Hepatitis B virus reactivation (HBVr) is a potentially serious disorder that is frequently induced by long-term immunosuppressive drug therapy. HBVr is more often seen in hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc)–positive patients (hereafter referred to as HBsAg-positive patients) but also occurs in patients with resolved infection as defined by negative HBsAg and positive anti-HBc. This clinical entity was first described nearly 50 years ago in the setting of cancer chemotherapy and kidney transplantation. Although specific cellular immunologic mechanisms have not been fully elucidated, the initial event is believed to be a disruption in the ability of the host immune system to control hepatitis B virus (HBV) replication. The best predictor of reactivation has been shown to be the level of HBV DNA at baseline. Patients who are HBsAg positive are 5 to 8 times more likely to develop HBVr than those with resolved infection who are HBsAg negative but anti-HBc positive. The immunologic potency and complexity of the drug regimen are also likely to be important factors. Reactivation is characterized by a sudden increase in serum HBV DNA level that is most often associated with a hepatitis flare several weeks later, as defined by an increasing alanine aminotransferase (ALT) level. Conventionally, reactivation is defined by the level of change in HBV DNA and ALT. In HBsAg carriers, this is often defined as either the de novo detection of HBV DNA or a ≥10-fold (1 log10) increase in HBV DNA level when compared with the baseline value before immunosuppressive drug therapy. A hepatitis flare is frequently determined to be present when there is at least a 2- to 3-fold elevation in ALT level above the patient’s baseline value or a predefined multiple of the upper limit of normal. In patients with resolved infection (HBsAg negative but anti-HBc positive), reactivation has been considered to occur with demonstration of reverse seroconversion to HBsAg-positive status.

The clinical spectrum of medical interventions that induce HBVr has greatly expanded in the past 2 decades and now includes several types of biological agents that are used in the fields of rheumatology, pulmonology, dermatology, neurology, gastroenterology, hepatology, nephrology, and transplantation medicine. Tumor necrosis factor (TNF) inhibitors may represent the predominant class of noncancer drugs that are capable of inducing HBVr because they are immunologically potent, widely used across specialties, and generally given on a long-term basis. In a recent systematic review, nearly 40% of HBsAg carriers and 5% of anti-HBc–positive but HBsAg-negative patients developed HBVr during TNF inhibitor therapy, nearly half of whom were undergoing treatment for inflammatory bowel disease. The fact that TNF inhibitors have been prescribed for more than 3 million people in the United States should raise concern, because this may result in several thousand cases of HBVr each year in the United States alone even when conservative prevalence rate estimates of HBsAg positivity of 0.4% and past infection of 3% are used.

B cell–depleting agents have also become increasingly implicated in HBVr. These drugs are used in patients with a variety of disorders, including leukemias, non-Hodgkin lymphoma, cryoglobulinemia, rheumatoid arthritis, and idiopathic thrombocytopenic purpura. Frequent reporting of rituximab-associated HBVr has led to a recent expanded box warning by the Food and Drug Administration (FDA) in which it is strongly recommended that all patients who are

Abbreviations used in this paper: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; AST, aspartate aminotransferase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, confidence interval; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation; PICO, population, intervention, comparison, and outcome; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RCT, randomized controlled trial; RR, relative risk; TACE, transarterial chemoembolization; TNF, tumor necrosis factor.
to undergo B cell–depletion therapy initially be screened for HBV and, if positive, referred to a specialist to evaluate the need for antiviral prophylaxis or close monitoring.9

Prior Management Recommendations

Several highly effective nucleos(t)ide analogues to treat hepatitis B have been licensed in the past 10 years. The newer agents, such as entecavir and tenofovir, have low resistance profiles, no significant drug-drug interactions, and an excellent safety record, which makes them suitable for long-term use. Real-world experience with both of these agents in more than 1200 patients has confirmed efficacy and safety features that are similar to those presented in registration trials.10 Nephrotoxicity is a potential concern with long-term use of tenofovir, but creatinine clearance rates in the above large study were shown to remain stable over 4 years; <1% of patients had increases of 0.5 mg/dL.

During the same period, several clinical trials have shown that the frequency of HBVr due to cancer chemotherapy can be reduced by screening for HBV followed by antiviral prophylaxis started before or at the time of initiation of chemotherapy in those found to be HBsAg positive. The frequent occurrence of HBVr during cancer chemotherapy and other immunosuppressive therapies has prompted the publication of several screening and treatment guidelines for patients who are to undergo long-term immunosuppressive drug therapy. There are 4 major sets of screening recommendations, including those by the Centers for Disease Control and Prevention (2008), the American Association for the Study of Liver Diseases (2009), the Asian Pacific Association for the Study of the Liver (2012), and the European Association for the Study of the Liver (2012).11–14 These guidelines vary in the types of screening tests recommended and the indications for prophylactic antiviral therapy, but each endorses HBsAg and anti-HBe screening as a critical first step for reducing the risk of HBVr. In striking contrast to these guidelines, the American Society of Clinical Oncology has published a provisional clinical opinion stating that there is insufficient evidence to recommend routine screening and this decision requires clinical judgment.15 Revision of these guidelines is urgently needed. Also, there are currently no specific screening or treatment guidelines for hepatitis B that have been published by the American Academy of Dermatology or the American College of Rheumatology. The variability in practice recommendations is confusing to clinicians and ensures that HBVr induced by immunosuppressive drug therapy will continue to be a serious health problem in the foreseeable future.

Another area that remains controversial is how long to continue prophylactic antiviral therapy. A recommendation has been made to continue treatment until 6 months after immunosuppressive drug treatment is discontinued and longer (possibly until therapeutic end points are reached) in the event that rituximab is used or in situations in which the baseline HBV DNA level is >2000 IU.12–14 Unfortunately, because many patients who undergo immunosuppressive therapy are not screened for HBV and therefore not given prophylactic antiviral therapy, guidelines about how long to treat are often nonactionable recommendations.

The Challenges Ahead and Relevance for the Field of Gastroenterology

Several surveys have indicated that HBV screening is frequently overlooked in patients who undergo long-term immunosuppressive therapy. Physician surveys have indicated that routine screening is performed by 20% to 40% of oncologists, 40% of dermatologists, and 70% of rheumatologists.16–18 There are currently no reliable data with regard to the frequency of screening by gastroenterologists or other specialists who use immunosuppressive therapies. However, in the past decade, the treatment of inflammatory bowel disease has been marked by increasing use of TNF inhibitors such as infliximab and several other biological agents are newly available,19 making this a relevant issue to address with gastroenterologists as well as other stakeholders.

Objectives of the Current Report

The primary purpose of the current report is to provide a technical review and critical update of the topic of HBVr due to immunosuppressive drug treatment. This review will focus on the results of clinical studies of the most frequently used oncological therapies and on biological agents that are either currently in use or soon will be used in various medical specialties. The review will not discuss other immunosuppressive states that can shape the natural history of hepatitis B, such as coinfection with human immunodeficiency virus, and it will not include descriptions of clinical studies in the areas of solid organ transplantation or hematopoietic stem cell transplantation.

Methods

Due to the clinical relevance of this area to gastroenterologists, a specific set of guidelines to prevent and treat HBVr in patients undergoing immunosuppressive drug treatment has been given high priority by the American Gastroenterological Association Institute. This is a 2-step process in which the previously mentioned technical review will be used to facilitate final recommendations. The American Gastroenterological Association is using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology in this technical review to assess the extent to which immunosuppressive drug therapy is likely to cause HBVr and the degree to which intervention can be anticipated to improve clinical outcomes.20 This was accomplished using a set of predetermined PICO (population, intervention, comparison, and outcome) questions, defining the importance of outcomes and rating the quality of evidence for those outcomes across studies. An accompanying report in this issue of Gastroenterology integrates the results of this technical review with the other GRADE criteria to produce a set of recommendations.21 HBVr is defined in this document as either the de novo appearance of HBV DNA in a patient previously known to have nondetectable HBV DNA or a ≥10-fold increase when compared with a baseline value. This virological definition does not require concomitant elevation of ALT level. Permissible surrogates were new detection of HBsAg or hepatitis B e antigen (HBeAg). Flares of hepatitis due to HBVr
are defined as elevated ALT level at least 3 times the baseline level that at a minimum is beyond the reference range.

**Literature Search**

An information specialist developed a literature search with input from the authors. All search results were imported using bibliographic management software for de-duplication and title and abstract screening. The following bibliographic databases were searched through the Ovid interface: EBM Reviews, Cochrane Central Register of Controlled Trials (July 2013), Cochrane Database of Systematic Reviews (July 2005 to July 2013), Health Technology Assessment (3rd quarter), EMBASE (1980 to 2013 week 35), and Ovid MEDLINE. We applied a search filter for systematic reviews, meta-analyses, and health technology assessments for questions on the use of antiviral therapy.

The primary search was performed from July to September 2013 and included all reports from 1998 to 2013 using the following search terms: hepatitis B, HBVr, anti-HBc, rituximab, immunosuppressive therapy, cancer chemotherapy, biological modifiers, antiviral prophylaxis, lamivudine, entecavir, telbivudine, and tenofovir (see Appendix 1 for search strategy). The initial search revealed 744 reports and their corresponding titles and abstracts. The authors discarded 606 reports by sequentially examining the titles and then the abstracts, and if applicable, the full text of the reports was retrieved. Reasons for exclusion were inappropriate content, such as relevance to solid organ transplantation or antiviral therapy in cohorts who were not treated with immunosuppressive drug therapy. We also excluded reports on bone marrow transplantation or hematopoietic stem cell transplantation due to the greater awareness of reactivation risk status and treatment policy in both HBsAg-positive and anti-HBc-positive patients. Case reports, abstracts, or conference proceedings were not preferred and were only used when there was a marked paucity of data. The remaining 98 references were sorted according to whether they would provide useful information to assess the individual PICO questions (see Appendix 2 for the trial flow diagram).

Major databases such as MEDLINE and conference reports were also searched by the authors for studies that addressed the baseline risk of HBVr and outcomes of interest in defined populations. Prevalence studies were not included in the final data analysis if they did not provide reasonable evidence for consecutive case reporting, if baseline HBV DNA data were unavailable, or if the study lacked definable criteria by which reactivation could be diagnosed. Editorials and letters were deselected, as were all observational studies in which it was believed that the study design could lead to an unacceptable level of confounding either in the diagnosis of reactivation or in the assessment of outcomes due to antiviral therapy.

Next, the authors systematically reviewed and partitioned the evidence for each outcome across studies, assessed the quality of evidence for each outcome, and then presented the evidence to answer each specific PICO question. The quality of the evidence was classified into 4 GRADE categories (high, moderate, low, and very low), and a summary of the evidence was documented in GRADE evidence profiles using GRADEpro software. According to GRADE criteria, evidence from randomized controlled trials (RCTs) started at high quality but was rated down if there was serious risk of bias, inconsistency or heterogeneity, indirectness, imprecision, and potential publication bias. Evidence from observational studies started at low quality but could be rated at a higher level if there was a large effect size. Observational studies were considered to be primarily helpful in determining the baseline risk of HBVr and providing additional information on patient outcomes.

