American Gastroenterological Association Institute
Technical Review on Prevention and Treatment of Hepatitis B
Reactivation During Immunosuppressive Drug Therapy

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Author disclosures: Perrillo: Consultant Gilead Sciences and Novartis
Gish: Consultant Gilead Sciences, Novartis, Abbvie, Merck, and Idenix
Falck-Ytter: Nothing to disclose

Author contributions: R. Perrillo, concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and critical revision of manuscript. Y. Falck-Ytter, concept and design, statistical analysis, interpretation of data, critical revision of manuscript; R. Gish, acquisition of data; analysis and interpretation of data; drafting and critical revision of manuscript.

Short Title: HBV Reactivation and Immunosuppressive drugs
Clinical Background

Hepatitis B reactivation (HBVr) is a potentially serious disorder that is frequently induced by chronic immunosuppressive drug therapy. HBVr is more often seen in HBsAg and anti-HBc-positive persons (hereafter referred to as HBsAg-positive) but also occurs in individuals with resolved infection as defined by a negative hepatitis B surface antigen (HBsAg) and a positive hepatitis B core antibody (anti-HBc). This clinical entity was first described nearly 50 years ago in the setting of cancer chemotherapy and kidney transplantation. While specific cellular immunologic mechanisms have not been fully elucidated, the initial event is thought to be a disruption in the ability of the host immune system to control hepatitis B virus (HBV) replication. The best predictor for 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 are persons with resolved infection who are HBsAg-negative but positive for antibody to hepatitis B core antigen (anti-HBc). 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 deoxyribonucleic acid (HBV DNA) that is most often associated with a hepatitis flare several weeks later as defined by an increasing ALT. Conventionally, reactivation is defined by both the level of change in HBV DNA and ALT. In HBsAg carriers this is often defined in the literature as either the de novo detection of HBV DNA or 10 fold (one log10) or greater increase in HBV DNA when compared to a baseline value before immune suppressive drug therapy. Hepatitis flare is frequently determined to be present when there is at least a two to three fold elevation in ALT above the patient’s baseline 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 upon demonstration of reverse seroconversion to HBsAg–positive status.

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

B-cell depleting agents have also become increasingly implicated in HBVr. These drugs are used in a variety of disorders including leukemias, non-Hodgkins 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 in which it is strongly recommended that all patients who are to undergo B-cell depletion therapy be initially screened for HBV and if positive referred to a specialist to evaluate the need for antiviral prophylaxis or close monitoring.

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 which are very similar to those presented in registration trials. Nephrotoxicity is a potential concern with long term use of tenofovir, but creatinine clearance rates in this large study were shown to remain stable over 4 years with <1% of patients having increases of 0.5 mg/dL.10

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 have thus prompted the publication of several screening and treatment guidelines for patients who are to undergo chronic immunosuppressive drug therapy. There are 4 major sets of screening recommendations including those by the Centers for Disease Control (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).13-14 These guidelines vary in the type of screening tests recommended and the indications for prophylactic antiviral therapy, but each endorses HBsAg and anti-HBc 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 which states 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 immune suppressive drug therapy will continue as a serious health problem in the foreseeable future.

Another area which remains controversial is how long to continue prophylactic antiviral therapy. Recommendation has been made to continue treatment until 6 months after immune suppressive drug therapy is discontinued and longer (possibly until therapeutic endpoints are reached in the event that rituximab is used or in situations where the baseline HBV DNA level is greater than 2,000 IU.12-14 Unfortunately, because many patients who undergo immune suppressive therapy are not screened for HBV and thereby not given prophylactic antiviral therapy, guidelines about how long to treat are often non actionable 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 chronic immunosuppressive therapy. Physician surveys have indicated that routine screening is done by 20-40% of oncologists, 40% of dermatologists, and 70% of rheumatologists.16-18 At the current time there are no reliable data with regard to the frequency of screening by gastroenterologists or other specialists who use immunosuppressive therapies. However, in the last decade, the treatment of inflammatory bowel disease has been marked by increasing use of TNF inhibitors such as infliximab and several other biologic agents are newly available19 making this a relevant issue to address with gastroenterologists as well as other stakeholders.

Objectives of Current Paper
The primary purpose of the current paper is to provide a technical review and critical update of the topic of hepatitis B reactivation due to immune suppressive drug treatment. This review will focus on the results of clinical studies with the most frequently used oncologic therapies and on those biologic agents
which are either currently in use or soon to find use in various medical specialties. The review will not
discuss other immunosuppressive states that can shape the natural history of hepatitis B, such as co-
infection with human immunodeficiency virus infection, nor will it 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 treatments has been given high priority
by the AGA Institute. This is a two-step process in which above mentioned technical review of the area
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
HBV reactivation and the degree to which intervention can be anticipated to improve clinical
outcomes. This was accomplished using a set of predetermined PICO (Patient Intervention Comparison
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. HBV
reactivation is defined in this document as either the de novo appearance of HBV DNA in an individual
previously known to have non-detectable HBV DNA or a 10 fold or greater increase in level when
compared to a baseline value. This virologic definition does not require concomitant ALT elevation.
Permissible surrogates were new detection of HBsAg or HBeAg. Flares of hepatitis due to HBVr are
defined as an ALT elevation of at least 3 times the baseline 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 EMB); Embase 1980 to
2013 week 35; Ovid Medline. We applied a search filter for systematic reviews, meta-analyses, and
health technology assessments for the questions on the use of antiviral therapy.

The primary search was accessed in July to September of 2013 and included all articles up to 1998 that
were using the search terms of hepatitis B, HBV reactivation, anti-HBc, rituximab, immunosuppressive
therapy, cancer chemotherapy, biologic modifiers, antiviral prophylaxis, lamivudine, entecavir,
telbivudine, and tenofovir (See Appendix 1 for search strategy). The initial search revealed 744
publications and their corresponding titles and abstracts. The authors discarded 606 publications by
sequentially examining the titles and then abstracts, and if applicable, after full text articles were
retrieved. Reasons for exclusion were inappropriate content such as relevance to solid organ
transplantation or antiviral therapy in cohorts who were not taking immune suppressive drug therapy.
We also excluded articles dealing with 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 trial flow diagram).

Major databases such as MEDLINE and conference reports were also searched by the authors for studies which addressed the baseline risk for HBVr and outcomes of interest in defined populations. Prevalence studies were not included in the final analysis of data 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 thought 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 the GRADEpro software. According to GRADE criteria, evidence from randomized, controlled clinical trials (RCTs) would start at high quality but rated down in the presence of serious risk of bias, inconsistency or heterogeneity, indirectness, imprecision and potential publication bias. Evidence from observational studies would start at low quality but were eligible to be rated up in the presence of large effect size. Observational studies were considered to be primarily helpful in the determination of baseline risk for HBVr and providing additional information on patient outcomes.

**Formulation of Patient Intervention Comparative Outcome (PICO) Questions**

PICO questions were devised by the authors and approved for further study by the AGA governing board in July of 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 above (Table 1). The following clinical outcomes were considered critical or important for decision making: 1) Severity of hepatitis; 2) disease morbidity, 3) resource utilization including the need for hospitalization; 4) liver related mortality; and 3) interruption of cancer chemotherapy or other immunosuppressive drug treatment (Table 1).

