

Tackling the Health Challenge posed by Hepatitis C in Puerto Rico: A Call for Immediate Public Health Actions

Cynthia M. Pérez, PhD*; Carmen E. Albizu-García, MD†; Esther A. Torres, MD‡

Within the past decade, researchers and hepatitis C specialists in Puerto Rico have highlighted the burden of hepatitis C and associated disease outcomes in the island to raise public awareness about this problem and set out a call to action to tackle prevention and control efforts, yet so far no concrete actions have taken place. The population-based studies on hepatitis C have documented that the main risk factor is the sharing of syringes and drug paraphernalia to inject drugs, that most seropositive individuals are unaware of their infection status, and that there are large knowledge deficits about the disease, its risk factors, and measures of prevention and control. The subject is further complicated by the fact that despite hepatitis C reporting is mandatory, there is no effective epidemiological surveillance system to provide the information needed for planning, implementation, monitoring, and evaluation of intervention strategies for this infection and access to medical and other existing therapies is limited. This document addresses the disparities in HCV infection and its adverse outcomes experienced among Puerto Ricans and attempts to set out strategies to address a public health response for hepatitis C at the meso and macro levels of the social-ecological model. Diverse organizations and major stakeholders are urged to mount an adequate response to hepatitis C by transforming current scientific evidence into public health actions to increase awareness, identify those who are actively infected, and link infected individuals into comprehensive care and treatment. [*PR Health Sci J* 2015;34:53-59]

Key words: Hepatitis C, Substance use disorders, Public health response

Hepatitis C, an infection of the liver caused by the hepatitis C virus (HCV), is the most common blood-borne infection in the United States (US). Between 60% and 85% of those infected develop chronic HCV infection. This chronic infection ranges from an asymptomatic phase without medical consequences to the development of cirrhosis with decompensation, hepatocellular cancer, and liver transplant, thus affecting productivity, quality of life, and life expectancy of affected individuals (1, 2). The interval between infection and the development of cirrhosis in non-immunocompromised patients is from 20 to 30 years. It is estimated that between 20% and 45% of patients with chronic hepatitis C develop cirrhosis, and of these, 1%-5% develop liver cancer annually (2).

HCV is transmitted by direct contact with the blood of an infected person. The main established risk factors for hepatitis C are: a) current or former injection drug use (sharing of syringes and drug paraphernalia to inject drugs), b) receipt of blood transfusions and organ transplants from infected donors before July 1992 or clotting factors before 1987, c) long-term hemodialysis, d) exposure to contaminated needles or instruments with HCV in health care settings, and e) birth to an HCV-infected mother (1, 2). In addition to these

high risk groups, the Centers for Disease Control (CDC) and Prevention recommends screening for HIV-infected patients, people who have evidence of chronic liver disease characterized by persistently high levels of liver enzymes, and all adults born between 1945 and 1965 (baby boomer generation) (1-3). HCV screening is currently of uncertain need in recipients of transplanted tissue, users of intranasal cocaine and other non-injecting drugs, persons with a history of tattooing or body piercing practices, persons with a history of multiple sex partners or sexually transmitted infections (except HIV), and long-term steady sex partners of HCV-infected individuals (1, 2).

*Department of Biostatistics and Epidemiology; †Center for Evaluation and Sociomedical Research, Graduate School of Public Health; ‡Department of Medicine, School of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, PR

The authors have no conflict of interests to disclose.

Address for correspondence: Cynthia M. Pérez, PhD, Professor, Department of Biostatistics and Epidemiology, Graduate School of Public Health, University of Puerto Rico Medical Sciences Campus, PO Box 365067, San Juan, PR 00936-5067. Email: cynthia.perez1@upr.edu

Recent data from the National Health and Nutrition Examination Survey (NHANES) indicate that 3.6 million adults (anti-HCV prevalence of 1.3%) in the US have past or current infection, of whom, 2.7 million (prevalence of 1%) have chronic HCV infection (4). When high-risk populations excluded in the NHANES sampling strategy (incarcerated individuals, homeless persons, and those on active military duty) are taken into account, the estimated number of seropositive individuals increases to 5.2 million (anti-HCV prevalence of 2%) (5). HCV infection is significantly more prevalent in African Americans than in non-Hispanic Whites and Mexican-Americans (4); however, prevalence differs markedly by Hispanic background. The Hispanic Community Health Survey/Study of Latinos (HCHS/SOL), a study of 16,415 Hispanic/Latino adults recruited following a multi-stage probability sampling of four US communities at the Bronx, Miami, Chicago, and San Diego, showed that the age-standardized prevalence of HCV antibody was highest in adults of Puerto Rican background (11.6%) (6).

