The future of functional cure programs

Combinations, novel biomarkers and timelines

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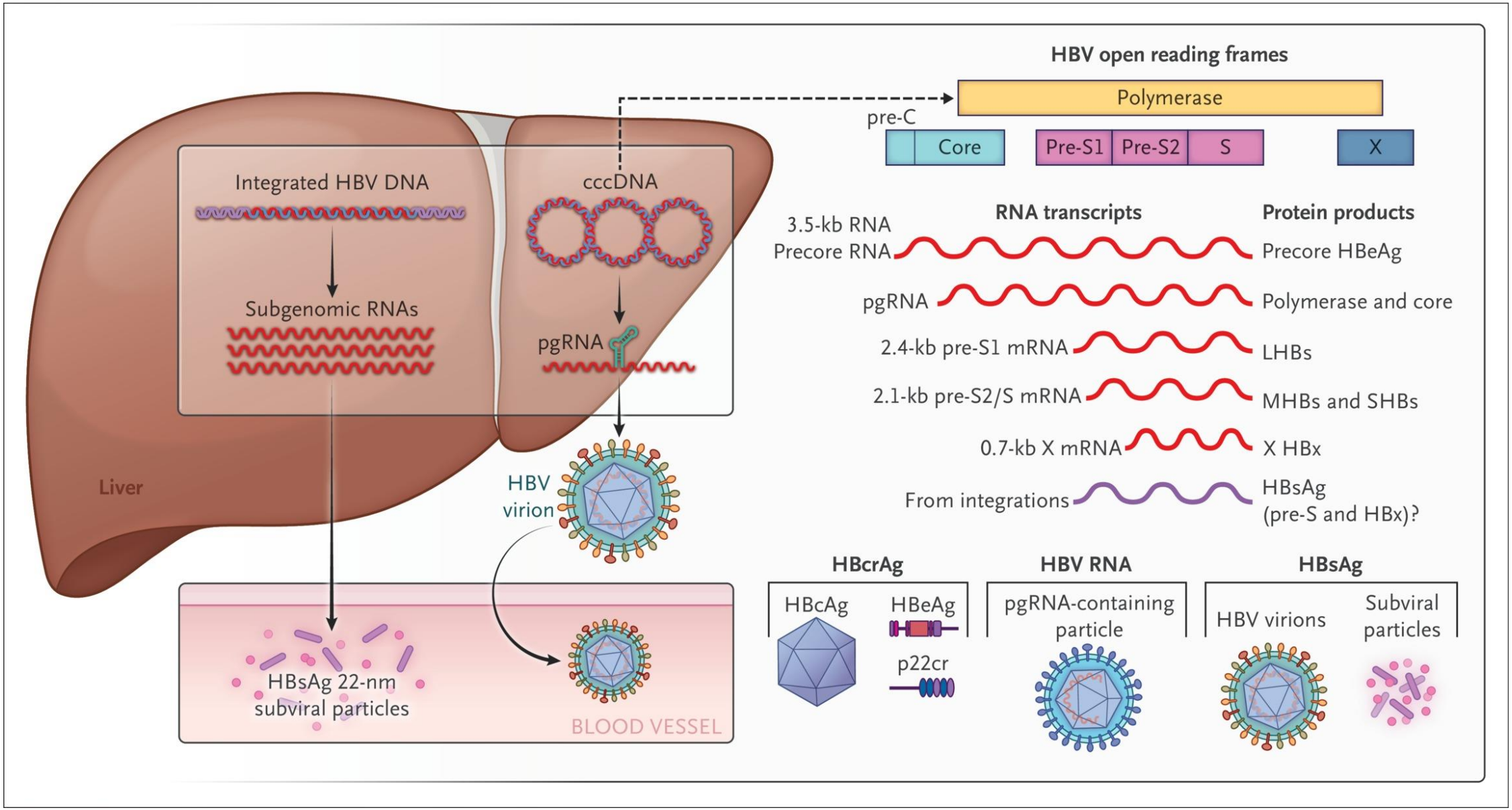
The future of functional cure programs

- Novel biomarkers
- Combinations
- Timelines

HBV Genome Open Reading Frames, RNA Transcripts, Protein Products, and Biomarkers.



Dusheiko Agarwal and Maini et al. N Engl J Med2023;388:55-69

Table 1. Phases of Hepatitis B Virus (HBV) Infection, Nomenclature, and Biomarkers.*

Variable	Phase					
	HBeAg-Positive Chronic HBV Infection	HBeAg-Positive Chronic Hepatitis B	HBeAg-Negative Chronic HBV Infection	HBeAg-Negative Chronic Hepatitis B	"Gray Zone"	Occult Hepatitis B
Other phase names	Immune tolerant	Immune (re)active	Inactive carrier state	HBeAg-negative disease	Indeterminate	None
Serologic testing						
HBsAg	Positive	Positive	Positive	Positive	Positive	Negative
Quantitative HBsAg ($\log_{10}$ IU/ml)†	3.5–4.5	3.5–4.5	2.5–3.5	2–3	2–3	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative	Negative
HBe antibodies	Negative	Negative	Positive	Positive	Positive	May be positive
HBV DNA (IU/ml)	Typically $>10^7$	Typically $>10^5$ to 10^7	$<10^3$	Typically $>10^3$ to $\leq 10^5$	2×10^3 (3.3 $\log_{10}$) to 2×10^4 (4.3 $\log_{10}$)	Low, at detection limit
Alanine aminotransferase	Near ULN	Elevated	Near ULN	Elevated	Fluctuates near ULN	Near ULN
Histologic features on liver biopsy	Minimal necroinflammation or fibrosis	Moderate-to-severe necroinflammation and varying degrees of fibrosis	Minimal necroinflammation and fibrosis	Moderate-to-severe necroinflammation or fibrosis	Minimal or low necroinflammation	Usually minimal or low necroinflammation; fibrosis can be present
cccDNA (assumed copy no./cell)‡	Relatively high	Relatively high	Relatively low, or transcriptional activity	Relatively low, or transcriptional activity	Relatively low, or transcriptional activity	Data uncertain
Integrated HBV DNA§	Present	Present	Present and accounts for majority of HBsAg	Present and accounts for majority of HBsAg	Present	Present
HBcrAg level	High	High	Low or undetected	Lower than HBeAg-positive states	May be detected	Data not available
HBV RNA level	High	High	Low or undetected	Lower than HBeAg-positive states	May be detected	Data not available

