Hepatitis Research and Development Combination Strategies

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Combination Treatment in CHB

- What do we want?
  - Functional cure: off-treatment sustained response and no need of long-term treatment
  - Reduce incidence of HCC
  - Complete cure
- Trade-off
  - Higher treatment cost
  - Possibly more adverse events
  - Patient inconvenience

Combination of immune modulator and direct antiviral agent

Logical partners

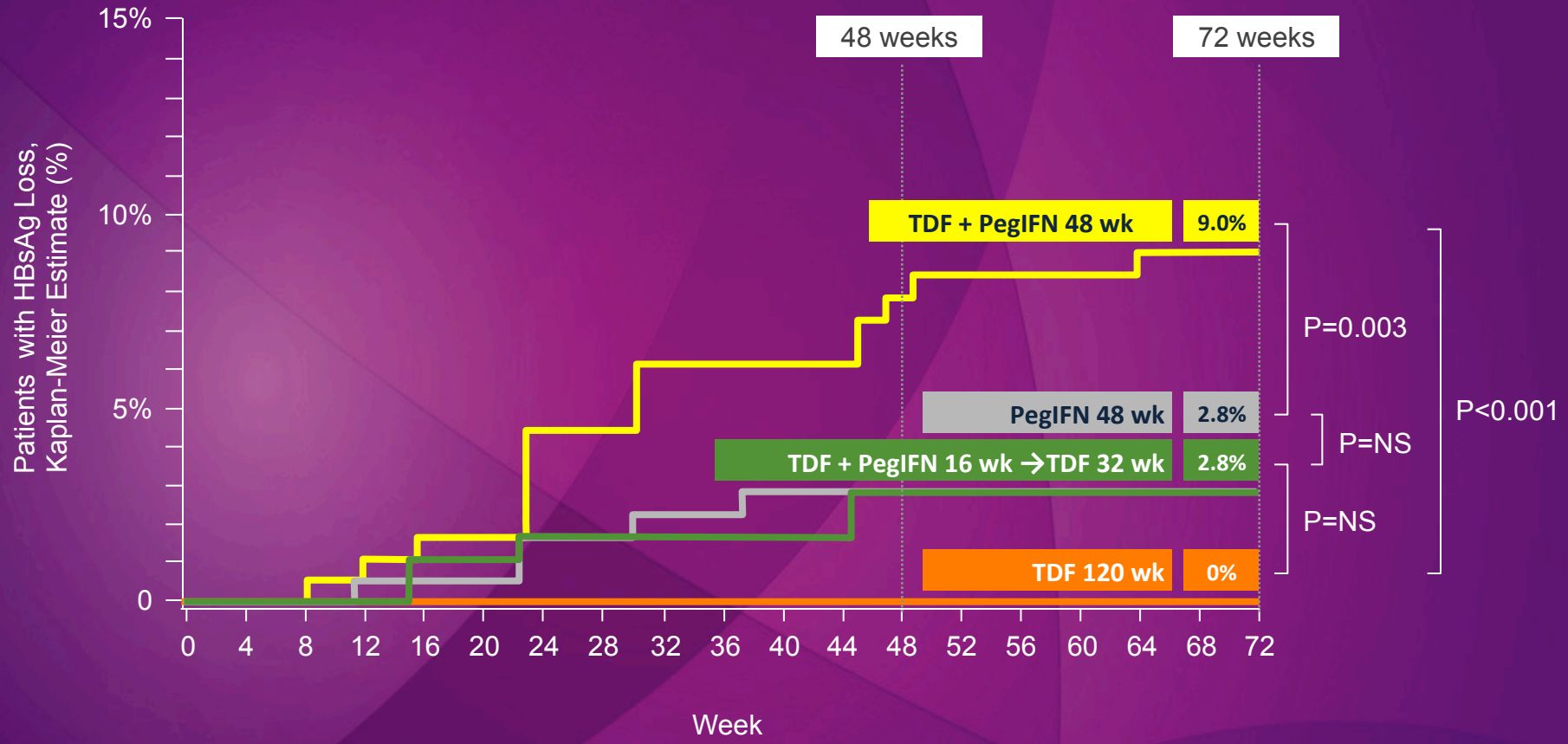
DOES THE CHOICE OF NA MATTER?

Combination therapy cannot improve sustained response to peginterferon

- Many studies on peginterferon combination therapy with lamivudine, adefovir or entecavir either simultaneous or staggered regimes
- Combination therapy can only increase on-treatment HBV DNA suppression but not sustained off-treatment response
- Currently, combination therapy of peginterferon and NA cannot be recommended

Lok ASF and McMahon BJ. Hepatology 2009
Sarin S et al., Hepatol Int 2016
EASL. J Hepatol 2012

Tenofovir and peginterferon is an exception Need to pick the right partner for combination therapy

