Updates on Hepatitis B

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Disclosures

In the last two years, I have served on the Data Adjudication Committee for a non-hepatology investigational drug for Novo Nordisk and the P&T Committee for Premera

Any conflicts of interest have been mitigated.

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Disclaimer

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AETC AIDS Education & Training Center Program Mountain West

Objectives

1. To define low, medium and high risk immunosuppressing regimens for hep B reactivation
2. To list ways that guidance for hep B therapy is changing
3. To describe the safety and efficacy of siRNA therapy for chronic hep B

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Background: HIV/HBV Coinfection

- Shared pathways for transmission: IDU, maternal to child, and sexual intercourse
- Globally, 5-20% of people living with HIV also have chronic hep B
  - Depends on geography (more common in sub-Saharan Africa and Asia)
- HIV coinfection significantly worsens natural history of HBV infection
  - Increased risk of chronic HBV
  - Higher HBV viral load and infectivity
  - Accelerated liver disease progression
- Reduced response to HBV treatment
- More reactivation of HBV

Georgios K. Nikolopoulo, Dimitrios Paraskevis, Eleni Hatzitheodorou, Zissis Moschidis, Vana Sypsa, Xenophon Zavitsanos, Victoria Kalapothaki, Angelos Hatzakis, Impact of Hepatitis B Virus Infection on the Progression of AIDS and Mortality in HIV-Infected Individuals: A Cohort Study and Meta-Analysis, *Clinical Infectious Diseases*, Volume 48, Issue 12, 15 June 2009, Pages 1763–1771, https://doi.org/10.1086/599110

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Case 1

Patient is a 40 yo man presents with 2 weeks of drenching night sweats and fatigue. He is diagnosed with stage III Hodgkin's lymphoma. His oncologist would like to start him on nivolumab + AVD (doxorubicin, vinblastine and dacarbazine). He is second generation Vietnamese-American and has never been screened for hepatitis B.

Should he be screened?

A) No, because he thinks he was vaccinated as a child growing up in Southern California.

B) No, because he should start chemotherapy immediately given the advanced nature of disease

C) Yes, because he will receive immunosuppressing therapy

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Case 1

He is screened and is HBsAg+, cAb+, ALT 25 IU/ml, and HBV DNA of 2,000 IU/ml. He has mild anemia but rest of his labs are normal. Should he start on antiviral prophylaxis?

A) Yes, because he will take a regimen containing anthracycline derivative and immune checkpoint inhibitor

B) Yes, because he has a high viral level of HBV

C) No, because there is a drug-drug interaction between both entecavir and tenofovir with his chemo regimen

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Background: Fulminant Hep B in Patients Receiving Chemotherapy and Immunosuppressants

- Greatest risk is in surface Ag+ patients (40-50% risk of reactivation and flare)
- Also occurs in patients with isolate core Ab+, but less often (4-14%)
- Any kind of chemotherapy can trigger
- Greatest risk with anti-CD20 antibodies

Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148(1):221. Perrillo RP, Martin P, Lok AS
Preventing hepatitis B reactivation due to immunosuppressive drug treatments. JAMA. 2015 Apr;313(16):1617-8. Hoofnagle JH. Reactivation of hepatitis B. Hepatology. 2009;49(5 Suppl):S156.

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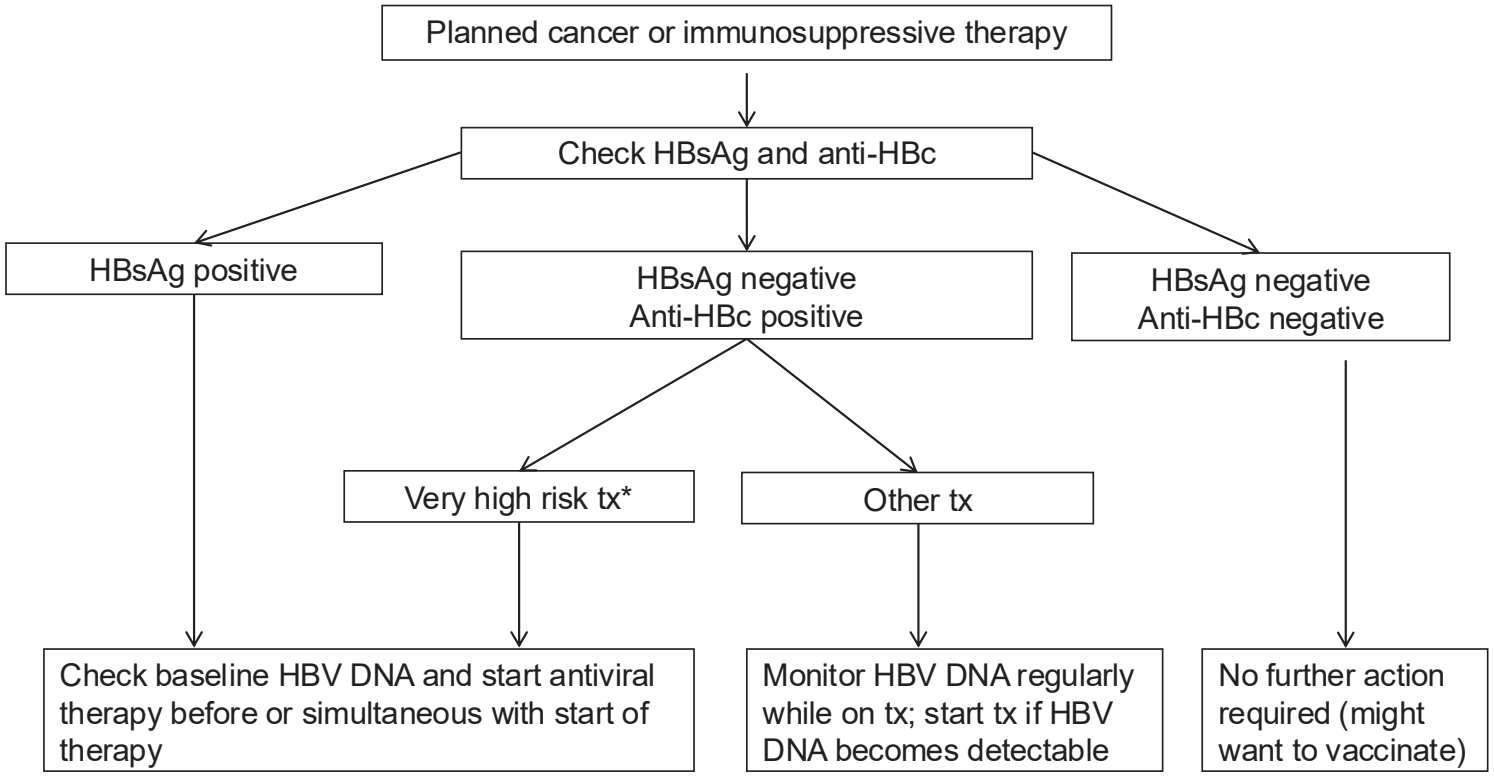
2015 AGA Guidelines