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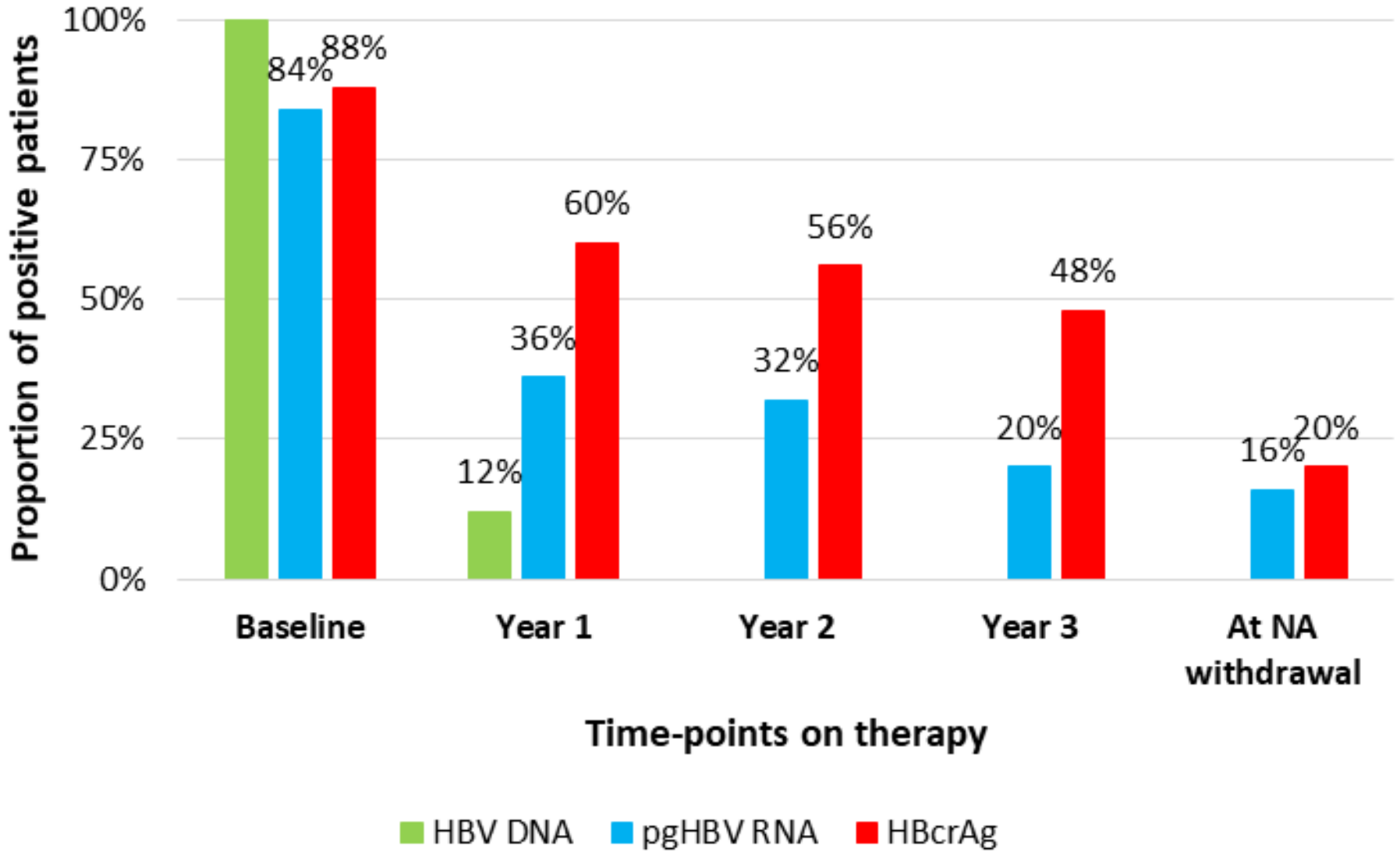
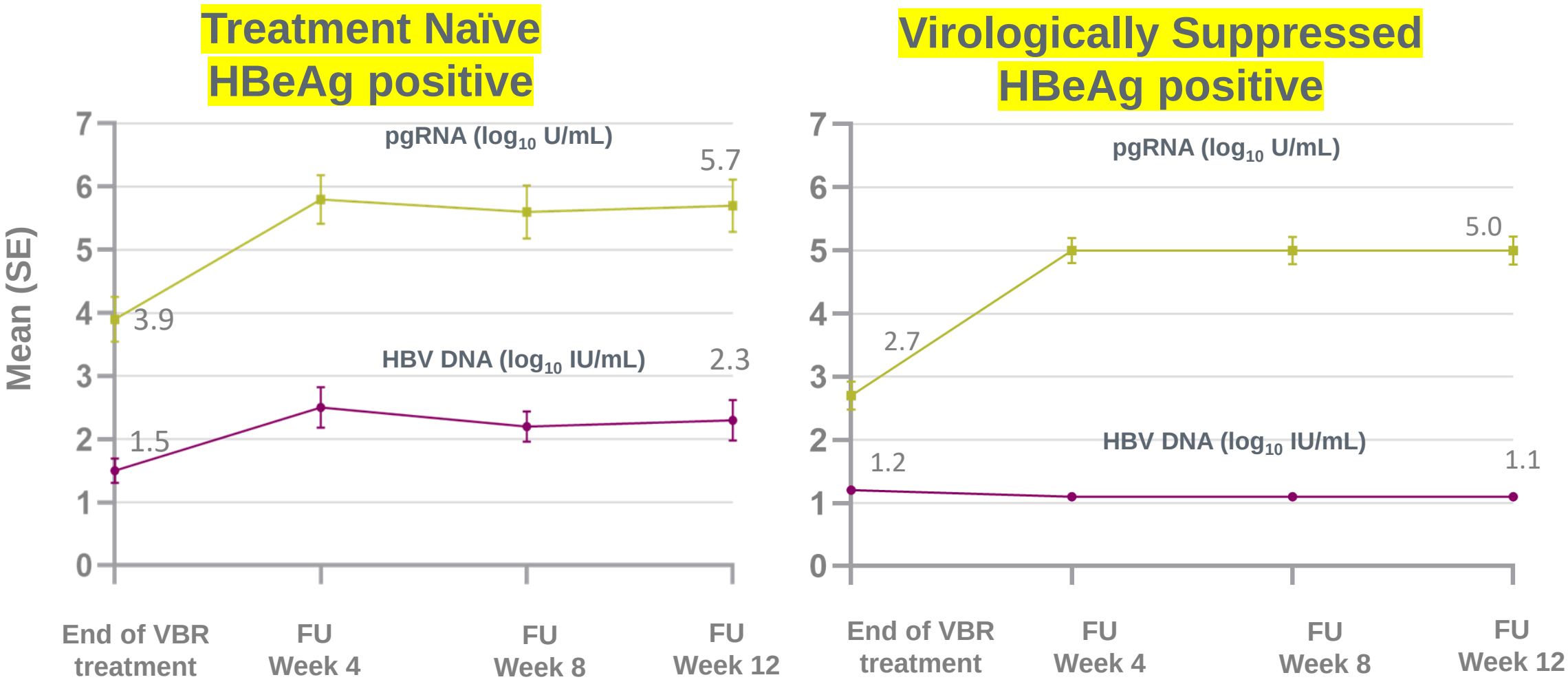
Proportion with positive biomarkers on therapy

Anti-HBe positive patients on nucleoside analogue therapy



Carey, I., et al. (2019). Hepatology DOI: 10.1002/hep.31026

HBV DNA and pgRNA recurrence in patients discontinuing vebicorvir



Discontinued VBR and remained on NrtI
(n = 21)

[a]At entry in Study 202.

Discontinued VBR and remained on NrtI
(n = 18)

[a]At entry in Study 201.

Yuen et al AASLD 2021 096

REEF-2: Demographics and Baseline Characteristics

NA suppressed HBeAg negative

Percentages or Mean Value (SD)	Placebos + NA (Control)	JNJ-3989 + JNJ-6379 + NA (Active)	Total
N	45	85	130
Demographics			
Female vs. Male (%)	35.6/64.4	31.8/68.2	33.1/66.9
Age, years	47.4 (10.55)	45.3 (10.10)	46.0 (10.27)
White (%)	66.7	65.9	66.2
Disease Characteristics			
HBsAg, $\log_{10}$ IU/mL	3.49 (0.703)	3.43 (0.530)	3.45 (0.594)
HBsAg level: <100 IU/mL (%)	1 (2.3)	0	1 (0.8)
HBV DNA <LLOQ (%)*	100	100	100
HBV RNA <LOD (%)†	97.7	92.8	94.4
HBcrAg <LLOQ (%)‡	75.0	65.9	69.0
ALT, U/L	23.9 (10.75)	24.2 (10.89)	24.1 (10.80)
Fibroscan score, kPa	5.02 (1.301)	5.23 (1.482)	5.16 (1.420)
Duration of NA at study entry, years	8.1 (4.48)	8.4 (4.79)	8.3 (4.67)
Stratification Factors			
Asian vs. Non-Asian (%)	17.8/82.2	21.2/78.8	20.0/80.0
Type of NA: ETV vs. TDF/TAF (%)§	37.8/62.2	38.8/61.2	38.5/61.5
HBsAg level: <1,000 vs. ≥1,000 IU/mL (%)	24.4/75.6	20.0/80.0	21.5/78.5

HBcrAg, hepatitis B core related antigen; LOD, limit of detection; SD, standard deviation.

*HBV DNA, LLOQ = 20 IU/mL. †HBV RNA, LOD = 2.49 $\log_{10}$ copies/mL. ‡HBcrAg, LLOQ = 3.0 $\log_{10}$ U/mL. §2 patients were on TAF.

