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Report from the International Conference on Viral Hepatitis - 2017

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Abstract

The International Conference on Viral Hepatitis 2017 brought exciting news on the treatment of viral hepatitis. The most recent estimates of the burden for hepatitis B virus and hepatitis C virus (HCV) infections were presented. The current gaps and prospects for regional and global eradication of viral hepatitis were discussed on the light of the WHO roadmap until 2030. Debates focused on hepatitis C and expectations using the new approved HCV pan-genotypic, once daily, oral direct-acting antivirals (DAAs), glecaprevir-pibrentasvir, and sofosbuvir-velpatasvir-voxilaprevir. The management of difficult-to-cure HCV patients included individuals who had failed prior DAAs, people who inject drugs, patients with decompensated cirrhosis, or renal insufficiency. Special patient populations such as children, pregnant women, persons with acute hepatitis C, or HIV coinfection were addressed separately. The use of HCV treatment as prevention was subject to debate, balancing the benefits on halting transmission and the risk for HCV reinfections and high medication costs. Complementary efforts on behavioral interventions and harm reduction programs were highlighted. Data from both clinical trials and real-world experience (i.e., from the US Veterans) were compared. Further debates addressed hepatic conditions that may alter the management and outcome of viral hepatitis, such as hepatitis B reactivation, non-alcoholic fatty liver disease, liver transplantation, and hepatocellular carcinoma. Finally, the recent data on often neglected hepatitis D and E virus infections were reviewed. **(AIDS Rev. 2018;20:57-69)**

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Key words

Hepatitis C. Hepatitis B. Hepatitis delta. Hepatitis E. HIV. Coinfection. Fatty liver disease. Antiviral therapy. Drug resistance. Epidemiology. Modeling. Transmission. Persons who inject drugs. Men having sex with men. Prevention. Tenofovir.

Introduction

Hepatologists, infectious diseases specialists, and other public health professionals from more than 15 countries convened in Chicago on October 9–10, 2017 for a new edition of the International Conference on Viral Hepatitis. The event was organized by the International Association of Providers of AIDS Care,

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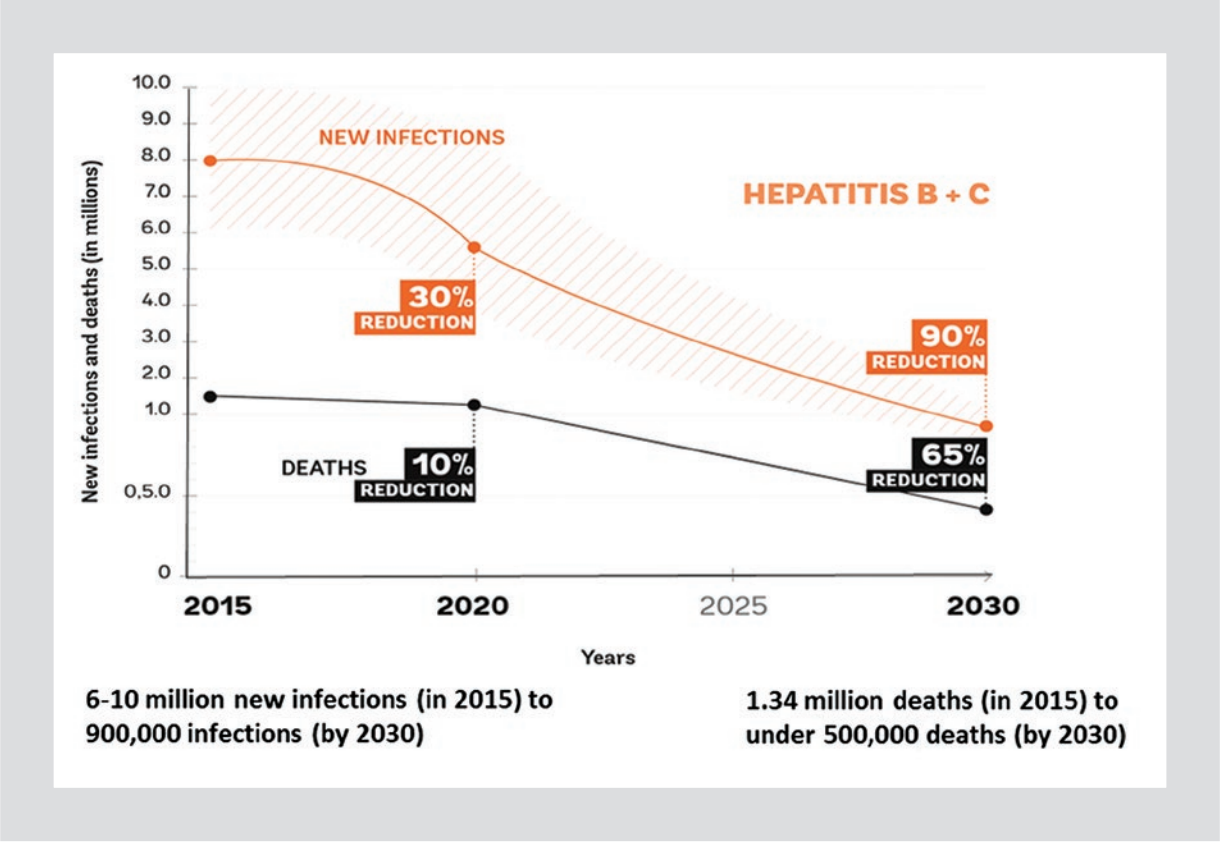

Figure 1. *The WHO roadmap proposal for eliminating viral hepatitis B and C as a major public health.*

in partnership with the alliance to eliminate HIV/hepatitis C virus (HCV) coinfection (AEH2C). It brought together a diverse panel of international experts that for 2 days discussed the most relevant topics on viral hepatitis. Attention was focused on new therapeutics and challenges for translating the good results from registration trials into success across all steps of the medical care cascade in the general population and globally.

Viral hepatitis - Current estimates and elimination plans

Philippa Easterbrook (Geneva, Switzerland) updated on the World Health Organization (WHO) plans for eliminating hepatitis B and C viral infections as a public health threat by 2030. Under the motto "thinking globally, acting locally," she highlighted the need to promote regional and national action plans to effectively control the hepatitis pandemics. Instead of pursuing unrealistically global eradication, the WHO aims to drastically reduce hepatitis B and C, reducing new infections by 30% and mortality by 10% in 2020 (Fig. 1). By 2030, these figures should be 90% and 65%, respectively. Only when viral hepatitis will no longer be a major public health threat, further efforts would allow pursuing global eradication[1].

The WHO estimates that worldwide 257 and 71 million people are living with chronic hepatitis B and C, respectively. In the year 2015, deaths due to viral hepatitis were 1.34 million, being two-thirds attributable to hepatitis B virus (HBV) and 30% to HCV (Fig. 2). Even more, worrisome is the expected increase in deaths due to viral hepatitis globally, in contrast with declines seen for other major infections, such as HIV, tuberculosis, or malaria (Fig. 3).

To provide antiviral therapy benefits at large scale, undiagnosed people must be unveiled. Key challenges in the current hepatitis testing response include lack of quality-assured serological and low-cost virological diagnostics, limited facilities for testing, inadequate data to guide country-specific hepatitis testing, stigmatization of those with or at-risk of viral hepatitis, and lack of guidelines on hepatitis testing for resource-limited settings[1]. The WHO hepatitis testing guidelines in low- and middle-income countries outline the public health approach to strengthen and expand current testing practices for

