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Authors

Chu, Carissa E
Wu, Feng
He, Xi
[et al.](#)

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Hepatitis C Virus Treatment Access Among Human Immunodeficiency Virus and Hepatitis C Virus (HCV)-Coinfected People Who Inject Drugs in Guangzhou, China: Implications for HCV Treatment Expansion

Carissa E. Chu,^{1,2} Feng Wu,³ Xi He,⁴ Kali Zhou,⁴ Yu Cheng,³ Weiping Cai,⁴ Elvin Geng,¹ Paul Volberding,¹ and Joseph D. Tucker^{2,3,5}

¹School of Medicine, University of California San Francisco; ²UNC-Project China, Guangzhou; ³School of Sociology and Anthropology, Sun Yat-sen University, Guangzhou, and ⁴Guangzhou Eighth People's Hospital, China; ⁵Institute of Global Health and Infectious Diseases, University of North Carolina at Chapel Hill

Background. Hepatitis C virus (HCV) treatment access among human immunodeficiency virus (HIV)/HCV-coinfected people who inject drugs is poor, despite a high burden of disease in this population. Understanding barriers and facilitators to HCV treatment uptake is critical to the implementation of new direct-acting antivirals.

Methods. We conducted in-depth interviews with patients, physicians, and social workers at an HIV treatment facility and methadone maintenance treatment centers in Guangzhou, China to identify barriers and facilitators to HCV treatment. We included patients who were in various stages of HCV treatment and those who were not treated. We used standard qualitative methods and organized data into themes.

Results. Interview data from 29 patients, 8 physicians, and 3 social workers were analyzed. Facilitators and barriers were organized according to a modified Consolidated Framework for Implementation Research schematic. Facilitators included patient trust in physicians, hope for a cure, peer networks, and social support. Barriers included ongoing drug use, low HCV disease knowledge, fragmented reimbursement systems, HIV exceptionalism, and stigma.

Conclusions. Expanding existing harm reduction programs, HIV treatment programs, and social services may facilitate scale-up of direct-acting antivirals globally. Improving integration of ancillary social and mental health services within existing HIV care systems may facilitate HCV treatment access.

Keywords. China; direct-acting antivirals; HCV; HIV; people who inject drugs.

Although hepatitis C infection treatment regimens have rapidly advanced, these benefits have yet to translate into improvements in clinical outcomes and systems of care [1]. Up to 30% of chronically infected hepatitis C virus (HCV) patients will progress to cirrhosis within 20 years, leading to end-stage liver disease and hepatocellular carcinoma [2, 3]. Hepatitis C virus has surpassed human immunodeficiency virus (HIV)-related deaths in several high-income nations [4].

Direct-acting antivirals (DAAs) have achieved over 90% sustained virological response (SVR) rates across all genotypes [5, 6]. Short duration, interferon-free regimens are now possible even for patients with HIV coinfection [7]. Direct-acting antivirals will not only improve SVR rates, but they also may reduce

dependence on laboratory testing and subspecialists [8]. The World Health Organization now recommends DAAs as standard of care for HCV [9] and that all HCV-positive adults, including people who inject drugs (PWID), should be assessed for treatment regardless of symptoms, ongoing drug use, or perceived disease severity [9]. Access to DAAs is an important global health priority for low- and middle-income countries, which continue to rely on interferon-based regimens [9]. In one European modeling study, a modest increase in HCV treatment rates from 8 to 15 per 1000 PWID could halve HCV prevalence within 15 years [10].

Hepatitis C virus/HIV-coinfected individuals have a 50% higher risk of mortality than HIV monoinfected patients and should be prioritized for treatment [9, 11]. It is unfortunate that coinfecting PWID also have the worst rates of treatment access [12, 13]. In one study of 845 coinfecting patients in the United States, <35% of patients eligible for treatment were referred for HCV care, and only 0.7% of the full cohort achieved SVR [14]. Even if cost is addressed, significant social and structural barriers hinder implementation of effective care for HCV among PWID [15–19]. Unless these barriers are reduced, scale up of DAAs is unlikely to be successful.

National leaders have prioritized improving access to HCV treatment in China [11], home to 30 million people living

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Correspondence: J. D. Tucker, University of North Carolina Chapel Hill Project-China, No. 2 Lujing Road, Guangzhou 510095, China (jdtucker@med.unc.edu).

