SUPPLEMENT ARTICLE

Management of Hepatitis C Virus/HIV Coinfection Among People Who Use Drugs in the Era of Direct-Acting Antiviral–Based Therapy

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Where active antiretroviral therapy (ART) is accessible, human immunodeficiency virus (HIV) is a survivable illness and effective ART can reduce HIV transmission. Chronic hepatitis C virus (HCV) has emerged as a threat to the survival of individuals harboring both HCV and HIV, due to high prevalence and aggressive disease course. The HCV/HIV coinfection epidemic has been driven by people who inject drugs (PWID), although incident HCV is rising among HIV-infected men who have sex with men in the absence of drug injection. Coinfected individuals warrant aggressive treatment of both viruses; although early ART initiation is recommended to reduce the rate of liver disease progression, the most effective way to decrease HCV-related morbidity and mortality in coinfection is to achieve HCV viral eradication. Direct-acting antiviral (DAA) agents will soon revolutionize HCV treatment. Clinical data are needed regarding the efficacy of DAAs in coinfected PWID. Drug–drug interaction studies between ART, DAAs, and opiate substitution therapy must be expedited. Coinfected PWID should have equitable and universal access to HIV/AIDS, HCV, and addiction prevention, care, and treatment. Essential basic steps include improving screening for both infections and engaging coinfected PWID in HIV and HCV care early after diagnoses. Developing strategies to expand access to HCV therapy for coinfected PWID is imperative to stem the HCV epidemic and limit the morbidity and mortality of those at greatest risk for HCV disease progression. The ultimate goal must be the elimination of HCV from all coinfected PWID.

Keywords. hepatitis C virus; HIV; HCV/HIV coinfection; people who inject drugs (PWID); direct-acting antivirals (DAAs).

EPIDEMIOLOGY OF HCV/HIV

The human immunodeficiency virus (HIV) epidemic has been linked to injection drug use since the first reports of AIDS-related illness, and drug use continues to fuel the global HIV pandemic. Although injection drug use accounts for 10% of HIV infections overall, this proportion rises to 30% outside of Africa, and HIV incidence continues to rise among people who inject drugs (PWID) [1]. Sharing HIV-contaminated needles is the most efficient means of spreading HIV after blood transfusion and is compounded by environmental conditions including stigma, discrimination, mental illness, poverty, and violence [1]. Unprotected sex is a further important HIV risk factor among PWID, in particular among women, female sex workers, and men who have sex with men (MSM). HIV-infected PWID transmit HIV sexually to noninjectors, and through vertical transmission to infants [1]. Whereas overall, 10% of HIV-infected persons are coinfected with HCV, among PWID, HCV coinfection rates range from 50% to >90% [2].

An Emerging Incident HCV Epidemic

While prevalent HCV/HIV is driven by injection drug use, increasingly, incident HCV among HIV-infected MSM is associated with non–injection drug use. HCV incidence is rising among HIV-infected MSM internationally [3, 4]. In the Swiss HIV Cohort Study, from

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1998 to 2011, HCV incidence rose 18-fold among HIV-infected MSM to an alarming rate of 4.1 cases per 100 person-years, while falling by 85% among PWID [5]. Most HIV-infected MSM acquiring HCV do not report injection drug use [4, 6]. In fact, among all HIV-infected persons, the majority of new HCV cases are occurring among non–PWID [5, 7, 8].

The reasons for this emerging epidemic are unclear. A conceptual model identifies a combination of drug use, sexual behaviors, and biologic factors (HIV status, syphilis) that work together to increase HCV risk [9]. The disturbing HCV incidence in a population previously thought to be at low risk motivates intervention. The European AIDS Treatment Network recommends quarterly screening for incident HCV in HIV-infected MSM, with the goal of rapid identification and treatment during the acute period of infection when interferon-based therapy is more successful [10–13].

NATURAL HISTORY OF HCV/HIV

Dual infection with HCV and HIV alters natural history of both diseases. HCV coinfection increases the risk of all-cause, AIDS-related, and liver-related death among HIV-infected people, despite use of antiretroviral therapy (ART) [14, 15]. HIV can accelerate HCV disease course, leading to more rapid progression to cirrhosis, liver failure, hepatocellular carcinoma (HCC), and increased HCV-related mortality [16–18]. Due to hastened progression and high prevalence in HIV-infected populations, HCV is a leading non-AIDS cause of death in HIV-infected persons in regions where ART is available [16, 18, 19]. The biologic basis for this is incompletely understood but may be related to impaired T-cell responses to HCV, to HIV's effect on hepatic cells, and to amplified microbial translocation promoting hepatic fibrosis [20, 21].

