SUPPLEMENT ARTICLE

Management of Mental Health Problems Prior to and During Treatment of Hepatitis C Virus Infection in Patients With Drug Addiction

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Psychiatric comorbidity is a common problem in patients with substance use disorders. Patients with psychiatric diseases and/or substance abuse have an increased risk for hepatitis C virus (HCV) infection. Furthermore, psychiatric problems occur frequently during antiviral treatment and may be associated with the use of interferon alpha (IFN-α) but also with the primary psychiatric condition. As a consequence, substance abuse and/or acute psychiatric problems are still important reasons for nontreatment of chronic HCV infection. However, prospective and controlled data from recent years showed that if an interdisciplinary treatment is provided, patients with substance use disorders and/or psychiatric diseases do not differ regarding sustained virologic response or IFN-α–associated complications such as depression when compared with controls. Moreover, depression as the most important acute IFN-α–associated psychiatric adverse event can be acutely treated or even prevented by antidepressant pretreatment. Other, more rare but severe complications such as mania, psychotic symptoms, or delirium need individual psychiatric interventions.

Keywords. hepatitis C; interferon; ribavirin; psychiatric adverse events; management; depression.

Substance use disorders and psychiatric morbidity are significantly more prevalent in chronic hepatitis C (CHC) patients than in the general population [1]. They are associated with an increased risk for infection, but emerging evidence suggests that they can also be related to the infection itself. In addition, antiviral therapy with interferon alpha (IFN-α) is often associated with the development of psychiatric side effects, which have a strong impact on quality of life, may reduce treatment compliance, and are risk factors for treatment failure [2]. Furthermore, IFN-α–induced mental side effects, reports of suicide attempts, the risk of reinfection after relapse in injection drug use, and the need for adherence to therapy and monitoring, both to ensure patient safety and successful treatment, were often used to regard injection drug use and psychiatric morbidity as a contraindication to antiviral therapy. As a consequence, most of these patients still remain untreated despite fulfilling the medical criteria for antiviral treatment of CHC [3]. On the other hand, because of the high prevalence of psychiatric morbidity in patients with drug addiction and the lack of routine psychiatric screening examinations, psychiatric comorbidity might remain unknown and patients might receive antiviral treatment without sufficient interdisciplinary support.

Research over recent years has contributed to develop different management strategies for the acute treatment or the prevention of psychiatric problems during antiviral therapies [2]. Especially in people who inject drugs (PWID), strategies to improve compliance and reduce or manage side effects during hepatitis C treatment are important to achieve the best possible

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therapeutic outcome. Consequently, an approach that integrates the expertise of a variety of disciplines, including specialists in addiction medicine, hepatology, infectious diseases, primary care, and psychiatry, has been advocated for the treatment of HCV among PWID [4].

MENTAL HEALTH AND HCV INFECTION

Injection drug use is the most common risk factor for HCV infection in most Western countries [5]. CHC prevalence within PWID populations varies widely, but most studies found rates between 60% and 90% [6]. Other psychiatric comorbidity (depressive, bipolar, anxiety, and psychotic disorders, as well as fatigue) are also significantly more prevalent in CHC patients than in the general population [1], especially in the group of PWID and in human immunodeficiency virus (HIV)–coinfected patients [7]. Cognitive disturbances have also been reported in about one-third of CHC patients [2], with an additive effect of HIV/HCV coinfection [8].

Although comorbidity is related to increased high-risk behavior, such as injection drug use [1], there are other involved factors. Stigmatization and the fact that patients have to cope with a chronic infectious disorder can also increase the risk of depression and anxiety. Finally, a number of studies now support the hypothesis that HCV directly or indirectly induces biological changes in the central nervous system, which may result in psychiatric symptoms [2].

