

Hepatitis B: long-term protection through vaccination and treatment

Virtual meeting

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The objectives of the two-day virtual meeting were as follows:

- to assess the long-term protection resulting from hepatitis B vaccination, and the scientific evidence from recent and/or ongoing follow-up studies
- to assess the long-term impact of hepatitis B vaccination strategies, illustrated by success stories
- to discuss the impact of growing vaccine hesitancy on long-term vaccination coverage, and
- further to discuss long-term hepatitis B vaccination in relation to the goals of the World Health Organization (WHO) to eliminate viral hepatitis by 2030, and
- to consider long-term outcomes of (new) HBV treatment and the discontinuation of treatment.

Part 1 – Long-term protection of HBV vaccination

In the 1970s, Alaskan natives had some of the highest rates of hepatitis B in the world, with high prevalences of liver cancer and cirrhosis. In 1981, a plasma-derived vaccine against hepatitis B was introduced. Follow-up of the long-term immunogenicity began at that time and the Alaska HBV Vaccine Demonstration Project in the west of the State has now been studying more than 1500 vaccinated children and adults for more than 35 years. In 1986, levels of antibodies to hepatitis B virus surface antigen (anti-HBs) ≥ 10 mIU/ml were found in 81% of subjects; the figure declined to 51% at 30 years and 47% at 35 years. Good evidence of cell-mediated immunity was demonstrated at 30 years. Studies are ongoing for the 35-year cohort, including some subjects who lived in villages where HBV was endemic. It appeared that, although they had been vaccinated successfully, they were exposed to HBV and subsequently infected asymptotically, as demonstrated by the presence of hepatitis core-specific T cells in their peripheral blood; thus it is clear that cell-mediated immunity is strong at 35 years and is probably maintained for at least 40 years. The long incubation period of HBV enables both cell-mediated and humoral immunity to abort any infection.

The Vax Demo 35 study continued the investigation of immunity and evaluated the effect of a booster dose of vaccine in those with anti-HBs levels < 10 mIU/ml. It revealed solid evidence of protection, with overall 86% having evidence of immunity (either having been boosted or with anti-HBs ≥ 10 mIU/ml at 35 years), including one group that had not received a booster dose in the interim. Higher anti-HBs antibody titres after the primary series of vaccination were associated with protective antibody titres at 35 years, but poor immune response was not associated with age, sex, body mass index, diabetes or co-morbidities.

The data show that primary immunization with plasma-derived vaccine provides immunity for at least 35 years, as is probably the case with recombinant vaccines, and that boosters are not needed. They support vaccinating children younger than 6 months.

Out of 320 followed for 35 years, originating from the original cohort of 1578 individuals, only 28 cases of non-persistent vaccine-breakthrough infections were detected, identified through their anti-HBc antibody positivity, some with only transient DNA.¹ None had had detectable illness, none

was immunocompromised and none developed chronic hepatitis. In other words, the vaccine protects against disease, as a vaccine should do, rather than against infection.

Responses to vaccination and policy implications

Variations in the responses to HBV vaccination were found in a study in Italy to be due to age at vaccination, sex, time interval before determination of antibodies and the level set for which the anti-HBs antibody titre was considered to be “protective”. Variables modifying the response include sex steroidal hormones, sex chromosomal genes and immune gene polymorphisms.

The findings that females appeared to have stronger responses than males when vaccinated at ages above one year led to a proposal to consider a concentration of anti-HBs antibodies ≥ 2 mIU/ml as sufficient to prompt a response to a booster dose even several years after initial vaccination and to predict effective protection.² Setting such a limit would carry implications for vaccination schedules as well as for surveillance of healthcare workers, professionals and medical students. A further proposal to initiate hepatitis B vaccination after one year of age, on the basis that in Italy the first administration of MMR vaccine had been delayed until 13–15 months of age³ at which time hepatitis B vaccine could also be given, was countered by the overwhelming evidence of the value of immunization with the hexavalent HBV-containing vaccine in earlier months of life.