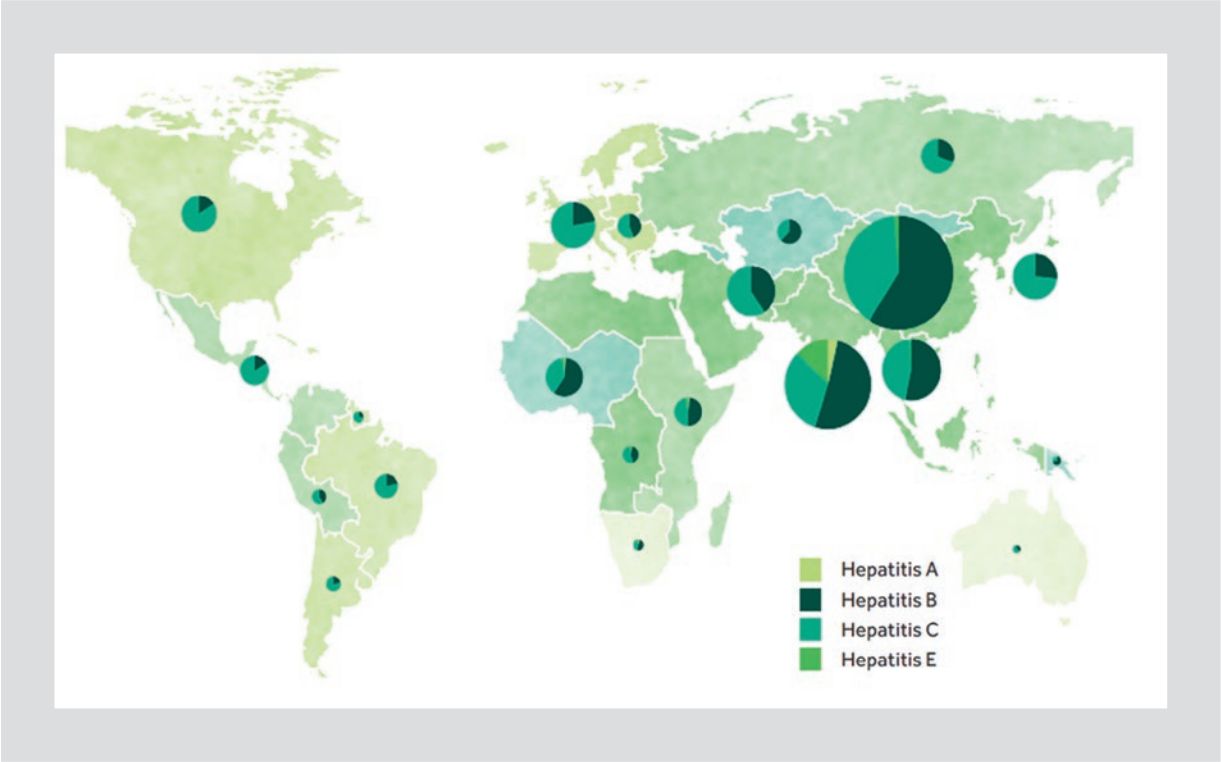

Figure 2. *Deaths due to viral hepatitis worldwide.*

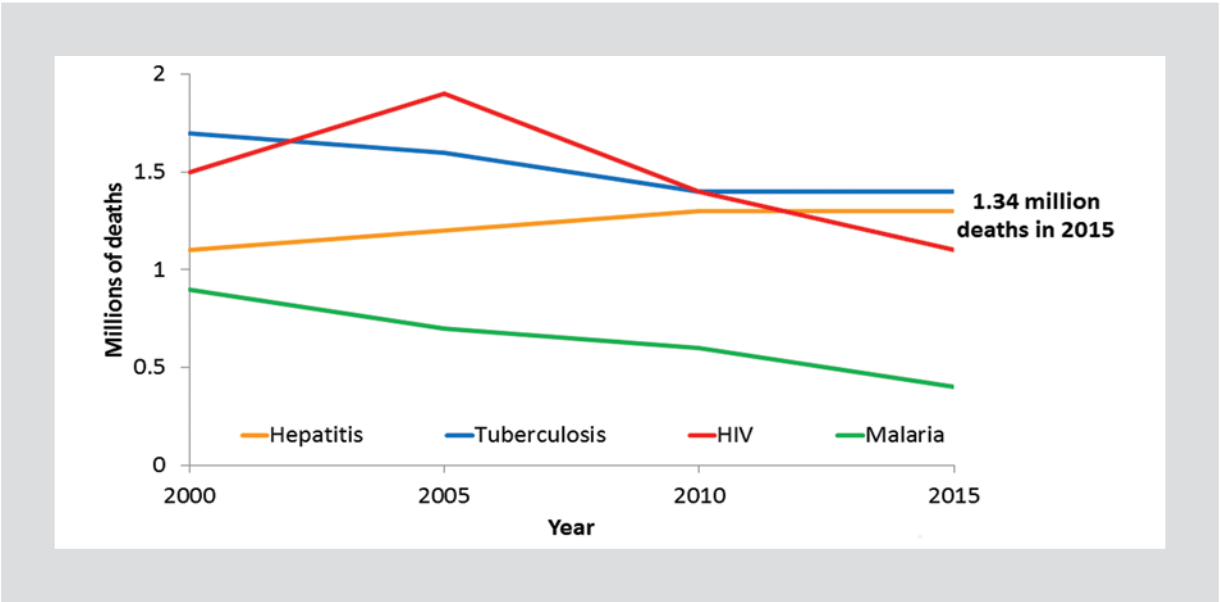

Figure 3. *Deaths due to major infectious diseases worldwide.*

viral hepatitis, specifying who to test (testing approaches), which assays to use (testing strategies) as well as interventions to promote linkage to medical care[1].

Future directions in hepatitis testing include strategies to improve access, near-patient or point-of-care assays for virological markers (nucleic acid testing and HCV core antigen), use of dried blood spot specimens, multiplex platforms to enable testing for multiple pathogens and potential self-testing for viral hepatitis[2]. In many places, medical services and facilities already developed to confront the HIV pandemic should be used[3].

John Ward (Atlanta, GA) discussed the last Centers for Disease Control and Prevention surveys on HCV

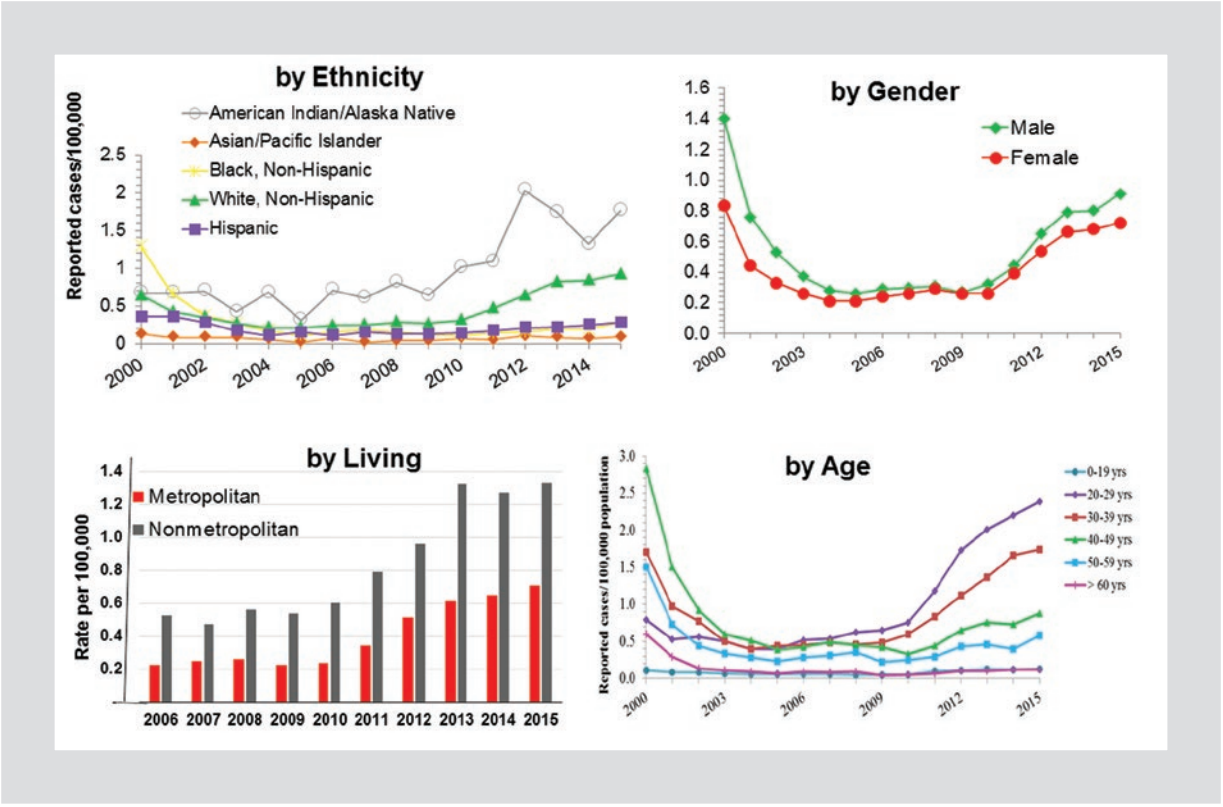

Figure 4. *Incidence of acute hepatitis C in the United States.*

epidemiology in the United States, where roughly 3 million people have chronic hepatitis C[4]. Although recommendations on HCV testing of "baby boomers" (individuals born between 1945 and 1965)[5] have been very successful in identifying asymptomatic carriers, much work still needs to be done for linking effectively the newly diagnosed population to medical care. The ultimate goal is to treat and cure hepatitis C in everyone infected[6,7].

