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Position Paper

Management of Hepatitis B virus infection in patients on treatment with immunosuppressants or immunomodulators: Position Paper of Associazione Italiana Studio del Fegato (AISF), Associazione Italiana di Oncologia Medica (AIOM), Gruppo Italiano per il Trapianto di Midollo Osseo (GITMO), Società Italiana di Reumatologia (SIR), Società Italiana Trapianti d'Organo (SITO), Società Italiana di Gastroenterologia (SIGE), Società Italiana di Malattie Infettive e Tropicali (SIMIT)

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ABSTRACT

Immunosuppressants and immunomodulators are increasingly used for the treatment of several oncologic and immune-mediated diseases. However, reducing or inhibiting the immune system's activity can interfere with the natural mechanisms responsible for Hepatitis B Virus (HBV) control and may potentially induce HBV reactivation (HBVr) in both Hepatitis B surface Antigen (HBsAg) positive patients (overt infection) and HBsAg negative/anti-Hepatitis B core (anti-HBc) positive carriers. Among factors contributing to the persistence of HBVr risk are insufficient awareness, the significant rate of patients not tested for HBV markers before immunosuppression/immunomodulation and the shortcomings in the correct management of anti-HBV therapy or prophylaxis. The risk of HBVr is influenced by the mechanism of action and the duration of immunosuppressants and immunomodulators, the underlying disease for which these drugs are used, and the virological patient's profile. However, HBVr can be prevented by the identification of at-risk patients through HBV screening in order to start anti-HBV therapy or prophylaxis. Following the need to have updated recommendations, primarily targeted to the Italian setting, on the management of HBV in patients on immunosuppressive and immunomodulator therapies, AISF, together with all the Scientific Societies mainly involved in their management, has promoted the drafting of a new dedicated document based upon available evidence at August 2025

1. Introduction

Hepatitis B Virus (HBV) represents one of the most important threats for public health. In 2022, the POLARIS Observatory estimated a global prevalence of 3.2 % (95 % uncertainty interval 2.7–4.0), corresponding to 257,5 [216,6–316,4] million individuals positive for Hepatitis B surface Antigen (HBsAg). The prevalence of HBV infection varies across Countries and ranges from low (<2 %; *i.e.*, United States, Canada, Western Europe) to intermediate (2–8 %; *i.e.*, Mediterranean Countries, the Middle East and parts of South America) and high (>8 %; *i.e.*, Western Africa, Eastern Asia) prevalence areas [1].

HBV infection can occur with different patterns (Phases) of infection, which are defined according to the combination of virological (HBV DNA), serological [HBsAg levels, Hepatitis B envelope Antigen (HBeAg)] and biochemical [alanine aminotransferase (ALT)] parameters. The four Phases of HBV infection are defined according to the recently published European Association for the Study of the Liver (EASL) guidelines [2]:

- Phase 1 - HBeAg positive chronic infection: HBeAg positive, high HBsAg and HBV DNA levels, normal ALT;
- Phase 2 - HBeAg positive chronic hepatitis: HBeAg positive, intermediate to high HBsAg levels, moderate to high HBV DNA levels, elevated ALT;
- Phase 3 - HBeAg negative chronic infection (old terminology "inactive carrier"): HBeAg negative, low (usually <1000 IU/mL) HBsAg, low (usually <2000 IU/mL) HBV DNA levels, normal ALT;
- Phase 4 - HBeAg negative chronic hepatitis: HBeAg negative, intermediate (usually >1000 IU/mL) HBsAg levels and usually >2000 IU/mL HBV DNA levels, elevated ALT.

A resolved HBV infection refers to a past infection and is defined by absence of HBsAg, presence of anti-Hepatitis B core (anti-HBc) ± antibodies against HBsAg (anti-HBs) [2,3].

Patient status can vary over time due to several factors, which include HBV interaction with the immune system or the use of specific anti-HBV treatments; therefore, HBV infection may be characterized by heterogeneous clinical presentations [2].

In recent years, immunosuppressants and immunomodulators have gained popularity in the treatment of several oncologic and immune-mediated diseases. However, modulation of immune response can interfere with the natural mechanisms responsible for HBV control and may potentially lead to HBV reactivation (HBVr), with a potential impact on patient's care. Importantly, despite the risk, interruption or early discontinuation of immunosuppressors and/or immunomodulators is not an acceptable approach [4] and should be avoided or otherwise discussed, as it compromises treatment efficacy and patient outcomes. In HBsAg negative/anti-HBc positive patients, although effective immune responses led to successful infection control, the persistence of the highly stable covalently close circular DNA (cccDNA) in liver cells represents the potential reservoir for HBVr upon immunosuppression [3]. This eventuality is not a trivial point considering the estimated prevalence of these subjects worldwide, which ranges from 19 % to 51 % in Western Countries [5].

Immunosuppressants target different stages of the immune response cascade (*i.e.*, adaptive, cellular or humoral) [6], whereas immunomodulators are able to regulate immune response, by enhancing the immune cascade. This latter mechanism of action is one of the key mainstays of immune checkpoint inhibitors (ICIs) able to enhance the natural host immune cell response towards neoplastic cells, by removing the perturbation (inhibition/escape) of the immune response signaling performed by the tumor itself via specific ligands expressed on neoplastic cells (*i.e.*, PD-1, PD-L1, CTLA4). In this line, at variance with "traditional" immunosuppressants, the boosting of T-cell functions could result in reinvigorating the HBV-specific T-cell responses [4,7]. Immunosuppressant drugs may remove the normal immune surveillance pressure against HBV, enhancing viral replication. This "first phase" of HBVr kick offs when the patient starts therapy, and is characterized by the increase in HBV replication within the liver, thus resulting in a widespread infection of the hepatocytes followed by an increase of serum HBV DNA levels. After withdrawal of immunosuppression, there is a "second phase", characterized by recovery of host immunity and rapid destruction of infected hepatocytes mediated by T-cells, thus resulting in acute reactivation of hepatitis. This latter phase usually begins six months after immunosuppression cessation, but in some cases may take place as late as 12–36 months after the end of treatment, due to a late immune-reconstitution phase. On the contrary, some immunomodulators may directly enhance the immune system response against HBV, thereby triggering the above "second phase", which is marked by serum ALT elevation ("hepatitis") potentially leading to an accelerated progression to chronic hepatitis B (CHB) and even liver failure [8–23].

1.1. Definitions

Definitions of HBVr may vary according to the patient's virological status:

- In HBeAg positive chronic infection (phase 1) and HBeAg negative (phase 4) or HBeAg positive (phase 2) CHB: $a \geq 2$ Log_{10} IU/mL HBV DNA elevation compared to baseline levels;
- In HBeAg negative chronic infection (phase 3): increase of HBV DNA >20,000 IU/mL;
- In HBsAg negative/anti-HBc positive subjects: de-novo detectable serum HBV DNA and/or HBsAg appearance (HBsAg seroreversion).

In addition to virological definition, HBVr-related hepatitis is defined as ALT increase to ≥3 fold the baseline values. HBVr-related hepatitis can reach up to 5–10-fold ALT increase with development of jaundice, and may result in acute liver failure, which is defined as a progressive decline in liver synthetic function and associated features of decompensation (ascites, hepatic encephalopathy). Acute liver failure might not reverse even after starting antiviral treatment and carries a high short-term mortality risk in absence of liver transplant (LT) [18–21]. The risk of HBVr is based on HBV markers and the planned immunosuppressive regimen and can be divided into high (risk of HBVr >10 %), moderate (risk of HBVr between 1–10 %) and low (risk of HBVr <1 %) [2,24].

1.2. Treatment strategies

The severity of HBVr is driven by the pre-treatment virological profile of HBV infection as well as by other factors, inluding stage of pre-existing liver disease, patient's age, concomitant exposure to hepatotoxic drugs and general health status. Moreover, HBVr may also indirectly impact on patients' care and survival, as it may cause discontinuation of the treatment prescribed for the underlying disease (*i.e.*, early withdrawal) [3,18–20]. However, HBVr can be prevented by the early identification of at-risk patients and using nucleos(t)ide analogues (NUCs).

In Italy, the following NUCs are available: lamivudine (LAM), characterized by low antiviral effect and high drug-resistance (R) rates and entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) characterized by no risk of drug-R. According to guidelines [2], in CHB patients with deteriorating renal function or low estimated glomerular filtration rate (eGFR), or osteopenia/osteoporosis, or older than sixty years, TAF or ETV should be preferred to TDF. However, according to Italian reimbursement rules, TAF could be used only in nucleoside-experienced patients with one of the aforementioned features while on TDF [25].

All HBsAg positive candidates to anti-HBV therapy [2] should be treated with life-long NUCs (ETV or TDF), regardless of concomitant oncological or immune-mediated diseases and/or the need to start immunosuppressants or immunomodulators. Conversely, HBsAg positive patients in absence of any indication to HBV treatment *per se* [2,22], requiring immunosuppressants or immunomodulators at high and/or moderate risk of reactivation should receive universal prophylaxis. Although according to Italian reimbursement rules LAM should be used in these patients, we suggest to use ETV or TDF prophylaxis.

In HBsAg positive individuals at low risk of HBVr, "pre-emptive prophylaxis", based on monitoring of HBV DNA every 3 months and initiation of ETV or TDF in case of ≥1 Log_{10} IU/mL HBV DNA elevation compared to baseline levels before clinical evidence of HBVr-related hepatitis, is recommended. If there are concerns about feasibility of HBV DNA monitoring, universal prophylaxis should be initiated (*see below*). This latter should be maintained for at least 12 months after immunosuppressants or immunomodulators withdrawals but until 18 months after completing treatment with B cell-depleting therapies.

