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Buprenorphine for Human Immunodeficiency Virus/Hepatitis C Virus–coinfected Patients:

Does It Serve as a Bridge to Hepatitis C Virus Therapy?

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Abstract

Objectives—Buprenorphine is associated with enhanced human immunodeficiency virus (HIV) treatment outcomes including increased antiretroviral therapy initiation rates, adherence, and $CD4^+$ cell counts among HIV-infected opioid-dependent individuals. Buprenorphine facilitates hepatitis C virus (HCV) treatment in opioid-dependent patients with HCV monoinfection. Less is known about buprenorphine's role in HIV/HCV coinfection.

Methods—We conducted a retrospective chart review to evaluate HCV care for HIV-infected buprenorphine patients in the first 4 years of buprenorphine's integration into a Rhode Island HIV clinic.

Results—Sixty-one patients initiated buprenorphine. All had HCV antibody testing; 57 (93%) were antibody-positive. All antibody-positive patients underwent HCV RNA testing; 48 (84%) were RNA-positive. Of these, 15 (31%) were not referred to HCV care. Among chronically infected patients, 3 received HCV treatment after buprenorphine; all had cirrhosis and none achieved viral eradication. At buprenorphine induction, most patients had inadequately controlled HIV infection, with detectable HIV RNA (59%) or $CD4^+$ cell count less than or equal to 350/μL (38%).

Conclusions—Buprenorphine has shown limited success to date as a bridge to HCV treatment within an HIV clinic. Buprenorphine's stabilization of opioid dependence and HIV disease may permit the use of HCV therapy over time.

Keywords

buprenorphine; hepatitis C virus (HCV); HIV/HCV coinfection; HCV treatment; opioid replacement therapy

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Chronic hepatitis C virus (HCV) infection is a significant public health problem and the leading cause of non-AIDS death among human immunodeficiency virus (HIV)–infected populations in the highly active antiretroviral therapy (HAART) era (Weber et al., 2006). Among HIV-infected individuals, the high prevalence of HCV infection is compounded by an aggressive HCV disease course, with lower rates of spontaneous clearance and hastened hepatic fibrosis progression (Pineda et al., 2007; de Ledinghen et al., 2008). Treatment of HCV with pegylated interferon plus ribavirin leading to sustained virologic response (SVR) is beneficial, resulting in decreased liver-related morbidity and mortality and decreased overall mortality (Berenguer et al., 2009; Backus et al., 2011). Thus, consensus guidelines recommend considering all HIV/HCV-coinfected persons for HCV treatment (Soriano et al., 2002; Ghany et al., 2009). Implementation of these guidelines is limited because most coinfected persons are current or former injection drug users. Injection drug use is the leading cause of HCV transmission in the United States yet remains among the main reasons HCV therapy is withheld (Falck-Ytter et al., 2002; Edlin et al., 2005). Developing strategies to expand access to HCV treatment for coinfected drug users is imperative to stem the HCV epidemic and limit the morbidity and mortality of those at greatest risk for HCV disease progression (Bruno et al., 2007; Berenguer et al., 2009; Singal et al., 2010).

Hepatitis C virus, HIV, and opioid dependence are overlapping epidemics. Opioid dependence and HCV are successfully treated concurrently in diverse settings (Mauss et al., 2004; Grebely et al., 2007; Litwin et al., 2009; Waizmann and Ackermann, 2010; Sasadeusz et al., 2011). Management of co-occurring opioid dependence is critical in optimizing HCV treatment safety, maximizing adherence for treatment efficacy, and preventing posttreatment reinfection. In the United States, methadone maintenance therapy has historically been the mainstay of opioid replacement therapy. Hepatitis C virus treatment, along with methadone maintenance therapy, is safe. Sustained virologic response rates among patients on methadone maintenance therapy are comparable with those of other populations (D. Sylvestre and B. Clements 2007; Bonkovsky et al., 2008; Litwin et al., 2009; Taylor et al., 2010). However, methadone has limited availability in many communities and is among the most regulated medications in the clinical armamentarium. US federal regulations prevent prescription of methadone maintenance therapy outside of licensed opioid treatment programs. Many people are not able to accept the lifestyle restrictions often required in methadone maintenance therapy. There are only slots for 20% of eligible individuals; thus, many cannot access methadone (Friedmann et al., 2003; Gryczynski et al., 2009). The potential for interactions between methadone and HAART is another concern (McCance-Katz et al., 2006a, 2006b, McCance-Katz and Mandell, 2010).

