New HBV/HDV Treatments

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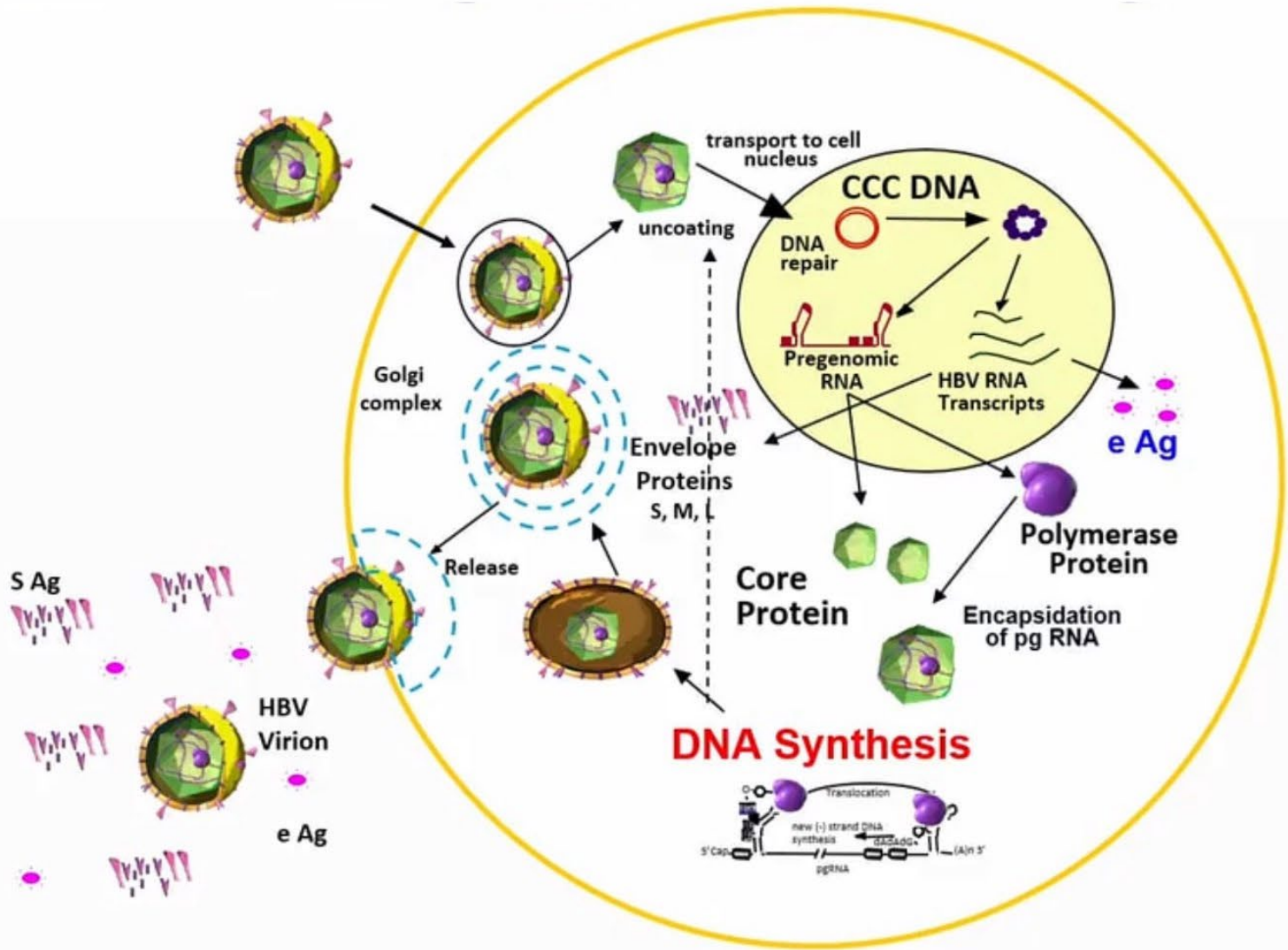
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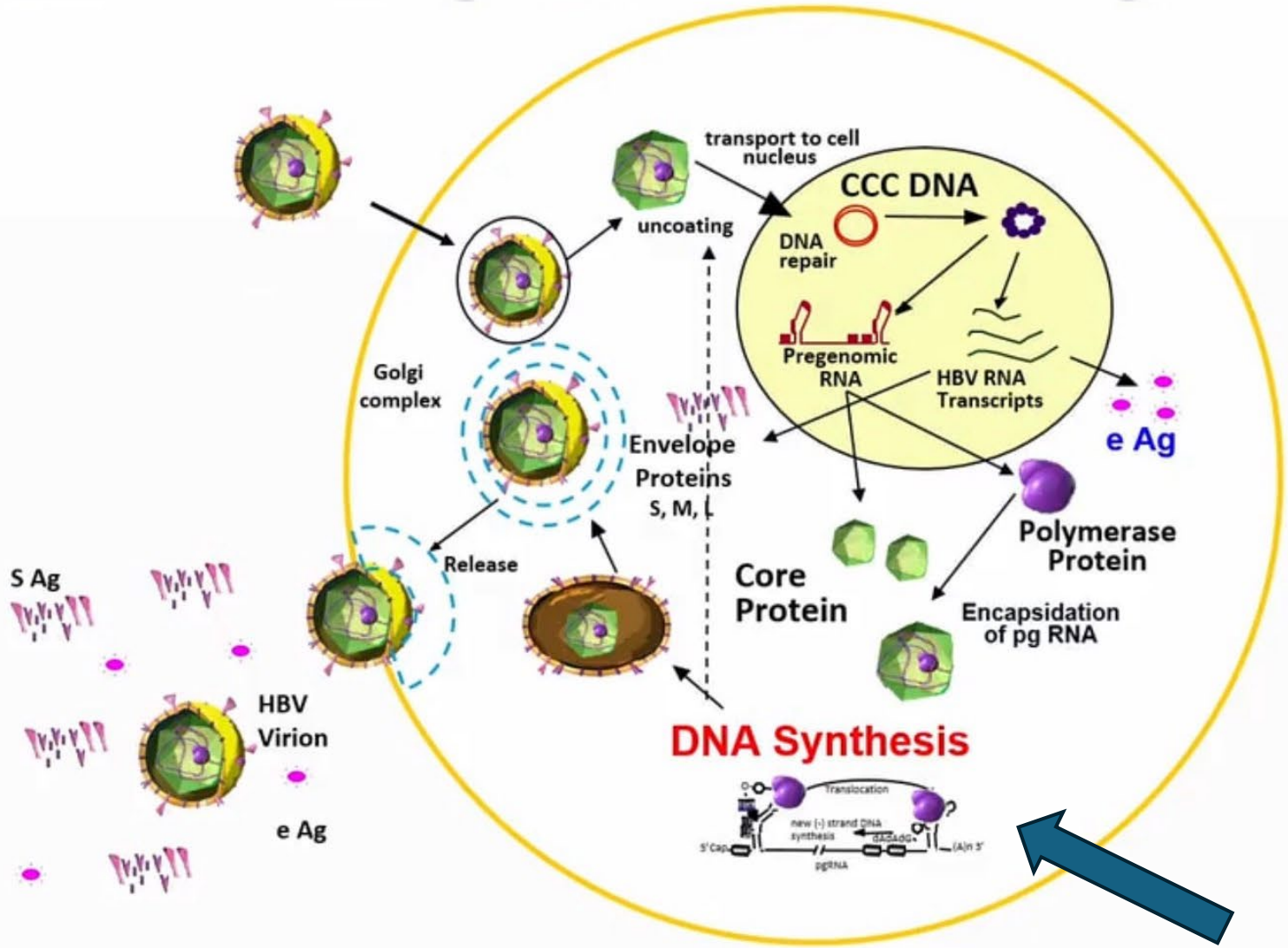
CCC DNA
uncoating
DNA repair
Pregenomic RNA
HBV RNA Transcripts
e Ag
Golgi complex
Envelope Proteins S, M, L
Release
S Ag
HBV Virion
e Ag
Core Protein
Polymerase Protein
Encapsidation of pg RNA
DNA Synthesis
Translocation
new (-) strand DNA synthesis
5' Cap
(A)n 3'
pgRNA

Nucleos(t)ide Analogues (NAs)

- Entecavir (ETV)
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)

- Inhibit HBV DNA polymerase
- Suppresses viral replication
- First-line NA therapies
  - long-term efficacy
  - favorable safety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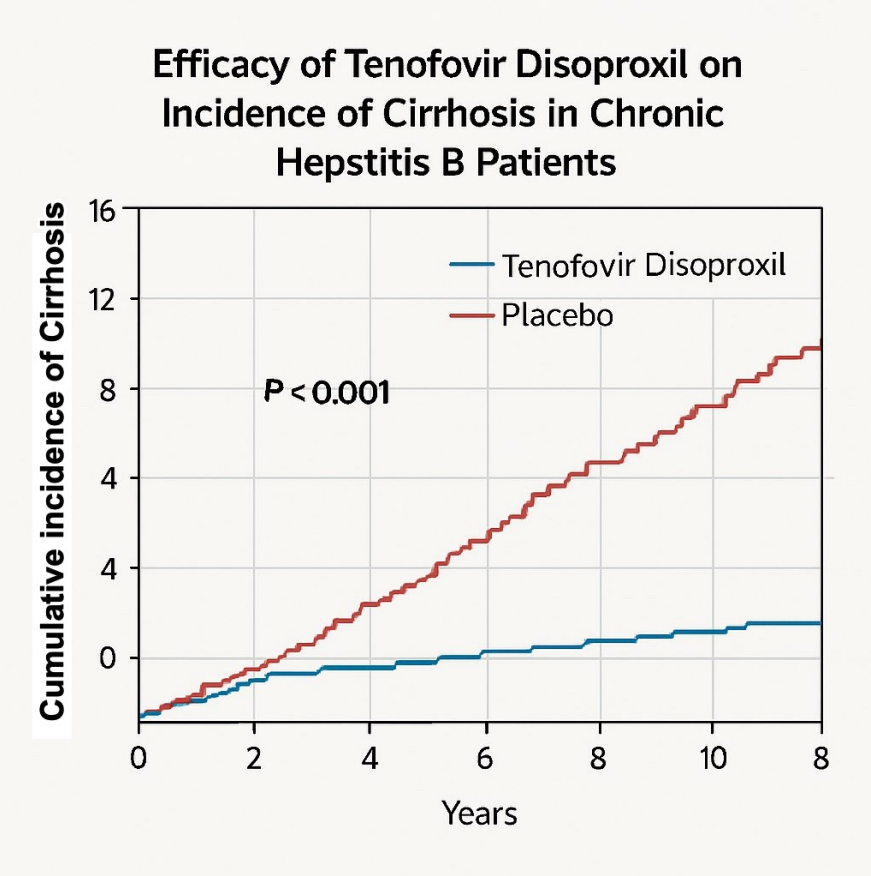
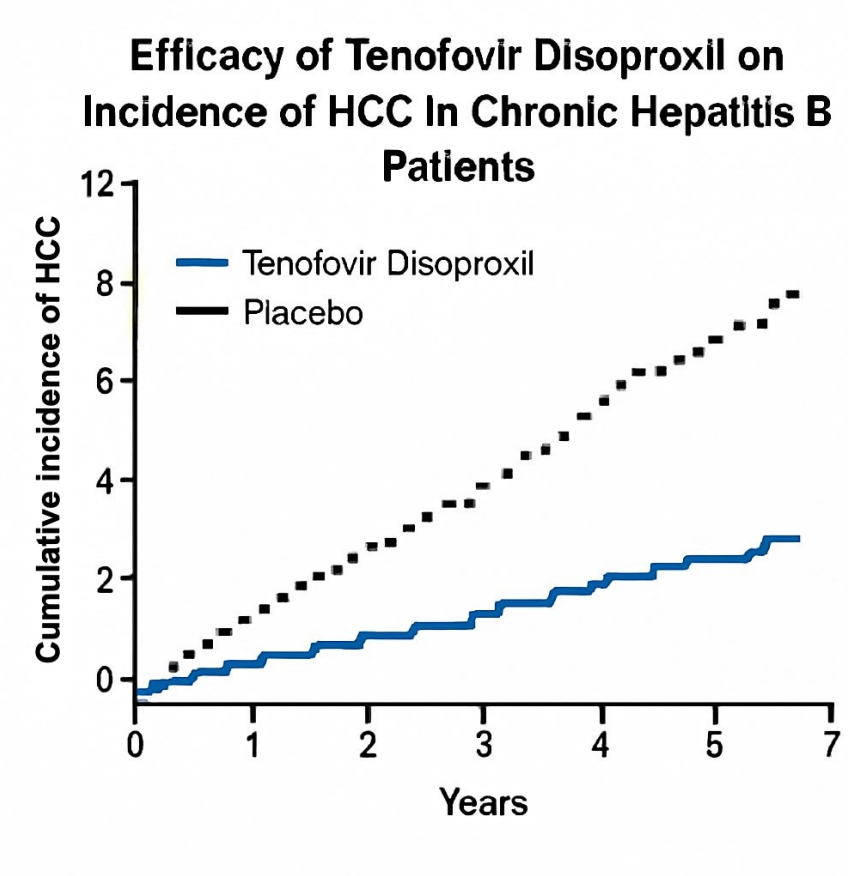
Nucleos(t)ide Analogues (NUCs)