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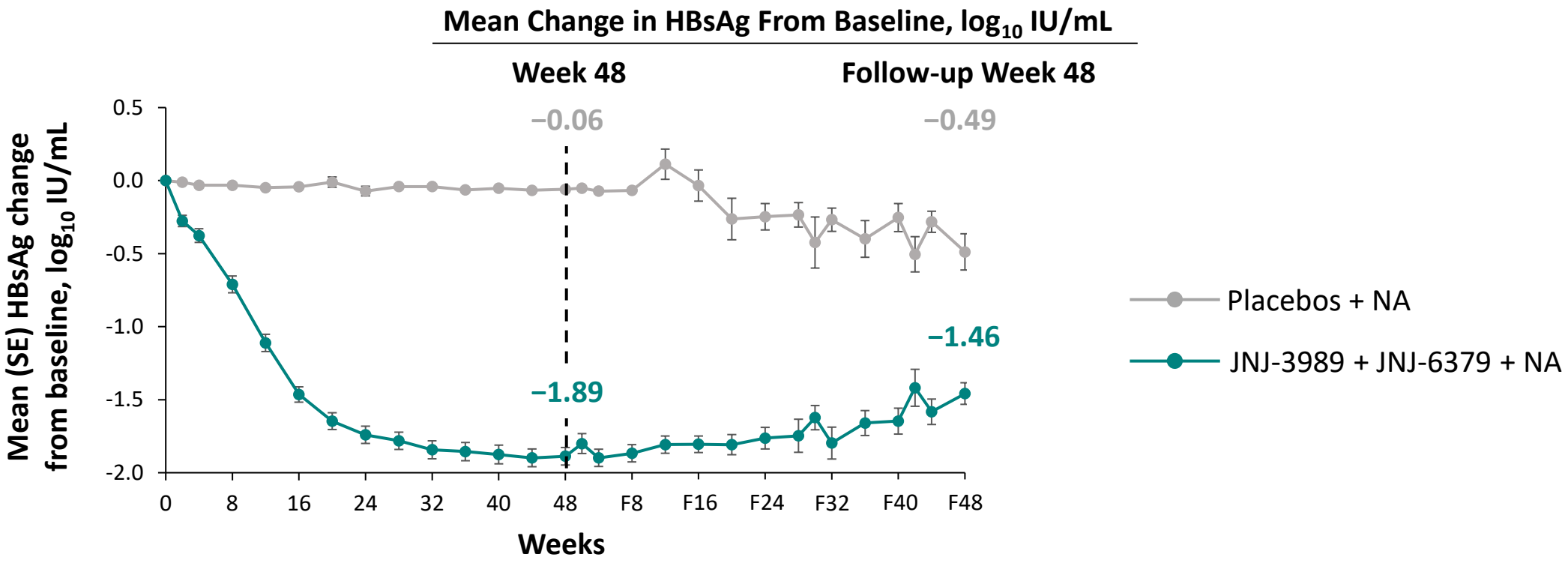
REEF-2: Change in HBsAg Over Time



In the JNJ-3989 + JNJ-6379 + NA arm:

- 31.6% of patients had declining* or stable† HBsAg levels from end of treatment to Follow-up Week 48
- 81.5% of patients had a HBsAg reduction from baseline of >1 $\log_{10}$ IU/mL at Follow-up Week 48

SE, standard error.
*Declining HBsAg: >0.2 $\log_{10}$ IU/mL reduction from end of treatment to Follow-up Week 48.
†Stable HBsAg: ±0.2 $\log_{10}$ IU/mL change from end of treatment to Follow-up Week 48.

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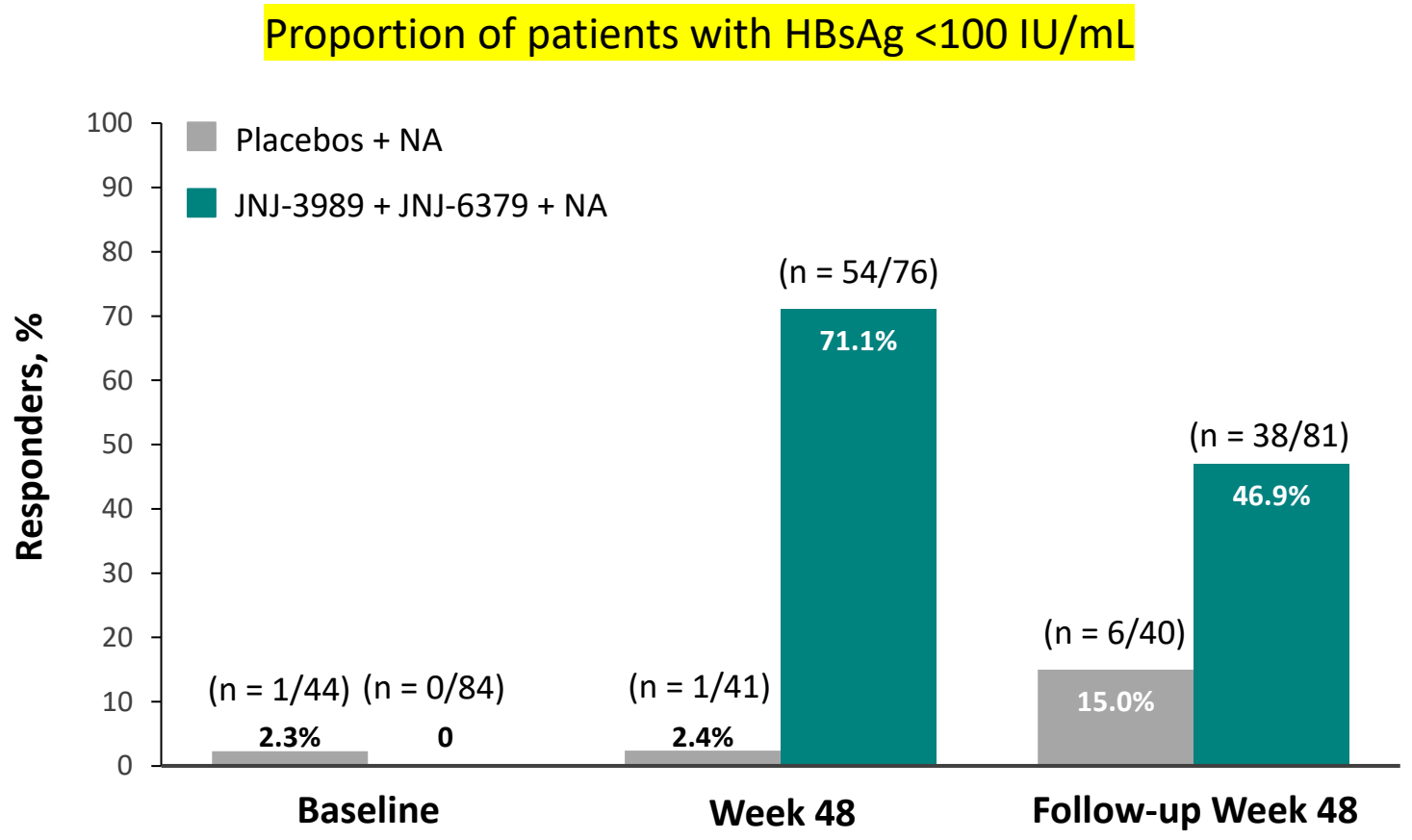
REEF-2: Proportion of Patients with HBsAg <100 IU/mL

No patients achieved HBsAg seroclearance* without restarting NA at Follow-up Week 24 (primary endpoint) or Follow-up Week 48



*HBsAg seroclearance defined as HBsAg <LLOQ (0.05 IU/mL).

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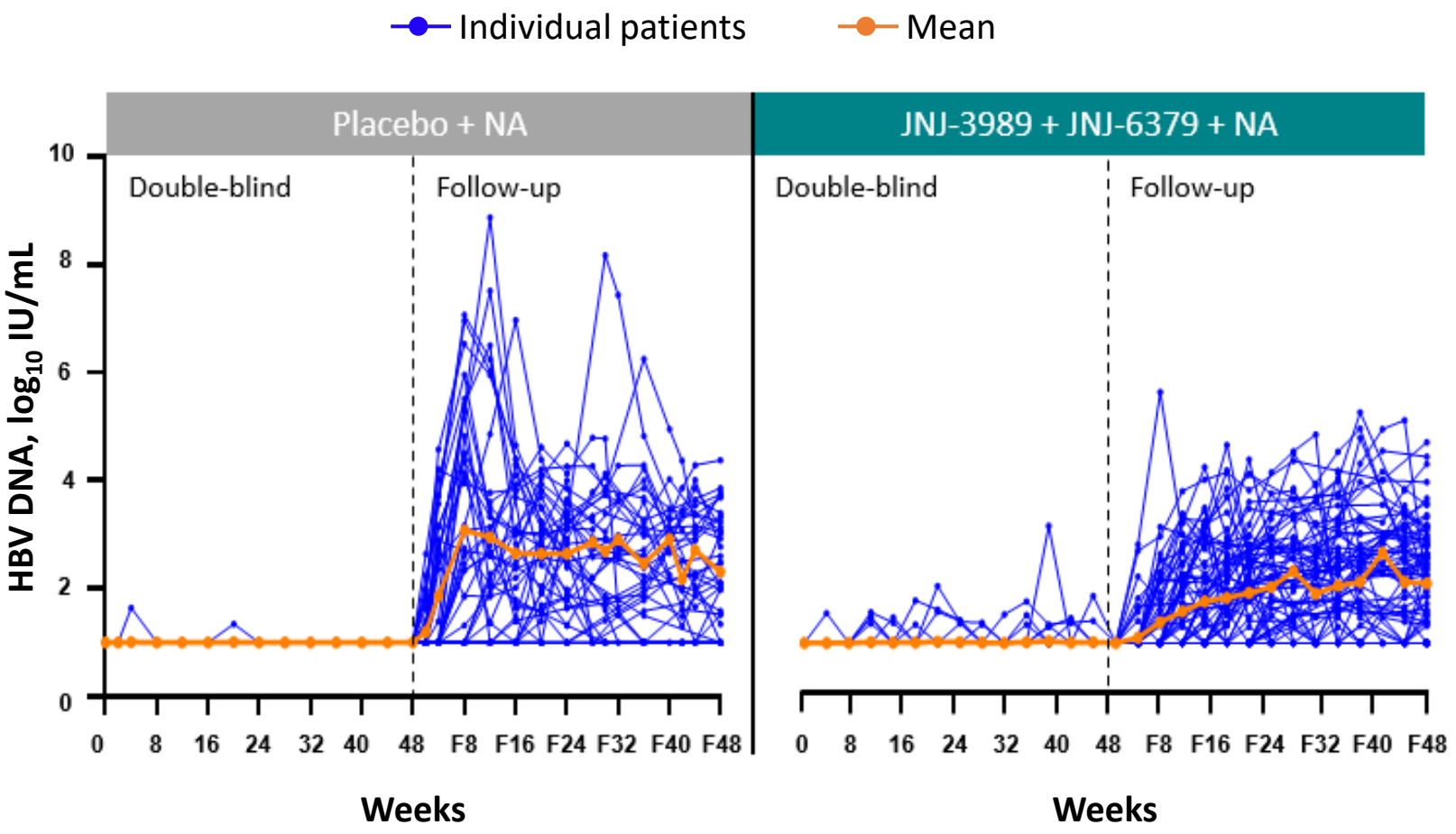
The future of functional cure programs

