

REVIEW

Public Health Considerations among People who Inject Drugs with HIV/HCV Co-Infection: A Review

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Received: October 11, 2018 / Published online: January 3, 2019
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ABSTRACT

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection among persons who inject drugs (PWID) is a major public health concern. There are limited data in clinical trials on the use of direct-acting antiviral (DAA) therapy for treatment of HCV in co-infected PWID. It is critical for these patients to gain access to treatment in order to decrease progression of liver disease and decrease transmission of both HIV and HCV. Additional harm reduction interventions, including needle and syringe programs and opioid substitution treatment, should be made available to this vulnerable population. Despite the importance of DAA treatment, the cost of DAA therapy and access to medical care is still a barrier to appropriate therapy. The purpose of this review is to present available data on the use of DAAs in co-infected PWID, review guideline recommendations for treatment and retreatment of HCV in co-infected PWID, provide cost considerations for DAA therapy, and provide recommendations

about caring for patients who continue to inject drugs.

Keywords: Co-infection; HCV; Hepatitis; HIV/AIDS; Injection drug use; Public health; PWID

BACKGROUND

A recent study estimated there were 15.6 million persons who inject drugs (PWID) globally [1]. It was also estimated that 52.3% (8.2 million people) of current PWID have been exposed to hepatitis C virus (HCV), while 17.8% (2.8 million people) of PWID are living with human immunodeficiency virus (HIV). Due to the overlapping routes of parenteral transmission, HIV and HCV infections are a major global public health concern. There were an estimated 2.3 million cases of HIV/HCV co-infection in individuals globally, of which 1.4 million (59%) were also PWID [2]. Eastern Europe and Central Asia have the greatest burden due to the large HIV-infected PWID population of 688,100, of which an estimated 83% (567,700 people) of PWID were co-infected with HIV/HCV. North America has an estimated 187,000 patients living with HIV (PLWH) who were also PWID. Of these, 153,300 PWID were co-infected with HIV/HCV. Additionally, there is evidence to support that, in high-income countries, PWID were the main risk group for HCV transmission,

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contributing to more than 90% of new infections in settings such as the United Kingdom (UK) [3].

International guidelines recommend prioritizing treatment in individuals at risk of transmitting HCV [4]. Unfortunately, a large number of HIV/HCV co-infected PWID remain untreated for HCV [5, 6]. Identifying the barriers that hinder the implementation of treatment in PWID is crucial to the success of therapy. Importantly, evidence supports the effectiveness of harm reduction interventions, such as needle and syringe programs (NSP) and opioid substitution treatment (OST), in reducing HIV transmission and HCV and HIV incidence [7]. Therefore, it is imperative to identify a treatment system that provides an opportunity for PWID to obtain treatment in order to prevent HIV and HCV transmission and reduce long-term morbidity in PWID. The information in this paper is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

GUIDELINE GUIDANCE

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) do not have specific treatment recommendations in PWID and are co-infected with HIV/HCV [4, 8]. Direct-acting antiviral (DAA) therapy continues to be the mainstay of therapy for HCV therapy with or without HIV, yet limited studies exist in PWID. Similar to HCV-monoinfected patients, cure rates are comparable around 95% sustained virologic response (SVR). However, many studies exclude PWID due to concerns regarding medication and protocol adherence. Active or recent drug use should not be considered a contraindication to HCV therapy, as the DAAs are safe and effective with a reduced length of treatment when compared to interferon-based management. Both guidelines recommend the use of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir to provide pan-genotypic coverage against HCV genotypes 1–6 and can be used in patients who are co-infected. The use of other

DAAs can be considered in this population as long as drug interaction potential is considered in the presence of antiretroviral therapy as well as opioid substitution therapy.