Contrary to what has been reported for HIV, hepatitis C is associated with excess mortality as shown by a significant increase in the age-adjusted mortality rate from 1999 to 2007 (7), underscoring the need for new policy initiatives to detect patients with chronic hepatitis and link them to appropriate care and treatment. Co-infection with hepatitis B virus (HBV) or HIV, chronic liver disease, and alcohol-related conditions were significantly associated with HCV-related deaths. In the absence of effective treatment, it is projected that the annual number of patients with cirrhosis, hepatic decompensation, liver cancer, and liver-related deaths in the US will double by 2020, mainly affecting people over 60 years due to aging of HCV-infected individuals (8). Fortunately, the treatment of hepatitis C has evolved significantly over the years, creating a unique opportunity to proactively identify strategies to address HCV infection. The incorporation of new oral free-interferon drugs (e.g., boceprevir, telaprevir, sofosbuvir, and simeprevir) that have proven effective in increasing the sustained response and reducing adverse effects is anticipated in the coming months (9-13). On April 2014, the World Health Organization released the first guidelines for hepatitis C treatment designed for policymakers, government officials, health care providers, and others working in low- and middle-income countries who are developing comprehensive programs for the screening, care, and treatment of HCV infected individuals (14).

Burden of Hepatitis C in Puerto Rico

Despite the Administrative Order 177 (January 1, 2003) that established the mandatory reporting of hepatitis C, there is no effective surveillance system that systematically collects and analyzes data on hepatitis C, hampering planning, implementation, and evaluation of intervention strategies for this infection. Current knowledge about hepatitis C in Puerto Rico is the result of several investigators' efforts who have prioritized hepatitis C in their research agenda. The first study in 1991 conducted among blood donors in the American Red

Cross found a prevalence of 0.79% in 32,080 donors, using a first-generation ELISA and second-generation confirmatory RIBA test (15). This prevalence had decreased to 0.12%-0.17% by 2004-2006 (Personal Communication, R. Casanova, American Red Cross). Another study in hemodialysis patients in the western region of Puerto Rico during 1997 and 1998 revealed a prevalence of 2% (16). The first study population-based study conducted in 2001-2002 in the municipality of San Juan found an overall seroprevalence of HCV of 6.3% (95% CI: 3.6%-10.9%) in the population aged 21-64 years (17). An islandwide serosurvey conducted between 2005 and 2008 showed that 2.3% (95% CI: 1.3%-4.2%) of the population aged 21-64 years in Puerto Rico had serological evidence of HCV infection (18). The prevalence of HCV infection increased to 2.7% in municipalities characterized by a high incidence of AIDS among injecting drug users. However, the seroprevalence of HCV infection is higher because the study excluded high-risk populations, such as incarcerated and homeless individuals. This study also showed that anti-HCV prevalence was significantly higher in individuals who were men, had public or no health insurance, had a history of injection drug use, tattooing and body piercing practices, receipt of blood transfusions before 1992, and imprisonment, and were positive to HBV and herpes simplex virus type 2. Of particular importance to public health efforts in Puerto Rico are the observations that an overwhelming majority (80%) of seropositive individuals were unaware of their HCV serostatus and that HCV prevalence was twice that of HIV (2.3% vs. 1.1%). Another study also showed that the vast majority of participants showed large knowledge deficits about hepatitis C, underscoring the need for targeted educational campaigns to increase awareness about HCV transmission and prevention (19). In terms of hepatitis C-related mortality, liver disease and cirrhosis occupied the 16th cause of death in 2010 in Puerto Rico (adjusted rate of 4.6/100,000) (20). In addition, liver cancer represented the fourth and fifth leading causes of cancer death in men (6%) and women (4.9%), respectively, and the eighth most common newly diagnosed cancer in men (2.8% of all incident cases) during 2005-2009 (21).

Hepatitis C in the Correctional System

A serosurvey conducted in the correctional population in Puerto Rico in 1998 revealed that 49.3% of the 11,530 inmates tested positive for HCV (22). In 2010-2011, the Puerto Rico Department of Health documented that the most prevalent chronic infection in their correctional institutions was hepatitis C (54.6%), whereas substance use disorder (46.3%) was the most prevalent mental health diagnosis (23). Notably, only 0.7% (21/3,033) of HCV-infected inmates were under treatment in contrast to 62% (310/501) for HIV infection. The absence of preventive measures, such as treatment for people addicted to opiates (most commonly injected drugs in Puerto Rico), clean needles, and condom use, along with the behaviors and adverse social conditions of prisoners promote a fertile ground for the transmission of HCV and other bloodborne pathogens.

