Hepatitis C Virus Infection: From Margin to Center in Rhode Island and Beyond

Physicians, Research Scientists and Public Health Experts Collaborate to Combat Rhode Island's Hepatitis C Epidemic

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BACKGROUND

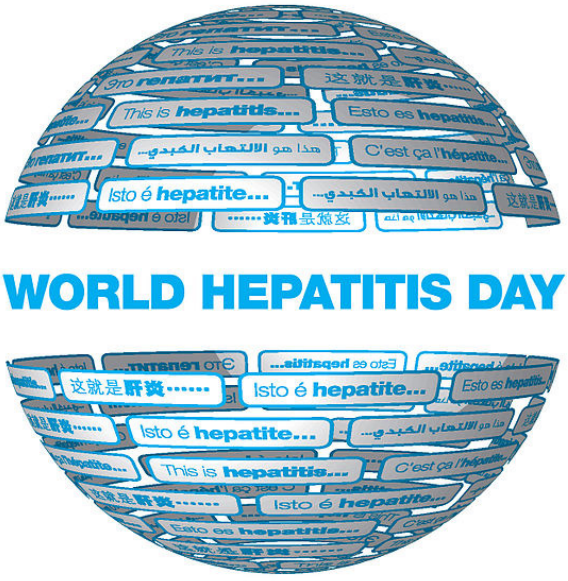
July 28 is World Hepatitis Day – in honor of Nobel Laureate Baruch Samuel Blumberg, MD, who discovered the hepatitis B virus (HBV), demonstrated it could cause liver cancer, developed the HBV vaccine, and implemented HBV vaccination worldwide. Each year on Dr. Blumberg's birthday, the World Health Organization (WHO) and partners acknowledge World Hepatitis Day to increase awareness of all types of viral hepatitis; strengthen prevention, detection and treatment; and promote action to improving access to care and control of these epidemics.

This year marks the convergence of many steps taken to address the global and national problem of hepatitis C virus infection (HCV). The WHO unveiled its first-ever HCV treatment guidelines.[1] The American Association for the Study of Liver Diseases/Infectious Diseases Society of America in partnership with the U.S. Centers for Disease Control and Prevention (CDC), developed HCV care recommendations.[2] The U.S. Department of Health and Human Services updated its Viral Hepatitis Action Plan.[3] Thus coinciding with World Hepatitis Day, this issue of the *Rhode Island Medical Journal* focuses on HCV, the biggest killer of Americans among the viral hepatidities.

More than 185 million people worldwide, 3% of the world's population, are living with HCV, of whom 350,000 die each year.[1] Three to 4 million people are newly infected annually. HCV is the most common chronic blood-borne infection in the U.S. Yet most people with HCV are unaware of their infection. Most individuals are asymptomatic when they become infected. They remain symptom-free for decades, during which time diagnosis will not occur without screening and the virus may be unknowingly be transmitted to others – until they develop severe liver disease including cirrhosis and liver cancer, and develop symptoms. This causes the "silent epidemic" we face today. HCV burdens healthcare systems due to high costs of treatment of end-stage liver disease and liver cancer. In the U.S., HCV is the leading reason for liver transplantation. Nevertheless, this epidemic has not been addressed in a comprehensive way in most locales.

HCV HISTORY

We have come a long way since 1957 when Alick Isaacs, a Scottish virologist, and his Swiss colleague Jean Lindenmann discovered interferon, a natural antiviral agent. This protein "interfered" with infections and cancers – thus their name, "interfer-on." Cynics dubbed their cytokine, "misinterpreton." Eventually interferon became the mainstay of HCV therapy. More than 50 years later we still use interferon alfa against HCV, HBV and melanoma.



In the 1970s, Harvey Alter, MD, at the National Institutes of Health (NIH), demonstrated that hepatitis acquired via transfusion was not due to hepatitis A or B. In 1987, Daniel Bradley, PhD, at the CDC, in collaboration with Chiron Corporation scientists, identified the virus. In 1988, Alter confirmed its presence in non-A, non-B hepatitis specimens. In 1989, the discovery of HCV was published in journal *Science*.[5,6] By 1992 the blood test was perfected that essentially eliminated HCV from the blood supply.

The first patients treated with interferon were cured in 1984 and 1985 before it was known that HCV caused their disease. Jay Hoofnagle and his NIH colleagues used interferon to treat patients with non-A, non-B hepatitis and observed normalization of hepatic enzymes.[7] It was not until 1991 that the U.S. Food and Drug Administration (FDA) approved the first alpha interferon, administered by subcutaneous injection three times weekly, to treat HCV.