**Formulation of PICO Questions**

PICO questions were devised by the authors and approved for further study by the American Gastroenterological Association Governing Board in July 2013. Each PICO question asks if an intervention affects patient outcomes in a positive or negative way, and each independently required a careful and coordinated search of the medical literature as described in the preceding text (Table 1). The following clinical outcomes were considered critical or important for decision making: severity of hepatitis; disease morbidity; resource utilization, including the need for hospitalization; liver-related mortality; and interruption of cancer chemotherapy or other immunosuppressive drug treatment (Table 1).

**Extraction of Data and Analytical Approach**

The numerator and denominator for each critical and important outcome were extracted from each study by using pretested data extraction sheets listing acceptable definitions for outcomes, such as HBVr, hepatitis, liver failure, liver-related mortality, and chemotherapy interruptions. When possible, the pooled relative risk (RR) was calculated for each outcome by using the Mantel-Haenszel random effect model in RevMan 5.2.24 Funnel plots were inspected for heterogeneity in addition to formal analysis of heterogeneity ($\chi^2$, $P < .1$) and residual heterogeneity that was not explained by chance ($I^2$). The number of studies was insufficient to formally test for funnel plot asymmetry to detect possible publication bias.

Because relative effects of interventions usually are stable across differing baseline risks, we initially pooled the results of all RCTs using antiviral regimens versus placebo from different populations and different antiviral regimens (Figure 1).25–29 Because relative effects appeared similar and little or no heterogeneity across studies was seen, the pooled relative effects were applied to typical baseline risks from different populations (those that were seen in the included RCTs but also from clinical settings in which baseline risks were not available directly from RCTs) to arrive at representative risk difference that would be most suitable to inform clinical guidance.

Because well-performed cohort studies from well-defined populations (eg, cancer or rheumatic disease) may provide accurate estimates of baseline risk of HBVr and because the risk of reactivation is markedly different based on the patient’s baseline HBV serological tests, a comprehensive review of those prevalence rates, mostly from observational studies, was performed. When pooled estimates of baseline risk were obtained from untreated control arms of RCTs in addition to well-performed cohort studies that enrolled consecutive, untreated patients, baseline risk was transformed to natural log proportions and pooled using the fixed effects inverse variance method in OpenMeta[analyst].30

**Baseline Risk**

The baseline risk of HBVr during immunosuppressive drug therapy can be assumed to be that which exists in the absence...
of an intervention to prevent HBVr. The baseline risk was assessed by review of 5 RCTs and 25 observational studies by extracting the number of HBVr events from the untreated or deferred treatment arms of those studies. A positive HBeAg status and high baseline level of serum HBV DNA have been shown to be predictive of reactivation after immunosuppressive drug therapy, which is consistent with a state of poorer immunologic control over viral replication before immune suppression.1,4,5 The baseline risk is also determined in part by the potency of the immunosuppressive drug regimen, and this will be addressed in the following section on drug risk. The level of uncertainty around the baseline risk estimates from the available literature was assessed and the confidence in the estimate judged as low, moderate, or high.

**Results**

**Risk Gradient of HBVr With Different Immunosuppressive Medications**

Answering any of the testing or intervention PICOs requires knowledge of the extent to which an immunosuppressive drug can be anticipated to cause HBVr. The authors classified drugs as low, moderate, or high risk based on the knowledge imparted from a review of all studies used in the analysis (Table 2). Low risk was considered to be evident whenever immunosuppressive drugs were in use for decades (eg, azathioprine) yet published reports either did not describe use of the drug as the sole agent responsible for.

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**Table 1. PICO Questions**

<table>
<thead>
<tr>
<th>Informal question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is antiviral prophylaxis needed for HBsAg-positive patients who will undergo ISDT?</td>
<td>All HBsAg-positive patients on ISDT associated with low, moderate, or high risk of HBVr</td>
<td>All oral antiviral drugs or any combination thereof</td>
<td>No antiviral prophylaxis</td>
<td>HBVr, liver disease; morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>2. Is antiviral prophylaxis needed for HBsAg-negative, anti-HBc-positive patients who will undergo ISDT?</td>
<td>Patients with isolated anti-HBc who undergo ISDT associated with low, moderate, or high risk of HBVr</td>
<td>All oral antiviral drugs or any combination thereof</td>
<td>No antiviral prophylaxis</td>
<td>HBVr, liver disease; morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>3. Does the presence of anti-HBs in addition to anti-HBc in HBsAg-negative patients confer additional protection against HBVr?</td>
<td>Patients with anti-HBc and anti-HBs who will undergo ISDT associated with low, moderate, or high risk of HBVr</td>
<td>All oral antiviral drugs or any combination thereof</td>
<td>No antiviral prophylaxis</td>
<td>HBVr, liver disease; morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>4. Is prophylactic treatment with third-generation nucleos(t)ide analogues more effective than treatment with first- or second-generation nucleos(t)ide agents?</td>
<td>Any patient undergoing antiviral prophylaxis for hepatitis B</td>
<td>Lamivudine, Adefovir, Telbivudine</td>
<td>Entecavir, Tenofovir</td>
<td>HBVr, liver disease; morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>5. Is HBV DNA monitoring followed by on-demand antiviral therapy as effective as prophylactic antiviral therapy?</td>
<td>Any patient treated with ISDT (malignant and nonmalignant disorders)</td>
<td>Regular HBV DNA testing during ISDT followed by antiviral therapy if HBVr occurs</td>
<td>Prophylactic treatment</td>
<td>HBVr, liver disease; morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>6. Is treatment of established HBVr with third-generation nucleos(t)ide agents more effective than treatment with first- or second-generation drugs?</td>
<td>Patients with delayed treatment</td>
<td>Lamivudine, Adefovir, Telbivudine</td>
<td>Entecavir, Tenofovir</td>
<td>HBVr, liver disease; morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>7. Should patients who will undergo long-term ISDT be screened for HBV before starting treatment?</td>
<td>Patients who will undergo more than 4 wk of ISDT for malignant and nonmalignant conditions</td>
<td>Testing of HBsAg and anti-HBc</td>
<td>No testing</td>
<td>HBVr, liver disease; morbidity and mortality; discrimination; treatment interruption; resource use</td>
</tr>
</tbody>
</table>

ISDT, immunosuppressive drug therapy.

aSearch included lamivudine, emtricitabine, entecavir, tenofovir, adefovir, telbivudine, or combination therapy.

bIncludes liver transplantation for patients without malignancy.
Figure 1. Meta-analysis of antiviral agents versus no prophylaxis across a variety of immunosuppressive regimens. The study by Huang et al. randomized HBsAg-negative/anti-HBc-positive patients to prophylaxis or therapeutic use of entecavir. The other studies enrolled HBsAg-positive patients only and prophylaxis with lamivudine was compared with deferred treatment. (1.1) The pooled estimates show an 87% relative risk reduction (RRR) of reactivation with prophylaxis (95% CI, 70%–94%). (1.2) The pooled estimates show an 84% RRR (95% CI: 58%–94%) of HBV-associated hepatitis flares.
HBVr (eg, reactivation occurred mostly or exclusively in combination with corticosteroids) or there were not a significant number of post-marketing reports. Use of a low-risk drug was anticipated to result in HBVr in <1% of cases for all drugs in this category and substantially <1% with most agents; use of a moderate-risk drug was anticipated to result in HBVr in >1% of cases but <10% of cases; and use of a high-risk drug was anticipated to result in HBVr in >10% of cases. Drugs that are in the same class as other high-risk drugs but in which there were no defined instances of HBVr in published reports or the FDA Adverse Event Reporting System were considered by the authors to be provisional high risk.

Azathioprine. The literature search did not reveal any reports of HBVr with maintenance azathioprine monotherapy, which may be used occasionally in the treatment of patients with autoimmune hepatitis. Azathioprine affects delayed hypersensitivity and cellular cytotoxic responses but has relatively little effect on antibody responses. Thus, it is not anticipated to have any major effect on neutralizing antibody to hepatitis B surface antigen (anti-HBs) concentration.
Early studies supported that azathioprine may have a permissive role in HBV replication by assessment of serum levels of core antigen, but these investigations antedated methods for detection of HBV DNA in serum or liver tissue and did not describe elevation of ALT levels during treatment. It is also difficult to attribute the increase in serum core antigen to azathioprine alone because some of the patients in these studies were treated concomitantly with glucocorticoids.32

In summary, despite long-standing use of this agent, the literature search did not reveal any cases in which azathioprine used alone was documented to cause HBVr. Due to the absence of applicable harms data, there is little uncertainty that the risk of HBVr from azathioprine when used alone is <1% and only moderate uncertainty that it is <0.1%. The effects of high-dose therapy alone (eg, ≥2.5 mg/kg) cannot be evaluated by the available data.

6-Mercaptopurine. 6-Mercaptopurine is an active metabolite of azathioprine, and the effects on the immune system are considered to be similar to those of the parent drug. The literature search did not reveal any cases in which HBVr was attributed to 6-mercaptopurine, either given alone or in combination with other immunomodulatory agents.

Due to the absence of applicable harms data, there is little uncertainty that the use of 6-mercaptopurine is associated with HBVr in <1% of cases and substantially <0.1% in patients who are HBsAg negative but anti-HBc positive.

Methotrexate. Use of methotrexate is widespread, and more cases of HBVr attributable to this agent have been reported than for any of the other traditional immunosuppressive drugs. However, all but 3 of these reports involved other immunomodulatory agents as well, such as monoclonal antibodies or corticosteroids.33–35 In a frequently cited case of methotrexate-induced HBVr, withdrawal of low-dose therapy (7.5 mg) was shown on 2 occasions to be associated with sudden increases in serum aminotransferase levels.33 The second episode resulted in fulminant hepatitis, which required liver transplantation. HBV DNA was not tested in serum, but there was evidence of replicative forms of HBV in liver tissue along with a diffuse lymphocytic infiltrate and hepatocytonecrosis consistent with chronic hepatitis B. In another relatively well-documented case, an elderly anti-HBc-positive woman with rheumatoid arthritis was treated with low-dose methotrexate for 10 months before having a nearly 5-log increase in HBV DNA level and subsequent 10-fold elevation in ALT level. The patient had low-level anti-HBs before initiation of methotrexate therapy that disappeared, followed by HBsAg seroreversion. Initiation of entecavir therapy allowed continued treatment with methotrexate, and the patient recovered uneventfully.34

Two of the 3 cases of HBVr with methotrexate mono-therapy were associated with an increase in serum aminotransferase levels on sudden discontinuation of the drug, which suggests a rebound in immunologic function directed to HBV. In both cases, however, there was poor documentation that the rebound was due to enhanced viral replication during treatment.

In summary, methotrexate has been in clinical use for more than 50 years, and only a small number of cases have been described in published reports in which HBVr was attributable to this agent when used alone. Based on these findings, there is little uncertainty that it causes HBVr in <1% of cases.