Hepatitis C, HIV/AIDS, and Injection drug use

Due to the similarity of HCV and HIV transmission routes, prevalence of HCV-HIV is common, affecting nearly 25%-30% of HIV-infected individuals; however, a higher prevalence of coinfection is found among HIV infected individuals who are injection drug users (24). This issue is of concern as HIV infection increases the progression of HCV-related liver disease, the risk of highly active antiretroviral therapy-related hepatotoxicity, and mortality. This biological interaction between HCV and HIV is worrisome given that Puerto Rico has been characterized by consistently having one of the highest incidence rates of HIV/AIDS in all states and territories of the US (25). In 2006, a study among 400 injecting drug users recruited from outdoor drug markets in the San Juan metropolitan area found that the prevalence of HCV, HIV, and HCV-HIV co-infection were 89%, 17%, and 9.6%, respectively (26). Moreover, 57% of injection drug users who had initiated drug injection within the year prior to the study interview were seropositive to HCV.

Comparative studies among injecting drug users in Puerto Rico and New York show that the frequency of drug injection is higher in Puerto Rico and the practice of injection occurs in higher risk environments (27-29). These observations may explain the higher rate of HIV seroconversion among islander Puerto Ricans compared to those living in New York (30). These differences can be partially explained by structural differences, including reduced availability of needle exchange programs, less access to treatment programs assisted by drugs, and lower utilization of health services in Puerto Rico (31).

In 1998, researchers at the Universidad Central del Caribe showed the effectiveness of the first needle exchange program established in Puerto Rico in significantly reducing the sharing of syringes and other injection equipment among injection drug users (32). Although there is ample evidence of the cost-effectiveness of science-based prevention strategies to reduce the transmission of HCV (33, 34), a recent study on the need for services for substance use disorders in Puerto Rico showed that 78.4% of individuals with drug abuse and dependence and 94.6% of those with alcohol abuse and dependence are not receiving services for their addictions (35).

Public Health response to HCV infection

In an effort to start developing a public health response to HCV infection in the US, the National Institutes of Health held consensus development conferences on the management of hepatitis C in 1997 and 2002 (1). The CDC also issued recommendations for the prevention and control of HCV infection and HCV-related chronic disease in 1998 (2) and later released the National Hepatitis C Prevention Strategy in 2001 (36). Federal legislation has also been proposed over the past decade to establish, promote, and support a comprehensive prevention, research, and medical management referral program for HCV infection, including the development of a national plan by the Department of Health and Human Services to

address HCV infection; however, most of these bills were not enacted in the US House of Representatives and Senate (*Hepatitis C Epidemic Control and Prevention Act*: S. 1143 and H.R. 3539 in 2003; S. 521 and H.R. 1290 in 2005; S. 1445 and H.R. 2552 in 2007; *Viral Hepatitis and Liver Cancer Control and Prevention Act*: H.R. 3974 2009 and S. 3711 in 2010; *Viral Hepatitis Testing Act*: S. 1809 and H.R. 3381 in 2011; *Viral Hepatitis Testing Act*: H.R. 3723 introduced in 2013 and S. 2538 in 2014). In 2010, the Institute of Medicine determined that the underlying factors hampering a public health response included the lack of knowledge and awareness about chronic viral hepatitis (among health-care and social-service providers, at-risk populations, general public, and policy makers) and insufficient understanding about the extent and seriousness of hepatitis C; thus, the Institute provided a framework for HCV and HBV prevention, education, control, research, and medical management (37). In response to the Institute of Medicine Report, the Department of Health and Human Services released in 2011 the *Action Plan for the Prevention, Care, and Treatment of Viral Hepatitis*, which provides a detailed guide to improve the prevention and linkage to care and treatment of infected individuals (38). To take into consideration new and anticipated therapies as well as the potential to improve access to viral hepatitis prevention, care, and treatment through the Patient Protection and Affordable Care Act (39), federal and nonfederal stakeholders updated the action plan in 2014 (40). The six priority areas of the updated plan are: a) education of health care providers and communities, b) improvement of diagnosis, care, and treatment, c) strengthening surveillance to detect viral hepatitis transmission and disease, d) elimination of vaccine-preventable viral hepatitis, e) reduction of viral hepatitis transmission associated with drug use, and f) protection of patients and health care workers from health-care associated viral hepatitis.