*Anti-CD20, stem cell txp

Di Bisceglie A, et al. Hepatology 2015;61:703-11. Barone M, Hepatology 2015;62: 40-6

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2025 Update

- Many new immunotherapies approved in last decade: checkpoint inhibitors, CAR-T therapy, tyrosine kinase inhibitors, etc.
- New data about safety after transarterial chemoembolization, Hep C directly acting antivirals
- Lower threshold of starting hep B antiviral prophylaxis

AGA Clinical Practice Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation in At-Risk Individuals
Ali, Faisal S. et al. Gastroenterology, Volume 168, Issue 2, 267 - 284

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Questions Asked By Committee

Table 1. Focused Questions and Corresponding PICO (Patients, Intervention, Comparator, and Outcome) Questions Addressed in These Guidelines

Question no.	Focused question	PICO question			
		Population	Intervention	Comparator	Outcome
1	Should patients presumed to be at risk of HBVr be screened for HBV markers?	Patients at risk for HBVr	Testing of HBsAg, anti-HBc, anti-HBs	No testing	HBV reactivation Hepatitis from HBV reactivation Chemotherapy/drug interruption Adverse events Resource use
2	Do patients at risk for HBVr who are anti-HBc–positive, HBsAg-negative require antiviral prophylaxis?	All patients who are anti-HBc–positive and at risk for HBVr	Antiviral prophylaxis	No antiviral prophylaxis + HBV-DNA monitoring	HBV reactivation Hepatitis from HBV reactivation Chemotherapy/drug interruption Adverse events Resource use
3	Do patients at risk for HBVr who are anti-HBc–positive and HBsAg-positive require antiviral prophylaxis?	All patients who are anti-HBc–positive and are also HBsAg-positive at risk for HBVr	Antiviral prophylaxis	No antiviral prophylaxis + HBV-DNA monitoring	HBV reactivation Hepatitis from HBV reactivation Chemotherapy/drug interruption Adverse events Resource use

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First Recommendation

For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone (strong recommendation, moderate evidence)

Implementation Considerations:

- Assumes the use of antivirals with a high barrier to resistance
- Antiviral prophylaxis should be started before start of immunosuppressing medications and continued at least 6 months after discontinuation of risk-imposing therapy (at least 12 months for B-cell-depleting agents)

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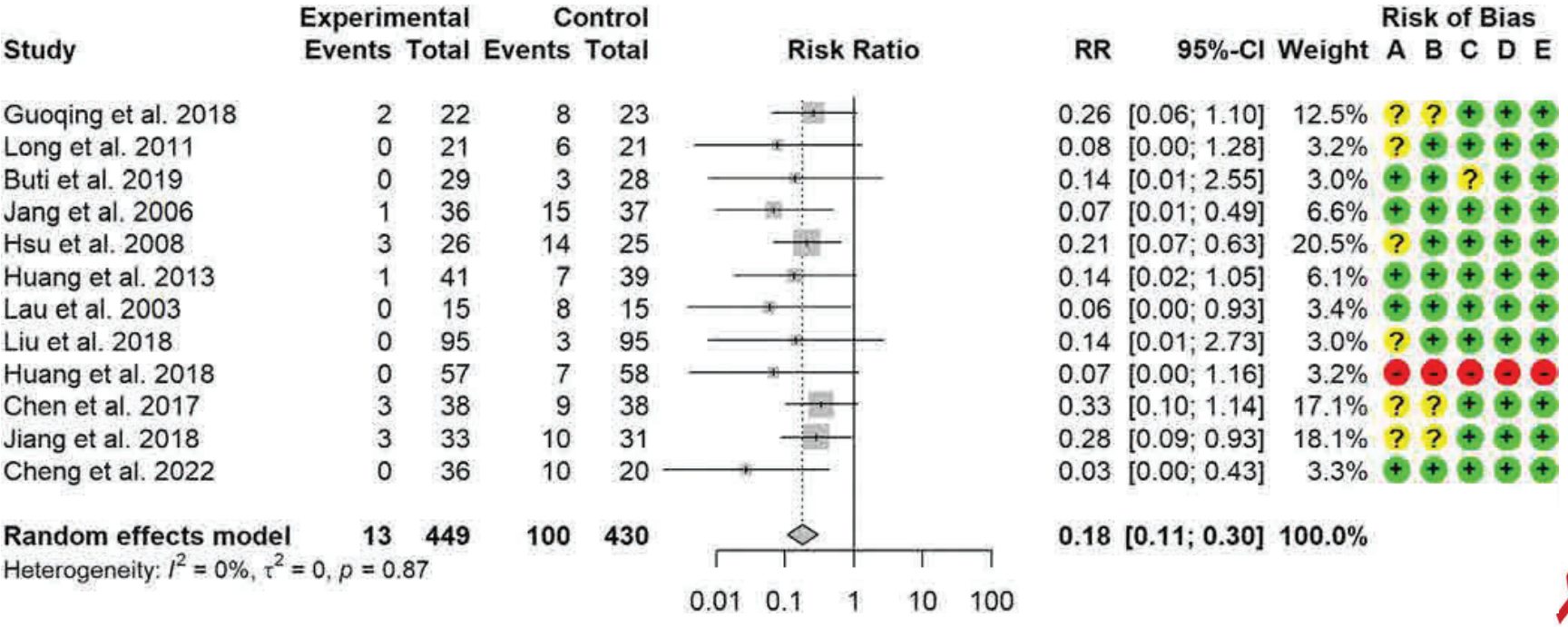
Evidence for First Recommendation