Recent data, however, highlight that incident hepatitis C infections are on the rise in the USA. Fig. 4 records the stratification of acute hepatitis C within the past years by ethnicity, gender, age, and living place. Looking at the graphics, it is clear that a distinct profile (young adults, white or native Americans, and those living in rural areas) has emerged as the major driver of current HCV epidemics in the USA, being mostly linked to opioid injection abuse. Thus, using only the birth cohort HCV screening recommendations, this population will be missed[8].

Natasha Martin (San Diego, CA) discussed the challenges to achieve global HCV control by 2030 following the WHO roadmap, expecting 90% reduction in new HCV infections and 65% drop in deaths. She stressed the high costs of oral direct-acting antivirals (DAAs) that preclude using these agents to treat everyone infected regardless liver fibrosis staging[9]. She focused on the large impact of persons who inject drugs (PWID) in fueling the HCV pandemic[10]. Although epidemiologic benefits have been reported in some studies treating hepatitis C in PWID and cutting transmission chains, it is clear that HCV reinfections may occur[11]. On the other hand, hepatitis C is rarely the major problem in PWID, in whom drug overdoses, bacterial infections, and crime can more often be fatal in the short-term[12]. Thus, there is a need to educate healthcare providers that, in providing the best care, they should value the whole person instead of focusing in only one disease. In a given PWID, better opportunities will come for curing the slowly harmful HCV infection once illicit drug use is well managed. In the meantime, priority efforts should focus on providing social support[13], education, clean needles, and/or oral opioid agonists[14].

To properly contextualize the current scenario of HCV and PWID in the USA, it is notable that drug overdose accounted for 64,070 deaths in 2016[15]. Overdoses represented more deaths than did AIDS at its peak in 1995. Although increased heroin use is largely contributing to this catastrophe, contamination of the

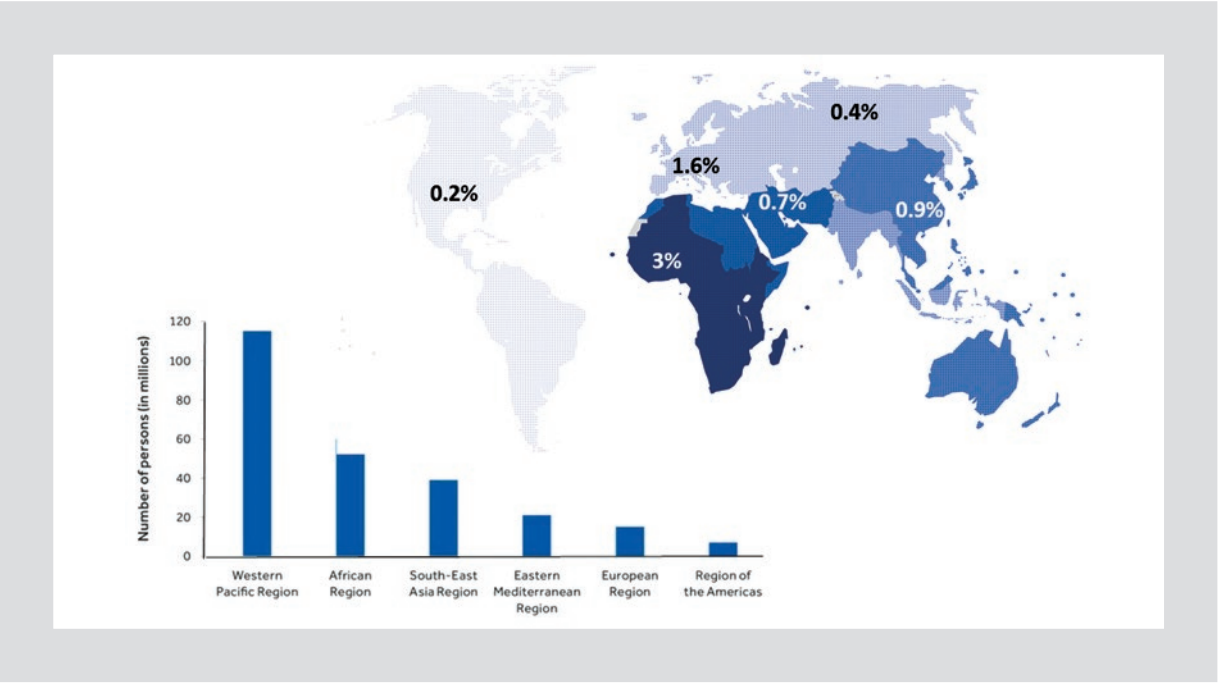

Figure 5. *Global distribution of chronic hepatitis B.*

heroin supply with illicitly manufactured fentanyl is the overwhelming driver of this recent increase in opioid-related overdose deaths[16]. Fentanyl is approximately 50 times as potent as heroin, which provides strong economic incentives for drug dealers to mix fentanyl with heroin, trafficking with smaller amounts that depict having stronger effects. Clearly, unnecessary exposure to medical prescription opioids must be reduced to prevent abuse with these drugs.

All the previous discussion on the convenience to treat hepatitis C in persons engaged in risk behaviors fits well within the current controversy between evidence-based medicine and precision medicine[17]. The major future challenge of precision medicine will be to expand the individualized knowledge that can confidently be brought to bear, moving beyond genomics[18], and to include aspects of lifestyle and environment[19]. This is the best way to ensure the optimal utilization of clinical medicine.

Hepatitis B

Of the 257 million people with chronic hepatitis B worldwide, more than two-thirds are living in Africa and Western Pacific (Fig. 5). In endemic areas, HBV is mostly transmitted from mother to newborns. Integration of hepatitis B vaccination into national immunization programs has resulted in substantial reductions of HBV transmission in these regions. The key strategy is birth dose and infant vaccination with the completion of the 3-dose schedule[20]. Dr. Easterbrook highlighted that globally still 16% of children do not complete the 3-dose immunization schedule and that <40% receive the birth dose (Fig. 6). Additional preventive measures include diagnosis of mothers at high risk of transmitting HBV, use of antivirals during pregnancy to decrease maternal HBV-DNA, and use of hepatitis B immunoglobulin at birth.

Treatment of hepatitis B since the times of interferon and lamivudine has progressed significantly. Robert Perrillo (Dallas, TX) reviewed the current HBV armamentarium (Table 1), highlighting the prospects for a functional cure that may largely halt HBV disease[21]. Clearance of serum hepatitis B surface antigen (HBsAg) and HBV-DNA should be an intermediate step in the path for truly HBV eradication, which would require the definitive elimination of the cccDNA or integrated HBV-DNA reservoir within hepatocytes[22].