- Novel biomarkers
- Combinations
- Timelines

REEF-2: HBV DNA Over Time in Individual Patients



Patients* with off-treatment virologic relapse† observed at any timepoint during the 48 weeks of follow-up, n (%)	Placebos + NA (N = 41)	JNJ-3989 + JNJ-6379 + NA (N = 77)
Peak HBV DNA		
HBV DNA >200 - 2,000 IU/mL	10 (24.4)	29 (37.7)
HBV DNA >2,000 - 20,000 IU/mL	12 (29.3)	18 (23.4)
HBV DNA >20,000 IU/mL	15 (36.6)	8 (10.4)

In each figure panel, the orange line is the mean for all patients. HBV DNA LLOQ = 20 IU/mL = 1.3 $\log_{10}$ IU/mL.
*Note: Restricted to patients who stopped NA at Week 48.
†Virologic relapse: confirmed HBV DNA > peak threshold.

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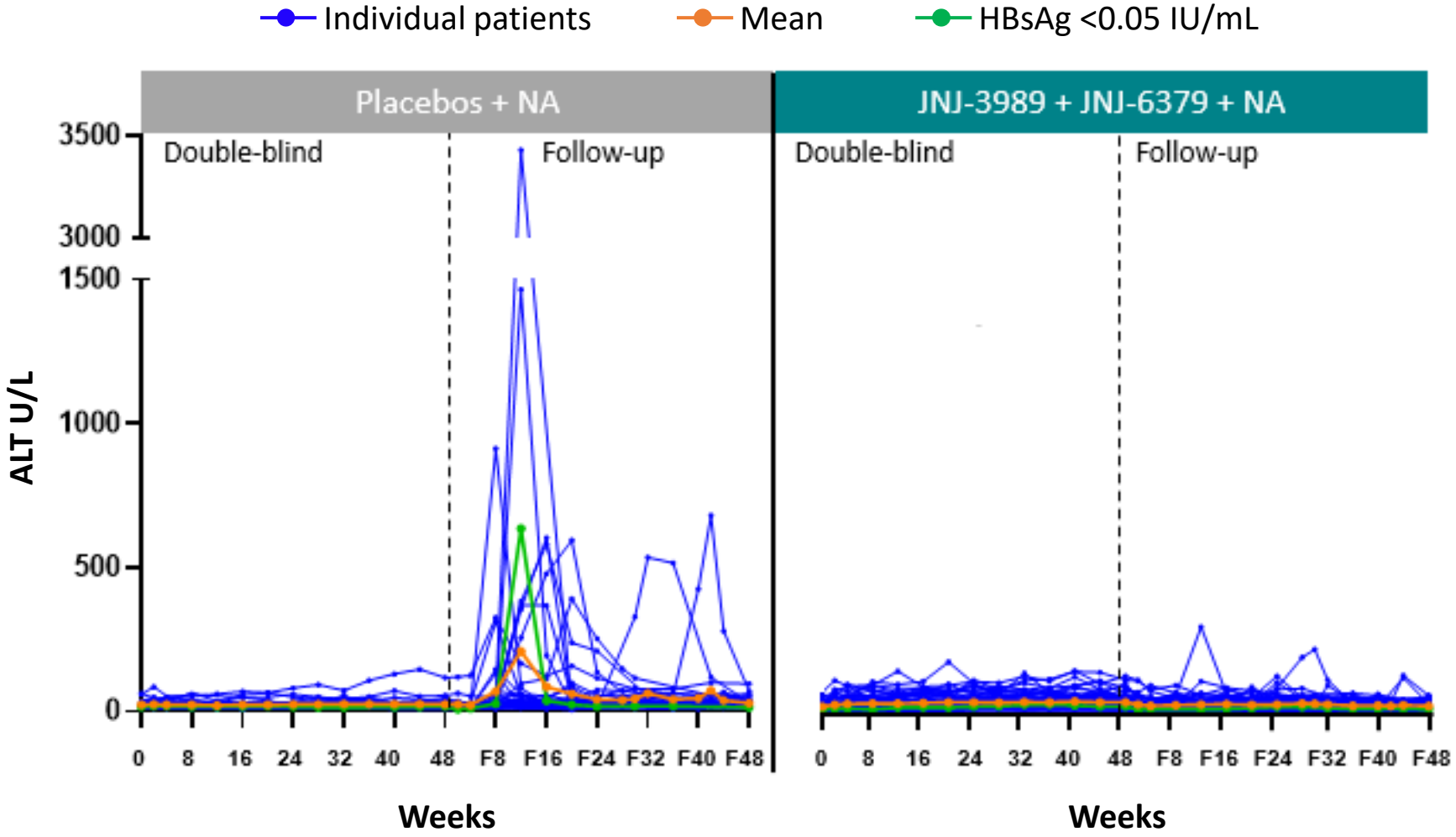
REEF-2: ALT Over Time in Individual Patients

All study interventions stopped including NA



ALT peak level during 48 weeks of follow-up, n (%)	Placebos + NA (N = 41)*	JNJ-3989 + JNJ-6379 + NA (N = 77)*
<3 × ULN	25 (61.0)	73 (94.8)
≥3 × ULN to <5 × ULN	2 (4.9)	2 (2.6)
≥5 × ULN to <10 × ULN	4 (9.8)	1 (1.3)
≥10 × ULN	10 (24.3)	1 (1.3)

In each figure panel, the orange line is the mean for all patients.
*Note: Restricted to patients who stopped NA at Week 48.

