. Zhao et al., 2015). Brain imaging studies confirmed the widespread of brain regions atrophy, which included the bilateral pallidum, left putamen, right inferior thalamus and inferior hippocampus (Janssen et al., 2015; Wade et al., 2015). Previous studies found HIV affected the impairment in global cognitive function, processing speed, memory, executive function, and working memory (Fellows, Byrd, & Morgello, 2014 2012; Fialho et al., 2015; Mayston et al., 2015; Meade et al., 2015).

Although several studies have documented neurocognitive impairment in patients with HIV/AIDS, but previous studies have been limited by lack of a guiding framework. As result, there is inability to gain comprehensive knowledge about potential etiologies, other contributing factors and its impact in patients with HIV/AIDS. In previous studies, there is still unclear information about risk factors of neurocognitive impairment. Knowing this factor is important to identify profile at risk patients and to thereby design effective intervention to prevent patients from dementia. Therefore, the extent of the problem remains unclear because the types, frequency, and severity of neurocognitive impairment that have not been explained among patients with HIV/AIDS. The purpose of this study is to develop a conceptual model neurocognitive impairment in patients with HIV/AIDS.

METHODS

The proposed conceptual framework was developed from the theoretical and empirical literature of two content are (a) pathophysiology of HIV/AIDS; and (b) pathophysiology of neurocognitive impairment. The inclusion criteria for studies to be reviewed were: (a) case-control or cohort studies or descriptive studies; and (b) measures of brain structure and function in relationship to cognitive outcomes in HIV/AIDS.
A literature search was conducted of articles published from 1998 through December 2015 using the PubMed, Embase, Cochrane Library and Ebscohost databases on evaluating the problem of neurocognitive impairment in HIV. The key words used for the search: HIV, AIDS; neurocognitive impairment; cognitive impairments; memory impairments; HIV-associated neurocognitive disorder; HAND; aging; neuropsychological measures; magnetic resonance imaging; and combinations of these terms. The search was limited to studies published in the English language.

This search resulted in a total of 36 articles and text book of neuropsychological. Studies were reviewed other factors might contribute to MCI, including regiment and adherence to HAART, comorbidity and Hepatitis C virus (HCV), substance used, mood and depressive symptoms. Knowledge of these areas facilitated design of the model with relevant concepts and relationships.

RESULTS

Overview of the Conceptual Model

Neuroinflammation is proposed as the primary etiology of the neurocognitive impairment in HIV/AIDS (Hazleton, Berman, & Eugenin, 2010). The cognitive domains that most likely to be affected were verbal/learning, attention/working memory, memory (learning/recall), executive function, and psychomotor speed (Antinori et al., 2007). Age, HAART, comorbidity, substance abuse, and depression were factors that might explain or contribute to neurocognitive impairment in these patients. Additional potential contributory factors are incorporated in the model as covariates (sex and education). The protective factors for prevent progression of neurocognitive impairment are adherence to HAART, social support, and exercise (see **Figure 1**).