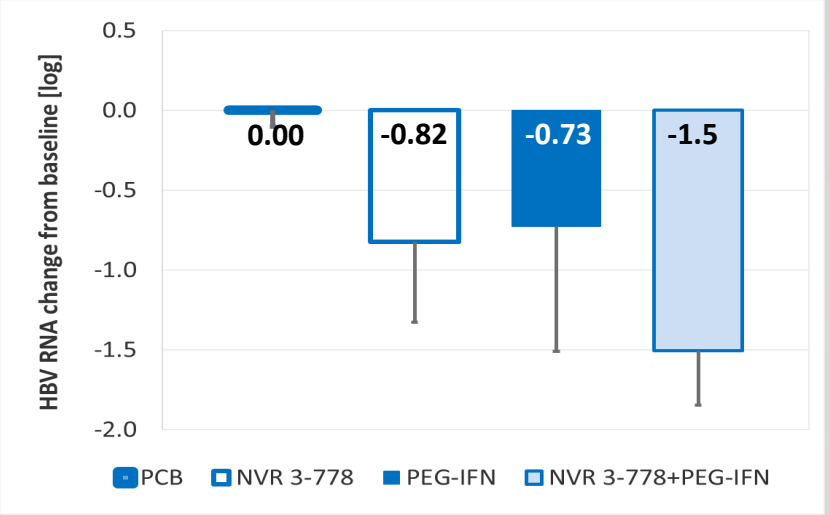


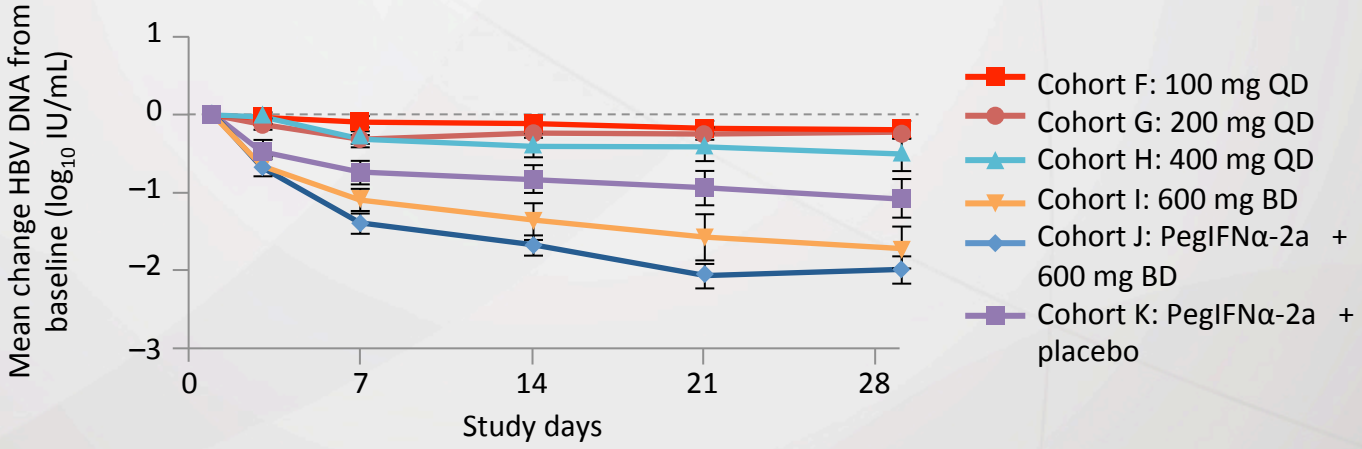
7 patients had HBsAg seroreversion on or after Week 48 (4 patients receiving TDF + PEG-IFN for 48 weeks and 3 with TDF + PEG for 16 weeks followed by TDF for 32 weeks

Marcellin P, … Chan HLY. Gastroenterology 2016;150:134-44

Maximum HBV DNA reduction with peginterferon and NVR 3-778 combination

- Additive effect of NVR 3-778 with PegIFN on HBV DNA (1.97 log IU/ml) and RNA (1.51 log copies/mL)





Yuen MF, et al. EASL 2016, Barcelona. LBO6

DOES TIMING OF COMBINATION MATTER?

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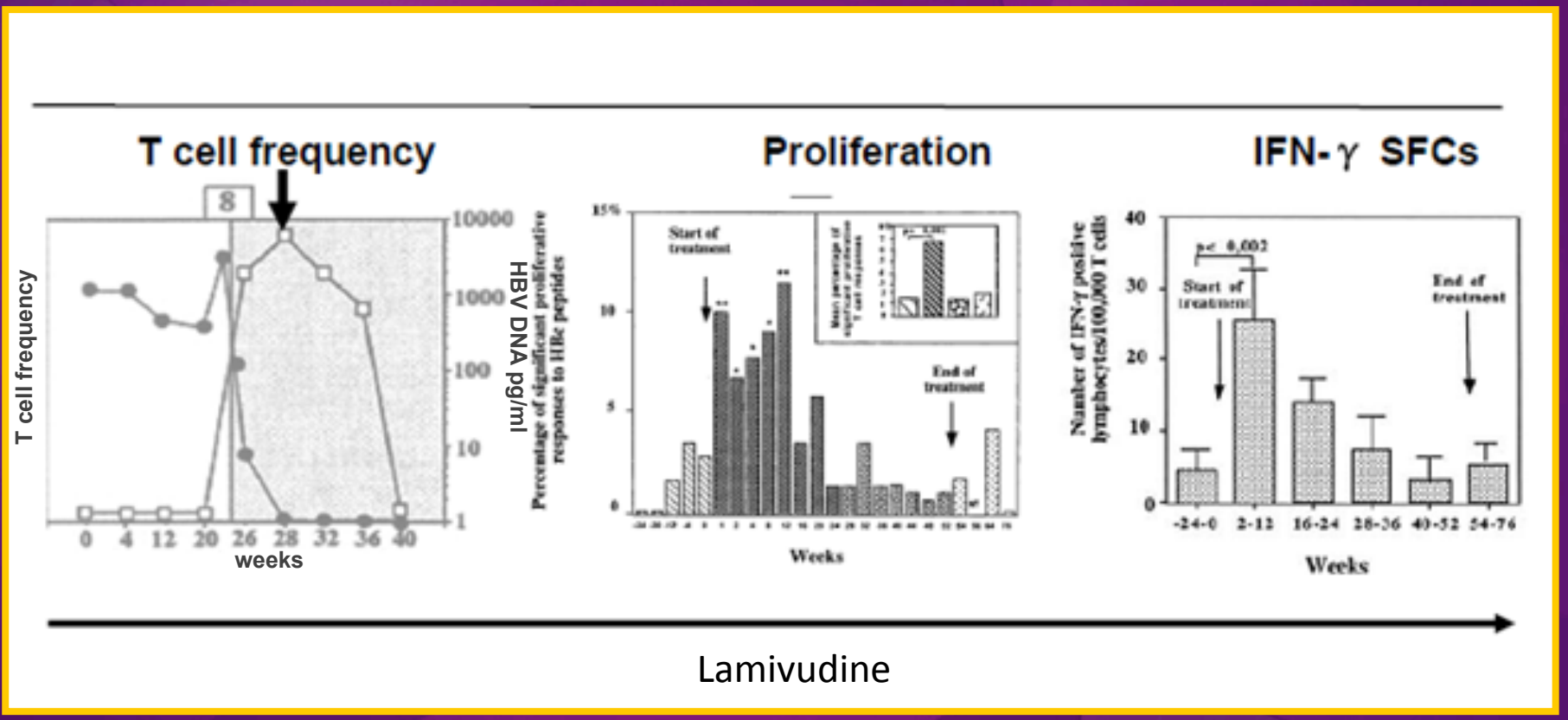
Rapid viral suppression transiently stimulates T cells at week 12