**Extraction of data and analytic approach**

Numerator and denominator for each critical and important outcome were extracted from each study using pre-tested data extraction sheets listing acceptable definitions for outcomes such as HBVr, hepatitis, liver failure, liver-related mortality and chemotherapy interruptions. When possible, pooled RR was calculated for each outcome using the Mantel-Haenszel random effect model in RevMan 5.2. Funnel plots were inspected for heterogeneity in addition to formal analysis of heterogeneity (chi-square, p<0.1) and residual heterogeneity that was not explained by chance (I-squared). The number of studies were insufficient to formally test for funnel plot asymmetry to detect possible publication bias.

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

As well done cohort studies from well-defined populations (e.g., cancer or rheumatic disease populations) may provide accurate estimates of baseline risks of HBV reactivation, and the risk of reactivation is markedly different based on the patient’s baseline HBV serologies, 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-done 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].

**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 randomized, controlled trials and 25 observational studies by either 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 immune suppressive drug therapy which is consistent with a state of poorer immunologic control over viral replication prior to immune suppression. The baseline risk is also determined in part by the potency of the immunologic drug suppressive 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 Immune Suppressive Medications**

Answering any of the testing or intervention PICOs requires knowledge of the extent to which an immunosuppressive drug can be anticipated to cause reactivation of hepatitis B. The authors classified drugs as either 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 (e.g., azathioprine), yet the literature either did not describe use of the drug to be the sole agent responsible for HBVr (e.g., reactivation occurred mostly or exclusively in combination with corticosteroids) and there was a lack of significant number of post-marketing reports. Use of a low risk drug is anticipated to result in HBVr in less than 1% of cases for all drugs in this category and substantially less than 1% with most agents. The authors designated moderate risk for those drugs in which based on the literature it could be anticipated that more than 1% but less than 10% of cases would develop HBVr. High risk drugs were considered to be those in which the anticipated frequency of HBVr is above 10%. Drugs which are in the same class as other high risk drugs but in which there were no defined instances of HBVr in the literature or FDA AERS were considered by the authors to be provisional high risk.

**Azathioprine**

The literature search did not reveal any reports of HBV reactivation with maintenance azathioprine monotherapy such as occasionally may be used 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 anti-HBs concentration that provides humoral immunity.

Early studies supported that azathioprine may have a permissive role on HBV replication by assessment of serum levels of core antigen, but these investigations antedated methods for detection of HBV DNA in serum or tissue and did not describe elevation in 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 with concomitantly treated with glucocorticoids.

In summary, despite longstanding 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 less than 1% and only moderate uncertainty it is less than 0.1%. The effects of high dose therapy alone (for example, 2.5 mg per kg or greater) cannot be evaluated by the available data.

6-Mercaptopurine

This is an active metabolite of azathioprine and the effects on the immune system are considered to be similar to the parent drug. The literature search did not reveal any cases where 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 less than 1% of cases and substantially less than 0.1% in patients who are HBsAg-negative but anti-HBc-positive.

Methotrexate

Methotrexate has received widespread use and there are more cases reported of HBVr that have been attributable to this agent than any of the other traditional immunosuppressives. However, all but three of these reports involved other immunomodulatory agents as well such as monoclonal antibodies or corticosteroids. In a frequently cited case of methotrexate induced HBVr, withdrawal of low dose therapy (7.5 mg) was shown on two occasions to be associated with sudden increases in serum aminotransferase levels. 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 hepatocyte necrosis 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 and subsequent 10 fold elevation in ALT. The patient had low level anti-HBs before initiation of methotrexate which disappeared followed by HBsAg seroreversion. Initiation of entecavir therapy allowed continued treatment with methotrexate and the patient recovered uneventfully.

Two of the three cases of HBVr on methotrexate monotherapy were associated with an increase in serum aminotransferase levels upon sudden discontinuation of the drug which suggests a rebound in immunological 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 the literature where HBVr was attributable to this agent when used alone.
Based on these findings there is little uncertainty that it causes reactivated hepatitis B in less than 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 were harmful in hepatitis B first occurred in the mid 1970s when it was demonstrated that HBsAg-positive patients with chronic hepatitis given corticosteroid therapy less often reached histological and biochemical endpoints when compared to disease matched HBsAg-negative counterparts.\(^{35}\) A few years later a placebo-controlled study demonstrated that long term 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.\(^{36}\) It was later shown that the HBV genome contains a transcriptional regulatory element (glucocorticoid responsive element) that is activated by corticosteroids.\(^{37}\) Thus, corticosteroids enhance viral replication by two potential mechanisms: depressed cytotoxic T cell function and direct stimulation of an HBV genomic sequence.\(^{37}\)

**Glucocorticoid withdrawal or pulse therapy.** Clinical studies showed that a marked increase in viral replication (as evaluated by DNA polymerase activity) and AST flare often occurred when prednisone was given in a decremental fashion over 12 weeks.\(^ {38}\) The increase in viral replication preceded AST flares by several weeks, and the AST values reached peak levels several weeks after corticosteroids were discontinued, a pattern consistent with HBVr. Investigators at the National Institutes of Health subsequently demonstrated that a 4 week course of prednisolone often resulted in prolonged reactivation of hepatitis B and worsened liver histology.\(^ {38}\) Increases in serum HBV DNA accompanied by flares of ALT have been shown to occur in 30 to 70% of patients in which a short course of corticosteroid therapy preceded either alpha interferon or lamivudine.\(^ {39-41}\) In one study sustained virologic response correlated with induction of Th1 helper cell activity and increased cytotoxic T cell function.\(^ {41}\) 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.\(^ {38-41}\)

The data that a short tapered regimen of glucocorticoids can result in HBV DNA reactivation appears robust because of similar selection criteria and consistent reporting in a fairly homogenous group of patients with chronic hepatitis B. It should be noted that each of these studies enrolled patients with HBeAg-positive chronic hepatitis B, however, 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 HBsAg-negative but anti-HBc-positive, and HBVr has not been reported in HBsAg-positive patients given glucocorticoids for two weeks or less.

**Chronic glucocorticoid therapy.** The literature review did not reveal cases of HBVr that were induced by maintenance corticosteroid monotherapy for chronic inflammatory disorders. It did, however, provide some information on the occurrence of HBVr during monotherapy for patients with asthma or chronic obstructive pulmonary disease. In a retrospective study 198 patients were either treated with inhaled corticosteroids (n = 126) or systemic corticosteroids (n = 72). Eleven percent of the latter developed HBVr as compared to 3.2% of the patients treated exclusively with inhaled corticosteroids (Odds Ratio of 3.8, 95% CI: 1.1-13.1, P =.03).\(^ {42}\) The investigators found that continuous use of systemic treatment for 3 months or greater was associated with more episodes of HBVr than intermittent treatment as was
continuous dosing at 20 mg or greater daily compared to lower doses. Due to the small sample size neither of these comparisons reached statistical significance. In a small randomized, controlled comparison of two chemotherapy regimens for non Hodgkins lymphoma, with the only difference being the use of high dose prednisolone in one, the cumulative incidence of HBVr at 9 months after starting chemotherapy was significantly greater in the steroid-containing regimen (73% men versus 38%, p = 0.03). 43

Our review did not reveal any reports of HBVr following chronic intraarticular injection of corticosteroids. However, unlike topical corticosteroids or ophthalmic administration, increased systemic levels of corticosteroids, adrenal suppression and a decrease in interleukins as well as TNF alpha levels have been observed after intraarticular administration. 44 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 there is a high degree of certainty that this would occur in substantially less than 1% of cases.