In all HBsAg negative/anti-HBc positive individuals at high and/or moderate risk of HBVr, universal prophylaxis with LAM is recommended, whereas individuals at low risk of HBVr should be candidate to "pre-emptive prophylaxis". Also, in this setting whenever "pre-emptive prophylaxis" cannot be adopted as a strategy, universal prophylaxis should be started [9,16,23–29]. The correct assessment of both the virological and clinical profile of HBV patients, as well as the risk of HBVr associated with the different drug class, are mandatory prior to start immunosuppressants and immunomodulators, since these baseline features are crucial for chosing the best therapeutic strategy (Table 1).

2. Methods for developing the statements

This position paper has been developed by the following Scientific Societies: Associazione Italiana Studio Fegato (AISF), Associazione Italiana di Oncologia Medica (AIOM), Gruppo Italiano pe ril Trapianro di Midollo Osseo (GITMO), Società Italiana di Reumatologia (SIR), Società Italiana Trapianti d'Organo (SITO), Società Italiana di Gastroenterologia (SIGE), Società Italiana di Malattie Infettive e Tropicali (SIMIT) with the aim to update a previous AISF document on prophylaxis and treatment of HBV in immunocompromised patients [16]. The above-mentioned Scientific Societies selected a committee of experts and one methodologist to draw up the position paper according to the methodology previously described (see supplementary material).

3. Statements

3.1. Baseline assessment

3.1.1. In patients planned to receive immunosuppressants or immunomodulators is HBV screening recommended?

Recommendation 1: We recommend HBV screening in all patients planned to receive immunosuppressants or immunomodulators.

Certainty of evidence: moderate; strength of recommendation: conditional for

No randomized controlled trials (RCTs) directly compared universal HBV screening (*i.e.*, all patients are tested for HBV) *vs.* risk-adaptive approaches (*i.e.*, only patients with risk factors for HBV infection or those planned to receive therapies associated with high-risk of HBVr are tested). However, three prospective studies conducted in oncological settings are available. Brasseur *et al.* performed a survey on potential risk factors for HBV infection in 388 French patients with solid cancers, showing that the use of a questionnaire on HBV risk factors - aimed to consider a selective screening - was associated with sensitivity and specificity of 46 % and 56 %, respectively, and with a positive predictive value of 9 % [30]. Ramsey *et al.* performed a multicenter cohort study in US including 3051 patients with newly diagnosed haematological and solid cancers planned to receive chemotherapy (CT), and showed that 21 % of HBsAg positive patients and 27 % of HBsAg negative/anti-HBc positive subjects did not have known risk factors for HBV infection [31]. Finally, Hwang et al. in US evaluated a 19-item for HBV risk on 2124 candidates to CT and identified a brief risk tool with a sensitivity approaching to 100 %, but with very low specificity (<15 %), demonstrating that >90 % of patients who completed the tool would still require HBV testing anyway [32]. Based on these data, in the oncological setting, universal HBV testing seems to be more effective in identifying patients at risk for HBVr, when compared to risk-based screening approaches.

Table 1
Summary of HBVr risk estimates[§] based on single medication.

	High risk	Moderate risk	Low Risk
HBsAg positive	Cytotoxic CT B cell-depleting agents Anti-TNF agents Kinase inhibitors Cytokine inhibitors CAR-T cell therapy JAK inhibitors Prednisone >20 mg/day (or equivalent) for ≥4 weeks Immunosuppression in the contest of SOT and HSCT Immune checkpoint inhibitors Proteasome inhibitors	Anti T-cell depleting therapies mTOR inhibitors, Cyclosporine	Azathioprine, Methotrexate, MMF, 6-mercaptopurine Any prednisone (or equivalent) doses for ≤1 week or ≤20 mg/day for ≥4 weeks
HBsAg negative/anti-HBc positive*	B cell–depleting agents Immunosuppression in the contest of HSCT Anti T-cell depleting therapy Proteasome inhibitors	Cytotoxic CT Kinase inhibitors Cytokine inhibitors CAR-T cell therapy JAK inhibitors Anti T-cell therapies Prednisone >20 mg/day (or equivalent) for ≥4 weeks Immunosuppression in the contest of SOT	Anti–TNF agents Immune checkpoint inhibitors Any prednisone (or equivalent) doses for ≤1 week or ≤20 mg/day for ≥4 weeks Azathioprine, Methotrexate, MMF, Cyclosporine, 6-mercaptopurine mTOR inhibitors

CT: chemotherapy; Anti-TNF: anti-tumor necrosis factor; CAR-T: chimeric antigen receptor-engineered; JAK Inhibitors: Janus kinase Inhibitors; SOT: solid organ transplant; HSCT: hematopietic stem cell transplantation; MMF: mycophenolate mofetil; mTOR: mechanistic target of rapamycin inhibitors.
§ The risk may be higher if immunosuppressant and/or immunomodulators are used in combination.
* if HBV DNA positive, management similar to HBsAg positive individuals.

In the setting of immune-mediated diseases, evidence comparing universal HBV screening *vs.* risk-adaptive models is lacking. In the past, expert opinion suggested that among patients with immune-mediated disorders, only those at high risk for HBV infection or those planned to receive treatments known to be associated with high risk of HBVr [including biological therapies, high-dose steroids, cyclophosphamide, mycophenolate mofetil] should be screened for HBV infection, while patients planned to receive treatments associated with low risk of HBVr could avoid screening [33,34]. However, current recommendations from European Alliance of Associations for Rheumatology (EULAR) state that all patients being considered for treatment with disease-modifying anti-rheumatic drugs (DMARDs), immunosuppressants and glucocorticoids should be screened for HBV [35–37]. Similarly, also in the setting of patients with inflammatory bowel diseases (IBD) there is no data comparing universal *vs.* risk-based HBV screening. However, in these patients, HBV vaccination is recommended with the aim to achieve anti-HBs >10 mIU/mL, thus indirectly suggesting the need for HBV screening in all IBD patients [38,39].

Cost-effectiveness of HBV screening strategies has been evaluated, showing heterogeneous results, mainly depending on the characteristics of tested populations. In patients with haematological cancers receiving treatment at high risk for HBVr [*i.e.*, rituximab (RTX)-based CT], universal HBV screening and subsequent antiviral treatment/prophylaxis according to screening results is cost-effective [40–42], compared to other strategies (*i.e.*, no screening or screening in high-risk patients, only). Conversely, results of cost-effectiveness analyses performed in the setting of solid tumours are more controversial, given that universal screening resulted to be cost-effective in some studies, but not in others [43–46]. No data are available from non-oncological settings.

3.1.2. In patients planned to receive immunosuppressants or immunomodulators, which HBV tests should be requested for screening?

Recommendation 2: We recommend that all patients planned to receive immunosuppressants or immunomodulators be tested at baseline for HBsAg, anti-HBc and anti-HBs. Both HBsAg positive and HBsAg negative/anti-HBc positive patients should be tested for serum HBV DNA.

Certainty of evidence: moderate; strength of recommendation: conditional for

In the absence of data comparing different screening strategies including different combination of tests, it should be advised that all onco-haematological patients should be screened for HBsAg, anti-HBc, and anti-HBs [47]. In fact, also HBsAg negative/anti-HBc positive subjects may be at risk of HBVr in absence of antiviral prophylaxis. Anti-HBs testing may be useful to identify those in need of HBV vaccination (HBsAg negative/anti-HBs negative/anti-HBc negative) or those with isolated anti-HBs positivity (HBsAg negative/anti-HBs positive/anti-HBc negative) in unvaccinated individuals that should be considered as a resolved HBV infection and managed accordingly as at risk of HBVr similarly to HBsAg negative/anti-HBc positive patients.

3.1.3. In HBsAg positive patients identified through HBV screening before immunosuppressants or immunomodulators, what baseline assessment are recommended?

Recommendation 3: We recommend that all HBsAg positive patients be referred to specialists to undergo full clinical and virological characterization and to decide about anti-HBV therapy or prophylaxis.

Certainty of evidence: moderate; strength of recommendation: strong for

All HBsAg positive patients should undergo detailed virological characterization and staging assessment, regardless of the need for immunosuppressive or immunomodulatory treatments [2]. The need of antiviral therapy should be based on their clinical, biochemical and/or virological features, independently on the need of immunosuppression/immunomodulation. In those with already established fibrotic damage, HBVr may have a worse course, characterized by liver failure and high mortality rates [48,49].

All HBsAg positive candidates to immunosuppressants and/or immunomodulators should receive ETV or TDF, either as treatment or prophylaxis (*see "Treatment strategies"*). Neverthless, independently of the aim of NUCs administration (treatment *vs.* prophylaxis), patients' management while on-NUCs follows international recommendations [2].

3.1.4. In HBsAg negative/anti-HBc positive individuals planned to receive immunosuppressants or immunomodulators could the evaluation of the anti-HBs titre be useful?

Recommendation 4: We suggest universal prophylaxis for all HBsAg negative/anti-HBc positive individuals undergoing high-risk immunosuppressive or immunomodulatory therapies, regardless of baseline anti-HBs titre.