In contrast to the multiple efforts undertaken in the US (1-3, 33, 34, 36-40) and elsewhere (14, 41), the lack of a coordinated public health response in Puerto Rico warrants an explanation. Longstanding scientific evidence has been available to justify a public health approach to reduce the spread of HIV and HCV among injectors. To increase awareness of hepatitis C and encourage at risk populations to undergo testing and promote actions to confront this condition, Law number 42 (January 3, 2003) designated May 19th as the National Hepatitis C Testing Day. However, the impact of this educational initiative on knowledge and health-seeking behavior remains unknown. Within the past decade, researchers and hepatitis C specialists have highlighted the burden of hepatitis C in the island to raise public awareness about this problem and set out a call to action to tackle prevention and control efforts, yet so far no concrete actions have taken place. The present report proposes public health strategies to reduce these and improve the public's health. The analysis and ensuing recommendations for hepatitis C prevention use the framework provided by the social-ecological model that emphasizes the linkages and relationships among

levels that may influence behaviors and associated health outcomes (42). Recommendations, although aligned with those included in the US Department of Human and Health Services action plan for the prevention, care, and treatment of viral hepatitis (38-40), are contextualized to the reality of the island, where persons who inject drugs, the largest at risk group for HCV and HIV, experience greater health disparities involving preventable causes of disease and illness than their counterparts in the US (43). Emphasis is placed on the factors at the meso and macro levels, including policies and public health actions, that need to be adopted and enforced to appropriately safeguard the health of this vulnerable population. Although individual level factors, such as HCV risk behaviors, can be modified through education to reduce the probability of contagion (44), the possibility of enacting the protective behaviors is conditional on many macro and meso structural factors. As occurs in Puerto Rico, criminalization of drug users and increases in police surveillance of active users in the community has been associated with increased risk of HIV (45). Other protective interventions within the continuum of harm reduction measures are not readily available in Puerto Rico (43). In addition, Puerto Rico experiences a gap in treatment availability that surpasses that of the US (35). Pharmacotherapy for persons who inject opioids is an effective intervention that is not readily accessible and fraught with inordinate regulations that affect treatment access and retention in the island (43). Therefore, our context requires prompt actions at the macro and meso levels if Puerto Rico is to adequately address the health needs of the population at greatest risk of HCV contagion.

Education to the general public, at-risk populations, policymakers, and health care providers

1) Implement health education programs for the general public, high-risk populations, and policymakers through awareness campaigns, health communication activities, and community outreach to promote education and knowledge about the risk factors, prevention, and transmission of HCV, importance of testing and counseling, medical management of the condition to prevent chronic liver disease, and identification of facilities that offer integrated care and service delivery for infected individuals.

2) Develop a health education and risk reduction program in correctional institutions in Puerto Rico.

3) Create a professional training program for health care and social service providers regarding the prevention, detection, and medical management of persons infected with HCV, HBV, and HIV in order to help them deliver better services to infected patients. Since stigma enacted in the treatment sector is a potential barrier to treatment entry and retention that can contribute to further health disparities in this vulnerable population (46), professional training also needs to address stigma towards drug users.

4) The Puerto Rico Department of Health should develop a website for the general public and health care providers to

provide updated guidelines for the diagnosis, treatment, and prevention of hepatitis C as well as patient education materials. In addition, a hepatitis hotline can be implemented to provide callers with accurate information, counseling, and referrals to services or resources in the community.

Screening for HCV infection in high-risk individuals

1) Health care professionals in the private and public sectors should routinely ask all patients about risk factors for HCV infection in order to identify who should be tested.

2) Support voluntary testing programs for hepatitis C in high risk individuals to assist in the early detection of HCV-infected individuals.

3) Hepatitis C risk-reduction counseling, before and after HCV testing, should be promoted. Counseling should review topics such as HCV transmission, risk of other infections and substance use disorders, importance of early diagnosis and treatment, therapeutic regimens, test results and meanings, vaccination against hepatitis A and hepatitis B, and risk reduction behaviors.

Medical management

1) Health care professionals are urged to provide HCV RNA test negative individuals education and interventions to reduce progression of liver disease by addressing alcohol use status, considering opioid substitution therapy in people with substance use disorders, and recommending vaccination against hepatitis A and hepatitis B.

2) Health care professionals are urged to provide HCV RNA test positive individuals education and interventions to reduce progression of liver disease by addressing alcohol use status, considering opioid substitution therapy in people with substance use disorders, and recommending vaccination against hepatitis A and hepatitis B. Moreover, health care professionals should refer these infected patients to specialist physicians (e.g., hepatologist, gastroenterologist, or infectious disease specialist) for further medical evaluation programs directed to determine its state of chronicity, presence of other comorbidities, eligibility for new antiviral therapies, and provide medical follow-up to monitor treatment efficacy and toxicity.

