

Schizophrenia and Comorbid Human Immunodeficiency Virus or Hepatitis C Virus

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Patients with schizophrenia are at significantly increased risk for infection with human immunodeficiency virus (HIV), hepatitis C virus, or both. Several factors underlie this increased risk, including substance abuse and high-risk sexual behavior. Although being sexually active tends to be less common among patients with schizophrenia than among nonpsychotic individuals, patients with schizophrenia who are sexually active are more likely than nonpsychotic individuals to engage in high-risk behavior. Many patients with schizophrenia have inadequate knowledge about the risks of HIV, but delivering factual information is not likely, by itself, to bring about behavioral changes that reduce the risk of exposure and transmission. Comorbidity of schizophrenia and life-threatening viral illnesses incurs a worse prognosis for both conditions. Nevertheless, effective pharmacotherapy exists, and antipsychotics and highly active antiretroviral treatments for HIV can be used together successfully. The clinical challenge is to encourage adherence to treatment and to coordinate the clinical services needed to address the diverse psychiatric and medical problems that coexist in this population.

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Patients with schizophrenia are at an increased risk for a variety of medical disorders, including chronic viral infections, of which the most serious are the diseases associated with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). It is generally recognized that the risk of HIV and HCV infection is higher in patients with schizophrenia than in the general population and that comorbidity implies a poorer prognosis.^{1,2} Consequently, the clinical management plan for patients with schizophrenia should include efforts aimed at prevention, early detection, and appropriate treatment of these infections.

The problem of comorbid serious infection in patients with schizophrenia is representative of the larger problem of medical illness in general in this population; because

of such factors as poverty, homelessness, social isolation, and substance abuse, these patients are at greater risk and less likely to have access to medical care than nonpsychotic individuals.³⁻⁶

This article reviews clinical issues associated with HIV or HCV infections in patients with schizophrenia, with emphasis on the prevalence of comorbidity, the psychiatric complications linked to these chronic infections, and the challenge of treatment in this patient population.

PREVALENCE

In a study of 931 patients with severe mental illness in the eastern United States,¹ the prevalence of HIV infection was 3.1%, or 8 times the estimated prevalence in the U.S. population. A review of 4 earlier studies sharing common methodology showed a slightly higher prevalence, ranging from 5.5% to 7.1%,² whereas a review of 11 studies employing diverse methodologies showed a much wider range of prevalence, from 4.0% to 22.9%.⁷

The greater prevalence of HIV infection in patients with schizophrenia can be seen in those on Medicaid. In a large cross-sectional study of Medicaid recipients,⁸ the odds ratio for treatment of comorbid HIV infection was 1.5 in patients with schizophrenia versus patients without severe mental illness; of interest, the likelihood of HIV infection is even higher among Medicaid patients with a major affective disorder (odds ratio = 3.8).

Despite the evidence linking serious mental disorders to an increased prevalence of HIV infection, clinical ef-

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forts to identify HIV-positive individuals within psychiatric populations have been inconsistent and thus inadequate. In a study of 300 inpatients with schizophrenia,⁹ only 17% had been tested for HIV within the preceding 6 months. Testing was more common among those with certain known risk factors for HIV, but even within this subgroup, the greater number of patients had not been recently tested.⁹ Although the prevalence of risk factors for HIV infection is known to be relatively high in patients with schizophrenia, mandatory screening of people with mental illness does not appear to be warranted.¹⁰

In the majority of cases involving comorbidity, psychotic disorders *precede* HIV infection.¹¹ On the other hand, a review of studies in patients with previously diagnosed HIV-spectrum illnesses² showed that new-onset psychosis occurred in 0.2% to 15% of patients in various studies, with the highest incidence reported in a study of patients with HIV-associated dementia. These studies also indicated that morbidity and mortality rates in patients with comorbid schizophrenia and HIV infection are higher than those associated with either condition alone, regardless of the order in which the conditions appeared.²

The onset of psychosis among HIV-positive individuals is not necessarily related to the infection. However, if the incidence of psychosis was found to increase as the stage of HIV infection progressed toward acquired immunodeficiency syndrome (AIDS), the implication would be that at least some episodes of new-onset psychosis in this population result from the effects of retroviral infection within the central nervous system (CNS).

