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# Challenges Facing a Rural Opioid Epidemic: Treatment and Prevention of HIV and Hepatitis C

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## Abstract

**Purpose of Review** This article reviews recent epidemiologic trends in HIV and hepatitis C virus (HCV) and strategies for treatment and prevention of these infections as they relate to the opioid epidemic.

**Recent Findings** Among people who inject drugs (PWID) in the United States (US), HIV diagnoses are decreasing, while HCV is increasing. Care for HIV and HCV relies heavily on specialist infrastructure, which is lacking in rural areas. Antiretrovirals for HIV and direct-acting antivirals for HCV are effective among PWID, yet multiple barriers make it difficult for rural injectors to access these treatments. Similarly, access to syringe service programs, medication-assisted therapy for opioid addiction, and pre-exposure prophylaxis for HIV are all limited in rural areas.

**Summary** Previous research on HIV and HCV among PWID has focused on urban or international populations, yet the US opioid epidemic is moving away from metropolitan centers. Increasing rurality of opioid injection brings unique challenges in treatment and prevention. Research into the care of HIV, HCV, and opioid use disorder among rural populations is urgently needed.

**Keywords** HIV · Hepatitis C · Opiate-related disorders · Substance abuse, intravenous · Rural health

## Introduction

The outbreak of HIV in rural Scott County, Indiana, is a cautionary tale for the potential of HIV and hepatitis C virus (HCV) to rapidly disseminate among people who inject opioids [1]. The episode highlighted the many challenges

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characterizing the current opioid epidemic, including a lack of public health and preventive care infrastructure, paucity of specialty services for persons with infectious diseases, and poor awareness of infectious complications of opioid use disorders.

Abuse of prescription opioids has shifted in recent years from oral to injection drug use (IDU), and opioid injectors who were previously dependent on oral formulations engage in injection practices carrying greater risks of HIV and HCV transmission [2, 3]. Historically, discussion around people who inject drugs (PWID) has focused on heroin use in larger cities, but in the current opioid epidemic, new injectors reside more often in nonurban areas [4, 5]. According to estimates from the Center for Diseases Control and Prevention (CDC), the counties at greatest risk for IDU-associated HIV outbreaks are largely rural [6••].

Data on infectious disease (ID) complications of the rural opioid epidemic are sparse, but we may apply lessons learned from managing HIV and HCV among urban PWID to improve care now and identify priorities for future research. The purpose of this review is to summarize existing knowledge about the management of HIV and HCV among PWID in the United States (US) and discuss ways in which

we can optimize treatment and prevention of these infections for rural PWID.

## What Are the Current Epidemiological Trends in HIV and HCV Among PWID in the US?

Between 2008 and 2014, new HIV diagnoses among PWID in the US fell 48%, driven by an approximately 50% decline among urban Black and Hispanic/Latino injectors [7•, 8]. In New York City, new HIV diagnoses among PWID plummeted from 195 in 2007 to 35 in 2013 [9]. IDU transmission in nonmetropolitan areas contributes to new HIV diagnoses in greater proportions than in urban settings [10]. Among White PWID in both urban and rural areas, a more modest decrease in HIV infections was seen from 2008 to 2010 and subsequently leveled off (Fig. 1) [7•].

These data are promising, but HIV screening among PWID remains infrequent overall. Recent surveys demonstrate that approximately half of PWID tested for HIV within the prior year [11, 12]. In Seattle, self-reported screening decreased from 64 to 47% from 2005 to 2015,
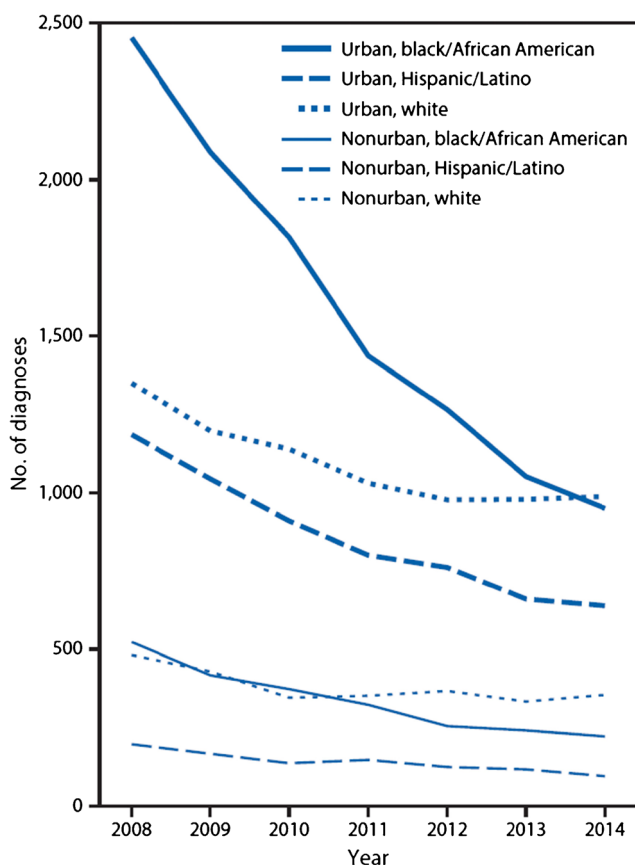


**Fig. 1** Diagnoses of human immunodeficiency virus (HIV) infection among persons who inject drugs—National HIV Surveillance System, USA, 2008–2014. Reprinted from Wejnert et al. [7]

while another result showed a decrease from 72 to 58% over the same period [11].

Infrequent testing is observed against a backdrop of ongoing risks for HIV acquisition among PWID. Syringe and needle sharing continues at high rates among White PWID while declining among Black and Hispanic/Latino injectors [7•]. Persons who inject together are often sexually active with one another, as well; substance abuse is linked with higher-risk sexual practices, including condomless sex and sex with multiple partners [13, 14]. Historically, under half of injectors living with HIV disclose their serostatus to drug-using partners [15]. Primary sex partners are most frequently aware, while disclosure is lower among casual partners and those who exchange sex for drugs [16, 17]. Awareness of serostatus among PWID networks remains poor. In one recently studied cohort, 45% were unaware of their last injecting partner's HIV status, and 38% did not know their last sex partner's serostatus, frequencies which increased over the prior decade [11].

