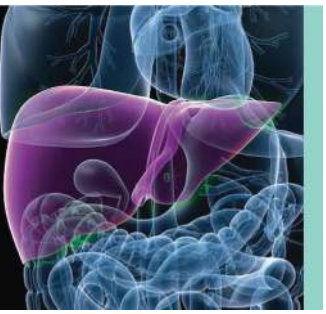

Reactivation of Hepatitis B Virus: A Review of Clinical Guidelines

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INTRODUCTION AND DEFINITIONS

Reactivation of hepatitis B virus (HBV) is a syndrome characterized by the reappearance of HBV particles in patients with previously resolved HBV or an increase in HBV viremia in patients with previously inactive chronic hepatitis B (CHB). Reactivation can occur spontaneously, but it is more commonly triggered by immunosuppressive (IS) therapies. Reactivation can cause significant morbidity and mortality but is preventable if at-risk individuals are identified through screening and started on antiviral prophylaxis (PPX) if indicated. Since this topic was last covered in the March 2015 issue of *Clinical Liver Disease*, screening and management guidelines have rapidly evolved, thus necessitating an updated review. This review highlights the importance of HBV screening in patients who are receiving chronic IS therapy, reviews current guidelines for screening and risk-stratifying patients for reactivation, and illustrates gaps between ideal and "real-world" HBV screening practices.

The definition of HBV reactivation varies between guidelines, but the general concept is similar. In patients with CHB (HBV surface antigen positive [$HBsAg^+$] for at least 6 months and measurable HBV DNA in the blood), reactivation is defined by a rise in HBV DNA above baseline. In patients with resolved HBV ($HBsAg^-$, anti-HBV-core antibody positive [anti-HBc^+]), reactivation is defined by

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ALT, alanine aminotransferase; anti-HBc, anti-HBV-core antibody; APASL, Asian Pacific Association for the Study of the Liver; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CS, corticosteroid; EASL, European Association for the Study of the Liver; ETV, entecavir; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HSCT, hematopoietic stem cell transplant; IS, immunosuppression; mRNA, messenger RNA; NA, nucleotide analog; NCTP, sodium taurocholate cotransporting polypeptide; PPX, prophylaxis; SCT, stem cell transplant; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TKI, tyrosine kinase inhibitor; TNF, tumor necrosis factor.

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TABLE 1. DEFINITIONS OF HBV REACTIVATION BASED ON SOCIETY GUIDELINES

	Reactivation of CHB	Reactivation of Resolved HBV
Baseline serologies	$HBsAg^+$, anti-HBc^+	$HBsAg^-$, anti-HBc^+
AASLD 2018 guidelines	Unknown DNA baseline: ≥10,000 IU/mL	Development of detectable DNA
	Known DNA baseline, previously undetectable: ≥1,000 IU/mL	OR
	Known DNA baseline, previously detectable: ≥100-fold increase	Development of HBsAg (also known as reverse seroconversion)
AGA 2015 guidelines	Unknown DNA baseline: not explicitly defined	Development of detectable DNA
	Known DNA baseline, previously undetectable: *de novo* detectable DNA	OR
	Known DNA baseline, previously detectable: ≥10-fold increase	Development of HBsAg (also known as reverse seroconversion)
		OR
		Development of HBeAg
APASL 2016 guidelines	Unknown DNA baseline: ≥20,000 IU/mL	Development of detectable DNA
	Known DNA baseline, previously undetectable: ≥100 IU/mL	OR
	Known DNA baseline, previously detectable: ≥100-fold increase	Development of HBsAg (also known as reverse seroconversion)
EASL 2017 guidelines	Not explicitly defined	Not explicitly defined

either the appearance of HBV DNA in the blood or conversion to the $HBsAg^+$ state. The latter process is known as reverse seroconversion (Table 1).[1-4]

PATHOPHYSIOLOGY

The key molecular agent driving HBV reactivation is covalently closed circular DNA (cccDNA). During an acute HBV infection, HBV viral particles enter hepatocytes by receptor-mediated endocytosis. The partially double-stranded HBV genome is imported to the nucleus, where both viral and host machinery complete a full-length cccDNA molecule, or mini-chromosome. This mini-chromosome persists as the reservoir for both new viral particles and more cccDNA (Fig. 1).[5] Although acute HBV infection in adults generally resolves without development of CHB,