PSYCHIATRIC SIDE EFFECTS OF ANTIVIRAL TREATMENT

Antiviral therapies based on pegylated or standard IFN-α, alone or in combination with ribavirin, are often associated with significant psychiatric side effects, which are estimated to occur in 30%–80% of all patients undergoing treatment for CHC [2]. Up to 70% of patients have been reported to suffer from mild to moderate depressive syndromes, whereas major depressive disorder (MDD) occurs in 15%–45% [2, 9]. Data so far indicate a similar incidence of depression between PWID and other CHC populations [10, 11].

In addition to depression, IFN-α is also associated with the occurrence of a wide range of other neuropsychiatric symptoms. Fatigue as the most prominent side effect occurs in up to 80% of patients. Anger, irritability, and/or hostility have also been reported to be distinct from depression and affect up to 50% of patients receiving IFN-α therapy. Sleep alterations, anxiety, and cognitive disturbances may occur in up to 50% of patients. In contrast, mania and psychosis represent more rare adverse events, developing in up to 3% of patients [2]. Finally, whereas suicidal thoughts have been reported in about 10% of patients undergoing IFN-α therapy, case reports of suicide or suicidal attempts remain only anecdotal [12].

Different treatment options such as standard versus pegylated IFN-α, type of peg-IFN-α (ie, 2a vs 2b), and associated ribavirin do not seem to have a significant influence on the incidence of psychiatric side effects. Currently available data suggest that the new antivirals telaprevir and boceprevir do not have specific neuropsychiatric side effects [2]. Nevertheless, with new antivirals the general management of psychiatric adverse events becomes more complicated because of possible drug–drug interactions (see article by Mauss in this supplement).

Dimensional analyses of symptoms developing during IFN-α treatment have revealed differential time courses: Neurovegetative and somatic symptoms, including fatigue, decreased appetite, pain, and gastrointestinal disorders, develop at early stages of treatment, usually as soon as the first weeks of therapy. These symptoms appear in a majority of patients treated with IFN-α and they remain persistent during the duration of treatment. Mood and cognitive symptoms, including depressive symptoms, anhedonia, memory disturbances, and concentration problems, develop at later stages of treatment, usually after week 4 of therapy, with a greater intensity of depressive symptoms after week 8 [13]. While most of the neuropsychiatric effects resolve with treatment cessation, cases of persistent, recurring, or new developing symptoms have been described [14].

Some patients with a history of drug or alcohol abuse, or patients during methadone maintenance treatment, may confound early side effects of IFN-α with drug or alcohol withdrawal symptoms, possibly followed by a relapse of abuse. Cravings might also be secondary to IFN-α–driven mood changes or be related to needles that are used for IFN-α therapy. However, rates of relapse in injection drug users seem to be relatively low (0%–17%) [15].

Predicting the occurrence of psychiatric adverse effects is an important area of clinical research, as ultimately it could lead to prophylactic interventions only in those at risk. Patients with higher levels of depressive symptoms at baseline were shown to reach higher depression scores during IFN-α treatment and to be more likely to develop clinically significant depression [2]. These findings have been replicated in PWID populations [11]. A personal history of major depression has also been found to be a risk factor, although this may be due to higher depressive baseline scores, rather than a specific effect [16]. Baseline sleep disturbances, older age, and organic brain impairment (eg, vascular diseases, AIDS encephalopathy) are also regarded as important risk factors. Poorer social functioning and social support were also associated with new-onset depression during treatment [11]. Finally, patients with drug addiction seem to have an increased risk of developing psychotic symptoms, possibly related to former abuse of hallucinogenic drugs [17].

MENTAL HEALTH MANAGEMENT PRIOR TO ANTIVIRAL TREATMENT

The decision to offer antiviral therapy should be individualized in current users of illicit drugs or alcohol (Figure 1) [5, 17]. For patients with drug addiction, treatment in a multidisciplinary group with an opiate substitution program should be provided [4, 17, 18].

In general, patients should be intensively informed about the possible mental changes and their association with IFN-α treatment. Knowledge about HCV and its treatment plays an important role in HCV assessment and treatment decisions among PWID [19]. The risk for severe psychiatric complications might be higher in patients who are not aware of their association with IFN-α; these patients might not seek medical advice in time. In particular, PWID appear more likely to discontinue antiviral treatment early in cases where psychiatric side effects occur and therefore need intensified pretreatment care [17, 20].

