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GUIDELINES

AGA Clinical Practice Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation in At-Risk Individuals

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BACKGROUND & AIMS: Hepatitis B reactivation (HBVr) can occur due to a variety of immune-modulating exposures, including multiple drug classes and disease states. Antiviral prophylaxis can be effective in mitigating the risk of HBVr. In select cases, clinical monitoring without antiviral prophylaxis is sufficient for managing the risk of HBVr. This clinical practice guideline update aims to inform frontline health care practitioners by providing evidence-based practice recommendation for the management of HBVr in at-risk individuals. **METHODS:** The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence and make recommendations. The panel conducted a systematic evidence review to identify new studies since publication of the first version of this clinical practice guideline in 2014. The Evidence to Decision framework was used to develop recommendations regarding the role of antiviral prophylaxis and monitoring without antiviral prophylaxis for management of HBVr. Clinical recommendations were based on the balance between desirable and undesirable effects, patient values, costs, and health equity considerations. **RESULTS:** The panel agreed on 4 recommendations. Based on evidence and baseline risk assessment, the panel made a strong recommendation in favor of antiviral prophylaxis for individuals at high risk of HBVr. For individuals at moderate risk of HBVr, a conditional recommendation was made in favor of antiviral prophylaxis. For individuals at low risk of HBVr, a conditional recommendation was made in favor of monitoring alone without antiviral prophylaxis. Monitoring should be performed at 1- to 3-month intervals, and must include assessment of hepatitis B viral load in addition to assessment of alanine aminotransferase. For individuals deemed to be at-risk of HBVr, the panel agreed on a strong recommendation in favor of testing for HBV; given universal Centers for Disease Control and Prevention screening guidance for hepatitis B for all adults 18 years and older by testing for HBV surface antigen, hepatitis B surface antibody, and total hepatitis B core antibody, stratifying screening practices by magnitude of HBVr risk is no longer needed. **CONCLUSIONS:** This document provides updated guidance for the management of HBVr in at-risk individuals. Limitations and gaps in the evidence are highlighted. This guideline is expected to require updating in 5 years from publication.

Keywords: Hepatitis B Reactivation; Antiviral Prophylaxis; Autoimmune Disease; Cancer Therapy; Immunosuppression.

Hepatitis B virus reactivation (HBVr) is characterized by a loss of immunologic suppression of HBV activity in patients who are either positive for HBV surface antigen (HBsAg) or HB core antibody (anti-HBc). HBVr is generally a consequence of chronic immunosuppression, induced either by drug therapy or by pathologic immunosuppression. The incidence of HBVr varies by the degree and mechanism of immunosuppression.[1] B cell–depleting agents, such as rituximab, are traditionally associated with a notably high risk of HBVr. Individuals' serologic status also modulates the risk of HBVr; reactivation is more likely among those who are HBsAg-positive than patients with resolved HBV infection, defined in this guideline as those who are HBsAg-negative, HBV DNA–negative, and anti-HBc–positive. These factors are projected in a measurable baseline risk of individuals to develop HBVr, which is defined as

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Abbreviations used in this paper: **AGA, American Gastroenterology Association; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CAR-T, chimeric antigen receptor T cell; CEA, cost-effectiveness analysis; DAA, direct-acting antiviral; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HBsAg, hepatitis B virus surface antigen; HBVr, hepatitis B virus reactivation; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; IL, interleukin; JAK, Janus kinase; 6-MP, 6-mercaptopurine; RCT, randomized controlled trial; RR, relative risk; TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitor; TNF, tumor necrosis factor.**

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the rate of HBVr among individuals who are either HBsAg-positive or anti-HBc–positive/HBsAg-negative, who are subject to exposures known to lead to HBVr, and whose risk is not being modulated by antiviral prophylaxis. The baseline risk of HBVr is the culmination of all risk factors that explain the variability in the rate of reactivation among individuals with different immunosuppressive exposures.

Objective of the Evidence Review and Guideline

In 2014, the American Gastroenterology Association (AGA) published their first guideline on the prevention and management of HBVr among individuals on immunosuppressive therapy.[2,3] Since that publication, multiple novel classes of immunosuppressive therapies have been developed and approved for clinical use. In addition, interventional therapies, such as transcatheter arterial chemoembolization (TACE) that can induce an immunosuppressed state, and thus are relevant to potential HBVr, have also been recognized. This guideline update aims to address the wide range of exposures that are suspected to increase the risk of HBVr, and for which guideline recommendations currently do not exist. In particular, the current update sought to provide guidance on the prevention and management of HBVr in individuals taking immune checkpoint inhibitors (ICIs), anti-interleukin (IL) therapies, chimeric antigen receptor T cell (CAR-T) therapies, cytokine/integrin inhibitor therapies, tyrosine kinase inhibitors (TKIs), anti T-cell therapies, and Janus kinase (JAK) inhibitors, and update the guidance provided for anti–tumor necrosis factor (TNF) therapies in light of new evidence. The current guideline update also sought to provide guidance on the prevention and management of HBVr among individuals undergoing TACE for hepatocellular carcinoma, and individuals who are co-infected with hepatitis C virus (HCV) and undergoing direct-acting antiviral (DAA) treatment. This guideline is not intended to dictate medical decision making, but are intended to provide evidence-based guidance to inform medical decision making. No single guideline can encompass the nuance of medical decision making that requires clinical judgment and contextualization of medical knowledge by individual values and preferences. Within this context, this guideline aims to provide guidance on the benefits and harms of antiviral prophylaxis and monitoring for HBVr as alternative strategies.

Target Audience

This guideline is intended to guide frontline health care practitioners, including primary care physicians, clinical advanced care providers (eg, nurse practitioners, pharmacists, and physician assistants), gastroenterologists, hepatologists, oncologists, rheumatologists, dermatologists, and other health care providers who are tasked with the prevention and management of HBVr in their clinical practice. In addition, this guideline is intended to provide guidance for patients with exposures that increase their risk of HBVr, as well as policy makers. Although the Guideline Panel is aware that this guideline and its recommendations will be read by a wide audience, including policy makers and industry representatives, it is primarily targeted toward health care providers who depend on our evidence-based, expert recommendations to inform their clinical practice and shared decision making with patients. We intend these recommendations to serve as a benchmark for high-quality HBV care and improve delivery and management of related health care services.

Methods

Overview

The recommendations presented herein were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[4]

Organization and Panel Composition, and Conflicts of Interest

The Guideline Panel included 7 guideline committee members, 5 of whom were hepatologists with clinical and research expertise in the subject matter, 1 senior GRADE methodologist, and 1 junior GRADE methodologist. The senior methodologist provided supervision and oversight of the evidence synthesis process, and actively participated with the junior methodologist on this work. The guideline committee members actively participated in review of the evidence, screening of studies captured through systematic review, and contributed to the development of recommendations.

All conflicts of interest were disclosed by the Guideline Panel members before initiation of the guideline development process and were adjudicated by the Chair of the AGA Clinical Guidelines Committee. All identified conflicts were managed according to AGA policies. The junior and senior methodologist had no conflicts relevant to the topic of this guideline. No Guideline Panel member needed to be excused from participation in the guideline process due to disqualifying conflicts of interest.

Document Review

The guideline underwent 30-day invited peer review and open public comment. Feedback from a patient was also received. Revisions to the guideline document were made to incorporate the feedback received from these processes. The AGA Governing Board subsequently reviewed and approved the manuscript.

Formulation of Clinical Questions and Determining Outcomes of Interest

The Guideline Panel met and generated clinical questions using the PICO format, outlining the population of interest (P), the intervention of interest (I), the comparator (C), and the outcomes of interest (O) (Table 1). Selected desirable and undesirable outcomes were consistent with the 2014 version of this guideline. Only outcomes that were deemed CRITICAL or IMPORTANT for decision making, based on the standardized definitions of CRITICAL and IMPORTANT outcomes put forth while using GRADE methodology,[5] were summarized by generating evidence profiles.