Corticosteroids. Of all the traditional immunosuppressive medications, corticosteroids have been most often implicated in the induction of HBVr. The observation that corticosteroids are harmful in patients with hepatitis B first occurred in the mid-1970s, when it was shown that HBsAg-positive patients with chronic hepatitis given corticosteroid therapy less often reached histological and biochemical end points when compared with disease-matched HBsAg-negative counterparts.36 A few years later, a placebo-controlled study in HBsAg-positive patients with chronic hepatitis showed that long-term treatment with prednisolone (10 mg) was associated with a delay in biochemical remission, earlier relapse after discontinuation, and a significant increase in the frequency of complications, including death, in HBsAg-positive patients.37 It was later shown that the HBV genome contains a transcriptional regulatory element (glucocorticoid responsive element) that is activated by corticosteroids.38 Thus, corticosteroids enhance viral replication by 2 potential mechanisms: depressed cytotoxic T-cell function and direct stimulation of an HBV genomic sequence.

Glucocorticoid withdrawal or pulse therapy. Clinical studies showed that a marked increase in viral replication (as evaluated by DNA polymerase activity) and aspartate aminotransferase (AST) flares often occurred when prednisone was given in a decremental fashion over 12 weeks.39 The increase in viral replication preceded AST flares by several weeks, and the AST values reached peak levels several weeks after treatment with corticosteroids was discontinued, which is a pattern consistent with HBVr. Investigators at the National Institutes of Health subsequently showed that a 4-week course of prednisolone often resulted in prolonged HBVr and worsened liver histology.40 Increases in serum HBV DNA levels accompanied by flares of ALT have been shown to occur in 30% to 70% of patients in whom a short course of corticosteroid therapy preceded treatment with either interferon alfa or lamivudine.41,42 In one study, sustained virologic response correlated with induction of T-helper 1 cell activity and increased cytotoxic T-cell function.42 These reactivation-induced flares of disease activity have been associated with rare fatalities despite protocol initiation of antiviral therapy upon discontinuation of the steroid priming regimen. All regimens started with moderate to high doses of glucocorticoids (30 to 60 mg daily), and tapering occurred over 4 to 12 weeks.39–42

The data showing that a short tapered regimen of glucocorticoids can result in HBV DNA reactivation appear robust because of similar selection criteria and consistent reporting in a fairly homogeneous group of patients with chronic hepatitis B.39–42 Each of these studies enrolled patients with HBsAg-positive chronic hepatitis B, and as such they would be anticipated to have high baseline levels (>20,000 IU) of serum HBV DNA. Thus, calculated risk estimates for pulse glucocorticoid therapy cannot be applied to all HBsAg-positive patients. The effects of such regimens
are unknown in patients who are HBsAg negative but anti-HBc positive.

We further attempted to see if there was any risk of HBVr in HBsAg-positive patients treated with varying doses of corticosteroids for <4 weeks because this is a practical concern for a variety of conditions, such as asthma and allergic disorders. The review did not reveal any data from which a precise risk estimate could be determined.

**Long-term glucocorticoid therapy.** The literature review did not reveal cases of HBVr that were induced by maintenance corticosteroid monotherapy for chronic inflammatory disorders. However, it provided some information on the occurrence of HBVr during monotherapy in patients with asthma or chronic obstructive pulmonary disease. In a retrospective study, 198 patients were treated with either inhaled corticosteroids (n = 126) or systemic corticosteroids (n = 72). Eleven percent of the patients treated with systemic corticosteroids developed HBVr compared with 3.2% of the patients treated with inhaled corticosteroids (odds ratio, 3.8; 95% confidence interval [CI], 1.1–13.1; P = .03). The investigators found that continuous use of systemic treatment for ≥3 months was associated with more episodes of HBVr than intermittent treatment, as was continuous dosing at ≥20 mg daily compared with lower doses. Because of the small sample size, neither of these comparisons reached statistical significance. In a small randomized, controlled comparison of 2 chemotherapy regimens for non-Hodgkin lymphoma, in which the only difference was the use of high-dose prednisolone in one of the regimens, the cumulative incidence of HBVr at 9 months after starting chemotherapy was significantly greater in the corticosteroid-containing regimen (73% vs 38%, P = .03).

Our review did not reveal any reports of HBVr after long-term intra-articular injection of corticosteroids. However, unlike topical corticosteroids or ophthalmic administration, increased systemic levels of corticosteroids, adrenal suppression, and a decrease in levels of interleukins as well as TNF-α have been observed after intra-articular administration. In addition, one case of pulmonary and joint tuberculosis has been reported. The possibility of HBVr due to repeated injections of corticosteroids cannot be totally excluded, but given the frequent use of this modality of therapy there is a high degree of certainty that this would occur in substantially <1% of cases.

In conclusion, moderate doses of glucocorticoids for ≥3 months have been shown to be associated with an increased risk of HBVr in HBsAg-positive patients. There is a high level of confidence that the true risk of HBVr with long-term systemic corticosteroid therapy is at least 10% when used in HBsAg carriers. The risk of HBVr from long-term glucocorticoid therapy is anticipated to be lower in HBsAg-negative, anti-HBc-positive patients. However, due to a paucity of data, a precise estimate cannot be provided (Table 2).

**TNF-α inhibitors and other biological agents.** Each of the 3 commonly used TNF-α inhibitors (etanercept, infliximab, and adalimumab) have been associated with HBVr. This is most likely explained by a class effect of these agents because TNF-α has been shown to be a first line of defense in viral infections. Rates of HBVr with these agents have generally been reported to be lower than those observed with highly immunosuppressive cancer chemotherapy. HBVr in HBsAg carriers has been reported to occur in 0% in small case series and up to 40% in large collective case series, whereas reactivation in HBsAg-negative, anti-HBc-positive patients has occurred in 0% to 5% of cases. Most cases of HBVr have occurred in patients treated for rheumatoid disease, with lower numbers reported in patients with Crohn’s disease and psoriasis, respectively. In many of these reports, it was unclear whether or not true cohorts were described to be able to calculate true proportions or rates. Also, many of the reported cases were being treated with other immunosuppressive agents, including prednisone, which might further augment the risk of reactivation. Overall, there is low confidence in the estimate of baseline risk for this class of immunosuppressive medications.

**Infliximab.** Infliximab is a chimeric monoclonal antibody to TNF-α that has been used to treat patients with Crohn’s disease, severe rheumatoid arthritis, and plaque psoriasis, among other conditions. In some case series, including a review of cases from Spain, infliximab has been associated with HBVr more often than the other TNF inhibitors; in a second series, HBVr attributable to infliximab was shown to be more frequently associated with severe biochemical abnormalities. Fatalities due to hepatitis B have been reported. However, this seemingly greater risk with infliximab is not a consistent finding, and many of the reported cases of HBVr during infliximab therapy were being treated with other immunosuppressive agents such as corticosteroids or methotrexate. In addition, comparative risk assessment between these agents is problematic when rates are derived from reported cases instead of well-performed consecutive cohorts that can accurately define risk.

**Other TNF-α inhibitors.** Several other TNF inhibitors (etanercept and adalimumab) have been linked to HBVr in small case series or individual case reports. Salvage therapy with antivirals has been used successfully, but the quality of the data on the risk of HBVr in HBsAg-positive patients as well as patients who are HBsAg negative but anti-HBc positive is low due to the small number of reported events and potential publication bias.

In summary, although there are no prospective, large-scale studies of the safety of TNF-α inhibitors and other biological agents in patients with active or resolved hepatitis B, the data from several large case series as well as data on file at the FDA indicate that TNF-α inhibitors induce HBVr. The percentage of patients who will develop HBVr with the more frequently used TNF-α inhibitors cannot be absolutely defined at present, but there are reasonable data to suspect that it is more than that described for traditional immunosuppressive drugs and less than that described for cancer chemotherapy, rituximab (see the following text), and glucocorticoids. A moderate level of confidence can be given to estimation that the risk of HBVr during anti-TNF monotherapy is between 1% and 10% in HBsAg carriers. The risk in patients who are HBsAg negative but anti-HBc positive is
considered to be lower (1%) because most case series to date have defined an absence of events. More accurate estimates of risk in both categories will require properly designed prospective studies and long-term follow-up because these drugs are often used for extended periods.

**Other biological agents.** Abatacept. Abatacept blocks costimulation of T lymphocytes and is currently used in advanced cases of rheumatoid arthritis. A single case was reported in which reactivation occurred after abatacept was added to a regimen of low-dose prednisone and daily leflunomide, an immunomodulatory pyrimidine synthesis inhibitor. In another retrospective case series, 4 HBsAg-positive patients given antiviral prophylaxis remained clinically stable, whereas an additional 4 HBsAg-positive patients not given prophylaxis developed HBVr. Unfortunately, the reasons for starting the patients on antiviral therapy were not described and the HBeAg status and baseline serum HBV DNA level were not known for most of the patients. Given the mechanism of action, it is likely that abatacept would be associated with a reactivation rate that is >1% but <10%; however, because of the paucity of data, there is little confidence in this estimate.

Tyrosine kinase inhibitors. Imatinib and nilotinib are specific tyrosine kinase inhibitors that are used to treat patients with chronic myelogenous leukemia and gastrointestinal stromal tumors. Several well-documented case reports and small case series have shown that this class of drugs induces HBVr in HBsAg-positive patients. The mechanism for reactivation remains unclear, but in vitro studies have shown that imatinib can inhibit T-cell activation and proliferation. In several of these studies, hepatitis flares occurred after the patients achieved a complete molecular or cytogenetic response, suggesting that the flare may be due to restoration of the immune response.

*Ustekinumab.* Ustekinumab is a human monoclonal antibody that is directed to interleukin-12 and interleukin-23 and is licensed in Europe, Canada, and the United States for treatment of severe plaque psoriasis. There are a few case reports of HBVr in HBsAg-positive patients. In one small series, 2 of 7 patients (29%) who did not receive antiviral prophylaxis experienced reactivation; one was an inactive carrier, and the other had HBeAg-negative chronic hepatitis B. No reactivation was reported in 3 HBsAg-negative patients who were anti-HBe positive. Given the mechanism of action, it is likely that ustekinumab would be associated with a reactivation rate that is >1% but <10%; however, due to the paucity of data, this estimate remains highly uncertain.

*Natalizumab and vedolizumab.* Natalizumab and vedolizumab are 2 recently developed inhibitors to the cell adhesion molecule α4 integrin found on lymphocytes. They have been used in the treatment of patients with inflammatory bowel disease. Experience in HBV-infected patients has thus far not been reported. A national registry of the safety of these agents is being kept, and further information on HBV-infected patients may become available in the future.

Further experience with these newer biological agents is needed, and the absence of reported cases cannot be taken as definitive evidence of low risk because of their short time of availability. The authors have little uncertainty in categorizing these drugs as having some risk of reactivation. This risk could prove to be the same as that of TNF or other cytokine inhibitors, but this estimate remains highly uncertain due to the lack of experience with these agents.

