QUALITY OF LIFE WITH MENTAL HEALTH HIV-INFECTED PATIENTS IN INDIA BEFOR AND AFTER ANTIRETROVIRAL THERAPR (ART)

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Abstract

Background: AIDS/HIV is a chronic pandemic disease with significant morbidity and mortality. Although with the advent of HAART an increase in life expectancy and improved QoL has been noticed, evidences regarding prevalence of mental disorders among PLHIV are largely ambiguous.

Aim: The present study aims to systematically review the evidences about the mental complications in PLHIV before and after HAART therapy.

1. **Methodology:** Literature search was conducted for past ten years (i.e from 2008 to 2019) using the electronic databases like PubMed, Google scholar, Google using combination of keywords “AIDS” OR “HIV” AND “quality of life” OR “health related quality of life” AND “neurocognition”, OR “cognitive deficit” OR “psychological complications” OR “mental health” OR “cognitive impairment” OR “depression” OR “anxiety” OR “dementia” AND “randomized controlled trials” OR “randomized clinical trials”, OR “cohort study”, OR “ meta-analysis”, OR “systemic review” OR “study”.

Results: A total of 27 studies were included in the current systematic review in which 25 were cross sectional studies and 2 were reviews. These 27 studies recorded the neuropsychological variables either as a component of HRQoL/QoL or through usage of specific tools for assessment of depression, anxiety and HAND. Overall based upon the included studies it is evident that the enhanced coexistence of depression, anxiety and HAND with AIDS/HIV is common worldwide. Further, it was observed that the role of HAART in reducing the prevalence of neuropsychological disorders with disease progression is largely meager.

Conclusion: It is recommended that baseline assessment of HRQoL, immune markers, and neuropsychological disorders may serve as better treatment strategy with improved outcomes. Further, considering the serious repercussions of mental disorders on HRQoL, it would be beneficial to incorporate additional treatment regimen for them in addition to HAART from the beginning.

Introduction

AIDS caused by a retrovirus HIV has been globally accepted as a pandemic problem with significant morbidity and mortality (World Health Organization WHO, 2014). It is estimated by United Nations Programme on HIV and AIDS (UNAIDS) that worldwide approximately 36.7 million people are already living with HIV (PLHIV) in 2016 which is likely to be increased with almost 1.8 million new infections each year (Global AIDS Update, 2017). The largest disease burden is shared by sub-Saharan Africa while India comes at the third position with approximately 20.89 lakh PLHIV (Global AIDS Update, 2017). Further, while approximately 2.23 million people have died from AIDS, the mortality rate was noticed to be declined to 2.12 million since 2007 (India HIV Estimations 2015 Technical Report,2015). This steady decline in mortality rate is attributed to the introduction of highly active antiretroviral therapy (HAART) which exert improved clinical and laboratory outcomes in terms of fewer opportunistic infections and overall management of HIV/AIDS as a chronic illness (Moore and Chaisson,1999; Fairall et al.2008; Sow et al.2007). Although, HAART has been established for its efficacy and significant benefits in reducing overall morbidity and mortality, it is also reported to exert unpleasant side effects and life-long medication thereby affecting cumulative health related quality of life (HRQoL) of PLHIV (Corless et al.2005; Nicholas et al.2005; Burgoyne and Tan, 2008).

HRQoL is defined as a multidimensional approach to address changes in overall health status including physical, mental, and social functioning aspects either due to disease and/or treatment (Bonomi et al.2000). In context of mental manifestations, neurocognitive disturbance and psychological problems such as depression and anxiety were extensively reported in PLHIV (Watkins and Treisman,2015; NIMH,2016). Neurocognitive disturbance in HIV is specifically defined as HIV-associated neurocognitive disorder (HAND) which includes HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Signh,2012; Janssen et al.1991; Ancuta et al.2008). The pathophysiology behind neurological complications involves the infiltration of HIV-infected immune cells through blood–brain barrier causing inflammation of the central nervous system by activating microglia and related pathways (Signh,2012; Janssen et al.1991; Ancuta et al.2008). Further, psychological complications further enhances the HIV associated morbidity and mortality due to poor HRQoL, prognosis, response and adherence to HAART (Vivithanaporn et al.2010; Hinkin et al.2002; Tozzi et al.2004; Heaton et al.2004).