The prevalence of HCV infection in the general population was estimated at 1.8% in a 1999 report,¹² but a 2003 report noted that the incidence appears to be falling due to better screening of blood donors and safer practices among intravenous drug users.¹³ As with HIV, the prevalence of HCV infection is higher in patients with mental illness than in the general population. A retrospective study of 1556 psychiatric inpatients showed that 8.5% were positive for HCV,¹⁴ and the previously mentioned study of 931 patients with severe mental illness reported an even higher prevalence of 19.6%.¹ However, there are no strong data on HCV prevalence rates associated with specific psychiatric diagnoses.

Reflecting the overlap in behavioral risk factors for these diseases, the prevalence of coinfection with HIV and HCV is substantial.^{1,15,16} This risk of coinfection and resultant poorer prognosis applies to patients with or without mental illness.

SCHIZOPHRENIA AND RISK OF HUMAN IMMUNODEFICIENCY VIRUS EXPOSURE

The main risk factors for HIV infection—unprotected sex with multiple partners and injection drug use (IDU)—are the same in patients with schizophrenia as in the gen-

eral population.¹ The increased prevalence of HIV infection among patients with schizophrenia therefore reflects increased rates of high-risk exposure, which may result in part from such factors as substance abuse; cognitive, excited, or positive symptoms; and vulnerability to sexual victimization.^{1,17}

Exposure Through Sexual Contact

Although overall rates of being sexually active tend to be lower in patients with schizophrenia than in the general population, sexual interest and activity do not disappear with this diagnosis.¹⁸ Moreover, high-risk behavior is relatively common among those patients who are sexually active.^{11,19}

For example, a study of 178 psychiatric patients¹⁷ showed that only 52% had been sexually active within the preceding 6 months. Within this subgroup, however, 58% never used condoms, 48% had multiple partners, 35% used drugs during sex, and 30% had traded sex for money or goods.¹⁷ Similarly, in a study of 1558 outpatients with mental illness (of whom 19% were diagnosed with schizophrenia or schizoaffective disorder),²⁰ 69% were sexually active during the previous year, and 23% of patients screened were considered to be at high risk for HIV infection. Another study²¹ showed that only 42 (44%) of 95 patients with schizophrenia were sexually active within the preceding 6 months, but high-risk behavior was common in this subgroup; 26 (62%) had multiple partners, 21 (50%) had traded sex, and 5 (12%) had at least 1 partner who injected drugs or was HIV positive.

With respect to the increased risk associated with male same-sex activity, 10% of the 42 sexually active patients in the aforementioned study reported current homosexual activity (3 men and 1 woman), but 22% of the full study population reported a prior history of homosexual activity, with similar data for men (16 of 69, 23%) and women (5 of 25, 20%).²¹ These findings are consistent with a review of studies (1990–1995) of HIV risk in patients with mental illness¹⁸; male homosexual activity was reported in 7% to 13% of study populations, in up to 30% of sexually active subgroups, and in 20% to 48% of HIV-positive subgroups.

The severity of psychiatric symptoms may be predictive of high-risk behaviors.²² For example, the likelihood of trading sex for money or goods was 5-fold higher in patients with high scores for excited symptoms, and the likelihood of having multiple sexual partners was 3-fold higher in those with high scores for positive symptoms.¹⁷

Exposure Through Injection Drug Use

Although IDU is a universally recognized risk factor for both HIV and HCV infection, there is little specific information about IDU in people with severe mental illness.^{11,23} In a review of studies published from 1990 to 1996,⁷ an estimated 1% to 8% of individuals with serious mental illness reported recent IDU, and 5% to 20% re-

ported some history of IDU. By comparison, in the general population, the total number of people aged 12 years or older who had engaged in IDU during the preceding year (averaged from 1999–2001 data) has been estimated at 338,000, with the highest rate (0.29%) among those aged 18 to 25 years.²⁴