In conclusion, moderate doses of glucocorticoids given for 3 or more 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 chronic systemic corticosteroid therapy is at least 10% when used in HBsAg carriers. The risk of HBVr from chronic 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).

Tumor necrosis factor alpha inhibitors and other biologic agents

Each of the three commonly used TNF alpha inhibitors (etanercept, infliximab, and adalimumab) have been associated with HBVr. This is most likely explained by a class effect of these agents since TNF alpha 1 has been shown to be a first line of defense in viral infections. 45 Rates of HBVr with these agents have generally been reported to be lower than that observed with highly immunosuppressive cancer chemotherapy. Hepatitis B reactivation 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. 2 3 46 48 Most cases of HBVr have occurred in patients treated for rheumatic 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 calculate true proportions or rates. Also, many of the reported cases have been on other immunosuppressive agents, including prednisone, which might further augment the risk for reactivation. Overall, there is low confidence in the estimate of baseline risk for this class of immunosuppressive medications.

Infliximab

This is a chimeric monoclonal antibody to TNF alpha which has been used to treat 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 and in a second series, HBVr attributable to infliximab was shown to be more frequently associated with severe biochemical abnormalities. 2 49 Fatalities due to hepatitis B have been reported. 50 However, this seeming greater risk from infliximab is not a consistent finding and many of the reported cases of HBVr during infliximab therapy have been treated concomitantly with other immunosuppressive agents such as corticosteroids or methotrexate. 2 49 In addition, comparative risk
assessment between these agents are problematic when rates are derived from reported cases instead of well-done consecutive cohorts that can accurately define risk.

**Other TNF Alpha Inhibitors**

Several other TNF inhibitors (etanercept and adalimumab) have been linked to HBVr in small case series or individual case reports. Salvage therapy with antiviral therapy has been used successfully but the quality of the data on the risk for HBVr in HBsAg-positive and those individuals 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 alpha inhibitors and other biologic agents in patients with active or resolved hepatitis B, the data available from several large case series as well as data on file at the FDA indicate that TNF alpha inhibitors induce reactivation of hepatitis B. The percentage of patients who will develop HBVr with the more frequently used TNF alpha inhibitors cannot be absolutely defined at the current time but there is reasonable data to suspect that it is more than that described for traditional immunosuppressives and less than cancer chemotherapy, rituximab (see below), and glucocorticoids. A moderate level of confidence can be given to estimation that the risk for HBVr during anti-TNF monotherapy is between 1% and 10% in HBsAg carriers. The risk in individuals who are HBsAg-negative but anti-HBc-positive is considered to be lower (1%) due to the fact that 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 given for very extended periods.

**Other Biologic Agents**

**Abatacept**

This drug blocks co-stimulation 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, four HBsAg-positive patients given antiviral prophylaxis remained clinically stable whereas an additional four 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 were not known in most of the patients. Given the mechanism of action, it is likely that abatacept would be associated with reactivation rate that is greater than 1% but less than 10%, but due to the paucity of data there is little confidence in this estimate.

**Tyrosine kinase inhibitors**

These agents (imatinib and nilotinib) are specific tyrosine kinase inhibitors that are used in chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST). Several well documented case reports and small case series have demonstrated 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

This is a human monoclonal antibody that is directed to interleukin 12 and 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 reactivated; one was an inactive carrier and the other had HBeAg negative chronic hepatitis B. No reactivation was reported in 3 patients HBsAg-negative patients with anti-HBc. Given the mechanism of action, it is likely that ustekinumab would be associated with reactivation rate that is greater than 1% but less than 10%, but due to the paucity of data this estimate remains highly uncertain.

Natalizumab and Vedolizumab

These are two recently developed inhibitors to the cell adhesion molecule α4 integrin found on lymphocytes. They have been used in 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 kept and further information in HBV infected patients may become available in the future.

Further experience with these newer biologic 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 for reactivation risk. This risk could prove to be the same as in 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 two 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 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 this way 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 due to ofatumumab, but the specific treatment indication was not included. The discrepancy in numbers of cases is due to the long lead time since FDA approval of rituximab.

Rituximab is frequently added to CHOP therapy for non-Hodgkin’s 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 which are unlikely to be attributable to the
other oncolgic agents used for lymphoma. One is that reactivation events may occur as late as 12 months after rituximab is discontinued at a time when there are waning anti-HBs titers.\textsuperscript{59, 60} Another feature that differentiates this drug is a high rate of HBsAg seroreversion (25 to 40\%) in patients with anti-HBc who reactivate.\textsuperscript{61, 62} 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 who are to be placed on rituximab or ofatumumab need to be screened for HBsAg and anti-HBc and referred to a specialist for further evaluation about the need for virologic monitoring and antiviral therapy.\textsuperscript{61}

The consistency of reports of rituximab-induced HBVr provide a high level of confidence that this drug should be considered as high risk for HBVr. Although a precise estimate of HBVr rate in HBsAg-positive patients is unavailable, the available evidence suggest that the majority of patients will eventually develop HBVr and in severe cases may require liver transplantation.\textsuperscript{64}

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.\textsuperscript{65} Pooled baseline risk estimates from the control arm of a randomized trial.\textsuperscript{25} and from untreated cohorts of well-done observational studies.\textsuperscript{61, 66-69} revealed a reactivation rate of 16.9\% (95\% CI: 13.1\%, 21.9\%) (\textbf{Figure 2}).

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

\textbf{Disease Outcomes of HBV Reactivation}

The literature review allowed assessment of the baseline risk for HBVr as well as the outcomes of reactivated hepatitis B through 5 randomized controlled trials and 25 observational studies which met the criteria defined in the Literature Review section above. The randomized controlled studies compared antiviral prophylaxis to deferred treatment. The observational studies included patients who were not given antiviral therapy or provided deferred treatment once the diagnosis of reactivation was made. All patients entered into these studies were either HBsAg-positive or had serologic profiles consistent with resolved infection. These different patients groups will be separately analyzed under PICO 1, 2, and 3 below. Baseline risk and disease outcomes could be most clearly assessed in three types of malignancy: lymphoma, breast cancer, and hepatocellular carcinoma and bone marrow or hematopoietic stem cell transplant.

\textbf{PICO 1. Is antiviral prophylaxis needed for HBsAg-positive patients who will undergo immunosuppressive drug therapy (IDST)?}

\textbf{Lymphoma}

Non-Hodgkin’s 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 two randomized controlled clinical trials that compared prophylactic antiviral therapy started before or at the time of initiation of chemotherapy to deferred or on demand treatment. A total of 40 untreated HBsAg-positive were included in these
The majority of 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 using a real time PCR method. Among the 40 patients, 22 (55%) developed HBVr which was consistent between studies (53%, 55%), and 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, two of which occurred after discontinuation of prophylactic lamivudine therapy. None of these patients were treated with rituximab. Data on frequency of interrupted cancer chemotherapy were not reported in either study.

Three observational studies met the criteria for inclusion in the analysis of data. Collectively these studies included 88 HBsAg-positive untreated patients. None of these CHOP-treated patients were exposed to rituximab, and deferred antiviral therapy was begun when the diagnosis of reactivation was made in two 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 was not reported in any of these studies.

Breast Cancer

A total of 154 untreated HBsAg-positive patients with breast cancer were derived from three studies, one of which was a randomized, controlled clinical trial of prophylaxis versus deferred treatment. 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 two 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. In one study a significant association between HBV reactivation and premature discontinuation or delay of chemotherapy was observed with a relative risk of 2.12 and a confidence interval of 1.11-4.03, P = 0.019. The same investigators reported early termination of cancer chemotherapy in 35% of the patients with HBVr.

