Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2018;20:236-239

Hot News

Hepatitis Delta Could Be More Frequent than Previously Thought

HDV is a unique defective agent that only infects humans and requires the presence of hepatitis B to complete its life replication cycle within hepatocytes. Accordingly, hepatitis delta is believed to occur exclusively in serum HBsAg+ individuals. Indeed, it has not been recognized in patients with resolved hepatitis B (*Aguilera* et al. *Eur J Gastroenterol Hepatol. 2018;30:1063-5*).

Hepatitis delta produces the most severe form of chronic viral hepatitis, with more rapid progression to cirrhosis and liver cancer than hepatitis B alone or hepatitis C. Furthermore, in contrast with successful antiviral therapies to treat HBV or HCV, to date, there is no efficacious treatment for hepatitis delta, although some experimental drugs including lonafarnib, REP-2139, and myrcludex will soon be tested in Phase 3 clinical trials (*Soriano* et al. *J Infect Dis. 2018;217:1173-6; Wedemeyer* et al., *Gut, In Press*).

Older studies suggested that the global rate of hepatitis delta was around 5% among HBsAg+ carriers, with absolute figures of 15-20 million people infected worldwide. However, a recent meta-analysis has concluded that roughly 15% of HBsAg+ carriers are seroprevalent for HDV (*Chen* et al., *Gut, In Press*). Given that, estimates for HBsAg+ carriers have been updated to 300 million people (*POLARIS Collaborators. Lancet Gastroenterol Hepatol. 2018;3:383-403*), the authors claimed that absolute numbers for the global burden of hepatitis delta nowadays would be > 60 million people.

Africa, the Amazon Basin, Eastern and Mediterranean Europe, Middle East, and parts of Asia (i.e., Iran and Mongolia) exhibit the highest rates of HDV carriage. Moreover, injection drug users and in less extent individuals with high-risk sexual behaviors, especially men having sex with men, display greater HDV rates than other HBsAg+ individuals (37%, 17% and 10%, respectively). The meta-analysis also confirmed prior findings about the increased rate of hepatitis delta in the HIV population (*Soriano* et al. *AIDS. 2017;31:875-84*).

Chen et al. acknowledged that HDV prevalence has ceased to decline and has even increased in Western Europe, in association with recent large waves of immigration from highly HDV endemic regions. Based on their data, the authors concluded that anti-HDV screening of all HBsAg+ individuals must be mandatory everywhere and that universal HBV vaccination must be further expanded.

Jose V. Fernandez-Montero[1] and Vicente Soriano[2]
[1]Department of Infectious Diseases, University Hospital Crosshouse, Kilmarnock, UK; [2]UNIR Health Sciences School and La Paz University Hospital Madrid, Spain

Longer Life Expectancy but still Accelerating Aging in HIV Patients under Antiretroviral Therapy

The current goal of HIV treatment is sustained undetectable plasma viremia. This aim is generally associated with good CD4 counts and the absence of opportunistic diseases. Recent advances in antiviral drug development allow to achieve this objective taking one single pill once daily in most HIV patients. Not surprisingly, life expectancy in treated HIV persons is approaching that of uninfected matched controls. However, in the absence of eradication, residual viral replication seems to keep elevated the inflammatory phenomena and immune activation that ultimately lead to increased rates of cardiovascular events, cancers and neurocognitive impairment, and among other age-related illnesses (*Stoff* et al. *Curr HIV/AIDS Rep 2017;14:184-199*). Estimating the extent of the disconnect between biological and chronological age has been a challenge to date.

At the Longevity World Forum (www.longevityworldforum.com), held in Valencia on November 2018, telomere lengths and epigenetic changes were proposed for monitoring aging. Thomas Stubbs (www.chronomics.com) reported that the extent of DNA methylation in saliva samples could represent an easy to take an accurate biomarker for aging estimates (*Stubbs* et al. *Genom Biol 2017;18:68*). Hypothetically, in HIV-infected individuals under successful antiretroviral therapy, this testing could inform about the extent of accelerating aging in a given patient comparing the biological estimate and his chronological age. In HIV+ individuals with the worst profiles, interventions for earlier diagnosis of age-related illnesses and preventive measures might be considered.