In the meantime, potent and safer drugs such as the nucleotide analog tenofovir may be given to HBsAg+ carriers with significant viremia. As with other major chronic viral epidemics, such as HIV or HCV, the benefits of complete suppression of HBV replication with antivirals have public health implications beyond keeping the patient healthy as transmissions are largely halted. Kosh Awargal (London, UK) addressed the treatment chronic hepatitis B patients with tenofovir alafenamide (TAF), the recently marketed new

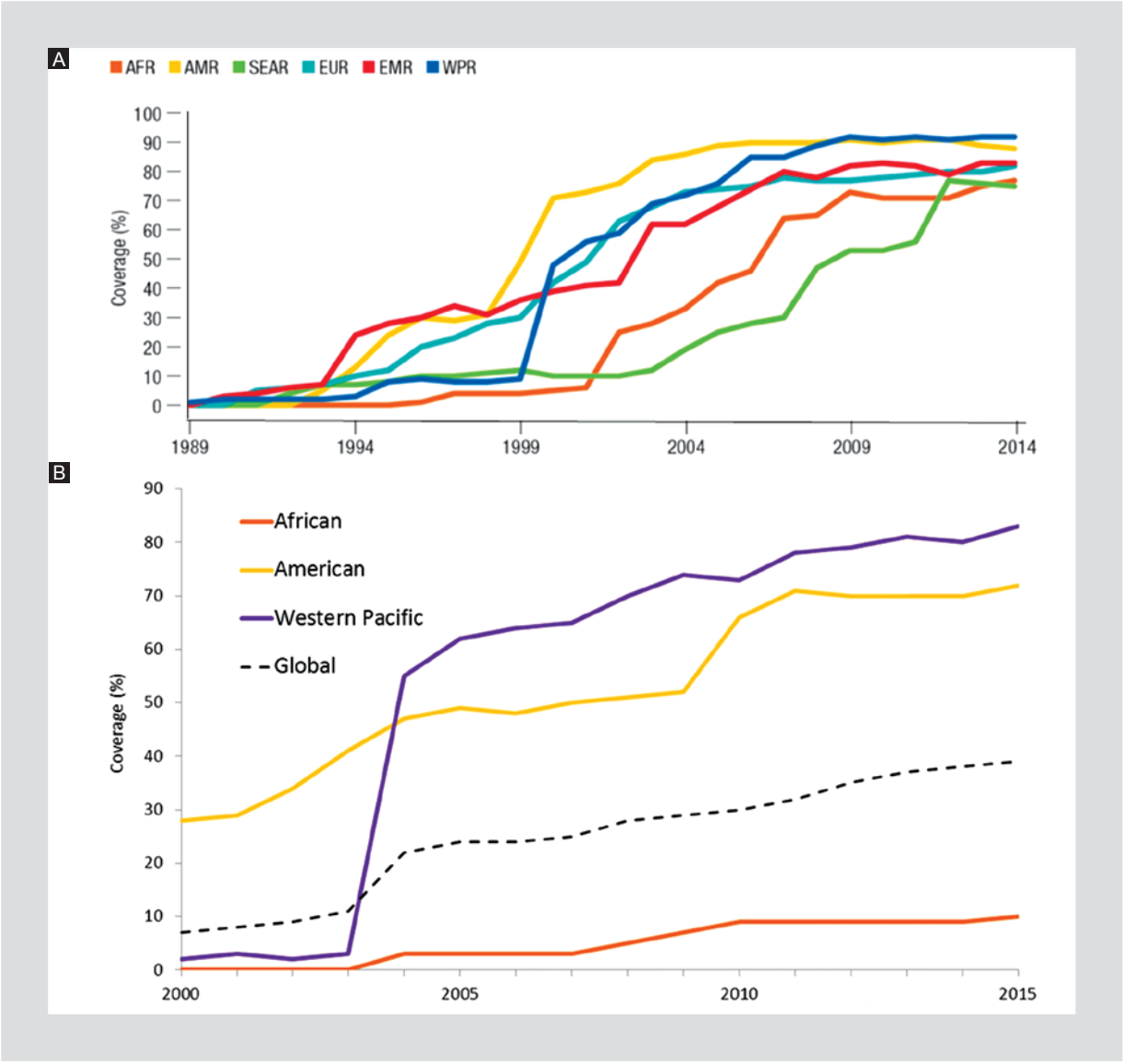

Figure 6. *Hepatitis B immunization of infants[20]. (**A**) 3-dose hepatitis B virus (HBV) vaccine coverage (2015): 84%. (**B**) HBV birth dose coverage (2015): 39%.*

formulation of tenofovir that reduces risk of kidney tubular damage. In the registration trials, once daily TAF was associated with the achievement of undetectable viremia and normalization of liver enzymes in most HBV subjects, although <5% of subjects experienced HBsAg clearance[23].

The global hepatitis B therapeutic cascade is far from ideal. By 2015, <10% of the 257 million people with chronic hepatitis B were diagnosed, with large geographical differences (Fig. 7). The number of treated patients with HBV was only of 1.7 million. Clearly, much work needs to be done, expanding testing and referral to treatment centers for achieving the WHO eradication goals by 2030. As shown in Fig. 8, tremendous gaps currently exist in diagnosis and treatment for either hepatitis B or C.

Hepatitis C

Roughly 100 million persons worldwide have serological evidence of current or past HCV infection[8]. Since 30% would be aviremic, estimates for chronic hepatitis C globally are of 71 million people. More than half of all people living with HCV live in 5 countries (China, Pakistan, India, Egypt, and Russia) (Fig. 9). Hepatitis C causes about 700,000 deaths each year. The preva-

Table 1. New HBV armamentarium[21]

Mechanisms of action		Drugs
Virus life cycle (antivirals)	Entry inhibitors	Myrcludex
	Polymerase inhibitors	TAF, CMX-157, AGX-1009, Besifovir, Lagociclovir
	Capsid blockers	GLS-4, NVR 3-778
	Release inhibitors	Rep-2139, Rep-2165
	cccDNA cleavage (gene editing)	CRISPR/Cas9
	Transcription inhibitors (RNA interference)	ARC-520, ARC-521
Host immune response (immunomodulators)	Innate immunity	GS-9620, Birinapant
	Adaptive immunity	Therapeutic vaccines (GS-4774), Engineered T cells

HBV: Hepatitis B virus.

lence is the highest in low- and middle-income countries, in which a significant number of past infections were iatrogenic, due to injections with contaminated recycled needles[1]. In contrast, in developed countries, infections are mainly caused by high-risk exposures and behaviors among specific populations, such as PWID or men who have sex with men (MSM)[8].

The advent of new DAAs has provided unprecedented rates of HCV clearance with short courses of oral therapy, transforming chronic hepatitis C infection into a curable condition[24]. The extraordinary clinical performance of DAAs and recent substantial price reductions and wide access in resource-limited settings has provided new impetus for potential control and elimination of hepatitis C as a public health threat, as claimed by the WHO[25].

Across all risk groups and regions, there is a consistently higher HCV prevalence among HIV-infected individuals, especially in PWID[3]. Worldwide, there are nearly 2.3 million persons with HIV-HCV coinfection (6.2% of HIV-positives), of which 60% are PWID[26]. These figures highlight the importance of routine HCV testing in all HIV-infected individuals.

Daniel Fierer (New York City, NY) discussed the sexual transmission of HCV, especially in MSM. Despite being considered an inefficient route of HCV transmission in the past, outbreaks of acute hepatitis C among MSM highlight that sex may be an important mechanism of contagion. Anal intercourse with the differential features of the rectal mucosa, exposure to multiple partners, and the concomitant use of drugs (*"chemsex"*), such as mephedrone and/or methamphetamine, altogether may act synergistically enhancing HCV susceptibility in MSM. The topic of the treatment of acute hepatitis C in these individuals was subject to debate between Kenneth Sherman (Cincinnati, OH), Donald Jensen (Chicago, IL), Natasha Martin (San Diego, CA), and Edward Cachay (San Diego, CA). The benefit of halting further HCV transmissions treating earlier should be balanced with the high cost of medications[27], the chance of spontaneous HCV clearance (roughly 30%), and the risk of HCV reinfection when risk behaviors persist.

Although the success rate of current DAA regimens is very high, a small subset of treated patients experiences treatment failure, often selecting HCV resistance-associated variants[28]. David Wyles (Denver, CO) noted that this is an important issue for NS5A inhibitors, whereas sofosbuvir very rarely selects for resistance mutations[29].

Massimo Puoti (Milano, Italy) provided an update on liver cancer in patients with viral hepatitis B and C. Hepatocellular carcinoma (HCC) is one of the most frequent cancers worldwide and closely linked to chronic HBV and HCV infections. The controversy that recently followed the claims for an increased incidence of HCC shortly following DAA cure[30] was discussed, acknowledging that new data does not support this concern[31].

