



NJ'S INFECTIOUS DISEASE SPECIALISTS

The Road to Cure of Hepatitis B

From Viral Suppression to Off-Drug Control

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DISCLOSURES

- Clinical Investigator – Gilead, Vir, Merck, Artubus, GSK, VIIV

HEPATITIS B THE ROAD TO CURE

GOALS OF THE DISCUSSION

- **DEFINE CURE**
- **REVIEW CURRENT TREATMENT RELATED TO THE CURE JOURNEY**
- **DISCUSS THE REASONS TO WORK FOR AND EXPECT A CURE OPTION**
- **REPORT ON THE LATEST ACTIVITY TOWARD A HEPATITIS B CURE**

HEPATITIS B CURE - DEFINITIONS

The pathogenesis of CHB depends on both HBV replication and its disruption of the immune response via the production of excess quantities of HBsAg²

FUNCTIONAL CURE IS DEFINED AS:



Undetectable HBV DNA^{1,3}

AND

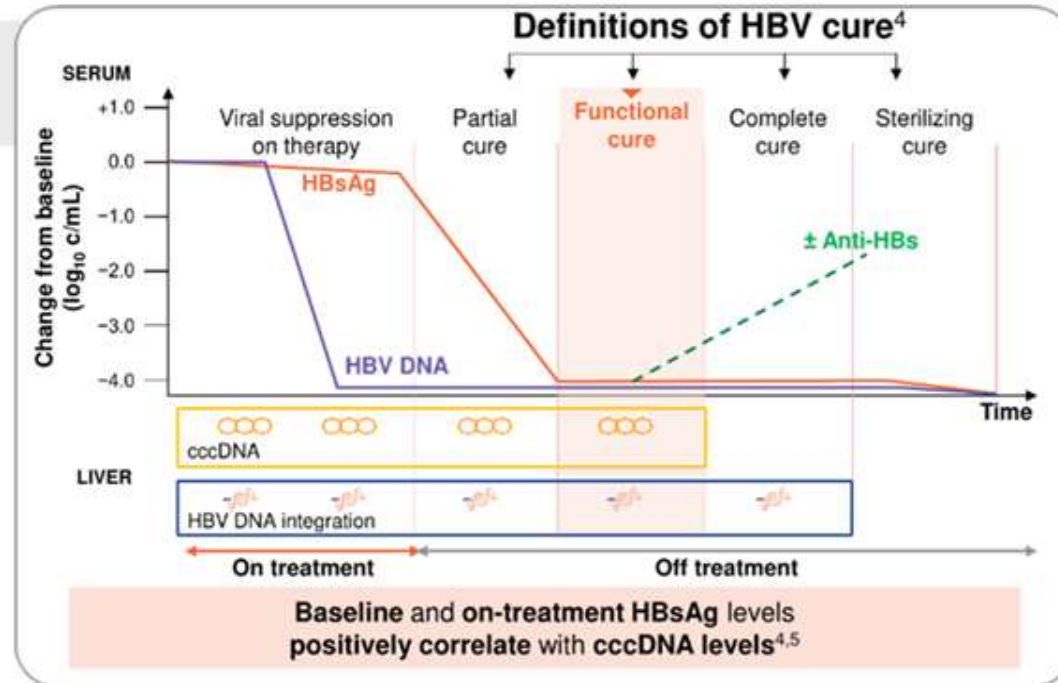


Undetectable HBsAg^{1,3}

THAT CONTINUES AT



24 weeks following cessation of all treatment^{1,3}



Sustained off-treatment HBsAg loss is rare with current HBV treatments⁶⁻⁸

Figure recreated from Testoni B et al. 2017, with permission from Thieme Media.³

anti-HB = anti-hepatitis B surface antibody; CHB = chronic hepatitis B; HBs = hepatitis B surface antibody; cccDNA = covalently closed circular DNA; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

1. European Association for the Study of the Liver. *J Hepatol* 2025; doi.org/10.1016/j.jhep.2025.03.018 [Epub ahead of print]. 2. Yardeni D et al. *Gastroenterology* 2023;164:42–60.e6; 3. Ghany MG et al. *J Hepatol* 2023;79:1254–1269; 4. Testoni B et al. *Semin Liver Dis* 2017;37:231–242; 5. Chuaypen N et al. *J Med Virol* 2017;89:130–138; 6. Marcellin P et al. *Liver Int* 2019;39:1868–1875; 7. Lok ASF. *Gut Liver* 2024;18:593–601; 8. Hanan N et al. EASL 2023. Poster SAT-158.

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WHAT CURRENT THERAPY ACHIEVES (AND DOES NOT)

- NAs: HBV DNA suppression; improved outcomes
- Peg-IFN: finite course; modest response; tolerability limits
- Gap: HBsAg loss (functional cure) uncommon on current standards
- Treatment prevents/reduces
 - Deaths, cancer and transmission risk
 - But still requires lifelong treatment

WHAT CURRENT THERAPY ACHIEVES AND DOES NOT Gilead 108 (eAG-) & 110 (eAg+)

Parameter	TAF6y	TDF2y→TAF6y	TDF3y→TAF6y
HBV DNA <29 IU/mL	571/600 (95)	117/125 (94)	165/170 (97)
HBV DNA <29 IU/mL with TND	385/600 (64)	71/125 (57)	103/170 (61)
Normalized ALT (central lab)	460/528 (87)	93/113 (82)	128/147 (87)
Normalized ALT (AASLD)	442/569 (78)	85/120 (71)	127/160 (79)
HBsAg loss	17/583 (3)	4/117 (3)	4/167 (2)
HBsAg seroconversion	12/583 (2)	4/117 (3)	3/167 (2)

Aliment Pharmacol Ther. 2024;60:1573–1586.