3) Establish facilities that offer integrated care and service delivery for hepatitis C. A multidisciplinary team that includes specialist physicians, primary care physicians, nurses, mental health/addiction counselors, nutritionists, case managers, and outreach workers is needed to deliver comprehensive care and treatment. Growing evidence supports that counseling activities and other prevention services are being successfully integrated into existing clinical services and public health programs, such as those that offer prevention and treatment of HIV, other sexually transmitted infections, and substance use disorders (47).

Prevention and treatment of substance use disorders

1) Expand the needle exchange programs and the scope of services provided to prevent the spread among injecting

drug users. These should include the following services as recommended by the CDC (34): a) HIV/AIDS education and counseling; b) condom distribution to prevent transmission of HIV and other sexually transmitted infections; c) referrals to substance abuse treatment and other medical and social services; d) distribution of alcohol swabs to help prevent abscesses and other bacterial infections; e) on-site HIV testing and counseling and crisis intervention; f) screening for tuberculosis, hepatitis B, hepatitis C, and other infections; and g) provision or facilitated referral to primary medical services.

2) Expand medication-assisted treatment (MAT) programs against opioid dependence, such as methadone and buprenorphine, to address the social and health needs of people with substance use disorders. Medication use in treatment significantly reduces drug injection and opportunities for acquisition and transmission of viruses that cause hepatitis B and C and HIV/AIDS. The annual cost of MAT of opioid dependence is estimated between \$4,000 and \$6,000 less than the cost of drugs for the treatment of HIV/AIDS and hepatitis B and C (48). A recent study conducted for ASSMCA in 2013 to inform expansion of MAT with methadone reveals overly restrictive practices in spite of patient needs that hinder expansion of take homes and the establishment of medication and mobile dispensing units to satisfy demand for services and improve geographic access for a large number of current participants (49). A large proportion of patients have to travel daily more than an hour to reach their treatment site. Efforts need to be expanded to improve client-centered, accessible services to close the current treatment gap, including use of mobile units that are known to enhance retention of patients in treatment (50).

Public Health Surveillance

1) Recognize the need to invest in the surveillance of hepatitis C as an essential tool to guide prevention efforts. This information will be useful to monitor trends in the prevalence of and risk factors for HCV infection, identify infected persons and link them to care and treatment, and support the development and ongoing evaluation of programs and policies to prevent hepatitis C and minimize its public health impact. Currently, the CDC estimate that approximately 10% of the new cases of hepatitis C and only two-thirds of cases of chronic HCV are reported through the National Notifiable Disease Surveillance System (51). To achieve the essential function of hepatitis C surveillance, the combination of different sources of information will be required due to the limitations of diagnostic tests for hepatitis C, the asymptomatic nature of the disease, and the time between infection and disease diagnosis.

2) Continue to promote hepatitis C reporting among health professionals, hospitals, and laboratories to ensure accurate reporting of all cases of hepatitis C to the Puerto Rico Department of Health.

Research

1) Design periodic serosurveys in the general population and high-risk populations to estimate the seroprevalence of hepatitis C, monitor risk behaviors, and assess health disparities.

2) Develop and evaluate evidence-based interventions that reduce hepatitis C incidence or risk behaviors.

3) Continue to promote the participation of patients with chronic hepatitis C in clinical trials to understand the impact of new antiviral therapies in our patient population.

Public Health advocacy and Policy

1) Build a Hepatitis C task force comprised of field experts, specialists in hepatology, infectious disease, and substance use disorders, primary care physicians, public health officers, community-based organizations, and affected communities, to guide prevention efforts and advocate for federal and non-federal funds to coordinate and implement an action plan for the prevention and control of hepatitis C.

2) Implement the Patient Protection and Affordable Care Act to expand coverage of commercial health plans and the government insurance plan (*Mi Salud* coverage) for the treatment and management of complications of chronic hepatitis C including liver transplantation.

Conclusions

Because there is currently no vaccine to prevent HCV infection, it is imperative to ensure that state and local authorities allocate fiscal resources required to establish surveillance, prevention, management, and medical management of hepatitis C as a public health priority in Puerto Rico. Governmental agencies and major stakeholders are urged to mount an adequate response to hepatitis C by transforming current scientific evidence into public health actions to increase awareness, identify those who are actively infected, and link them into comprehensive care and treatment.

