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The Challenges of Hepatitis B Treatment in the US-Associated Pacific Islands

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In 1993, the Medical School Hotline was founded by Satoru Izutsu PhD (former vice-dean UH JABSOM), it is a monthly column from the University of Hawai'i John A. Burns School of Medicine and is edited by Kathleen Kihmm Connolly PhD; HJH&SW Contributing Editor.

The Challenges of Hepatitis B Treatment in the US-Associated Pacific Islands

Instituting hepatitis B therapy in a low-resource Pacific Island setting is challenging. During 2018, members of the University of Hawai'i Department of Family Medicine and Community Health (DFMCH) participated in the "Tuberculosis (TB) and Leprosy Free Majuro" campaign in the Republic of the Marshall Islands (RMI) to identify and treat people with TB and Hansen's disease (formerly called leprosy).¹ The question of how to institute a vertical hepatitis B elimination program that dovetails with strengthening the primary health care system was highlighted. In this discussion, parallels are drawn with how treatment became available for HIV/AIDS and hepatitis C, two other viral diseases for which there was at one time no political will to treat in resource-poor settings.

Hepatitis B in the Marshall Islands

A 2009 study estimated that Marshallese women who are older than 30 years have a very high hepatitis B surface antigen (HBsAg, indicative of chronic infection with the virus) prevalence of 9.5%.² Since hepatitis B is mostly transmitted by vertical, mother-to-child transmission or early in childhood, boys and girls are equally likely to contract hepatitis B (and therefore develop chronic hepatitis B), thus the prevalence in men is likely similar. Because newborn vaccination against hepatitis B started in the late 1980s, the prevalence is lower in those under 30 years old. Although alcohol is used by a minority of the population (19.3%), there is a greater frequency of drinking among men and those younger than 44. Additionally, those who drink often engage in heavy, episodic drinking even at early ages.³ In Micronesia, chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma,^{4,5} are primarily driven by hepatitis B.

TB and Leprosy Free Majuro

The intent of the TB and Leprosy Free Majuro campaign was to attempt to reach the entire population of Majuro, the capital

atoll of the Republic of the Marshall Islands. The initial screening sites, located in the population center, were two elementary schools, which were not in session during the summer. A mobile screening site was later set up for more distant populations. For those about to receive treatment for latent TB infection (LTBI), a screening algorithm for individuals at risk of underlying undiagnosed hepatitis B was instituted with blood testing for transaminases on patients 40 years or older and those with significant alcohol consumption (the definition of "significant" being up to the prescriber). Elevated transaminases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), indicate ongoing hepatocellular damage from liver diseases such as alcohol and hepatitis B. Patients who met campaign criteria for a diagnosis of LTBI were started on LTBI medications the same day and instructed to go to Majuro Hospital for venipuncture. Those with AST or ALT greater than 80 units per liter, approximately twice the upper limit of normal, would have further testing for hepatitis B surface antigen (the only hepatitis B serology available at Majuro Hospital).

Although Hepatitis B was not a focus of the TB and Leprosy Free Majuro campaign, there were concerns that the isoniazid and rifapentene that were planned to be dispensed to about 7000 individuals with LTBI would precipitate liver toxicity and contribute to liver failure in vulnerable individuals with underlying undiagnosed chronic hepatitis B infection. Such an adverse outcome would violate the ethical precept *primum non nocere* (first, do no harm) and tarnish the image of an overburdened public health system. Additionally, given the history of exploitation and unethical medical testing by American physicians in the Marshall Islands in the years after World War II,^{6,7} it was imperative to protect all screening participants from unintended, iatrogenic harm.

During the 6-month campaign, no known cases of severe hepatotoxicity, requiring intensive care admission and support, occurred.

Hepatitis B Care in the Marshall Islands

The RMI Ministry of Health (RMI MOH) continues to make an effort to universally vaccinate infants against hepatitis B (the primary measure to prevent mother-to-child transmission) despite logistical challenges. Health care workers must periodically travel by boat to remote atolls to reach patients. As a secondary preventive measure, hepatitis B immune globulin (HBIG) is administered to infants born to mothers with hepatitis B to bind to any circulating virus.

There is no systematic screening of adults for hepatitis B in the Marshall Islands, despite the high prevalence of chronic hepatitis B infection. Antiviral medications for hepatitis B remain prohibitively expensive, thereby limiting access for the developing small island nation. The formal government off-island referral system sends most patients to the Philippines. Because of the high costs of such referrals, policy limits these referrals to only those patients with a predicted >50% survival after 5 years. Thus, patients who develop complications such as liver failure or hepatoma generally do not receive referral under the formal system. For those who need antiviral treatment, the only alternative for many patients is to migrate to the US. However, health insurance coverage is difficult to obtain for such migrants.⁸

Global Health Equity – Who Qualifies? Which Diseases Qualify?

To draw lessons for expanding hepatitis B treatment, the history of how treatment became available for HIV/AIDS and hepatitis C is reviewed. These are two viral diseases, which at one time were not being treated in resource-poor settings. Hepatitis B is in the phase of neglect that these other diseases were once in prior to the more widespread availability of treatment.

HIV/AIDS

While Highly Active Antiretroviral Therapy (HAART) for HIV/AIDS became available in 1996, it was initially deemed too complicated and too expensive to treat individuals in low-resource settings. In the early 2000s, Médecins Sans Frontières (MSF) and Partners in Health (PIH) demonstrated that therapy could indeed be delivered. Paul Farmer's address at the 14th International AIDS Conference in Barcelona in 2002 was pivotal.⁹ This was followed by the President's Emergency Plan for AIDS Relief (PEPFAR), which was announced in January 2003, with \$15 billion pledged to fight HIV/AIDS over 5 years; and the Global Fund to Fight AIDS, TB, and Malaria, with pledges of \$4.8 billion by 2004.