Certainty of evidence: low; strength of recommendation: conditional for

No RCTs have been conducted to assess the role of anti-HBs titre in the prediction of HBVr in immunosuppressed patients, and evidence come only from observational studies. In the setting of onco-haematological disorders, some studies [10,27,50] demonstrated that undetectable anti-HBs at baseline is an independent risk factor for HBVr by multivariate analysis. An aggregate data meta-analysis of 20 studies [51] in HBsAg negative/anti-HBc positive individuals showed a risk of HBVr of 14 % (95 % CI 9.4–19 %) in 388 anti-HBs negative *vs.* 5 % (95 % CI 3.0–7.0 %) in 1284 anti-HBs positive patients. Presence of anti-HBs reduced the HBVr risk with a pooled OR of 0.21 (95 % CI 0.14–0.32) *vs.* absence of anti-HBs. Moreover, a Taiwanese cost-effective analysis conducted in patients with lymphoma treated with RTX-based CT showed that universal prophylaxis was cost-effective when compared to pre-emptive prophylaxis only in the subgroup of patients with negative anti-HBs [52]. Other studies conducted in this setting identified a baseline anti-HBs titre >100 mIU/mL as a significant protective factor for HBVr [27,53,54]. Conversely, low baseline anti-HBs with high anti-HBc titre [55], or negative anti-HBs with detectable HBV DNA [27] were identified as independent risk factors for HBVr. However, prospective studies clearly showed that anti-HBs titre can decrease during immunosuppressant treatment [10,27], as well as following hematopoietic stem cell transplantation (HSCT) [55,56] both in patients who develop or not HBVr. Therefore, baseline anti-HBs titre is not accurate enough to predict HBVr risk in the onco-haematologic setting.

Several retrospective studies conducted in unprophilaxed HBsAg negative/anti-HBc positive individuals treated with RTX or with DMARDs for rheumatoid arthritis (RA) reported an independent association between negative or low (<100 mIU/mL) anti-HBs titre and the risk of HBVr [57–60]. Two studies reported 20 % and 30 % risk of HBVr among anti-HBs negative *vs.* 4.8 % and 4.0 % in anti-HBs positive patients, respectively [57,59]. Also in this case, anti-HBs titre significantly decreases after 2 years of RTX [57], although patients with baseline titre >100 mIU/mL have a significantly lower probability of anti-HBs loss [61].

A prospective study, including patients with rheumatic diseases receiving DMARDs, reported that anti-HBs titre changed during follow-up and that negative anti-HBs levels (at baseline or during follow-up) were significantly associated with higher risk of HBVr [62].

3.1.5. How to manage HBsAg negative/anti-HBc positive individuals with detectable serum HBV DNA before immunosuppression or immunomodulation?

Recommendation 5: We recommend that all HBsAg negative/anti-HBc positive individuals who have detectable serum HBV DNA levels at baseline and are planned to receive immunosuppressants or immunomodulators be managed as HBsAg positive individuals and therefore we suggest considering universal prophylaxis with ETV or TDF instead of LAM.

Certainty of Evidence: High for the need of treatment; very low for the type of NUC; Strength of Recommendation: Strong for need of treatment; conditional for type of NUC

HBsAg negative/anti-HBc positive individuals may have detectable serum HBV DNA by currently available assays [3]. In these individuals, HBV genomes are in the form of episomal cccDNA and in a low state of replication; thus, the detectability of serum HBV DNA is intermittent, and, when detectable, is usually at a low range. As a consequence, the prevalence of detectable HBV DNA in serum is variable and depends on several factors. They include the studied population, the assay sensitivity, and whether blood samples were collected at one or more time points [63]. Studies conducted in HBsAg negative/anti-HBc positive individuals have shown a higher risk of HBVr in those with detectable viremia [64]. In this setting, no RCTs directly compared LAM *vs.* ETV or TDF as universal prophylaxis, however the use of the latter should be considered due to their low long-term resistance risk [2].

3.2. Risk of HBVr and management of HBsAg positive patients undergoing immunosuppressants or immunomodulators (Table 2)

3.2.1. Corticosteroids

Recommendation 6: In all HBsAg positive patients undergoing prednisone >20 mg/day (or equivalent) for ≥4 weeks universal prophylaxis with ETV or TDF is recommended. Conversely, patients receiving any prednisone (or equivalent) doses for ≤1 week or low dose (≤20 mg/day) for ≥4 weeks, pre-emptive prophylaxis is recommended.

Certainty of evidence: moderate; strength of recommendation: strong for

Administration of prednisone (or equivalent) ≥20 mg/day for ≥4 weeks is considered to significantly increase the risk of HBVr (high risk) [2,22,24]. Conversely, patients treated with any prednisone (or equivalent) doses for ≤1 week or low dose (≤20 mg/day) for ≥4 weeks are considered to be at low risk of HBVr. Pulse therapy (*i.e.*, methylprednisolone >250 mg/day for 1–3 days) poses a moderate-to-high risk of HBVr [65]. Kim *et al.* [66] described HBVr in 8/72 (11 %) HBsAg positive patients not receiving NUCs; all patients presented HBVr-related hepatitis but none of them reported liver decompensation or death. Yang et al. [67] reported a mortality rate for HBVr of 2.5 % (36/1447) in HBsAg positive patients treated with steroids without NUCs, whilst none of those on NUCs ($n = 209$) died due to HBVr.

3.2.2. Immune-checkpoint inhibitors (ICIs)

Recommendation 7: We recommend that all HBsAg positive patients treated with ICIs receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

According to published studies, the rates of HBVr in HBsAg positive patients treated with ICI without NUCs are up to 100 % compared to only 1 % (13 out of 1282 patients) in those under NUCs (68–80). Neverthless, the risk of HBVr-related hepatitis was similar between the two groups (<1 %), and no patients experienced liver decompensation or liver-related death.

3.2.3. Cytotoxic chemotherapy (CT)

Recommendation 8: We recommend that all HBsAg positive patients treated with cytotoxic CT receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

In the study by Karaca *et al.* [81] 133 HBsAg positive patients received CT due to solid tumours without NUCs, and 17 (12.8 %) of them experienced HBVr. In the study by Kim *et al.* [82], 23 out of 111 (20.7 %) HBsAg positive women receiving CT due to breast cancer developed HBVr in absence of NUCs and it was often associated with acute hepatitis.

3.2.4. Tumor necrosis factor-alpha antagonists (anti-TNFα)

Recommendation 9: We recommend that all HBsAg positive patients treated with anti-TNFα receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

In published studies, HBVr was reported in up to 60 % of HBsAg positive patients treated with anti-TNFα in absence of NUCs. Main risk factors for HBVr were high baseline HBV DNA levels, the exposure to more than one immunosuppressant agent and prolonged treatment duration (83–88).

3.2.5. Kinase inhibitors (KIs)

Recommendation 10: We recommend that all HBsAg positive patients treated with KIs receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

Although KIs are not properly recognized as immunosuppressants, their use in HBsAg patients has been associated with HBVr after a tumour response, thus supporting the hypothesis that immune restoration may lead to HBVr. In fact, *in vitro* studies have reported that such theraphies can inhibit T-cell activation and proliferation, with subsequent restoration of the function of plasmacytoid dendritic cells, the well-known crucial effectors in innate immunity [89,90]. Overall, among 227 HBsAg positive patients treated with KIs for solid and non-solid tumours without antiviral prophylaxis, 24 (10,5 %) and 18 (7.9 %) had virological and biochemical HBVr, respectively (91–94).

3.2.6. Proteasome inhibitors

Recommendation 11: We recommend that all HBsAg positive patients treated with proteasome inhibitors receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

The incidence of HBVr was notable in patients with multiple myeloma (MM) receiving bortezomib-containing regimens. Use of LAM prophylaxis may reduce but will not preclude the risk, which has been observed in nearly 20 % of the patients (95–98).

3.2.7. Cytokine inhibitors and Janus kinase (JAK) inhibitors

Recommendation 12: We recommend that all HBsAg positive patients treated with cytokine inhibitors or JAK inhibitors receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

Rates of HBVr in HBsAg positive patients treated with cytokine inhibitors for rheumatic diseases ranged between 25 % and 100 % in absence of NUCs (99–104). Recently, a meta-analysis including 6 studies conducted in HBsAg positive patients affected by RA and treated with anti-interleukin (IL)-6, reported an overall HBVr risk of 6.7 % (95 % CI 0–31.1). This risk increased up to 37 % (95 % CI 0–99.1) in patients not taking NUCs [104]. Retrospective studies analysing the risk of HBVr in small cohorts of patients affected by rheumatological disorders treated with anti-IL6 (tocilizumab), JAK inhibitors (tofacitinib) or abatacept, and including either subjects on NUCs or not, reported that only patients not on NUCs experienced HBVr (33–100 %) [105–108]. Cantini et al. in a meta-analysis including studies in rheumatological and dermatological patients treated with biological drugs, estimated a pooled rate of HBVr of 15.4 % (95 % CI 1.2–41.2 %) [84]. Wang et al. performed a meta-analysis on the rate of HBVr in patients with psoriasis and HBV infection (either active or resolved) treated with biological drugs. Ten observational studies were included (n = 238), of which 36 patients were HBsAg positive. In this subgroup, the pooled HBVr rate was 4.1 % (95 % CI 0.0–17.9 %). No HBVr occurred among patients receiving NUC prophylaxis [109]. El Jamaly et al. reported a 19.1 % (95 % CI 7.3–41.2 %) rate of HBVr in chronic carriers of HBV treated with ustekinumab [110]. Limited data exist on HBVr among patients treated with JAK inhibitors.

