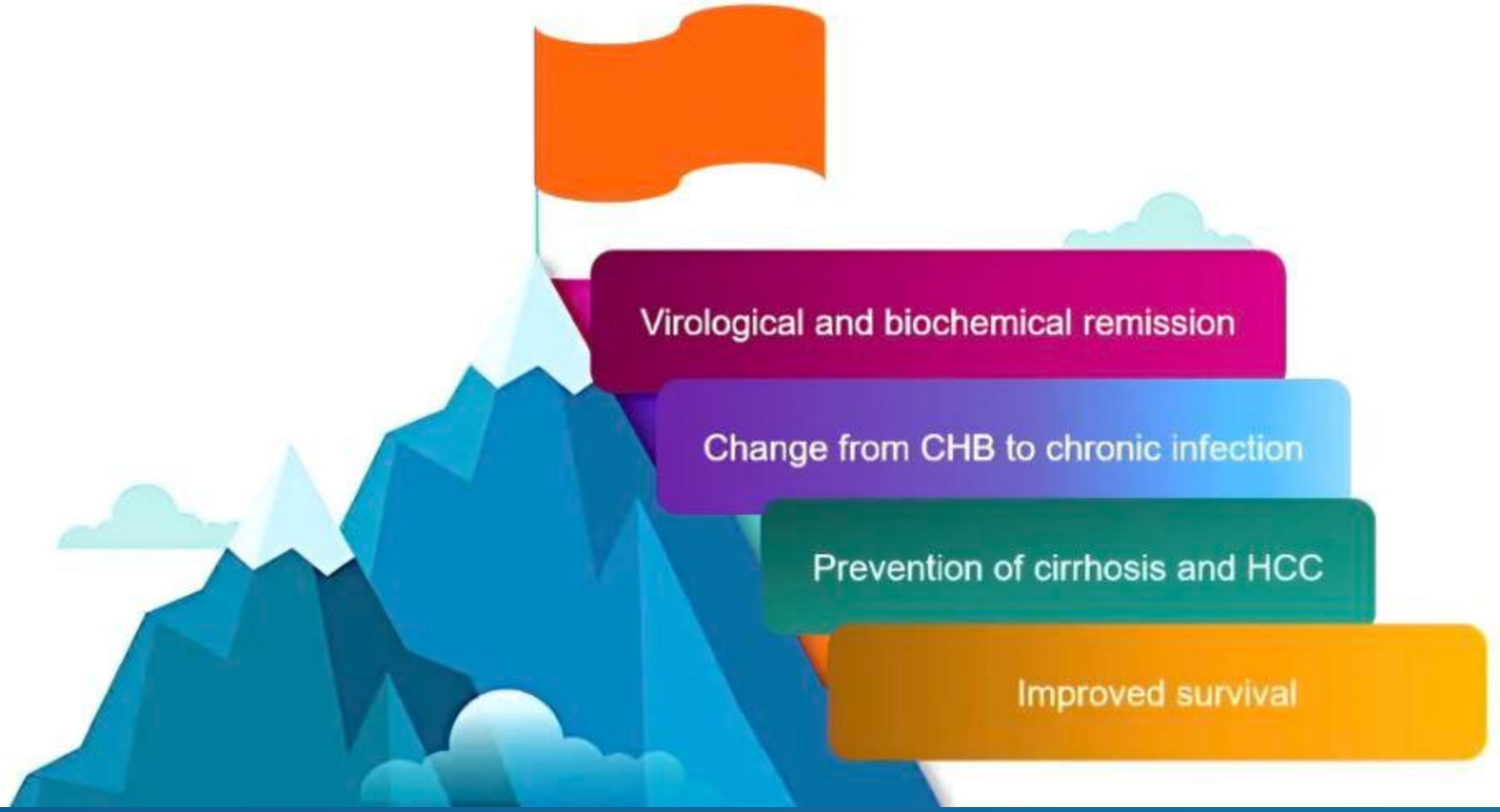
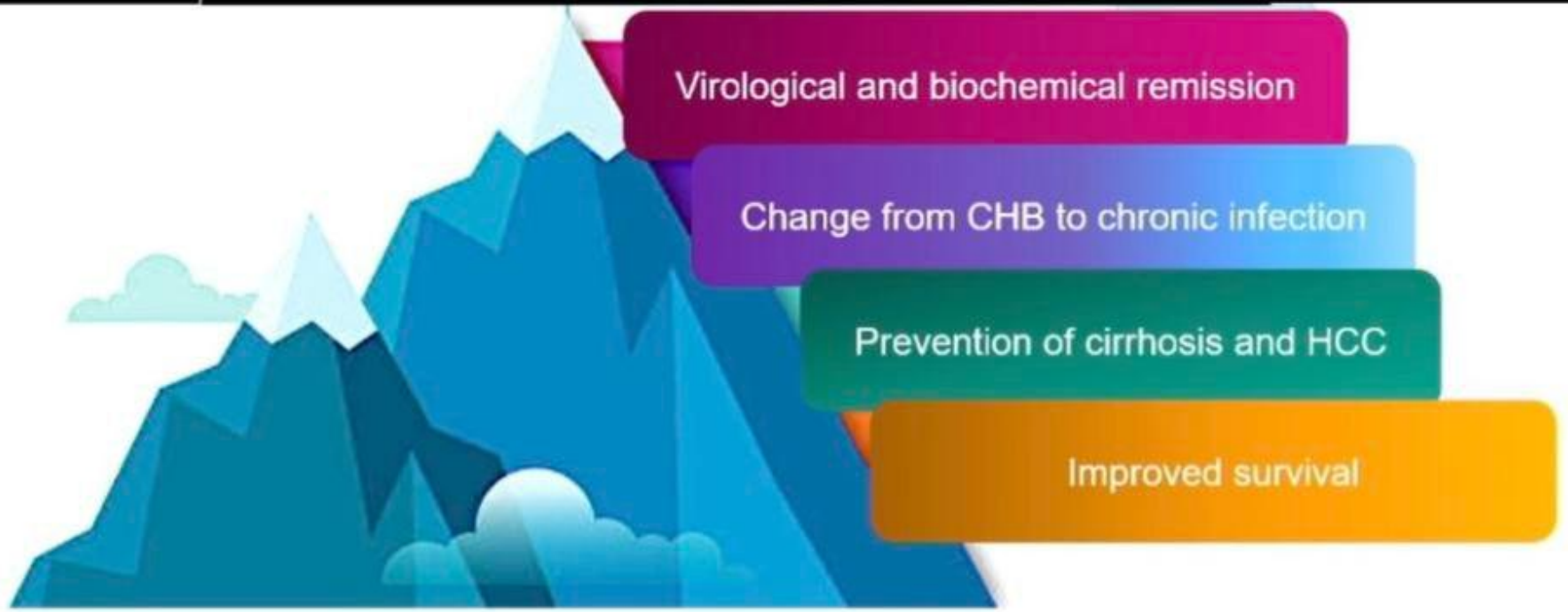
Which HBV treatments will reach the clinics?

د ابتسام بوشي
الهيئة العامة لمشفى دمشق

Feasible therapeutic endpoints for CHB



Ideal therapeutic endpoints for CHB



CHB= chronic hepatitis B, HCC= hepatocellular carcinoma

Incremental benefits of HBsAg loss compared to HBV DNA suppression

Potential benefits	Proven benefits
Further reduction in HCC risk	Evidence in support but risk not eliminated
Further reduction in risk of other cancers and extrahepatic manifestations	Unknown
Eliminate need for long-term therapy	If HBsAg loss is sustained during long-term follow-up, to be determined
Decrease overall cost of treatment	High cost of cure therapy may not offset cost of long-term generic NA
Eliminate need for long-term monitoring	Maybe, if HBsAg loss occurs at young age, before cirrhosis, and in those with no family history of HCC
Remove stigma of HBV infection, improve quality of life	Possible, needs to be confirmed
Further reduction in transmission	Unlikely

Strategies aimed at functional cure

- Inhibit HBV DNA replication
- Decrease HBsAg production or release
- Stimulate immune response and/or remove immune blockade

Antiviral therapies: what's NOT new?

Current HBV Treatment Options in Clinical Practice

Peg-IFN

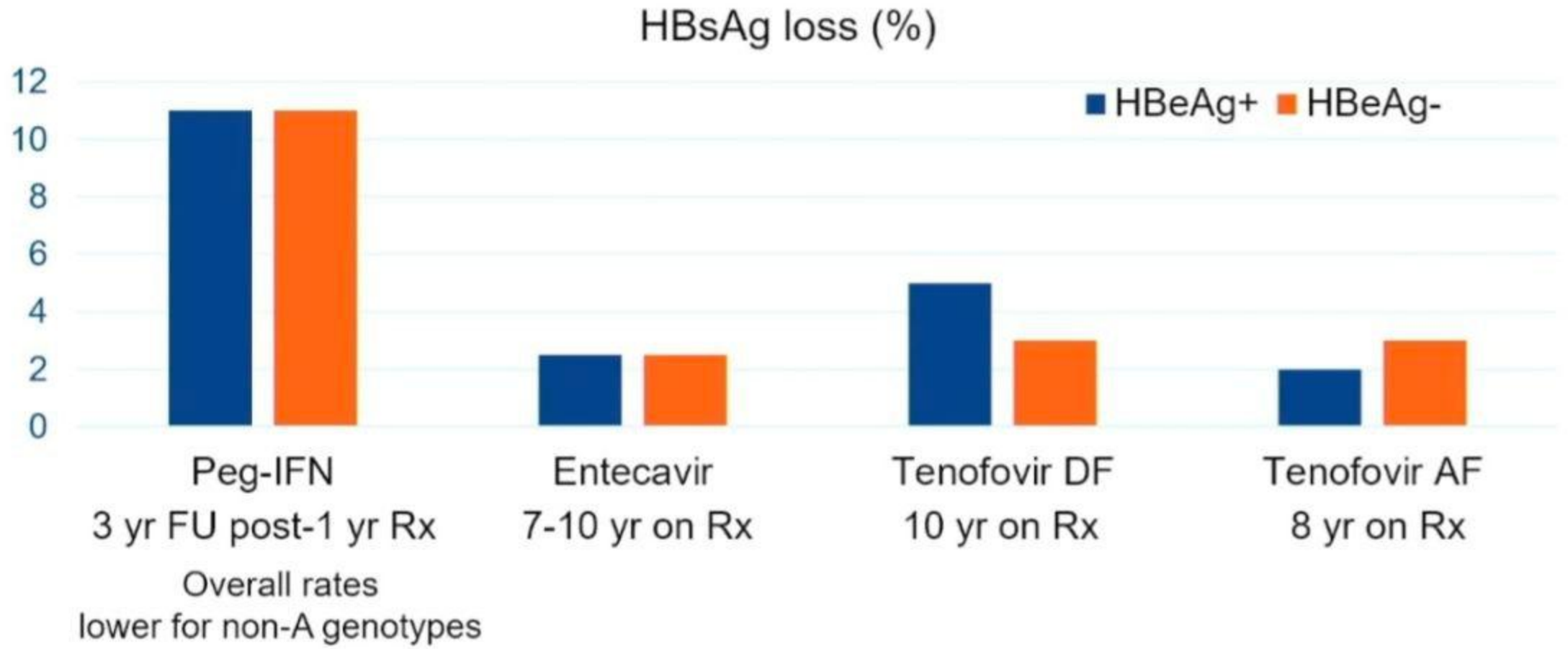
(Pegylated Interferon 2a)