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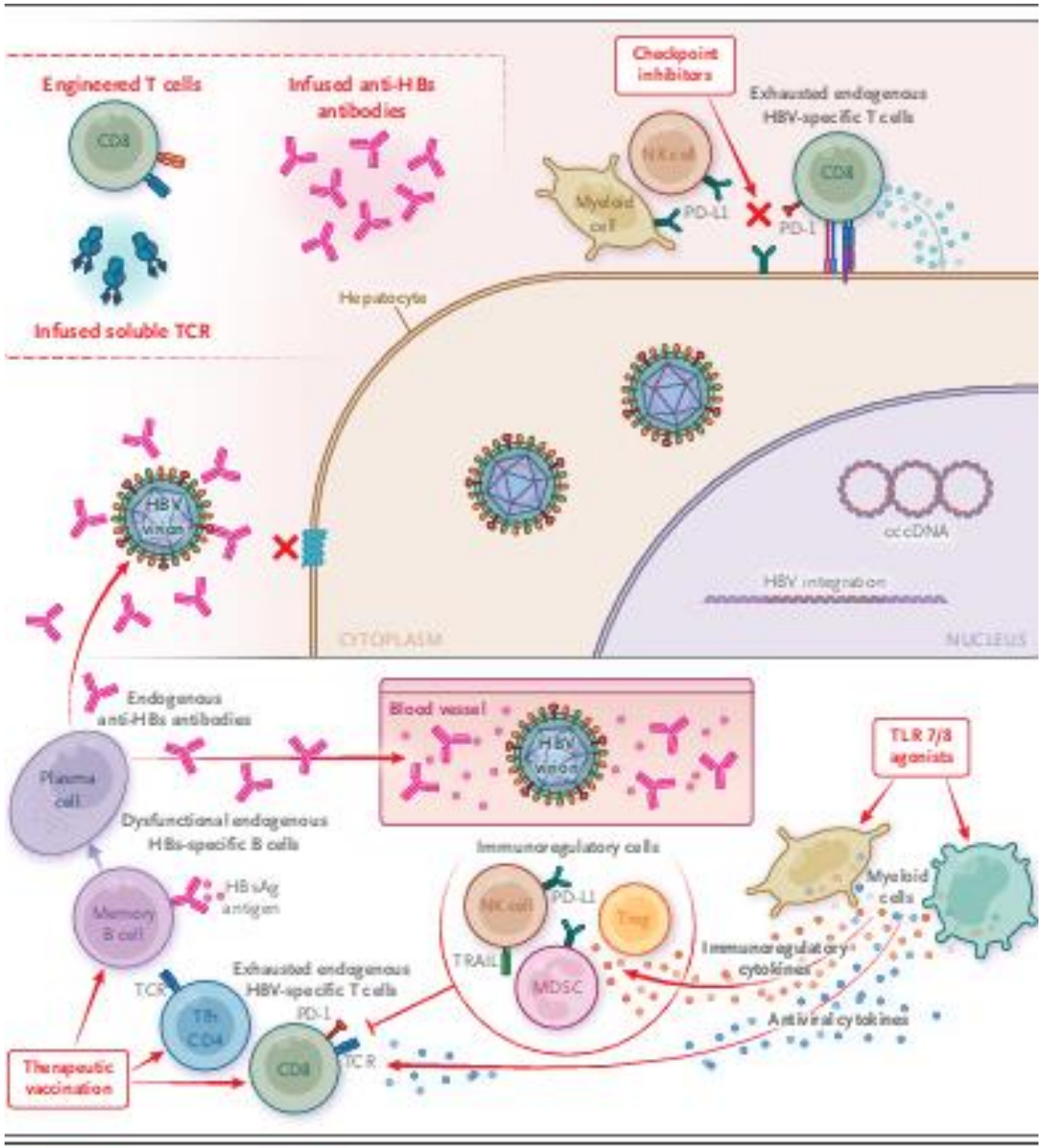
Combinations

- Early data suggest that new direct antiviral agents alone are insufficient to restore effective immunologic control.
- Therefore, immunomodulatory treatments
  - To restore and replenish exhausted, sparse, or dysfunctional HBV-specific T-cell and B-cell responses
  - By activating or replacing endogenous immunity are being researched

Potential molecular and immunotherapeutic targets



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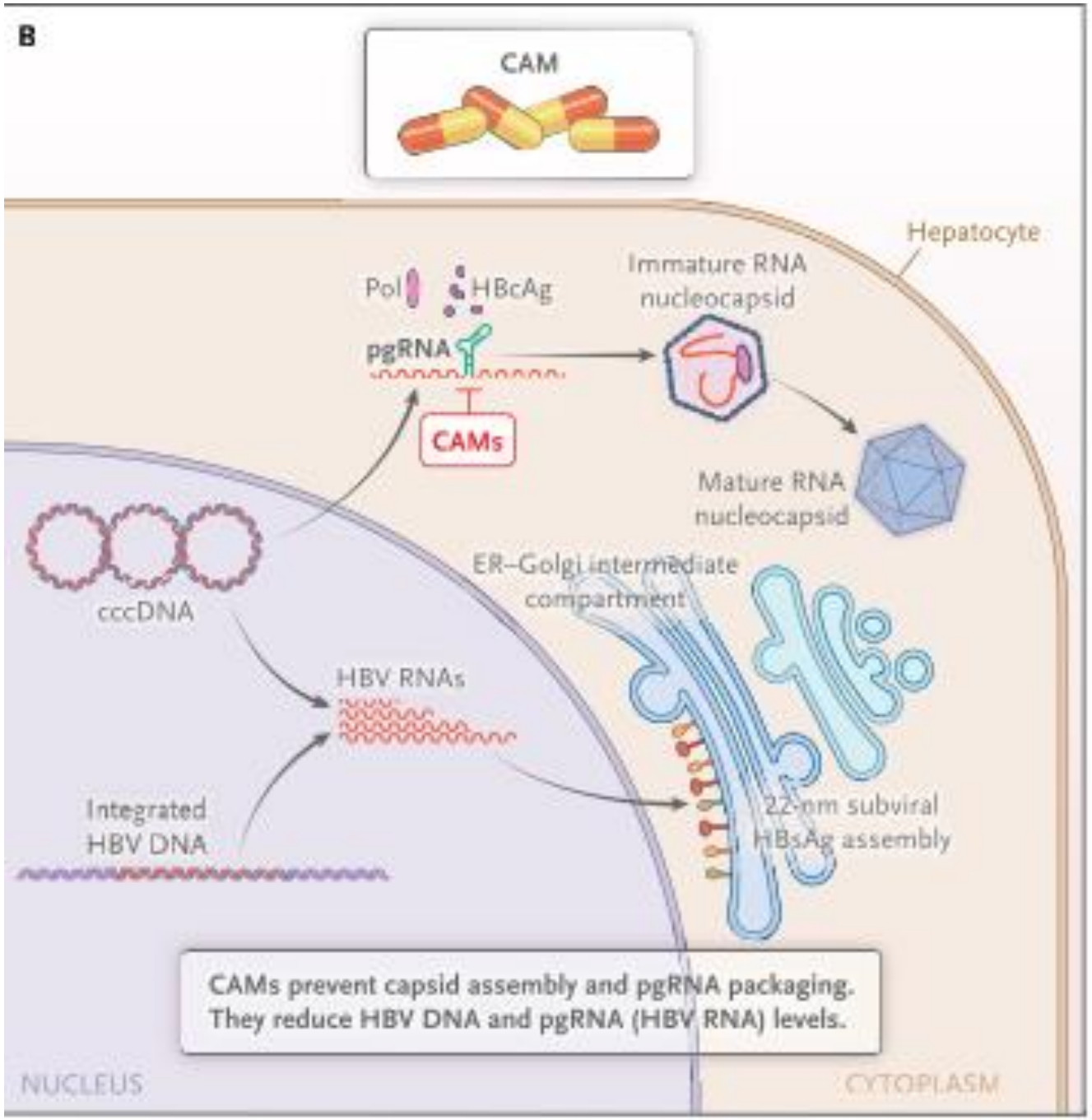

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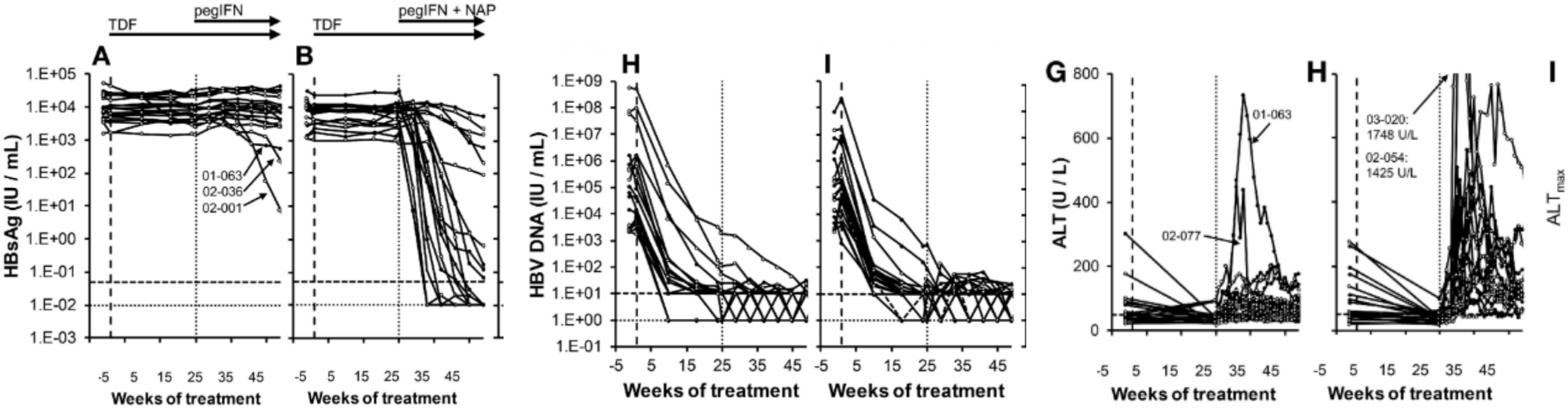
48 Weeks REP 2139 or REP 2165, Tenofovir Disoproxil, and Pegylated Interferon Alfa-2a 401 study

HBeAg negative patients with chronic HBV infection naïve to nucleoside therapy.