- 12 RCTs
- 82% reduction in risk of HBVr (95% CI: 70-89%)



Second Recommendation

For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone (conditional recommendation, moderate evidence)

Implementation Considerations:

- Assumes the use of antivirals with a high barrier to resistance
- Shared decision-making model: if patients place a higher value on avoiding long-term use of antiviral therapy and associated costs, could monitor q 1-3 months with HBV DNA and ALT

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Third Recommendation

For individuals at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis (conditional recommendation, moderate evidence)

Implementation Considerations:

- Assumes regular and sufficient follow-up that ensures continued monitoring
- Patients who value avoiding the small risk of reactivation (particularly those on >1 immunosuppressing medication) may reasonably select antiviral therapy

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Fourth Recommendation

For individuals at potential risk of HBVr, the AGA recommends testing for hepatitis B (Strong recommendation, moderate evidence)

Implementation Considerations:

- Given universal CDC screening guidance for HBV for all adults >18 yo with HBVsAg, cAb, and sAb, stratifying screening practices is no longer needed
- It is reasonable to test for serologic markers alone initially, followed by HBV DNA if sAg or cAb are positive

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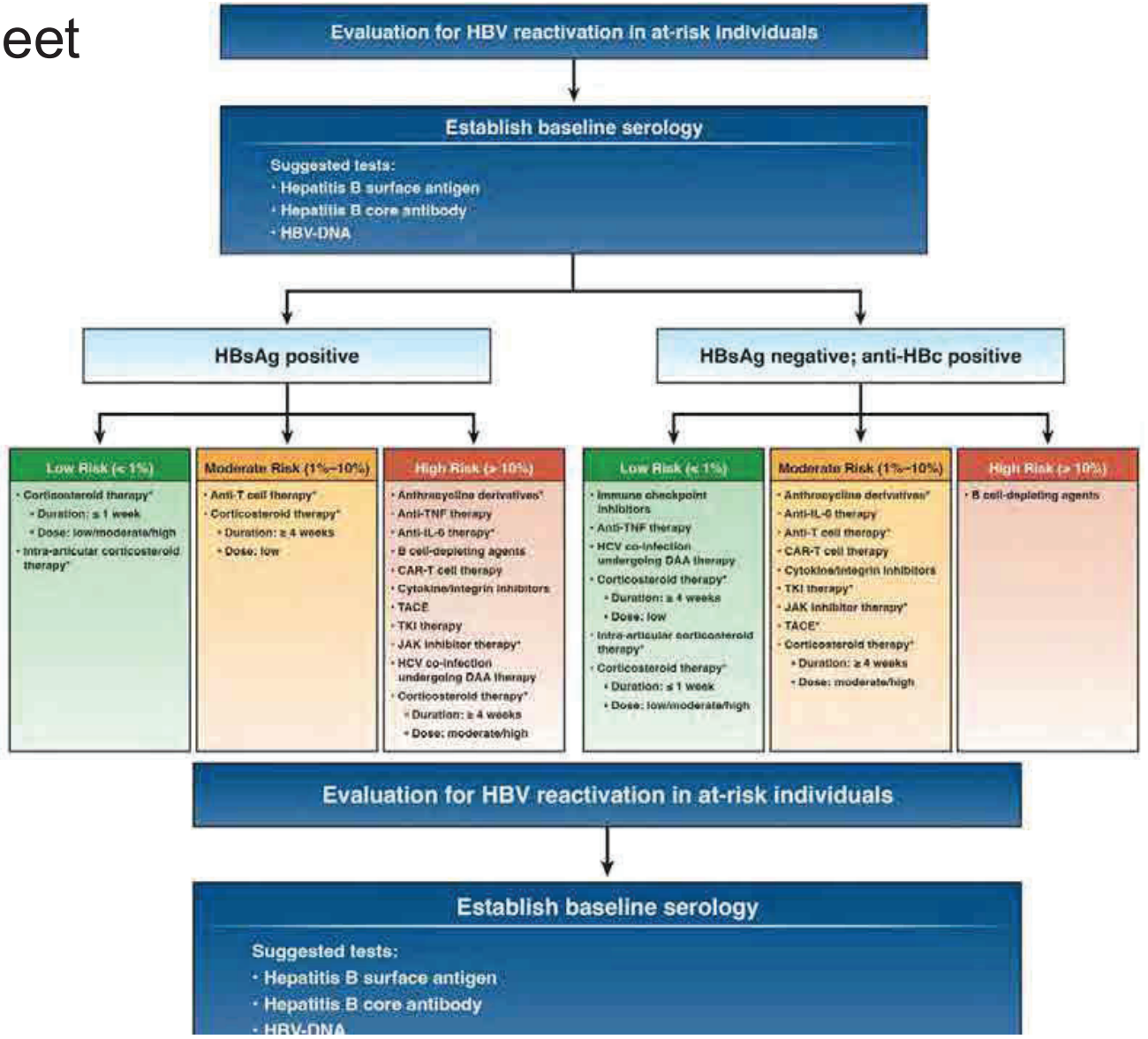
Data Flowsheet