NAs

(Nucleos(t)ide Analogues)

ETV, TDF, TAF

Low rates of HBsAg loss with interferon or nucleos(t)ide analogue monotherapy



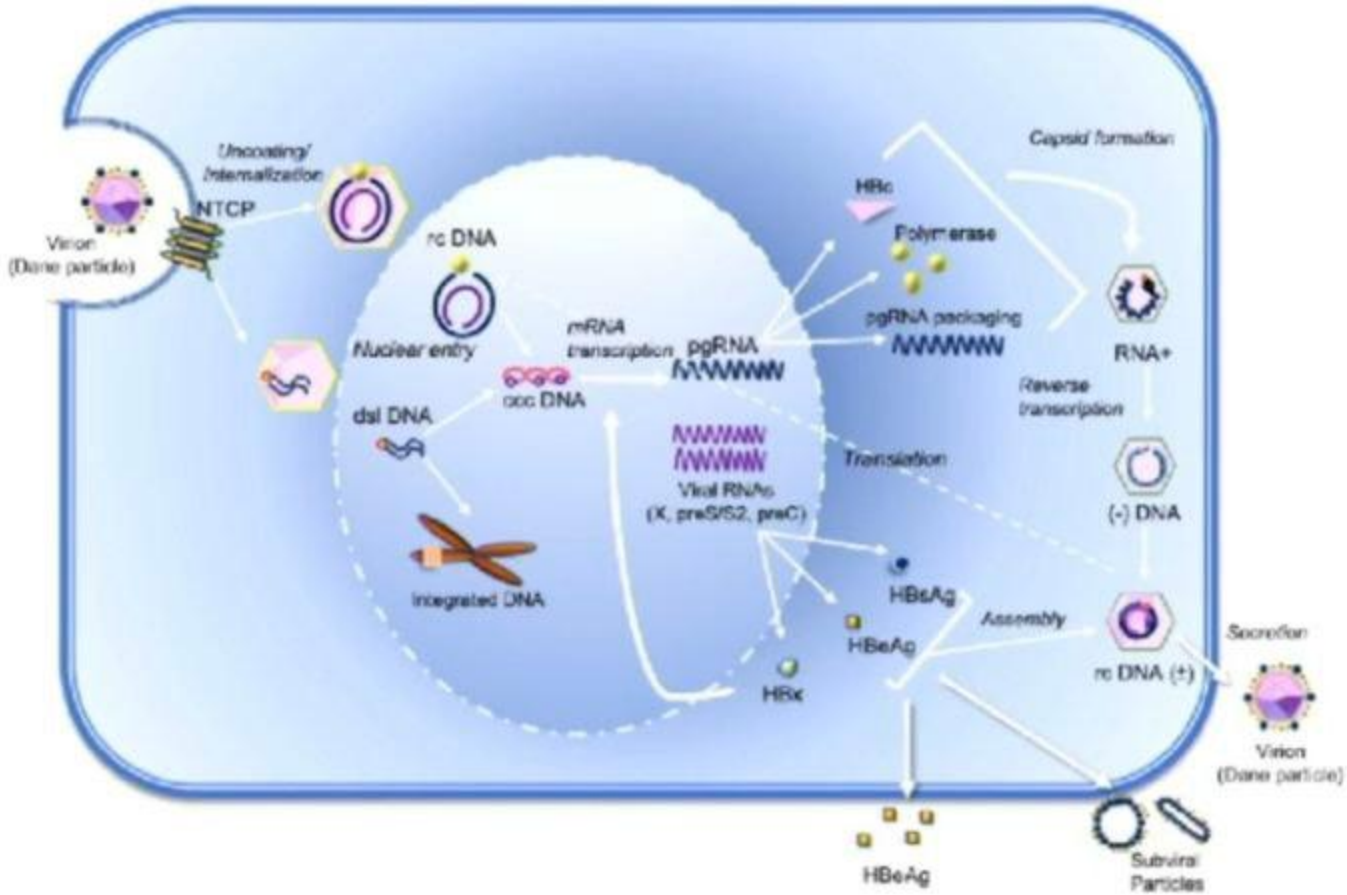
Replication inhibition

- Nucleos(t)ide analogue (NA)
  - Backbone therapy: obligatory or optional?
- Capsid assembly modulator (CAM)
  - 1st generation CAM: additive effect in combination with NA, also decrease HBV RNA, drug resistance as monotherapy
  - 2nd generation CAM: robust inhibition with no drug resistance after 96 weeks monotherapy
- Entry inhibitor
  - Limited data, bulevirtide limited effect, new agents?
- siRNA / ASO
  - Variable, inadequate inhibition as monotherapy particularly for HBeAg+ patients
- Peg-interferon (peg-IFN)
  - Modest inhibition, less potent than NA

New HBV antiviral targets aim at functional cure

Mechanisms interfering with virus life cycle

1. Entry inhibitors
2. Capsid assembly modulators (CAMs)
3. Small interfering RNAs (siRNAs)
4. Antisense oligonucleotides (ASOs)
5. Nucleic acid polymers (NAPs)



Modified from M Papatheodoridi et al. Expert Opin Pharmacother 2022

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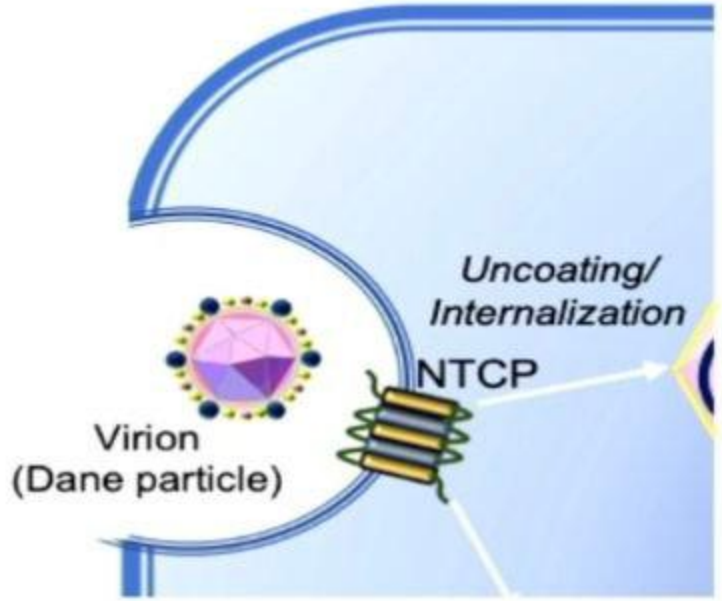

Blocking NTCP: sodium taurocholate cotransporter

Modified from M Papatheodoridi et al. Expert Opin Pharmacother 2022

NTCP Blocker

Bulevirtide

- Minimal effect on HBsAg decline
- No HBsAg loss
- Some decline of serum HBV DNA

Impossible extrapolation from BLV use in CHD:
Low serum HBV DNA levels, combination of BLV with NA

EASL HDV CPGs. J Hepatol 2023;79:433–60

Recommendations

- All patients with CHD and compensated liver disease should be considered for treatment with BLV **(LoE 3, strong recommendation, consensus).**
- The optimal dose and duration of treatment have not yet been defined **(LoE 5, consensus).** Until further data become available, long-term treatment with BLV, 2 mg once daily, may be considered **(LoE 5, weak recommendation, consensus).**
- The combination of pegIFNα and BLV may be considered in patients without pegIFNα intolerance or contraindications **(LoE 5, weak recommendation, consensus).**