Predictably, a history of IDU is more frequent among those psychiatric patients who are HIV-positive than among those who are HIV-negative. In a study of HIV-positive patients with chronic mental illness in New York City,²⁵ 64% of patients reported a lifetime history of IDU, and 26% reported having sex with an injection drug user. In a similar study from Los Angeles, the corresponding figures were 44% and 56%, and the authors noted that HIV infection in the general (nonpsychiatric) population is more often associated with IDU in New York City and with male homosexual activity in Los Angeles.²⁶ Epidemiologic data from Australia suggest that the prevalence of hepatitis C antibodies among people injecting drugs for < 3 years is 20%.²⁷ This rate triples at 6 years, with > 60% of drug abusers developing the antibody.²⁷

Knowledge of Risks

Misinformation about HIV risks is common among patients with schizophrenia but also in the general population. In particular, there are many widely held false beliefs about how HIV can and cannot be transmitted. In a survey of AIDS knowledge in patients with severe mental illness,¹⁷ the median score was 23 correct answers to 28 questions, but 91 (51%) of the 178 patients mistakenly believed that HIV infection can be transmitted through casual contact. Of interest, a similar proportion of the general population holds this same misperception. In surveys taken in 1997 and 1999, almost half of respondents believed that HIV infection can be transmitted through various forms of casual contact, and these percentages were actually higher than those reported in similar surveys from 1991.²⁸

The correlation between high-risk behavior and inadequate or mistaken information is not consistently found. In 1 study,²⁹ 54 psychiatric outpatients had an average score of 75% on a test of AIDS knowledge, which was significantly ($p < .001$) lower than the score achieved by a comparator group of 168 high school students. For example, 42% of the patients were unaware of the risks associated with IDU. Furthermore, the authors found a significant correlation between lack of information and high-risk behavior.²⁹ On the other hand, a brief test of AIDS knowledge in 151 psychiatric outpatients revealed a wide range of incorrect answers (from 6% who believed that exclusively heterosexual men cannot get AIDS to 40% who believed that donating blood can result in AIDS), but better knowledge did not necessarily lead to safer behavior.³⁰ As with the general population, educating people with mental illness about HIV infection risks often results in increased knowledge but not in decreased high-risk behavior.³¹ The level of AIDS knowledge

may be lower in patients with schizophrenia than in patients with other mental disorders,^{18,32} and patients with schizophrenia are more likely to change their behavior if they believe they can affect the likelihood of becoming infected than if they are simply provided with factual information about HIV infection risks.³³

HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED DEMENTIA

The presence of HIV in the CNS reflects the neuro-invasive, neurotropic, and neurovirulent properties of the virus.³⁴ As the stage of HIV disease progresses, opportunistic infections and neoplasms may also contribute to the characteristic adverse neurologic and psychiatric effects seen in this population, including cognitive deficits, affective disorders, and psychosis.³⁵

More than half of patients with HIV infection will eventually develop symptomatic neurologic complications.³⁶ Psychiatric complications in patients with HIV infection can adversely affect the prognosis of both conditions because cognitive and affective problems lead to reduced treatment adherence and increased high-risk behavior.³⁵

The range of psychiatric complications relating to CNS infection with HIV and opportunistic pathogens is broad. In addition to the characteristic HIV-associated dementia, patients may develop psychotic or affective disorders or delirium; in some cases, these symptoms may also be related to substance abuse, the side effects of HIV-related medications, or undiagnosed medical complications.³⁷

Patients infected with HIV may develop mild cognitive and/or motor dysfunction or more severe dementia. Dementia due to HIV disease is described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision,³⁸ as a dementia considered to be a direct consequence of the infection. No specific diagnostic criteria are offered, but clinical manifestations commonly include deficits in memory and concentration, apathy, and social withdrawal; psychotic symptoms, delirium, and motor abnormalities may also occur.⁴⁵ The onset of symptoms is often insidious, occurring years after exposure and CNS involvement.³⁹

