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Commentary

Ten priorities for expanding access to HCV treatment for people who inject drugs in low- and middle-income countries

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ABSTRACT

Of the estimated 130–150 million people who are chronically infected with hepatitis C virus, around 90% reside in low- and middle-income countries. People who inject drugs are disproportionately affected by HCV, with a global estimated prevalence (based on serological reports of HCV antibodies) of 67%; worldwide over 10 million people who inject drugs are infected with HCV. Treatment for HCV has improved dramatically in recent years with the arrival of new direct acting antivirals (DAAs) and this is stimulating considerable efforts to scale up access to treatment. However, treatment coverage among the general population is less than 10% in most countries, and coverage for people who inject drugs is generally much lower. It is estimated that globally around 2 million people who inject drugs need treatment for HCV. The DAAs offer significant potential to rapidly expand access to treatment for HCV. While the ideal combination therapy remains to be established, key characteristics include high efficacy, tolerability, pan-genotypic activity, short treatment duration, oral therapy, affordability, limited drug–drug interactions, and availability as fixed-dose combinations and once daily treatments. This paper outlines 10 key priorities for improving access to HCV treatment for people who inject drugs: (1) affordable access to direct acting antivirals; (2) increased awareness and testing; (3) standardization of treatment; (4) simplification of service delivery; (5) integration of services; (6) peer support; (7) treatment within a framework of comprehensive prevention; (8) tracking progress; (9) dedicated funding; and (10) enabling policies.

Introduction

Of the estimated 130–150 million people who are chronically infected with hepatitis C virus, around 90% reside in low- and middle-income countries (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013). People who inject drugs are disproportionately affected by HCV, with a global estimated prevalence of 67%; worldwide over 10 million people who inject drugs are estimated to be infected with HCV (Aceijas & Rhodes, 2007; Nelson et al., 2011), compared to around 1.7 million with living HIV (UNODC, 2014); this number is far higher if individuals with HCV who have either temporarily or permanently ceased injecting drugs are included. Around half of the world's estimated 12.7 million (range 8.9–22.4 million) people who inject drugs live in low or middle income countries, including 1 million in Africa, 1.1 million in Latin America and the Caribbean, and 4.7 million in Asia (UNODC, 2014). In these countries, health budgets are generally limited, there is a lack of appropriate diagnostics and drugs, health insurance mechanisms are often inadequate and, as a consequence, out-of-pocket healthcare payments are common.

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The World Health Organization (WHO) identifies people who inject drugs as a key target group for HCV screening, prevention and treatment (WHO, 2010). Considering that the majority of people with HCV who inject drugs reside in low- and middle-income settings, improving access to HCV diagnosis and treatment for this priority group will require ensuring access to affordable treatment delivered through models of care that are adapted to settings with limited health resources.

Until recently, the standard treatment for HCV comprised 6–12 months of pegylated-interferon and ribavirin, which is associated with frequent and sometimes severe side-effects and low rates of treatment success. The arrival of new direct acting antivirals (DAAs) is stimulating considerable efforts to scale up access to treatment. The DAAs are administered for a shorter time, have fewer side effects, and high rates of treatment success, allowing for effective public policy action to address the large burden of HIV in resource-limited settings (Ford et al., 2014).

In 2014 Member States of the WHO endorsed a resolution requesting WHO to examine the feasibility of and strategies needed for the elimination of HCV with a view to setting global targets for treatment and care (WHO, 2014c). Modeling studies have suggested that improved access to effective HCV treatment can reduce the prevalence of HCV among people who inject drugs (Durier, Nguyen, & White, 2012; Martin et al., 2011). Modelling has also suggested that prioritizing people who inject drugs for treatment will substantially impact incident transmission as in many countries the majority of incident infections occur among people who inject drugs. In contrast, prioritizing people with moderate/advanced fibrosis has the greatest impact on severe liver mortality but is suboptimal in terms of averting incident infection (Innes, Goldberg, Dillon, & Hutchinson, 2014). However, while treatment efficacy, defined as sustained virological suppression (SVR), now exceeds 90%, treatment coverage is less than 10% in most countries (Grebely & Dore, 2014), and coverage for people who inject drugs is generally lower than for the general population (Mathers et al.), with some studies estimating that less than 2% of people who inject drugs are receiving treatment (Alavi et al., 2014; Iversen et al., 2014). According to one recent report, around 2 million people who inject drugs globally are estimated to need treatment for HCV, based on current clinical criteria (Medecins du Monde/International Network of People who use Drugs, 2014).