MEDICAL MANAGEMENT OF HCV/HIV

Coinfected individuals warrant aggressive treatment of both viruses. It has long been recognized that sustained virologic response (SVR) rates are lower in coinfection than in HCV monoinfection. Some of this may be due to biological and treatment-specific factors, but much may be linked to other issues found frequently in coinfected populations including unstable socioeconomic circumstances, stigma, racial barriers, and competing priorities for healthcare. This is particularly true for individuals who have acquired disease through injection drug use. Improvements in HIV and HCV treatment and delivery, provide new hope that simple, well-tolerated, and effective treatment for both viruses may become widely available.

Screening and Diagnosis

The first challenge for providing universal treatment for HIV and HCV in coinfection is to improve screening for both infections. HIV testing rates are improving, yet many HCV infections in HIV-infected individuals remain undiagnosed. In a report of long-term outcomes in a cohort of >2000 HIV-infected individuals, a third of whom were HCV antibody positive, mortality was 50% higher in the coinfected group. Of concern, 30% of HCV-coinfected persons were unaware of their HCV status [22]. Screening guidelines in HIV-infected populations support HCV antibody testing at HIV diagnosis and yearly thereafter to aid in the detection of often asymptomatic HCV infection (particularly relevant given the recent increases in newly acquired HCV infections seen within certain subgroups; see Epidemiology section) [13, 23]. Guidelines also advocate HCV RNA testing in the setting of new or unexplained alanine aminotransferase elevations and/or symptoms and risk exposure. If infection is confirmed, testing for HCV genotype, evaluation for other causes of liver disease, healthy liver lifestyle counseling, and evaluation and care for cirrhosis including screening for HCC should be performed [9]. HCV screening should be accompanied by education about prevention, transmission, natural history, and evolving therapies.

Treating HIV

Therapy for HIV infection is the cornerstone of effective medical management in coinfection. ART transforms HIV from a lethal process to a chronic, manageable disease; reduces AIDS-related morbidity and mortality and all-cause mortality; and is cost-effective in underresourced and well-resourced locales [24]. Twenty-three antiretroviral agents (ARVs) now exist in 6 mechanistic classes including 3 one-tablet, once-a-day combinations. Furthermore, the groundbreaking findings of a 2011 HIV Prevention Trials Network study verified the concept of HIV treatment as prevention [25]. This international randomized trial provided the strongest evidence to date that early ART initiation reduces rates of heterosexual transmission of HIV type 1 and clinical events, indicating both personal and public health benefits.

Previously, concerns around drug-induced liver injury (DILI) often discouraged clinicians from prescribing ART in coinfection. Although some earlier ARVs (ritonavir, nevirapine, stavudine, and didanosine) are associated with hepatotoxicity, mitochondrial toxicity, and/or steatosis, development of less hepatotoxic ARVs has reduced this risk. Additionally, untreated HIV may lead to high levels of immune activation, infection of hepatic stellate cells, and generation of inflammatory cytokines, thus promoting hepatic fibrosis and supporting the rationale to treat HIV early, especially in coinfection [20, 21]. Several studies suggest that better HIV control and higher $CD4^+$ cell counts may be associated with slower fibrosis progression [26]. It is now clear that although coinfection increases risk of ART-related hepatotoxicity, liver disease progression is slower in patients receiving ART, and benefits outweigh risk. Irrespective of $CD4^+$ cell count, HIV RNA level, HIV-related symptoms, and

opportunistic infections, early ART introduction is recommended to reduce the rate of progression of hepatic disease. In most cases, ART should precede HCV treatment, to decrease HIV-related morbidity and mortality and diminish HIV transmission. Treatments for HIV and HCV should not be started simultaneously, so that patients can adjust to each regimen sequentially. The most recent Department of Health and Human Services (DHSS) guidelines now state, "For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding DILI. Therefore, ART should be considered for HIV/HCV-coinfected patients, regardless of $CD4^+$ count (BII)" [27]. Given the wider availability of "liver-friendly" ART, including all 4 first-line regimens recommended by DHSS guidelines, ART can be safely prescribed to most coinfected individuals—but only if issues of access, cost, and adherence are overcome.

Access and adherence are particularly relevant to PWID, who are less likely to be offered ART, and more likely to initiate ART at lower $CD4^+$ cell counts than other populations [28, 29]. This is due in part to the perception that PWID may be less compliant with treatment and more likely to develop HIV drug resistance than other individuals. However, when appropriate support is provided, there is little evidence to support this. In fact, a recent meta-analysis examining ARV drug resistance in HIV-infected PWID versus non-IDUs found no difference in observed rates of resistance [30].

