

Chronic Viral Hepatitis: Current Management and Future Directions

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The past decade has seen transformation in the strategies for identifying and managing viral hepatitis, most dramatically the transformation of hepatitis C virus from a mostly chronic affliction to a curable disease that is accessible to wide populations through direct-acting antiviral therapies. More recently, shifting of hepatitis C virus burden to younger patients driven by intravenous drug use has shaped screening recommendations. Future work focusing on effective screening, linkage to care, treatment initiation, and post-cure management will allow countries to work toward meeting goals of eliminating viral hepatitis as a major public health threat. Concurrently, hepatitis B virus has also seen advances in management using oral nucleos(t)ide therapies with high-resistance barriers. However, virologic cure remains elusive in the setting of viral genetic persistence within the hepatocyte nucleus, even with suppressive antiviral therapy. Future directions include a refined definition of “cure,” new biomarkers, and development of therapies targeting multiple pathways in the viral pathogenic and replication pathway. Progress is additionally being made on the management of hepatitis D infection. This review summarizes the recent evolution in disease characteristics, associated affected population, and changes in our understanding of management for these infections. We also discuss future directions in the management of viral hepatitis, including discussion on issues related to management before and after antiviral therapy. *Conclusion:* We summarize recent advances in the identification and management of viral hepatitis, which hold the potential to markedly reduce disease burden and therefore associated liver-related complications. However further work is needed to adequately identify and manage these diseases. (*Hepatology Communications* 2020;4:329-341).

Viral hepatitis continues to contribute to the burden of liver disease in the United States, causing chronic hepatitis, cirrhosis and decompensated disease, liver cancer, and extrahepatic manifestations. However, this past decade has experienced a sea of change in our ability to identify, diagnose, and manage these diseases, most notably with development of curative direct-acting antiviral (DAA) therapies for chronic hepatitis C virus (HCV) infection. Numerous advances in treatment development and strategies have been made in chronic hepatitis B virus (HBV) and hepatitis D virus (HDV) as well. This

review aims to summarize the current epidemiology and management strategies available for chronic viral hepatitis, including future directions and areas where further work is needed.

Hepatitis C: From Chronic Malady to Robust Cure

Of the viral hepatitis, none has seen as much transformation in available pharmacologic treatment

Abbreviations: AASLD, American Association for the Study of Liver Diseases; cccDNA, covalently closed circular DNA; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; NA, nucleos(t)ide analog; pgRNA, pregenomic RNA; PWID, people who inject drugs; SVR, sustained virologic response; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Received September 23, 2019; accepted December 21, 2019.

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DOI 10.1002/hep4.1480

Potential conflict of interest: N. Reau consults for Gilead, Abbott, AbbVie. She researches for Abbott.

options as for chronic HCV, which has been viewed previously as a chronic infection with only modest cure rates (sustained virologic response [SVR] up to 63%) with interferon-based therapies.⁽¹⁾ However, now it has become a disease with multiple, well-tolerated, finite therapies with SVR rates greater than 95% across nearly all patient and viral characteristics. Availability of such treatment has altered the landscape of patient populations who are able to receive treatment, as well as which patients should have access to these safe, effective treatments.

CHANGING EPIDEMIOLOGY AND SCREENING RECOMMENDATIONS

Hepatitis C remains one of the most prevalent chronic liver diseases in the United States and beyond, but the infected population is shifting toward a younger, treatment-naïve population without cirrhosis. The estimated worldwide anti-HCV antibody seropositivity is 100 million people, with viremia in 71 million.⁽²⁾ In a prevalence study of the Global Burden of Disease project, HCV genotype 1 was most common (46.2% of cases), although other genotypes also contribute a large proportion of disease burden (genotype 3: 30.1%; genotype 2, 4, and 6: 22.8%; genotype 5: <1%).⁽³⁾ A meta-analysis reported global HCV prevalence of 2.5%, ranging from 1.3% in the Americas to 2.9% in Africa.⁽⁴⁾ In the United States, an epidemiological study of the National Health and Nutrition Examination Survey (NHANES) revealed serologic antibody positivity in 1.7% (4.1 million) adults, with viremia seen in 1.0% (2.4 million) in 2013 to 2016.⁽⁵⁾ In 2017, the Centers for Disease Control estimated 44,700 new cases of acute HCV infection, with an estimated 2.8 million people with chronic HCV in the United States.⁽⁶⁾

