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25 Jahre Transplantationsmedizin Leipzig

Viral hepatitis in immunocompromised patients

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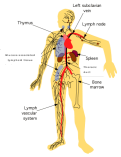
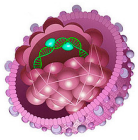
Chronic HBV infection: Host vs virus



vs

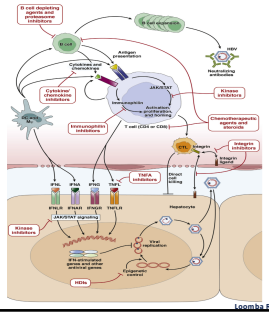


Immunosuppression: increase of HBV replication

⬇

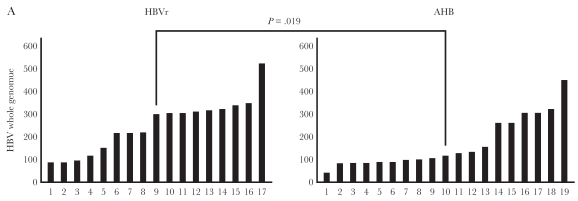
HBV reactivation/exacerbation*
(>80% symptomatic, perhaps fulminant)
**usually after immune constitution*

Mechanisms of HBV reactivation under immunsuppressive therapies



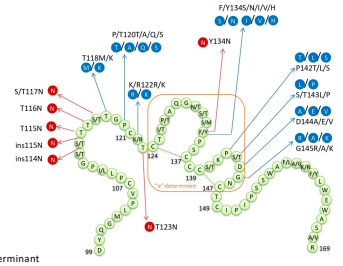
Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

Comparison of the frequency of mutation sites in the hepatitis B virus (HBV) whole genome between HBV derived from HBV reactivation (HBVr) and acute hepatitis B (AHB) patients



Sakamoto K et al. J Infect Dis 2019; epub

Major hydrophilic region (MHR) of HBsAg with the most frequent mutations and additional N-linked glycosylation (NLG) sites found in reactivated HBV



orange rectangle—"a" determinant
within MHR; in blue—the most frequent mutations; in red—additional NLG sites

Lazarevic I et al. Viruses 2019; 11: 778

Definitions of HBV reactivation

VIROLOGIC

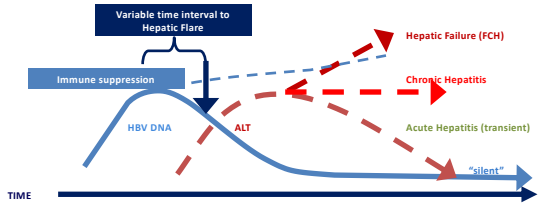
- Defined as reappearance or increase of HBV DNA > 1 log or > 20.000 IU/mL in patients with previously resolved, inactive or active HBV infection
- (Reverse HBsAg seroconversion)

BIOCHEMICAL

- Hepatitis is defined by ALT > 3 x ULN and severe hepatitis by a > 10-fold ALT increase from baseline

Sanchez MJ, et al. J Hepatol 2009;51:1091–1096.

Patterns and outcome of HBV reactivation



FCH = fibrosing cholestatic hepatitis

Adapted from Lau GKK, *et al. Crit Rev Oncol Hematol* 1999;31:71-76.

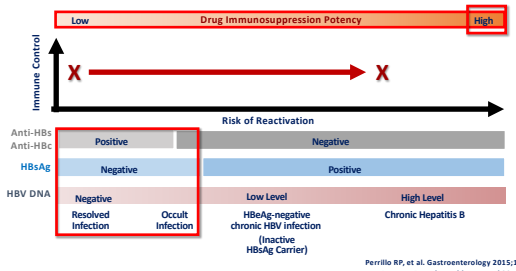
Who is at risk?

Settings associated with HBV reactivation

- Chemotherapy for cancer, haematological malignancies
  - Especially rituximab, corticosteroids, others
- Autoimmune diseases, e.g. rheumatoid arthritis (RA), inflammatory bowel disease (IBD)
  - Corticosteroids, anti-TNFs, …
- Transplantation
  - Solid organ and bone marrow

1. Sorrell MF, *et al. Ann Intern Med* 2009;150:104–110. 2. Lok ASF, McMahon BJ. *Hepatology* 2009;50(3):1–36. 3. Yeo W, & Johnson PJ. *Hepatology* 2006;43:209–220. 4. Sanchez MJ, *et al. J Hepatol* 2009;51:1091–1096.

HBV Reactivation Risk Assessment



Perrillo RP, et al. Gastroenterology 2015;148:221-244
Bessone F, et al. World J Hepatol 2016;8:385-394

Drug immunsuppression potency assessment

Risk of HBV reactivation associated with immunsuppressive therapies

HBsAg-positive patients

High risk of reactivation

> 10%

- B-cell–depleting agents including rituximab, ofatumumab, natalizumab, alemtuzumab, and ibritumomab
- High-dose corticosteroids
- Anthracyclines including doxorubicin and epirubicin
- More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab
- Local therapy for HCC including TACE
- Systemic chemotherapy

Moderate risk of reactivation

1-10%

- Less potent TNF-α inhibitors including etanercept
- Cytokine-based therapies including abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab
- Immunophilin inhibitors including cyclosporine
- Tyrosine-kinase inhibitors including imatinib and nilotinib
- Proteasome inhibitors such as bortezomib
- HDIs
- Moderate-dose corticosteroids **Definition of moderate dose?**

Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

Risk of HBV reactivation associated with immunsuppressive therapies

HBsAg-positive patients

Low risk of reactivation <1%	Antimetabolites, azathioprine, 6-mercaptopurine, and methotrexate Short-term low-dose corticosteroids **Definition of short term?** Intra-articular steroid injections (extremely low risk)

Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

Risk of HBV reactivation associated with immunsuppressive therapies

Risk of reactivation in HBsAg-negative and anti-HBc positive patients[9]

High risk of reactivation	B-cell–depleting agents including rituximab, ofatumumab, natalizumab, alemtuzumab, ibritumomab
Moderate risk of reactivation	High-dose corticosteroids Anthracyclines including doxorubicin and epirubicin More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab Systemic cancer chemotherapy including HCC
Level of evidence?	Cytokine-based therapies including abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab Immunophilin inhibitors including cyclosporine Tyrosine-kinase inhibitors including imatinib and nilotinib Proteasome inhibitors such as bortezomib HDIs

Definition of moderate dose?

Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

Risk of HBV reactivation associated with immunsuppressive therapies

Risk of reactivation in HBsAg-negative and anti-HBc positive patients[9]

Low risk of reactivation	Moderate- and low-dose prednisone Antimetabolites, azathioprine, 6-mercaptopurine, and methotrexate

Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

Immunosuppressive drugs and risk of HBV reactivation

Drug Class	Drug	Risk of Reactivation		Recommendations
		HBsAg+	HBsAg −/anti-HBc+	
B-Cell depleting agents	Rituximab[62] Ofatumumab Alemtuzumab Ibrutinib	30%–60%	24.00%	Prophylaxis
Checkpoint inhibitors	Nivolumab Ipilimumab			
Anthracycline derivatives	Doxorubicin[63] Epirubicin	15%–30%	>10%	Prophylaxis
TNF-α inhibitors	Infliximab Etanercept[64] Adalimumab[65] Certolizumab Golimumab	39% 1%–5% 12%–39%	5%	Prophylaxis Prophylaxis
Cytokine and integrin inhibitors	Abatacept[19,20,48,66] Ustekinumab Natalizumab Mogamulizumab[22] Vedolizumab	1%–10%	1% 12.50%	 Prophylaxis

Sasadeusz J et al. Clin Liver Dis 2019; 23: 521–534

Immunosuppressive drugs and risk of HBV reactivation

Drug Class	Drug	Risk of Reactivation		Recommendations
		HBsAg+	HBsAg −/anti-HBc+	
Tyrosine kinase inhibitors	Imatinib[67] Nilotinib Dasatinib Ibrutinib Erlotinib	1%–10%	1%	Monitor/ prophylaxis
Steroids duration >4 wk	High dose >20 mg[68]	10%–15%	<1%	Prophylaxis if HBsAg+
	Moderate dose 10–20 mg orally >4 wk[69,70]	5%–10%		Monitor/ prophylaxis
	Low dose <10 mg orally >4 wk or less	<1%		Monitor/ prophylaxis
Duration <2 wk	Intra-articular[71]	<1%	<0.1%	Usual care
Antimetabolites	Azathioprine[72]	<1%	<0.1%	Usual care
	6-MP			Usual care
	Methotrexate	<1%	<0.1%	Usual care

Sasadeusz J et al. Clin Liver Dis 2019; 23: 521–534

Newer drugs that may lead to HBV reactivation and probably need prophylaxis include the following

- B-cell inhibitors, including ofatumamab, ustekinamab, natalizumab, ibrotumomab, and obinuzumab
- PI3Kδ inhibitors, including idelasib
- Anti-CD38 agents, including daratumumab
- JAK inhibitors, including ruxolitinib
- T-cell inhibitors (CTLA-4), including abatacept
- Cytokine and chemokine inhibitors, including tocilizumab and mogamulizumab
- Proteasome inhibitors, including bortezomib

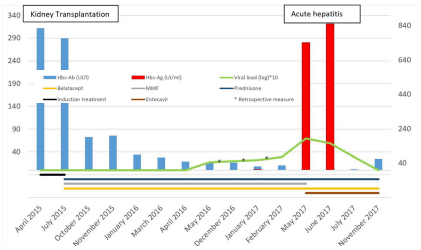
Sasadeusz J et al. Clin Liver Dis 2019; 23: 521–534

Agents with reported cases of HBV reactivation

Agent	Target	Use	Reports of Reactivation	Timing of Reactivation
Tocilizumab	IL-6	Rheumatoid arthritis Castleman disease	7 cases[6,40-44]	8 wk to 5 y
Mogamulizumab[45]	Anti-CCR4	T-cell leukemia and lymphoma	2 cases[8,45,46]	Following X cycles of CHOP and THP-CHOP
Brentuximab vedotin	CD30	Relapsed or refractory Hodgkin lymphoma and T-cell lymphoma	1 case[47]	
Abatacept	CTLA-4	Rheumatoid arthritis	17 cases[c,19,20,48,49]	
TACE[50,51]	HCC		80+ cases[d,52]	
Ibrutinib	IL2	B-cell non-Hodgkin lymphoma	4 cases[53,54]	5 mo
Ruxolitinib[55]	JAK1 JAK2	Myelofibrosis	1 case[56]	4 wk
Pomalidomide[57]	Angiogenesis	Multiple myeloma	1 case[e,57]	6 cycles
Bortezomib	T cells	Hematopoietic stem cell transplantation	11 cases[58-61]	1–3 y

Sasadeusz J et al. Clin Liver Dis 2019; 23: 521–534

Hepatitis B virus reactivation during belatacept treatment after kidney transplantation

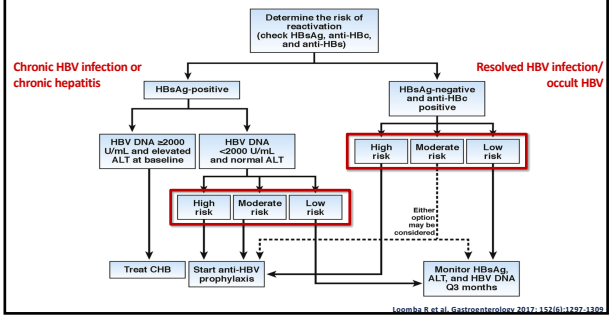


Belatacept binds costimulatory ligands CD80 or CD86 on dendritic cells, preventing the full activation of naïve T cells

Cambier M-L et al. Transpl Infect Dis. 2019;00:e13170

Managing HBV infection under immunosuppressive therapies?