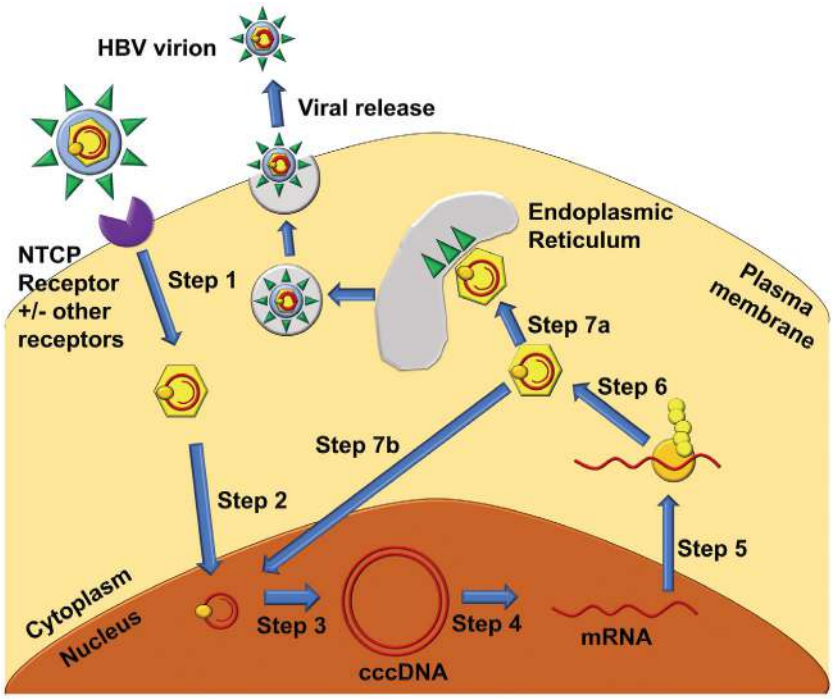

FIG 1 HBV life cycle. Step 1: viral particles (blue spheres) are first internalized through receptor-mediated endocytosis by binding cell surface transporters (purple spheres; NCTP). Step 2: nucleocapsids (yellow hexagons) are then uncoated in the cytoplasm, releasing the partially double-stranded viral genomes (single red circles) that are imported into the nucleus. Step 3: viral genomes are converted to cccDNA molecules. Step 4: cccDNA serves as a template for viral mRNA, which in step 5 is exported to the cytoplasm. Step 6: cytoplasmic mRNA is translated to produce the viral surface, core, polymerase, and X proteins. Viral capsids assemble, incorporating genomic viral RNA, which is reverse transcribed back into a viral DNA genome. Step 7: the resulting nucleocapsid cores can either enter the endoplasmic reticulum to be exported from the cell (step 7a) or recycle their genomes into the nucleus to replenish the reservoir of cccDNA (step 7b). Reproduced with permission from *New England Journal of Medicine*. Copyright 2014, Massachusetts Medical Society.

persistent cccDNA still poses a risk for reactivation. It is important to recognize that both patients with CHB and patients with resolved HBV are at risk for HBV reactivation in the setting of chronic immunosuppression. Where HBV is endemic, reported HBV reactivation rates with immunosuppression are as high as 41.5% (resolved HBV) and 70% (CHB).[2,6] Specific factors dictating whether reactivation will occur are not well understood.

STAGES OF HBV REACTIVATION

Clinically, HBV reactivation manifests in several ways, including: (1) silent reactivation, elevated viral load without overt hepatitis; (2) HBV-associated hepatitis, elevated viral load and evidence of clinical, biochemical, or histological hepatitis; and (3) fulminant liver failure, elevated viral load with hepatic synthetic dysfunction, encephalopathy, and coagulopathy.

SCREENING AND RISK STRATIFICATION

Several professional societies have published screening and treatment guidelines for HBV reactivation. Slight differences aside, the overarching principles hold (Fig. 2 and Table 2).[1-4] Prevention of HBV reactivation is critical and requires: (1) recognizing the need to screen patients about to receive IS therapies, (2) stratifying risk based on virological data and IS regimen, and (3) tailoring management