Political pressure from mobilized people and activists, notably people living with HIV/AIDS (PLWHA), and deaths among some prominent individuals, led to these funding decisions by the governments of developed countries. In addition, pharmaceutical

corporations were pressured to allow generic HIV medications to be manufactured and distributed. Thus, even today, people with HIV/AIDS continue to be relatively well-supported. The RMI, with a vanishingly small number of people living with HIV, has a stock of antiretroviral medications supplied by the United Nations Development Programme (UNDP), and receives regular continuing education from the AIDS Education & Training Center.

Hepatitis C

Although a long political struggle was necessary to pressure pharmaceutical corporations on intellectual property rights in order to allow access to antiretroviral drugs for HIV, the recent treatment program implemented in Egypt is an example of access to modern hepatitis C antivirals progressing rather rapidly.

While hepatitis C therapy was spectacularly expensive in the US, in 2015, the Egyptian government made a deal with a pharmaceutical corporation to offer a treatment course that costs the government \$900, and comes at no cost to the patient. Gilead Sciences provides sofosbuvir (used in combination with other antivirals) to the Egyptian government at prices that make it affordable for Egyptians to be treated for hepatitis C. At this time (2015) a treatment course in the US cost \$84,000;¹⁰ a newer therapy currently cost \$27,580.¹¹ Of note, the effective treatment of hepatitis C leads to cure of the infection.

Implications for hepatitis B

Over the past two decades, the treatment of hepatitis B has progressed such that effective oral medications are now available. As with HIV, the treatment must be ongoing, with most patients needing lifelong therapy. In fact, one of the hepatitis B medications (tenofovir) is also an HIV medication. Ironically, in the Marshall Islands, it is available for HIV, but not for hepatitis B. Thus, when market mechanisms fail, public policy must ensure the delivery of life-saving medications to those who need them. The history of advocacy for HIV treatment serves as a reminder that advocacy for hepatitis B treatment is needed.

Comprehensive or Selective Primary Health Care?

In 1987, at the Joint WHO/UNICEF Conference in Alma-Ata, USSR (now Almaty, Kazakhstan), the Declaration on Primary Health Care (PHC) called for health systems to strive to be practical, scientifically sound, socially acceptable, universally accessible, and affordable. This vision of comprehensive PHC was viewed by some quarters of the international development community as too expensive and disruptive to the established world order. PHC was thus undermined by calls for "Selective Primary Health Care" (SPHC),¹² a rubric emphasizing directing resources toward specific diseases with high prevalence, morbidity, and mortality, and established means of control. SPHC thus

emphasized vertical programs and technical solutions. Among such programs were infant vaccinations, breast-feeding, malaria treatment, and oral rehydration packets.

SPHC is alive and well today in the RMI. Within public health, departments are organized along funding lines from the US Centers for Disease Control and Prevention. Meanwhile, the hospitals (Majuro Hospital and Lerioj Kitlang Hospital in Ebeye, the second population center) and their staffs are supported by the Department of the Interior. Thus, at the national level, TB services are separate from Non-Communicable Disease (NCD) services. NCD is part of public health and is separate from the Outpatient Department. The “TB and Leprosy Free Majuro” campaign, while a temporary project, was a vertical program that drew upon the resources, human and material, of the formal health services of the RMI.

Human Resources for Health

One problem with the proliferation of vertical programs is the scarcity of human resources for health in a setting like the Marshall Islands. The RMI is unable to produce enough health care workers to serve its population. The majority of physicians practicing in the RMI are international medical graduates, mostly from the Philippines.

With each vertical program introduced into the RMI, a number of physicians and administrators are drawn away from caring for the general medical needs of the populace. Each program has its own reporting mechanisms and requirements, sometimes requiring off-island travel. What is needed is a hepatitis B program that does not negatively affect and further burden the already strained primary care system.

The “TB and Leprosy Free” campaigns of 2017-2018 in the RMI tried to minimize the number of health care personnel drawn from other programs by bringing in expatriate workers. Nonetheless, the sizable cost of providing travel, food, and lodging to rotating teams of American volunteers to support the campaigns was primarily borne by the RMI government. Despite early signs of success in screening the majority of the urban Marshallese population for TB, large-scale, short-term, capital-intensive interventions like this would not be appropriate to address hepatitis B in the RMI. With a HBsAg prevalence of 9 to 10% in those over age 30, a program of hepatitis B screening and treatment at the next clinic or hospital encounter makes more sense.

Conclusion

Hepatitis B does not have a specific home within the RMI health system and continues to be a neglected disease with

high burden. The DFMCH’s involvement in mass TB and leprosy screenings raised ethical and clinical concerns over the potential unintended negative consequences of the intervention. Additionally, large-scale interventions such as these are not appropriate solutions for all public health concerns — and they are no replacement for robust, integrative primary health care systems. The historical trend in global health since Alma Ata has been a consistent shift away from primary health care towards top-down, donor-driven, and market-based vertical programming. As a consequence, low-resource countries like the RMI have little support to develop integrated services necessary for effective primary health care. Instead, the RMI remains reliant on US donor priorities and expensive off-island referrals.

As strategies are formulated to improve hepatitis B services in places like the RMI, plans should be explicit on how to make hepatitis B screening and care an integral part of comprehensive primary care. People living with hepatitis B and their allies in medicine and public health need to advocate for public policy to lower cost and make hepatitis B medications more widely available. It should be ensured that hepatitis B care does not draw financial or human resources away from the primary care system. Doing so supports an on-going commitment towards greater health equity across the globe, including the far-flung atolls of the Marshall Islands.

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