While HIV garnered national attention from the Scott County outbreak, HCV incidence has increased widely across the US, with a threefold increase in reported cases of acute HCV from 2010 to 2015 and a disproportionate rate of HCV among nonurban populations [18, 19]. As of 2015, Appalachian states had some of the highest rates of reported acute HCV cases, most notably West Virginia (3.4 cases per 100,000), Kentucky (2.7), and Tennessee (2.6). However, similarly high rates were seen in Massachusetts (3.7), Indiana (2.1), and New Mexico (1.9), confirming that HCV's spread is not geographically limited [19].

Acute HCV cases reflect only a portion of the true burden of incident infections, since only 15–30% of those with newly acquired HCV become symptomatic [20]. The majority of persons with HCV (75%) establish chronic infection, with 5–25% progressing to cirrhosis within 10–20 years [21]. It is this long delay before the development of liver disease that has prompted US screening recommendations to focus on individuals born between 1945 and 1965, most of whom likely acquired HCV through the reuse of medical equipment [22]. Although recommendations for birth cohort screening are appropriate to help mitigate liver disease in an aging population, comparatively few of these individuals have behavioral risks for forward transmission. Focusing on testing and treatment of "baby boomers" may divert attention and resources from active injectors at current risk for acquiring and transmitting HCV [23].

HCV is transmitted by blood more efficiently than HIV. While HIV infection may occur following 0.3% of healthcare-associated, contaminated needlestick injuries, HCV results in infection in 3–9% of such incidents; numbers are likely higher for both in the setting of IDU [24, 25]. HIV may survive anywhere from 6 days in dried blood to over 4 weeks in a sealed syringe [26, 27]. In

contrast, viable HCV particles can persist on inanimate surfaces for over 6 weeks [28]. For both HIV and HCV, the transmission risk is related to the volume of blood involved; high dead space syringes, which harbor larger quantities of residual blood, pose the greatest risk among PWID [29, 30]. In one study, such syringes comprised nearly half of those available from three major retail pharmacy chains in the US [31].

Because HCV does not induce durable immunity, individuals who spontaneously clear the virus or are successfully treated may be infected again [32]. Further, some opioid use networks segregate by HCV status, a practice that concentrates one's risk of reinfection [33].

## What Barriers Prevent Rural PWID from Accessing HIV and HCV Testing and Treatment?

### Lack of Specialty Healthcare

Compared with urban areas, far fewer physicians practice in rural areas of the US—a phenomenon driven primarily by a lack of specialty providers (Fig. 2) [34]. In the absence of local specialists, primary care providers (PCPs) must decide whether to refer to a distant provider or independently manage the patient's condition. Perhaps owing to a lack of familiarity with advances in antiretroviral therapy (ART) and limited training on the subject, most PCPs refer HIV patients to specialists, even though the decreased complexity and toxicity of ART regimens have made HIV treatment in their practices much more feasible. Although it imposes additional burdens on patients, this approach is probably reasonable; clinical outcomes among people living with HIV (PLWH) are associated with the level of provider experience in managing HIV disease, regardless of one's specialty training [36]. In rural communities, social- and stigma-related factors often make it difficult for PCPs to accumulate enough patients to develop robust HIV expertise [37•].

HCV care in rural America has clear parallels to HIV, with a scarcity of HCV-savvy providers resulting in patient referral to hepatology and (to a lesser extent) ID specialists in more urban areas [38]. The ascendance of safe, efficacious, and well-tolerated direct-acting antivirals (DAAs) has prompted some specialists to call upon PCPs to treat HCV [39]. However, many such providers do not feel ready to take on this role; at one center, less than 10% felt comfortable treating HCV, regardless of a patient's substance abuse [40]. Concerns and uncertainties about treating PWID for HCV further



**Fig. 2** Active physicians per 100,000 population by physician specialty and urbanization level: USA, 2010. Reproduced with permission using data from Meit et al. [34, 35]
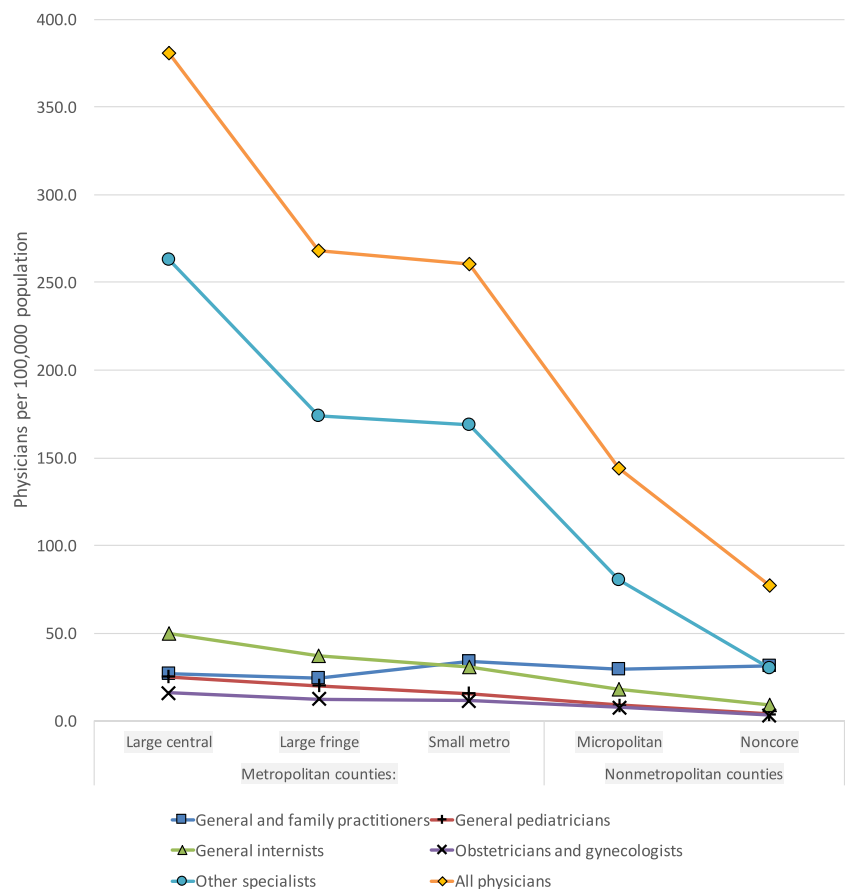
complicate matters. Indeed, even among hepatologists, the overwhelming majority report is that they would not treat HCV in a person with active IDU [41].