Because buprenorphine is a partial rather than full agonist at the μ-opioid receptor, it has less potential for abuse, respiratory depression, and overdose (Jasinski et al., 1978; Bickel et al., 1988). Buprenorphine thus provides an opportunity to integrate HCV and HIV care with addiction treatment in a single outpatient office setting. Buprenorphine is associated with enhanced HIV treatment outcomes, including increased HAART initiation rates, adherence, and $CD4^+$ cell counts among HIV-infected opioid-dependent individuals (Moatti et al., 2000; Altice et al., 2011). Fewer interactions exist between buprenorphine and HAART than between methadone and HAART (Sullivan and Fiellin, 2005; Gruber et al., 2012; Vergara-Rodriguez et al., 2011). Buprenorphine is safe and effective in combination with pegylated

interferon plus ribavirin (Conway et al., 2004; Chossegros et al., 2008). In a prospective, observational study of HCV treatment among drug users in France, genotype 1 and 4 patients receiving buprenorphine had higher SVR rates rather than those receiving methadone (Chossegros et al., 2008).

Buprenorphine effectively bridges street-recruited, HCV-monoinfected heroin injectors to HCV therapy (D. L. Sylvestre et al., 2006; D. L. Sylvestre and J. E. Zweben, 2007). Coinfected drug users face further challenges including HIV/AIDS, the need for HAART and polypharmacy, accelerated HCV disease course with less time available for effective intervention, and comorbidities prevalent in HIV infection such as coronary artery disease. Compared with HCV and HIV monoinfection, coinfection is associated with more severe psychiatric illness, ongoing drug abuse, poverty, homelessness, and incarceration (Rosenberg et al., 2005). Buprenorphine's utility in stabilizing coinfected drug users toward HCV treatment and improving HCV, HIV, and addiction outcomes remains unclear.

In 2005, the Miriam Hospital Immunology Center in Providence, RI, was 1 of 10 sites to be awarded a grant by the Health Resources and Services Administration to integrate buprenorphine into an HIV clinic (Cheever et al., 2011). There is a paucity of literature on HCV treatment among coinfected individuals on buprenorphine. We sought to examine whether buprenorphine was a facilitator of HCV therapy among coinfected patients and, if not, why coinfected patients who received buprenorphine did not initiate HCV therapy.

METHODS

The Immunology Center serves 1400 HIV-infected patients, approximately 30% of whom are current or former opioid users. In 2001, the on-site Coinfection Clinic was established to provide longitudinal, comprehensive HCV care to more than one-third of those who are coinfected with chronic HCV. In 2005, 5 Immunology Center physicians were licensed to prescribe buprenorphine. Clinic patients are informed of the availability of buprenorphine on an ongoing basis, with buprenorphine education sessions led by a nurse. Patients may request to meet with the buprenorphine nurse and/or physicians. Furthermore, HIV physicians discuss buprenorphine with their patients during routine office visits and then refer them into buprenorphine care. Patients are inducted during clinic hours by a nurse or physician. The Clinical Opiate Withdrawal Screen is used to assess opioid withdrawal (Wesson and Ling, 2003). During the first day of induction, patients receive a series of doses over several hours. In the first week of induction, a nurse evaluates patients daily until dose stabilization occurs. The buprenorphine/naloxone formulation (Suboxone; Reckitt Benckiser Pharmaceuticals Inc, Richmond, Va) is utilized.