Impact of vaccination in Europe

The 53 Member States of the WHO European Region have seen major advances in implementing HBV vaccination over 25 years. Policies vary but every country is implementing vaccination, with most by 2020 having policies for either universal vaccination of newborns ($n = 23$) or infants or children ($n = 48$). Thirty countries implement selective vaccination of newborns at risk, rather than universal vaccination of newborns, with 29 reporting screening of pregnant women and mostly high coverage rates. Regional data (Table 1) show that coverage rates for three doses of hepatitis B vaccine were higher than 90% in 2018–2020 but fell with the arrival of COVID-19, in some counties to less than 80%. Already in 2016–2020 low rates were seen in Ukraine for a variety of reasons including vaccine hesitancy and supply problems, and are not likely to improve given the war situation.

Table 1. Coverage with three doses of hepatitis B vaccine in Member States of the WHO European Region, 2018–2020

Hepatitis B vaccine coverage, three doses	Number of countries (% of reporting countries) by year		
	2018	2019	2020
$\geq 90\%$	38 (83%)	41 (85%)	30 (68%)
80–89%	4 (9%)	4 (8%)	11 (25%)
$< 80\%$	4 (9%)	3 (6%)	3 (7%)
Total number of reporting countries	46	48	44

Source: WHO Immunization Dashboard.

Nevertheless, vaccination has given striking results: by 2019, only three countries in central Asia still had high incidence rates of hepatitis B and 25, mainly in western Europe, had low or very low rates. In 2016–2019, altogether 35, 19 and 17 countries met the coverage targets for, respectively, three doses of hepatitis B vaccine, the birth dose and screening of pregnant women for HBsAg.⁴

National figures, however, can hide discrepancies and not all are reliable. Although few countries have done population-based representative serosurveys, several of those that have done so showed much higher rates of HBsAg prevalence in foreign-born subjects ($>1\%$) compared with the indigenous populations (0.1%). A similar discrepancy is found from the screening of pregnant

women: although several countries, including Croatia, Denmark and the UK, reported overall rates of 0.1–0.4%, the rates in Denmark and Italy among foreign-born women were much higher.

In 2021, WHO's Regional Committee for Europe adopted the European Immunization Agenda 2030⁵ with indicators and control targets for hepatitis B for 2030, and was due to consider a regional strategy for achieving WHO's 2030 elimination targets later in 2022.^a The Hepatitis B Regional Working Group of the European Technical Advisory Group of Experts on Immunization has begun the process of the validation of attainment of targets, although COVID-19 has delayed progress. At the beginning of 2020 Italy and the Netherlands had been so validated.

Vaccine hesitancy, COVID-19 and responses

Although WHO has created a strategic advisory group of experts (SAGE) working group on vaccine hesitancy,⁶ concerns continue that loss of confidence in vaccines is derailing vaccine campaigns generally (and outbreaks of measles have been reported in unvaccinated groups). Vaccine hesitancy has also been linked to decreasing coverage of HBV vaccine with consequent undermining of progress towards viral hepatitis elimination, exacerbating existing barriers in health systems to universal access to HBV vaccination.⁷ Scaling up the birth dose coverage of HBV vaccine remains the key to elimination of HBV. Disruptions in vaccination efforts due to COVID-19 may not delay elimination but may result in an increase in HBV-related deaths in the 2020 birth cohort.

Recent findings in 19 countries of people's increased willingness to accept COVID-19 vaccines are encouraging, although studies have focused on public trust in governments about COVID-19 rather than on routine vaccines. Furthermore, the requirements and mandates for HBV vaccination are many and varied, presenting complexities. Health professionals need to set examples about vaccination but even they themselves report hesitancy, which could derail vaccination campaigns. More education (pre- and in-service), training, advocacy and coherent messaging (as well as understanding of the reasons for hesitancy) are needed.