Hepatocellular Carcinoma

A number of studies over the past 10 years have attempted to characterize the risk that HBsAg-positive patients have for HBVr from local ablation, surgical resection, or systemic chemotherapy treatment of HCC in HBsAg-positive patients. The fact that transarterial chemoembolization (TACE) can precipitate HBVr has been well documented and it attributed to systemic exposure to chemotherapy by means of arteriovenous shunting. Five studies, including one randomized controlled trial of prophylactic versus on demand antiviral therapy, included HBsAg-positive patients. Collectively, these studies incorporated a total of 545 untreated HBsAg carriers in which 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 and associated with early termination of TACE in 3 (20%) of patients. 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 greater than $10^4$ copies (2,000
IU/ml) independently predicted HBVr (P = 0.046). The borderline significance of this observation was probably based on the small number of events.

In the largest of the observational studies 320 patients had TACE with epirubicin and/or mitomycin. HBeAg was positive in 20.3% of patients at baseline and HBV DNA was log 10 IU. Fifty-six (17.5%) of these patients reactivated after one or more courses of TACE of which only 26 (46%) had reactivation-related hepatitis. Rates of HBVr were significantly lower (1.5%, p < 0.0001) 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 at baseline between the two groups.

In a more recent study by the same group of investigators who conducted the randomized, controlled trial above, 119 patients were treated with TACE using either adriamycin or a more immunologic suppressive combination of epirubicin and cisplatin. These patients were compared to 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 to local ablation as the reference population, the adjusted hazard ratio for TACE with adriamycin was 2.45 (confidence interval of 0.92-6.49); for TACE with combination agent therapy 4.19 (CI 1.35-13.00), and for TACE with the two drug regimen and radiotherapy 10.17 (CI 3.78-27.40). While the authors mention that 10 patients with HBVr developed hepatic failure, it was not mentioned which group they were in. 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 individuals in who were waiting to receive therapy for hepatocellular carcinoma. HBeAg was detected at baseline in 46 (67.1%) of TACE-treated patients and 30% of the previously non-treated patients. The follow up in controls was short (mean 59.4 ± 56 days). There was no difference in HBVr events between the TACE-treated (4.3%) and controls 2 (10%). Hepatitis due to HBVr subsided spontaneously without treatment in one month in most of the patients. Unfortunately, the investigators used an insensitive technique for the assessment of quantitative HBV DNA (Digene II, Digene Corp., USA) with a lower limit of sensitivity of 141,000 copies/mL. This provided an opportunity for underestimation of HBVr frequency in individuals with low baseline HBV DNA.

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 a total of 37 patients (36%) developed HBVr which was considered to be severe in 23 (62%). Reactivation was associated with jaundice in 18 (49%) and disruption in chemotherapy resulted in 32 (86%), including 26 who had premature discontinuation. The most striking finding in this study was the high death rate (n = 12, 30%) 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 a high risk of 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 anti-rheumatic agents (DMARDs) or TNF alpha inhibitors. In a large series from Spain, nearly 40% of HBsAg carriers demonstrated reactivation when placed on chronic TNF inhibitor therapy, but this figure represented pooled data from multiple centers and many patients received complex immune suppressive 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 non-detectable HBV DNA by PCR at baseline but a 3 to 4 log increase in HBV DNA during treatment. Hepatitis did not occur in either. In a second study from Japan, HBVr occurred in 2 out of 5 HBsAg carriers treated with TNF alpha 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 DMARDs and several were started on antiviral therapy because of elevated baseline HBV DNA and a positive HBeAg status.

**PICO 2. Is antiviral prophylaxis needed for HBsAg-negative, anti-HBc-positive patients who will undergo ISDT?**

**Lymphoma**

Four hundred and one patients who were HBsAg-negative but anti-HBc-positive were included in the analysis. None were given prophylactic antiviral therapy. The mean frequency of HBVr in the studies was considerably lower in these patients when compared to the data derived above in HBsAg carriers (mean of 12.2% with range of 3.2% to 23.8%) (Table 3). Death due to reactivation was very uncommon, but occurred. Most of these patients were treated with rituximab in addition to CHOP or other combination regimens. In a controlled comparison between RCHOP and CHOP, a significantly greater number of patients given RCHOP developed HBVr (5 of 21 versus 0 of 25, respectively, \( P = .015 \)).

**Hepatocellular Carcinoma**

The baseline risk for 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. 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 to 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 all had at least a one log increase in HBV DNA at the time HBVr was detected (range 1.6 x 10^3 to 6/4 x 10^6 IU per mL). Hepatitis was mild in all cases and improved with lamivudine. 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 for HBVr in HBsAg-negative, anti-HBc-positive patients with rheumatic disease was described in relatively few studies. In a study involving 188 untreated patients given a variety of disease modifying anti-rheumatic agents, 2 (1%) developed HBVr. Both cases had been taking 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. This case was classified as severe, but the patient recovered uneventfully after entecavir was started allowing her to continue on methotrexate. In a third study 0 of 67 patients developed reactivation during complex immunotherapy with TNF alpha inhibitors often taken in combination with methotrexate or
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 to 56). These data suggest that the risk of HBVr in anti-HBc-positive patients is considerably lower than that found in serologic counterparts given cancer chemotherapy.

In summary, when compared to HBsAg-positive patients, individuals who are HBsAg-negative, anti-HBc-positive appear to have a lower risk of HBVr when exposed to moderate risk immune suppressive 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 immune suppressive drugs which are in the low risk category. By 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 randomized controlled trials that compared antiviral therapy (lamivudine in 4, entecavir in 1) to deferred treatment (after HBVr was diagnosed) were considered to be highest quality evidence available. These five 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 confined the analysis to those who were HBsAg-positive. The pooled effect of antiviral prophylaxis was calculated as the Risk Ratio (RR) 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 five studies to meaningfully evaluate, pooled estimate showed a RR of reactivation of 0.13 (95% CI: 0.06; 0.3) and a RR of HBV associated hepatitis of 0.16 (95% CI: 0.06; 0.42) across varying baseline risks (including varying HBV serologies) (Figure 1; panel 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 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 reduced chemotherapy treatment interruptions).

In summary, HBsAg-positive and anti-HBc-positive (HBsAg-negative) patients, when exposed to high risk immunosuppressive agents, 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 flares per 1000 (from 290 fewer to 470 fewer). Even if the baseline risk is 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 alpha 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 patients treated (from 35 fewer to 47 fewer) and 42 fewer hepatitis flares 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 1,000 (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 above drug risk calculations, antiviral prophylaxis with immunosuppressive agents in the low risk group (e.g., azathioprine) would result in only 1 fewer reactivations per 1000 (from 1 fewer to 1 fewer) when assuming the baseline risk to be 0.1%. See table 4: GRADE evidence profile for PICO 1 and 2.

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 above studies had detectable anti-HBs.\textsuperscript{51, 66-69, 71} Among these 252 patients who were anti-HBs positive, HBV reactivation was observed in 11 (4.3%), a frequency which is only slightly lower than 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 these studies. Further studies have been done in patients given RCHOP which suggest a relationship exists between 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 RCHOP. Eight patients lost anti-HBs and one developed “reverse” HBsAg seroconversion (or seroreversion). None of 10 cases with pre-treatment anti-HBs above 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% confidence interval, 0.000-0.302, \(P = 0.014\)).\textsuperscript{72}

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 titers or level affects the risk of reactivation with rituximab. Therefore, decision on using antiviral prophylaxis should not 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 first or second generation nucleos(t)ide agents?

