

Treatment of Psychiatric Disorders in Children and Adolescents with HIV/AIDS

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Published online: 20 March 2010
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Abstract We could not have predicted that HIV/AIDS would become one of our greatest public health challenges worldwide when the first cases were identified in the 1980s. More than 22 million people have died from the disease, and HIV is now the seventh-leading cause of death in the United States among 15- to 24-year-olds. At the beginning of this pandemic, most HIV infections of youth were acquired congenitally. Prenatal screening of pregnant women, early detection, and antiretroviral therapies have reduced mother-to-child transmission. Children born with HIV infections are now young adults living with HIV, while other adolescents are acquiring HIV primarily through high-risk behaviors. Associations between psychiatric symptoms and poor health outcomes have been recognized among adults. Few studies have examined these factors among youth. We review what is known about psychiatric syndromes among HIV-positive youth, and their treatments.

Keywords Adolescents · HIV/AIDS · Psychiatric disorders · Adolescent HIV · Mental health

Introduction

In 2003, 4.8 million people worldwide (range, 4.2–6.3 million) became newly infected with HIV. More than 22 million people have died since the first cases of AIDS were

identified in 1981. At the end of 2006, more than 1 million individuals in the United States were living with HIV infection (21% were undiagnosed) [1].

In 2008, the Centers for Disease Control and Prevention (CDC) estimated that 56,300 people were newly infected with HIV in 2006 (the most recent year for which data are available) [2]. More than half (53%) of these new infections occurred in gay and bisexual men. Black men and women were strongly affected and were estimated to have an incidence rate that was seven times as high as the incidence rate among whites [1, 3].

The cumulative estimated number of deaths of people with AIDS in the United States through 2007 was 583,298. This included 557,902 adults and adolescents [2].

Prenatal detection of HIV infection among women and the use of antiretroviral therapies to prevent transmission have caused the rates of congenitally acquired HIV to decline dramatically in developed countries. At the end of 2002, there were only 9,300 cases of AIDS in children younger than 13 years of age in the United States. In 2003, only 59 cases of congenitally acquired cases were reported to the CDC [4]. For children who were born too early to benefit from these advances, they are now young adults living with this chronic condition. Many of these young adults are beginning to have their own children [5].

Although the number of reported new cases of congenitally acquired HIV is low, many more young people are being infected. The CDC reports that adolescents account for 50% of new HIV infections and 25% of new sexually transmitted disease cases reported annually [4]. Recent incidence data collected through 2006 confirm that HIV is an epidemic primarily of young people. More infections occurred among young people 13–29 years of age than in any other age group, accounting for 34% of all new infections [2]. The most common modes of transmission among adolescents

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and young adults were male-to-male sexual transmission (accounting for 42% of all cases), high-risk heterosexual contact (31%), and injection drug use (21%). Most cases of new infections were among blacks, and 19% were among Hispanics.

Psychiatric Conditions in the Context of Pediatric HIV/AIDS

The associations between adolescents with mental health conditions and the greater risk of HIV transmission have been well-supported by a growing body of evidence. Specifically, the evidence suggests that psychiatrically ill adolescents are more likely to be sexually active, to engage more often in unprotected intercourse, and to have multiple sexual partners than their peers without psychiatric conditions [6, 7]. The evidence further suggests that they are more likely to have an early sexual debut and histories of sexually transmitted diseases, more likely to use drugs or alcohol when having sex, and less likely to use condoms [5]. These findings underline the importance of identifying psychiatric illness in preventing HIV transmission.

Prevalence estimates of psychiatric disorders among HIV-positive adolescents have varied widely. Many of the studies have limited generalizability due to small sample sizes, different study designs, and differing methods for ascertainment of diagnosis. Although clinical reports suggest high rates of mental health problems among perinatally infected adolescents [8], few well-controlled studies have examined rates of psychiatric disorders among adolescents who have vertically or behaviorally acquired HIV disease [9, 10••].

