Neuropsychiatric Aspects of Coinfection With HIV and Hepatitis C Virus

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By AIDS Reader [1]

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In the United States, an estimated 150,000 to 300,000 people are infected with both HIV and hepatitis C virus (HCV), representing about 15% to 30% of all persons living with HIV infection and 70% to 90% of injection drug users. The longer life expectancy of HIV-infected persons since the advent of highly active antiretroviral therapy has highlighted the effect of chronic hepatitis C, which has become a major cause of morbidity and mortality among HIV-infected persons. The neurocognitive and psychiatric consequences of HIV/HCV coinfection are far reaching and significantly influence the clinical presentation, care, and outcomes of coinfected persons.

At the same time, the etiology and pathophysiology of neuropsychiatric syndromes associated with HIV/HCV coinfection remain poorly understood, as do the unique nuances of clinical assessment and treatment. This presents a clinical dilemma, particularly in light of the high and growing rate of HIV/HCV coinfection. In addition to the far-reaching influence of coinfection, the resulting neuropsychiatric complications may correlate with a decline in functionality, medication nonadherence, and poorer medical outcomes. A thorough understanding of the etiology, pathophysiology, assessment, and treatment of the syndromes would probably benefit clinicians who face the unique challenge of treating the complications and, thereby, helping to improve the quality of life of coinfected persons.

The goals of this review include an elucidation of the neurocognitive and psychiatric aspects of HIV infection, hepatitis C, and HIV/HCV coinfection; a discussion of the clinical implications and integrated models of care for coinfected persons who have neuropsychiatric comorbidities; and suggestions for future research directions.

NEUROCOGNITIVE ASPECTS OF HIV INFECTION

Neurocognitive sequelae of HIV infection are widely recognized, and diagnostic criteria were established in 1991 by a Working Group of the American Academy of Neurology AIDS Task Force. Two categories, HIV-associated dementia (HAD) and HIV-associated minor cognitive-motor disorder, were identified and distinguished primarily by the degree of the patient’s impairment. Inclusion of a third category, asymptomatic neurocognitive impairment, has been proposed; it is differentiated from the other categories by including in its criteria a lack of obvious functional decline. Cherner and colleagues found slightly increased sensitivity, specificity, and positive predictive value using the 3-category diagnostic nomenclature in predicting HIV-related neuropathology at autopsy.

The most common neurocognitive impairments in persons with HIV infection are found on measures of complex attention, mental flexibility, psychomotor speed, and verbal retrieval, which probably reflect an underlying deficit in controlled (versus automatic) attentional processing. General intelligence, verbal skills, visuoperception, and recall of successfully encoded information remain relatively unaffected except in cases of severe HAD. This pattern of deficits on neurocognitive testing is often said to reflect “subcortical” dysfunction and is consistent with neuropathological studies showing abnormalities primarily in the white matter and basal ganglia. However, cortical abnormalities also may be present and may be more extensive than previously recognized. Neurocognitive dysfunction has proved to be an important clinical consideration for persons with HIV infection because even subtle impairment can interfere with abilities to perform activities of daily living, such as medication adherence and driving. Moreover, the presence of neurocognitive dysfunction is a strong indicator of CNS involvement, which can influence treatment decisions. For example, cognitively impaired persons may respond to agents designed to enhance the penetration of antiretroviral drugs into the CNS, or they may be candidates for existing or future neuroprotective therapies. Thus, assessment of neurocognitive functioning is recommended for all persons with...
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HIV/AIDS, especially those at greatest risk for neurocognitive impairment, such as persons who are older than 60 years and who have high HIV RNA levels or uncontrolled viral replication, low CD4 counts, and/or functional limitations associated with neurocognitive complaints. A combination of list learning and psychomotor speed tasks—specifically the combination of Hopkins Verbal Learning Test–Revised (HVLT-R), which assesses verbal learning and memory (immediate recall, delayed recall, delayed recognition); Grooved Pegboard Test (with either the nondominant or dominant hand), which is a timed test that is sensitive to motor slowing; Trail Making Test B, which is a test of perceptual motor speed, attention, and visuospatial tracking; and the combination of HVLT-R and Wechsler Adult Intelligence Scale–Third Edition Digit Symbol Test, which assesses processing speed—have been found to be more accurate than the HIV Dementia Scale in screening for neurocognitive impairment. The sensitivity rates of these assessments were higher (i.e., 75%) than those reported for a variety of other screening batteries.

