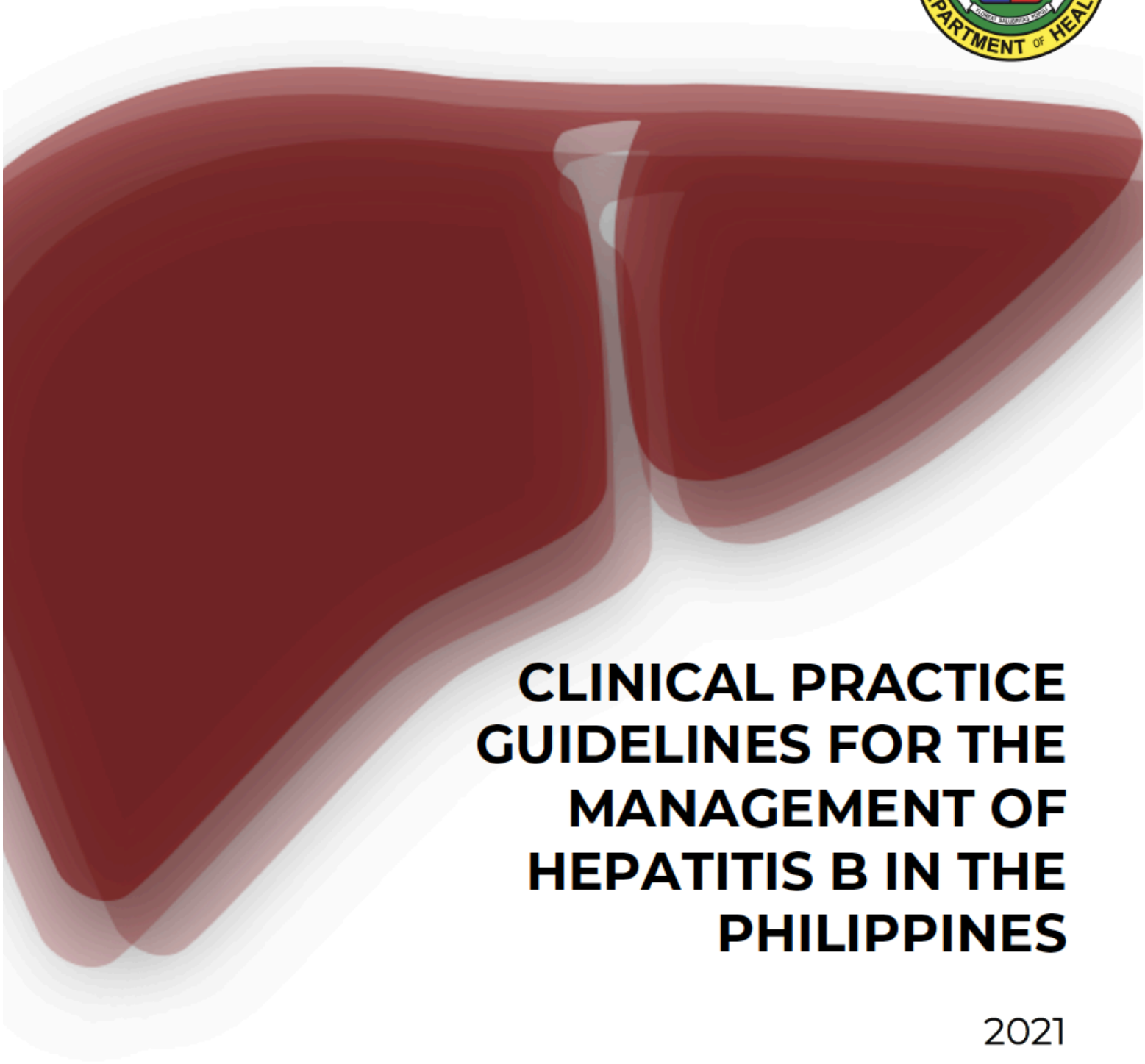

CLINICAL PRACTICE GUIDELINES FOR THE MANAGEMENT OF HEPATITIS B IN THE PHILIPPINES

2021

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DISCLAIMER

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of hepatitis B. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

LIST OF ABBREVIATIONS AND ACRONYMS

AASLD	American Association for the Study of Liver Diseases
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AE	adverse events
AFP	alpha fetoprotein
aHR	adjusted hazard ratio
AKI	acute kidney injury
ALT	alanine transaminase
AMMI	Association of Medical Microbiology and Infectious Disease
APASL	Asian Pacific Association for the Study of the Liver
APRI	AST to platelet ratio index
ARR	absolute risk reduction
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
CASL	Canadian Association for the Study of the Liver
CDC	Centers for Disease Control and Prevention of the United States
CHB	chronic hepatitis B
CI	confidence interval
CKD	chronic kidney disease
CLIA	chemiluminescent immunoassay
CP	Consensus Panel
CPG	clinical practice guidelines
CTP	Child-Turcotte-Pugh score
DM	diabetes mellitus
DOH	Department of Health
DRPI	drug price reference index
EASL	European Association for the Study of the Liver
eGFR	estimated glomerular filtration rate
EIA	enzyme immunoassay
ELISA	enzyme-linked immunoassay
ERE	Evidence Review Experts
EPP	exposure prone procedures
EtD	Evidence to Decision
ETV	entecavir
EPP	exposure prone procedures
FDA	Food and Drug Administration
FIB4	Fibrosis 4 Index for Liver Fibrosis
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HAV	hepatitis A virus
HBeAg	hepatitis B e antigen
anti-HBs	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HBV DNA	hepatitis B virus DNA
HCC	hepatocellular carcinoma
HCV	hepatitis C virus

HCW	healthcare workers
HDV	hepatitis D virus
HepA	hepatitis A
HepB	hepatitis B
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRS	hepatorenal syndrome
HSP	Hepatology Society of the Philippines
ICBS	International Consortium for Blood Safety
ICE	Institute of Clinical Epidemiology
ICER	incremental cost-effectiveness ratio
LAM	Lamivudine
LdT	Telbivudine
LGU	local government unit
LLQ	lower limit of quantitation
LLV	lower level viremia
LR	likelihood ratio
LT	liver transplantation
MEIA	microparticle enzyme immunoassay
MELD	Model for End-Stage Liver Disease
MeSH	Medical Subject Headings
MTCT	mother-to-child transmission
NA	nucleos(t)ide-analogue
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NPV	negative predictive value
NRTI	nucleotide reverse transcriptase inhibitors
NS	not significant
PCR	polymerase chain reaction
PhilHealth	Philippine Health Insurance Corporation
PEG-IFN	pegylated-interferon
PHP	Philippine pesos
PICO	Population-Intervention-Comparator-Outcome
PIEALT	persistently or intermittently elevated ALT
PNALT	persistently normal ALT
POGS	Philippine Obstetrical and Gynecological Society, Inc.
PPV	positive predictive value
PSM	propensity score matched/ing
QALY	quality-adjusted life years
QoL	quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized clinical trial
RDT	rapid diagnostic tests
RPHA	reverse passive hemagglutination assay
RR	relative risk
SC	Steering Committee
SHEA	Society for Healthcare Epidemiology of America
Sn	sensitivity
Sp	specificity
TAF	tenofovir alafenamide

TDF	tenofovir disoproxil fumarate
ULN	upper limits of normal
USPSTF	US Preventive Services Task Force
WHO	World Health Organization

EXECUTIVE SUMMARY

Hepatitis B infection is a highly prevalent disease in the Philippines affecting at least 7.3 million individuals and continues to be one of the leading causes of mortality and morbidity locally. Despite the implementation of nationwide expanded immunization programs as well as integration of hepatitis services at the primary care level, the management of these patients still prove to be challenging.

In this clinical practice guideline (CPG), we aimed to provide updated, evidence-based recommendations for the management of Hepatitis B in the Philippines. It is expected to benefit various end-users, including public health professionals, clinicians, researchers, policymakers and local government units, patients and their advocacy groups.

This CPG was developed using the standard methodology detailed in the DOH CPG Manual 2018. The CPG Development Task Force was composed of separate working groups. Thirteen priority guideline questions were identified by Lead CPG Developers. Current best available evidence (up to April 2021) were comprehensively searched and summarized by Evidence Review Experts. A multi-sectoral panel of representatives and experts formulated consensus recommendations. The GRADE method was used to determine the level of certainty of evidence and the direction and strength of each recommendation.

A total of twenty one recommendations were produced in these guidelines (Table 1). Although the certainty of evidence across different questions varied from very low to high, majority of interventions were strongly recommended primarily due to their anticipated net benefits.

Table 1. Summary of Final Recommendations, 2021 Clinical Practice Guidelines on the Management of Hepatitis B in the Philippines

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
	PREVENTION		
1	We recommend HBV catch-up vaccination among children 18 years old and younger with incomplete or unknown HBV vaccination to decrease prevalence of HBsAg, HBV detection, and increase anti-HBs seroconversion.	Moderate ⊕⊕⊕◯	Strong
2	We recommend catch-up vaccination of healthy adults with no serological evidence of immunity or previous vaccination to decrease the incidence of acute hepatitis B.	Low ⊕⊕◯◯	Strong
3	We recommend vaccination of pregnant women with no serological evidence of immunity to prevent horizontal transmission. However, there is insufficient evidence that this would decrease mother-to-child transmission.	Very low ⊕◯◯◯	Strong
4	There is insufficient evidence to recommend prophylactic administration of HBIG in infants born to mothers of unknown maternal HBV status. HBIG administration is only recommended for infants born to HBsAg-positive mothers. (*We only recommend HBIG for infants born to HBsAg-positive mothers.)*	Very low ⊕◯◯◯	Strong
5	We recommend the use of tenofovir disoproxil fumarate (TDF) for pregnant patients with chronic hepatitis B (CHB) with viral load ≥ 200,000 IU/mL from the 28th week of pregnancy until at least the delivery among pregnant patients with chronic hepatitis B infection for the prevention of mother-to-child transmission of hepatitis B.	Low ⊕⊕◯◯	Strong
	TREATMENT		
6A	We recommend the use of TDF or TAF or ETV among HIV-negative non-cirrhotic adults with chronic hepatitis B infection with elevated ALT and HBV DNA ≥ 2,000 IU/mL to attain biochemical, serologic, and virologic outcomes and to delay fibrosis progression.	Low ⊕⊕◯◯	Strong
6B	We recommend either TDF or ETV among HIV-negative non-cirrhotic adults with chronic hepatitis B infection in decreasing risk of HCC.	Very low ⊕◯◯◯	Strong
6C	We recommend the use of TAF over TDF among patients with indications for treatment who have pre-existing renal insufficiency and bone mineral disease.	Moderate ⊕⊕⊕◯	Strong
6D	We recommend the use of TDF over no antiviral treatment among HIV-negative non-cirrhotic children aged 12-18 years old with chronic hepatitis B infection with ALT ≥ 2x ULN and HBV DNA ≥ 18,000 IU/mL in decreasing risk for persistent liver inflammation and viremia.	Moderate ⊕⊕⊕◯	Strong
6E	We suggest the use of ETV over no antiviral treatment among HIV-negative non-cirrhotic children aged two to eighteen (2-18) years old with chronic hepatitis B infection with persistently elevated ALT ≥ 1.5x ULN and HBV DNA ≥ 18,000 IU/mL in decreasing risk for chronic liver inflammation, viremia, and non-HBeAg seroconversion.	Moderate ⊕⊕⊕◯	Conditional
7A	We recommend treatment with ETV or TAF or TDF for HIV-negative adults with chronic hepatitis B and compensated liver cirrhosis to decrease all-cause mortality, hepatitis B-related mortality, decompensating events and HCC.	Low ⊕⊕◯◯	Strong

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
7B	We recommend the use of TAF over TDF among chronic hepatitis B patients with compensated liver cirrhosis who have pre-existing renal insufficiency and bone mineral disease.	Moderate ⊕⊕⊕◯	Strong
7C	We recommend TDF (aged 12 to 18 years) or ETV (aged 2 to 18 years) for HIV-negative children and adolescents with CHB cirrhosis.	Low ⊕⊕◯◯	Strong
8A	There is insufficient evidence to recommend treatment of healthcare workers with chronic hepatitis B performing exposure-prone procedures to target HBV DNA levels to reduce procedure-related transmission of HBV.	Very low ⊕◯◯◯	None
8B	Healthcare workers who meet the target HBV DNA levels can be allowed to perform exposure prone procedures (EPP) provided they are referred to an institutional expert review panel for care.	Consensus statement	
	SCREENING AND DIAGNOSIS		
9	We recommend screening for all Filipino adults and adolescents for hepatitis B. This is incumbent on the availability of pre- and post-test counseling and linkage to care.	Low ⊕⊕◯◯	Strong
10	In resource-limited settings, we suggest using a single elevated ALT in combination with HBV DNA ≥ 2000 IU/mL to guide initiation of antiviral treatment in adults with chronic hepatitis B infection.	Very low ⊕◯◯◯	Conditional
	MONITORING		
11	We recommend periodic monitoring of ALT and HBV DNA to determine treatment eligibility in order to decrease hepatitis B-related outcomes.	Very low ⊕◯◯◯	Strong
12	We recommend periodic monitoring using HBV DNA, AFP, platelet count, albumin, creatinine among chronic hepatitis B patients with compensated liver cirrhosis on treatment to improve hepatitis B-related outcomes and decrease adverse drug effects.	Very low ⊕◯◯◯	Strong
13A	We recommend periodic monitoring among adult patients with chronic hepatitis B without liver cirrhosis on treatment using HBV DNA, ALT, APRI, FIB4, and creatinine to improve hepatitis B-related outcomes and decreasing adverse effects.	Very low ⊕◯◯◯	Strong
13B	We recommend monitoring of non-cirrhotic pediatric patients with chronic hepatitis B on antiviral treatment using HBV DNA, anthropometrics, creatinine, and bone mineral density at least annually.	Low ⊕⊕◯◯	Strong

Chapter 1. INTRODUCTION

Hepatitis B infection is a serious problem worldwide affecting approximately 240 million people.[1-3] This disease is highly prevalent in the Asia Pacific region with the Philippines having an estimated prevalence of 16.7% or 7.3 million Filipinos in 2013.[4] This prevalence represents more than twice the average prevalence in the Western Pacific region.[5] Despite the implementation of a nationwide expanded immunization program in 1995 to decrease its transmission, hepatitis B and the sequelae of its chronic infection remain as one of the leading causes of mortality and morbidity in the Philippines.

In 2014, the Hepatology Society of the Philippines developed consensus statements on the management of hepatitis B in the Philippines using a modified Delphi process. These statements included guides on screening and vaccination, general management, indications for assessment of fibrosis, indications for treatment, post-treatment monitoring, and duration of antiviral treatment.[5] Recommendations on the management of antiviral drug resistance and management of special populations were also tackled. Several international organizations have also published and updated their guidelines on this topic, namely, the American Association for the Study of Liver Diseases (AASLD) in 2009 and 2015, the Asian Pacific Association for the Study of the Liver (APASL) in 2012 and 2015; the European Association for the Study of the Liver in 2012 and 2017 and the World Health Organization in 2015. Although drafted comprehensively in ideal settings, these guidelines have been difficult to adopt on a wide scale due to limited resources. The WHO guidelines were primarily formulated to be used by low- to middle- income countries in scaling up their country-wide programs for hepatitis B prevention care and treatment. These recommendations, however may need to be revisited in the advent of changing knowledge on the management of this disease.

In 2019, the Department of Health (DOH) launched pilot sites for the integration of hepatitis services at the primary care level. These sites that include several municipalities in Pampanga, Bataan, Nueva Ecija, and Bulacan now have on-the-ground experience on how hepatitis B is managed at the primary care level. Preliminary reports on prevalence show a 4% seropositivity rate among 52,339 individuals tested in the primary sites of Central Luzon from August 2019 to July 2020.[6] This number may be an underestimate of the true prevalence of chronic hepatitis B because the primary centers cater to routine clients and not the general population. From this number, more than half are lost to follow-up due to difficulty in complying with treatment eligibility and treatment monitoring guidelines prescribed by the latest CPGs. Other issues that were observed in the pilot sites include adult and adolescent catch-up vaccination, pre- and post-exposure prophylaxis, as well as minimum diagnostic tests to increase compliance and follow-up.[6]

This CPG was developed to serve as a guide for healthcare workers when choosing cost-effective, evidence-based interventions for the management of patients with Hepatitis B infection in primary care.

Objectives of the CPG

This clinical practice guideline (CPG) aims to provide updated, evidence-based recommendations for the management of Hepatitis B in the Philippines.

Scope

This CPG will cover identified priority clinical questions in Hepatitis B prevention, screening, diagnosis, treatment and monitoring.