Resumen

En la última década, investigadores y especialistas de la hepatitis C en Puerto Rico han hecho un llamado a las agencias pertinentes para aumentar la concienciación sobre este problema de salud pública e implantar estrategias de prevención y control; sin embargo, los esfuerzos dirigidos a combatir la hepatitis C han sido infructuosos hasta la fecha. Los estudios poblacionales sobre hepatitis C han documentado que el factor de riesgo principal es el uso compartido de equipo contaminado para la inyección de drogas, que la mayoría de las personas infectadas desconocen su estado de infección, y que el conocimiento sobre la enfermedad, sus factores de riesgo y las medidas de prevención y control es limitada en la población general. El tema se complica aún más por el hecho de que a pesar de que la hepatitis C es una enfermedad de declaración obligatoria, no existe un sistema de vigilancia

epidemiológico efectivo que suministre la información necesaria para la planificación, la implantación, el monitoreo y la evaluación de estrategias de intervención para esta infección y el acceso a la terapia farmacológica vigente es limitado. Este documento describe las disparidades en la hepatitis C y los eventos adversos relacionados experimentados por los puertorriqueños e intenta establecer estrategias para el abordaje de una respuesta de salud pública para la hepatitis C, enfatizando los niveles meso y macro del modelo socio-ecológico. Se insta a las diversas organizaciones y las partes interesadas a desarrollar una respuesta adecuada para la hepatitis C mediante la transformación de la evidencia científica acumulada en acciones de salud pública para aumentar el conocimiento, identificar personas con infección activa y vincular a las personas infectadas a la atención y el tratamiento integral.

Acknowledgments

The authors would like to thank Dr. Erick Suárez, Dr. Juan Carlos Reyes, Dr. María del Carmen Santos, Dr. Adelaida Ortiz, Dr. Jorge Santana, Dr. Rafael Pastrana, Dr. Marcia Cruz, Dr. Federico Rodríguez, Dr. Doris Toro, and Dr. Ángel Mayor for their critical reading and valuable comments of an early draft of the manuscript.