Table 1. Focused Questions and Corresponding PICO (Patients, Intervention, Comparator, and Outcome) Questions Addressed in These Guidelines

Question no.	Focused question	PICO question			
		Population	Intervention	Comparator	Outcome
1	Should patients presumed to be at risk of HBVr be screened for HBV markers?	Patients at risk for HBVr	Testing of HBsAg, anti-HBc, anti-HBs	No testing	HBV reactivation Hepatitis from HBV reactivation Chemotherapy/drug interruption Adverse events Resource use
2	Do patients at risk for HBVr who are anti-HBc–positive, HBsAg-negative require antiviral prophylaxis?	All patients who are anti-HBc–positive and at risk for HBVr	Antiviral prophylaxis	No antiviral prophylaxis + HBV-DNA monitoring	HBV reactivation Hepatitis from HBV reactivation Chemotherapy/drug interruption Adverse events Resource use
3	Do patients at risk for HBVr who are anti-HBc–positive and HBsAg-positive require antiviral prophylaxis?	All patients who are anti-HBc–positive and are also HBsAg-positive at risk for HBVr	Antiviral prophylaxis	No antiviral prophylaxis + HBV-DNA monitoring	HBV reactivation Hepatitis from HBV reactivation Chemotherapy/drug interruption Adverse events Resource use

A patient representative provided feedback on selected outcomes, balance between desirable and undesirable outcomes, and, when applicable, how patients' values and preferences may affect the strength of recommendations.

Search Strategy

Detailed search strategy, including searched databases can be found in Supplementary Table 1. An additional Health Disparities and Minority Health Search Strategy was deployed to identify potential issues around equity that could arise from recommendations in this guideline.

Outcomes of Interest

In keeping with the definitions established in the 2014 guideline,[3] we defined HBVr as either the de novo appearance of HBV-DNA in a patient with previously undetectable HBV-DNA or ≥10-fold increase in HBV-DNA value compared with their baseline. Permissible surrogates were new detection of HBsAg or hepatitis B e antigen. We defined a hepatitis flare due to HBVr as an elevation in serum alanine aminotransferase level at least 3 times the baseline level that, at a minimum, is beyond the reference range. Additional outcomes of interest were interruption of treatment (eg, chemotherapy) and adverse events from antiviral prophylaxis against HBVr.

We identified variability in the definitions used by randomized controlled trials (RCTs), as well as nonrandomized studies in the definitions used to define HBVr and hepatitis due to HBVr. Examples of these variations include an increase in HBV-DNA to an absolute value of 2000 IU/mL, and an increase in serum alanine aminotransferase above an absolute value of 100 IU/L. The panel agreed that such deviations from the definitions outlined were acceptable, as they were in keeping with standard clinical practice.

Study Selection

The Guideline Panel, with consensus, agreed on inclusion and exclusion criteria that were aligned with the PICO questions. The screening process was conducted using Covidence[6] software (Melbourne, Australia) and is illustrated in Supplementary Figure 1. Two members of the Guideline Panel conducted title and abstract screening. Each of the full-text articles selected were screened by the junior methodologist and a Guideline Panel member. The full-text articles finally selected were reviewed by the Guideline Panel for selection. Any conflicts were resolved by consensus among the panel members.

Ascertainment of Risk Categories

The previous AGA guideline on prevention and treatment of HBVr during immunosuppressive drug therapy[3] outlined low- (<1%), moderate- (1%–10%), and high- (>10%) risk categories for HBVr. These thresholds represented risk values that guided medical decision making; low- and high-risk categories represented thresholds below and above which the decision to monitor and start antiviral prophylaxis could be made with higher certainty, respectively. In contrast, the moderate-risk category (encompassing baseline risk of 1%–10%) represented the variability in individual risk aversion when antiviral

prophylaxis should be considered and, given a reasonable discussion of risks, benefits, preferences, and values takes place, one may opt to monitor for reactivation instead of using antiviral prophylaxis. In the current guideline update, we designed and conducted a survey for empirical validation of these risk thresholds for HBVr. Our survey was designed from a patient's perspective and provided the options to select antiviral prophylaxis or monitoring instead of prophylaxis at various baseline risk values to ascertain distinct risk thresholds. In addition, our survey provided the option to consider or nearly always choose surveillance over antiviral prophylaxis; this flexibility in the degree of commitment to either of the 2 choices was designed to reflect the strength of preferences and risk averseness, thereby allowing validation and recalibration of risk categories. The survey was administered, in sequence, to the Guideline Panel, the AGA Governing Board, to attendees of the AGA Guideline Symposium at Digestive Disease Week 2024, and subsequently to the public at large through the AGA's social media representatives on X (formerly Twitter). Our survey was conducted through the REDCap consortium.[7]

Data Extraction and Analysis

Data from RCTs comparing preventive antiviral prophylaxis with monitoring followed by antiviral therapy when HBVr occurred were extracted to compute a pooled relative risk (RR) for each outcome of interest, which included the risk of HBVr, the risk of hepatitis flares attributed to HBVr, the risk of chemotherapy interruption, and the risk of adverse events associated with antiviral prophylaxis.

Because relative effects of interventions are generally stable across various baseline risks, we used all RCTs, including studies of different populations, as well different antiviral regimens, to generate pooled RRs. We used the inverse-variance method for study weighting, along with a random-effects model to compute pooled RR. Heterogeneity was assessed using the I^2 statistic. The pooled relative effects were subsequently applied to various baseline risks representative of different populations and risk categories, thereby computing risk differences with and without antiviral prophylaxis for these population categories.

Baseline risk estimates were obtained from the control arm of RCTs by performing a meta-analysis of proportions. In the absence of RCTs, baseline risks for various population groups were obtained from observational studies that:

- included consecutive individuals at risk of HBVr who were not on antiviral prophylaxis;
- provided appropriate baseline serology status of the included cohort;
- defined HBVr and/or hepatitis flares after HBVr in a manner that fell within the umbrella of acceptable definitions for these outcomes agreed on by the Guideline Panel experts and that corroborated the definitions of HBVr and hepatitis flares from HBVr as used in RCTs; and
- provided a description of a follow-up duration, which would either include the duration of exposure (eg, immunosuppressive therapy) or duration of follow-up from initial exposure (eg, start of immunosuppressive therapy).

We sought to include cohort studies or studies that most closely resembled inception cohort studies and excluded case series without a clear definition of the overall cohort (ie, lacking the denominator for meta-analysis of proportions), case reports, and case-control studies. We used the inverse-variance method along with a fixed-effects model to generate pooled baseline risks. We used the Freeman-Tukey double arcsine transformation to stabilize the variances in order to compute accurate proportions close to the margins. For comparative meta-analysis, as well as for meta-analysis of proportions, we used STATA software (StataCorp LLC, College Station, TX). We used the open-source software R (The R Project for Statistical Computing) to generate forest plots with imbedded graphical risk of bias presentation. We assumed class effect when assigning risk categories to drugs; the estimated risk of HBVr was applied to the entire drug class instead of limiting it to the drugs that were included in studies that provided data on HBVr.

Certainty Assessment

The risk of bias in RCTs was assessed using the Cochrane risk-of-bias tool for randomized trials, version 2. Certainty of the evidence was assessed using the GRADE approach (Tables 2 and 3) for each outcome and overall across outcomes using GRADEpro guideline development software (Evidence Prime).[8] The following domains are considered when assessing certainty using the GRADE approach: risk of bias, inconsistency in effect estimates, indirectness, imprecision of effect estimates, risk of publication bias, and presence or absence of a large effect estimate, as well as the potential impact of residual confounding. Results of these assessments are summarized in evidence profiles.