Scharko [9] reviewed studies that used *DSM* criteria to determine the prevalence of psychiatric disorders among HIV-infected youth. He found eight studies that examined psychiatric disorders among HIV-positive youth that met these criteria. The author found high prevalence rates of psychiatric disorders: 28.6% with attention-deficit/hyperactivity disorder (ADHD), 24.3% with anxiety disorders, and 25% with depression. Study limitations included small sample sizes, unclear modes of infection, unclear diagnostic methods, and wide variations in the ages of sample and use of control groups [9]. One well-controlled study examining behavioral problems in perinatally infected children found high rates of behavioral problems. However, these investigators also found that the rates of these disorders did not differ from those of a control group of children who were perinatally exposed to—but not infected with—HIV, suggesting that HIV infection was not a likely contributor to the development of behavioral problems [11]. Another study found high rates of psychiatric hospitalization among perinatally infected children and adolescents when compared

with their non-HIV-infected peers. In this study, most were admitted, with the primary diagnoses being depression, ADHD, and oppositional defiant disorder [8]. One small study of HIV-infected youth 6–15 years of age found high rates of depression (47%) and attentional problems (29%); however, these findings were associated with declining immune function, further suggesting that depression may be associated with encephalopathy and worsening immune function [12].

A few studies have examined rates of psychiatric disorders among HIV-infected youth, using structured interviews to obtain psychiatric diagnosis. Pao and colleagues [13] used the Structured Clinical Interview for *DSM* Disorders to evaluate 34 HIV-positive adolescents attending an urban clinic for current and lifetime rates of psychiatric disorders. In this sample, 68% had a diagnosis of depression, 59% substance abuse, and 29% conduct disorder. They further found that most of these youth had psychiatric disorders preceding their diagnosis and that about half of them had a current affective disorder. Compared with estimated rates of psychiatric disorders among community samples of adolescents (10%–22%), HIV-positive adolescents experienced these disorders at significantly higher rates [13, 14].

In another study using the Diagnostic Interview Schedule for Children to determine the presence of psychiatric disorders in 47 perinatally infected youth 9–16 years of age, 55% of youth evaluated met criteria for a psychiatric disorder, with anxiety disorders being the most prevalent (40%), followed by ADHD (21%) and disruptive behavior disorders (24%) [10••]. These recent well-controlled studies of psychiatric diagnoses among perinatally acquired HIV-positive youth suggest rates of psychiatric disorders ranging from 48% [15] to 61% [10••]. When evaluating all the evidence of psychiatric disorders among HIV-positive adolescents, these studies suggest high rates of psychiatric illnesses among adolescents who have acquired their HIV infections behaviorally and perinatally.

Treatment

When considering psychotropic medication use for HIV-positive individuals receiving antiretroviral therapies, developmental, environmental, social, and family factors must be considered. A comprehensive assessment should include information from the child or adolescent and collateral information from schools, primary care providers, specialists, counselors, family members, and others involved in caretaking. A thorough family psychiatric history and history of recent life events and stressors are extremely important in reaching diagnostic conclusions.

One must also consider many complex and interacting factors when evaluating psychiatric symptoms and other

behavioral problems presenting in the context of HIV disease. Biological factors, including the direct or indirect effects of the virus on the central nervous system, genetic factors, prenatal exposure to substances, opportunistic infections, adequacy of medical care, and other environmental factors impact the presentation of these symptoms. Additionally, most youth exposed to HIV live in demographically distressed areas affected by poverty, family stress, and alcohol and substance abuse [5]. It is important to remember that an effective treatment plan should be developed with a multidisciplinary team, include families or other caregivers, and must occur in a biopsychosocial and developmental context. Medications should be used as one component of a comprehensive treatment plan for youth with HIV disease.

Recommendations for pharmacologic treatment of psychiatric disorders in HIV-infected youth have been based on studies of adult populations that suggest that medications commonly used to treat psychiatric symptoms in non-medically ill populations—psychostimulants, antidepressants, and antipsychotic medications—are useful in the treatment of those disorders in the medically ill, including those who are HIV-positive [16]. For youth with psychiatric conditions, the recommendations for pharmacotherapies are largely empirical and based on clinical experience [5].