Chronic Hepatitis B: The Global Challenge & The Goal of Functional Cure

GLOBAL HEALTH CHALLENGE




Over 250 Million People
Affected Worldwide



Leading Cause of Liver Cancer

CURRENT STANDARD OF CARE (SOC)



Nucleos(t)ide
Analogues



Often Requires
Lifelong Therapy



Low Functional Cure Rate
(Typically ~1%)

THE GOAL: FUNCTIONAL CURE

Functional Cure:
Sustained Undetectable HBsAg (Viral Protein)
& Undetectable HBV DNA in Blood



At least 24 Weeks
After Finite Course
of Treatment

✓ HBsAg
(Undetectable)

✓ HBV DNA (Undetectable)

BENEFITS OF FUNCTIONAL CURE



Significant Reduction
in Long-Term Liver
Complications
(Including Liver Cancer)



Significant
Reduction in
All-Cause Mortality

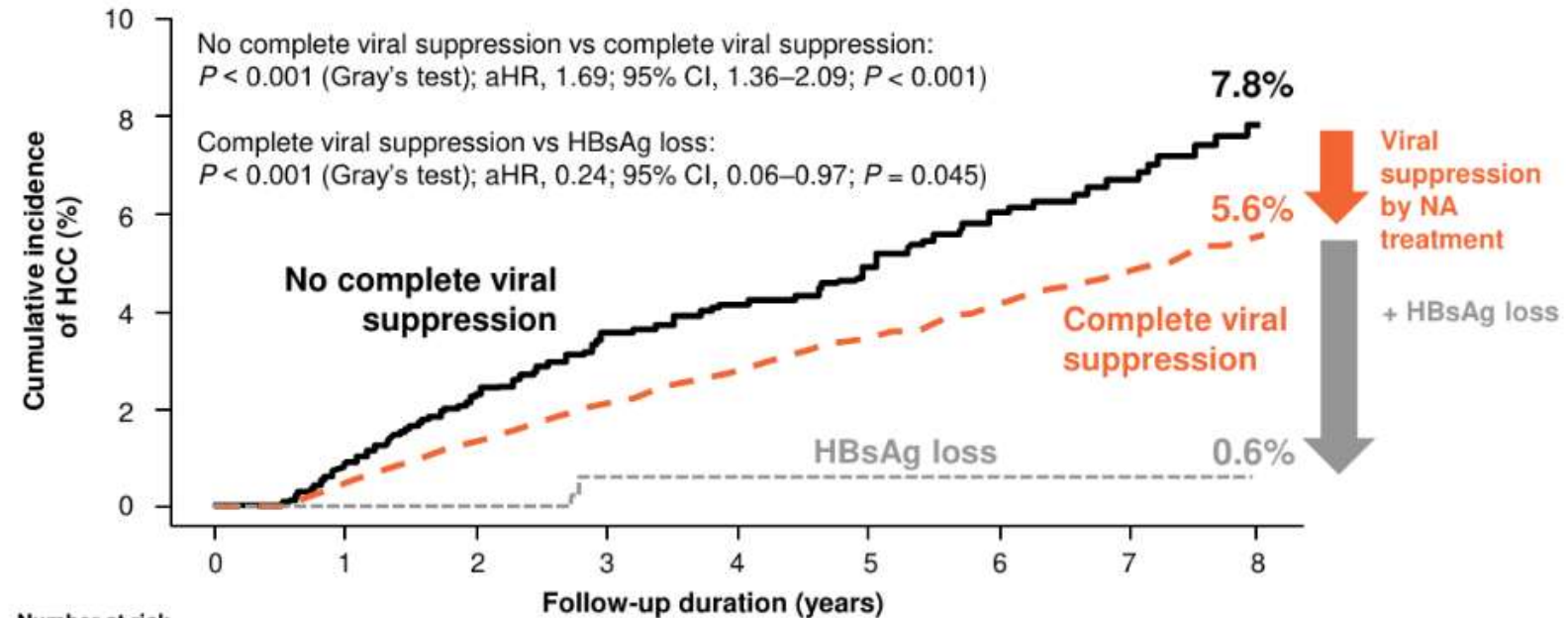


Improved
Long-Term
Health Outcomes

WHY HBV CURE NOW – THERAPEUTIC ADVANCES

- Most patients currently remain on lifelong therapy
- Cure efforts are being accelerated by:
 - new antigen-lowering agents (siRNA/ASO (antisense oligonucleotides), mAbs)
 - new direct-acting agents (capsid, entry, etc.)
 - renewed focus on immune restoration
- Recognition of significant clinical benefits for cure