Target audience

The following users are expected to benefit from this CPG:

1. Public health professionals, such as provincial, city, rural and municipal health officers, program managers, public health nurses, midwives and barangay health workers
2. Private practitioners
3. Researchers
4. Policymakers and local government officials
5. Non-government organizations and advocacy groups

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Chapter 2. GUIDELINE DEVELOPMENT METHODOLOGY

OVERVIEW

Guideline preparation

This CPG followed the standard methodology described in the 2018 Manual for Clinical Practice Guideline Development by the DOH. [7]

The Institute of Clinical Epidemiology (ICE), under the National Institutes of Health of the University of the Philippines Manila was the facilitating agency for this CPG. The CPG task force was composed of the following working groups: Lead CPG Developer/Steering Committee (SC), Evidence Review Experts (ERE), and the Consensus Panel (CP). The individual members of these working groups were identified and convened after adequately coordinating with appropriate stakeholders and specialty societies.

The SC along with key stakeholders, namely DOH, PhilHealth, patient advocates, program managers from DOH primary care pilot sites, and private and public physicians, identified key areas that need to be addressed by the CPG through a series of consultative meetings. These areas included variations in practice, limitations in applicability of current recommendations in program implementation, and underuse or overuse of health technology. Data from the pilot sites in the form of demonstration reports, performance updates or interim reports that have been submitted to DOH were solicited to identify current processes or practices in the program implementation that warrant evidence review and guidance. Brainstorming sessions were also done involving project managers and the DOH to formulate key questions for research on the limitations in the applicability of current recommendations, as well as practices that may still need guidance and supportive evidence. Questions arising from these activities, as well as those nominated by the program managers were summarized and prioritized by the SC using an online form. The SC then finalized the scope and the final list of questions and forwarded them to the ERE for initiation of evidence synthesis.

The SC selected members of a Consensus Panel (CP) based on their knowledge, expertise, and potential conflicts of interest. The CP was composed of 14 multi-sectoral representatives such as private and public practitioners, primary and specialty care physicians, stakeholders, program managers and patient advocates, and members of the academe. These representatives were nominees of various specialty groups and acted as representatives of their respective organizations. Pilot program managers, patient advocates, and stakeholders were invited to represent the views of patients and the public.

Evidence synthesis

Related clinical guidelines were appraised and reviewed for their quality and validity using the AGREE II tool.[8] Guidelines that had an overall score of 75% with no domain garnering a score lower than 75% were considered to be of good quality. When available, systematic reviews and meta-analyses that dealt with a clinical question were also evaluated and critically-appraised. Only high-quality existing systematic reviews were considered in making draft recommendations.

To obtain primary studies, a universal search strategy for hepatitis B and related concepts was used. Depending on the clinical questions, concepts and search terms were derived and jointly finalized by the Steering Committee and the ERE. The following databases and trial registries were searched: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov, EU Clinical Trials Register, Chinese Clinical Trial Registry, and the International Clinical Trials Registry Platform (ICTRP). No date and language restrictions were applied. All search strategies were reviewed by the ERE project manager. Inclusion and exclusion criteria were applied as appropriate depending on the theme being analyzed (i.e., diagnosis or treatment). Two ERE independently appraised the directness, methodological quality, results, and applicability of the eligible studies for each guideline question. Meta-analyses were done to obtain overall estimates of effect for each outcome. When study results cannot be combined statistically, a narrative synthesis was done along with summary tables. Draft recommendations were then formulated based on the evidence.

A certainty level or quality rating was determined for the entire body of evidence evaluated for each research question. The certainty of evidence represents the degree of confidence that the estimates of the treatment effect or test accuracy lie close to the actual effects of interest. For questions that had varying levels of certainty across outcomes, the lowest quality among the outcomes rated as critical was considered as the final certainty level.

Evidence derived from randomized controlled trials (RCTs) was initially assigned a “high” quality, while evidence from observational studies was given a “low” rating. The initial ranking of RCTs was downgraded in case of serious risk of bias, inconsistency between studies, indirectness, imprecision, and publication bias. On the other hand, the ranking of observational studies was upgraded when there was a large and consistent effect, a dose-response relationship between the outcomes and degree of exposure, or plausible confounders that are expected to diminish the observed effect. The overall certainty (quality) of evidence and strength of recommendations were rated using the GRADE method (Grading of Recommendations, Assessment, Development, and Evaluations.[9,10]

The ERE was organized by a project leader who has expertise on CPG development and evidence-based medicine. The project leader oversaw the retrieval and appraisal of evidence, as well as the creation and drafting of recommendations. A separate project manager coordinated the operations of the ERE with the assistance of an administrative associate. Final evidence summaries were prepared by a technical writer to ensure that the recommendations were uniform, concise, and clear. These were then submitted to the consensus panel (CP) for initial review prior to the actual CP meetings.

Evidence to decision

Virtual *en banc* meetings with the 14 Consensus Panel members, were conducted over eight sessions (May 28, and 31; June 4, 7, 9, 14, and 16, 21) lasting two hours each. A skilled meeting

facilitator headed the CP meetings. Evidence summaries and draft recommendations were presented by the ERE for discussion and consensus voting. Evidence profiles were prepared for each key question using GRADEpro and Guideline Development Tool accessible through https://gradepro.org/. Outcomes considered critical and important for decision-making for healthcare providers and consumers were identified by the CP through an online survey. A quorum of 75% of the panelists was needed for each meeting to proceed.

Generation of recommendations

The Consensus Panel evaluated the direction and strength of each recommendation based on the: 1) overall certainty of evidence for each question, 2) balance between benefits and harms, 3) values and preferences of patients, 4) economic impact and burden on patients 5) cost and resource use and 6) other considerations that may arise during the discussion. Equity was incorporated in each step of the process following the Knowledge Management Plus (KM+) Equity Criteria described in the DOH Manual for Clinical Practice Guideline Development.[7] Panelists voted either "YES," "NO," or "ABSTAIN" on each draft. Consensus was reached when there was at least 75% agreement among panelists for both the direction and strength of recommendation. When consensus was not reached, each panelist was asked to explain the rationale behind their vote, then another round of voting commenced. The process was repeated up to three times until a consensus was reached. Questions that were not settled within a single meeting were subjected to the same consensus building process in the subsequent meeting; this precluded the need for a modified Delphi approach.

A standardized language was used to indicate the direction and strength of each recommendation. (e.g., *We suggest* for conditional, *We recommend* for strong recommendations). A *strong recommendation* was given when the consensus panel was confident that the desirable effects of the intervention or test outweigh its undesirable effects, or vice versa. A *conditional recommendation* was given when the panel was less certain about the trade-offs because of the absence of high-quality evidence, imprecise estimates of benefit or harm, limited applicability of the recommendations to certain populations or settings, or when the anticipated benefits come at a high cost.

Table 2. Certainty in the effect estimates (quality of evidence) in GRADE

Certainty	Definition and Implications	Randomized trials	Observational studies
HIGH ⊕⊕⊕⊕	The group is very confident that the true effect lies close to that of the estimate of the effect. (Further research is very unlikely to change confidence in the effect estimate)	No serious flaws in study quality	Extremely strong association and no major threats to validity
MODERATE ⊕⊕⊕◯	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (Further research is likely to have an important impact)	Serious flaws in design or execution; quasi-experimental design	Strong consistent association and no plausible confounders
LOW ⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. (Further research is very likely to have an important impact)	Very serious flaws in design or execution	No serious flaws in study quality
VERY LOW ⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. (The estimate of effect is very uncertain)	Very serious flaws and at least one other serious threat to validity	Serious flaws in design and execution

Funding and management of conflicts of interest

This CPG was funded by the DOH. The funding body did not influence the contents of the CPG for the thirteen questions that were prioritized. The SC formulated the guideline questions but had no participation in the evidence syntheses, drafting of the recommendations, and voting on final recommendations during the consensus panel meetings. All individuals involved in these guidelines were required to disclose potential conflicts of interest that have existed in the past 4 years. The SC assessed the individual interests for the panelists and decided that there were no substantial conflicts of interest that may have introduced bias in their decision making (Appendix 1).

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Chapter 3. EVIDENCE AND FINAL RECOMMENDATIONS

1. Should catch-up vaccination be recommended to children with incomplete or unknown vaccination status to reduce all-cause mortality, hepatitis B-related morbidity and mortality and hepatocellular carcinoma and horizontal transmission of hepatitis B?

We recommend HBV catch-up vaccination among children 18 years old and younger with incomplete or unknown HBV vaccination to decrease prevalence of HBsAg, HBV detection, and increase anti-HBs seroconversion.

Strength of recommendation: **Strong**
Certainty of evidence: **Moderate** ⊕⊕⊕◯

Hepatitis B virus (HBV) universal vaccination has been shown to be effective in decreasing the incidence of HBV-related morbidities and mortality including chronic HBV infection[11-15], fulminant hepatic failure in infancy[16] and childhood hepatocellular carcinoma[17-20]. For individuals who, for whatever reason, have not received or completed HBV vaccination, catch-up vaccination may be done. However, evidence on the effectiveness of catch-up vaccination in decreasing HBV-related morbidity and mortality is limited.

EVIDENCE TO DECISION

Benefits and harms

One cross-sectional study from Canada showed that catch-up vaccination in children aged 9 to 18 years old decreased HBsAg positivity, reduced HBV DNA detection and increased anti-HBs seroconversion.[14]

Certainty of evidence

The certainty of evidence was deemed moderate based on a good quality observational study with a large treatment effect on the outcomes of decreased risk of HBsAg positivity, reduced HBV DNA detection and increased anti-HBs seroconversion.

Other considerations

Cost

In China, a cost effectiveness analysis was done to assess the hepatitis B catch-up program.[21] Using a Markov model, the catch-up immunization program of children 1-19 years old was shown to have a 97% chance of being cost-saving and a 98% chance of having an incremental cost effectiveness ratio (ICER) of less than $2,500 per QALY gained.[21] Similarly, in Shandong China, HBV catch-up program was dominant compared to no vaccination in preventing symptomatic acute hepatitis B, HBsAg carriers, disease progression to cirrhosis, development of hepatocellular carcinoma, and reducing deaths due to HBV infection.[22]

In the Philippines, the approximate unit cost of one vial of pediatric or adult HBV vaccine ranges from PHP 250 to 300, which translates to approximately PHP 1,000 for the entire vaccination series. HBV treatment with oral nucleos(t)ide analogue for at least 1 year ranges from PHP 18,250 to 91,250 at a cost of PHP 50-250 per tablet. If the patient decompensates and requires liver transplant, the cost is about PHP 5,000,000.

Recommendations from other groups

The CDC Advisory Committee on Immunization Practices (ACIP) as of February 2021 recommends vaccination following the schedule listed below:[23]

a. unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months;
b. adolescents 11–15 years old may use an alternative 2-dose of adult recombinant formulation schedule with at least 4 months between doses;
c. adolescents ≥ 18 years old may receive a 2-dose series of adjuvanted Hep B vaccine at least 4 weeks apart;
d. adolescents ≥ 18 years old may receive the combined Hep A and Hep B vaccine as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

On the other hand, the American Academy of Pediatrics 2021 recommends the following:

a. administer the 3-dose series to those not previously vaccinated at 1 month interval for the first two doses and the third dose after eight weeks or at least 16 weeks from the first dose;
b. a 2-dose series 4 weeks apart of adult formulation is licensed for children aged 11 through 15 years;

The Philippine Foundation for Vaccination 2021 recommends administering three doses at 0, 1, and 6 months for 1-18 year old children who have not been previously vaccinated.[15]

CONSENSUS ISSUES

The panel strongly recommends catch-up vaccination for children on the basis of the following: (1) the high endemicity of HBV in the Philippines, (2) impact of hepatitis B on patients' quality of life, (2) high-level evidence on the benefits of catch-up vaccination for this population (i.e., reduced HBsAg positivity and HBV DNA, and increased anti-HBs seroconversion detection), (3) these benefits outweighing potential adverse effects, and (4) vaccination being cheaper than treating the disease.

Health equity issues were also considered before this consensus was reached. The cost and the feasibility of the treatment may penalize the marginalized and those living in remote areas. Good planning, appropriate health financing mechanisms, and government support are recommended to manage this risk.

SUMMARY OF FINDINGS

Table 3. Catch-up HBV vaccination for children with incomplete or unknown vaccination status.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Catch-up vaccination	No vaccination	Relative (95% CI)	Absolute (95% CI)		
HBsAg prevalence	1	4/1869 (0.2%)	50/2004 (2.5%)	**RR 0.08** (0.03, 0.24)	**23 fewer per 1,000** (from 24 fewer to 19 fewer)	Favors vaccination	MODERATE ⊕⊕⊕⊕
HBV DNA detection	1	3/1868 (0.2%)	38/2001 (1.9%)	**RR 0.08** (0.03, 0.27)	**17 fewer per 1,000** (from 18 fewer to 14 fewer)	Favors vaccination	MODERATE ⊕⊕⊕⊕
Anti-HBs detection	1	635/1871 (33.9%)	329/2007 (16.4%)	**RR 2.07** (1.84, 2.33)	**175 more per 1,000** (from 138 more to 218 more)	Favors vaccination	MODERATE ⊕⊕⊕⊕

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2. Should vaccination be recommended to healthy adult patients with no evidence of hepatitis B immunity to reduce hepatitis B-related outcomes?

We recommend catch-up vaccination of healthy adults with no serological evidence of immunity or previous vaccination to decrease the incidence of acute hepatitis B.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

Among adults who have not been previously exposed to hepatitis B infection or whose exposure and vaccination status is unknown, the effect of vaccination on the risk of developing hepatitis B infection and its sequelae is unclear.[25] Evidence on the benefit of vaccinating adult healthy populations in reducing hepatitis B-related outcomes requires evaluation.

EVIDENCE TO DECISION

Benefits and harms

No RCTs directly investigated the effects of catch-up vaccination among healthy adults in reducing hepatitis B-related outcomes. Three observational studies were found describing the effectivity of vaccination that included catch-up vaccination of all eligible adults in decreasing HCC prevalence and acute hepatitis B incidence.

A prospective cohort study done in Korea among an exclusively male population showed a large reduction in the incidence of HCC among vaccinated persons that is comparable to persons with natural immunity, when compared to chronic carriers.[26] A cross-sectional study in Alaska in 1987 showed that after a mass vaccination program that included catch-up vaccination of susceptible adults, incidence of acute symptomatic hepatitis B significantly dropped after completion of the mass immunization project.[27] A similar study in a highly endemic area in Italy showed a significant decrease of incident acute hepatitis B cases after mass HBV vaccination.[28]

Certainty of evidence

Certainty of evidence is low due to serious indirectness and study design limitations.

Other considerations

Cost

The cost of vaccination in the Philippines is approximately PHP 1000 (PHP 250-300/dose). Treatment for chronic hepatitis B is more expensive at PHP 50-250 per day for an indefinite period. Moreover, the cost of decompensated liver disease and possible liver transplantation may be insurmountable.

Recommendations from other groups

ACIP recommends vaccination of adults at risk of HBV infection, including universal vaccination of adults in settings in which a high proportion have risk factors for HBV infection and vaccination of adults requesting protection from HBV without acknowledgement of a specific risk factor.[29]

Follow-up testing is recommended for those who remain at risk of infection, such as HCWs, infants of HBsAg-positive mothers, sexual partners of persons with CHB, chronic hemodialysis patients, and immunocompromised persons, including those with HIV. Furthermore, annual testing of hemodialysis patients is recommended given that immunity wanes rapidly in these individuals who are at a high risk of continued exposure to HBV.

Booster doses are not indicated in immunocompetent individuals if the primary vaccination series is completed, as long-term follow-up studies indicate that immune memory persists despite declining anti-HBs levels.[29]

For individuals undergoing postvaccination serological testing, especially immunocompromised patients (such as persons on dialysis or with chronic inflammatory conditions, including HIV), a booster injection is advised by American Association for the Study of Liver Diseases (AASLD) when the anti-HBs titer falls below 10 mIU/mL.[30]

Local guidelines from the Philippine Society for Microbiology and Infectious Diseases (2018) recommend standard hepatitis B vaccination schedule of 0-1-6 months to confer long term protection among those who need immediate protection and rapid seroconversion among high-risk groups *(strong recommendation, very low quality of evidence)*.[31]

CONSENSUS ISSUES

Despite the low certainty of evidence and the unclear role or influence of factors like age, comorbidities, etc., the panel strongly recommends catch-up vaccination for adults to decrease the incidence of acute hepatitis B. Aside from theoretically being cheaper than hepatitis treatment, which can be particularly costly for chronic cases, vaccination can decrease the incidence of complications. However, the panel assessed vaccination's effectiveness for decreasing HCC cases to be insufficient. To ensure equal access to its benefits, vaccination programs would require government financing and support.

While the recommendation given is strong, the panel acknowledges the need for better-quality evidence. Similarly, further research is needed to evaluate the effects of adult catch-up vaccination as a public health strategy.

SUMMARY OF FINDINGS

Table 4. Catch-up HBV vaccination for adults with incomplete or unknown vaccination status.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Catch-up vaccination	No vaccination	Relative (95% CI)	Absolute (95% CI)		
HCC incidence (3 yr follow up)	1	8/100,000 (0.0%)	216/100,000 (0.2%)	**RR 0.04** (0.02, 0.07)	**2 fewer per 1,000** (from 2 fewer to 2 fewer)	Favors vaccination	LOW ⊕⊕◯◯
Acute hepatitis B (3-6 yr follow up)	2	24/100,000 (0.0%)	306/100,000 (0.3%)	**RR 0.08** (0.05, 0.11)	**3 fewer per 1,000** (from 3 fewer to 3 fewer)	Favors vaccination	LOW ⊕⊕◯◯

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3. Should vaccination be recommended to pregnant women who have no serological evidence of hepatitis B immunity to prevent maternal to fetal transmission and horizontal transmission?