3.2.8. B-cell depleting agents

Recommendation 13: We recommend that all HBsAg positive patients treated with B-cell depleting agents receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

B-cell depleting agents have been initially conceived to eliminate B cancerous cells and are now widely used to treat also autoimmune disorders. They target CD19, CD20, CD38 and B-cell activating factor (BAFF). The rates of HBVr among HBsAg positive patients with haematological malignancies treated with RTX+CT without NUC ranges from 40 % to 80 %, and despite the initiation of antiviral therapy at the time of HBVr, up to 40 % of patients ultimately died as a consequence of acute liver failure (111–133). More recently, several studies confirmed the role of NUCs in the prevention of HBVr in patients treated with RTX for either onco-haematological or non-haematological disease (134–138). Huang *et al.* evaluated 3702 adults with newly diagnosed diffuse large B-cell lymphoma (DLBCL) receiving RTX-based CT, and reported that median overall survival was significantly reduced in HBV patients not taking NUCs, wherease no differences were found between HBsAg negative and positive patients on NUCs. Interestingly, in patients

on LAM the risk of HBVr was not fully abrogated, being between 20 and 37 % [135].

Several new monoclonal antibodies targeting different pathogenic pathways and causing profound B-lymphocyte depletion (along with T-lymphocyte) are nowaday available in clinical practice or are currently under investigation in active clinical trials: anti-CD20 (ocrelizumab, ofatumumab, obinutuzumab), anti-CD22 (inotuzumab, ozogamicin), anti-CD52 (alemtuzumab), anti-CD30 (brentuximab vedotin), anti-integrins (natalizumab), anti-CD38 (daratumumab, isatuximab), anti-CD19 (blinatumomab or inebilizumab). However, HBsAg positive patients were excluded from most trials, whilst someother warranted prophylactic use of NUCs. Ocrelizumab, ofatumumab, obinutuzumab, alemtuzumab, brentuximab vedotin, natalizumab, daratumumab and isatuximab are associated with a high risk of HBVr in patients with HBV infection, whereas no increased risk of HBVr due to anti-CD19 use were reported [50,138–148].

3.2.9. CAR T-cell therapy

Recommendation 14: We suggest that all HBsAg positive patients treated with chimeric antigen receptor-engineered (CAR) T-cell therapy receive universal prophylaxis with ETV or TDF.

Certainty of evidence: low; strength of recommendation: conditional for

In the last years, chimeric antigen receptor-engineered (CAR) T-cell therapy has been used in different haematological diseases. No data on CART-cell therapy use are available for HBsAg positive patients not on NUCs. Conversely, HBVr has been reported in up to 20 % of HBsAg positive patients despite NUCs use; no information is available regarding the risk of HBVr-related hepatitis although no deaths due to HBVr were reported [149–153].

3.2.10. Solid organ transplant (SOT): kidney, heart, lung and liver in HBsAg positive recipients

Recommendation 15: We recommend that all HBsAg positive patients treated with immunosuppressants for SOT receive universal prophylaxis with ETV or TDF pre- and post-transplant.

Certainty of evidence: moderate; strength of recommendation: strong for

In kidney transplant (KT), HBsAg positivity is associated with a significant high risk of death independently of the viremic phase. Untreated patients with CHB present an accelerated course towards cirrhosis (5.3–12 %/year), decompensation and HCC [154,155]. In heart (HT) and lung transplant (LuTX) recipients, the evolution of HBV-related disease is accelerated in untreated CHB, whereas the risk of post-transplant HBVr is over 50 % in originally inactive subjects (phase 3) (156–158).

In HBsAg positive patients receiving LT, the risk of post-transplant HBVr is over 80 % in the absence of pre- and post-LT treatment/prophylaxis [159]. The Position Statement and Recommendations by the European Liver and Intestine Transplantation Association (ELITA) advise that management of HBV-related infection before and after LT should be driven by the following criteria: pre-LT serum HBV DNA levels (undetectable *vs.* detectable); presence of HDV co-infection and patient's adherence. In patients with undetectable serum HBV DNA levels at LT two options can be considered: the short-term (4 weeks) anti-HBV specific immunoglobulins (HBIg) in combination with ETV or TDF and then only antiviral monotherapy or the ETV or TDF monotherapy immediately post LT. In patients with detectable serum HBV DNA levels at LT, ETV or TDF+HBIg for at least one year after HBV DNA negativity is advised and then only long-term antiviral monotherapy. Long-term combination of ETV or TDF+HBIg is recommended for patients with low adherence to antiviral drugs and for those with HDV co-infection [160].

A recent multicentric, retrospective Italian study, including 1205 LT recipients (60.8 % with HCC), reported 3.1 % and 2.1 % HBV recurrence in patients transplanted with and without HCC, respectively. Recipients on life-long HBIg+NUCs experienced lower rates of HBV recurrence than those withdrowning HBIg or those who received NUCs alone (2.3 % *vs.* 6.2 % *vs.* 1.9 % *vs.* 8 %, respectively; $p = 0.042$). In patients transplanted for HCC, HBV recurrence was independently associated with tumor recurrence [161].

3.2.11. Organ transplantation from HBsAg positive donors

Recommendation 16: We suggest that recipients of grafts from HBsAg positive donors be considered for transplantation after risk-benefit assessment and patient consent, as these recipients are at high risk of de-novo HBV infection. All patients who receive a LT from an HBsAg positive donor should be treated life-long with ETV or TDF. In the case of non-liver organ transplants from an HBsAg positive donor, HBIg+ETV or TDF are recommended. In the case of a stem cell transplant or a living donation of a solid organ from an HBsAg positive donor in the latter should started ETV or TDF before donation.

Certainty of evidence: moderate; strength of recommendation: conditional for

According to the Italian National Transplant Center [162], the use of grafts from HBsAg positive patients is allowed. Grafts from HBsAg positive/anti-HDV negative donors can be allocated to subjects with the same virological profile (HBsAg positive/anti-HDV negative) or, after informed consent signature, in HBsAg negative individuals (± anti-HBs). In case of negative or low (<10 mIU/mL) anti-HBs, both intra-operative HBIg and long-term ETV or TDF are recommended. Patients with HDV infection should not receive HBsAg positive liver grafts as HDV re-infection is highly likely under such conditions, leading to poor outcomes [160]. All livers from HBsAg positive donors should undergo histological evaluation for fibrosis stage assessment. In case of LT recipients, ETV or TDF must be continued indefinitely while HBIg prophylaxis is not necessary as the transplanted liver is already infected with HBV and reinfection cannot be prevented. Recipients of heart, lungs, kidneys and HSC from HBsAg positive donors should receive for the first 6 months HBIg in addition to ETV or TDF, if the recipient does not have a sufficient anti-HBs concentration (ideally >100 mIU/mL) at the time of transplantation, and then long-term ETV or TDF, with regular monitoring of HBsAg and HBV DNA.

In recipients of KT from HBsAg positive donors, the risk of de-novo HBV infection ranges from 10 % *vs.* up to 100 % in those receiving or not receiving NUCs, respectively (163–165). A study from South Korea reported that the risk of HBV infection without NUCs was 52.9 %, and that no NUCs administration (HR 7.34; 95 %CI 1.51–35.69) and HBV DNA ≥1000 IU/mL before SOT (HR 4.39; 95 % CI 1.08–17.81) were associated with an increased risk of HBVr [164]. A meta-analysis conducted in the setting of HT reported that, among 65 HBsAg positive recipients, NUCs were administered to 16 % of patients pre-HT and to 72 % of patients post-HT. The authors did not report data on HBV infection, however mortality due to HBV-related hepatic failure was observed in 7 % of patients 1-year after HT [166]. Hearts from HBsAg positive donors can be safely transplanted into anti-HBs positive recipients since in published studies they survived without any liver-related event (167–169).

Table 2
Management of patients with current (HBsAg positive) or resolved (HBsAg negative/anti-HBc positive) HBV infection undergoing immunosuppressants and/or immunomodulators.

Setting	Drug	HBsAg positive	HBsAg negative/Anti-HBc positive
Haematolgy	B-cell depleting agents Cytotoxic CT Kinase inhibitors JAK inhibitors CAR-T cell therapy Proteasome inhibitors Immunosuppression in the contest of HSCT	Universal prophylaxis with ETV or TDF	Universal prophylaxis with LAM
Oncology (solid tumours)	Cytotoxic CT Kinase inhibitors JAK inhibitors Cytokine inhibitors Immune-checkpoint inhibitors		Pre-emptive prophylaxis*
SOT Rheumatology Dermatology Gastroenterology	Immunosuppression in the contest of SOT Azathioprine, Methotrexate, MMF, Cyclosporine, 6-mercaptopurine, mTOR inhibitors Anti-TNF agents JAK inhibitors Prednisone >20 mg/day (or equivalent) for ≥4 weeks		
Any setting	Any prednisone (or equivalent) doses for ≤1 week or ≤20 mg/day for ≥4 weeks	Pre-emptive prophylaxis*	

CT: chemotherapy; JAK Inhibitors: Janus kinase Inhibitors; CAR-T: chimeric antigen receptor-engineered; HSCT: hematopoietic stem cell transplant; anti-TNF: anti-tumor necrosis factor; MMF: mycophenolate mofetil; mTOR: mechanistic target of rapamycin inhibitors; LAM: lamivudine; SOT: solid organ transplant; ETV: entecavir; TDF: tenofovir disoproxil fumarate
* Based on monitoring of serum HBV DNA every 3 months and initiation of ETV or TDF in case of ≥1 Log10 IU/mL HBV DNA elevation compared to baseline levels before clinical evidence of HBVr-related hepatitis. If there are concerns about feasibility of HBV DNA monitoring, universal prophylaxis should be initiated.