Since the introduction of highly active antiretroviral therapy in 1996, the incidence of moderate to severe HAD has decreased significantly, but the incidence and prevalence of milder forms of neurocognitive dysfunction have increased, with prevalence estimated to be as high as 40%. Although some persons with HIV may experience improvements in neurological and neurocognitive symptoms after beginning antiretroviral therapy, no antiretroviral regimen has been shown to eliminate completely neurocognitive dysfunction. These findings suggest that the virus itself is not solely responsible for neurocognitive dysfunction. There is accumulating evidence that chronic CNS inflammation secondary to the virus infection, in combination with genetic differences in the host immune response, may play a primary role in neurocognitive impairment.

PSYCHIATRIC ASPECTS OF HIV INFECTION

The high prevalence, challenges, and importance of recognizing and treating psychiatric disorders in HIV-positive persons are well documented. In HIV-positive adults, the estimated lifetime prevalence of major depressive disorder is 29% to 36%, which is 2 to 3 times higher than the prevalence seen in the general population; the estimated lifetime prevalence of dysthymia is 26%; generalized anxiety disorder, 16%; and panic disorder, 11%. High rates of posttraumatic stress disorder (PTSD) also are seen among patients with HIV disease, up to 30% to 50%. Depression has been associated with more HIV-related symptoms. Substance use disorders also are significant concerns in HIV-positive persons, since injection drug use accounts for 24% of HIV infection transmission in the United States, and the increasing use of methamphetamine places abusers at an increased risk for acquiring or transmitting HIV infection. Furthermore, patients with psychiatric disorders may be more likely to engage in high-risk behaviors, such as injection drug use and sexual indiscretion, possibly attributing to the overrepresentation of psychiatric disorders in the HIV-infected population. Neuropsychiatric features such as apathy and irritability, which are more likely to reflect HIV-associated CNS involvement than are depression and anxiety, are more common with advanced illness.

In a 2007 retrospective review, HIV infection was present in 1.2% of the psychiatric outpatients, about 4 times the occurrence of HIV infection in the general population. The major diagnostic categories that had a high prevalence of HIV infection were substance use disorders (5%), personality disorders (3.1%), bipolar disorders (2.6%), and PTSD (2.1%). Psychiatric disorders in HIV-positive persons may be related to primary effects of the virus, such as pathological abnormalities in the frontal-subcortical circuitry associated with apathy and irritability, or secondary etiologies, such as mania occurring in late-stage HIV infection, or they may be related to psychosocial effects, such as psychological reactions to losses, lack of social support, stigmatization associated with HIV/AIDS, and comorbid medical conditions. Psychiatric comorbidities,
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specifically depression and alcohol abuse or dependence, were predictors of discontinuing combination antiretroviral therapy. Difficulties with treatment adherence may be related to psychiatric comorbidities resulting in neurocognitive deficits, apathy, and hopelessness.

Incorporating screening tools, specifically for depressive, anxiety, and substance use disorders, can facilitate the recognition of comorbid psychiatric disorders. The Beck Depression Inventory–Fast Screen and the Patient Health Questionnaire 9 (PHQ-9) have been helpful in screening, monitoring, and treating patients with depression, and the CAGE Questionnaire and Michigan Alcohol Screening Test have been helpful in screening for alcohol abuse or dependence.

A compilation of the features of HIV infection are summarized in Table 1.