We recommend vaccination of pregnant women with no serological evidence of immunity to prevent horizontal transmission. However, there is insufficient evidence that this would decrease mother-to-child transmission.

Strength of recommendation: **Strong**
Certainty of evidence: **Very Low** ⊕◯◯◯

Pregnancy is a period wherein both screening and intervention can be done to address newborn health. It is also the time when previously unvaccinated women seek consultation with the healthcare system and provide an opportunity to incorporate immunization to address the health of the mother and to prevent maternal to fetal and horizontal transmission of vaccine preventable diseases.[32] As vertical transmission is the most common form of hepatitis B transmission in the Philippines,[33] vaccination has been done as a measure to decrease hepatitis B infection in infants through the formation of protective antibodies that may pass through the placental barrier.[34]

EVIDENCE TO DECISION

Benefits and harms

No RCTs directly compared vaccination versus no vaccination for susceptible pregnant patients to prevent MTCT of hepatitis B. Instead, nine cohort studies investigated the efficacy, safety, and maternal transfer of antibodies to neonates after giving hepatitis B catch-up immunization during pregnancy.

Among the pregnant women given hepatitis B vaccine during pregnancy, 389 out of 486 (80%) showed seroconversion.[35-41] Of the 185 infants of mothers who were vaccinated, 158 (85%) had seroprotective levels of antiHBs.[35,36,38,42] There were no serious adverse events reported after administration of the vaccine.[35,36,40,41,42,43]

Certainty of evidence

The overall certainty of evidence was rated very low due to serious risk of bias (i.e., issues on comparability) and study design limitations, serious indirectness for the outcomes of seroconversion and maternal transfer of antibodies.

Other considerations

Recommendations from other groups

The American College of Obstetricians and Gynecologist (ACOG) and the Centers for Disease Control recommend prenatal screening for all pregnant women for hepatitis B. According to the

ACOG, all pregnant women who are HBsAg negative and who are at risk for hepatitis B infection should be specifically targeted for immunization.[37]

The Philippine Obstetrical and Gynecological Society, Inc (POGS), through its immunization for Filipino women task force, recommends that all HBsAg-negative pregnant women seeking STD treatment who have not been vaccinated should receive hepatitis B vaccination (Grade III, Level B).[44]

CONSENSUS ISSUES

The overall certainty of evidence was deemed very low due to issues with the studies' designs (i.e., fair-quality observational studies), comparability, and indirectness for two outcomes (i.e., seroconversion and maternal transfer of antibodies). Despite this limitation, the panel strongly recommends catch-up vaccination for pregnant women for the following reasons: (1) the high incidence of HBV, (2) the potential benefits of vaccination outweighing the risks, (3) current prenatal care practices already involving HBV vaccination and HBV antibody and antigen screening, and (4) the cost-effectiveness of vaccination. With regard to the treatment's risk benefit ratio, it was agreed upon that HBV vaccination poses minimal to no risks to infants and it may even offer them protection. More evidence is needed to evaluate the effectiveness of vaccination in decreasing the incidence of MTCTs. Nevertheless, as vaccination during pregnancy might be the only window of opportunity for mothers to get vaccinated, this recommendation will likely promote maternal health by decreasing the chances of horizontal transmissions.

SUMMARY OF FINDINGS

Table 5. Catch-up HBV vaccination for pregnant women with no serological evidence of hepatitis B immunity.

Outcomes	Studies	Effect	Certainty of evidence
Seroconversion after vaccination	7	Of the pooled 486 pregnant women from 7 studies, 389 (80%, 95% CI 70-92%) developed protective levels of antibodies	VERY LOW ⊕◯◯◯
Adverse events	7	Of the 4 studies which enumerated adverse events (n=265), pain (n=30), fatigue (n=10) and headache (n=5) were the most frequent complaints. The remaining three reported no serious adverse events.	LOW ⊕⊕◯◯
Maternal transfer of antibodies	4	Of the pooled 185 infants of mothers who were vaccinated 158 (85%) tested positive for protective levels of anti-HBs at birth, surrogate outcome of maternal-fetal transfer of antibodies and protection from infection.	VERY LOW ⊕◯◯◯

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4. Should administration of hepatitis B immunoglobulin be recommended to be given to infants born to mothers of unknown hepatitis B virus status to reduce maternal to fetal transmission?

There is insufficient evidence to recommend prophylactic administration of HBIG in infants born to mothers of unknown maternal HBV status.

HBIG administration is only recommended for infants born to HBsAg-positive mothers.

Strength of recommendation: **Strong**
Certainty of evidence: **Very Low** ⊕◯◯◯

A younger age at infection of hepatitis B is associated with an increased risk of chronic infection, where around 15-25% may later suffer from complications like cirrhosis, liver failure, and HCC. Among infants that may be infected by vertical transmission—the predominant form of transmission in the Philippines—90% may develop chronic infection.[45,46] In a review of outpatient charts of 768 pregnant patients from the Philippine General Hospital by Carpio et al. in 2015, it was shown that 9.6% of patients were HBsAg seropositive, reflecting the need for interventions to minimize maternal to fetal transmission.[47] There is a need to investigate whether prophylactic administration of HBIG among infants of unscreened or mothers with unknown hepatitis B status is effective in reducing vertical transmission.

EVIDENCE TO DECISION

Benefits and harms

No RCTs or observational studies were found that directly answer whether HBIG prophylaxis among infants of mothers with unknown maternal status decreases hepatitis B maternal to fetal transmission. Instead, 8 RCTs were found on the detection of HBsAg and the development of anti-HBs after the administration of HBIG plus vaccine versus vaccine alone, and one RCT comparing the persistence of HBsAg between HBIG administered infants versus placebo.[50, 57-64]

Pooled analysis of 8 RCTs failed to show statistically significant difference in HBsAg detection between the two groups, and pooled analysis of 4 RCTs did not show statistical difference in anti-HBs seroconversion between the two groups. When compared to placebo, HBIG decreased HBsAg detection.

Certainty of evidence

The overall certainty of evidence was rated very low due to risk of bias concerns, indirectness, inconsistency, and imprecision.

Other considerations

Cost

A 2013 cost-effectiveness study[52] suggested that the best vaccination strategy depends on the prevalence of HBV in the area and the willingness-to-pay threshold. The study did not consider other factors such as manpower, prior maternal screening, and infrastructure for health service delivery of any of the strategies. Among areas with high endemicity (HBV carrier rates of 15%), universal vaccination with no screening for HBsAg and no HBIG administration had the lowest cost but prevented the fewest infections. On the other hand, universal vaccination plus screening for HBsAg and HBIG administration had the highest cost, highest ICER (increment cost/per incremental infection averted), but averted the most number of infections.[51]

In the Philippines, the drug price reference index (DRPI) of 0.5mL HBIG and pediatric Hepatitis B vaccine are PHP 1,163.00 and PHP 133.72, respectively. The cost of HBsAg testing may range from PHP 220-300.[54-54]

Recommendations from other groups

According to the recommendation of the HSP released last 2020, all pregnant women should be screened for hepatitis B to help prevent vertical transmission. It is also recommended that infants born to mothers with chronic hepatitis B should receive a prophylaxis of 0.5ml HBIG plus the first dose of the hepatitis B vaccine within 12 hours of birth to decrease the rate of transmission from 90% to 10%.[46]

The CDC recommended that all infants born to women with unknown hepatitis B status must be given a hepatitis B vaccine shot without HBIG within 12 hours of birth. If the mother is then tested to be HBsAg positive, the infant must receive a dose of HBIG within 7 days. If the mother was never tested and the hepatitis status is not determined, HBIG is not necessary for the infant. However, among preterm infants with a birthweight of <2,000 grams, HBIG must be given to augment the immunogenicity of the hepatitis B vaccine if the HBsAg status of the mother cannot be determined within 12 hours of birth. HBIG administration is also recommended within 12 hours of birth among infants born to unknown maternal hepatitis B status but with evidence of infection such as a positive HBV DNA, HBeAg positive status or mothers known to be chronically infected.[55-56]

CONSENSUS ISSUES

A strong recommendation was given for the vaccination of infants born to mothers who turn out to be positive on HBsAg screening. The following points support this recommendation: (1) pregnant women come to primary care centers without being ever screened, (2) it is not possible to do HBsAg determination in at least 80% of sites, (3) UHC now provides access to HBsAg testing, (4) the current practice of pediatricians is to routinely give HBIG to HBV-positive mothers, and (5) the side effects of screening or HBIG appear to be minimal, at least in practice.

The panel acknowledged, however, that current evidence is insufficient to make any recommendations for or against HBIG for infants of mothers with unknown HBV status. The need to know mothers' HBV status prior to vaccination highlights the importance of HBsAg testing.

In principle, the present recommendations are viewed as fairly feasible to implement. As vaccination is considered a standard of care, the recommendation to give HBIG is made together with universal HBV vaccination for all infants at birth. However, the following implementation

challenges must be managed: 1) its high cost, 2) its limited accessibility in most places, and 3) the need to administer it within 24 hours after HBsAg test results are known.

SUMMARY OF FINDINGS

Table 6. HBIG for infants born to mothers of unknown status.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		HBIG	Placebo	Relative (95% CI)	Absolute (95% CI)		
HBsAg status	8	34/926 (3.7%)	53/1147 (4.6%)	**RR 0.71** (0.47 to 1.06)	**13 fewer per 1,000** (from 24 fewer to 3 more)	NS	VERY LOW ⊕◯◯◯
Anti-HBs	4	463/709 (65.3%)	444/641 (69.3%)	**RR 0.95** (0.88 to 1.02)	**35 fewer per 1,000** (from 84 fewer to 14 more)	NS	LOW ⊕⊕◯◯

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5. Should treatment be recommended to pregnant patients with chronic hepatitis B infection to decrease all-cause mortality, hepatitis B-related morbidity and mortality, prevalence and incidence of chronic hepatitis B infection?

We recommend the use of tenofovir disoproxil fumarate (TDF) for pregnant patients with chronic hepatitis B (CHB) with viral load ≥ 200,000 IU/mL from the 28th week of pregnancy until at least the delivery among pregnant patients with chronic hepatitis B infection for the prevention of mother-to-child transmission of hepatitis B.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

Mother-to-child transmission (MTCT) of HBV still accounts for most cases of CHB infection. Even though immunization against HBV, together with the administration of hepatitis B immune globulin at birth, has reduced the risk of MTCT, immunoprophylaxis fails in 10 to 30% of infants born to mothers with high level of viremia.[65-67] Antiviral agents that inhibit HBV replication have been administered to pregnant women with a high viral load and may reduce the risk of MTCT. Tenofovir disoproxil fumarate (TDF), a nucleotide analogue and a potent inhibitor of HBV polymerase, is the only approved nucleotide analogue with high efficacy against HBV but no detected clinical resistance to date.[68] TDF is classified as a pregnancy category B drug and has been widely used in HIV and HIV/HBV co-infection and may be useful in preventing MTCT. In a recent meta-analysis on peripartum antiviral prophylaxis for reducing the risk of HBV MTCT, TDF was concluded to be effective.[67]

EVIDENCE TO DECISION

Benefits and harms

Five RCTs were found on the use of TDF among pregnant patients with chronic hepatitis B for the prevention of MTCT and hepatitis B-related morbidity.[45,46,48-50] Pooled results of four trials showed that compared to no treatment/placebo, TDF was associated with significant reduction in MTCT of hepatitis B virus (HBV).[65,66,68,69] There were also no differences in maternal and infant adverse events, fetal development, and infant growth between the treatment and control groups.

Certainty of evidence

There was high certainty of evidence on the outcome of MTCT, while the outcomes on maternal and infant safety were deemed low to moderate due to inconsistency and imprecision.

Other considerations

Cost

TDF costs approximately PHP 1440/bottle of 30 tablets or about 48 pesos/tablet, with an estimated total cost of treatment PHP 4,032 for a minimum of 12 weeks.

Recommendations from other groups

The WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥ 200,000 IU/mL receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth to prevent mother-to-child transmission of hepatitis B. This is in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose (conditional recommendation, moderate quality of evidence).[71]

CONSENSUS ISSUES

Despite the low certainty of evidence associated with tenofovir, the panel strongly recommends its use among pregnant women primarily because of its benefits, safety profile, and cost-effectiveness. It should be noted that the perused safety data were taken from studies involving pregnant women with HIV and not HBV. Aside from benefitting the mother, vaccination will also provide additional protection to the infant since the main cause of HBV in babies is MTCT. This recommendation should not be used to discriminate against the use of pharmacologic treatments other than tenofovir.

Overall, this recommendation is deemed feasible because it is already consistent with the current practice of local obstetricians. However, this treatment can be costly, especially if required for a long period. Government financing, strategic planning, and support are vital to maximizing accessibility, as well as patients' adherence to treatment.

SUMMARY OF FINDINGS

Table 7. TDF for pregnant patients with chronic hepatitis B infection.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		TDF	No treatment	Relative (95% CI)	Absolute (95% CI)		
MTCT	4 (n=672)	0/357 (0.0%)	27/315 (8.6%)	**RR 0.06** (0.01, 0.24)	**81 fewer per 1,000** (from 85 to 65 fewer)	Benefit	HIGH ⊕⊕⊕⊕
Maternal hepatic flares	1	9/154 (5.8%)	5/157 (3.2%)	**RR 1.84** (0.62, 5.35)	**27 more per 1,000** (from 12 fewer to 139 more)	NS	MODERATE ⊕⊕⊕◯
Infant safety	4	Pan et al – no difference TDF vs. control Jourdain et al. – 27% TDF, 24% placebo w/ at least 1 SAE, NS Lin et al – no difference Sun et al – no difference				TDF similar to control	LOW ⊕⊕◯◯
Maternal safety	5	Pan et al. – higher creatinine (7% vs. 0, P=0.006) and ALT (45% vs. 30%, P=0.03) in TDF vs. placebo Jourdain et al. – no difference Lin et al – 2/59 (3%) patients in TDF group experienced nausea and vomiting, but continued TDF with symptomatic treatment Pan et al - one mother in the TDF group (1%) withdrew from the trial owing to grade 2 nausea. Chandran et al. – nausea seen with LAM and TDF in 33.5 and 31%, respectively (p = 0.715), NS Sun et al. – reported no severe adverse reaction				TDF similar to control	LOW ⊕⊕◯◯

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6. Should treatment be recommended to patients with chronic hepatitis B infection without liver cirrhosis to decrease hepatitis B-related outcomes?

A. We recommend the use of TDF or TAF or ETV among HIV-negative non-cirrhotic adults with chronic hepatitis B infection with elevated ALT and HBV DNA ≥ 2,000 IU/mL to attain biochemical, serological, and virologic outcomes and to delay fibrosis progression.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

B. We recommend either TDF or ETV among HIV-negative non-cirrhotic adults with chronic hepatitis B infection in decreasing risk of HCC.

Strength of recommendation: **Strong**
Certainty of evidence: **Very Low** ⊕◯◯◯

C. We recommend the use of TAF over TDF among patients with indications for treatment who have pre-existing renal insufficiency and bone mineral disease.

Strength of recommendation: **Strong**
Certainty of evidence: **Moderate** ⊕⊕⊕◯

D. We recommend the use of TDF over no antiviral treatment among HIV-negative non-cirrhotic children aged 12-18 years old with chronic hepatitis B infection with ALT ≥ 2x ULN and HBV DNA ≥ 18,000 IU/mL in decreasing risk for persistent liver inflammation and viremia.

Strength of recommendation: **Strong**
Certainty of evidence: **Moderate** ⊕⊕⊕◯

E. We suggest the use of ETV over no antiviral treatment among HIV-negative non-cirrhotic children aged two to eighteen (2-18) years old with chronic hepatitis B infection with persistently elevated ALT ≥ 1.5x ULN and HBV DNA ≥ 18,000 IU/mL in decreasing risk for chronic liver inflammation, viremia, and non-HBeAg seroconversion.

Strength of recommendation: **Conditional**
Certainty of evidence: **Moderate** ⊕⊕⊕◯

Among non-cirrhotic patients treatment options to prevent progression to liver cirrhosis and to decrease HCC incidence are PEG IFN, nucleoside analogues and nucleotide analogues. Among all drugs registered, most of the established guidelines around the world advocate the use of ETV, TDF and TAF as the first-line agents for the treatment of chronic hepatitis B due to its high genetic barrier for resistance. Furthermore, these three drugs have been easily available in the Philippine

market for use. Though the use of IFN is still recommended by most treatment algorithms, the use of PEG-IFN is beyond the scope of this document.

EVIDENCE TO DECISION

Benefits and harms

Six RCTs[88-93] and 10 cohort studies[85, 94-100, 104] provided data on the effects of TDF, TAF, and ETV on various outcomes among non-cirrhotic CHB patients.