In the United States, although the disease burden from HCV is decreasing, the clinical characteristics of those with chronic infection is evolving. Overall, HCV prevalence has decreasing nearly 2-fold, from 1.6% to 0.9% over the past 20 years.⁽⁷⁾ Additionally, the distribution of affected age groups is thought to have become bimodal, with a disproportionate number of new HCV cases seen in those aged 20 to 39 years and 40 to 59 years.⁽⁸⁾ It has been proposed that this bimodal distribution has developed due to the increase in people who inject drugs (PWID), a population in whom prevalence of chronic HCV has been estimated to be approximately 73.4% (range 20%-80% globally), corresponding to 1.5 million people in the United States.⁽⁹⁾ Another suggested epidemiological change based on a recent modeling analyses is that in contrast to the previous population consisting of treatment-experienced patients, most of the treatable patients are now anticipated to be treatment-naïve and without cirrhosis.⁽¹⁰⁾ However, despite anticipated decreased disease incidence, disease burden is still expected to be substantial based on a modeling study finding that, driven primarily by a lack of disease identification, 560,000 patients will not know about their chronic infection, 320,000 patients will die, 157,000 will develop hepatocellular carcinoma, and 203,000 patients will develop decompensated cirrhosis in the next 35 years.⁽¹¹⁾

Optimizing HCV screening holds the key to disease identification, yet effective screening has persistently been a challenge in the United States. A recent study of screening strategies identified that reflex nucleic acid testing after a positive serum antibody result was cost-effective and adequately sensitive for viremia.⁽¹²⁾ However, identifying who to screen has been challenging. Most current screening recommendations until recently had called for both risk-factor and cohort-based approaches. The American Association

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for the Study of Liver Diseases (AASLD) currently recommends one-time screening for individuals with associated risk behaviors (PWID or with intranasal drug use) or risk exposures (hemodialysis, unregulated parenteral exposure, health care workers with exposure to HCV-infected blood, children born to HCV-infected women, prior recipients of transfusions or organ transplants, and history of incarceration) and for those in the birth cohort (born between 1945 and 1965), regardless of the presence of risk factors.⁽¹³⁾ However, due to the expanding young population and the anticipated aging of the baby boomer generation, the U.S. Preventive Services Task Force is in the process of expanding its recommendations to screen to all adults aged 18 to 79 years, a screening recommendation that is distinct from other organizations, and potentially cost-effective compared with birth cohort screening.^(14,15) Although a monumental step forward, this one-time screen runs the risk of missing individuals screened before engaging in high-risk behaviors. Additionally, targeted micro-elimination may be an effective strategy to reduce HCV disease burden on those at high risk for disease, and has been reported to be cost-effective in the U.S. prison population,⁽¹⁶⁾ men who have sex with men, injection drug use, and maternal-to-child transmission.^(17,18) Although guideline recommendations are important for guiding practices, they will ultimately need to be adopted by both practitioners and medical societies.

EVOLUTION OF MANAGEMENT PRINCIPLES AND THERAPIES FOR CHRONIC HEPATITIS C VIRUS INFECTION

Our understanding of treatment-eligible populations has developed in tandem with DAA therapies and an evolving definition of cure. Although in prior years there was need to define safe populations for antiviral treatments, current recommendations suggest treating all individuals diagnosed with HCV infection regardless of risk for reinfection, hepatic fibrosis stage, or prior-treatment status. Additionally, the definition of SVR has been shortened to be the absence of viremia 12 weeks after treatment completion, as 99% of patients with SVR12 have been found to have persistent viral clearance at 24 weeks.⁽¹⁹⁾ This finding has reduced the heterogeneity of treatment endpoints in treatment studies,

whereas prior studies used 24 or even 48 weeks to define HCV cure.

Multiple societies have made recommendations for patient screening, including considerations for country-specific policies, to identify populations to perform screening (Table 1). Identification through screening remains challenging. Prior AASLD guidance had recommended screening all Americans born between 1945 and 1965.⁽²⁰⁾ However, recent updates broaden the screening to include all U.S. adults aged 18 years or older,⁽²¹⁾ paralleling the recommendations made by the U.S. Preventive Services Taskforce to test those 18 to 79 years old.⁽¹⁴⁾ Identifying an optimally inclusive screening strategy will allow us to move toward treating the largest proportion of the chronic HCV-infected population.