Cure rates were abysmal – less

than 10% for genotype 1, which accounts for 75% of U.S. infections. By 1998, ribavirin, a nucleoside analogue active against some RNA and DNA viruses, with unclear mechanism of action, was approved for use with interferon, to be taken twice daily in pill form. Pegylation, the attachment of large polyethylene glycol (PEG) molecule to interferon, prolonged the half-life, reduced clearance and extended therapeutic action. The FDA approved the first once-weekly pegylated interferon in 2001. At this time, one was still considered a charlatan if you stated that HCV was curable.

Although cure rates remained low with PEG-interferon plus ribavirin, cure was established to be beneficial. HCV viral eradication decreases liver-related morbidity and mortality, as well as overall mortality. While there were many systems-, provider-, and patient-level barriers to treatment, interferon itself was central. Interferon is a "hard sell." Physicians must ask patients who feel well to take injections for up to a year. These may cause depression, suicidality, cytopenias, fatigue, flu-like symptoms, bacterial infection and permanent thyroid dysfunction and vision loss, to name a subset of potential adverse effects. Ribavirin causes a dose-dependent, reversible hemolytic anemia that has precipitated myocardial infarction, respiratory distress and death. Ribavirin is teratogenic for both women and men. Taking the time to evaluate and treat comorbidities to permit this therapy, manage co-existing disorders, shepherd patients safely through, manage side effects by titrating interferon and ribavirin doses and adding adjunct medications, is poorly reimbursed in our current medical system. Given the low efficacy, toxicity, poor tolerability, contraindications, dangers, extended duration of therapy and low reimbursement for providers, it is no wonder that a minority of patients have been treated and cured. Consequently, mortality from HCV in the U.S. has continued to increase and now exceeds that from HIV infection.[8]

DIRECT-ACTING ANTIVIRAL AGENTS (DAAs)

Cure rates with immune-modulating therapy remained stagnant until the advent of direct-acting antiviral agents (DAAs) in 2011. A better understanding of HCV's life cycle resulted in development of DAA pills that stop the virus' ability to copy itself. DAAs directly interfere with HCV replication by targeting viral proteins that inhibit enzymes and steps in viral replication. Combining DAAs from various classes yields consistent, astonishingly high cure rates (100% in some studies), brief treatment durations (perhaps 4 weeks within a few years), and vastly improved tolerability and safety. This transformative breakthrough in antiviral therapeutics is unprecedented; it is as if we are experiencing three decades of gradual improvements in antiretroviral therapies for HIV condensed into a few years. Four DAAs are now available; already the first two are obsolete in the U.S., supplanted by safer, more effective DAAs with simpler dosing schedules.

As of December 2013, we entered the era of interferon-free and ribavirin-free therapies. We now have a simple genotype 1 option of 2 pills, once daily, for 12 weeks, leading to cure in over 90% of patients. By the end of 2014, the FDA is expected to approve the first combination pill – one pill integrating 2 DAAs, once daily – to cure HCV. We are approaching ideal regimens with high-cure rates in all genotypes and subpopulations (interferon treatment-experienced, patients with cirrhosis), with minimal to no side effects. Physicians and patients alike must stay on top of the rapidly changing standard of care.[2] Treatment paradigms will continue to shift as new agents become available.

THE PROBLEM OF THE BABY BOOMERS

Screening with a blood test identifies people so they may be engaged in care and treatment, and evaluated for cirrhosis (Determining if a person has cirrhosis is always the first step in HCV

COMMENTARY

What price for a cure?

LYNN E. TAYLOR, MD

DAAs are not expensive drugs to manufacture. The high pricing of the new pills will limit their impact. Already payers are devising schemes to ration these potentially life-saving medications. Some algorithms are aligned with principles of distributive justice,[11] such as prioritizing patients with advanced liver scarring. Other rules support long-held prejudices and misperceptions rather than evidence-based science, about certain people with HCV being more deserving than others, about some subpopulations being more able to adhere to DAAs than others. Removing interferon from the treatment armamentarium will not eradicate barriers for people who use drugs and alcohol, for people who are poor and underinsured. We need advocacy from diverse stakeholders and political action to dismantle the hurdles that have been built over decades. We need experts to step up and participate. Otherwise, non-specialists in payer organizations and business people in medical organizations who prioritize lucrative types of medical practice, will make decisions about which patients we can treat.

