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## The Beginning of a New Era in Understanding Hepatitis C Prevention

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### Abstract

Hepatitis C virus (HCV) infection is a staggering problem in the United States and worldwide. In the United States, HCV is responsible for 12,000 deaths each year, and is the most common blood borne pathogen and a leading cause of liver transplantation. While over 4 million people in the United States and 180 million worldwide (3%) are chronically infected, most are not aware of their diagnosis. The disease burden and mortality from HCV infection are predicted to increase in the United States 2- to 3-fold over the next 10 to 20 years as the number of persons with long duration of infection grows. This will greatly impact individual and public health and will lead to a substantial economic burden as well. Most HCV-related mortality is occurring in men under 60 years of age (and disproportionately among non-Hispanic Black men [1]), making HCV a leading infectious cause of years of potential life lost, as well as an important cause of premature mortality. Death due to HCV infection is the most frequent cause of non-AIDS-related death for HIV-infected persons with access to highly active antiretroviral therapy [2].

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Since the discovery of a reliable test for antibodies to HCV in 1990 [3], we have learned a great deal about the virus - that it leads to chronic infection in approximately 85% of exposures, that those who are infected have an average chance of 20% of developing cirrhosis after 20 years, and that those who consume alcohol, as well as those who are coinfecting with HIV, are much more likely to progress to cirrhosis and death than others. Although HCV is curable, and antiviral HCV treatment leading to viral eradication reduces liver-related morbidity and mortality, treatment with pegylated interferon plus ribavirin is burdensome, toxic, expensive and ineffective for half of those attempting therapy [4–6]. Treatment initiation rates are low across varied settings [7–11]. Most patients diagnosed with chronic HCV infection have not received antiviral therapy. This is due, in part, to restrictive treatment criteria excluding patients with concomitant substance use that led to the infection in the first place [12]. The treatment landscape is on the verge of a paradigm shift with the impending launch of Specifically Targeted Antiviral Therapy (STAT-C) to inhibit HCV-specific enzymes. Along with higher anticipated cure rates will come higher costs of therapy, increased toxicity, thrice daily pill dosing and the introduction of resistance. The lack of an HCV vaccine and limitations of treatment highlight the imperative of developing strategies to prevent HCV transmission.

Although perinatal and sexual transmission occur, including sexual transmission among HIV-infected men who have sex with men [13], the HCV epidemic is predominantly driven by the injection of illicit drugs [14]. Before 1992, when widespread screening of the blood supply began in the United States, HCV was also commonly spread through blood transfusions and organ transplants. Testing of blood donors for HCV RNA by means of nucleic acid amplification was introduced in the United States as an investigational screening test in

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mid-1999 to identify donations made during the window period before seroconversion [15]. In the United States iatrogenic transmission has almost completely been eliminated with screening of the blood supply. However there are still incidents of transmission such as the 2007 HCV outbreak at a free-standing private endoscopy clinic in Nevada, resulting from reuse of syringes and use of single-use medication vials on multiple patients [16–17].

Outside of the United States, one of the worst iatrogenic outbreaks of HCV infection occurred in Egypt where, from the 1960s to the 1980s, a mass campaign to eradicate schistosomiasis using repeated intravenous antischistosomal therapy inadvertently infected a generation. Decades later the overall prevalence of HCV antibody is 15–20% of the general population [18]. Clearly, the intravenous aspect of this campaign markedly increased the transmission rate. In the absence of mass treatment campaigns using intravenous medication, similar outbreaks are not anticipated. However, acute HCV infection is typically clinically silent, and routine screening for HCV is not recommended or done, so iatrogenic transmission of HCV may be more common than we know.

During intravenous injection by injection drug users (IDU), blood (and any blood borne virus such as HCV) is typically drawn up into the syringe in order to locate the vein, thus contaminating the inside of the syringe and creating an effective tool for transmission of whatever blood borne pathogen is then lining the syringe. Injection drug users (IDUs) often lack knowledge about safe injection practices and the need for sterility and also often lack the necessary tools (i.e., sterile syringes, diluent, mixing containers (cookers), filters (cotton)) to prevent viral transmission.

Injection drug use remains a hidden and stigmatized behavior. Addiction is a chronic relapsing disease that is highly treatable, although most people do not get the treatment that they need. Preventive efforts should focus on IDUs but this has not transpired on the massive scale required. IDUs have been overlooked in part because of the challenges working with this population, the difficulty in finding IDUs and the underlying stigma. In the United States, society's major response to addiction in terms of resources has been to criminalize and further drive underground the behavior, often alienating people from treatment, leading to negative health and social consequences. Most IDUs are incarcerated at some point, and this has contributed to an unprecedented rate of incarceration. Although this 'intervention' is expensive and ultimately ineffective -- while we work to redirect policies and resources towards evidence-based prevention, treatment and harm reduction -- mass incarceration makes it easier to find IDUs and provides opportunity to address prevention, diagnosis and treatment of addiction and HCV infection in the correctional setting.

HCV is much more prevalent than HIV among IDUs, and yet why this is has not been fully elucidated. Are key determinants the differences in viral viability in syringes, the concentration of the virus, the volume of blood remaining in the syringes or other factors? The increased prevalence of HCV among IDUs certainly contributes to the difference (with a higher prevalence of HCV, a given syringe is more likely to have been used by someone with HCV than HIV), but probably does not explain it completely. Answering these questions has, until very recently, been hampered by the inability to culture HCV and the lack of a small animal model of HCV transmission.

In this issue of the Journal, Paintsil et al have contributed to our understanding of the biological mechanisms of HCV transmission by developing an experimental model of IDU using cultured virus from HCV-contaminated syringes. This group is the first to develop a microculture assay to detect viable HCV in small volumes of blood laced in syringes. This work suggests that duration of survival of HCV in used syringes and the amount of residual blood inside the syringe are important parameters in understanding transmission. The ability to use cultured virus to

explore transmission mechanisms and develop prevention interventions has the potential to revolutionize the field. There has already been an improved understanding of the role of biocides for HCV treatment [19].

Heimer's earlier work employed similar methodologies to illuminate the transmission dynamics of HIV during IDU [20–21]. His group demonstrated that HIV can survive in a syringe for months. This finding, along with his team's elegant mathematical modeling studies, proved that reducing syringe circulation time could lead to reduced HIV transmission. This provided critical early evidence in support of needle exchange programs (NEPs). NEPs have had a huge impact on reducing HIV transmission. NEPs do not seem to have had as dramatic an effect on reducing HCV transmission, and understanding why that is, and perhaps how to improve what they do, may be addressed by this methodology. Furthermore, while non-injection drug use has been epidemiologically linked to HCV transmission, perhaps through the use of contaminated drug-sniffing implements [22–23], it is possible that non-injection drug use is really just a marker for illicit, undetected IDU. Using simulated laboratory studies with cultured virus should contribute to understanding the mechanism(s) and relative contribution of non-injection drug use to HCV transmission.

It is estimated that an individual IDU injects about 1,000 times a year and that persons with diabetes who use insulin inject once or twice a day. HCV transmission remains unrestrained among IDUs, with incidence rates ranging from 16%–42% per year [24]. This novel investigation provides robust evidence about the dynamics of viral transmission with syringes, using simulated injecting practices. More importantly, the ability to culture HCV heralds a new era in which the combination of basic laboratory, epidemiologic and ethnographic research should allow a much more precise understanding of HCV transmission and pave the way for designing and targeting future public health interventions to prevent HCV infection.

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