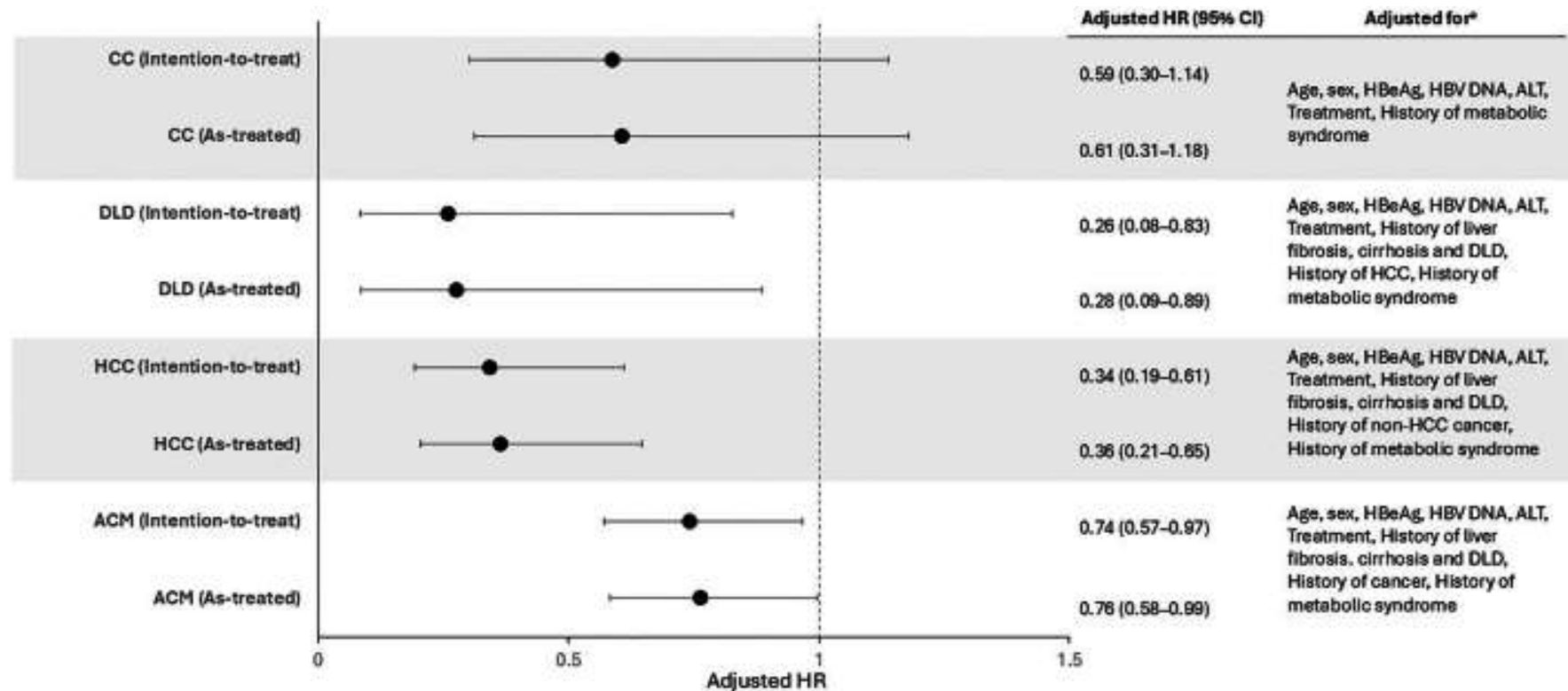
HEPATITIS B SURFACE ANTIGEN LOSS AND CLINICAL OUTCOMES



Follow-up duration (years)									
Number at risk									
No complete viral suppression (n)	2764	2715	2003	1555	1221	996	741	542	385
Complete viral suppression (n)	17,123	17,010	15,053	12,680	10,429	8402	6248	4353	2891
HBsAg loss (n)	376	376	354	318	274	231	182	126	80

Yip T, Wong G, Chan H et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. Journal of Hepatology, 2018; 70, 361-370

HEPATITIS B SURFACE ANTIGEN LOSS AND CLINICAL OUTCOMES



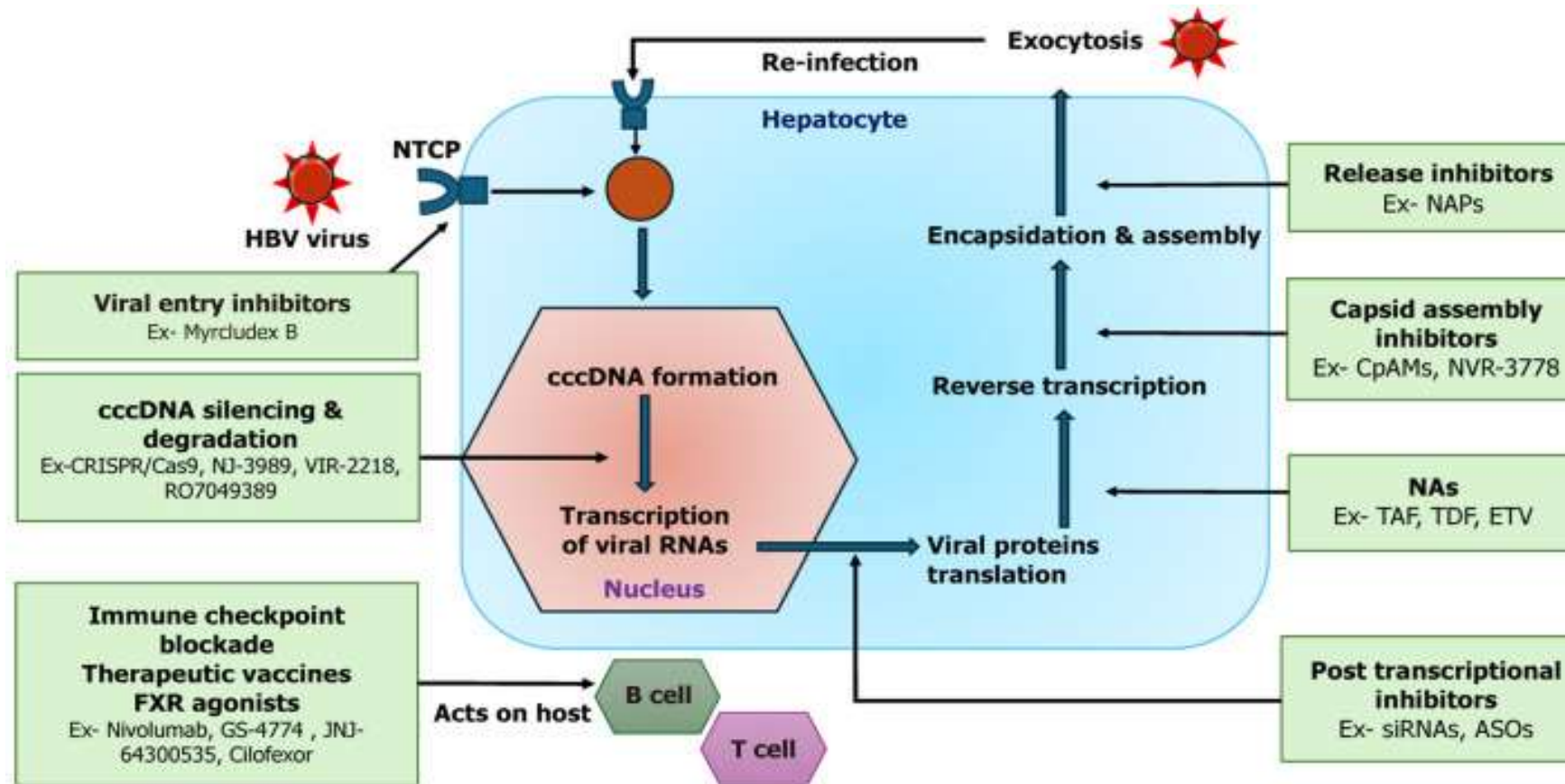
CC – cirrhosis, DLD – decompensated liver disease,
HCC – Hepatocellular carcinoma, ACM – all cause mortality

Lau W, et al Hepatitis B Surface Antigen Loss and Improved Clinical Outcomes in Asians with Chronic Hepatitis B Virus Infection. Gastro Hep Adv. 2025 Nov 6;5(2):100844. doi: 10.1016/j.gastha.2025.100844. PMID: 41487459; PMCID: PMC12757638.