Although the opportunity to incorporate other vaccines into the COVID-19 vaccination programmes was attractive (for instance, during the 15-minute waiting time after vaccination), the urgency and speed of the latter generally precluded any such steps. Exceptionally, however, the arrival of COVID-19 caused viral hepatitis outreach programmes in Spain to rethink their approaches, leading to the introduction of aspects of these programmes into those for COVID-19 vaccination.⁸ Novel strategies were introduced to overcome health system barriers and bring marginalized populations such as migrants and other under-served populations into contact with health and community services and to lower vaccine hesitancy.⁹ The success seen with hepatitis C programmes¹⁰ underlines the potential for introducing services for hepatitis B; experience is still sketchy because of the current focus on COVID-19 but use of mobile testing units proved successful and reached marginalized and unvaccinated groups. Combining strategies such as testing and vaccination can help to increase uptake of services, but the focus on COVID-19 has deflected attention from other vaccination campaigns. Another encouraging example is Albania, where the health authorities have built on the experience with COVID-19 and introduced a web-based system for linking surveillance and vaccination data from private and public laboratories for HIV, viral hepatitis and COVID-19.

Group discussion

Participants consider two questions.

Question 1. Based on the available scientific evidence, should a booster dose for hepatitis B be recommended in general population and/or for healthcare professionals, medical students and risk groups?

^a The regional action plan for ending the epidemic of viral hepatitis was adopted in September 2022 (see resolution EUR/RC72/R4).

Hepatitis B vaccine does what it is intended to do: it prevents disease rather than infection. Rates of acute infection have tumbled as the vaccine has been introduced across the world, as have the numbers of chronic carriers of HBV and of cases of hepatocellular carcinoma. The response of vaccinees to boosters (whether natural or administered), in particular the convincing and encouraging data from the 35-year follow-up of vaccinated children in Alaska, indicates the presence of cell-mediated immunity to HBV, even if more supporting data are still scarce. For the general population, the available scientific evidence is clear: there is no need for booster doses of hepatitis B vaccine.

From the public health perspective, loss of antibody to HBsAg does not lead to symptomatic infection or chronic hepatitis B. Some vaccinees do not respond to vaccination with production of anti-HBs and data on their subsequent morbidity are lacking. Questions remain about those whose levels of antibody lie between 1 and 10 mIU/ml. There are currently no markers to identify people who are at risk of progressing to disease or chronic infection. But for the moment the consensus was that policy does not need to be changed.

Certain groups, however, may benefit from screening and boosting as appropriate. Different approaches may be needed for healthcare providers, medical and healthcare students, and people at high risk such as injecting drug users or special populations such as dialysis patients. Options include (1) boost all and then test or (2) test and then boost those whose antibody concentrations are <10 mIU/ml. Another potential approach that should be considered is for screening household or similarly close contacts through the use of rapid point-of-care tests for HBsAg using capillary blood specimens obtained from a finger stick, once performance of such tests (especially sensitivity) has been improved. The results would be used for decisions about vaccinating on the spot and establishing links to care as appropriate.

Given a lack of solid data, it was suggested that a meta-analysis of studies on antibody responses to HB vaccination, including vaccinees whose antibody concentrations lie in the range 1–10 mIU/ml, and of morbidity in vaccine recipients would be useful. Moreover, any such analysis should include studies of the cost-effectiveness of preventing one HBV infection through a booster dose and a strategy of screening before boosting, including the costs of screening before boosting as opposed to universal boosting.

Question 2. Can we continue as we are or are there threats to the high coverage rates and is it necessary to take special initiatives to counter these threats?

Work towards WHO's elimination goals for viral hepatitis set for 2030 needs to be kept high on the public health, policy and research agenda. Improving and maintaining high coverage rates of hepatitis B vaccination are crucial, especially given the long-term prevention of liver cirrhosis and hepatocellular carcinoma. Furthermore, efforts to raise the rates of administration of the birth dose of HBV vaccine must continue in countries where they are low and HBsAg prevalence is high or intermediate and where not all births occur in healthcare facilities. Even though coverage rates for vaccination of young people may be high, attention should also turn to raising average figures (ensuring also that averages do not hide broad discrepancies) for unvaccinated adults and people with co-morbidities, people among whom coverage rates are low, and other groups such as refugees and immigrants from countries where the prevalence is high.

The dangers of the politicization of vaccines and public health need to be recognized and countered, especially with other challenges than viral hepatitis to public health. The growing hesitancy towards vaccines in general and potentially hepatitis B vaccine too is another major concern. The introduction of new vaccines against COVID-19 initially exacerbated hesitancy but subsequent greater acceptance seems to have lowered the risk of spill-over to hepatitis B vaccination, especially as the HBV vaccine

is very different in that it prevents long-term disease and mortality and can be seen as an anti-cancer vaccine. This aspect could open the door to synergies with noncommunicable disease programmes.