Drawing on lessons learnt from scaling up access to HIV treatment in low- and middle income countries, this article outlines ten key priorities for expanding access to HCV treatment for people who inject drugs.

1. Affordable access to direct acting antivirals

WHO guidelines make clear that people should not be excluded from HCV treatment programmes on the basis of injecting drug use, but such exclusion persists, either directly or because they are considered ineligible for health insurance (WHO, 2014a). Reasons cited for limiting access to treatment for people who inject drugs included concerns about poor adherence, increased susceptibility to side effects, risk of reinfection, and financial constraints. For people who inject drugs, fear of side effects associated with interferon-based treatment is cited as one of the main barriers to initiating and adhering to treatment, and the most important consideration for deciding against treatment (Harris & Rhodes, 2013; Munoz-Plaza et al., 2008; Swan et al., 2010).

Of these cited concerns, the currently high cost of DAAs is a critical barrier to improving access. Several systematic reviews have shown that even with interferon-based therapy, adherence to treatment among people who inject drugs is not worse than for the general population, and comparable treatment outcomes can be achieved (Aspinall et al., 2013; Hellard, Sacks-Davis, & Gold, 2009). The use of DAAs should further improve adherence, and will reduce provider and patient concern about treatment side effects. Documented rates of reinfection are low, subsequent to improved immune response to re-exposure, coupled with the impact of SVR on modifying risk practices, and should no hold back treatment (Grady, Schinkel, Thomas, & Dalgard, 2013).

The current very high cost of direct acting antivirals – at over $50,000 per treatment course in some countries – has led to strict rationing of these drugs to reduce the budgetary impact on health services. Rationing is a consequence of high drug prices, and every effort should be made to reduce their cost. In the short term, difficult decisions may be required as to who gets treated first, but they should not be made on the basis of injecting drug use status.

Efforts are underway to reduce the price of DAAs. Several countries, notably Egypt, have managed to negotiate a price of less than US$1000 for 12 weeks of sofosbuvir (a direct-acting antiviral) for patients treated in the public sector. Estimated production costs for this and other HCV DAAs are reported to be even lower, so further price reductions can be anticipated (Hill, Khoo, Fortunak, Simmons, & Ford, 2014).

Successful strategies for reducing drug prices and increasing affordability are highlighted by the global effort to expand access to antiretroviral therapy for people living with HIV/AIDS provides (Ford, Calmy, & Mills, 2011). The most effective proven way to substantially reduce HIV drug prices has been unrestricted generic competition, often supported by civil society. Several generics manufacturers are poised to produce generic versions of DAAs, provided patents do not act as a barrier to production. In India, the patent for sofosbuvir was recently rejected, a decision which if upheld could help facilitate generic production. The granting of patents has also been opposed in several other countries (WHO, 2015).

Experience from HIV shows that guaranteeing the quality of generic drugs is critical. Initially donors were unwilling to purchase generic drugs citing concerns about quality, but this was responded to through the creation of the UN/WHO prequalification programme. Other factors supporting access to affordable antiretrovirals included the use of legal instruments to promote generic access, notably more stringent patentability standards and examination, compulsory licenses and patent oppositions; increased price transparency through public price reporting by WHO and Médecins Sans Frontières; and price reductions and voluntary licensing agreements from originator pharmaceutical companies.

All these options have the potential to increase the affordability of DAAs. In the case of price reductions and voluntary licenses from pharmaceutical companies, a critical difference with HIV is that the dominant burden of HCV infection is in middle-income countries. Further, a number of countries previously classified as low income have transitioned into middle-income country status. Countries with a high burden of HCV and large numbers of people who inject drugs like China, Ukraine and Argentina have generally been excluded from eligibility for the price reductions and voluntary licenses from pharmaceutical companies and high levels of patent protection are pursued in these countries, limiting access to generic drugs (WHO, 2014b).

2. Increased awareness and testing

A recent study among people who inject drugs in India found that more than half of the study population had not heard of HCV despite infection rates of over 30% in this population; this low level of knowledge translated into low testing rates and consequently poor awareness of HCV status in those who were infected (Solomon et al., 2015). Low levels of awareness about HCV have been reported in other settings (Ti et al., 2013; Treloar et al., 2011).