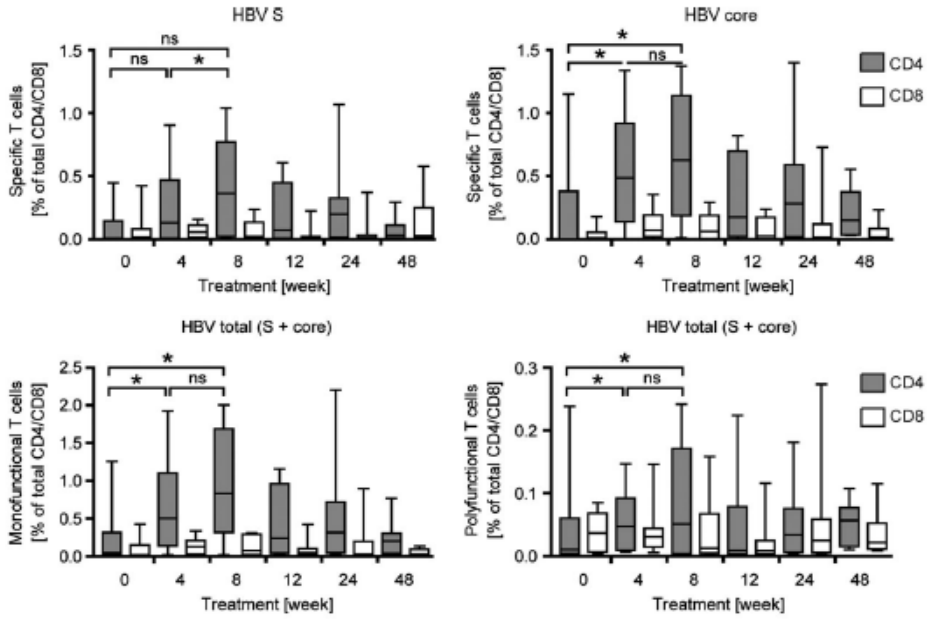
12 cases of lamivudine treated HBeAg-positive CHB patients
T immune response 6 months before LMV, 12 month LMV therapy and 6 month after LMV



Boni C,et al.J Clin Invest 1998,102(5):968-957.
Bonic C,et al. J Hepatol 2003,39:596-605.

CD4 and CD8 T cell stimulation among NA treated patients with add-on IFN therapy

12 CHB patients (3 HBeAg +) on NA (1 LMV, 2 LMV+ADV, 6 ETV, 1 ETV+ADV, 2ETV+TDF)
Add-on peginterferon alfa-2a therapy



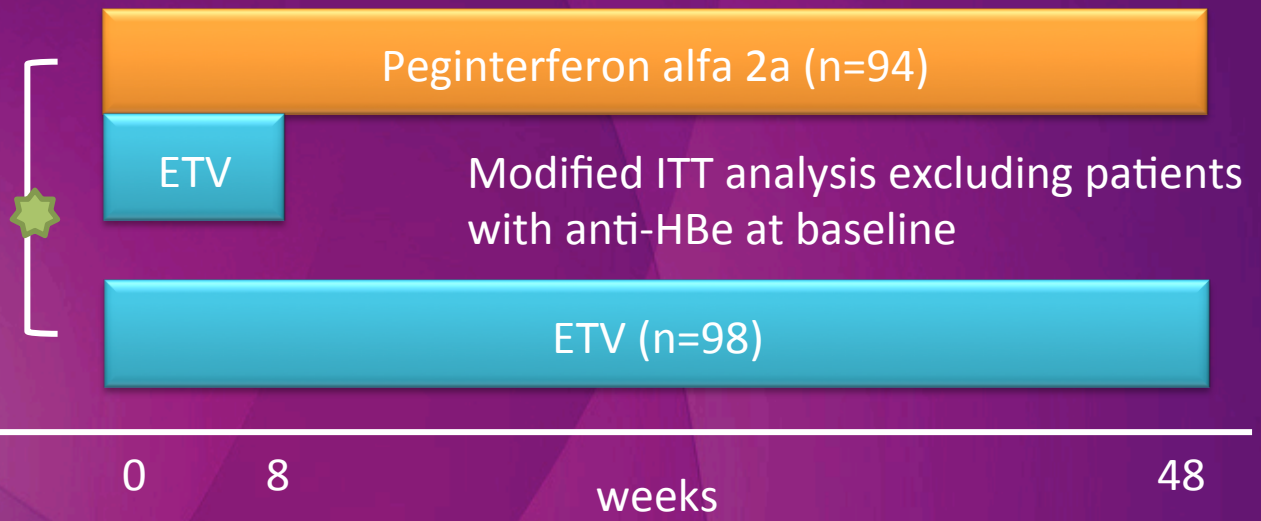
PIFN stopped after 12 weeks due to no s decline (7)
PIFN stopped due to adverse events (3)
PIFN for 48 weeks in s loss (2)