While a plethora of studies demonstrated the poor and improved HRQOL in PLHIV when compared with HIV free and HAART adhered HIV population respectively (Moore and Chaisson,1999; Fairall et al.2008;

Sow et al.2007; Murri et al.2003; Wig et al.2006; Pérez et al.2009; Jelsma et al.2005; Louwagie et al.2007), evidences regarding the status of neurocognitive and psychological disorders in PLHIV at various stages of engagement in HIV care is not clear. Therefore, the present study aims to systematically review the evidences about the mental complications in PLHIV before and after HAART therapy.

Methodology

The literature search was conducted for past ten years (i.e from 2008 to 2019) using the electronic databases like PubMed, Google scholar, Google. The search was conducted using the combination of keywords "AIDS" OR "HIV" AND "quality of life" OR "health related quality of life" AND "neurocognition", OR "cognitive deficit" OR "psychological complications" OR "mental health" OR "cognitive impairment" OR "depression" OR "anxiety" OR "dementia" AND "randomized controlled trials" OR "randomized clinical trials", OR "cohort study", OR " meta-analysis", OR "systemic review" OR "study". Only English language articles were searched and incorporated in the analysis.

All randomized controlled trials irrespective of double blind, single blind or open, interventional studies, pilot studies, systematic reviews and meta-analysis were considered as eligible studies. Studies that compared the PLHIV with normal control, with or without therapy were selected although it has been ensured that all studies must have included mental health as primary or secondary parameter. Further studies conducted over adults above 18 years were only selected however studies conducted exclusively over one gender or specific age group for instance over aged population were excluded from the study design. Further, studies focused on specific pathologies in PLHIV in addition to mental complications or studies using interventions other than HAART were also not selected for this review in order to increase the study homogeneity.

Results

A total of 27 studies were included in the current systematic review to assess the evidences about the neuropsychological health variables in PLHIV as represented in Table 1. Among the 27 studies, 11 studies recorded the neuropsychological variables as a component of HRQoL or QoL, remaining reports used the specific tools to assess depression, anxiety and HAND. In addition, the included studies involve 25 cross sectional studies and 2 reviews.

Among the 11 studies that investigated the mental health as a component of HRQoL, 10 studies showed overall poor mental performance including high depression and anxiety in PLHIV (Ledo et al.2018;

Nyongesa et al. 2018; Emuren et al.2017; Thomas et al.2017; Deshmukh et al.2017; Maimaiti et al.2017; Surur et al.2017; Betancur et al.2017; Akinboro et al.2014; Briongos-Figuero, 2011; Campos et al.2009). Further five studies unanimously reported depression as a major psychological disorder which overall negatively affect the QoL of PLHIV (Nyongesa et al.2018; Emuren et al.2017; Deshmukh et al.2017; Maimaiti et al.2017; Betancur et al.2017; Briongos-Figuero, 2011). Similarly, in terms of the affect of HAART treatment in reduced predisposition to mental disorders, 5 studies reported positive effect. While studies conducted by Ledo et al. 2018 and Betancur et al.2017 reported poor QoL including mental domains in HIV naïve and poor treatment adhering patients, cross sectional studies conducted by Akinboro et al.2014, Campos et al.2009 and Thomas et al.2017 highlighted the significant effect of ART over modulation of psychological health and overall HRQoL scores specifically during the initial treatment period. On the contrary, remaining six studies demonstrated enhanced prevalence of depression and therefore poor QoL irrespective of ART administration. These studies additionally reported the significant association between female gender, smoking, and low CD4 count and worsened neuropsychological health and overall HRQoL.