- **Highly effective in suppressing HBV DNA levels**
- **Often leads to undetectable DNA (<20 IU/ml)**



Marcellin P, et al. N Engl J Med 2013



Papatheodoridis et al., J Hepatol 2015

Nucleos(t)ide Analogues (NAs)

Safety Profile:

- TAF >> TDF in:
  - Hypophosphatemia
  - Osteopenia/osteoporosis
  - Renal insufficiency

- ETV is an alternative for TAF

- ETV is not associated with kidney or bone damage

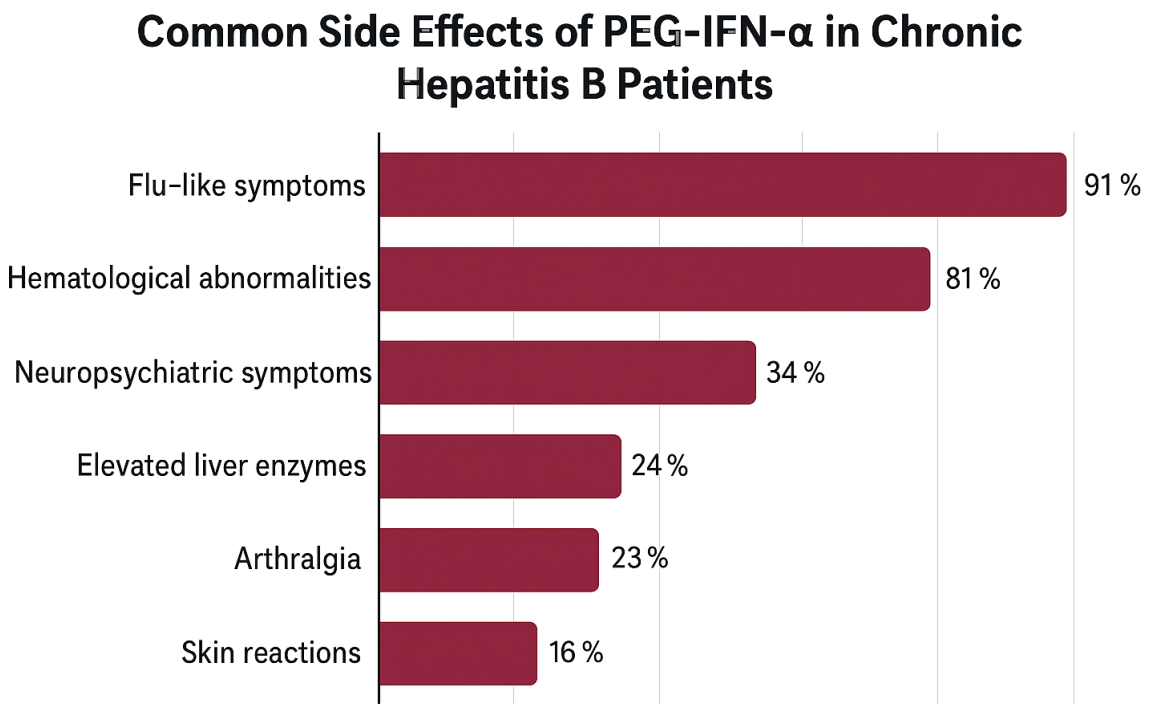
Pegylated Interferon Alpha (PEG-IFNa)

- Stimulates host immune response
- Influence HBV life cycle - Epigenetic silencing of cccDNA
- HBeAg/HBeAb seroconversion
- HBsAg loss
- Improve liver histology
- Reduce HCC incidence

PEG-IFNa

Significant side effects

- Combination with NAs: no advantage over monotherapy



EASLD 2025

Initial Assessment in HBsAg+ Individual

- **qHBVDNA** - Critical for treatment/monitoring
- **HBeAg** - Classify infection phase, replication marker
- **HbeAb** - Define disease phase, assess evolution/response to Tx
- **HBcAb(IgM)** - Differentiate acute from chronic exacerbation
- **qHBsAg** - Characterize disease phase, define prognosis, guide Tx
- **HBV Genotype** - Stratification for IFN-Tx, estimate HCC risk
- **HDV, HCV, HIV Screening** - Impact on therapy

New Viral Biomarkers (Emerging)

- HBcrAg (core-related antigen)
  - Reflects cccDNA pool
  - indicates high viraemia
- HBV RNA
  - Reflects cccDNA pool
  - still limited evidence
- Quantitative Anti-HBc
  - Reflects immune response
  - associated with disease activity

Treatment Goals for Chronic Hep B

- ↓morbidity (cirrhosis, decompensation, HCC) & ↑survival
- Persistent suppression of HBV DNA (undetectable)
- Ultimate Goal: HBsAg loss (functional cure)
- Additional Endpoints
  - Normalization of ALT
  - HBeAg loss & anti-HBe seroconversion (with HBV DNA <2000 IU/ml)
  - Improvement of liver fibrosis
  - Improvement of HBV-associated extrahepatic manifestations
  - Improvement of HRQoL
  - Prevention of HBV transmission
  - Prevention of HBV reactivation (HBVr)

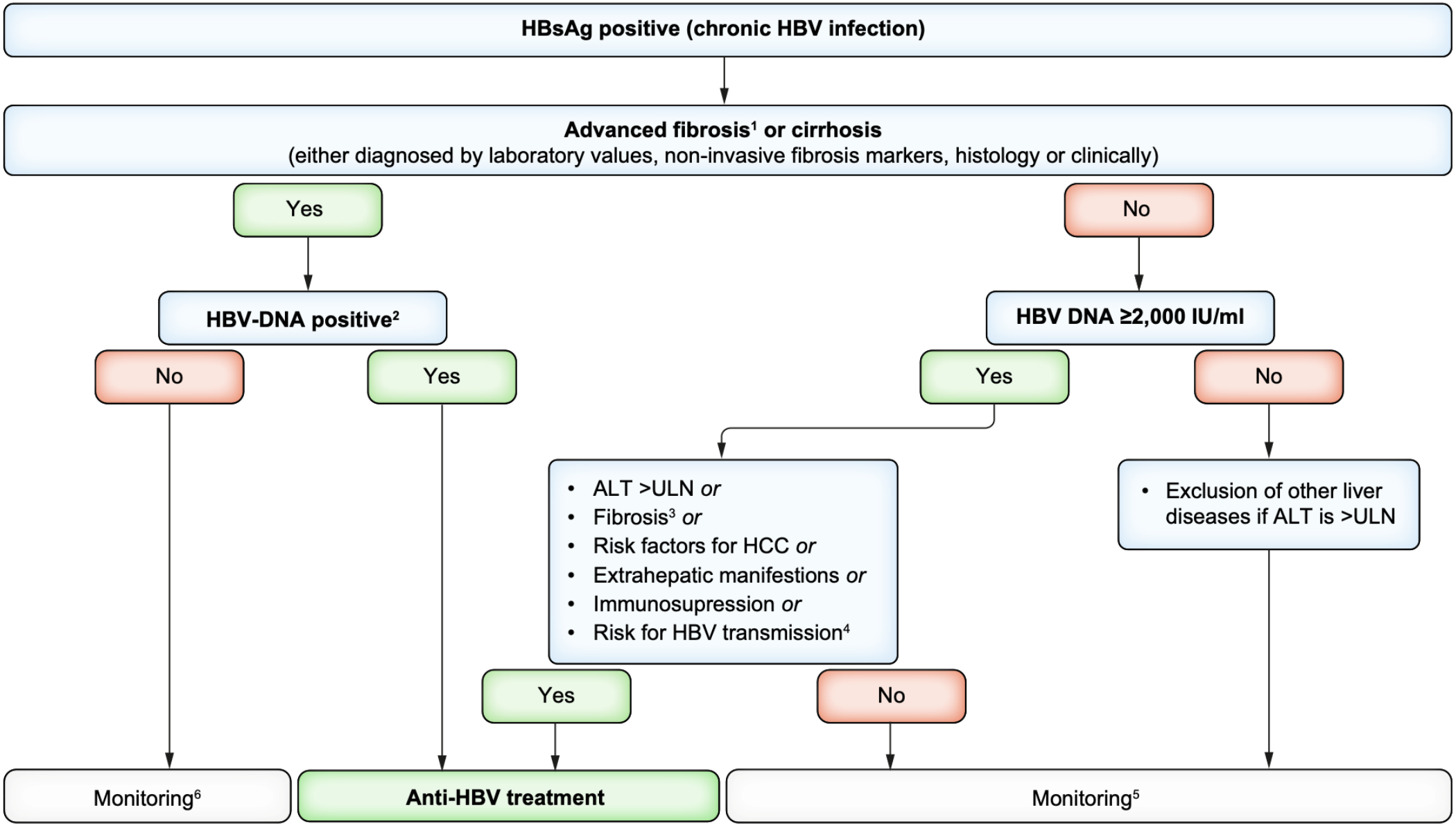


Fig. 1. Treatment indication for chronic HBV infection. [1]Equivalent of ISHAK F ≥4/Metavir F ≥3 (non-invasive assessment is preferred, LSM > 8 kPa). [2]Sensitive NAT assay (lower limit of detection <20 U/L). [3]Equivalent of ISHAK ≥F3/Metavir ≥F2 (non-invasive assessment is preferred, LSM > 7 kPa). [4]The threshold values for HBV DNA vary depending on the activity and risk of transmission. Important: Tenofovir in pregnant women with HBV DNA ≥200,000 IU/ml. [5]Anti-HBV treatment in HCC, HIV co-infection, extrahepatic manifestations, immunosuppression. [6]Anti-HBV treatment in immunosuppression. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; LSM liver stiffness measurement; ULN, upper limit of normal.

Table 8. Risk factors that have been associated with HCC risk in individuals with chronic HBV infection.

Risk factor	Comments and references
Viral factors	
HBV DNA*	Non-linear risk starting with >2,000 IU/ml[11,161,163] Highest risk in HBeAg-positive individuals with 6-7 log_{10} IU/ml (lower risk if HBV DNA is ≥8 log_{10})[207]
HBsAg	High HBsAg (≥1,000 IU/ml) in HBeAg-negative individuals[163]
HBeAg*	In overall analyses, positive HBeAg (in individuals older than 30 years) is associated with HCC[163,166,167]
HBcrAg	Prognostic marker for occurrence and recurrence;[164,165,208] importance of HBcrAg in HBeAg-negative infection[209]
HBV genotype	Genotype C,[197] genotype A (*e.g.* in The Gambia[199]), genotype F in Alaska native persons,[197] genotype D in India[210]
Core promoter mutations	Present[169,211]
Viral coinfections	HDV,[212,213] HCV,[167,184,214] HIV[215]
Host factors	
Cirrhosis	Strongest risk factor for HCC[161,167,169] HCC risk remains after viral suppression[170,171]
Low platelets*	Indicator for cirrhosis[195]
Family history of HCC	Independent risk factor in all phases of chronic HBV infection[192,193,216]
Age*	HCC risk increases with age, with most studies focusing on individuals older than 30 years[161,185] Evidence increases with age ≥35,[166] ≥40,[163] ≥50.[167] HCC risk varies in different age groups for men and women and for different ethnic groups[191]
Sex*	Higher risk among males[161,166,169,185]
ALT*	Elevated (or in the upper normal range)[63,166,167,185]
Type 2 diabetes mellitus (T2D)	T2D is independently associated with HCC.[183,217,218] Glycaemic burden is associated with HCC.[219] T2D is included in HCC risk scores[168,218] However, one analysis showed that T2D was not independently associated with HCC in chronic HBV infection[179]
Steatotic liver disease (SLD)	Conflicting data: - Increased risk of HCC and cirrhosis[188] - Lower risk of HCC, cirrhosis, and mortality[180,182,189]
Body mass index (BMI)	High BMI ≥30,[179] HR stronger in females[178]
Metabolic syndrome	Multiple (≥3) metabolic risk factors or increasing burden of metabolic dysfunction are associated with HCC[180–182,190]
Cigarette smoking	Present[181,184–187]
Alcohol consumption	Heavy alcohol intake ≥60 g/d[161]
Ethnicity	Evidence low or absent: - Birth in Africa/Oceania: linked to very early-onset HCC[194] - Sub-Saharan Africans with HBV in Europe: lower HCC incidence, similar risk factors to general population[195] - Western *vs.* Eastern studies: no significant age-adjusted differences in HCC incidence[161]
Environmental factors	
Aflatoxin B1 (AFB1)	In high-exposure areas, AFB1 and HBV synergistically increase HCC risk; reducing aflatoxin exposure could lower HCC cases by 23%[198]
Air pollution	Association between fine particulate matter and HCC[200,201]

HCC Risk Assessment

Table 13. HCC risk assessment using PAGE-B and mPAGE-B scores.[441,446]

PAGE-B: Low risk: 0-9; intermediate risk: 10-17; high risk: ≥18

Age (years)	Points	Sex	Points	Platelets (µmol/L)	Points
16-29	0	Female	0	>200	0
30-39	2	Male	6	100-199	6
40-49	4			<100	9
50-59	6				
60-69	8				
≥70	10				

mPAGE-B: Low risk: 0-8; intermediate risk: 9-12; high risk: ≥13

Age (years)	Points	Sex	Points	Platelets (µmol/L)	Points	Albumin (g/dl)	Points
16-29	0	Female	0	>250	0	≥4.0	0
30-39	3	Male	2	200-250	2	3.5-4.0	1
40-49	5			150-200	3	3.0-3.5	2
50-59	7			100-150	4	<3.0	3
60-69	9			<100	5		
≥70	11						

HCC, hepatocellular carcinoma.

