Editorial

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Excluding people who use drugs or alcohol from access to hepatitis C treatments – Is this fair, given the available data?

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Revolutionary new drugs to cure hepatitis C virus (HCV) infection represent one of the most important breakthroughs in clinical medicine in recent decades. However, high pricing of these well-tolerated, highly efficacious all-oral regimens and high demand (actual or anticipated) has led many payers in the United States and other countries to exclude people who have recently used illicit drugs, injectable drugs or alcohol (with the definitions of "use" varying by jurisdiction) from access to these treatments [1]. With wholesale prices of USD $1,125 per day for combined therapy [2], there is a clear basis upon which to argue for price reduction, particularly given that clinical recommendations state that treatment is indicated for people with HCV at all disease stages [3,4]. While we support those advocating for price reduction, the intention of this article is to consider the ethical and evidentiary basis of the restrictions that have been instituted to date. We will examine restrictions to assess whether they meet evidenced-based medical and public health criteria, and whether they satisfy the principle of justice [5].

Rationing or restricting access to healthcare goods, while unpopular, is a common practice in healthcare systems, although not always acknowledged as such [6]. Ethical criteria for rationing may include calculations such as cost-benefit analysis and cost effectiveness, but these alone are insufficient to capture the moral complexity of issues surrounding illness, health, recovery and death [7]. Distributive criteria need also to consider the 'rule of rescue' [8] – the duty to provide care for those at risk of avoidable death – and the principle of justice within which like cases are treated as like and people are not subject to arbitrary exclusions on the basis of irrelevant behaviours or characteristics [5]. Determining whether or not like cases are like is critical and we propose that, in healthcare contexts, like/unlike be determined by the presence or absence of salient differences between patient or population groups. A salient difference should only be established on the basis of available evidence. These are the ethical and evidentiary considerations when evaluating the restrictions that have been instituted to date.

So far, many payers have limited the reimbursement of new HCV therapies to people with advanced liver disease, while people who use drugs and those with alcohol misuse have been deemed ineligible from reimbursement irrespective of disease stage, which has effectively excluded this group from accessing treatment. The criteria forming the basis for these restrictions varies by jurisdiction, but includes recent drug use (with varying definitions of what constitutes "recent"), recent injecting drug use, treatment with opioid substitution therapy (OST), heavy alcohol use and alcohol misuse. We will now consider possible justifications for these exclusions and the implications of these decisions from ethical and evidentiary perspectives.

Prioritizing patients with more advanced liver disease (severe fibrosis or cirrhosis) has been the most common form of restriction [2]. Given the high risk of progression to decompensated cirrhosis and hepatocellular carcinoma among patients with advanced fibrosis, HCV treatment for those with advanced liver disease meets the criterion of providing priority healthcare for the worst-off, who are otherwise at risk of death. While this is a justifiable priority, limiting access to those with advanced liver disease is a poor public health strategy because successful treatment of HCV infection reduces progression of liver disease [9], reduces all-cause mortality in people with advanced liver disease [10] and treatment of those with greatest risk of transmission (e.g. people who inject drugs [PWID]) represents a potential tool to help stop onward HCV transmission among PWID [11]. Furthermore, the feasibility of prioritizing treatment to people with advanced liver disease (e.g. stage $\geqslant$F2) is somewhat compromised by the fact that few specialists are recommending and willing to biopsy all patients, and non-invasive liver diseases

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staging tools (e.g. transient elastrography) are not available everywhere and, most importantly, not reimbursed.