In terms of neuropathology, HIV-associated dementia (formerly called AIDS dementia complex) is characterized by diffuse destruction of white matter and subcortical structures, with reactive astrogliosis. Thus, it has more in common with the dementia that may occur in Parkinson's disease than with cortical dementias such as Alzheimer's disease, and parkinsonian motor symptoms may accompany the neuropsychiatric symptoms.^{39,40}

The cognitive and motor deficits associated with HIV infection in the CNS may reflect, respectively, involvement of the hippocampus and basal ganglia.⁴¹ The development of dementia is probably an indirect process in which HIV affects dopaminergic activity and stimulates the pro-

duction of cellular toxins; these events in turn lead to neuronal degeneration and neurotransmitter dysregulation, both of which contribute to cognitive loss.⁴² It appears that neuronal damage results from a type of encephalopathy characterized by the fusion of mononuclear phagocytes with noninfected cells to form multinucleated giant cells.⁴³ A variety of humoral factors contribute to neurotoxicity in HIV-infected patients, including cytokines (tumor necrosis factor- α [TNF- α] and interleukin 1 beta [IL-1 β]) and free radicals (nitric oxide and superoxide); these toxins and others may be elaborated by immune-stimulated uninfected macrophages, which comprise the majority of macrophages in the brains of AIDS patients, as well as by the smaller number of HIV-infected macrophages.⁴⁴ Other mechanisms, such as the death of astrocytes, are also involved in HIV-associated dementia.^{41,44}

DUAL PHARMACOTHERAPY

Treatment of the HIV infection involves a complex regimen of antiretroviral medications referred to as highly active antiretroviral treatment, designed to reduce viral load and bolster the immune system's ability to fight new infections. Five classes of antiretroviral medications are available: nucleoside analog reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, nucleotide analogs, and entry inhibitors.⁴⁵ Interferon and ribavirin are used in the management of HCV,⁴⁶ with the goal of treatment being the cure of infection and cessation of liver disease progression.

In patients with schizophrenia and HIV infection, dual administration of antipsychotics and antiretrovirals may be necessary. Thus, all parties involved in treatment management should be cognizant of the clinical issues that exist in coadministering these medications.

Effects of Antipsychotics on HIV Replication

To assess antipsychotic drugs for antiretroviral activity, an *in vitro* study⁴⁷ was conducted with the conventional antipsychotics haloperidol, fluphenazine, thiothixene, and chlorpromazine and the atypical antipsychotics clozapine, risperidone, sertindole, and quetiapine, along with their various respective metabolites. Two of the metabolites of clozapine were able to inhibit HIV type 1 replication in tissue culture at subcytotoxic concentrations, but no significant antiviral activity was observed with any of the other compounds tested.

Antipsychotic drugs in patients with schizophrenia with or without comorbid HIV infection may reduce the psychotic symptoms that may be contributing to high-risk behavior. The possibility that these agents may offer the additional advantage of antiretroviral activity is intriguing, but its clinical relevance has not been demonstrated.

Effects of Antiretrovirals on Psychotic Symptoms

Antiretroviral drugs do not have antipsychotic activity. To the contrary, case reports on HIV-positive patients have described the onset of psychotic and depressive symptoms attributable to treatment with antiretroviral agents.^{48,49} In individual cases in which antiretroviral therapy is temporally linked to the onset of psychotic symptoms, initiation of antipsychotic medication may alleviate the symptoms. If psychotic symptoms persist despite such treatment or are very severe, it may be necessary to discontinue the antiretroviral regimen and, after stabilizing the patient, resume a new antiretroviral regimen that does not include the offending agent.⁴⁸

Cotherapy for Psychosis and Hepatitis C Virus Infection

The mainstay of therapy for HCV infection is interferon- α , which may cause depression and other changes in mental status. Consequently, the use of this therapy in patients with chronic psychosis has been questioned.^{50,51} On the other hand, restricting a necessary treatment is viewed by others as unwarranted. Careful monitoring is the best approach to treating patients with a history of mental illness for HCV infection.