Five oral nucleos(t)ide analogue drugs are currently approved for HBV treatment (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 HBV reactivation and has been shown in systematic reviews to reduce the risk of HBVr.\textsuperscript{82} However, lamivudine is associated with a high rate of drug resistance when used beyond one year. Rates of lamivudine resistance of 20% at one year and 30% at two years have been reported in non-immunocompromised patients and would be anticipated to be even higher in patients on immune suppressive drug treatment.\textsuperscript{83} Due to the fact that cancer chemotherapy regimens often fall short of one year and lamivudine resistance is very 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.\textsuperscript{84-87} The literature search, however, revealed only a few studies comparing the effectiveness of these two 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 randomized controlled trial of entecavir versus lamivudine prophylaxis has been reported in abstract form.\textsuperscript{85} 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 (HBVr 30% for lamivudine versus, 6.6% for entecavir, \textit{P} = 0.001). Moreover, chemotherapy disruption due to hepatitis B also occurred significantly less frequently in patients given entecavir (18.3% versus 1.6%, respectively, \textit{P} = 0.002). The number of cases in which prophylaxis has been attempted with telbivudine or adefovir studies in some of these studies is too small to evaluate and indirect evidence have shown that resistance development is of concerns which makes those drugs less suitable.

Collectively, these studies provide some useful data but the analysis is complicated by non-randomized enrollment, physician preference in treatment assignments, inconsistencies in reporting pre-chemotherapy HBV DNA, and other features which 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 virologic breakthroughs due to lamivudine-resistant 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 and was less common in patients who were given lamivudine as prophylactic as opposed to deferred therapy (22.9% versus 59.1%, \textit{P} < 0.001).\textsuperscript{86}

In summary, based on a single, head-to-head randomized, controlled study of entecavir vs. lamivudine, it appears that antivirals with high barrier to resistance given for prophylaxis confer a higher efficacy against HBVr (RR 0.22, 95% CI 0.08; 0.61) which is due to a significantly lower rate of virologic 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 antivirals having 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 disruption 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.\textsuperscript{86} 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 to lamivudine. \textbf{See Table 6: GRADE evidence profile for PICO 4.}

**PICO 5. Is HBV DNA monitoring followed by on demand antiviral therapy associated with different outcomes than prophylactic antiviral therapy?**

This PICO question addresses the consideration that regular monitoring of HBV DNA 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 randomized, controlled trials that compare both means of drug administration.\textsuperscript{74-28} These have been described in detail above. When taken collectively, the observational studies included in this review provide data on a large populations 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 HBV reactivation, and perhaps most importantly for addressing this question, inconsistently report any outcomes other than the frequency of reactivation, severe elevation of ALT, and reactivation related death. Also, the existing studies differ somewhat in the regularity with which HBV DNA monitoring is carried out 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. Cost of routine HBV genomic testing is a secondary but important practical issue and one which would need addressment before implementation of a defined policy.

PICO 6. Is treatment of established HBVr with third generation nucleos(t)ide agents more effective than first or second generation drugs?

The literature review did not allow direct comparison of the clinical effectiveness of third generation oral antivirals with earlier generation antivirals in patients who developed HBVr during immune suppressive 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. Moreover, both drugs were well tolerated.

There is emerging data on the use of entecavir in patients who reactivate while on cancer chemotherapy for hematological malignancies, and although trials are ongoing the authors came upon no published reports of tenofovir in this setting.

In non-immunosuppressed populations, entecavir is associated with a significantly higher rate of non-detectable HBV DNA when compared to lamivudine. What is likely to be of greater importance when making the decision as to which agent to use for antiviral prophylaxis, however, is the much higher rate of drug resistance with lamivudine, particularly when the need for therapy extends beyond 6-12 months. The duration of antiviral therapy is often prolonged in individuals who reactivate due to a number of factors including the severity of clinical presentation and the need for continuing immune suppression drug therapy long-term (well beyond 6 months). Moreover, the use of immune suppressive 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 non-immunosuppressed patients and this data combined with its greater antiviral potency makes 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 to entecavir (and by inference, greater than lamivudine) and the virtual absence of drug resistance over 6 years of continuous use. None of the currently used oral antivirals have interactions with drugs metabolized by the cytochrome P450 3A4 pathway. The only dose adjustment of 3rd generation HBV medications is when renal insufficiency is present. See Table 7: GRADE evidence profile for PICO 6.

PICO 7. Should patients who will undergo long term immune suppressive drug therapy be screened for HBV before starting?

An appropriate answer to this question requires clear understanding of the downsides as well as upsides of routine screening in patients who are to undergo immune suppressive drug therapy. The downsides include the emotional concerns of patients engendered by the diagnosis of either active or resolved HBV infection that may impact 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 for HBsAg. The risk of a false positive 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 tests 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 hepatitis B reactivation revealed compelling data to indicate that patients who are found to be HBsAg-positive as well as those individuals with resolved infection exposed to high risk drug regimens have a considerable risk for HBV reactivation and its health consequences, and this risk for HBVr can be greatly reduced by prophylactic antiviral therapy. Once HBV reactivation occurs, it has implications for serious medical outcomes, interruption in medical (e.g., cancer) therapy and increased resource utilization. Many of these patients are not candidate 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 prior to initiation of immune suppressive drug therapy.

The cost of routine HBV screening for patients who are to undergo immune suppressive drug therapy needs consideration in making a general recommendation on whether routine screening is a medically wise policy. Thus far, there is scant data on cost effectiveness of screening all patients who will undergo immune suppressive drug therapy. However, in a decision model study in lymphoma patients treated with CHOP and rituximab, a strategy of screen-all was a dominant strategy when compared to screening only patients who were at high risk vs. 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 individuals 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 immune suppressive drug regimens or equally importantly when moderate risk drugs are used.

In summary, the downsides of testing for hepatitis B are limited and the choice of screening prior to immune suppressive drug treatment hinges on being able to define a pre-test 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 (>10%). In situations where the risk is low (<1%), however, it is reasonable to conclude that the need for screening be determined according to the recommendations outlined by the Centers for Disease Control and Prevention and the U.S. Preventive Services Task Force, which reflects the anticipated population prevalence. In addition, screening for hepatitis B may even be cost-effective in the very low-risk population (<0.3%; general U.S. population).
Limitations of Current Evidence and Future Directions

This review has demonstrated 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 to a baseline sample determination. However, the general low rate of screening for hepatitis B in patients about to undergo immune suppressive drug therapy limits the ability to apply these criteria. One alternative that has been used in some studies, therefore, 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 HBV reactivations 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 HBV reactivation and in particular, at the earliest stage possible. For these reasons, future studies should only use a PCR based assay that is able to detect 25 or less IU of HBV DNA per mL.

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 (silent), (2) increased ALT without jaundice (mild), (3) increased ALT and concomitant jaundice (moderate), (4) jaundice and signs of liver failure (severe); and (5) fatal. A simple system of grading such as this would allow investigators the ability to perceive how often ALT abnormalities are absent when virologic criteria have been satisfied and further define the relationships between biochemically “severe” hepatitis and emergence of liver failure.