New HBV antiviral targets aim at functional cure

Mechanisms interfering with virus life cycle

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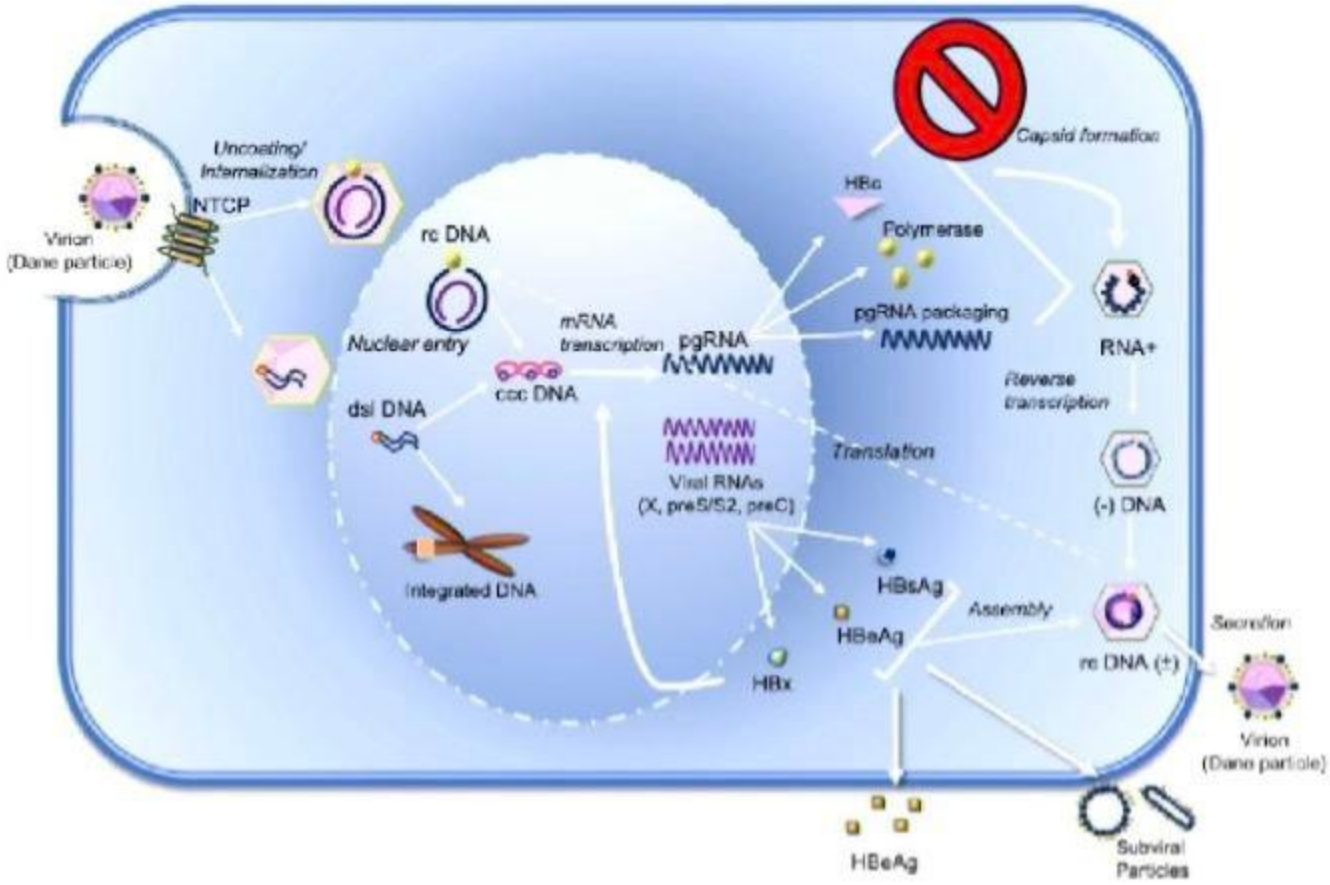
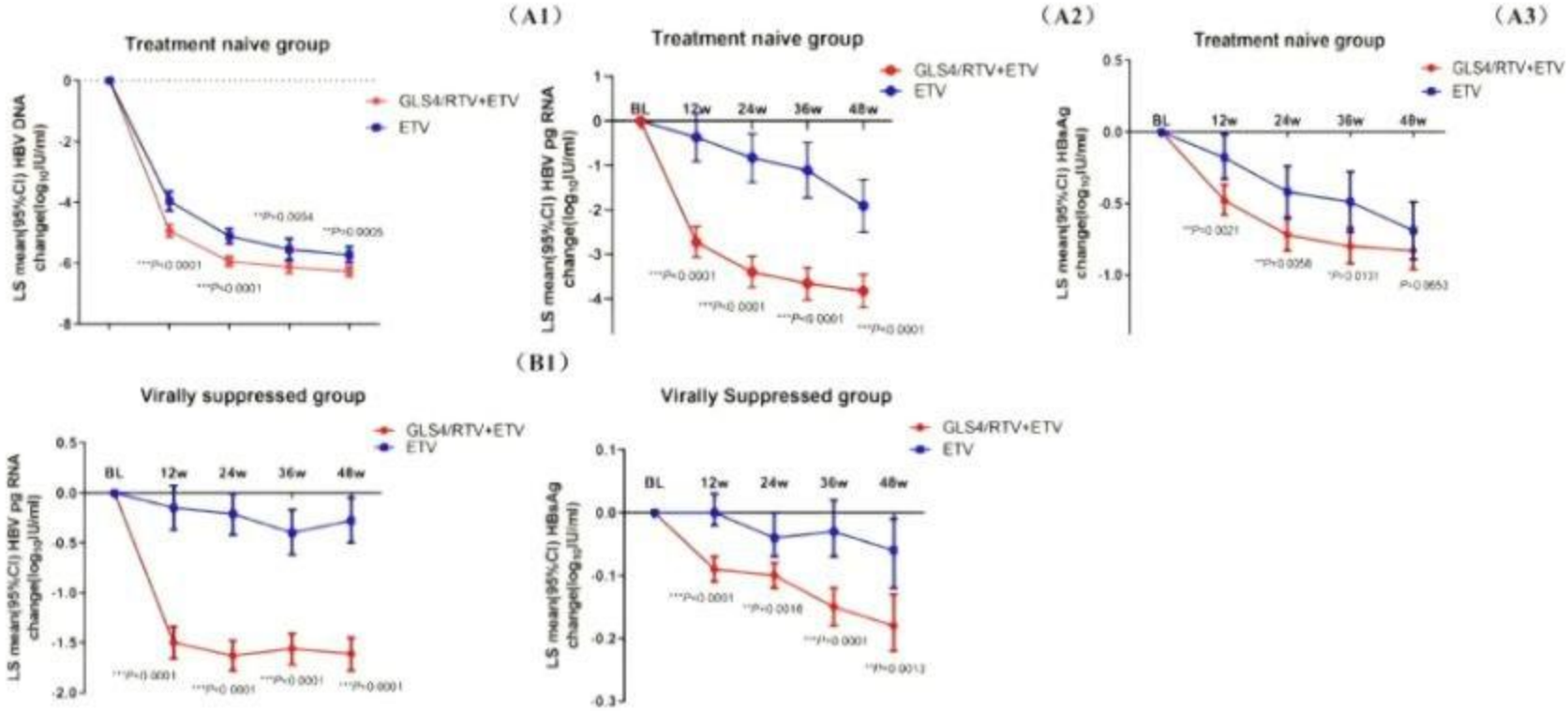


Modified from M Papatheodoridi et al. Expert Opin Pharmacother 2022

GLS4

NCT04147208, Phase 2b

GLS4 + ETV was **superior** than ETV alone in **HBV DNA, HBV pgRNA and HBsAg decline** at 48wks **both** in NA-naïve and NA suppressed patients.



*GLS4 was ritonavir (RTV) boosted

New HBV antiviral targets aim at functional cure

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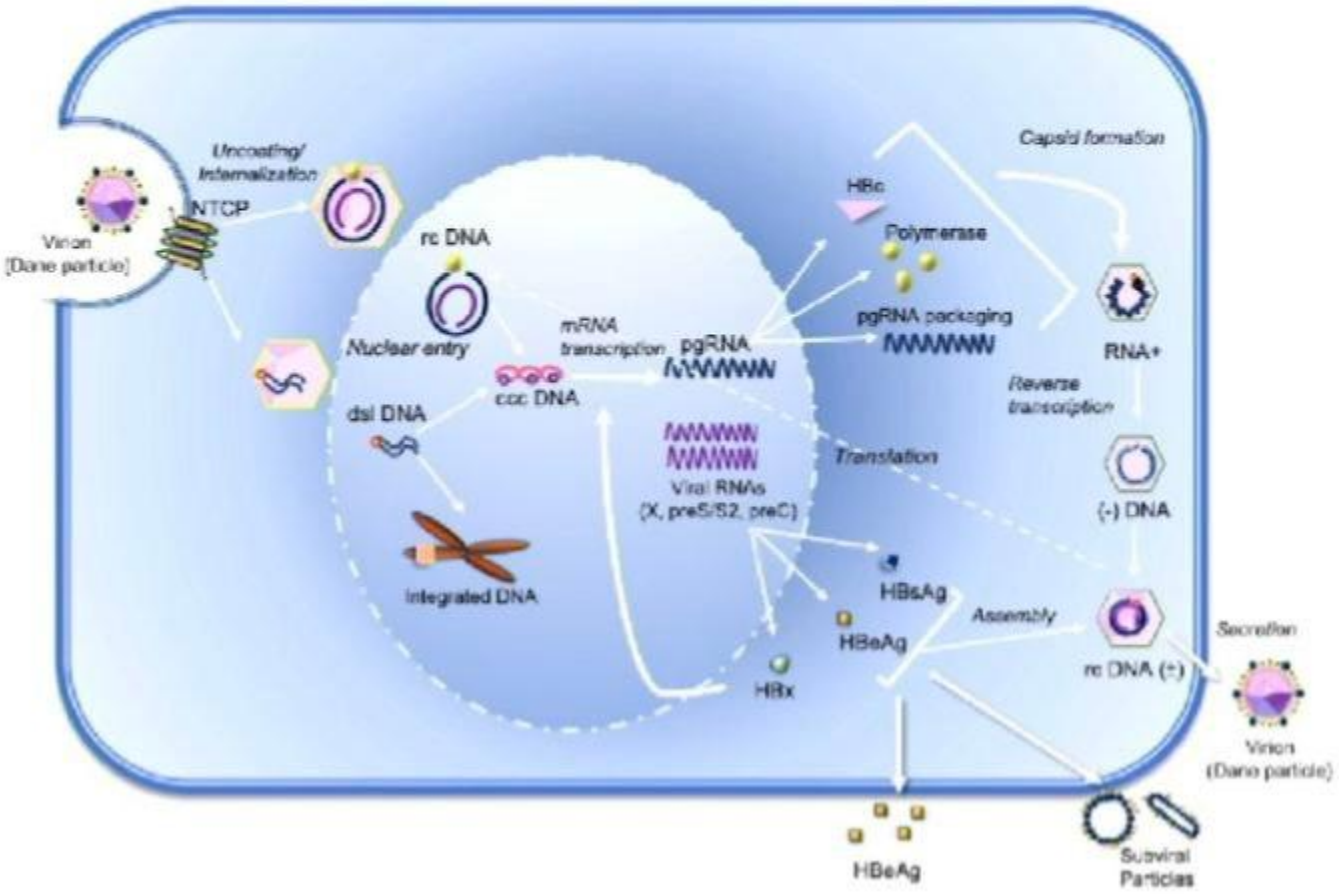


siRNA

	Imdusiran (IDR, AB729)	Xalnesiran (RG6346)	Elebsiran (VIR-2218)
Phase 2 trials	NCT04980482 IM-PROVE I	NCT04225715 PIRANGA	NCT03672188/ NCT05970289
Key points	✓ Combinations of siRNA with Peg-IFN (24-48wks) offer increased HBsAg loss rates 2x-3x times than monotherapy of siRNA.		
	up to 16%,	up to 23%	up to 33%
	✓ Small number of study patients		
	N=43	N=159	N=84/ 55
	✓ Most patients who achieved HBsAg loss had baseline **HBsAg <1,000** (or <3,000) IU/mL		
	✓ All patients were on continued NA treatment		
References	Yuen MF, et al. J Hepatol. 2021.	Hou J. et al N Engl J Med 2024.	Yuen MF et al. Lancet Gastro & Hep 2024; Poster No LBP-016

ASO

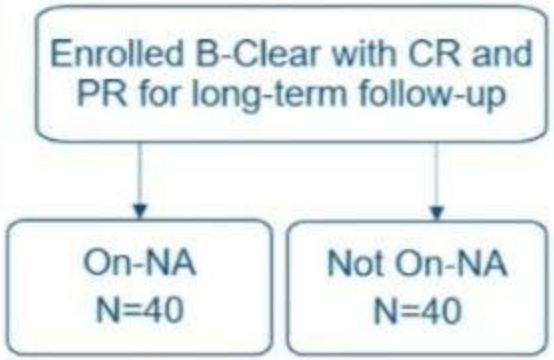
Bepirovirsen

Recruiting/Active Phase 3 trials: B-Well 1 & 2

NCT04449029, Phase 2b B-Clear

Bepirovirsen 300mg with loading dose for 24wks	On-NAs	Not-on NAs
HBsAg loss at EOT / at 24wks post EOT, %	26 / 12	29 / 14

MF Yuen et al. NEJM 2022



NCT04676724, Phase 2b B-Sure

No TOP-268 & THU-259 Lim SG et al. EASL 2025

Most patients with CR maintained functional cure for up to 18 months (after NA discontinuation: 8/11) or up to 27 months (if not on-NAs: 6/8)

CR = Complete response= HBsAg <0.05 IU/mL and HBV DNA < LLOQ. (<20 IU/mL).
PR = Partial response= HBsAg <100 IU/mL and HBV DNA <LLOQ