In a few instances such as Spain, COVID-19 has enabled new initiatives for reaching marginalized communities with hepatitis services, but novel strategies for outreach and overcoming health system barriers still need developing. Meanwhile, activities such as continuing education, communication and advocacy are vital, with messaging that is specific for hepatitis B and its long-term and anti-cancer benefits.

Despite the fact that hepatitis B vaccines have been in use in parts of Europe for some 40 years, data are not available to demonstrate the long-term impact of HBV vaccination. A recommendation of the group would be to promote the achievements made and to document their impact.

Part 2 – Long-term treatment of hepatitis B

More than 250 million people globally are chronically infected with hepatitis B virus. Although most of these infections remain asymptomatic, chronically infected people run a 100-fold increased risk of liver-related complications, including cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), indicating the importance of screening and appropriate linkage to care.

The past few years have seen changing epidemiology and better insights into the natural history of infection, the development of diagnostic tools and new approaches to therapy, including the introduction of second-generation nucleos(t)ide analogues (NAs) and their discontinuation after long-term treatment.

Pegylated interferon was the mainstay of treatment for many years but does not provide a functional cure, which is currently seen as persistent loss of HBsAg. It remains an option in patients with non-advanced liver disease, but its applicability is limited owing to low efficacy and poor tolerance. In recent years, second-generation NAs, especially those with a high-barrier to resistance, namely entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide, are giving excellent clinical results, but a similar lack of functional cure has meant the need for long-term treatment.

Current treatments aim to persistently inhibit replication of HBV and to normalize alanine aminotransferase (ALT) activity, but that is not a functional cure. Functional cure has been found to be difficult to achieve, with rates of loss of HBsAg of merely 0.15–0.33% per year depending on HBV genotype. Life-long treatment runs the risk of the development of resistance and altered immune responses. It may also reduce compliance (a low rate of 75% was reported from Taiwan), and may cause side-effects including induction of severe acute exacerbations (sometimes fatal) – severe virological flares have been described but are infrequent (see RETRACT-B study quoted in reference 18). Reduced adherence to the treatment regimen and loss to follow-up are inevitable and can result in severe virological and biochemical flares or hepatic failure.

Long-term treatment with NAs has been shown in many studies in Asia and the USA to be safe and generally well tolerated (with very few reports of kidney failures or bone fractures, although there have been cases of lactic acidosis and hypophosphataemia and other side effects in HIV-infected patients who received the same antiviral agents), but longer-term studies are needed. Long-term treatment produces good virological (i.e. HBV DNA suppression) and excellent clinical outcomes. Second-generation NAs result in almost universal suppression of HBV DNA and long-term treatment can reverse liver fibrosis, prevent liver decompensation and the need for liver transplants, as well as prevent progression towards cirrhosis. HCC incidence is largely reduced during long-term NA treatment, but not completely prevented, thereby requiring a continuation of HCC surveillance.

Loss of HBsAg is, however, rare and slow¹¹ but on top of complete suppression of HBV viraemia it results in a lower risk of progression to HCC¹². Given that cirrhosis and HCC are long-term outcomes, virological endpoints for treatment success have been defined: currently HBV DNA suppression, HBeAg seroconversion and clearance of HBsAg (with or without seroconversion to anti-HBs) have been proven to be associated with beneficial long-term clinical outcomes, and are therefore accepted as surrogate endpoints. In addition, HBsAg loss is taken to mean functional cure, allowing withdrawal of NA treatment.

Clinically patients receiving long-term NA treatment have survival rates similar to those in the general population, with only cirrhosis and HCC reducing survival: a European study showed a survival rate of 94% after eight years in patients without baseline cirrhosis or HCC.¹³ Such good survival rates can be attributed to compliance with treatment, provision of advice about healthy behaviour as well as regular monitoring.