When compared to placebo, TDF was associated with lower risk for persistent liver fibrosis progression (liver biopsy), liver inflammation (ALT elevation), and viral replication (HBV DNA). TDF was comparable to ETV in reducing HCC incidence and suppressing disease activity. Similarly, TAF was shown to be non-inferior to TDF in terms of viral replication suppression (HBV DNA), resolution of liver inflammation (ALT normalization), and disease activity suppression (HBeAg). TAF was associated with a lower risk of bone resorption (bone mineral density) and kidney function decline (creatinine clearance) compared to TDF.

TDF was associated with greater decline in kidney function (estimated glomerular filtration rate) compared to ETV. However, these two drugs were comparable in their effects on osteopenia/osteoporosis based on one cross-sectional study including patients treated for >18 months.[98] Drug resistance events were not reported in the RCTs and observational studies for all 3 drugs.

Two RCTs involving non-cirrhotic pediatric patients showed that TDF and ETV use was associated with a decreased risk for persistent liver inflammation (ALT) and lower persistent viral replication (HBV DNA).[104, 105]

Certainty of evidence

Certainty of evidence was assessed as very low for HCC incidence due to issues on imprecision and study design limitations, moderate for fibrosis progression due to indirectness, and low for biochemical, virologic, and serologic outcomes due to imprecision and inconsistency. Among studies on pediatric patients, outcomes on persistent liver inflammation and persistent viral replication were of moderate certainty of evidence due RCTs that were downgraded due to issues on directness.

Other considerations

Cost

TDF was concluded to be the most cost-effective oral antiviral compared with other agents in both non-cirrhotic and cirrhotic patients. At a threshold of C$50,000 per QALY gain ceiling, first-line TDF monotherapy was the most effective strategy among NA-naive patients with or without cirrhosis. Furthermore, all strategies using TDF as first-line antiviral were more cost-effective than first-line use of any other NA. Specifically, the total net benefits for NA-naive patients with cirrhosis were as follow: TDF then LAM C$219,587, TDF then TDF+LAM C$219,306, and TDF then TDF+LAM then ETV C$219,305. Among lamivudine-resistant patients with or without cirrhosis, shifting to TDF monotherapy was also the most cost-effective second-line treatment, with a total net benefit of C$346,373.[101]

At a threshold ICER of €50,000 per QALY gained, TDF was associated with lower costs and higher efficacy (€30,959 per QALY) compared with ETV (€46,498 per QALY). Conversely, telbivudine (€62,051 per QALY), and adefovir (€82,824 per QALY) did not have favorable ICER compared with natural history of disease. Furthermore, among the monotherapies, only tenofovir had an ICER per QALY below the threshold of €23,000–34,000 set by the National Institute for Health and Clinical Excellence (NICE). The analysis of patients with cirrhosis confirms the results obtained with the CHB cohort though with higher ICERs (tenofovir €68,833.82 per QALY vs ETV €89,758.12 per QALY).[101]

Recommendations from other groups

Multiple societies have advocated the use of tenofovir as an agent of choice for the treatment of CHB.[106-111] Antiviral therapy is likewise suggested for pediatric patients with chronic hepatitis B cirrhosis.

CONSENSUS ISSUES

Despite the very low to moderate certainty of evidence, the panelists voted for a strong recommendation because they were convinced that there is enough data on the beneficial effects of antivirals in preventing liver-related outcomes, particularly hepatocellular carcinoma. The panel emphasized the need to monitor patients for initiation of treatment and the type and dosage of treatment considering renal status.

The feasibility of monitoring patients who are eligible for treatment was the primary barrier discussed in implementation. The availability of certain diagnostics is limited in rural areas (e.g., only one access point for HBeAg was available for an entire province), so the possibility of alternative parameters (e.g., APRI alone) was raised. However, the group agreed that evidence of liver damage (e.g., ALT, APRI) and viral replication (e.g., HBV DNA) are required in the decision to initiate treatment.

As for non-cirrhotic pediatric patients, the panel gave one strong recommendation for TDF and one conditional recommendation for ETV based on the moderate certainty of evidence showing net benefit. Feasibility issues were the primary reason for lowering the strength of recommendation. The need for and feasibility of a more definitive measure (i.e., a liver biopsy) was a major point of contention. As there may be other reasons for elevated ALT and HBV DNA levels in children, some panel members were concerned about subjecting children to a potentially prolonged medication period without a definite diagnosis of liver fibrosis. On the other hand, the panel acknowledged that the cost, material resources, and specialists required to do a biopsy might delay or hinder patients' treatment. To address this dilemma, the panel decided to recommend treatment based on ALT and HBV DNA levels with a caveat. For this recommendation to be successfully implemented in the primary health care setting, co-management with specialists will be key.

SUMMARY OF FINDINGS

Table 8. TDF compared to no treatment in CHB without cirrhosis.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		TDF	No treatment	Relative (95% CI)	Absolute (95% CI)		
Incidence of HCC	1	504 participants 1.7/1000 person years	504 participants 6.22/1000 person years	**aHR 0.27** (0.07 to 0.99)	**5 fewer per 1,000** (from 6 fewer to 0 fewer) **5 fewer per 1,000** (from 6 fewer to 0 fewer)	Benefit	VERY LOW ⊕◯◯◯
Persistent fibrosis progression (3 yr follow up)	1	19/73 (26.0%)	34/73 (46.6%)	**RR 0.56** (0.35 to 0.88)	**384 fewer per 1,000** (from 567 fewer to 105 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Persistent liver inflammation in patients with chronic HBV infection (3 yr follow up)	1	21/74 (28.4%)	39/75 (52.0%)	**RR 0.55** (0.36 to 0.83)	**234 fewer per 1,000** (from 333 fewer to 88 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Viremia/Persistent viral replication in patients with chronic HBV infection (3 yr follow up)	1	11/74 (14.9%)	66/75 (88.0%)	**RR 0.17** (0.10 to 0.29)	**730 fewer per 1,000** (from 792 fewer to 625 fewer)	Benefit	MODERATE ⊕⊕⊕◯

Table 9. TAF vs TDF for CHB patients

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		TDF	Placebo	Relative (95% CI)	Absolute (95% CI)		
HBeAg-negative with ALT > 2x							
Resolution of liver inflammation in (44-96 wks follow up; assessed with: ALT normalization - study Central Lab cut-offs)	2	387/472 (82.0%)	177/242 (73.1%)	**RR 1.12** (1.03 to 1.22)	**88 more per 1,000** (from 22 more to 161 more)	Benefit	MODERATE ⊕⊕⊕◯
Suppression of viral replication (44-96 wks follow up; assessed with achieving HBV DNA <29 IU/ml)	2	525/570 (92.1%)	257/280 (91.8%)	**RR 1.00** (0.96 to 1.05)	**0 fewer per 1,000** (from 37 fewer to 46 more)	NS	MODERATE ⊕⊕⊕◯
HBeAg-positive							
Resolution of liver inflammation in (44-96 wks follow up; assessed	2	789/1074 (73.5%)	360/536 (67.2%)	**RR 1.09** (1.02 to 1.17)	**60 more per 1,000** (from 13 more to 114 more)	Benefit	MODERATE ⊕⊕⊕◯

with: ALT normalization - study Central Lab cut-offs)							
Suppression of viral replication (44-96 wks follow up; assessed with achieving HBV DNA <29 IU/ml)	2	794/1162 (68.3%)	413/584 (70.7%)	**RR 0.97** (0.91 to 1.03)	**21 fewer per 1,000** (from 64 fewer to 21 more)	NS	MODERATE ⊕⊕⊕◯
Suppression of disease activity (44-96 wks; assessed with HBeAg loss)	2	201/1130 (17.8%)	85/570 (1 4.9%)	**RR 1.19** (0.95 to 1.50)	**28 more per 1,000** (from 7 fewer to 75 more)	NS	MODERATE ⊕⊕⊕◯
Suppression of disease activity (44-96 wks; assessed with HBeAg seroconversion)	2	157/1130 (13.9%)	58/570 (10.2%)	**RR 1.37** (1.03 to 1.81)	**38 more per 1,000** (from 3 more to 82 more)	Benefit	MODERATE ⊕⊕⊕◯

Table 10. TDF compared to placebo for CHB infection among pediatric patients.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		TDF	Placebo	Relative (95% CI)	Absolute (95% CI)		
Persistent liver inflammation (72 wks)	1	9/35 (25.7%)	29/42 (69.0%)	**RR 0.37** (0.20 to 0.68)	**435 fewer per 1,000** (from 552 fewer to 221 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Persistent Viral Replication Assessed by HBV DNA > 400 copies/ml(72 wks)	1	6/52 (11.5%)	54/54 (100.0%)	**RR 0.12** (0.06 to 0.25)	**880 fewer per 1,000** (from 940 fewer to 750 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Persistent Disease Activity Assessed by non-HBeAg loss (72 weeks)	1	38/48 (79.2%)	41/48 (89.4%)	**RR 0.93 (0.77 to 1.12)**	**76 fewer per 1,000** (from 248 fewer to 129 fewer)	Inconclusive	MODERATE ⊕⊕⊕◯

Table 11. ETV compared to placebo for CHB infection among pediatric patients.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		TDF	Placebo	Relative (95% CI)	Absolute (95% CI)		
Persistent liver inflammation (48 wks; assessed with non-ALT normalization)	1	39/120 (32.5%)	46/60 (76.7%)	**RR 0.42** (0.32 to 0.57)	**445 fewer per 1,000** (from 521 fewer to 330 fewer)	Benefit	MODERATE ⊕⊕⊕◯

Persistent Viral Replication (48 wks; assessed with HBV DNA > 300 copies/mL)	1	61/120 (50.8%)	58/60 (96.7%)	**RR 0.53** (0.44 to 0.63)	**454 fewer per 1,000** (from 541 fewer to 358 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Persistent disease activity (48 wks; assessed with non-HBeAg seroconversion)	1	91/120 (75.8%)	54/60 (90.0%)	**RR 0.84** (0.74 to 0.96)	**144 fewer per 1,000** (from 234 fewer to 36 fewer)	Benefit	MODERATE ⊕⊕⊕◯

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7. Should treatment be recommended to patients with chronic hepatitis B infection with compensated liver cirrhosis to decrease hepatitis B-related outcomes?

A. We recommend treatment with ETV or TAF or TDF for HIV-negative adults with chronic hepatitis B and compensated liver cirrhosis to decrease all-cause mortality, hepatitis B-related mortality, decompensating events and HCC.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

B. We recommend the use of TAF over TDF among chronic hepatitis B patients with compensated liver cirrhosis who have pre-existing renal insufficiency and bone mineral disease.

Strength of recommendation: **Strong**
Certainty of evidence: **Moderate** ⊕⊕⊕◯

C. We recommend TDF (aged 12 to 18 years) or ETV (aged 2 to 18 years) for HIV-negative children and adolescents with CHB cirrhosis.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

Among patients with CHB infection, the mortality rate differs according to the study population. Patients with cirrhosis are estimated to progress to hepatic decompensation at a rate of 3% annually. The 5-year survival rate is 84% in patients with compensated cirrhosis, but it decreases to 14%-35% in individuals with decompensated cirrhosis.[112-114]. In the cirrhotic patient, the 5-year cumulative risk of developing hepatocellular carcinoma ranges from 10-17%.[115] Therefore, further hepatic insults be prevented with treatment.

EVIDENCE TO DECISION

Benefits and harms

There was 1 RCT comparing TDF and ETV[116], 2 RCTs on ETV versus LAM[117,118], and 3 RCTs on TDF versus TAF[119-121]. Fifteen cohort studies assessed the efficacy of ETV and TDF among adult patients with cirrhosis from CHB infection. Majority of the studies compared the efficacy of TDF with ETV, and excluded patients with decompensated cirrhosis. Currently, no RCTs or observational studies have assessed the effect of tenofovir on pediatric patients with CHB cirrhosis.

Among HIV-negative adults with CHB cirrhosis, treatment with either ETV or TDF compared to placebo decreased all-cause and liver-related mortality, decompensating events, and incidence of HCC. TDF performed the same as ETV, but was better in improving cirrhosis.

Two indirect RCTs that involved non-cirrhotic pediatric patients found ETV and TDF to have high rates of HBV DNA clearance and ALT normalization, without significant increase in adverse events.[122-123] Outcomes on mortality, morbidity, prevention of cirrhosis, and reduction of HCC occurrence were not reported.

Certainty of evidence

The certainty of evidence for the use of ETV and TDF among HIV-negative cirrhotic adults was deemed very low due to high. Some observational studies were downgraded due to issues on directness and imprecision, while some good quality observational studies were upgraded due to strength of association. Among HIV-negative pediatric patients, the certainty of evidence for the use of ETV and TDF was deemed moderate because of the indirectness of the available RCTs.

Other considerations

Cost

Overall, results show that tenofovir is the most cost-effective oral antiviral compared with other agents in both non-cirrhotic and cirrhotic patients. At a threshold of $50,000 per QALY gain ceiling, first-line TDF monotherapy was the most effective strategy among NA-naive patients with or without cirrhosis. Among lamivudine-resistant patients with or without cirrhosis, shifting to TDF monotherapy was also the most cost-effective second-line treatment, with a total net benefit of C$346,373.[124]

At a threshold of €50,000 ICER per QALY gained, tenofovir was associated with lower costs and higher efficacy (€30,959 per QALY) compared with ETV (€46,498 per QALY). Conversely, telbivudine (€62,051 per QALY), and adefovir (€82,824 per QALY) did not have favorable ICERs compared with natural history of disease. Furthermore, among the monotherapies, only tenofovir had an ICER per QALY below the threshold of €23,000–34,000 set by the National Institute for Health and Clinical Excellence (NICE). The analysis of patients with cirrhosis confirms the results obtained with the CHB cohort though with higher ICERs (tenofovir €68,833.82 per QALY vs ETV €89,758.12 per QALY).[124]

Recommendations from other groups

Several practice guidelines[125-130] worldwide, including local consensus statements[130], advocate for the treatment of all patients with CHB cirrhosis, whether compensated or decompensated, and regardless of HBV DNA levels, HBeAg status, or ALT levels. Monotherapies with either tenofovir or entecavir are preferred because of their potency and minimal risk of antiviral resistance.

The HSP also suggest that for those with hepatic decompensation, treatment should be initiated promptly with entecavir or tenofovir (high quality of evidence, strong recommendation).[130] Tenofovir alafenamide (TAF) is a potential option for patients with decompensated cirrhosis, but long-term data on the safety of TAF in this population are lacking.[130]

Antiviral therapy is likewise suggested for pediatric patients with chronic hepatitis B cirrhosis. Tenofovir is recommended for children age 12 and above, given a high genotypic barrier to resistance and a favorable side effect profile.[125-129] Although not yet approved for the treatment of CHB in patients < 12 years of age, the use of tenofovir might be safe in younger children, as it is already widely used (and FDA-licensed) for patients older than 2 years of age with HIV infection.[128] No local recommendations for children exist as of writing.

CONSENSUS ISSUES

Despite the low certainty of evidence, the panel strongly recommends ETV or TAF or TDF for HIV-negative adults with chronic hepatitis B and compensated liver cirrhosis. This recommendation was made primarily because of the following considerations: (1) anything that can prevent decompensation and HCC will improve survival, (2) treatment may decrease the severity of fibrosis, and (3) antiviral therapy is much cheaper than the treatment for decompensation and HCC (i.e., a liver transplant). As for HIV-negative adults with pre-existing renal insufficiency and bone mineral disease in addition to chronic hepatitis B and compensated liver cirrhosis, the panel strongly recommends TAF over TDF. This recommendation is consistent with the moderate certainty of evidence showing benefit with TAF.

The recommendation for HIV-negative children and adolescents with chronic hepatitis B and cirrhosis is TDF (for 12- to 18-year-olds) and ETV (for 2- to 18-year-olds). The panel strongly recommends these treatments despite the low certainty of evidence, because any safe treatment that can be given to them as soon as possible to prevent complications would be valuable. Children and adolescents still have much to contribute to society. Although other treatments for pediatric hepatitis exist, the steering committee focused on TDF and ETV, because they are cheaper (TDF, in particular) and easier to secure. They also have a good safety profile and a high barrier of resistance. The latter is important for children, who will require long-term treatment. The committee did not find any clinical trials investigating the effect of other drugs (e.g., interferon, lamivudine [LAM], adefovir [ADV], and telbivudine [TEL]) on children with cirrhosis. Existing studies looked only at children without cirrhosis, so further research in this area is recommended. Since these children need to be put on medication for a long time, researchers may also look for better treatments that can shorten their treatment period.

For all three recommendations to be realized, accessible programs and adequate financing mechanisms are necessary. Existing programs have to be expanded as these medications are currently not available nationwide. Furthermore, even if they were available, some patients might not be able to sustain treatment because of its costs.