3.2.12. Hematopoietic stem cell transplantation (HSCT) in HBsAg positive recipients

Recommendation 17: We recommend that all HBsAg-positive patients receiving HSCT, whether allo- or auto-transplant, receive universal prophylaxis with ETV or TDF.

Certainty of evidence: moderate; strength of recommendation: strong for

Several studies and a systematic review (170–180) addressed the risk of HBVr in HBsAg positive patients undergoing allo- or auto-HSCT. Overall, HBVr rates in HBsAg positive allo-HSCT recipients were 14.3 %–100 % in patients not on NUCs *vs.* 0–67 % in those taking antivirals. More recently, a long-term retrospective study reported rates of HBVr in HBsAg positive patients receiving HSCT from anti-HBs negative *vs.* anti-HBs positive donors (HR=0.255, $p < 0.001$), thus suggesting a potential role for donors' anti-HBs status. Moreover, the risk of HBVr was lower in HBsAg positive recipients experiencing no or mild Graft *versus* Host Disease (GvHD) than in those with moderate/severe GvHD (HR 0.201, $p = 0.020$) [174]. Concerning the use of different antiviral prophylaxis in HBsAg positive allo-HSCT recipients, a retrospective cohort study with a historical control group showed a rate of 23.5 % of HBVr in patients treated with LAM *vs.* 2.1 % in patients receiving ETV [175]. Siyahian *et al.* [180] in a meta-analysis on 2067 allo-HSCT patients from 10 studies reported that the cumulative HBVr rate in allo-HSCT patients receiving LAM was 11.5 % (range 5–30 %) while in those receiving ETV was 1.9 % (range 0–2.67).

In HBsAg positive patients receiving auto-HSCT, rates of HBVr ranged from 0 to 50 % in those not on NUCs and from 8 to 27 % in those taking NUCs [176,177,181,182]. No data are available on the efficacy of different antivirals.

Whereas HBsAg patients with CHB are treated according to international recommendations [2] no studies are available regarding the optimal duration of antiviral prophylaxis in the setting of allo- or auto-HSCT in phase 1 and 3 patients (Table 2).

3.3. Risk of HBVr and management of HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators (Table 2)

3.3.1. Corticosteroids

Recommendation 18: We recommend that all HBsAg negative/anti-HBc positive patients treated with corticosteroid monotherapy receive pre-emptive prophylaxis.

Certainty of evidence: low; strength of recommendation: conditional for

Overall, 5 studies analyzed the risk of HBVr in HBsAg negative/anti-HBc positive patients receiving steroids; however, most patients received additional treatments for their underlying disorder (183–187) (Table S1). In 424 patients receiving steroids (maintained *vs.* pulse doses) for any rheumatological indication, a retrospective single-center study reported 0.7 % HBVr during a median follow-up of 131 months [184]. In another retrospective, multicenter study including 12,997 patients receiving steroids, HBVr occurred in 1 % [185]. HBVr-related hepatitis occurred in few patients, with no cases of liver failure reported. Positive anti-HBs titers was identified as a protective factor against HBVr. Time-weighted average prednisone dose >20 mg/day was associated with HBVr in two studies [183,187], whereas dose or duration of corticosteroids did not correlate with HBVr in the others two [185,186]. In all studies, a control group with patients already on NUCs was lacking.

3.3.2. Immune-checkpoints inhibitors (ICIs)

Recommendation 19: We recommend that all HBsAg negative/anti-HBc positive patients treated with ICIs receive pre-emptive prophylaxis.

Certainty of evidence: low; strength of recommendation: conditional for

Overall, eleven studies and one case series investigated the risk of HBVr in HBsAg negative/anti-HBc positive patients receiving ICIs without antiviral prophylaxis. They globally reported an extremely low (0.14 %) risk of HBVr among 1417 patients, with no cases of HBVr-related hepatitis (68–75,188–192) (Table S2).

3.3.3. Cytotoxic chemotherapy (CT)

Recommendation 20: We recommend that all HBsAg negative/anti-HBc positive patients treated with conventional cytotoxic CT in the onco-haematological setting receive universal prophylaxis with LAM, while we recommend pre-emptive prophylaxis in solid tumor setting.

Certainty of evidence: low; strength of recommendation: conditional for

There are few studies investigating the risk of HBVr in HBsAg negative/anti-HBc positive patients receiving only conventional cytotoxic CT for onco-haematological diseases or solid tumours (193–201). These studies greatly differ in terms of patients' population, type of tumour and of cytotoxic regimen; also rates of HBVr are heterogeneous. Furthermore, with the exception of the retrospective study by Shoji *et al.* [201], analysing the risk of HBVr in glioma patients receiving temozolomide, all published studies involved subjects who received complex treatment regimens, as composed by several drugs, sometimes owning to different pharmacological classes. This prevents the assessment of HBVr risk associated with each single molecule. In studies of patients with onco-haematological disorders treated with RTX-free CT, the overall rate of HBVr was 5.7 % (10/173), with documented cases of HBVr-related liver failure and death. Conversely, patients with solid tumours receiving conventional cytotoxic CT alone displayed a HBVr rate of 5.0 % (6/120) without serious liver-related events (Table S3). A decision curve analysis based on the results of a meta-analysis showed a small benefit with the use of antiviral prophylaxis in patients with solid tumor treated with RTX-free CT [29].

3.3.4. Tumor necrosis factor-alpha antagonists (anti-TNFα)

Recommendation 21: We recommend that all HBsAg negative/anti-HBc positive patients treated with anti-TNFα receive pre-emptive prophylaxis.

Certainty of evidence: low; strength of recommendation: conditional for

The risk of HBVr in HBsAg negative/anti-HBc positive patients receiving anti-TNFα has been investigated in several studies [58,85,86,202–223). Currently, data are available for three main drugs in this class: infliximab, adalimumab and etanercept. There is limited data available for golimumab and certolizumab. To date, available studies vary in terms of sample-size (ranging from 7 to 178 patients), underlying disease and observational follow-up (12–75 months). The vast majority of subjects enrolled in these studies did not receive antiviral prophylaxis since ETV, TDF or LAM were used in only 4 out of 18 studies, in selected subgroups of patients. In the seven studies reporting HBVr, only 9 cases of HBVr were described, with HBVr rates not exceeding 3.0 % (range 0.3–3.0 %). Time to HBVr was highly variable, and ranged from 2 to 68 months after anti-TNFα initiation. In most cases, HBsAg did not reappear, and HBV DNA became spontaneously undetectable despite continued anti-TNFα. Only two patients experienced HBVr-related hepatitis, both while on concomitant immunosuppressive therapy with methotrexate and steroids. No cases of liver failure were reported (Table S4).

3.3.5. Kinase inhibitors (KIs)

Recommendation 22: We recommend that all HBsAg negative/anti-HBc positive patients treated with KIs in the onco-haematological setting receive universal prophylaxis with LAM, while we recommend pre-emptive prophylaxis in other settings.

Certainty of evidence: low; strength of recommendation: conditional for

Kinase Inhibitors are used to treat onco-haematological disorders, immune-rheumatological diseases and some solid tumours (*i.e.*, lung cancer), however most studies have been conducted in the onco-haematological setting. Currently, only data for some drugs in this class are available: acalabrutinib, afatinib, dasatinib, erlotinib, gefitinib, ibrutinib, imatinib, nilotinib, osimertinib, ponatinib and zanubrutinib. Data on the use of KIs in solid tumours are limited to a single retrospective monocentre study and a few cases [91,92,224–241). In this setting, a large study conducted in patients affected by lung cancer [240] reported a HBVr rate of only 0.06 % (1 out of 1594); no HBVr were detected in the six patients on NUCs prophylaxis. In the onco-haematological setting, KIs use was associated with HBVr rates close to 10 % (0–9.5 %). In all cases of HBVr, the introduction of NUCs therapy resulted in a progressive decline of HBV DNA, with no cases of liver failure or HBVr-related deaths. Importantly, all patients displaying HBVr while on KIs had previously received RTX (Table S5).

3.3.6. Janus kinase (JAK) inhibitors

Recommendation 23: We recommend that all HBsAg negative/anti-HBc positive patients treated with JAK inhibitors in the onco-haematological setting receive universal prophylaxis with LAM, while we recommend pre-emptive prophylaxis in other settings.

Certainty of evidence: low; strength of recommendation: conditional for

The risk of HBVr in HBsAg negative/anti-HBc positive patients receiving JAK inhibitors has been investigated in a few studies

[105,242–250). Data are currently available for three drugs owning to this class: tofacitinib, baricitinib and ruxolitinib. No data are currently available for other JAK inhibitors (*i.e.*, abrocitinib, filgotinib, upadacitinib, fedratinib). Ruxolitinib is the only JAK inhibitor for whom data are available in the onco-haematologic setting. Its use in patients not on NUCs has been associated with HBVr rates ranging from 0 to 26.7 % [246,247]. In the rheumatology setting, the use of tofacitinib or baricitinib was associated with a risk of HBVr between 0 and 4 % [243,244] (Table S6).

3.3.7. Cytokine inhibitors

Recommendation 24: We recommend that all HBsAg negative/anti-HBc positive patients treated with cytokine inhibitors receive pre-emptive prophylaxis.