References

- National Institutes of Health Consensus Development Conference. Management of Hepatitis C. *Hepatology* 2002;36: S3-20.
- Centers for Disease Control and Prevention. Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease. *Morbidity and Mortality Weekly Report* 1998;47:1-39.
- Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012;61:(RR-4) 1-32.
- Denniston MM, Jiles RB, Drobeniuc J, Klevens M, Ward JW, McQuillan GM, Holmberg SD. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* 2014;160:293-300.
- Chak E, Tlal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: An estimate of true prevalence. *Liver Int* 2011;31: 1090-1101.
- Kuniholm MH, Jung M, Everhart JE, Cotler S, Heiss G, McQuillan G, Kim RS, Strickler HD, Thyagarajan B, Youngblood M, Kaplan RC, Ho GY. Prevalence of hepatitis C virus infection in US Hispanic/Latino adults: results from the NHANES 2007-2010 and HCHS/SOL studies. *J Infect Dis* 2014;209:1585-1590.
- Ly KM, Xing J, Klevens M, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012;156:271-278.
- Davis GL, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV of prevalence and disease progression. *Gastroenterol* 2010;138: 513-521.
- Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013;368:34-44.
- Cammà C, Petta S, Cabibbo G, Ruggeri M, Enea M, Bruno R, Capursi V, Gasbarrini A, Alberti A, Craxi A; WEF Study Group. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. *J Hepatol* 2013;59:658-66.
- Cammà C, Petta S, Enea M, Bruno R, Bronte F, Capursi V, Cicchetti A, Colombo GL, Di Marco V, Gasbarrini A, Craxi A; WEF Study Group. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. *Hepatology* 2012;56:850-860.
- Sulkowski MS, Naggie S, Lalezari J, Fessel WJ, Mounzer K, Shuhart M, Luetkemeyer AF, Asmuth D, Gaggar A, Ni L, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Rodriguez-Torres M, Dieterich D; PHOTON-1 Investigators. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA* 2014;312:353-61.
- Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott J, Peeters M, Lenz O, Ouwkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): A randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014;384:414-26.
- World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. World Health Organization, 2014. Available at: <http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/>. Accessed on May 2014.
- Martínez J, Rubio C, Ohárriz JJ, et al. Hepatitis C Antibody in Healthy Puerto Rican Blood Donors: Prevalence, Hepatic Functional and Histological Abnormalities. *Bol Asoc Med PR* 1992;84:94-96.
- López-Navedo PJ, Lebrón-Rivera R, González-Trápaga J, et al. Prevalence of hepatitis C virus infection at three hemodialysis units in the western region of Puerto Rico. *Bol Asoc Med P R* 1999;91:100-102.
- Pérez CM, Suárez E, Torres EA, Román K, Colón V. Seroprevalence of Hepatitis C Virus and Associated Risk Behaviors: A Population-Based Study in San Juan, Puerto Rico. *Int J Epidemiol* 2005;34:593-599.
- Pérez CM, Marrero E, Meléndez M, Adrovet S, Colón H, Ortiz AP, Soto-Salgado M, Albizu C, Torres EA, Suárez E. Seroepidemiology of viral hepatitis, HIV, and herpes simplex type 2 in the household population aged 21-64 years in Puerto Rico. *BMC Infect Dis* 2010;10:76.
- Soto-Salgado M, Suárez E, Ortiz AP, Adrovet S, Marrero E, Meléndez M, Colón HM, Albizu C, Santos MD, Torres E, Pérez CM. Knowledge of viral hepatitis among Puerto Rican Adults: Implications for Prevention. *J Community Health* 2011;36:565-573.
- Departamento de Salud, Secretaría Auxiliar de Planificación y Desarrollo, División de Análisis Estadístico. Boletín de Mortalidad: 2009 y 2010. San Juan, Puerto Rico, 2012.
- Rivera-Méndez E, Díaz Miranda OL, Arroyo Quijano CA, Torres E, Pérez N, Ortiz-Ortiz K, Ortiz AP. Cáncer hepático en Puerto Rico. Registro Central de Cáncer, Centro Comprensivo de Cáncer Universidad de Puerto Rico. Vol. 5 (1), Junio 2012.
- Pérez CM, Albizu C, Peña M, Torres EA, Reyes JC, Colón H, Ortiz AP, Suárez E. Hepatitis C in Puerto Rico: A time for public health action. *PR Health Sci J* 2007;26:339-344.
- Departamento de Salud. Salud de la población correccional en Puerto Rico: Año 2010. Secretaría Auxiliar de Planificación y Desarrollo, San Juan, Puerto Rico, 2013.
- Thomas DL, Leoutsakas D, Zabransky T, Kumar MS. Hepatitis C in HIV-infected individuals: Cure and control, right now. *J Int AIDS Soc* 2011;14:22.
- Centers for Disease Control and Prevention. Rates of diagnoses of HIV infection among adults and adolescents, by area of residence, 2011—United States and 6 dependent areas. *HIV Surveillance Report* 2011. Available at: <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/>. Accessed August 27, 2013.
- Reyes JC, Colón HM, Robles RR, Ríos E, Matos TD, Negrón J, Marrero CA, Calderón JM, Shepard E. Prevalence and correlates of hepatitis C virus infection among street-recruited injection drug users in San Juan, Puerto Rico. *J Urban Health* 2006;83:1105-1113.
- Deren S, Robles R, Andia J, Colón HM, Kang SY, Perlis T. Trends in HIV seroprevalence and needle sharing among Puerto Rican drug injectors in Puerto Rico and New York: 1992-1999. *J Acquir Immune Defic Syndr* 2001;26:164-169.