Discontinuation of NA Therapy

Not Recommended

- **Advanced liver disease (especially cirrhosis)**
- **Concomitant liver diseases**
- **Immunosuppressive treatment**
- **HIV coinfection**

Discontinuation of NA Therapy

1. Confirmed HBsAg loss (two measurements 6 months apart)

2. HBeAg-positive patients without advanced liver disease
   - Can stop 12 months after HBeAg/HBeAb seroconversion and undetectable HBV DNA if close monitoring is guaranteed.

3. HBeAg-negative patients without advanced liver disease
   - Can stop if HBV DNA is undetectable for at least 3-4 years, HBsAg level is low (e.g., <1,000 IU/ml for Caucasians, <100 IU/ml for Asians), and close monitoring is guaranteed.

HBcrAg and HBV RNA can further aid stratification.

Discontinuation of NA Therapy

Post-Discontinuation Monitoring

- **Monthly for 6 mo, then q 3-12 mo**
- **HBV DNA and ALT**
- **HBV DNA > 10,000 IU/ml → Restart Tx**

Acute Hep B

- Given the high spontaneous clearance rate of HBsAg during acute HBV infection in adults, antiviral treatment is NOT REQUIRED in this clinical setting … as long as synthetic liver function is not impaired

Pregnancy

- On Tx:
  - Tenofovir (TDF, TAF) - continue
  - ETV or adefovir -- switch to tenofovir (TDF, TAF)
  - PEG-IFNa -- switch to tenofovir (TDF, TAF)

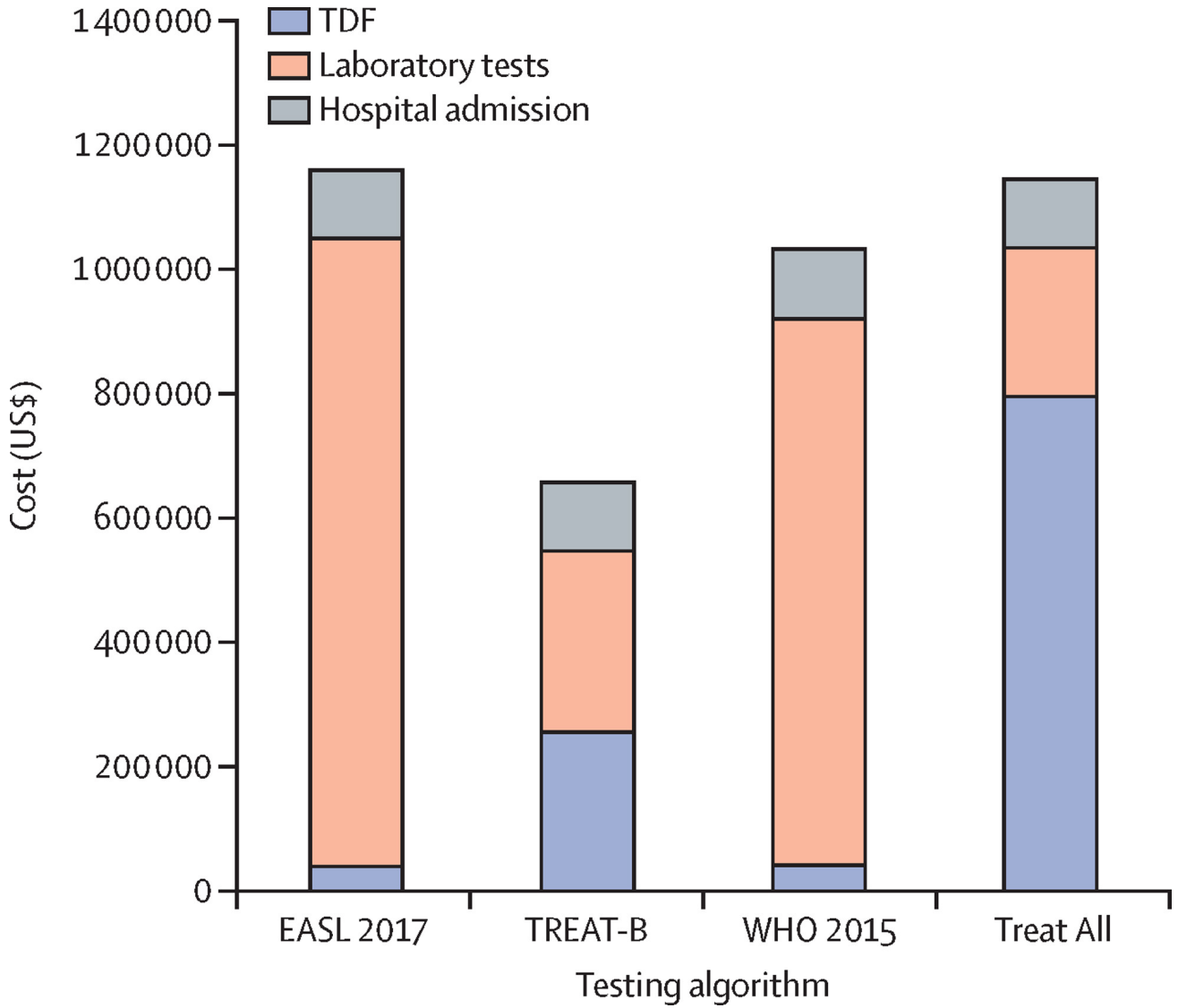
- Not on Tx:
  - Start Tenofovir (TDF, TAF) if:
    - HBV DNA levels > 200,000 IU/ml
    - Ideally before last trimester
    - If HBV DNA not available → Treat all HBeAg+ cases

- Newborns can be breastfed

The "Treat All" Approach

"Treat All" Approach

- Guidelines are complex - DNA level, ALT, fibrosis severity
- No truly "quiescent" disease phase in CHB
- Cirrhosis and HCC risk still present
- Even in patients with low HBV DNA levels



Impact analysis for a cohort of 5000 individuals aged 20 years with chronic hepatitis B virus infection.

Nguyen, et al. The Lancet Global Health 2024

"Treat All" Approach

Potential Caveats

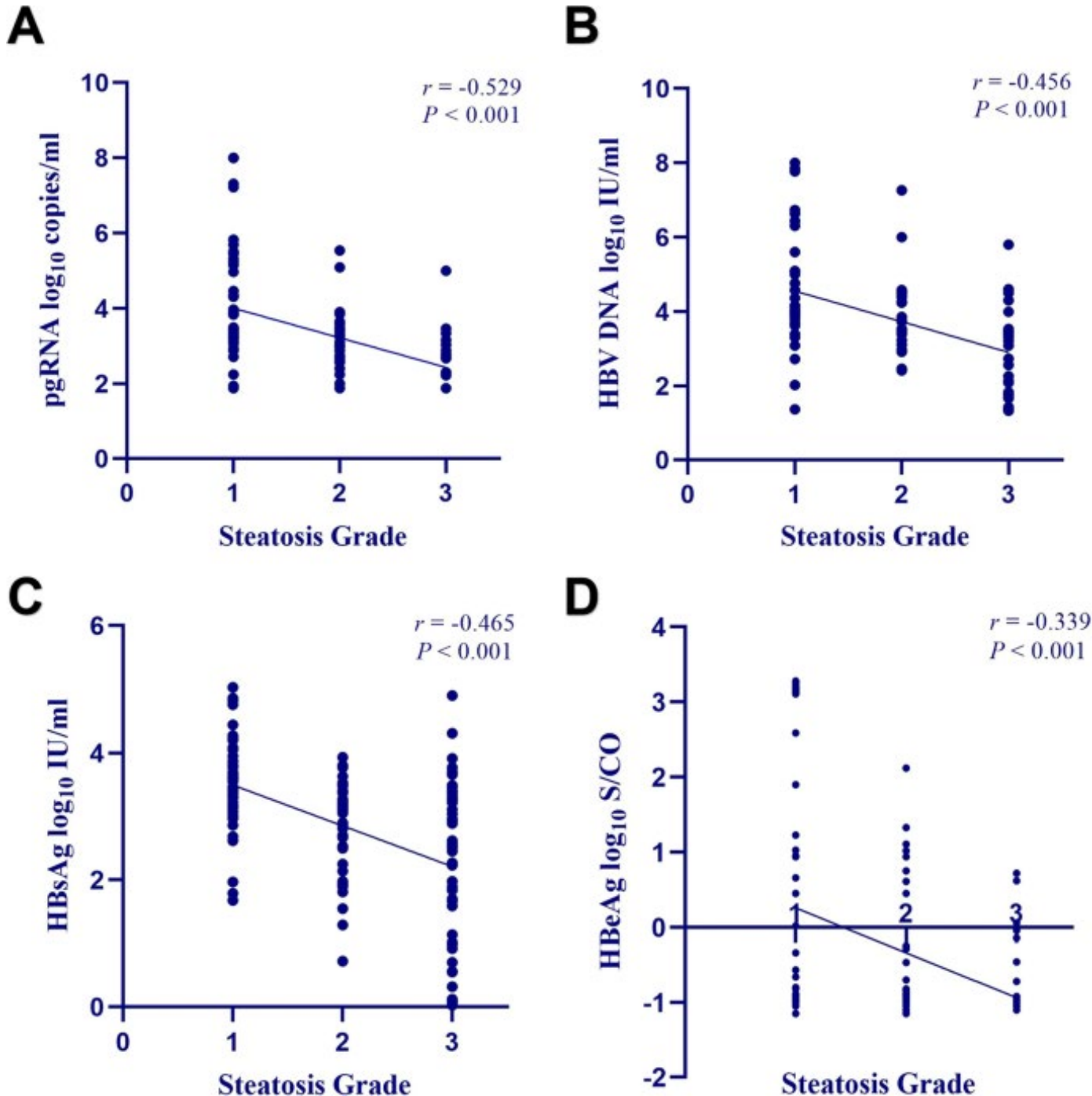
- ? Long-term side effects
- ? Patient acceptability issues

"Treat All" Approach

- WHO guideline for areas with limited HBV DNA testing:
- ‘all HBsAg-positive individuals with persistently elevated ALT levels’
- Benefit of reducing complications outweighs potential side effects.

Coexistence of HBV and MASLD

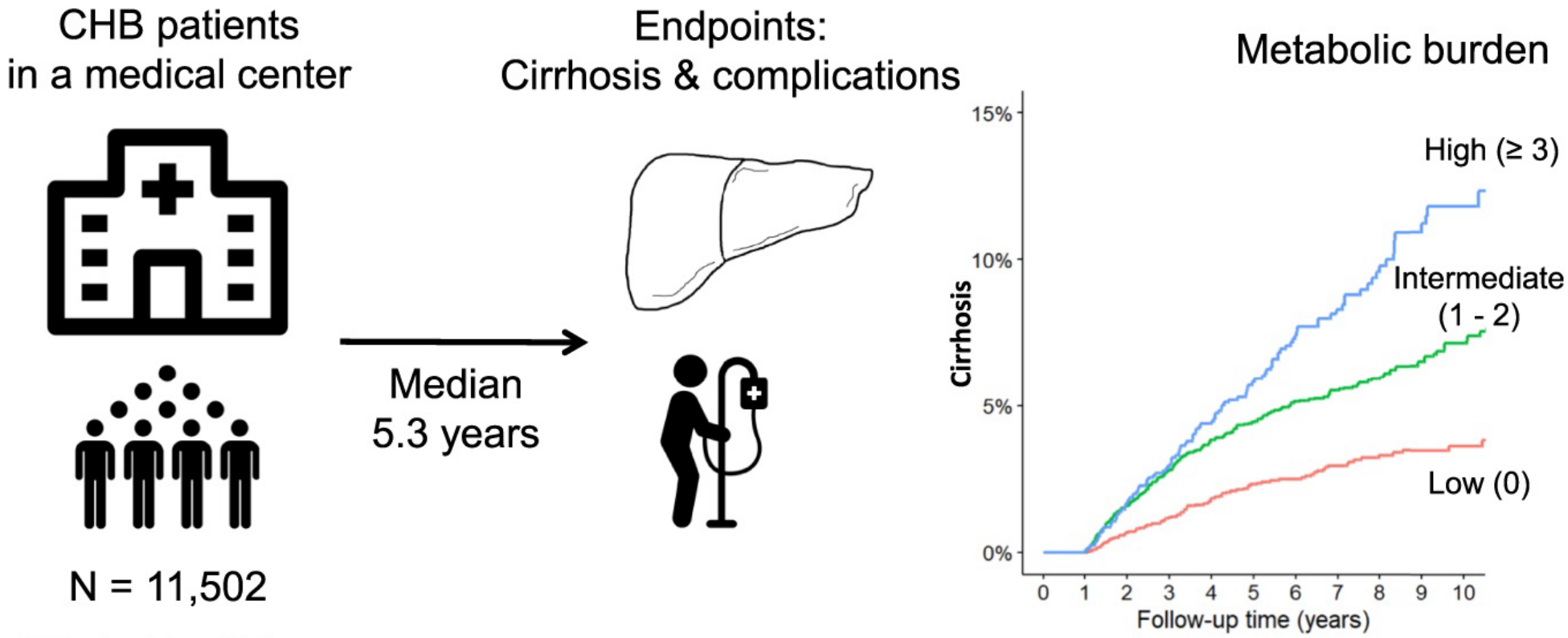
- Not rare (14-70%)
- Is MASLD protective?!
- Cross-sectional
- 272 HBV infected patients
- Tx-naïve or off-Tx for > 6mo
- Limitations:
  - longitudinal follow-up needed
  - the study lacked liver biopsy