Another consideration in choosing to use pharmacotherapy to treat psychiatric symptoms in HIV-positive youth is the potential for drug interactions for those using highly active antiretroviral therapy. Many psychotropic medications, as well as antiretroviral medications, are widely metabolized by the cytochrome P450 system, especially the subgroups 3A4 and 2D6, and have a strong potential for drug–drug interactions. Hepatic enzyme systems may be inhibited or induced by medications that are metabolized by the liver, with the potential for increasing or decreasing levels of one or both. Although the clinical significance of many of these interactions is unclear, certain classes of antiretroviral classes are known to pose the greatest risk for changes in drug levels that are significant in HIV-positive individuals. The protease inhibitors, specifically ritonavir, have the greatest impact on the inhibition of 3A4, and to a lesser extent on 2D6. [17];

Efavirenz has been shown to induce CYP3A4, which potentially decreases plasma levels of coadministered medications principally metabolized by this pathway [17].

The absence of evidence guiding clinicians' prescribing practices for HIV-infected youth requires that clinicians proceed carefully and thoughtfully. The benefits of treatment must outweigh the risks, and the potential for side effects must be considered. The heightened sensitivities to side effects that may exist in youth with neurological effects of HIV and the potential for children and adolescents to respond to lower doses of medications must be considered when choosing medications. A thorough discussion with the youth

and family and comprehensive education about side effects and adverse effects should take place. When choosing medications and dosing, the clinician must consider the child's weight, body mass index, Tanner stage, and status of medical illness; potential drug interactions; and the side effects of medications [18•].

Mood Disorders

The prevalence of depressive disorders increases in frequency from childhood to adolescence for HIV-negative and HIV-positive populations [14]. Similar to adult populations, depressed mood and irritability of at least 2 weeks' duration are criteria. Complicating this diagnosis in the HIV-positive child or adolescent, however, is the overlap between the vegetative symptoms of depression and the symptoms of the medical illness, or the side effects of HIV treatments. Symptoms such as anorexia, fatigue, or other somatic complaints may be related to depression or HIV disease. When establishing the diagnosis, evaluation for worsening of medical status, poor adherence to antiretroviral therapy, drug resistance, recent stressors with resulting adjustment disorder, and other psychological factors should be considered.

Although antidepressants of all classes have been prescribed to HIV-positive children and adolescents based on the adult literature, selective serotonin reuptake inhibitors are the most commonly prescribed antidepressant medications, although no evidence currently exists to support differences in efficacy. However, only fluoxetine has been approved for the treatment of depression in children and adolescents, as it has the greatest empirical support [19]. Amitriptyline is approved for treatment of depression in patients older than 12 years of age. Tricyclic antidepressants (TCAs) have been used empirically to help with pain syndromes, insomnia, and anxiety, but their sedating side effects and potential for toxicity in overdose limit their usefulness [20]. Fluoxetine and its metabolite, norfluoxetine, may inhibit CYP3A3 and CYP3A4, contraindicating its use with macrolide antibiotics, azole antifungal medication, and several other medications [21]. Citalopram and mirtazapine are commonly used due to fewer drug interactions and more favorable side effect profiles. Additionally, mirtazapine has been helpful in promoting weight gain and sleep. Careful monitoring for the emergence of suicidal ideation is warranted with the use of the antidepressant medications during treatment.

The presence of bipolar disorder in prepubertal youth and adolescents and its clinical presentation have been supported by a large evidence base, although no studies have examined the prevalence of these disorders in HIV-positive youth [22]. Grandiosity, elevated and expansive mood, racing thoughts, decreased need for sleep, and hypersexuality can also present

in the pediatric population and can occur with other childhood psychiatric disorders, such as ADHD and substance abuse. Treatment recommendations for children and adolescents with bipolar disorder are similar to those recommended for adults, with the caveats that drug interactions, hepatotoxicity, and side effect profiles must be considered in the presence of HIV disease [23].

Attention-Deficit/Hyperactivity Disorder

Several studies suggest high rates of ADHD in HIV-infected youth [9, 10••], though few studies have examined the use of psychotropic medications in this group. ADHD is characterized by sustained impulsivity, poor attention, and hyperactivity whose onset is prior to 7 years of age. The efficacy of psychostimulants in the treatment of ADHD in non-medically ill populations is well-validated and is the pharmacotherapeutic treatment of choice for this disorder. Although psychostimulants are commonly prescribed in HIV-positive children, few studies have evaluated their dosage or efficacy in the HIV-positive population.

Empiric data suggest initiating treatment at the same dosages as those in the non-medically ill population and titrating those dosages as recommended. Stimulant medications have few drug–drug interactions, making them relatively safe in combination with antiretrovirals [24]; however, it is important to observe for side effects.