Since the approval of telaprevir and boceprevir in 2011 with SVR rates of 65% to 75%, the landscape of antiviral therapy for chronic HCV has expanded, with development of well-tolerated, pan-genotypic, all-oral, DAA therapies available to a variety of special populations (Table 2). Additionally, recent updates to the AASLD recommendations have developed a simplified approach to treat chronic HCV, recommending glecaprevir/pibrentasvir for 8 weeks or sofosbuvir/velpatasvir for 12 weeks in all patients with HCV who are treatment-naïve, noncirrhotic, with normal renal function and without comorbid infections.⁽²¹⁾

Despite earlier data of heterogenous safety and efficacy across different treatment groups, current therapies for chronic HCV infection are safe and effective across a variety of patient populations, with high SVR rates in decompensated cirrhosis (>85%), end-stage renal disease (>95%), human immunodeficiency virus co-infection (>95%), or history of prior DAA failure (>90%), status following liver transplantation (>95%), and across all HCV genotypes (>95%).⁽²²⁻²⁵⁾ High SVR despite multiple patient comorbidities targeting all viral genotypes thus raises the question about whether defining “special populations” or treatment subgroups is still a pertinent need.

FUTURE DIRECTIONS

HCV elimination is possible with DAA therapies. However, beyond issues of screening, there are issues that limit diagnosis, referral, and treatment for all infected patients. From a health-services perspective, the World Health Organization has set five service

TABLE 1. SOCIETY-BASED RECOMMENDATIONS FOR SCREENING AND TREATMENT FOR HCV INFECTION

Society	Year of Guideline/ Guidance	Screening	Indication for Treatment	Comments
World Health Organization ^(78,79)	2017 (Screening)	Strategies for country-specific testing policy: <ul style="list-style-type: none"> • High-risk behaviors • Past generalized exposures that have since been removed ("birth cohort" testing) • Generalized population epidemic with high prevalence (whole population testing) 	All individuals diagnosed with HCV infection who are 12 years of age or older, regardless of disease stage Including MSM, PWID, and incarcerated individuals, with the exception of pregnant women	Strong recommendation, moderate quality of evidence
AASLD, Infectious Disease Society of America (IDSA) ⁽¹³⁾	2018 (Treatment)	<ul style="list-style-type: none"> • Risk behavior, risk exposure, or other conditions* • One-time, routine opt-out HCV testing in all patients 18+ years old, in those younger than 18 years, one-time testing in those with risk exposures or behaviors 	All patients with chronic HCV, except for those with a short life expectancy who cannot be remediated by HCV therapy, liver transplantation, or another directed therapy	Periodic repeat testing for persons with risk exposures, behaviors, conditions, or circumstances. Annual testing for PWID and MSM who are sexually active without protection
EASL ⁽⁸⁰⁾	2018	Screening strategies for HCV infection should be defined according to the local epidemiology of HCV infection, ideally within the framework of national plans	All treatment-naïve and treatment-experienced patients with HCV infection, who are willing to be treated and who have no contraindications [†] for treatment, should be treated	Patients with decompensated (Child-Pugh B or C) cirrhosis and an indication for liver transplantation with a MELD score ≥ 18 -20 should be transplanted first and treated after transplantation [‡]
U.S. Preventive Services Task Force ⁽¹⁴⁾	2019 (in progress)	Screening strategies may include screening of populations at risk for infection, birth cohort testing, and general population testing in areas of intermediate to high seroprevalence ($\geq 2\%$ -5%) Adults ages 18 to 79 years	Treatment is generally not recommended in patients with limited life expectancy due to non-live-related comorbidities	Recommendation currently in draft form (public comment through 9/23/2019) Update to previous recommendations to screen high-risk and birth cohort ⁽⁸¹⁾

*Risk behaviors: injection drug use and intranasal illicit drug use. Risk exposures: hemodialysis, parenteral exposures, health care workers after exposure, children born to HCV-infected women, prior recipients of transfusions or organ transplants, and ever incarcerated. Other conditions: HIV infection, sexually active about to start HIV postexposure prophylaxis, unexplained liver chemistry abnormalities, and solid organ donors.

[†]Use of certain cytochrome P450 inducing agents (carbamazepine, phenytoin) are contraindicated with all regimens. Regimens consisting of protease inhibitor must not be used in patients with Child-Pugh B or C decompensated cirrhosis or in patients with previous episodes of decompensation. In patients with eGFR < 30 mL/min/1.73 m², sofosbuvir should only be used if no alternative treatment approved for use in severe renal impairment is available.

[‡]If the wait time on the liver transplant list is more than 6 months, then patient can be treated before transplantation, although the clinical benefit is not well established.
Abbreviations: eGFR, estimated glomerular filtration rate; MELD, Model for End-Stage Liver Disease; MSM, men who have sex with men.