Why is it so hard to cure hepatitis B

- **High levels of HBsAg production** → immune exhaustion
- **cccDNA** → difficult for immune system and antivirals to penetrate, remains even after sAg loss
- **Integrated HBV DNA into host** → occurs early in course of infection, leads to de novo hepatocarcinogenesis

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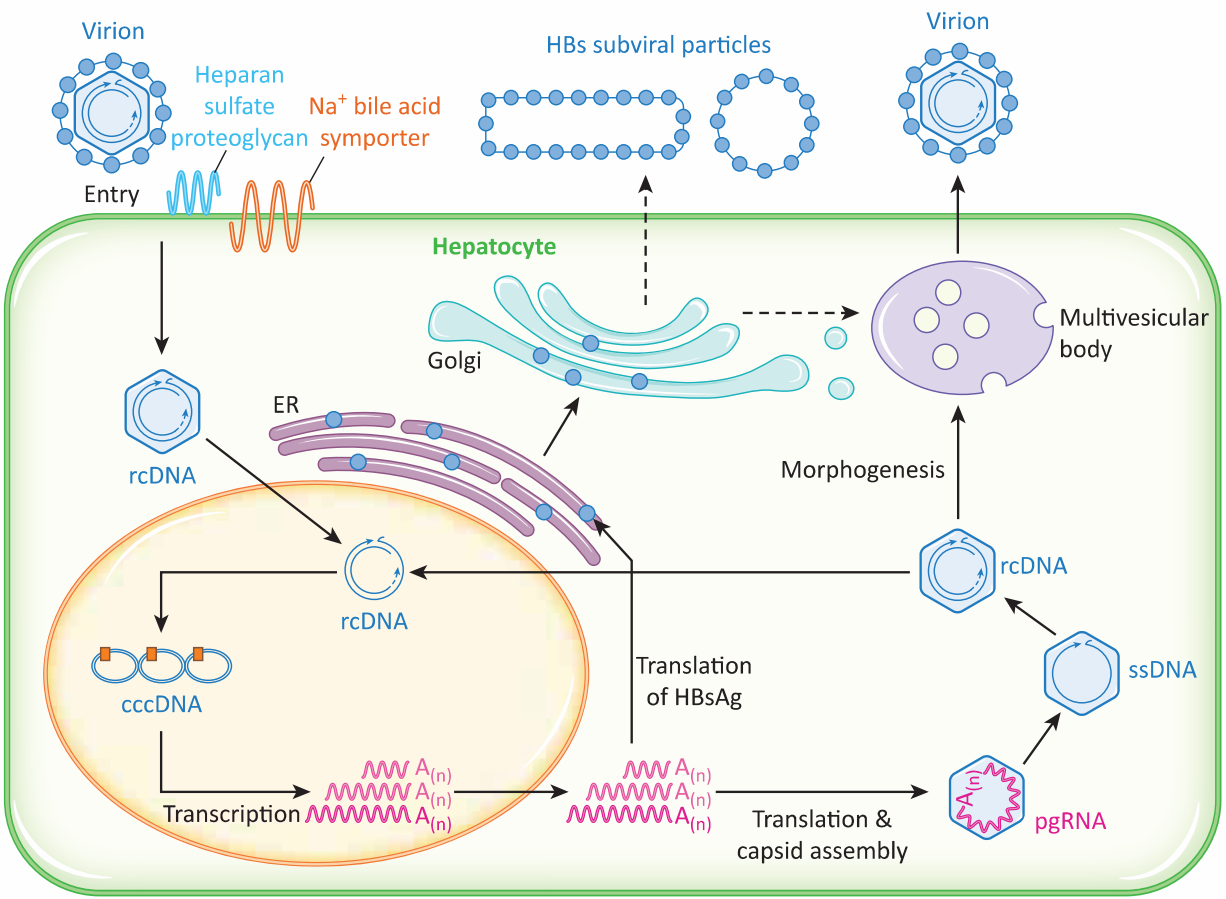
Review of HBV Lifecycle



C Shih, et al
Trends in Microbiology, April 2018, Vol.26, No. 4

What are the pros/cons of antiviral therapy for Hep B?

Pros:

- Decreased chance of transmission
- Theoretically lower risk of HCC
- Some chance of functional cure
- Low side effects of meds
- Peace of mind

Cons:

- Cost of antivirals
- Going off and causing a flare
- Slight risk of renal and bone toxicity with TDF

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Hep B Guidelines

AASLD (2015, updated 2018)

- The AASLD suggests that adults with compensated cirrhosis and low levels of viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level.
- The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB.
- The AASLD recommends antiviral therapy for adults with immune-active CHB (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications.
- Immune-active CHB is defined by an elevation of ALT >2 ULN or evidence of significant histological disease plus elevated HBV DNA above 2,000 IU/mL (HBeAg negative) or above 20,000 IU/mL (HBeAg positive).