## Cost, Insurance, and Rationing of Care

The high cost of treating and medically monitoring PLWH was recognized early on as a major barrier to persistence in HIV care. Successful advocacy efforts led to the passage of the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act in 1990, establishing a variety of federal programs to support the medical and psychosocial needs of uninsured and underinsured PLWH. Ryan White CARE Act-funded programs demonstrate how coordinated efforts addressing both medical and non-medical needs can effect major changes in disease-specific patient outcomes. Recipients of Ryan White services are more likely to be on ART and to achieve virologic suppression, compared to patients with other types of healthcare coverage [42]. Because of insurance coverage for HIV and associated conditions and the safety net provided by Ryan White programs (including the AIDS Drug Assistance Program), it is relatively rare for PLWH to be unable to access HIV treatment resources or medications.

The situation is substantially different for individuals living with HCV, however. The exorbitant cost of early DAA regimens prompted most public and private insurers to institute restrictions on medication access at the patient level (e.g., requiring advanced liver fibrosis or documentation of sobriety to be eligible for treatment) or the provider level (e.g., limiting prescribers to hepatology and ID practices) [43]. Until very recently, obtaining DAAs for Medicaid beneficiaries had been especially challenging. This is a significant problem for PWID, since 30% of those with opioid addiction are insured by Medicaid [44]. In one multistate cohort, 46% of all DAA prescriptions for Medicaid recipients were denied outright, with an additional 25% authorized after an initial denial [45]. As competition in the marketplace drives down the cost of DAAs, restrictions are being loosened or lifted altogether [46].

In one cohort of HCV-seropositive drug users in rural Appalachia, only 32% were insured, and those subjects with insurance were over twice as likely to follow up with healthcare providers for HCV [47]. Regardless of specific risks, only 8% of participants received treatment for HCV, underscoring the barriers to care among a population hard-hit by the opioid epidemic.

Paradoxically, prescribing DAAs is often easier for patients without insurance. Perhaps with the lessons from AIDS advocacy efforts in mind, manufacturers have instituted patient assistance programs enabling access to treatment for uninsured individuals with HCV, thus leaving only the costs of laboratory studies and office visits for the patient to shoulder. This is still a significant burden for patients and staff to execute (and one without available Ryan White-like resources to leverage) but is much more manageable than if one had to pay tens of thousands of dollars out-of-pocket for a DAA regimen.

Use of DAAs among substance users remains an area of controversy, principally because of concerns about nonadherence and reinfection [48••]. For many specialists, reluctance to treat PWID for HCV is a reflection of standards of care in the interferon era, in which high adherence to a grueling, 48-week regimen of treatment was necessary to achieve sustained virologic response (SVR). Shorter treatment durations and improved potency, efficacy, and tolerability of DAAs have dramatically shifted the calculus, but practice patterns have yet to catch up to current guidelines, which recommend DAA therapy for essentially all patients regardless of current drug use [49].

## What Is the Efficacy of HIV and HCV Treatment among PWID?

Advances in ART have expanded options, simplified dosing, and reduced toxicity, but successful management requires retention in care and medication adherence. The vast majority of PWID retained in HIV care are prescribed ART (89–92%), yet only 71–75% of those are virologically suppressed [50]. PWID have historically been less likely to persist in HIV care, receive ART, and achieve virologic suppression, but recent findings from one large, urban HIV clinic indicate rates of suppression among PWID are converging toward those of non-users [51–53]. In rural areas, however, it is likely that PLWH will lag behind in these key metrics. Rural PLWH tend to enter care with more advanced HIV disease and have higher mortality [54, 55].

Accumulating data show that treating HCV-infected substance abusers with DAAs is highly efficacious [48••]. Post hoc analyses of DAA trials found SVR rates of 96–97% among participants on medication-assisted therapy (MAT), including some with ongoing drug use [56, 57]. In dedicated studies of DAAs among MAT recipients, SVR rates were similar in populations with and without ongoing drug use [58, 59]. Among recent injectors receiving DAAs, SVR was attained in 85–100% [60]. Preliminary results from small, "real-world" treatment cohorts are reassuring, with retrospective studies of current or former PWID confirming rates of SVR of at least 80% [61, 62]. Ten-year data from a large HCV program showed no negative effect of recent or prior IDU on treatment adherence or therapeutic response [63].

## How Can We Best Optimize HIV and HCV Treatment Outcomes Among PWID?

### Substance Abuse Treatment

Drug abuse support services are a key component in improving care for PLWH with addiction. The use of buprenorphine or methadone for MAT can improve HIV outcomes. One prospective study found that buprenorphine-based therapy was associated with significant improvements in ART use and CD4 count [64]. Methadone maintenance has been linked to improved HIV-specific outcomes; those on methadone have higher odds of adherence and virologic suppression [65].

HIV care providers need to be cautious in opioid prescribing practices for their patients. PLWH receive long-term prescriptions for opioids at high rates and are more likely to receive higher doses [66, 67]. HIV care providers have reported poor adherence to prescribing guidelines and low confidence in identifying abuse, but these results predate the current, heightened awareness of the opioid epidemic [68]. Newly released guidelines from the HIV Medicine Association are available to help HIV providers manage chronic pain in their patients [69].

Clinical trials and cohort analyses support the efficacy of offering DAAs to individuals on MAT. Retention in regular substance abuse care likely selects for individuals who will remain sufficiently engaged in care for HCV to complete therapy. In one study, individuals retained in buprenorphine treatment were more likely to be referred to an HCV specialist and offered antiviral therapy [70]. Given the high prevalence of HCV among individuals with any lifetime IDU, offering HCV therapy through the substance abuse treatment infrastructure is a sensible option and can leverage existing, multidisciplinary services to support DAA therapy [71].