TABLE 2. RECOMMENDED TREATMENTS FOR CHRONIC HCV INFECTION*

Regimen	Treated Genotypes	Duration (weeks)	Efficacy	Treatable Special Populations	Special Considerations
Daclatasvir/sofosbuvir	1, 2, 3, 4	12	93%-100%	Decompensated cirrhosis Following liver transplant with/without cirrhosis HIV/HCV coinfection when antiretroviral cannot be changed to accommodate recommended regimens (GT1,4)	Add RBV for decompensated cirrhosis
Elbasvir/grazoprevir	1, 3, 4	12	91%-100%	Treatment-experienced (PEG/RBV) with/without cirrhosis Severe renal impairment	GT1a: Alternative regimen if high-fold resistance variants to NS5A GT3: Add sofosbuvir for PEG/RBV experienced with compensated cirrhosis Not for decompensated cirrhosis or following liver transplant with cirrhosis
Glecaprevir/pibrentasvir	1, 2, 3, 4, 5, or 6	8	94%-100%	Treatment-experienced (PEG/RBV) with/without cirrhosis [†] Following liver transplant without cirrhosis Severe renal impairment Following kidney transplant with/without cirrhosis	Not for decompensated cirrhosis or following liver transplant with cirrhosis 12-week duration for special populations 8-week duration for compensated cirrhosis
Ledipasvir/sofosbuvir	1, 4, 5, or 6	12	93% to 100%	PEG/RBV experienced with/without cirrhosis Decompensated cirrhosis Following liver transplant with/without cirrhosis (compensated or decompensated) Following kidney transplant with/without cirrhosis	8-week duration for treatment-naïve, non-black, HIV-negative, HCV RNA < 10 ⁶ IU/mL, without cirrhosis 24-week duration and add RBV for decompensated cirrhosis with sofosbuvir failure Add RBV for decompensated cirrhosis, following liver transplant
Sofosbuvir/velpatasvir	1, 2, 3, 4, 5, or 6	12	96%-100%	Treatment-naïve, PEG/RBV, or DAA experienced without cirrhosis (± decompensation) PEG/RBV with/without NS3 protease inhibitor experienced Following liver transplant with decompensated cirrhosis	Add voxilaprevir for NS5A failure (including NS3 protease inhibitors) with/without cirrhosis (not for decompensated cirrhosis or following liver transplant with cirrhosis) 24-week duration and add RBV for decompensated cirrhosis with DAA failure including NS5A

*Simplified regimen for treatment-naïve, nonpregnant patient with normal renal function and HCV mono-infection, without cirrhosis or history of liver transplantation: glecaprevir/pibrentasvir for 8 weeks or sofosbuvir/velpatasvir for 12 weeks.

[†]Also non-NS5A failure with/without cirrhosis.

Abbreviations: CKD, chronic kidney disease; PEG, pegylated interferon; RBV, ribavirin.

coverage targets for elimination of viral hepatitis as a public health threat by 2030, including targeting vertical transmission prevention, blood and injection safety, PWID harm reduction, and antiviral treatment provision.⁽²⁶⁾ However, a recent Markov modeling analysis found that 36 of 45 (80%) high-income

countries/territories would be projected to not meet these elimination targets by this time, including the United States.⁽²⁷⁾ Further aggressive policy measures will be needed if this benchmark were to be met.

Providing treatment would ultimately only treat the 7% to 11% with known chronic HCV infection,

but it does not account for those undiagnosed or not offered treatment.⁽²⁸⁾ Thus, more work is needed to identify those suffering attrition during the process steps required from testing to treatment, by which loss to follow-up would result in persistent infection, described as the HCV treatment cascade.^(29,30) As an illustrative example, Rege et al. found in an analysis of two large national laboratory databases from 2013 to 2016, that 89.4% of patients diagnosed with chronic HCV infection did not receive prescription for antiviral therapy. In this study, 46.7% of patients did not have genotype testing, and 57.3% did not have liver chemistries, suggesting that patients suffer attrition at an early phase of the care cascade.⁽³¹⁾ Future work to target the care cascade gaps will help to identify those for whom treatment could be offered: HCV screening, diagnosis, patient communication regarding chronic infection, care linkage, and fibrosis staging. Concurrently, development of HCV vaccinations and subsequent provision implementation strategies will be important to reduce population disease burden.