Algorithm of managing HBV infection under immunsuppressive drugs

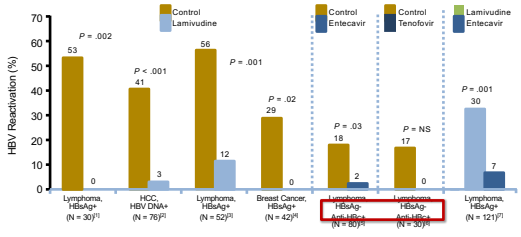


Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

Prevention of HBV reactivation in patients with resolved HBV infection (HBsAg negative, anti-HBc positive)

THE EVIDENCE

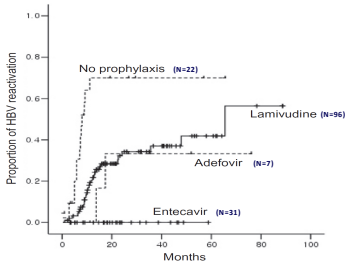
Randomized, Controlled Trials of HBV Prophylaxis



1. Lau GK, et al. Gastroenterology. 2003;125:1742-1749; Jang JW, et al. Hepatology. 2006;43:233-240; Hsu C, et al. Hepatology. 2008;47:844-853; Long M, et al. Breast Cancer Res Treat. 2011;127:705-712; Huang YH, et al. J Clin Oncol. 2013;31:2765-2772; 5421-5422; 7. Huang H, et al. JAMA. 2014;312:2521-2530

Which drug is preferred?

Comparison of HBV reactivation based on the type of anti-viral prophylaxis in HBsAg+ patients

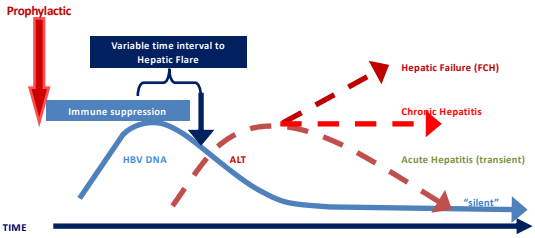


Kim SJ et al. Eur J Cancer 2013; 49: 3486

Prevention of HBV reactivation

- Strategies?
- Prophylactiv or preemptive?

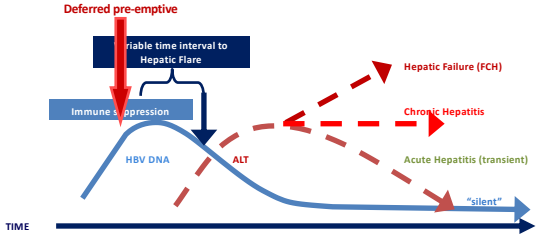
Prevention of HBV reactivation



FCH = fibrosing cholestatic hepatitis

Adapted from Lau GKK, et al. Crit Rev Oncol Hematol 1999;31:71-76.

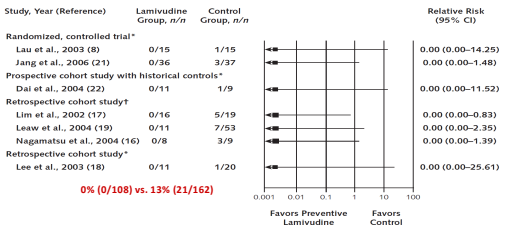
Prevention of HBV reactivation



FCH = fibrosing cholestatic hepatitis

Adapted from Lau GKK, et al. Crit Rev Oncol Hematol 1999;31:71-76.

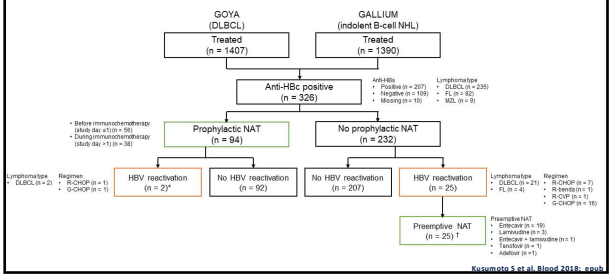
Prophylactic versus deferred lamivudine forest plot of clinical trials assessing HBV-related liver failure



† preventive vs. no lamivudine

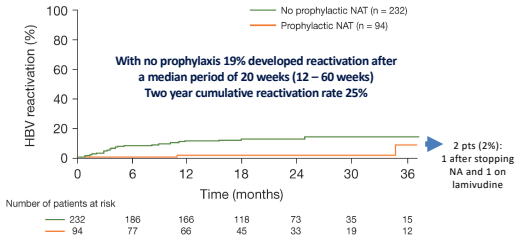
Loomba R et al. Ann Intern Med 2008; 148: 519

Risk of HBV reactivation in B-cell lymphoma under obinutuzumab or rituximab in resolved anti-HBc positive infection



Kusumoto S et al. Blood 2018; epub

Risk of HBV reactivation in B-cell lymphoma under obinutuzumab or rituximab in resolved anti-HBc positive infection



Kusumoto S et al. Blood 2018; epub

Risk of HBV reactivation in B-cell lymphoma under obinutuzumab or rituximab in resolved anti-HBc positive infection

- HBV DNA monitoring-guided preemptive nucleos(t)ide therapy can prevent HBV-hepatitis during anti-CD20 immunochemotherapy in B-cell NHL.
- Prophylactic nucleos(t)ide therapy can prevent HBV reactivation and may be appropriate for high-risk patients.