WHO and other key United Nations agencies promote HCV testing as part of the comprehensive package of prevention and care for people who inject drugs (WHO, UNODC, & UNAIDS, 2012), but in several countries, lack of testing availability remains a major barrier. There is a need for simplified diagnostics. The ideal would be a rapid test that reliably detects HCV antibody and HCV core antigen as a single test, to allow for once-stop diagnosis. While awaiting such a test, recent studies have suggested that dried blood spot testing could help increase access to diagnostic testing and uptake of hepatitis C services among people who inject drugs (McAllister et al., 2014; McLeod et al., 2014).

There are good individual and public health reasons why people with hepatitis C who inject drugs should know their status irrespective of treatment opportunities. Awareness of HCV infection – and its prevalence among communities – can mobilize people to demand treatment, as well as promoting positive behavior to limit the risk of disease progression (notably alcohol consumption) and onward transmission. On the other hand, knowledge of status in the absence of treatment has been associated with reduced quality of life among people who inject drugs, and on this basis it has been argued that testing should not be pursued unless treatment is offered (McDonald et al., 2013). This was the case for HIV a decade ago, where it was argued that offering routine testing was inappropriate in the absence of treatment, as it offered little benefit to the individual (Bayer & Edington, 2009). When HIV testing was offered in settings when treatment was not available, the proportion of patients accepting HIV testing in some settings was three times lower than in settings where treatment was available (Sabapathy, Van den Bergh, Fidler, Hayes, & Ford, 2012). As has been shown for HIV, widespread availability of DAAs can be anticipated to improve the willingness of individuals to engage with health education programmes, accept HCV testing, and if positive to adopt practices to reduce the risk of onward transmission.

3. Standardization of treatment

After decades of neglect, there is now a rich pipeline of novel therapies in development for HCV, with over 25 new drugs and combinations in development as of the end of 2014. While renewed innovation is welcome, the delivery of HCV treatment at scale in resource-limited settings will likely be facilitated by the prioritization of a limited number of key drugs to standardize treatment. In the case of HIV, global treatment guidelines have evolved over the last decade from recommending eight potential first line regimens in 2006 to a single preferred regimen in 2013 (Vitoria, Vella, & Ford, 2013). This rationalization has been endorsed by most national governments in high burden countries, and is also supported by major donors as a way to improve supply chain efficiencies and leverage further price reductions through bulk procurement.

Similarly, for the delivery of HCV treatment at scale, it will be important to define a limited number of standardized regimens to assist procurement and simplify prescribing and reduce prescribing error. While the ideal combination therapy remains to be established, key characteristics include high efficacy, tolerability, pan-genotypic activity, short treatment duration, oral therapy, affordability, limited drug–drug interactions, and availability as fixed-dose combinations and once daily treatments (Ford et al., 2014).

4. Simplification of service delivery

Traditional models of HCV treatment delivery rely on specialist clinicians in secondary and tertiary centres, with interferon injections often administered as directly observed therapy. The numerous side effects of interferon and ribavirin, and high failure rates associated with certain genotypes has led to a reliance on multiple laboratory investigations including baseline genotyping, frequent viral load testing, and full blood chemistry measures to guide therapy and support decisions to stop in case of non-response to treatment or severe drug related adverse events.

The DAAs offer the potential to greatly simplify service delivery, possibly to the point that patients would only require laboratory testing at the beginning and after the end of treatment to diagnose infection and confirm cure (Ford et al., 2014). The simplification of laboratory testing and clinical oversight would in turn promote the possibility of increasing access to treatment through decentralization of service delivery to primary care level, overseen by non-specialized health workers, with specialist time dedicated to managing complicated cases. This approach has been progressively adopted in the field of HIV for the management of uncomplicated adult and paediatric HIV therapy, with rates of treatment success equivalent to care delivered by specialists (Fairall et al., 2012).

The limited availability of HCV treatment even in high-income countries has led to the establishment of pilot programmes to assess the feasibility of delivering HCV treatment at primary care centres overseen by non-specialist health workers. These programmes have reported outcomes similar to care delivered by specialists using pegylated interferon-based therapy (Hill, Butt, Alvarez, & Krajden, 2008; Mitruka et al., 2014). While such approaches have potential to help expand access to care, training and supervision will be required to ensure quality.