Specialty care access is another area for future consideration in the optimization of HCV care, and expansion of the provider pool who provide antiviral therapies would increase the capacity for HCV treatment. Alternative models of HCV care have been reported with DAA therapies provided by non-hepatology providers. Studies of non-hepatologist-driven HCV care has reported success in treating infected patients when led by nurses,⁽³²⁾ pharmacists,⁽³³⁾ and primary care providers.⁽³⁴⁾ As more chronically infected patients are identified, growth scaling of the provider pool to treat this expanding patient population may result in improved care access for larger number of patients in need of treatment. This will become increasingly important as systems consider alternative payment models to increase therapy access, such as the “Netflix model” of subscription payment to drug companies adopted by Louisiana,⁽³⁵⁾ or a dedicated linkage-to-care program in Philadelphia, which reported linkage to care in over two-thirds of patients infected with HCV.⁽³⁶⁾

Solid-organ transplantation capacity can be expanded through improved HCV-positive organ use. Wooley et al. conducted a single-center, open-label pilot trial of patients receiving organ transplantation from HCV-infected donors of various genotypes (n = 44 with 36 lung and 8 heart transplants) who received 4 weeks of sofosbuvir and velpatasvir immediately after

transplantation. The authors found that, on follow-up, all 35 patients (100%) were alive with excellent graft function and undetectable viral load 6 months after transplantation.⁽³⁷⁾ Further data are needed regarding outcomes associated with liver transplantation, as well as optimal treatment duration and timing.

DAA-treatable populations have expanded to include those with end-stage renal disease, coinfection with HBV or human immunodeficiency virus, and pediatric populations. However, some populations are still in need of further research. For example, DAA therapy in pregnant women is still not currently recommended and more data are needed regarding the safety and efficacy to prevent vertical transmission. Beyond maternal-to-child transmission risk, pregnancy may be the only time when patients have access to continuous care, thus being a potential opportune time to receive treatment. Additionally, guidance for treatment for those with acute HCV infection (occurring in the first 6 months of infection) has recently changed to recommend treatment in these patients after diagnosis and without a waiting period to assess for viral clearance.⁽¹³⁾ If DAA treatments become more cost-effective in the future, future research in optimal treatment regimen and timing may become useful in preventing acute HCV infection from progressing to chronic infection, and minimizing comorbidity resulting from acute infection and transmission with horizontal spread.

Despite robust SVR rates in most patients, the presence of HCV resistance-associated amino acid substitutions can result in lower cure rates in some patient groups, including genotype 1a/3, cirrhosis, and nonresponders to prior interferon-based treatments. Developing strategies to detect and account for viral resistance to DAAs will be necessary, as with continued treatment, the population of chronically infected patients shifts toward treatment-experienced, DAA-refractory patients.

Finally, as large numbers of patients achieve HCV cure, further knowledge will be needed of post-SVR management, particularly regarding who need closer monitoring. Although patients with cirrhosis will still require indefinite subspecialty care, determination of surveillance of those with advanced fibrosis is not clear. For example, there is a question regarding the need for surveillance for hepatocellular carcinoma in these patients, and one study reported the cost-effectiveness of surveillance in those with cirrhosis,

but not in those with F3 fibrosis.⁽³⁸⁾ Another population in need of further research is those with obesity, owing to the risk for nonalcoholic fatty liver disease, which has arisen as the most prevalent chronic liver disease in the world and the fastest-growing indication for liver transplantation in the United States.⁽³⁹⁻⁴¹⁾ A recent nationwide study found a 160% increase in NAFLD prevalence in the past 30 years, despite stable or decreasing prevalence of chronic HBV, HCV, and alcoholic liver disease.⁽⁷⁾ Weight gain after HCV cure has been suggested in small prospective studies.^(42,43) Additionally, it is unclear whether weight gain occurs or is associated with alternation in the natural history of HCV from cure, but is clinically important given the high worldwide prevalence of obesity and the multisystemic complications associated with excess weight, including NAFLD⁽⁴⁴⁾ (Table 3).

Hepatitis B Virus: Still in Need of Definitive Cure

Although current therapies for chronic HBV are associated with high viral suppression rates, patients generally require lifelong therapy, and true virologic clearance remains elusive. HBV management has generally been approached with viral suppression using antiviral therapies. This section will detail recent developments, including recent development of a new effective first-line antiviral and future therapeutic strategies under investigation.