Sitong Yi, et al. Virology Journal 2024

Co-existence of HBV and MASLD

Metabolic Burden Aggravates Cirrhosis in CHB



*CHB, chronic hepatitis B

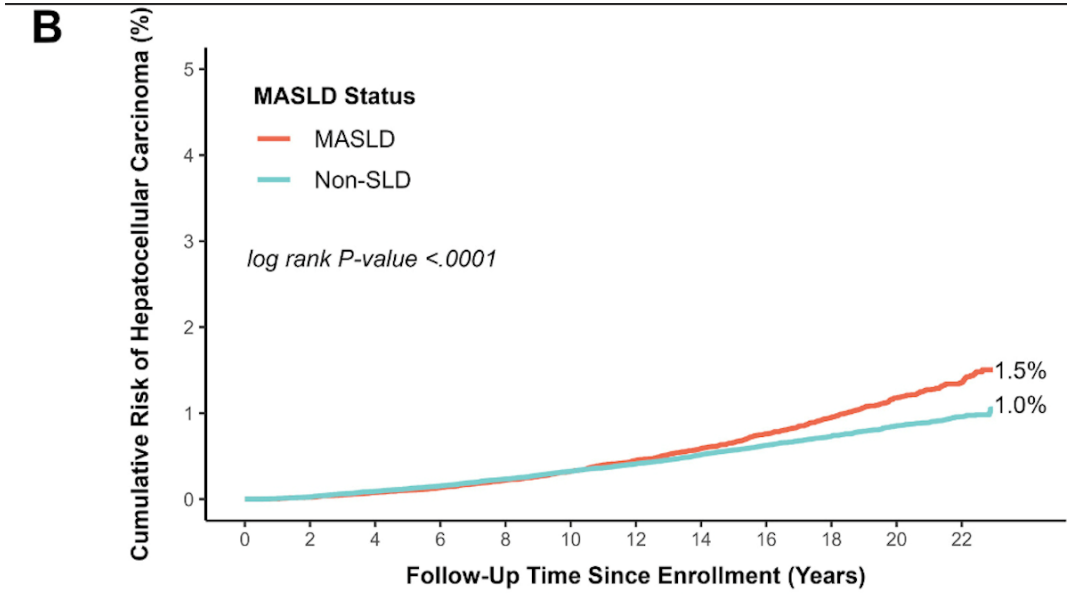
Huang et al. *Am J Gastroenterol.* 2025. doi:10.14309/ajg.0000000000002915

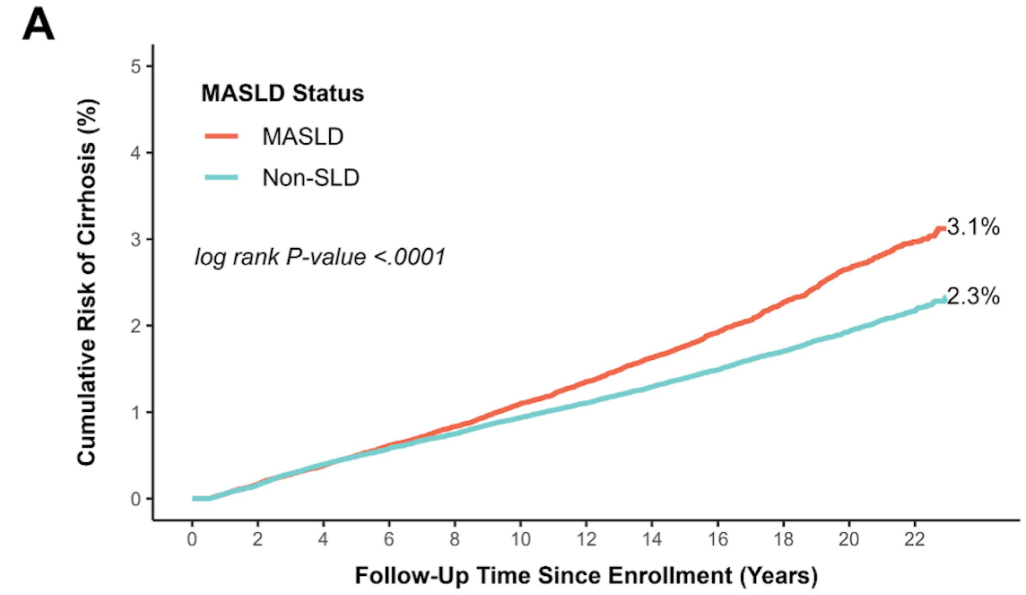
All icons above are from Noun Project.

AJG The American Journal of GASTROENTEROLOGY

Co-existence of HBV and MASLD

- 336,866 adults >30yr
- prospectively enrolled during 1997–2013 - Mean 15yr F/U
- 5562 new cases of cirrhosis
- 2273 new cases of HCC





Huang et al. Am J Gastroenterol. 2025

Statin Use in chronic hep B

Statin Use in chronic hep B

- Associated with reduced risk of HCC in chronic hepatitis B
- Shown in various observational studies and meta-analyses
- Lipophilic (atorvastatin) >> ~~Hydrophilic (rosuvastatin~~)
- Longer duration of statin exposure linked to greater benefits
- Statins may act as chemopreventive agents against HCC by mitigating fibrosis progression

Singh et al. Gastroenterology 2013
Hsiang et al. J Hepatol 2015
Li et al. BMC gastroenterology 2020

Emerging Therapeutic Strategies

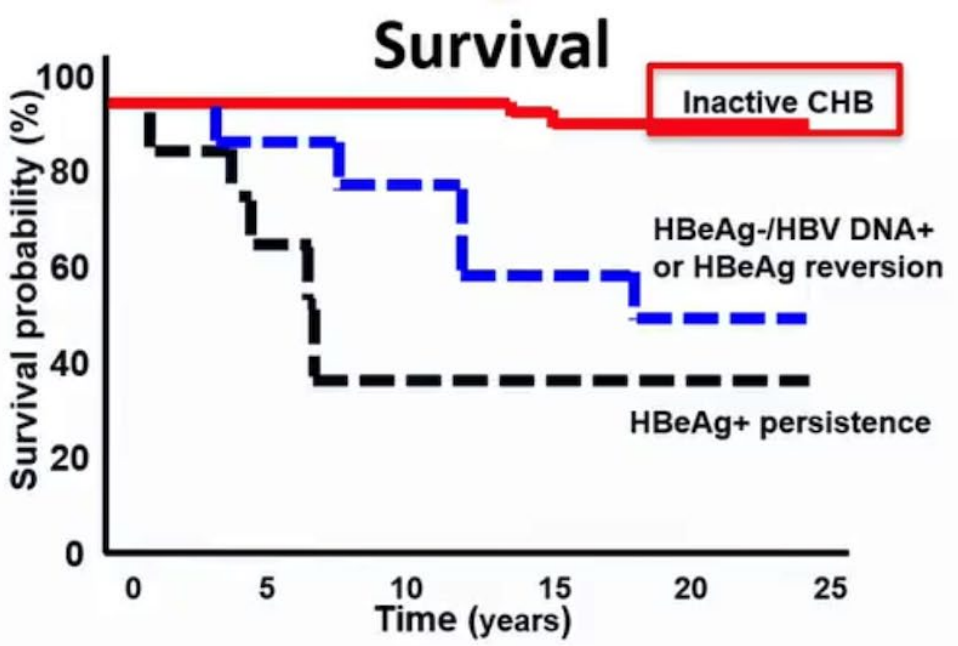
Current therapy is highly effective

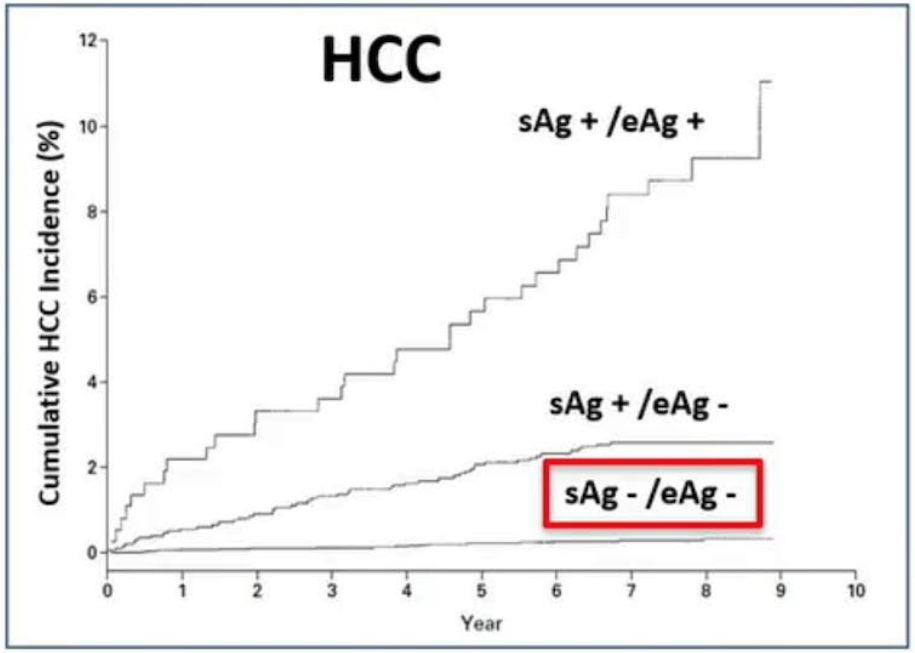
- Current therapy taken long-term
  - Suppresses HBV DNA
  - Normalizes ALT
  - Prevents fibrosis progression
  - Promotes fibrosis regression - even in cirrhosis
  - Prevents and even reverses hepatic decompensation
  - Reduces, but does not eliminate, the risk of HCC
  - Rarely leads to HBsAg loss/seroconversion

This (and HCV DAAs) have lead to great interest in HBV curative regimens

What are the goals of new HBV therapy?

Learning from natural history





- Very inactive disease and ideally HBsAg loss associated with excellent long-term and cancer-free survival
- ***A good goal for therapy***

Goals of Therapy

Complete Cure

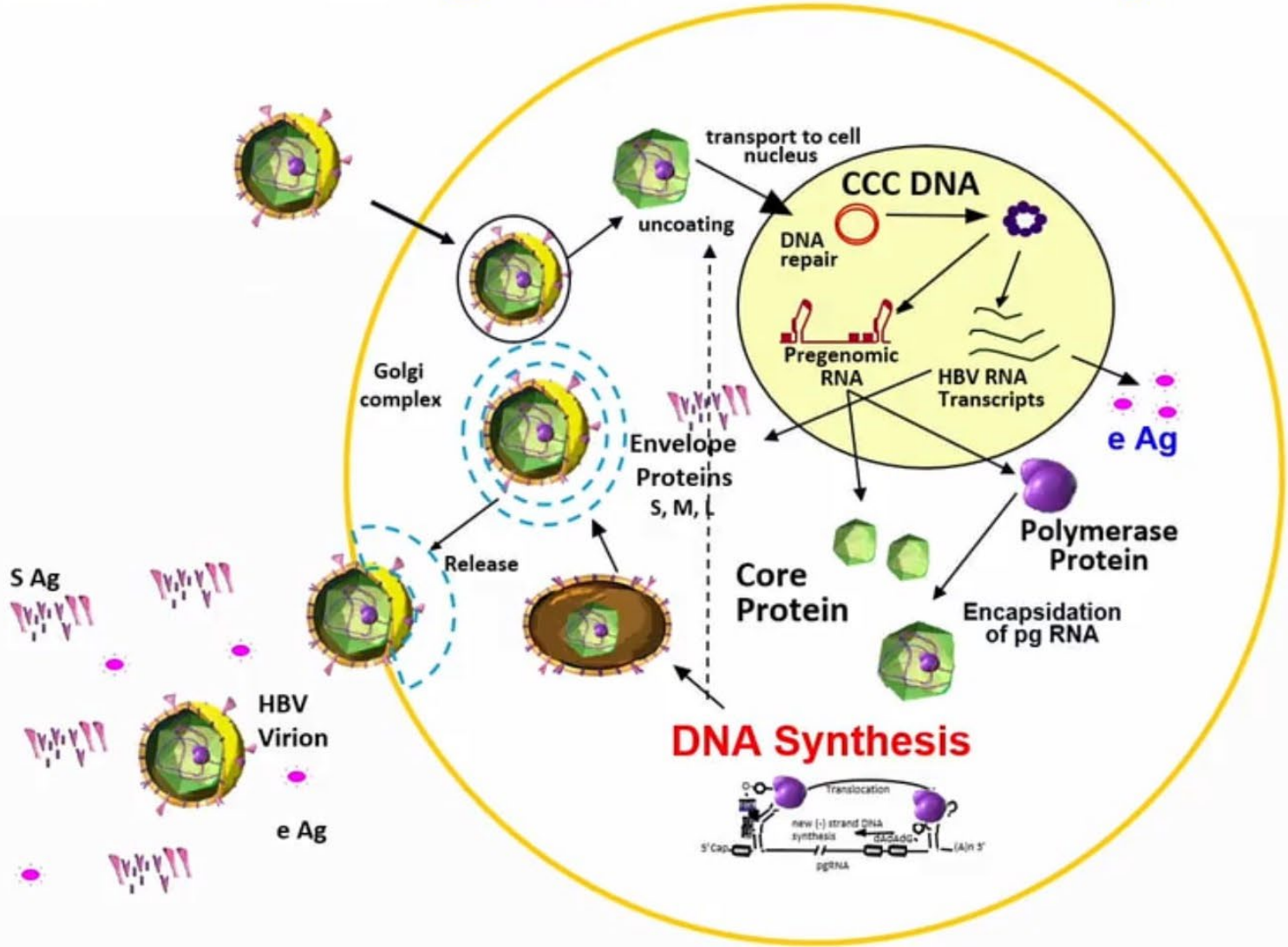
- True cure = all traces of HBV gone from the liver (ie. like HCV)
- This is **VERY** difficult (if not impossible) → cccDNA + integrated HBV DNA