Kusumoto S et al. Blood 2018; epub

The natural course of HBV reactivation -

How risky is a watch and wait strategy?

The natural course of HBV reactivation in patients with resolved HBV infection receiving B-cell antibodies ?

- HBsAg negative and anti-HBc positive under rituximab- or obinutuzumab-containing regimens (N=83)
- Monitored every 4 weeks
- Sixteen (19%) patients developed HBV reactivation after a median duration of 20 weeks (IQR, 12–60)
- All patients were HBsAg negative at the time of reactivation.
- HBV reactivation was significantly more common in baseline anti-HBs-negative patients when compared to anti-HBs positive patients (45.1% vs 15.7%; p=0.001)

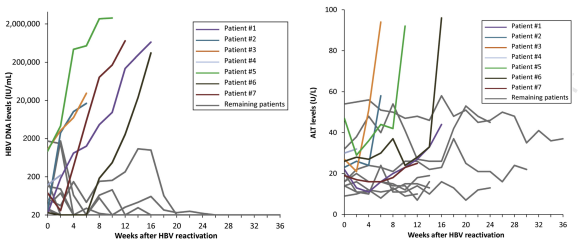
Seto WK et al. Clin Gastroenterol Hepatol 2018; epub

The natural course of HBV reactivation in patients with resolved HBV infection receiving B-cell antibodies ?

- 15/16 patients entered biweekly monitoring,
- 7 (44%) subsequently developed active HBV disease, occurring at a median of 10 weeks (IQR, 4–16) after reactivation
- Three patients seroreverted to HBsAg positivity
- 2 patients developed ALT >2 ULN (92 and 96 U/L, respectively)
- 2 patients developed both HBsAg seroreversion and ALT >2 ULN (58 and 94 U/L, respectively)

Seto WK et al. Clin Gastroenterol Hepatol 2018; epub

Monitoring and treatment of patients undergoing immunotherpay with anti-CD20 and resolved HBV infection



Seto WK et al. Clin Gastroenterol Hepatol 2018; epub

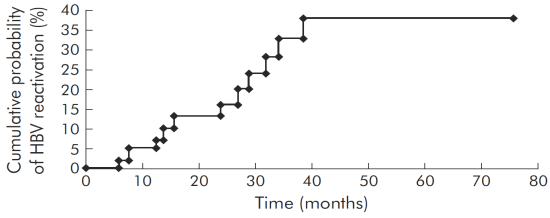
Natural course of HBV reactivation - Conclusion

- Not all occult HBV carriers progressed to active biochemical hepatitis after HBV reactivation. With very frequent monitoring, we were able to show that an HBV DNA level of 2000 IU/mL was an optimal cutoff threshold for progression to active HBV
- Despite virological reactivation, anti-HBV therapy might only be needed for patients with higher levels of viral activity

Seto WK et al. Clin Gastroenterol Hepatol 2018; epub

Duration of prophylactic antiviral regimens?

Cumulative probability of HBV reactivation after withdrawal of pre-emptive lamivudine therapy in HBsAg positive patients with haematological malignancy on completion of chemotherapy (N=46)



Lamivudine withdrawal 3 months after completion of chemotherapy

Hui CK et al. Gut 2005; 54: 1597

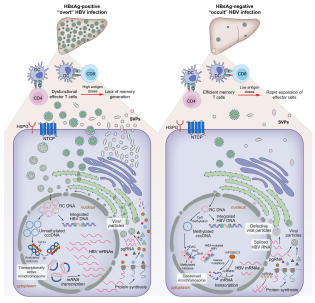
Duration of HBV Prophylaxis for Patients Receiving Immunosuppressive Therapy - Guideline recommendations

- Duration
  - Varies among guidelines
  - 6 months post immunosuppressive therapy if HBV DNA < 2000 IU/mL OR until treatment goals reached if > 2000 IU/mL (AASLD)[1]
  - 6 months post immunosuppressive therapy OR 12+ mos if B-cell–depleting agent (AGA, ASCO)[2,3]
  - 12 months post immunosuppressive therapy (EASL, APASL)[4,5]
  - 18 months for B-cell depleting agents (i.e. rituximab) (EASL)[6]

1. Lok AS, et al. Hepatology 2009;50:661-662, 2. Reddy KR, et al. Gastroenterology 2015;148:215-219, 3. Hwang JP, et al. J Clin Oncol 2015;33:2212-2220, 4. EASL CPG J Hepatol 2012;57:167-185. 5. Sarin SK, et al. Hepatol Int 2016;10:1-98; 6. EASL CPG J Hepatol 2017; 67: 370

Why do some patients with resolved (HBsAg-negative, anti-HBc positive) HBV infection reactivate but others not?

Risk of HBV reactivation – presence of occult HBV infection?



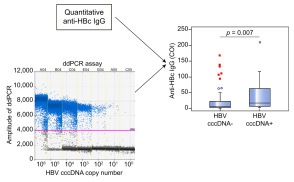
Definition

- **Occult HBV infection (OBI)** is defined as the presence of replication-competent HBV DNA (*i.e.* episomal HBV covalently closed circular DNA [cccDNA]) in the liver and/or HBV DNA in the blood of people who test negative for hepatitis B surface antigen (HBsAg) by currently available assays.

Raimondo G et al. J Hepatol 2019; 71: 397–408

Biomarkers to predict the reactivation risk?

Quantitative anti-HBc levels to predict occult HBV infection (cccDNA positive livers)

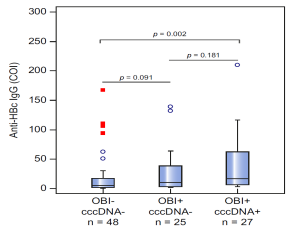


- HBV covalently closed circular DNA (cccDNA) is responsible for viral persistence decades after liver disease resolution.
- A latent occult HBV infection is identified by the presence of the antibody to the HB-core antigen (anti-HBc).
- HBV cccDNA is detectable and quantifiable in 27 out of 100 anti-HBc-positive liver donors.
- Serum anti-HBc IgG levels are associated with the finding of intrahepatic HBV cccDNA.