EVOLVING DISEASE BURDEN AND EPIDEMIOLOGY

HBV remains a global public health issue. A recent, large epidemiologic pooled analysis of 161 countries found HBV surface antigen (HBsAg) prevalence of 3.61%, comprising 248 million chronically infected individuals and ranging between 0.20% in the Americas to 22.38% in Africa. In the United States, HBsAg seroprevalence was 0.27%, corresponding to 843,724 individuals with chronic HBV infection.⁽⁴⁵⁾

ADVANCES IN VACCINATION

Improvements in HBV vaccination strategy is one key to reducing disease burden. Universal vaccination

programs in hyperendemic regions, such as the one implemented in 1984 for infants in Taiwan, have been associated with reduced HBV carrier and liver cancer rates.^(46,47) Additionally, ease of vaccination dosing would increase uptake by patients and providers. In a recent, large, phase 3, multicenter, randomized, blinded, active-controlled trial of healthy patients, Heyward investigated a two-dose regimen (given at 0 and 4 weeks) of HBsAg-1018 (HEPLISAV-B), a vaccine containing HBsAg combined with a toll-like receptor 9 agonist adjuvant designed to improve vaccine immunogenicity.⁽⁴⁸⁾ Compared with the three-dose, 6-month regimen, HBsAg-1018 was found to induce a higher seroprotection rate through 1 year following vaccination, with comparable safety. This vaccine was approved in 2018 for all persons aged 18 years or older for vaccination against HBV.⁽⁴⁹⁾

MANAGEMENT: VIRAL SUPPRESSION IS KEY

If treatment is indicated, the choice of antiviral agent should be a medication with a high barrier to viral resistance. Studies of pivotal trials have revealed low long-term (up to 8 years) rates of HBV resistance to entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). Thus, these three antiviral drugs have become the only oral therapies recommended by the AASLD and European Association for the Study of the Liver (EASL).⁽⁵⁰⁻⁵²⁾ TAF, a nucleotide reverse-transcriptase inhibitor and prodrug of tenofovir, was approved in the United States in 2016 and has emerged as one effective first-line antiviral therapy. TAF benefits from more efficient hepatocyte drug delivery compared with TDF, which allows lower allowable TAF doses. For this reason, TAF may be associated with lower risk for renal dysfunction and reduced bone mineral density compared with TDF.⁽⁵³⁾ An analysis of two large, randomized, phase 3 controlled trials found significantly lower bone mineral density at 96 weeks in patients receiving TDF compared with TAF (hip: -2.51% TDF vs. -0.33% TAF; spine: -2.57% TDF vs. -0.75% TAF; $P < 0.001$ for both) and renal function (median glomerular filtration rate: -4.8% TDF vs. -1.2% TAF; $P < 0.001$), with TAF noninferiority for HBV viral suppression.⁽⁵⁴⁾ The recent 2017 EASL Guidelines and 2018 AASLD Guidance update have added TAF as a first-line preferred HBV therapy to TDF, ETV,

TABLE 3. INDICATIONS FOR TREATMENT OF CHRONIC HBV INFECTION

Indications to Initiate Treatment		Potentially Treat*	Do Not Treat
AASLD	Treat		
	HBeAg-positive ALT elevated but <2× ULN and HBV DNA > 20,000 IU/mL	HBeAg-positive ALT elevated <2× ULN and HBV DNA ≥ 2,000 IU/mL, persistent >6 months	HBeAg-positive ALT normal and HBV DNA > 20,000 IU/mL
EASL	Or	Or	Or
	HBeAg-negative ALT ≥ 2× ULN and HBV DNA > 2,000 IU/mL	ALT elevated ≥ 2× ULN and HBV DNA 2,000 to 20,000 IU/mL, persistent >6 months Or HBeAg-negative ALT normal but HBV DNA ≥ 2,000 ALT elevated and HBV DNA ≥ 2,000	HBeAg-negative ALT normal and HBV DNA < 2,000 IU/mL
EASL	Should be treated	May be treated	Do not treat
	HBeAg-positive or HBeAg-negative Chronic HBV infection† Cirrhosis with/without decompensated and any detectable HBV DNA, regardless of ALT HBV DNA > 20,000 IU/mL and ALT > 2× ULN, regardless of degree of fibrosis	HBeAg-positive chronic HBV infection and age >30 years, regardless of severity of liver histological lesions HBeAg-positive or negative Chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations	Undetectable HBV DNA, normal ALT, and mild or no liver necroinflammation and fibrosis

Note: ALT upper limit of normal is defined as 35 U/L for males and 25 U/L for females.

*If staging indicates fibrosis ≥ F2 or activity ≥ A3, then treat regardless of HBV DNA or ALT, unless ALT normal and HBV DNA < 2,000 IU/mL.

†HBV > 2,000 IU/mL, ALT elevated, with at least moderate liver necroinflammation or fibrosis.