*Rituximab and ofatumumab.* Rituximab and ofatumumab are the 2 licensed B cell–depleting agents that are used primarily but not exclusively to treat hematologic malignancy. The American Society of Clinical Oncology provisional guidelines specifically categorize the use of rituximab as “highly immunosuppressive.” Ofatumumab was approved in 2009 and has been used to treat chronic lymphocytic leukemia in patients with advanced disease that is not responsive to other treatments. Rituximab was approved in 1997 and is used to treat non-Hodgkin lymphoma and chronic lymphocytic leukemia as well as rheumatoid arthritis, vasculitis, and essential mixed cryoglobulinemia. Both drugs are classified as anti-CD20–directed monoclonal antibodies. These drugs lead to nearly complete depletion of B cells in the blood with partial depletion in the bone marrow. They have a profound effect on antibody production, and the loss of anti-HBs during rituximab therapy in patients with evidence for past infection has been relatively well described.

Rituximab is seldom used as single-agent therapy for malignant disorders but has been used as such in patients with severe plaque psoriasis, idiopathic thrombocytopenia, and rheumatoid arthritis.

A recent review of the FDA Adverse Event Reporting System identified 109 cases of HBV-related acute liver injury caused by rituximab and 3 cases caused by ofatumumab, but the specific treatment indication was not included. The discrepancy in the numbers of cases is due to the long lead time since FDA approval of rituximab.

Rituximab is frequently added to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy for non-Hodgkin lymphoma but also has been used as maintenance therapy in some patients with poorly treatable malignancy. Several relatively unique features of rituximab-induced HBVr have been described that are unlikely to be attributable to the other oncological agents used for lymphoma. One is that reactivation events may occur as late as 12 months after rituximab is discontinued, at a time when anti-HBs titers are waning. Another feature that differentiates this drug is a high rate of HBsAg seroreversion (25%–40%) in patients who are anti-HBe positive. This is often associated with acute liver injury, and its occurrence has been rarely described in patients receiving antiviral prophylaxis. Concerns about the safety of B cell–depleting agents in patients with underlying HBV infection has led the FDA to recommend that all patients to be treated with rituximab or ofatumumab should be screened for HBsAg and anti-HBe and referred to a specialist for further evaluation about the need for virological monitoring and antiviral therapy.

The consistency of reports of rituximab-induced HBVr provides a high level of confidence that this drug should be considered as high risk for HBVr. Although a precise estimate of the HBVr rate in HBsAg-positive patients is unavailable, the available evidence suggests that most patients will eventually develop HBVr and in severe cases may require liver transplantation.
Even patients who are deemed to have resolved hepatitis B (HBsAg negative, anti-HBc positive) remain at significant risk for HBVr and liver failure-related death.66 Pooled baseline risk estimates from the control arm of a randomized trial66 and from untreated cohorts of well-performed observational studies62,67–70 revealed a reactivation rate of 16.9% (95% CI, 13.1%–21.9%) (Figure 2).

In summary, for rituximab, there is very little uncertainty that the risk of HBVr is >10% for both HBsAg-positive and HBsAg-negative, anti-HBc-positive patients; the effect of the drug on the frequency of HBVr is additive or synergistic to that of other chemotherapeutic agents used for non-Hodgkin lymphoma. Although the data on HBVr are limited for ofatumumab, the similarity in the mechanism of action and the small number of well-defined cases of HBVr provide very little uncertainty that all B cell–depleting drugs should be classified as high risk.

**Disease Outcomes of HBVr**

The literature review allowed assessment of the baseline risk of HBVr and the outcomes of HBVr through 5 RCTs and 25 observational studies that met the criteria defined in the preceding text. The RCTs compared antiviral prophylaxis with deferred treatment, and the observational studies included patients who were not given antiviral therapy or were provided deferred treatment once reactivation was diagnosed. All patients entered into these studies were either HBsAg positive or had serological profiles consistent with resolved infection. These different patient groups are separately analyzed in the following text. Baseline risk and disease outcomes could be most clearly assessed in 3 types of malignancy: lymphoma, breast cancer, and hepatocellular carcinoma.

**PICO 1. Is antiviral prophylaxis needed for HBsAg-positive patients who will undergo immunosuppressive drug therapy?** *Lymphoma.* Non-Hodgkin lymphoma is the most common form of hematologic malignancy associated with HBVr and constitutes the majority of cases of HBVr in most large cancer centers. Experience with antiviral prophylaxis during cancer chemotherapy is available in 2 randomized controlled clinical trials that compared prophylactic antiviral therapy started before or at the time of initiation of chemotherapy with deferred or on-demand treatment. A total of 40 untreated HBsAg-positive patients were included in these trials.25,28 Most patients in both studies were HBeAg negative, and HBV DNA was detectable at baseline in 27% of patients in one study that used a hybrid capture assay (lower limit of detection of 142,000 copies) and more consistently found in the second study using a real-time polymerase chain reaction method. Among the 40 patients, 22 (55%) developed HBVr, which was consistent between studies (53% and 55%); most cases (86%) had biochemical evidence of hepatitis, which resulted in hepatic failure in 4 patients (10%). Three deaths due to hepatitis B were reported in these studies, 2 of which occurred after discontinuation of prophylactic lamivudine therapy. None of these patients were treated with rituximab. Data on the frequency of interrupted cancer chemotherapy were not reported in either study.

Three observational studies met the criteria for inclusion in the data analysis. Collectively, these studies included 88 HBsAg-positive untreated patients.44,71,72 None of these CHOP-treated patients were exposed to rituximab, and deferred antiviral therapy began when reactivation was diagnosed in 2 of the studies. These studies varied in reporting of HBeAg status at baseline and used varying methods of HBV DNA detection with different sensitivities. The mean frequency of HBVr and hepatitis attributable to viral reactivation varied from 48% to 54% and 33% to 100%, respectively. Death due to reactivated hepatitis and liver failure was reported in 3 cases (3.4%). Data on frequency of interruption of cancer chemotherapy were not reported in any of these studies.

**Breast cancer.** A total of 154 untreated HBsAg-positive patients with breast cancer were derived from 3 studies, one of which was a randomized controlled clinical trial of prophylaxis versus deferred treatment.29,73,74 Overall, 28 of the 154 patients (18.1%) developed HBVr, and this was associated with hepatitis in approximately 60% of cases. Anthracycline-based therapy was used by all investigators, and glucocorticoids were routinely administered in 2 studies. One death due to HBVr-associated fulminant hepatitis was reported in the entire group of 154 patients, but HBVr was listed as the cause of delay or early discontinuation of cancer chemotherapy in 60% to 70% of cases.5,75 In one study, a significant association between HBVr and premature...
discontinuation or delay of chemotherapy was observed with an RR of 2.12 and a CI of 1.11 to 4.03 (P = .019). The same investigators reported early termination of cancer chemotherapy in 35% of patients with HBVr.

**Hepatocellular carcinoma.** A number of studies over the past 10 years have attempted to characterize the risk of HBVr from local ablation, surgical resection, or systemic chemotherapy of hepatocellular carcinoma in HBsAg-positive patients. The fact that transarterial chemotherapy (TACE) can precipitate HBVr has been well documented and is attributed to systemic exposure to chemotherapy by means of arteriovenous shunting. Five studies, including one RCT of prophylactic versus on-demand antiviral therapy, included HBsAg-positive patients. Collectively, these studies incorporated a total of 545 untreated HBsAg carriers in whom TACE was the single modality of care.

In the randomized controlled clinical trial involving prophylactic versus on-demand antiviral therapy, 15 of 37 patients (40.5%) treated with TACE developed HBVr. Among these 15 patients, hepatitis was severe in 11 patients and associated with early termination of TACE in 3 patients (20%). One death due to HBVr was reported. Most (75%) of the patients who were not prophylactically treated were HBeAg negative. A multivariate analysis revealed that baseline HBV DNA level >10^4 copies (2000 IU/mL) independently predicted HBVr (P = .046). The borderline significance of this observation was probably based on the small number of events.

In the largest of the observational studies, 320 patients underwent TACE with epirubicin and/or mitomycin. HBeAg was positive in 20.3% of patients at baseline, and HBV DNA level was 4 log_10 IU. Fifty-six (17.5%) of these patients had reactivation after one or more courses of TACE, of whom only 26 (46%) had reactivation-related hepatitis. Rates of HBVr were significantly lower (1.5%, P < .0001) in a comparator group of patients given prophylactic antiviral therapy. Of note, the frequency with which HBVr occurred was similar (15.7%) in 121 Child–Pugh A patients who underwent surgical resection only. This was not explainable by differences in HBeAg status or HBV DNA level at baseline between the 2 groups.

In a more recent study by the same group of investigators who conducted the RCT described in the preceding text, 119 patients were treated with TACE using either adriamycin or a more immunologically suppressive combination of epirubicin and cisplatin. These patients were compared with patients who were treated with other forms of local ablation and TACE combined with radiotherapy. This study showed that high-level viremia and high-level treatment intensity were the major risk factors for HBVr. When compared with local ablation as the reference population, the adjusted hazard ratio for TACE with adriamycin was 2.45 (95% CI, 0.92–6.49), for TACE with combination therapy was 4.19 (95% CI, 1.35–13.00), and for TACE with the 2-drug regimen and radiotherapy was 10.17 (95% CI, 3.78–27.40). Although the investigators mentioned that 10 patients with HBVr developed hepatic failure, their treatment group was not indicated. The single death occurred in a patient who was treated with TACE and radiotherapy.

Sixty-nine HBsAg-positive patients were evaluated in a study that compared the frequency of HBVr after a single course of TACE with that observed in patients who were waiting to undergo therapy for hepatocellular carcinoma. HBeAg was detected at baseline in 46 (66.7%) of TACE-treated patients and 30% of the previously nontreated patients. The follow-up in controls was short (mean of 59.4 ± 56 days). There was no difference in HBVr events between the TACE-treated patients (4.3%) and controls (10%). Hepatitis due to HBVr subsided spontaneously without treatment in 1 month in most patients. Unfortunately, the investigators used an insensitive technique for the assessment of quantitative HBV DNA (Digene II; Digene Corp, Gaithersburg, MD) with a lower limit of sensitivity of 141,000 copies/mL. This provided an opportunity for underestimation of the frequency of HBVr in patients with low baseline HBV DNA levels.

The baseline risk and outcome for HBsAg-positive patients undergoing systemic chemotherapy was evaluated in a study in which 102 untreated patients were treated with adriamycin or a combination of cisplatin, adriamycin, and 5-fluorouracil, combined with interferon alfa-2b. In this study, 37 patients (36%) developed HBVr, which was considered to be severe in 23 patients (62%). Reactivation was associated with jaundice in 18 patients (49%) and disruption in chemotherapy resulted in 32 patients (86%), including 26 patients who had premature discontinuation. The most striking finding in this study was the high death rate (n = 12; 32.4%) due to reactivation. Five of the deaths occurred in patients who were treated with on-demand lamivudine therapy and most of these patients had cirrhosis, which put them at high risk for liver failure.

**Rheumatic conditions.** The literature review revealed a marked paucity of high-quality studies in HBsAg carriers who underwent treatment with traditional disease-modifying antirheumatic agents or TNF-α inhibitors. In a large series from Spain, nearly 40% of HBsAg carriers had reactivation when placed on long-term TNF inhibitor therapy, but this figure represented pooled data from multiple centers and many patients received complex immunosuppressive drug therapy, thus limiting the usefulness and limit of confidence that can be placed in the data.