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with HCV infection. Two thirds of PWID are HCV positive [20], and an estimated 6% of patients enrolled in methadone treatment are HIV/HCV coinfectd (approximately 80 000 individuals) [21]. China’s large methadone treatment system and HIV care system provide an opportunity to examine facilitators and barriers to HCV treatment access among coinfectd PWID. The purpose of this study was to explore social and structural factors affecting HCV treatment access in Guangzhou, China in order to inform the development of strategies for expanding access.

METHODS

Site

Our research sites included the outpatient HIV clinic at the Guangzhou Eighth People’s Hospital (a high-volume referral center for HIV management and treatment within the province), the adjacent inpatient hospital, and 2 district-based methadone clinics. Twenty-seven patients were recruited from clinic, and 2 patients were admitted to the hospital for treatment of opportunistic infections and interviewed on the ward. Field observation at clinics took place for 1 month before interviews.

Subject Recruitment

A purposive sample of HCV/HIV-coinfectd PWID were recruited and interviewed from October 2013 to March 2014. We included physicians and social workers to gain a better understanding of the local social environment, but we focused on patient narratives to develop a nonmedical perspective. Verbal consent was obtained from all participants. All participants received a phone card worth 100 RMB (approximately 16 US Dollars [USD]) for their participation.

Interviews

A semistructured, in-depth interview guide (Supplementary 1) was field tested among 8 patients, 2 inpatient physicians, and 3 key informants. Trained interviewers fluent in the local language (Cantonese or Mandarin) conducted interviews in a private location. Interview duration was 30 to 120 minutes. Interviews were audio-recorded if consent to record was provided; if not, field notes were taken. The interview guide included questions regarding the patients’ experience with HCV treatment, HCV/HIV clinical history, injection drug use habits, and sociodemographic information. Emergent themes were explored further in subsequent interviews until thematic saturation was reached. We defined thematic saturation as the point at which further interviews did not yield new themes or trends.

Analysis

Our methodological approach was inductive in which themes were derived from empirical data, influenced by discourse analysis and grounded theory [22, 23] Interview transcripts were primary sources and were translated from Chinese to English. Transcripts were analyzed using Atlas.ti (version 7; ATLAS.ti

Scientific Software Development GmbH, Berlin, Germany). Initial coding was undertaken by 2 independent authors after examining 5 transcripts separately and developing a list of preliminary themes. These themes were discussed at length between the 2 researchers; any discrepancies were discussed with a third, senior investigator. The themes were then organized into a hierarchy based on their relationships with one another (Supplementary 2). These themes were also tested in subsequent participant interviews for validity. All transcribed data was examined based on the coding book.

We analyzed the preliminary themes using an adapted version of the Consolidated Framework for Implementation Research (CFIR) [24]. The CFIR domains included the following: (1) intervention characteristics, (2) individuals involved, (3) internal environment, and (4) external environment [24]. Intervention characteristics include cost, complexity, adaptability, sources, and evidence strength and quality. The individuals involved embody the knowledge and beliefs about intervention, self-efficacy, individual stage of change, identification with an organization, and other personal attributes. The inner environment includes structural characteristics, culture, and the implementation climate. Finally, the outer environment describes patient needs and resources, peer pressure, and external policies and incentives. We classified the barriers and facilitators to HCV treatment into this framework to present the hierarchy and interrelatedness of our findings.

Institutional Review Board

This study was approved by the University of North Carolina, Chapel Hill Institutional Review Board and the Guangzhou Eighth People’s Hospital Institutional Review Board.

RESULTS

Interview transcripts from 29 patients, 8 physicians, and 3 social workers were analyzed (Table 1). Four patients (14%) had undergone interferon-based HCV treatment. No patients had received DAAs. Factors associated with HCV treatment access were organized based on (1) individuals involved, (2) intervention

Table 1. Patient Population and Demographic Data

Age (Years)	27–53
Gender	28 M, 1 F
Enrolled in methadone treatment	12 (41%)
Guangzhou resident	17 (59%)
Inpatient participant	2 (6%)
Highest education level attained	Elementary: 9 (31%) Middle: 13 (45%) High School: 6 (21%) College: 1 (3%)
History of HCV treatment	4 (14%)
Unemployment rate	13 (45%)
Average income (USD/year)	\$3150
History of detention	22 (76%)

Abbreviations: HCV, hepatitis C virus; USD, US Dollars.

characteristics, (3) inner environment, and (4) outer environment (Figure 1). Physician and social worker data generally corroborated and extended patient perspectives.

