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Review Article

Psychotic Disorders with HIV Infection: A Review

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Abstract

Background: Psychosis and HIV/AIDS are comorbid in some subjects. Their association might be simply coexisting or complex - psychosis enhances the risk to contract or protract HIV infection, and HIV/AIDS increases the risk to develop psychosis in terms direct effect of HIV on CNS or prescribed medications.
Objective: This review focused on the association of psychosis and HIV/AIDS with conceptual issues in their coexistence and management. Method: A literature review was conducted using PubMed and Google Scholar databases from 1970 to January 2012 to identify studies focused on HIV, AIDS, psychosis, psychiatric disturbances and side effects of antiretroviral therapy and antipsychotics.
Results: We review the limited research available on association of HIV and psychosis. Up to one-fourth of the subjects (3%-23%) with psychotic disorders were HIV positive. In contrast, the prevalence of new-onset psychosis among patients with HIV infection ranges 0.23-15.2%. Psychosis is also found to be associated with medical conditions, substance dependence and more importantly with medications used to treat HIV/AIDS, especially efavirenz.
Conclusions: A thorough evaluation of HIV- AIDS patients with psychotic symptoms requires a comprehensive history and physical examination to rule out other known causes of psychosis. Atypical antipsychotics especially risperidone, followed by clozapine and olanzapine are supported for the treatment of new-onset psychosis in HIV positive subjects (German J Psychiatry 2013; 16(1): 43-48).

Keywords: HIV, AIDS, Psychosis, HAART, side effects

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Introduction

The efficacy of HAART (highly active antiretroviral therapy) has resulted in increased life expectancy in subjects with HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome), turning HIV/AIDS into a chronic medical illness (Perkin & Akman, 2006). As with any other chronic medical illness, there is significant psychological distress due to a wide variety of factors. Physical factors may include declining health, repeated stressful disease phases, physical ailments, pain, discomfort, concurrent alcohol or drug abuse or dependence, and medication side-effect, and need for constant monitoring of viral load and CD4 cell counts. Social factors may include lack of appropriate treatment facilities, poor access to the health care, low educational level, financial problems, and disability (Wight et al., 2003). Family factors may include AIDS in the spouse, poor family support, the impact on significant others like partner, spouse, and family members. Psychological factors may include disclosure of HIV status, loss of significant others/social support, uncertainty and unpredictability of future, stigma and social discrimination, shame and blame, cognitive decline. The global stress from

these factors may lead to increased psychiatric morbidity (Wight et al., 2003).

Conversely, persons with severe mental illness are known to be vulnerable to HIV infection. Factors such as sexual abuse, homelessness and impaired judgment regarding sexual relationships, use of alcohol and other drugs of abuse make psychiatric patients vulnerable to enter casual or coercive sexual relationship associated with higher risk to contract HIV infection (Chandra et al., 2005). Western studies documented HIV infection rate among patients with severe mental illness ranging 3-23%, much higher than in general population (Cournos& McKinnon, 1997; Rosenberg et al., 2001; McDaniel et al., 2000). The common psychiatric diagnoses in this population are schizophrenia, schizoaffective disorder, bipolar disorder, and substance use disorders (Rosenberg et al., 2001; McDaniel et al., 2000). Occurrence of sexual coercionand abuse of severely mentally ill increases the HIV risk among women (Chandra et al., 1999).

In HIV infection the mental health professionals have an important role to play to: identify and modify behavioural factors related to the acquisition of infection or affecting the course of disease; describe the significance and inner consequences of the diagnosis; and determine the usefulness of interventions. With this background we are now focusing our review on the relationship between HIV infection and psychosis. A literature review was conducted using PubMed and Google Scholar databases from 1970 to January 2012 to identify studies focused on HIV, AIDS, psychosis, psychiatric disturbances and side effects of antiretroviral therapy and antipsychotics. With this we found 2600 articles/web pages in Google Scholar and 253 articles in PubMed, and out of this search we included 47 articles, consisting of original research, reviews and case reports, in our review.