### Co-location of Services

For PWID, regardless of HIV or HCV infection status, co-location of mental health, substance use, social work, and pharmacy services in a single venue may help to optimize outcomes. This model, adopted by many clinics serving PLWH, is well-suited to address the needs of high-risk populations such as those with opioid abuse [72, 73]. Strong consideration should be given to implementing MAT options wherever possible. Opioid users living with HIV are more likely to use buprenorphine or other MAT if administered at their "parent" HIV clinic, rather than having to visit another center [74]. Rural and community health centers are an attractive option to house such multidisciplinary programs but must be adequately and sustainably resourced in order to succeed.

Similar to HIV, untreated psychiatric illness, and ongoing drug use among those living with HCV have adverse effects on the ability to achieve SVR [75]. Because current DAA regimens are of short duration (8–24 weeks), mobilization of mental health, substance use, and social work services for HCV-infected patients must necessarily be more rapid than with PLWH, who are often in care longitudinally for years at a single center. While many HIV clinics offer such comprehensive, multidisciplinary services, strict funding restrictions often prohibit their use for HIV-uninfected individuals. Peer-based group substance abuse treatment and directly observed therapy have been studied but are not widely available [71]. One solution adaptable to the existing healthcare infrastructure is patient navigation. In one large, urban public health department, navigators successfully guided individuals with IDU, homelessness, alcohol use, and other mental health conditions through the HCV care process, leading to SVR rates of 91% among those treated [76].

## What Are the Current Best Practices in HIV and HCV Prevention Among PWID?

In addition to the prevention of HIV and HCV, providers caring for opioid abusers should be mindful of hepatitis B virus, sexually transmitted diseases, and bacterial infections such as endocarditis and cellulitis. On a population level, a multifaceted approach incorporating routine screening, linkage to prevention and treatment resources, MAT, and harm reduction strategies are needed to reduce incident infections and keep PWID as healthy as possible [77].

### Harm Reduction and Syringe Services Programs

Syringe service programs (SSPs) have been proven to prevent HIV and HCV infections in international and urban US settings, but systematic evaluation of the role of SSPs for infection control among rural PWID in the US is lacking [78, 79]. SSPs provide an opportunity for PWID, a population otherwise difficult to access for public health interventions, to receive condoms and naloxone kits, access testing for viral infections, and be referred to specialist care for MAT, HIV, and HCV. They can also ensure access to low dead space syringes, further decreasing the likelihood of viral transmission among injecting partners. Combining prevention methods reduces HCV transmission among PWID, and higher rates of SSP use would likely contribute the greatest population effect on disease transmission, conferring a "herd immunity" benefit on PWID not utilizing SSPs [80].

Unfortunately, the accessibility of syringe service programs (SSPs) varies across the US, depending on state and local laws [81]. Nationally, SSPs are unevenly distributed and tend to be clustered in urban areas [82]. An estimated 80% of young people with HCV (as a surrogate marker of IDU) reside over 10 mi from a SSP, with larger geographic coverage gaps in the South and Midwest [82].

## Effects of MAT on HIV and HCV Prevention

Among real-world cohorts of PWID, engagement in MAT reduces HIV acquisition by 54% [83]. MAT helps reduce a variety of hazardous behaviors, including IDU, syringe sharing and high-risk sexual practices, such as having multiple partners [84]. MAT also confers a protective benefit on HCV acquisition, with hazard ratios for acquisition ranging from 0.18 to 0.47 for those on MAT [85].

Currently, the MAT infrastructure is insufficient to address the burden of opioid use, especially in rural areas [86]. Of all US physicians permitted to prescribe buprenorphine, over 91% are in urban areas [87]. This lack of providers creates a bottleneck for users in need; among buprenorphine prescribers in one survey, only 60% were accepting new patients [88]. In interviews with PCPs who do not prescribe MAT, almost half cited lack of institutional support as a factor [89]. Thus, health system administrators play an important role in ensuring access to services needed by their patient population. However, as for HIV and HCV treatment, MAT services impose additional burdens on patients in terms of transportation costs, wait-list times, and the visit frequency required to participate [90].

## Treatment as Prevention

Large clinical trial and cohort data have proven that virologic suppression with ART renders PLWH non-infectious to others—a principle referred to as "treatment as prevention" [91, 92]. Although such data are lacking for HCV, it is reasonable to conceptualize the potential public health impact of DAAs in a similar framework. PWID constitute an important, active reservoir of HCV, so eliminating active, chronic infections among injectors intuitively should reduce forward transmission and the risk of reinfection after treatment [93]. This idea is supported by modeling studies, but robust, real-world analyses are still needed [94, 95].

## HIV Pre-exposure Prophylaxis Among People Who Inject Drugs

Consistent use of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as pre-exposure prophylaxis (PrEP) is efficacious in reducing sexual transmission of HIV, but the effect of PrEP against injection-related exposures may be less robust [96]. In the Bangkok Tenofovir Study, use of TDF (without FTC) reduced HIV acquisition by 49% among all users and 84% among those who were highly adherent [97, 98]. But, this study relied on directly observed PrEP administration and could not isolate whether the effect on HIV acquisition was due to parenteral or sexual transmission. These methodological questions have led some to voice concerns about implementing PrEP for PWID, even though it is

currently recommended for this purpose in the US [99, 100]. Expanding PrEP among PWID is a challenge, however. Some PWID may not be interested in taking PrEP [101]. Further, providers are less willing to prescribe PrEP for PWID than for any other risk group [102]. To date, the use of DAAs as PrEP for HCV has not been investigated.

## Learning from Scott County, Indiana: Addressing Risks in Ohio and North Carolina

The 2014–2015 outbreak of 181 new HIV infections among PWID in rural Indiana was a direct result of widespread local opioid abuse, lack of access to syringe services programs (SSPs), and limited health infrastructure (including resources for HIV and HCV testing) [1]. With lessons from this incident in mind, public health officials are examining rural communities across the US and taking steps to mitigate the risk for a similar event [6••]. Without concerted efforts to invest in rural healthcare infrastructure and develop sustainable resources to address the health and prevention needs of opioid users, that risk is unfortunately very real.