Individuals Involved

Positive Patient-Physician Relationships Facilitated Treatment

Long-term patient-physician relationships facilitated engagement in care. Human immunodeficiency virus patients formed closer relationships with infectious disease specialists and ancillary staff due to a model of HIV care that involved a multidisciplinary care team, frequent follow up, and continuity of care. As a result, HIV physicians played an important role in recommending HCV treatment and setting expectations for treatment outcomes, side effects, and adherence.

Later, my [HIV] doctor told me that my HCV viral load had reached more than 10 million [and] that hepatitis C could be treated [. . .] He started prescribing the medication and I have been on hepatitis C treatment for more than a month.

– Patient, 39M, treated

Social acceptance of patients by infectious disease and substance abuse specialists also increased trust and willingness to accept treatment.

The infectious diseases hospitals are much better, just like the methadone clinic. The physicians there are closer to our type of patients.

– Patient, 38M, treated

The Hope for Cure Was a Strong Motivator for Treatment

Patients were willing to bear the financial and physical cost of treatment for a chance to achieve a SVR. Unlike HIV treatment, the HCV treatment course seemed finite and allowed patients to feel hopeful about being cured. Patients were able to plan ahead, both financially and emotionally.

If you want to be cured, there are no real problems, you just need to look at your attitude. Adherence is a bit inconvenient, but you just need to make sure you want to be cured. If you have a ‘waiting to die’ attitude, the outcomes would be very different.

– Patient, 39M, treated

Ongoing Injection Drug Use Was a Perceived Disincentive for Treatment

Providers and patients believed that ongoing drug use would have a significant negative impact on medication compliance and clinic follow up.

How would they have the money to get hepatitis C treatment? His first priority is drugs. These people simply do not work. If they do not work, where does the money come from? Even if they earn a bit, they would spend it on drugs. How can they treat hepatitis C?

– Patient 39M, untreated

Some providers considered patients’ personal financial and social circumstances before recommending treatment, omitting a discussion about HCV entirely if they thought their patient was

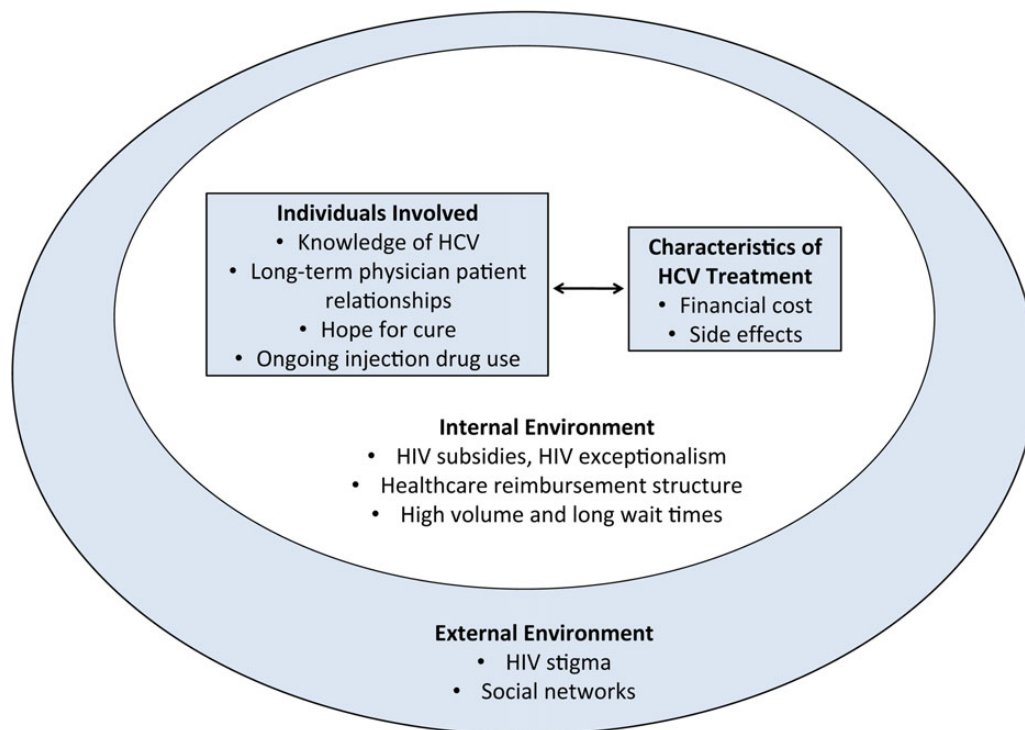


Figure 1. Factors impacting hepatitis C virus (HCV) treatment among people who inject drugs in Guangzhou, China. HIV, human immunodeficiency virus.

poor. Furthermore, PWID actively using drugs were mistrustful of the medical system for fear of being identified, arrested, and detained; these individuals were unlikely to seek care even if diagnosed.