NEUROCOGNITIVE ASPECTS OF HEPATITIS C
Neurocognitive dysfunction in the form of hepatic encephalopathy has long been recognized in persons with cirrhosis secondary to chronic liver diseases, such as chronic hepatitis C. Hepatic encephalopathy can range from subtle deficits in attention/executive functioning, learning, and psychomotor speed not obvious on clinical examination (ie, minimal hepatic encephalopathy) to frank delirium, coma, and death. Neurocognitive dysfunction in the form of minimal hepatic encephalopathy has been found in more than 50% of patients who have undergone evaluation for liver transplantation and is associated with work-related disability and driving difficulties.

The epidemic of hepatitis C led to the discovery of neurocognitive dysfunction in persons with chronic liver disease who do not have cirrhosis. It is now recognized that approximately 33% of persons chronically infected with HCV experience neurocognitive dysfunction. As in HIV-infected persons, frontal-subcortical circuits appear to be affected most and have been found through the use of a variety of methods that include neuropsychological tests, proton magnetic resonance spectroscopy, and P300 event-related potentials.

To complicate matters further, the only FDA-approved treatment of chronic hepatitis C, interferon alpha (IFN-α), usually administered in combination with ribavirin, also is associated with neurocognitive dysfunction primarily in frontal-subcortical systems.

The negative effect of IFN-α on neurocognition in hepatitis C suggests that cytokines play a role in the etiology of CNS dysfunction as exhibited by these persons. Chronic immune system activation in response to chronic hepatitis C probably results in ongoing production of IFN-α and other cytokines known to affect neurocognition. Cytokines are thought to affect brain functioning indirectly via multiple pathways that include transmission of signals through the vagus nerve or other visceral afferent neuronal pathways, induction of secondary messengers, and stimulation of neuroendocrine pathways and various neurotransmitter systems. A direct effect of the HCV on the brain also is possible, such as a local inflammatory response triggered by the virus.

PSYCHIATRIC ASPECTS OF HEPATITIS C
Clinically significant emotional distress is evident in 35% of HCV-infected patients not receiving antiviral therapy, with a strong correlation between high levels of neuropsychiatric symptomatology and decreased health-related quality of life. Comorbid psychiatric disorders are highly prevalent among HCV-infected persons. Lifetime rates of psychiatric disorders range from 80% to 95%, and the most common is substance use disorder. Current rates of psychiatric disorders are also high, ranging from 31% to 58%.

Depression has been reported to be the most common disorder among untreated HCV-positive persons, with 1 particular study reporting a lifetime prevalence of depressive disorders of 42% and a
current prevalence of 28\%. The level of prevalence is comparable with rates of depression in HIV-infected persons. Dwight and colleagues have identified a very high correlation between depressive symptoms and fatigue, although no association was found between depression and severity of hepatic disease, comorbid medical illnesses, or any sociodemographic factors. Fatigue has been the most common symptom reported by HCV-infected persons, ranging from 40\% to 100\%.\textsuperscript{71}

Anxiety disorders come as the second most common disorder, with rates ranging from 18\% to 26\%; generalized anxiety disorder and PTSD are the most prevalent, depending on the clinical setting.\textsuperscript{69}

Other psychiatric disorders, such as bipolar disorder, psychotic disorders, and personality disorders, have not been well examined in HCV-infected patients, but a preliminary study found prevalence rates of 6\%, 17\%, and 30\%, respectively, among a population of veterans.\textsuperscript{69}

A number of valid and reliable screening and rating instruments are available for psychiatric and substance use disorders. The Veterans Affairs Hepatitis C Resource Center Program has developed an instrument that provides screening for depression, PTSD, and substance use disorders and conceptualized a guide for the early screening and management of psychiatric and substance use disorders in hepatitis C clinics that could be easily adapted for other clinical settings.\textsuperscript{72}

In addition, dose-dependent, reversible neuropsychiatric toxicity is reported in up to 30\% to 40\% of chronic HCV-infected patients treated for 6 to 12 months with IFN-α alone or with IFN-α/ribavirin combination therapy. The disorders include anxiety, depression, irritability, cognitive impairment, and mood lability. Less common manifestations include confusion, psychosis, mania, severe depression, and suicidality. The development of these manifestations often requires the discontinuation of IFN-α. In most cases, these symptoms decrease gradually over the course of 2 to 4 weeks.