A retrospective chart review was undertaken to identify HIV-infected patients inducted on buprenorphine for the treatment of opioid dependence at the Immunology Center from April 2005 to April 2009. A research assistant and a nurse reviewed each patient chart and extracted data from physician-dictated notes and laboratory reports. The chart review was not blinded. All data, including information for the case studies, was collected by chart review. Reasons for lack of referral were collected from physician-dictated notes. Data extracted included sex, race, ethnicity, presence of HCV antibody testing, HCV antibody

results, presence of plasma HCV RNA testing, plasma HCV RNA results, presence of HCV genotype testing, HCV genotype results, HIV status at the time of initial buprenorphine induction (including $CD4^+$ cell count, HIV plasma viral load, HAART use), buprenorphine maintenance doses, referral to HCV care, HCV treatment initiation, and whether SVR was achieved. Statistical analysis was not performed because of the available sample size.

RESULTS

At least a single dose of buprenorphinewas administered to 61 patients during the study period (Figure 1). Of the 61 patients, 16 (26%) were female, 38 (62%) Caucasian, 12 (20%) black, 2 (3%) Native American, 9 (15%) race unknown, and 20 (33%) Hispanic. Four (6.5%) patients did not complete induction. For those who continued buprenorphine, maintenance doses ranged from 2 to 32 mg, with a mean dose of 16.25 mg.[1]

All 61 patients had documentation of HCV antibody testing, and 57 (93%) had an HCV antibody-positive result. All patients with a positive HCV antibody result received plasma HCV RNA testing: 9 (16%) of the 57 HCV antibody-positive patients had no detectable serum HCV RNA and 48 (84%) had detectable HCV RNA. Hepatitis C virus genotyping was performed on 40 (83%) of the 48 chronically infected HCV patients with subtypes as follows: 65% genotype 1, 12.5% genotype 2, 12.5% genotype 3, 5% genotype 4, 2.5% mixed genotype, and genotype unknown for 1 patient.[2]

Eight (17%) of the 48 patients with chronic HCV infection received HCV treatment. Five of the 8 patients received HCV treatment before the buprenorphine induction; 1 achieved SVR. This patient received HCV treatment while incarcerated. Three patients received HCV treatment after buprenorphine induction at the Immunology Center; none achieved SVR. The first of these 3 patients had compensated cirrhosis and Child-Pugh score of 5. He completed 6 months of pegylated interferon plus ribavirin therapy (Case Study 1). A second patient, with history of general anxiety disorder, major depression, ongoing cocaine use, compensated cirrhosis, and Child-Pugh score of 6, insisted on initiating HCV therapy despite potential risks. She discontinued HCV therapy at week 2 after development of jaundice and elevated bilirubin. She restarted HCV therapy after a 4-month hiatus and was again rapidly discontinued because of development of jaundice, elevated bilirubin, and hepatic encephalopathy. The third patient, with compensated cirrhosis and Child-Pugh score of 5, schizophrenia, and alcoholism, suspended alcohol use several months before HCV treatment initiation. He achieved rapid virologic response and early virologic response. Treatment was terminated at week 30 because of development of hepatic encephalopathy. Of these 3 patients, 2 continued buprenorphine during HCV therapy whereas the third elected to switch back to methadone before HCV therapy initiation.

Among the 48 patients with a positive HCV RNA result, 15 (31%) were not referred to HCV care. The most common reasons for lack of referral included physician impression that HCV care was not warranted because HCV was asymptomatic, HCV disease was stable, or the

[1]Maintenance dose is unknown for 1 patient.
[2]Patient was treated for HCV during incarceration. Full care records from the prison were not available.

patient was too unstable regarding addiction and/or psychiatric illness to be referred. In one case, there was no mention of HCV diagnosis in the medical record. Among patients who had at least 1 HCV appointment but did not undergo HCV treatment, reasons included that the patient declined, was in the process of preparing for, or had contraindications to therapy. Of the 4 patients with a negative HCV antibody result, all had 2 to 3 subsequent HCV antibody tests. Findings from all results were negative. Among the 9 patients who spontaneously resolved HCV infection, all had between 1 and 8 repeat HCV RNA tests to screen for reinfection. Findings from all results were negative.