In a study from China, 2 of 23 untreated HBsAg carriers developed reactivation. Both of these patients were treated with methotrexate and prednisone (5 mg/day) and either leflunomide or hydroxychloroquine, and each had nondetectable HBV DNA by polymerase chain reaction at baseline but a 3- to 4-log increase in HBV DNA level during treatment. Hepatitis did not occur in either patient. In a second study from Japan, HBVr occurred in 2 of 5 HBsAg carriers treated with TNF-α inhibitor therapy. In both studies, the baseline risk from any individual drug as well as the outcome related to HBVr cannot be reliably assessed because many patients were treated with glucocorticoids in addition to disease-modifying antirheumatic agents and several were started on antiviral therapy because of elevated baseline HBV DNA level and a positive HBeAg status.
**PICO 2. Is antiviral prophylaxis needed for HBsAg-negative, anti-HBc-positive patients who will undergo immunosuppressive drug therapy?** *Lymphoma.* In total, 401 patients who were HBsAg negative but anti-HBc positive were included in the analysis.\(^62,67-70,72\) None of the patients were given prophylactic antiviral therapy. The mean frequency of HBVr in the studies was considerably lower in these patients when compared with the data derived from HBsAg carriers (mean, 12.2%; range, 3.2%–23.8%) (Table 3). Death due to reactivation was very uncommon but did occur. Most of these patients were treated with rituximab in addition to CHOP or other combination regimens. In a controlled comparison between rituximab plus CHOP (R-CHOP) and CHOP, a significantly greater number of patients treated with R-CHOP developed HBVr (5 of 21 vs 0 of 25, respectively; \(P = .015\)).\(^62\)

**Hepatocellular carcinoma.** The baseline risk of HBVr in HBsAg-negative, anti-HBc-positive patients was evaluated in a study that included 43 patients who received one or more cycles of TACE containing mitomycin C.\(^81\) Four patients (9.3%) developed reactivation after a median of 3.5 cycles. Surprisingly, reactivation was reported to occur several months after completion of TACE (median, 3 months; range, 1–5 months). The study defined reactivation by HBsAg seroreversion, which occurred in all patients, and all patients were HBV DNA negative (<200 IU) at baseline but had at least a 1-log increase in HBV DNA level when HBVr was detected (range, \(1.6 \times 10^4\) IU/mL to \(6.4 \times 10^4\) IU/mL). Hepatitis was mild in all cases and improved with lamivudine therapy. Exploratory analysis suggested that reactivation frequency was associated with the number of cycles and the presence of elevated bilirubin levels coexisting with cirrhosis. The small number of events precludes any conclusions on outcomes, and further studies are needed.

**Rheumatic conditions.** The baseline risk of HBVr in HBsAg-negative, anti-HBc-positive patients with rheumatic disease was described in relatively few studies. In a study involving 188 untreated patients treated with a variety of disease-modifying antirheumatic agents, 2 patients (1%) developed HBVr.\(^80\) Both patients had been treated with either leflunomide or methotrexate plus glucocorticoids (5 mg), and both recovered fully without antiviral therapy. In a second study, 1 of 45 anti-HBc-positive patients (2.2%) developed reactivation.\(^34\) This case was classified as severe but the patient recovered uneventfully after entecavir was started, allowing her to continue methotrexate therapy. In a third study, 0 of 67 patients developed reactivation during complex immunotherapy with TNF-\(\alpha\) inhibitors often taken in combination with methotrexate or glucocorticoids.\(^\) Among 21 anti-HBc-positive patients who received TNF-\(\alpha\) inhibitor therapy (10 of whom also received methotrexate), none developed HBVr during a mean duration of treatment of 27 months (range, 7–56 months).\(^10\) These data suggest that the risk of HBVr in anti-HBc-positive patients is considerably lower than that found in serological counterparts given cancer chemotherapy.

In summary, when compared with HBsAg-positive patients, patients who are HBsAg negative and anti-HBc positive appear to have a lower risk of HBVr when exposed to moderate-risk immunosuppressive drugs such as TNF-\(\alpha\) inhibitors; however, due to the paucity of data, a precise estimate of baseline risk was not possible (Table 2). The existing data support that the risk may be partially attributable to the concomitant use of other immunosuppressive drugs that are in the low-risk category. In contrast, when high-risk agents such as rituximab are used in anti-HBc-positive patients, high rates of reactivation in excess of 10% occur and antiviral prophylaxis can be anticipated to result in similar absolute risk reduction as described for HBsAg-positive patients (Table 2).

**Treatment effect in patients given prophylactic antiviral therapy (PICO 1 and PICO 2).** Results from 5 RCTs that compared antiviral therapy (lamivudine in 4 RCTs and entecavir in one RCT) with deferred treatment (after HBVr was diagnosed) were considered to be the highest-quality evidence available.\(^55-59\) These 5 studies collectively included a total of 139 patients who were given prophylactic treatment and 137 controls who were offered on-demand treatment once the main study outcome (HBVr) had occurred. One of the studies only enrolled HBsAg-negative, anti-HBc-positive patients, whereas the others

### Table 3. HBVr in 401 HBsAg-Negative, Anti-HBc-Positive Patients Treated With Chemotherapy for Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Author, reference (year)</th>
<th>n</th>
<th>Rituximab</th>
<th>Patients with HBVr (%)</th>
<th>Patients with hepatitis due to HBVr (%)</th>
<th>Patients with acute liver failure (%)</th>
<th>Deaths due to HBVr (%)</th>
<th>Interruption of chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lok et al(^62) (1991)</td>
<td>45</td>
<td>No</td>
<td>2 (4.4)</td>
<td>2 (4.4)</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Yeo et al(^62) (2009)</td>
<td>46</td>
<td>Yes, some</td>
<td>R-CHOP: 5/21 (23.8)</td>
<td>5 (10.8)</td>
<td>1 (2.1)</td>
<td>2 (2.1)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Matsue et al(^70) (2010)</td>
<td>56</td>
<td>Yes, all</td>
<td>CHOP: 0/25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td>Cheung et al(^77) (2011)</td>
<td>10(^a)</td>
<td>Yes, in 4</td>
<td>5 (8.9)(^a)</td>
<td>5 (8.9)</td>
<td>1 (1.7)</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td>Koo et al(^80) (2011)</td>
<td>62</td>
<td>Yes, all</td>
<td>2 (3.2)</td>
<td>2 (3.2)</td>
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<td>1 (1.6)</td>
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</tr>
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<td>Hsu et al(^80) (2014)</td>
<td>143</td>
<td>Yes, all</td>
<td>27 (18.9)</td>
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<td>0</td>
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</tr>
<tr>
<td>Huang et al(^80) (2013)</td>
<td>39</td>
<td>Yes, all</td>
<td>7 (17.9)</td>
<td>2 (5.1)</td>
<td>0</td>
<td>0</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

\(^a^\)All treated successfully treated with entecavir.

\(^b^\)All were occult HBV carriers and low-level HBV DNA was detected at baseline.

\(^c^\)Patient was treated with rituximab.
confined the analysis to those were HBsAg positive. The pooled effect of antiviral prophylaxis was calculated as the risk ratio by summarizing studies reporting reactivation rates with or without prophylactic antiviral therapy. Whereas there were too few cases of acute liver failure and liver-related deaths in these 5 studies for meaningful evaluation, the pooled estimate showed a relative risk of reactivation of 0.13 (95% CI, 0.06–0.23) and a relative risk of HBV-associated hepatitis of 0.16 (95% CI, 0.06–0.42) across varying baseline risks (including varying HBV serological profiles) (Figure 1; panels 1.1 and 1.2). There was little or no heterogeneity across studies. However, the evidence was judged as moderate due to a combination of a borderline low number of events and some uncertainty whether the reduction in reactivation events would consistently lead to improvement of patient-important outcomes (such as severe hepatitis, liver failure, or death or a reduction in interruptions of chemotherapy).

In summary, when exposed to high-risk immunosuppressive agents, HBsAg-positive and anti-HBC-positive (HBsAg-negative) patients exhibit a high baseline risk of reactivation in excess of 10%. Based on a typical reactivation rate of 50% in HBsAg-positive patients, antiviral prophylaxis would result in 435 fewer reactivation events per 1000 (from 350 fewer to 470 fewer) and 420 fewer cases per 1000 (from 290 fewer to 470 fewer). Even if the baseline risk were at the lower end of this risk category (10%), 87 fewer HBVr per 1000 would be prevented (from 70 fewer to 94 fewer).

Moderate-risk agents, such as TNF inhibitors, are expected to be associated with a 1% to 10% reactivation rate in HBsAg-positive patients. Assuming a typical 5% reactivation rate in this group, antiviral prophylaxis would result in 44 fewer reactivation events per 1000 (from 35 fewer to 47 fewer) and 42 fewer hepatitis cases per 1000 (from 29 fewer to 47 fewer). Even if HBVr occurred in 2% of these patients, prophylactic therapy would result in 17 fewer cases per 1000 (from 14 fewer to 19 fewer).

Although the true risk of HBVr from the use of moderate-risk drugs is likely to be substantially less for HBsAg-negative, anti-HBC-positive patients as compared with patients who are HBsAg positive, the lack of high-quality data makes the absolute risk estimate uncertain.

In contrast to the preceding drug risk calculations, antiviral prophylaxis with immunosuppressive agents in the low-risk group (eg, azathioprine) would result in only 1 fewer reactivation per 1000 (from 1 fewer to 1 fewer) when assuming the baseline risk to be 0.1% (Table 4).

**PICO 3. Does the presence of anti-HBs in addition to anti-HBc in HBsAg-negative patients confer additional protection against HBVr?** It has been suggested that the presence of anti-HBs antibodies may provide additional protection against reactivation. More than two-thirds of anti-HBC-positive patients in the previously described studies had detectable anti-HBs. Among these 252 patients who were anti-HBs positive, HBVr was observed in 11 (4.3%), a frequency only slightly lower than that of the total group of anti-HBc-positive patients. The small number of cases did not allow comparison as to whether these patients who had anti-HBs had clinically less severe hepatitis.

The titer or level of anti-HBs was not reported in any of these studies. Further studies have been performed in patients treated with R-CHOP, which suggests that a relationship exists between the initial anti-HBs titer and continued detectability of anti-HBs during treatment. In one study involving 29 patients with lymphoma, paired sera were available before and after a median of 6 cycles with R-CHOP. Eight patients lost anti-HBs, and one developed "reverse" HBsAg seroconversion (or seroreversion). None of the 10 cases with a pretreatment anti-HBs level >100 mIU/mL became anti-HBs negative, and reactivation did not occur. Multiple logistic regression showed lower pretreatment anti-HBs titer to be the only independent factor predicting the loss of anti-HBs (odds ratio, 0.003; 95% CI, 0.000–0.302; P = .014).