Treating HCV

ART may lessen the accelerated liver disease progression in coinfection but does not fully correct for it. In a meta-analysis of studies examining fibrosis rates in coinfected individuals in the ART era, ART partially, but not fully, corrected the adverse impact of HIV on HCV progression [31]. Similarly, the Veterans Cohort Study recently reported that long-term liver disease–related outcomes were higher in their coinfected versus HCV-monoinfected population, despite the fact that all HIV-infected patients were on ART [32]. The most effective way to reduce morbidity and mortality from liver disease in coinfection is to achieve SVR. SVR reduces hepatic fibrosis progression, liver stiffness, serum inflammatory markers of fibrosis, rates of hepatotoxicity, and overall mortality, as well as subsequent liver-related events (liver-related death, decompensation, HCC, or transplant) [33–38].

Treatment with pegylated interferon and ribavirin (peg-IFN/RBV) has typically resulted in SVR rates that are 10%–15% lower in HIV-infected individuals. For genotype 2/3 infections treated for 48 weeks, SVR rates have ranged from 44% to 73%, although this can be enhanced with weight-based RBV dosing. Data exist to support shortening treatment duration to 24 weeks in those with rapid virologic response; however, this is recommended only for those with low baseline HCV loads and minimal fibrosis—a fraction of the coinfected population. Genotype 1 SVR rates have been dismal, from 14% to 38%. Low SVR rates, treatment toxicities, polypharmacy, and the need for liver biopsy deter coinfected individuals from attempting treatment, while these factors plus comorbidities prevalent in HIV deter physicians from prescribing HCV therapy.

HCV TREATMENT AMONG HCV/HIV-COINFECTED PWID

The goal of HCV viral eradication in coinfection has been challenging. Although international guidelines endorse considering all coinfected patients for HCV treatment [27, 39], implementation of these guidelines has been limited because most coinfected persons are current or former PWID. Historically, HCV therapy has been underused in this population. Few data are available regarding chronic HCV treatment outcomes among coinfected PWID (Supplementary Table 1). Most studies of chronic HCV treatment efficacy in PWID involve HCV monoinfection; monoinfection data do not demonstrate differences in SVR rates between PWID and non-IDUs. Across the 11 published studies involving coinfected PWID [40–50], 9 reported HCV treatment initiation specifically by HIV status, but SVR was not delineated by HIV status and is therefore unknown in more than half (6) of these. Data are lacking to consider coinfected PWID for HCV treatment differently than non-IDUs.

DAAs in HCV/HIV

HCV treatment is rapidly evolving; in 2011, the first HCV protease inhibitors (PIs), boceprevir and telaprevir, were approved. Boceprevir- and telaprevir-based regimens significantly increase treatment efficacy for genotype 1 patients, regardless of HIV status. Treatment outcomes in coinfection from phase 2b studies with telaprevir and boceprevir have been reported [51]. In the telaprevir study, 38 genotype 1 treatment-naive coinfected participants were treated with telaprevir plus peg-IFN/RBV for 12 weeks, followed by an additional 36 weeks of peg-IFN/RBV. Outcomes were compared to 22 coinfected controls treated with peg-IFN/RBV for 48 weeks. SVR at week 24 data (defined as an undetectable HCV RNA level 24 weeks after treatment discontinuation) demonstrated efficacy to be considerably greater in the triple- (74%) versus the dual-therapy arm (45%). Adverse events occurred more frequently with triple therapy, and the pill burden was sizeable, particularly for those on efavirenz who were required to take 3 telaprevir pills 3 times daily. However there was no difference according to ART use and no loss of HIV control.

Although formal drug–drug interaction studies were not performed between telaprevir and ARVs, drug levels of telaprevir and ARVs the participants were already taking were measured. These results provided reassurance that interactions with

Table 1. Antiretroviral Agents Suitable for Concomitant Treatment of HIV and Hepatitis C Virus in the Context of Opioid Substitution Therapy

	Antiretroviral Agents, by Class			
HCV PI	NRTI	NNRTI	PI	II
Boceprevir	Tenofovir[a] Abacavir Lamivudine Emtricitabine	Etravirine[b]	An ongoing study is evaluating drug–drug interactions between boceprevir and HIV PIs	Raltegravir
Telaprevir	Tenofovir[a] Abacavir Lamivudine Emtricitabine	Etravirine Rilpivirine Efavirenz (telaprevir dose must be increased from 750 mg/tid to 1125 mg/tid)	[a]Atazanavir/ritonavir	Raltegravir

Abbreviations: HIV, human immunodeficiency virus; II, HIV integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; tid, 3 times a day.