North Carolina (NC) and Ohio (OH) are in some ways emblematic of the challenges faced in preventing ID complications from the current opioid epidemic. Both are geographically large with multiple urban, metropolitan hubs separated by wide, mostly rural areas. Acute HCV cases and drug-related deaths are rising but vary by region within each state [103, 104]. Twenty-nine of 100 counties in NC and 31 of 88 counties in OH are part of Appalachia, the region hardest-hit by the opioid epidemic [105]. Eleven of the 220 counties nationwide identified by the CDC as being at highest risk for a Scott County-like outbreak are in OH, with another five in NC; all but one of these 16 are in Appalachia [6••].

Despite the similarities of their opioid epidemics, NC and OH have diverged in two key policy areas: Medicaid expansion and SSPs. In 2014, OH chose to expand its Medicaid program, opening eligibility to all adults with incomes below 138% of the federal poverty level [106]. This led to over 700,000 new enrollees, the vast majority of whom would not have access to health insurance otherwise [106]. Among enrollees in 2015, over two-thirds were White and nearly a quarter resided in rural or Appalachian areas. In contrast, NC opted not to expand Medicaid; as of 2015, its uninsured rate was 11%, compared with OH's 6% [107]. Medicaid expansion's true impact on outcomes and disease prevention among opioid abusers remains to be seen, but Medicaid expansion appears to have increased insurance coverage among heroin abusers (but not those with other opioid use disorders) [108]. Expansion states have significantly increased buprenorphine prescriptions, over time [109]. With respect to SSPs, although both NC

and OH have legalized these programs, the implementation differs substantially by state. As of October 2017, NC has at least 23 programs, covering many disparate regions of the state, while OH has eight—four of which are based in major cities [110, 111].

In response to the needs of rural providers at the front-lines of the opioid epidemic, initiatives to train PCPs on HIV, HCV, and opioid-related issues and to provide telehealth consultations are proliferating. Project ECHO (Extension for Community Healthcare Outcomes) has pioneered a telemedicine consultation model that has demonstrated success in treating large numbers of patients with HCV in distant areas and in prison settings [112]. In NC, the Carolina Hepatitis C Academic Mentorship Program (CHAMP) was launched as a statewide effort to facilitate training in HCV management for providers in more remote, rural locations [113]. In 2017, the National Institute of Drug Abuse and CDC funded multiyear projects in both states, aimed at building an infrastructure of non-specialist providers to address HCV and HIV treatment among PWID in counties hardest hit by the opioid epidemic. The commitment of public health officials and academic medical centers to respond to the Scott County wake-up call is heartening, but much work remains to be done in the field; these projects are important first steps toward sustainable change.

## Conclusions

The experience of a large, rural outbreak of HIV and HCV has prompted a renewed focus on the prevention and care of HIV and HCV among individuals with opioid use disorders and PWID. Although this topic has long been studied, the existing literature and clinical experience are overwhelmingly drawn from international and urban US populations. The current epidemic of opioid abuse, which has significantly affected nonmetropolitan and rural areas in the US, highlights shortcomings in existing infrastructure for comprehensive treatment of addiction, HIV and HCV. The most immediate needs are the rapid deployment of MAT programs and SSPs as well as the scaling up of HCV treatment in at-risk communities. Research focusing on people with opioid and heroin abuse in rural areas is needed to help translate existing principles to this unique population. Urgent attention to these tasks will be critical to curbing the spread of HCV and preventing another major outbreak of HIV.

## Compliance with Ethical Standards

## References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Peters PJ, Pontones P, Hoover KW, Patel MR, Galang RR, Shields J, et al. HIV infection linked to injection use of oxymorphone in Indiana, 2014–2015. N Engl J Med. 2016;375:229–39.
2. DeBeck K, Wood E, Dong H, Dobrer S, Hayashi K, Montaner J, et al. Non-medical prescription opioid use predicts injection initiation among street-involved youth. Int J Drug Policy. 2016;34:96–100.
3. Al-Tayyib AA, Koester S, Riggs P. Prescription opioids prior to injection drug use: comparisons and public health implications. Addict Behav. 2017;65:224–8.
4. Jones CM, Logan J, Gladden RM, Bohm MK. Vital signs: demographic and substance use trends among heroin users—United States, 2002-2013. MMWR Morb Mortal Wkly Rep. 2015;64:719–25.
5. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Annu Rev Public Health. 2015;36:559–74.
6.•• Van Handel MM, Rose CE, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. JAIDS J Acquir Immune Defic Syndr. 2016;73:323–31. **CDC predictive model of US counties at high risk for an outbreak of HIV or HCV due to injection drug use (IDU). Article identifies specific counties of concern, which are largely rural and Appalachian.**
7.• Wejnert C. Vital signs: trends in HIV diagnoses, risk behaviors, and prevention among persons who inject drugs—United States. MMWR Morb mortal Wkly Rep. 2016;65:1336–42. **Report of trends in IDU-related HIV diagnoses from 2008 to 2014 stratified by race and urban residence. Demonstrates that new diagnoses due to IDU are rapidly dropping in urban, racial/ethnic minorities but leveling off among nonurban, White persons.**
8. Diagnoses of HIV infection in the United States and dependent areas, 2015. HIV surveillance report. 2016.
9. Des Jarlais DC, Arasteh K, McKnight C, Feelemyer J, Campbell ANC, Tross S, et al. Consistent estimates of very low HIV incidence among people who inject drugs: New York City, 2005–2014. Am J Public Health. 2016;106:503–8.
10. HIV Surveillance in Urban and Nonurban Areas n.d.
11. Burt RD, Tinsley J, Glick SN. A decline in HIV testing among persons who inject drugs in the Seattle area, 2004–2015. JAIDS J Acquir Immune Defic Syndr. 2017;75:S346–51.

12. Cooley LA, Wejnert C, Spiller MW, Broz D, Paz-Bailey G, NHBS study Group. Low HIV testing among persons who inject drugs—national HIV behavioral surveillance, 20 U.S. cities, 2012. Drug Alcohol Depend. 2016;165:270–4.

13. Friedman SR, Mateu-Gelabert P, Ruggles KV, Goodbody E, Syckes C, Jessell L, et al. Sexual risk and transmission behaviors, partnerships and settings among young adult nonmedical opioid users in New York City. AIDS Behav. 2017;21:994–1003.

14. Clayton HB, Lowry R, August E, Everett Jones S. Nonmedical use of prescription drugs and sexual risk behaviors. Pediatrics. 2016;137:e20152480.