At buprenorphine induction, 36 (59%) of the 61 patients had a detectable serum HIV RNA. Twenty-three (38%) had $CD4^+$ cell counts less than or equal to 350/μL; of these, 9 (39%) had $CD4^+$ cell counts less than or equal to 200/μL. At induction, 7 (11%) patients had recently restarted or were inconsistently taking HAART whereas 24 (39%) patients were not taking HAART.

We present 2 cases illustrating the dual uses of buprenorphine in coinfection beyond care of opioid dependence, as a facilitator of HIV and HCV therapies.

Case Study 1: Prescribing Buprenorphine to Facilitate HCV Therapy in a Coinfected Heroin Injector

A 63-year-old African American, coinfected male with compensated cirrhosis Child-Pugh 5, HCV genotype 1, high HCV RNA viral load with bipolar disorder on Lithium Carbonate, initiated buprenorphine in 2005 in an attempt to stabilize his heroin injection to permit HCV therapy. As a long-term nonprogressor, his HIV disease was well-controlled without HAART. For several years before buprenorphine induction, he was on and off methadone maintenance therapy with recurrent relapses to heroin injection including unsafe injection practices (eg, injecting in his neck). He declined HCV therapy for 4 years out of fear of psychiatric decompensation as he had prior hospitalizations for mania. The HCV physician planned to stabilize him on buprenorphine for 12 to 24 weeks before layering on HCV therapy (D. L. Sylvestre and J. E. Zweben, 2007). After 9weeks of buprenorphine therapy, he had stopped using heroin and wanted to initiate HCV treatment. He felt that he had gotten his life back and had not felt as well in 20 years. His HCV treatment course was uneventful; he felt nothing. He was 100% adherent to weekly nurse-administered pegylated interferon injection visits. Treatment was discontinued after 24 weeks by the physician because of virologic nonresponse (null responder). Six years post-HCV therapy, the patient's Child-Pugh score remains 5, and he continues on buprenorphine and serves as a leader of a coinfection support group. The patient experienced 2 relapses to heroin injection, one after he chose to taper off buprenorphine and a second after leaving a nursing facility with inadequately treated postsurgical pain. He has not used injection drugs, heroin, or other opioids since restarting buprenorphine. We perceive that he succeeded in initiating HCV treatment because as an HIV long-term nonprogressor, there was no need to stabilize HIV disease before treating HCV. Essentially, this patient is similar to HCV-monoinfected patients taking buprenorphine to facilitate HCV therapy. Insufficient attention to how long it can take to engage coinfected opioid-dependent patients in HCV care contributed to HCV treatment initiation at a stage of advanced fibrosis.

Case Study 2: Buprenorphine as a Means to Stabilize Opioid Dependency and HIV Disease

Upon incarceration, a 30-year-old coinfected Latino man was seen by one of our HIV physicians who prescribed buprenorphine. Medical history was significant for chronic HCV genotype 1; paranoid schizophrenia with depression and anxiety; polysubstance addiction with heroin, cocaine, and marijuana; and self-mutilation with cutting. Last use of HAART was 9 months prior. $CD4^+$ cell count was 195/μL with HIV RNA 14,261/ml. At this initial visit, HAART (lopinavir/ritonavir/tenofovir/emtricitabine) and sulfamethoxazole/trimethoprim were resumed. He was referred into psychiatric care. Buprenorphine was not available in the prison.