SUMMARY OF FINDINGS

Table 12. Tenofovir compared to no treatment in CHB cirrhosis.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Tenofovir	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (5 yr follow up)	1	4/797 (0.5%)	32/291 (11.0%)	**HR 0.06** (0.02 to 0.15)	**103 fewer per 1,000** (from 108 fewer to 93 fewer)	Benefit	HIGH ⊕⊕⊕⊕
Hep B-related mortality (5 yr follow up)	1	4/797 (0.5%)	21/291 (7.2%)	**HR 0.10** (0.04 to 0.27)	**65 fewer per 1,000** (from 69 fewer to 52 fewer)	Benefit	HIGH ⊕⊕⊕⊕
Decompensating events (5 yr follow up)	1	7/797 (0.9%)	63/291 (21.6%)	**HR 0.28** (0.11 to 0.76)	**150 fewer per 1,000** (from 190 fewer to 47 fewer)	Benefit	MODERATE ⊕⊕⊕◯
HCC (5 yr follow up)	2	74/863 (8.6%)	67/357 (18.8%)	**HR 0.43** (0.28 to 0.67)	**102 fewer per 1,000** (from 131 fewer to 59 fewer)	Benefit	MODERATE ⊕⊕⊕◯

Table 13. ETV compared to no treatment in CHB cirrhosis.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		ETV	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (4-6 yr follow up)	1	10/450 (2.2%)	88/450 (19.6%)	**HR 0.40** (0.25 to 0.64)	**112 fewer per 1,000** (from 143 fewer to 66 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Hep B-related mortality (4-6 yr follow up)	1	6/450 (1.3%)	75/450 (16.7%)	**HR 0.22** (0.08 to 0.59)	**127 fewer per 1,000** (from 152 fewer to 65 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Decompensating events (16 mo. Follow up)	1	Lower probability of hepatic events in ETV group: 3-year: 21.6 vs 33.9% 5-year: 25.5 vs. 45.8%				Benefit	LOW ⊕⊕◯◯
HCC (5 yr follow up)	1	31/450 (6.9%)	115/450 (25.6%)	**HR 0.40** (0.25 to 0.64)	**144 fewer per 1,000** (from 184 fewer to 83 fewer)	Benefit	MODERATE ⊕⊕⊕◯
Safety (4-6 yr follow up)	1	No significant adverse reactions were reported through 4 years.				Benefit	LOW ⊕⊕◯◯

Table 14. Tenofovir compared to ETV in CHB cirrhosis.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Tenofovir	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (5 yr follow up)	5	111/3675 (3.0%)	171/36880 (0.5%)	**HR 0.85** (0.54 to 1.34)	**1 fewer per 1,000** (from 2 fewer to 2 more)	NS	VERY LOW ⊕◯◯◯
Regression of cirrhosis (5-9.6 yrs follow up)	1	189/256 (73.8%)	56/91 (61.5%)	**RR 1.20** (1.00 to 1.43)	**123 more per 1,000** (from 0 fewer to 265 more)	NS	VERY LOW ⊕◯◯◯
Hepatitis B-related mortality (33-66 mos follow up)	2	Not statistically different between TDF and ETV arms (HR 1.47 [95% CI 0.65-3.30], p value = 0.356). Another study also reported no significant differences (p value = 0.107) (n=2032)				NS	VERY LOW ⊕◯◯◯
HCC in all cirrhotics (33-78 mos follow up)	8	288/3831 (7.5%)	438/3849 (11.4%)	**HR 0.79** (0.65 to 0.96)	**23 fewer per 1,000** (from 38 fewer to 4 fewer)	Benefit	VERY LOW ⊕◯◯◯
Decompensating events (33-66 mos follow up)	2	7/267 (2.6%)	17/346 (4.9%)	**HR 0.76** (0.19 to 3.00)	**12 fewer per 1,000** (from 40 fewer to 91 more)	NS	VERY LOW ⊕◯◯◯
Adverse events (follow up: 48 weeks; assessed with: Drug-related AE)	1	10/56 (17.9%)	22/109 (20.2%)	**RR 0.88** (0.45 to 1.73)	**24 fewer per 1,000** (from 111 fewer to 147 more)	NS	HIGH ⊕⊕⊕⊕
Hepatitis B-related mortality in NA-naive patients (33-66 mos follow up)	2	The risk of liver-related deaths was not statistically different between TDF and ETV arms (HR 1.47 [95% CI 0.65-3.30], p value = 0.356). Another study also reported no significant differences (p value = 0.107).				NS	VERY LOW ⊕◯◯◯
Cost-effectiveness (ICER)	1	At a threshold of C$50,000 per QALY gained ceiling, first-line TDF monotherapy is the most effective strategy among NA-naive patients with or without cirrhosis. Furthermore, all strategies using TDF as first-line antiviral were more cost-effective than first-line use of any other NA. Among lamivudine-resistant patients with or without cirrhosis, shifting to TDF monotherapy was also the most cost-effective second-line treatment, with the total net benefit of C$346,373.				TDF most cost-effective	LOW ⊕⊕◯◯

Table 15. Tenofovir compared to placebo in pediatric patients with CHB cirrhosis.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Tenofovir	No treatment	Relative (95% CI)	Absolute (95% CI)		
Virologic response (72 wks follow up)	1	46/52 (88.5%)	0/54 (0.0%)	**RR 96.5** (6.10, 1526)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Benefit	MODERATE ⊕⊕◯◯
ALT normalization	1	26/35 (74.3%)	13/42 (31%)	**RR 2.40** (1.46, 3.92)	**433 fewer per 1,000** (from 142 more to 904 more)	Benefit	MODERATE ⊕⊕◯◯
HBeAg loss (72 wks follow up)	1	10/48 (20.8%)	7/48 (14.6%)	**RR 0.58** (0.30, 1.15)	**61 fewer per 1,000** (from 102 fewer to 22 more)	NS	MODERATE ⊕⊕◯◯
Any adverse event (72 wks follow up)	2	44/52 (84.6%)	48/54 (88.9%)	**RR 0.95** (0.82, 1.11)	**44 fewer per 1,000** (from 160 fewer to 98 more)	NS	MODERATE ⊕⊕◯◯
Drug resistance (72 wks follow up)	1	None of the patients who did not have virologic breakthrough and virologic response had resistance to TDF.					MODERATE ⊕⊕◯◯

Table 16. ETV compared to placebo in pediatric patients with CHB cirrhosis.

Outcomes	Studies	Effect		Interpretation	Certainty of evidence
		Relative (95% CI)	Absolute (95% CI)		
HBV DNA suppression	1	**RR 14.8** (3.7 to 58.3)	**15 fewer per 1,000** (from 58 fewer to 4 fewer)	Benefit	MODERATE ⊕⊕◯◯
HBeAg seroconversion	1	**RR 2.4** (1.1 to 5.5)	**2 fewer per 1,000** (from 6 fewer to 1 fewer)	Benefit	MODERATE ⊕⊕◯◯
ALT normalization	1	**RR 2.9** (1.8 to 4.7)	**3 fewer per 1,000** (from 5 fewer to 2 fewer)	Benefit	MODERATE ⊕⊕◯◯
Any adverse events	1	**RR 0.85** (0.70 to 1.03)	**115 fewer per 1,000** (from 230 fewer to 23 more)	Inconclusive	MODERATE ⊕⊕◯◯

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8. Should treatment of healthcare workers with chronic hepatitis B infection be recommended to prevent procedure-related transmission?

A. There is insufficient evidence to recommend treatment of healthcare workers with chronic hepatitis B performing exposure-prone procedures to target HBV DNA levels to reduce procedure-related transmission of HBV.

Strength of recommendation: **None**
Certainty of evidence: **Very Low** ⊕◯◯◯

B. Healthcare workers who meet the target HBV DNA levels can be allowed to perform exposure prone procedures (EPP) provided they are referred to an institutional expert review panel for care.

(Consensus statement)

Despite widespread vaccination, HBV infection remains one of the most transmitted blood-borne pathogens encountered especially in the healthcare setting following percutaneous exposure. Among published cases of healthcare provider-to-patient transmission, at least 75% occurred as a result of an HBeAg-positive personnel with variable degrees of viremia measured through HBV DNA level.[131] Thus, there is a need to review the effect of antiviral treatment among infected HCWs in preventing occupational transmission. Moreover, a significant viral cut-off level needs to be established for which an HCW should be prevented from performing exposure-prone procedures and to signal initiation of antiviral therapy.

EVIDENCE TO DECISION

Benefits and harms

No RCTs were found directly investigating whether treatment is effective for this specific population. The search focused on objective evidence including HBV DNA level and procedure-related risk factors that could establish horizontal transmission from a healthcare worker to a patient. No RCTs or prospective studies were also found evaluating the effect of antiviral therapy on preventing horizontal transmission of hepatitis B among HCWs to patients.

Indirect evidence came from eight observational studies (3 retrospective cohort, 1 case report, 1 case series and 3 cross-sectional studies) demonstrating an association between HBV DNA levels with procedure-related transmission.[132-139] Based on the pooled results from these studies, the cumulative transmission rate of hepatitis B among infected HCWs to patients ranged from 0.5 to 13%. Sera from transmitting healthcare personnel, who were mostly surgeons, were found to contain an HBV DNA level from as low as 2.5×10^5 to as high as 5×10^9 gEq/ml. Infection rates were higher among patients receiving blood products during surgery and for longer surgeries (i.e. > 5 hrs); however, these differences were not statistically significant.

Certainty of evidence

Overall certainty of evidence was very low due to study design limitations inherent to observational studies, serious imprecision from small sample sizes and wide confidence intervals,

and serious indirectness from the absence of trials specifically evaluating effects of antiviral treatment in preventing occupational transmission.

Other considerations

Recommendations from other groups

Several countries and regions have issued differing recommendations in managing HBV-infected healthcare providers based on circulating viral burdens. HBV DNA level has been used over HBeAg status in determining infectivity due to several studies documenting increased levels of viremia despite seronegative HBeAg. According to a 2008 study, adopting a more stringent threshold (i.e., <200 IU/mL) for allowing exposure prone procedures would restrict practice of 58% of HBV-positive HCWs in UK and >94% in the Netherlands.[140]

With the advent of approved analogs (e.g., entecavir, tenofovir) possessing potent antiviral activity and very low rates of drug resistance, latest guidance from CDC and APASL have adopted a more liberal cut-off level of <1,000 IU/mL for allowing providers to perform EPP. Furthermore, the SHEA and European consensus recommended an HBV DNA cut-off of 10^4 gEq/ml (2×10^3 IU/mL) to strike a balance between the risk of transmission and loss of specialist HCWs.[141-143]

CONSENSUS ISSUES

Although the panel believed that treatment may probably reduce disease transmission, current best available evidence does not sufficiently answer whether antiviral therapy that solely targets reducing HBV DNA levels would benefit patients who perform EPPs. In addition, an HBV DNA level considered safe enough to allow HCWs to perform EPPs and prevent occupational transmission has not been identified. The treatment's impact on health equity, cost-effectiveness, and acceptability to HCWs also remains uncertain.

The panel also acknowledged that identifying HCWs with high HBV DNA levels may result in a significant reduction in the already limited number of available specialists in the country. Preventing HCWs with hepatitis B infection from working may also inadvertently lead to discrimination. Currently, very few hospitals have a policy for allowing infected HCWs to perform EPPs. As such, a consensus statement was made despite the lack of high-quality evidence to highlight the importance of screening HCWs and ensure that they receive care and follow up from a multidisciplinary institutional expert review panel prior to allowing them to perform EPPs. The institutional expert review panel will be tasked to monitor, counsel, follow-up and initiate treatment among these HCWs when necessary.

SUMMARY OF FINDINGS

Table 17. Outcomes associated with EPPs performed by HCWs with hepatitis B infection.

Outcomes	Studies	Number of patients		Effect		Interpretation	Certainty of evidence
		Procedure by an HBV infected surgeon	Control	Relative (95% CI)	Absolute (95% CI)		
Risk of HBV transmission from HCW to patient	1 (n=246)	24/115 (21%)	7/131 (5.3%)	**RR 3.9** (1.8 to 8.7)	**155 more per 1,000** (43 more to 411 more)	Harm	VERY LOW ⊕◯◯◯
Total OR duration	1 (n=112)	--	--	**OR 4.2** (1.5 – 11.5)	**--**	Harm	VERY LOW ⊕◯◯◯
Complications	1 (n=112)	--	--	**OR 3.7** (1.0-13.4)	**--**	Harm	VERY LOW ⊕◯◯◯

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9. Should screening for hepatitis B be offered in highly endemic populations to decrease all-cause mortality, hepatitis B-related morbidity and mortality, liver cirrhosis, and hepatocellular carcinoma?

We recommend screening for all Filipino adults and adolescents for hepatitis B. This is incumbent on the availability of pre- and post-test counseling and linkage to care.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

In the Philippines where seroprevalence of HBV infection among adults was reported to be 16.7% (167 per 1,000), chronic hepatitis B (CHB) is a main public health problem.[144] Screening the population for hepatitis B using rapid HBsAg will not only identify cases of CHB but can potentially decrease HBV-related complications and mortality when timely linkage to care is done.[145] This review summarizes evidence on the accuracy of RDTs in screening for hepatitis B and presents data on the efficacy of interventions for the management of patients with and without hepatitis B.

EVIDENCE TO DECISION

Benefits and harms

There are currently no RCTs directly showing benefit of HBV screening on reducing all-cause mortality and improving HBV-related outcomes among asymptomatic, apparently healthy individuals in highly endemic areas.

One observational study showed the effectiveness of vaccination programs that were implemented after mass screening.[146] In a highly endemic area, there were reported decreased incidence rates of acute hepatitis after vaccinating susceptible individuals as well as decreased case fatality rates of HCC among chronically infected individuals who underwent serial monitoring. Long-term observational studies on antiviral treatment for HBV infection showed decreased risk for HCC and hepatitis B-related mortality and morbidity among patients who received treatment.

Twelve observational studies provided data on the diagnostic accuracy of rapid hepatitis B surface antigen (HBsAg) for detecting HBV infection in highly endemic populations.[147-158] The pooled sensitivity was 87.1% (95% CI 82.3% to 90.8%) and the pooled specificity was 99.6% (95% CI: 99.3% to 99.8%). No screening-related adverse events were reported.

Certainty of evidence

The overall certainty of the evidence was very low because of issues on indirectness, imprecision and heterogeneity, downgrading the quality of evidence by two levels.

Other considerations

Cost

In the Philippines, Bioland (Chungbuk, Korea) tests for HBsAg (NanoSign HBs) and anti-HBs (NanoSign anti-HBs) are available. The cost for both tests is approximately $1.00 (~50 pesos).[144] The number needed to screen to identify one HBV infection ranged from 32 to 148,[159] translating into $32 to $148 spent to identify one HBV infection. In one study, the cost of treating non-cirrhotic immune active chronic hepatitis B (CHB) infection was $1293 per patient. Since the seroprevalence of HBV infection in the Philippines is 16.67% or 167 per 1,000 individuals, this translates to $215,931 per 1,000 per year if these individuals would develop immune-active CHB infection. Thus, HBV screening using RDTs can be considered cost-effective to prevent incurring CHB-related medical expenses.[160]

Recommendations from other groups

Several guidelines have also proposed the use of targeted or focused-screening approach for screening HBV infection among individuals.[159,161] In the systematic review of the US Preventive Services Task Force (USPSTF) on screening for HBV infection in non-pregnant adolescents and adults, three studies focusing on patients with risk factors (i.e., immigration from high prevalence country, other demographic risk factors, and/or behavioral risk factors) were evaluated.[160-162] Although there were no studies that focused on clinical outcomes, screening strategies among these high-risk populations would identify nearly all cases of HBV infection while screening about the population.

The WHO recommended to conduct focused testing in the following populations: (a) adults and adolescents from populations most affected by HBV infection (who are either part of a population with high HBV seroprevalence or who have a history of exposure and/or high-risk behaviors for HBV infection); (b) adults, adolescents, and children with a clinical suspicion of chronic viral hepatitis; (c) sexual partners, children and other family members, and close household contacts of those with HBV infection; (d) health-care workers (low quality of evidence, strong recommendation). Furthermore, WHO recommends mandatory screening of blood donors.[161]

CONSENSUS ISSUES

Despite the low certainty of evidence regarding its benefits, the panel still decided to make a strong recommendation in favor of mass HBV screening due to its anticipated benefits. The high accuracy of screening will allow more Hep B cases to be detected earlier, which will allow treatment to be initiated before associated complications appear. It will also help identify susceptible individuals who can be vaccinated. Moreover, the costs of treating HBV and its complications (i.e., HCC, liver transplantation) greatly outweigh the cost of screening. Given that the prevalence of Hep B continues to remain high locally despite the existing vaccination program, enhancing mass screening is viewed a crucial step towards achieving the goal of controlling HBV.

However, the panel acknowledged several factors that need to be addressed first to ensure that a national HBV screening program can be successfully implemented and the targets set for Hepatitis B reduction can be met. First, screeners must be cognizant of their competency on pre- and post-screening care. Lack of access to pre- and post-test counselling in patients undergoing screening may be a key driver of patient attrition. As access points for treatment are already available in the sub-national level, government (i.e., LGUs, health authorities) must ensure that

clear linkage to care is available for patients after screening and that a comprehensive Hep B program is established.