WHY HBV IS HARD TO CURE: PERSISTENCE BIOLOGY

- cccDNA persists in hepatocyte nuclei
- Integrated HBV DNA continues producing HBsAg
- Chronic antigen exposure → immune exhaustion/tolerance

THE HEPATITIS B VIRUS LIFE CYCLE - THERAPEUTIC INTERVENTION POINTS



**Cure strategy
= multi-node
interruption +
immune
restoration**

WHY COMBINATION THERAPY IS THE DOMINANT HYPOTHESIS

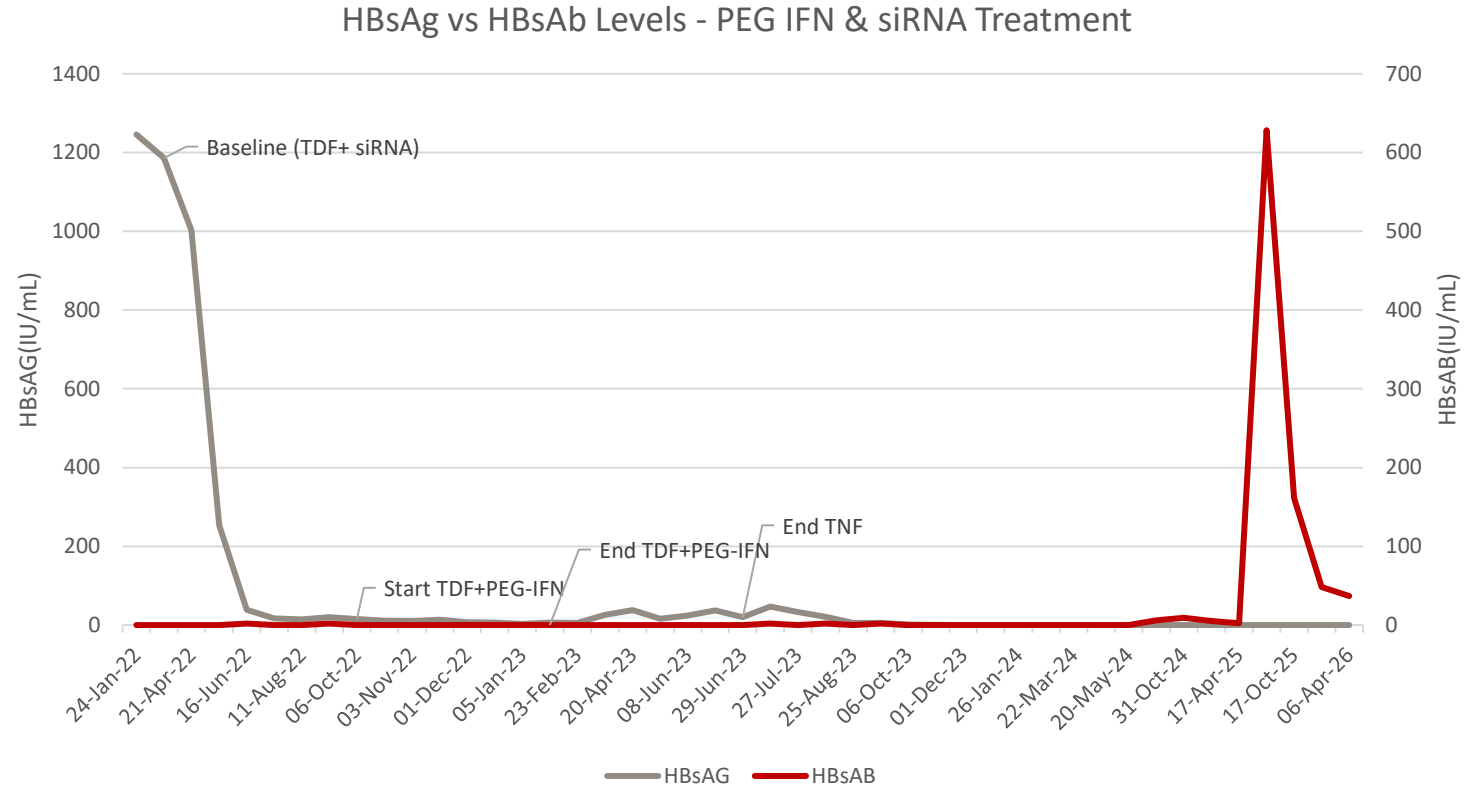
- HBV DNA suppression $\neq$ HBsAg loss
- What is needed is
 - reduce virion production,
 - lower circulating HBsAg, and
 - facilitate immune re-control
- Most promising: NA backbone + antigen-lowering + immune agent

PROOF OF CONCEPT EXISTS SPONTANEOUS HBSAG CLEARANCE EXISTS

- Natural HBsAg clearance occurs (uncommon but real)
- Clinical trials of novel therapeutics continue to demonstrate efficacy albeit in selected individuals and with low frequency – no more than 30%

PROOF OF CONCEPT EXISTS

- 52-year-old, Indian, male, with BMI 39, chronic hepatitis B enrolled into a clinical trial which included and siRNA injection and PEG IFN injection
- Received 24 weeks siRNA followed by 12 weeks PEG
- Remained on DAA throughout and then stopped 60 weeks after treatment and followed off all treatment
- Remains functionally cured for 2.5 years



CURE-TRIAL DATA POINTS ID CLINICIANS SHOULD TRACK

- Virologic: HBV DNA
- Antigen: qHBsAg
- Antibody: HBsAB quant
- Host: ALT flares, immune signatures
- Outcome: durability off therapy (months matter)

THERAPUETIC CLASSES BEING DEVELOPED TO ACHIEVE THIS

- Suppress viral replication – NA Backbone
- Debulk Antigen: siRNA, ASO, mAb
- Enhance immune response – PEG IFN, MAB, therapeutic vaccine, ASO

ANTIGEN REDUCTION: siRNA (CLASS CONCEPT)

- Double stranded RNA
- RNA interference → decreased HBV transcripts (HBsAg ± others by design)
- Goal: large qHBsAg declines on-treatment; evaluate HBsAg loss off-treatment
- Issues: immune boost, durability, ALT flares

ARBUTUS siRNA PROGRAM — IMDUSIRAN

Up to 50% of Patients with Baseline HBsAg $\leq 1,000$ IU/mL Achieved Functional Cure with Imdusiran + PEG-IFN α Combination Treatment

- siRNA agent administered subcutaneously
- Inhibits viral replication by silencing all HBV transcripts:
 - Lowers HBV DNA and HBV-derived antigens, including HBsAg
- Pan-genotypic activity across all evaluated HBV genotypes (A to E)¹