The role of genotypes was underlined, with different types seen in different geographical regions and different outcomes. For instance, five genotypes are seen in Alaska, with high rates of B and C, as in Asia. Genotype F is strongly associated with risk of HCC whereas in Africa genotype A prevails and exposure to aflatoxin exacerbates the risk of cancer. The genotype pattern in Taiwan is changing with time. Rather than focusing on issues of ethnicity, it might be better to look at HBV genotype. It would also be relevant to issues of screening.

Murine model

Seroconversion to anti-HBs antibodies is usually attributed to increased responsiveness of HBV-specific T cells, but a causal link between serum HBsAg levels and activation of CD8+ T cells has not been established.¹⁴ Therefore, in order to examine host–virus interactions, replication-competent transgenic mice depleted of circulating HBsAg and implanted with HBV-specific CD8+ T cells have been studied. Clearance of serum HBsAg had only a minimal effect on the expansion of HBV-specific naïve CD8+ T cells undergoing intrahepatic priming and had no impact on the capacity of CD8+ effector T cells to induce liver pathology; it also had no effect on the antiviral activity of interleukin-2-based immunotherapeutic approaches. The implications are that therapy that might reduce HBsAg levels is unlikely to increase virus-specific CD8+ T cell immunity and should be coupled with treatment that does activate T cell immunity.

Finite therapy

Especially in countries where HBV infection is endemic, life-long or long-term treatment increases the costs of treatment. In Taiwan, for instance, estimates put the number of people with chronic hepatitis B at about two million, with an individual cost of treatment of about US\$ 2200 per annum. As insurance does not cover life-long treatment, patients are given continuous NA treatment for three years, after which it is withdrawn. Patients are then followed up to observe the durability of clinical remission. (About half of patients have clinical relapses, and almost all have virological relapses; only patients with clinical relapses are re-treated.)¹⁵

A growing body of evidence now favours systematic discontinuation of long-term NA treatment of HBeAg-negative non-cirrhotic subjects after suppression of HBV to low or undetectable levels but without a functional cure, that is to say “finite therapy”. Different virological phases follow NA discontinuation:¹⁶ first comes a lag phase lasting anywhere up to 12 months; then a reactivation phase of up to three months affecting HBV DNA levels, HBsAg levels and ALT activities; followed by a consolidation phase.¹⁷ The HBV DNA flares observed during the reactivation phase are often transient and most likely represent a trigger for inducing a long-term immune control by HBV-specific CD8+ T cells, and therefore do not need immediate interventions but close follow-up and evaluation; harmful flares can be terminated by reintroducing treatment. In chronic HBV infection

continued stimulation of HBV-specific CD8+ T cells by HBV antigens may exhaust the host antiviral responses. The resurgence of HBsAg after discontinuation of treatment may trigger immune memory B cells and reactivate exhausted T cells, leading to the eventual decline in HBsAg; but in some cases the T cells may remain in a state of exhaustion and be unable to suppress the antigen.

Outcomes range from HbsAg loss and sustained virological response (a “healthy carrier” state, with a HbsAg decline of about 40%) to an intermediate state or chronic hepatitis B requiring re-treatment. Low HbsAg levels at the time of initial cessation of treatment (<1000 mIU/ml) strongly predict a positive long-term response to NA discontinuation associated with a higher likelihood of HBsAg clearance.

Much increased rates of loss of HBsAg, up to 20–30% over two to three years of follow-up, have been reported, with highest cumulative rates in patients with sustained responses after discontinuation of initial treatment. In the short term, prognosis seems as good as for patients with spontaneous loss of HBsAg. Nevertheless, the results are varied. In the RETRACT-B study of an international and multicentre cohort of more than 1500 chronic hepatitis B patients who were virally suppressed, HBeAg-negative, noncirrhotic with low HBsAg levels and who stopped NA therapy,¹⁸ the cumulative probability of HBsAg loss (>30% after 48 months of follow-up) was higher in Whites than in Asians and in those with low HBsAg levels at the end of therapy (<1000 mIU/ml in Whites or <100 mIU/ml in Asians), with predictors of a favourable outcome in multivariate analysis being Caucasian ethnicity and HBsAg levels <100 mIU/ml. Virological and clinical relapse, with reintroduction of treatment after four years, was seen in 56% of patients, and flares were seen in a third. Again, stringent monitoring of the patients is vital so that decisions can be made in good time to ensure safety but not too early to halt clearance of HBsAg and achievement of functional cure.