The relative effects obtained from pooled analysis of RCTs were applied to the varying baseline risks of exposures of interest. In our analyses, there were situations when the baseline risk had to be estimated from a low event rate or relatively limited sample size; in these circumstances, if the 95% CI of the baseline risk (modeled worst-case scenario) crossed clinically important risk thresholds used to define low-, moderate-, and high-risk categories, this was considered to impact precision of baseline risk estimate (Figure 1).

Development of Recommendations

The evidence studied and the evidence profiles generated are translated to guideline recommendations using the GRADE Evidence to Decision framework, which takes into consideration the overall certainty of evidence, the balance of benefits and harms, patient values and preferences, feasibility, acceptability, and cost-effectiveness of the intervention, and the impact of the intervention on equity. Using these domains, the Guideline Panel reached consensus for all recommendations. The phrase "the AGA recommends" is used for strong recommendations, whereas "the AGA suggests" is used for conditional recommendations.

Table 2. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessment, Development and Evaluation Framework[4]

Implication	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

NOTE. Strong recommendations are indicated by statements that lead with "we recommend" and conditional recommendations are indicated by statements that lead with "we suggest."

Recommendations

A summary of all the recommendations in this guideline is provided in Table 4. A clinical decision support tool that may assist clinicians in making pharmacologic management decisions for patients with HBVr is presented in Figure 2.

Recommendation 1: For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone. (*Strong recommendation, moderate certainty evidence*)

Implementation Considerations:

- This recommendation assumes the use of antivirals with a high barrier to resistance.
- Antiviral prophylaxis should be started before start of medications that impose risk of HBVr and should be continued for at least 6 months after discontinuation of risk-imposing therapy (at least 12 months for B cell–depleting agents).

We identified 12 RCTs[9–20] comparing antiviral prophylaxis in patients who were HBsAg-positive and/or anti-HBc–positive/HBsAg-negative with monitoring alone, who were offered on-demand rescue therapy at the occurrence of HBVr (Supplementary Tables 2 and 3); antiviral prophylaxis was associated with an 82% relative reduction in the risk of HBVr (95% CI, 70%–89%), as well as a 72% relative reduction in the risk of hepatitis flare from HBVr (95% CI, 50%–90%; Table 5, Supplementary Table 4, and Figure 3). As established previously, although these effect estimates are considered large, the magnitude of absolute effect is expected to vary by differing baseline risks. Consequently, the tradeoffs between a desirable effect from the intervention and the undesirable consequences also vary by differing baseline risks and may be sensitive to individuals' values and preferences. As values of patients differ in terms of risk averseness and perception of benefit, thresholds for risk categorization may vary accordingly. The previously published thresholds for low, moderate, and high-risk categories were reproducible and the Guideline Panel opted to retain them for the current iteration of the guideline. Of note, the following HBVr risk assessments are based on single agent exposure, and risk of immune-modulating

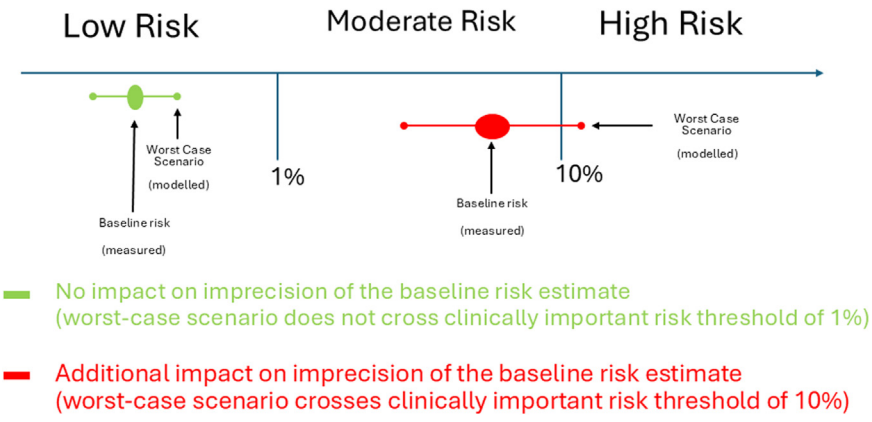

Figure 1. Graphical depiction of imprecision assessment for baseline risk estimates. Effect estimates with 95% CIs that cross the clinically important risk thresholds of 1% and 10% suffer from imprecision that impacts the certainty in the estimate of such effects.

Table 3. Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations Assessment, Development and Evaluation Framework[4]

Certainty of evidence	Definition
High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕◯	We are 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.
Low ⊕⊕◯◯	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
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.

medications used in combination (eg, with corticosteroids) may require additional adjustment.

For patients at "high risk," the baseline risk of HBVr from the exposure of interest is expected to be >10% (Table 6 and Supplementary Table 5) and included the following:

1. Anthracycline derivatives: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "moderate-risk" category, Recommendation 2).
2. B cell–depleting agents: When used in individuals who are HBsAg-positive or HBsAg-negative/anti-HBc–positive.
3. Anti–TNF agents: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "low-risk" category, Recommendation 3).
4. TKIs: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–

Table 4. Executive Summary of Recommendations and Implementation Considerations

Recommendations and implementation considerations
Recommendation 1: For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone. (*Strong recommendation, moderate certainty evidence*) **Implementation Considerations:** • This recommendation assumes the use of antivirals with a high barrier to resistance. • Antiviral prophylaxis should be started before start of medications that impose risk of HBVr and should be continued for at least 6 months after discontinuation of risk-imposing therapy (at least 12 months for B cell–depleting agents).
Recommendation 2: For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone. (*Conditional recommendation, moderate certainty evidence*) **Implementation Considerations:** • This recommendation assumes the use of antivirals with a high barrier to resistance. • Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use, and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative) may reasonably select active monitoring over antiviral prophylaxis, with careful consideration of feasibility and likelihood of adherence to long-term monitoring. Monitoring should be performed at 1- to 3-month intervals, and must include assessment of hepatitis B viral load in addition to assessment of alanine aminotransferase.
Recommendation 3: For individual at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis. (*Conditional recommendation, moderate certainty evidence*) **Implementation Considerations:** • This recommendation assumes regular and sufficient follow-up that ensures continued monitoring. • Patients who place a higher value on avoiding the small risk of reactivation (particularly those who may be on more than 1 low-risk immunosuppressive medication) and a lower value on the burden and cost of antiviral therapy may reasonably select antiviral therapy.
Recommendation 4: For individuals at risk of HBVr, the AGA recommends testing for hepatitis B (*Strong recommendation, moderate certainty evidence*) **Implementation Considerations:** • Given universal Centers for Disease Control and Prevention (CDC) screening guidance for hepatitis B for all adults aged ≥18 years by testing for HBsAg, anti-HBs, and total anti-HBc, stratifying screening practices by magnitude of HBVr risk is no longer needed. • It is reasonable to test initially for serologic markers alone (at minimum for HBsAg, anti-HBc) followed by viral load testing (HBV-DNA) if HBsAg and/or anti-HBc is positive.

