The hepatitis C virus (HCV) epidemic has reached a new era, with calls for global elimination (1) and early evidence of the benefits of national elimination programs. Key to plans for elimination are expanded screening and linkage to care strategies, universal access to direct-acting antiviral (DAA) therapy, and provision of prevention and harm reduction strategies to minimize incident infection and re-infection. There is no population where the benefits of these strategies are clearer and their role in elimination efforts more critical than for people who inject drugs (PWID). The strategies for elimination come at an opportune time in the United States, where we are gripped with another crisis, the opioid epidemic. The intersection of injection drug use and blood-borne infections has played out over decades and in many communities, recently in Scott County, Indiana, (2) and Lowell, MA, (3) where rapid human immunodeficiency virus (HIV) dissemination occurred in the setting of pre-existing HCV transmission networks.

Prior to the DAA era, uptake of HCV therapy among PWID was low. Although studies in the interferon era suggested that response rates with pegylated-interferon and ribavirin were comparable for PWID compared to non-PWID, (4) there remained significant barriers for PWID, including the side-effect profile, length of therapy (24-48 weeks), lack of access to care, and provider and insurer policies restricting treatment for those with addictive disorders. With the advent of DAA therapies, many of these barriers were surmountable, involving improved safety profiles, shortened treatment durations to 8-12 weeks, and patient-assistance programs that offer access to DAA for patients without health insurance; yet, some barriers remain. Specifically, many insurers and even some providers continue to consider active or recent drug use as a contraindication to curative DAA therapy. But what does the evidence show?

On the contrary, in this issue of Hepatology Communications, Janjua et al. (5) add to the growing body of literature suggesting that PWID can achieve high rates of sustained virologic response (SVR), which is the virologic surrogate for cure, when there is access to DAA therapies. Furthermore, these authors uniquely contribute to the current literature by describing treatment outcomes and predictors of SVR in the large real-world British Columbia Hepatitis Testers Cohort (BC-HTC). All individuals in the BC-HTC are registered in the publicly funded single-payer health care
system with centralized services, resulting in universal access to testing results, medical visits and hospitalizations, dispensed prescriptions, and deaths. The use of a single-payer system limits the selection bias introduced by other real-world cohorts due to variations in access by insurer policies and provider preferences. The analysis included all patients with HCV infection who received either ledipasvir/sofosbuvir (LDV/SOF) or sofosbuvir/velpatasvir (SOF/VEL), both combinations of a nonstructural (NS)5B nucleoside inhibitor and a NS5A inhibitor. The analysis also classified patients as either receiving opioid agonist therapy (OAT) or not receiving OAT and as recent PWID (within 3 years of start of DAA therapy), past PWID (more than 3 years from start of DAA therapy), or non-PWID.

This was a large sample, with 5,283 evaluable patients of which 390 were off-OAT/recent injecting drug users (IDUs), 598 off-OAT/past IDUs, 515 off-OAT/non-IDUs, 609 on-OAT/IDUs, and 171 on-OAT/non-IDUs. All subgroups achieved an SVR >90%, with SVRs of 91%, 95%, 96%, 93%, and 95%, respectively. Overall recent or active IDU was associated with a small but significant decrease in SVR, although the authors argue that some of this increased risk of treatment failure was driven by a higher loss to follow-up and death during follow-up. This highlights a conundrum present in many “real-world” HCV cohorts, namely the interpretation of “intention to treat” versus “per-protocol” analyses. The authors also note that re-infection rates in PWID and other high-risk populations, including men who have sex with men (MSM), are high, and without sequencing, patient treatment failure may be misclassified as relapse instead of re-infection. These limitations aside, this study adds to the growing literature showing that the majority of PWID can be engaged in therapy and achieve SVR. While SVR may be lower when compared to non-PWID, an SVR rate of >90% yields benefits on both the individual and community level.