HIV associated neurocognitive disorder (HAND) was studied by 8 studies either alone or as mixed diagnosis out of which 7 studies reported mild to severe HAND when compared either with healthy control or within HIV positive patients (Kumar et al.2019; Yusuf et al.2017; Balaini et al.2017; Estiasari et al.2015; Habib et al.2013; Achappa et al.2013; Wang et al.2013). Only a single study conducted by Nyongesa et al. 2018 reported no significant effect of HIV over neurocognitive skills. Out of 8 studies, 6 studies included patients on HAART for different duration and majorly reported no response. While Balaini et al.2017 and Nyongesa et al.2018 found no association between HAND and cART regimen, studies conducted by Yusuf et al.2017, Achappa et al.2013, Wang et al. 2013 found mild to severe HAND prevalence irrespective of HAART administration. The positive effect of long term administration of ART over HAND was recorded by Kumar et al. 2019 whereas study performed by Estiasari et al. 2015 reported poor cognitive performance and high Prevalence rate in absence of HAART treatment. In case of HAND major factors that were found to be associated with poor cognitive performance were long duration of HIV diagnosis, low CD4 count, low educational status, severity of illness, psychiatric diseases and substance use, anemia, low body mass index, increasing age, and female gender.

A total of 6 studies assessed depression and anxiety in PLHIV where 5 studies recorded high prevalence (Adeoti et al.2018; Ramachandra and Badiger, 2018; Hafeez T, 2018; Betancur et al.2017; Tesfaw et al. 2016) and one showed no significant occurrence (Gauiran et al. 2018.) All these studies included the patients on ART for variable duration, hence higher prevalence of depression and anxiety in these patients indicate no significant effect of treatment. Major correlates demonstrated by these studies include female gender, age, smoking, homosexuality, unprotected sex, unemployment, low CD4 count, non-disclosure of

HIV status, perceived HIV stigma, poor social support, HIV stage III, poor medication adherence, divorce, and co-morbid TB illness.

Few number of studies (n=4) has assessed anxiety alone among PLHIV in which 3 were cross sectional studies and one was a review (Brandt et al.2017; Mirghani and Elbadawi,2017; Shukla et al.2016; Belete et al.2014). Overall, the three cross sectional studies demonstrated low to high anxiety rate with variable severity irrespective of ART and interestingly study conducted by Belete et al.2014 reported higher anxiety prevalence in ART receiving patients when compared with HIV naïve patients. Similarly, review did by Brandt et al. 2017 demonstrated consistent relationship between increased anxiety prevalence and HIV medication non-adherence, substance use behavior, poor QoL, and suicidal tendency in PLHIV. Further, increased anxiety prevalence was associated with poor educational status, single marital status, perceived treatment side-effects, female gender, and perceived stigma about their HIV status.

Table 1: Summary of studies included to assess the mental health in HIV patients

Author, Year	Study type and characteristics	Intervention	Comparator	Variables	Outcomes
Kumar et al.2019	Clinical study N=200 HIV patients (M=130, F= 70) N=200 control	N= 182 on HAART	Healthy control	-HAND	-One-fourth of all HIV patients had HAND. -Higher CD4 counts and a greater duration of ART decreases HAND predisposition.
Ledo et al.2018	Cross sectional study. N=104 (M = 79; F = 25)	No intervention	Within the group	- HRQoL	- Lower HRQoL in female patients specifically for Mental Component Summaries (MCS) of HRQoL. - Female gender and smoking as predictors for MCS.
Nyongesa et al.2018	A descriptive cross-sectional study. N=167 (M=48, F=119)	HAART (n=84)	Healthy community control (n=83)	- Non-verbal intelligence, verbal working memory and executive functioning. - Depression	- No major effect of HIV infection on neurocognitive tests. - Increased depression scores in HIV patients.