Given that genetics plays an important role in the most prevalent diseases of the elderly and the cost of human whole genome sequencing has drop significantly during the last couple of years, is it time to move HIV patients into precision medicine? Manuel Corpas (www.cambridgeprecisionmedicine.com), chair of the conference, emphasized that the road for personalized medicine is highly dependent on the inclusion of genomic information into the clinical management of each patient. Along with family history and lifestyle, knowledge of individual gene variants would allow risk prediction for many diseases (*Reyes-Palomares* et al. *BMC Genom 2016;17:232*). Nowadays, the major challenge is the interpretation of genome data rather than the collection of high-quality whole genome sequences.

Pharmacogenomics would be a particularly important application of whole genome sequencing in HIV+ patients, as polypharmacy is frequent in this population and would be even more frequent as subjects become older. Along with information on drug interactions for antiretrovirals, which is accessible at several websites (i.e., www.hiv-druginteractions.org), advice for drug avoidance or dosing changes should also consider gene variants involved in hypersensitivity reactions and/or processes of (absorption, distribution, metabolism, and excretion). Several companies are developing software (i.e., g-Nomic, www.eugenomic.com) that integrate information from both drug interactions and pharmacogenomics for predicting drug exposure and assist clinicians in drug prescription more wisely in a given patient, to optimize treatments and avoid drug-related side effects.

Testing individual's whole genome following saliva collection currently may cost < 1000 dollars and is expected to become cheaper. Growing evidence supports that genomic information should be part of the clinical chart for each patient. Consideration of genetics may improve prevention and treatment management at the individual level, which is the goal of precision medicine, the most optimal way to provide health care to distinct persons.

Vicente Soriano and Octavio Corral
UNIR Health Sciences School Madrid, Spain

Hepatitis E Virus, the Uninvited Intruder in Western Kitchens

Hepatitis E virus (HEV) has been known since the early 1980s as a cause of epidemic acute hepatitis of orofecal transmission in developing countries, mostly in Africa and Eastern Asia. In the past years, we have learned that this agent may also be cause of this self-limited clinical picture in Western countries (in Europe, North America, or Japan), and even become chronic in patients with underlying immunodepression, as those HIV infected. For this reason, the European Association for the Study of Liver Diseases (EASLD) has recently released its clinical practice guidelines on HEV infection (*EASLD. Clinical Practice Guidelines on HEV Infection. J Hepatol 2018;68:1256-1271*).

While HEV genotypes 1 and 2 have humans are only hosts, and responsible of waterborne epidemics in developing countries, HEV genotypes 3 and 4 have been identified as the zoonotic cause of human infection after ingestion of products from diverse mammals (mainly pigs, but also boar, deer, etc.). To date, it is estimated that up to 2 million people catch HEV infection every year in Europe. People working in the food chain of potentially infected animals are at high risk, but also wherever pork is consumed in the form of undercooked sausages, particularly if they contain pork liver (i.e., French figatellu). Waterborne infection is possible if stool from infected animals cause contamination of the environment. Human to human HEV transmission has not been documented in Western countries. Hotspots of HEV infection in Europe are southwest France, the Netherlands, Scotland, western Germany, Czech Republic, central Italy, and western/central Poland. Surprisingly enough other countries as Spain or Portugal with frequent use of pork products as part of traditional cuisine have much lower HEV seroprevalence (*Horn et al. Epidemiologic estimates of HEV infection in European countries. Infect 2018 [in press)]*).

Although acute genotype 3 hepatitis E is only symptomatic in 5% of the cases, today this is the leading cause of viral hepatitis in Western countries, ahead of acute hepatitis A or B. While usually self-limited, severe acute hepatitis E is more frequent in older patients, those with chronic liver conditions (i.e., steatosis, alcohol abuse, and chronic viral hepatitis) or in pregnant women. Of note HEV reinfection is possible, although subsequent exposures are usually more benign.