[a] Monitoring for toxicity is recommended.

[b] In healthy volunteers, boceprevir decreased etravirine area under the curve, C_{max}, and C_{min}, but clinical significance is not clear; when etravirine is coadministered with methadone or buprenorphine, clinical monitoring is recommended and dose adjustments may be necessary.

Sources: De Kanter C, Blonk M, Colbers A, et al. The influence of the HCV protease inhibitor boceprevir on the pharmacokinetics of the HIV integrase inhibitor raltegravir. In: 19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, 5–8 March 2012. Abstract 772LB.

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tenofovir, atazanavir, and efavirenz plus telaprevir were manageable. Other ARVs that may be coadministered with telaprevir-based treatment include raltegravir, etravirine, rilpivirine, and 3 additional nucleoside reverse transcriptase inhibitors (NRTIs) (Table 1). However, telaprevir dose increase is necessary with concomitant efavirenz, clinical and laboratory monitoring for hyperbilirubinemia is recommended with atazanavir, and increased monitoring is warranted with tenofovir.

In the boceprevir study, similar outcomes were observed [52]. Sixty-four coinfected genotype 1 treatment-naive participants were randomized to 4 weeks of peg-IFN/RBV, followed by 44 weeks of peg-IFN/RBV/boceprevir, compared to 34 participants randomized to peg-IFN/RBV for 48 weeks. Again the SVR at week 12 data (defined as an undetectable HCV RNA level 12 weeks after treatment discontinuation) showed a similar efficacy benefit (61% in triple vs 27% in dual arm), but adverse events were greater in the triple arm. Although HIV breakthrough was similar in both arms (2 on triple and 3 on dual therapy), a subsequent drug–drug interaction study on healthy volunteers demonstrated considerable interactions between boceprevir and the HIV PIs. Area under the curve concentrations for darunavir, atazanavir, and lopinavir were reduced by 34%–44% in the presence of boceprevir, leading to a subsequent Food and Drug Administration recommendation not to use these drugs with boceprevir. Additionally, fosamprenavir, ritonavir, and efavirenz are not recommended in combination with boceprevir. ARVs that may be coadministered with boceprevir-based treatment include raltegravir, etravirine, and 4 NRTIs (Table 1). In summary, although these drugs offer efficacy benefit, restrictions on ARV use, additional pill burden, and toxicity impede their widespread use.

OST IN HCV/HIV COINFECTION

HCV, HIV, and opioid dependence are overlapping epidemics. HCV-monoinfected PWID can be successfully treated for HCV with and without opioid substitution therapy (OST) [53]. OST facilitates HCV treatment among PWID in diverse settings [44, 45], reduces HIV acquisition, and is associated with enhanced HIV treatment outcomes (including increased ARV initiation rates, adherence, and $CD4^+$ cell counts). Fewer interactions exist between buprenorphine and ARVs than between methadone and ARVs [54–56].

Opioid Substitution Treatment With DAAs

PWID and individuals on OST were excluded from the first HCV PI studies in coinfection. Among all coinfection telaprevir studies to date, exclusion criteria regarding PWID and OST are heterogeneous, ranging from no mention of excluding PWID or use of OST, to excluding individuals with alcohol intake and/or substance abuse that may represent an obstacle for participation. Among all coinfection boceprevir studies to date, exclusion criteria regarding PWID and OST are similarly varied. Some do not

mention excluding PWID or use of OST, whereas others exclude individuals with active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements; those receiving OST but not enrolled in an OST maintenance program; those with current evidence of substance abuse within 3 years of screening; those with a history of a clinical diagnosis within the past 6 months of substance abuse prior to day 1; or those with any current evidence of substance abuse of alcohol or other drugs. Some HCV-monoinfection PI studies have allowed inclusion of persons on OST, although safety and treatment outcome data have not been presented in this subpopulation. Fortunately, pharmacokinetic studies suggest that OST can be coadministered with boceprevir and telaprevir; although dose adjustments may not be necessary, clinical monitoring for withdrawal symptoms is recommended.