New HBV antiviral targets aim at functional cure

Mechanisms interfering with virus life cycle

1. Entry inhibitors
2. Capsid assembly modulators (CAMs)
3. Small interfering RNAs (siRNAs)
4. Antisense oligonucleotides (ASOs)
5. Nucleic acid polymers (NAPs)

- ✓ Inhibition of HBsAg secretion
- ✓ Reduction of serum HBsAg levels
- ✓ Restoration of immunomodulation and host-mediated clearance

Only **REP-2139 and REP-2165** in phase 2 study

(Bazinet M. et al, Gastroenterology 2020)

Despite high rates of HBsAg loss

- Frequent ALT flares (even > 1000 U/L)
- No confirmatory studies since then

HBsAg reduction: decrease production or release

- siRNA/ASO
  - siRNA monotherapy: 2-3 log reduction, maintain lower HBsAg level during follow up but negligible HBsAg loss
  - Naked ASO – off-treatment HBsAg loss achieved without addition of immune modulator
- Release inhibitor
  - Nucleic acid polymer (REP 2139/2165), 39% functional cure in combination with peg-IFN and TDF in 1 small trial
- CAM
  - 1st generation – no effect
  - 2nd generation – HBsAg decrease mainly in HBeAg+ patients but not loss
- Entry inhibitor
  - Limited data, bulevirtide no effect in HBV/HDV, new agents?
- Peg-IFN
  - Monotherapy: low rate of HBsAg loss
  - Augments HBsAg loss as add-on to NA
  - Variable increase in HBsAg loss in combination with siRNA/ASO: concurrent or sequential, optimal duration?
- Gene editing/epigenetic modification
  - Proof-of-concept studies: promising preclinical data, long-term safety and efficacy to be determined

Is naked ASO the answer to functional HBV cure? Long-term follow-up of participants who received Bepirovirsen

- Of those with undetectable HBsAg (<0.05 IU/mL) ≥6 months off Bepi, 57% and 73% in the groups with vs. without concomitant NA had sustained functional cure (FC) during long-term follow-up
- Few with HBsAg <100 IU/mL 6 months off Bepi achieved functional cure during long-term follow-up
- **Overall long-term functional cure in 16/457 participants, mainly those with low baseline HBsAg**

Bepirovirsen + NA, n=227 in B-Clear

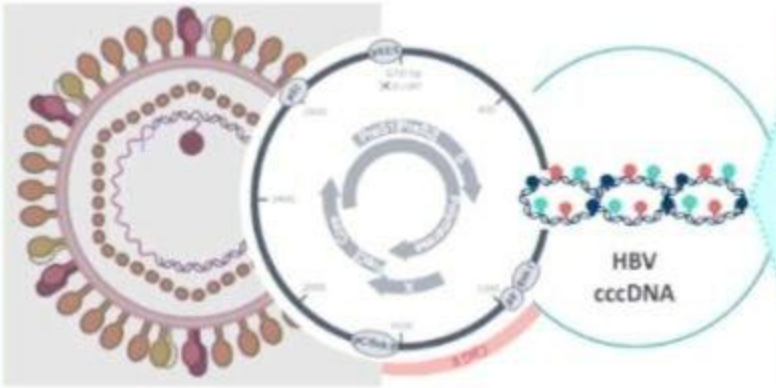
Months off Bepi	HBsAg <0.05 IU/mL	HBsAg <100 IU/mL
6	14	26
9 (off NA)	10/14	22/26
15	8/10 FC	7/22 (2 FC)
21	8/8 FC	5/7 (2 FC)
27	8/8 FC	4/5 (2 FC)

Bepirovirsen only, n=230 in B-Clear

Months off Bepi	HBsAg <0.05 IU/mL	HBsAg <100 IU/mL
6	11	5
9	8/11 FC	1/5
21	8/8 FC	1/1
27	6/6 FC	1/1

Lim SG, 2025 EASL THU-259 & TOP-268

Next generation HBV cure aiming at HBV eradication



CRISPR/Cas9 → EBT-107, Excision BioTherapeutics

ARCUS mRNA →
No LBP-038, Yucov A. et al.
PBGENE-HBV, Precision BioSciences
First-in-human clinical trial- Phase 1
3participants
Safe, well tolerated, (lowest dose cohort 0.2mg/kg)
Valiidation of preclinical data until now
Ie. eliminating cccDNA

Epigenetic silencing →
AASLD 2024 Poster No 0152
TUNE-401, Tune Therapeutics
Preclinical data
Strong, durable silencing of
Integrated HBV DNA in Hep3B cells

International HBV meeting, Chicago 2024
CRMA-1001, Chroma medicine/ nChroma Bio

Take away messages

Latest phase 2b trials reveal that **combinations** including translation inhibitors offer increasing **HBsAg loss rates** (**ASO> SiRNA**, possibly by restoring immune response)

Phase 3 trials are ongoing

Ongoing/latest trials are assessing **durability of response** in the post-treatment period

Some newer **CAM** molecules offer **profound HBV viral load** decline but no functional cure

Preclinical data from next generation antivirals use **gene editing or silencing** strategies in order to **target cccDNA** (± integrated HBV DNA)

Rationale for an immunotherapeutic approach

- Current antivirals safe & effective but:
  - lifelong treatment, risk of HCC and stigma not eliminated
- New antivirals unlikely to be able to eliminate all HBV cccDNA and integrated DNA

- Most infected adults resolve HBV infection and maintain residual virus under successful long-term immune control

  –blueprint for immunotherapy

- Multiple aspects of immunity are defective in chronic HBV

  …….but the virus remains susceptible to immune control

Goal of immunotherapeutic approaches

Complement antivirals for termination of therapy with sAg loss and/or sustained viral control

Short-term:

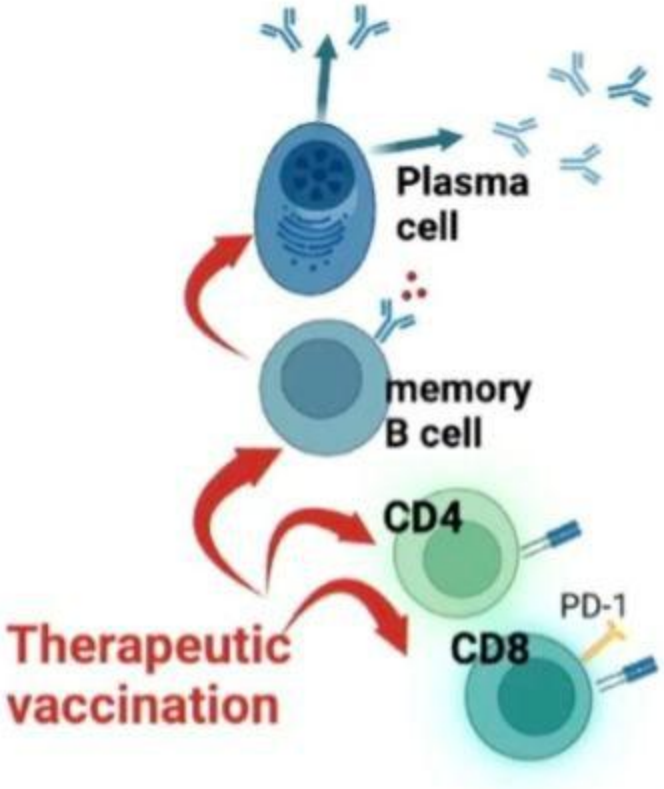
- Act in tandem with antivirals to clear infected hepatocytes
  - Cytolytic clearance / non-cytolytic removal

Long-term:

- Provide robust immunosurveillance
  - to limit viral reactivation and spread from residual cccDNA
  - to limit HCC development from integrated DNA

Enhancing therapeutic vaccination in chronic hepatitis B

Boost existing +/- induce de-novo HBV-specific adaptive immunity



Vaccine optimisation:

- Inclusion of all major HBV antigens
- Coverage of all major genotypes
- Immunogenic platform able to induce CD4, CD8 and humoral immunity
- Heterologous prime & boost

Host response optimization:

- Disease phase
- Age/duration of infection
- Route of acquisition: vertical/horizontal
- Viral antigen burden, genotype
- Specific immunotherapeutic boosting

Therapeutic vaccines as a backbone for functional cure: the new generation of platforms

BARINTHUS BIOTHERAPEUTICS VTP300

ChAdOx prime, MVA boost

VIRION THERAPEUTICS VRON-0200

ChAdOx with CPI

Brii Biosciences BRII-179

Recombinant proteins

TherVacB

Protein prime, MVA boost

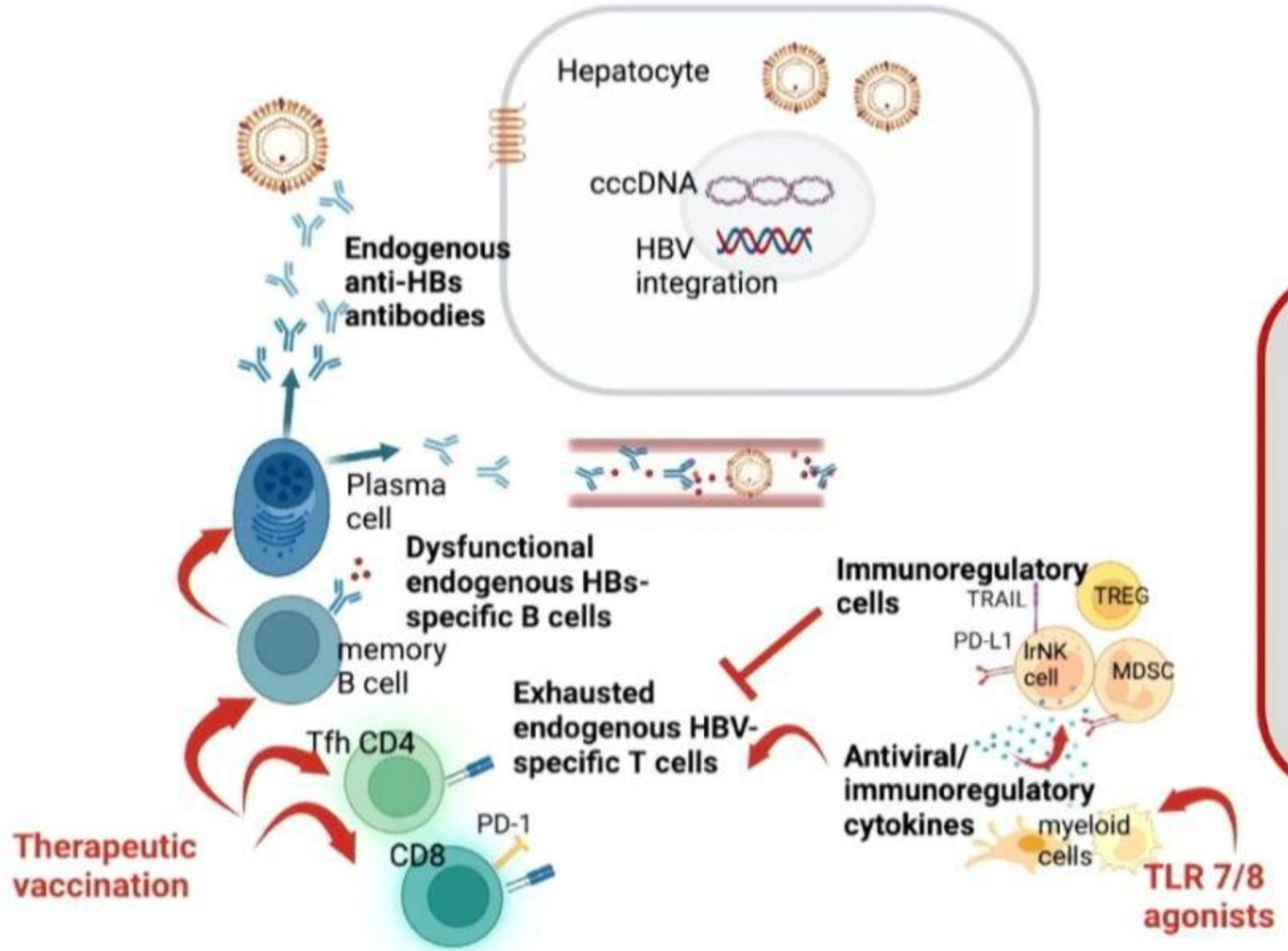
AstriVax Therapeutics

Yellow fever-based vector

GILEAD

Arenavirus-based vector

Endogenous immunotherapeutic approaches



TLR agonists

Pros:

Broad MOA

Oral administration

Cons:

Unfocused MOA

Non antigen-specific

Poor efficacy as single agent

Endogenous immunotherapeutic approaches

Checkpoint inhibitors

Pros:

Rescue exhaustion

Track record in cancer

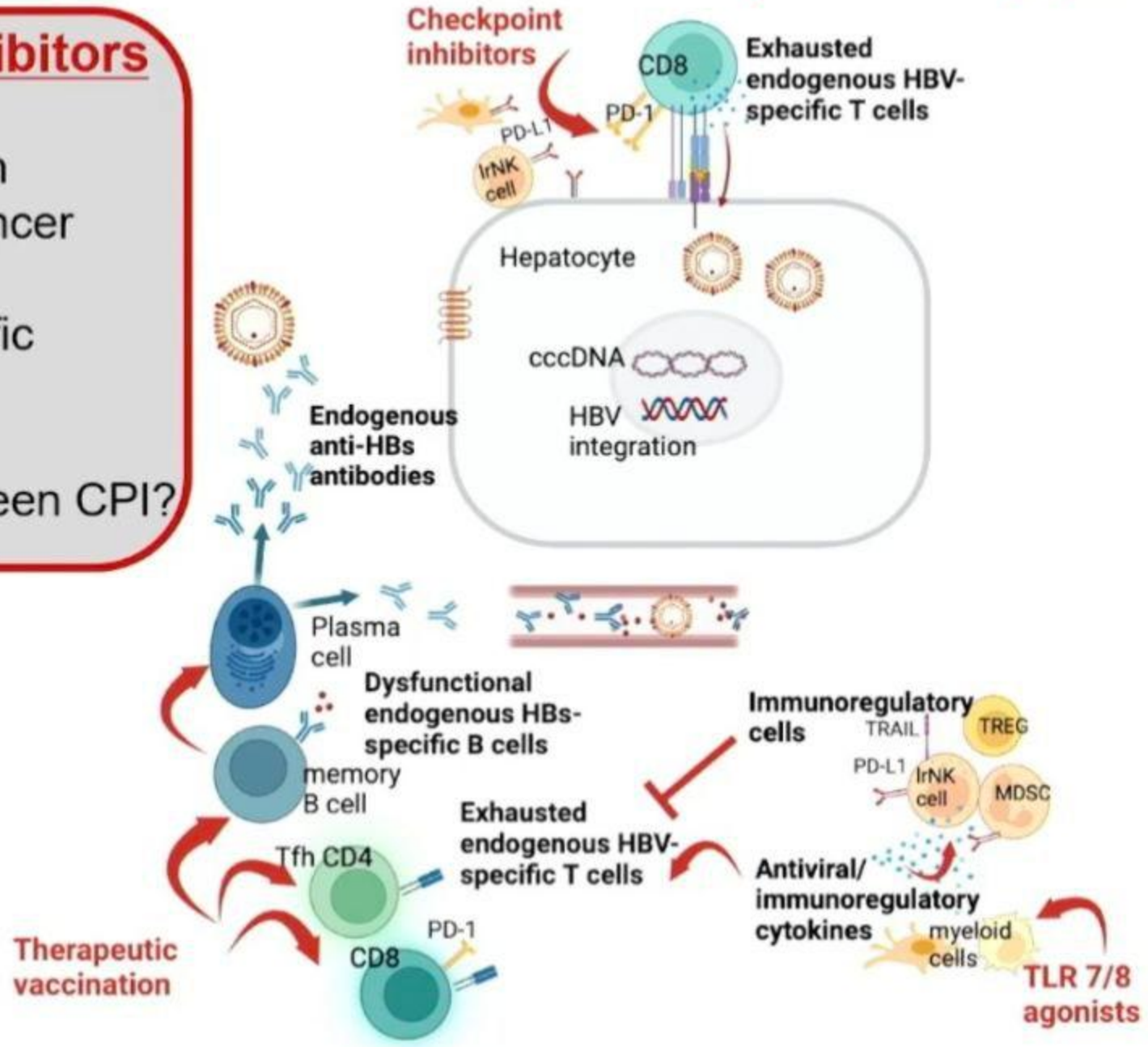
Cons:

Non antigen-specific

Toxicity risks

Require infusion

Redundancy between CPI?



HBV immunotherapy: Replacement approaches

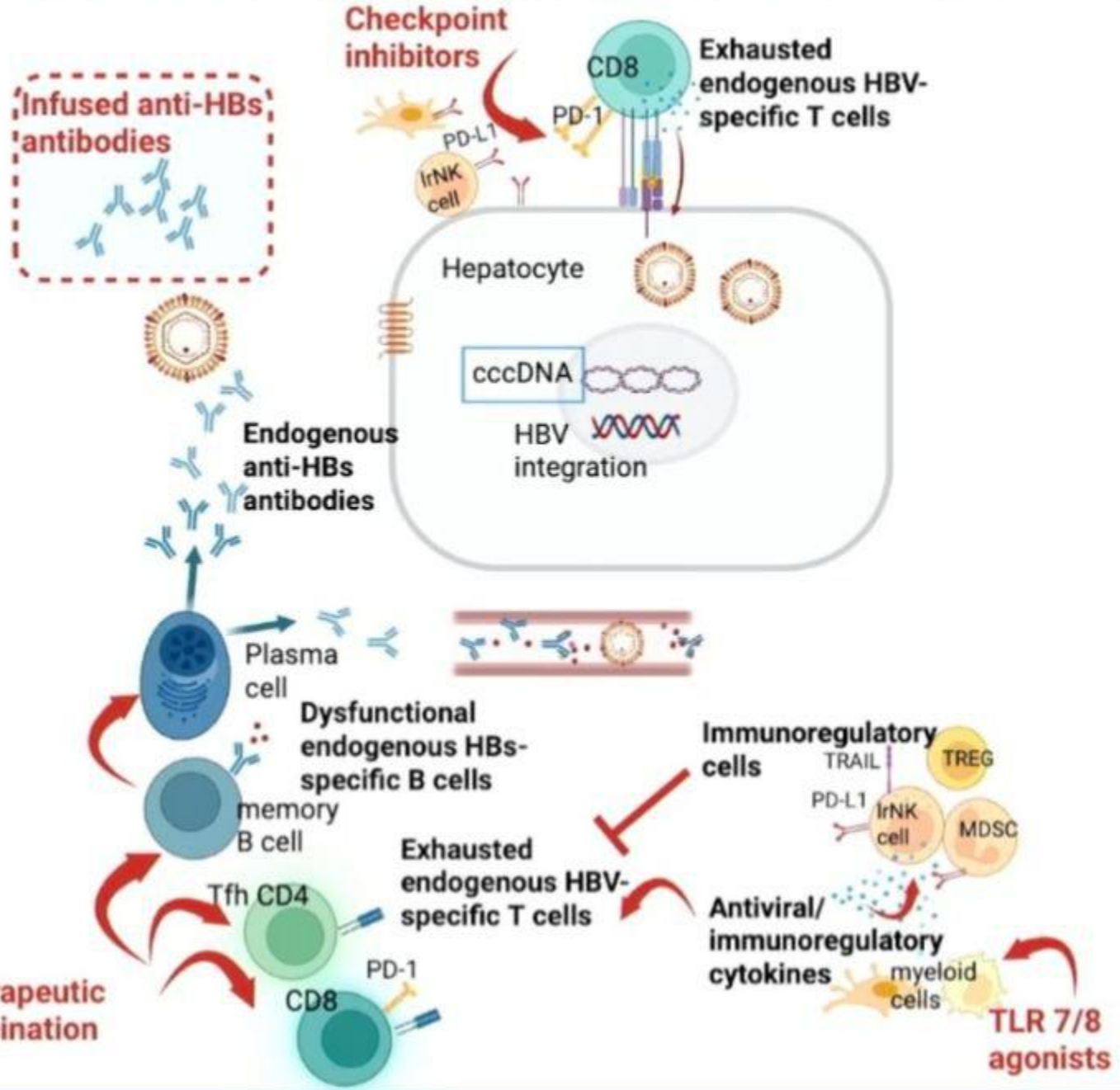
Monoclonal Antibodies

Pros:

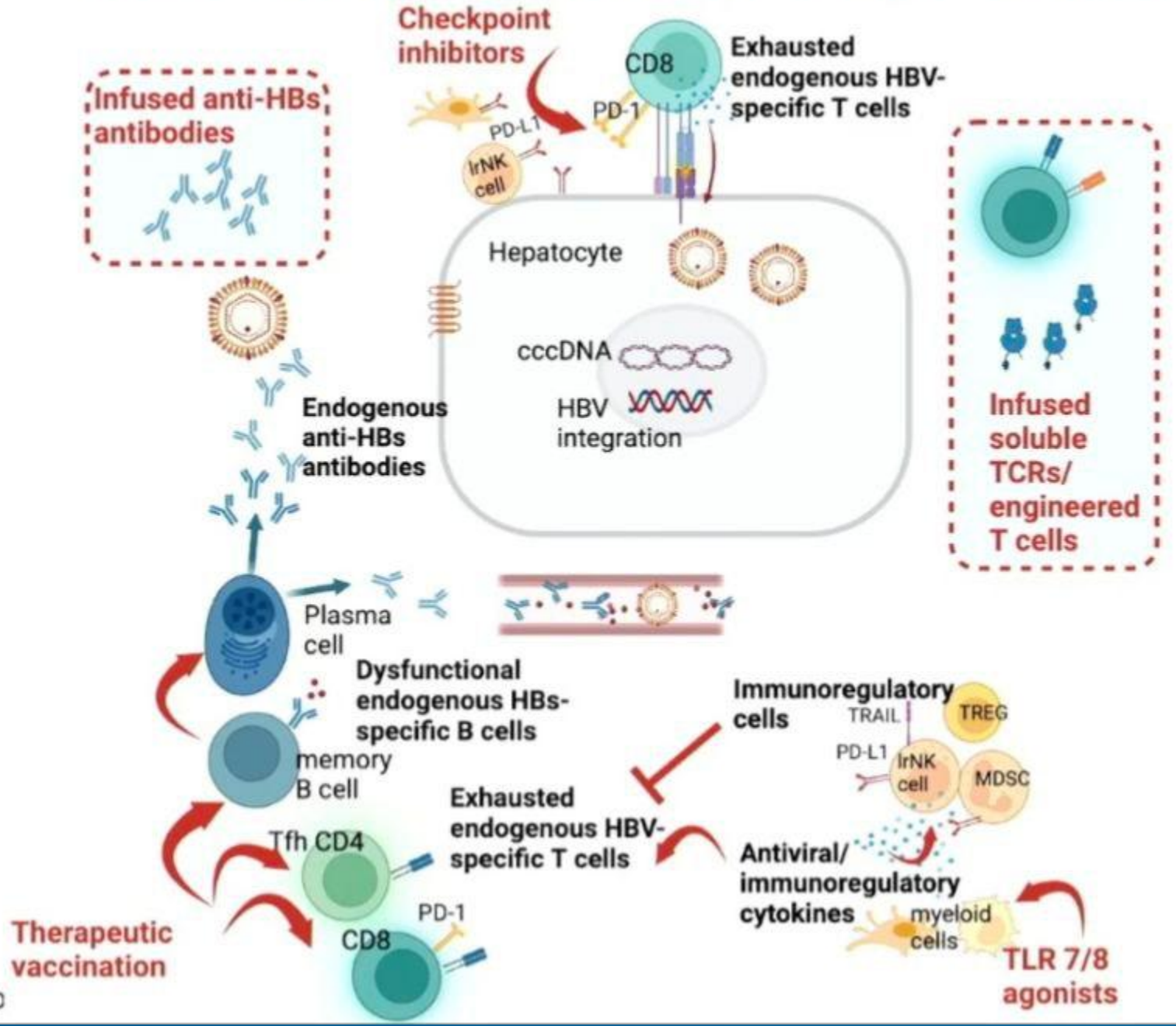
Bypass exhaustion
Antigen-specific
Promising in HIV
Vaccinal effect?

Cons:

Require infusions
HBsAg sink
Durability?



HBV immunotherapy: Replacement approaches



Engineered T cells/ T cell engagers

Pros:

Bypass exhaustion

Antigen-specific

Cons:

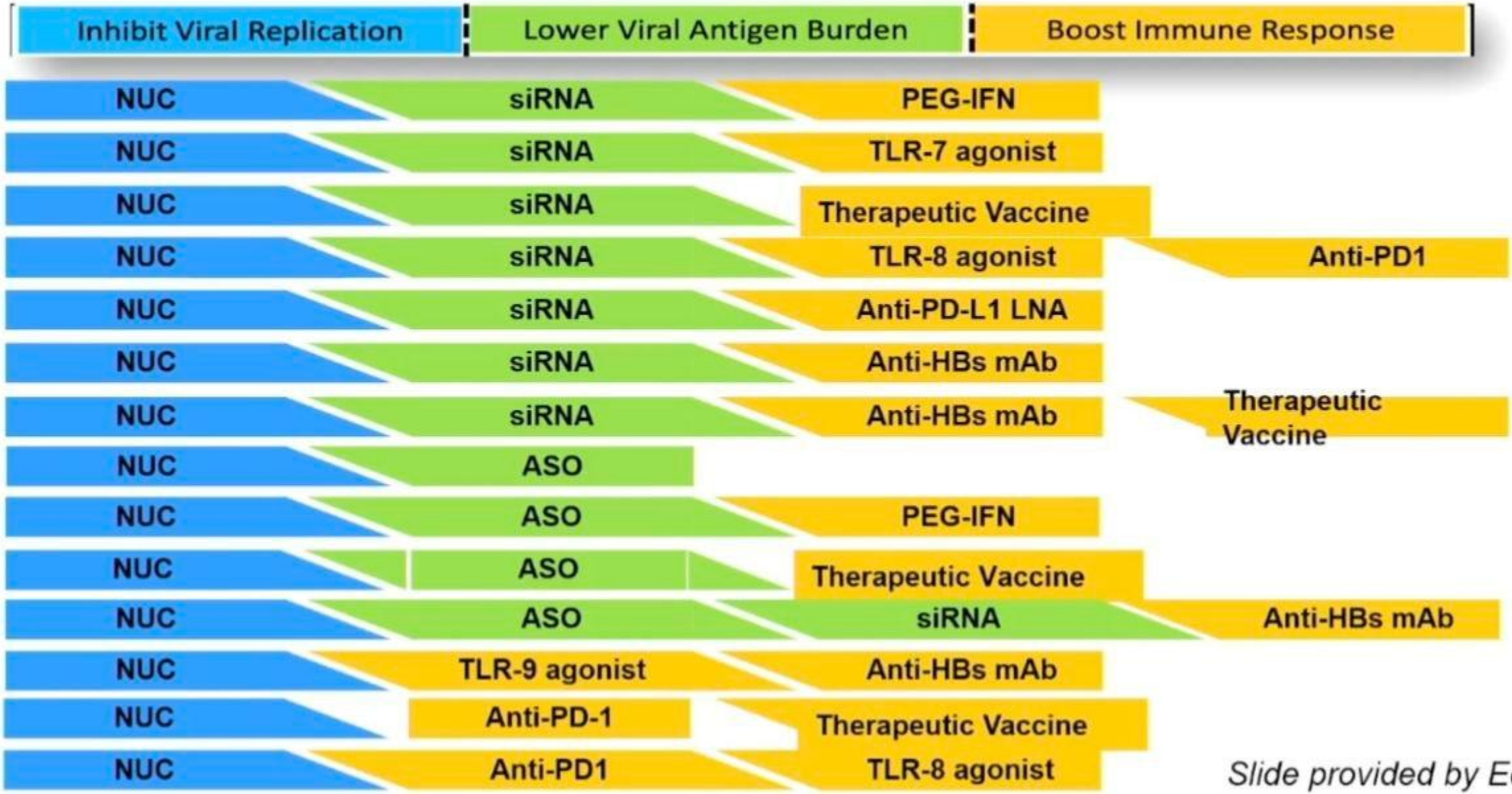
Require infusions

Laborious synthesis

HLA-restricted

Combination trials for immunotherapy of HBV

Completed and Ongoing Platform Studies



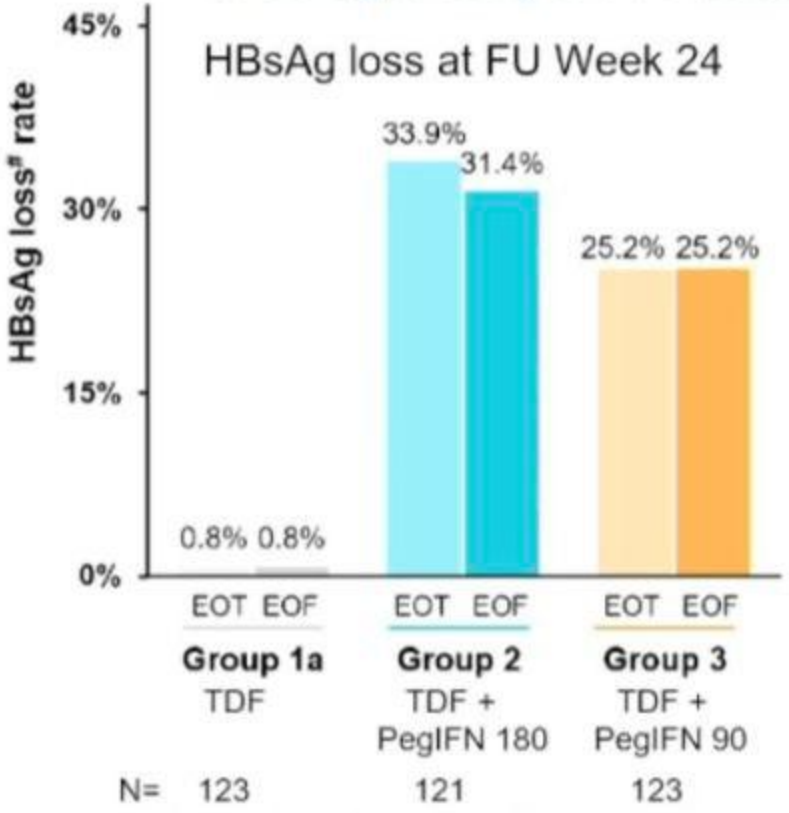
Slide provided by Ed Gane

Recovery of HBV-immune response in patients with low HBsAg level

Low HBsAg by targeting its production does not have the same effect as spontaneous or NA-related low HBsAg

Interferon add-on in patients receiving NA with suppressed HBV DNA

TDF 300 mg +/- intermittent PegIFN α2b 180 or 90 ug weekly x 144 weeks

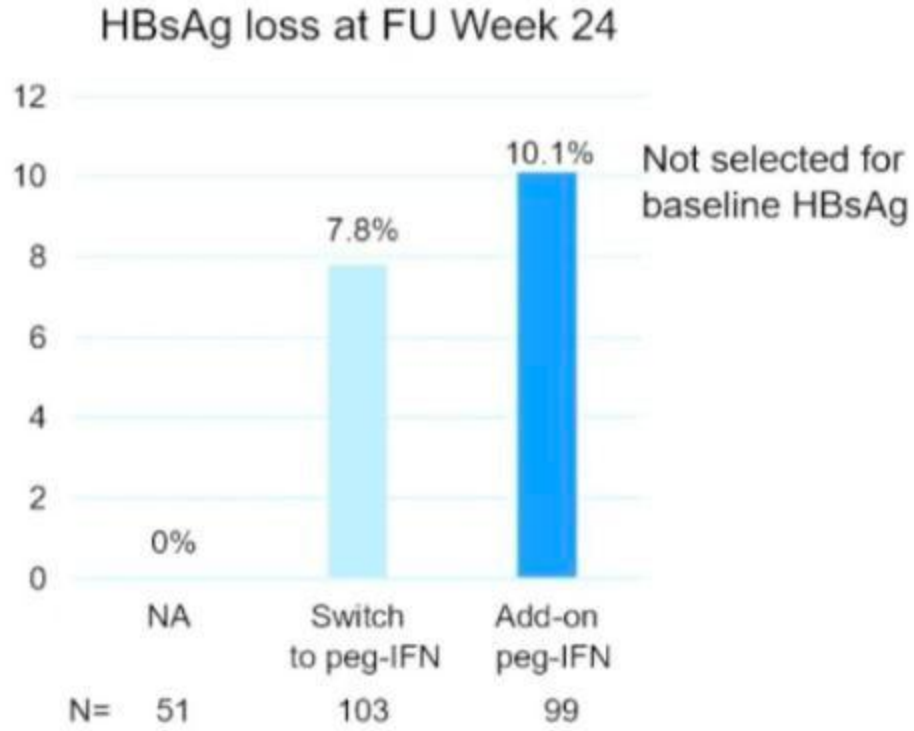


Baseline HBsAg <1500 IU/mL

Applicable only to
- patients with low baseline HBsAg
- with no contraindications to IFN, AND
- able to tolerate IFN