Due to a lack of studies that have used anti-HBs titers to guide whether or not to initiate antiviral prophylaxis, there is insufficient evidence to determine if anti-HBs titer or level affects the risk of reactivation with rituximab. Therefore, a decision on using antiviral prophylaxis cannot be based on the presence or titers of anti-HBs when anti-HBC is present.

**PICO 4. Is prophylactic treatment with third-generation nucleos(t)ide analogues more effective than treatment with first- or second-generation nucleos(t)ide analogues?** Five oral nucleos(t)ide analogue drugs are currently approved for treatment of HBV: lamivudine, adefovir, entecavir, telbivudine, and tenofovir. As the first approved drug in this class, lamivudine has been used for a number of years as prophylaxis against HBVr and has been shown in systematic reviews to reduce the risk of HBVr. However, lamivudine is associated with a high rate of drug resistance when used beyond 1 year. Rates of lamivudine resistance of 20% at 1 year and 30% at 2 years have been reported in nonimmunocompromised patients and would be anticipated to be even higher in patients on immunosuppressive drug treatment.

Due to the fact that cancer chemotherapy regimens often fall short of 1 year and lamivudine resistance is uncommon in patients before 6 to 9 months of therapy, it has been suggested that lamivudine can be used as first-line therapy for prophylaxis in this situation. This offers the advantages of reduced cost and broad availability worldwide.

More recent studies have shown that entecavir is also effective for reactivation prophylaxis. However, the literature search revealed only a few studies comparing the effectiveness of these 2 drugs used as prophylaxis (Table 5). Several of these studies have reported lower rates of HBVr with entecavir, but the data are weakened by physician preference for drug assignment and potential publication bias. A single RCT of entecavir versus lamivudine prophylaxis has been reported in abstract form. This study found a significantly higher rate of HBVr in the lamivudine arm during a median follow-up of 40 months, which was presumably due to drug resistance (30% for lamivudine vs 6.6% for entecavir; P = .001). Moreover, disruption of chemotherapy due to hepatitis B also occurred significantly less frequently in patients treated with entecavir (18.3% vs
Table 4. GRADE Evidence Profile for PICO 1 and 2: Should Antiviral Prophylaxis Versus No Prophylaxis Be Used for Prevention of HBVr With Immunosuppression?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Study event rates (%)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>With placebo/ close monitoring</td>
<td>With antiviral prophylaxis</td>
</tr>
<tr>
<td>(no. of studies), follow-up</td>
<td>Overall quality of evidence</td>
<td></td>
</tr>
<tr>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>HBV reactivation* (critical outcome; assessed with new HBV DNA detection or increase by 10-fold, negative to positive HBeAg, negative to positive HBsAg)</td>
<td>276 (5 studies)25-29</td>
<td>12–18 mo</td>
</tr>
<tr>
<td></td>
<td>Moderate HBV risk 50 HBVr per 1000</td>
<td>44 fewer HBVr per 1000 (from 35 fewer to 47 fewer)</td>
</tr>
<tr>
<td></td>
<td>High HBV risk 500 HBVr per 1000</td>
<td>435 fewer HBVr per 1000 (from 350 fewer to 470 fewer)</td>
</tr>
<tr>
<td>HBV hepatits flare* (critical outcome; assessed with ALT level &gt;3 times the upper limit of normal or &gt;100)</td>
<td>276 (5 studies)25-29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate HBV risk 50 flares per 1000</td>
<td>42 fewer flares per 1000 (from 29 fewer to 47 fewer)</td>
</tr>
<tr>
<td></td>
<td>High HBV risk 500 flares per 1000</td>
<td>420 fewer flares per 1000 (from 290 fewer to 470 fewer)</td>
</tr>
<tr>
<td>Chemotherapy disruption (important outcome; assessed with either discontinuation or delay of 7 days or more)</td>
<td>(5 studies)25-29</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. The source was our own analysis (see text for study details and forest plot in Figure 1).

a Although liver failure and death from HBVr have been reported in retrospective observational studies, comparative effects from interventions on these outcomes are unreliable and did not occur in the RCTs included in this analysis. Due to the strong relationship with HBVr, followed by HBV hepatitis flare and subsequent liver failure and death, similar relative effects on those end points can be assumed.

b Allocation concealment was uncertain in 3 of 5 studies but not judged to be of sufficient severity to rate down; studies were not blinded, but the outcome was objective and not rated down.

c There is some uncertainty whether an improvement in this outcome is consistently associated with improvement of patient-important outcomes as well when comparing prophylactic pre-emptive treatment with monitoring only followed by treatment when indicated. This is a borderline judgment. Other borderline judgments for this outcome (such as risk of bias and imprecision) were folded into a single down rating accordingly.

d Fragility may be present but not rated down because the rating down for indirectness was borderline as well.
1.6%, respectively; \( P = .002 \). The number of cases in which prophylaxis has been attempted with telbivudine or adefovir in some of these studies is too small to evaluate and indirect evidence has shown that development of resistance is of concern, which makes those drugs less suitable.

Collectively, these studies provide some useful data, but the analysis is complicated by nonrandomized enrollment, physician preference in treatment assignments, inconsistencies in reporting HBV DNA levels before chemotherapy, and other features that might promote some degree of bias. One of the important clinical issues raised, however, has been the high rate of lamivudine failure. Investigators in the Asia Lymphoma Study Group reported virological breakthroughs due to lamivudine-resistant

<p>| Table 5. Studies Using Entecavir Prophylaxis, Either Alone or Compared With Lamivudine |
|----------------------------------------|--------|------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Author, reference, reference</th>
<th>No. of patients enrolled</th>
<th>Type of cancer and chemotherapy</th>
<th>Study design</th>
<th>Frequency of HBVr, no. (%)</th>
<th>Frequency of hepatitis due to HBVr, no. (%)</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al88</td>
<td>123c</td>
<td>Lymphoma R-CHOP in 70%</td>
<td>Multicenter, nonrandomized controlled</td>
<td>89 LVD 18 (20.2)d</td>
<td>11 (12.4)d</td>
<td>One death due to LVD resistance; 5 patients end chemotherapy early</td>
</tr>
<tr>
<td>Chen et al85</td>
<td>40d</td>
<td>Hematologic malignancies RTX in 46% ETV vs 0% LVD</td>
<td>Retrospective drug use audit</td>
<td>14 LVD 1 (7.1)</td>
<td>1</td>
<td>Virological breakthrough in one during second year of LVD</td>
</tr>
<tr>
<td>Huang et al86</td>
<td>121</td>
<td>Lymphoma R-CHOP in all</td>
<td>Randomized controlled</td>
<td>60 LVD 8 (13)</td>
<td>5 (8)</td>
<td>Chemotherapy interrupted in 11 (18.3%)</td>
</tr>
<tr>
<td>Kojima et al87</td>
<td>84</td>
<td>Lymphoma R-CHOP in all</td>
<td>Prospective review</td>
<td>12 ETV 0</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td>Kim et al89</td>
<td>127g</td>
<td>Lymphoma R-CHOP in some</td>
<td>Retrospective multinational</td>
<td>96 LVD 30 (31.3)</td>
<td>Not stated</td>
<td>3 deaths due to hepatic failure; frequent virological breakthrough</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31 ETV 0</td>
<td>Not stated</td>
<td>1 death due to hepatic failure</td>
</tr>
</tbody>
</table>

LVD, lamivudine; ETV, entecavir; RTX, rituximab.

a95% were HBsAg positive.
bDifferences not statistically different.
cPhysicians decided which drug to use based on clinical status and ability to pay for drug.
dIn total, 15 had chronic hepatitis B and 25 had resolved infection.
eIncludes 9 HBsAg-positive and 3 occult carriers.
fAll patients had HBV DNA monitoring during treatment and up to 1 year after chemotherapy was stopped.
g44 patients were HBsAg positive and the remaining 83 were HBsAg-negative, anti-HBc positive. All but 2 HBV reactivations occurred in HBsAg-positive patients.
HBV in more than 20% of 127 HBsAg-positive cases who were treated with rituximab in addition to CHOP. Reactivation was reported to occur both during and after cessation of lamivudine therapy and was less common in patients who were treated with lamivudine as prophylactic therapy as opposed to deferred therapy (22.9% vs 59.1%; P < .001).89

In summary, based on a single, head-to-head RCT of entecavir versus lamivudine, it appears that antiviral agents with a high barrier to resistance used for prophylaxis have higher efficacy against HBVr (risk ratio, 0.22; 95% CI, 0.08–0.61), which is due to a significantly lower rate of virological breakthrough meeting the criteria for HBVr. Extrapolating from the findings of this study, 234 fewer reactivations per 1000 (from 117 fewer to 276 fewer) would be anticipated to occur with antiviral agents with a high barrier to resistance, such as entecavir and tenofovir. In addition, 125 fewer hepatitis flares per 1000 (from 133 fewer to 0 fewer) and 167 fewer chemotherapy disruptions per 1000 (from 60 fewer to 181 fewer) would be achieved. The evidence was rated as moderate in quality due to imprecision (small sample size, few events). However, there is at least moderate confidence in the effect based on indirect evidence from the results of the entecavir registration trials.90,91 The same can be said for tenofovir due to the lack of resistance shown during long-term use and the superior antiviral potency when compared with lamivudine (Table 6).

**PICO 5. Is HBV DNA monitoring followed by on-demand antiviral therapy as effective as prophylactic antiviral therapy?** This PICO question addresses the consideration that regular monitoring of HBV DNA levels may allow early detection and treatment of HBVr and the latter may attenuate liver injury and improve patient outcomes, which differ little from those observed in patients given prophylactic antiviral therapy. The best evidence that improved outcomes are achievable with prophylactic antiviral therapy as opposed to deferred treatment comes from RCTs that compare both means of drug administration.55–59 These have been described in detail in the preceding text. When taken collectively, the observational studies included in this review also provide data on a large population of patients, and the data suggest that the overall rate of HBVr is considerably lower when prophylactic antiviral therapy is compared with on-demand treatment. Most of these studies are poor in quality, use slightly different definitions of HBVr, and, perhaps most importantly for addressing this question, inconsistently report any outcomes other than the frequency of reactivation, severe elevation of ALT level, and reactivation related to death. Also, the existing studies differ somewhat in the regularity with which HBV DNA monitoring is performed and in the methodology used for quantification, both of which can influence the timing at which HBVr is first appreciated. The observational studies do not allow valid cross-comparisons between studies. Thus, no consensus can be achieved on how HBV DNA monitoring may be most efficiently conducted based on these studies.

In summary, the most appropriate HBV DNA monitoring interval needed to achieve good clinical outcomes with deferred antiviral therapy cannot be determined from the existing data, and concerns remain as to whether the intensity of monitoring achieved in highly resourced trials can successfully be reproduced in regular care. The cost of routine HBV genomic testing is a secondary but important practical issue and one that would need to be addressed before implementation of a defined policy.

**PICO 6. Is treatment of established HBVr with third-generation nucleos(t)ide agents more effective than treatment with first- or second-generation drugs?** The literature review did not allow direct comparison of the clinical effectiveness of third-generation oral antiviral agents with earlier-generation antiviral agents in patients who developed HBVr during immunosuppressive drug therapy. However, a recent meta-analysis has shown equivalent improvement in 3-month survival with either entecavir or lamivudine in cases of acute-on-chronic liver failure due to hepatitis B.92 Moreover, both drugs were well tolerated.