Upon community reentry, the patient resumed heroin injection, approximately a half gram daily. One month later, in February 2009, he made his first outpatient HIV appointment with the physician he met during incarceration. The patient understood his opioid dependence and HIV infection well and was eager to discontinue heroin. He was strongly opposed to methadone maintenance therapy that he had tried previously. He perceived that buprenorphine, which he bought on the street, helped tremendously. He was asked to return to the clinic in the morning in opioid withdrawal, which he did, for successful buprenorphine induction. He was referred to a 12-step program and outpatient psychiatric care where he started valproic acid, alprazolam, fluoxetine, and quetiapine. He resumed HAART and sulfamethoxazole/trimethoprim. By March, $CD4^+$ cell count was 274/μL with HIV RNA of 514/ml. By April he was feeling well on 24 mg of buprenorphine daily and remained adherent to HAART and psychiatric medications. He continued to contend with anxiety and depression but was no longer cutting himself. By July 2009, HIV RNA was nondetectable with $CD4^+$ 485/μL, without relapse to heroin, and with improvement in his psychiatric health, sense of well-being, and relationship with his wife. The patient's medical record did not include mention of HCV evaluation or treatment. He typifies many coinfected opioid-dependent patients, with numerous immediate health concerns taking precedence over HCV. The challenge is to bring HCV into consideration before advanced liver disease develops.

DISCUSSION

Despite the availability of HCV treatment within an HIV clinic, the introduction of buprenorphine did not lead to high rates of HCV treatment in opioid users during the first 4 years of buprenorphine's use. There are many potential reasons for this. In an HIV clinical setting, and in coinfection in general, control of HIV/AIDS takes priority over HCV disease. The primary purpose of buprenorphine is to treat opioid dependence, facilitate HAART, and control HIV infection, rather than to advance HCV treatment. Many of the coinfected patients had not achieved HIV viral suppression or immunologic recovery at the time of buprenorphine initiation. Treating HCV was not a specific goal in the integration of buprenorphine into our HIV clinic. Buprenorphine was prescribed specifically to foster HCV therapy in only 1 patient. These priorities differ from those in previous research involving HCV-monoinfected patients in which buprenorphinewas specifically used to promote HCV treatment (D. L. Sylvestre et al., 2006).

Buprenorphine may be more successful in engaging patients with antiviral agents for HIV rather than for HCV, because of the inherent difficulties of interferon-based therapy. The multiple contraindications and adverse effects of HCV treatment do not exist to the same extent with HAART, whereas treatment outcomes are better for HIV than for chronic HCV. Patient refusal rates may be higher and physician recommendations lower for HCV versus HIV therapy, in coinfection. Interferon administration can be especially challenging in coinfection. HIV coinfection is a marker for greater psychosocial instability with respect to housing, employment, and educational and economic advantage when compared with HCV- and HIV-monoinfected populations (Rosenberg et al., 2005). Among HIV-infected individuals, HCV-coinfected patients are more likely to have diagnoses of psychiatric illness and drug and alcohol misuse and are less likely to have received HAART, compared with HIV-monoinfected patients (Backus et al., 2005; Goulet et al., 2005). In our study, the only patient achieving SVR underwent HCV therapy during incarceration, demonstrating that the correctional setting offers opportunity to treat HCV in complex patients (Allen et al., 2003; Chew et al., 2009).

The benefit-to-risk ratio in HCV treatment should improve with interferon-free regimens (Lok et al., 2012). Buprenorphine's role as an HCV treatment catalyst in coinfection may show more promise with the availability of safer, better-tolerated HCV treatment regimens. Direct acting antiviral agents for HCV are anticipated to increase SVR rates in coinfection. Buprenorphine's use, in combination with direct acting antivirals, is under investigation. Some of these novel medications may be more compatible with buprenorphine than with methadone.