Patients with increased T cell activity
S specific CD4 66.6%
S specific CD8 58.3%
Core specific CD4 83.3%
Core specific CD8 83.3%

Sprinzl MF, et al. J Viral Hepat 2014;21:633-41.

Peginterferon increases HBeAg seroconverision and HBsAg loss among patients with low HBeAg title on ETV

HBeAg positive CHB on ETV x 9-36 mos
HBV DNA <1000 copies/ml + HBeAg <100 PEIU/ml

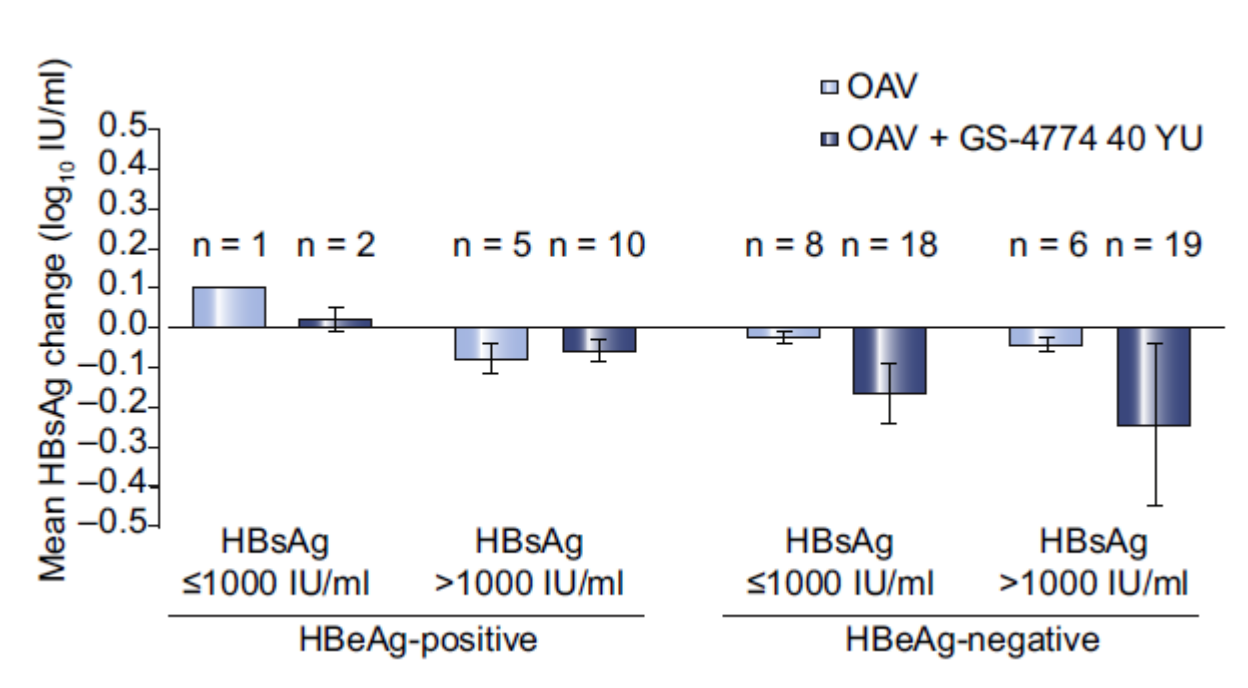


Outcome	Peginterferon α2a	Entecavir	P
HBeAg seroconversion	14.9%	6.1%	0.047
HBeAg loss	38.1%	33.3%	0.64
HBsAg loss	8.5%	0	0.0028
HBsAg seroconversion	4.3%	0	0.056

Ning Q, et al. J Hepatol 2014;61:777

No significant decline in HBsAg with therapeutic vaccine GS-4774 among patients on long-term antiviral drugs