				- QoL	- No correlation between neurocognitive scores and QoL but strong association between depression and QoL.
Adeoti et al.2018	A cross-sectional study N=753 (M=165, F= 588) HIV positive = 424, HIV negative = 329)	ART for 6 months	Healthy control	- Anxiety and depression	- High prevalence of depression and anxiety disorders and their co-morbid occurrence. -More frequent in females
Ramachandra and Badiger,2018	A cross sectional study N=169 (M=110, F=59)	ART	Within the group	- Anxiety and depression	- Females were prone to anxiety (62.1%) and depression (59.4%). - Association between disease diagnosis age and depression.
Hafeez T,2018	Comparative study N=168 (M=120, F= 48)	N=85 on HAART and N= 83 without treatment	HIV naive	- Anxiety and depression	- Both depression and anxiety were higher among HIV/AIDS patients who are not on treatment. - Depression is primarily higher irrespective of treatment. - Females and unmarried male with CD4 < 500 are more prone for depression and anxiety.
Gauiran et al.2018	Cross-sectional analytic study. N=417 (M=408, F= 9)	N=362 on ART	Within the group	- Anxiety and depression	-Low prevalence rate of anxiety and/or depression (10.1%),

					-Significant associates were cigarette smoking, homosexuality, unprotected sex, unemployment, female sex and non-disclosure of status
Emuren et al.2017	Cohort N=1668 (M=1552, F=116)	HAART (n=1257)	Within HAART treatment	- HRQoL	- Depression accounted for over 60% of the psychological comorbidity and most predictive factor of HRQOL
Thomas et al.2017	Large cross-sectional survey done in Zambia and South Africa. Zambia: 19733 respondents (M= 5428; F = 14305) (HIV positive = 4128) South Africa: 18612 respondents (M= 5816; F = 12796) (HIV positive 4012).	In Zambia: N=1585 on HAART In South Africa: N = 1236 on HAART	HIV negative and HIV naive	HRQoL	- No significant difference in overall HRQoL scores between HIV positive and negative individuals where ART has been used for more than 5 years. - Improved HRQoL scores between HIV-positive and negative individuals who had initiated ART less than 5 years previously
Deshmukh et al.2017	A cross-sectional study N=754 (M=460, F=294)	ART	Within the group	- Depression, anxiety and stress scale-21 - QOL	- Depression was seen in 50% of the patients - Depression more prevalent in females - Depressed patients have overall lower QOL.
Maimaiti et al.2017	Consecutive case series N=679 (M=411, F=268)	ART	Within the group	- HRQoL	- 69% HIV cases showed depressive symptoms.

Surur et al.2017	Cross-sectional study N=400 (M= 181, F = 219)	HAART	Within the group	- HRQoL	- All domains of HRQoL were found to be moderate however the psychological health was found to be lower than remaining domains.
Betancur et al.2017	Cross-sectional study. N= 47 (M=14, F=33)	ART	Within the group	- Socio-demographic variables, depression and anxiety in poor adherence to HAART HIV patients	- 59.5% participants presented moderate to severe depressive symptoms. - Poor QoL in non-adhering patients with mental health as the most affected variable. -Females constituted the higher proportion of non-adherent patients.
Brandt et al.2017	Review	NA	NA	- Anxiety	- Anxiety and disease severity/progression (n =6) = no relation (n = 4), negative relation (n=1), and positive relation (n=1). - Anxiety and HIV medication adherence (n=13) = positive relation between increased anxiety and HIV medication non-adherence (n=10). - Consistent significant relation between anxiety symptoms and substance use behavior (n=4)

					- Anxiety and sexual risk (n=9) = positive relationship (n=4), no relations (n=2), and negative relations (n=2). - Consistent relationship between anxiety and lower QoL. - Consistent relationship between anxiety and suicidal thoughts, behaviors and history (n=4)
Mirghani and Elbadawi,2017	A cross-sectional analytic study N=352 (M= 220, F = 132)	ART	Within the group	- Anxiety	-High anxiety rate in HIV/AIDS patients especially among illiterate, widowed/divorced
Yusuf et al.2017	Cross-sectional study N=418 (M= 93, F = 325)	ART	Within the group	-HAND	-Prevalence rate of 19%. - Major correlates were duration of HIV diagnosis, low CD4 count and high detectable viral load during ART, low educational status, and severity of illness.
Balaini et al.2017	Prospective observational study N=41 (M=25, F=16)	HAART	Within the group	-HAND	-HAND is common among HIV patients with asymptomatic neurocognitive impairment as the most prevalent type. - No association between HAND and cART regimen.
Shukla et al.2016	Hospital-based cross-sectional study N=170 (M=110, F=60)	ART	Within the group	- Anxiety	- All patients showed anxiety with 92.1% showed mild anxiety while remaining