Most patients with drug addiction suffer from psychiatric comorbidity (Figure 2). Therefore, psychiatric screening before antiviral treatment is crucial. In case of preexisting psychiatric conditions, interdisciplinary care of the patients should be organized.

Because regular alcohol consumption leads to accelerated fibrosis progression and possibly reduced response to antiviral therapy, it is important to ensure that patients abstain from regular alcohol consumption. If patients cannot, treatment for alcohol dependence should be attempted before the initiation of antiviral therapy [23]. Pretreatment of psychiatric conditions such as depression, anxiety, personality disorders, schizophrenia, or epilepsy will also need an intensive optimization of drugs with regard to possible interactions and a stabilization of the patients for at least several weeks before antiviral treatment is started.

Although most clinicians are diligent about screening for depression, suicidality, and ongoing alcohol and/or illicit drug use, there are a number of other significant psychosocial issues that can complicate treatment and reduce adherence. They include subclinical mood, personality, or behavioral symptoms (eg, irritability, impulsivity), and general life instability and inadequate resources (eg, no access to healthcare and insurance, transportation, housing, limited financial resources, and chaotic interpersonal or living environments) [24]. Measurement of social functioning prior to treatment may provide a useful tool for predicting who may be at risk of developing psychiatric side effects during HCV treatment and require enhanced psychiatric assistance and monitoring [11]. Furthermore, strategies to improve psychological adjustment to chronic medical illness, develop adaptive coping skills to handle daily stressors and side effects, increase social support, reduce stigmatization, and promote lifestyle changes (alcohol use, nutrition, exercise, work) should be implemented, as all of them significantly improve treatment adherence [2].

MENTAL HEALTH MANAGEMENT DURING ANTIVIRAL TREATMENT

The patient's psychiatric condition should be monitored during IFN-α therapy to early detect treatment-related changes (Figure 1). A reasonable schedule for general HCV patients would be monthly visits during the first 12 weeks of treatment, followed by visits at 8- to 12-week intervals thereafter until the end of therapy [5]. However, in cases of psychiatric comorbidity or drug addiction, monitoring should be done every 2–4 weeks during the first 3 months, and then every 4–6 weeks until 12–24 weeks after antiviral therapy [2]. At each visit, patients should be questioned regarding the presence of side effects and depression. Psychiatric symptoms can be easily overlooked during routine clinical exams, as evidenced by a recent study which found that only 32% of patients who developed MDD during treatment were correctly identified as "depressed" by clinicians [25]. Thus, increased education of both treating nurses/physicians and patients is necessary to allow improved early detection of psychiatric symptoms [17]. Furthermore, the use of brief, validated screening tools is recommended, such as BDI (Beck Depression Inventory), CES-D (Center for Epidemiologic Studies Depression Scale), PHQ-9 (Patient Health Questionnaire), HADS (Hospital Anxiety and Depression Scale), or MDI (Major Depression Inventory) [25]. These scales can be used to monitor and quantify the severity of psychiatric symptoms. However, they are not diagnostic instruments, and a diagnosis of depression should be confirmed by an experienced mental health professional.

Formal psychiatric referral should be provided if the treating physician is unable to diagnose correctly or to manage psychiatric problems; the initial management has failed; the psychiatric situation is complex or uncertain; there is an identified or suspected risk of suicide, alcohol, or substance abuse; there is a complex and difficult social situation; multiple psychotropic drugs are necessary; or psychotherapeutic treatment is required. Hospitalization may be necessary in cases of high suicide risk, lack of response to treatment, psychotic symptoms, psychotic depression, disorientation, and symptoms of delirium [2]. Discontinuation of antiviral treatment because of psychiatric complications should be decided on a case-by-case basis, but in most cases treatment can be continued without dose reduction or discontinuation if an adequate therapeutic management of the psychiatric side effects is offered [17, 26].

