

# Hepatitis B Virus Screening, Prophylaxis, and Reactivation in Inflammatory Bowel Disease Patients Undergoing Biologic Therapy: Real-Life Data from a Tertiary Center in Türkiye

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## What is already known on this topic?

- Hepatitis B virus (HBV) reactivation is a well-recognized complication in patients receiving immunosuppressive and biologic therapies, particularly among those with hepatitis B surface antigen (HBsAg) or HBV DNA positivity.
- Current international guidelines recommend antiviral prophylaxis for HBsAg-positive patients, while suggesting that HBsAg-negative, anti-HBc-positive patients may be managed with close monitoring rather than routine prophylaxis.
- Long-term real-life data on HBV reactivation risk in inflammatory bowel disease (IBD) patients, especially from HBV-endemic regions, remain limited.

## What does this study add to this topic?

- This long-term real-world study demonstrates that no cases of HBV reactivation occurred in IBD patients receiving anti-tumor necrosis factor (TNF) therapy when a risk-adapted screening, prophylaxis, and monitoring strategy was implemented.
- Antiviral prophylaxis effectively prevented HBV reactivation in all HBsAg or HBV DNA-positive patients, while no reactivation occurred in isolated anti-HBc IgG-positive patients who did not receive prophylaxis.

## Abstract

**Objective:** Chronic hepatitis B virus (HBV) infection poses a risk of viral reactivation in patients receiving immunosuppressive therapies, including anti-tumor necrosis factor (TNF) agents. This study aimed to evaluate HBV screening practices, antiviral prophylaxis, and reactivation outcomes in patients with inflammatory bowel disease (IBD) undergoing biologic therapy at a tertiary referral center in Turkey.

**Methods:** Patients diagnosed with IBD who initiated biologic therapy between 2009 and 2025 were retrospectively reviewed. Demographic and clinical characteristics, HBV serologic status, antiviral prophylaxis, vaccination history, and HBV reactivation events were recorded. Chronic HBV infection was defined as persistent hepatitis B surface antigen (HBsAg) positivity for more than 6 months. Occult HBV infection was defined as HBsAg negativity with anti-HBc positivity and detectable HBV DNA. HBV reactivation was defined as the reappearance of HBV DNA or HBsAg in patients with previously undetectable levels, or a greater than 10-fold increase in HBV DNA, in accordance with EASL 2025 criteria.

**Results:** A total of 437 patients were included (59% male; mean age  $33.2 \pm 12.8$  years), of whom 72% had Crohn's disease. Anti-HBc positivity was detected in 70 patients (16%). Five patients (1.1%) were HBsAg positive, and 1 patient had occult HBV infection; all 6 received antiviral therapy. Overall, 12 patients (2.7%) received antiviral prophylaxis. During a mean biologic exposure of  $33.5 \pm 28.6$  months, no HBV reactivation occurred in patients receiving or not receiving antiviral therapy. HBV vaccination was documented in 25.8% of patients, with loss of vaccine-acquired immunity observed in 18.5%. Among patients with natural immunity, 15.1% experienced anti-HBs seroreversion.

**Conclusion:** Real-life data from this tertiary IBD center demonstrate appropriate HBV screening and antiviral prophylaxis in high-risk patients. The absence of HBV reactivation supports close monitoring rather than routine prophylaxis in intermediate-risk groups. Periodic reassessment of HBV serology is recommended due to antibody loss during immunosuppressive therapy.

**Keywords** Antiviral prophylaxis, biological therapy, HBV reactivation, hepatitis B virus, inflammatory bowel disease, screening

## Introduction

Hepatitis B virus (HBV) reactivation may occur long after apparent recovery due to persistence of covalently closed circular DNA (cccDNA) or integrated viral DNA within hepatocytes, enabling latency and reactivation under immunosuppression.<sup>1</sup> Thus, individuals with prior HBV exposure remain at lifelong risk during immunosuppressive therapy. Clinically, reactivation ranges from asymptomatic aminotransferase fluctuations to severe hepatitis or hepatic decompensation.<sup>2-4</sup> Case series in patients with inflammatory bowel disease (IBD), Behcet disease, and other autoimmune disorders, particularly under anti-tumor necrosis factor (TNF) therapy, have reported HBV reactivation, including severe hepatitis in HBsAg-positive individuals.<sup>5-7</sup> In contrast, those with resolved infection (anti-HBs and anti-HBc IgG positivity) and normal aminotransferases did not show reactivation.