Emphasis was also given regarding the stigma associated with having a positive HBV-screen result, along with reported patient experiences related to workplace discrimination. The panel argued, however, that the normalization of screening may actually reduce this stigma and increase awareness and patient empowerment. Also, acceptance for HBV screening is reported to be high, at least among pregnant patients.

SUMMARY OF FINDINGS

Table 18. Outcomes associated with mass HBV screening.

Outcomes	Studies	Pooled estimate (95% CI)	Interpretation	Certainty of evidence
Sensitivity	12	**87.1%** (82.3% - 90.8%)	High	LOW ⊕⊕◯◯
Specificity	12	**99.6%** (99.3% - 99.8%)	High	LOW ⊕⊕◯◯

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10. Should a single, elevated ALT in combination with HBV DNA be used in the assessment of disease activity to guide initiation of treatment?

In resource-limited settings, we suggest using a single elevated ALT in combination with HBV DNA ≥ 2000 IU/mL to guide initiation of antiviral treatment in adults with chronic hepatitis B infection.

Strength of recommendation: **Conditional**
Certainty of evidence: **Very Low** ⊕◯◯◯

Alanine aminotransferase (ALT) is a significant predictor of liver fibrosis among adults with CHB infection.[165-168] However, ALT levels fluctuate over time. Several clinical practice guidelines recommend initiating treatment among patients with persistent ALT of ≥2x ULN after 3-6 months of observation together with increased HBV DNA.[169-171] This would rule out other causes of increased ALT. However, the repeated follow up and diagnostic tests result in poor adherence and increased financial barriers. These factors have been found to contribute to the low diagnosis and treatment rates of hepatitis B infection, particularly in Asia.[172] Determining whether a single ALT elevation in combination with HBV DNA is enough to guide treatment would hopefully overcome this barrier.

EVIDENCE TO DECISION

Benefits and harms

No evidence was found comparing single elevated ALT in combination with HBV DNA versus persistent elevation in ALT combined with HBV DNA in determining disease activity. One observational study showed a significantly increased incidence and risk of liver fibrosis among a combined group of patients with persistently and intermittently elevated ALT versus persistently normal ALT.[173] Another observational study showed that having persistently or intermittently elevated ALT is a significant predictor of liver fibrosis.[168] One observational study found an increased risk of developing HCC among patients with transient abnormal ALT (at least 1 ALT level ≥ 45 U/L but <50% of ALT measurements <45 U/L) and persistently abnormal ALT versus persistently normal ALT.[174] No evidence was found applicable for children.

Certainty of evidence

Certainty of evidence is very low because of risk of bias due to confounding and indirectness since patients with persistently or intermittently elevated ALT were grouped together for analysis.

Other considerations

Recommendations from other groups

Three practice guidelines recommend monitoring ALT levels for 3-12 months to determine persistent elevation in combination with increased HBV DNA load prior to treatment.[169-171] A clinical practice guideline by the AASLD 2018 recommends ALT monitoring for persistent or intermittent increase prior to treatment if initial ALT measurements are >ULN but <2x ULN and if

HBV DNA levels are less than 2,000 IU/mL.[171] Two guidelines (EASL 2017, Asian consensus 2019) recommend initiating treatment without repeated ALT measurements.[172,176]

CONSENSUS ISSUES

The panel made a conditional recommendation in favor of single ALT elevation and HBV DNA testing primarily due to its anticipated net benefit. The certainty of this effect, however, lacks the support of high-quality studies and is only based on expert opinion. Testing can possibly lead to prompt treatment, prevent worsening of outcomes, and minimize the number of CHB patients lost to follow up. In addition, overtreatment with antivirals has not been reported to cause significant health complications.

Serial ALT testing, by convention, has been the practice standard among hepatologists to avoid overtreatment. Although serial testing is desired, this may not always be feasible in some settings. Testing may be cost-prohibitive especially for patients from lower socio-economic groups and some areas may not readily have resources to allow frequent ALT or HBV DNA testing.

SUMMARY OF FINDINGS

Table 19. Association between ALT and hepatitis-B outcomes.

Outcomes	Studies	Effect Estimates	Certainty of evidence
Incidence and risk of liver fibrosis	1	Persistently Normal ALT (PNALT) = 2/74 (2.7%) Persistently or Intermittently Elevated ALT (PIEALT) = 39/159 (24.5%) (p < 0.001) PIEALT OR = 11.70 (95% CI 2.74 - 49.92)	LOW ⊕⊕◯◯
Intermittent ALT increase as a predictor of liver fibrosis	1	Persistently or Intermittently Elevated ALT (PIEALT) OR = 4.304, (95% CI 2.870 - 6.452)	LOW ⊕⊕◯◯
Transient increased ALT as risk for hepatocellular carcinoma	1	Hazard Ratio: High normal = 1.63 (95% CI 0.73-3.61) Transient abnormal = 3.08 (95% CI 1.41-6.71) Persistent abnormal = 5.75 (95% CI 2.71-12.23)	LOW ⊕⊕◯◯

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11. Should periodic disease activity monitoring with ALT and HBV DNA be used among non-cirrhotic patients with chronic hepatitis B infection who have not started treatment to determine proper initiation of treatment and prevention of hepatitis B-related outcomes?

We recommend periodic monitoring of ALT and HBV DNA to determine treatment eligibility in order to decrease hepatitis B-related outcomes.

Strength of recommendation: **Strong**
Certainty of evidence: **Very Low** ⊕◯◯◯

The natural history of CHB is variable and dynamic, with reversion from inactive to active disease states occurring even without symptoms. Long-term follow-up and laboratory monitoring is critical to detect significant fluctuations that would warrant treatment initiation in patients with previously less active disease. The factors that most frequently enable patients to become treatment eligible during follow-up were a rise in ALT, HBV DNA, or both. This highlights the importance of periodic monitoring to identify patients with CHB who would benefit from antiviral therapy.[177]

EVIDENCE TO DECISION

Benefits and harms

Three observational studies conducted among patients with HBeAg-positive CHB infection showed that a persistently normal ALT is associated with decreased risk of liver disease progression.[178-180] However, one observational study demonstrated a higher incidence of HCC and mortality in untreated patients of this group compared to treated immune active patients.[181]

Five observational studies conducted among patients with HBeAg-negative Chronic Hepatitis B infection showed that a persistently normal ALT was associated with a decreased risk of liver disease progression.[180,182-185] In four observational studies that monitored HBV DNA, 3 studies did not show a difference in the risk of liver disease progression between patients with HBV DNA < 2000 IU/ml versus HBV DNA ≥ 2,000 to 20,000 IU/ml, while a large cohort study showed that the incidence of liver cirrhosis increases with increasing HBV DNA levels.[194]

One observational study among patients with HBeAg-negative Chronic Hepatitis B infection demonstrated a lower risk of HCC and mortality among patients with ALT < 2X ULN.[183] In addition, a large cohort study showed that the incidence of HCC increases with increasing HBV DNA levels.[186]

Three observational studies conducted among HBeAg-negative patients with fluctuating ALT and HBV DNA levels showed a lower risk of liver disease progression with normal ALT compared to ALT up to 1-2x ULN.[180, 183, 186] One observational study showed that the incidence of HCC, as well as mortality and liver transplantation was higher in patients with HBV DNA between 2,000-20,000 IU/ml, compared to those in the inactive carriers. Another study showed an increased incidence of HCC in this group compared to patients already on oral nucleos(t)ides.

Children diagnosed with Chronic Hepatitis B have a low risk of developing liver cirrhosis and HCC and may be safely monitored and not treated.

Certainty of evidence

The overall certainty of evidence for adults across studies was deemed low due to issues on inconsistency and imprecision. The overall certainty of evidence for the pediatric age group was rated low due to risk of bias from study design and imprecision.

Other considerations

Cost

Cost effectiveness studies show that the monitor and treatment strategy in inactive carrier states, and treatment of patients in the immune tolerant phase may be cost-effective. A study in China implementing a lifelong monitoring for inactive Chronic Hepatitis B carriers, assuming an adherence to monitoring of 35%, found that implementing a monitor and treat strategy is cost-effective, with an ICER of US$ 2996 per QALY gained. However, this did not result in a substantial reduction in HCC or CHB-related deaths. Increasing the percentage of monitoring adherence, percentage of active CHB treated, and percentage of treatment adherence to 50%, 65%, and 85%, respectively, lowered the ICER to $808, with a reduction in CHB-related death by almost 10%, compared to the current practice.[187] On the other hand, a study in Korea showed that starting antiviral treatment in patients in the immune-tolerant Chronic Hepatitis phase may be more cost effective than delaying treatment until the HBeAg-positive active hepatitis phase, with treatment being more cost effective with higher HCC risk and decreasing drug costs.[188]

Table 20. Monitoring frequency across studies

Diagnostic test	Frequency across studies
ALT (liver function tests)	6 months (3-12)
HBV DNA	6 months (3-12)
AFP	6 months (3-12)
Liver ultrasound	6 months

Table 21. Estimated cost of monitoring according to frequency.

Diagnostic Test	Unit Cost (Php)	Quarterly	Every 6 months	Annually
ALT	180.00-200.00	720.00-800.00	360.00-400.00	180.00-200.00
AFP	700.00-1000.00	2,800.00-4000.00	1,400.00-2000.00	700.00-1,000.00
HBV DNA	3,800.00-5,000	15,200.00-20,000.00	7,600.00-10,000.00	3,800.00-5,000.00
Liver ultrasound	500.00-800.00	2,000.00-3,200.00	1,000.00-1,600.00	500.00-800.00
Estimated Annual Cost		20,720.00-28,000.00	10,360.00-14,000.00	5,180.00-7,000.00

Recommendations from other groups

The Hepatology Society of the Philippines recommends monitoring of ALT every 3 to 6 months for those who do not yet meet the criteria for treatment. Treatment initiation is indicated for persistently elevated ALT ≥2 times ULN and HBV DNA ≥20,000 IU/ml if HBeAg-positive and ≥2,000 IU/ml if HBeAg-negative.[189]

WHO recommends at least annual monitoring of the following: ALT levels (and AST for APRI), HBsAg, HBeAg for HBeAg-positive patients, and HBV DNA levels. Assessing presence of cirrhosis is also recommended using non-invasive tests (APRI score or FibroScan) in those without cirrhosis at baseline. More frequent monitoring for disease progression may be indicated in persons who have intermittently abnormal ALT levels or HBV DNA levels that fluctuate between 2000 IU/mL and 20,000 IU/mL *(where HBV DNA testing is available)* and in HIV-coinfected persons. Treatment is initiated among non-cirrhotic patients at least 30 years of age who have persistently abnormal ALT and HBV DNA >20,000 IU/ml regardless of HBeAg status. Where HBV DNA testing is not available, treatment may be based on persistently abnormal ALT levels alone regardless of HBeAg.[190]

An Asian Consensus Recommendation recommends monitoring of ALT every 3 months, HBV DNA every 6-12 months, and non-invasive testing for liver fibrosis every 12 months. In HBeAg-negative HBV-infected patients with HBV DNA <2000 IU/mL, they recommend ALT every 6-12 months, HBV DNA and liver fibrosis testing every 2-3 years. In HBeAg-negative HBV-infected patients with HBV DNA ≥2000 IU/mL, ALT monitoring is recommended every 3 months for the first year and every 6 months thereafter; HBV DNA should be monitored every 3 years, while liver fibrosis assessment, by noninvasive means or by liver biopsy, should be conducted at least every 3 years. Treatment is initiated if HBV DNA ≥ 2,000 IU/ml and ALT > ULN. Treatment may be warranted regardless of HBV DNA and ALT level depending on HCC risk (>30-year-old, moderate fibrosis, first degree relative with cirrhosis or HCC; extrahepatic manifestations).[191]

AASLD recommends monitoring of ALT and HBV-DNA at 3–6-month intervals for patients who are HBeAg positive with normal ALT and high baseline HBV DNA. A more frequent approach to monitoring should be performed if ALT becomes elevated. In patients who remain HBeAg-positive with HBV-DNA > 20,000 IU/mL after a 3- to 6-month period of elevated ALT levels > 2x ULN (i.e., >50 U/L for women and >70 U/L for men), liver biopsy or noninvasive tests of fibrosis should be considered, particularly in patients over age 40 who have been infected with HBV from a young age. Patients with evidence of fibrosis may be considered for antiviral treatment. Patients who are HBeAg negative, anti-HBe positive, with normal ALT and HBV DNA less than 2000 IU/mL should have ALT and HBV determination every 3 months during the first year to verify that they are truly in the “inactive phase” and then every 6-12 months, thereafter. As in HBeAg-positive patients, monitoring of ALT level should be more frequent if ALT becomes elevated. If ALT becomes elevated, other causes of possible elevation of ALT should be explored and evidence of liver disease severity should be assessed. Treatment should be considered for patients with evidence of liver fibrosis (>F2), ALT more than 2x ULN, and HBV DNA > 2,000 IU/ml.[192]

EASL recommends that patients with HBeAg positive chronic HBV infection who are younger than 30 years should be followed at least every 3–6 months. Patients with HBeAg-negative chronic HBV infection and serum HBV DNA <2,000 IU/ml should be followed every 6–12 months, while patients with HBeAg-negative chronic HBV infection and serum HBV DNA >2,000 IU/ml should

be followed every 3 months for the first year and every 6 months thereafter. Treatment is intiated for any HBeAg as long as HBV DNA ≥2,000 IU/ml or any ALT elevation.[193]

Children with CHB should undergo physical examination and measurement of serum ALT and HBeAg/anti-HBe levels every 6 months (C1). In HBeAg-positive patients with persistently elevated ALT, their levels should be monitored every 3 months for at least one year. In HBeAg-negative patients, ALT and HBV DNA levels should be measured every 4 months within the first year to rule out HBeAg-negative hepatitis. After confirmation of the inactive carrier status (normal ALT and HBV DNA <2000 IU/ml), patients should be monitored every 6 months. Full blood count and liver function tests should be performed yearly. HCC surveillance with liver ultrasound should be done every 6–12 months, depending on the stage of fibrosis. AFP, although widely used, was recently shown to provide insufficient sensitivity and specificity for effective surveillance. Lifetime follow-up is warranted even for inactive carriers, because of the risk of cirrhosis, HCC and reactivation of HBV infection, with seroreversion to HBeAg-positive status or progression to HBeAg-negative hepatitis.[193]

CONSENSUS ISSUES

Although current available evidence on the net benefit and cost-effectiveness of these tests are sparse and require further investigations, the panel made a strong recommendation in favor of serial monitoring to reduce the number of patients lost to follow-up and potentially minimize costs associated with CHB complications. A minimum monitoring strategy that can diagnose liver disease progression and signal timely treatment ideally includes HBV DNA and periodic ALT monitoring along with serological classification using HBeAg, fibrosis scoring systems, and transient elastography.

Fibrosis scoring systems may underestimate the risk for hepatocellular carcinoma, and, as ALT may poorly correlate with liver disease activity, reliance on HBV DNA, as was shown in the evidence to be more clearly associated with HCC risk at levels ≥ 2,000 IU/ml even for single determinations, was advocated. The use of this HBV DNA cutoff may also be applied for any level ALT or any HBeAg status, making it a more reliable single test to initiate treatment. While periodic monitoring using ALT may be done to establish with higher certainty that the ALT elevation is from HBV disease activity, when combined with HBV DNA, the decision to treat may be more warranted.

Resource limitations, however, may impede timely determination of treatment eligibility as many areas in the Philippines do not have access to HBeAg, and transient elastography. Frequent testing would also be costly, especially to individuals belonging in low socio-economic groups. Unless these become part of the national hepatitis program, the successful implementation and compliance to this recommendation will be difficult.

SUMMARY OF FINDINGS

Table 22. HBeAg-positive Chronic Hepatitis B infection (immune tolerant phase).

Outcomes	Studies	No. of events	No. of individuals	Effect	Certainty of evidence
Liver disease progression in HBeAg-positive CHB infection with persistently normal ALT	3	45	587	event rate 0.27 per 1 (0.07 to 1.11)	⨁⨁◯◯ LOW
HCC risk in HBeAg-positive CHB infection compared to treated HBeAg positive Chronic Hepatitis as assessed by incidence ratio	1	24	413	event rate 2.54 per 100-person year(s) (1.54 to 4.18)	⨁⨁⨁◯ MODERATE
Mortality in HBeAg-positive CHB infection compared to treated HBeAg positive Chronic Hepatitis as assessed by incidence ratio	1	18	413	event rate 3.38 per 100-person year(s) (1.85 to 6.16)	⨁⨁⨁◯ MODERATE

Table 23. HBeAg-negative Chronic Hepatitis B infection (inactive carrier phase).