Achieved HBsAg loss (≤ 0.05 IU/mL) at time point, n/N (%)	A1: IDR (6 doses) + NA + IFN 24W N=12	A2: IDR (4 doses) + NA + IFN 24W N=13	B1: IDR (5 doses) + NA + IFN 12W N=8	B2: IDR (4 doses) + NA + IFN 12W N=10
EOT				
All	4/12 (33)	3/13 (23)	0/8	0/10
BL HBsAg < 1000 IU/mL	4/6 (67)	2/7 (29)	0/6	0/4
24W Post-EOT				
All	4/12 (33)	2/13 (15)	0/8	0/10
BL HBsAg < 1000 IU/mL	4/6 (67)	2/7 (29)	0/6	0/4
FC				
All	3/12 (25)	2/13 (15)	0/8	1/10 (10)
BL HBsAg < 1000 IU/mL	3/6 (50)	2/7 (29)	0/6	0/4

BL, baseline; EOT, end of IFN treatment; FC, functional cure; HBsAg, hepatitis B surface antigen; IDR, imdusiran; IFN, pegylated interferon alfa-2a; NA, nucleos(t)ide analogue; W, week.

Treatment with IFN for 24 vs 12 weeks and continuation of imdusiran during IFN treatment led to greater HBsAg declines and more subjects reaching and maintaining HBsAg loss and functional cure

Imdusiran plus 24 weeks of PEG-IFN α was generally safe and well-tolerated – no SAEs; no AEs leading to discontinuation

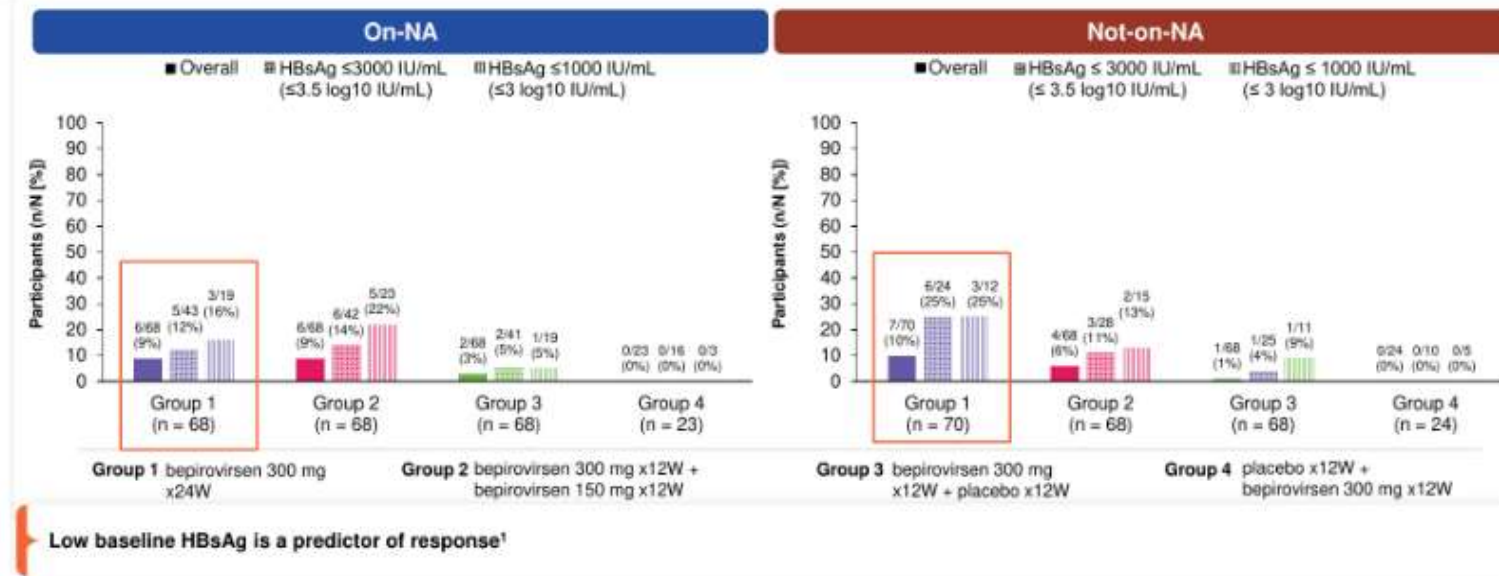
1. Yuen MF et al., Poster 5036 Cohort A1, AASLD 2024

ANTIGEN REDUCTION: ANTISENSE OLIGONUCLEOTIDES (ASO)

- Single stranded DNA
- Reduces HBV DNA
- HBsAg lowering to reset host response
- Baseline HBsAg may predict response
- Hypothesized to stimulate the immune system via toll like receptors

GSK ASO PROGRAM (BEPIROVIRSEN) — B Clear and B Sure

Participants achieving HBsAg < 0.05 IU/mL and HBV DNA < LLOQ sustained for 24 weeks off-treatment by baseline HBsAg level



B CLEAR- Group 1

9% of patients on NA treatment and 10% of patients not on NA treatment

- HBsAg levels below(LLOQ) and
- HBV DNA levels below the LLOQ,-
- 24 weeks post last dose.

Sustained response rates were highest in subjects with low baseline HBsAg (< 1000 IU/mL) with 16% and 25% of patients respectively.

Figure independently created by GSK using data from Yuen MF, et al. N Engl J Med 2022;387(21):1957-68 (article and supplement) and data on file.

HBsAg = hepatitis B surface antigen; NA = nucleos(t)ide analog; W = week.

¹ Yuen MF, et al. N Engl J Med 2022;387(21):1957-68 (article and supplement). © GSK. Data on file RFF-214351 2021. © GSK. Data on file RFF-214351 2021.