The review also disclosed a number of areas where critical outcome data on HBVr are not being reported. The available data focuses 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, it begs exploration of the more numerically dominant but underreported issue of how interruption of chemotherapy due to HBVr affects cancer progression and cancer-free survival. If meaningful differences could be shown between patients who have early chemotherapy discontinuation due to HBVr, those who reactivate but complete chemotherapy with slight or no delay, and individuals who neither reactivate 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 being 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 US 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 persons, 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 individuals have frequent HBV DNA monitoring unless they are on prophylactic antiviral therapy.\textsuperscript{12-14} 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 HBV DNA 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.\textsuperscript{22} Should HBV DNA testing be done 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 non-malignant disorders because of differences in the baseline risk that HBVr will occur during immune suppressive drug treatment? What are the cost implications for HBV DNA monitoring indefinitely as might be needed in patients who take biologic agents long-term 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 biologic agents for non-malignant 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 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 individuals 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 has 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.\textsuperscript{33} In addition, cost-effectiveness studies are needed with the large group of patients who are currently taking moderate risk drugs such as TNF alpha 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 that hepatitis B vaccination has in preventing HBVr is an area that has been somewhat neglected. However, it is conceivable that higher neutralizing antibody titers prior to immune suppressive therapy may offer some protection when B cell depleting agents are used in patients with resolved infection. To be most effective, it is required that vaccine delivery occur in advance of immune suppression. It remains an open question, however, as to whether a single booster dose given to those known to have been previously vaccinated successfully or with documented resolved hepatitis B might help protect them against HBVr during B cell depleting drug therapy. This could be studied relatively easily.

In summary, the review of the literature on this topic indicates that much more study needs to be given to improving the health outcomes of patients who are to undergo immune suppressive 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.
Table 1: PICO questions (Patients/Populations, Intervention, Comparator, Outcomes)

<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. Do HBsAg-positive patients who will undergo ISDT* need antiviral prophylaxis?</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. Do HBsAg-negative, anti-HBc-positive patients who will undergo ISDT require</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>antiviral prophylaxis?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Does the presence of anti-HBs in HBsAg negative, anti-HBc-positive patients</td>
<td>Patients with anti-HBc and anti-HBs who will undergo ISDT associated with low, moderate, or high risk</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>confer additional protection against reactivation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Is prophylactic treatment with third generation nucleos(t)ide analogues more</td>
<td>Any patient having antiviral prophylaxis for hepatitis B</td>
<td>Lamivudine Adeovir Telbivudine</td>
<td>Entecavir Tenofovir</td>
<td>HBVr, liver disease morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>effective than first or second generation agents?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Is HBV DNA monitoring followed by on demand antiviral therapy associated with</td>
<td>Any patient treated with ISDT (malignant and non-malignant 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>different outcomes than prophylactic antiviral therapy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Is treatment of established HBVr with third generation nucleos(t)ide agents</td>
<td>Delayed treatment patients</td>
<td>Lamivudine Adeovir Telbivudine</td>
<td>Entecavir Tenofovir</td>
<td>HBVr, liver disease morbidity and mortality; treatment interruption; resource use</td>
</tr>
<tr>
<td>more effective than first or second generation agents?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Should patients who will undergo long term ISDT* be screened for HBV before</td>
<td>Patients who will undergo more than 4 weeks of ISDT for malignant and non-malignant 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>
<tr>
<td>starting?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ISDT = immune suppressive drug therapy
*Search included lamivudine, emtricitabine, entecavir, tenofovir, adefovir, telbivudine or combination therapy
†Includes liver transplantation for patients without malignancy
Table 2. Risk groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>HBVr Drug Risk Estimates</th>
<th>Potential Disorders for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBsAg positive or anti-HBc positive</td>
<td></td>
</tr>
<tr>
<td><strong>Low risk group</strong> &lt; 1%</td>
<td><strong>Traditional immunosuppressive agents:</strong> azathioprine, 6-mercaptopurine, methotrexate</td>
<td>Inflammatory bowel disease, psoriasis, sarcoidosis, autoimmune liver disease, arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: &lt; 1% (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: &lt; 1% (A)</td>
</tr>
<tr>
<td></td>
<td><strong>Intraarticular corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: &lt;&lt; 1% (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: &lt;&lt; 1% (A)</td>
</tr>
<tr>
<td></td>
<td><strong>Corticosteroids for ≤ 1 week</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: &lt; 1% (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: &lt; 1% (A)</td>
</tr>
<tr>
<td><strong>Moderate risk group</strong> 1% to 10%</td>
<td><strong>TNF alpha inhibitors:</strong> (etanercept, adalimumab, infliximab)</td>
<td>Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: 1-10% (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: 1% (C)</td>
</tr>
<tr>
<td></td>
<td><strong>Other cytokine inhibitors and integrin inhibitors</strong> (abatacept, ustekinimab, natalizumab, vedolizumab)</td>
<td>Plaque psoriasis, inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: 1-10% (C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: 1% (C)</td>
</tr>
<tr>
<td></td>
<td><strong>Tyrosine kinase inhibitors</strong> (imatinib, nilotinib)</td>
<td>Chronic myelogenous leukemia, gastrointestinal stromal tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: 1-10% (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: 1% (C)</td>
</tr>
<tr>
<td><strong>Corticosteroids (≥ 4 weeks)</strong></td>
<td></td>
<td>Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: 1-10% (C) (low dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: 1-10% (C) (any dose)</td>
</tr>
<tr>
<td><strong>High risk group</strong> &gt; 10%</td>
<td><strong>Corticosteroids (≥ 4 weeks)</strong></td>
<td>Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: &gt;10% (B) (high dose*)</td>
</tr>
<tr>
<td></td>
<td><strong>Anthrapyline derivatives such as doxorubicin and epirubicin</strong></td>
<td>Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias; transarterial chemoembolization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: 15-30% (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: &gt;10% (B)</td>
</tr>
<tr>
<td></td>
<td><strong>B cell depleting agents such as rituximab and ofatumumab</strong></td>
<td>Lymphoma/leukemia, rheumatoid arthritis, idiopathic thrombocytopenic purpura, cryoglobulinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg pos/anti-HBc pos: 30-60% (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HBsAg neg/anti-HBc pos: &gt;10% (A)</td>
</tr>
</tbody>
</table>

Confidence in evidence:
- (A) High confidence that the estimate lies within group risk boundaries
- (B) Moderate confidence that the estimate lies within group risk boundaries
- (C) Little or no confidence that the estimate lies within group risk boundaries

*High dose steroids: prednisone ≥ 20 mg or equivalent
### Table 3. Hepatitis B Reactivation in 401 HBsAg-Negative, Anti-HBc-Positive Patients Treated with Chemotherapy for Non-Hodgkins 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>Chemo-therapy interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lok&lt;sup&gt;71&lt;/sup&gt; 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&lt;sup&gt;61&lt;/sup&gt; 2009</td>
<td>46</td>
<td>Yes, some</td>
<td>RCHOP: 5 of 21 (23.8)&lt;br&gt;CHOP: 0 of 25</td>
<td>5 (10.8)</td>
<td>1 (2.1)</td>
<td>1 (2.1)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Matsue&lt;sup&gt;69&lt;/sup&gt; 2010</td>
<td>56</td>
<td>Yes, all</td>
<td>5 (8.9)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>5 (8.9)</td>
<td>1 (1.7)</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td>Cheung&lt;sup&gt;66&lt;/sup&gt; 2011</td>
<td>10</td>
<td>Yes, in 4</td>
<td>1 (10)</td>
<td>1 (10)∞</td>
<td>0</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td>Koo&lt;sup&gt;68&lt;/sup&gt; 2011</td>
<td>62</td>
<td>Yes, all</td>
<td>2 (3.2)</td>
<td>2 (3.2)</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Hsu&lt;sup&gt;≥7&lt;/sup&gt; 2013</td>
<td>143</td>
<td>Yes, all</td>
<td>27 (18.9)</td>
<td>10 (6.9)</td>
<td>0</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td>Huang&lt;sup&gt;≥7&lt;/sup&gt; 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>