Reasons for restricting access to life-saving HCV therapies based on drug and alcohol use are much harder to justify. Over the past year, many State Medicaid committees and private payers in the United States have implemented restrictions that exclude those who have recently used illicit drugs, injecting drugs, or are receiving OST (e.g. methadone or buprenorphine); and those with heavy alcohol use or those with alcohol misuse from receiving new potentially life-saving HCV therapies (irrespective of disease stage) [2]. Among the 42 State Medicaid committees, 37 (88%) include drug and/or alcohol use or abuse in their eligibility criteria, with 50% requiring a period of abstinence and 64% requiring urine drug screening [2]. The various criteria are considerably heterogeneous across jurisdictions. These drug and alcohol-related restrictions for new HCV treatments generally apply to the poorest and most underserved patients with HCV infection. Underserved populations, such as PWID, are disproportionately affected by HCV infection. In high income countries, the majority (80%) of new cases of HCV infection occur among PWID, with most (60%) existing infections among former and current PWID [12,13]. A large proportion of PWID have been infected with HCV for two or more decades and many have progressed to advanced fibrosis [9]. Rates of advanced liver disease complications, associated healthcare costs, and liver-related morbidity and mortality among PWID are rising [9]. As such, PWID represent a key affected population, requiring access to new treatments to stem the growing burden of HCV-related disease.

Justifications for these restrictions that have been given are: that people who use or inject drugs and those with alcohol misuse cannot adhere to the treatment regime; that they have worse outcomes than other patients at comparable disease stages; a higher likelihood of HCV re-infection; and that there is a lack of data on treatment outcomes with the new interferon-free HCV therapies in this population. However, these reasons are not based on evidence.

Recent international recommendations have reviewed the evidence on drug use and interferon-based treatment for HCV infection [3,4,14,15]. There is now compelling evidence that HCV treatment is safe and effective for PWID [15–18]. In two systematic reviews of interferon-based studies assessing treatment for PWID (one specifically focusing on those with recent injecting at the time of treatment initiation), the overall sustained virological response (SVR) was 56% [17,18]. These response rates are comparable to responses in non-drug using populations in large randomized controlled trials of interferon-based treatment [19]. A history of injecting drug use does not generally compromise adherence, treatment completion, or SVR, although some studies have found lower treatment completion. Recent injecting drug use at treatment initiation has limited impact on adherence, treatment completion, or SVR [15–18]. Despite that interferon-based treatment for HCV infection is poorly tolerated (side effects include depression and mimic opioid withdrawal), HCV treatment does not have an impact on OST treatment (OST, e.g. methadone or buprenorphine) or increase drug use. Occasional injecting drug use during HCV treatment does not seem to impact adherence, treatment completion, or SVR. However, lower adherence and SVR has been observed in persons with frequent injecting drug use (daily/every other day) during treatment. In adherent people, alcohol use has no negative impact on SVR [20,21]. Although there is concern that HCV re-infection may negate the potential benefits of treatment, the reported rates of re-infection following successful HCV treatment among PWID are low (1–5% per year) [15,17].

The decision to exclude people who use drugs from accessing new HCV therapies in the United States is a step backwards in time. Initial guidelines for the management of HCV by the National Institutes of Health (NIH) in 1997 also excluded PWID from consideration for therapy, citing concerns about adherence, increased susceptibility to side effects (e.g. depression) and HCV re-infection [22]. However, following concerted advocacy [23] and given improved evidence demonstrating similar safety and efficacy of interferon-based HCV therapy among PWID and non-PWID, the NIH guidelines were revised in 2002 to encourage the treatment of HCV infection for PWID [24].

International guidelines from the American Association for the Study of Liver Disease (AASLD)/Infectious Diseases Society of America (IDSA), the European Study for the Association of the Liver (EASL), the International Network for Hepatitis in Substance Users and the World Health Organization now all recommend treatment for HCV infection among people who use drugs [3,4,14,15,25].

Although data on the use of novel DAA-based therapies among current PWID is limited, there are some data among people receiving OST. In phase II/III clinical trials, rates of SVR are similar among people receiving OST as compared to those not receiving OST [26–28]. Among participants in phase II/III clinical trials receiving OST with HCV genotype 1, SVR was 94% in those treated with ledipasvir and sofosbuvir (with or without ribavirin) [27], and 96% in those treated with paritaprevir/ritonavir, ombitasvir, dasabuvir (with or without ribavirin). Similarly, in a study of genotype 1 participants receiving OST (n = 38) treated with the all-oral combination of paritaprevir/ritonavir, ombitasvir, dasabuvir, and ribavirin, the overall SVR was 97% [29]. Results from the ongoing CO-STAR study, a phase III randomized clinical trial to study the efficacy and safety of the combination regimen of MK-5172/MK-8742 in treatment-naïve participants with chronic HCV genotype 1, 4, and 6 infection who are on OST, are eagerly anticipated.