					moderate to severe anxiety symptoms. - Anxiety severity was associated with educational status, perceived side-effects during last one month and duration of treatment.
Tesfaw et al.2016	Institution based cross-sectional study. N=417 (M= 166, F = 251)	ART	Within the group	- Anxiety and depression	-41.2 % had depression and 32.4 % had anxiety while 24.5 % showed co-morbid depression and anxiety. -Major correlates for depression were perceived HIV stigma, poor social support, HIV stage III and poor medication adherence. - Major correlates for anxiety were female gender, divorce, co-morbid TB illness and perceived HIV stigma.
Estiasari et al.2015	Cross-sectional study N=82 (M=56, F= 26)	No treatment	Healthy control	-HAND	-Poor cognitive performance of HIV subjects in comparison to healthy controls. -Prevalence rate of 51% in HIV naïve patients.
Belete et al.2014	Institute based cross -sectional study N=436 (M= 174, F = 262)	72% on HAART	HIV naïve patients	- Anxiety	- Anxiety prevalence rate was 22.2%. - Major anxiety correlates were female gender,

					divorced and perceived stigma about their HIV status. - Patients on ART showed 2.7 times more prevalence of anxiety in comparison to HIV naïve patients
Akinboro et al.2014	Cross-sectional study N=491 (M=144, F=347)	N=393 on HAART	Within the group	WHO-QoL	- Participants with CD4 count ≥ 350 cells /mm3 had better QOL scores in the physical, psychological and level of independence domains. - Subjects on antiretroviral therapy (ART) reported significantly better QOL in the physical, psychological, level of independence and spirituality domains.
Habib et al.2013	Random effects meta-analysis of prospective studies	NA	NA	-HAND	-HIV associated with NCI. - ART lowers NCI by 63% and 77% when compared to HIV naïve patients and 6 months treatment respectively. -Psychiatric diseases and substance use further enhances NCI prevalence.
Achappa et al.2013	Cross sectional study	N=88 on HAART	Within the group	-HAND	-91 out of 101 patients had HAND.

	N=101 (M = 69, F = 32)				-Risk factors were low CD4 cell counts, anemia, low body mass index, increasing age, and female gender.
Wang et al.2013	Cross-sectional survey N=309 (M=272, F= 37)	N=236 on HAART	Within the group	-HAND	- Higher prevalence rate of HAND in HIV-infected patients with a baseline CD4 count ≤ 350 cells/µL. -Major correlates were old age, female gender, low level of education, and a longer period of EFV use in HAART regimens
Briongos-Figuero,2011	cross-sectional study N=150 (M=112; F = 38)	ART	Within the group	- Depression - HRQoL	- Depression significantly and negatively affected all HRQL domains including Mental Health Summary (MHS)
Campos et al.2009	A prospective adherence study. N=262	ART	Baseline values without ART treatment	- Quality of life - Anxiety and depression symptoms	- Improved QoL after four months of ART - Lack of anxiety and depression symptoms associated with good QoL.

Discussion

The present study evaluated the evidences about the prevalence of common neuropsychological health disorders viz. HAND, depression, and anxiety among PLHIV. Further, the review also focused on the impact of HAART in decreasing the predisposition of mental disorders in PLHIV, if any. Overall based upon the included studies it is evident that the enhanced coexistence of depression, anxiety and HAND with AIDS/HIV is common worldwide. This coexistence of mental disorders with HIV/AIDS can be understood in terms of pathophysiology mechanisms as well as social factors.