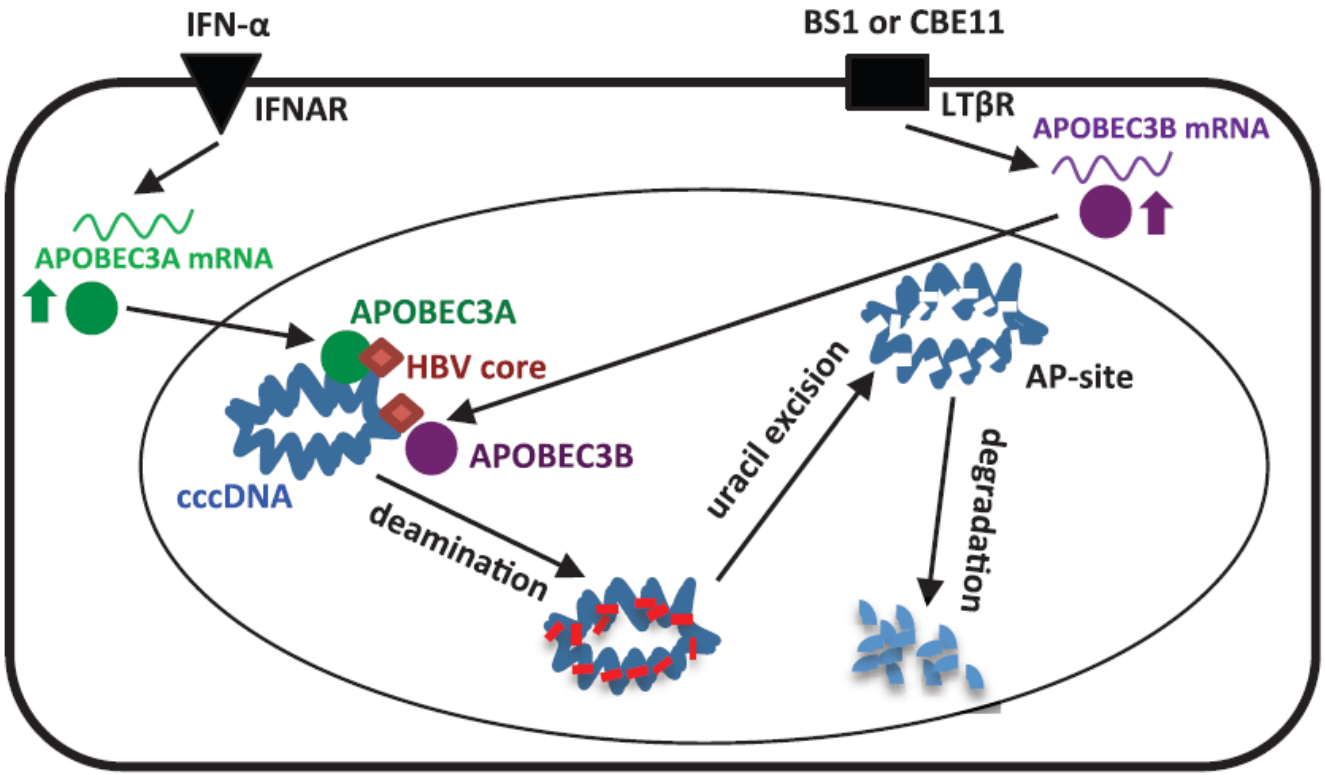
- GS-4774 is a yeast-based vaccine expressing recombinant X, large S and core HBV antigens
- Randomized controlled trial in CHB patients on oral antiviral (OAV) for >1 year; on GS-4774 every 4 weekly until week 20 and OAV till week 48



No HBsAg loss in all patients

Lok AS, et al. J Hepatol 2016;65:509-16

Interferon may still be here for a while cccDNA clearance by interferon-alpha



Lucifora et al. Science 2014;343:1221

ANY ROLE OF DIRECT ANTIVIRAL COMBINATION?

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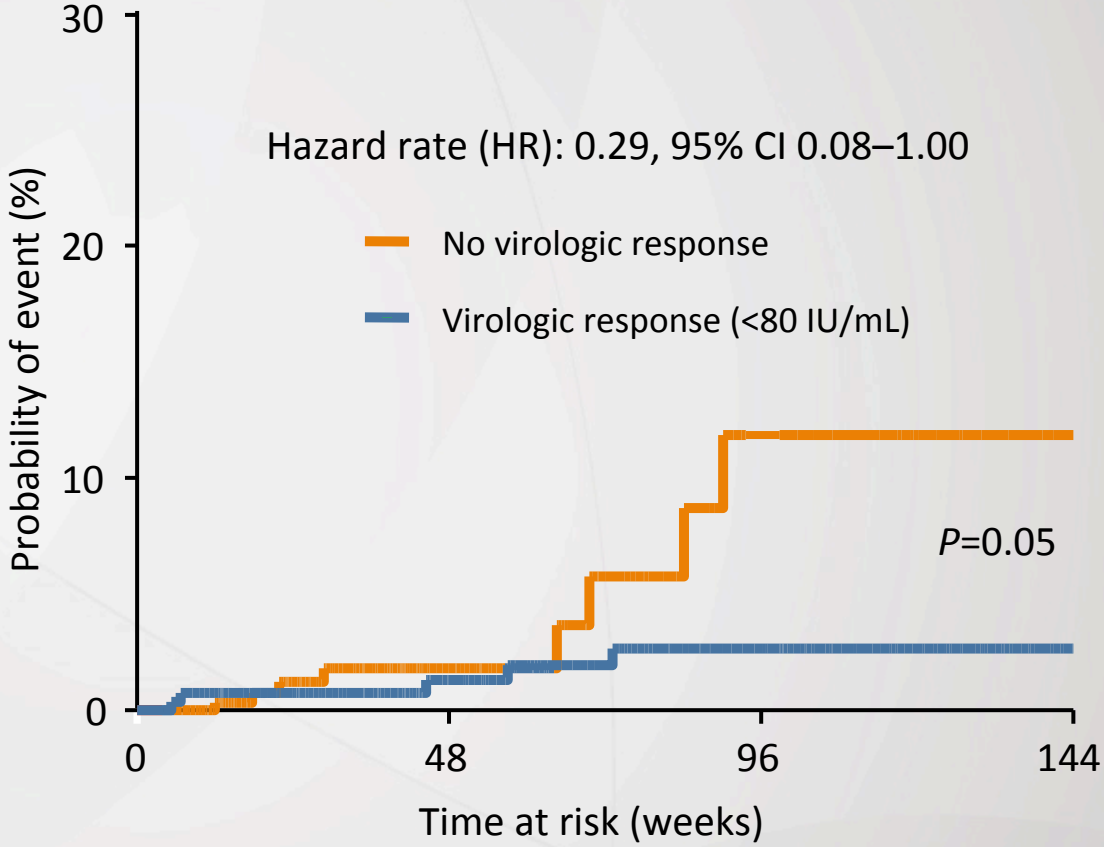
VIRGIL ETV study
Virologic response is associated with a lower probability of disease progression