Implementation research is needed to validate the feasibility of different simplification approaches to delivering DAA-based therapy and develop an adequate package of care for people who inject drugs adapted to their needs. For people who inject drugs, collocated/integrated models of care should further incorporate the delivery of opioid substitution therapy in services that provide hepatitis treatment, and vice versa. This is facilitated by the fact that opioid substitution therapy delivered by non-specialists at primary care has already been shown to be feasible (Seidenberg, Rosemann, & Senn, 2013).

5. Integration of services

Many individuals with HCV are lost along the cascade of care from diagnosis to sustained virological suppression (Yehia, Schranz, Umscheid, & Re, 2014). Integration of services is an important way to increase access to HCV treatment and care, and can reduce the risk of loss to follow up by reducing the need to transfer between services to receive treatment and care. Successful models of integration of HCV care within different services have been documented, including opioid substitution clinics, general practitioner clinics, prisons, and secondary/tertiary care settings (Bruggmann & Litwin, 2013; Lloyd et al., 2013). Service integration has been found to lead to improved patient outcomes in other areas, including HIV and TB, maternal, new-born, and child health services (Suthar, Rutherford, Horvath, Doherty, & Negussie, 2014). Considering the high rates of HIV/HCV coinfection in some settings, integration of HCV-related services, as well as services for other common health concerns faced by people who inject drugs, into existing HIV programmes for people who inject drugs is a clear way to increase access to treatment, and this strategy is endorsed by WHO.

6. Peer support

The low uptake of HCV services has been partly explained by stigma, discrimination, criminalization of drug use, and lack of trust between patients and health workers. Peer support has been

put forward as one way to overcome these barriers (Crawford & Bath, 2013).

Peer support is associated with improved uptake of and outcomes on treatment for a number of infectious and non-communicable diseases, including HIV/AIDS (Mills et al., 2014), drug-resistant tuberculosis (Horter, Stringer, Venis, & Du Cros, 2014), asthma (Shah et al., 2001), diabetes (Small et al., 2013), and cancer (Hoey, Ieropoli, White, & Jefford, 2008). Peer support models have also shown some promise in HCV management for people who inject drugs. In Australia, for example, a peer-based integrated model of hepatitis C care at a community drug and alcohol clinic was developed with the aim of increasing uptake in treatment and found to have a high level of patient and provider acceptability (Norman et al., 2008). Further research is needed to elaborate the specific contribution peer support can make to improving uptake and outcomes of HCV treatment for people who inject drugs.

7. Treatment within a framework of comprehensive prevention

Concern about HCV reinfection among people who inject drugs has been cited as a reason why treatment has been held back. Rates of reinfection have been found to be relatively low (Grady et al., 2013), with one recent meta-analysis estimating a reinfection rate of just over 2% a year over five years (Hill, Simmons, Saleem, & Cooke, 2015). Although reinfection rates in the setting of IFN-free therapy have been low, most of these studies were retrospective and included patients who were more likely to be retained in care, and further prospective evaluations are needed.

Thus, while concerns about reinfection should not be a reason to limit treatment of HCV for people who inject drugs, scale up of treatment should be accompanied by appropriate prevention interventions. The following specific recommendations are recommended by the World Health Organization for people who inject drugs: rapid hepatitis B vaccination regimen; incentives to increase uptake and completion of the hepatitis B vaccination schedule; sterile needle and syringe programmes that also provide low dead-space syringes to people who inject drugs; opioid substitution therapy to treat opioid dependence; and education to reduce HCV risk behaviour (WHO, 2014a).

8. Tracking progress

In public health, what gets measured gets done (Chan, 2007). Global estimates of the number of people who inject drugs is limited, in particularly in the Caribbean and sub-Saharan Africa region, where only a minority of countries report data. Where data do exist, there are issues of inconsistency in definitions used in prevalence estimations that make between-country comparisons difficult (Mathers et al., 2008). Similarly, only a quarter of countries report prevalence estimates for HCV among people who inject drugs, and available data is limited in representativeness and of variable quality; reliable data on HCV-associated morbidity and mortality are also lacking in many countries (Aceijas & Rhodes, 2007; Nelson et al., 2011). This is especially the case in low- and middle-income countries, where little data is available even in the general population. Programmatic data on hepatitis treatment in-turn is poorly developed in most regions of the world.