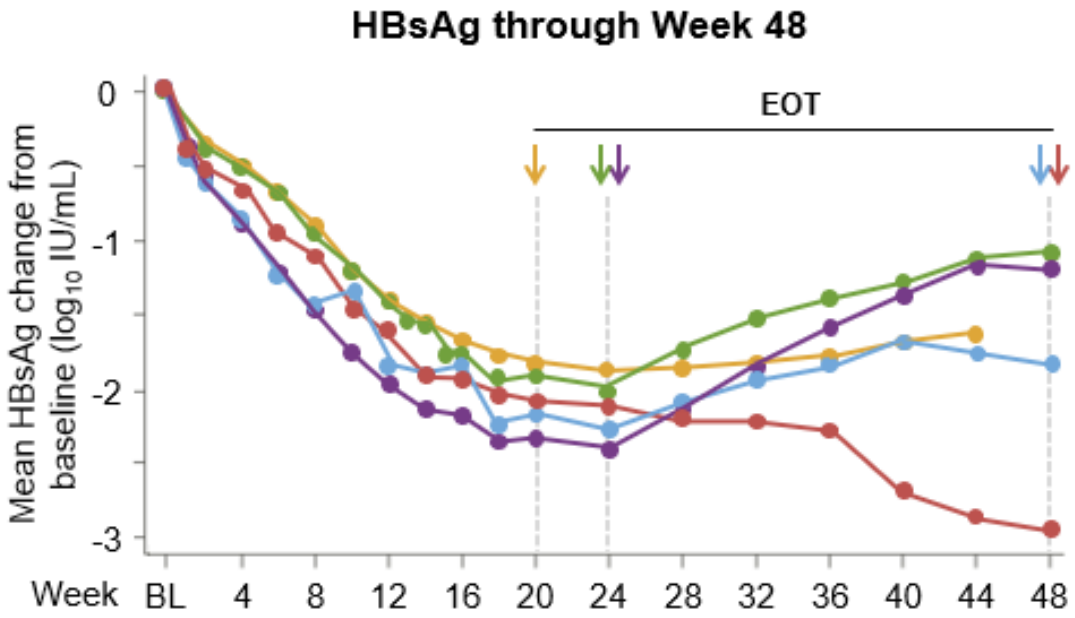


Changes in serum HBsAg, HBV DNA, ALT during the first 48 weeks of therapy

Bazinet M, Gastroenterology 2020;158:2180-2194.

48 week efficacy data VIR 2218 (siRNA) alone and in combination with PEG IFN alpha

HBeAg positive and negative



Mean ±SD (n)	HBsAg Mean change from baseline (log_{10} IU/mL)		
	Week 24	Week 36	Week 48
VIR-2218 × 6	–1.9 ±0.25 (15)	–1.8 ±0.39 (15)	–1.6 ±0.42 (15)[a]
VIR-2218 × 6 lead-in + pegIFNα × 12	–2.0 ±0.69 (15)	–1.4 ±0.80 (15)	–1.1 ±0.83 (15)
VIR-2218 × 6 + pegIFNα × 24	–2.4 ±0.71 (16)	–1.6 ±0.66 (16)	–1.2 ±0.54 (17)
VIR-2218 × 6 + pegIFNα × ≤48	–2.3 ±0.86 (16)	–1.8 ±1.62 (16)	–1.8 ±1.71 (16)
VIR-2218 × ≤13 + pegIFNα × ≤44	–2.1 ±0.62 (13)	–2.3 ±0.81 (13)	–2.9 ±1.36 (13)

HBsAg seroclearance

n (%)	VIR-2218 × 6 (n=15)	VIR-2218 × 6 lead-in + pegIFNα × 12 (n=15)	VIR-2218 × 6 + pegIFNα × 24 (n=5)	VIR-2218 × 6 + pegIFNα × ≤48 (n=18)	VIR-2218 × ≤13 + pegIFNα × ≤44 (n=13)
At any time up to Week 48	0	1 (7)	1 (6)	4 (22)	4 (31)
At Week 48	0	1 (7)	0	3 (17)	4 (31)
With anti-HBs (>10 mIU/mL) at Week 48	0	1 (7)	0	3 (17)	4 (31)

Lower HBsAg levels achieved with concurrent VIR 2218 and PEG IFN compared to VIR-2218 monotherapy

Longer duration VIR 2218 and PegIFNα (48 weeks) most effective regimen: 2.9 log_{10} reduction in HBsAg and 31% HBsAg loss

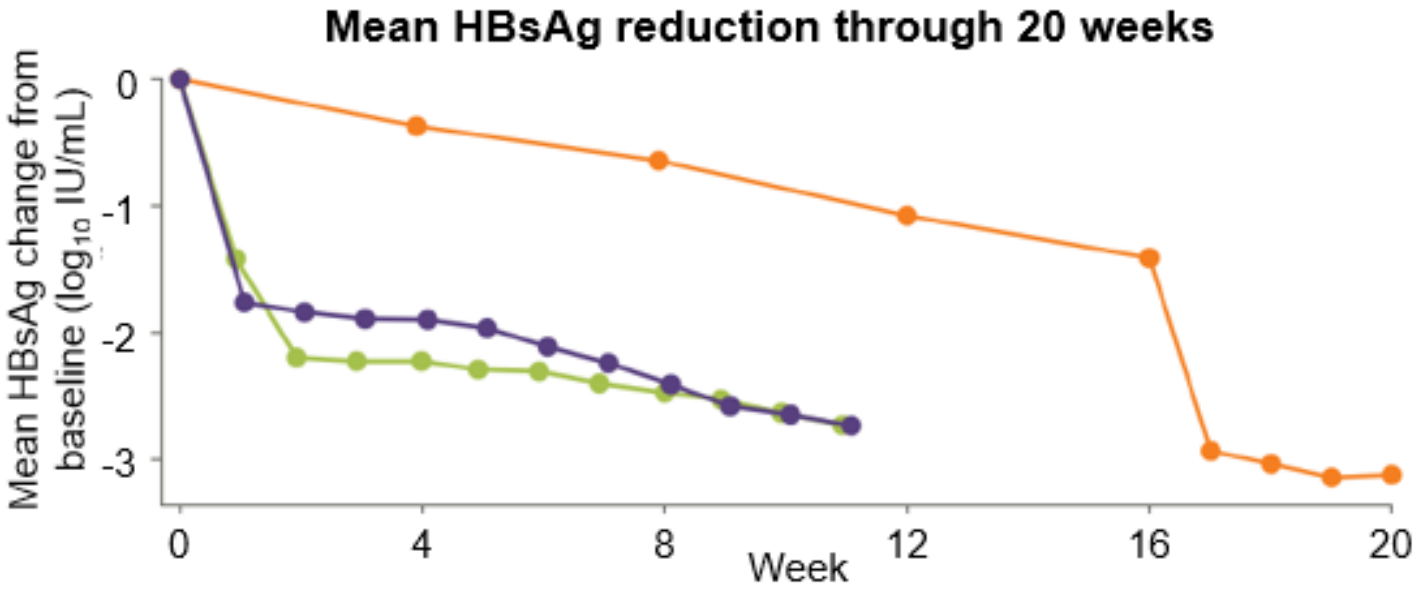
Cohort 5: 2/5 (40%) HBsAg < 1500 IU/ml versus 2/8 (25%) HBsAg > 1500 IU/ml achieved HBsAg loss

Yuen et al AASLD 2022 Oral 19

MARCH: preliminary efficacy siRNA (VIR 2218) + neutralising monoclonal antibody (VIR-3434)