Sanjeev Arora (Albuquerque, NM) discussed the Extension for Community Healthcare Outcomes (ECHO)

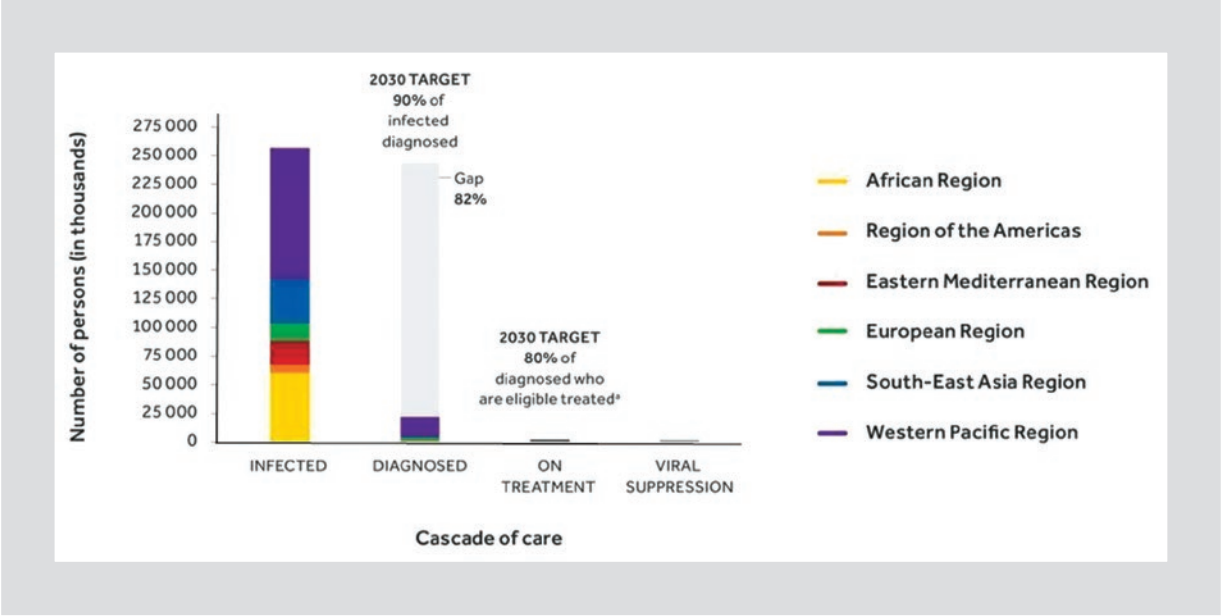

Figure 7. *Hepatitis B therapeutic cascade.*

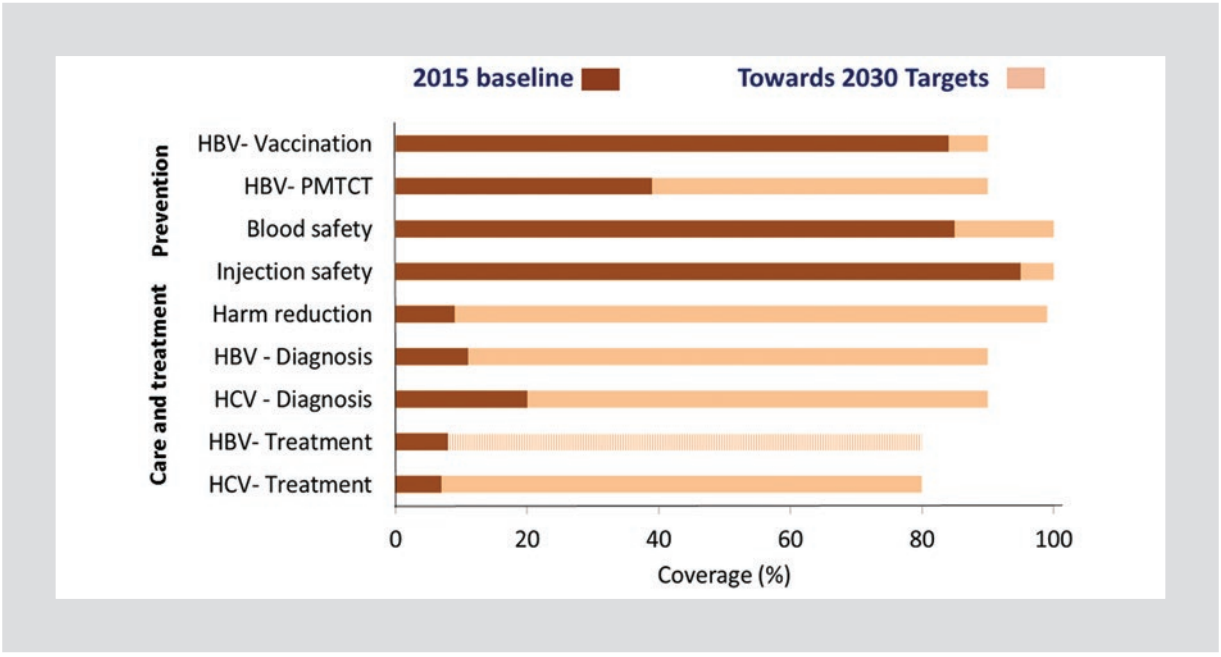

Figure 8. *Hepatitis B and C global elimination strategy.*

telementoring model for hepatitis C[32]. The ECHO project enables primary care providers to deliver best-practice care for complex conditions to underserved populations. For hepatitis C, its implementation has translated into higher numbers of cured HCV patients in the US Veterans system[33]. In other countries, similar benefits were obtained in Argentina where a clinic provided video conferencing support and training by specialists to physicians from Patagonia who treated patients with hepatitis C[34]. Finally, a recent analysis found that ECHO would be cost-effective to find and treat more patients with chronic hepatitis C in the USA using existing primary care providers[35]. Altogether, complementary telemedicine seems to be an effective alternative for improving medical care[36], enhancing the global HCV cascade.

Nancy Reau (Chicago, IL) addressed the new current standard of care for hepatitis C in the USA, following the approval of the triple combo from Gilead and

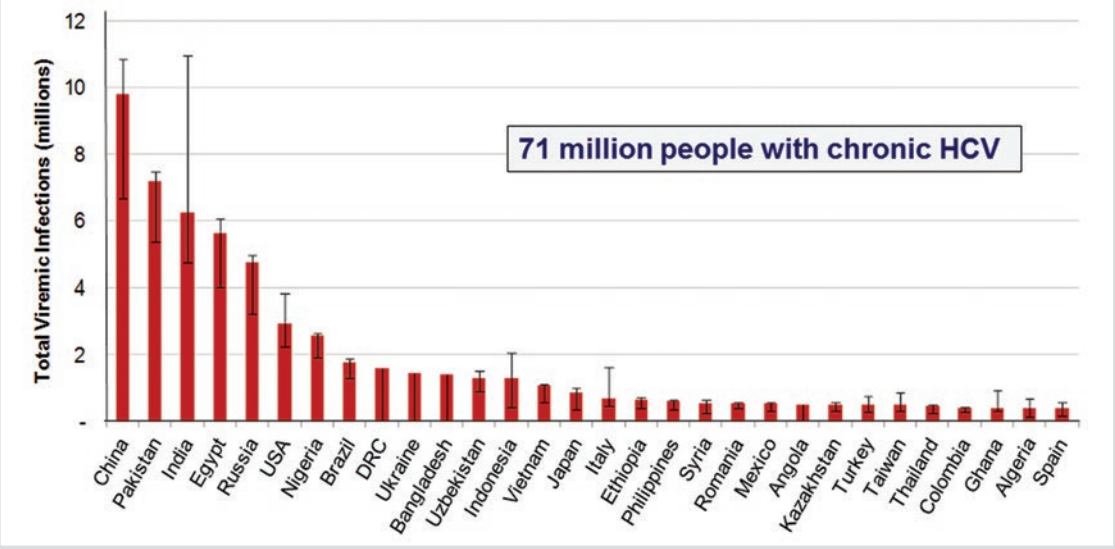

Figure 9. *Countries with the highest numbers of individuals with HCV infection.*

the new dual combo from AbbVie. Whereas 8 weeks of pibrentasvir-glecaprevir are the preferred option as initial therapy of non-cirrhotics, sofosbuvir-velpatasvir-voxilaprevir would be the best choice for retreatment of prior DAA failures[24]. However, regardless liver fibrosis stages, at this time, HIV-HCV-coinfected individuals should receive 12 weeks of DAA therapy.