15. Latkin CA, Knowlton AR, Forman VL, Hoover DR, Schroeder JR, Hachey M, et al. Injection drug users' disclosure of HIV seropositive status to network members. AIDS Behav. 2001;5:297–305.

16. Latka MH, Mizuno Y, Wu Y, et al. Are feelings of responsibility to limit the sexual transmission of HIV associated with safer sex among HIV-positive injection drug users? J Acquir Immune Defic Syndr. 2007;46:S88–95.

17. Nasarruddin AM, Saifi RA, Othman S, Kamarulzaman A. Opening up the HIV epidemic: a review of HIV seropositive status disclosure among people who inject drugs. AIDS Care. 2017;29:533–40.

18. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. Clin Infect Dis. 2014;59:1411–9.

19. Centers for Disease Control and Prevention. Viral hepatitis surveillance: United States, 2015 n.d.

20. Busch MP, Shafer KAP. Acute-phase hepatitis C virus infection: implications for research, diagnosis, and treatment. Clin Infect Dis Off Publ Infect Dis Soc Am. 2005;40:959–61.

21. Ray SC, Thomas DL. Hepatitis C. Mand. Douglas Bennetts Princ. Pract. Infect. Dis. Updat. Ed. 8th ed., Philadelphia, PA: Elsevier/Saunders; 2015, p 1904–1927.e11.

22. Joy JB, McCloskey RM, Nguyen T, et al. The spread of hepatitis C virus genotype 1a in North America: a retrospective phylogenetic study. Lancet Infect Dis. 2016;16:698–702.

23. Jordan AE, Perlman DC. The shift in emphasis from risk-based to age-based hepatitis C virus (HCV) testing in the US tends to remove injection drug use from discourse on HCV. Subst Use Misuse. 2017;52:340–50.

24. Henderson DK. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures: a prospective evaluation. Ann Intern Med. 1990;113:740–6.

25. MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: rates, routes, and cofactors. Epidemiol Rev. 1996;18:137–48.

26. van Bueren J, Simpson RA, Jacobs P, Cookson BD. Survival of human immunodeficiency virus in suspension and dried onto surfaces. J Clin Microbiol. 1994;32:571–4.

27. Abdala N, Stephens PC, Griffith BP, Heimer R. Survival of HIV-1 in syringes. J Acquir Immune Defic Syndr Hum Retrovirology Off Publ Int Retrovirology Assoc. 1999;20:73–80.

28. Paintsil E, Binka M, Patel A, Lindenbach BD, Heimer R. Hepatitis C virus maintains infectivity for weeks after drying on inanimate surfaces at room temperature: implications for risks of transmission. J Infect Dis. 2014;209:1205–11.

29. Binka M, Paintsil E, Patel A, et al. Survival of hepatitis C virus in syringes is dependent on the design of the syringe-needle and dead space volume. PLoS One. 2015;10

30. Zule WA. Low dead-space syringes for preventing HIV among people who inject drugs: promise and barriers. Curr Opin HIV AIDS. 2012;7:369–75.

31. Oramasionwu CU, Bailey SC, Moore HN, Oramasionwu CO, Russell AL, Zule WA. Dead space in over-the-counter syringes: the implications for HIV and HCV transmission. Int J Drug Policy. 2015;26:1282–4.

32. Sacks-Davis R, Aitken CK, Higgs P, Spelman T, Pedrana AE, Bowden S, et al. High rates of hepatitis C virus reinfection and spontaneous clearance of reinfection in people who inject drugs: a prospective cohort study. PLoS One. 2013;8:e80216.

33. Rowe C, Santos G-M, Raymond HF, Coffin PO. Social mixing and correlates of injection frequency among opioid use partnerships. Int J Drug Policy. 2017;41:80–8.

34. Meit, Michael, Knudson, Alana, Gilbert, Tess, et al. The 2014 update of the rural-urban Chartbook 2014.

35. Individual data tables: The 2014 Update of the Rural-Urban Chartbook 2014.

36. Gallant JE, Adimora AA, Carmichael JK, Horberg M, Kitahata M, Quinlivan EB, et al. Essential components of effective HIV care: a policy paper of the HIV medicine Association of the Infectious Diseases Society of America and the Ryan white medical providers coalition. Clin Infect Dis. 2011;53:1043–50.

37.• Schafer KR, Albrecht H, Dillingham R, Hogg RS, Jaworsky D, Kasper K, et al. The continuum of HIV care in rural communities in the United States and Canada: what is known and future research directions. J Acquir Immune Defic Syndr. 2017;75:35–44. **Comprehensive review of HIV trends in rural North America and challenges in treating and improving outcomes in this population**

38. Westergaard RP, Stockman LJ, Hyland HA, Guilfoyle SM, Fangman JJ, Vergeront JM. Provider workforce assessment in a rural hepatitis C epidemic: implications for scale-up of antiviral therapy. J Prim Care Community Health. 2015;6:215–7.

39. Shiffman ML. A balancing view: we cannot do it alone. Am J Gastroenterol. 2007;102:1841–3.

40. Thomson M, Konerman MA, Choxi H, Lok ASF. Primary care physician perspectives on hepatitis C management in the era of direct-acting antiviral therapy. Dig Dis Sci. 2016;61:3460–8.

41. Asher AK, Portillo CJ, Cooper BA, Dawson-Rose C, Vlahov D, Page KA. Clinicians' views of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs. Subst Use Misuse. 2016;51:1218–23.

42. Bradley H, Viall AH, Wortley PM, Dempsey A, Hauck H, Skarbinski J. Ryan White HIV/AIDS program assistance and HIV treatment outcomes. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016;62:90–8.

43. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for Medicaid reimbursement of Sofosbuvir for the treatment of hepatitis C virus infection in the United States. Ann Intern Med. 2015;163:215–23.

44. The Henry J. Kaiser Family Foundation: Medicaid's role in addressing the opioid epidemic. 2017. http://www.kff.org/infographic/medicaids-role-in-addressing-opioid-epidemic/. Accessed 15 Sept 2017.

45. Lo Re III V, Gowda C, Urick PN, et al. Disparities in absolute denial of modern hepatitis C therapy by type of insurance. Clin Gastroenterol Hepatol. 2016;14:1035–43.