Functional cure

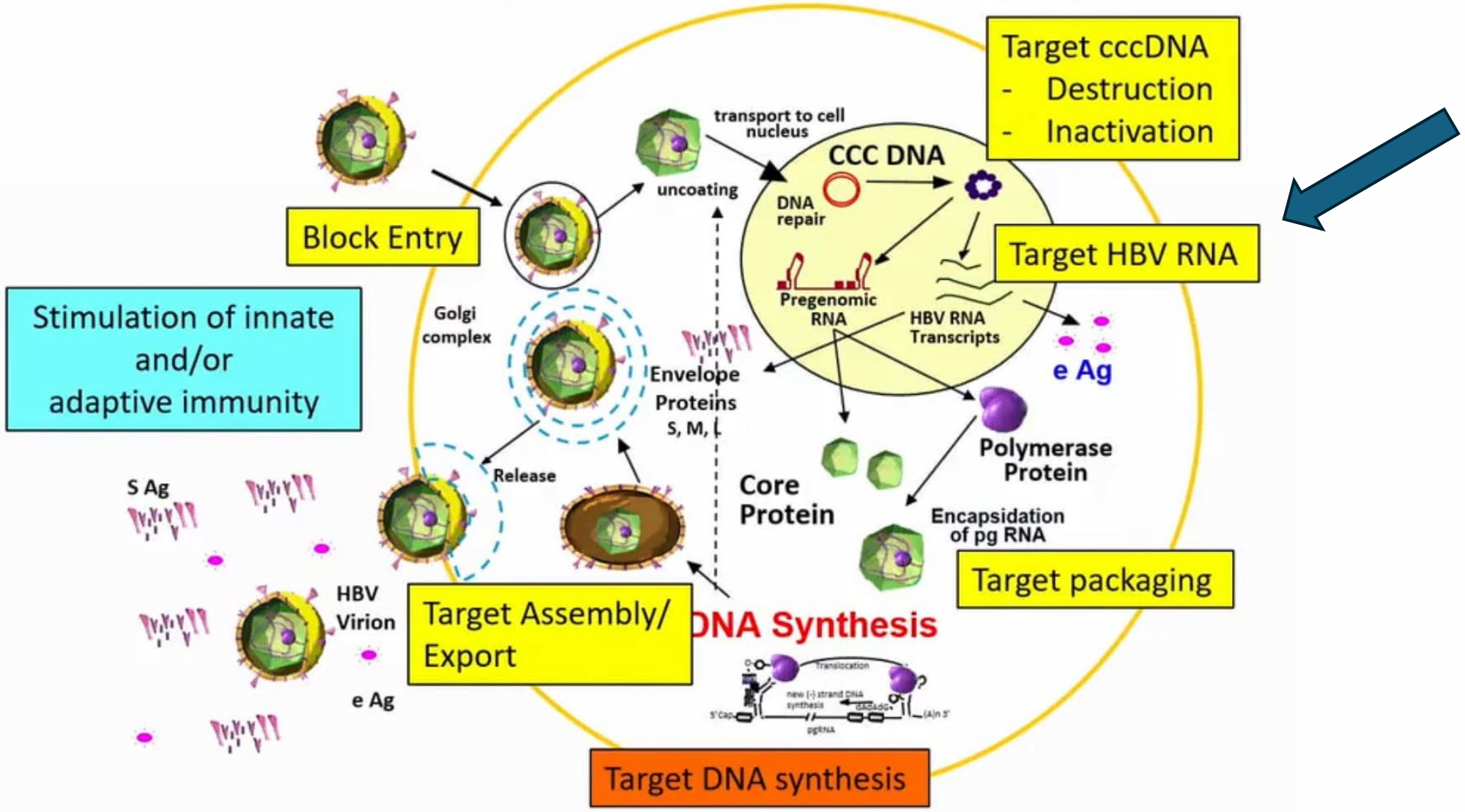
- HBsAg loss (ideally with HBsAb formation)

  Or possibly...
- Sustained off treatment inactive disease without HBsAg loss ('partial cure')
  - HBeAg –ve
  - DNA undetectable
  - normal ALT
  - normal histology