Dr. Reau pointed out the advantages of current HCV medications, being simpler, safer, and given for shorter periods. At the same time, she acknowledged that some issues should leave HCV-cured patients in care, including the residual increased risk for liver cancer in patients with advanced liver fibrosis (F3) or cirrhosis[37], the chance of HCV reinfection in persons engaged in risky behaviors, and complications of coinfections, including HBV reactivation. To this end, Fred Poordad (San Antonio, TX) pointed out that HBV rebounds during or shortly after a DAA course in chronic hepatitis C patients are rare and mostly seen in patients in whom HBsAg+ was ignored. Hence, serological characterization of HBV should be performed before prescribing DAA. Close monitoring of HBV-DNA and liver enzymes are warranted in those with HBsAg+. Moreover, prescription of anti-HBV nucleos(t)ide analogs (i.e., tenofovir) may be considered in the subset HBV viremic[38].

Given shared transmission routes, HIV coinfection is relatively frequent in patients with viral hepatitis B and C. Globally, 2.7 million are HIV/HBsAg+ and 2.3 million are HIV/anti-HCV. Whereas the long-term use of tenofovir permits controlling both HBV and HIV replication in most dually infected persons, DAA should be given to cure hepatitis C in HIV-coinfected patients. Although most results from trials using DAA in HIV-HCV coinfected patients have been as good as in HCV-monoinfected persons, several real-world studies have suggested that responses could be lower in this population[39-41]. Table 2 records the reasons that may support this conclusion. Considerations on drug-drug interactions and comorbidities are among the most important[42,43]. Thus, although HIV-HCV-coinfected patients should no longer be considered a difficult-to-treat group, they deserve to be considered as a special patient population[44].

Wendy Spearman (Cape Town, South Africa) summarized the current HCV scenario in South Africa, a country of 55 million people, of whom only 10% are white. Although genotype 5 is the most prevalent (35%) HCV variant, followed by genotype 1 (31%), all other HCV clades are circulating. In contrast to Western countries, most HCV infections are iatrogenic due to unsafe blood transfusions or injections and reuse of syringes for parenteral medications or vaccinations. However, injection drug use of illicit opioids is on the rise, as shown in a recent global meta-analysis that pointed out that the largest numbers of PWID are seen in low- and middle-income countries in Africa[10].

Michael Charlton (Chicago, IL) and Helen Te (Chicago, IL) discussed the impact of DAA on liver

transplantation, acknowledging that end-stage liver disease due to chronic hepatitis C is declining as a reason for hepatic transplantation, whereas fatty liver disease, whether alcohol-related or not, is on the rise[45]. This largely reflects the huge benefits of high HCV cure rates using DAA, both pre- and post-transplantation[46].

Hepatitis D

Globally, 5-10% of individuals with chronic hepatitis B are superinfected with the hepatitis delta virus (HDV). Vicente Soriano (Madrid, Spain) highlighted that chronic hepatitis D is often misdiagnosed despite causing the most severe form of chronic viral hepatitis[47,48]. The virus is transmitted parenterally. Accordingly, PWID represents a large reservoir of the 15 million people HDV-infected worldwide[49].

To date, peginterferon-α was the only approved therapy for chronic hepatitis delta. However, clearance of serum HDV-RNA is achieved in less than one-third of treated patients, being relapses frequent on drug discontinuation[50]. Long-term administration of anti-HBV nucleos(t)ide analogs, such as tenofovir, has been associated only occasionally with virological and histological benefits in hepatitis delta patients[51-53]. Thus, there is an unmeet therapeutic need for HDV infection. Within the past couple of years, several compounds have entered phase II trials as therapy for chronic hepatitis delta (Table 3).

In a phase 2b trial, 120 hepatitis delta patients received myrcludex (a viral entry inhibitor) subcutaneously (2, 5, or 10 mg) along with oral tenofovir for 24 weeks. A dose-dependent effect on serum HDV-RNA was noticed with a mean drop of 2.4 log for the highest dose. Injection site reactions were the main adverse event. Delta viremia declined slowly, over weeks, and most likely would have become negative in most patients with a longer treatment length. However, no significant changes in serum HBsAg concentrations were seen[54].

Oral lonafarnib, a farnesyltransferase inhibitor (50, 75, and 100 mg) boosted with ritonavir 100 mg was tested in a phase 2 trial that included 21 hepatitis delta patients. All received anti-HBV nucleoside analogs concomitantly. HDV replication was 95% blocked in all patients with a slow serum HDV-RNA drop regardless lonafarnib doses. Estimates for complete HDV clearance should have occurred after 1 year of therapy[55].

Finally, a recent study conducted in Moldova reported the results treating 12 patients with delta hepatitis with weekly intravenous REP-2139, a HBsAg release inhibitor[56]. Nine patients cleared serum HDV-RNA and 5 became negative for HBsAg after clearing HBV-DNA. This unprecedent success has prompted further development of nucleic acid polymers with subcutaneous formulations.

Table 2. Impaired DAA response in real-world HIV-HCV coinfection

More prevalent predictors of treatment failure
Advanced liver fibrosis and cirrhosis
Greater serum HCV-RNA levels
More frequent difficult genotypes G3 and G1a in Europe
Blacks more represented in the USA
Drug adherence challenges
Neuropsychiatric illnesses
Social unstability - homeless
Active addiction - drugs and alcohol
Increased risk for drug-drug interactions
Scarce experience in patients with low CD4 counts +/- detectable plasma HIV-RNA

HCV: Hepatitis C virus, DAA: Direct-acting antiviral.

Table 3. Therapeutic landscape for hepatitis delta

Immunomodulators: Peginterferon-α
Anti-HBV agents
Nucleos(t)ide analogs: Tenofovir
Entry inhibitors: Myrcludex-B
Gene therapy (nucleic acid polymers): REP-2139
Specific anti-HDV drugs
Prenylation inhibitors: Lonafarnib
Gene therapy (RNA interference)
Therapeutic vaccines

HCV: hepatitis C virus, HDV: hepatitis delta virus.

Hepatitis E

Hepatitis E virus (HEV) is the most frequent cause of acute hepatitis globally. Kenneth Sherman (Cincinnati, OH) updated current knowledge on this often forgotten virus[57]. The family Hepeviridae includes enterically transmitted small non-enveloped positive-sense RNA viruses. HEV is responsible for self-limiting acute hepatitis in humans and several mammalians. However, the infection may become chronic in immunocompromised individuals (organ transplants, advanced HIV infection, or chemotherapy for cancers)[58,59].