HCV MEDICATION TRIALS IN PEOPLE WITH HIV/HCV CO-INFECTION

The United States (US) Food and Drug Administration (FDA) had approved ledipasvir/sofosbuvir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, and grazoprevir/elbasvir as single-tablet DAAs which have been shown to be safe and effective for use in patients co-infected with HIV/HCV. Clinical trials supporting the use of these single-tablet DAAs as treatment in the HIV/HCV co-infected population are represented in Table 1 with rates of SVR ranging from 95 to 100%, yet specific data in PWID is not reported [9–14]. Each clinical trial included patients co-infected with HIV/HCV, both on and off antiretroviral therapy (ART) at the time of screening visit, and addressed the handling of data from PWID. ENDURANCE-1 and EXPEDITION-2 both included PWID in the final analysis, and overall rates of SVR for the entire study populations were 100% and 98%, respectively [9, 10]. In ENDURANCE-1, 28% of the total study population reported injection drug use (IDU), while in EXPEDITION-2, 6–9% of total study population reported IDU within 12 months of screening and 45–63% reported IDU more than 12 months prior to screening. The National Institute of Allergy and Infectious Diseases (NIAID) ERADICATE study required all opioid-dependent subjects to participate in supervised treatment, with no mention of specifics on urine drug screening (UDS) or pharmacological agents used for OST [11]. Results from NIAID ERADICATE represented SVR rates of 100% in ART-naïve patients and 97% in ART-experienced patients. ION-4 and ASTRAL-5 excluded patients with clinically relevant drug abuse (not defined) or positive drug screen within 12 months of study enrollment [12, 13]. Interestingly, UDS was only collected at the initial screening visit. C-EDGE CO-INFECTION also excluded patients with clinically relevant

Table 1 Clinical trials supporting the use of DAAs in the HIV/HCV co-infected population [9–14]

Clinical trial	Population	Exclusion criteria ^a	HCV treatment history	Genotype	Length of therapy	SVR ₁₂
Trials including PWID						
ENDURANCE-1 [9]	HIV co-infected (Naïve: CD4 ≥ 500, VL < 1000; experienced: CD4 ≥ 200, VL < 40 on ART × 8 weeks)	Cirrhosis	Treatment-naïve or experienced with IFN, PEG-IFN ± RBV, or SOF + RBV ± PEG-IFN	1	8 or 12 weeks	100% of co-infected (n = 33)
Glecaprevir/pibrentasvir						8-week group (n = 15)
						12-week group (n = 18)
EXPEDITION-2 [10]	HIV co-infected (Naïve: CD4 ≥ 500; experienced: CD4 ≥ 200, VL < 20 on ART × 8 weeks)	Decompensated cirrhosis	Treatment-naïve or experienced with IFN, PEG-IFN ± RBV, or SOF + RBV ± PEG-IFN	1–6	8 weeks no cirrhosis; 12 weeks cirrhosis	98% overall (n = 153)
Glecaprevir/pibrentasvir						
Trials excluding PWID						
NIAID ERADICATE [11]	HIV co-infected (Naïve: CD4 ≥ 500 or stable CD4 with VL < 500; experienced: CD4 ≥ 100, VL < 50 on ART × 8 weeks)	Cirrhosis	Treatment-naïve	1, 1a, 1b	12 weeks	100% of patients not on ART (n = 13)
Ledipasvir/sofosbuvir						97% of patients on ART (n = 37)
ION-4 [12]	HIV co-infected (CD4 ≥ 100, VL < 50 on ART × 8 weeks)	Decompensated cirrhosis	Treatment-naïve and experienced	1,4	12 weeks	96% overall (n = 335)
Ledipasvir/sofosbuvir						

Table 1 continued

Clinical trial	Population	Exclusion criteria ^a	HCV treatment history	Genotype	Length of therapy	SVR ₁₂
ASTRAL-5 [13] Sofosbuvir/ velpatasvir	HIV co-infected (CD4 ≥ 100, VL < 50 on ART × 8 weeks)	Decompensated cirrhosis	Treatment-naïve or IFN-experienced	1–6	12 weeks	95% overall (n = 101) 95% treatment-naïve (n = 75) 97% treatment-experienced (n = 31) 100% compensated cirrhosis (n = 19)
C-EDGE CO-INFECTION [14] Grazoprevir/elbasvir	HIV co-infected (Naïve: CD4 ≥ 500, VL < 50,000; experienced: CD4 ≥ 200, VL < 20)	Decompensated cirrhosis	Treatment-naïve	1, 1a, 1b, 4	12 weeks	96% overall (n = 218) 100% compensated cirrhosis (n = 35)