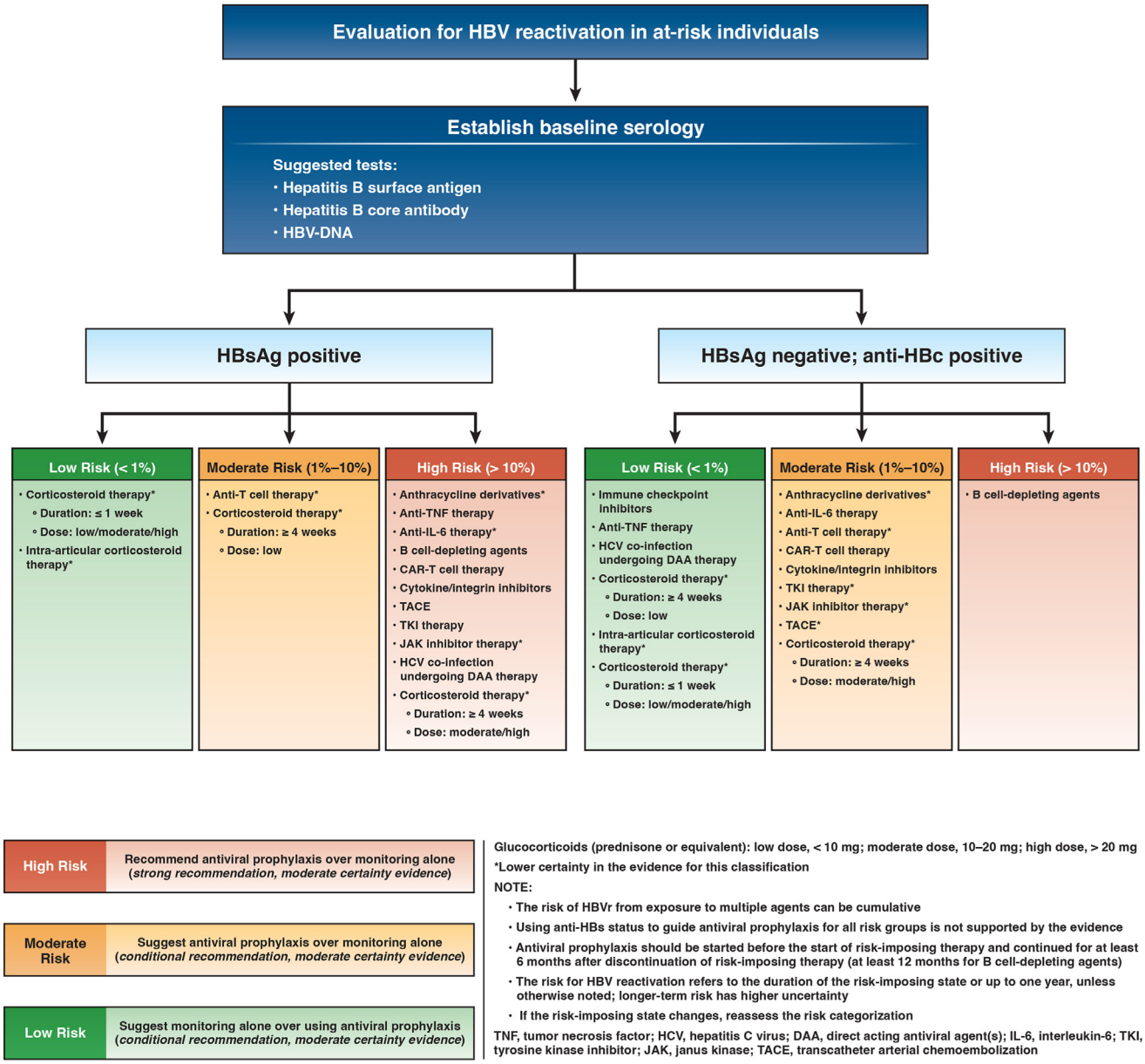

Figure 2. *Clinical Decision Support Tool:* HBVr. Summary of the risk classification and recommendations on antiviral prophylaxis for frontline practitioners.

positive individuals, please refer to the "moderate-risk" category, Recommendation 2).

5. Cytokine/integrin inhibitors: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "moderate-risk" category, Recommendation 2).
6. CAR-T cell therapy: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "moderate-risk" category, Recommendation 2).
7. Anti-IL6 agents: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc-positive individuals, please refer to the "moderate-risk" category, Recommendation 2).
8. JAK inhibitors: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "moderate-risk" category, Recommendation 2).
9. Individuals with HCV co-infection undergoing treatment with a DAA agent: Applicable to individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "low-risk" category, Recommendation 3).

Table 5. Summary of Findings Table of Antiviral Prophylaxis Compared With No Prophylaxis for Prevention of Hepatitis B Virus Reactivation in At-Risk Individuals

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	
				Risk with no prophylaxis	Risk difference with antiviral prophylaxis
HBVr (IMPORTANCE: Critical)	879 (12 RCTs)	⨁⨁⨁◯ Moderate[a]	0.18 (0.11–0.30)	1 per 1000 50 per 1000 500 per 1000	Low risk 1 fewer per 1000 (1 fewer to 1 fewer) Moderate risk 41 fewer per 1000 (45 fewer to 35 fewer) High risk 410 fewer per 1000 (445 fewer to 350 fewer)
HBV flare (IMPORTANCE: Critical)	624 (9 RCTs)	⨁⨁⨁◯ Moderate[b]	0.22 (0.10–0.50)	1 per 1000 50 per 1000 500 per 1000	Low risk 1 fewer per 1000 (1 fewer to 1 fewer) Moderate risk 39 fewer per 1000 (45 fewer to 25 fewer) High risk 390 fewer per 1000 (450 fewer to 250 fewer)
Chemotherapy interruption (IMPORTANCE: Important but not critical)	124 (2 RCTs)	⨁◯◯◯ Very low[c,d]	0.31 (0.05–1.84)	403 per 1000	278 fewer per 1000 (383 fewer to 339 more)
Adverse events (IMPORTANCE: Important but not critical)	141 (2 RCTs)	⨁⨁◯◯ Low	1.08 (0.47–2.49)	104 per 1000	8 more per 1000 (55 fewer to 156 more)

NOTE. The risk categories shown are representative of anticipated baseline risks and are chosen to illustrate risk differences. The risk in the intervention group (and its 95% CI) is based on the assumed baseline risks in the comparison group and the relative effect of the intervention (and its 95% CI).
[a]The clinical effect of a change in HBV-DNA / serologies may / may not translate into patient important outcomes.
[b]Fragility Index: 5.
[c]Lack of overlap in CI of the 2 studies.
[d]Very few events and a CI that is suggestive of a very large effect in favor of prophylaxis and an effect in favor of control.

10. TACE: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc–positive individuals, please refer to the "moderate-risk" category, Recommendation 2).

11. Corticosteroid therapy in moderate dose (10–20 mg prednisone dose or equivalent) or high dose (>20 mg prednisone daily or equivalent) for ≥4 weeks: When used in individuals who are HBsAg-positive (please refer to the "moderate-risk" [Recommendation 2] and "low-risk" categories [Recommendation 3] for additional guidance stratified by individual serology status, dose, and duration of corticosteroid therapy).

For individuals at high risk of HBVr, the magnitude of absolute reduction in the risk of reactivation is expected to be the largest; at a representative baseline risk of 50%, antiviral prophylaxis would lead to 410 fewer cases of HBVr and 390 fewer hepatitis flares from HBVr per 1000 individuals.

Recommendation 2: For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone. (*Conditional recommendation, moderate certainty evidence*)

Implementation Considerations:

- This recommendation assumes the use of antivirals with a high barrier to resistance.
- Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use, and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative) may reasonably select active monitoring over antiviral prophylaxis, with careful consideration of feasibility and likelihood of adherence to long-term monitoring. Monitoring should be performed at 1- to 3-month intervals, and must include assessment of hepatitis B viral load in addition to assessment of alanine aminotransferase.