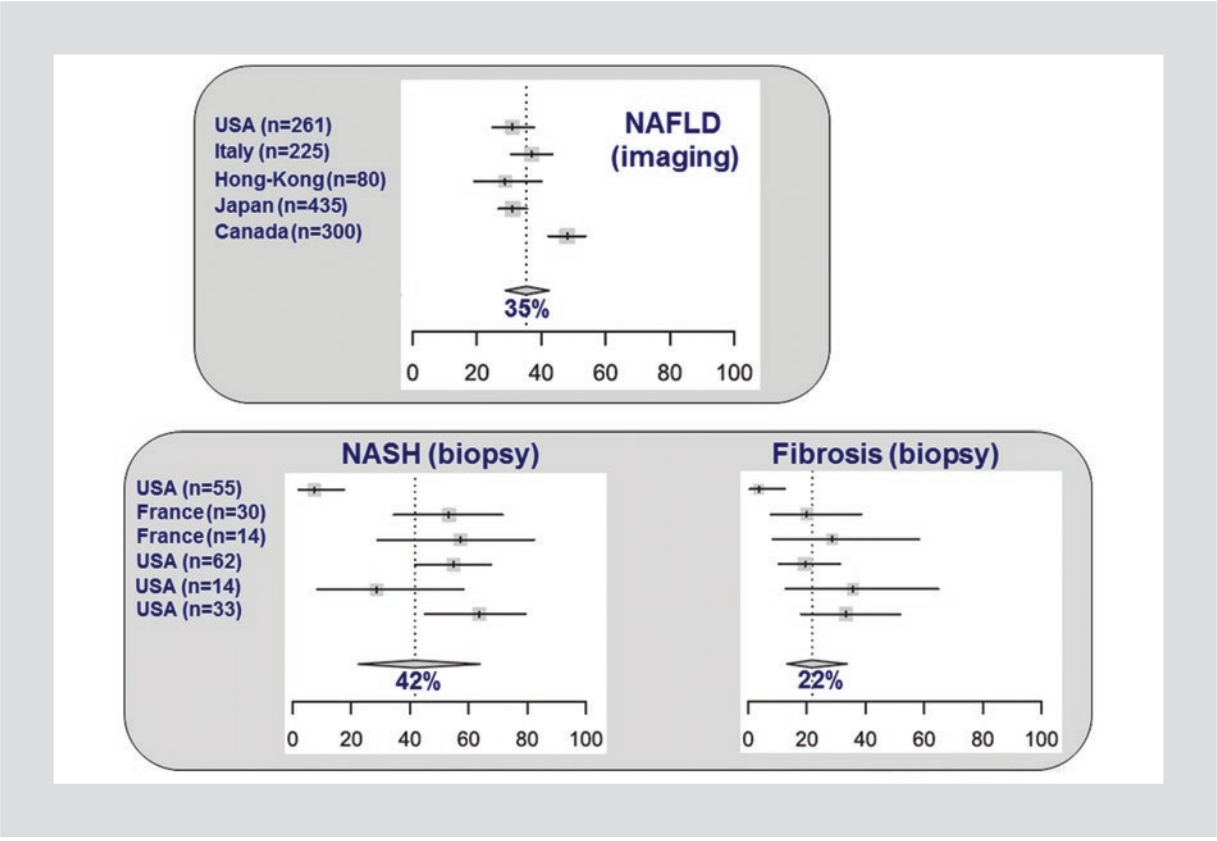

Figure 10. *Prevalence of fatty liver disease in the HIV population*[65].

Manifestations of disease, source of infection, and route of transmission vary by HEV genotype worldwide. In developing regions in Asia, Africa, and South America, water-borne transmission outbreaks of self-limited acute hepatitis E due to endemic HEV genotypes 1 or 2 are common. Foreign tourists may acquire HEV infection. By contrast, in industrialized regions, human infection by HEV genotypes 3 or 4 may occur after eating uncooked meat from pigs and other mammals. Then, hepatitis E behaves as a zoonosis, occasionally causing chronic hepatitis E[57].

Extrahepatic manifestations of HEV infection, i.e., Guillain-Barré syndrome, neuralgic amyotrophy, glomerulonephritis, and pancreatitis have been described occasionally. Nonetheless, HEV is frequently unidentified or misdiagnosed as drug liver injury (hepatotoxicity) in patients with liver enzymes elevations. Diagnosis is challenged by the lack of commercial tests. In chronic hepatitis E, the use of ribavirin has been shown to be curative[60]. However, viral clearance has also been obtained reducing/switching immunosuppressants in organ transplant recipients. An effective vaccine has been approved in China but is not available elsewhere.

Fatty Liver Disease

As overweight and obesity are increasing in humans across all societies, fatty liver disease is increasing worldwide. The condition is defined histologically by the recognition of fat in >5% of hepatocytes. It is referred as a non-alcoholic fatty liver disease (NAFLD) when found in patients that deny alcohol abuse (>42 g or roughly 3 units/daily). A subset of these individuals develops liver inflammation and ultimately fibrosis. Non-alcoholic steatohepatitis (NASH) has become one of the leading causes of cirrhosis and liver transplantation in the United States[61].

Edward Cachay (San Diego, CA) addressed fatty liver disease in HIV-infected patients, a rapidly rising complication as the HIV population ages[62]. As viral hepatitis can be well controlled (HBV) or eliminated (HCV), hepatic involvement in the metabolic syndrome (dyslipidemia, hypertension, diabetes, and obesity) is becoming a major cause of end-stage liver disease in the HIV population[63].

Although a genetic predisposition for fatty liver disease has been demonstrated, involving specific PNPLA3 polymorphisms, HIV infection is independently associated

with an increased risk of NASH in patients with NAFLD[64]. On the other hand, there is an ethnic predisposition for NASH, being Hispanics more frequently affected than Caucasians or Blacks. This may partially explain some geographical heterogeneity in the rate of NAFLD in HIV-infected patients (Fig. 10) which currently affects more than one-third of the HIV population[65].

Although a confident diagnosis of NAFLD/NASH relies on liver biopsy, non-invasive tools are increasingly widely used. Liver ultrasound depicts low sensitivity for fatty liver disease, as >30% of fatty hepatocytes should be present to provide a characteristic brighter than normal. Using elastography (Fibroscan), a controlled attenuated parameter may provide information on fat deposition, besides hepatic stiffness[66]. Finally, hepatic magnetic resonance imaging is the most sensitive non-invasive procedure for recognizing NAFLD. Liver fibrosis progression in patients with NASH generally occurs slowly, over the decades, but 20% of patients may experience a rapid progression to cirrhosis and liver decompensation[67].

In the absence of any specific treatment for NASH, HIV providers must focus on preventive efforts, mostly addressing weight and insulin resistance. In addition, antiretrovirals with a friendly metabolic profile should be chosen. Finally, Dr. Cachay pointed out that ultimately the recognition of fatty liver disease in the aging HIV+ population acts a surrogate for further metabolic complications. Thus, modifications in lifestyle (diet and exercise) and prescription of specific medications[61] must be considered along with choosing metabolic friendly antiretrovirals.

Conclusions

Viral hepatitis B and C are a major cause of cirrhosis, liver cancer, and death in HIV-infected worldwide. Efforts to eliminate HBV and HCV pandemics as a public health threat by 2030 are led by the WHO, encouraging national programs for expanding HBV vaccination and increasing diagnosis as well as treatment opportunities. The AEH2C is focusing on expanding access to antivirals by reducing prices, reaching underserved groups, and patients with HIV-HCV coinfection. In this regard, the use of generic medicines[68] and the involvement of general practitioners would be of great value.

Attention should move to other causes of liver disease than viral hepatitis B and C, as the use of successful antivirals expands. Persons living with HIV are at high risk for developing NAFLD/NASH. Following a diagnosis of "fatty liver" is essential to assess liver fibrosis staging. In the absence of specific treatment for NASH, preventive efforts addressing weight and insulin resistance must be prioritized. Antiretrovirals with a safer metabolic profile should be preferred.

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References

1. Easterbrook P;WHO Guidelines Development Group. Who to test and how to test for chronic hepatitis C infection - 2016 WHO testing guidance for low- and middle-income countries. J Hepatol. 2016;65 (suppl 1):46-66.
2. Easterbrook P, Roberts T, Sands A, Peeling R. Diagnosis of viral hepatitis. Curr Opin HIV AIDS. 2017;12:302-314.
3. Easterbrook P, Johnson C, Figueroa C, Baggaley R. HIV and hepatitis testing: global progress, challenges, and future directions. AIDS Rev. 2016;18:3-14.
4. Rosenberg E, Hall E, Sullivan P, et al. Estimation of state-level prevalence of HCV infection, US states and District of Columbia, 2010. Clin Infect Dis. 2017;64:1573-81.
5. Smith B, Morgan R, Beckett G, Falck-Ytter Y, Holtzman D, Ward J. HCV testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med. 2012;157:817-22.
6. Reau N, Fried M, Nelson D, et al. HCV Council - critical appraisal of data: recommendations for clinical practice in a rapidly evolving therapeutic landscape. Liver Int. 2016;36:488-502.
7. Kanwal F, Bacon B, Beste L, et al. HCV infection care pathway - A report from the American Gastroenterological Association Institute HCV Care Pathway Work Group. Gastroenterology. 2017;152:1588-98.
8. Ward J. Global elimination of HCV. Gastroenterol Hepatol (NY). 2016;12:632-5.
9. Rein D, Wittenborn J, Smith B, Liffmann D, Ward J. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for HCV. Clin Infect Dis. 2015;61:157-68.
10. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health (in press)
11. Fraser H, Martin N, Brummer-Korvenkontio H, et al. Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. J Hepatol (in press)
12. Soriano V, Gallego L. Viral hepatitis: treating hepatitis C in injection drug users. Nat Rev Gastroenterol Hepatol. 2013;10:568-9.
13. Katz M. Homelessness - challenges and progress. JAMA (in press)
14. Martin N, Skaathun B, Vickerman P, Stuart D. Modeling combination HCV prevention among HIV-infected MSM and PWID. AIDS Rev. 2017;19:97-104.
15. Collins F, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793-5.
16. Nardini C, Annoni M, Schiavone G. Mechanistic understanding in clinical practice: complementing evidence-based medicine with personalized medicine. J Eval Clin Pract. 2012;18:1000-5.
17. Tonelli M, Shirts B. Knowledge for precision medicine mechanistic reasoning and methodological pluralism. JAMA 2017;318:1649-50.
18. US Centers for Disease Control and Prevention. Provisional counts of drug overdose deaths as of August 6, 2017. https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates. Accessed November 3rd, 2017.
19. Dowell D, Noonan R, Houry D. Underlying factors in drug overdose deaths. JAMA (in press)
20. Nelson N, Easterbrook P, McMahon B. Epidemiology of HBV infection and impact of vaccination on disease. Clin Liver Dis. 2016;20:607-28.
21. Soriano V, Barreiro P, Benitez L, Peña JM, de Mendoza C. New antivirals for the treatment of chronic hepatitis B. Expert Opin Investig Drugs. 2017;26:843-51.
22. EASL. Clinical Practice Guidelines on the management of HBV infection. J Hepatol. 2017;67:370-98.
23. Buti M, Gane E, Seto W, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1:196-206.