Anxiety Disorders

Anxiety disorders seem to be common among HIV-positive youth and are frequently comorbid with other psychiatric disorders. Social and specific phobias, separation anxiety disorders, agoraphobia, generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder have been reported, but the prevalence rates of specific anxiety disorders among HIV-positive youth have not been described [10••]. When they are present in HIV-positive youth and significant enough to interfere with normative function, cognitive and behavioral therapies are indicated. The use of selective serotonin reuptake inhibitors and TCAs have demonstrated efficacy in more severe cases of anxiety disorders that have not responded to effective evidence-based psychotherapeutic interventions [25].

Post-traumatic Stress Disorder

The epidemiology of HIV in the United States and its geographic distribution heighten the risks for exposure to environmental stressors for HIV-positive youth. Most

HIV-positive women reside in poor urban communities, thus increasing the risk of exposure to trauma for youth living with HIV. Most perinatally exposed youth live in inner cities, in which stress, poverty, and trauma are prevalent [26]. Trauma related to traumatic events and medical procedures place HIV-positive youth at risk for post-traumatic stress disorder (PTSD) and/or traumatic stress [27]. The evidence further suggests that trauma exposure may adversely impact adherence to treatment recommendations among HIV-positive youth [28].

Only a few studies have examined the prevalence of PTSD and post-traumatic stress symptoms (PTSS) among HIV-positive youth. In one such study, PTSD and PTSS symptoms in a sample of HIV-positive youth—30 adolescents and young adults with HIV/AIDS—were evaluated using a trauma symptom checklist keyed to *DSM-IV* PTSD symptoms. These investigators found high rates of PTSD (13.3%) and PTSS (20%) in the sample. They reported high rates of PTSD and PTSS in response to receiving a diagnosis of HIV infection. Even higher rates of PTSD and PTSS (23.3% and 23.3%) were observed when examining other traumatic life events experienced by this same group of adolescents [28]. This is one of the few studies to examine PTSD among a population of HIV-positive adolescents.

Treatment studies for adolescents with PTSD suggest that cognitive-behavioral therapies focused on PTSD symptomatology are more effective than other therapies in the management of symptoms, and that medications can be helpful, although support for medication use in adolescents is lacking [29].

Unfortunately, the care provided to youth to prolong life may itself be a source of anxiety for children with chronic illnesses, and the presence of medical trauma has been well-supported by the evidence [27]. For children and adolescents experiencing anxiety related to procedures, benzodiazepines used in low doses, such as lorazepam, in conjunction with distraction techniques and psychotherapy have been helpful. Clonazepam has been used as an adjunct to psychotherapy for children and adolescents experiencing more pervasive and prolonged anxiety. Benzodiazepines may cause sedation and behavioral disinhibition, especially in patients with central nervous system disease, and should be monitored closely.

Antihistamines have been used to sedate anxious children but are not recommended for the treatment of anxiety. Additionally, the anticholinergic properties of antihistamines can precipitate or worsen delirium.

Delirium and Dementia

Although few studies have specifically examined pediatric delirium, the available evidence suggests that the clinical

presentation of delirium in the pediatric population is very similar to that of adults with delirium and that the *DSM-IV* diagnostic criteria are applicable across the lifespan. The clinical findings of impaired attention and responsiveness, fluctuating levels of consciousness and orientation, confusion, affective lability, and sleep disturbance are present in pediatric patients with delirium. What seems to differ is that the findings of paranoia, perceptual disturbances, and memory impairment are less common in younger children. The most common etiologies were underlying medical conditions [30]. Treatment recommendations for pediatric delirium are largely based on the same principles of management recommended for adults. Providing a calm environment, developmentally appropriate strategies to maintain orientation, and environmental cues that support orientation and decrease confusion is recommended. Low doses of atypical antipsychotic agents have been used empirically [30]. It should be pointed out, however, that in one recent case report, the atypical agent risperidone failed to adequately address symptoms of delirium in an adolescent with HIV-associated dementia, requiring the use of a typical agent, haloperidol, to effectively address the symptoms of delirium [31].