Potential targets in the lifecycle



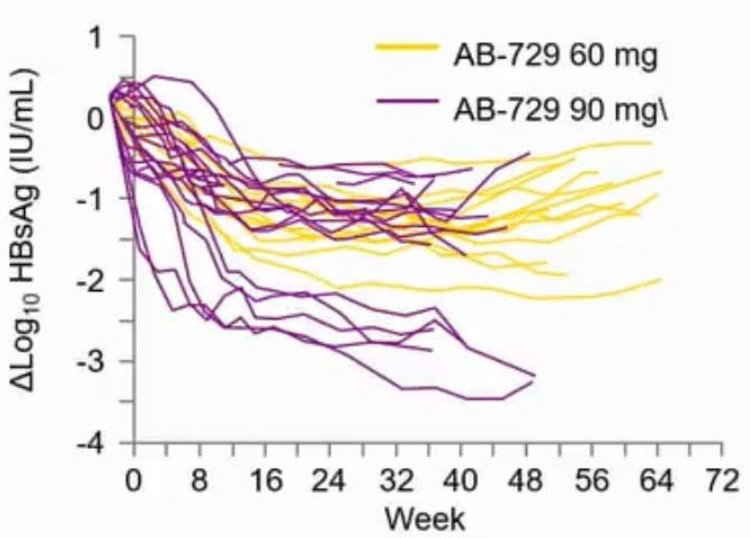
Potential targets in the lifecycle



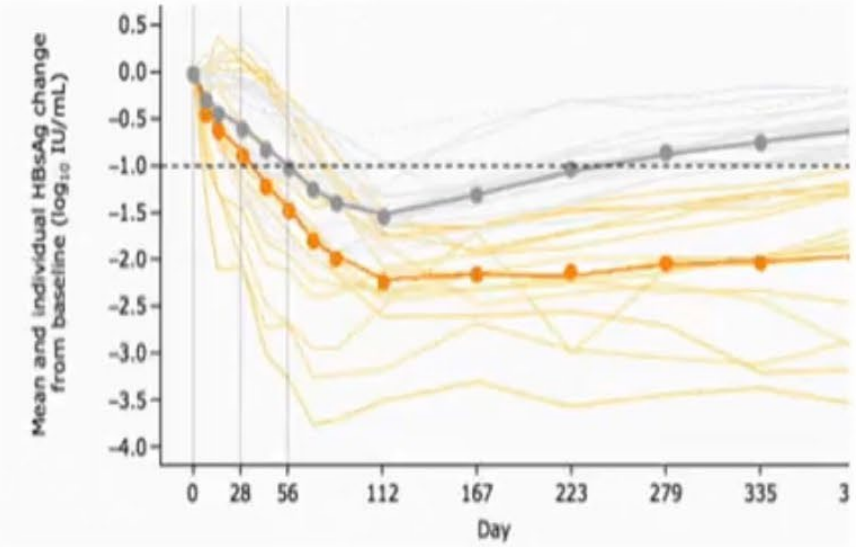
RNA inhibitor – siRNA

Subcutaneous injection

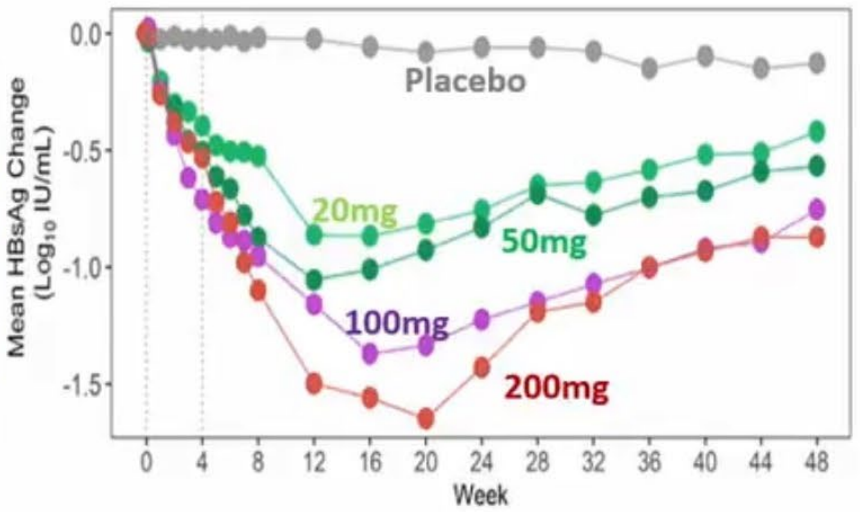
AB-729 (60/90 mg) + Nuc



JNJ-3989 (ARO-HBV) + Nuc



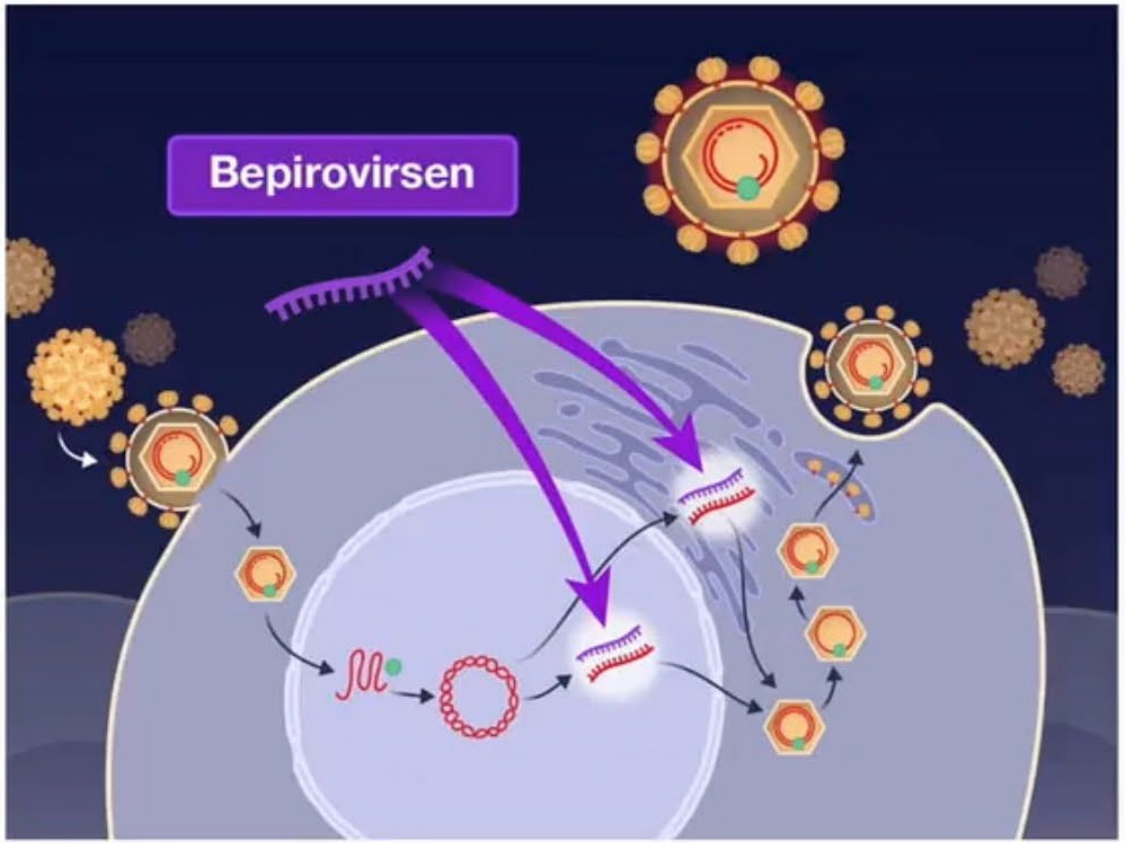
VIR 2218 + Nuc



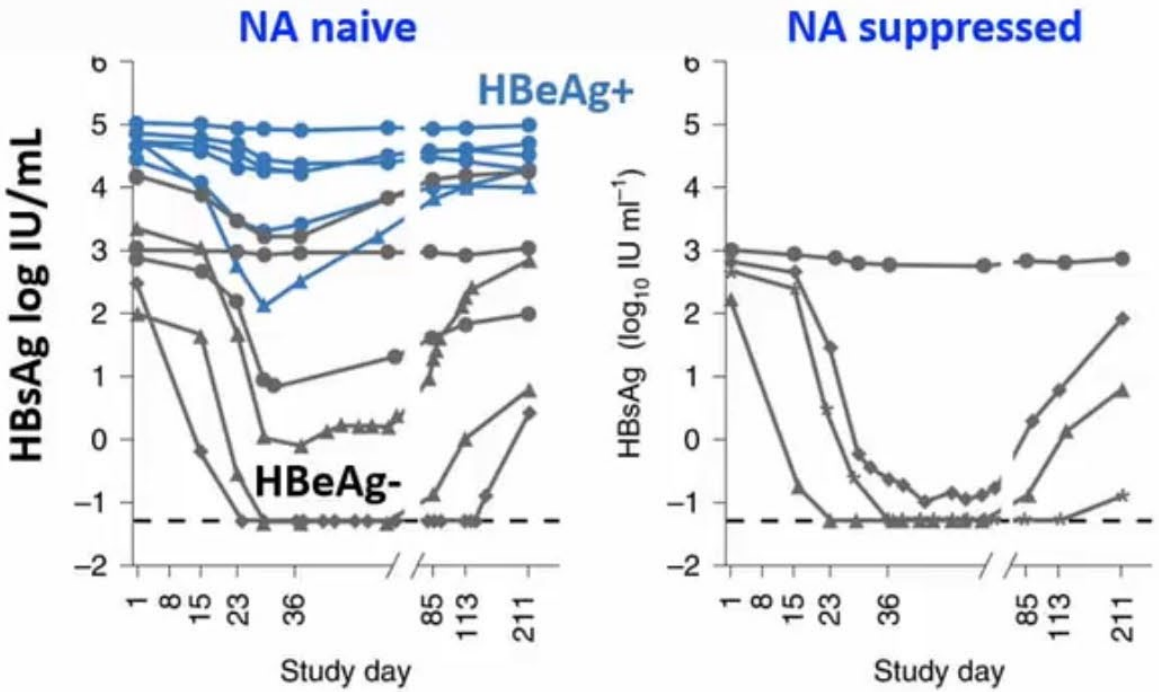
- Fairly consistent results – initial decline → **plateau – why?**
- Off-treatment – **sustained response ~40%** - what does this mean? Immune control?
- **Infrequent dosing, minimal toxicity, minimal/no resistance**

Antisense oligonucleotide – Bepirovirsen

- Similar concept to RNAi
- ASO binds HBV RNA species and degraded by RNase H rather than Ago



- Subcutaneous injection
- Dosed days 1, 4, 8, 11, 18 and 22
- Treatment-naïve and NA-suppressed

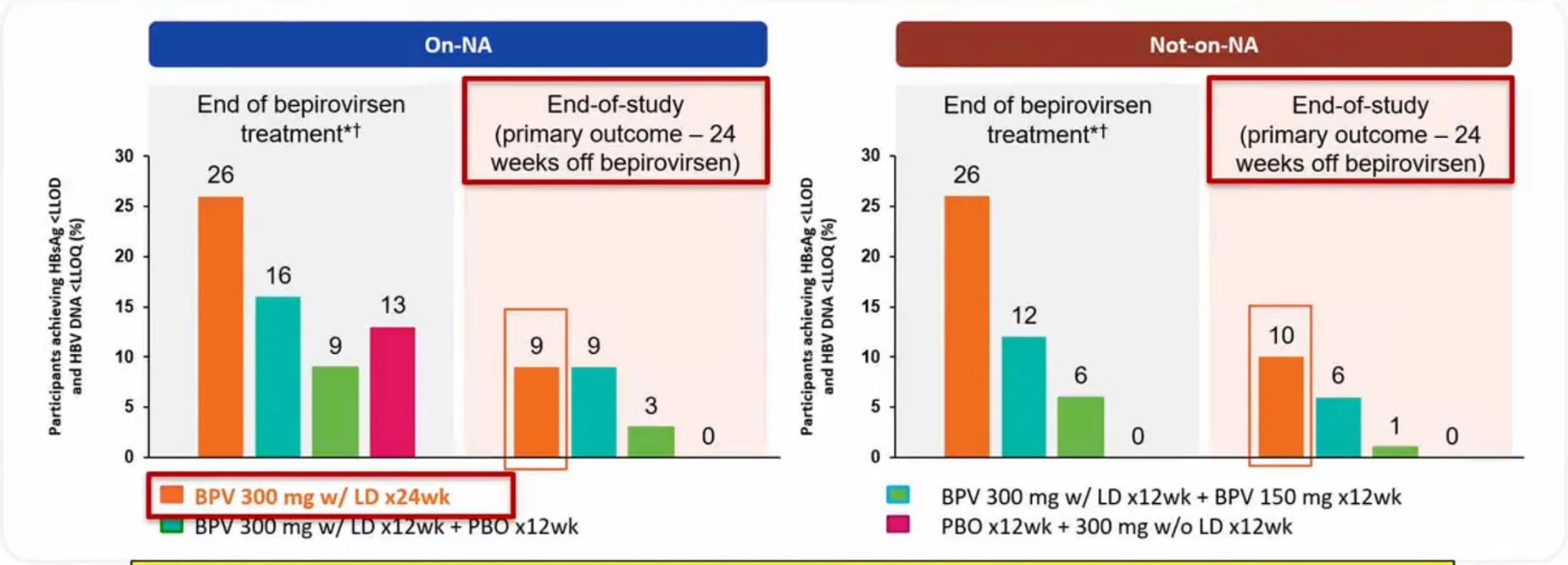


Greatest effect in HBeAg-negative CHB

Yuen Nature Medicine 2021
Yuen NEJM 2022

B-Clear: Phase 2 of ASO (bepirovirsen) +/- NA

CHB, **HBsAg>100 IU/mL**, on **stable NA** (DNA<90 IU/mL) or **not on NA** (DNA>2000)
Stratify by eAg and HBsAg <> 1000 IU/mL. **Primary endpoint → HBsAg loss & HBV DNA<20 IU/mL 6m off Tx**

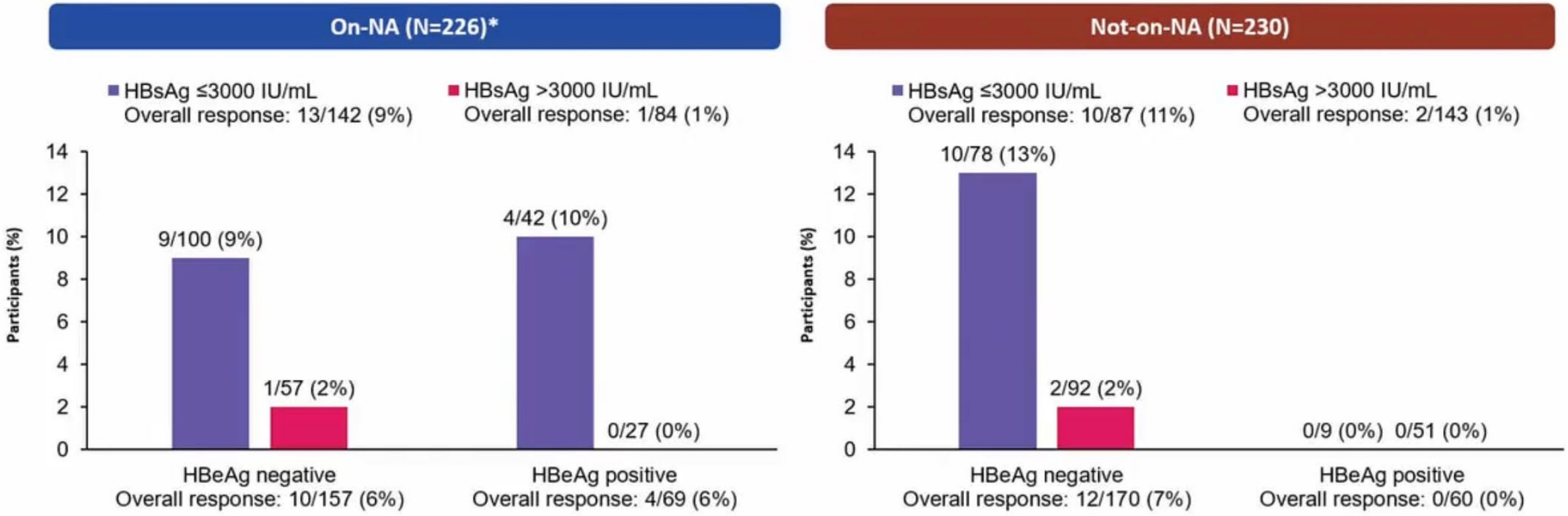


Very effective on treatment → drop-off after stopping

Yuen, et al. EASL 2022 NEJM 2022

Predictors of Response

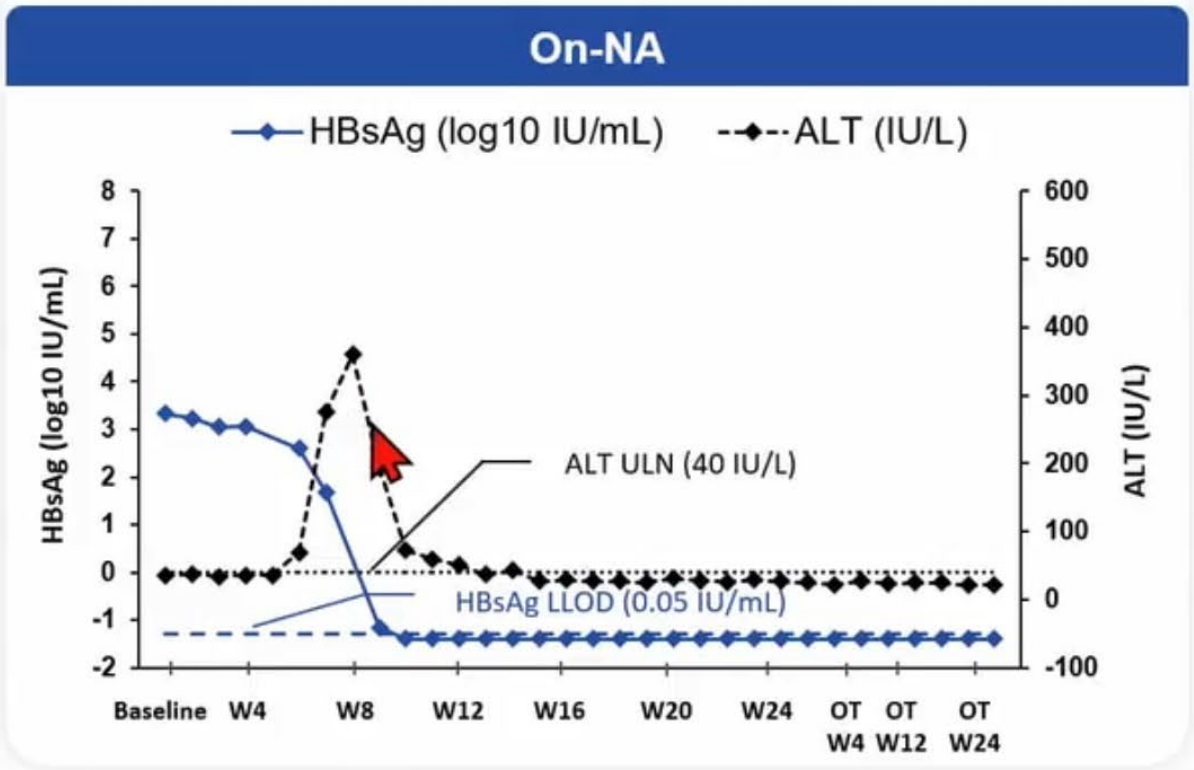
Proportion of participants achieving the primary outcome by baseline HBsAg levels (>/≤3000 IU/mL) and HBeAg status