To return to the ethical considerations that we propose for evaluating the restrictions that have been instituted to date, our argument is that the exclusions are unjust. There is no good evidence for establishing a salient difference between non-alcohol and non-drug using populations of HCV infected people and populations of HCV infected people who use (or are recent users of) alcohol and drugs. Both populations should be treated as 'like' on the basis of established outcome measures, potential benefits and any other established health-related evidence. Decisions to provide new HCV treatments to people with drug and alcohol use, including PWID, must be undertaken on the basis of clinical and public health requirements rather than a common co-existing disorder, such as addiction.

Furthermore, even if it could be shown that treatment is less effective for people who use drugs and alcohol, it does not follow that it is equitable or just to exclude them. For example, it would have been unacceptable to withhold pegylated-interferon and ribavirin from patients co-infected with HIV and HCV genotype 1, even though cure rates in this population were significantly lower than in HCV mono-infection [30,31]. This demonstrates that lower efficacy in a population group is not a sufficient basis to justify restricted access. In the case of people who use drugs and alcohol, withholding effective healthcare from these groups,

both of which are socially marginalised and bear a significant burden of HCV disease, is patently unfair and potentially socially corrosive.

Given the available data, it is unethical to withhold HCV treatment from people who use drugs. Potential life-saving therapies for the treatment of lung cancer or asthma are not withheld from current smokers. Similarly, therapies for type 2 diabetes are not withheld from those who are overweight and do not adhere to dietary recommendations. Substance use criteria are not used to restrict access to antiretroviral therapy for HIV/AIDS. Based on current restrictions, in many jurisdictions in the United States a PWID with HIV/HCV co-infection would be unable to access new HCV therapies, even if they had advanced liver disease, but would be able to access antiretroviral therapy in early HIV disease.

Good governance requires that people have access to essential healthcare services, and in high income countries, this should be interpreted as including fair access to comprehensive care for avoidable illness, irrespective of drug and or alcohol use. Discriminatory policies that limit access to potentially life-saving therapy have been identified as human rights abuses of PWID in the context of HIV [32], and this is equally so in the context of new HCV treatments given the disproportionate burden of disease experienced by this population and the lack of any clinical justification for the exclusion.

The high prices of new therapies may preclude universal access, but payers should not be empowered to limit particular groups from access to life-saving treatment in the absence of valid justifications based on evidence. Further, despite substantial reductions in pricing for new HCV therapies over the previous year (discounting of around 50%), there has been no corresponding change in restriction policies. Decisions for prioritizing patients for more immediate therapy need to be made based on clinical criteria. The AASLD/IDSA recommendations state that HCV treatment is recommended for all patients with chronic HCV infection (irrespective of disease stage) [3]. The recommendations do however state that patients who are at the *highest priority for immediate treatment* include patients with advanced fibrosis (METAVIR F3) or compensated cirrhosis (METAVIR F4), due to the higher risk for severe complications (e.g. hepatic decompensation or hepatocellular carcinoma). Patients with moderate fibrosis (METAVIR F2) are listed in the next priority group as a *high priority for treatment* due to their high risk for complications [3]. Rather than recommending exclusion of PWID, these guidelines in fact include PWID with earlier liver disease stages among a second-order priority group due to potential HCV treatment as prevention benefit. There is also evidence demonstrating that HCV treatment for current and former PWID is cost-effective, particularly when potential prevention benefits are considered [33].

We strongly recommend that all restrictions on access to new HCV treatments based on drug or alcohol use or opioid substitution treatment be removed. There is no good ethical or health based evidence for such discriminations. Nor do the restrictions make clinical, public health or health economic sense.

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