The high prevalence of psychiatric disorders in HCV-infected persons is multifactorial. Persons with psychiatric and substance use disorders are at greater risk for becoming infected with HCV. Hepatitis C in persons with severe mental illness, defined by (a) a diagnosis of a major mental illness, (b) disability in important life spheres, and (c) persistence of illness and disability, and with substance use disorder called “co-occurring disorder” is associated with psychiatric illness severity, ongoing drug abuse, poverty, homelessness, incarceration, and minority status.\textsuperscript{75}

Pathophysiological explanations similar to those suggested above for neurocognitive manifestations may be implicated.\textsuperscript{76}

In addition, genetic factors may play a role in increasing susceptibility to neuropsychiatric dysfunction.\textsuperscript{77}

The features of hepatitis C are summarized in Table 2.

**NEUROCOGNITIVE ASPECTS OF HIV/HCV COINFECTION**

Evidence for an additive effect of HIV/HCV coinfection on neurocognitive dysfunction is increasing. Reaction time and processing speed, in particular, are slower in coinfected persons than in persons who have either HIV infection or hepatitis C. In studies examining the effect of hepatitis C on neurocognitive functioning in HIV-infected drug users, hepatitis C has been found to negatively affect neurocognitive functioning even after considering HIV-related variables and drug use. Richardson and colleagues found that 52.9\% (37/70) of women drug users coinfected with HIV/HCV exhibited clinically significant neurocognitive dysfunction compared with 37.3\% (28/75) who had HIV infection alone and 37.0\% (10/27) who had HCV infection alone.
Given the increased probability and severity of neurocognitive deficits in coinfected populations, the assessment of neurocognitive functioning is vital in identifying persons at risk for functional impairment and possibly HAD and/or hepatic encephalopathy. Fortunately, the neurocognitive functions affected by HIV infection and hepatitis C are similar, and the brief screening batteries suggested by Carey and colleagues for HIV-associated neurocognitive impairment are likely to be sensitive to neurocognitive deficits in coinfected persons. The presence of neurocognitive dysfunction in patients with hepatitis C may have treatment implications that are important in managing coinfection.

The etiology of increased neurocognitive dysfunction in HIV/HCV-coinfected persons is unknown. As noted above, substance use cannot explain the additive effect, nor can depression or fatigue. It is likely that a synergistic effect of the 2 viruses is responsible. For example, both HIV and HCV replicate in monocytes/macrophages and B and T cells, and HIV infection has been shown to facilitate HCV replication in macrophages. Also, greater liver fibrosis may exacerbate neurocognitive dysfunction in coinfected persons, especially given that HIV has been shown to accelerate the progression of liver fibrosis in persons with hepatitis C.

**PSYCHIATRIC ASPECTS OF HIV/HCV COINFECTION**

Coinfection with HIV and HCV presents complex clinical challenges for the health care provider. Researchers have used several studies in an attempt to elucidate the aspects of psychiatric syndromes that are unique to coinfection. Data remain quite limited and, in some cases, contradictory. Nevertheless, by translating available research findings to patient care in the clinical setting, we hope to assist health care providers in efforts to improve the quality of life for their coinfected patients.

In a cohort of 6782 HIV/HCV-coinfected veterans, 76.1% met criteria for a comorbid mental health illness: the most common diagnoses were major depressive disorder (56.6%) and substance use disorders (68%). A smaller cross-sectional review of psychiatric illness in 62 coinfected persons suggests that the most common diagnoses include past depression (71%), current depression (42%), past cocaine dependence (73%), past opioid dependence (81%), and past alcohol dependence (47%). Other common diagnoses in this study include past dysthymia (19%), PTSD (19%), past childhood conduct disorder (16%), and past and current generalized anxiety disorder (11% and 10%, respectively). While data on rates of anxiety and psychotic disorders in HIV/HCV-coinfected persons remain sparse, depression and substance use disorders represent significant documented comorbidities in the coinfected population.