Retrospective cohort study in 10 large European centers
Study population (N=372)

Median follow-up 20 (3–51) months

98 patients have liver cirrhosis



*** Composite endpoint: Hepatic decompensation, jaundice, variceal bleeding, ascites or encephalopathy, HCC, death.**

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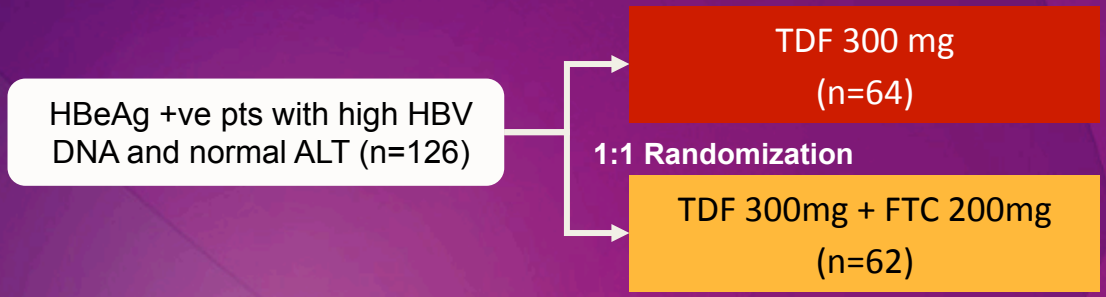
Zoutendijk R, et al. Gut 2013;62:760-5

Combination of tenofovir and emtricitabine improves viral suppression in HBeAg-positive patients with high viral load

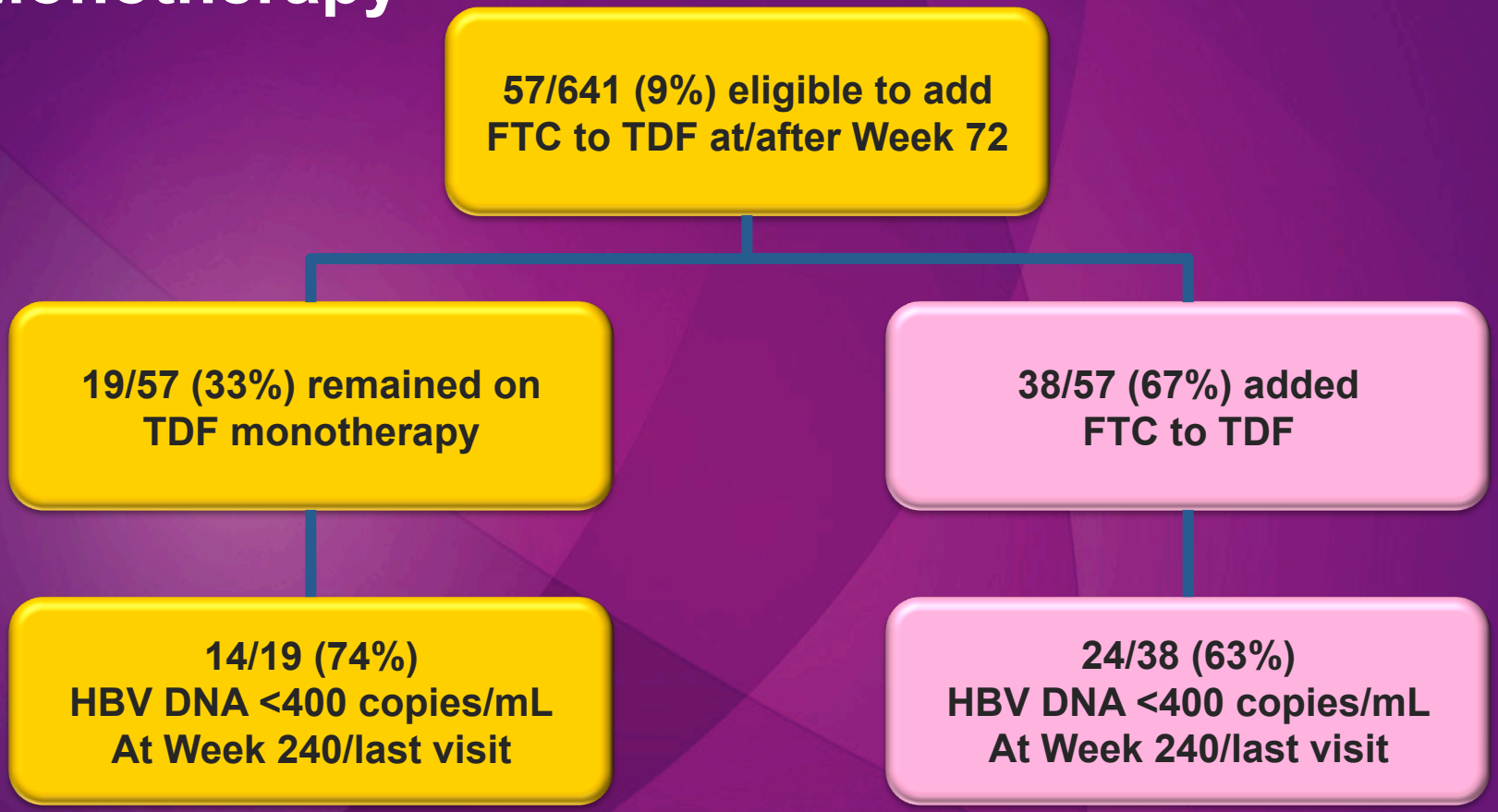


Response = HBV DNA < 69 IU/ml at week 192

	TDF n=64	TDF/FTC n=62	p-value
Primary endpoint			
HBV DNA <69 IU/mL	55%	76%	0.016
Secondary endpoints			
HBeAg seroconversion	5%	0%	0.244
HBsAg loss	0%	0%	