Drug-Drug Interactions

In patients with comorbid psychosis and HIV, concomitant therapy with antipsychotic and antiretroviral drugs raises the possibility of drug-drug interactions. The atypical antipsychotics are metabolized primarily by the hepatic cytochrome P450 (CYP) system, and cotherapy with drugs that inhibit or stimulate cytochrome enzyme activity could result in increases or decreases in plasma levels of the antipsychotic.⁵² For example, ritonavir (600–1000 mg/day) reduced systemic exposure from a single 10-mg dose of olanzapine in 14 healthy volunteers (olanzapine is metabolized by CYP1A2 isozyme and glucuronosyltransferases, both of which are induced by the protease inhibitor).⁵³ On the other hand, ritonavir and indinavir inhibit the CYP2D6 and CYP3A4 isozymes that metabolize risperidone and could therefore result in increased exposure to given doses of risperidone during cotherapy.^{54,55} Simultaneous use of antipsychotics and protease inhibitors should include close monitoring so that the antipsychotic dosage can be adjusted if necessary. The general rule of start low and go slow is the most helpful approach.

Practice guidelines published by the American Psychiatric Association recommend that depot antipsychotics be avoided in patients with advanced HIV.⁴⁵ In patients receiving concomitant antipsychotic and antiretroviral therapy, dosage adjustment of the antipsychotic may be necessary to minimize potential adverse events. Patients receiving clozapine and antiretroviral medications should be closely monitored for agranulocytosis and seizures. Pimozide is contraindicated in combination with protease

inhibitors because of the risk of fatal arrhythmias. As with administration of any dual therapy, simple strategies such as starting at low dosages and escalating dosages slowly, providing the least complicated dosing schedule possible, considering the adverse event profiles of the medications, and maintaining awareness of the drug metabolism and clearance pathways are all helpful in minimizing and potentially preventing serious and unnecessary complications.

TREATMENT CHALLENGES

Lifestyle Modification

A growing body of evidence indicates that psychosocial interventions in general and learning-based therapies in particular can be used effectively in patients with schizophrenia.⁵⁶ In schizophrenic patients at risk for contracting or transmitting HIV infection, cognitive-behavioral interventions can reduce high-risk behaviors, although the benefits tend to wane without reinforcement. For example, 52 men and women with mental illness participated (by random assignment, either at once or at a later date) in 4 weekly 90-minute sessions devoted to education and skills relevant to preventing the sexual transmission of HIV infection.⁵⁷ Compared with patients on the waiting list, those who participated in the program were significantly less likely to engage in unprotected sex and more likely to use condoms over the next month; however, in a smaller number of patients from whom longer follow-up data were available, only some of the benefits were retained after 2 months.⁵⁷ These methods, which are costly and time-consuming in research trials, have not been widely used in publicly funded facilities.¹¹

A number of public health initiatives could reduce the risk of HIV infection in individuals with mental illness, starting with routine and consistent use of a history-based risk-classification system. Testing and counseling should be provided for all patients with risk histories, and these individuals may be considered for intensive behavioral intervention programs. HIV education aimed at patients and the public is essential. Programs to provide condoms and to encourage drug injection equipment replacement or cleansing with bleach remain socially and politically controversial but should be encouraged as ways to reduce the spread of HIV and HCV infections through sexual contact and IDU.

A major barrier to effective intervention has been inadequate awareness of the increased risk of HIV infection in this population, even on the part of clinicians who care for these patients.¹⁸ Furthermore, those clinicians who are aware of the risks may be reluctant to discuss sexual activity with individuals with mental illness for fear of being perceived as encouraging it. At the same time, patient advocacy groups may be reluctant to publicize the prevalence of HIV infection in people with schizophrenia for

fear that patients will be doubly stigmatized. The result of such concerns is that testing, education, and risk-reduction programs are not employed when they could do the most good; instead, clinical intervention is often deferred until the patient has become infected with HIV and is in need of antiretroviral therapy.