Certainty of evidence: low; strength of recommendation: conditional for

Regarding the risk of HBVr in HBsAg negative/anti-HBc positive patients receiving cytokine inhibitors, consistent data from large dermatological and rheumatological cohorts are only available for three drugs: tocilizumab (anti IL-6), ustekinumab (anti IL-12/23) and secukinumab (anti IL-17A). For other drugs, such as anakinra (anti IL-1), ixekizumab (anti IL-17), risankizumab (anti IL-23), dupilumab (anti IL-4/13), mepolizumab (anti IL-5), tildrakizumab (anti IL-23) and guselkumab (anti IL-23), only case reports or case series have been published [58,60,99–103,206,213,251–261). Nine out of 15 studies did not report any HBVr in patients with RA or psoriasis treated with tocilizumab, ustekinumab and secukinumab. The majority of these studies included subjects not receiving antiviral prophylaxis, while only one study included a patient taking LAM. In the six studies reporting HBVr, the risk ranged from 1.5 % to 5.2 %, although neither HBVr-related hepatitis or liver failure were described. According to published data, concomitant immunosuppressive therapy seems to increase the risk of HBVr, as three out of seven patients with HBVr across the studies included were taking cytokine inhibitors in association with MTX and/or steroids at the time of reactivation. In large, long-term follow-up retrospective studies conducted in the rheumatology setting the risk of HBVr ranged between 2 % and 8 % [62,262–272). HBVr occurred mainly as HBsAg seroreversion or detectable HBV DNA with normal ALT, while HBVr-related hepatitis or liver failures were rare. Older age (>70 years), negative anti-HBs titre at baseline, exposure to multiple (>3) classes of biological drugs or combination with steroids were identified as risk factors for HBVr (Table S7).

3.3.8. Proteasome inhibitors

Recommendation 25: We recommend that all HBsAg negative/anti-HBc positive patients treated with protease inhibitors receive universal prophylaxis with LAM.

Certainty of evidence: low; strength of recommendation: conditional for

The risk of HBVr in HBsAg negative/anti-HBc positive patients receiving proteasome inhibitors has been assessed only in patients treated with bortezomib (Bortezomib), whilst no data are available for other proteasome inhibitors (ixazomib and carfilzomib). They come from two case reports and two retrospective studies [97,273–275). In one retrospective study HBVr occurred in 2/7 (28,5 %) patients receiving bortezomib and lenalidomide for MM, despite NUC prophylaxis [97] whereas, in the other one, none of 22 patients with amyloidosis experienced HBVr due to bortezomib-based CT, during a median follow-up of 11 months [275].

3.3.9. B-cell depleting agents

Recommendation 26: We recommend that all HBsAg negative/anti-HBc positive patients treated with B-cell depleting agents receive antiviral prophylaxis with LAM.

In onco-haematological setting: Certainty of Evidence: Moderate; Strength of Recommendation: Strong for. In non onco-haematological setting: Certainty of Evidence: Low; Strength of Recommendation: Conditional for

Most data on B-cell depleting agents in HBsAg negative/anti-HBc positive individuals refer to RTX used in both onco-haematological and non onco-haematological settings. HBsAg negative/anti-HBc positive patients receiving RTX-based CT due to onco-haematological disorders (mainly B Non-Hodgkin Lymphoma) carry a high risk of HBVr, ranging from 10 % up to >30 %. Pooled risk of HBVr was 11 % (95 % CI 7 %–17 %) in a meta-analysis of studies including patients not receiving antiviral prophylaxis [29]. HBVr resulted in HBVr-related hepatitis in up to 30 % of cases, with several cases of death due to liver failure. Overall mortality ranged between 14 % and 44 %. Older age (>60 years), advanced stage of haematologic disease, male sex, multiple RTX cycles and negative anti-HBs titre have been identified as risk factors for HBVr [10,27,51,137,194,196,199,276–312). NUCs prophylaxis has been extensively reported to reduce the risk of HBVr in patients undergoing RTX-based CT in the onco-haematological setting. In one randomized, controlled trial, risk of HBVr was 2 % *vs.* 18 % in patients undergoing or not antiviral prophylaxis, respectively [28]. These figures have been consistently replicated across both retrospective and prospective studies, reporting HBVr rates between 0 and 4 % in patients on NUCs prophylaxis [278,279,281,286,291,292,295–297,311,312]. One RCT reported similar HBVr rates in patients maintaining NUCs prophylaxis for 6 *vs.* 12 months after RTX discontinuation (2.3 % *vs.* 4.9 %, respectively) [279]. A decision curve analysis estimated the number of unnecessary antiviral prophylaxis needed to effectively prevent one HBVr between 8 % and 24 % [29].

In HBsAg negative/anti-HBc positive patients receiving RTX due to rheumatic diseases, risk of HBVr without prophylaxis was lower than that observed in the onco-haematological setting, ranging between 2 % and 9 %. Nevertheless, cases of overt HBVr-related hepatitis and some deaths due to decompensation and liver failure have been described. As already observed in the onco-haematological setting, positive anti-HBs titre was reported to partially protect from HBVr [58,60,61,212,223,228,286,313–317). Fewer data, compared to RTX, are available for other B-cell depleting agents. Ofatumumab has been mentioned alongside with RTX in the FDA warning for increased HBVr risk [146]. Ocrelizumab has been evaluated in the context of neurological diseases in some retrospective and prospective studies conducted in limited patient populations, and has been associated with a HBVr risk of 0–6 % (318–321). Obinutuzumab data have been reported as aggregate data with RTX in onco-haematologic diseases [50,312,321], while two studies evaluated daratumumab in combination with proteasome inhibitors in the context of MM and amyloidosis [275,322]. Small case series are available for alemtuzumab in chronic lymphatic leukaemia and HSCT [323,324], while only one case report is available with inebilizumab [325]. No data are currently available for the other B-cell depleting agents (blinatumomab, belimumab, isatuximab, combotox, veltuzumab, ublituximab, ocaratuzumab) (Table S8).

3.3.10. Solid organ transplant (SOT)

Recommendation 27: We recommend that HBsAg negative/anti-HBc positive patients receiving SOT undergo pre-emptive prophylaxis.

Certainty of evidence: low; strength of recommendation: strong for

In HBsAg negative/anti-HBc positive recipients of SOT, the overall risk of HBVr without NUCs prophylaxis ranged between 2 % and 10 %. Most data have been generated in the setting of KT, whereas few data are available for HT and LuTX; no studies have been conducted in other SOT settings. Induction and maintenance immunosuppressive regimens were heterogeneous across studies. They mostly included steroids, anti-IL-2 agents (basiliximab) or anti-thymocyte globulins for induction, and steroids, calcineurin inhibitors (tacrolimus, cyclosporin) and MMF as maintenance treatment. In some studies, RTX or other T-cell depleting agents (belatacept) were also used. HBVr mainly occurred as de-novo detectable HBV DNA or HBsAg seroreversion; cases of HBVr-related hepatitis were rare, and were efficiently rescued by NUCs treatment. Liver failures were also rare. Positive anti-HBs titre confers lower risk of HBVr, whilst rejection, ABO blood type-incompatible transplantation and RTX use were associated with increased HBVr risk [165,168,326–346). In HBsAg negative/anti-HBc positive recipients of SOT undergoing NUCs prophylaxis, HBVr risk ranged between 2.5 % and 4.7 % [165,327,332,341]. However, a recent meta-analysis of 16 retrospective studies conducted in 2913 anti-HBc positive recipients was not able to draw any conclusion concerning the benefit of NUCs prophylaxis in non-liver SOT [327] (Table S9).

3.3.11. Transplantation of kidney, heart, and lung, from an HBsAg negative/anti-HBc positive donor

Recommendation 28: We suggest that non-liver grafts from HBsAg negative/anti-HBc positive donors be preferentially used in HBsAg positive or anti-HBs positive±anti-HBc recipients. In all HBV-naïve recipients we suggest pre-emptive prophylaxis.

Certainty of evidence: low; strength of recommendation: conditional for

Non-liver organs, such as heart, lung, kidney, do not contain cccDNA and therefore the risk of HBV transmission is generally very low, although exists if HBV DNA is present in the donor's blood [2,3]. Successful HBV vaccination of the recipient appears to further reduce the risk of HBV transmission and is therefore recommended for all patients [158,347]. However, many patients with organ failure have an impaired immune response, which may result in a suboptimal response to standard recombinant vaccines. Moreover, the presence of anti-HBc in recipients is associated with protection against HBV transmission. On the contrary, kidney, heart and lung grafts from HBsAg negative/anti-HBc positive donors to HBV naïve patients (HBsAg negative/anti-HBs negative/anti-HBc negative) have a low risk of HBV transmission (348–357) (Table S9).

3.3.12. Transplantation of liver from an HBsAg negative/anti-HBc positive donor

Recommendation 29: There is a risk of de-novo HBV infection if a liver grafts from HBsAg negative/anti-HBc positive donor is transplanted into a naive (HBsAg negative/anti-HBc negative/anti-HBs negative) or in a HBsAg negative/anti-HBc negative/anti-HBs positive recipient, and therefore in such cases long-term use of ETV or TDF is recommended. The risk is particularly low in a recipient with a resolved HBV infection (HBsAg negative/anti-HBc positive±anti-HBs) and therefore pre-emptive prophylaxis is recommended.