Psychosis may precede HIV infection, HIV infection may cause psychosis either directly or indirectly, or a common etiologic factor may predispose to both HIV infection and psychosis (Howarth &Cournos, 2006). Pathophysiology of psychosis in HIV infection is complex and a multifactorial aetiology is believed to be quite likely (Sewell et al., 1994). Psychosis is more common among people with HIV infection than general population and factors contributing may include direct effect of HIV on CNS, opportunistic infection, CNS neoplasm, medications, substance use disorder and other psychological stresses (McDaniel et al., 2000). Those at high risk for HIV infection and those with a first episode psychosis share several features such as young adulthood, high-risk sexual behaviour and intravenous drug use (Sewell et al., 1994).

Psychotic symptoms in HIV infection can be a part of delirium, dementia or any other organic brain syndrome and can contribute to difficulties in medical care and residential placement. Individuals with psychosis show greater neuropsychological impairment, higher rates of stimulant abuse and higher mortality rate at follow up (Sewell et al., 1994). Patients with no HIV-related neurological disease or acute metabolic dysfunction were categorized as having 'primary psychosis' and those with opportunistic cerebral infection or metabolic encephalopathy related to pulmonary, hepatic and renal failure were diagnosed with 'secondary psychosis' (Alciati et al., 2001).

Psychotic Disorder due to HIV infection (293.xx) may occur at any stage but are usually late complications of HIV infection (Doyle &Labbate, 1997), and pose a dilemma as to whether the presentation is organic or functional. A further complicating fact is that the age range of the peak incidence for HIV infection is similar to that for schizophrenia and mood disorders in the general population (Sewell, 1996). Therefore establishing a causal relationship between HIV infection and psychiatric morbidity may be difficult. Yet, regardless of which illness comes first, their co-occurrence is associated with higher morbidity and mortality than expected with either illness alone.

The high co-prevalence suggests a possible aetiological association between HIV infection and psychosis (Navia et al., 1986). Some studies have reported equal or lesser prevalence of psychosis in HIV infected subjects as compared to general population (Halstead et al., 1988; Prier et al., 1991; Nebhinani et al, 2011). Along the same lines others have argued that these cases could in fact represent either coincidental schizophrenia or bipolar disorder and HIV infection or HIV-related organic hallucinosis, delusional or affective syndromes with or without associated dementia (AIDS-dementia complex) (Vogel-Scibilia et al., 1988). The use of the term psychosis in describing AIDS-related behavioural syndromes seems misleading, and should be replaced by specific categories of a standard classificatory system like the DSM-IV-TR.

Psychotic disorders that precede HIV infection/HIV infection in subjects with psychosis

Prevalence

Psychiatric patients have substantial rates of HIV seropositivity, ranging 3%-23% (Cournos& McKinnon, 1997; Rosenberg et al., 2001; McDaniel et al., 2000; Susser et al., 1995; Mashaphu&Mkize, 2007). Comparative seropositivity rate in India is currently 2.11%. Though lower than that in the West, it is alarming considering the increase from 0.47% in 1993 to 5.33% in 1997 (Chandra et al., 1999). Sexual coercionand abuse of severely mentally ill increases the HIV risk among women. The most common psychotic diagnoses are schizophrenia, schizoaffective disorder and bipolar disorder, commonly with comorbid substance dependence, which in turn enhances the likelihood of HIV infection (Chandra et al., 1999). Halstead et al(1988) reported rate of functional psychosis with HIV at 0.2% while Alciati et al(2001) reported prevalence rate of 1.05% for primary psychosis (similar to functional psychosis).

Risk behaviour s/factors

Persons with severe mental illness, especially those with psychotic disorders, are at risk for developing comorbid HIV

infection and AIDS. As they may engage in high risk sexual activity in form of unprotected sex with multiple or casual partners (Susser et al., 1995), lack of risk awareness, impaired judgment, substance abuse, and the potential for sexual victimization and drug use behaviour s that place them at high risk for HIV infection. Substance use alone can predispose to psychosis as well as HIV infection (Howarth & Cournos, 2006).

