An Epidemiologic Update on Hepatitis C Infection in Persons Living With or at Risk of HIV Infection

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Due to shared routes of transmission, coinfection with both human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) is relatively common and results in accelerated liver disease, driving morbidity and mortality. Deaths related to HCV now exceed deaths related to HIV in the United States, and co-infected patients bear a significant proportion of that mortality. This burden may be addressed by novel antiviral therapies that promise increased rates of cure or by enhanced access to liver transplantation, but these are costly interventions. Ultimately, the future burden of coinfection is addressed by greater understanding of who is at risk for development of each infection, thus guiding preventive efforts. Key recent reports regarding the US burden of morbidity and mortality due to HCV and groups at risk for coinfection are reviewed, with a focus on recently described HCV occurring among young injection drug users and men who have sex with men. Given the lack of available vaccine against HCV, enhanced detection and surveillance is a vital component of our public health strategy to combat HCV.

Keywords. sexual transmission; epidemiology; viral infection; incidence; prevalence; perinatal transmission; men who have sex with men.

The worldwide burden of hepatitis C virus (HCV) is extraordinarily high, with estimates that 170 million persons may be infected, five times higher than the worldwide estimates for those infected with human immunodeficiency virus type 1 (HIV-1). In the United States alone, there are an estimated 3.4–4.9 million individuals living with chronic HCV infection [1]. As these 2 viruses also share risk factors for transmission, HIV-1/HCV coinfection is relatively common. Up to 25% of the approximately 1.2 million people infected with HIV-1 in the United States also have HCV [2]. Those unfortunate enough to harbor both viruses will face particular challenges with accelerated liver disease, the costs and adverse effects of treatment, and barriers to care; these issues are described elsewhere in this supplement. No vaccine against either of these viruses has yet to be deployed, emphasizing the importance of other preventive and surveillance strategies, especially as those living with one virus are at risk for the other. In this article we will briefly review data emerging about the current overall burden of HIV-1/HCV and highlight evolving trends in the convergence of these epidemics, with a public health focus on where to devote resources to prevent further morbidity and mortality. We will also explore new paradigms regarding testing for HCV among the highest risk groups.

MORBIDITY AND MORTALITY DUE TO HCV-RELATED LIVER DISEASE CONTINUES TO INCREASE AMONG “BABY-BOOMERS”

An increasing burden due to HCV-related liver disease has been projected, taking into account that
millions of persons were infected three or four decades ago and the progression to cirrhosis over that timeframe [2]. These projections are proving to be increasingly accurate; a review of 2007 death certificate data strongly suggests that deaths related to HCV now exceed those caused by HIV in the United States (15,106 and 12,734, respectively) [3]. This is despite the fact that successful eradication of the virus for those with advanced fibrosis and cirrhosis radically reduces liver-related mortality for those chronically infected, including HIV/HCV co-infected persons [4]. Numerous barriers to care have been identified, including: (1) lack of knowledge of the infection, due to its mostly asymptomatic nature and undertesting of those at risk; (2) a limited number of providers capable and willing to treat HCV; (3) psychosocial barriers that prevent successful evaluation and treatment; (4) significant cost of current HCV regimens, and (5) interferon-based treatments, when applied, were fraught with side effects and, until recently, were often not successful. Just as novel antiviral therapies are arriving with promise of enhanced efficacy and fewer side effects (as expected with interferon-free regimens), projected morbidity and mortality due to HCV is unfolding before us.

As HCV-related liver disease is accelerated in the presence of HIV, those with HIV/HCV co-infection represent a significant proportion of this burden. Studies show that viral hepatitis (driven largely by HCV) is the most likely non-AIDS cause of death for those living with HIV [4] and that HCV antibody positivity (a correlate of viremia) increases the overall risk of death [5]. Thus efforts to identify candidates for treatment and provide access to antivirals are approaches that could be implemented to reduce the substantial morbidity and mortality associated with HCV, including for co-infected persons [4].

The risk factors for HCV are known; this virus is most efficiently transmitted via exposure to contaminated blood, in addition to inefficient sexual and perinatal transmission. Persons with repeated risks such as injection drug users (IDUs) or exposure to blood-derived products prior to interventions to decrease bloodborne pathogen transmission are at immense risk for HCV. However, even a single exposure may result in transmission, and certain exposures are likely to be underreported (such as brief experimentation with injection drugs) or were commonplace (such as nosocomial transmission in the 1970s and 1980s, before the HIV epidemic resulted in broad changes in needle safety practices). Survey data in the United States indicate that a large number of persons at risk for HCV-related liver complications are simply unaware of the infection [6]. The implication is that risk factor-based screening has failed to identify most individuals infected with HCV in the United States.