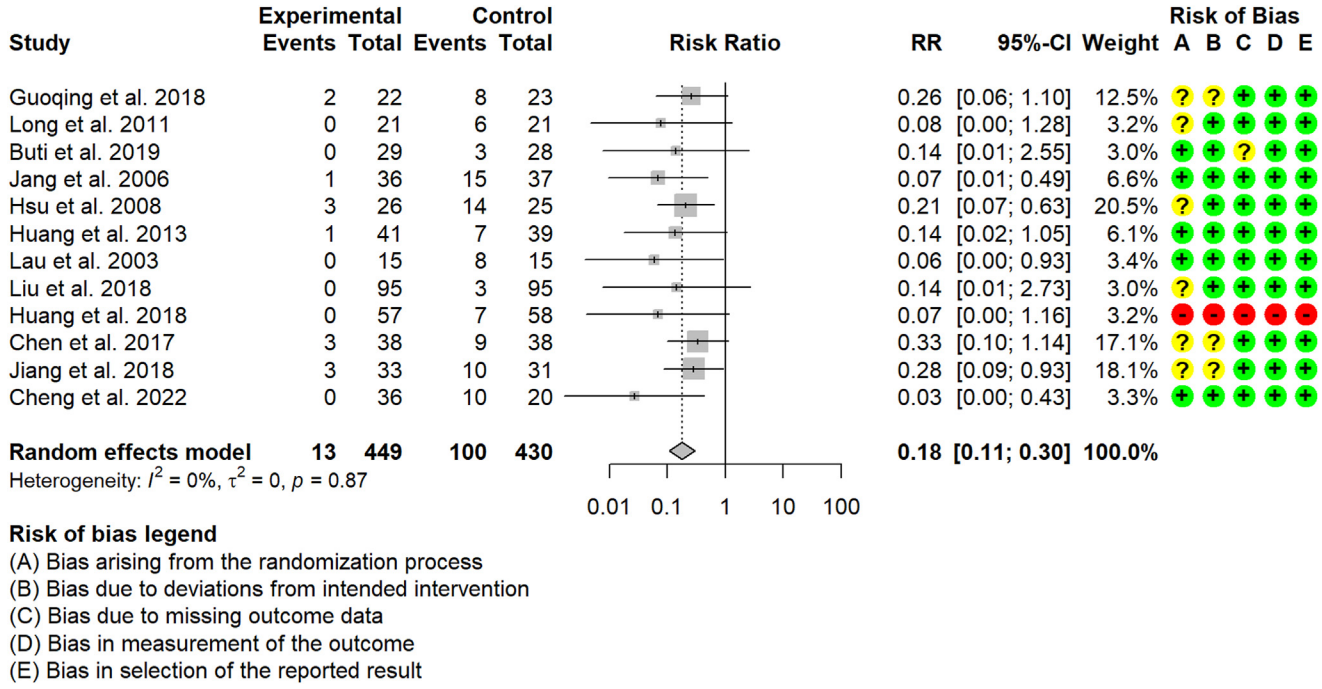

Figure 3. Meta-analysis of randomized trials comparing antiviral prophylaxis with no prophylaxis.

For patients at "moderate risk," the baseline risk of HBVr from the exposure of interest is expected to be between 1% and 10% (Table 6 and Supplementary Table 5) and included the following:

1. Anthracycline derivatives: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).
2. ICIs: When used in individuals who are HBsAg-positive (for use in HBsAg-negative/anti-HBc-positive individuals, please refer to the "low-risk" category, Recommendation 3).
3. Anti T-cell therapy: When used in individuals who are HBsAg-positive or HBsAg-negative/anti-HBc–positive.
4. TKIs: When used in individuals who are HBsAg-negative/anti-HBc–positive.
5. Cytokine/Integrin inhibitors: When used in individuals who are HBsAg-negative/anti-HBc-positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).
6. CAR-T cell therapy: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).
7. Anti-IL6 agents: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).
8. JAK inhibitors: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).
9. Corticosteroid therapy in moderate dose (10–20 mg prednisone dose or equivalent) or high-dose (>20 mg prednisone daily or equivalent) for ≥4 weeks: When used in individuals who are HBsAg-negative/anti-HBc–positive (please refer to the "high-risk" [Recommendation 1] and "low-risk" categories [Recommendation 3] for additional guidance stratified by individual serology status, dose and duration of corticosteroid therapy).
10. TACE: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).
11. Corticosteroid therapy in low dose (<10 mg prednisone dose or equivalent) for ≥4 weeks: When used in individuals who are HBsAg-positive/anti-HBc–positive (please refer to the "high-risk" [Recommendation 1] and "low-risk" categories [Recommendation 2] for additional guidance stratified by individual serology status, dose, and duration of corticosteroid therapy).

For individuals at moderate risk of HBVr, the magnitude of absolute reduction in the risk of reactivation is less than that seen among high-risk individuals, but remains clinically

Table 6. Summary of Baseline Risk by Exposure of Interest

Exposure	Baseline risk if HBsAg-positive/ anti-HBc–positive	Baseline risk if HBsAg-negative/ anti-HBc–positive
Anthracycline derivatives Drugs: doxorubicin; epirubicin	HIGH[a]	MODERATE[a]
Anti-TNF therapy Drugs: infliximab; adalimumab	HIGH	LOW
Anti-IL6 therapy Drug: tocilizumab	HIGH[a]	MODERATE[a]
Anti-T cell therapy Drug: abatacept	MODERATE[a]	MODERATE
B cell–depleting agents Drugs: rituximab; ofatumumab	HIGH	HIGH
CAR-T cell therapy	HIGH[a]	MODERATE
Cytokine/integrin inhibitors Drugs: ustekinumab; secukinumab	HIGH	MODERATE
HCV co-infection undergoing DAA therapy	HIGH	LOW
ICIs Drugs: nivolumab; pembrolizumab; ipilimumab	MODERATE	LOW
JAK inhibitors Drugs: tofacitinib, baricitinib	HIGH[a]	MODERATE[a]
TACE	HIGH	MODERATE[a]
TKI therapy Drugs: imatinib, sunitinib	HIGH	MODERATE[a]
Methotrexate, 6-mercaptopurine, and azathioprine	Low[a]	Low[a]
Categorization of corticosteroid therapy		
Corticosteroid therapy Duration: ≥4 wk Dose: moderate/high dose	HIGH[a]	MODERATE[a]
Corticosteroid therapy Duration: ≥4 wk Dose: low dose	MODERATE[a]	LOW[a]
Corticosteroid therapy Duration: ≤1 wk Dose: low/moderate/high dose	LOW[a]	LOW[a]
Corticosteroid therapy, intra-articular	LOW[a]	LOW[a]

NOTE. Risk estimate based on single medication exposure and may be higher if used in combination with other immunosuppressive medications. Glucocorticoids: prednisone (or equivalent): low dose, <10 mg; moderate dose, 10–20 mg; high dose, >20 mg. The risk for HBV reactivation refers to the duration of the risk-imposing state or up to 1 year, unless otherwise noted; longer-term risk has higher uncertainty. If risk-imposing state changes, reconsider risk categorization.
[a]There is lower certainty in the estimate of baseline risk.

important. At a representative baseline risk of 5%, antiviral prophylaxis would lead to an anticipated 41 fewer cases of HBVr per 1000 individuals and 39 fewer hepatitis flares from HBVr per 1000 individuals.

Recommendation 3: For individuals at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis. (*Conditional recommendation, moderate certainty evidence*)

Implementation Considerations:

- This recommendation assumes regular and sufficient follow-up that ensures continued monitoring.
- Patients who place a higher value on avoiding the small risk of reactivation (particularly those who may be on more than 1 low-risk immunosuppressive medication) and a lower value on the burden and cost of antiviral therapy may reasonably select antiviral therapy.

For patients at "low risk," the baseline risk of HBVr from the exposure of interest is expected to be <1% (Table 6 and Supplementary Table 5) and included the following:

1. Methotrexate, 6-mercaptopurine (6-MP), and azathioprine: When used in individuals who are HBsAg-positive or HBsAg-negative/anti-HBc–positive.
2. Intra-articular steroid injection: When used in individuals who are HBsAg-positive or HBsAg-negative/anti-HBc–positive.
3. Corticosteroid therapy in moderate-dose (10–20 mg prednisone dose or equivalent) or high-dose (>20 mg prednisone daily or equivalent) for <1 week: When used in individuals who are HBsAg-positive or HBsAg-negative/anti-HBc–positive (please refer to the "moderate-risk" [Recommendation 2] and "high-risk" categories [Recommendation 1] for additional guidance stratified by individual serology status, dose and duration of corticosteroid therapy).
4. Corticosteroid therapy in low dose (<10 mg prednisone dose or equivalent) for ≥4 weeks: When used in individuals who are HBsAg-negative (please refer to the "moderate-risk" [Recommendation 2] and "high-risk" categories [Recommendation 1] for additional guidance stratified by individual serology status, dose and duration of corticosteroid therapy).
5. Anti-TNF agents: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).