Impact. Impact of severe mental illness like schizophrenia on HIV-AIDS may be crucial. In general, psychotic disorders may alter the course of HIV infection by impairing immune function or influencing behaviour (Hinkin et al., 2001); however, there is scanty published literature on the possible effects of schizophrenia on the progression of HIV-spectrum illness. Diseases such as HIV may lead to greater morbidity and mortality in patients with schizophrenia than in the general population because patients with schizophrenia may have difficulty in explaining symptoms to medical personnel and complying with medical care, and may receive less attention from medical personnel about physical complaints (Sewell, 1996). In addition, individuals with schizophrenia may be more susceptible to the stresses related to HIV infection and may have fewer resources to address these issues (Sewell, 1996).

New onset psychosis in individuals with HIV infection

New-onset psychosis can occur in the setting of HIV infection; it may occur with an opportunistic infection (like CNS lymphoma), with AIDS-related dementia, as medication side effect, or with asymptomatic HIV infection (Perry & Jacobsen, 1986). Mostly such psychosis occurs in the later stages of HIV infection, usually in the context of AIDS. Less often it occurs with positive past psychiatric history, no antiretroviral therapy, and lower global cognitive performance compared to non-psychotic HIV-positive subjects (De Ronchi et al., 2000).

Neuropsychiatric symptoms occasionally serve as the initial indicator of HIV infection, as psychosis sometimes occurs early in the course of an organic mental syndrome and in the absence of other signs of AIDS. There are several case reports describing psychosis as the presenting manifestation of HIV infection (Harris et al., 1991; Volkow et al., 1987; Halstead et al., 1988).

Prevalence. Reports of the prevalence of new-onset psychosis among patients with HIV infection have varied widely (0.23%–15.2%) (Navia et al.,1986; Halstead et al., 1988; Prier et al., 1991; Harris et al., 1991; Susser et al., 1997).

Presentation. Most common presentation is in forth decade (Vogel-Scibilia et al., 1988; Sewell et al., 1994; Susser et al.,1997; Alciati et al., 2001; Huffman &Fricchione, 2005) with predominance of paranoid delusions (54%-100%) and hallucinations (75%-88%) (Sewell et al., 1994; Alciati et al., 2001; Harris et al., 1991). Higher cognitive impairment (Sewell et al., 1994), and higher comorbid substance dependence (Sewell et al., 1994; Susser et al., 1997) were reported in psychosis group compared to non-psychosis group with HIV infection, and rapid deterioration was seen in subjects with structural brain changes (Harris et al., 1991).

Several cases have been reported with catatonia in patients with HIV infection (Volkow et al., 1987; Huffman & Fricchione, 2005). Compared to schizophrenia, new onset psychosis in HIV infected subjects less commonly have bizarre delusions and Schneiderian first rank symptoms; more commonly have eventual remission of psychosis; need antipsychotics in lesser dosages and for shorter duration; have a variable clinical course; and are more likely to have full remission of psychosis (Harris et al., 1991).

Etiopathogenesis. Pathogenesis of new-onset psychosis in HIV infection has been explained by a number of hypotheses: brain damage from some other opportunistic infection (Sewell et al., 1994); an inferior immune response in the CNS that allows greater damage from infectious pathogens (Sewell et al., 1994); subcortical neurodegeneration caused by HIV itself or in the presence of other viral infections (Hinkin et al., 2001); psychosis secondary to HIV encephalopathy (Doyle &Labbate, 1997; Halstead et al., 1988) or an underlying dementia (El-Mallakh, 1992); and high levels of intracellular free calcium, leading to inappropriate neurotransmitter release (El-Mallakh, 1992). Additional potential factors reported to be associated with the development of psychosis are: history of substance abuse disorder, affective disorder, untreated HIV infection, cognitive impairment, and dementia (Sewell et al., 1994; Alciati et al., 2001; De Ronchi et al., 2000). Thus no single factor is likely to fully explain the pathogenesis of new-onset psychosis in HIV disease. Hence, continued examination of such hypotheses is needed to obtain valuable insight into their prevention and treatment.