Wang GQ AASLD 2024

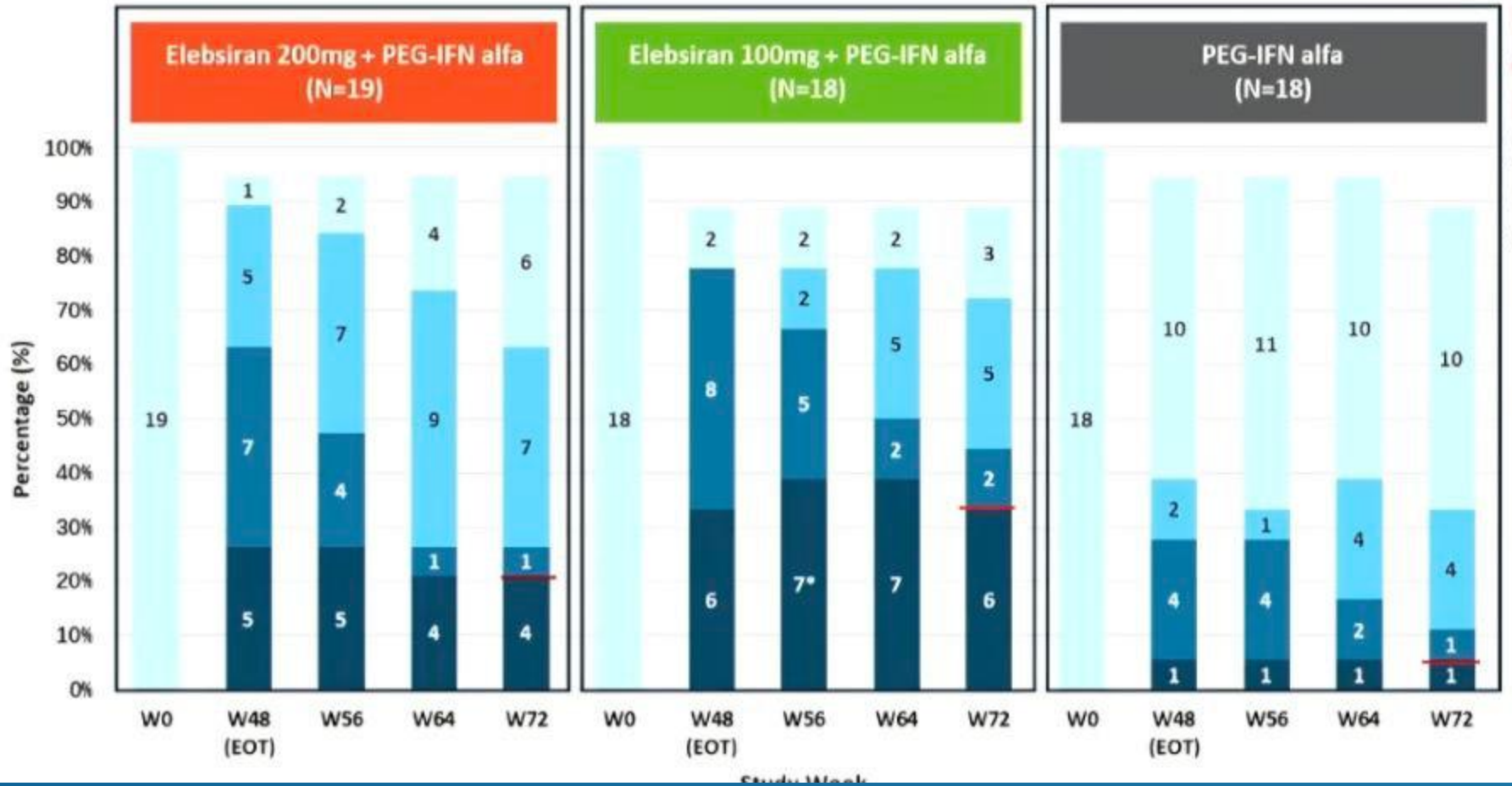
Continue NA vs. Peg-IFN switch or add-on x 48 weeks



Lim SG, Clin Gastroenterol Hepatol 2022; 20: e228

ENSURE Study: Does adding peg-IFN to siRNA increase functional cure?

Elebsiran (siRNA) + peg-IFN vs. peg-IFN x 48 weeks in patients on NA



Functional cure rate higher in elebsiran + peg-IFN than peg-IFN alone

21.1% & 33.3% vs. 5.6%

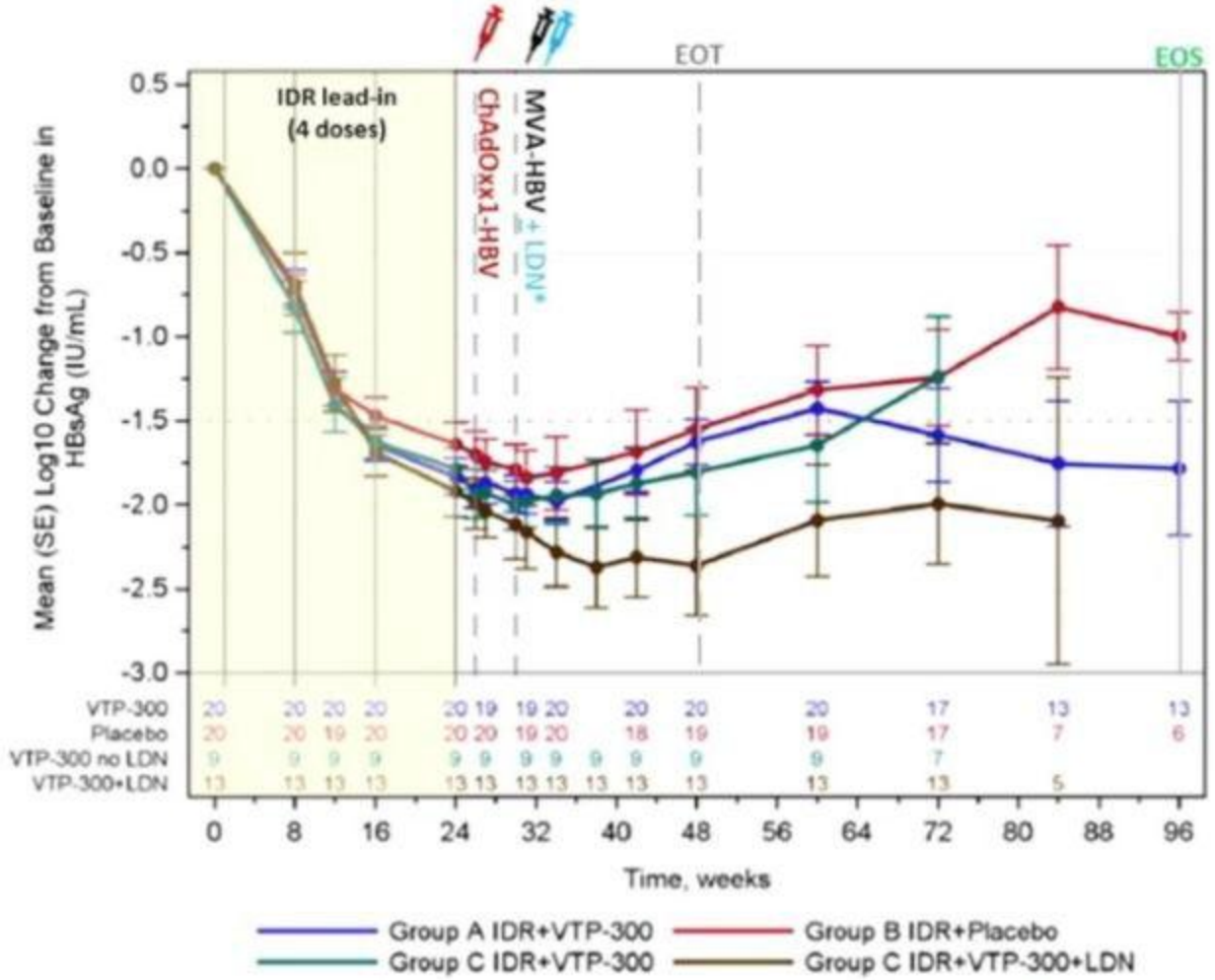
(also shown to be higher than siRNA alone in other studies)

First study to include peg-IFN alone for comparison

Jia J, 2025 EASL LBP-016

Combination of sAg reduction (siRNA) +/-therapeutic vaccination +/- checkpoint modulation

IM-PROVE II: lead-in Imdusiran + VTP300 ± low-dose nivolumab



IDR + Placebo

IDR + VTP-300

IDR + VTP-300

IDR + VTP-300 + nivolumab

2 patients achieved functional cure with anti-HBsAb
-ALL had baseline HBsAg <500 IU/mL

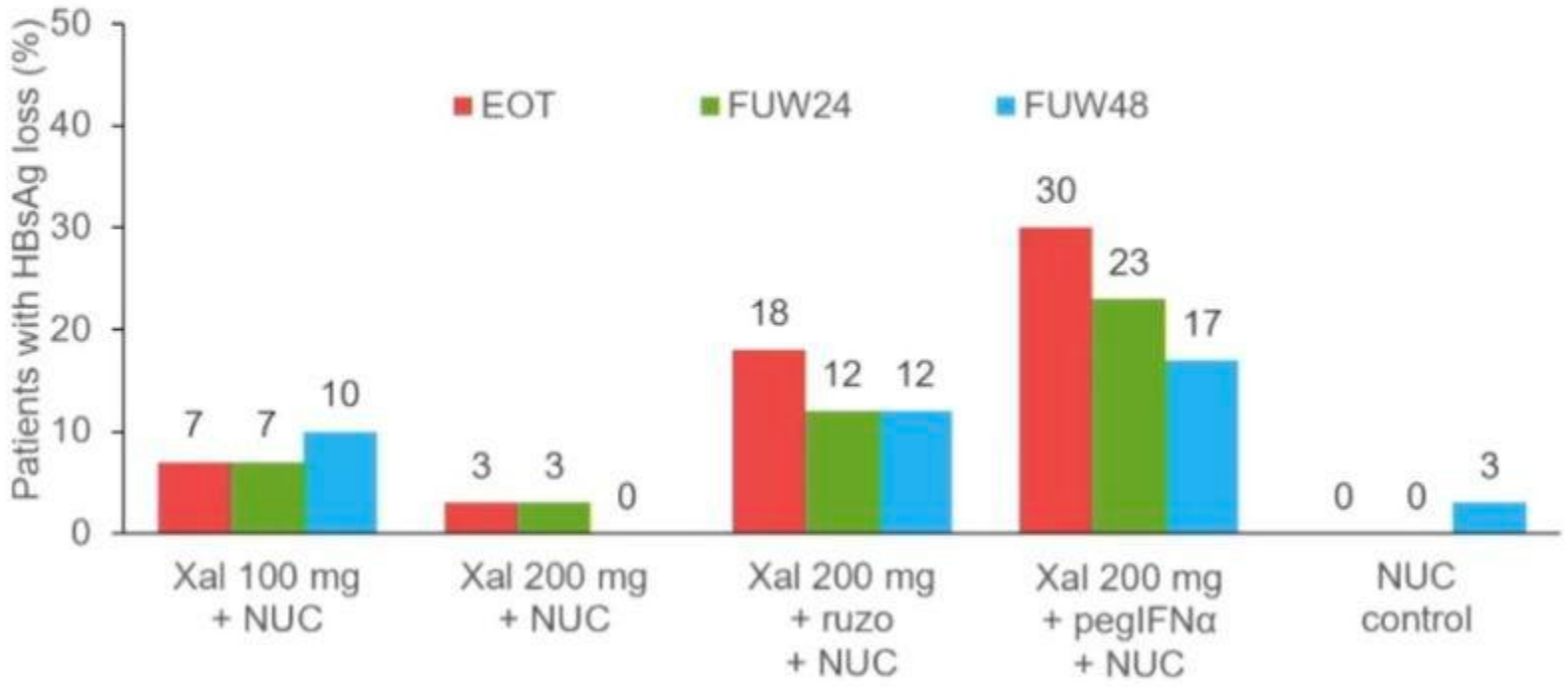
More sustained off-treatment viral control upon addition of vax to siRNA