HBV Primary Care Workgroup (2020)

- For persons without cirrhosis, treatment is recommended if the HBV DNA level is greater than 2,000 IU/mL and the ALT level is elevated, regardless of HBeAg status. For this purpose, elevated ALT is defined as greater than 25 U/L in females and greater than 35 U/L in males that is persistent for at least 3 to 6 months.
- Treatment is recommended for all persons with cirrhosis, regardless of HBV DNA level, ALT level, or HBeAg status.

https://www.aasld.org/practice-guidelines/chronic-hepatitis-b; Tang AS, Thornton K, et al. https://www.hepatitisb.uw.edu/go/hbv/initial-treatment/core-concept/all#hepatitis-b-treatment-guidance-recommendations-hbv-primary-care-workgroup

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Hep B Guidelines (continued)

EASL (2017)

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

WHO (2024)

HBV DNA	ALT level	Fibrosis Level	Treat?
>2,000 IU/ml	>19 IU/L for women, >30 IU/L for men, at least twice	-	Yes
		APRI >0.5 or F2 or greater on TE	Yes
		Clinical cirrhosis; APRI >1 or F4 on TE	Yes
		Presence of coinfections, comorbidities, immune suppression, extrahepatic manifestations, family history of liver cancer or cirrhosis	Yes

https://www.who.int/publications/i/item/9789240090903; European Association For The Study Of The Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98

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siRNA: Multiple Mechanisms of Action

1. Targeting HBV RNA:

- siRNAs are designed to be complementary to specific sequences within HBV RNA, including pgRNA and mRNA.

2. RNA Interference (RNAi):

- Once inside the cell, siRNAs are processed by the cell's machinery into a RNA-induced silencing complex (RISC).

3. mRNA Degradation:

- The RISC complex, containing the siRNA, then binds to the target HBV mRNA, leading to mRNA degradation and silencing of the targeted gene.

4. Reduced Viral Protein Production:

- By reducing the levels of HBV mRNA, siRNAs effectively lower the production of viral proteins, including HBsAg, HBcAg, HBeAg, and HBV polymerase.

5. Suppression of Viral Replication:

- Reduced viral protein production leads to a decrease in viral replication, including the suppression of HBV cccDNA, the stable form of HBV DNA responsible for its persistence.

6. Potential Immune Reconstitution:

- By significantly reducing HBV viral antigens, siRNAs may indirectly enhance the host's immune response against the virus, which is a key advantage over other antiviral treatments that may only suppress viral replication but not directly target the viral reservoir.

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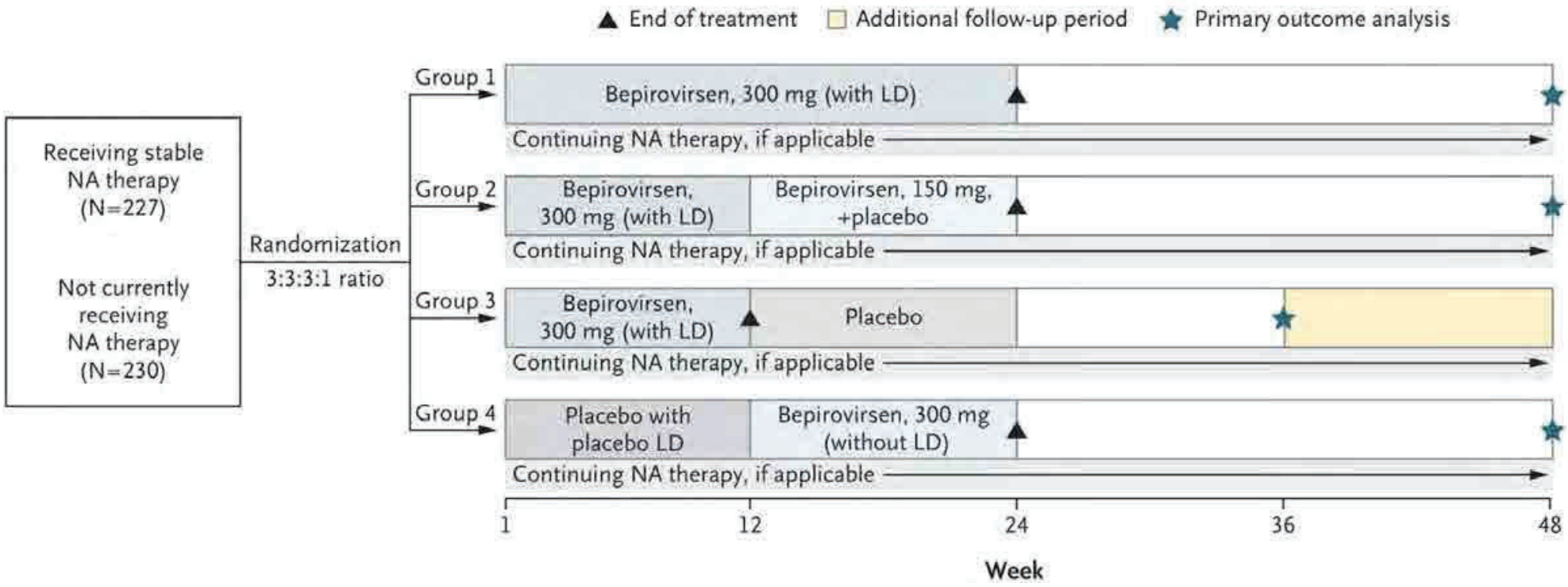
Phase 2 Study of Bepirovirsen