Certainty of evidence: low; strength of recommendation: conditional for

In LT setting, the risk of de-novo HBV infection in recipients of a HBsAg negative/anti-HBc positive graft in absence of any prophylaxis is high (on average around 50 %) (358–364). Among these patients, overt hepatitis and/or chronic infection with liver fibrosis progression have also been described. It is preferable to allocate liver graft from HBsAg negative/anti-HBc positive donors to the following sub-groups of recipients: HBsAg positive (since these patients still have to undergo long-term prophylaxis); those with resolved HBV infection (HBsAg negative/anti-HBc positive±anti-HBs), since previous contact with HBV are protective factors against de-novo HBV infection; and vaccinated patients (HBsAg negative/anti-HBs positive), although vaccination seems to be less protective than the serological profile of previous contact (365–383) (Table S9).

3.3.13. Hematopoietic stem cell transplantation (HSCT)

Recommendation 30: We suggest that HBsAg negative/anti-HBc positive recipients of HSCT as well as recipients of HSC from HBsAg negative/anti-HBc positive donors receive universal prophylaxis with LAM.

Certainty of evidence: low; strength of recommendation: conditional for

In HBsAg negative/anti-HBc positive patients receiving HSCT, large retrospective and prospective studies reported that HBVr risk ranged between 4 % and 50 % in absence of NUCs prophylaxis [10,56,177,179,303,384–400). Time to HBVr varied from 27 days to 91 months, and clinical presentation included overt hepatitis in up to 20 % of cases. In addition, deaths due to liver failure were reported, despite rescue treatment with NUCs. On the other hand, several studies and a meta-analysis reported that HBVr risk in patients receiving NUCs prophylaxis (LAM, ETV or Telbivudine) with heterogeneous durations (6–30 months) ranged between 2 % and 11 %, [176,180,388,393]. Allo-HSCT carried a higher risk of HBVr compared to auto-HSCT; moreover, older age (>60 years), negative anti-HBs titre, presence of GvHD and repeated/multiple concomitant CT courses were independently associated with an increased risk of HBVr. In HSCT setting, anti-HBc positive as well as vaccinated donors were protected against the risk of HBVr [385]. Nevetheless, most published studies did not provide this information. (Table S10).

Only few data are available regarding HSCT from HBsAg negative/anti-HBc positive donors. In this setting, the risk of HBsAg seroreversion appears to be negligible in anti-HBc positive recipients but greater in naïve HBV recipients [394].

3.4. Management of antiviral prophylaxis in HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators

3.4.1. What is the best strategy to manage HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators according to the risk of HBVr?

Recommendation 31: We suggest that HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators at moderate/high risk of HBVr receive universal prophylaxis with LAM while in those at low-risk pre-emptive prophylaxis is preferred.

Certainty of evidence: low; strength of recommendation: conditional for

In HBsAg negative/anti-HBc positive patients, antiviral prophylaxis with LAM is recommended when using drugs associated with a moderate/high HBVr risk. For low-risk drugs the pre-emptive prophylaxis, based on monitoring of serum HBV DNA every 3 months followed by initiation of ETV or TDF in case of ≥1 Log_{10}

IU/mL HBV DNA elevation compared to baseline levels before clinical evidence of HBVr-related hepatitis is recommended. Whenever regular HBV DNA monitoring cannot be implemented, universal prophylaxis should be preferred. Although ETV and TDF have high potency against HBV and low resistance rates for long-term use, LAM prophylaxis is the favored strategy in HBsAg negative/anti-HBc positive patients. Since the risk of LAM-R is related to baseline levels of HBV DNA, which are usually low/undetectable in such patients, LAM should be potent enough to maintain suppressed HBV replication without risk of virological failure due to the emergence of drug-R.

3.4.2. How long should antiviral prophylaxis be administered in HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators?

Recommendation 32: We suggest that HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators receive universal prophylaxis for up to 12 months after the end of treatment. However, patients treated with B-cell depleting agents or undergoing HSCT should receive universal prophylaxis for up to 18 months after the end of treatment and subsequently monitored following prophylaxis discontinuation (see below) given the risk of late HBVr.

Certainty of evidence: low; strength of recommendation: conditional for

Time of immunological reconstitution has been considered the surrogate information to set the duration of antiviral prophylaxis. Evidences supporting prosecution for up to 6–12 months after immunosuppression/immunomodulation discontinuation mainly come from both RCTs [278,395–397) and prospective non-RCTs [398,399], which compared antiviral treatment/prophylaxis (LAM in most cases) *vs.* monitoring in HBsAg positive patients. Although no data comparing different durations of antiviral prophylaxis in HBsAg negative/anti-HBc positive patients receiving immunosuppressive or immunomodulatory therapies are available, those treated with B-cell depleting agents or those undergoing HSCT should be prophylaxed up to 18 months after end of any immunosuppressants or immunomodulators, given that they are at higher risk of HBVr following immune system reconstitution. Conversely, in patients not treated with potent immunosuppressants or immunomodulators, the duration of universal prophylaxis after the end of therapy may be reduced to 12 months [9,16,23,24,26,27,400]. However, there is no consensus on current international guidelines regarding duration of antiviral prophylaxis in HBsAg negative/anti-HBc positive patients undergoing treatments at higher risk of HBVr. The American Association for the Study of Liver Diseases (AASLD) recommends that optimal duration of NUCs prophylaxis should be at least 6 months after immunosuppression/immunomodulation discontinuation; both the American Gastroenterological Association (AGA) and the American Society of Clinical Oncology (ASCO) suggest to maintain antiviral prophylaxis for 6–12 months; the European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts (ESGISH) considers 12–18 months of antiviral prophylaxis after drugs withdrawal, while EASL and AISF guidelines recommend 18 months of antiviral prophylaxis after immunosuppression/immunomodulation discontinuation in patients planned to receive B-cell depleting agents or HSCT [2,16,22,24,47,401,402]. In this setting, long-life prophylaxis has been proposed by some authors [170,403]. In the setting of immune-mediated diseases, EULAR recommends at least 6 months of antiviral prophylaxis after immunosuppression/immunomodulation discontinuation [36].

3.4.3. How to monitor HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators on antiviral prophylaxis?

Recommendation 33: We suggest that HBsAg negative/anti-HBc positive patients on universal prophylaxis because of immunosuppression or immunomodulation be monitored with HBsAg assay every 6 months.

Certainty of evidence: low; strength of recommendation: conditional for

Since the risk of LAM-R emergence in HBsAg negative/anti-HBc positive patients with undetectable serum HBV DNA at baseline is null, patients could be monitored by HBsAg assay every 6 months. Hovewer it is essential to remember adherence to prophylaxis and it might be useful to monitor serum HBV DNA by PCR assay in patients with poor adherence, in those who take LAM at reduced doses according to eGFR and/or for long-time as in all these cases the risk of LAM-R is increased. Moreover, due to the risk of late HBVr after withdrawal of NUCs, HBV DNA monitoring (monthly during the first 3 months and subsequently every 3 months for at least 12 months following prophylaxis discontinuation) is needed [10,26–28,404–413).

3.4.4. How to monitor HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators without antiviral prophylaxis?

Recommendation 34: We suggest that HBsAg negative/anti-HBc positive patients undergoing immunosuppressants or immunomodulators at low risk of HBVr, in the absence of universal prophylaxis, be monitored with serum HBV DNA every 3 months during treatment and up to 18 months after discontinuation of immunosuppression/immunomodulation.

Certainty of evidence: very low; strength of recommendation: conditional for

In the study by Kusumoto et al. [27], 269 patients treated with RTX-based CT were followed-up with HBV DNA and the threshold of >11 IU/mL was used to start ETV treatment. HBVr occurred in 22 patients, but no cases of HBVr-related hepatitis were observed in patients with HBV DNA between 11 and 432 IU/mL. Paul et al. [51] reported no cases of HBVr-related hepatitis among lymphoma patients treated with RTX or obintuzumab in absence of antiviral prophylaxis; in this study patients underwent regular HBV DNA monitoring (every 3/4 weeks), and NUCs were started if HBVr occurred. ASCO suggests both HBsAg and HBV DNA monitoring every 3 months, with immediate start of antiviral therapy in case of HBsAg seroreversion or HBV DNA >1000 IU/mL, in patients receiving high-risk regimens but no NUCs prophylaxis. Conversely, in patients receiving regimens at low risk of HBVr, ASCO suggests testing HBsAg and ALT every 3 months. In these patients, HBV DNA testing is reserved to those experiencing a hepatitis flare, while antiviral treatment is recommended only in case of HBsAg seroreversion or HBV DNA >1000 IU/mL [47]. EASL recommends to perform HBsAg and/or HBV DNA every 3 months [2], while AASLD and APASL recommend HBV DNA monitoring every 1–3 months, up to 12 months after discontinuation of immunosuppression/immunomodulation [22,414].

In clinical settings at lower risk of HBVr, several retrospective studies have been published. In patients affected by immune-mediated diseases treated with biological or conventional immunosuppressive therapies without antiviral prophylaxis, HBsAg and HBV DNA monitoring performed every 3 [212,415] or 6 [86,203,207,214] months was safe, as it effectively

avoided the occurrence of HBVr-related hepatitis. However, cost-effectiveness analyses comparing prophylaxis *vs.* pre-emptive prophylaxis showed discordant results [52,416]. Therefore, timing of HBV DNA monitoring in absence of antiviral prophylaxis should take into account several factors, which include the following: willingness and/or capability to adhere to clinical follow-up, duration of immunosuppression/immunomodulation and risk of HBVr related both to the drug and the underling disease.

3.4.5. Which is the best antiviral prophylaxis strategy in HBsAg negative/anti-HBc positive patients when no information is available regarding the risk of HBVr for new molecules?