DAA price reform will require social and political action. Some are already able to negotiate much lower DAA prices – countries with universal healthcare systems, countries with high disease prevalence. Egypt negotiated a deal whereby sofosbuvir, a pan-genotypic (effective against genotypes 1-6) DAA that may be used without interferon, costs 1% of the U.S. price. These issues go way beyond those of HCV. The U.S. bears research and development costs and pharmaceutical company profits for drugs for many diseases, while middle- and lower-resourced countries and nations with universal health care pay less. The pressure for lower drug prices must remain in the context of our promise to treat more patients. By lowering DAA prices to facilitate treatment for everyone in need, drug manufacturers

care). Baby Boomers who never suspected they were infected are now discovering their liver disease in advanced form. One in 30 U.S. Baby Boomers, those born from 1945-1965, has HCV, comprising 75% of the U.S. epidemic. In 2013, the CDC revised its guidelines to recommend 1-time screening for everyone born from 1945 to 1965, in addition to risk-based screening. The U.S. Preventive Services Task Force supports this recommendation.

CHALLENGES AHEAD

Excitement over the striking advances in therapeutics is tempered by concerns about challenges ahead. Without a parallel revolution in treatment delivery, HCV-related morbidity and mortality in the U.S will continue to rise.[9] Will we be able to treat enough patients in time to avert the looming disaster of early illness, suffering and death, as Baby Boomers infected in the 1960s–1990s progress to cirrhosis? Will we be able to treat enough patients in time to avoid the enormous costs of the complications of cirrhosis? "…treatment of half or all of HCV persons with these new agents would reduce cirrhosis by 15.2% and 30.4%, respectively, after just 10 years."[10] (*See Commentary: What Price for a Cure*?)

CONTRIBUTORS

This issue of the Journal features articles on various aspects of the RI HCV epidemic. We address key domains including epidemiology, prevention, screening, treatment, public health policy and advocacy.

Tackling HCV begins with understanding the scope of the problem. In, "Estimating the True Prevalence of Hepatitis C in Rhode Island," authors **ELIZABETH KINNARD, BA**; **OMAR GALÁRRAGA, PhD**; **BRANDON MARSHALL, PhD**, and I model the first estimates of the disease burden in our state.

Public health leadership and initiatives provide foundation for combating RI's HCV epidemic. "Prevention and Control of Hepatitis C in Rhode Island," by **NICOLE ALEXANDER-SCOTT, MD**; **ANGELA LEMIRE**, **H. ELSA LARSON, MA, MS**; and **UTPALA BANDY, MD, MPH**, delineates the RI Department of Health's commitment to addressing HCV.

The DAA drug pipeline is robust, with many DAAs under investigation. The rapid development of multiple classes of DAAs demonstrates that HCV research field has benefited from the arduous path of HIV therapeutics.[17] Who better to discuss, "Therapeutic Revolution in Antiviral Medications for Hepatitis C Virus Infection," than **KAREN TASHIMA, MD**, RI's leader in studies of antiretroviral agents for HIV.

An anti-HCV vaccine remains elusive. Incident HCV occurs due to nosocomial transmission. HCV outbreaks have occurred due to lack of infection control in U.S. healthcare facilities, primarily at ambulatory surgery centers.[18,19] HCV maintains infectivity for weeks after drying on inanimate surfaces at room temperature.[20] Most incident HCV in the U.S. is due to use of injection equipment contaminated with HCV. Evidence-based preventive interventions exist via needle exchange programs (NEPs). The Congressional ban on federal funding for NEPs has thwarted expanded preventive efforts. Providence is one of only 166 U.S. cities with a NEP. In, "ENCORE: Rhode Island's Needle Exchange Program," **RAYNALD JOSEPH, AARON KOFMAN, MD**; **SARAH LARNEY, PhD**; and **PAUL FITZGERALD, MSW**, focus on the history and current status of this critical prevention program.

In accordance with CDC recommendations, RI could and should become the first state to implement statewide HCV screening of Baby Boomers among primary care physicians using electronic medical records (EMRs). **ROLAND MERCHANT, MD, MPH, ScD**; **JANETTE BAIRD, PhD**; **TAO LIU, PhD**, and I, in, "Hepatitis C Seroprevalence among The Miriam Hospital and Rhode Island Hospital Adult Emergency Department Patients," consider one approach to RI HCV screening to date.