Genotype 3 and 4 HEV infection may remain chronic in subjects with immune compromise. The most common cases are subjects under immune suppressive therapy after organ transplantation or those with HIV infection and CD4 counts below 200 cells/μL. Of note, progression to advance liver fibrosis or overt cirrhosis may just take a few years in this scenario of chronic viral hepatitis plus depressed immunity.

While treatment of acute hepatitis E is merely symptomatic, in case of chronic infection viral eradication

should be pursued to prevent further liver damage. If possible, immunity should be improved, by optimizing antiretroviral therapy in case of HIV infection or by reducing the dose of immunosuppressive therapy in case of organ transplantation. In addition, several studies have proven that around 12 weeks of ribavirin, pegylated-interferon, or both may achieve HEV eradication.

In summary, genotype 3 HEV has become a leading cause of acute hepatitis in Western countries. Food precautions are the best mean of prevention, and avoidance of undercooked pork products should be advised in pregnant women, individuals with chronic liver conditions or those with severe immune compromise, HIV-infected patients included.

Pablo Barreiro
Hospital Carlos III- La Paz Madrid, Spain

Should HIV Patients be concerned about Occult Hepatitis B?

In HIV disease, infection is universally followed by chronification, and therefore, recognition of anti-HIV antibodies always reflects HIV persistence. In hepatitis B, chronic infection was thought to be reliably picked-up by detecting serum hepatitis B virus surface antigen (HBsAg). However, this view has been challenged following a better understanding of the virus life cycle and reports of episodes of hepatitis B virus (HBV) reactivation and transmission from individuals with negative serum HBsAg. This so-called occult B infection (OBI) has attracted so much attention that the European Association for the Study of the Liver endorsed one special workshop on October 1-2, 2018, in Taormina, Italy, to address this topic. Herein, we highlight aspects with especial relevance for the HIV population.

Exposure to HBV is followed by the development of acute hepatitis B, which can be clinically symptomatic or not. In adults, most HBV infections occur following sexual exposure and are self-limited with the development of anti-hepatitis B core (HBc) and anti-HBs. In contrast, in endemic regions, mother-to-child transmission of HBV is common and most newborns progress to chronicity, defined by the persistence of serum HBsAg. Among individuals with chronic HBV infection who are untreated, lifelong 15-30% will progress to cirrhosis, which may lead to liver failure and/or hepatocellular carcinoma.

In between chronic and resolved HBV infection, individuals with OBI enter an HBsAg-negative phase characterized by fluctuating low-level serum HBV-DNA. Most exhibit anti-HBc and occasionally anti-HBs. Although the risk for liver disease in this population is very low, they may experience overt HBV reactivation under immunosuppression. Furthermore, OBI donors may transmit HBV following blood transfusions and organ transplantation (*Candotti* et al*., Gut, In Press*). Considering OBI as an additional phase in the natural history of HBV infection is important. As shown in figure 1, roughly 2 of 7.7 billion people living in the world have been infected with HBV. Of them, the majority has developed apparent immunity and 290 million are chronic HBsAg+ carriers (*POLARIS. Lancet Gastroenterol Hepatol. 2018;3:383-403*).