Recommendation 37: When no data is available regarding the risk of HBVr for specific new molecules, we suggest that HBsAg negative/anti-HBc positive patients receive prophylaxis according to evidences borrowed from similar drug classes.

Certainty of evidence: very low; strength of recommendation: conditional for

Both immunosuppressants and immunomodulators approved to treat oncological and/or immune-mediated diseases are constantly evolving. Thus, data on HBVr risk may be lacking, especially for newly approved molecules, and decisions on antiviral treatment or prophylaxis need to be personalized case by case. It could be useful to take into account the same information used to guide clinical decision on NUCs administration in similar settings and/or when molecules owning to the similar class are used.

3.5. Management of HBVr in patients undergoing immunosuppressive or immunomodulatory therapies

3.5.1. Which anti-HBV drug should be administered in the case of HBVr?

Recommendation 35: We suggest that patients showing HBVr be treated with ETV, TDF or TAF.

Certainty of evidence: very low; strength of recommendation: conditional for

There is a lack of evidence regarding the optimal pharmacological treatment for HBVr, as no studies compared the effectiveness of ETV, TDF, TAF *vs.* LAM in patients experiencing HBVr during or after immunosuppression/immunomodulation. However, several clinical trials provided indirect evidence that ETV or TDF resulted in lower rates of treatment failures and of virological resistance (417–420). Therefore, ETV or TDF should be the treatment of choice for HBVr, due to their predictable high potency and long-term antiviral efficacy, finally leading to HBV DNA undetectability in virtually all compliant patients. Their favourable safety profile allows also for administration in cases of liver impairment [2,22,421]. Very few information is available to guide the choice of the best NUC to be used, although indirect evidence from studies comparing ETV and TDF in preventing HBVr can be borrowed to deduce their similar efficacy in treating HBVr in patients on immunosuppressive therapy [422]. TDF is recommended in all previously LAM-exposed patients. The potential role of TAF in HBVr management is also emerging [423]. Alongside this, it is univocally recommended to use ETV, TDF or TAF to treat HBVr although prescribing rules may influence drug selection, in some cases.

3.5.2. Which antiviral should be preferred as prophylaxis in HBsAg negative/anti-HBc positive candidates to multiple cycles of immunosuppressants and/or immunomodulators?

Recommendation 36: We suggest that HBsAg negative/anti-HBc positive patients undergoing multiple cycles of immunosuppressants or immunomodulators receive universal prophylaxis with ETV or TDF instead of LAM, since the risk of LAM-R may emerge with long-term use.

Certainty of evidence: low strength of recommendation: conditional for

Long-term LAM use in immunocompromised patients may fail due to the emergence of R [413,417–420). Although comparative data in this setting are not available, the use of ETV or TDF is prudentially suggested. Alternatively, regular HBV DNA monitoring by a sensitive PCR assay with the aim of early detection of LAM-R emergence and subsequent initiation of TDF treatment rescue may be an option.

3.5.3. In viremic HBsAg positive patients is there any HBV DNA threshold to be reached following NUCs initiation (as either treatment or prophylaxis) before immunosuppressants or immunomodulators start?

Recommendation 38: We suggest that immunosuppressors be initiated in HBsAg positive patients regardless of HBV DNA values, once universal prophylaxis has been initiated. Conversely, in HBsAg positive candidates to immunomodulators the latter should be started only when undetectable (or <500 IU/mL) serum HBV DNA values have been reached.

Certainty of evidence: very low; strength of recommendation: conditional for

Currently, no literature data exist to support the need of reaching specific HBV DNA targets (through NUCs) before initiation of immunosuppressants and/or immunomodulators [9,23,395–397). ASCO recommends not to delay the start of anti-cancer treatment while waiting for screening tests' results [47], independently of the type of cancer. In the setting of IBD, European Crohnś and Colitis Organisation (ECCO) guidelines recommend to start NUCs treatment or prophylaxis 2 weeks before the introduction of immunosuppressants [39]. HBsAg positive patients receiving ICIs the risk of HBVr remains despite NUCs administration and/or undetectable HBV DNA levels at baseline [75,76]. In RCTs conducted on HCC patients, atezolizumab plus bevacizumab could be administered to HBsAg positive patients only if they had HBV DNA <500 IU/mL within 28 days before immunotherapy initiation [424]. On-treatment, 2 % of them experienced HBVr, but no HBV-r hepatitis [425]. Similarly, in the registration trial of durvalumab plus tremelimumab, HBsAg patients with low/undetectable HBV DNA (≤2000 IU/mL) while on-NUCs were enrolled, however the incidence of HBVr had not been reported [426].

4. Conclusion

Immunosuppressive and immunomodulation therapies are of strategic importance in the management of patients with cancer or inflammatory diseases, yet they often subvert host immunocompetence to the point of inducing HBVr and/or acceleration of a pre-existing liver damage. In the absence of antivirals - prescrived as either therapy or prophylaxis - the majority of patients with an overt HBV infection will experience HBVr. The risk is not negligible also in some subjects previously exposed to HBV (HBsAg negative/anti-HBc positive). Therefore, all patients candidated to immunosuppressants and/or immunomodulators - independently of their clinical indication - should be screened for HBsAg, anti-HBs and HBc, at baseline. This indication is supported by the prevalence of HBV in the general population worlwide and the potential risk of severe, sometimes fatal, HBVr. The risk of HBVr is influenced by both the mechanism of action and the duration of immunosuppressants/immunomodulators, as well as by other factors, including the underlying disease for which these drugs are used and

the patient's virological profile. All HBsAg positive patients should be referred to a hepatologist, in order to set-up the appropriate follow-up and undergo a complete diagnostic work-up, beyond the need of immunosuppression or immunomodulation. In these patients, the choice of anti-HBV treatment *vs.* universal prophylaxis *vs.* pre-emptive prophylaxis is finally influenced by their virological status and the type of systemic therapy they are candidate to. In line with international recommendations [2,24], HBsAg positive patients with an *a priori* indication to antiviral treatment should be maintained on ETV, TDF or TAF indefinitively (or at least till the HBsAg seroclearance), whereas those whithout an indication to antiviral treatment should be maintained on ETV, TDF universal prophylaxis up to 12/18 months after the end of immunosuppressive and/or immunomodulatory therapies. Moreover, we suggest that HBsAg negative/anti-HBc positive patients undergoing drugs at moderate/high risk of HBVr should undergo universal prophylaxis with LAM, whilst pre-emptive prophylaxis could be preferred in HBsAg negative/anti-HBc positive patients undergoing therapies at low risk. This latter option is acceptable when also patient's adherence to the monitoring schedule is guaranteed, otherwise universal LAM prophylaxis is recommended. Once initiated, LAM prophylaxis should be generally maintained up to 12 months after the end of immunosuppression/immunomodulation, with the exception of subjects treated with B-cell depleting agents or receiving HSCT, that should continue LAM prophylaxis up to 18 months after withdrawal of immunosuppression. Of course, the choice of using LAM as prophylaxis is influenced by Italian reimbursement rules, which currently does not allow the use of third generation NUCs. However, when possible, ETV or TDF could be preferred to LAM as prophylaxis [2,24] in moderate to high risk HBsAg negative/anti-HBc positive patients undergoing immunosuppression or immunomodulation. HBV monitoring - either on- or off- NUCs - is crucial, as it leads to early identification of HBVr, making NUCs rescue able to prevent the progression to HBVr-related hepatitis to liver failure and death, which may occur in almost all cases. Although the use of novel immunomodulatory agents is rapidly expanding, the evidence base on HBVr risk remains limited and fragmented. Given the paucity of data and the heterogeneity of existing study designs, some recommendations are necessarily supported by low levels of evidence and weak strength of recommendations, underscoring the need for more robust and methodologically sound research. Randomized controlled studies, while essential to establish robust safety data ande define optimal prophylactic strategies, are unlikely to be feasible in this setting. Real-world studies, despite their methodological constraints, are expected to play a pivotal role in generating clinically meaningful evidence, particularly for HBsAg negative/anti-HBc positive patients. The growing use of novel immunomodulatory agents therefore presents a unique opportunity to advance our understanding of HBVr risk and to refine prophylactic strategies through collaborative, high-quality research. Until stronger data become available, clinical decision-making must rely on a cautious and patient-centered approach, while the hepatology and immunology communities should actively prioritize efforts to close this critical knowledge gap.

Declaration of competing interest

MV: speaking and teaching for Gilead Science, AbbVie, Advanz Pharma, IPSEN, Kedrion. RD: speaking, teaching and advisory board for Gilead Science and AbbVie; consultant and advisory board for Madrigal. CC: speaking for AstraZeneca, Roche, Eisai, MSD, Ipsen; advisory Board for Ipsen, MSD. BD: advisory board for AstraZeneca, Roche, MSD, Eisai, Novocure, Servier, BMS; speaking for Roche, Incyte, AstraZeneca; Research grant by AstraZeneca, Roche, Servier. GDO: speaking and teaching for AbbVie, Gilead, GSK, Viatris. SF: speaking, teaching and advisory board for AbbVie, Gilead, MSD, Novartis, Roche, Eisai, Ipsen, Mirum, Kedrion, AstraZeneca. NP: advisory board and travel grants for AbbVie, Gilead. PT: speaking for AbbVie, Gilead, AstraZeneca, Roche; adviry board for Gilead, Ipsen. VC: speaking and/or advisory board for Advanz, Alfa-sigma, Echosens, Ipsen, Gilead, GSK, Mirum, Roche.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.10.025.

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