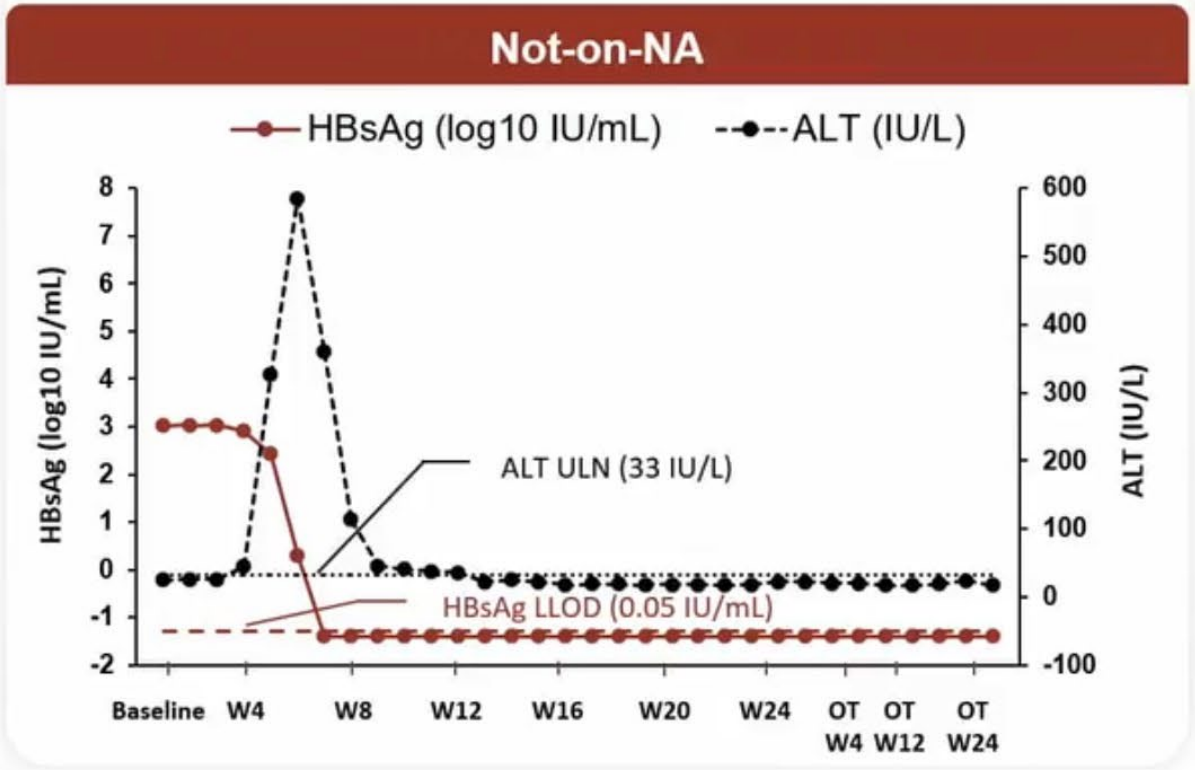


- **Baseline qHBsAg key predictor of response**
- **qHBsAg>3,000 IU/mL associated with very low response rate**

Yuen, et al. EASL 2022 NEJM 2022

ALT flares

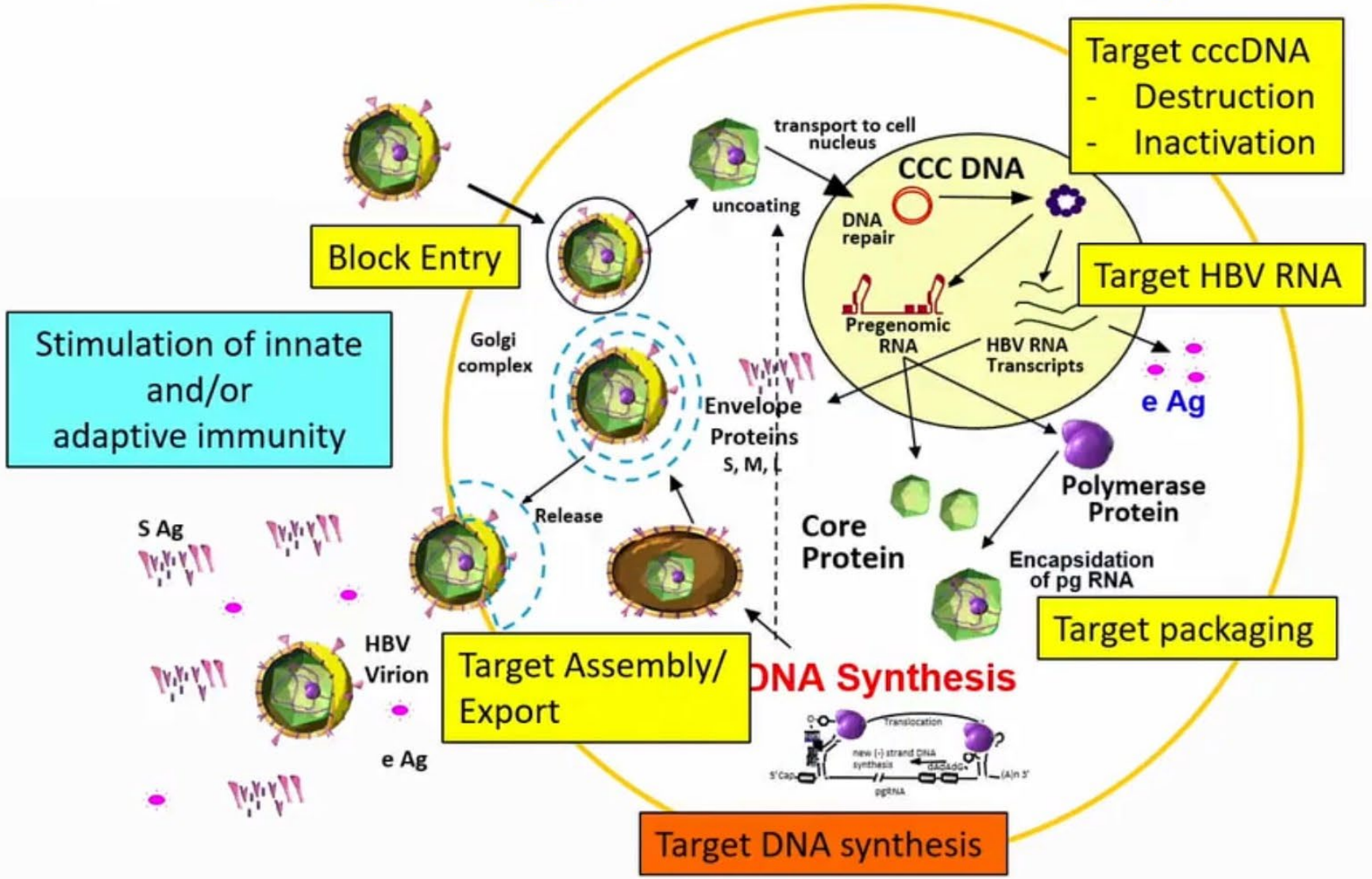




- Well tolerated but **predictable ALT flares** with HBsAg decline

Yuen, et al. EASL 2022 NEJM 2022

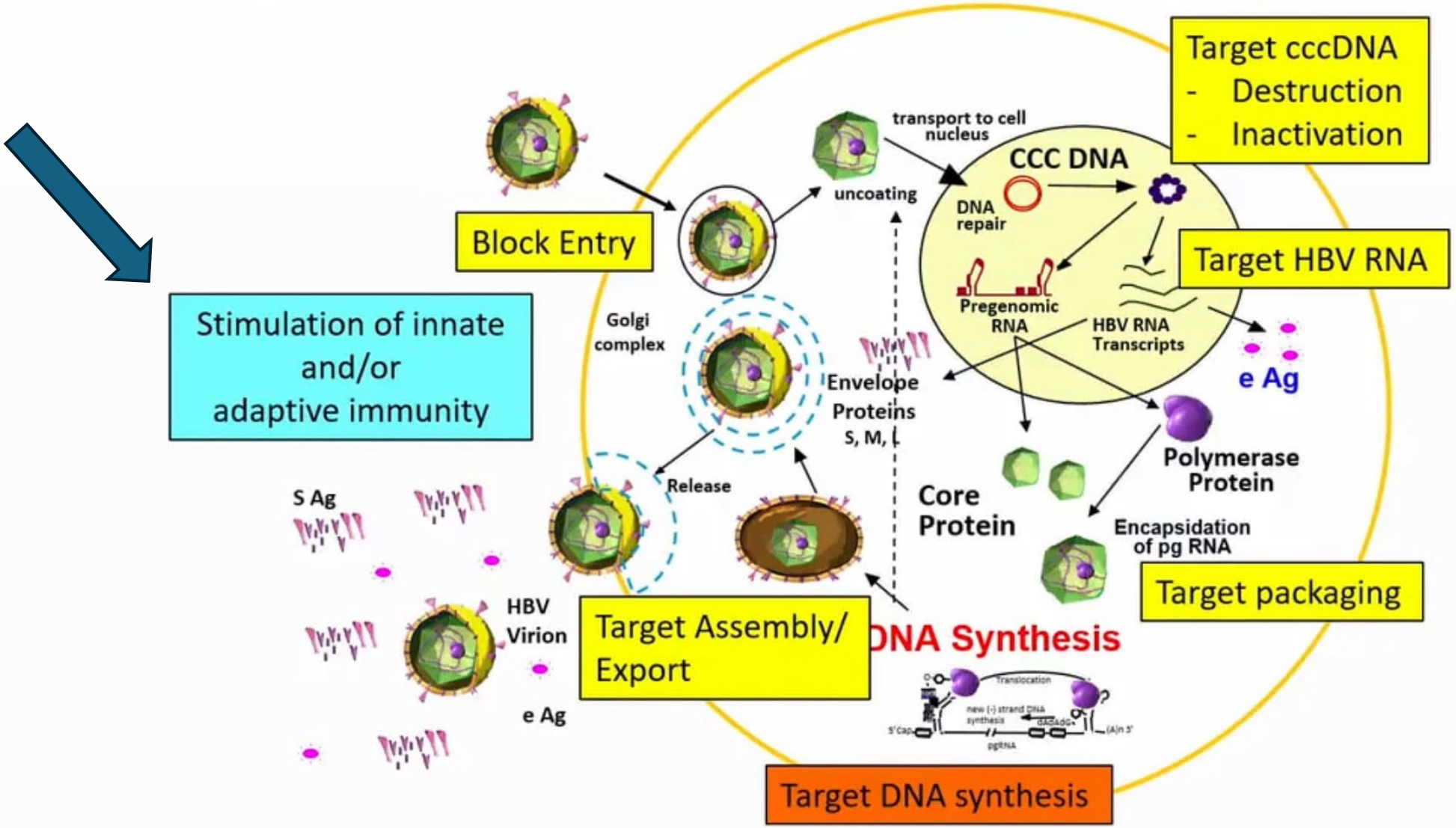
Potential targets in the lifecycle



Gene editing or epigenetic silencing

- The future is almost here…
- Promising therapies with:
  - CRISPR-Cas
  - ARCUS (another nuclease like CRISPR-Cas)
  - Epigenetic silencing
- Holds potential to target cccDNA and integrated HBV DNA → **makes 'complete cure' potentially possible**
- *Will it be enough?*
- *Will it be safe?*
- *Will people take it (even if it's safe)?*

Potential targets in the lifecycle



Immunotherapies

Innate

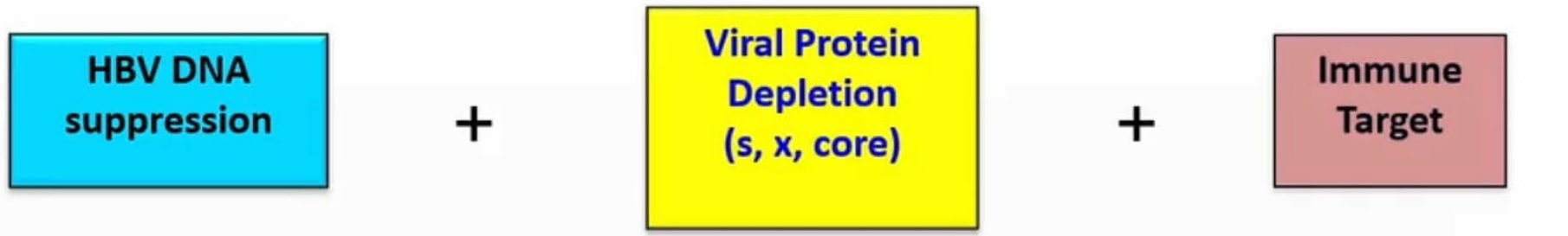
- Cytokine therapy
  - IFN
- TLR agonists
  - TLR7, TLR8
- RIG-I agonists

Adaptive

- Monoclonal Ab (entry inhibitor)
- Therapeutic vaccine
- Checkpoint inhibitors
  - PD-1
  - PD-L1

Immune restoration through inhibition of viral antigens

Attractive combinations



Nuc	RNAi	TLR/RIG-I agonist
+/- CAM +/- RNAi +/- cccDNAi	Nucleic Acid Polymers cccDNAi	αPD1/PDL1 Therapeutic vaccine

Mix and match…complicated matrix!



A tight race…
But slower than
we would like!