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Therefore, careful interpretation of HBV serology is essential before biologic therapy in IBD, requiring appropriate screening and risk-based prophylaxis and monitoring.

Briefly, according to the EASL guideline, all patients should have hepatitis B prophylaxis with tenofovir or entecavir during anti-TNF or Janus kinase inhibitors (JAK) therapy if they have HBsAg positivity and/or HBV DNA positivity.<sup>8,9</sup> Hepatitis B surface antigen (HBsAg)-negative, anti-HBc-positive, HBV DNA-negative individuals who will receive an immunosuppressive regimen with moderate or low risk of reactivation (anti-TNF, anti-interleukin-12/23 agents, JAK inhibitors) do not need to be treated and should be monitored closely.<sup>8,9</sup> In the 2018 AASLD guideline, antiviral prophylaxis is recommended for patients with HBsAg positivity prior to initiating immunosuppressive therapy.<sup>10</sup>

In this retrospective study, we aimed to investigate HBV virological markers, the rate of prophylaxis, and the incidence of HBV reactivation among IBD patients receiving anti-TNF therapy.

## Methods

Patients diagnosed with IBD who initiated biological therapy between 2009 and 2025 were included in the study. Clinical characteristics and treatment-related data were retrospectively reviewed from patient files and the hospital registry system. Chronic HBV infection was defined as HBsAg positivity persisting for more than 6 months. Occult HBV infection was defined as HBsAg-negative and anti-HBc-positive status with detectable HBV replication. HBV reactivation was defined as the reappearance of HBV DNA (>100 IU/mL) or HBsAg in a patient with previously undetectable levels, or a >10-fold increase in HBV DNA compared to baseline.<sup>8</sup>

Due to the retrospective nature of the study, the requirement for written informed consent was waived by the local ethics committee. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

## Statistical Analysis

Statistical analysis was performed using standard descriptive and comparative methods. Continuous variables were expressed as mean  $\pm$  standard deviation (SD) or median (range), as appropriate. Categorical variables were summarized as numbers and percentages.

Comparisons between patients who received antiviral prophylaxis and those who did not were performed using the Student's *t*-test for normally distributed continuous variables and the Mann-Whitney U-test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

The duration of biological therapy was compared between groups using independent-sample tests. HBV reactivation was assessed descriptively, as no reactivation events occurred during follow-up.

A *P*-value <.05 was considered statistically significant. All analyses were conducted retrospectively based on available clinical and laboratory data.

## Ethics Approval

The study protocol was reviewed and approved by the Ethics Committee of Cerrahpaşa Faculty of Medicine (Approval No.: 1472932; Date: January 2, 2026).

## Results

A total of 437 patients were included, of whom 59% (*n* = 258) were male, with a mean age at diagnosis of  $33.2 \pm 12.8$  years. Crohn's disease (CD) accounted for 72% of cases, while 28% had ulcerative colitis (UC). The mean duration of biological therapy was  $37.9 \pm 29.4$  months. The majority of patients were treated with anti-TNF agents, especially infliximab (*n* = 250, 57%) and adalimumab (*n* = 100, 23%). Due to reimbursement policies, patients who used vedolizumab (*n* = 25, 6%) and Ustekinumab (*n* = 5, 1%) were anti-TNF experienced. Overall, 115 patients had more than 2 biological agents (26%).

Anti-HBc positivity was detected in 70 patients (16%, 70/437) prior to anti-TNF therapy. Among these, 33 patients were anti-HBs positive (7.5%, 33/437). HBV DNA testing was performed in 21 of the 70 anti-HBc-positive patients, and detectable HBV DNA was identified in one patient (Table 1).

Thirty-seven patients were anti-HBs negative, of whom 5 were HBsAg positive (1.1%); HBV DNA positivity was detected in 4 of these 5 cases. All 5 HBsAg-positive patients, as well as one occult HBV case (HBsAg-negative, HBV DNA-positive), received antiviral therapy. In addition, 6 patients with anti-HBs positivity without DNA positivity were also treated with antivirals. Two were diagnosed with corticosteroid-dependent ulcerative colitis. The characteristics of these patients are presented in Table 2. Overall, in the whole group, 12 patients (2.7%) received antiviral therapy. Among these patients, 8 had infliximab, 2 had adalimumab, and 2 had more than one biologic agent. The mean biologic treatment duration in this group was  $34.5 \pm 27.7$  months. Among 32 patients (7.3%) with isolated anti-HBc positivity, HBV DNA was tested in 5 patients and was negative in all. None of these patients received antiviral treatment. The mean duration of anti-TNF use was  $27 \pm 25.7$  months in this group. The duration of treatment was not significantly different from those who had antiviral treatment (*P* = .2291).