Characteristics of Hepatitis C Virus Treatment

The Most Pervasive Barrier to Hepatitis C Virus Treatment Access Was Financial Cost

It's not that people don't want to get treated. It's that they don't have the financial means, so they are forced to give up.

– Patient, 39M, untreated

Personal poverty was a common theme, related to a history of injection drug use, prior incarceration, HIV coinfection, and lack of employment. Patients often relied on the government subsistence allowance of 500–600 RMB per month (approximately 80 to 100 USD) to meet their basic living needs. In comparison, the cost of a full 48-week course of peg-interferon and ribavirin cost 60 000 RMB (approximately 9600 USD).

90% of the people who got our kind of disease are relatively poor. In general, our type of people [PWID] do not have work for long periods of time [. . .] I have no guarantee of basic needs such as three meals a day. How could I afford this treatment?

– Patient, 39M, untreated

Although HIV care was provided for free for all patients, HCV testing and treatment were not free. Supplemental insurance (a quarterly allowance for inpatient and outpatient health expenditures) was available only to patients registered at an urban address. Patients often delayed treatment as they saved money to support treatment. Many patients borrowed from families to meet the high cost of HCV treatment.

We need to wait until we save enough money. You can't start treatment for one month and then stop for a month, it won't work. . . but I'm worried about my liver getting worse.

– Patient, 43M, untreated

Inner Environment

Structural Barriers in the Health System Affected Access to Hepatitis C Virus Treatment

Fragmented reimbursement systems resulted in healthcare disparities in which tests and treatments were covered for some patients but not for others. This resulted in delays in both diagnosis and seeking care.

In an urban city, residents are allowed to have a free blood test once a year. Not in rural areas. People in rural areas usually don't choose to go to hospital until they have a severe problem.

– Patient, 47M, untreated

Furthermore, outpatient visits ranged from 3 to 8 minutes each, with long patient wait times. A single provider could

see from 30 to 100 patients a day. Patient visits were often focused on HIV first; discussions of HCV and treatment options were rare.

Human Immunodeficiency Virus Coinfection Often Competed With Hepatitis C Virus Care

At times, HIV infection was a direct impediment to HCV treatment. National treatment guidelines stated that coinfecting patients should have a CD4 count >200 to be eligible for HCV treatment, which excluded many PWID [9, 25]. Human immunodeficiency virus was also given higher priority than HCV, such that healthcare delivery, funding streams, and social services were focused on HIV, reflecting HIV exceptionalism [26]. As a result, healthcare needs related to HCV were often overshadowed, with much less disease knowledge and prioritization for HCV.

I thought HCV, in contrast to HIV, was not a big problem. I thought HIV treatment was more important. The fear of HIV is much greater than HCV [. . .] there is not much publicly available medical information.

– Patient, 40M, untreated

Furthermore, HIV-coinfecting patients were seen exclusively by HIV doctors, whereas HCV-monoinfecting patients were typically seen by hepatologists. As a result, there were systematic differences in the quantity and quality of HCV care. There were instances where patients reported that physicians did not discuss their HCV-positive diagnosis and focused solely on HIV management. From the perspective of the physicians, some felt that their patients would not be able to afford, tolerate, or adhere to HCV treatment and therefore withheld the discussion.

To be honest, for those who had HIV, which is already a heavy burden, HCV treatment will cost several tens of thousands of yuan a year. Some people have the will but not the ability. It all depends on your circumstances.

– Patient, 42M, treated

Human immunodeficiency virus exceptionalism resulted in lack of information and familiarity with HCV infection. There was pervasive uncertainty about the long-term health consequences of chronic HCV infection, treatment length, anticipated side effects, and chances for treatment success. Some coinfecting patients were not aware of their HCV status and therefore did not seek treatment.

I had no idea about my HCV, I just knew that most drug addicts have it.

– Patient, 41M, untreated

Decreased public awareness resulted in ambivalence about the disease.

