



## Time to end treatment restrictions for people with hepatitis C who inject drugs



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Hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality worldwide. Ongoing transmission is mostly driven by people who inject drugs (PWID), among whom global HCV antibody prevalence is 52.3%.<sup>1</sup> Although direct-acting antiviral therapy has made this infection curable in most patients, PWID remain largely untreated. Despite guidelines recommending treatment for people who use drugs,<sup>2</sup> stigma towards this disenfranchised population has resulted in insurance restrictions and reluctance from providers to offer appropriate medical therapy.<sup>3</sup>

In *The Lancet Gastroenterology & Hepatology*, Jason Grebely and colleagues<sup>4</sup> demonstrate the efficacy of pan-genotypic direct-acting antiviral therapy in PWID with recent injection drug use. 103 patients were treated for 12 weeks with sofosbuvir and velpatasvir, and 94% achieved sustained virological response 12 weeks after completion of treatment. Notably, although three patients were lost to follow-up, there were no documented cases of treatment failure. The SIMPLIFY study supports what health-care providers of people who use drugs have long understood: substance use alone does not determine a patient's interest in medical care and should not preclude access to effective medical treatment.

Although this study effectively shows that PWID enrolled in a clinical trial can maintain sufficient adherence to achieve HCV cure, these findings might not be generalisable to all PWID. Participants were recruited from existing clinical sites, and therefore were probably already engaged in medical care; 77% reported stable housing and only 26% reported at least daily injection drug use. Therefore, as with other clinical trials, these participants might represent a more stable population than that in the real world.

It should also be noted that, as part of the clinical trial, patients received more monitoring, support, and incentives than might be feasible in the real world, including weekly appointments for medication dispensation, monetary incentives for the return of blister packs, and clinic visits. Further, since the 103 patients were seen at 19 study sites worldwide, each site was probably only managing a few PWID at a time.

Given the current opioid epidemic, outcomes of HCV treatment in injectors of heroin and other opioids are particularly relevant. Patients engaged in stable opioid substitution therapy have excellent adherence and sustained virological response;<sup>5</sup> however, outcomes of people who misuse opioids and are not on such therapy remain unknown. Because enrolment was open to people who injected any substance, it is unclear how many patients eligible for opioid substitution therapy were receiving it during HCV treatment. A clarification of the effect of opioid substitution therapy on HCV outcomes is needed, especially in an era in which global access to this therapy remains sparse.<sup>6</sup>

More importantly, although this study reinforces that PWID can be effectively cured with direct-acting antivirals, it does not clarify how overall outcomes for this patient population can be optimised. HCV treatment could serve as a rare opportunity to engage high-risk patients in care and therefore is a crucial chance to try to reduce harm in this population. However, since patients in this study did not have any measured change in drug use behaviors and four participants died due to illicit drug overdose, it is clear that HCV treatment alone will not be sufficient to reduce harm. This situation reinforces the need for the integration of evidence-based strategies that will reduce HCV reinfection and the risk of opioid overdose, HIV acquisition, and other harms associated with drug use. In particular, engagement in needle and syringe programmes, initiation of opioid substitution therapy in people with opioid use disorders, and provision of naloxone to prevent opioid overdose should be considered to improve overall outcomes.<sup>7-9</sup> As we expand the responsibility of HCV treatment to primary care providers and addiction specialists,<sup>10</sup> so too should we consider the role that HCV specialists can have in managing addiction.<sup>11</sup>

Overall, the SIMPLIFY study provides exciting new data reinforcing that PWID can and should be treated with direct-acting antivirals. An understanding of how such care can be given to PWID in real-world settings, including prisons and jails, is crucial, but can only be achieved with the repeal of insurance restrictions and

Published Online  
January 5, 2018  
[http://dx.doi.org/10.1016/S2468-1253\(18\)30001-3](http://dx.doi.org/10.1016/S2468-1253(18)30001-3)  
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sobriety requirements. This study provides the scientific burden of proof that persistence of these restrictions is unwarranted and unsupported by data. We now need to focus on ways to capitalise on the provision of HCV treatment for PWID and optimise engagement with this patient population to not only cure HCV but also reduce harms associated with substance use while they are engaged in health care.

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ESR reports grants from Merck and Gilead Sciences. SKa reports reports grants from Gilead Sciences. SKo declares no competing interests.

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## FOCUS4: a new trial design for evaluation of targeted drugs in colorectal cancer?

The molecular phenotype of colorectal cancer is highly heterogeneous, with several molecularly defined subgroups that are of relevance for understanding the biological behaviour of the cancer and also the efficacy of drugs<sup>1</sup>—for instance, *RAS* mutations occur in 45% of colorectal cancers, *BRAF* mutations in 9%, *HER2* amplification in 4%, and *PIK3CA* mutations in 14%, among many others. This heterogeneity is also highly relevant for the design of new trials that require a more selective, economic, and rapid approach. An important issue in this context is the potential for multiple changes in the mutational profile during drug treatment; indeed, the molecular profile can even vary across different metastatic lesions in the same patient.<sup>2</sup> Therefore, there could be major differences in outcome if the investigational drug or combination of drugs is applied as first-line treatment rather than in later stages of the disease, as is traditionally done. A potentially appropriate place for an experimental drug to be tested is during the period after the end of induction therapy, where either no active maintenance or fluorouracil (or derivative thereof), with or without bevacizumab, is given.

Two trials—FOCUS4 in the UK, and the international MODUL trial<sup>3</sup>—have introduced the concept of the umbrella trial design using an adaptive platform of several (flexible) cohorts of colorectal cancer patients, in which a single trial tests multiple targeted agents after induction therapy, during the maintenance phase, on the basis of the molecular aberrations present in the patients' tumours. FOCUS4 includes several cohorts with different molecular phenotypes, comparing new targeted agents versus placebo maintenance, and a “no biomarker” cohort comparing standard capecitabine versus placebo, acting as a standard control arm across the trial.

The first outcome data from the FOCUS4 trial<sup>4</sup> are reported in *The Lancet Gastroenterology & Hepatology*: the results from cohort D, which included patients with colorectal cancers that were wild-type for *RAS*, *BRAF*, and *PIK3CA* and had no *PTEN* loss. The drug being tested in this cohort was an oral pan-HER tyrosine kinase inhibitor, AZD8931, chosen on the basis of preclinical and molecular data that showed that combined inhibition of



Published Online  
December 15, 2017  
[http://dx.doi.org/10.1016/S2468-1253\(17\)30402-8](http://dx.doi.org/10.1016/S2468-1253(17)30402-8)  
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