Outcomes	Studies	No. of events	No. of individuals	Effect	Certainty of evidence
Liver disease progression in HBeAg negative CHB infection with persistently normal ALT	4	96	1014	event rate 0.61 per 1 (0.33 to 1.13)	⨁⨁◯◯ LOW
Risk of cirrhosis in HBeAg negative CHB infection with ALT <2x ULN HBeAg positive Chronic Hepatitis as assessed by incidence ratio	1	28	2752	event rate 0.16 per 1 (0.1 to 0.25)	⨁⨁⨁⨁ HIGH
Liver disease progression in HBeAg negative CHB infection with HBV DNA	4	36	613	event rate 0.82 per 1 (0.63 to 1.08)	⨁⨁⨁◯ MODERATE
Incidence of cirrhosis in HBeAg negative CHB infection with HBV DNA between 54 to 1786 IU/ml	1	261	2850	event rate 2.1 per 100000-person year(s) (1.1 to 4)	⨁⨁⨁◯ MODERATE
Risk HCC in HBeAg negative CHB infection with ALT < 2x ULN	1	7	2752	event rate 0.10 per 1 (0.04 to 0.26)	⨁⨁⨁◯ MODERATE
Incidence of HCC in HBeAg negative CHB infection with HBV DNA between 54 to 1786 IU/ml	1	164	2925	event rate 1.4 per 100000-person year(s) (0.5 to 3.8)	⨁⨁⨁◯ MODERATE
Risk of Mortality in HBeAg negative CHB infection with ALT < 2x ULN	1	36	2752	event rate 0.33 per 1 (0.2 to 0.56)	⨁⨁⨁◯ MODERATE

Table 24. HBeAg-negative Grey Zone (Fluctuating ALT and HBV DNA levels).

Outcomes	Studies	No. of events	No. of individuals	Effect	Certainty of evidence
Liver disease progression in HBeAg negative with fluctuating ALT and HBV DNA levels (normal ALT vs ALT 1-2x ULN)	3	33	2555	event rate 0.48 per 1 (0.33 to 0.69)	⨁⨁⨁⨁ HIGH
Incidence of HCC in HBeAg negative with fluctuating ALT and HBV DNA levels (UMA vs IC)	1	63	396	event rate 4.77 per 100-person year(s) (3.54 to 6.44)	⨁⨁⨁◯ MODERATE
Incidence of HCC in HBeAg negative fluctuating ALT and HBV DNA levels (UMA VS NUC-VR)	1	16	152	event rate 3.485 per 1 (1.234 to 9.3846)	⨁⨁⨁◯ MODERATE
Incidence of Mortality in HBeAg fluctuating ALT and HBV DNA levels (UMA VS IC)	1	38	396	event rate 2.0 per 100-person year(s) (1.41 to 2.84)	⨁⨁⨁◯ MODERATE

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12. Should periodic disease activity monitoring be done among patients with chronic hepatitis B infection with compensated liver cirrhosis who are on treatment to determine medication compliance, drug toxicities, and to prevent hepatitis B-related morbidity and mortality and development of HCC?

We recommend periodic monitoring using HBV DNA, AFP, platelet count, albumin, creatinine among chronic hepatitis B patients with compensated liver cirrhosis on treatment to improve hepatitis B-related outcomes and decrease adverse drug effects.

Strength of recommendation: **Strong**
Certainty of evidence: **Very Low** ⊕○○○

Monitoring for virologic response during treatment is important because treatment options have different successes in achieving endpoints. Resistance can also emerge, especially during long-term therapy. Different studies and guidelines have recommended the use of serum aminotransferase levels, HBV DNA level, hepatitis B e antigen (HBeAg) and antibody (anti-HBe), hepatitis B surface antigen (HBsAg) or antibody (anti-HBs), and liver histology as methods for monitoring treatment response.[195] Aside from monitoring for treatment response, other outcomes such as treatment compliance, drug toxicities, and HBV-related outcomes can also be evaluated.

EVIDENCE TO DECISION

Benefits and harms

Only indirect evidence from observational studies were found on the relationship of HBV DNA, AFP and platelet with hepatitis B-related outcomes, as well as medication adherence and its correlation to disease progression and hepatocellular carcinoma. Several observational studies monitored creatinine and bone mineral density to identify drug toxicity. No studies were done on children.

Adherence to medications and surveillance during treatment decreased risk for complication of chronic hepatitis B infection and progression to hepatocellular carcinoma.[196-199] Positive HBeAg, elevated baseline HBV DNA levels, and higher quantitative HBsAg were predictors of poor virologic response.[200] Low platelet count, elevated AFP levels, and elevated HBV DNA levels were associated with an increased risk of hepatocellular carcinoma.[201-209]

In terms of safety, antiviral medications such as tenofovir increased creatinine and decreased eGFR; hence the need to monitor kidney function during treatment.[210-212] However, it did not increase the risk of osteopenia compared to patients who did not receive treatment.[212-213]

Certainty of evidence

The overall certainty of evidence was deemed very low due to serious risk of bias and inconsistency across studies.

Other considerations

Cost

Table 21. Cost Considerations

Diagnostic Test	Unit Cost (Php)	Quarterly	Every 6 months	Annually
Platelet Count	120.00-250.00	480.00-1000	720.00-1500	120-250
AFP	700.00-1000.00	2,800-4000	1,400-2000	700-1,000
HBV DNA	3,800.00-5,000	15,200-20,000	7,600-10,000	3,800-5,000
Creatinine	95.00-200.00	380-800	190-400	95-200
Liver ultrasound	500-800	2,000-3,200	1,000-1,600	500-800
Estimated Annual Cost		20,860-29,000	10,910-15,500	5,215-7,250

Recommendations from other groups

WHO recommends annual monitoring of ALT, HBsAg, HBeAg, and HBV DNA during treatment. Treatment adherence must also be monitored regularly. For patients with compensated or decompensated cirrhosis, the guidelines recommend closer monitoring of at least every three months for the first year. Lastly, annual monitoring of renal function in patients on long-term tenofovir or entecavir is recommended.[214]

AASLD recommends renal safety monitoring by periodically checking serum creatinine, phosphorus, urine glucose, and urine protein among patients on TDF. For patients on nucleos(t)ide therapy, the group suggested monitoring of HBV DNA every 3 months until HBV DNA is undetectable and then every 3-6 months thereafter.[215]

APASL also recommends regular monitoring of the efficacy and safety of nucleus(t)ide therapy. Measuring HBV DNA levels is recommended at month 3 and 6 of therapy and then every 3-6 months for low genetic barrier and every 6 months for high genetic barrier drugs. The recommended frequency of serum ALT, HBeAg, and anti-HBe measurement is every 3 months. Monitoring of serum creatinine and serum phosphate levels is also recommended every 3 months.[216]

CONSENSUS ISSUES

Despite the very low certainty of evidence due to indirectness and inconsistencies of studies, the panel strongly recommends monitoring among chronic hepatitis B patients with liver cirrhosis. The panelists highlighted its importance in reducing complications and monitoring of outcomes, but raised issues on costs, equity, acceptability, and feasibility. Since it requires periodic testing, monitoring may become too expensive and challenging for patients to sustain. Aside from this, testing services and facilities may not be readily available to patients, especially those in rural areas. Considering this limitation, it is necessary to determine which test or combination of tests will be the most beneficial to use in monitoring. However, this question was not directly answered by the studies. In terms of feasibility, expanding accessibility to these diagnostic tests becomes crucial in management. Monitoring may also require funding and support from the local and

national government for successful and sustainable implementation. Despite these issues, the panel mentioned its importance in preventing HCC among treated patients. They argued that the costs of monitoring are still cheaper when compared to the costs of HCC treatment. It may potentially be cost-effective or even cost-saving long term, but a formal economic evaluation is needed.

SUMMARY OF FINDINGS

Table 22. Monitoring strategies using diagnostic tests and risk of outcomes.

Monitoring strategy used	Studies (patients)	Analysis	Outcome	Effect Estimate (95% CI)	Interpretation	Certainty of evidence
Albumin (3-6 months)	2 (n=1200)	Normal vs. low	HCC	**HR 0.61** (0.42, 0.83)	Normal albumin, lower risk	VERY LOW ⊕◯◯◯
Platelet count (3-12 months)	5 (n=4960)	Low vs. normal	HCC	**HR 1.33** (1.04, 1.70)	Lower platelet, increased risk	VERY LOW ⊕◯◯◯
AFP (3-12 months)	4 (n=4103)	High vs. low	HCC	**HR 2.06** (1.10, 3.86)	High AFP, increased risk	VERY LOW ⊕◯◯◯
HBV DNA (6-12 months)	1 (n=591)	High vs. low	HCC	**HR 1.18** (1.05, 1.33)	High HBV DNA, increased risk	VERY LOW ⊕◯◯◯
	1 (n=419)		Complete virologic response	**HR 0.86** (0.74, 0.99)	Increasing HBV DNA, decreasing virologic response	VERY LOW ⊕◯◯◯
Liver ultrasound (3-6 months)	4 (n=4430)	Optimal vs. suboptimal surveillance	HCC	Tumor ≤ 4cm (28% vs. 60%, p=0.084) BCLC A or B (72% vs. 40%, p=0.152)	Not significant (trend towards small tumor size)	VERY LOW ⊕◯◯◯
Creatinine (12 months)	3 (n=1332)	TDF, ETV, telbivudine and without treatment	Kidney injury	--	Decreased eGFR for TDF	VERY LOW ⊕◯◯◯
Bone mineral density (at least 2x during treatment)	2 (n=1263)	TDF, entecavir and without treatment	Osteopenia/ osteoporosis	--	No significant change in BMD from baseline	VERY LOW ⊕◯◯◯

Table 22. Monitoring treatment compliance and risk of outcomes.

Monitoring treatment compliance		Findings	Interpretation	Certainty of evidence
Ha et al. (2011)	Cohort of HBeAg negative patients on ETV and ADV	Incomplete viral suppression was shown to be more likely due to medication non-adherence (no effect estimate)	Adherence leads to viral suppression	VERY LOW ⊕◯◯◯
Shin et al. (2018)	Non-compliance to medications and: 1) all-cause mortality 2) liver-related mortality	1) HR 4.96 (2.19, 11.27) 2) 14.29 (3.49, 58.47) 3) HR 2.86 (1.76, 4.64) 4) HR 2.86 (1.93, 4.25)	Non-adherence increases risk fo all-cause mortality, liver-related mortality,	VERY LOW ⊕◯◯◯

Monitoring treatment compliance		Findings	Interpretation	Certainty of evidence
	3) HCC 4) cirrhotic complications		HCC, and cirrhotic complications	
Lee et al. (2020)	Poor adherence and: 1) composite death and liver transplantation 2) renal failure	1) HR 1.38 (1.27, 1.50) 2) HR 2.62 (2.20, 3.12)	Non-adherence increases risk of death, LT, and renal failure	VERY LOW ⊕◯◯◯
Wang et al. (2016)	Compliance to HCC surveillance Cirrhosis vs. no cirrhosis	38.4% vs. 21.6% (P<0.001) (cirrhotics were compliant) Adherent patients had smaller tumor sizes (p<0.08)	Compliance to HCC surveillance trends towards earlier HCC (smaller tumor size	VERY LOW ⊕◯◯◯

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13. Should periodic disease activity monitoring be done among non-cirrhotic patients with chronic hepatitis B infection who are on treatment to determine medication compliance, drug toxicities, and prevention of hepatitis B-related morbidity and mortality and development of HCC?

A. We recommend periodic monitoring among adult patients with chronic hepatitis B without liver cirrhosis on treatment using HBV DNA, ALT, APRI, FIB4, and creatinine to improve hepatitis B-related outcomes and decreasing adverse effects.

Strength of recommendation: **Strong**
Certainty of evidence: **Very Low** ⊕◯◯◯

B. We recommend monitoring of non-cirrhotic pediatric patients with chronic hepatitis B on antiviral treatment using HBV DNA, anthropometrics, creatinine, and bone mineral density at least annually.

Strength of recommendation: **Strong**
Certainty of evidence: **Low** ⊕⊕◯◯

Monitoring of CHB patients on treatment evaluates sustained viral suppression, disease progression, and adherence to therapy. This can serve as a guide in deciding which patients should continue or discontinue treatment.[217] Infrequent monitoring has also been previously found to possibly lead to interruption or prolongation of treatment or increase the risk of a patient being lost to follow-up.[217] It is important to determine how to best approach monitoring among non-cirrhotic, CHB patients, on antiviral therapy to ascertain compliance to medication, disease progression and risk for hepatitis B-related morbidity or hepatocellular carcinoma.

EVIDENCE TO DECISION

Benefits and harms

Indirect evidence was obtained from 20 observational studies that monitored HBV DNA, ALT, platelet count, APRI and FIB4, and their correlation to HBV-related outcomes.

Twenty observational studies were reviewed that reported on the predictors of hepatitis B-related disease progression and hepatocellular carcinoma among non-cirrhotic patients on treatment. Elevated ALT was associated with increased risk for worse liver-related outcomes, while higher baseline ALT and lower baseline HBV DNA were associated with increased virological response.[234-237] Increased ALT[228], HBV DNA[228], APRI[227,229-232] and FIB-4 index[227, 228] were associated with an increased risk of HCC development, while platelet counts[228,233] did not seem to affect HCC risk. Subsequent adherence to HCC surveillance is associated with earlier cancer stages and smaller tumor sizes on diagnosis of HCC.[222]

Three studies showed that tenofovir was associated with decreasing renal function over time, but none of the studies reviewed have assessed whether this is associated with increased risk of

dialysis.[218-220] Similarly, although treatment effects on bone mineral density were explored in 2 studies[220-221], none have specifically reported on the incidence of fractures.

RCTs on children show that the antivirals and placebo had similar adverse events for both groups except for one study on lamivudine which showed more adverse events in the placebo group.[223-226]

Certainty of evidence

Overall, certainty of evidence for studies involving adults was deemed very low due to issues on indirectness, inconsistency and imprecision. For studies on children, certainty of evidence was ranged from low to moderate across outcomes due to issues with imprecision and inconsistency.

Other considerations

Cost

The following table provides an overview of the costs of periodic monitoring in CHB patients on antiviral therapy:

Table 23. Costs of periodic monitoring in CHB patients on antiviral therapy

Diagnostic Test	Unit Cost (Php)	Quarterly	Every 6 months	Annually
Complete Blood Count with Platelet*§	120.00-250.00	480.00-1000.00	240.00-500.00	120.00-250.00
AST*§	185.00-200.00	740.00-800.00	370.00-400.00	185.00-200.00
ALT*	180.00-200.00	720.00-800.00	360.00-400.00	180.00-200.00
AFP	700.00-1000.00	2,800.00-4000.00	1,400.00-2000.00	700.00-1,000.00
Complete Blood Count with Platelet*§	120.00-250.00	480.00-1000.00	240.00-500.00	120.00-250.00
AST*§	185.00-200.00	740.00-800.00	370.00-400.00	185.00-200.00
ALT*	180.00-200.00	720.00-800.00	360.00-400.00	180.00-200.00
AFP	700.00-1000.00	2,800.00-4000.00	1,400.00-2000.00	700.00-1,000.00
HBV DNA	3,800.00-5,000	15,200.00-20,000.00	7,600.00-10,000.00	3,800.00-5,000.00
Creatinine	95.00-200.00	380.00-800.00	190.00-400.00	95.00-200.00
Liver ultrasound	500.00-800.00	2,000.00-3,200.00	1,000.00-1,600.00	500.00-800.00
Estimated Annual Cost		22,320.00-30,600.00	11,160.00-15,300.00	5,580.00-7,650.00

*Components of FIB4
§Components of APRI

Recommendations from other groups

WHO recommends that all patients with CHB infection undergo testing for ALT, AST (for APRI), HBsAg, HBeAg, and HBV DNA levels at baseline, as well as non-invasive tests like FibroScan and APRI score. Those who are on treatment should be followed up regularly and assessed for adherence to medication in every visit. As part of HCC surveillance, abdominal ultrasound and

AFP must be done every 6 months in non-cirrhotic patients aged >40 years old or who have a family history of HCC. Patients who are on long-term antiviral therapy, specifically entecavir and tenofovir, should have monitoring of renal function yearly.[217]

Similarly, APASL recommends that patients on TDF or ADV be monitored for renal function and bone density quarterly. The association also recommends that HBeAg, anti-HBe, and ALT be done every 3 months in CHB patients on NA therapy. HBV DNA should be included in the tests done on the 3rd month and 6th month of treatment and then repeated 3-6 months thereafter in patients on lamivudine, adefovir or tenofovir, and every 6 months in patients on entecavir and tenofovir. [238]

CONSENSUS ISSUES

The panel strongly recommended periodic monitoring in both adult and pediatric patients with chronic hepatitis B without liver cirrhosis, despite the very low certainty of evidence. The panelists considered periodic monitoring as an important part of treatment. They argued that its benefits in prevention and early intervention of liver cancer far outweigh its costs, considering that HCC treatment is not a viable option for many patients. Government funding will be needed to sustain the long-term costs of periodic monitoring. Aside from costs, concerns on availability of tests and accessibility to services and facilities were raised. Not all tests are available nationwide and accessibility to tests largely depend on the resources of LGUs.

SUMMARY OF FINDINGS

Table 24. Monitoring strategies using diagnostic tests and risk of outcomes.