46. Andrews M, HC. Drug's lower cost paves way for Medicaid, prisons to expand treatment. Kais Health News. 2017;

47. Stephens DB, Young AM, Havens JR. Healthcare contact and treatment uptake following hepatitis C virus screening and counseling among rural Appalachian people who use drugs. Int J Drug Policy. 2017;47:86–94.

48.•• Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. Nat Rev Gastroenterol Hepatol. 2017. **Extensive review of recent studies of direct-acting antivirals (DAAs) for people who inject drugs (PWID). While some providers may have concern about use of**

DAAs for PWID, emerging prospective and retrospective studies support their effectiveness.

49. AASLD-IDSA: Recommendations for testing, managing, and treating hepatitis C. n.d. http://www.hcvguidelines.org/. Accessed 9 Mar 2017.

50. Hall HI, Frazier EL, Rhodes P, Holtgrave DR, Furlow-Parmley C, Tang T, et al. Differences in human immunodeficiency virus care and treatment among subpopulations in the United States. JAMA Intern Med. 2013;173:1337–44.

51. Rebeiro PF, Abraham AG, Horberg MA, Althoff KN, Yehia BR, Buchacz K, et al. Sex, race, and HIV risk disparities in discontinuity of HIV care after antiretroviral therapy initiation in the United States and Canada. AIDS Patient Care STDs. 2017;31:129–44.

52. Hanna DB, Buchacz K, Gebo KA, Hessol NA, Horberg MA, Jacobson LP, et al. Trends and disparities in antiretroviral therapy initiation and virologic suppression among newly treatment-eligible HIV-infected individuals in North America, 2001–2009. Clin Infect Dis. 2013;56:1174–82.

53. Lesko CR, Tong W, Moore RD, Lau B. Retention, antiretroviral therapy use and viral suppression by history of injection drug use among HIV-infected patients in an urban HIV clinical cohort. AIDS Behav. 2017;21:1016–24.

54. Lopes BLW, Eron J, Mugavero MJ, et al. HIV care initiation delay among rural residents in the southeastern United States, 1996 to 2012. J Acquir Immune Defic Syndr. 2017;76:171–6.

55. Ohl M, Tate J, Duggal M, Skanderson M, Scotch M, Kaboli P, et al. Rural residence is associated with delayed care entry and increased mortality among veterans with human immunodeficiency virus infection. Med Care. 2010;48:1064–70.

56. Grebely J, Mauss S, Brown A, Bronowicki JP, Puoti M, Wyles D, et al. Efficacy and safety of Ledipasvir/Sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: analysis of phase 3 ION trials. Clin Infect Dis. 2016;63(11):1405–11.

57. Grebely J, Dore GJ, Zeuzem S, Aspinall RJ, Fox R, Han L, et al. Efficacy and safety of Sofosbuvir/Velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: analysis of phase 3 ASTRAL trials. Clin Infect Dis. 2016;63:1479–81.

58. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. Elbasvir-Grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med. 2016;165:625–34.

59. Lalezari J, Sullivan JG, Varunok P, Galen E, Kowdley KV, Rustgi V, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol. 2015;63:364–9.

60. Boglione L, Mornese Pinna S, De Nicolò A, et al. Treatment with direct-acting antiviral agents of hepatitis C virus infection in injecting drug users: a prospective study. J Viral Hepat. 2017;24:850–7.

61. Read P, Lothian R, Chronister K, Gilliver R, Kearley J, Dore GJ, et al. Delivering direct acting antiviral therapy for hepatitis C to highly marginalised and current drug injecting populations in a targeted primary health care setting. Int J Drug Policy. 2017;47:209–15.

62. Norton BL, Fleming J, Bachhuber MA, Steinman M, DeLuca J, Cunningham CO, et al. High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic. Int J Drug Policy. 2017;47:196–201.

63. Elsherif O, Bannan C, Keating S, McKiernan S, Bergin C, Norris S. Outcomes from a large 10 year hepatitis C treatment programme in people who inject drugs: no effect of recent or former injecting drug use on treatment adherence or therapeutic response. PLoS One. 2017;12:e0178398.

64. Altice FL, Bruce RD, Lucas GM, Lum PJ, Korthuis PT, Flanigan TP, et al. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. J Acquir Immune Defic Syndr. 2011;56:S22–32.

65. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend. 2006;84:188–94.

66. Brunet L, Napravnik S, Heine AD, Leone PA, Eron JJ. Longitudinal opioid use among HIV-infected patients, 2000 to 2014. J Acquir Immune Defic Syndr. 2017;75:77–80.

67. Edelman EJ, Gordon K, Becker WC, Goulet JL, Skanderson M, Gaither JR, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. J Gen Intern Med. 2013;28:82–90.

68. Lum PJ, Little S, Botsko M, Hersh D, Thawley RE, Egan JE, et al. Opioid-prescribing practices and provider confidence recognizing opioid analgesic abuse in HIV primary care settings: JAIDS. J Acquir Immune Defic Syndr. 2011;56:S91–7.

69. Bruce RD, Merlin J, Lum PJ, et al. 2017 HIVMA of IDSA clinical practice guideline for the management of chronic pain in patients living with HIV. Clin Infect Dis. n.d.

70. Norton BL, Beitin A, Glenn M, DeLuca J, Litwin AH, Cunningham CO. Retention in buprenorphine treatment is associated with improved HCV care outcomes. J Subst Abus Treat. 2017;75:38–42.

71. Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. Clin Infect Dis. 2013;57:S56–61.

72. Zaller N, Gillani FS, Rich JD. A model of integrated primary care for HIV-positive patients with underlying substance use and mental illness. AIDS Care. 2007;19:1128–33.

73. Proeschold-Bell RJ, Heine A, Pence BW, McAdam K, Quinlivan EB. A cross-site, comparative effectiveness study of an integrated HIV and substance use treatment program. AIDS Patient Care STDs. 2010;24:651–8.

74. Lucas GM, Chaudhry A, Hsu J, Woodson T, Lau B, Olsen Y, et al. Clinic-based treatment for opioid-dependent HIV-infected patients versus referral to an opioid treatment program: a randomized controlled trial. Ann Intern Med. 2010;152:704–11.