Abbreviations: ALT, alanine aminotransferase; CHB, chronic hepatitis B; ULN, upper limit of normal.

and pegylated interferon. Additionally, these recommendations include considerations for choosing TAF over TDF, including advanced age, reduced bone density, and chronic renal insufficiency (Table 4).^(51,52)

FUTURE DIRECTIONS: NEW DEFINITIONS, BIOMARKERS, AND THERAPEUTIC APPROACHES

Clarification of treatment endpoints based on patient serological status may allow more clarity of treatment goals when developing drugs targeting multiple pathways in the viral replication pathway. Although the ideal goal would be to halt all forms of HBV replication (termed “sterilizing cure” or “virologic cure”), this may be unrealistic due to the persistence of viral covalently closed circular DNA (cccDNA) in the liver, and with it the risk of reactivation with immunosuppression event after treatment completion. A recent consensus conference for HBV treatment endpoints provided guidance for HBV treatment endpoint goals in therapeutic drug design, including “functional cure,” whereby after a finite course of therapy, HBV DNA is not detectable and HBsAg loss has persisted for 6 months following treatment. “Partial functional cure,” defined as detectable

HBsAg but persistently undetectable HBV DNA 6 months after treatment, is considered an intermediate goal for antiviral therapies.^(55,56) Designation of these clear-but-distinct endpoints will allow benchmarking of the progress of novel therapy development.

More research on the biomarkers of treatment efficacy will allow better assessment of HBV cure. Biomarkers may assist in posttreatment monitoring and in identifying those potentially able to be successful with antiviral therapy discontinuation. Decrease in quantitative HBsAg levels has been associated with viral clearance,^(57,58) and is routinely monitored over the course of antiviral treatment, allowing differentiation of immune tolerance and immune clearance in hepatitis B e antigen (HBeAg)-positive patients.⁽⁵⁹⁾ Hepatitis B core-related antigen (HBcrAg) is one new biomarker under investigation. HBcrAg has been correlated with cccDNA levels, can predict posttreatment recurrence of hepatocellular carcinoma during antiviral therapy, and can identify patients who may successfully discontinue therapy.⁽⁶⁰⁻⁶²⁾ Pregenomic RNA (pgRNA), an intermediate genome-length RNA transcribed from cccDNA, has also been associated with cccDNA levels and may be a clinical marker for viral replication activity.⁽⁵⁹⁾ These viral molecules

TABLE 4. CONSIDERATIONS FOR ANTIVIRAL SELECTION FOR HBV TREATMENT

AASLD

Guidance statements	No preference between ETV or TDF regarding potential long-term risks of renal and bone complications TAF is associated with lower rates of bone and renal abnormalities than TDF In cases of suspected TDF-associated renal dysfunction and/or bone disease, TDF should be discontinued and substituted with TAF or ETV, with consideration for any previously known drug resistance
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EASL

Indications for selection of ETV or TAF over TDF	Age > 60 years Bone disease Chronic use of medications that worsen bone density (including steroids) History of fragility fractures Osteoporosis Renal dysfunction eGFR <60 mL/min/1.73 m ² Albuminuria >30 mg/24 hours or urinalysis with moderate qualitative proteinuria Hypophosphatemia (<2.5 mg/dL) On hemodialysis
Recommendation statements	Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous treatments

Abbreviations: eGFR, estimated glomerular filtration rate; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

hold promise as surrogate markers for HBV viral activity in conjunction with standard biomarkers in present clinical use.

Current approved treatments for chronic HBV fall into two classes: nucleos(t)ide reverse transcriptase inhibitors, also known as nucleos(t)ide analogs (NAs), and interferon alpha. Additionally, additional NAs are currently in development, including other tenofovir prodrugs besifovir and metacavir.⁽⁶³⁾ Unfortunately, even though NAs effectively suppress viral replication, they do not lead to virologic cure. Thus, most patients require indefinite oral therapy, as although partial functional cure is readily achievable with current therapies, complete functional cure is achieved in a minority and virologic cure in even fewer patients.⁽⁶⁴⁾

Development of new treatments for chronic HBV is needed, concurrently with a better understanding of the HBV replication life cycle. For treatments to theoretically achieve virologic cure, inhibition of cccDNA and viral replication is needed. Towards this goal, multiple drugs targeting multiple therapeutic targets (Table 5) are in development. Viral entry inhibitors such as Myrcludex B competes for viral binding for viral entry into the hepatocyte and would play a role in treating both HBV and HDV.⁽⁶³⁾ Other targets include viral migration to the hepatocyte nucleus, viral uncoating, cccDNA production and integration, viral replication through DNA synthesis, as well as the production and secretion of viral particles (Dane particles).⁽⁵⁵⁾ New drug development coupled with research on combination therapies hold promise for effective viral virologic cure.