Psychosis associated with HIV related medical conditions

CNS opportunistic diseases, including toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), tuberculous meningitis, and CNS neoplasms, such as lymphoma or Kaposi's sarcoma, or disturbances associated with these disorders may alter the mental status with the commonest presentation being delirium (Howarth &Cournos, 2006). Several cases have been reported of psychosis presenting a manifestation of opportunistic infection, including tubercular meningitis presenting as paranoid psychosis, and progressive multifocal leukoencephalopathy (PML) presenting as catatonia (Howarth & Cournos, 2006).

Psychosis associated with substance use disorders

Several studies have found strong association of substance dependence in new onset psychosis subjects with HIV infection compared to subjects without psychosis (Sewell et al., 1994; Susser et al., 1997). Hence, diagnosis of substance induced psychotic disorder should be considered in HIV infected subjects who use alcohol or other drugs and devel-

op psychotic symptoms during or within a month of substance-related intoxication or withdrawal.

Psychosis associated with HIV medications (HAART)

Since the virus is present in the central nervous system (CNS), it is essential that HAART drugs cross the blood-brain barrier. Efavirenz passes through this barrier satisfactorily and can reduce the deleterious central effects of the human immunodeficiency virus. However, up to 50% patients treated with efavirenz report some CNS side effects (mainly vivid dreams, insomnia and mood symptoms), although most of these are mild & transient but some individuals also experience significant psychiatric disturbance such as mania, depression, suicidal thoughts, psychosis, and hallucinations (Cavalcante et al., 2010).

Implications of the CYP2B6-G516T polymorphism have been highlighted in HIV-infected patients receiving efavirenz therapy as it impairs the clearance of efavirenz and leads to more side effects. Patients who are known to have the CYP2B6-G516T variants warrant close monitoring of efavirenz therapy to avoid potential development of high concentrations of the drug as it decreases efavirenz clearance and may lead to toxicity and, therefore, psychosis. Age and CYP2B6-G516T variants are independently associated with oral efavirenz clearance (Saitoh et al., 2007).

On the basis of current knowledge, however, patients receiving efavirenz therapy who develop significant and prolonged psychiatric symptoms, especially after the initiation of therapy or a dose increase, should be tested at least to determine drug concentrations (to rule out toxicity) and, possibly also for detection of the CYP2B6-G516T genotype.

There are several reports of medication induced psychosis, especially with efavirenz (Garza et al., 2001; Blanch et al., 2001; Poulsen& Lublin, 2003;Hasse et al., 2005; Lowenhaupt et al., 2007), and less commonly with nevirapine (Jan Wise, 2002; Foster et al., 2003), and zidovudin (Maxwell et al., 1988; O'Dowd &McKagney, 1988); all showed recovery on discontinuation of the causative agent.

Management of psychosis in HIV infected individuals

Evaluation. The clinical evaluation of HIV-AIDS patients with psychotic symptoms requires a comprehensive history taking and physical examination, to rule out other known causes of psychosis. A careful history should include information about the onset and course of the patient's symptoms. Signs of medical illness, drug intoxication, or medication toxicity should be considered during the examination (Sewell et al., 1994).

Treatment. Medication side-effects and drug–drug interactions are important considerations when patients are prescribed antipsychotic agents for the treatment of new-onset psychosis while concomitantly receiving HAART. For example, the enzymatic inhibition seen with protease inhibitors may lead to increased serum levels of antipsychotic agents and a greater potential for side-effects. Similarly, the ability of protease inhibitors and some atypical antipsychotic agents to cause weight gain and dyslipidemia may lead to negative long-term outcomes such as diabetes, hypercholesterolemia, and cardiovascular events. The ability of some antiretroviral agents (e.g. zidovudine, efavirenz) to cause CNS effects (e.g. nightmares, hallucinations) may also complicate the treatment of psychiatric disorders. Caution should thus be exercised when deciding on the pharmacological treatment of psychosis in HIV-infected individuals.