HIV physicians correctly identified HCV infection, yet this did not always result in referral for HCV care. HIV physicians had misperceptions about the asymptomatic nature of chronic HCV disease. They withheld HCV referral because of concerns that their patients were not stable enough to undergo HCV treatment. Medical education is needed to ensure that physicians of coinfected patients understand that contemporary HCV care includes more than pharmacotherapy, and that with HCV treatment, close monitoring can preempt clinical and psychosocial decompensation. At a minimum, all coinfected patients should receive HCV care that includes comprehensive HCV education and evaluation of liver disease. Education should encompass information about how to limit disease progression even without HCV antiviral medications (eg, alcohol reduction) and about the growing list of treatment options (Sulkowski and Spach, 2011). Co-occuring conditions often prolong the timeline to HCV therapy initiation but should not delay HCV referral. Conversely, the potential need to stabilize relative contraindications to HCV treatment supports earlier engagement in HCV care, so there is adequate time to address barriers. Consequences of late intervention include development of end-stage liver disease, hepatocellular carcinoma, and liver-related mortality. The importance of timely HCV intervention in our patients is made clear by the fact that all patients treated for HCV after buprenorphine induction had cirrhosis at HCV treatment commencement, making treatment more difficult and less effective.

A key limitation to this study is its small sample size, which is due to the fraction of patients inducted on buprenorphine during the study period. Our experience is that when buprenorphine was introduced into our clinic, it was not immediately accepted. There was

skepticism among those who had never heard of buprenorphine. Many patients had long-standing relationships with methadone clinics and feared switching from methadone maintenance therapy to buprenorphine. Patients requiring higher methadone doses, more than 80–90 mg, were unable to switch to buprenorphine, as it is most effective for patients on lower methadone doses. Polysubstance use, prevalent among our population, presented another obstacle. Patients use many other classes of drugs along with opioids, most commonly, benzodiazepines, stimulants (cocaine, methamphetamine), and alcohol. Initially, buprenorphine was prescribed to a narrow group of patients with opioid dependence only. As physicians gained experience, they considered buprenorphine for opioid-dependent patients using other drugs concomitantly, and the number of patients taking buprenorphine expands by 2010. Lastly, patients often receive opioid prescriptions from their HIV physicians for chronic pain, including long-acting morphine sulfate (MS Contin). Typically, these patients with chronic pain and addiction are disinterested in discontinuing their prescribed narcotics to start buprenorphine.

Other limitations include the retrospective nature of the study and limited access to data through chart review. We did not collect HIV data longitudinally. We have information neither on intervening substance use nor on coexisting psychiatric illness, which may have impacted HCV care. We are not able to consider the degree of liver fibrosis, also a factor in HCV referral and treatment. These data were not systematically collected in the context of a clinical program.

We are witnessing the genesis of an integrated program for HIV, HCV, and buprenorphine. It is possible that over time, buprenorphine will stabilize opioid dependence and HIV disease in a growing proportion of patients, leading to greater HCV treatment uptake rates. The challenge is to address chronic HCV before it is too late. Although the majority of our patients inducted on buprenorphine had chronic HCV, only 3 (6%) received HCV therapy after the use of buprenorphine, all were cirrhotic by the time HCV therapy began, and none achieved SVR. If we wait to engage coinfected patients in care for chronic HCV until they are deemed ideal HCV treatment candidates, some will not receive treatment early enough for it to be beneficial.

CONCLUSIONS

Coinfected opioid-dependent patients should be engaged in HCV care early after HIV and HCV diagnoses. It may take time to adapt to HAART and buprenorphine and gain control of HIV disease, before HCV treatment may be added. During this time, patients should have access to education and evaluation of HCV, the commonly coexisting third chronic disease. If HCV remains too distant a priority, hepatic fibrosis may progress, and opportunities for effective HCV therapy missed. Although to date buprenorphine has shown limited success as a bridge to HCV treatment within a Rhode Island HIV clinic, it may be an important tool over time and in other settings, to help ensure that coinfected opioid-dependent individuals can be offered the lifesaving possibility of effective HCV treatment.