Overall supportive treatment, behavioral therapy, or cognitive therapy may all increase adherence to antiviral treatment and reduce symptoms of depression and anxiety, but so far trials are lacking. However, if psychiatric complications arise

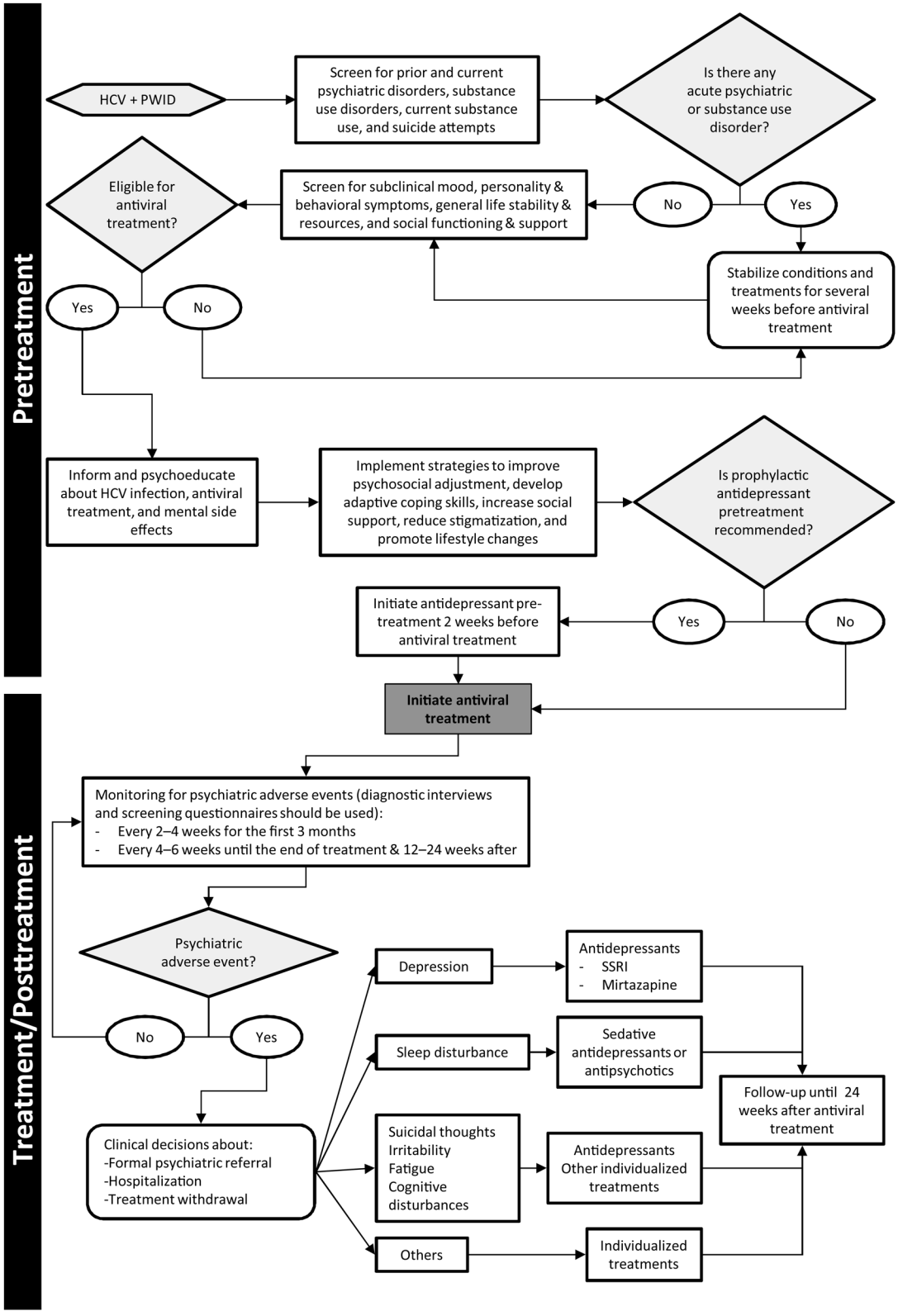

Figure 1. Clinical pathway for the management of mental health prior to and during treatment of hepatitis C virus infection in patients with drug addiction. Abbreviations: HCV, hepatitis C virus; SSRI, selective serotonin reuptake inhibitor; PWID, people who inject drugs.