Cavigila et al. J Hepatol 2018; 69: 301-307

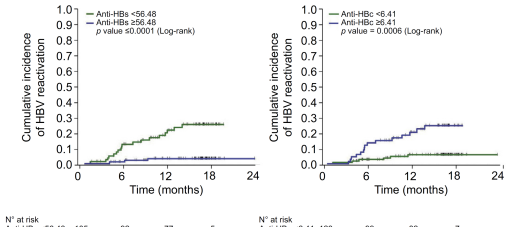
Clinical utility of quantitative anti-HBc levels

- **Serum levels of anti-HBc (COI) correlate with cccDNA positivity in OBI (*p*=0.002)**
- **The median levels of anti-HBc IgG were**
  5.1 (3.0–8.7) in OBI-/cccDNA-
  10.4 (3.6–31.3) in OBI+/cccDNA-
  17.0 (7.0–39.2) in OBI+/cccDNA+



Cavigila et al. J Hepatol 2018; 69: 301-307

Quantification of HBV core antibodies may help to predict HBV reactivation in resolved HBV infection



N° at risk

Anti-HBs <56.48	105	92	77	5
Anti-HBs ≥56.48	87	65	44	4

N° at risk

Anti-HBc <6.41	123	99	82	7
Anti-HBc ≥6.41	69	58	39	2

Yang H-C et al. J Hepatol 2018; 69: 286

Risk of Hepatitis B Virus Reactivation in Patients With Inflammatory Arthritis Receiving Disease-Modifying Antirheumatic Drugs: A Systematic Review and Meta-Analysis

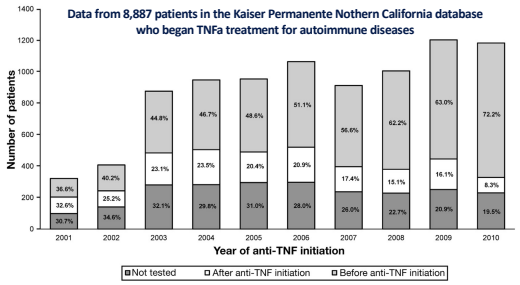
Lin T-C et al. Arthritis Care Res 2018; 70: 724

Table 2. Pooled HBV reactivation rates in inflammatory arthritis patients with resolved HBV without antiviral prophylaxis*

	No.	Event	Pooled rate, % (95% CI)	P†
Total	1,032	16	1.6 (0.8–2.6)	0.27
TNF inhibitors	629	8	1.4 (0.5–2.6)	0.26
Non-TNF biologics	69	3	6.1 (0.0–16.6)	0.08
Nonbiologic DMARDs	334	5	1.7 (0.2–4.2)	0.23

Lin T-C et al. Arthritis Care Res 2018; 70: 724

Risk of HBV reactivation under long-term TNFa antagonists



Pauly MP et al. Clin Gastroenterol Hepatol 2018; 16: 1964

Risk of HBV reactivation under long-term TNFa antagonists

- In patients treated with TNF antagonists for autoimmune diseases:
- HBV reactivation in 39% of patients who were HBsAg+ before therapy
- No reactivation in patients who were HBsAg-negative and anti-HBc-positive before therapy
- Patients should be screened for HBV infection before anti-TNF therapy; HBsAg+ patients should receive prophylactic antiviral therapy, but not HBsAg-negative, anti-HBc+ patients

Pauly MP et al. Clin Gastroenterol Hepatol 2018; 16: 1964

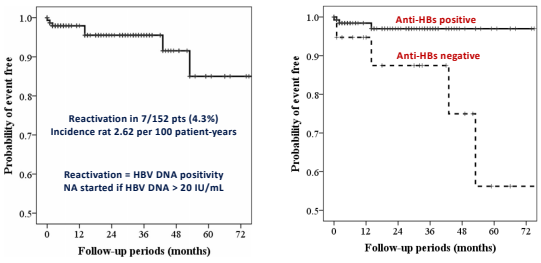
Incidence of reactivation from resolved HBV infection in rheumatoid arthritis patients treated with biological DMARDs

N=152

bDMARDs = abatacept (n = 29), golimumab (n = 26), etanercept (n = 25), tocilizumab (n = 25), adalimumab (n = 19), infliximab (n = 17) and certolizumab pegol (n = 11)

Watanabe T et al. Int J Rheum Dis 2018; epub

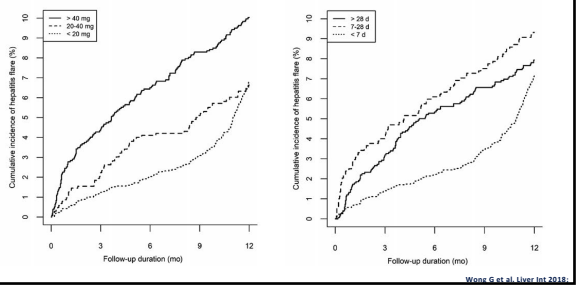
Incidence of reactivation from resolved HBV infection in rheumatoid arthritis patients treated with biological DMARDs



Watanabe T et al. Int J Rheum Dis 2018; epub

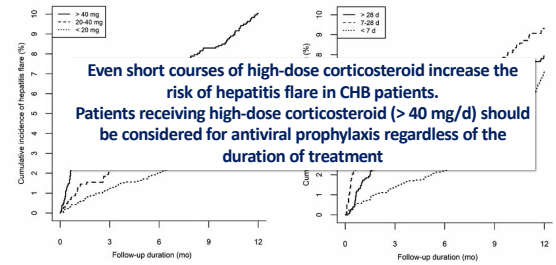
and the risk of steroids….?