ART antiretroviral therapy, *CD4* cluster domain 4 (in cells/mm³), *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IDU* injection drug use, *IFN* interferon, *PEG-IFN* pegylated interferon, *PWID* people who inject drugs, *RBV* ribavirin, *SOF* sofosbuvir, *UDS* urine drug screen, *VL* HIV-1 viral load (in copies/mL)

^a For an extensive list of exclusion criteria please refer to individual clinical trials

drug abuse (not defined) within 12 months of study enrollment, but did not require UDS at enrollment or any time during the study period [14]. No virologic failure was noted in any of these trials, while NIAID ERADICATE and C-EDGE CO-INFECTION each had patients with transient viremia who later achieved viral suppression with no change in ART [11, 14].

Overall, limited studies evaluate the use of DAAs in HIV/HCV co-infected PWID. ENDURANCE-1 and EXPEDITION-2 demonstrated high rates of SVR in PWID using glecaprevir/pibrentasvir for treatment of HCV [9, 10]. These trials represented the DAA with the most data in the HIV/HCV co-infected PWID population. Despite the limited availability of data, both these studies demonstrate that a HCV cure can be achieved despite all of the considerations and/or concerns regarding active or prior drug use.

COST CONSIDERATIONS

While the efficacy of the DAA regimens for HCV infection is well established, cost is still a major concern when considering large-scale access to these medications. The sticker price for HCV treatment is substantially higher than many other medications on the market today. However, the cost-avoidance achieved with these regimens should also be considered. Complications of untreated chronic HCV infection include end-stage liver disease/cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and ultimately death. In 2017, the average total cost for a liver transplant in the United States was US\$812,700. This included, in addition to the surgery, the 30-day pre-transplant work-up, procurement of the organ, hospitalization, post-transplant follow-up, and all medications throughout the process [15]. While mortality associated with hepatocellular carcinoma is decreasing, the overall hospitalization costs have been steadily increasing. One study noted a \$15,153 increase in the cost per hospitalization between the years 2002 and 2011, after adjusting for inflation [16]. Medical treatment for HCV may decrease the overall economic burden of end-stage liver disease and

cirrhosis, which are costly to our healthcare system. Furthermore, the treatment cost also prevents reinfection or further infection of other injection drug users in the PWID population. Even when taking into consideration the high price of medications, the cost-avoidance achieved through treating this patient population rather than delaying treatment has been shown to be cost-effective [17].

The price tag on DAA therapy varies globally, but remains unaffordable to a majority of patients living with HCV [18]. Some low- and medium-income countries have licensing agreements with pharmaceutical companies for tiered pricing of certain DAAs, but these agreements do not include the middle-income countries which suffer the highest burden of HCV infections. For example, Central and Eastern European countries have the highest costs for DAA therapies, despite having the highest burden of HIV/HCV co-infected patients. Low-cost generic DAAs available in India have led to improved patient outcomes and increased cost savings related to HCV treatment, but the cost of testing and diagnosis still remain high [19]. Generic DAAs are expected to become available in the US in early 2019, which could potentially lead to increased access to treatment and a reduction in the economic burden of HCV [20].