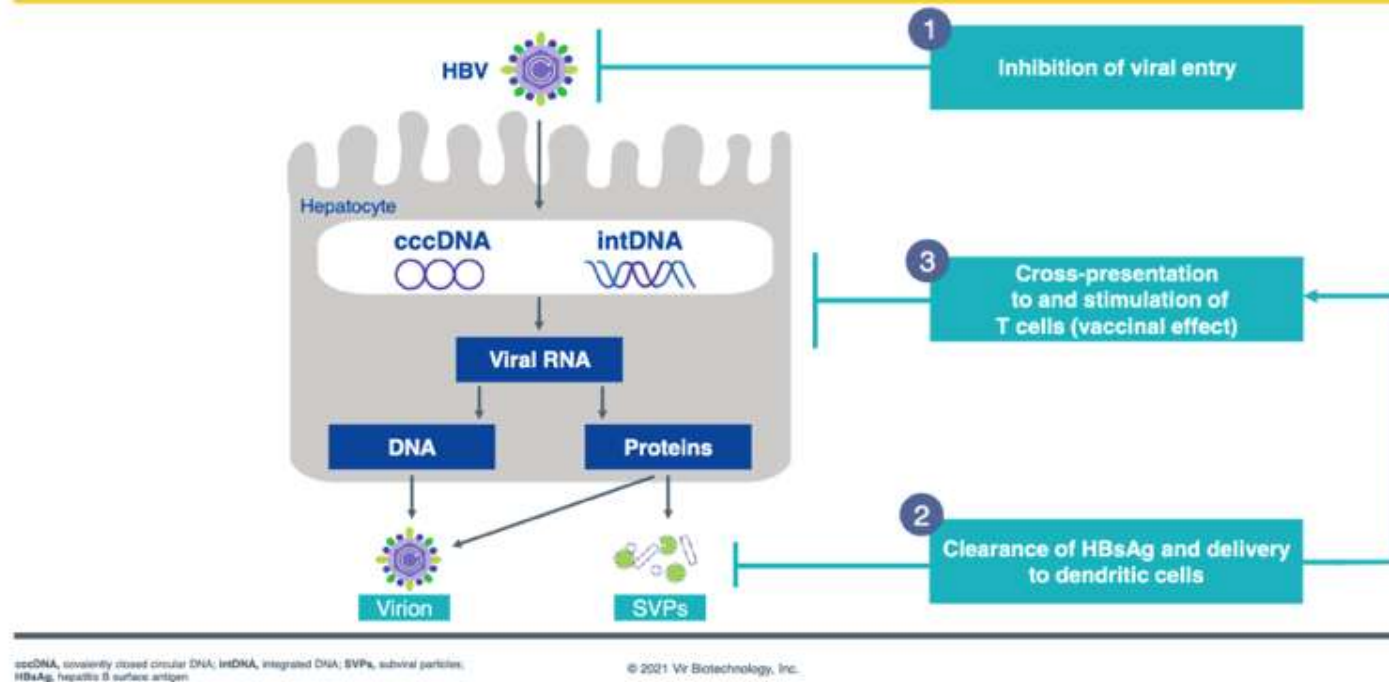
MED-US-12401 v2

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Yuen MF, Lim SG, et al; B-Clear Study Group. Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection. N Engl J Med. 2022 Nov 24;387(21):1957-1968. doi: 10.1056/NEJMoa2210027. Epub 2022 Nov 8. PMID: 36346079.

ANTI-HBS MONOCLONAL ANTIBODIES: WHY INTERESTING

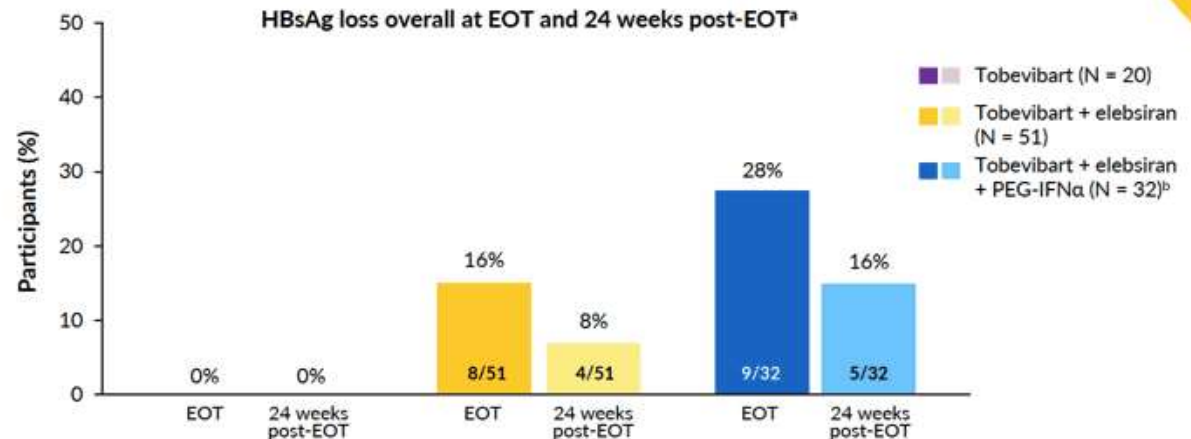
VIR-3434: HBV-neutralizing mAb with multiple potential mechanisms of action



VIR siRNA PROGRAM — mAb + siRNA +/- PEG IFN

- siRNA antigen lowering; often combined: siRNA + mAb ± PEG IFN
- Can combined antigen lowering + clearance increase functional cure?
- Immune therapy enhancement?

Tobevibart + Elebsiran ± PEG-IFN α Result in HBsAg Loss at EOT and at 24 Weeks Post-EOT in Overall Population (Primary Endpoint)



HBsAg loss at EOT and at 24 weeks post-EOT was highest for tobevibart + elebsiran + PEG-IFN α

EOT, end of treatment; HBsAg, hepatitis B surface antigen; PEG-IFN α , pegylated interferon alfa-2a.

^aHBsAg loss defined as HBsAg <0.05 IU/mL (lower limit of quantification). ^bEOT and 24 weeks post-EOT data available for N = 32/50 participants enrolled.