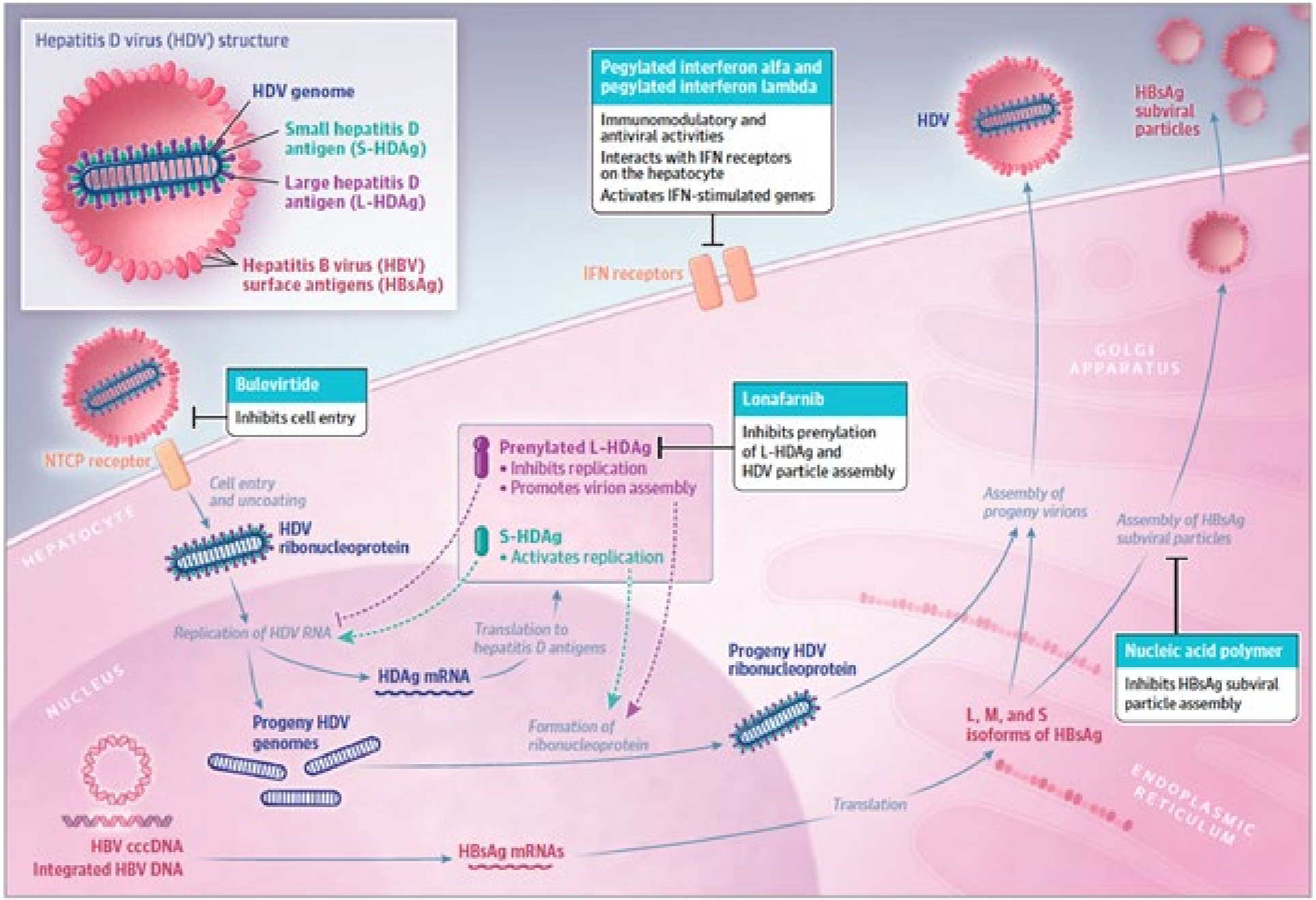


New HDV Treatments

Chronic Hepatitis D (CHD)

- Most severe form of chronic viral hepatitis
- Requires HBsAg for replication and propagation
- Estimated 10-20 million people worldwide
- Global prevalence: 5-15% of HBsAg+ individuals

Figure 1. Hepatitis D Virus (HDV) Structure, Life Cycle, and Antiviral Targets



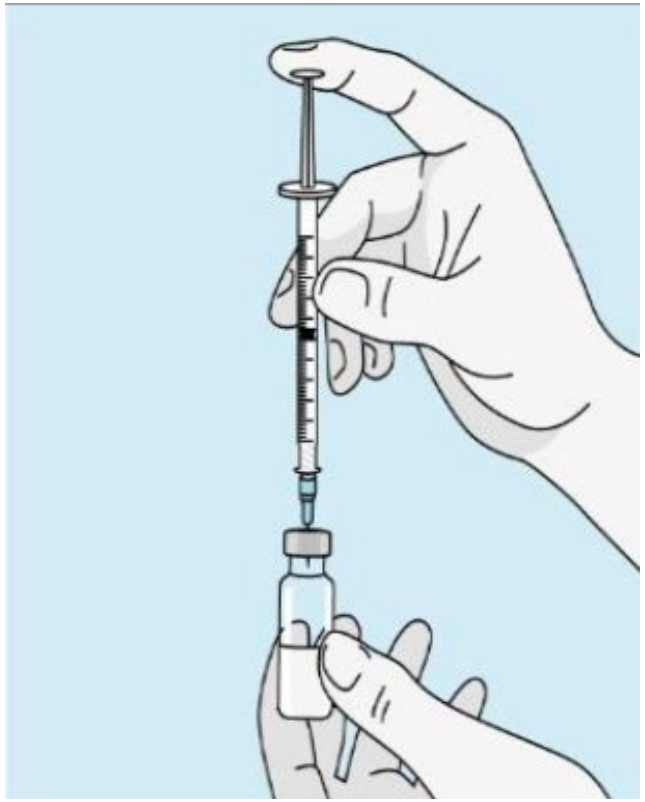
Treatment for CHD

Pegylated Interferon Alfa (PegIFN)

- Mechanism of Action: Prevents cell-to-cell spread of HDV and induces an antiviral state by destabilizing HDV RNA.
- Used off-label for many years
- Limitations:
  - Significant side effects
  - contraindications (advanced liver disease)
  - late relapse after treatment cessation.
  - Low efficacy rates (10-20% sustained off-Tx virologic responses)

Bulevirtide (BLV)

- First approved anti-HDV drug
- Entry inhibitor that blocks the NTCP receptor
- Prevents the entry of HBsAg-coated viral particles into hepatocytes
- Inhibits infection of previously uninfected cells
- Monotherapy Efficacy (2 mg/day) after 96 weeks:
  - 64% biochemical response
  - 79% virological response
  - 54% combined response



Bulevirtide (BLV)

- Generally safe and well-tolerated.
- Common side effects:
  - dose-dependent ↑bile acids (pruritus is infrequent, ~10%)
  - injection-site reactions
- Serious adverse events are rare
- discontinuation due to adverse events is uncommon.
- Improves biochemical markers (ALT, AST, GGT), liver stiffness (LSM), and liver function parameters (albumin, platelet count)
- Studies show low cumulative incidence of de novo HCC (3.0%) and decompensation (2.8%) over 96 weeks.

Combination Therapy (BLV + PegIFN)

Pegylated Interferon Alfa-2a, 180 μg

48 weeks

once weekly



24 Patients

Bulevirtide, 2 mg

96 weeks

daily

+

Pegylated Interferon Alfa-2a

first 48 weeks

once weekly

50 Patients

Bulevirtide, 10 mg

96 weeks

daily

+

Pegylated Interferon Alfa-2a

first 48 weeks

once weekly

50 Patients

Bulevirtide, 10 mg

96 weeks

daily



50 Patients

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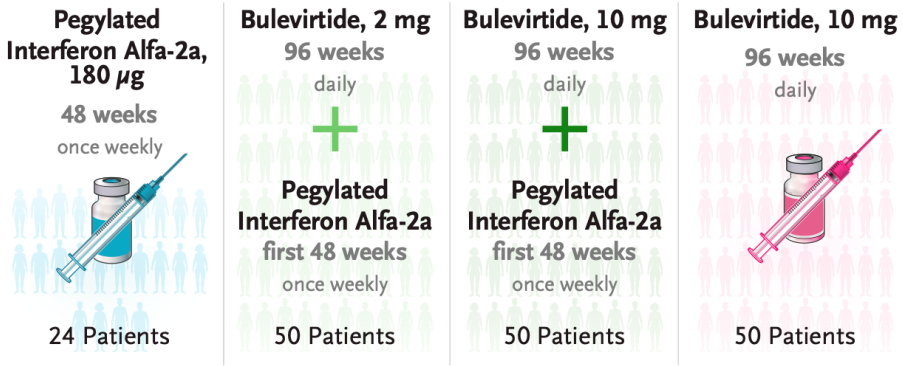

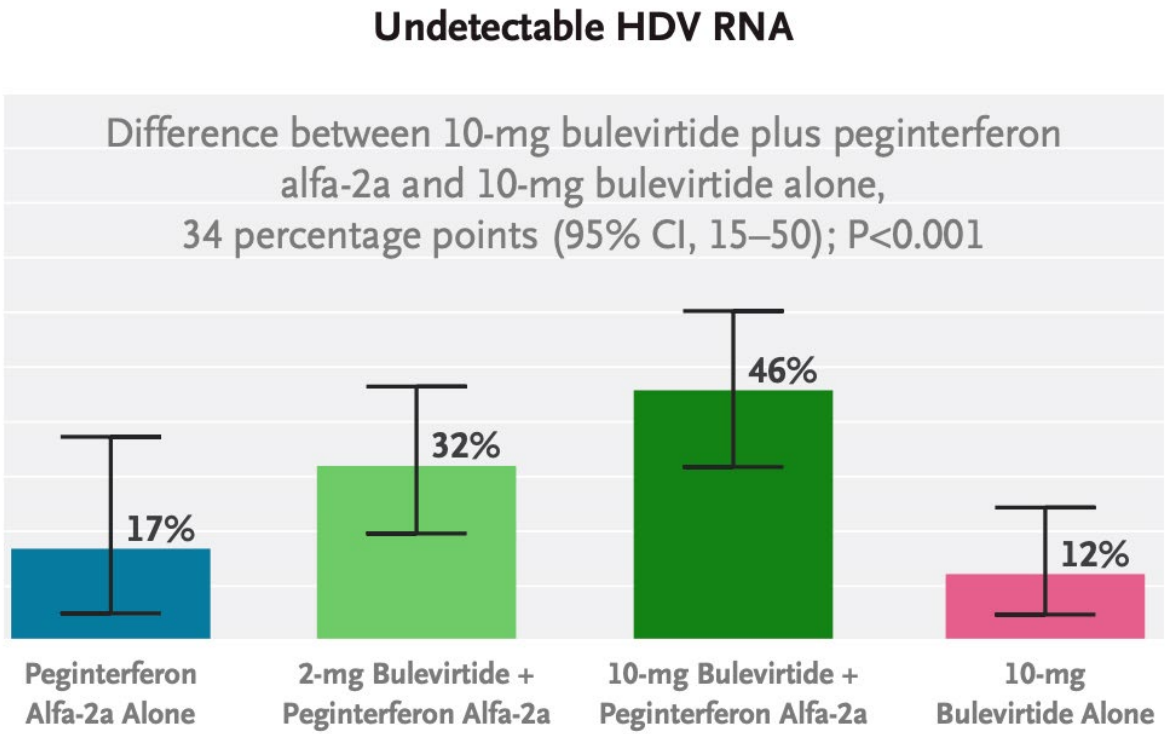

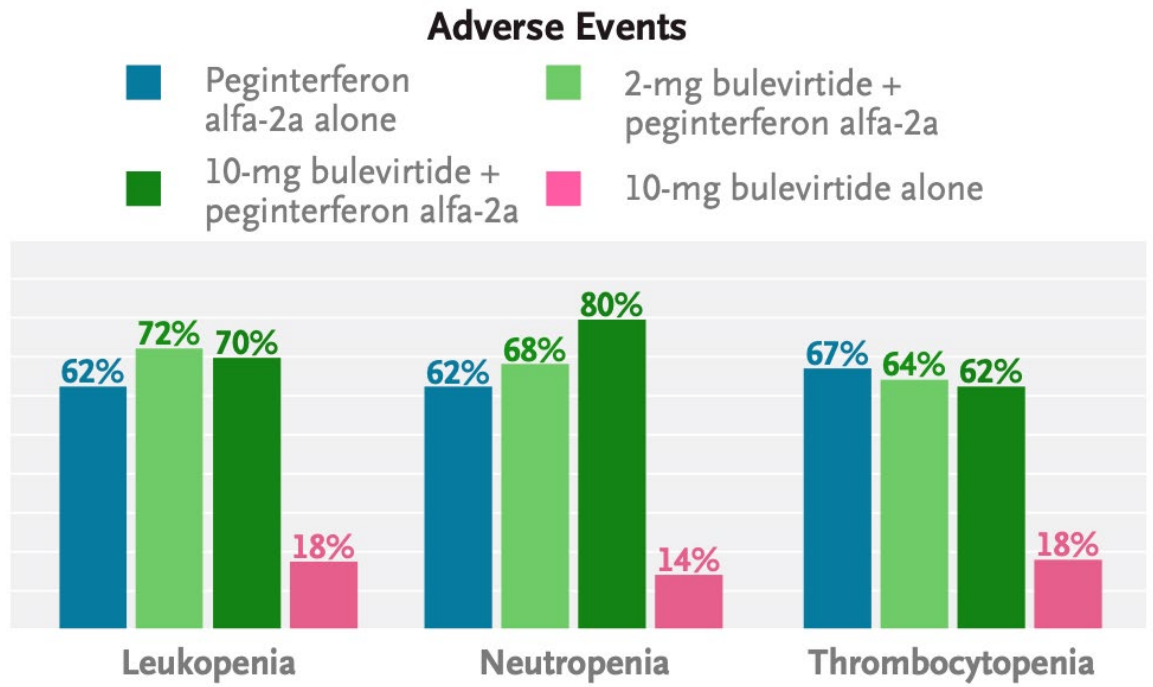

Asselah, et al 2024, NEJM

Key unmet needs

? Standardized HDV RNA assays

? Robust biomarkers for disease progression

? Optimal duration of bulevirtide treatment

? Clear predictors of treatment response

Thank You