Chan HL, et al. Gastroenterology 2014;146:1240-8

Studies 102/103: Adding FTC does not improve viral suppression vs Maintaining TDF Monotherapy



All subjects analyzed with >400 copies/mL had no TDF resistance detected.

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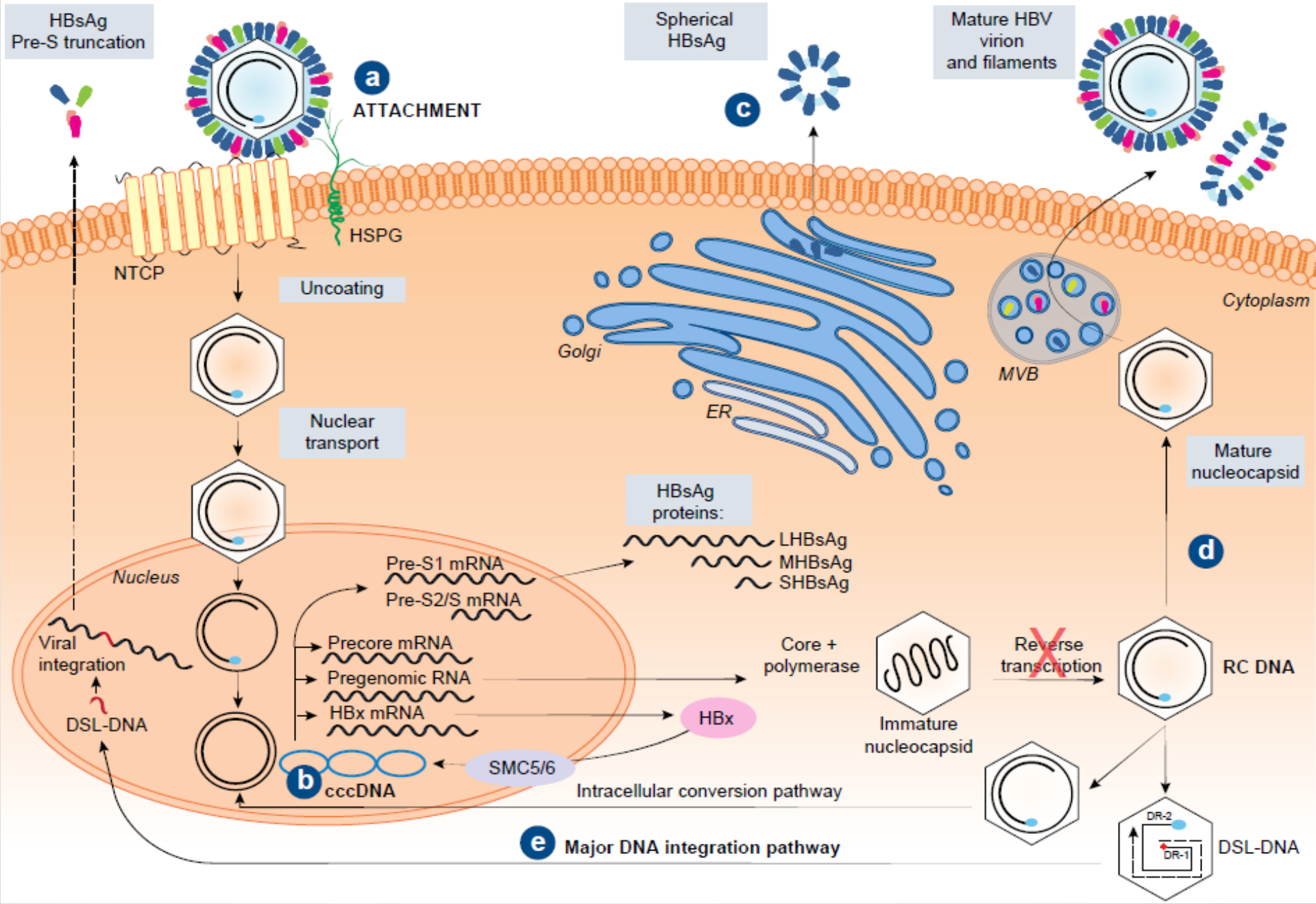
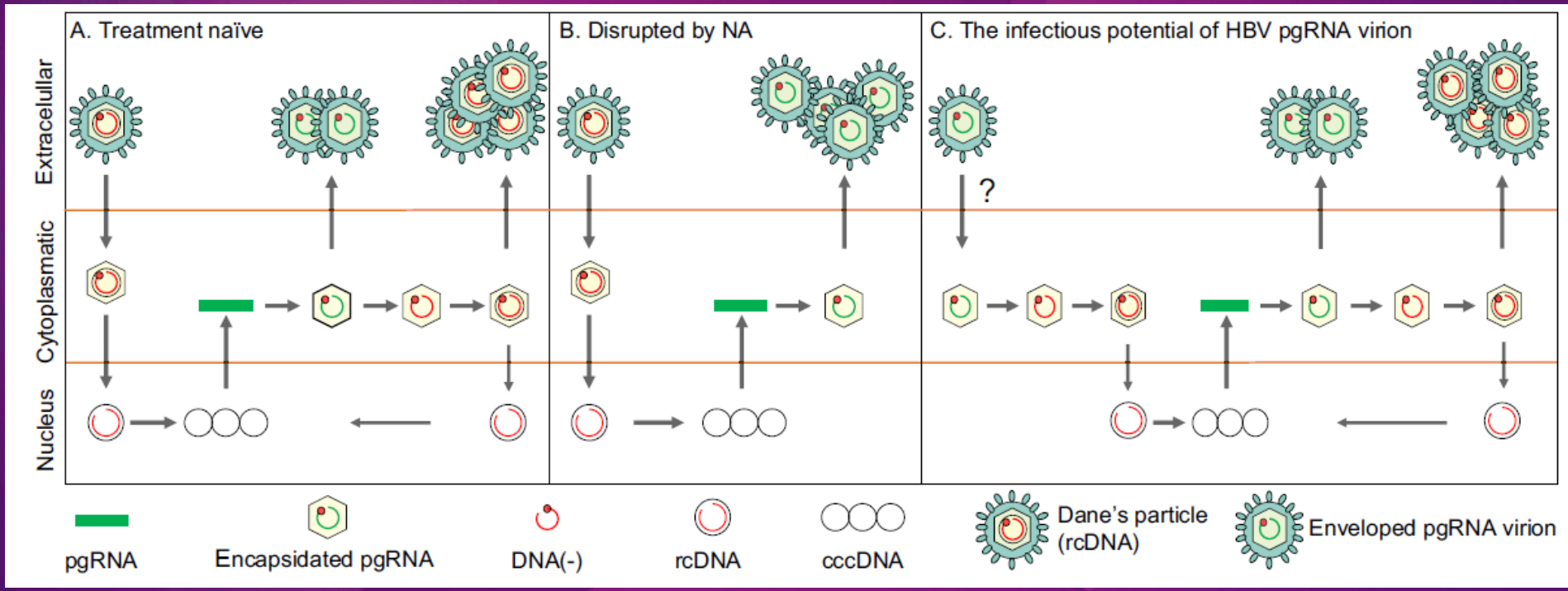
Marcellin P, et al. AASLD 2011. Oral 238.