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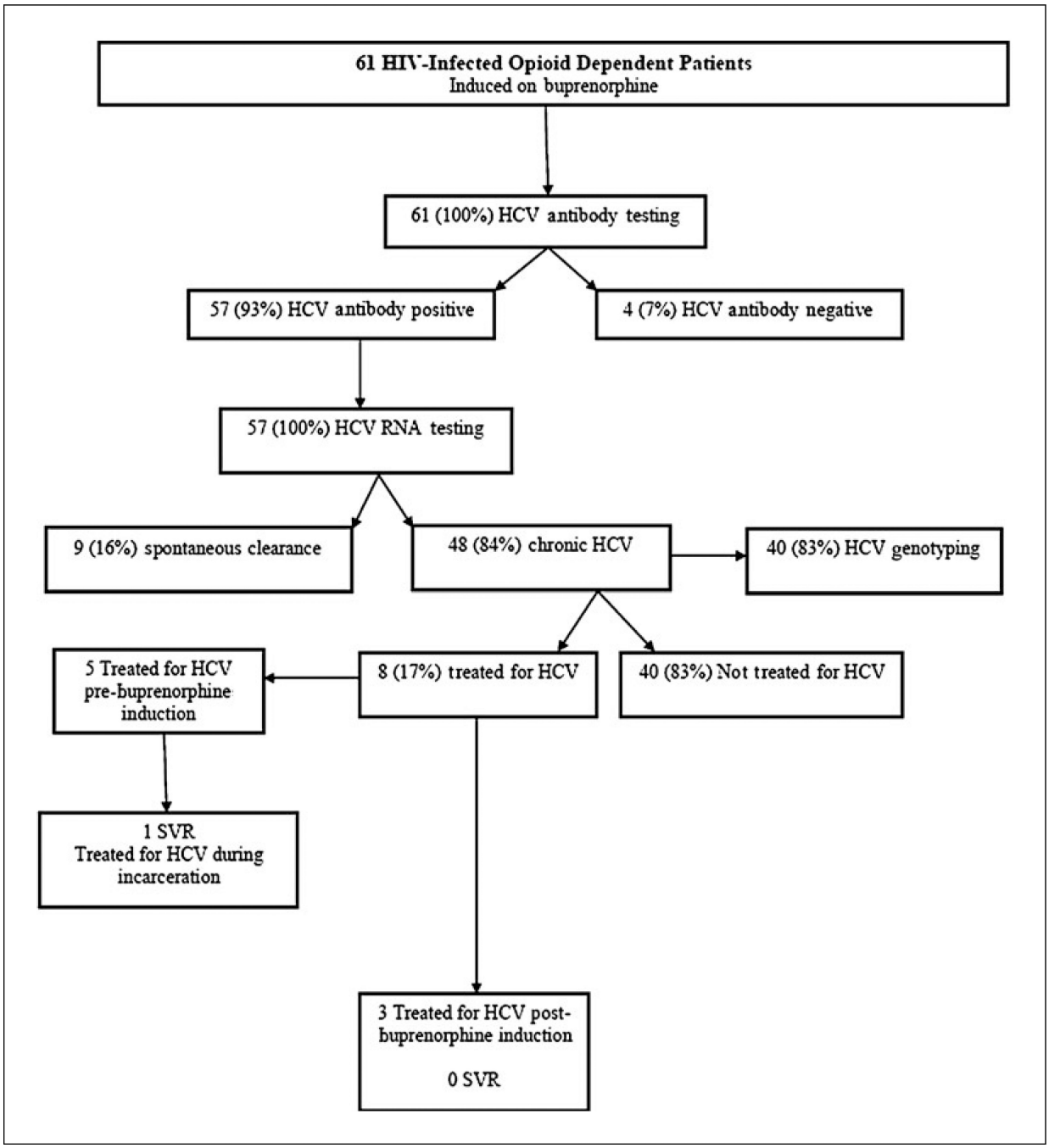

FIGURE 1.

Hepatitis C virus (HVC) testing and treatment among HIV/HCV-coinfected patients undergoing buprenorphine therapy. HIV indicates human immunodeficiency virus; SVR, sustained virologic response.