No HBV reactivation occurred in patients receiving antiviral therapy (5 HBs Ag positive and 1 occult HBV) or in those with isolated anti-HBc IgG positivity who did not receive antiviral treatment (*n* = 32).

The duration of anti-TNF use was  $33.5 \pm 28.6$  months in the group of patients who did not receive antiviral therapy. The duration of anti-TNF use was not statistically significant between patients who had antiviral treatment and those who did not. (*P* = .75).

**Table 1.** Immunoprophylaxis Rate According to the HBV Status of the Group

	At the initiation of the treatment (n = 437)	Prophylaxis	Reactivation
Anti HBc Ig G (+)/HBs Ag (+)/HBV DNA (+), n (%)	4 (0.9)	4 (100)	Not occurred
Anti HBc Ig G (+)/HBs Ag (+)/HBV DNA (–), n (%)	1 (0.2)	1 (100)	Not occurred
Anti HBc Ig G (+)/HBs Ag (–)/DNA (+), n (%)	1 (0.2)	1 (100)	Not occurred
Anti HBc Ig G (+)/HBs Ag (–)/HBV DNA (–), n (%)	64 (14.6)	6 (9.3)	Not occurred

HBV, hepatitis B virus.

**Table 2.** Clinical and Laboratory Findings of the Patients who Received Antiviral Prophylaxis

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	M	F	M	F	M	M
Age at IBD diagnosis (years)	48	30	36	31	51	28
HBsAg	+	+	+	+	+	-
Age at start of anti-TNF therapy, years	48	30	58	33	57	31
HBeAg/Anti-HBe	-/+	-/+	-/+	-/+	-/+	-/+
HBV DNA at baseline (IU/mL)	<50	9000	200	1250	88	1140
Follow-up time, mo	26	112	20	46	42	48
HBV DNA at last visit	Undetectable	Undetectable	Undetectable	Undetectable	Undetectable	Undetectable
Other immunosuppressive therapy	Azathioprine (5 years)	—	Azathioprine (6 months)	Azathioprine (11 years), Budesonide (3 years)	Azathioprine (8 years)	Azathioprine (7 years)
Antiviral treatment	Tenofovir	Lamivudine → Tenofovir	Tenofovir	Tenofovir	Tenofovir	Lamivudine → Tenofovir
Outcome/Prognosis	HBsAg positive	HBV DNA positivity under lamivudine → switched to tenofovir	HBsAg positive	HBsAg positive	HBsAg seroconversion (-), anti-HBs (+)	HBV DNA positivity under lamivudine → switched to tenofovir

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

During follow-up, HBV DNA positivity was detected in 2 HBsAg-positive patients receiving lamivudine, and antiviral therapy was subsequently switched to tenofovir. Table 2 provides a summary of the clinical and laboratory findings among patients who underwent antiviral therapy.

The HBV vaccination rate in the cohort was 25.8% (113/437), defined as anti-HBc IgG-negative and anti-HBs-positive. Loss of vaccine-acquired immunity during anti-TNF therapy was observed in 21 of 113 patients (18.5%). Furthermore, among 33 patients with natural immunity, 5 experienced seroreversion of anti-HBs (15.1%).

## Discussion

In this study conducted at a tertiary IBD treatment center in Turkey, the evaluation of patients receiving anti-TNF therapy in daily practice with respect to chronic hepatitis B was examined. A total of 70 patients were anti-HBc positive, comprising 33 with natural immunity and 32 with isolated anti-HBc positivity. Within the isolated anti-HBc group, HBV DNA was detectable in one patient. There were 5 HBsAg-positive patients, 4 of whom had detectable HBV DNA. All 6 patients with HBsAg positivity and/or detectable HBV DNA received targeted antiviral prophylaxis. A total of 31 patients with isolated anti-HBc positivity were managed without antiviral treatment. The absence of HBV reactivation in both the prophylaxis and observation groups confirms that a rigorous screening and monitoring protocol effectively mitigates reactivation risks.