* All treated successfully treated with entecavir
π All were occult HBV carriers and low level HBV DNA was detected at baseline
∞ Patient was treated with rituximab
Table 4. GRADE evidence profile for PICO 1 and 2: Should antiviral prophylaxis vs. no prophylaxis be used for prevention of HBV reactivation with immunosuppression?
Source: own analysis (see text for study details and forest plot in figure 1)

<table>
<thead>
<tr>
<th>Participants (studies) Follow up</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Overall quality of evidence</th>
<th>Study event rates (%)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV reactivation</strong>* (CRITICAL OUTCOME; assessed with: HBV DNA detection or increase by 10 fold; negative to positive HBeAg; neg to positive HBsAg)</td>
<td>276 (5 studies) 12-18 months</td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td>⊕⊕⊕⊖ ⊕⊖⊖⊖ MODERATE¹ ² ³ due to indirectness</td>
<td>50/137 (36.5%)</td>
<td>5/139 (3.6%)</td>
<td>RR 0.13 (0.06 to 0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>50/137 (36.5%)</td>
<td>5/139 (3.6%)</td>
<td>RR 0.13 (0.06 to 0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>50/137 (36.5%)</td>
<td>5/139 (3.6%)</td>
<td>RR 0.13 (0.06 to 0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>50/137 (36.5%)</td>
<td>5/139 (3.6%)</td>
<td>RR 0.13 (0.06 to 0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>50/137 (36.5%)</td>
<td>5/139 (3.6%)</td>
<td>RR 0.13 (0.06 to 0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>50/137 (36.5%)</td>
<td>5/139 (3.6%)</td>
<td>RR 0.13 (0.06 to 0.3)</td>
</tr>
<tr>
<td><strong>HBV hepatitis flare</strong>* (CRITICAL OUTCOME; assessed with: ALT &gt; 3 x UNL or over 100)</td>
<td>276 (5 studies)</td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td>⊕⊕⊕⊖ MODERATE¹ ² ³ due to indirectness</td>
<td>31/137 (22.6%)</td>
<td>4/139 (2.9%)</td>
<td>RR 0.16 (0.06 to 0.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>31/137 (22.6%)</td>
<td>4/139 (2.9%)</td>
<td>RR 0.16 (0.06 to 0.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>31/137 (22.6%)</td>
<td>4/139 (2.9%)</td>
<td>RR 0.16 (0.06 to 0.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>31/137 (22.6%)</td>
<td>4/139 (2.9%)</td>
<td>RR 0.16 (0.06 to 0.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>no serious imprecision³</td>
<td>undetected</td>
<td></td>
<td>31/137 (22.6%)</td>
<td>4/139 (2.9%)</td>
<td>RR 0.16 (0.06 to 0.42)</td>
</tr>
</tbody>
</table>
Chemotherapy disruption (IMPORTANT OUTCOME)

<table>
<thead>
<tr>
<th>5 studies</th>
<th>500 flares per 1000</th>
<th>420 fewer flares per 1000 (from 290 fewer to 470 fewer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 between HBVr, followed by HBV hepatitis flare and subsequent liver failure and death, similar relative effects on those endpoints can be assumed.

1 Allocation concealment uncertain in 3 of 5 studies - not judged to be of sufficient severity to rate down; studies not blinded, but outcome objective - not rated down

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

3 Fragility may be present, but not rated down as the rating down for indirectness was borderline as well.
Table 5. Studies Using Entecavir Prophylaxis, Either Alone or Compared to Lamivudine

<table>
<thead>
<tr>
<th>Author, Ref no.</th>
<th>Number 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 87</td>
<td>123*</td>
<td>Lymphoma RCHOP in 70%</td>
<td>Multicenter, non-randomized controlled</td>
<td>18 (20.2) ∞</td>
<td>11 (12.4) ∞</td>
<td>One death due to LVD-resistance; 5 patients end chemotherapy early</td>
</tr>
<tr>
<td></td>
<td>89 LVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 ETV</td>
<td></td>
<td></td>
<td>4 (11.8) ∞</td>
<td>0 ∞</td>
<td>Chemotherapy completed in all</td>
</tr>
<tr>
<td>Chen 84</td>
<td>40*</td>
<td>Hematological Malignancies RTX in 46% ETV vs 0% LVD</td>
<td>Retrospective drug use audit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 LVD</td>
<td></td>
<td></td>
<td>1 (7.1)</td>
<td>1</td>
<td>Virologic breakthrough in 1 during 2nd year of LVD</td>
</tr>
<tr>
<td></td>
<td>26 ETV</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>Hepatitis flare due to premature withdrawal of ETV</td>
</tr>
<tr>
<td>Huang 85</td>
<td>121</td>
<td>Lymphoma RCHOP in all</td>
<td>Randomized, controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 LVD</td>
<td></td>
<td></td>
<td>8 (13)</td>
<td>5 (8)</td>
<td>Chemotherapy interrupted in 11 (18.3%)</td>
</tr>
<tr>
<td></td>
<td>61 ETV</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>Chemotherapy interrupted in 1 (1.6%)</td>
</tr>
<tr>
<td>Study</td>
<td>Number</td>
<td>Treatment</td>
<td>Study Design</td>
<td>ETV</td>
<td>HBcα</td>
<td>Other Complications</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----</td>
<td>------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Kojima86</td>
<td>84</td>
<td>Lymphoma R CHOP in all</td>
<td>Prospective review</td>
<td>0</td>
<td>0</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 ETVδ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72 anti-HBcα</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (4.2)</td>
<td>1 (1.4)</td>
<td>Hepatitis due to monitoring failure</td>
</tr>
<tr>
<td>Kim88</td>
<td>127**</td>
<td>Lymphoma RCHOP in some</td>
<td>Retrospective multinational</td>
<td>30 (31.3)</td>
<td>Not stated</td>
<td>3 deaths due to hepatic failure; frequent virologic breakthrough</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>96 LVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31 ETV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 95% were HBsAg-positive. ** Physicians decided which drug to use based on clinical status and ability to pay for drug. ∞ Differences not statistically different. ¥ 15 chronic hepatitis B; 25 resolved infection. δ Includes 9 HBsAg-positive and 3 occult carriers. α All patients had HBV DNA monitoring during treatment and up to one year after chemotherapy was stopped.
### Table 6. GRADE evidence profile for PICO 4: Should antivirals with high barrier to resistance vs lamivudine be used for prophylaxis of HBVr in patients undergoing immunsuppression?1

**Source:** Huang et al.85 Presented at 2013 ASCO annual meeting. Data taken from slide set.

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (studies) Follow up</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>HBV reactivation (CRITICAL OUTCOME; assessed with: HBV DNA detection or increase by 10 fold; negative to positive HBeAg; neg to positive HBsAg)</td>
<td></td>
</tr>
<tr>
<td>121 (1 study) 40 months⁵</td>
<td>no serious risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV hepatitis flare (CRITICAL OUTCOME; assessed with: ALT &gt; 3 x UNL or over 100)</td>
<td></td>
</tr>
<tr>
<td>121 (1 study) 40 months⁵</td>
<td>no serious risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy disruption (IMPORTANT OUTCOME; assessed with: Either discontinuation or disruption of 7 days or more)</td>
<td></td>
</tr>
<tr>
<td>121 (1 study) 40 months⁵</td>
<td>no serious risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ The only RCT found used entecavir.
² There remains some uncertainty whether an improvement of this outcomes is consistently associated with improvement of patient-important outcomes as well when comparing prophylactic pre-emptive treatment to monitoring only followed by treatment when indicated. This is a borderline judgment.
³ Fragility present. Total number of events low and sample size low.
⁴ Relative risk not reported. RR was calculated using chi-square statistics in openepi (openepi.com). If zero events were reported, 0.5 events were added to be able to calculated RR.
⁵ 8.8 months to 63 months
Table 7. GRADE evidence profile for PICO 6: Should antivirals with high barrier to resistance vs lamivudine be used for established HBV reactivation?