Although the presence of HIV-associated dementia has been well-described among adults with HIV disease, this late-appearing neuropsychiatric presentation has not been well-described in the pediatric population [32]. HIV-related progressive and static encephalopathies have been well-described among perinatally infected youth [33]. In the previously mentioned case report of an adolescent presenting with delirium and HIV-associated dementia, these authors suggested that this presentation may be a harbinger for new neurologic findings among HIV positive adolescents. The presentation of neurologic disease may be changing, as adolescents with perinatally acquired HIV and adolescents with behaviorally acquired HIV are living longer with this chronic illness and may increasingly present with this late-occurring sequelae of HIV disease [31].

Psychotherapeutic Interventions

Few studies have specifically examined the outcomes of psychotherapeutic interventions for HIV-positive youth. Most studies have focused on interventions for adherence to medical treatments and risk reduction. Cognitive and behavioral therapies, insight-oriented therapies, and group therapies have demonstrated varying degrees of efficacy for decreasing psychological distress, improving adherence to treatment, and relieving the symptoms of depression and anxiety among adults with HIV disease [34]. Current treatment recommendations for HIV-positive youth with psychiatric disorders are the same evidence-based psycho-

therapies recommended for youth not affected by HIV disease and extrapolated from adult studies.

However, a few studies suggest that group interventions can decrease psychological distress, improve peer support, encourage safer sexual behaviors, improve adherence to medical treatments and safe sex practices, and improve self-care and overall quality of life for HIV-positive youth [35, 36]. Other psychosocial programs developed to help adult caretakers of HIV-positive youth that teach effective parenting skills, monitoring of medical treatment, and support for increasing social networks have been useful. HIV prevention programs using behavioral strategies have been effective in increasing safe sex practices [36]. Effective treatments for HIV-positive youth must involve the family and incorporate adjunctive interventions aimed at providing support, guiding behaviors, and monitoring treatment adherence.

Conclusions

Despite the challenges, most children and adolescents living with HIV infection are doing well. These youths, who were once not expected to live long, are now living into young adulthood and coping with their chronic illness. This increased longevity has changed the clinical and social environment for youths living with HIV, bringing new demands and challenges. The demands for adherence to complicated medication regimens, the uncertainty about mortality when living with a treatable but still incurable disease, and normal developmental challenges for adolescents all converge to increase the burden of their illness and the demands of living with this chronic condition.

Psychiatric conditions are increasingly recognized among HIV-positive youth. The evidence firmly supports the relationships among the presence of psychiatric illness and increased risks for acquisition and transmission of HIV disease, decreased adherence to safe sexual practices and antiretroviral therapy, and worse medical and psychosocial outcomes [37, 38].

Identification of psychiatric disorders in HIV-positive youth should occur in the context of a comprehensive biopsychosocial assessment. Multiple informants involved in the life of the child or adolescent care, including caregivers, schools, and medical providers, are needed. Given the unique circumstances of children affected by HIV disease, the psychosocial assessment is essential. HIV disease is still associated with significant stigma, forcing families affected by HIV disease to make decisions about disclosure of their illnesses to other family members, schools, and social contacts. Youth born with HIV disease also face issues of parental loss, as well as the potential loss of other family members. Assessment of changes in health status,

cognitive status, and adherence to antiretroviral treatments and safe health practices, including an assessment of sexual practices and safe sex behaviors, should be included [39].

Psychotropic treatments for behavioral conditions among HIV-positive youth should occur within the biopsychosocial framework. Although few treatment studies have focused specifically on treatments for psychiatric conditions among medically ill children and adolescents, and even fewer have focused on HIV-positive youth, the few available studies suggest that interventions currently used for non-HIV-positive children and adolescents may be effective. Attention must be given to potential drug interactions with other medications, side effect profiles, and ease of administration for youth who may already be using antiretroviral therapy.

Psychiatrists can play an important role in the prevention of HIV infection and in slowing this epidemic. Identification and treatment of psychiatric conditions among HIV-negative youth can decrease risky behaviors contributing to HIV infection. Identification and treatment of HIV-positive youth with psychiatric conditions can increase adherence to antiretroviral therapy, thus decreasing risks for drug resistance and disease progression and promoting safe sex practices and other health-sustaining behaviors. Psychiatrists are well-positioned to improve the quality of life of youth affected by HIV and their families.

Disclosure No potential conflict of interest relevant to this article was reported.

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