Risk factors for clinical relapses after stopping treatment include age, host genetics and cirrhosis. ALT activities may rise abruptly five-fold higher than normal for chronic hepatitis B and HBV DNA concentrations may also rise. The timing of off-treatment flares differs with the NA used. Specifically, flares after TDF withdrawal occur significantly more early than after ETV cessation. Both virological and biochemical flares can have abrupt onset, and rarely may be severe. A double-edged sword, they might mark transitions to inactive disease or clearance of infection, but in certain scenarios they might also lead to hepatic decompensation or death.¹⁹ Decisions about when to recommence treatment are crucial, and criteria need to be established urgently. Biochemical markers can indicate the need to re-treat.

Nevertheless, the criteria for both discontinuing and recommencing treatment after flares have not yet been defined or agreed, although there is consensus that intense off-treatment monitoring is mandatory. Known risk factors for clinical relapse after discontinuation of therapy include older age, liver cirrhosis and prior treatment history. Levels of HBsAg at end of treatment are not correlated with time to relapse or flare severity.

Baseline viral markers associated with HBsAg loss were low levels of intrahepatic HBV DNA (<0.2 copies/cell) and of intrahepatic HBV RNA, corresponding to a decreased transcription of covalently-closed circular (ccc) HBV DNA.²⁰ (Upon infection, HBV establishes a pool of cccDNA in the nucleus of infected hepatocytes where antiviral agents have little or no effect on it.²¹) The patients who remained off-therapy after discontinuation of long-term NA treatment had high levels of HBV-specific CD8+ cells with CD107a, IFN γ and IFN γ /TFN α markers. However, controversy still dogs predictors of relapses. Only HBsAg serum levels at NA discontinuation seem to be the most robust predictive marker of the probability of subsequent off-treatment HBsAg seroclearance, and,

although newer viral markers such as HBV RNA and HBcrAg seem promising, further research is required.

Immediately upon infection, the HBV genome integrates into the host genome, where it resides invulnerable to antiviral agents. Recent studies have elucidated that a large fraction of circulating HBsAg originates from integrated HBV DNA and not from epigenomic cccDNA. Current tests cannot however distinguish between the two HBsAg fractions in serum. Recent developments include serum HBV RNA quantification as a possible marker of viral rebound and clinical relapse²² and monitoring the kinetics of the three glycoprotein isoforms (L, M and S) of HBsAg²³ for any association with flares. The results of a multinational trial of an assay for serum HBV-related core antigen, a potential marker for monitoring HBV reactivation as an alternative to HBV DNA,²⁴ are due soon. The lack of clear biomarkers for predicting outcomes of cessation of NA treatment hampers the introduction of this approach in clinical practice.²⁵

Guidelines

In 2020 the Spanish Association for the Study of the Liver issued a revised version of its 2012 consensus document on the treatment of hepatitis B infection with updated guidance on the management of chronic infection.²⁶ The treatment of choice is the long-term administration of an NA with high barrier to resistance (entecavir, tenofovir or tenofovir alafenamide): entecavir or tenofovir alafenamide are recommended in decompensated cirrhosis, chronic kidney disease and osteoporosis, tenofovir disoproxil fumarate and tenofovir alafenamide in HIV infection and tenofovir disoproxil fumarate in pregnancy.²⁷ As in the EASL guidelines, treatment should be started immediately for patients with HBV DNA concentrations of >2000 mIU/ml, high ALT activities, patients with compensated liver cirrhosis and those with decompensated liver disease. All patients must be monitored for the risk of progression to advanced liver disease and development of hepatocellular carcinoma. In line with the European guidelines the Spanish guidelines also recommend screening of all newly detected cases of HBsAg positivity for hepatitis D virus infection.

The need for monitoring of patients, including ultrasonography every 3–6 months, was emphasized by all the speakers.