There are emerging data on the use of entecavir in patients who experience reactivation while on cancer chemotherapy for hematologic malignancies. Although trials are ongoing, the authors found no published reports of tenofovir in this setting.

In nonimmunosuppressed populations, entecavir is associated with a significantly higher rate of nondetectable HBV DNA when compared with lamivudine.90,91 What is likely to be of greater importance when deciding which agent to use for treatment, however, is the much higher rate of drug resistance with lamivudine, particularly when the need for therapy extends beyond 6 to 12 months.94 The duration of antiviral therapy is often prolonged in patients who experience reactivation due to a number of factors, including the severity of clinical presentation and the need for continuing immunosuppressive drug therapy on a long-term basis (well beyond 6 months). Moreover, the use of immunosuppressive drug therapy would be anticipated to encourage high levels of viral replication, in turn enhancing the chance for selection of lamivudine-resistant HBV.

In summary, entecavir results in far fewer cases of drug resistance than lamivudine in nonimmunosuppressed patients. These data, combined with its greater antiviral potency, make entecavir a more suitable first-line approach whenever possible to prevent HBVr. The same can be said of tenofovir due to equivalent or even greater antiviral potency when compared with entecavir (and, by inference, greater than lamivudine) and the virtual absence of drug resistance over 6 years of continuous use.94 None of the currently used oral antiviral agents have interactions with drugs metabolized by the cytochrome P450 3A4 pathway. The only dose adjustment of third-generation HBV medications is when renal insufficiency is present (Table 7).

**PICO 7. Should patients who will undergo long-term immunosuppressive drug therapy be screened for HBV before starting treatment?** An appropriate answer to this question requires clear understanding of the downsides as well as the upsides of routine screening in patients who are to undergo immunosuppressive drug
Table 6. GRADE Evidence Profile for PICO 4: Should Antiviral Drugs With a High Barrier to Resistance Versus Lamivudine Be Used for Prophylaxis of HBVr in Patients Undergoing Immunosuppression?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants (no. of studies), follow-up</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>HBV reactivation (critical outcome; assessed with new HBV DNA detection or increase by 10-fold; negative to positive HBeAg; negative to positive HBsAg)</td>
<td></td>
</tr>
<tr>
<td>121 (1 study), 40 mo</td>
<td>No serious risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| HBV hepatitis flare (critical outcome; assessed with ALT level >3 times the upper limit of normal or >100) |
| 121 (1 study), 40 mo | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious | Undetected | Moderate due to imprecision | 8/60 (13.3) | 0/61 (0) | RR, 0.06 (0.004–1.0) | 133 flares per 1000 |
| | | | | | | | | | | 125 fewer flares per 1000 (from 133 fewer to 0 fewer) |

| Disruption of chemotherapy (important outcome) |
| 121 (1 study), 40 mo | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious | Undetected | Moderate due to imprecision | 11/60 (18.3) | 1/61 (1.6) | RR, 0.09 (0.01–0.67) | 183 per 1000 |
| | | | | | | | | | | 167 fewer per 1000 (from 60 fewer to 181 fewer) |

NOTE. The source was Huang et al., and the only RCT that provided comparison between entecavir and lamivudine.

\[a\]The median range was 8.6 to 62.3 months.

\[b\]There remains some uncertainty whether an improvement of this outcome is consistently associated with improvement of patient-important outcomes; this also applies when comparing prophylactic pre-emptive treatment with monitoring only followed by treatment when indicated. This is a borderline judgment.

\[c\]Fragility was present. The total number of events was low, and the sample size was small.

\[d\]RR was not reported. RR was calculated using \(\chi^2\) statistics in openepi (openepi.com). If zero events were reported, 0.5 events were added to be able to calculate the RR.
Table 7. GRADE Evidence Profile for PICO 6: Should Antiviral Drugs With a High Barrier to Resistance Versus Lamivudine Be Used for Treatment of Established HBVr?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Study event rates (%)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants (no. of studies), follow-up</td>
<td>With antiviral drugs with high barrier to resistance</td>
<td>With lamivudine</td>
</tr>
<tr>
<td>Risk of bias</td>
<td>Risk</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Failure of virological response (critical outcome; assessed with undetectable HBV DNA)</td>
<td>2278 (7 RCTs), 52 wk</td>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>Development of viral resistance at 5 y (critical outcome)</td>
<td>183 (1 RCT follow-up study), 5 y</td>
<td>No serious risk of bias</td>
</tr>
</tbody>
</table>

NOTE. The sources are Liu et al,103 Woo et al,104 Petersen and Buti,105 Chang et al,106 and Kitrinos et al.93

a Although statistical heterogeneity was detected, each study included both HBeAg-negative and -positive infections and showed a superior effect of entecavir over lamivudine, making the detected heterogeneity clinically less relevant. Not rated down.

b Indirect evidence from head-to-head RCTs of entecavir versus lamivudine in HBeAg-positive and -negative chronic hepatitis B. The comparative antiviral effects are not expected to differ in established reactivated hepatitis B.

c Comparable superior effects were shown for tenofovir (indirect comparisons) in a network-meta-analysis. The viral response of tenofovir vs lamivudine was as follows: odds ratio, 23.3 (95% CI, 6.2–76).104

d Indirect evidence from long-term (5-year) follow-up of chronic hepatitis B therapy. Comparable development of resistance is expected in established HBVr when the duration of treatment is expected to exceed 6 months.

e This is assumed based on the observed frequency between the entecavir and lamivudine cohorts.

f Rate is from Petersen and Buti.105 Other rates were 16% at year 1, 40% at year 2, and 61% at year 3.

g Estimated based on reported rates.

h Based on data on entecavir (0.55% at 5 years). No detectable resistance has been reported after 6 years of treatment with tenofovir in 347 HBeAg-negative and -positive patients (Kitrinos et al106).
therapy. The downsides include the emotional concerns of patients engendered by the diagnosis of either active or resolved HBV infection that may affect a patient’s health or emotional state. A diagnosis of chronic HBV infection will also have an impact on future health care costs if long-term therapy is applied. This includes costs attached to initial and subsequent assessments with appropriate follow-up testing, including surveillance for hepatocellular carcinoma when appropriate. There may be additional financial costs of routine HBV screening associated with family screening and vaccination of household contacts. These costs notwithstanding, it can be argued that diagnosis of active infection will lead to better supplementary testing and assessment for the potential need for treatment as well as the need for vaccination of close contacts, both of which serve the well-being of the public. A third possible disadvantage of universal screening comes from the potential for a false-positive blood test result for HBsAg. The risk of a false-positive result for HBsAg, however, would be greatly minimized by routine anti-HBc screening because a positive result for HBsAg is almost universally associated with a positive anti-HBc. Besides, false-positive HBsAg test results are very rare and almost always occur in low-prevalence populations in accordance with Bayes’ theorem.

These seeming deterrents for HBV testing must be weighed against the medical disadvantages of not testing. The current review of the literature on HBVr revealed compelling data indicating that patients who are found to be HBsAg positive as well as patients with resolved infection exposed to high-risk drug regimens have a considerable risk of HBVr and its health consequences, and this risk can be greatly reduced by prophylactic antiviral therapy. Once HBVr occurs, it has implications for serious medical outcomes, interruption in medical (eg, cancer) therapy, and increased resource utilization. Many of these patients are not candidates for liver transplantation if fulminant hepatitis were to occur due to their underlying disease. Importantly, the decision to use prophylactic antiviral therapy can only reasonably be made if the HBV status of the patient is determined before initiation of immunosuppressive drug therapy.

The cost of routine HBV screening for patients who are to undergo immunosuppressive drug therapy needs to be considered when making a general recommendation on whether routine screening is a medically wise policy. Thus far, there are scant data on the cost-effectiveness of screening all patients who will undergo immunosuppressive drug therapy. However, in a decision model study in patients with lymphoma treated with CHOP and rituximab, a strategy of screening all patients was dominant when compared with screening only patients who were at high risk versus no screening. It was important that this study not only showed universal screening to be cost-effective but also cost-saving. A second study found universal screening to possibly be cost-effective in patients at high risk for hepatitis B who are in need of adjuvant chemotherapy. It remains to be seen if further studies will prove HBV screening to be cost-saving or cost-effective with other high-risk immunosuppressive drug regimens or equally important when moderate-risk drugs are used.

In summary, the downsides of testing for hepatitis B are limited and the choice of screening before immunosuppressive drug treatment partially hinges on being able to define a pretest probability threshold that makes screening followed by antiviral prophylaxis or regular monitoring cost-effective. Although there was insufficient evidence to answer this question, the authors conclude that the cost of testing is likely outweighed by the benefits when the baseline risk for reactivation is moderate (≥1%, <10%) or high (>1%). In situations in which the risk is low (<1%), however, it is reasonable to conclude that the need for screening should be determined according to the recommendations outlined by the Centers for Disease Control and Prevention and the US Preventive Services Task Force, which reflects the anticipated population prevalence.

Limitations of Current Evidence and Future Directions

This review has shown a need for consensus on a standardized definition of HBVr. Standard criteria for diagnosing and grading HBVr would increase the validity of making cross-study comparisons and provide further clarity in systematic reviews of the area. Many studies have used the arbitrary criterion of a 10-fold increase or de novo detection of serum HBV DNA when compared with a baseline sample determination. However, the general low rate of screening for hepatitis B in patients about to undergo immunosuppressive drug therapy limits the ability to apply these criteria. One alternative that has been used in some studies is to use an absolute cutoff level of serum HBV DNA at the time that increasing serum aminotransferase levels have been appreciated. However, it may be difficult to separate naturally occurring disease exacerbations from true HBVr when these criteria are used. The review also revealed a surprising number of assay methodologies with varying sensitivities to evaluate HBV DNA level. Substantial differences in the lower limit of detection of the various assays limits the ability to detect HBVr and, in particular, at the earliest stage possible. For these reasons, future studies should only use a polymerase chain reaction–based assay that is able to detect ≤25 IU/mL HBV DNA.

There is also a need to systematically classify the biochemical abnormalities (ALT or AST) and degree of severity of HBVr. Severe hepatitis, for example, is often gauged as one in which there is a 5- to 10-fold or greater elevation in aminotransferase levels above the upper limit of normal or when there is lower ALT elevation with conspicuous clinical symptoms. These patients may not have a different outcome from milder cases unless there is concomitant liver failure or protracted disease. Thus, one can argue that, as reported, the designation of “severe hepatitis” may have little clinical meaning and more explicit, patient-important outcomes should be defined. One way of dealing with this issue is a system of grading HBVr on a 5-point scale proposed recently by Hoofnagle in which the following designations are used: (1) without change in ALT level (silent), (2) increased ALT level without jaundice


might be needed in patients who take biological agents on a long-term basis for benign conditions? Addressing this issue will not be easy because it will require large-scale studies to ensure adequate power to determine statistically meaningful differences in outcomes between various monitoring strategies. One way of reconciling this dilemma is to have the pharmaceutical industry and federal funding agencies incorporate the expertise of the academic hepatology community during the process of protocol development for new cancer therapeutics and biological agents for nonmalignant conditions. Currently, many of these protocols exclude patients with known hepatitis B. An alternative course of action is to actively screen and enroll anti-HBc-positive patients into various monitoring or treatment strategy protocols, perhaps stratifying patients by baseline HBV DNA level and anti-HBs using a randomized controlled design. This need not prolong the pathway to drug development if undertaken not only in North America but also in highly endemic regions of the world where anti-HBc-positive patients are far more commonly encountered and from which most of the published literature on reactivated hepatitis due to immunosuppressive medications has been derived.