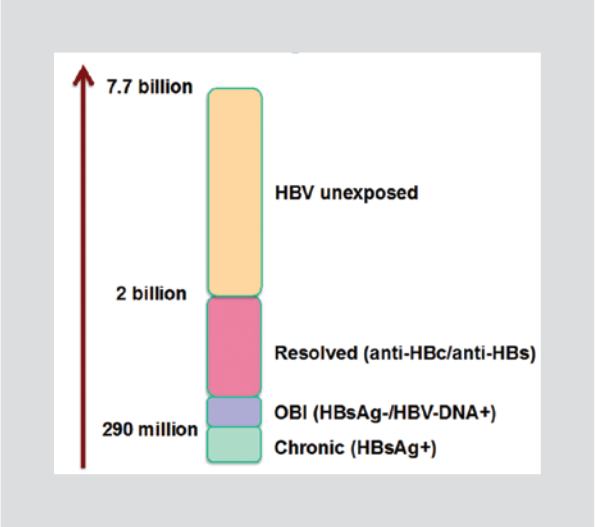

Figure 1. *Worldwide population according to hepatitis B virus status.*

A clear distinction between OBI and resolved hepatitis B cannot be made since detection of HBV-DNA might hypothetically be possible in all individuals once infected with HBV, following HBsAg clearance from their serum. Hence, the number of persons with possible OBI might be huge (up to 2 billion!). Accordingly, increased sensitivity of the newest HBV-DNA diagnostic tests and repeated testing over time is already unveiling larger OBI populations.

Efforts for diagnosing OBI in any given person are justified based on the risk for developing clinical complications. Liver disease in OBI patients has been extensively evaluated, with slightly increased risk for both cirrhosis and liver cancer (*Pollicino* et al. *J Hepatol. 2014;61:688-9*). More recently, the interest has shifted to explore whether OBI could support hepatitis delta virus (HDV) superinfection, given the severity of delta hepatitis, 10% rate among HBsAg+ carriers and claims of a sort of independent HDV persistence in the liver. Preliminary findings, however, suggest that delta hepatitis does not exist in the absence of serum HBsAg in

patients with resolved hepatitis B (*Aguilera* et al. *Eur J Gastroenterol Hepatol. 2018;30:1063-5*).

Given the shared transmission routes for HIV and HBV and the immune impairment produced by HIV, initial reports claimed that OBI was more frequent in AIDS patients. By contrast, the current scenario shows that OBI is negligible in the HIV population. One explanation is that HBV immunization and recall vaccination campaigns have been very active in this group. A second and most important reason points out to the wide use of antiretroviral regimens that include anti-HBV active agents, that is, tenofovir, lamivudine, and/or emtricitabine. They are recommended either as the treatment for all HIV carriers or as pre-exposure prophylaxis for uninfected individuals at risk. The consequences are that HBV reactivations associated with HIV-related immunodeficiency have become very rare. Furthermore, HBV suppression with these antivirals has drastically reduced the likelihood of transmission from OBI carriers and/or acquisition by uninfected exposed individuals (*Shilaih* et al. *J Infect Dis. 2016;214:599-606*).

Enthusiasm unabated, however, new tenofovir-sparing antiretroviral regimens are becoming popular and might account for a resurgence of OBI in the HIV setting. Given that dual combinations (i.e., rilpivirine plus dolutegravir), triple-drug one pill coformulations (i.e., lamivudine and abacavir plus dolutegravir), and long-acting antiretrovirals (i.e., cabotegravir) would increasingly being use in HIV-infected persons, efforts for the proper diagnosis and management of OBI are warranted.

Chronic hepatitis B screening usually includes only HBsAg testing. Other serological markers, such as HBV core and surface antibody (anti-HBc and anti-HBs) that indicates resolved HBV infection and immunity, are not routinely performed. Yet, serum HBV-DNA may be detectable in up to 10% of HBsAg-/anti-HBc+ cases, representing OBI. Based on the new data, in all HIV patients with anti-HBc planned to receive immunosuppressants for any reason (cancer, transplantation, rheumatoid conditions, etc.), the presence of low-level serum HBV-DNA should be discharged using sensitive tools such as individual nucleic acid testing, and repeated testing would be worth for excluding OBI.

Antonio Aguilera[1] and Vicente Soriano[2]
[1]Microbiology Department, Complexo Hospitalario Universitario Santiago (CHUS) & University of Santiago, Santiago de Compostela, Spain; [2]UNIR Health Sciences School and La Paz University Hospital Madrid, Spain