Adherence to Pharmacotherapy

As in all forms of pharmacotherapy, adherence to antiretroviral therapy varies inversely with the frequency and severity of symptomatic adverse events. Adverse effects associated with protease inhibitors include gastrointestinal and metabolic disturbances; side effects of nucleoside reverse transcriptase inhibitors include gastrointestinal symptoms, lactic acidosis, and neuropathies; and nonnucleoside reverse transcriptase inhibitors have been linked to skin rashes, hepatotoxicity, and psychiatric disturbances.⁵⁸

Some patients with schizophrenia tend to show poor adherence to medication in general, including antipsychotic medication^{59,60} and drug treatment for nonpsychiatric conditions.⁶¹ Risk factors identified to be predictors of nonadherence in patients with schizophrenia include poor insight, prior history of nonadherence, negative attitude, substance abuse, lack of social or family support, and poor therapeutic alliance.⁶⁰ Maintaining close contact with patients through medical and social services should be part of a proactive effort to encourage and facilitate adherence.

Nonpsychotic individuals may also show inadequate adherence to antiretroviral therapy, possibly because of AIDS-related neurocognitive deficits; complex medication regimens can be a particular problem in the face of cognitive loss.⁶² There is some evidence that treatment adherence is as good or better in HIV-positive patients with schizophrenia as in those without schizophrenia, possibly because the former group may be under closer medical supervision.⁶³ In a study determining antiretroviral adherence in 45 HIV-positive patients with serious mental illness (including 24 with bipolar depression and 12 with schizophrenia),⁶⁴ mean adherence, defined as the percentage of prescribed doses taken, was 66%, ranging widely from over 90% in 18 patients to < 50% in 14 patients. The implication is that many psychiatric patients are able to adhere to prescribed medication, although overall adherence to treatment regimens in this population remains inadequate.

COORDINATING MENTAL AND PHYSICAL HEALTH CARE

In patients with comorbid schizophrenia and HIV or HCV infections, coordination of mental and physical health care is essential because each condition can adversely affect the prognosis of the other. Fortunately, mental health care and HIV services delivered in the public

sector are of surprisingly high quality in some regions, and, in many locales, special funds have been provided for the treatment of HIV-infected people with mental illness. It also appears that HIV-infected people with mental illness may be more likely to receive appropriately coordinated care than people with mental illness with other chronic medical conditions.

Mental health care providers are in the best position to help psychiatric patients obtain HIV-related services, such as prevention programs, risk assessment, antibody testing, counseling, and medical care.²³ Psychiatrists, HIV infection specialists, and other involved clinicians should all assume responsibility for maintaining open lines of communication and coordinating the mental and physical health care services they provide for patients with comorbid schizophrenia and HIV. All personnel involved in their care should work cooperatively and proactively to create a coordinated and comprehensive management regimen, to foster treatment adherence, and to monitor changes in either condition.

CONCLUSION

The comorbidity of schizophrenia and viral infections, such as HIV and HCV, is an emerging area, for which more data are needed regarding the impact these conditions and their treatments may have on patients. It is critical that mental health professionals are cognizant of the increased risk of HIV and HCV infections among people with mental illness and are willing to discuss the risk associated with these infections with their patients and their patients' families/caregivers. Management of schizophrenia in the presence of comorbid HIV or HCV infection requires special considerations. With proper awareness and coordination on the part of the medical community, caregivers, and patients, these conditions can be optimally and successfully managed, and long-term complications can at least be potentially delayed.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), indinavir (Crixivan), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), ribavirin (Rebetol, Copegus, and others), risperidone (Risperdal), ritonavir (Norvir), thiothixene (Navane and others).

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