Eligibility: adults, qsAg>100 Iu/ml, if on NA HBV DNA <90 IU/ml and ALT <2xULN, if NA naïve HBV DNA>2000 IU/ml and ALT <3xULN, no HIV, HDV or HCV, no cirrhosis

Yuen M-F et al. N Engl J Med 2022;387:1957-1968

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Results

Table 2. Primary Outcome (Intention-to-Treat Population).*

Variable	Receiving NA Therapy				Not Receiving NA Therapy			
	Group 1 (N=68)	Group 2 (N=68)	Group 3 (N=68)	Group 4 (N=23)	Group 1 (N=70)	Group 2 (N=68)	Group 3 (N=68)	Group 4 (N=24)
Primary-outcome event — no. of participants (%)†	6 (9)	6 (9)	2 (3)	0	7 (10)	4 (6)	1 (1)	0
Point estimate of response — % (95% credible interval)	9 (0–31)	9 (0–43)	3 (0–16)	2 (0–8)‡	10 (0–38)	6 (0–25)	2 (0–6)‡	2 (0–8)‡

* Participants were randomly assigned (in a 3:3:3:1 ratio) to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). Loading doses of bepirovirsen (300 mg, in groups 1, 2, and 3) or placebo (in group 4) were administered on days 4 and 11.

† The primary outcome was an HBsAg level below the lower limit of detection (0.05 IU per milliliter) and an HBV DNA level below the lower limit of quantification (20 IU per milliliter) maintained for 24 weeks after the planned end of bepirovirsen treatment, without newly initiated antiviral medication.

‡ Shown are point estimates and credible intervals from post hoc unstratified Bayesian analysis owing to nonconvergence of the prespecified stratified Bayesian hierarchical model. Additional details are provided in the Methods section in the Supplementary Appendix.

Among patients with baseline qsAg <3000 Iu/ml, 12-25% had durable sAg loss and HBV DNA suppression

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Safety Data

Adverse Event	Receiving NA Therapy				Not Receiving NA Therapy			
	Group 1 (N=68)	Group 2 (N=67)	Group 3 (N=68)	Group 4 (N=23)	Group 1 (N=70)	Group 2 (N=67)	Group 3 (N=68)	Group 4 (N=24)
	number of participants (percent)							
Visits at wk 1–12 (when group 4 received placebo)								
Any adverse event	53 (78)	57 (85)	52 (76)	10 (43)	63 (90)	55 (82)	59 (87)	13 (54)
Any grade 3 or 4 adverse event†	5 (7)	9 (13)	5 (7)	0	10 (14)	9 (13)	7 (10)	0
Any serious adverse event‡	1 (1)	1 (1)	3 (4)	0	3 (4)	0	0	0
Adverse events of special interest§								
Injection-site reaction	38 (56)	47 (70)	43 (63)	3 (13)	50 (71)	41 (61)	46 (68)	3 (12)
Vascular inflammation and complement activation	24 (35)	31 (46)	30 (44)	1 (4)	45 (64)	38 (57)	42 (62)	6 (25)
Thrombocytopenia	12 (18)	9 (13)	11 (16)	3 (13)	21 (30)	17 (25)	19 (28)	4 (17)
Increased ALT level	7 (10)	10 (15)	6 (9)	0	15 (21)	12 (18)	11 (16)	1 (4)
Renal injury	2 (3)	6 (9)	6 (9)	0	5 (7)	3 (4)	9 (13)	1 (4)
All visits								
Any adverse event	56 (82)	59 (88)	53 (78)	16 (70)	65 (93)	60 (90)	62 (91)	19 (79)
Any adverse event leading to discontinuation of trial agent	2 (3)	3 (4)	3 (4)	0	3 (4)	1 (1)	5 (7)	0
Any grade 3 or 4 adverse event†	7 (10)	11 (16)	8 (12)	0	16 (23)	15 (22)	13 (19)	4 (17)
Any serious adverse event‡	1 (1)	1 (1)	4 (6)	0	6 (9)	2 (3)	3 (4)	0
Adverse events of special interest§								
Injection-site reaction	41 (60)	49 (73)	43 (63)	11 (48)	52 (74)	41 (61)	49 (72)	12 (50)
Vascular inflammation and complement activation	30 (44)	34 (51)	31 (46)	10 (43)	49 (70)	40 (60)	46 (68)	12 (50)
Thrombocytopenia	19 (28)	16 (24)	12 (18)	6 (26)	32 (46)	21 (31)	21 (31)	6 (25)
Increased ALT level	7 (10)	10 (15)	6 (9)	6 (26)	20 (29)	19 (28)	16 (24)	5 (21)
Renal injury	4 (6)	9 (13)	6 (9)	2 (9)	7 (10)	6 (9)	9 (13)	3 (12)