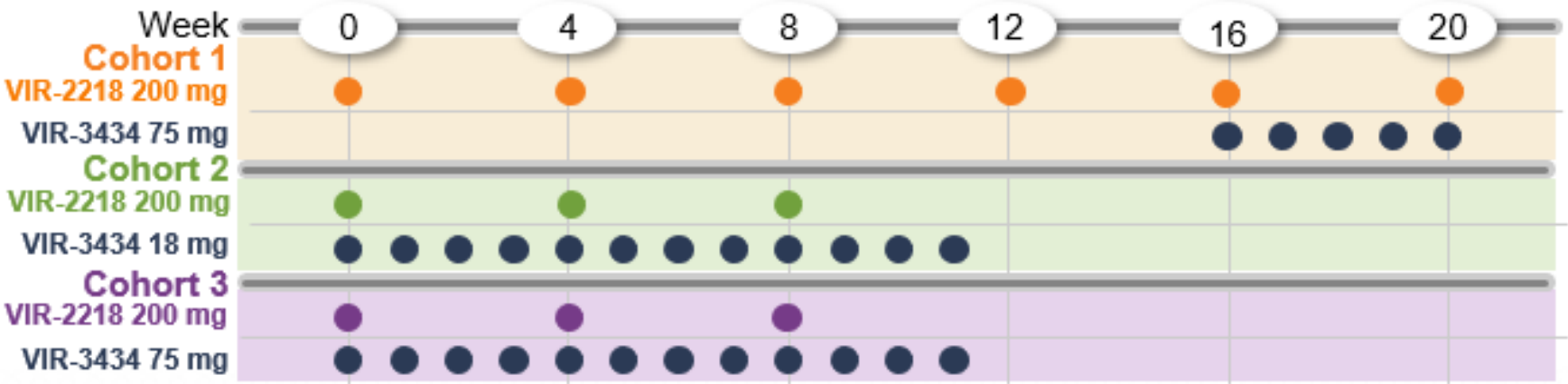
On nucleoside analogues

Demographics: cohort 2 and 3 greater percentage with baseline HBsAg <1000 IU/ml



Mean ±SD HBsAg change from baseline at EOT (log_{10} IU/mL)

Cohort 1	–3.1 ±0.4
Cohort 2	–2.7 ±0.3
Cohort 3	–2.7 ±0.6

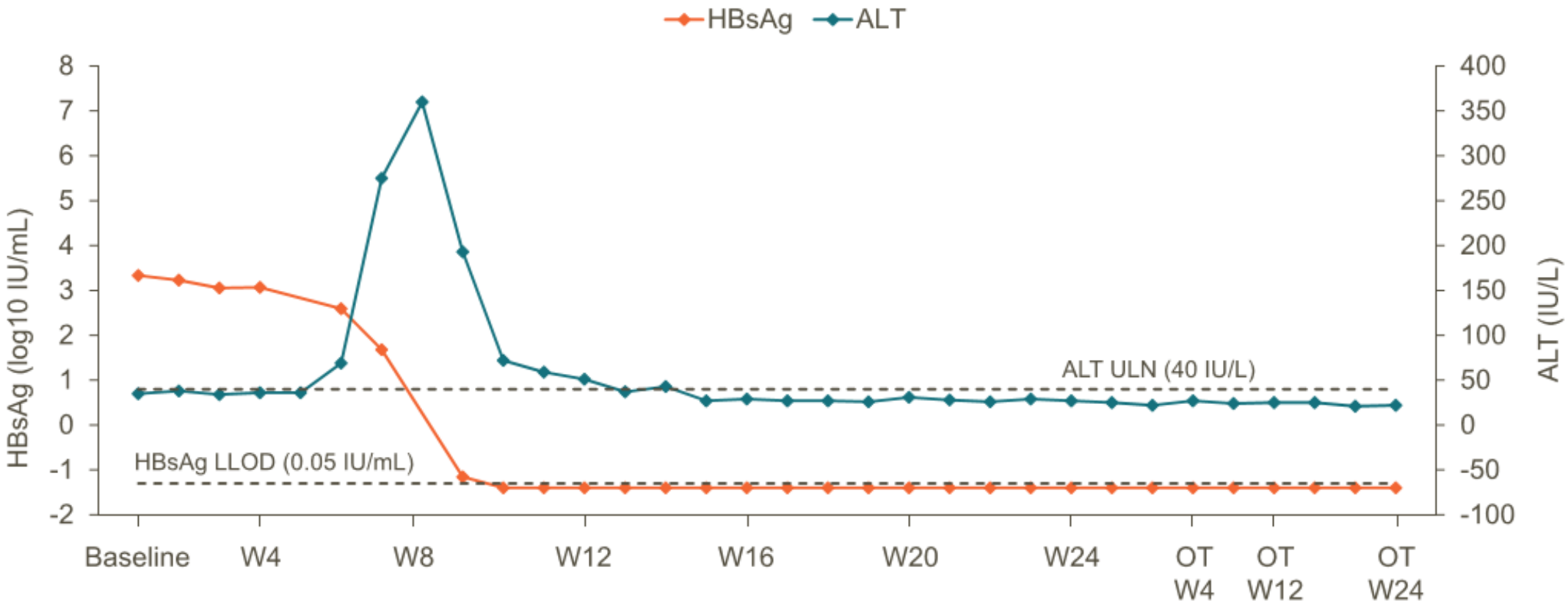


HBsAg kinetics: additive reductions from VIR-2218 and VIR-3434

Neutralising or Fc engineered immune effector function and induced cytotoxicity?

Gane et al AASLD 2022 oral 18

Most ALT elevations occurred in association with HBsAg decline



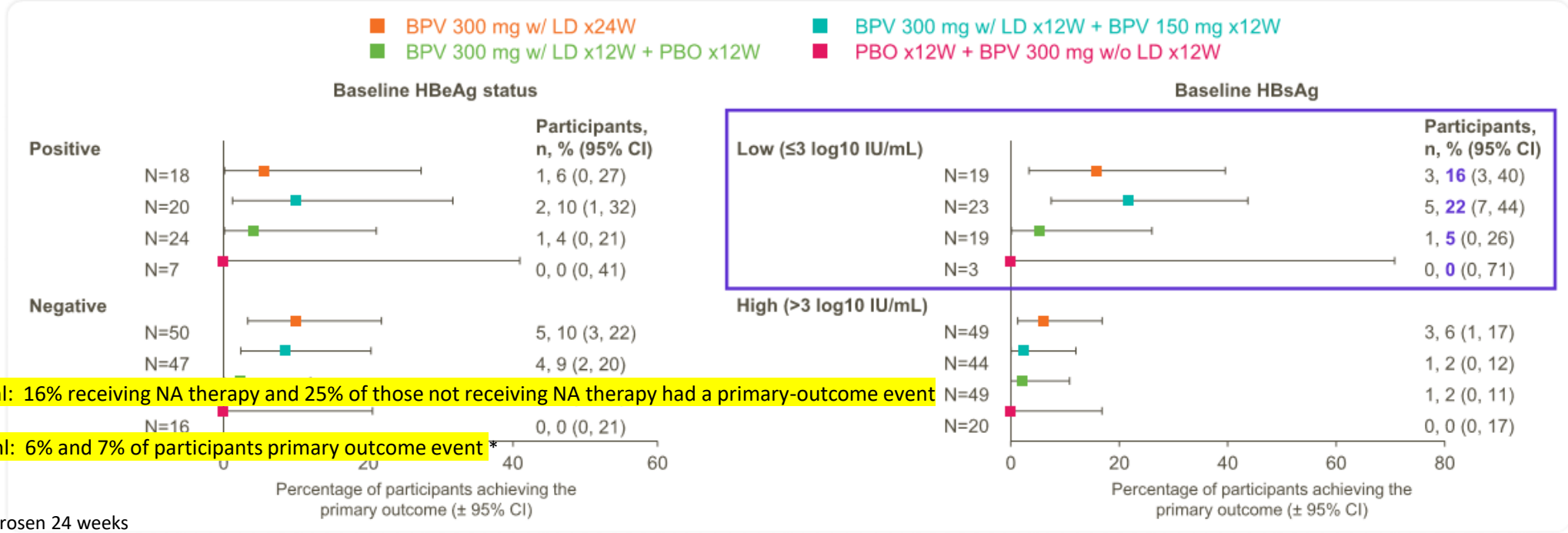
39 participants had ALT increase ≥3 x ULN; most (97%) elevations occurred in association with HBsAg decline (>0.4 log from baseline).

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

HBsAg seroclearance and HBV DNA loss Bepivirosen B-CLEAR

On nucleoside analogue population

ITT population



*HBsAg ≤3 log_{10} IU/ml: 16% receiving NA therapy and 25% of those not receiving NA therapy had a primary-outcome event

*HBsAg >3 log_{10} IU/ml: 6% and 7% of participants primary outcome event *

Group 1 300 mg bepivirosen 24 weeks

Primary outcome was achieved in a similar proportion of HBeAg negative and positive participants (Arm 1: 10% vs 6%).