The effect of steroid peak dose and duration on the risk of hepatitis flares in chronic HBV infection



Wong G et al. Liver Int 2018;

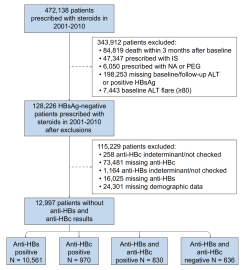
The effect of steroid peak dose and duration on the risk of hepatitis flares in chronic HBV infection



Even short courses of high-dose corticosteroid increase the risk of hepatitis flare in CHB patients.
Patients receiving high-dose corticosteroid (> 40 mg/d) should be considered for antiviral prophylaxis regardless of the duration of treatment

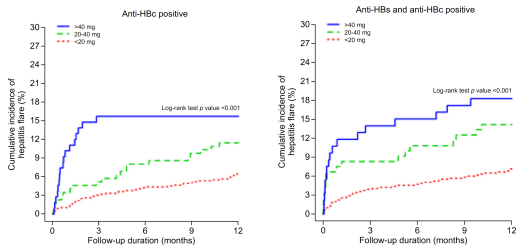
Wong G et al. Liver Int 2018;

Risk of hepatitis B surface antigen seroreversion after corticosteroid treatment in patients with previous HBV exposure



Wong G L-H et al. J Hepatol 2020; 15: 585

1-year cumulative incidence of hepatitis flare after corticosteroid treatment in HBsAg-negative patients according to different peak daily doses of corticosteroid and anti-HBs/anti-HBc status



Wong G L-H et al. J Hepatol 2020; 15: 585

Risk of hepatitis B surface antigen seroreversion after corticosteroid treatment in patients with previous hepatitis B virus exposure

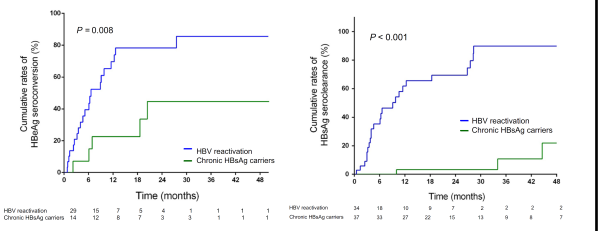
Highlights

- HBsAg^{-} patients (anti-HBc^{+} but anti-HBs^{-}) are at increased risk of HBsAg seroreversion after corticosteroid therapy.
- The peak daily dose of corticosteroid is a more important risk factor for hepatitis flares than treatment duration.
- In contrast, dose and duration of corticosteroid use are not associated with the risk of HBsAg reversion.

Wong G L-H et al. J Hepatol 2020; 15: 585

Outcome of HBV flares associated with reactivation?

Early Hepatitis B Surface Antigen Seroclearance Following Antiviral Treatment in Patients with Reactivation of Resolved Hepatitis B



Lee HL et al. Dig Dis Sci 2019, April epub

HCV is different from HBV
No long-term or latent reservoir

HBV	HCV
Treatment	Treatment
Long-term suppression of viral replication[1]	*Viral eradication*
Life-long risk of reactivation	No risk of reactivation after eradication

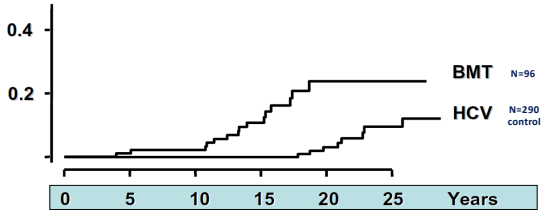
cccDNA = covalently closed circular DNA

1. Pawlotsky JM. *J Hepatol* 2008;134:405-415

Impact of HCV infection in patients receiving anti-cancer therapies or stem cell transplantation

- Increase in viral replication
- Transient hepatitis, rarely fibrosing cholestatic hepatitis
- Faster fibrosis progression
- Potential risk factor for veno-occlusive disease
- Increased rate of drug-induced liver injury (DILI)
- Effect on survival?

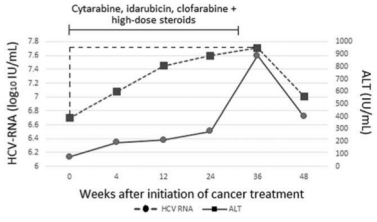
Incidence of cirrhosis in bone marrow transplant patients with chronic HCV infection



According to Peffault de Latour et al. Blood 2004; 103: 1618, and J Hepatol 2008; 48: 1008

Hepatitis C reactivation in patients receiving cancer treatment

A representative case of HCV reactivation



Torres HA et al. Hepatology 2018; 67: 36

Immunosuppressive therapies and HCV infection

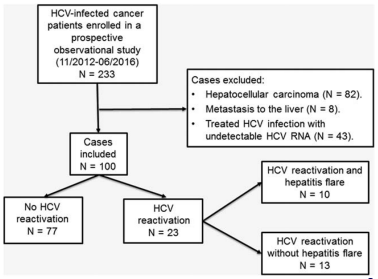
Drug (Class)	Experience in HCV infection	Effects on HCV infection
Steroids	+++	Replication ↑ Fibrosis progression ↑
Azathioprine	+	-
Mycofenolat Mofetil	+++	± anti-viral effect?
Cyclosporine A	+++	± anti-viral effect? Fibrosis progression↓?
Tacrolimus	+++	? Fibrosis progression ↑
Methotrexat	(+)	?
Anti-TNFα	(+)	No negative effects
Rituximab	+	Viremia ↑ ?