6. ICIs: When used in individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "moderate-risk" category, Recommendation 2).

7. Individuals with HCV co-infection undergoing treatment with a DAA agent: Applicable to individuals who are HBsAg-negative/anti-HBc–positive (for use in HBsAg-positive individuals, please refer to the "high-risk" category, Recommendation 1).

For individuals at low risk of HBVr, the absolute magnitude of reduction in the risk of reactivation is small, such that most individuals who are reasonably risk averse would opt for no antiviral prophylaxis, but with active monitoring of their HBV status; at a representative baseline risk of 0.1%, antiviral prophylaxis would lead to 1 fewer case of HBVr and hepatitis flare from HBVr per 1000 individuals. However, risk averseness and feasibility/practicality of long-term monitoring vary at an individual level, and there may be circumstances where individuals would opt for antiviral prophylaxis, despite the trivial magnitude of reduction in the risk of HBVr and its consequences.

Recommendation 4: For individuals at potential risk of HBVr, the AGA recommends testing for hepatitis B (*Strong recommendation, moderate certainty evidence*)

Implementation Considerations:

- Given universal Centers for Disease Control and Prevention (CDC) screening guidance for hepatitis B for all adults aged ≥18 years by testing for HBsAg, anti-HBs, and total anti-HBc, stratifying screening practices by magnitude of HBVr risk is no longer needed.
- It is reasonable to test initially for serologic markers alone (at minimum for HBsAg, anti-HBc) followed by viral load testing (HBV-DNA) if HBsAg and/or anti-HBc is positive.

The CDC, in their updated guidance, recommended universal screening for HBV for adults aged ≥18 years by testing for HBsAg, hepatitis B surface antibody, and total anti-HBc.[21] For individuals with exposures that render them at risk of HBVr and whose HBV status is not known, the panel agreed to recommend screening per CDC guidance. Furthermore, for risk-based screening, the CDC recommended testing of all people, irrespective of their age, if they have had exposures that render them at risk of HBVr. The CDC recommends continued periodic testing while the exposure persists. It is important to highlight that individuals who meet criteria for treatment of HBV based on current clinical practice guidelines should receive antiviral therapy regardless of their risk of HBVr.

Summary of Evidence

Baseline Risk

Corticosteroid therapy. The risk categorization of corticosteroids for HBVr was adapted from the 2014 AGA Guideline on HBVr[3]; no changes were made to the original categorization. Evidence informing the risk of HBVr with corticosteroid use is difficult to generate, partly because most patients on corticosteroids are also on adjunct immunomodulators, which likely augments the risk of HBVr. The recommendations made in 2014 drew on the indirect body of evidence on the use of corticosteroids and their association with a higher risk of HBVr among select patient populations, such as those with non-Hodgkins lymphoma undergoing chemotherapy along with high-dose prednisolone,[22] patients with chronic HBV who have relatively higher baseline HBV-DNA levels,[23,24] and patients with asthma or chronic obstructive pulmonary disease.[25] Over the past decade, studies have emerged suggesting that the risk of HBVr with corticosteroid therapy is likely mediated by the dose and duration of systemic corticosteroid therapy.[26,27] The highest risk of HBVr from corticosteroid therapy has been found to be imposed by high-dose therapy when administered for ≥4 weeks[27]; it is plausible that this risk would be even higher among individuals who are HBsAg-positive than those who are anti-HBc–positive. In contrast, the lowest risk imposed by corticosteroids is likely from low-dose therapy in individuals who are HBsAg-negative and anti-HBc–positive. The risk of HBVr with moderate- or high-dose therapy in individuals who are HBsAg-positive, a population group that is by definition high risk, may also be low when corticosteroids of these dose ranges are administered for ≤1 week.

Similar to the original guideline, the risk of HBVr imposed by local corticosteroid therapy, such as intra-articular corticosteroid injections, was considered to be low, and no changes to this classification were made.

Anti–tumor necrosis factor therapy. Evidence on the baseline risk of HBVr among individuals undergoing anti-TNF therapy was derived from 14 nonrandomized studies enrolling a total of 1555 individuals.[28–41] The follow-up time for the body of evidence ranged from 1 to 10 years. The baseline risk of HBVr among HBsAg-negative/anti-HBc–positive individuals on anti-TNF therapy was 2 per 1000 (Supplementary Figures 2 and 3) and, as such, this population group was categorized to be at a "low-risk" of HBVr (<1%). In contrast, the baseline risk of HBVr among HBsAg-positive individuals undergoing anti-TNF therapy was noted to be 332 per 1000, characterizing this population group to be at a "high risk" of HBVr. We performed sensitivity analyses stratifying studies by their follow-up duration; the risk of HBVr in the single study with the longest follow-up duration (10+ years) was 11 per 1000. Furthermore, a subgroup analysis of the larger studies (>100 individuals per study) showed that the baseline risk of HBVr was 5 per 1000. Based on the findings of our sensitivity analyses, it was determined that annualization of events would lead to a lower rate of HBVr than the observed value, and that the nonannualized computed risk of HBVr

likely represents the worst-case scenario. Given that such time adjustment would not lead to a further downgrade in the risk categorization of HBsAg-negative/anti-HBc–positive individuals undergoing anti-TNF therapy, we deferred attempts at annualization of the event-rate.

Immune checkpoint inhibitors. We identified 10 studies of patients with cancer undergoing therapy with ICIs, including anti–PD-L1/anti–PD-1 agents, as well as anti–CTLA-4 agents[42–49]; 8 of these studies informed the baseline risk of HBVr in HBsAg-negative/anti–HBc–positive individuals, and 5 studies provided data for baseline risk computation of individuals who were HBsAg-positive.[50,51] None of the studies stratified data by ICI type. The mean/median follow-up duration for these studies ranged from 4 to 14 months. The baseline risk of HBVr for HBsAg-negative/anti-HBc–positive patients was <0.1%, based on data from 1214 patients (Supplementary Figures 4 and 5). In contrast, for HBsAg-positive/anti-HBc–positive patients undergoing ICI therapy, the risk of HBVr was 70 per 1000; thus, this population group was categorized to be at "moderate risk" of HBVr. The upper bound of the 95% CI for the estimated HBVr risk was 160 per 1000, crossing the high-risk category threshold (>10%, or 100 per 1000), thereby leading to imprecision in the estimated risk. Consequently, the certainty in estimate of the baseline risk of HBVr among HBsAg-positive patients undergoing ICI therapy was downgraded from moderate to low.

Individuals with hepatitis C virus co-infection undergoing direct-acting antiviral treatment. We identified 11 studies that provide data for computation of the baseline risk of HBVr in the HCV co-infection cohort undergoing DAA therapy.[52–62] The time to assessment of HBVr was 12 weeks from initiation of DAA therapy in all but 2 studies that reported HBVr at 24 weeks. The pooled baseline risk of HBVr in this cohort of patients who were HBsAg-negative/anti-HBc–positive was 2 per 1000 (Supplementary Figures 6 and 7), categorizing them to be at a "low risk" of HBVr. In contrast, in patients who were HBsAg-positive, the pooled baseline risk of HBVr was 240 per 1000, categorizing them to be at a "high risk" of HBVr. Only 1 RCT compared antiviral prophylaxis to monitoring with on-demand antiviral therapy in the setting of HBVr in patients with HCV co-infection undergoing treatment with a DAA agent.[14] Although no HBVr events were noted during entecavir therapy, a cumulative incidence of HBVr that exceeded 90% was noted 12 weeks after cessation of entecavir. In light of these data and the opinions of the panel members, it is reasonable to extend antiviral prophylaxis beyond the 12–24 weeks of DAA therapy to 6–12 months after cessation of DAA therapy, tailored by clinician judgment and patient preference.