Those born between 1945 and 1965 or the so-called “baby boomer” generation are a demographic group that carries about a 3%–4% prevalence of HCV and is estimated to represent approximately two-thirds of the total infected population [1]. A single anti-HCV antibody test applied broadly would capture a large proportion of those who are chronically infected and at risk for future liver complications. Repeat testing is likely unnecessary as there is unlikely to be ongoing exposure among most members of this group. This screening recommendation, recently published by the Centers for Disease Control and Prevention (CDC) [7], will need to be carried out by non-specialists and there will be challenges to implementation including provider knowledge gaps, added provider burden, and cost. Nonetheless, this so-called baby-boomer screening paradigm promises to save a substantial number of lives and is as cost-effective as many other commonplace screening interventions applied in primary care [8]. This paradigm is not dissimilar to that guiding testing for HIV, recommended as a one-time test for all adults by the CDC, and combined testing is of added importance as up to 15% of newly discovered HIV is among adults over 50 [9].

All persons discovered to have HCV via this age-based screening should also be screened for HIV infection. Because HIV typically comes to clinical attention sooner than HCV due to its shorter latency until manifestations, it is not likely that baby-boomer screening will uncover a large burden of HIV/HCV co-infected persons. In parallel there are ongoing and substantial efforts to expand HIV screening, and the current standard of care is to screen all those living with HIV for HCV at baseline. Overall, continued identification of cases of each virus should help to uncover the hidden burden of HIV/HCV co-infection.

Increased attention has been paid to healthcare acquired infections in recent years due to instances of outbreaks of bloodborne viruses in healthcare settings, including dramatic outbreaks that resulted in large-scale investigations [10]. Nosocomial transmission, even if sporadic, may be an even more relevant concern as the baby-boomer population, with their higher rates of HCV infection, develop other medical issues as they age and increase their healthcare utilization. Moreover, healthcare workers have recently been implicated in transmission in the hospital setting by exposing patients to their own HCV, motivated by diverting injectable medications for their own use [11]. Thus, although many safeguards are in place to reduce nosocomial transmission, particularly via careful screening of the blood supply and universal precautions, hospital systems need to remain hypervigilant regarding safety practices to prevent the often silent transmission of HCV. Due to their sporadic nature, it is almost impossible to identify cases of nosocomial transmission in a timely way via current disease surveillance systems.

SURVEILLANCE UNCOVERS A NEW EPIDEMIC OF HCV AMONG YOUNG PERSONS

This leads to another key challenge to understanding the HCV epidemic in the United States, including its impact on
people infected with HIV: the lack of adequate HCV disease surveillance in most jurisdictions. These initiatives are largely underfunded (or not funded at all) at both state and federal levels [12]. Thus, a full public health perspective on the prevalence of HIV-1/HCV coinfection is limited by jurisdictions’ lack of infrastructure to process, manage and analyze the high volume of HCV laboratory test results and case reporting forms.

One of the key findings from the few jurisdictions with relatively robust surveillance is an increase of HCV infection among adolescents and young adults [13]. In Massachusetts, the use of a highly automated, web-based surveillance system has allowed the detection of a major shift in the demographics of HCV. Since 2007, the Massachusetts Department of Public Health has received over 1000 reports of cases of HCV infection annually among people between the ages of 15 and 25.

Figure 1: Age distribution of newly reported confirmed cases of hepatitis C virus (HCV) infection in Massachusetts for 2002 (A, n = 6368) and 2011 (B, n = 5194). The data confirm the shift previously reported [13] from a unimodal to a bimodal age distribution over this decade. Data are based on case report forms by reporting clinicians, triggered by a positive HCV antibody or HCV viral load test.
years. As seen in Figure 1, the number of cases in the younger age group has increased considerably since 2002, leading to a bimodal distribution. Also of note are the data regarding gender of these 2 age groups. Although among the older cohort, males comprise approximately 70% of cases, among the younger cohort, the distribution of cases between genders is closer to equal. Because both acute and chronic HCV rarely present with significant symptoms, it is likely that the burden of infection among adolescents and young adults is even higher due to undiagnosed infection. The majority of cases for whom risk behavior data are available report past or current injection of heroin [13].

This uptick in HCV incidence may be a marker for where the HIV epidemic, and therefore cases of HIV-1/HCV coinfection, may be found in the future. This alarming trend has been noted in other jurisdictions [14]; however, this has not yet led to a substantial increase in resources to identify and/or prevent new infections. Although there have been conflicting data on the most effective means of preventing HCV infection among injection drug users, recent evidence supports the use of multicomponent prevention programs, including access to sterile injection distribution, opiate replacement therapy and drug rehabilitation as an effective tool for this purpose [15]. However, federal funding for HIV prevention for injection drug users has been decreased in recent years due to the lower incidence of HIV infection. This decrease has occurred despite evidence of ongoing risky behavior in this population: approximately 9% of the 48,100 new US HIV infections in 2009 occurred in IDUs [16] and, in addition to sharing drug paraphernalia, risks such as unprotected sex and multiple partners remain quite prevalent [17]. Because most HCV prevention efforts are integrated into other public health infrastructure, especially those related to HIV services, the reductions in HIV funding for drug user prevention programs are coming at a time when HCV incidence data indicate that they are urgently needed.