The review also revealed a paucity of data on the cost-effectiveness of universal screening for HBV. The available data have provided somewhat discrepant results. However, the finding of cost savings in one study that incorporated aggressive chemotherapy in the model signals a need for further study with other high-risk therapies. In addition, cost-effectiveness studies are needed with the large group of patients who are currently taking moderate-risk drugs such as TNF-α inhibitors. The findings of these studies may allow better discrimination of economic thresholds for screening that can be translated into health care policy.

Finally, the protective role of hepatitis B vaccination in preventing HBVr is an area that has been somewhat neglected. This has special relevance for patients with inflammatory bowel disease. The literature reflects that many patients with inflammatory bowel disease may ultimately need immunosuppressive drug therapy, but relatively few have been vaccinated. Whereas patients with inflammatory bowel disease who have not been placed on immunosuppressive drug therapy have been shown to have good antibody responses, this rapidly wanes during treatment. Studies with more highly immunogenic vaccines and a booster dose strategy appear warranted to assess the level and durability of protection during immunosuppressive drug therapy.

Also, it is conceivable that high neutralizing anti-HBs titers (>100 IU) may offer some protection against HBVr when B cell–depleting agents are used in patients with resolved infection. It remains an open question as to whether a booster dose given immediately before the initiation of B cell–depleting therapy followed by repeat dosing during treatment in patients with waning anti-HBs titers might reduce the rate of or clinically attenuate HBVr. However, until such time that these issues can be further resolved, prophylactic antiviral therapy offers a far easier clinical solution.

In summary, the review of the literature on this topic indicates that much more study is needed to improve the health outcomes of patients who are to undergo

The review also disclosed a number of areas in which critical outcome data on HBVr are not being reported. The available data focus on immediate or short-term outcomes, such as the number of episodes of acute liver failure or the number of liver-related deaths attributed to HBVr. Because both of these important outcomes occur infrequently, even in patients treated with intensive cancer chemotherapy, exploration of the more numerically dominant but underreported issue of how interruption of chemotherapy due to HBVr affects cancer progression and cancer-free survival is needed. If meaningful differences could be shown among patients who have early discontinuation of chemotherapy due to HBVr, those who have reactivation but complete chemotherapy with slight or no delay, and those who neither have reactivation nor require adjustment in therapy, it could promote an awareness by the oncology community of the medical benefits of screening and early intervention. Although the data are incomplete on the frequency of drug interruption due to HBVr, several studies have reported that this occurs in 40% or more of cases, with the predominant outcome of early discontinuation rather than delay in reinstitution of chemotherapy.

Another pressing issue is how to best manage patients who are HBsAg negative but anti-HBc positive. Anti-HBc positivity is detectable in at least 3% of the general population in the United States, and rates in excess of 50% have been reported in Southeast Asia and China and immigrants to the United States from these regions. In both settings, the seroprevalence of anti-HBc is 5 to 10 times greater than the HBsAg carrier state, which means that despite the lower rates of reactivation known to occur in HBsAg-negative and anti-HBc-positive patients, the sheer number of HBVr cases in this group may equal or surpass that occurring in HBsAg carriers. Currently, major liver societies recommend that anti-HBc-positive patients undergo frequent HBV DNA monitoring unless they are on prophylactic antiviral therapy. However, this recommendation is based on low-quality data. Many experts have adopted the potential value of HBV DNA monitoring followed by on-demand treatment if the HBV DNA level increases, but this has been shown not to be as safe as a preventive therapy strategy and no standards have been set as to how to best approach routine monitoring. Should HBV DNA testing be performed monthly, bimonthly, or even less frequently in anti-HBc-positive patients? Should different standards be in place for patients with malignancy versus those being treated for nonmalignant disorders because of differences in the baseline risk that HBVr will occur during immunosuppressive drug treatment? What are the cost implications for HBV DNA monitoring indefinitely, as might be needed in patients who take biological agents on a long-term basis for benign conditions?
immunosuppressive drug therapy and may unknowingly (or even knowingly) have hepatitis B. Hopefully, this can be achieved with reasonable incremental cost or, better yet, reduced costs.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.10.038.

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Conflicts of interest
The authors disclose the following: R.P.P. has served as a consultant for Gilead Sciences and Novartis. R.G. has served as a consultant for Gilead Sciences, Novartis, AbbVie, Merck, and Idenix. Y.T.F.-Y. discloses no conflicts.
Appendix 1. Search Strategy

Search date: September 4, 2013

Search filter applied: RCTs/SRs/MAs/HTAs (for antiviral therapy question only); all study designs included for screening question

Limits: 1995 – current; Case reports, editorials, letters and notes removed.

Databases searched: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2013>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 2013>, EBM Reviews - Health Technology Assessment <3rd Quarter 2013>, Embase <1980 to 2013 Week 35>, Ovid MEDLINE(R) <1946 to August Week 3 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 03, 2013>

Search Strategy:

1. exp *Hepatitis B/ or exp *Hepatitis B Virus/ (96819)
2. exp Hepatitis B Surface Antigens/ use mesz,cctr,coch,clhta (17313)
3. exp hepatitis B surface antigen/ use emez (24081)
4. exp Hepatitis B Antibodies/ use mesz,cctr,coch,clhta (9068)
5. hepatitis B antibody/ use emez (6365)
6. (hepatitis b or hbv or hbsag or anti-HBc or anti-HBs).ti,ab. (149957)
7. or/1-6 (167891)
8. exp Immunosuppressive Agents/ use mesz,cctr,coch,clhta (275112)
9. exp immunosuppressive agent/ use emez (518948)
10. exp Antineoplastic Protocols/ use mesz,cctr,coch,clhta (124161)
11. exp Immunosuppression/ use mesz,cctr,coch,clhta (52207)
12. exp immunosuppressive treatment/ use emez (118814)
13. exp Immunocompromised Host/ use mesz,cctr,coch,clhta (19108)
14. exp immunocompromised patient/ use emez (7399)
15. exp Antineoplastic Agents/ use mesz,cctr,coch,clhta (878840)
16. exp antineoplastic agent/ use emez (1351760)
17. exp chemotherapy/ use emez (341171)
18. Antibodies, Monoclonal/ use mesz,cctr,coch,clhta (187808)
19. exp monoclonal antibody/ use emez (320133)
20. exp Tumor Necrosis Factor-alpha/ use mesz,cctr,coch,clhta (102327)
21. exp Cytotoxicity, Immunologic/ use mesz,cctr,coch,clhta (48046)
22. exp immunocytotoxicity/ use emez (14685)
23. exp Neoplasms/dt [Drug Therapy] (883052)
24. exp cancer patient/ use emez (101078)
25. (immunocompromis* or immunosuppress* or chemotherap*).ti,ab. (927819)
26. or/8-25 (3589791)
27. exp Mass Screening/ use mesz,cctr,coch,clhta (104081)
28. screen*.ti,ab. (1040493)
29. exp screening/ use emez (417398)
30. or/27-29 (1264047)
31. exp Virus Activation/ use mesz,cctr,coch,clhta (5844)
32. exp virus reactivation/ use emez (6860)
33. exp Recurrence/ use mesz,cctr,coch,clhta (170501)
34. exp recurrent infection/ use emez (10241)
35. exp prophylaxis/ use emez (643286)
36. (reactivat* or prophylaxis or recurrence or prophylactic or re-activat* or pre-empt* or preempt*).ti,ab. (763837)
37. or/31-36 (1483719)
38. exp Lamivudine/ (32361)
39. (Zefix or Heptovir or Epivir or 3tc or lamivudine).ti,ab. (18873)
40. exp Entecavir/ use emez (3798)
41. (Entecavir or Baraclude or Entaco or Entaliv).ti,ab. (3362)
42. exp Adefovir/ use emez (3877)
43. (Adefovir or bis-POM PMEA or Preveon or Hespera).ti,ab. (5350)
44. exp Emtricitabine/ use emez (4579)
45. (Emtricitabine or Emtriva or Coviracil or Truvada or Atripla).ti,ab. (2867)
46. exp Tenofovir/ use emez (8996)
47. (Tenofovir or TDF or PMPA or Viread or Reviro).ti,ab. (9756)
48. exp telbivudine/ use emez (1722)
49. (telbivudine or Sebivo or Tyzeka).ti,ab. (1203)
50. (3424-98-4 or 147127-20-6 or 143491-57-0 or 134678-17-4 or 106941-25-7 or 142217-69-4 or 134680-32-3 or 209216-23-9 or 137530-41-7 or...
143491-54-7 or 143491-57-0 or 147127-19-3).rn. (35417)

or/38-50 (49828)

(Meta Analysis or Controlled Clinical Trial or Randomized Controlled Trial).pt. (917026)

Meta-Analysis/ use mesz,cctr,coch,clhta (50071)

Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez (86913)

(meta analytic or metaanalytic or pooled analysis or systematic adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane or ((health technolog* or biomedical technolog*) adj2 assess*).ti,ab. (369668)

exp Random Allocation/ use mesz,cctr,coch,clhta or exp Double-Blind Method/ use mesz,cctr,coch,clhta or exp Control Groups/ use mesz,cctr,coch,clhta or exp Placebos/ use mesz,cctr,coch,clhta (344981)

Randomized Controlled Trial/ use emez or exp Randomization/ use emez or exp RANDOM SAMPLE/ use emez or Double Blind Procedure/ use emez or exp Triple Blind Procedure/ use emez or exp Control Group/ use emez or exp PLACEBO/ use emez (637332)

or/52-58 (3031904)

7 and 26 and 30 and 37 (605)

7 and 37 and 51 and 59 (515)

60 or 61 (1069)

limit 62 to yr="1995 -Current" (1050)

remove duplicates from 63 (789)

limit 64 to (editorial or letter or note or case reports or comment) [Limit not valid in CCTR,CDSR,CLHTA,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained] (44)

Case Report/ use emez (1939567)

64 not (65 or 66) (707)
Appendix 2. Study Flow Diagram

Records identified through database searching (n = 1050)

Additional records identified through other sources (n = 40)

Records after duplicates removed (n = 744)

Records screened (n = 744)

Records excluded (n = 606)

Full-text articles assessed for eligibility (n = 138)

Studies included in qualitative synthesis (n = 98)

Studies included in quantitative synthesis (meta-analysis) (n = 5)

Full-text articles excluded (solid organ, bone marrow, or hematopoietic stem cell transplant) (n = 40)