Gane E, et al. EASL 2025 Outcomes of 48 Weeks of Therapy and Subsequent 24-Week Post-Treatment Period With Tobevibart (VIR-3434) and Elebsiran (VIR-2218) With or Without Pegylated Interferon Alfa-2a in Chronic Hepatitis B Virus Infection: Findings From the MARCH Study

PEG-IFN: 'OLD DRUG,' NEW ROLE

- Provides immune stimulation + antiviral effects
- Tolerance a challenge - may add value when baseline qHBsAg is low and/or after debulking
- Requires careful selection and monitoring

ALT FLARES: EFFICACY SIGNAL VS SAFETY EVENT

- ALT increases may reflect immune-mediated clearance vs drug toxicity/unsafe inflammation
- Risk management: cirrhosis status, bilirubin/INR monitoring, stopping rules, rescue NA

WHAT ENDPOINTS MATTER MOST

- Highest value: durable HBsAg loss off therapy
- Near-term wins: deep sustained HBsAg lowering
- Ability to stop NA safely in subsets
- Patient reported outcomes

HDV DEPENDS ON HBSAG: HBV CURE STRATEGIES CAN CURE HDV

- HDV requires HBsAg to assemble/release
- Therefore, HBsAg loss = functional cure for HBV and effectively curative for HDV replication
- Implication: HBV antigen-lowering + anti-HBs mAbs may be two-for-one in HBV/HDV

WHERE ARE WE NOW

- Multiple classes now produce meaningful biologic effects
- Functional cure achievable in a subset but we need more study on
 1. durability
 2. scalability
 3. safety
 4. simplification

We are no longer debating *whether* HBV can be functionally cured-but *who, how, and how safely*. ID Clinicians will play a central role in identifying, treating, and following these patients

HBV CURE THERAPIES IN CLINICAL TRIALS

Inhibit HBV DNA replication

- Nucleos(t)ide analogues
- Capsid assembly modulators
- PegIFN- α
- siRNA, ASO
- Entry inhibitors

Inhibit HBsAg production or secretion

- Production: siRNA, ASO, second generation capsid assembly modulators, pegIFN- α
- Secretion: nucleic acid polymer

Stimulate or revive HBV-specific immune response

- Innate immune response: TLR7 or TLR8 agonists
- Adaptive immune response: therapeutic vaccines
- Antibody to HBsAg
- Remove immune blockade: checkpoint inhibitors
- PegIFN- α

WHAT TO WATCH IN THE NEXT 12–24 MONTHS

- Best combinations and sequencing: NA + siRNA/ASO + mAb ± peg-IFN + therapeutic vaccines
- Validated predictors: baseline qHBsAg thresholds; early on-treatment kinetics
- Durability off therapy (≥ 24 –48 weeks)
- Implementation: shorter regimens, fewer injections, accessible biomarkers

TAKE AWAY POINTS

- **Beyond Suppression: Functional Cure** (HBsAg loss) is the new gold standard.
- **The Power of Combination:** The future is "**Reduction + Restoration**"
- **Targeting the Reservoir:** cccDNA/integrated DNA remains the ultimate barrier.
- **Clinical Insights:** remember to mind the **ALT flares**, remember to tract qHBsAG
- **A Shift in Outlook:** Moving from "lifelong management" to "finite duration therapy."

REFERENCES

- Marrapu S, Soni JR, Kamal K, Kumar R. Hepatitis B functional cure: Current and future perspective. World J Hepatol. 2025 Oct 27;17(10):110107. doi: 10.4254/wjh.v17.i10.110107. PMID: 41179730; PMCID: PMC12576716.
- Lok ASF. **Toward a Functional Cure for Hepatitis B.** Gut and Liver 2024;18:593-601. <https://doi.org/10.5009/gnl240023>
- Remember that like Hepatitis C, Hepatitis B is a viral infection of the liver. These infections can cause a liver disease if we do not successfully control the infection. This is an infection we should be treating. The future will provide opportunity to provide curative therapy.
- Rnahass@idcare.com
- QUESTIONS?
- Thank you



Solving the challenges
of infectious diseases

The current environment for infectious diseases



Federal policy and funding uncertainty affecting research and public health



Increasing misinformation and erosion of trust in science



Growing demand for infectious disease expertise across healthcare systems

How IDSA is responding



Opposing Research and
Public Health Funding Cuts

Defending USAID & PEPFAR

Protecting the Public Health
Workforce

Litigation Against Unlawful
Vaccine Changes

Filling the Information Void

Media and Congressional
Engagement

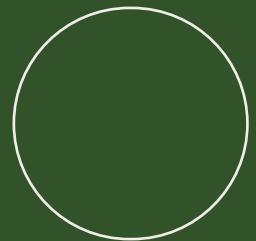
Proposed regulation on federal grant rules



Grant determinations in the hands of political appointees with political alignment used as a key criteria for grants



Prohibiting the use of grant funds for journal publication



Severely limiting grant use for conference attendance and professional memberships

IDSA's strategy to respond



Collaboration with
professional
societies &
advocacy groups



Urging Congress to
block
implementation



Local action

Why affiliates like South Carolina matter



State and regional societies bring IDSA's national priorities into local health systems, public health departments and policymaking

Affiliates help recruit and mentor the next generation of infectious diseases clinicians

Local societies often lead advocacy on reimbursement, workforce and public health policy at the state level

Regional networks strengthen coordination during outbreaks and emerging infectious disease threats