Hepatitis C reactivation in patients receiving cancer treatment

- Reactivation was defined as an increase in HCV-RNA 1 $\log_{10}$ IU/mL over baseline and
- hepatitis flare as an increase in alanine aminotransferase to 3 times the upper limit of normal

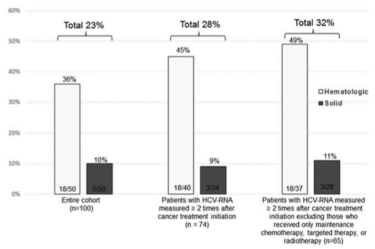
Torres HA et al. Hepatology 2018; 67: 36

Hepatitis C reactivation in patients receiving cancer treatment



Torres HA et al. Hepatology 2018; 67: 36

Hepatitis C reactivation in patients receiving cancer treatment



Torres HA et al. Hepatology 2018; 67: 36

Hepatitis C reactivation in patients receiving cancer treatment

Independent predictors of HCV reactivation

Potential Predictor	OR (95% CI)	*P*
High-dose steroids (>600 mg equivalent prednisone versus <600 mg equivalent)	5.05 (1.40-20.23)	0.01
Rituximab use (yes versus no)	9.52 (2.19-49.12)	0.001
Baseline HCV-RNA (>6 $\log_{10}$ IU/mL versus <6 $\log_{10}$ IU/mL)	0.12 (0.03-0.46)	<0.001

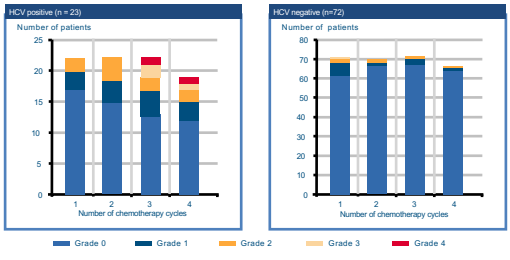
Torres HA et al. Hepatology 2018; 67: 36

Hepatitis C reactivation in patients receiving cancer treatment

- HCV reactivation occurred in 23% of HCV-infected patients receiving cancer treatment, and most had an unremarkable clinical course
- However, reactivation can affect the cancer treatment plan
- Our findings suggest that HCV infection should not contraindicate cancer therapy and infected patients should have access to multiple cancer treatments with close monitoring while receiving regimens associated with HCV reactivation

Torres HA et al. Hepatology 2018; 67: 36

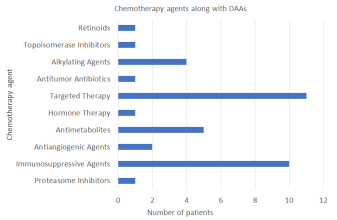
Hepatotoxicity during chemotherapy in HCV-infected patients with diffuse large B-cell NHL



Besson et al. *J Clin Oncol* 24: 953 (2006)

Should we start DAAs together with anti-cancer treatment?

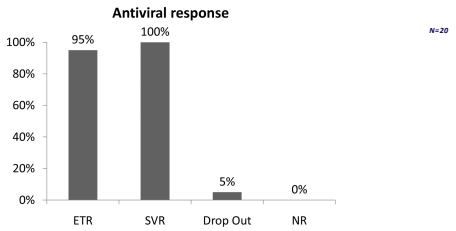
DAA treatment in concomitance with chemotherapy – is it safe?



Type of direct-acting antiviral treatment	N (%)
Total	21
Sofosbuvir + Ledipasvir +/– Ribavirin [f]	11 (52)
Sofosbuvir + Ribavirin	6 (29)
Sofosbuvir + Simeprevir	3 (14)
Sofosbuvir + Daclatasvir	1 (5)

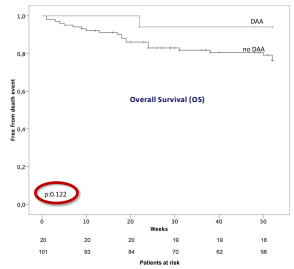
Economides MP et al. Aliment Pharmacol Ther 2016; 44: 1235

DAA treatment in HCV-infected patients with diffuse large B-cell lymphoma in concomitance with chemotherapy



Persico M et al. Hepatology 2018; 67: 48

DAA treatment in HCV-infected patients with diffuse large B-cell lymphoma in concomitance with chemotherapy



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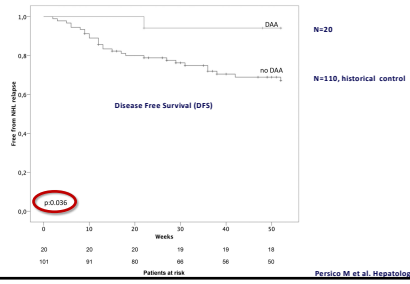
DAA treatment in HCV-infected patients with diffuse large B-cell lymphoma in concomitance with chemotherapy



Persico M et al. Hepatology 2018; 67: 48

DAA treatment in HCV-infected patients with diffuse large B-cell lymphoma in concomitance with chemotherapy

In conclusion, our data confirm a pathogenic role for HCV in the development of NHL and suggest that AVT with DAA may represent a useful and safe approach for HCV-positive NHLs in combination with chemotherapeutic regimens in order to reinforce the remission of the neoplastic disease.

Persico M et al. Hepatology 2018; 67: 48

Hepatitisvirus Scrrening fpr all Cancer patients?

- Universal screening of patients with newly diagnosed cancer for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV is not routine in oncology practice, and experts disagree about whether universal screening should be performed.
- Screening all 1.6 million patients with newly diagnosed cancer in the United States for HBV, HCV, and HIV each year will increase the cost of cancer care and may have low yield and negligible influence on patient outcomes

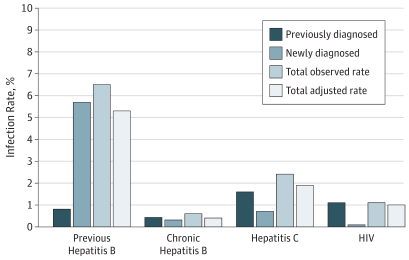
Ramsey SD et al. JAMA Oncol Jan 2019 online

Hepatitis B Virus, Hepatitis C Virus, and HIV Infection Among Patients With Newly Diagnosed Cancer From Academic and Community Oncology Practices

- General viral hepatitis screening in patients with cancer before starting cancer therapy?
- What is the prevalence of HBV, HCV and HIV infection among patients with newly diagnosed cancer?