Cytokine/integrin inhibitors. We identified 5 studies of individuals on ustekinumab/secukinumab therapy enrolling a total of 108 individuals, all of whom were being treated for autoimmune disease (4 studies of patients with psoriasis and 1 study of patients with axial spondylarthritis).[63–67] The follow-up duration ranged from 9 to 24 months. The risk of HBVr among HBsAg-negative/anti-HBc–positive patients undergoing cytokine/integrin therapy was 13 per 1000 (Supplementary Figures 8 and 9), categorizing this population to be at "moderate risk" of HBVr. For HBsAg-positive patients undergoing cytokine/integrin therapy, the risk of HBVr was 260 per 1000, categorizing this population to be at a "high risk" of HBVr.

Anti-IL6 therapy. We identified 5 studies that provided data to compute HBVr rate for HBsAg-negative/anti-HBc–positive patients undergoing anti-IL6 therapy with tocilizumab; 2 of the studies included patients who received a single dose of tocilizumab in the setting of SARS CoV-2 infection, whereas the remaining 3 studies included patients with rheumatoid arthritis who were on tocilizumab for at least 3 months.[33,68–71] The follow-up ranged from 1 to 154 months. There was concern for spurious effect from co-interventions; nearly the entire cohort of the 3 studies on long-term tocilizumab was on low-dose corticosteroid therapy. In addition, there were sporadic comments in studies suggesting that some patients had previously been treated with rituximab. Based on data from a cohort of 204 patients, the pooled rate of HBVr was <0.1%; the upper bound of the 95% CI for the risk of HBVr was 13 per 1000 (Supplementary Figure 10), crossing the moderate-risk category threshold (>1% baseline risk), leading to imprecision in the estimate of this risk. Consequently, the certainty in estimate of the baseline risk of HBVr among HBsAg-negative/anti-HBc–positive patients undergoing anti-IL6 therapy was downgraded from moderate to low.

We did not find any studies of HBsAg-positive patients undergoing anti-IL6 therapy who were not on antiviral prophylaxis; this finding is in line with current clinical practice because this patient subgroup is considered to be significantly immunosuppressed and is pre-emptively prescribed antiviral prophylaxis while undergoing anti-IL6 therapy. Based on biological plausibility, the panel agreed to categorize HBsAg-positive patients undergoing anti-IL6 therapy to be at a "high risk" of HBVr, while recognizing that there is uncertainty surrounding this classification due to absence of evidence for empirical assessment of the risk of HBVr.

Tyrosine kinase inhibitor therapy. Data on the risk of HBVr among patients undergoing TKI therapy were obtained from 4 observational studies; 3 of these studies informed the baseline risk of HBVr in HBsAg-negative/anti-HBc–positive individuals (n = 71), and 3 studies provided data for baseline risk computation of individuals who were HBsAg-positive (n = 106).[72–74] The follow-up duration was provided in 2 studies and ranged from a mean of 12.4 months to a median of 45.8 months. The largest study of HBsAg-negative/anti-HBc–positive patient, enrolling a total of 36 patients, did not provide data on the duration of follow-up. The risk of HBVr for HBsAg-negative/anti-HBc–positive patients on TKI therapy was <0.1% (Supplementary Figures 11 and 12), with no HBVr events reported in any of the 3 studies. However, the upper bound of 95% CI for this baseline risk estimate was suggestive of an HBVr risk of 22 per 1000, crossing the threshold of moderate risk category (>1%). The lack of events, and the 95% CI crossing a clinically important risk threshold are factors contributing to the imprecision in the estimate of

HBVr risk in this population group, which decreases the certainty of this estimate from moderate to low. Furthermore, there were multiple case reports of HBVr among patients undergoing TKI therapy published in the literature,[75] and biological plausibility suggests that the true HBVr risk among HBsAg-negative/anti-HBc–positive patients undergoing TKI therapy is more likely to resemble the simulated risk of 22 per 1000 than the current effect estimate. Therefore, the panel agreed to categorize HBsAg-negative/anti-HBc–positive patients undergoing TKI therapy to be at a "moderate risk" of HBVr. In contrast, HBsAg-positive patients undergoing TKI therapy had a pooled HBVr risk of 110 per 1000, categorizing this population group to be at "high risk" of reactivation.

Anti–T-cell therapy. We identified 3 studies reporting the baseline risk of HBVr among individuals undergoing anti–T-cell therapy with abatacept (n = 125); all patients were under treatment for autoimmune disease, with 2 of the 3 studies comprising exclusively of patients with rheumatoid arthritis, and 1 of the studies comprising a mixed cohort, the majority of whom had rheumatoid arthritis.[36,76,77] The follow-up duration ranged from 24 to 154 months. The cumulative risk of HBVr among HBsAg-negative/anti-HBc–positive patients undergoing treatment with abatacept was 46 per 1000 (Supplementary Figures 13 and 14), categorizing this population group to be at a "moderate risk" of reactivation. Only 1 study provided data to compute baseline HBVr risk for HBsAg-positive patients undergoing abatacept therapy; the computed risk of HBVr in this population group was <0.1%, with the upper bound of 95% CI suggesting a baseline HBVr risk of 44 per 1000. The lack of events, the extremely small sample size (34 patients from a single study), the 95% CI crossing the threshold of moderate-risk from low-risk category are factors contributing to the very serious imprecision in the estimate of HBVr risk in this population group, which decreases the certainty of this estimate from moderate to very low. Furthermore, biological plausibility suggests that the true risk of HBVr in HBsAg-positive patients undergoing treatment with abatacept is more likely to resemble the simulated risk of 44 per 1000 than the current effect estimate. Therefore, the panel agreed to classify HBsAg-positive patients undergoing abatacept therapy to be at a "moderate-risk" of HBVr.

Chimeric antigen receptor T cell therapy. We identified 7 studies that provided data to compute the risk of HBVr among HBsAg-negative/anti-HBc–positive patients undergoing CAR-T cell therapy.[78–84] In all studies, patients who were HBsAg-positive were on antiviral prophylaxis, which was expected in this subset of the population (ie, patients with leukemia, lymphoma, and myeloma) since they are generally under treatment with multiple agents, including B cell–depleting agents such as rituximab, which classifies them as a high-risk group. On the same note, there were concerns regarding a spurious effect from co-intervention and recent use of B cell–depleting agents in some of the patients who were HBsAg-negative/anti-HBc–positive and were not on antiviral prophylaxis. Based on a pooled sample of 161 patients, the risk of HBVr in HBsAg-negative/anti-HBc–positive patients on CAR-T cell therapy was 21 per 1000 (Supplementary Figure 15), classifying this population group to be at a "moderate risk" of reactivation. Given the high-risk nature of these patients and because this population group is expected to be undergoing multiple co-interventions or to have had temporal exposure to therapeutics that pose a high risk of HBVr while undergoing CAR-T cell therapy, practitioners are likely to take into account the potential for additive effect or may opt for antiviral prophylaxis due to the temporality of exposure to agents such as rituximab. Due to biological plausibility, and in keeping with current practice, the panel agreed to classify HBsAg-positive patients undergoing CAR-T cell therapy to be at a "high risk" of HBVr. Similar to other exposures, the panel acknowledged there is uncertainty surrounding this classification of HBsAg-positive patients due lack of data for empirical assessment of their baseline risk.

Transarterial chemoembolization. We computed the baseline risk of HBVr in patients undergoing TACE from the data of 3 RCTs; 1 of the trials enrolled patients who were HBsAg-positive and the 2 remaining trials did not explicitly mention the HBsAg status of their cohort.[9,18,19] Based on data from 91 patients, the risk of HBVr among individuals undergoing TACE was noted to be 180 per 1000, categorizing this population group to be at a "high risk" of reactivation. The panel agreed to categorize HBsAg-negative/anti-HBc–positive individuals undergoing TACE to be at a "moderate risk" of HBVr, owing to biological plausibility and the high risk of HBVr noted in HBsAg-positive individuals, while acknowledging that there exists uncertainty with this classification due to absence of evidence for empirical assessment of baseline risk.