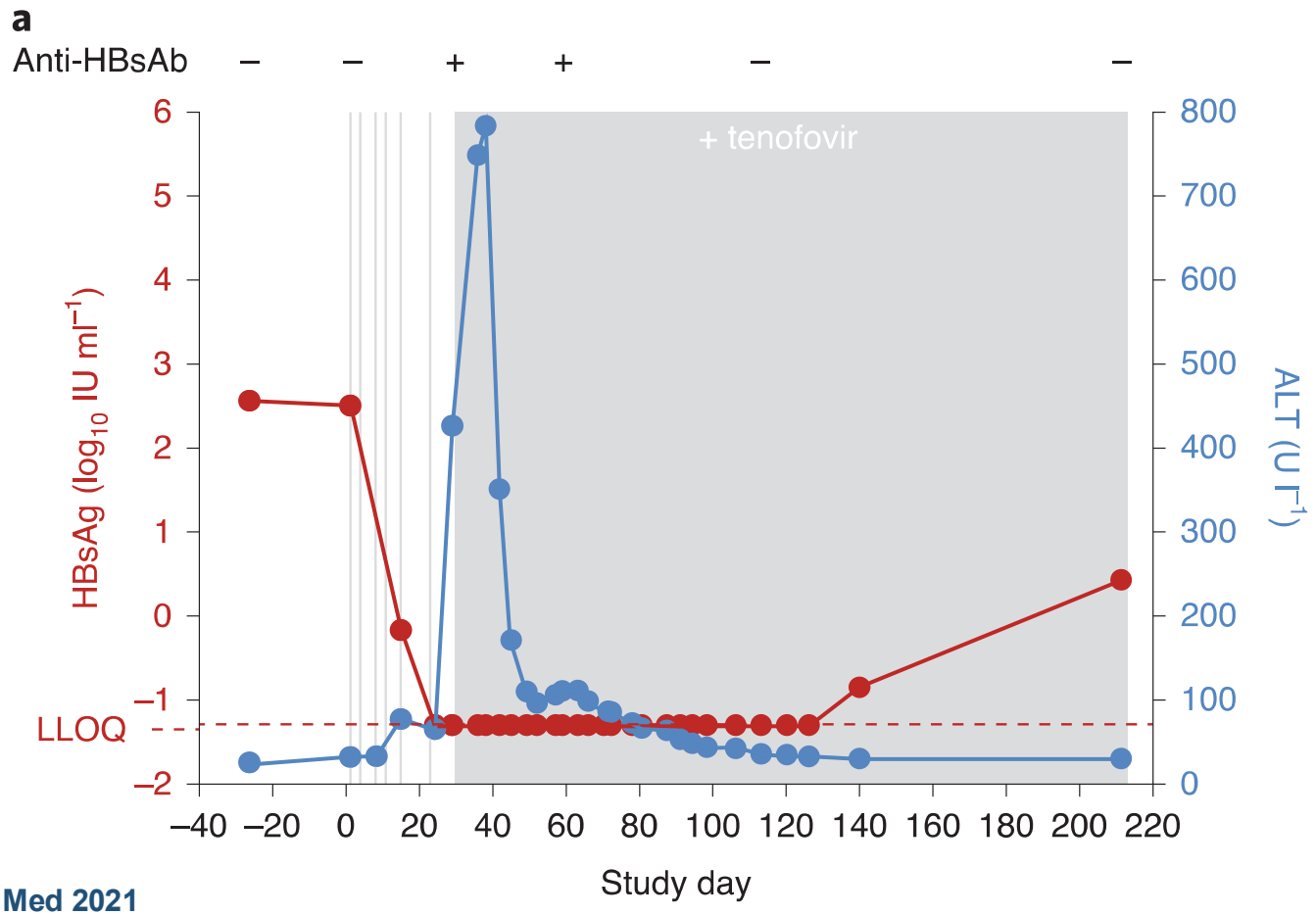
Participants were randomly assigned (in a 3:3:3:1 ratio) to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). Loading doses of bepirovirsen (300 mg, in groups 1, 2, and 3) or placebo (in group 4) were administered on days 4 and 11. In group 2, one participant receiving NA therapy and one not receiving NA therapy did not receive any bepirovirsen treatment and were therefore not included in the safety population.

† Adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1. Grade 1 indicates a mild event, grade 2 a moderate event, grade 3 a severe event, grade 4 a potentially life-threatening event, and grade 5 death.

‡ A serious adverse event is defined as an adverse event that, at any dose of bepirovirsen or placebo, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or clinically significant disability or incapacity, or is a congenital anomaly or birth defect.

§ The adverse events of special interest were defined according to standardized *Medical Dictionary for Regulatory Activities* (MedDRA) queries or MedDRA high-level terms or individual preferred terms (see Table S9 in the Supplementary Appendix). The adverse event of special interest "vascular inflammation and complement activation" included preferred terms such as injection-site pruritus and injection-site swelling. Injection-site reactions were the most commonly reported events in the trial.

ALT Flares



Yuen MF, et al. Nature Med 2021

Findings

- In this phase 2b trial, bepirovirsen at a dose of 300 mg per week for 24 weeks resulted in sustained HBsAg and HBV DNA loss in 9 to 10% of participants with chronic HBV infection
- ALT flares happen on bepirovirsen, typically at time of sAg clearance
- Being on a NA and having a baseline quant sAg <3000 IU/ml are predictive of response
- Larger and longer trials are ongoing, enrolment complete