People don't think treating HCV is important. They believe HCV won't cause harm for a long time and rarely results in

cirrhosis . . . most patients are unwilling to treat HCV because they don't know about it.

– Social worker, 25M

Human Immunodeficiency Virus Coinfection Also Facilitated Access to Resources and Support

Patients with HIV infection could qualify for additional health-care funds for medications and laboratory testing, as well as social support from nonprofit social work organization focused on HIV. This funding offset the cost of HCV treatment and was an important facilitator for treatment. Additional funding could be obtained for inpatient services for HIV-infected patients, and physicians would sometimes admit patients to the hospital to reduce out of pocket HCV treatment costs.

[HCV treatment] feels a bit expensive, but I am relatively lucky, the “Red Ribbon Organization” gives me 600 RMB subsidy every month, 3 months is 1800 RMB. Last time I saw the doctor, I spent all of it.

– Patient, 39M, treated

Human immunodeficiency virus diagnosis was also an entry point into the healthcare system, which led to an HCV diagnosis. Patients hospitalized with opportunistic infections were routinely tested for HCV. A positive diagnosis meant that some patients who became medically eligible for HCV treatment could receive it.

I thought I was young and robust, so I did not know about the HCV until my HIV was diagnosed.

– Patient, 40M, untreated

Outer Environment

Pervasive Human Immunodeficiency Virus Stigma Impacted Access to Hepatitis C Virus Treatment

We are the marginalized people, the most marginalized of society.

– Patient, 29M, untreated

Stigma was often tied to HIV status and history of injection drug use. Patients from rural areas reported pervasive stigma, even refusal of medical treatment, at their local hospitals, requiring them to travel long distances to find providers willing to take HIV-positive patients. Once outside of their area of residence, however, their HCV treatment was no longer covered, and financial challenges prevailed. Stigma against HIV-infected individuals reflected a moralistic attitude toward the disease and drug use. This was often internalized into a tainted sense of self.

If you were walking in the street and a normal person told you that he used to be a drug user, you would turn around and leave, because deep down you would think, he must be a bad guy. Even if you changed to a good guy, you are still bad.

– Patient, 29M, untreated

Stigma impacted disclosure, increased the sense of vulnerability, and rendered patients hesitant to discuss HCV with providers.

Talking about my HCV will do little help. If I talk about it aren't I just exposing myself?

– Patient, 40M, untreated

Fear of disclosure among peers perpetuated ongoing HCV transmission and decreased interest in HCV treatment, particularly if storing and injecting interferon would expose their disease status.

Social Support Promoted Awareness About Hepatitis C Virus Treatment

Patients found support among peers in the HIV clinic or the methadone clinic. A common identity resulted in greater trust. A peer-to-peer network, sometimes supported by formal community-based organization (CBO) activities, was important for disseminating information about treatment. Friends were important resources for identifying which hospitals and providers would provide compassionate care for the patient population. Friends and family were also important sources of moral support.

My friend is hopeful [about being cured of HCV] because his friends have also been through treatment and they support him.

– Patient, 39M, treated

Social workers played a critical role as well. They provided individual and group counseling to support medication adherence, abstinence from injection drug use, and daily attendance at methadone clinics. Social workers also provided job counseling to ease reintegration into employment. Social workers also played a role in connecting previously treated patients with patients currently contemplating treatment. However, they were also severely limited by time constraints and often traveled long distances to cover multiple sites.

DISCUSSION

This study presents the social and structural challenges to HCV treatment access among coinfecting PWID. Other studies have demonstrated that HCV treatment outcomes improve when social factors unique to PWID are addressed [6–8, 10]. Our study favors acknowledgement of these social factors among PWID in a densely populated Chinese city. These factors also play a critical role in the management of other chronic diseases among this population, particularly in a primary care setting [27].

We found that social and peer networks facilitated HCV treatment access. These networks filled important roles with counseling, emotional support, linkage to community resources, and addiction recovery. This is consistent with literature showing that nonjudgmental treatment settings with peer-led support groups reduce stigma, facilitating treatment access and adherence [28]. Prior studies have demonstrated the

effectiveness of using multidisciplinary team including peers to enhance community-based treatment programs [17, 29]. The importance of peers in contributing to HCV treatment access suggests that involving PWID CBOs and related groups may improve access.