BARINTHUS Arbutus BIOPHARMA

Wong GL, et al. EASL 2025

Combination of sAg reduction (siRNA) +/-TLR7 agonist +/- PegIFNα

Piranga: NUC + Xalniseran ± Ruzotolimod/PegIFN for 48 weeks



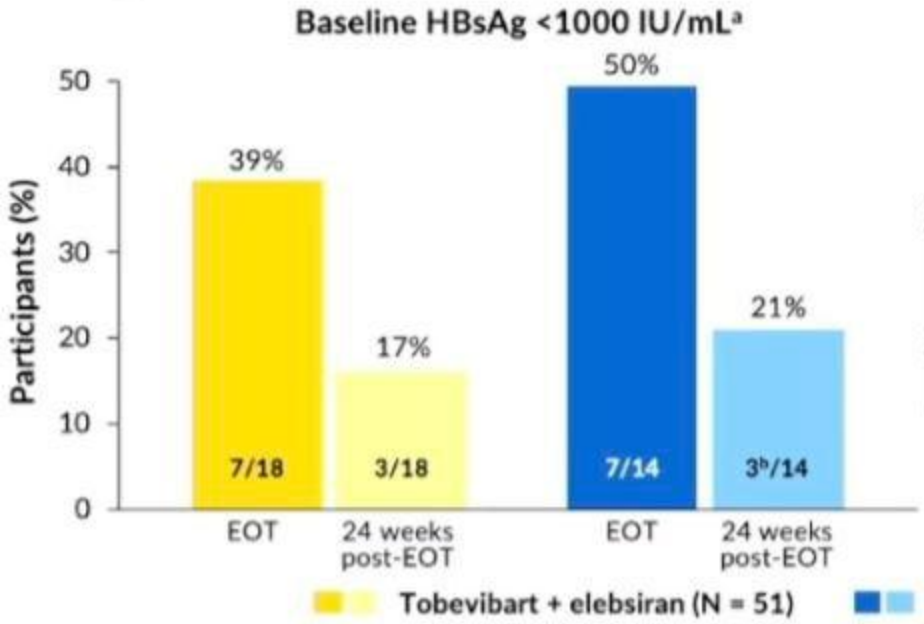
Combo of siRNA + immunomodulator increased HBsAg loss
But ONLY if baseline HBsAg<1000 IU/ml

Hou JL et al, NEJM Dec 2024

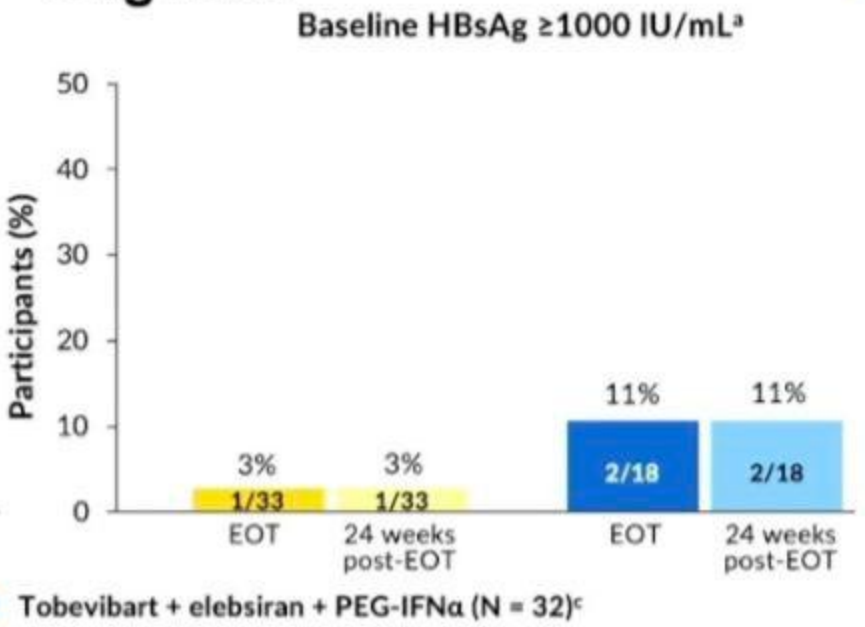
Combination of sAg reduction (siRNA) + anti-HBs mAb +/- Peg-IFNα

MARCH: NUC + Elebsiran ± Tobevibart ± Peg-IFNα (48 weeks)

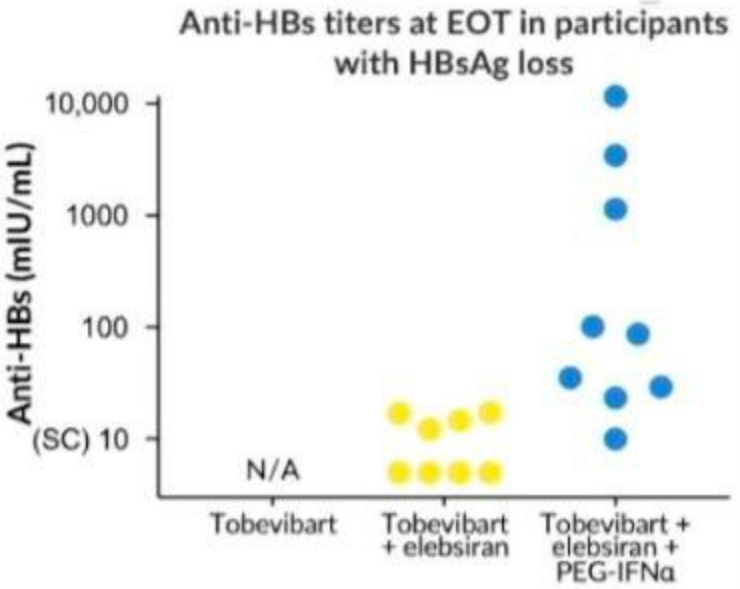
sAg loss



sAg loss



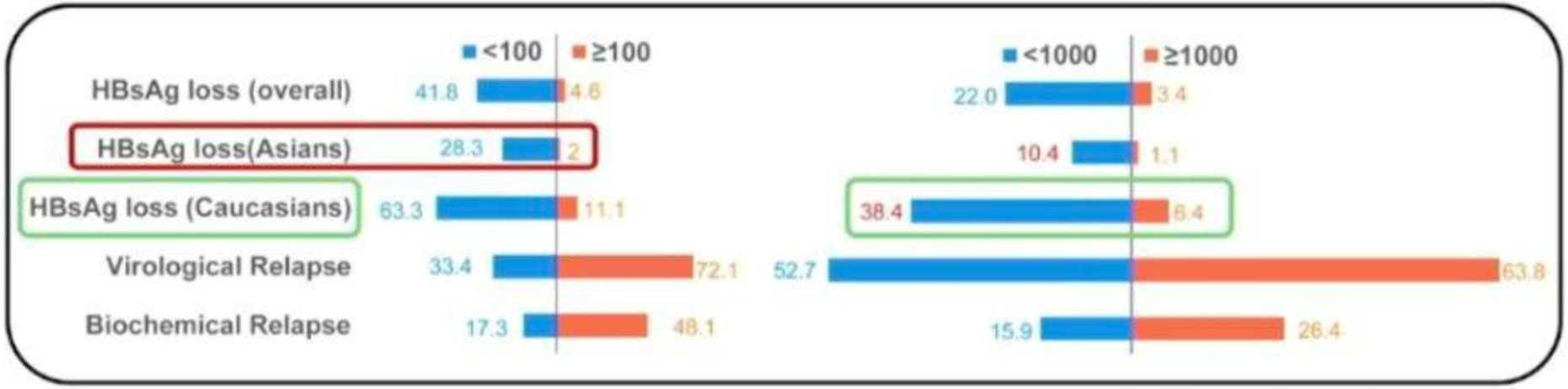
Anti-HBsAg Ab



Withdrawing NA to increase HBsAg loss

- Systematic review and meta-analysis of 24 articles, 7 non-Asian
- 3732 patients followed for 9.8-111.6 months off NA
- HBsAg loss in 1-63%, EOT HBsAg strong predictor of efficacy, lower EOT HBsAg required for Asians to achieve HBsAg loss
- Biochemical relapse in 16-48%, hepatic decompensation in 1%
- Applicable to ~30% Caucasian and ~10% Asian patients

qHBsAg thresholds for stopping Nucleoside Analogue therapy



Lim SG, Clin Gastroenterol Hepatol 2024; 22: 2403

Desired characteristics of HBV cure therapy

- Safe
  - For all stages of CHB including decompensated cirrhosis, post-liver transplant
  - For all ages, with comorbidities (e.g., CKD, HIV), negligible drug interactions
- Efficacious
  - High rate of HBsAg loss after a finite course of treatment regardless of baseline HBsAg level
  - Sustained response >1 year off-treatment
- Simple
  - Finite duration, preferably ≤1 year
  - Easy to administer, preferably oral, once daily
  - Limited pre-treatment characterization and on- and off- treatment monitoring
- Affordable and accessible

Which class of new HBV treatment do you think will be the first to be approved for clinical use?

1. CAM (capsid assembly modulator)
2. ASO (antisense oligonucleotide)
3. siRNA (small interference RNA)
4. Therapeutic vaccine
5. Liver-targeted check point inhibitor

Which class of new HBV treatment do you think will be the first to be approved for clinical use?

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Thank You!
Combination of Drugs to
Achieve HBV Functional Cure