In our cohort, all patients underwent baseline HBV serological screening prior to the initiation of biological therapy. However, HBV DNA testing among isolated anti-HBc Ig G-positive patients was performed in only a limited number of cases, reflecting real-world clinical practice rather than a protocol-driven surveillance strategy. This observation is consistent with previously published real-world data demonstrating suboptimal adherence to HBV

screening and monitoring recommendations in patients receiving immunosuppressive therapy, including anti-TNF agents. In a large retrospective cohort study, Paul et al<sup>11</sup> reported that fewer than half of patients initiating anti-TNF therapy underwent appropriate HBV screening prior to treatment, highlighting a substantial gap between guideline recommendations and routine clinical practice. A recent systematic review protocol highlighted the lack of standardized criteria for HBV reactivation and the substantial heterogeneity in HBV DNA monitoring practices across studies evaluating anti-TNF therapy.<sup>12</sup>

In our study, the rate of antiviral use among patients who were anti-HBc IgG positive but HBsAg and HBV DNA negative was 9.3%. Similarly, a study from Turkey reported that 14% of the patients with anti-HBc IgG positivity received antiviral therapy.<sup>13</sup> In our cohort, none of the 32 patients with isolated anti-HBc IgG positivity who did not receive antiviral therapy experienced HBV reactivation. Similarly, Sayar et al<sup>13</sup> reported no cases of reactivation among 90 patients who did not receive antiviral therapy. These findings suggest that the risk of HBV reactivation in patients with isolated anti-HBc IgG positivity may be low. A Turkish cohort study including 272 HBsAg-negative, anti-HBc-positive patients with rheumatologic, gastrointestinal, or dermatologic diseases reported an antiviral use rate of 11%, with no reactivation observed.<sup>1</sup> Consistent with these observations, a meta-analysis including 2252 HBsAg-negative/anti-HBc positive patients, predominantly from non-IBD (rheumatologic) cohorts, reported an overall pooled HBV reactivation rate of 2.0% across biologic/targeted synthetic therapies; notably, the pooled reactivation rate in the TNF- $\alpha$  inhibitor subgroup was 0.0%.<sup>14</sup> On the other hand, in our study prophylaxis was administered to 6 patients with isolated anti-HBc IgG positivity despite negative HBV DNA. Although prophylaxis was not required in these cases, the presence of steroid-dependent ulcerative colitis in 2 of these patients may partially explain this practice.

The absence of reactivation in this cohort may be partly explained by the relatively lower intensity of immunosuppression in IBD compared with hematologic malignancies, where combination regimens and B-cell-depleting therapies are more frequently used.<sup>4</sup> Emerging evidence indicates that HBV reactivation rates in anti-HBc positive patients receiving anti-TNF therapy for IBD are substantially lower than those reported in oncologic settings.<sup>14,15</sup>

An important finding of our study is that, although no HBV reactivation was observed, a considerable proportion of patients experienced loss of protective anti-HBs antibodies during biological therapy, occurring in 15% of vaccinated patients and in 18% of patients with natural immunity. The loss of immune response acquired either through vaccination or past infection under immunosuppressive treatment suggests a potential risk for future HBV reactivation, particularly in patients with resolved infection. Declining anti-HBs titers under immunosuppression have been associated with an increased risk of subsequent virological reactivation, supporting the concept that loss of serological immunity may precede virological relapse.<sup>3,8</sup> But it should be emphasized that no clinically evident HBV reactivation was observed during follow-up in our cohort, even in cases where anti-HBs seroreversion occurred.

In this cohort, lamivudine was initiated in accordance with reimbursement regulations at the time, rather than as a preferred antiviral strategy. Given the higher risk of viral resistance with prolonged lamivudine therapy, 2 HBsAg-positive patients developed HBV DNA positivity during follow-up. Both patients were successfully managed by switching to tenofovir, and no further virological complications were observed during the observation period.

A major strength of this study is its reliance on real-world data collected over a 16-year period, reflecting biological therapy practices, encompassing both prophylaxis and non-prophylaxis groups, and providing long-term follow-up, particularly among anti-HBc IgG positive patients who did not have prophylaxis. The limitations of this study include its retrospective design. HBV-DNA monitoring was performed inconsistently among isolated anti-HBc positive patients. This limited testing raises the possibility of under-detection of subclinical reactivation.

In summary, our study showed that HBsAg-positive and/or HBV DNA-positive IBD patients receiving anti-TNF therapy benefited from antiviral prophylaxis, with no reactivation observed. Notably, anti-HBc-positive but HBsAg-negative patients who did not receive prophylaxis also remained free of reactivation.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Cerrahpaşa Faculty of Medicine (Approval No.: 1472932; Date: January 2, 2026).

**Informed Consent:** Due to the retrospective nature of the study, the requirement for written informed consent was waived by the local ethics committee. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

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