CONSIDERATIONS WHEN CARING FOR PATIENTS WHO CONTINUE TO INJECT DRUGS

When treating a person who injects drugs with newly diagnosed HIV/HCV co-infection, as with all patients, medication therapy for both infections should be initiated as soon as possible to prevent the progression of liver disease and decrease transmission of the viruses. However, caring for co-infected patients who continue to inject drugs presents health care providers with potential challenges including reinfection, transmission, and nonadherence to antivirals and monitoring programs. Co-infected PWID should be counseled on the risk of reinfection with HCV after achieving SVR with DAAs. Reinfection is defined as the recurrence of HCV

RNA after achieving SVR and demonstration that the infection is caused by a different strain of HCV [4]. In a study reviewing HCV reinfection in co-infected patients 36–75 months after achieving SVR with either Peg-IFN + RBV or Peg-IFN + RBV + DAA, the reinfection rates were estimated to be 8.72 cases per 100 person-years in patients who continued to inject drugs [21]. In Part B of the C-EDGE CO-STAR study evaluating HCV reinfection and injecting risk behavior following grazoprevir/elbasvir therapy in patients receiving OST for at least 3 months, the overall reinfection rate was 2.3 cases per 100 person-years [22]. Data were further extrapolated to show reinfection rates of 4.2 cases per 100 person-years for those who reported continued IDU during the OST treatment period. While this patient population was around 8% co-infected PWID, further data on reinfection rates in HIV/HCV co-infected patients are limited. A meta-analysis showing higher HCV reinfection incidence in PWID is mostly driven by the HIV-positive MSM cohort, which cannot be extrapolated to the general HIV/HCV population [23]. Patients who become reinfected with HCV should be monitored for spontaneous clearance of infection for at least 3 months prior to restarting therapy [4]. In Part A of the C-EDGE CO-STAR study, 6 out of 301 patients had probable reinfection, and 50% of these patients had spontaneous clearance of virus [24]. Based on EASL and AASLD-IDS guidelines, patients who continue to inject drugs should be tested bi-annually or annually for HCV reinfection [4, 8]. If reinfection is detected, retreatment should be made available to these patients. The combination of sofosbuvir/velpatasvir/voxilaprevir is the regimen of choice for retreatment in patients who failed IFN-free, DAA therapy, although safety and efficacy data on this combination are lacking in the HCV/HIV co-infected population [4].

The distribution of HCV genotypes/subtypes that previously exhibited specific geographical locations are becoming more prevalent in PWID [25, 26]. Potential drivers of HCV genotype transmission have been hypothesized and include opiate drug trafficking, increased global travel, and immigration. In the general population. Genotype 1 is the most common

genotype seen in North America, accounting for approximately 80% of reported cases [25]. In PWID, genotype 1a accounts for approximately 70% of reported cases in North America, followed by genotypes 1b, 2, and 3, each occurring at rates of about 10% [26]. In other geographical areas of the world with a high burden of IDU, genotypes vary in PWID. For example, the most common genotypes in Eastern Europe are 1a, 1b and 3, while the most common genotypes in Central Asia are 1a, 1b, 2, 3, and 4. In a study comparing HCV genotypes and subtypes between HIV-positive and HIV-negative patients living in Spain, they found genotype 1 represented 74.6% of HIV-negative and 58.5% of HIV-positive patients ($p < 0.01$) [27]. In addition, HCV subtype 1a was the most common in HIV-positive patients (32.1%) and subtype 1b was the most common in HIV-negative patients (53.8%), while there was an increase in the prevalence of genotype 4 among the HIV/HCV co-infected population. The increasing distribution of HCV genotypes amongst PWID supports the use of pangenotypic DAAs in this high-risk population when genotypic testing cannot be performed.

Beginning at diagnosis and continuing with each health care encounter, it is important to address and evaluate the patient's illicit drug use. Studies have shown that, in the HIV populations, ART is equally efficacious for PWID when patients are not actively using drugs [28]. Illicit drugs have been linked to depression and anxiety, which is a strong predictor of poor adherence and potentially poor treatment outcomes. Persons living with HIV who inject drugs have lower rates of ART adherence if they have additional risk factors for non-adherence, such as recent incarceration or lack of access to rehabilitation programs. Consequently, management of substance use disorders is often necessary to successfully eradicate HCV and appropriately manage HIV. Therefore, OST should be considered in combination with DAA therapy when HCV treatment is being suggested for HIV/HCV co-infected patients who continue to inject drugs. In patients living with HIV, OST is associated with a twofold increase in adherence to ART and a 45% increase in virologic suppression [29]. In patients living with HCV,