HIV-infected individuals are particularly susceptible to extrapyramidal (EPS) including tardive dyskinesia (TD) induced by conventional antipsychotic agents (Sewell et al., 1994; Hriso et al., 1991). One study reported the risk as more than twice that in non-AIDS patients after controlling for the mean medication dose and body weight, and still higher in the relatively young subjects (78% developed EPS depending on the antipsychotic dose) (Hriso et al., 1991). Similarly, a 6-week study of haloperidol and thioridazine in the treatment of new-onset psychosis in HIV-seropositive adults showed high rates of motor side-effects with conventional antipsychotic agents at low doses (Sewell et al., 1994).

The sensitivity of HIV-seropositive adults to EPS is attributed to HIV involving the basal ganglia to cause a loss of dopaminergic neurons (Berger &Nath, 1997). Also, because of their dopamine blockade in the nigrostriatum, conventional antipsychotic medications may produce or exacerbate EPS (Berger &Nath, 1997). Unfortunately, current antiretroviral therapies do not seem to increase CNS levels of dopamine (Gisslen et al., 1994) or improve the clinical symptoms of parkinsonism in patients with HIV infection (Mirsattari et al., 1998).

As patients with HIV-associated psychosis are more sensitive to extrapyramidal side effects, so they require lower doses than other patients with psychosis (Halstead et al., 1988; Harris et al., 1991). Many published case reports (Dettling et al., 1998; Maha& Goetz,1998; Meyer et al., 1998; Zilkis et al., 1998) and case series (Singh & Catalan, 1994; Singh et al., 1997; Lera&Zirulnik, 1999) support the use of atypical antipsychotics in the treatment of new-onset psychosis in HIV positive subjects. The available data on psychotropics is extracted from open studies, as yet we don't have controlled trials in this population.

The most frequently investigated medication is risperidone, followed by clozapine and olanzapine. The use of atypical antipsychotic agents at relatively low doses is generally reported to lead to improvements in psychopathology without causing or exacerbating EPS. Risperidone (1mg-3.3 mg) (Maha& Goetz, 1998; Zilkis et al., 1998; Singh & Catalan, 1994; Singh et al., 1997), clozapine (mean 27 mg) (Dettling et al., 1998; Lera&Zirulnik, 1999) and olanzapine (10 mg) (Meyer et al., 1998) has been reported to lead to significant reduction in psychopathology with lesser risk for EPS. Nonetheless, the potential for antipsychotic-induced side-effects and overlapping toxicity between antiretroviral treatment and antipsychotic medications should lead to the careful selection of medications.

Conclusions

HIV infection with CNS involvement causes a variety of psychiatric complications. Increased life expectancy with HAART has led to concern for increased incidence of psychiatric manifestations in the AIDS survivors. HIV infection should be considered in all patients with new-onset psychosis, especially those with late-onset or atypical psychosis, or those with HIV risk factors. Similarly, it is also reasonable to consider co-morbid HIV infection in psychotic patients. Although the differential diagnosis in this population is extensive, drug toxicity must not be overlooked, and the treatment of drug toxicity may lead to resolution of symptoms. To avoid making erroneous associations between a drug and a possible side-effect of psychosis requires a thorough psychiatric assessment.

Both HIV care programs and psychiatric care clinics should be made aware of the frequent association of HIV infection and mental illness. Psychiatrists are in a better position to actively educate their patients on prevention of HIV infection. The need for implementation of risk-reduction programs in psychiatric facilities needs to be emphasized as a significant proportion of patients could be infected with HIV.

Research must be broadened in order to determine the prevalence of HIV infection in populations such as older adults and those with psychiatric illness. Research findings support the call for early intervention strategies that target reduction of sexual risk behaviour in the context of persistent mental illness. The usefulness of HIV prevention and harm reduction is highlighted in reducing the acquisition of HIV infection, contrary to that access to such preventive strategies remains substantially low in subjects with mental illness.

Cross-sectional studies have suggested that psychosis may negatively impact the morbidity and mortality associated with physical disease, but longitudinal, prospective multicentric studies to increase the external validity of study findings. Well-designed clinical trials are needed to gain a better understanding of how to treat individuals with HIV and psychotic illness safely and effectively.

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