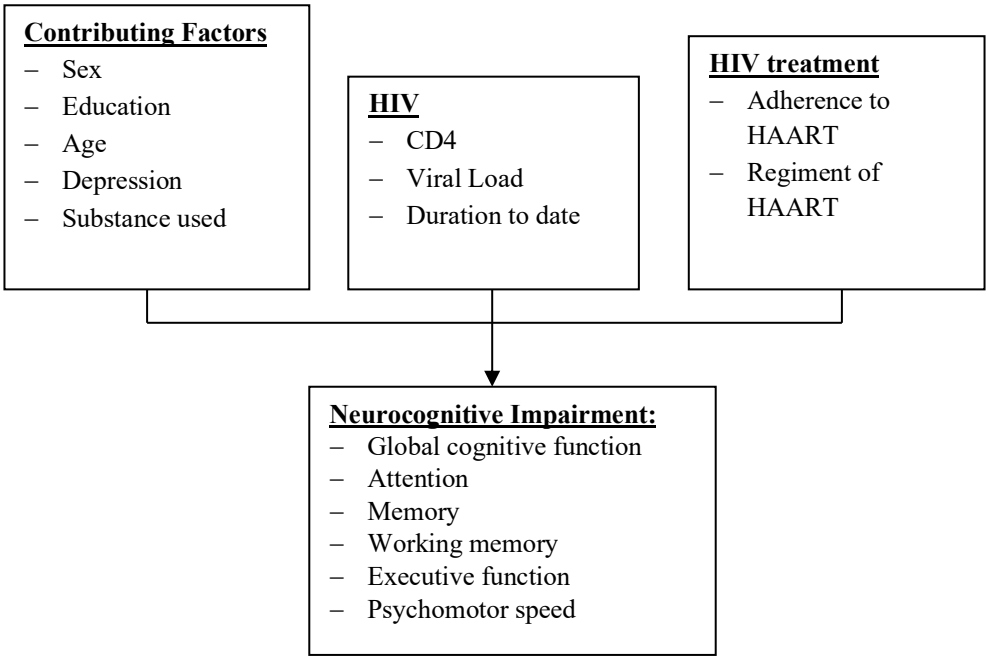

Figure 1 Conceptual framework of neurocognitive impairment in HIV/AIDS

Neurocognitive Impairment in HIV/AIDS

Cognitive function is defined as the ability to learn, retrain, and recall information; it is also reflecting a complexity of set intellectual function such as judgment and evaluation. The impairment in cognitive function is distinguished by impairment of memory at earlier, and or working memory, executive function, processing speed, and attention. In HIV, neurocognitive impairment is categorized as: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Antinori et al., 2007).

ANI is defined by performance at least 1 SD below the mean of demographically adjusted normative scores in at least two cognitive areas (attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory, including learning and recall, simple motor skills or sensory perceptual abilities); these criteria specify that at least five cognitive domains be examined or observed. Finally, the impairment does not occur solely as part of a delirium (i.e., a confusional state secondary to opportunistic CNS disease, vascular insult, metabolic derangement, drug effects, or other systemic disorders) and, as in all AAN criteria, the diagnosis is possible only if the cognitive impairment cannot be explained by other co morbidities (Antinori et al., 2007).

The MND defined by HNRC is similar to the MCMD previously defined by AAN but, in addition to criteria for asymptomatic neurocognitive abnormality, MND requires that there also be impairment in everyday functioning. Specifically, MND is defined by the following features: 1) an acquired mild-to-moderate impairment in cognitive function documented by a score of at least 1 SD below demographically corrected norms on tests of at least two different cognitive domains, 2) the cognitive impairment interferes, at least mildly, with activities of daily living, 3) the impairment does not meet criteria for delirium or dementia, and 4) the impairment is not fully explained by co morbid conditions (Antinori et al., 2007).

Finally, diagnosis of HAD according to these suggested criteria requires 1) acquired moderate-to-severe cognitive impairment,

documented by a score at least 2 SD below demographically corrected normative means in at least two different cognitive areas, 2) marked difficulty in ADLs due to the cognitive impairment, 3) the impairment does not meet criteria for delirium, and 4) the impairment is not adequately explained by co morbid conditions (Antinori et al., 2007).

Potential etiologies of neurocognitive impairment in HIV/AIDS

Soon after HIV infection, as early as 15 days (Hazleton et al., 2010), HIV enters the central nervous system (CNS). So far, three major mechanisms postulated HIV neuroinflammation: (Mrus, Williams, Tsevat1, Cohn, & Wu) "Trojan Horse hypothesis", entry of HIV into the brain takes place by the migration of infected monocytes, which differentiate into perivascular macrophage. (Simone, Vapiwala, Hampshire, & Metz) Entrance of HIV by transcytosis of brain microvascular endothelial cells. (Molony et al.) The direct entrance of the virus, once the virus is in the brain, it infects productively macrophages and microglia (del Palacio, Alvarez, & Munoz-Fernandez, 2012; Hazleton et al., 2010). The neuroinflammation can be detected and monitored by measurement of viral load in cerebrospinal fluid (CSF). Several groups have reported a positive correlation between CSF viral load and the observed degree of cognitive dysfunction in patients with HIV/AIDS (Brew, Pemberton, Cunningham, & Law, 1997; McArthur et al., 1997), and the highest concentrations of virus are observed in those subcortical structures most frequently affected in patients with severe of neurocognitive impairment. However, the neuroinflammation predicted to be continuing as time progresses.