Monitoring strategy used	Studies (patients)	Analysis	Outcome	Effect Estimate (95% CI)	Interpretation	Certainty of evidence
ALT (3-6 months)	1 (n=487) 1 (n=192)	ALT≤200 U/L ALT≥40 U/L vs < 40	Liver-related outcomes	**HR 0.32** (0.13, 0.75) **HR 2.19** (0.94, 5.15)	Increased risk with elevated baseline ALT	VERY LOW ⊕◯◯◯
	2 (n=967)	ALT≥2xULN	Virologic response	**RR 1.00** (1.00, 1.00) **HR 1.88** (1.48, 2.38)	Higher baseline ALT, increased probability of virologic response	VERY LOW ⊕◯◯◯
	1 (n=532)	ALT≥40 U/L vs <40	HCC	**HR 2.93** (1.56, 5.50)	Elevated ALT increases risk	VERY LOW ⊕◯◯◯
HBV DNA (3-12 months)	2 (n=967)	High vs. low	Virologic response	**RR 0.20** (0.12, 0.35)	High HBV DNA, lower virologic response	VERY LOW ⊕◯◯◯
HBV DNA (6-12 months)	1 (n=532)	2,000-19,999 20,000-199,999 ≥200,000	HCC	**HR 3.33** (1.31, 8.48) **HR 5.32** (2.05, 13.8) **HR 5.16** (2.08, 12.8)	High HBV DNA, increased risk	LOW ⊕⊕◯◯
FIB-4 (6 months)	2 (n=2468)	≥1.3	HCC	**HR 2.56** (1.67, 3.92)	Increased risk for HCC, for FIB-4 ≥1.3	LOW ⊕⊕◯◯

Monitoring strategy used	Studies (patients)	Analysis	Outcome	Effect Estimate (95% CI)	Interpretation	Certainty of evidence
APRI (6 months)	4 (n=3213)	≥above cutoffs per study	HCC	**HR 2.86** (1.56, 4.61)	Increased risk for HCC for ≥APRI cutoff	VERY LOW ⊕◯◯◯
Platelet (at least 2x during treatment)	2 (n=2198)	< 100,000	HCC	**HR 1.54** (0.44, 5.35)	No significant difference	VERY LOW ⊕◯◯◯
Crea (6-12 months)	3 (n=915)	Rise in crea/decrease in eGFR	Treatment safety	--	LdT increased eGFR; ETV and TDF decreased eGFR (all not clinically significant	VERY LOW ⊕◯◯◯
Bone mineral density (12 months)	2 (n=1460)	Decrease in hip and spine BMD	Treatment safety	--	Treatment did not increase risk of osteopenia/ osteoporosis	VERY LOW ⊕◯◯◯
Anthropometrics for children (every follow-up)	2 (n=371)	Measurement of height for age, weight for age, BMI z scores	Treatment safety – growth	--	Treatment had no effect on anthropometrics	LOW ⊕⊕◯◯

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Chapter 4. RESEARCH GAPS

Several RCTs are currently investigating the effects of curative or preventive treatments for CHB infections. There is an ongoing one-arm, open-label study on the early initiation of maternal TDF prior to 20 weeks of gestation.[239] The aim of this study is to determine the appropriate time in pregnancy to initiate TDF treatment of HBV in order to reach HBV DNA <100 IU/mL at delivery. The primary outcome measures of this trial are time to HBV DNA suppression and the proportion of women with undetectable HBV DNA at delivery.

A randomized controlled trial of tenofovir DF (NCT016514033 age: 2 to 12 years) in children and adolescents with chronic HBV infection was recently completed in the US.[240] Another randomized controlled trial of tenofovir alafenamide (TAF) (NCT02932150, age: 2 to 18 years) in children and adolescents with chronic HBV infection over a period of 240 weeks is in progress.[241]

Promising therapies have recently been developed against new targets in the HBV replication cycle, as well as immunotherapies that can restore the host's immune response to HBV.[242]

The following topics were identified as potential future research topics:

Table 25. Research gaps

Domain	Topic
Prevention	1. Effects of mass catch-up vaccination in targeted populations such as children 2. Effectiveness of catch-up vaccination for pregnant women in reducing MTCT and horizontal transmission 3. Cost-effectiveness of administering HBIG for infants, including costs associated with treating complications of chronic infection 4. Efficacy of HBIG prophylaxis among infants of mothers with known maternal status in preventing complications of vertical transmission of infection later in life 5. Optimal time to initiate and discontinue the administration of TDF for preventing MTCT 6. Efficacy of TDF in preventing MTCT among women whose infants did not receive HBIG
Treatment	7. Novel therapies affecting infection resolution among CHB patients, including those with and without liver cirrhosis 8. Randomized controlled trials assessing the efficacy and safety of tenofovir monotherapy for children 9. Long-term effects of antiviral therapy on reversal of cirrhosis 10. Effects of antiviral therapy among healthcare workers infected with HBV in terms of preventing procedure-related transmission 11. Comparative studies of tenofovir and other antivirals in children to optimize treatment algorithms
Screening, Diagnosis, and Monitoring	12. Optimal frequency of monitoring and surveillance 13. Local studies on cost-effectiveness of HBV screening 14. Determining the most accurate and cost-effective diagnostic test and frequency of testing among resource-limited countries to guide the initiation of treatment 15. Effects of the timing of monitoring (i.e., every 3 months vs 6 months vs 12 months) on disease progression, compliance, and adverse reactions of antiviral therapy on chronic HBV patients with or without cirrhosis receiving treatment 16. Optimal frequency of monitoring of HBV status for adults and children 17. Effects of monitoring among CHB patients who are not yet on treatment 18. Prospective, longitudinal studies on the clinical outcomes of treated children, including validating the use of biochemical and virologic outcomes

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242. Tenofovir Alafenamide (TAF) in Children and Adolescents With Chronic Hepatitis B Virus Infection - Full Text View - ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/show/NCT02932150 Accessed: 2021-07-23

Chapter 5. MONITORING AND EVALUATION

External Review

The CPG will be submitted for external review from Department of Health to obtain feedback on consensus recommendations, assess quality of the guideline development process, and evaluate applicability and feasibility for local implementation. Rating scales and open-ended questions will be used to collect data. These will be summarized by the Steering Committee and incorporated in the final manuscript.

Dissemination

The full manuscript of the CPG will be submitted to the DOH National Clearinghouse for promotion and uptake of the recommendations that include activities such as releasing department memoranda to notify stakeholders, publicizing the CPG through the DOH newsletter, press releases, news articles, social media, and NGOs.

The final CPG manuscript will be made available both in print and in digital form. This CPG will be presented to potential trainers and stakeholders from public and private institutions through virtual orientations. A training guide in the form of a lecture slide set will also be created for potential users of the CPG. The SC will develop a simplified version of this CPG and make it available in a format ready for reproduction and dissemination to patients in clinics and hospitals.

Implementation

Quality indicators will be formulated by the Steering Committee in the CPG to guide the DOH in monitoring and evaluation of the effectiveness of this CPG. Monitoring the use of this CPG may also be a subject of research by interested parties.

Updating of the guidelines

This CPG will be reviewed 3 years after its inception. Updates or revisions may be indicated if there are identified gaps in the current knowledge on the subject, newly released evidence from large-scale studies, approval of new interventions or therapies, changes in values placed on outcomes, changes in resources available for healthcare, or if there is a need for new guidance on a particular topic.

Chapter 6. AUTHORSHIP, CONTRIBUTIONS, ACKNOWLEDGEMENT

This project was made possible through the initiative and funding from the DOH. While instrumental in the inception of this CPG, the DOH did not impose any conditions nor exerted any influence in formulating the final recommendations.

Steering Committee. The steering committee spearheaded the preparatory work for the CPG, supervised the evidence review and facilitated the formulation of the recommendations. It organized the evidence reviewers and the consensus panel. The SC is responsible fot he overall organization and management of the project and is accountable for the overall quality of this CPG.

> *Dr. Jose D. Sollano, Jr. Dr. Theodora Cecile G. Magturo, Dr. Edhel S. Tripon, Dr. Cybele Lara R. Abad, Dr. Marjorie I. Santos, Dr. Novette Regina M. Lagunzad, Dr. Eric B. Yasay*

Technical Working Group. The Institute of Clinical Epidemiology of the University of the Philippines Manila undertook extensive technical work in (1) the objective search, appraisal, summarization, and synthesis of evidence summaries with (2) presenting the evidence in the panel meeting, and (3) documenting and writing the final output.

> *Dr. Eric B. Yasay (Lead), Mrs. Maria Vanessa C. Villarruz-Sulit (Project Manager), Dr. Sally Jane G. Velasco-Aro, Dr. Sarah Jean C. Bellido, Dr. Kathryn R. Baltazar-Braganza, Dr. Jairus B. Cabajar, Dr. Elvie Victonette B. Razon-Gonzalez, Dr. Germana Emerita V. Gregorio, Dr. Alinda Mae C. Gordola, Dr. Henry Winston C. Li, Dr. Jacqueline Michelle D. Melendres, Dr. Lester Jan A. Olimba, Dr. A. Nico Najar I. Pajes, Dr. Sahra May O. Paragas, Dr. Nikko Theodore V. Raymundo, Dr. Clarence Pio Rey C. Yacapin, Dr. Marissa M. Alejandria (Technical Adviser) and Dr Leonila F. Dans (Technical Adviser)*

Consensus Panel. This CPG is instrumental because it incorporates patient values and preferences, equity and implementation issues, and point of views of different stakeholders from varied sectors of society who lent their time, effort, and expertise in scrutinizing the scientific evidence to be able to localize the decision-making process. The dedicated panel members are composed of the following:

> *Dr. Juliet O. Sio-Aguilar (Philippine Society for Pediatric Gastroenterology and Nutrition), Dr. Sybil Lizanne R. Bravo (Philippine Obstetrical and Gynecological Society), Dr. Roberto N. De Guzman Jr. (Philippine Society of Digestive Endoscopy), Dr. Ronaldo E. Lapitan (Philippine Academy of Family Physicians), Dr. Dax Ronald O. Librado (Philippine Society of General Internal Medicine), Mr. Joseph Michael D. Manlutac (Hepatitis B Program Manager), Mr. Christopher Munoz (Patient Advocate, Yellow Warriors Society Philippines), Dr. Janus P. Ong (Hepatology Society of the Philippines), Dr. Diana A. Payawal (Philippine College of Physicians), Mr. Melbert B. Reyes (Philippine Nurses Association), Dr. Arthur Dessi E. Roman (Philippine Society for Microbiology and Infectious Diseases), Dr. Gerard Danielle K. Sio (Philippine College of Occupational Medicine), Dr. Marilou G. Tan (Philippine Pediatric Society), and Dr. Ira I. Yu (Philippine Society of Gastroenterology).*

This project would not have been successful without the leadership and guidance of Dr. Marissa M. Alejandria and Dr. Leonila F. Dans. The developers of this guideline would also like to give special thanks to Dr. Jose Gerad Belimac for facilitating the inception meetings, Dr. Lia Aileen M. Palileo-Villanueva for facilitating the consensus panel meetings and Mr. Howell Henrian G. Bayona for drafting the manuscripts for the CP meetings and the final manuscript.

Appendix 1. DECLARATION OF CONFLICTS OF INTEREST

Steering committee

No.	Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
1	Jose D. Sollano, Jr., MD	Gastroenterology	University of Santo Tomas	Receives honoraria from A. Menarini, Getz Pharma as a resource speaker; Co-author, APASL guidelines
2.	Theodora Cecile G. Magturo, MD, MHA	Program Manager	Department of Health – Food and Waterborne Diseases Prevention and Control Program	None
3.	Edhel S. Tripon. MD	Gastroenterology	Hepatology Society of the Philippines	Receives fees as consultant/Medical Director and owns stocks (<5%), Amihan Medical Ventures; Research grant for CANDLE Study (HCC and Hepatitis B in Filipinos-Cohort Study) under PCHRD-DOST; honoraria as speaker for hepatology-related topics, Viatris (May 2021) and Megalife (March-September 2021); President (2021-2022) and Board Member (2017-2021), HSP
4.	Cybele Lara R. Abad, MD	Infectious Diseases	University of the Philippines Manila – Philippine General Hospital (UP-PGH)	Received honoraria as webinar speaker on HBV/HIV from Menarini (2020)
5.	Marjorie I. Santos, MD	Obstetrics and Gynecology	Philippine Obstetrical and Gynecological Society	None
6.	Novette Regina M. Lagunzad, MD	Pediatric Gastroenterology	UP – PGH	None
7.	Eric B. Yasay, MD	Gastroenterology	UP – PGH	Project manager; 2021 Hepatitis B CPG

Consensus panel

No.	Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
1	Juliet Sio-Aguilar, MD, MSc	Pediatric Gastroenterology	Philippine Society for Pediatric Gastroenterology and Nutrition (PSPGHAN)	None
2	Sybil Lizanne R. Bravo, RPh, MD, MSc	Obtetrics and Gynecology, Reproductive Infectious Disease	Philippine Obstetrical and Gynecological Society	None

No.	Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
3	Roberto N. De Guzman Jr., MD	Adult Gastroenterology	Philippine Society of Digestive Endoscopy	Received honorarium as consultant, Menarini (2021)
4	Ronaldo E. Lapitan, MD	Family Medicine	Philippine Academy of Family Physicians	None
5	Dax Ronald Librado, MD	Internal Medicine	Philippine Society of General Internal Medicine	None
6	Joseph Michael D. Manlutac	Hepatitis B Pilot Program Manager	Department of Health – Central Luzon	Lobbying for support for the Hepatitis B pilot demo (Aug 2019- Sep 2020)
7	Christopher Munoz	Patient Advocate	Yellow Warriors Society Philippines	None
8	Janus P. Ong, MD, MPH	Adult Hepatology	Hepatology Society of the Philippines	Receives honoraria as advisor from Menarini (2021); Research support from Gilead (2020-present); Co-author HSP 2018 update to hepatitis C; Editorial board member, World Journal of Hepatology; Technical Working Group Member, Viral Hepatitis TWG, DOH and Strategic and Technical Advisory Committee, WPRO
9	Diana Alcantara-Payawal, MD, DTMH, FPCP, FPSG, FPSFDE	Adult Hepatology	Philippine College of Physicians	Consensus panel member and co-authored the 2020 APASL CPG on Hepatitis B reactivation; Senior editorial role, 2020 Asian Consensus recommendations on optimizing the diagnosis and initiation of treatment of Hepatitis B; Received speaker's fees for PSG Digestive Disease Week Satellite Dinner
10	Melbert B. Reyes, RN	Nursing	Philippine Nurses Association, Inc.	None
11	Arthur Dessi E. Roman, MD, MTM, FPCP, FPSMID	Adult Infectious Diseases	Philippine Society for Microbiology and Infectious Diseases	Treasurer and Board Member, PSMID
12	Gerard Danielle K. Sio, MD, MOH	Occupational Medicine	Philippine College of Occupational Medicine	None
13	Marilou G. Tan, MD	Pediatric Gastroenterology	Philippine Pediatric Society	President, Philippine Society for Pediatric Gastroenterology, Hepatology and Nutrition
14	Ira I. Yu, MD	Adult Hepatology	Philippine Society of Gastroenterology	President, PSG

Evidence reviewers

No.	Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
1	Sally Jane G. Velasco-Aro, MD	Pediatric Infectious Diseases	UP – PGH	None
2	Sarah Jean C. Bellido, MD	Gastroenterology	St. Luke's Medical Center Quezon City	None
3	Kathryn Baltazar-Braganza, MD	Developmental Pediatrics	UP Manila	None
4	Jairus Cabajar, MD	Internal Medicine	N/A	None

No.	Name	Area of Expertise	Affiliation	Summary of Disclosure or other relevant interest
5	Elvie Victonette B. Razon-Gonzalez, MD	Internal Medicine	West Visayas State University Medical Center, Medicus Medical Center	None
6	Germana Emerita V. Gregorio, MD	Pediatric Gastroenterology	UP – PGH	None
7	Alinda Mae Gordola, MD	Internal Medicine	UP – PGH	None
8	Henry Winston C. Li, MD, RMT	Gastroenterology	UP – PGH	None
9	Jacqueline Michelle D. Melendres, MD, FPDS, GDip(ClinEpi)	Dermatology	UP Manila	None
10	Lester Jan A. Olimba, MD	Gastroenterology	UP – PGH	None
11	A. Nico Nahar Pajes, MD	Internal Medicine	UP – PGH	None
12	Sahra May O. Paragas, MD	Clinical Epidemiology	UP Manila	None
13	Nikko Theodore V. Raymundo, MD	Gastroenterology	St. Luke's Medical Center Global City	None
14	Clarence Pio Rey C. Yacapin, MD, FPCS, MSc (cand.)	Laparoscopic Surgery	Asian Hospital and Medical Center	None
15	Eric B. Yasay, MD	Gastroenterology	UP – PGH	Project manager; 2021 Hepatitis B CPG
16	Maria Vanessa V. Sulit, RN, MSc	Clinical Epidemiology	Asia-Pacific Center for Evidence-Based Healthcare, Inc.	Receives fees as consultant from UP Manila for 3 months, honoraria from Stroke Society of the Philippines; Treasurer, APC-EBH