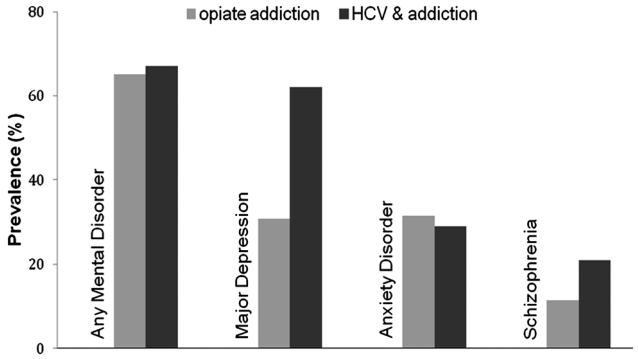

Figure 2. Prevalence of psychiatric comorbidity in patients with drug addiction with or without chronic hepatitis C virus (HCV) infection. Results are based on Regier et al [21] for opiate addiction and psychiatric comorbidity and Litwin et al [22] for HCV, addiction, and psychiatric disorders. Abbreviation: HCV, hepatitis C virus.

during IFN-α-treatment, acute pharmacological intervention becomes necessary and psychotherapy should not be offered alone [2, 17].

IFN-α–associated depression has been related to changes in serotonin signaling and a central nervous system serotonergic deficit [27], thus providing the rationale for the therapeutic use of selective serotonin reuptake inhibitors (SSRIs). They can be considered to be the first choice for treatment, as demonstrated in open-label studies, case reports, and a randomized, double-blind, placebo-controlled trial [28, 29]. For IFN-α–induced depression, a subthreshold treatment strategy has been suggested to start antidepressant treatment when depression scores are increasing, even at a low level [30]. However, an evidence base to support this is lacking. To reduce adverse events and increase adherence, treatment with antidepressants should be started at a low dose, and then a dose increase can be guided by effect and tolerability criteria. In general, a therapeutic relevant antidepressive effect can be expected after 8–14 days of treatment. In case of nonresponse, adherence should be assessed, serum levels could be monitored, and the dose can be escalated before patients are switched to a different antidepressant or a combination of two antidepressants with a different profile (eg, citalopram and mirtazapine). The frequency and severity of adverse events due to SSRIs are comparable between HCV patients and non-HCV patients [31]. Currently available data do not indicate negative effects of antidepressants on sustained virologic response or an increase of treatment discontinuation because of side effects [17, 32–34]. If patients respond to acute pharmacological treatment, the antidepressant should be continued through antiviral therapy and for 6–12 weeks after the end of treatment [14]. Another antidepressant, mirtazapine, has been suggested to be a better choice of treatment in cases where insomnia or anorexia develops [35]. Other alternatives that were successfully used in single cases have recently been summarized and can be considered in cases of nonresponse [29]. Psychostimulants should normally not be used in PWID.

For other IFN-α–associated psychiatric complications, no specific trial data are available, and symptomatic treatment should be individualized. Management of sleep disturbance appears important because it is a risk factor for the development of depression. Normally, benzodiazepine-like drugs such as zopiclone or zolpidem may be used for patients with interrupted or shortened sleep patterns. However, although the risk of addiction is markedly reduced compared with other benzodiazepines, these drugs should be avoided if possible in patients with drug addiction. Sedative antidepressants (mirtazapine, trimipramine) or antipsychotics may alternatively be used.

Fatigue might be ameliorated by antidepressant treatment, especially if there are also depressive symptoms [13]. But fatigue may be distinct from depression and related to basal ganglia alterations and decreased dopaminergic function [27]. One prospective and controlled trial showed a positive effect of ondansetron [36], but data have not been confirmed so far. Single case reports also indicate some partial positive effects of tryptophan [37], bupropion [38], or modafinil [39].