Source: Liu et al.101; Woo G et al.102; Petersen J, Buti M.103; Chang TT et al.104; Kitrinos KM et al.92.

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong> (studies) Follow up</td>
<td><strong>Study event rates (%)</strong></td>
</tr>
<tr>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td><strong>failure of virologic response</strong> (CRITICAL OUTCOME; assessed with: undetectable HBV DNA)</td>
<td></td>
</tr>
<tr>
<td>2278 (7 RCTs) 62 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>viral resistance development at 5 years</strong> (CRITICAL OUTCOME)</td>
<td></td>
</tr>
<tr>
<td>183 (1 RCT follow-up study) 5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Although statistical heterogeneity was detected, each study included (both e-antigen negative and positive infections) demonstrated a superior effect of entecavir over lamivudine, making the detected heterogeneity clinically less relevant. Not rated down.

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

3 Comparable superior effects were demonstrated for tenofovir (indirect comparisons) in a network-meta-analysis: viral response tenofovir vs. lamivudine: odd ratio 23.3 (95% CI 6.2; 76). Woo et al 2010.

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

5 Assumed, based on observed frequency between entecavir and lamivudine cohorts.

6 Rate from Petersen et al. 2012 Other rates: 16% at year 1, 40% at year 2, 61% at year 3.

7 Estimated based reported rates.

8 Based on entecavir data (0.55% at 5 years). No detectable resistance has been reported after 6 years of tenofovir treatment in 347 e antigen negative and positive patients (Kitrinos et al. 2014).
Figure 1.

1.1 HBV reactivation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antivirals</th>
<th>control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>1.1.1 entecavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang 2013</td>
<td>1</td>
<td>41</td>
<td>7</td>
<td>15.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>41</td>
<td>39</td>
<td>14.4%</td>
<td>0.14 [0.02, 1.05]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 1.91 (P = 0.06)</td>
<td></td>
</tr>
</tbody>
</table>

1.1.2 lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antivirals</th>
<th>control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Lau 2003</td>
<td>0</td>
<td>15</td>
<td>8</td>
<td>15.4%</td>
</tr>
<tr>
<td>Jang 2006</td>
<td>1</td>
<td>36</td>
<td>15</td>
<td>16.6%</td>
</tr>
<tr>
<td>Hsu 2008</td>
<td>3</td>
<td>26</td>
<td>14</td>
<td>51.5%</td>
</tr>
<tr>
<td>Long 2011</td>
<td>0</td>
<td>21</td>
<td>6</td>
<td>8.1%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>98</td>
<td>98</td>
<td>84.6%</td>
<td>0.13 [0.06, 0.32]</td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.65, df = 3 (P = 0.65); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.52 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.2 HBV hepatitis flare

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antivirals</th>
<th>control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>1.2.1 entecavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang 2013</td>
<td>1</td>
<td>41</td>
<td>1</td>
<td>13.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>41</td>
<td>39</td>
<td>13.0%</td>
<td>0.95 [0.06, 14.69]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.04 (P = 0.97)</td>
<td></td>
</tr>
</tbody>
</table>

1.2.2 lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antivirals</th>
<th>control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Lau 2003</td>
<td>0</td>
<td>15</td>
<td>7</td>
<td>15.4%</td>
</tr>
<tr>
<td>Jang 2006</td>
<td>1</td>
<td>36</td>
<td>11</td>
<td>24.4%</td>
</tr>
<tr>
<td>Hsu 2008</td>
<td>2</td>
<td>25</td>
<td>12</td>
<td>50.1%</td>
</tr>
<tr>
<td>Long 2011</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>Not estimable</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>98</td>
<td>87.0%</td>
<td>0.12 [0.04, 0.35]</td>
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<tr>
<td>Total events</td>
<td>3</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.41, df = 2 (P = 0.81); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.91 (P &lt; 0.00001)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Total (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antivirals</th>
<th>control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.35, df = 3 (P = 0.50); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.66 (P &lt; 0.0002)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 1.89, df = 1 (P = 0.17); I^2 = 47.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favors antivirals</td>
<td>Favors controls</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Figure 1 Legend. Meta-analysis of antiviral agents vs. no prophylaxis across a variety of immunosuppressive regimens. The study of 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 to deferred treatment. Panel 1.1: The pooled estimates demonstrate an 87% relative risk reduction (RRR) of reactivation with prophylaxis (95% confidence interval (CI): 70% to 94%). Panel 1.2: The pooled estimates demonstrate an 84% RRR (95% CI: 58%; 94%) of HBV associated hepatitis flares
**Figure 2** Legend: Pooled baseline risk estimate without prophylaxis of HBVr with rituximab in patients who have recovered from hepatitis B infection (HBsAg-negative, anti-HBc-positive).
Appendix 1

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  (Zeffix 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 Hepsera).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).rm. (35417)
51  or/38-50 (49828)
52  (Meta Analysis or Controlled Clinical Trial or Randomized Controlled Trial).pt. (917026)
53  Meta-Analysis/ use mesz,cctr,coch,clhta (50071)
54  Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez (86913)
55  (meta analy* or metaanaly* 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)
56 exp Random Allocation/ use mesz, ctr, coch, clhta or exp Double-Blind Method/ use mesz, ctr, coch, clhta or exp Control Groups/ use mesz, ctr, coch, clhta or exp Placebos/ use mesz, ctr, coch, clhta (344981)

57 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)

58 (random* or RCT or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab. (2205521)

59 or/52-58 (3031904)

60 7 and 26 and 30 and 37 (605)

61 7 and 37 and 51 and 59 (515)

62 60 or 61 (1069)

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

64 remove duplicates from 63 (789)

65 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)

66 Case Report/ use emez (1939567)

67 64 not (65 or 66) (707)
Appendix 2: Study flow diagram

- **Identification**: Records identified through database searching (n = 1050) and Additional records identified through other sources (n = 40).

- **Screening**: Records after duplicates removed (n = 744).

- **Eligibility**: Records screened (n = 744) and Full-text articles assessed for eligibility (n = 138) with Full-text articles excluded (solid organ, bone marrow, or hematopoietic stem cell transplant) (n = 40).

- **Included**: Studies included in qualitative synthesis (n = 98), Studies included in quantitative synthesis (meta-analysis) (n = 5).
References:


48. Mori S. Past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or nonbiological disease-modifying antirheumatic drugs. Mod Rheumatol 2011;21:621-627.


63. Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. JAMA 2013;310:1664.