Furthermore, neurocognitive impairment also reported associated with advance stage of HIV, CD4 count, viral load, years living with HIV. Studies reported that lower CD4 count, high viral load, advance HIV disease are predictor of neurocognitive impairment (Chan, Kandiah, & Chua, 2012; Hua et al., 2013; Odiase, Ogunrin, & Ogunniyi, 2007; Yusuf et al., 2014). Hua et al explained that regional brain volume reduction was linked to lower CD4 count, with a 1–2% white matter volume reduction for each 25-point reduction in CD4 (Hua et al., 2013). Another study reported each years living with HIV increased neurocognitive impairment (Attonito et al., 2014; Yusuf et al., 2014). Moreover, high rate of mild cognitive impairment is present at all stages of HIV infection but severe of impairment associated with advance HIV. Reduced cortical and subcortical volumes in addition to metabolite abnormalities persist in HIV patients associated with advanced disease stage (Thompson et al., 2005)Therefore, stage of disease, presented in lower CD4 count and high viral load, duration of illness are believed to contribute to increased neurocognitive impairment.

Neuroimaging studies have provided important insights into the pattern and extent of CNS damage associated with HIV infection in term of: Mrus et al. (2005) Cellular injury and inflammatory response, and (Simone et al.) Structural brain atrophy (Hua et al., 2013; J. Zhao et al., 2015). It was supported by several study that found regional metabolite disturbances, including increases in choline and myoinositol, along with decreases in N-acetyl aspartate, reflecting inflammation and neuronal injury, respectively, in the frontal white matter and subcortical nuclei (Sacktor et al., 2005). Furthermore, studies reported 15-20% atrophy in white matter, and widespread regions included the bilateral pallidum, left putamen and right inferior thalamus and inferior hippocampus (Chiang et al., 2007; Janssen et al., 2015; Wade et al., 2015). White matter and subcortical structures are the most affected brain regions that considered had strong association with neurocognitive impairment.

In addition to different brain regions affected, neuroimaging studies also documented different cognitive domain impaired. Studies also reported impairment, including global cognitive function, processing speed, memory, executive function, and working memory (Fellows et al., 2014 2012; Fialho et al., 2015; Mayston et al., 2015; Meade et al., 2015).

There is not one prototypical pattern of neurocognitive impairment in specific domains, one may have impaired on global cognitive function but some may have memory impairment.

Other potential etiologies and contributing factors

Although evidence is strong for HIV neuroinflammation as the etiology for cognitive impairment among patients with HIV, other factors common in HIV have been associated with neurocognitive impairment in chronically ill people. Age is one such factor because aging increases the incidence of dementia-related disorders, and it might be an indirect proxy for diminished cognition. Studies have been proved that older people with HIV at the most risk of neurocognitive impairment (Fazeli et al., 2014; Mindt et al., 2014). However, age can be independently caused of neurocognitive impairment. Therefore, the associations and interactions among HIV, age, and neurocognitive impairment require further investigation in order to identify profiles of patients most likely to experience neurocognitive impairment.

In addition, the effect of HAART is controversy, whether HAART is protective factors or risk factors of neurocognitive impairment. Evidence have been shower that before HAART introduced, the incidence of neurocognitive impairment was increased, but after HAART implemented, HAD have been decreased significantly (Heaton et al., 2010). In contrast with HAD, mild cognitive impairment in HAART era, it's noted higher prevalent among patients with HIV/AIDS (Fazeli et al., 2014; Fialho et al., 2015; Meade et al., 2015; Yusuf et al., 2014; T. Zhao et al., 2015). The other postulated that HAART is not completely suppress viral infection in the CNS, so that patients with HIV still at risk of getting neurocognitive impairment (Hazleton et al., 2010; Meeker, Asahchop, & Power, 2014; Nightingale et al., 2014; Woods, Moore, Weber, & Grant, 2009). Incomplete viral suppression are associated with poor adherence to HAART (Fazeli et al., 2014), dropout (Yusuf et al., 2014). Long term used of HAART also associate with neurocognitive impairment that caused different damage on brain (Letendre et al., 2008).