Irritability is a difficult-to-treat symptom, which is possibly caused by sleep disturbance, depression, mixed state, mania, psychosis, or worsening of agitation and impulsivity in patients with personality disorders. While irritability as a symptom of depression might improve after treatment with antidepressants, symptoms may exacerbate if irritability is related to mania. In those cases, a mood stabilizer or antipsychotic medication should be considered and acute intervention with benzodiazepines might become necessary [40].

Cognitive disturbances can be related to depressive symptoms, so antidepressants should be initiated as first-line treatment. However, no specific treatment is known to be effective for acute or long-lasting cognitive disturbances unrelated to depression.

PREVENTIVE STRATEGIES

The detection of IFN-α–related depressive symptoms relies on close observation and may be missed [25]. Moreover, any delay in initiating antidepressant therapy may lead to a reduction of patients' quality of life, an increased risk of treatment discontinuation, a worsening of depressive symptoms, and the development of suicidal thoughts [41]. Thus, preventive strategies have been developed.

From a psychological approach, a concomitant and continuous psychotherapeutic support program in a multidisciplinary medical team with psychiatric counseling has recently been shown to be able to reduce acute psychiatric complications and the need for pharmacological interventions during antiviral

therapy [42]. However, in a second trial, a cognitive-behavioral intervention to prevent depression in a group of methadone maintenance treatment patients was not successful [43].

From a psychopharmacological approach, preventive strategies using antidepressants as a pretreatment have been the most studied. Three open-label trials were initially conducted with patients with psychiatric risk factors: previous history of interferon-induced depression [44], major depressive disorder in remission [45], or preexisting depression and drug addiction [46]. In all 3 studies, antidepressants were able to reduce the incidence of IFN-α–induced depression. More recently, 6 prospective, randomized, placebo-controlled trials have been published [33, 34, 41, 47–49]. In 4 of them [33, 34, 48, 49], antidepressant pretreatment with paroxetine, citalopram, or escitalopram did not reduce the incidence of IFN-α–induced MDD or the overall severity of depressive symptoms. However, in one study, antidepressant treatment did reduce the increase of depressive symptoms during treatment, but it was measured only by questionnaires, and diagnostic criteria of MDD were not assessed [47]. Finally, the largest trial to date by Schaefer et al demonstrated a clear positive effect of escitalopram on the incidence and severity of depression during treatment in patients without prior psychiatric disorders [41].

Regarding PWID, results from few open-label studies conducted so far offer also positive results [46, 50]. In addition, methadone maintenance treatment has been described as an independent predictor of less long-term worsening of depressive symptoms [51].

SUMMARY AND CONCLUSIONS

Drug addiction is often associated with psychiatric comorbidity influencing treatment decision and outcome in patients with CHC. However, there is currently sufficient evidence that PWID do not have in general an increased risk for the development of major or severe depression during antiviral treatment with IFN-α. In addition, psychiatric comorbidity is not associated with an increased risk for early antiviral treatment discontinuation, lower compliance, lower sustained virologic response rates, or the development of depression during IFN-α treatment. In case of psychiatric comorbidity, case-by-case decisions for HCV treatment with IFN-α are recommended. Relative contraindications are acute major and uncontrolled psychiatric disorders and uncontrolled alcohol or drug abuse. In those cases, a psychiatric treatment is recommended before antiviral treatment is initiated.

Acute psychiatric adverse events of IFN-α such as depression can be successfully managed in most cases without the need of treatment discontinuation or dose reduction. Depression-specific symptoms are highly responsive to serotonergic antidepressants. Prophylactic antidepressant treatment is so far recommended in case of previous history of IFN-induced depression and with acute depressive symptoms at baseline.

Hepatitis C infection in patients with drug addiction can successfully be treated with IFN-α–based treatments, but specific interdisciplinary care is needed. So far, the best setting for antiviral therapy in PWID is a substitution treatment program.

Notes

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