75. Robaeys G, Grebely J, Mauss S, Bruggmann P, Moussalli J, de Gottardi A, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Clin Infect Dis. 2013;57:S129–37.

76. Ford MM, Johnson N, Desai P, Rude E, Laraque F. From care to cure: demonstrating a model of clinical patient navigation for hepatitis C care and treatment in high-need patients. Clin Infect Dis. 2017;64:685–91.

77. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis. 2013;57:S39–45.

78. Wodak A, Cooney A. Do needle syringe programs reduce HIV infection among injecting drug users: a comprehensive review of the international evidence. Subst Use Misuse. 2006;41:777–813.

79. Abdul-Quader AS, Feelemyer J, Modi S, Stein ES, Briceno A, Semaan S, et al. Effectiveness of structural-level needle/syringe programs to reduce HCV and HIV infection among people who inject drugs: a systematic review. AIDS Behav. 2013;17:2878–92.

80. Hagan H, Pouget ER, Jarlais D, et al. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. J Infect Dis. 2011;204:74–83.

81. Campbell CA. State HCV incidence and policies related to HCV preventive and treatment services for persons who inject drugs—

United States, 2015–2016. MMWR Morb Mortal Wkly Rep. 2017;66:465–9.

82. Canary L, Hariri S, Campbell C, Young R, Whitcomb J, Kaufman H, et al. Geographic disparities in access to syringe services programs among young persons with hepatitis C virus infection in the United States. Clin Infect Dis. 2017;65:514–7.

83. MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ. 2012;345

84. Karki P, Shrestha R, Huedo-Medina TB, et al. The impact of methadone maintenance treatment on HIV risk behaviors among high-risk injection drug users: a systematic review. Evid-Based Med Public Health. 2016;2

85. Vickerman P, Page K, Maher L, Hickman M. Opiate substitution treatment and HCV prevention: building an evidence base? Addict Abingdon Engl. 2014;109:2060–1.

86. Perlman DC, Jordan AE, Uuskula A, Huong DT, Masson CL, Schackman BR, et al. An international perspective on using opioid substitution treatment to improve hepatitis C prevention and care for people who inject drugs: structural barriers and public health potential. Int J Drug Policy. 2015;26:1056–63.

87. Andrilla, CHA, Coulthard, C, Larson, EH. Changes in the supply of physicians with a DEA DATA waiver to prescribe buprenorphine for opioid use disorder. Data Brief #162 2017.

88. Andrilla CHA, Coulthard C, Larson EH. Barriers rural physicians face prescribing buprenorphine for opioid use disorder. Ann Fam Med. 2017;15:359–62.

89. Hutchinson E, Catlin M, Andrilla CHA, Baldwin LM, Rosenblatt RA. Barriers to primary care physicians prescribing buprenorphine. Ann Fam Med. 2014;12:128–33.

90. Sigmon SC. Access to treatment for opioid dependence in rural America: challenges and future directions. JAMA Psychiatry. 2014;71:359–60.

91. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365:493–505.

92. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016;316:171–81.

93. Hickman M, De Angelis D, Vickerman P, et al. HCV treatment as prevention in people who inject drugs—testing the evidence. Curr Opin Infect Dis. 2015;28:576–82.

94. Zelenev A, Li J, Mazhnaya A, Basu S, Altice FL. Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study. Lancet Infect Dis. 2018;18:215–24.

95. Echevarria D, Gutfraind A, Boodram B, Major M, del Valle S, Cotler SJ, et al. Mathematical modeling of hepatitis C prevalence reduction with antiviral treatment scale-up in persons who inject drugs in metropolitan Chicago. PLoS One. 2015;10:e0135901.

96. Mayer KH, Ramjee G. The current status of the use of oral medication to prevent HIV transmission. Curr Opin HIV AIDS. 2015;10:226–32.

97. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381:2083–90.

98. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. AIDS. 2015;29:819–24.

99. Miller WC, Hoffman IF, Latkin CA, Strathdee SA, Shoptaw S. HIV antiretroviral prophylaxis for injecting drug users. Lancet. 2013;382:853.

100. Preexposure prophylaxis for the prevention of HIV infection in the United States—2014: a clinical practice guideline n.d.

101. Stein M, Thurmond P, Bailey G. Willingness to use HIV pre-exposure prophylaxis among opiate users. AIDS Behav. 2014;18:1694–700.

102. Edelman EJ, Moore BA, Calabrese SK, Berkenblit G, Cunningham C, Patel V, et al. Primary care physicians' willingness to prescribe HIV pre-exposure prophylaxis for people who inject drugs. AIDS Behav. 2017;21:1025–33.

103. Surveillance for Viral Hepatitis - United States, 2015 2017.

104. AmFAR Opioid & Health Indicators Database. n.d. http://opioid.amfar.org/. Accessed 11 Sept 2017.

105. Counties in Appalachia - Appalachian Regional Commission. n.d. https://www.arc.gov/counties. Accessed 11 Sept 2017.

106. Seiber EE, Berman ML. Medicaid expansion and ACA repeal: evidence from Ohio. Am J Public Health. 2017;107:889–92.

107. Health Insurance Coverage of the Total Population. Henry J Kais Fam Found. 2016.

108. Feder KA, Mojtabai R, Krawczyk N, Young AS, Kealhofer M, Tormohlen KN, et al. Trends in insurance coverage and treatment among persons with opioid use disorders following the Affordable Care Act. Drug Alcohol Depend. 2017;179:271–4.

109. Wen H, Hockenberry JM, Borders TF, Druss BG. Impact of Medicaid expansion on Medicaid-covered utilization of buprenorphine for opioid use disorder treatment. Med Care. 2017;55:336–41.

110. Syringe Exchange Programs in North Carolina | NC Department of Health and Human Services. n.d. https://www.ncdhhs.gov/divisions/public-health/north-carolina-safer-syringe-initiative/syringe-exchange-programs-north. Accessed 30 Oct 2017.

111. North American Syringe Exchange Network: Ohio Syringe Exchange Programs. n.d. https://nasen.org/directory/oh/. Accessed 30 Oct 2017.

112. Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011;364:2199–207.

113. Welcome to CHAMP — Carolina Hepatitis Academic Mentorship Program. n.d. https://www.med.unc.edu/champ. Accessed 16 Sept 2017.