In turn, guidance for management of patients with chronic hepatitis B^b has been reviewed, with some (but not all) national and international guidelines being revised and updated. Although still based on HBeAg status, presence of HBV DNA and liver enzyme activity, there remain divergences between the various guidelines, with those in Europe being more liberal than those in Asia or the USA. Furthermore, guidelines are not always followed in practice. A study of nearly 13,000 patients in the USA found that more than a quarter were not adequately evaluated and, although 11–14% of the rest met American or European criteria for treatment, only 54–60% of the latter received treatment within 12 months.²⁸

Not only screening for HBsAg was emphasized but screening for hepatitis D virus infection was recommended for every hepatitis B virus-infected subject. This recommendation has been included in EASL guidelines, whereas in the USA the AASLD guidelines recommend such screening only for

^b The European Association for the Study of the Liver (EASL) recently introduced a revised terminology: chronic HBV infection refers to viral infection with no rise in activity of alanine aminotransferase, and chronic hepatitis for patients in whom alanine aminotransferase activity is persistently raised, the latter being an indicator for treatment (Furquim d'Almeida A, Ho E, Van Hees S, Vanwolleghem T. Clinical management of chronic hepatitis B: A concise overview. *United European Gastroenterol J.* 2022;10(1):115-123. doi:10.1002/ueg2.12176).

high-risk subjects, even though it was agreed these may be difficult to identify, for example, immigrants from countries with a high prevalence of HDV and those with high ALT activities.

Panel discussion

Participants considered two questions:

Question 1. Currently is there sufficient scientific evidence to endorse discontinuation of treatment for patients with chronic hepatitis B virus infection in common practice?

Question 2. If yes, when and how should treatment be discontinued? If no, what information do we need for an evidence-based decision?

Generally, participants endorsed the conclusion that there is not enough scientific evidence to stop treatment in all patients with chronic hepatitis.

As, at its outset, chronic hepatitis is asymptomatic, diagnosis is the first step. WHO's targets for elimination by 2030 include 80% of those eligible for treatment being treated; that means improving diagnosis and early diagnosis must then lead to early treatment. At present, the rate of diagnosis is low across the world and better tests for viraemia (or other markers of infection) such as point-of-care tests and more testing are necessary. The 80% target is certainly ambitious, and must involve the screening of populations for HBsAg or raised ALT activities, little of which is done outside Asia. hepatitis B

The introduction of vaccination against hepatitis B benefited from an existing infrastructure for routine vaccinations and from the inclusion of hepatitis B vaccine into multivalent vaccines. It was also supported by political commitment. Globally, pressure must continue to be applied to raise and maintain hepatitis B vaccination rates, including coverage with the birth dose, and to keep WHO's 2030 elimination goals high on the public health agenda.

Clinicians deal with treatment failures whereas the public health community deals with failure to treat, a much larger problem. WHO's updated global health sector strategy on viral hepatitis for 2022–2030 does emphasize linkage to care, which is vital given that 30–40% of people with chronic hepatitis B do not have access to doctors.

Issues and needs

Generally, there is no base for introducing universal screening for HBsAg (as opposed to the standard response of screening only so-called high-risk groups) as there was for vaccination. Experiences with other programmes, however, have presented opportunities for integrating HBV screening into existing structures and programmes and of mobilizing the necessary resources: in some countries in Africa, for instance, people are routinely screened for HIV infection and in the USA screening of all adults for HCV infection was accepted once it was established that there were successful treatments. Incorporation of activities to prevent hepatitis B into other programmes such as those for COVID-19, as exemplified in Spain, should be encouraged and developed.

For health workers and medical students, policy decisions still need to be decided upon: should the policy be (1) boost all and then test or (2) test and then boost those with anti-HBs concentrations <10 mIU/ml?

Increasing awareness in the general population of chronic hepatitis B and its burden could help to increase the demand for screening. It was suggested that the VHPB should try to mobilize demand at grass-roots levels, to which politicians would respond. Increasing awareness could be complimented with advocacy for routine screening for HBsAg, not just in countries where the disease is endemic but elsewhere where there might also be a risk of stigmatization about being tested for HBV

infection in countries where it is not endemic. Other areas of action for all concerned parties are to understand and counter vaccine hesitancy, with health professionals taking a greater role as well as anthropological and social behavioural studies of the best ways forward, and continued outreach to vulnerable or hard-to-reach/under-served populations, from those with risk behaviours to migrants and women who do give birth outside health facilities.