In terms of biological mechanisms, occurrence of HAND in HIV patients was attributed to the CNS viral reservoir and neuroinflammatory pathways (Cysique et al.2015). It is hypothesized that both CNS and peripheral monocytes and macrophages serve as HIV reservoirs due to longer life span and rescue mechanisms from HIV infection or immune surveillance (Zhu et al.2002; Bacchus et al.2013; Campbell et al.2014; He et al.1997; Lavi et al.1997). Further, due to the chronic nature of disease, a constant low-grade immune activation and inflammation persists which act as a potential contributor to HAND (Freund et al.2010; Cysique et al.2013). Similarly, mood disorders particularly depression and anxiety have been associated with cortical and subcortical regions in HIV negative patients (Drevets and Neuroimaging ,2000; Sheline,2000). However, their direct role in increased psychological vulnerability among HIV positive patients is still not clear. In addition, hypothalamus–pituitary–thyroid (HPT) and hypothalamic–pituitary–adrenal (HPA) axis dysfunction has also been established in mood disturbances which may play significant role in the pathogenesis of depression and anxiety in PLHIV (Langford et al.2011). Overactivation of HPA axis may further increase the HIV disease progression through enhanced cortisol secretion which in turn can alter T-lymphocyte cytokine production, destruction of CD4 lymphocytes and therefore stimulated HIV replication (Sadock and Sadock, 2005). Moreover, elevated cortisol secretion proportionally influenced the nor-epinephrine synthesis which further stimulates HIV replication (Cole et al.1998). Elevated tryptophan degradation which serves as a serotonin precursor is also illustrated in PLHIV. Increased tryptophan degradation further reduces immune activation as well as reduced serotonin synthesis together causing enhanced HIV disease and psychological disorders progression (Schroecksnadel et al.2008).

Neuropsychological disorders in PLHIV were largely related with stressful life events and diminished social support (Leserman et al.2002; Ironson et al.2005). The present review also observed that major correlates for enhanced neuropsychological disorders involve social factors such as being female, HIV stigma, low education and income status, societal isolation, poor family support, smoking and substance use. Larger vulnerability of females towards mental disorders can be attributed to factors such as increased exposure to acute life events, lower social status and network, and financial problem (NACA, 2012). HIV stigma serves as one of the leading factor in increased preponderance of depression and anxiety. Stigma results in enhanced fatigue levels, isolation, loneliness and felling of worthlessness (Rodkjaer et al.2010; Bhate and Munjal,2014; Berhe and Bayray,2013). Similarly, social relationship domain not only help in preventing mental disorders but also significantly affect overall QoL in PLHIV as it provides safety, security and financial support. Smoking and substance use bidirectionally indicate status of mental problems as well as disease progression and therefore interventions to stop them are inherent part of HIV management (Chang et al.2017; Ruggles et al.2017).

Based upon the present review, the role of HAART in reducing the prevalence of neuropsychological disorders with disease progression is largely meager. This poor effect of HAART can be attributed to irreversible CNS damage occurred during the early disease course before the start of intervention, sustained neuroinflammation, viral replication and load in CNS while on HAART (Becker et al.2011; Dahl et al.2014). In-addition, an observational study also demonstrated the neurotoxic effect of HAART specifically by the antibiotics used as first line of treatment (Bacchus et al.2013). Patients CD4 count also serve as a prognostic factor for HAART response against mental disorders as a low or nadir CD4 count indicate advanced disease state and immune damage.

- Overall, based upon the current evidences while it can be concluded that the prevalence of neuropsychological disorders increased with HIV disease which negatively influenced the cumulative QoL of PLHIV and HAART is not sufficient on its own to manage them, several important caveats has been noticed in the available literature. First more than 50% studies assessed mental complications as a component of HRQoL thereby considering it as a secondary objective. Second, methodologies and study design used to assess mental disorders varied significantly which can largely impact the study outcomes. Third, studies examining the impact of neuropsychological disorders on disease progression have not been addressed due to the inclusion of subjective questioners and lack of analysis of immune system biomarkers. Fourth, although most of the studies used patients on HAART the treatment duration, baseline disease as well as mental status and follow up time was not mentioned. Therefore it is recommended that baseline assessment of HRQoL, immune markers, and neuropsychological disorders may serve as better treatment strategy with improved outcomes. Further, considering the serious repercussions of mental disorders on HRQoL, it would be beneficial to incorporate additional treatment regimen for them in addition to HAART from the beginning.

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