Our research suggests that HCV treatment access is facilitated by integration with existing health delivery systems serving co-infected PWID. Other studies have demonstrated success with HCV treatment delivery in HIV clinics, prison health services, and methadone maintenance programs [17, 30, 31]. These are settings in which PWID at high risk for both HIV and HCV are most likely to be identified, and targeted interventions may be helpful [32]. Our research is also consistent with existing outcomes and cost-effectiveness literature showing that integration of HCV and HIV services may facilitate psychosocial support, financial subsidies, community health worker networks, and early monitoring of adverse effects for patients [33].

Our finding that patient-physician trust facilitated HCV treatment access suggests that interpersonal relationships play an important role in treatment decisions. Our interviews with physicians corroborated this finding that longitudinal relationships were important in facilitating acceptance and adherence to medical treatment. This is consistent with research from Australia demonstrating that trusting relationships between HCV-positive patients and their health workers can reduce stigma, increase healthcare service utilization, and reduce risk behaviors [29]. Long-term physician patient relationships allow expression of caring, concern, and compassion, which are important aspects of trust and treatment decisions [34]. Thus, providing the time and opportunity to nurture physician-patient relationships may contribute to increased rates of HCV treatment.

We found that poverty and high drug costs limited HCV treatment access. Hepatitis C virus treatment costs (both DAAs and interferon-based regimens) are prohibitive in the absence of generic formulations and reimbursement reform. A 12-week course of sofosbuvir currently costs approximately 84 000 USD in China, approximately 70 times the subsistence allowance provided over the same period of time [35]. Discussions have begun to include DAAs in the list of essential medicines, and Gilead has announced generic licensing and tiered pricing strategies to remove barriers for treatment implementation in 91 developing countries [36, 37]. However, China, Brazil, Russia, and other middle-income countries with high burden of HCV have been excluded from this list [35].

Finally, we found that hopefulness about cure increases motivation for testing and treatment. The development of DAAs provides an opportunity to mobilize communities, improve screening, and increase health-seeking behaviors. This is consistent with findings from qualitative research showing that hopefulness for an HIV cure may increase uptake of HIV testing [38]. As increasing numbers of HCV-positive PWID become

interested in DAA treatment, linkage to care and retention will become critical priorities [39].

The strengths of this fieldwork are its location and in-depth focus on PWID, a large but marginalized population heavily affected by HCV. Our study site is also a strength—Guangzhou is a rapidly growing economy that has prioritized infectious disease research and healthcare reform, and progress here may be emblematic of large-scale change in China. This study may provide insight into HCV treatment implementation in other middle-income countries. Our empiric findings may inform harm reduction and HCV treatment programs in the United States, where PWID continue to be marginalized, integration of mental health and social interventions is poor, HIV coinfection is prevalent, and morbidity and mortality from HCV are on the rise.

Our study has multiple limitations. First, this is a single qualitative study that used purposive sampling. Broader inferences made from these data should be made with caution. Second, we were only able to interview 1 woman, and there may be sex differences in treatment access [16, 40]. Third, all HCV treatment provided to patients was interferon-based, which may not be transferrable to DAAs. Well tolerated oral regimens with very high rates of SVR and cure may mitigate some of the barriers identified in our study, including concerns about side effects, need for frequent follow up (and geographic limitations), and feelings of hopelessness. When asked, all patients unanimously agreed that a pill (ie, ribavirin) was much preferred to a needle (ie, interferon) as a route of drug administration, especially when needles were associated with intravenous drug abuse. By extension, DAAs may have higher acceptability and adherence rates.

However, changing the drug itself will not effect change on systems level—cost, stigma, and marginalization of PWID will continue to be an enormous barrier for DAAs. Middle-income countries such as China, Brazil, Russia, Ukraine, Philippines, and Mexico are seen as emerging markets for DAAs and were excluded from generic licensing agreements. A report from Médecins Sans Frontières' estimated that 49 million individuals living with HCV in middle-income countries were excluded from these agreements [41].

CONCLUSIONS

Direct-acting antivirals are currently our greatest tool for controlling the global HCV epidemic. This feat will be possible only by combining highly efficient, well tolerated drug combinations, active screening strategies, and improved access to care for PWID. This study provides in-depth study of the factors impacting access to current HCV treatment regimens. These findings may be transferrable to other settings, and they have been corroborated by other studies in low-, middle-, and high-income countries. Ongoing qualitative evaluation of DAA access in PWID is critical for guiding interventions. Future policy priorities should be

focused on addressing the specific needs of PWID and improving linkage and retention in healthcare systems.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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