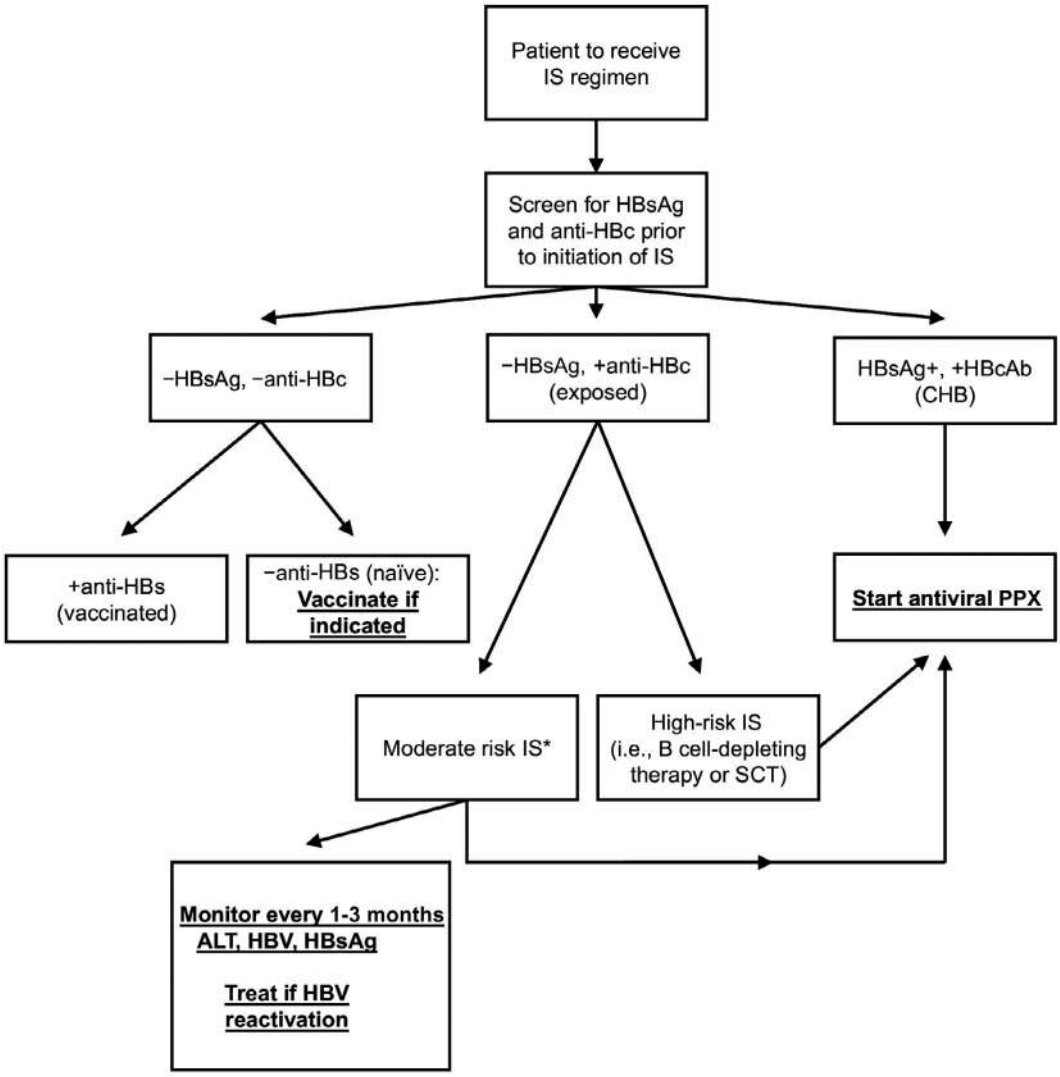

FIG 2 Proposed algorithm for the screening and management of patients at risk for HBV reactivation. *Moderate risk immunosuppression is defined by AGA guidelines as noted in Table 2.

TABLE 2. SCREENING AND MANAGEMENT GUIDELINES FOR HBV REACTIVATION

Society	Screen?	HBV Status	Risk Stratification and Management Strategy	Choice of NA	NA Duration	Monitoring after PPX
AASLD	Yes (HBsAg, anti-HBc)	CHB	PPX	ETV, TDF, TAF	6-12 months after IS	Continue up to 12 months after NA withdrawal (especially if B cell–depleting therapy)
		Resolved HBV	High-risk therapy (rituximab; SCT): PPX Other therapies: PPX or on-demand therapy (monitor every 1-3 months with ALT, HBV DNA, HBsAg)	ETV, TDF, TAF	6-12 months after IS	Continue up to 12 months after NA withdrawal (especially if B cell–depleting therapy)
APASL	Yes (HBsAg, anti-HBc)	CHB	PPX	Consider ETV or tenofovir (due to high barrier to resistance)	12 months after IS	No comment
		Resolved HBV	Rituximab in lymphoma: either PPX or monitoring (further studies needed) Detectable HBV DNA: PPX Undetectable HBV DNA: on-demand therapy (monitor every 1-3 months with ALT and HBV DNA)	Consider ETV or tenofovir (due to high barrier to resistance)	No comment	No comment
AGA	Yes if moderate-to-high risk for reactivation* (HBsAg, anti-HBc, DNA if positive)	CHB	High risk (B cell–depleting therapy; anthracycline, moderate-dose CS daily ≥4 weeks): PPX Moderate risk (TNF-α therapy, cytokine inhibitor, integrin inhibitor, TKI, low-dose CS): PPX preferred, can consider on-demand therapy	Recommend antivirals with high barrier to resistance	6-12 months after IS (12 months if B cell–depleting therapy)	No comment
		Resolved HBV	High risk (B cell–depleting therapy): PPX Moderate risk (TNF-α inhibitor, cytokine inhibitor, integrin inhibitor, TKI, low-dose CS): PPX preferred, can consider on-demand therapy	Recommend antivirals with high barrier to resistance	6-12 months after IS (12 months if B cell–depleting therapy)	No comment
EASL	Yes (HBsAg, anti-HBc, anti-HBs)	CHB	PPX	ETV, TDF, TAF	12 months after IS; 18 months after IS (if rituximab)	Every 3-6 months during PPX, continue 12 months after NA withdrawal
		Resolved HBV	High risk (rituximab for oncological indication; SCT): PPX Moderate or low risk: on-demand therapy (monitor HBsAg and/or HBV DNA every 1-3 months; treat if +DNA or reverse seroconversion)	ETV, TDF, TAF	18 months after IS (if rituximab)	Continue 12 months after NA withdrawal