The relative effect of coinfection, compared with HIV and HCV mono-infections, on the prevalence and severity of depression is unclear. Many studies suggest similar rates and degrees of depression and fatigue in addition to other psychiatric conditions, such as anxiety disorders, in coinfected persons relative to those infected with HIV or HCV alone. A cohort study (N = 131) by von Giesen and colleagues suggests increased prevalence and severity of depression in coinfected persons relative to HCV-infected persons. Two noteworthy studies of HIV-infected persons suggest an association between comorbid hepatitis C and more severe and highly prevalent depressive symptoms in the HIV population. In a study of 264 HIV-infected persons, Clifford and colleagues found that the coinfected persons tended to present with more depressive symptoms than those with HIV infection alone. A questionnaire study of 484 HIV-positive persons conducted by Braitstein and colleagues found that HCV-positive persons presented with significantly worse depression scores, increased fatigue, and poorer quality of life. A multivariate analysis of the Braitstein study suggests that these findings are probably attributable to social and demographic factors, rather than to hepatitis C alone. Despite the somewhat contradictory findings in studies of rate and degree of depression in coinfected versus mono-infected persons, research has consistently shown staggering rates of depression in persons with comorbid HIV infection and hepatitis C. These rates well exceed those of the population at large and are generally higher than those seen in studies of other chronic medical illnesses, including coronary artery disease, diabetes mellitus, chronic breathing disorders, stroke, and cancer. These findings underscore the importance of incorporating screening tools for depression—in addition to any predisposing psychosocial factors in the HIV/HCV-coinfected population—into the many levels of health care for coinfected persons, particularly because rates of medical and psychotherapeutic treatment of depression remain poor among the medically ill. In efforts to customize approaches to screening and assessment and to clarify goals for the treatment of depression in persons with coinfection, the quality of depressive symptoms in relation to infection status also has been a topic of investigation. In a study investigating this issue in injection drug users, HCV-seropositive persons were found to have higher indicators of psychological...
stress, phobia, and psychoticism: HIV-positive persons reported more hopelessness and preoccupation with being ill, and coinfected persons more frequently reported somatic complaints.97 A study by Hilsabeck and colleagues93 partially replicated these findings and suggests that coinfection tends to focus clinical complaints on somatic symptoms, but there were no significant group differences for depression, anxiety, fatigue, or quality of life. This finding was further supported by Clifford and colleagues,94 whose group found that HIV/HCV-coinfected persons tended to present more frequently with somatic depressive symptoms and depressive affect than the HIV-infected persons in the study.

While research remains limited in this domain, findings clearly suggest a strong focus on the somatic elements of psychiatric disease in coinfection. As such, it would strongly benefit health care providers to focus screening questions for depression on associated physical symptoms that include fatigue, changes in energy and appetite, and pain associated with depression. We postulate that the same probably holds true in screening for other psychiatric disorders among coinfection and strongly encourage the use of screening tools for depression: the PHQ version of the Primary Care Evaluation of Mental Disorders diagnostic instrument may be the most clinically useful depression screen.

The PHQ-998 includes the 9 items used to evaluate a major depressive episode; therefore, a diagnosis can be made directly from the PHQ-9. To further simplify screening, a 2-question screen has a sensitivity of 83% and a specificity of 92% for the major depressive disorders diagnosis among patients seen in a primary care setting.99 Such simple screening measures should be incorporated into the standard assessment of patients in the HIV primary care setting to better identify patients who are in need of treatment.100

