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Title: How to eliminate HCV infection by antiviral treatment

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The advent of new HCV treatments (Direct Acting Antivirals, DAAs) with >90% sustained viral response (SVR) rates in 8 to 12 weeks has ushered in an era of excitement about the possibility of elimination of HCV transmission. Tantalizing theoretical mathematical models predicting dramatic reductions in HCV chronic prevalence and incidence with scale-up of HCV treatment for those at risk of transmission have fueled this optimism[1]. Recent reports of a substantial dramatic reduction in HCV incidence (~50% in 2 years) among HIV-infected MSM in the Netherlands after the roll-out of DAA therapy[2] has provided the first piece of empirical evidence that HCV treatment as prevention may be more than just a theoretical idea.

One major question is how the availability of DAAs translates in terms of numbers of individuals treated. In this issue, Zimmerman and authors describe the real-world treatment rates achieved in the DAA era in Germany, a setting where in theory all patients are eligible for treatment regardless of disease stage (Zimmerman et al. Real-world treatment for chronic hepatitis C infection in Germany. Analyses from drug prescription data, 2010 – 2015). The authors report an estimated 160,000 patients in Germany with diagnosed chronic HCV infection, and even more who are undiagnosed. Yet despite no restrictions on treatment in Germany, Zimmerman et al. estimated only 7,000 patients were treated within the statutory health insurance system (covering 85% of the German population) during 2014, and just over 20,000 in 2015, below that

which would have been expected based on the numbers of individual in need of therapy. We are not surprised that universal access to treatment alone is not sufficient for achieving rapid and comprehensive provision of DAA therapy to those in need of it.

First, improvements are needed in HCV diagnosis and assessment. As Zimmerman et al. note, no HCV screening policy exists in Germany, and studies have found 35-65% of those testing positive for HCV in general practices and emergency rooms were unaware of their status. Globally, many remain unaware of their HCV infection, including those at risk of transmission[3]. In settings where people who inject drugs (PWID) are a main risk group for transmission, targeted case-finding programs in addiction services, primary care, and prisons may be highly effective and cost-effective[4,5]. Nevertheless, in many developing country settings the costs of diagnosis and confirmation of HCV infection are still prohibitively high. Additionally a lack of data surrounding the epidemiology of HCV in many country settings developed and developing makes it difficult to develop efficient targeted case-finding strategies and to establish the cascade of care (from the burden of disease to diagnosed cases, treated and cured)[5]

Second, universal access to therapy is likely required. Undoubtedly one of the most important issues facing HCV elimination is the high cost of DAA therapy, which continues to lead to prioritization of therapy in many settings. Indeed, Zimmerman et al. speculated that despite theoretical universal access to HCV treatment regardless of disease stage in Germany, physicians may have prioritized patients with advanced disease and put others on hold. Nevertheless, they note that ambiguities in the reimbursement system and fear of rejected claims may have led to a reluctance of clinicians to prescribe DAA therapy. In other settings prioritization and denial of insurance reimbursements may be a reality. European guidelines still prioritize HCV therapy for those with more advanced liver disease[6]. In the US, IDSA/AASLD guidelines no longer recommend treatment prioritization[7], but insurers in many states continue to restrict therapy for those with less advanced disease[8]. This has important consequences for the HCV elimination agenda. Although prioritization of individuals with more severe liver disease may be an economic way of preventing end-stage liver disease and HCV-related mortality, it may work at odds to the prevention agenda. For example, PWID tend to be younger with less advanced liver disease and therefore strategies which target more severe liver disease may have little to no impact on the epidemic. Indeed, mathematical modeling in the UK showed that current prioritization of therapy to individuals with F3 or cirrhosis would have virtually no effect on HCV incidence among PWID[9]. However, analyses have shown that in many settings with low-moderate HCV prevalence among PWID it is more cost-effective to prioritize early therapy for individuals at risk of transmission due to substantial prevention benefits[10]. Still, concerns about costs of therapy and potential costs of retreatment of reinfections persist. Ongoing studies will shed light on the risk of reinfection in the DAA era, but studies in the IFN-era consistently show that the risk of reinfection among PWID after SVR is relatively low[11,12]. Nevertheless, as observed in the US, Medicaid restrictions based on drug use history[8] (counter to IDSA/AASLD guidelines[7]) will hamper

efforts to deliver HCV treatment to those at risk of transmission in order to prevent new infections.

Third, once access is ensured, HCV treatment needs to be scaled-up, in particular to those at risk of transmission. Unfortunately, several barriers continue to thwart the scale-up of HCV treatment for these populations, particularly PWID. Studies have indicated that PWID are willing to undergo HCV therapy[13], yet many who are diagnosed remain untreated. Provider concerns surrounding potential poor treatment outcomes among PWID persist, despite clinical trial evidence that DAA treatment outcomes among PWID are comparable to the broader population[14,15]. Additionally, established programs have been successful at treating HCV among PWID even in the IFN-based era; the most effective programs are built on existing infrastructure for drug user health such as addiction clinics, community health centers, and prisons.

Fourth, HCV treatment needs to be combined with prevention scale-up to enhance impact, reduce reinfection, and ensure stable reductions in transmission occur. Harm reduction intervention such as opiate substitution therapy and needle and syringe programs are effective at reducing an individuals' risk of HCV acquisition, particularly in combination[16,17], and are crucial for enabling any treatment intervention to effectively treat current PWID. Combination HCV treatment and harm reduction strategies can potentially act synergistically to reduce HCV incidence[18], as well as prevent reinfection post treatment. However, across the globe the coverage and quality of harm reduction service provision is often low[19]. In settings with differing modes of transmission other prevention interventions are likely required, such as efficient blood screening, effective sterilization of medical equipment, education of unofficial health care providers, and initiatives to prevent mother-to-child transmission and between men who have sex with men.

Overall, the promise of HCV treatment as prevention is enormous, and universal access like in Germany is an important necessary, but as Zimmerman et al demonstrate not always sufficient, first step.

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