HDV: Emerging Therapies

HDV is a defective RNA virus that requires HBsAg expression as an envelope protein to mediate viral entry and complete its life cycle. HDV infection presents as either HBV-HDV coinfection or HDV superinfection in those with chronic HBV infection. HBV-HDV coinfection is considered among the most severe forms of viral hepatitis, with risk of developing acute liver failure as well as higher risk for development of cirrhosis, hepatocellular carcinoma, and mortality compared with HBV infection alone.^(65,66)

A recent systematic review and meta-analysis of 182 articles reported a HDV worldwide pooled prevalence in the overall HBsAg-positive population of 11% and in those with intravenous drug use as high as 38%.⁽⁶⁷⁾ Additionally, a study of the U.S. NHANES revealed HDV antibody seropositivity in 33% to 47% of adult HBsAg carriers.⁽⁶⁸⁾ This suggests higher HDV disease burden than previously believed (previously estimated to be only 5%).⁽⁶⁹⁾ Further epidemiologic studies are needed to clarify the current disease burden of HDV, which in turn may help identify optimal screening strategies. Current recommendations for HDV screening suggest testing for human immunodeficiency virus (HIV)-positive patients, persons who inject drugs, men who have sex with men, those at risk for sexually transmitted diseases, and immigrants from areas of highly endemic regions.⁽⁵²⁾

The only currently recommended treatment for HDV infection is pegylated interferon-alfa 2a or 2b, which is associated with suppression rates of only

TABLE 5. THERAPEUTIC TARGETS FOR HBV DRUGS IN DEVELOPMENT

Virus Life Cycle Step	Therapeutic Drug Class
Virus entry into hepatocyte	Entry inhibitors
Virus intracytoplasmic migration to nuclear periphery and nuclear import	Tubulin production inhibitor
Viral uncoating and intranuclear rcDNA release	No current drugs
cccDNA production, integration, epigenetic modification	cccDNA inhibitors (e.g., lymphotoxin beta receptor agonist)
	Epi-drugs
	Interferon alpha
Modification of cccDNA to pgRNA, pgRNA packaging for nuclear export	Small interfering RNA
pgRNA reverse transcription to progeny rcDNA and capsid packaging	Capsid assembly modulators
	Interferon alpha
Viral replication through DNA synthesis	Nucleoside analogs
Capsid incorporation of HBsAg and secretion from hepatocytes	Secretion inhibitors
	Interferon alpha

Abbreviations: ccc, covalently closed circular; DNA, deoxyribonucleic acid; HBsAg, hepatitis B virus surface antigen; pg, pregenomic; rc, relaxed circular; RNA, ribonucleic acid.

25% (range 17%–43%) after 12 months of treatment.^(70,71) NAs are not indicated for treatment of HDV infection, as they were not found to contribute further efficacy,⁽⁷¹⁾ but may nevertheless be indicated if concomitant chronic HBV DNA were present. Newer agents are under investigation, including HDV prenylation inhibitors (Lonafarnib), virion secretion inhibitors (REP 2139), and viral entry inhibitors (Myrcludex B) in phase 3 studies.^(72–75) Further targeted mechanisms, including RNA interference (ARC-520), have been proposed as having potential to treat both HBV and HDV.^(76,77)

Conclusion

Rapid, significant advances in the diagnosis and management for viral hepatitis has changed the landscape of the treatment of viral hepatitis in the past decade. Treatment options for hepatitis C currently hold the potential for eradication in the future if reduction in new cases can be coupled with widespread disease identification and treatment. Clearly defining hepatitis B cure endpoints, in conjunction with effective biomarkers and therapies targeting multiple pathways that focus on prevention of viral replication machinery, holds the key to virologic cure and ultimately eradication. Progress on hepatitis D infection grows in tandem with that of hepatitis B, and future work in epidemiology and pharmacotherapy are needed. Finally, although hepatitis A and hepatitis E are generally approached using supportive measures due their self-limited nature, more knowledge regarding management is needed for the minority of patients who develop protracted or chronic disease. Finally, in all viral hepatitis, the recognition of high-risk groups coupled with development of optimal screening and vaccination will hold the key for mitigating public health burden from these infections.

Author Contributions: A.D. and N.S.R. participated in the research, writing, and editing of this manuscript.

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