OST does not appear to affect SVR or adherence to DAA therapy [30, 31]. Most of the DAAs that the FDA approved for use in HIV/HCV co-infected patients are considered safe for co-administration with methadone, buprenorphine, and buprenorphine/naloxone [32–37]. Daclatasvir, ombitasvir/paritaprevir/ritonavir, and ombitasvir/paritaprevir/ritonavir plus dasabuvir increase levels of buprenorphine, requiring increased monitoring for adverse effects without any dose adjustments [38–40]. It is important to build a relationship of trust with these patients, and not only provide medical support for their HIV/HCV infections but also assist in connecting them with additional providers to manage comorbidities affecting adherence to medication therapies. This primarily includes a multidisciplinary approach to treating the patients' substance use disorders and psychiatric illnesses. It is prudent to stabilize these patients and provide them with the resources necessary to appropriately manage their HIV and HCV. Further harm-reduction strategies, such as connecting patients with needle exchange programs and/or clinics providing sexually transmitted infection screenings and free condoms, are also important.

There is growing evidence supporting the use of antiviral-based interventions, also known as treatment as prevention (TasP), to reduce transmission of HIV and HCV in PWID [41]. TasP leads to a reduction in the viral burden and infectious potential of patients who continue to engage in high risk behavior. These patients should be counseled on both sexual and injection drug use risk reduction behaviors to avoid transmission and reinfection. Furthermore, patients should be provided with access to naloxone rescue products, and both the patients and family members should be counseled on the signs and symptoms of opioid overdose and appropriate use of naloxone.

Patients enrolled in care for their HIV/HCV can also serve as an access point to enroll other high-risk patients. Respondent-driven sampling (RDS) has become a popular method both in the US and other countries to enroll high-risk patients into studies aiming to treat and prevent HIV and HCV [42–45]. In these studies, "seeds" are identified in high-risk areas and provided with coupons to

enroll additional patients for screening and education for HIV and HCV. Similar approaches can be considered in the real-world population by providing patients with educational materials and resources to recruit other PWID into care. At a teaching hospital in Australia, hepatitis B and C screening and treatment was incorporated into the OST setting by a multidisciplinary staff, leading to successful enrollment of high-risk patients into care [46]. By enhancing patient care models in the HIV/HCV co-infected population, more patients can receive access to treatment, decreasing the global burden of HCV.

CONCLUSION

As healthcare providers, the efficacy of HCV treatment and maintaining HIV virologic suppression are top priorities. Although the PWID population is commonly excluded in HIV/HCV co-infection trials, in those that did include this population, successful cure was achieved. These results could therefore be extrapolated to other PWID, especially taking into consideration the large percentage of persons with HIV/HCV co-infection being PWID. Arguably, this population makes a good target population for treatment. Novel approaches to providing this treatment should be considered, including meeting these patients in the community. Facilities providing OST, clean needle exchanges, or any type of substance dependence or mental health counseling are key places to engage, link, and retain PWID with HIV/HCV co-infection from the community into care. Furthermore, providing HCV treatment to PWID can lead to large cost avoidance when taking into consideration the decreased need for liver transplantation, hepatocellular carcinoma and spread of infection through injection drug use. Since many HCV genotypes are prevalent in this patient population, a pan-genotypic agent could be optimal first line. Glecaprevir/pibrentasvir is an ideal agent considering the short duration of therapy and limited drug interactions with both HIV and OST therapies. Ultimately taking into account all aspects of care, such as cost, access and efficacy, an interdisciplinary medical team is well

equipped to provide treatment to prevent HIV and HCV transmission and reduce long-term morbidity in PWID.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Rachel M. Murdock, Marisa B. Brizzi, Omar Perez and Melissa E. Badowski have nothing to disclose.

Compliance with ethics guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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