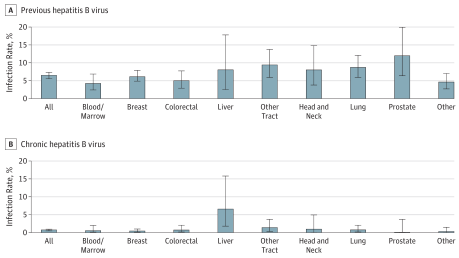
Ramsey SD et al. JAMA Oncol Jan 2019 online

Total observed rate is the sum of rates for patients with previously and newly diagnosed viral infection (N=3051)



Ramsey SD et al. JAMA Oncol Jan 2019 online

Observed Infection Rates by Type of Virus and Cancer



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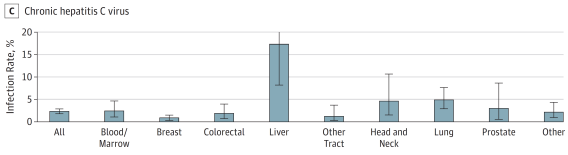


Ramsey SD et al. JAMA Oncol Jan 2019 online

Hepatitis B Virus, Hepatitis C Virus, and HIV Infection Among Patients With Newly Diagnosed Cancer From Academic and Community Oncology Practices

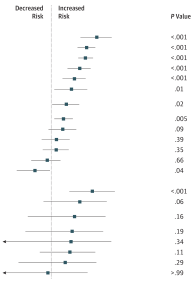
- Among patients with viral infections,
- 42.1% with chronic HBV
- 31.0% with HCV, and
- 5.9% with HIV were newly diagnosed through the study

- Hepatitis virus screening in patients with newly diagnosed cancer before starting treatment may be warranted to prevent viral reactivation and adverse clinical outcomes
- Universal screening for HIV infection may not be warranted

Ramsey SD et al. JAMA Oncol Jan 2019 online

Association of Important Predictive Factors and Incidence of Viral Infection

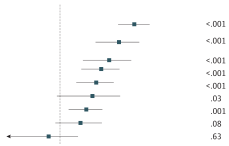
Question	Present Rates, %	Absent Rates, %	Odds Ratio (95% CI)	P Value
Previous HBV				
Sexual contact with HIV-positive person	35.9	6.1	8.66 (4.08-17.66)	<.001
Self-reported infection with HCV or HIV	23.3	5.4	5.32 (3.52-7.93)	<.001
Born in high HBV prevalence region	20.6	4.8	5.11 (3.61-7.18)	<.001
Injected drug use	19.6	6.0	3.85 (2.21-6.44)	<.001
Unprotected sex with high-risk person	16.2	6.0	3.01 (1.75-4.98)	<.001
Sexual contact with hepatitis-positive person	15.2	6.3	2.67 (1.19-5.40)	.01
Unprotected set with MSM, multiple, or anonymous partners	12.0	6.2	2.04 (1.06-3.68)	.02
Diagnosis or treatment for STD	10.4	6.0	1.81 (1.18-2.73)	.005
Blood transfusion between 1978-1985	10.6	6.3	1.76 (0.89-3.22)	.09
Needle-stick exposure	8.1	6.4	1.30 (0.64-2.40)	.39
Household contact with hepatitis-positive person	8.1	6.4	1.29 (0.69-2.25)	.35
High-risk occupation	5.5	6.5	0.83 (0.40-1.55)	.66
Completed HBV vaccine (3 or more doses)	3.3	6.8	0.47 (0.20-0.96)	.04
Chronic HBV				
Born in high HBV prevalence region	2.6	0.4	7.04 (2.39-19.97)	<.001
Needle-stick exposure	2.0	0.5	3.83 (0.70-13.75)	.06
Unprotected set with MSM, multiple, or anonymous partners	1.7	0.6	3.05 (0.34-13.21)	.16
Unprotected sex with high-risk person	1.5	0.6	2.73 (0.30-11.80)	.19
Sexual contact with hepatitis-positive person	1.5	0.6	2.58 (0.06-16.99)	.34
Diagnosis or treatment for STD	1.3	0.5	2.46 (0.59-7.90)	.11
Self-reported infection with HCV or HIV	1.1	0.6	1.97 (0.22-8.50)	.29
Household contact with hepatitis-positive person	0.5	0.6	0.87 (0.02-5.62)	>.99



Ramsey SD et al. JAMA Oncol Jan 2019 online

Association of Important Predictive Factors and Incidence of Viral Infection

HCV				
Injected drug use	23.9	1.7	17.87 (9.61-32.42)	<.001
Tested because of blood exposure, injected drug use, or transfusion before 1992	16.7	2.1	9.20 (3.78-20.21)	<.001
Tested because of symptoms	13.2	2.2	6.78 (2.48-15.95)	<.001
Blood transfusion between 1978-1985	9.6	2.1	4.94 (2.27-9.85)	<.001
Tested because born between 1945-1965	8.0	2.1	4.04 (1.87-8.02)	<.001
Self-reported infection with HIV	7.7	2.3	3.54 (0.90-10.11)	.03
Snorted cocaine	5.6	2.1	2.80 (1.44-5.12)	.001
Needle-stick exposure	5.0	2.3	2.26 (0.85-5.06)	.08
High-risk occupation	1.5	2.5	0.61 (0.12-1.89)	.63



Ramsey SD et al. JAMA Oncol Jan 2019 online