Cornberg M, … Chan HL. J Hepatol 2016 [in press]

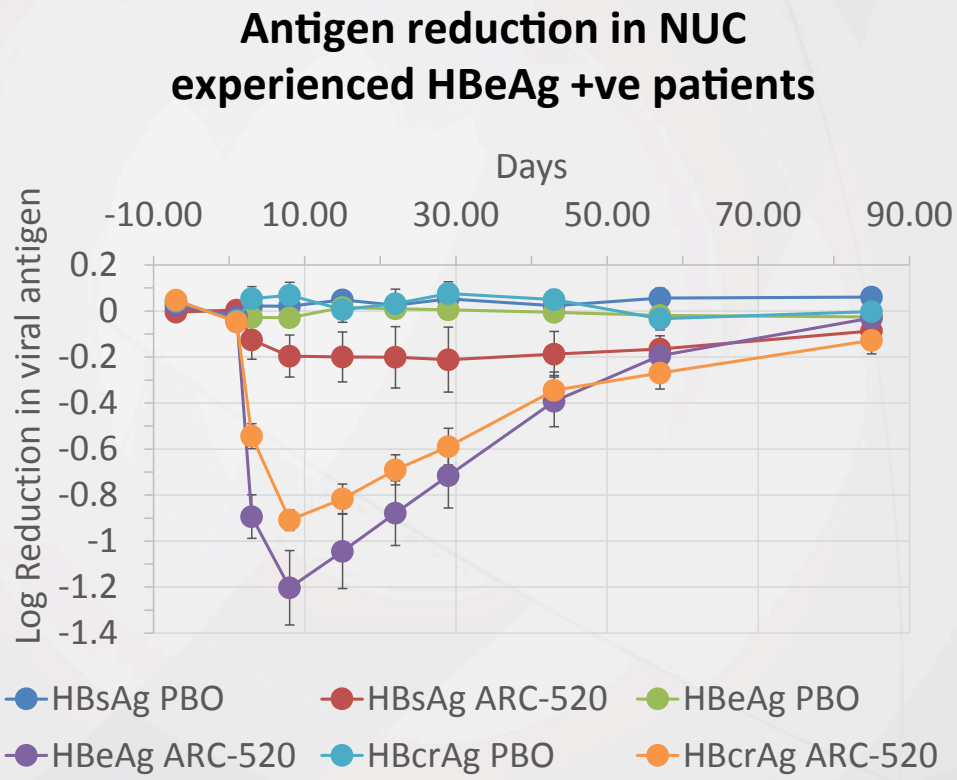
NA only suppresses HBV DNA but not HBV RNA production

Experiments in HepG22.2.15 cells, primary hepatocytes, HBV transgenic mice and CHB patients



Wang J, et al. J Hepatol 2016;65:700-10

Dramatic HBeAg reduction but little HBsAg reduction in treatment-experienced patients with ARC-520



- Single 4 mg/kg dose on day 1

Yuen MF, et al. AASLD 2015, San Francisco. #LB-9

Insights in combination strategies

- Viral suppression + immune modulation is probably needed
- Both treatment naïve and NA treated patients
- Pick the right candidates for combination
- May need cccDNA inhibition/clearance
- Complete viral suppression of other HBV ORFs and pgRNA