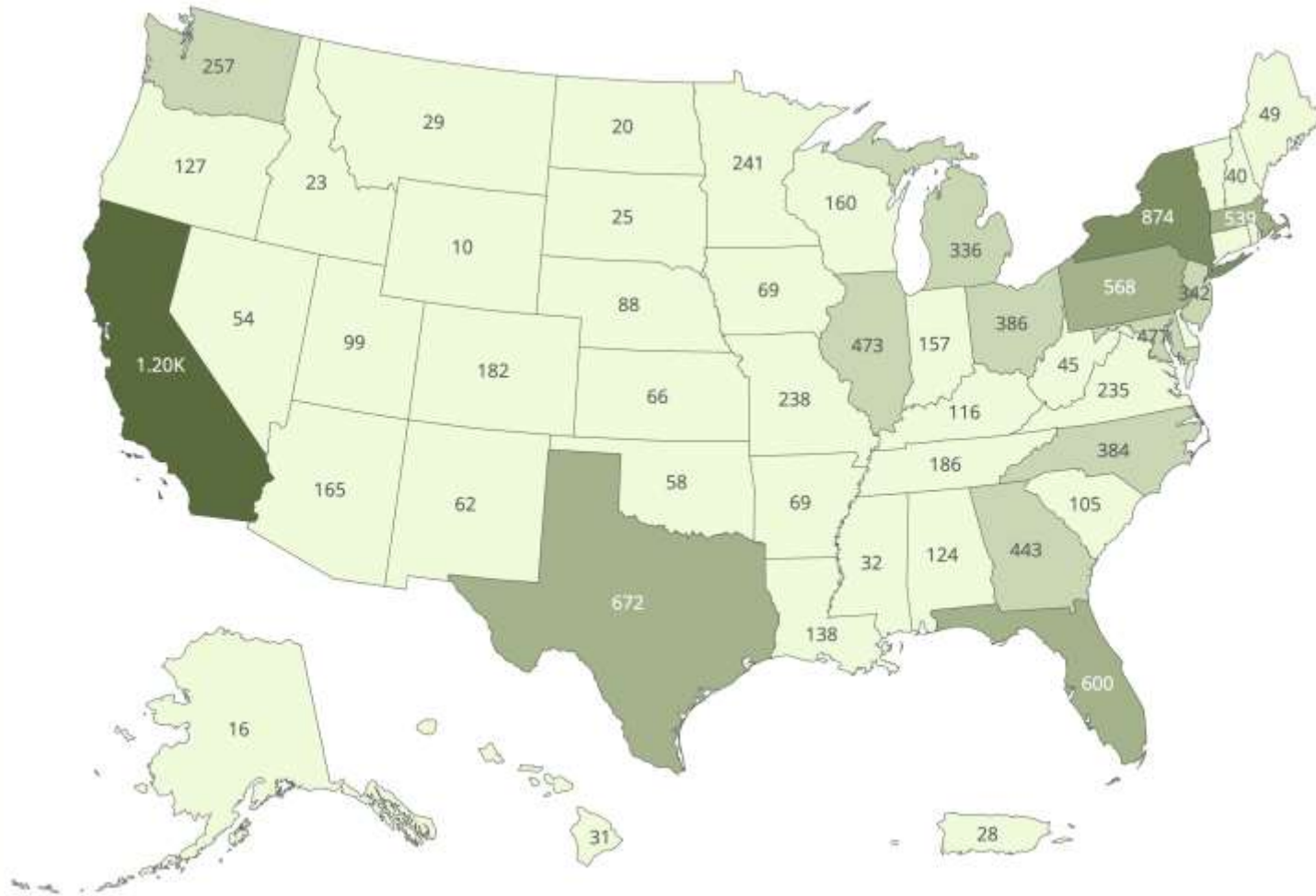
Strong affiliate partnerships make IDSA's national voice more credible and effective



- Strengthening partnerships with affiliates is a priority for IDSA



The community of IDSA



IDSA



Bringing together the curiosity, compassion and knowledge of our members to strengthen the field of infectious diseases, advance science and advocate for health equity.

Join Today!

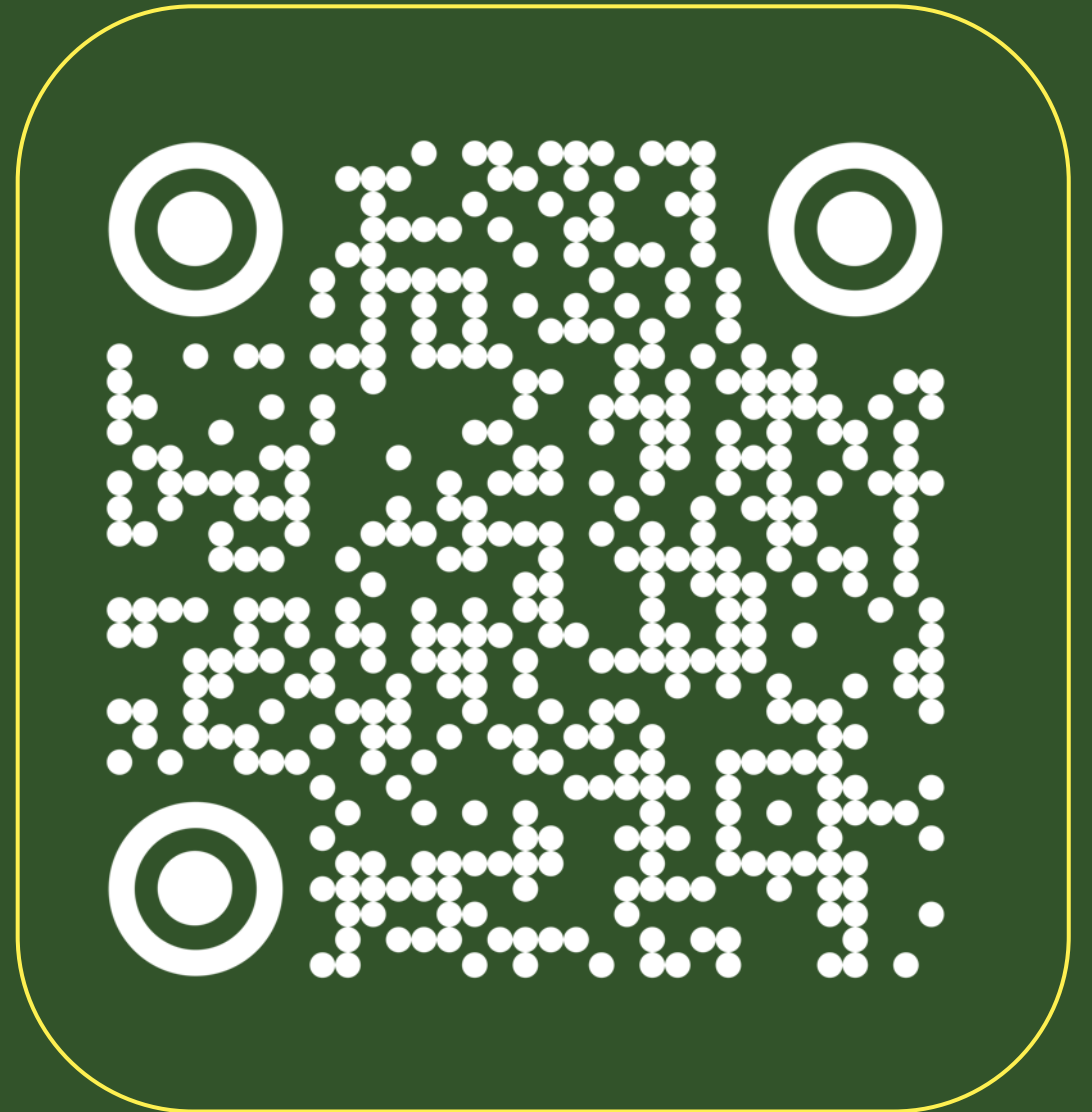


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Questions?