Guidelines are separated by professional society. Recommended screening tests are included in parentheses. Management strategies are stratified based on a combination of HBV serological status and potency of IS regimen.

*Per AGA guidelines, patients with a >10% and >1% risk for reactivation are considered high and moderate risk, respectively.

based on risk to close monitoring with on-demand antiviral therapy or antiviral PPX.

Most guidelines recommend that any patient due to receive chronic immunosuppression or cytotoxic chemotherapy should be screened for HBsAg and anti-HBc regardless of endemicity.[1,2,4] Unfortunately, actual practice patterns fall short of this. A review of HBV screening patterns at a cancer center showed that only 16.7% of 10,729 patients had HBV serologies checked.[7] Among those screened, the prevalence rate of CHB was 1.5% and the prevalence rate of isolated anti-HBc positivity was 7.4%, suggesting that many at-risk patients were missed. Studies from other specialty practices reported similarly low screening rates,[8] highlighting the need for closer investigation of screening practices.

After screening for HBV, the next step is risk stratification based on virological status and IS regimen. Patients with CHB have a higher risk than patients with resolved HBV.[1-4] Among IS regimens, hematopoietic stem cell transplant (HSCT) recipients and B cell–depleting therapies (e.g., rituximab) confer the highest risk. The American Gastroenterological Association (AGA) suggests that anthracyclines (e.g., doxorubicin) and moderate-dose corticosteroids (CSs; ≥10 mg of daily prednisone or equivalent for ≥4 weeks) confer higher risk than other IS agents.[3]

MANAGEMENT

The final step in preventing HBV reactivation is tailoring management based on risk stratification. For patients with CHB, antiviral PPX should be started before and continued well after cessation of immunosuppression, generally 12 to 18 months if high-potency therapies are used and 6 to 12 months for other agents.[1-4] Once PPX is withdrawn, the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommend continued biochemical monitoring, citing a large proportion of reactivation cases occurring after antiviral withdrawal.[1,4]

Guidelines generally agree that resolved HBV patients on high-potency immunosuppression should be treated similarly to immunosuppressed patients with CHB, with PPX starting before immunosuppression, continued PPX 12 to 18 months after cessation, and monitoring for 12 months after antiviral withdrawal.[1,3,4] For resolved HBV patients not on a high-potency regimen, the guidelines are more divergent. AASLD and EASL recommend these patients be monitored with serial labs (alanine aminotransferase [ALT], HBV DNA, HBsAg) at 1- to 3-month intervals and up to 12 months after cessation of therapy with on-demand antiviral therapy if needed.[1,4] Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend using the presence or absence of HBV DNA to stratify patients to PPX or monitoring, respectively.[2]

As for choice of antivirals, the majority of guidelines recommend the nucleoside inhibitors tenofovir and entecavir (ETV) as first-line therapy for both PPX and treatment, citing several meta-analyses demonstrating higher efficacy and barriers to resistance compared with lamivudine.[1,3] Yang et al.[9] showed that the rate of HBV reactivation was significantly lower in the ETV group (11/228 patients or 4.82%) compared with the lamivudine group (66/365 patients or 18.08%). Similarly, a prospective cohort by Picardi et al.[10] demonstrated significantly lower HBV reactivation rates with tenofovir disoproxil fumarate (TDF; 0/39 patients) compared with lamivudine (15/38 patients or 39.47%). Notably, no studies to date have investigated tenofovir alafenamide (TAF) as a prophylactic agent.[1]

CONCLUSION

HBV reactivation is a serious condition associated with significant morbidity and mortality. Reactivation is avoidable if at-risk patients are appropriately identified through screening and triaged to an appropriate treatment strategy. Current guidelines recommend that patients at the highest risk, including patients with CHB receiving B cell–depleting therapies and cytotoxic regimens, or HSCT recipients, should receive PPX before starting immunosuppression and continue PPX well beyond the cessation of immunosuppression. Patients at intermediate risk may consider PPX or monitoring as reasonable options. This review of HBV screening practices suggests there is more work to be done to improve HBV screening rates.

CORRESPONDENCE

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