24. Behara R, Reau N. Updates on hepatitis C virus therapy in the direct-acting antiviral era. Curr Opin Gastroenterol. 2017;33:115-9.
25. Lanini S, Easterbrook P, Zumla A, Ippolito G. Hepatitis C: global epidemiology and strategies for control. Clin Microbiol Infect. 2016;22:833-8.
26. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. 2016;16:797-808.
27. Kantarjian H, Shilpa P. Hepatitis C: when high drug prices preclude patients' benefits. Cancer (in press)
28. Benítez-Gutiérrez L, Barreiro P, Labarga P, et al. Prevention and management of treatment failure to new oral hepatitis C drugs. Expert Opin Pharmacother. 2016;17:1215-23.
29. Wyles D, Luetkemeyer A. Understanding HCV drug resistance: clinical implications for current and future regimens. Top Antivir Med. 2017;25:103-9.
30. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016;65:719-26.
31. Cucchetti A, D'Amico G, Trevisani F, et al. Effect of direct-acting antivirals on future occurrence of hepatocellular carcinoma in compensated cirrhotic patients. Dig Liver Dis (in press)
32. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for HCV infection by primary care providers. N Engl J Med. 2011;364:2199-207.
33. Beste L, Glorioso T, Ho P, et al. Telemedicine specialty support promotes hepatitis C treatment by primary care providers in the Department of Veterans Affairs. Am J Med. 2017;130:432-8.
34. Marciano S, Haddad L, Plazzotta F, et al. Implementation of the ECHO® telementoring model for the treatment of patients with hepatitis C. J Med Virol. 2017;89:660-4.
35. Rattay T, Dumont I, Heinzow H, Hutton D. Cost-effectiveness of access expansion to treatment of HCV infection through primary care providers. Gastroenterology (in press)
36. Tuckson R, Edmunds M, Hodgkins M. Telehealth. N Engl J Med. 2017;377:1585-92.
37. Soriano V, Benitez L, Arias A, Barreiro P, de Mendoza C. Need to face liver cirrhosis after HCV cure with antivirals. EBioMedicine 2017;24:24-5.
38. Pockros P. Black box warning for possible HBV reactivation during DAA therapy for chronic HCV infection. Gastroenterol Hepatol (NY). 2017;13:536-40.
39. Cachay E, Wyles D, Hill L, et al. The impact of direct-acting antivirals in the hepatitis C-sustained viral response in HIV-infected patients with ongoing barriers to care. Open Forum Infect Dis. 2015;2: ofv168.
40. Arias A, Aguilera A, Soriano V, et al. Rate and predictors of treatment failure to all-oral HCV regimens outside clinical trials. Antivir Ther. 2017;22:307-12.
41. Neukam K, Morano L, Rivero-Juárez A, et al. HIV-coinfected patients respond worse to direct-acting antiviral-based therapy against chronic hepatitis C in real life than HCV-monoinfected individuals: a prospective cohort study. HIV Clin Trials. 2017;18:126-34.
42. Soriano V, Labarga P, Fernandez-Montero JV, et al. Drug interactions in HIV-infected patients treated for hepatitis C. Expert Opin Drug Metab Toxicol. 2017;13:807-16.
43. Soriano V, Berenguer J. Extrahepatic comorbidities associated with hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS. 2015;10:309-15.
44. Cachay E, Soriano V. Is HIV still a special population for the treatment of hepatitis C? AIDS. 2016;30:2001-3.
45. Goldberg D, Ditah I, Saeian K, et al. Changes in the prevalence of HCV infection, non-alcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology. 2017;152:1090-9.
46. Te HS. Recurrent hepatitis C: the bane of transplant hepatology. Hepatology. 2014;59:21-3.
47. Fernández-Montero JV, Vispo E, Barreiro P, et al. Hepatitis delta is a major determinant of liver decompensation events and death in HIV-infected patients. Clin Infect Dis. 2014;58:1549-53.
48. Béguelin C, Moradpour D, Sahli R, et al. Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. J Hepatol. 2017;66: 297-303.
49. Soriano V, Sherman K, Barreiro P. Hepatitis delta and HIV infection. AIDS. 2017;31:875-84.
50. Yurdaydin C, Keskin O, Kalkan C, et al. Interferon treatment duration in patients with chronic delta hepatitis and its effect on the natural course of the disease. J Infect Dis (in press)
51. Soriano V, Vispo E, Sierra-Enguita R, et al. Efficacy of prolonged tenofovir therapy on hepatitis delta in HIV-infected patients. AIDS. 2014;28:2389-94.
52. Soriano V, Barreiro P, de Mendoza C. Tenofovir for hepatitis delta. Hepatology. 2016;63:1395-6.
53. Béguelin C, Friolet N, Moradpour D, et al. Impact of tenofovir on hepatitis delta virus replication in the Swiss HIV Cohort Study. Clin Infect Dis. 2017;64:1275-8.
54. Wedemeyer H, Alexandrov A, Bogomolov P, et al. Interim results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of myrcludex B in combination with tenofovir in patients with chronic HBV/HDV co-infection. Hepatology 2017;66 (suppl):20-1.
55. Dubey P, Koh C, Surana P, et al. Modelling hepatitis delta virus dynamics during ritonavir boosted lonafarnib treatment – the LOWR HDV-3 study. Hepatology 2017;66 (suppl):21.
56. Bazinet M, Pântea V, Cebotarescu V, et al. Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial. Lancet Gastroenterol Hepatol. (in press)
57. Murrison L, Sherman K. The enigma of hepatitis E virus. Gastroenterol Hepatol (NY). 2017;13:484-91.
58. Madejón A, Vispo E, Bottecchia M, Sánchez-Carrillo M, García-Samaniego J, Soriano V. Lack of hepatitis E virus infection in HIV patients with advanced immunodeficiency or idiopathic liver enzyme elevations. J Viral Hepat. 2009;16:895-6.
59. Sherman K, Terrault N, Barin B, Rouster S, Shata M;HIV-TR Investigators. Hepatitis E infection in HIV-infected liver and kidney transplant candidates. J Viral Hepat. 2014;21: e74-7.
60. Neukam K, Barreiro P, Macías J, et al. Chronic hepatitis E in HIV patients: rapid progression to cirrhosis and response to oral ribavirin. Clin Infect Dis. 2013;57:465-8.
61. Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? J Hepatol (in press)
62. Soriano V, Barreiro P, Sherman K. The changing epidemiology of liver disease in HIV patients. AIDS Rev. 2013;15:25-31.
63. Crum-Cianflone N, Dilay A, Collins G, et al. Non-alcoholic fatty liver disease among HIV-infected persons. J Acquir Immune Defic Syndr. 2009;50:464-73.
64. Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study. Aliment Pharmacol Ther. 2015;41:368-78.
65. Maurice J, Patel A, Scott A, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. AIDS. 2017;31:1621-32.
66. Macías J, Pineda JA, Real L. Non-alcoholic fatty liver disease in HIV infection. AIDS Rev. 2017;19:35-46.
67. Singh S, Allen A, Wang Z, Prokop L, Murad M, Loomba R. Fibrosis progression in non-alcoholic fatty liver vs non-alcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13:643-54.
68. Jensen D, Sebhatu P, Reau N. Generic medications for hepatitis C. Liver Int. 2016;36:925-8.