Along with an increase in HCV among young IDUs is a potential impact on perinatal transmission of HCV. While the risk of HCV transmission from an infected mother to her child is relatively low (estimated at 3%–5%) [18], a greater burden of HCV infection among females of childbearing age suggests that there are likely to be more opportunities for transmission by virtue of a larger population of infected mothers. Should a parallel increase of HIV infection be seen in this population, the risk for HCV transmission to children could be augmented given the impact that HIV can have on perinatal HCV transmission [19]. Current guidelines suggest that providers should screen the children of HCV-positive women for transmission [20], but there are no parallel recommendations to screen pregnant women, thus limiting the likelihood of detecting perinatal cases. Although there are no proven interventions at this time to interrupt perinatal transmission due to the difficulties of using interferon and ribavirin among pregnant women, it is possible that new paradigms may emerge. Improved data collection and follow-up of HCV infected mothers and their newborns are needed to determine effective policies and public health response.

### Table 1: Recent Epidemiological Observations Regarding Hepatitis C Virus (HCV), Their Implications, and Potential Responses

<table>
<thead>
<tr>
<th>Epidemiological trend</th>
<th>Implications</th>
<th>Potential responses</th>
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<tbody>
<tr>
<td>Increased morbidity and mortality related to HCV, lack of diagnosing HCV infection</td>
<td>Increased healthcare utilization</td>
<td>“Baby-boomer” screening Access to evaluation and treatment Access to liver transplantation</td>
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<tr>
<td>HCV incidence rising among young injection drug users</td>
<td>Most cases are not symptomatic so not easily identified Coepidemic with opiate abuse Young women affected; may result in more cases of perinatal transmission</td>
<td>Improved public health surveillance Access to opiate substitution Access to HIV and HCV testing Multipronged HCV prevention Access to opiate substitution Access to needle exchange Access to drug rehabilitation HIV prevention Improved recognition of perinatal transmission</td>
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<tr>
<td>HCV incidence rising among HIV-positive men who have sex with men</td>
<td>Coepidemic with sexual risks, noninjection drugs Accelerated fibrosis in HIV/HCV coinfection</td>
<td>Regular screening for both behaviors and acute HCV infection Identification and treatment of co-existing STDs Access to drug rehabilitation Decreasing risky behaviors, use of barriers Access to interferon-based treatments with higher efficacy and less complexity than those used during chronic disease</td>
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Abbreviations: HIV, human immunodeficiency virus; STD, sexually transmitted disease.
A SYNDROME OF SEX, DRUGS, AND HCV

New HCV infection may also occur after HIV-1 infection. Over the past decade, outbreaks of HCV infection in HIV-infected men who have sex with men (MSM) have been reported from Europe, the United States, and Australia [21]. These outbreaks are a result of a syndemic of high-risk sexual behavior and noninjection drug use, especially crystal methamphetamine. Risk factors for transmission include a higher number of partners, group sex, other ulcerogenital sexually transmitted diseases, sexual acts that involve trauma and bleeding, and exposure to semen.

After infection, persistent viremia is the usual outcome, which then confers risk for liver disease progression. At least one study has detected a high rate of significant liver fibrosis shortly after recognition of HCV [22], although the progression toward cirrhosis may eventually slow down over time [23]. Nonetheless, as chronic HCV in the context of HIV has an accelerated course compared to those without HIV and remains complicated and costly to treat; even as more effective therapies arrive, it remains a high priority to prevent chronic infection. Prevention of initial exposure to HCV among HIV-infected MSM also needs to be addressed urgently, although few public health efforts have been proven thus far.

Overall, high rates of response to interferon-based therapies for acute HCV (usually defined as the first 6 months of infection) have been reported in both HIV-1 negative and HIV-1 positive hosts (59%-90%) [24]. These are much higher rates than treatment applied during the chronic phase, especially for genotypes 1 or 4 despite less intensive and shorter regimens typically used to treat acute disease. Given the relatively high cost of addressing chronic disease, identifying acute HCV infection will allow providers to offer effective treatment. Testing yearly HCV antibodies and work-up of liver function test abnormalities in HIV-positive MSM are together a cost-effective approach [25].

AVOIDING THE “DOUBLE TROUBLE” OF COINFECTION

Multiple approaches are necessary to achieve successful HCV and HIV prevention, identification of new cases, and linkage to care. Effective treatments for both infections are available and provide an ability to stem the tide of increasing morbidity and mortality due to HCV-related liver disease. Moreover, persons remain at risk for HCV, especially young persons abusing opiates and HIV-positive MSM. Addressing the groups at highest risk would be best accomplished with an integrated, multprunged approach, acknowledging that there are complicated forces driving these risk behaviors, namely, the increase in opiate prescription, diversion, and addiction [26], and the syndemic of high-risk sex, noninjection drugs, and HIV among MSM. Other responses include access to testing, provision of care for those already infected with HCV, and prevention efforts for those at high risk but yet to be infected with either virus (Table 1). Increased funding for prevention and linkage to care targeting these populations is needed at the federal, state, and local levels. All of these endeavors would benefit from improved surveillance in more jurisdictions to identify outbreaks earlier and to assess the burden of HCV and HIV/HCV coinfection, informing how we devote our currently limited resources to combat viral hepatitis [12]. These joint efforts between providers, public health systems, and epidemiologists will remain vital to address the current morbidity and mortality related to HCV and HIV and to avoid future burden of these 2 infections.

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