There are now examples of treatment as prevention in HCV infection, including in MSM and PWID. In the Aids Therapy Evaluation in the Netherlands (ATHENA) cohort, lifting of restrictions on DAA access in MSM with HIV and HCV infections was followed by a 51% decrease in incident HCV infection. Iceland initiated a nationwide elimination program in 2016 with scale-up of DAA (Treatment as Prevention for Hepatitis C [TraP HepC]). Due to the high risk for transmission, treatment of PWID is a point of emphasis for this program along with harm reduction efforts and educational campaigns. An interim analysis reported lower SVR in current PWID but an overall SVR of 90%. Similarly, there was a 53% decrease in incident HCV infection and a 72% decrease in viremia among PWID at the addiction hospital from 2015 to 2017.

While the rates of treatment response reported here are in line with prior reports, there were unexpected findings reported by the authors. Shorter treatment duration (8 weeks versus 12 weeks) and SOF/VEL were associated with not achieving SVR, and this held true when the analysis was restricted to LDV/SOF and genotype 1. LDV/SOF is approved by the U.S. Food and Drug Administration as a 12-week treatment course for initial therapy of genotype 1 infection. In patients without cirrhosis and with a baseline viral load <6 million IU/mL, there are data supporting efficacy with 8 weeks; yet, there are populations where some clinical trial and real-world data have suggested differences in SVR based on 8 weeks versus 12 weeks of therapy. For example, patients who are black may have a higher relapse rate when treated with 8 weeks of therapy. This may be due to a higher unfavorable interleukin (IL)28B T allele frequency or other genetic differences. Retrospective studies, such as the one reported here, cannot appropriately account for baseline predictors of treatment failure. It is also possible that the weaknesses inherent in the study design produced unreliable results. For example, the grouping of PWID was based not on survey data or questionnaires but rather on a validated algorithm with a sensitivity of 78% and specificity of 83%; thus, risk of misclassification was high.

The finding of lower SVR in patients treated with SOF/VEL versus LDV/SOF was also unexpected. The most obvious explanation would be that SOF/VEL, which is a pangenotypic regimen, was used for treatment of all genotypes, including genotype 3, which has consistently shown lower SVR rates, especially in the setting of severe liver disease and/or prior treatment failure. While genotype 3 infection had a lower SVR than other genotypes with SOF/VEL, this was only a numerical difference, and when the analysis was restricted to only genotype 1, the difference remained. The use of proton pump inhibitors, which is not recommended above 20 mg daily dose equivalent for either LDV/SOF or SOF/VEL, is not
reported in this paper, which could be a confounder due to a greater negative effect on VEL absorption. The prospective TraP HepC study group used LDV/SOF until October 2016 when they switched to SOF/VEL and thus will have the ability to conduct analyses assessing differences in treatment responses between the two regimens while controlling for known confounders.

A growing body of literature supports testing and treating PWID for HCV infection. The study An Efficacy and Safety Study of Grazoprevir + Elbasvir in the Treatment of Chronic Hepatitis C Virus (HCV) Genotype (GT)1, 4, or 6 Infection in Treatment-Naïve Participants Who Are on Opiate Substitution Therapy (C-EDGE CO-STAR) was a phase 3, randomized, placebo-controlled trial of PWID who had been on OAT for ≥3 months and maintained ≥80% adherence to appointments.(9) This trial included patients with HIV infection, compensated cirrhosis, and active drug use, and the treatment was 12 weeks of elbasvir/grazoprevir, an NS5A inhibitor/NS3 protease inhibitor combination. Overall SVR was 91%, with the lowest SVR in patients with genotype 6 infection. Active drug use was detected in urine drug screens in 60% of subjects and was not a predictor of SVR. The Sofosbuvir and Velpatasvir for Hepatitis C Virus Infection in People With Recent Injection Drug Use (SIMPLIFY) trial was a phase IV, open-label, single-arm study that was not a predictor of SVR. The Sofosbuvir and Velpatasvir for Hepatitis C Investigation Team. A large HCV transmission network enabled a fast-growing HIV outbreak in rural Indiana, 2015. EBioMedicine 2018;37:374-381.

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