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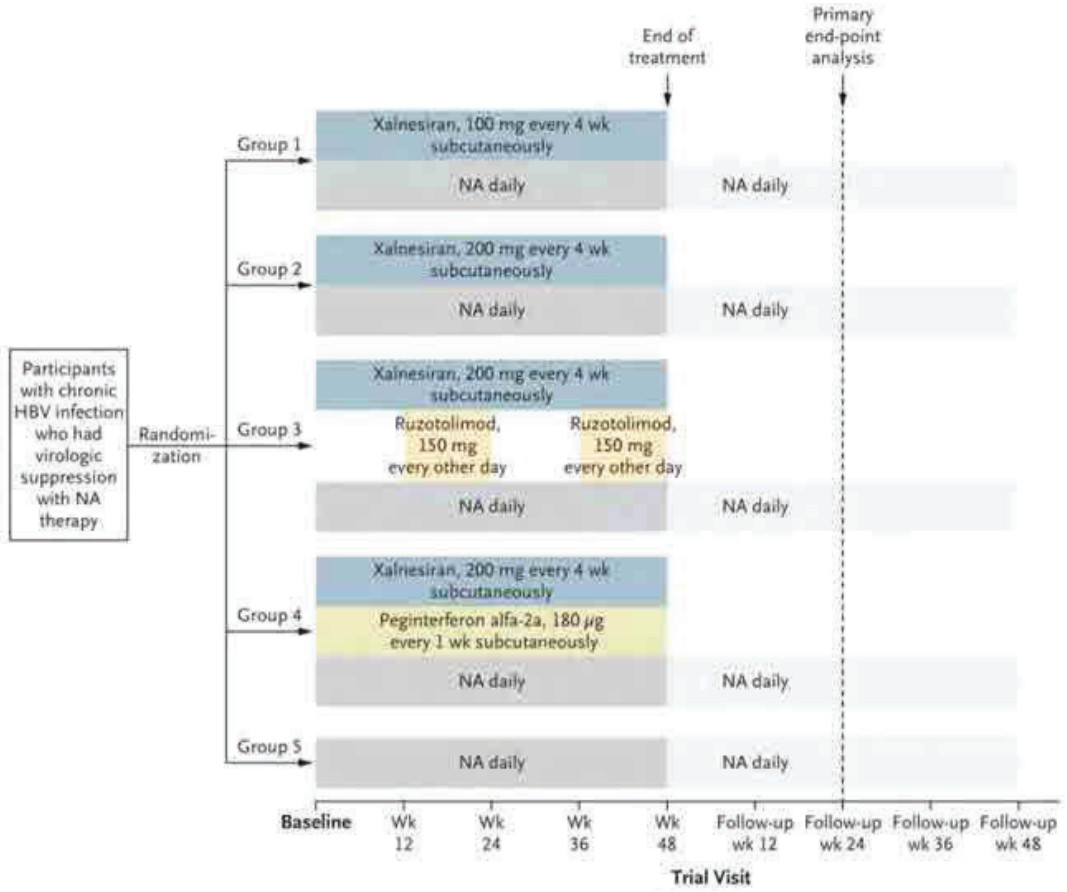
siRNA + immunomodulator: Xalnesiran



Hou J et al. N Engl J Med2024;391:2098-2109

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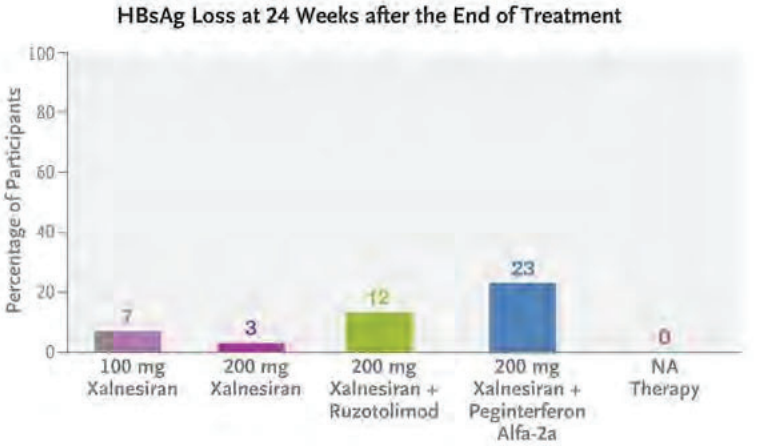
Results

The NEW ENGLAND JOURNAL of MEDICINE

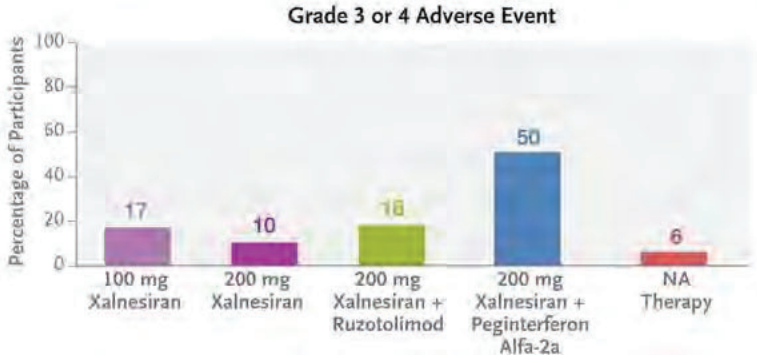
RESULTS

The percentage of participants with HBsAg loss at 24 weeks after treatment ended was highest with xalnesiran plus ruzotolimod and xalnesiran plus peginterferon alfa-2a.

HBsAg seroconversion (a secondary end point) occurred most often with xalnesiran plus peginterferon alfa-2a.



Grade 3 or 4 adverse events were not uncommon; the most frequent such event was an elevated alanine aminotransferase level, which was most often observed in the group treated with xalnesiran plus peginterferon alfa-2a.



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siRNA treatment summary

- See an initial sAg decline (up to 2-4 log after 48 weeks) but then plateaus
- Need to combine with other agents
- Rebound if stop therapy but see lower pre-set level of HBV DNA and sAg

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Treatment Paradigm: Combination Therapy

TDF
TAF
Entecavir

siRNA
Entry inhibitor
Capsid inhibitor
Antisense molecule

Therapeutic vaccine
Monoclonal Ab
TLR 8 or 9 agonist
Interferon
Checkpoint inhibitor

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Summary

- Screen patients for HBVsAg, cAb, and sAb before starting immunosuppressive therapies
- Updated recommendations suggest a lower threshold for starting antivirals, but requires shared-decision making
- Promising improvement in HBV therapy with surface Ag clearance rates approaching 25-30% after one year
- More complicated!
- Interferon coming back?
- Importance of testing for quant sAg for future therapies

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