28. Colón HM, Robles RR, Deren S et al. Between-city variation in frequency of injection among Puerto Rican injection drug users: East Harlem, New York, and Bayamón, Puerto Rico. *J Acquir Immune Defic Syndr* 2001;27:405-413.
29. Deren S, Kang SY, Colón HM et al. Migration and HIV risk behaviors: Puerto Rican drug injectors in New York City and Puerto Rico. *Am J Public Health* 2003;93:812-816.
30. Deren S, Kang SY, Colón HM, Andía JF, Robles RR. HIV incidence among high-risk Puerto Rican drug users: A comparison of East Harlem, New York and Bayamón, Puerto Rico. *J Acquir Immune Defic Syndr* 2004;36:1067-1074.
31. Robles RR, Matos TD, Colón HM et al. Determinants of health care use among Puerto Rican drug users in Puerto Rico and New York City. *Clin Infect Dis* 2003;37:S392-S403.
32. Robles RR, Colón HM, Matos TD, Finlison HA, Muñoz A, Marrero CA, García M, Reyes JC. Syringe and needle exchange as HIV/AIDS prevention for injection drug users in Puerto Rico. *Health Policy* 1998;45:209-220.
33. Centers for Disease Control and Prevention (CDC). Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the U.S. Department of Health and Human Services. *MMWR Recomm Rep* 2012;61(RR-5):1-40.
34. Academy for Educational Development. A comprehensive approach: Preventing blood-borne infections among injection drug users. Available at: <http://www.cdc.gov/idu/pubs/ca/comprehensive-approach.htm>. Accessed May 1, 2015.
35. Reyes JC, Colón HM. Puerto Rico Mental Health and Anti-Addiction Services Administration. Puerto Rico Substance Abuse Needs Assessment Program: 2008 Household Study Final Results. San Juan, 2009.
36. Division of Viral Hepatitis, National Center for Infectious Diseases, Centers for Disease Control and Prevention. National Hepatitis C Prevention Strategy: A Comprehensive Strategy for the Prevention and Control of Hepatitis C Virus Infection and its Consequences, Summer 2001.
37. Institute of Medicine. Hepatitis and liver cancer: A national strategy for prevention and control of hepatitis B and C. Washington, DC: National Academy Press, 2010.
38. US Department of Human and Health Services. Combating the silent epidemic of viral hepatitis: Action plan for the prevention, care & treatment of viral hepatitis. May 12, 2011. Available at: <http://www.hhs.gov/ash/initiatives/hepatitis/> Accessed May 2011.
39. National Alliance of State and Territorial AIDS Directors. The Affordable Care Act and the silent epidemic: Increasing the viral hepatitis response through health reform. March 2013. Available at: <http://nastad.org/docs/Primer-ACA-Hepatitis-March-2013.pdf>. Accessed on June 2014.
40. US Department of Human and Health Services. Combating the silent epidemic of viral hepatitis: Action plan for the prevention, care & treatment of viral hepatitis – Updated, 2014-2016. Available at: <http://aids.gov/pdf/viral-hepatitis-action-plan.pdf/> Accessed May 2014.
41. World Health Organization. Prevention & Control of Viral Hepatitis Infection: Framework for Global Action. World Health Organization, Geneva, 2012. Available at: <http://www.who.int/csr/disease/hepatitis/Framework/en/>, Accessed May 2014.
42. Stokols D. Translating social ecological theory into guidelines for community health promotion. *Am J Health Promotion* 1996;10:282-298.
43. Deren S, Gelpí-Acosta C, Albizu-García CE, González Á, Des Jarlais DC, Santiago-Negrón S. Addressing the HIV/AIDS epidemic among Puerto Rican people who inject drugs: the need for a multiregion approach. *Am J Public Health* 2014;104:2030-2036.
44. Garfein RS, Golub ET, Greenberg AE, Hagan H, Hanson DL, Hudson SM, Kapadia F, Latka MH, Ouellet LJ, Purcell DW, Strathdee SA, Thiede H; DUIT Study Team. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. *AIDS* 2007;21:1923-1932.
45. Friedman SR, Cooper HLF, Osborne AH. Structural and social contexts of HIV risk among African Americans. *Am J Public Health* 2009;99:1002-1008.
46. Albizu-García CE, Caraballo JN, Caraballo-Correa G, Santiago S, Méndez A, Rivera-Suazo S. Assessing stigma towards drug users among health care providers. Poster presentation at the 2014 College of Problems in Drug Dependence Conference, San Juan, Puerto Rico.
47. Buffington J, Jones TS. Integrating viral hepatitis prevention into public health programs serving people at high risk for infection: Good public health. *Public Health Rep* 2007;122 Suppl 2:1-5.
48. Substance Abuse and Mental Health Services Administration. The ADSS cost study: Costs of substance abuse treatment in the specialty sector. Office of Applied Studies, DHHS Publication No. SMA 03-3762, Analytic Series A-20. Rockville, MD, 2003.
49. Alvarado R, Lugo M, Serra M, Rodríguez-Adames J, Conde A, Quiñones V, Melecio R, Ayala G, Albizu-García CE. Aceptabilidad de Expansión de Dispensación "take home" (TH) entre Participantes y Proveedores de Centros de Tratamiento Integral Asistido por Medicamentos (CTIAM) de San Juan y Bayamón de ASSMCA. August 22, 2013, Final Report to ASSMCA of study conducted as requirement for EVAL 6650: Practicum in Health Services Evaluation. Graduate School of Public Health, University of Puerto Rico.
50. Greenfield L, Brady JV, Besteman KJ, et al. Patient retention in mobile and fixed-site methadone maintenance treatment. *Drug and Alcohol Dependence* 1996;42:125-131.
51. Ward JW, Valdiserri RO, Koh HK. Hepatitis C virus prevention, care, and treatment: From policy to practice. *Clin Infect Dis* 2012;55(Suppl 1):S58-S63.