Substance use presents another significant comorbidity among the coinfection population. In their cross-sectional review of 69 coinfection persons, Ryan and colleagues92 found that rates for dependence on stimulants, cannabis, alcohol, cocaine, and opiates were, respectively, 11%, 19%, 47%, 73%, and 81% for past dependence and 2%, 3%, 10%, 16%, and 13% for current dependence. A comparison between this sample and a matched 49-person sample of HIV-infected persons revealed significantly higher probability of coinfection persons having a history of opiate dependence, cocaine dependence, or stimulant dependence. What is more, this study suggests that the likelihood of depression secondary to substance use is significantly greater in coinfection persons than in HIV-infected persons.92

Contrary to this finding, another study showed a high rate of both current and lifetime alcohol abuse and drug abuse but not significantly higher rates of lifetime psychiatric illness.101 Backus and colleagues91 further demonstrated significantly higher rates of alcohol and other substance abuse among 6782 coinfection veterans relative to 11,567 who were infected with HIV alone. The negative influence of depressive symptoms and substance use on quality of life for coinfection persons has been clearly established. A cross-sectional survey of 115 persons conducted by Marcellin and colleagues102 revealed the negative influence of depressive and fatigue symptoms on quality of life for more than half of the coinfection persons. While there are no clear indicators of significantly worsened quality of life that is primarily due to coinfection,95 studies consistently demonstrate that the comorbid mental health conditions and psychosocial stressors often associated with coinfection are independent predictors of diminished quality of life.35,102

In evaluating for salient indicators of poor quality of life in coinfection persons, Marcellin’s group
suggests that self-reported fatigue and depression are the most accurate, further pointing to the need to screen for depression and its somatic correlate, fatigue, in coinfectected patients on all levels of patient care. As untreated psychiatric and substance use disorders negatively affect quality of life, they may also indirectly, but significantly, worsen morbidity and mortality in HIV/HCV-coinfected persons.

The features of HIV/HCV coinfection are summarized in Table 3.

**CLINICAL CHALLENGES OF HIV/HCV COINFECTION**

Being positive for both HCV and HIV is likely to be a marker for multiple coexisting problems, such as psychiatric and addictive disorders as well as social problems, such as lack of housing, support, and transportation, that contribute to poor access to care and to treatment barriers. People who are coinfectected with HIV and HCV do experience poor quality of life. Unique to the setting of coinfection is the lack of treatment of one infection that appears to hasten the progress of the other. That is, untreated HIV infection is a risk factor for more rapid progression of liver impairment in persons with hepatitis C, and worsened liver impairment due to hepatitis C is a major cause of morbidity and mortality in the HIV-infected population. A team approach to disease management has been explored in an attempt to coordinate and integrate the delivery of disparate services by the many providers to address such complex and intertwined problems.

Cointected patients represent unique challenges and puzzles in the evaluation and treatment process. The neuropsychiatric and cognitive manifestations could be either occurring in the context of the coinfection or preexisting to the current illness or even induced by the side-effect profile of the patient’s medication regimen. Medical and psychiatric concerns about hepatitis C treatment tolerance are more significant in cointected patients than in monoinfected patients, especially when they undergo treatment of both conditions simultaneously. Hepatitis C and IFN-α/ribavirin combination therapy are known to exacerbate the liver toxicity caused by antiretroviral therapy, placing a significant burden on the patient’s liver. Hepatitis C medications can also interact with some HIV medication regimens and have harmful effects. Furthermore, neuropsychiatric symptoms are commonly associated with antiviral therapy for hepatitis C, and cointected persons may be more adversely affected by hepatitis C antiviral therapy, knowing that persons with pretreatment psychiatric manifestations may be more susceptible to developing neuropsychiatric disorders.

These issues can influence the treatment decision-making process in the timing and sequencing of initiating hepatitis C and HIV infection therapy. Substance abuse and psychiatric illness are among the most common reasons for the exclusion of cointected persons from hepatitis C and HIV therapy because they are thought to be potential barriers to treatment adherence and tolerance. For example, more than 50% of persons coinfectected with HCV and HIV have alcohol problems. The importance of continued alcohol use is related not only to accelerating the progression of liver disease but also to the observation that alcohol use is associated with reduced response rates to IFN-α. Current guidelines recommend that abstinence be achieved before beginning IFN-α treatment, especially in cointected persons who also have decreased IFN-α response rates and more rapidly progressive liver disease.