Methotrexate, 6-mercaptopurine, and azathioprine. The current guideline made no changes to the categorization of the antimetabolite immunosuppressive agents provided in the 2014 AGA Guideline.[3] These include methotrexate, 6-MP, and azathioprine. Our literature search did not identify any studies that could provide an estimate of baseline risk of HBVr among individuals using azathioprine. From the perspective of biological plausibility, azathioprine does not have a significant impact on antibody responses. Similarly, we did not find any studies that could provide a baseline risk estimate for HBVr with 6-MP use or methotrexate use. Given that these medications have been in use for multiple decades, and in the absence of HBVr cases directly attributable to these agents, there is little uncertainty that the risk of HBVr with monotherapy of azathioprine, 6-MP, and methotrexate is <1%. However, in the absence of evidence, the categorization of these drugs as low risk is conditional until studies that verify these statements are published.

Janus kinase inhibitors. We identified 3 studies that provided data for computation of baseline risk of HBVr in patients undergoing JAK inhibitor therapy.[85–87]; 3 provided data on patients who were HBsAg-negative, anti-HBc–positive (n = 354), and 2 on patients who were HBsAg-positive (n = 12). All studies included patients with rheumatoid arthritis on tofacitinib or baricitinib. The cumulative baseline risk of HBsAg-negative/anti-HBc–positive patients undergoing JAK inhibitor therapy was 18 per 1000

(Supplementary Figures 16 and 17); based on these data, JAK inhibitor therapy in anti-HBc–positive patients was classified as a "moderate-risk" exposure. Data on HBsAg-positive patients was relatively less robust and suffered from serious imprecision. The baseline risk of HBVr in this cohort was 333 per 1000; JAK inhibitor therapy in HBsAg-positive patients was therefore classified as a "high-risk" exposure.

The certainty in HBVr risk classification of HBsAg-negative/anti-HBc–positive patients, as well as HBsAg-positive patients, was downgraded from moderate to low due to concerns surrounding imprecision in the estimate of the baseline risk.

Gut-specific anti–T cell therapy. There is currently insufficient evidence to accurately assess the risk of HBVr with vedolizumab. A prospective nationwide registry from Taiwan assessing the safety and efficacy of vedolizumab among patients with inflammatory bowel disease reported a single case of HBVr in a patient with Crohn's disease who was an HBV carrier (presumed anti-HBc–positive) and who was also on corticosteroid therapy and azathioprine.[88] This patient had also had dose escalation of his azathioprine. Further evidence is needed before a recommendation on risk categorization of gut-specific anti–T cell therapy for HBVr can be performed.

Duration of Antiviral Prophylaxis

To date, 3 RCTs have compared the duration of antiviral prophylaxis after withdrawal of the exposure of interest.[14,89,90] When comparing a longer with a shorter duration of prophylaxis (3 months after withdrawal of exposure in 1 study; 6 months in 2 studies), a RR of 0.99 (95% CI, 0.76–1.28) for HBVr and a RR 1.24 (95% CI, 0.46–3.39) for hepatitis flare from HBVr were found on pooled analysis of these trials. The certainty in these effect estimates was downgraded to "low" due to concerns regarding very serious imprecision. On subgroup analysis, 2 RCTs comparing 12 months of antiviral continuation after cessation of exposure with 6 months found a RR of 1.07 (95% CI, 0.68–1.68) for HBVr and a RR of 1.35 (95% CI, 0.45–3.99) for hepatitis flare from HBVr. These findings suggest that the current body of evidence suffers from imprecision. The panel concluded that antiviral prophylaxis should be continued for at least 6 months after cessation of exposure of interest. However, in cases when the risk of HBVr is considered high, extension of antiviral therapy to 12 months is reasonable. In cases of exposure to B cell–depleting agents, antiviral prophylaxis should be extended to at least 12 months after end of exposure to B cell–depleting agents, given several case reports of delayed HBVr beyond 12 months.

Cost-Effectiveness of Antiviral Prophylaxis

Our search did not identify any published studies that provided direct evidence of the cost-effectiveness of providing antiviral prophylaxis for low, moderate, and high baseline risk categories. A recent cost-effectiveness analysis (CEA) by Fujita et al[91] comparing antiviral prophylaxis with HBV-DNA monitoring, followed by on-demand antiviral therapy, used a transition probability of 6% for baseline risk of HBVr, which corresponds to a moderate-risk class exposure. The incremental cost-effectiveness ratio for prophylactic antiviral therapy was US$132,048 per quality-adjusted life-year, which was higher than the study willingness-to-pay threshold of US$45,662 (converted from Japanese yen). One major limitation of this CEA was that the probability for HBVr in the antiviral prophylaxis arm was 2.1%; given that antiviral prophylaxis can provide a RR reduction of 82%, for a baseline risk of 6%, this should translate to a transition probability of 1.1% with antiviral prophylaxis. Applying this lower probability of HBVr with antiviral prophylaxis could lead to a lower incremental cost-effectiveness ratio that may fall within the umbrella of an acceptable willingness-to-pay threshold of $50,000–$100,000. Furthermore, this analysis sheds light only on the moderate-risk class of exposures. One could extrapolate that, if the above-mentioned adjustments to the model are made, antiviral prophylaxis is likely to be cost-effective for high-risk cases, may be cost-effective for moderate-risk cases, and may not be cost-effective for low-risk cases. Formal CEAs evaluating CEA thresholds based on the risk categories in this guideline are needed.

Equity Considerations

The additional Health Disparities and Minority Health Search Strategy identified no potential issues around equity that could arise from recommendations in this guideline.

Harms of Antiviral Prophylaxis

The undesirable consequences of antiviral therapy were considered small or trivial in the nexus of medical decision making when prescribing antiviral prophylaxis. With use of tenofovir disoproxil fumarate, there can be concern regarding its impact on renal function and bone mineral density, although the overall effect on these domains remains small to trivial. Tenofovir alafenamide does not adversely impact renal function or bone mineral density compared with tenofovir disoproxil fumarate.[92] Although these antiviral medications are covered by most insurance plans, in some instances, out-of-pocket costs may act as a barrier to administration of antiviral therapy.

Hepatitis B Surface Antibody and Risk of Hepatitis B Reactivation

Four of the RCTs used to generate an evidence profile for antiviral prophylaxis efficacy reported anti-HBs status of their patients; the pooled proportion of patients who were anti-HBs–positive in the control arm of these RCTs was 65% (95% CI, 58%–72%). A combined meta-analysis of RCTs and nonrandomized studies reported that patients who were anti-HBs–positive and underwent rituximab therapy had a baseline risk of 6.6%.[93] However, the upper bound of the 95% CI for their pooled analysis in this patient subgroup was 14.4%. These findings suggest that being anti-HBs–

positive may not mitigate the risk of HBVr. Hence, the panel agreed that anti-HBs status should not be used to make recommendations regarding prophylaxis in patients at risk of HBVr.

Knowledge Gaps

As the armamentarium of immunotherapeutics evolves, it will be crucial to search for, use, and maintain studies that provide baseline HBV serologies; include a clear definition of HBVr; and enroll a large, nonselective cohort that can guide categorization of risk of HBVr. Although we were able to generate updated guidance and include new therapies in our risk categories, there remains uncertainty in certain risk categorizations, as highlighted above, particularly due to concerns surrounding imprecision of the estimate of baseline risk, which is a consequence of the lack of a robust body of evidence, as well as from lack of evidence altogether, which necessitates drawing on biological plausibility and expert consensus. This limitation can be ideally addressed by maintenance of national registries when feasible. Technological innovation may enable the establishment and maintenance of an online repository that is updated periodically to provide accurate estimates of baseline risk of HBVr for different exposures of interest; this should be an area of future research.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.11.008.

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