Target setting has been critical to driving scale up access to ART with a successive round of global targets from 3 by 5 (3 million people in treatment by 2005) to 15 by 15 (15 million by 2015 by 2015). The latest HIV targets, set in mid 2014, have evolved from numbers on treatment to targets along the cascade of care. The 90–90–90 targets aim to achieve 90% knowledge of HIV status among those infected, 90% of those who are positive linked to care, and 90% of those receiving treatment being virologically suppressed by 2020 (http://www.unaids.org/en/resources/documents/2014/90-90-90).

WHO, together with partner UN agencies has supported the development of guidance on target settings for universal access to HIV prevention, treatment and care for people who inject drugs (WHO et al., 2012), and is in the process of establishing global targets for testing, prevention and treatment of HCV, including for people who inject drugs The achievement of these targets will depend on improvements in effective data collection and reporting at the country level, as well as standardization of the key data points in hepatitis programming to allow within- and between-country comparisons. Efforts to improve access to treatment will need to be accompanied by efforts to support data collection to measure progress.

9. Increased funding to support scale up of treatment

The arrival of highly active antiretroviral therapy for HIV in 1996 changed the prognosis from a few additional life years to the management of HIV as a chronic disease. However, the initial cost of treatment was prohibitive, and cost effectiveness analyses concluded that funding should be directed at prevention rather than treatment (Marseille, Hofmann, & Kahn, 2002). As prices came down, donors began to support treatment – some later admitting to have delayed doing so for too long (Boseley, 2003). In addition to major bilateral donor support, new international funding mechanisms were established to support scale up, including The President's Emergency Plan for AIDS Relief, the Global Fund to fight AIDS, TB and Malaria, UNITAID, and the Clinton Health Access Initiative. Governments of affected countries also increased their contribution to fighting HIV, including through the establishment of specific taxation schemes and other funding models. In 2013, global contributions to funding for HIV/AIDS programmes in low- and middle-income countries was estimated at over $US 19 billion (http://www.avert.org/funding-hiv-and-aids.htm).

At least for the short term, dedicated HCV funding will be needed to scale up treatment coverage. As was the case for HIV, a critical first step will be to reduce the cost of treatment. UNITAID and the Global Fund have expressed a willingness to support scale up of HCV treatment, within the context of HIV co-infection. Further international funding will be critical to support treatment scale up, particularly in the poorest countries, and increased commitment from national governments will also be critical, particularly in middle-income countries where most people with HCV live, to increase their commitment to HCV while at the same time securing treatment at an affordable price to ensure access for all.

10. Enabling policies

The DAAs will facilitate HCV treatment scale-up for people who inject drugs, but the benefits of these medications are limited by numerous structural barriers to health care for people who inject drugs, including stigma, poverty, homelessness, criminalization and mass incarceration. Unless tensions are resolved between the public health approach, which views drug dependence as a chronic, relapsing condition, and the public security agenda, which applies criminal and administrative penalties to drug use and possession, comprehensive HCV prevention and treatment for people who use drugs will be severely hampered. Globally, just 8% of opiate users have access to opioid substitution therapy, and people who inject drugs receive on average just 2 needle/syringes per month (Mathers et al., 2010). At this rate, universal access to HCV (or HIV) prevention and treatment is unattainable. Punitive laws and

policies that perpetuate violence against and incarceration of people who inject drugs and inhibit access to essential harm reduction services including opioid substitution therapy and needle and syringe programmes undermine these global efforts.

Among the lessons to be learned from the scale up of treatment for people living with HIV is the need to prioritize human rights protections for highly marginalized groups such as people who inject drugs. While there has been a remarkable increase in access to treatment for people living with HIV overall, this increase has been substantially lower for people who inject drugs and other key populations (WHO, 2013). People who use drugs should be active participants in the design, implementation and monitoring of HCV treatment programmes. Hepatitis C treatment for people who use drugs should be delivered in the context of a human rights framework, addressing stigma, poverty, homelessness and criminalization so that equitable access is ensured.

Conclusions

The scale up of HIV treatment over the last decade is viewed as one of the most successful programmes in global health. From this experience, a number of important lessons can be applied to rapidly expand access to effective screening, care and treatment of HCV and other epidemic infectious diseases in low- and middle-income countries. The DAAs offer significant potential to rapidly expand access to treatment for HCV. The first critical step will be to ensure access at an affordable price.

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