Neurocognitive impairment might be associated with other issues such as; co morbidity, depression and substance used. In Meta-analysis that review 24 studies found HIV co-infection more sever from neurocognitive impairment compare to HIV mono-infection (Fialho et al., 2015). Other observational study also found that Hepatitis C virus co-infection increases neurocognitive impairment severity (Vivithanaporn et al., 2012). Furthermore, depression is considered as important predictor of neurocognitive impairment in patients with HIV/AIDS (Fazeli et al., 2014; Mayston et al., 2013; Meade et al., 2015; Mindt et al., 2014; Salama et al., 2013; Yusuf et al., 2014). Some studies have been investigated the association between depression and risk of neurocognitive impairment not only in HIV but also in other chronic disease or Alzheimer disease. Hence, Depression may cause poor concentration, lack of interest and apathy (Gibbie et al., 2006). Another is substance used that frequently co-occurs with HIV and may further impair NC functioning. HIV infection and heavy drug or alcohol use have been observed to have synergistically negative effects on NC functioning and the progression of HAND (Attonito et al., 2014). Some studies reported drug abuse (e.g. cocaine & methadone) and alcohol use increased risk of neurocognitive impairment in patients with HIV/AIDS (Meade et al., 2015; Sassoon, Rosenbloom, Fama, Sullivan, & Pfefferbaum, 2012; Yusuf et al., 2014).

Furthermore, sex has not been thoroughly evaluated in past studies of impairment in patients with HIV/AIDS. Prevalence of neurocognitive impairment both in man and female remain same at adult age (Holguin et al., 2011; Nakku et al., 2013). However, gender specific issues related to menopause not yet been investigated or did not report menopausal status and use of estrogen replacement therapy that might affect on

cognitive deficits neurocognitive impairment. Evidence showed estrogen decline in menopause stage was increased risk of neurocognitive impairment (Epperson, Sammel, & Freeman, 2013). Then, education on average is a benefit for cognitive function (Lezak, 2004). Study reported that lower education is associated with neurocognitive impairment (Chan et al., 2012; Mayston et al., 2013; Smith et al., 2012). Therefore, it's important to address gender and education for further investigation.

DISCUSSION

This literature review shows that being infected with HIV and increased age is independent factors on HAND. Evidence has indicated that there are neurobiological changes and brain abnormalities among people living with HIV/AIDS, which may affect cognitive functioning. It is urgent to have a conceptual model that will guide further studies to investigate comprehensive knowledge of neurocognitive impairment among patients with HIV/AIDS. Guiding framework could be used to examine the deficits systematically as well as provide a structure for investigating etiologies of the deficits and determining how cognitive deficits influence outcomes in heart failure. In most past studies, there still lack of information about other potential etiologies or contributing factors of neurocognitive impairment among patients with HIV/AIDS. Therefore, the model represents an important step in advancing knowledge of the complex and important problem of cognitive deficits and heart failure. It is now ready for testing, validating, and revise.

The neurocognitive impairment model might need to be revised in the future as new knowledge is gained. Neurocognitive impairment is an independent predictor of early mortality and is associated with many difficulties in activities of daily living (Ezeabogu, Copenhaver, & Potrepka, 2012; Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Heaton et al., 2004; Vivithanaporn et al., 2012; Yeung, Krentz, Gill, & Power, 2006), increased health care cost (Yeung et al., 2006), poor quality of life (Thein et al., 2007). Those impairment, specifically in memory, can seriously affected to the ability of patients to accurately follow their medication regiment, thus further reducing their health-related quality of life and increasing the occurrence of morbidity and mortality. Self-management related to a complex of medication regimen and management of risk behavior is necessary for patients with HIV/AIDS (Fialho et al., 2015).

CONCLUSION

This conceptual model provides systematically and comprehensive knowledge of neurocognitive impairment in patients with HIV/AIDS. Testing of the model is potential to make unique contribution to the body of knowledge. This model can be used to identify profile of patients with HIV/AIDS who are more likely to develop neurocognitive impairment.

Declaration of Conflicting Interest
None declared.

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Author Contribution
All authors contributed equally in this study.

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