In some countries, health ministries have issued political statements and made commitments, but not always is practice aligned with them; countries may have endorsed WHO's goals but not launched a screening programme. Politicians need to be held to account in such cases. Policies on reimbursement of the costs of treatment of chronic hepatitis B vary across countries and governments, some covering the costs of life-long treatment and others not. Discontinuation of treatment and subsequent possible re-treatment complicates the issues, and more data and health economics studies are vital.

Much research continues to need to be done in the scientific and clinical domains. Some of the top priorities identified were as follows.

- Continued studies of the duration of immunity after vaccination against hepatitis B and a better understanding of cell-mediated immunity and immune memory in long-term immunity
- Clinical studies of vaccinees who have apparently lost immunity, together with the development of surrogate markers for those people who have been vaccinated against hepatitis B but need boosting because of low or undetectable levels of antibodies to HBsAg
- Side effects of long-term NA therapy
- The role of cell-mediated immunity after discontinuation of treatment of chronic hepatitis B, for examples in clinical and virological relapse and flares, including immunological predictors of their outcomes; the mechanisms underlying the virus-specific dysfunctionality of T cells in chronic hepatitis B need to be understood
- The role of genotypes of hepatitis B virus in outcomes and responses to treatment
- Endpoints for antiviral treatment and clinical outcome, from viral suppression to seroconversion and loss of HBsAg
- More data on the activity of new antiviral agents against integrated HBV DNA and its products
- Discontinuation of treatment (“finite therapy”):
 - further studies of host characteristics and of biomarkers for selecting HBeAg-negative patients for cessation of treatment and the criteria for restarting treatment after relapses need to be identified and standardized;
 - well-designed, prospective randomized clinical trials that include consideration of host responses, ethnicity and baseline factors, such as end-of-treatment levels of HBsAg and HBV DNA, with more representative subjects (e.g. race, age, geographical location) than hitherto;
 - strategies for practice (including degree of loss of HBsAg, effectiveness of action at different levels of HBsAg and HBV DNA, and ALT activities and what cut-off levels to apply);
 - more data on clinical outcomes after cessation of treatment and their durability, including studies on the inactive carrier state that can be achieved;
 - more details on the immunological responses during treatment (e.g. CD8+ cells, memory cells, cccDNA and the source of HBsAg in flares)
 - issues around information for patients about consequences of discontinuation of treatment;
 - continued strict monitoring of patients whose treatment is stopped (for clinical outcomes, development of drug resistance and virological studies, such as for S-region variation) with guaranteed continued access to care and close follow-up.
- Can we even depend on loss of circulating HBsAg as a biomarker because of uncertainty about its source? There is a need to distinguish HBsAg produced by integrated HBV DNA from that produced by free virus (unintegrated), including studies with small interfering RNA.

- International validation and standardization of assays (e.g. hepatitis B core-related antigen (HBcAg) and point-of-care tests) and new biomarkers.
- Revision and harmonization of guidelines for clinical practice and management.

¹ Bruce MG, Bruden D, Hurlburt D, Morris J, Bressler S, Thompson G, et al. Protection and antibody levels 35 years after primary series with hepatitis B vaccine and response to a booster dose. *Hepatology*. 2022; 76:1180–1189. <https://doi.org/10.1002/hep.32474>.

² Trevisan A, Frasson C, De Nuzzo D, Nicolli A, Scapellato ML. Significance of anti-HB levels below 10 IU/L after vaccination against hepatitis B in infancy or adolescence: an update in relation to sex. *Hum Vaccin Immunother*. 2020;16(2):460-464. doi: 10.1080/21645515.2019.1656483. Epub 2019 Sep 5. PMID: 31487228; PMCID: PMC7062447.

³ Italian immunization schedule (<https://www.epicentro.iss.it/en/vaccines/immunization-schedule-italy>).

⁴ Khetsuriani N, Mosina L, Van Damme P, Mozalevskis A, Datta S, Tohme RA. Progress Toward Hepatitis B Control — World Health Organization European Region, 2016–2019. *MMWR Morb Mortal Wkly Rep* 2021;70:1029–1035. DOI: <http://dx.doi.org/10.15585/mmwr.mm7030a1>

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