COMMENTARY continued

will receive less money per pill but will garner greater societal commitment to treat more individuals. When considering costs, we must consider the costs of not treating, costs of advanced liver disease, and costs of removing people at the prime of their lives from the workforce. As Harvard's Camilla Graham, MD, teaches us, we must use the metric of cost per cure when comparing DAA regimens.[12]

Eliminating HCV is technically feasible. Eliminating HCV can provide economic benefits, enhance capacity to address other health challenges, and ameliorate healthcare disparities.[13,14] Eliminating HCV is likely going to be cost-effective, but up-front resources will be needed.[15,16] Barriers to eliminating HCV in the U.S. include lack of NIH funding earmarked for HCV research, sparse federal funding for HCV prevention and care, underinsured and disenfranchised populations disproportionately affected by HCV, and low reimbursement for HCV care. How will we build the infrastructure to get the new drugs to the people who need them? How will we utilize scientific breakthroughs to benefit those in need? Rational decision-making requires change at the governmental, health systems, pharmaceutical industry and payer levels. For example, the ban on Medicare negotiating drug prices means that Baby Boomers will overpay. The crisis over DAA costs should prompt deliberate, thoughtful discourse and plans about what to do about HCV in RI, and stimulate development of a business case for a cost-saving HCV model. ❖

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References

1. WHO Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014. http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/
2. AASLD, IDSA, IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed April 24, 2014.
3. Action Plan for the Prevention, Care and Treatment of Viral Hepatitis. Updated 2014-2016. http://www.cdc.gov/hepatitis/HHS-ActionPlan.htm
4. Gravitz L. HCV Introduction: a smouldering public-health crisis. *Nature.* 2011 Jun 8;474(7350):S2-4. doi: 10.1038/474S2a.
5. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science.*1989;244:359-362.
6. Kuo G, Choo QL, Alter HJ, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science.* 1989 Apr 21;244(4902):362-4.
7. Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med*. 1986 Dec 18;315(25):1575-8.
8. Ly KN, Xing J, Klevens RM, et al. The increasing mortality from viral hepatitis. *Ann Int Med*. 2012 Feb 21;156(4):271-8.
9. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010 Feb;138(2):513-21, 521.
10. Kanwal F, El-Serag HB. Hepatitis C Virus Treatment: The Unyielding Chasm Between Efficacy and Effectiveness. *Clin Gastroenterol Hepatol.* 2014 Mar 4. pii: S1542-3565(14)00349-8.
11. Aronsohn A, Jensen D. Distributive justice and the arrival of direct-acting antivirals: who should be first in line? *Hepatology.* 2011 Jun;53(6):1789-91.
12. Graham C. Cost of Cure vs Cost of Treatment with Camilla S. Graham, MD, MPH. HCV CONSULTS. 2014 Apr;1(1):20-21.
13. Grebely J, Dore GJ. Can hepatitis C virus infection be eradicated in people who inject drugs? *Antiviral Res.* 2014;104:62-72.
14. Dowdle WR, Cochi SL. The principles and feasibility of disease eradication. *Vaccine.* 2011;29 Suppl 4:D70-3.
15. Sadana R, Blas E. What can public health programs do to improve health equity? *Public Health Rep*. 2013;128 Suppl 3:12-20.
16. Chan K, Lai MN, Groessl EJ, et al. Cost effectiveness of direct-acting antiviral therapy for treatment-naive patients with chronic HCV genotype 1 infection in the veterans health administration. *Clin Gastroenterol Hepatol*. 2013;11(11):1503-10.
17. McGovern BH, Abu Dayyeh BK, Chung RT. Avoiding therapeutic pitfalls: the rational use of specifically targeted agents against hepatitis C infection. *Hepatology*. 2008 Nov;48(5):1700-12. Erratum in: *Hepatology*. 2009 Mar;49(3):1059.
18. Thompson ND, Perz JF, Moorman AC, Holmberg SD. Nonhospital health care-associate hepatitis B and C virus transmission: United States, 1998-2008. *Ann Intern Med.* 2009;150(1):33-9.
19. Perz JF, Thompson ND, Schaefer MK, Patel PR. US outbreak investigations highlight the need for safe injection practices and basic infection control. *Clin Liver Dis*. 2010;14(1):137-51.
20. Paintsil E, Binka M, Patel A, Lindenbach BD, Heimer R. Hepatitis C virus maintains infectivity for weeks after drying on inanimate surfaces at room temperature: implications for risks of transmission. *J Infect Dis.* 2014 Apr 15:209(8):1205-11.

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'C' is for Cure: A WaterFire Lighting for RI Defeats Hep C

Saturday, July 26
Full Lighting – Sunset 8:11 pm

Please join us for this special WaterFire on Saturday, July 26. We will raise awareness; build Community, Connection, Cooperation and Camaraderie around HCV; help diminish stigma; inspire those living with HCV to seek cure; and have a family-oriented, artistic, musical, creative, enchanting, free summer night out on the town. This Waterfire will include entertainers, food, music and HCV testing. WaterFire Providence is an independent, non-profit arts organization whose mission is to inspire its visitors by revitalizing the urban experience, fostering community engagement and creatively transforming the city. WaterFire centers around the installation of 80 bonfires floating on Providence's rivers, with 65,000 people attending each WaterFire event.