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

The future of functional cure programs

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- Combinations
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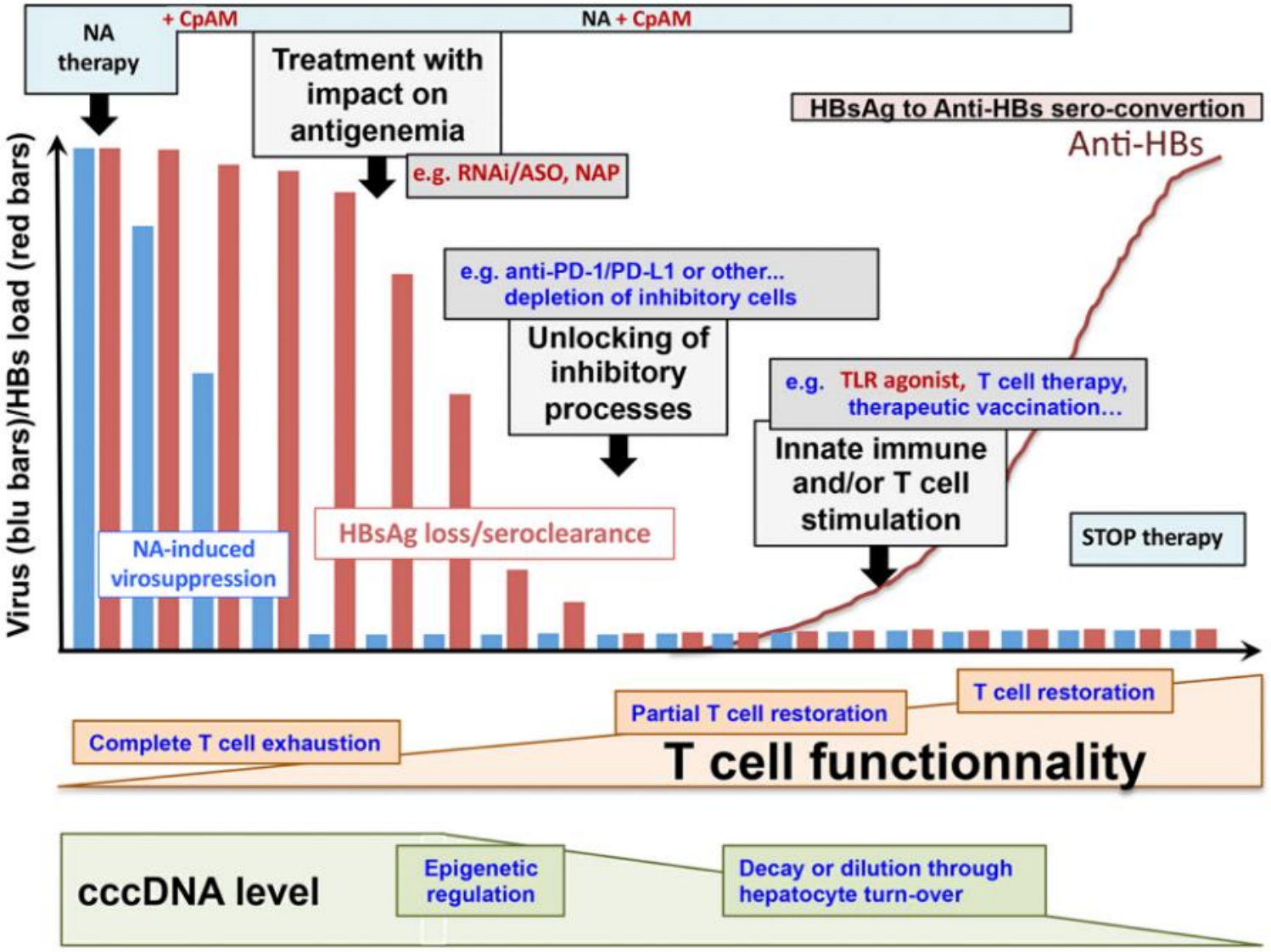
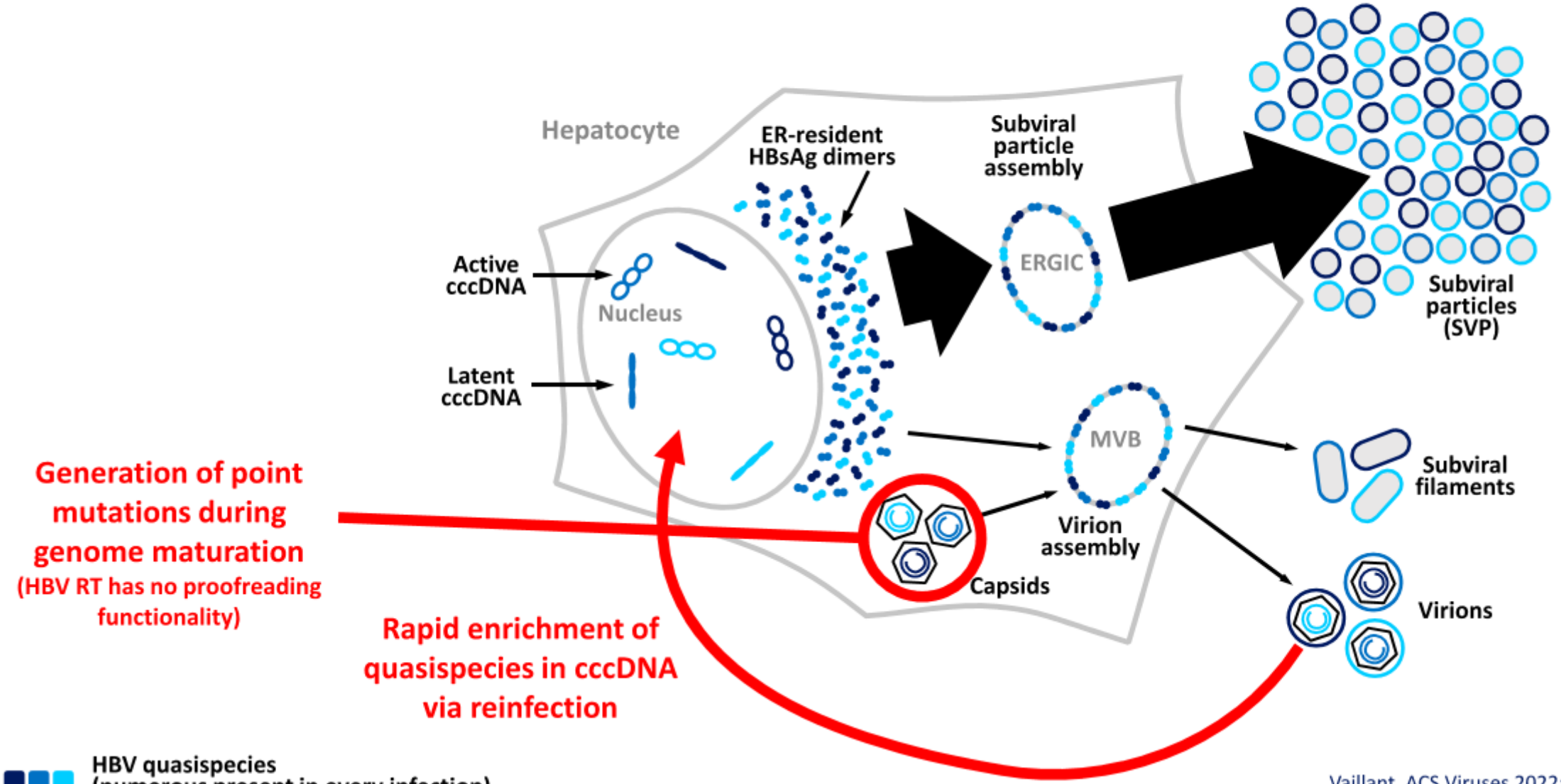
A road map of strategies, combinations and timelines



Durantel, D. (2023). Antiviral Res: 105515.

Sources of genetic variability in HBV infection



Vaillant, ACS Viruses 2022; 14: 2052

Preclinical research approaches

- These include X gene targeting, cccDNA or RNA
- Destabilization or cccDNA reduction
- Host targets or targeting by CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats
- And associated Cas9 homing endonucleases) to base edit cccDNA.

Conclusions

- Myriad challenges to HBV cure remain: Encouraging learning curve, but not megatrend
- Maintaining momentum requires
  - Defining realistic endpoints: HBsAg decline a proxy for progress?
  - Will have to be remunerative to ensure continued investment
  - Patient involvement required
- New biomarkers and technological advances
  - Illustrate the two sources of HBsAg
  - Refine HBeAg-negative states
  - Improve indications for treatment
- Trend lines pointing in the right direction (False comfort?)
- Additive combinations observed
- **We should not lose sight of fact that current levels of treatment are insufficient**
- **Cardinal responsibility is to improve awareness and access with existing treatments**