More recently, active substance abuse and psychiatric illness have been considered more as relative contraindications to IFN-α therapy. Current guidelines recommend that treatment be delivered on a case-by-case basis, with decisions made by the patients with their physicians on the basis of a balanced assessment of the risks and benefits. For instance, patients have been removed from treatment if they become severely depressed, but recent studies show that depression in this context can be treated successfully while patients continue to receive IFN-α therapy. Another example of successful treatment was seen in cointected injection drug users employing a multidisciplinary approach that included specialists in hepatitis C therapy and in medical, mental health, and addiction care.

A study on treatment with antiretroviral regimens compared disease progression in cointected persons with disease progression in persons infected with HIV alone and found that cointected persons started antiretroviral therapy later and had lower CD4 counts at initiation. The cointected patients may have experienced delayed access to care or possibly lack of a consistent source of medical care. Poverty, homelessness, social marginalization, and mistrust of the health care system contribute to barriers to treatment.

Socially and culturally marginalized persons are particularly vulnerable to these issues. This is accentuated by some provider-associated factors such as lack of comfort in combining treatments of HIV infection and hepatitis C; insufficient training; and judgmental attitudes in managing these patients, especially when alcohol or drug use and persistent psychiatric manifestations are present.
Furthermore, medical providers also have difficulty in gaining access to necessary psychiatric and substance abuse consultations, collaboration, and psychiatric and substance abuse services.\textsuperscript{112} Patient-centered care is essential for successfully treating coinfected persons.

Because services for persons with complex comorbidities, especially neuropsychiatric disorders, are usually provided by different disciplines in varying settings, fragmentation of care can lead to catastrophic consequences, such as lack of treatment and poor medication adherence, and eventually to poor outcomes. In the integrated treatment model, strategies to enhance communication and ongoing collaboration should facilitate an integrated interdisciplinary approach. Different models for integration of care for HIV/HCV-coinfected patients have been tested, including HIV/HCV co-located clinics, integrating care for hepatitis C into primary care for HIV infection, and substance abuse treatment and integrated care for opioid addiction.\textsuperscript{113} Although evidence for effectiveness consists primarily of observational studies of demonstration programs, targeted integrated strategies have the highest potential to improve outcomes.\textsuperscript{114} The components of a comprehensive treatment plan for coinfected patients are summarized in Table 4.

**CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS**

HIV/HCV coinfection appears to have an additive negative effect on neurocognitive functioning compared with HIV or HCV monoinfection. The mechanism for this interaction has yet to be determined but is probably related to the combined effects of each virus on similar neural cells (eg, macrophages, astroglia) in frontal-subcortical circuits, enhanced HCV replication in the context of an immunocompromised host, chronic immune system activation, impaired liver functioning, and host genetic factors.

In order to decipher this complex interaction, multidisciplinary research teams will be needed to examine relationships between brain functioning using neurocognitive testing and sophisticated neuroimaging techniques (eg, magnetic resonance spectroscopy, functional MRI, and diffusion tensor imaging); viral replication within cells of monocyte lineage; effects of cytokines, chemokines, and other neurochemicals; and genetic determinants of the host immune response. Elucidation of the role of cytokines is of particular interest given the increasing move toward using biological agents to treat disease.\textsuperscript{115} Predictors of who is most likely to develop neurocognitive dysfunction and how or whether it can be prevented are important questions.

The clinical effect of neurocognitive deficits in patients who are coinfected with HIV/HCV is another essential avenue of study. It is unknown whether coinfected patients encounter greater difficulties in performing activities of daily living or whether they are more susceptible to HAD or hepatic encephalopathy. Furthermore, neurocognitive dysfunction secondary to coinfection may interact with aging and neurodegenerative disease processes, resulting in earlier disease manifestation and more severe deficits.

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