Opiate Substitution Treatment With ART and DAAs

Selecting ART for patients on methadone involves consideration of drug–drug interactions. Among the single-tablet regiments, Complera (rilpivirine/tenofovir/emtricitabine) cannot be used with methadone due to an increased risk of QTc prolongation and torsade des pointes. Efavirenz, the backbone of Atripla (efavirenz/tenofovir/emtricitabine), lowers methadone plasma concentration; dose adjustments are typically needed to avert withdrawal symptoms. Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine) can be coadministered with methadone and buprenorphine, but there are no available data on drug–drug interactions with boceprevir or telaprevir.

Complex drug–drug interactions may exist between ARVs, DAAs, and OST. A list of ARVs suitable for concomitant treatment of HIV and HCV in the context of OST is provided in Table 1. ARV options may be further limited by multidrug resistance or financial constraints. Cotreatment of HCV and HIV is further complicated by overlapping drug toxicities, increased pill burden, and food restrictions.

Failure to perform drug–drug interaction studies that facilitate inclusion of high-prevalence patient groups in clinical trials perpetuates a vicious cycle; after approval, treatment is often withheld due to lack of information on safety, efficacy, and tolerability. Clinicians treating coinfected patients on stable OST with advanced liver disease—individuals most likely to benefit from successful HCV treatment—often do so without adequate data. To date, drug–drug interaction studies with ARVs and HCV PIs have been performed only in healthy volunteers. Drug levels may be different in HIV-infected and HCV/HIV-coinfected patients, especially those with hepatic impairment.

INVESTIGATIONAL DAAs IN HCV/HIV

Developments in HCV therapeutics will likely revolutionize HCV treatment for coinfected individuals in the near future. It is anticipated that over time, difficulties seen with the first-generation HCV PIs, including those of toxicity and drug–drug interactions, are likely to disappear. Studies are already under way with several second-generation drugs including simeprevir, faldeprevir, and daclatasavir, all of which have improved tolerability profiles. One of the most exciting drugs in development is sofusbuvir—a potent, tolerable direct-acting nucleotide polymerase inhibitor with a high genetic barrier to resistance, currently in phase 3 studies in monoinfection and coinfection. A phase 1b study of 19 coinfected individuals suggests that HCV declines observed with 7 days' sofosbuvir monotherapy are identical to those in HCV monoinfection [57]. Drug–drug interaction studies with ARVs have begun; in a phase 1, fixed-sequence, 4-cohort study involving healthy volunteers, pharmacokinetic interactions between sofusbuvir and common ARVs demonstrated no clinically significant interactions or change in levels of either HIV or HCV drug [58].

ENHANCING DELIVERY OF CARE

Given the barriers to treatment that often exist for coinfected PWID (lack of engagement in healthcare, incarceration, mental health disorders, and fractured social networks), urgent attention is needed to improve mechanisms through which this disenfranchised group can be treated. Programs that enhance engagement, retention, and adherence including directly observed therapy, supervised dispensing, patient–provider support, and OST have been shown to be effective. There are a growing number of successful models of HCV care for coinfected PWID in settings including HIV clinics, community health centers, hospitals, and prisons. Common facilitators include multidisciplinary care, integrated addiction services, peer-based support, psychiatric care, "one-stop shopping," risk reduction, case management, and nursing assessment. These approaches require implementation on a larger scale than that currently achieved, with investment in infrastructure at the healthcare service level.

CONCLUSIONS

Coinfected PWID are among the most likely to be affected by HCV but are the least likely to have access to HCV treatment. Benefits of therapeutic advances in HCV will be limited for coinfected PWID until barriers are overcome and HCV care enhanced on a massive scale. Only a revolution in HCV treatment delivery, similar to that occurring in HCV treatment development, will avert decades of preventable morbidity and mortality. Coordinated approaches to prevention and treatment of HCV/HIV among PWID are imperative.

Coinfected PWID should have equitable and universal access to HIV/AIDS, HCV, and addiction prevention, care, and treatment. Drug use itself is not a contraindication to HCV therapy and treatment should not necessarily be deferred until this is

"stabilized." Coinfected PWID must be engaged in HCV care early after HIV and HCV diagnoses. It may take time to adapt to ART and gain control of HIV before HCV treatment may be initiated. During this time, patients should have access to HCV education and evaluation. The stage of HCV, status of HIV, and patient preference should drive the timing of HCV therapy while DAAs evolve. If treatment is deferred, reevaluation should occur biannually and relative contraindications should be addressed.

In summary, the ultimate goal must be the elimination of HCV from all coinfected PWID. To achieve this, substantial issues of cost, access, and treatment delivery will need to be overcome. Ensuring that all coinfected PWID receive comprehensive HIV care and consideration for HCV treatment is the important first step.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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