Nucleic Acid Polymers for the Treatment of Chronic HBV:

A new therapeutic alternative.

Oligonucleotide Therapeutics Society 2014
Oct 12-15, San Diego, U.S.A.

Nucleic Acid Polymers (NAPs) in HBV therapy

- prevent subviral particle (SVP) formation in HBV infected hepatocytes
  (aptameric interaction with ApoH blocks HBsAg assembly into SVPs)
- aptameric interaction is sequence independent but length and PS dependent
- NAPs can be engineered to remove off target effects:
  - immunostimulation
  - off target hybridization
  - off target sequence specific aptameric interactions

REP 2055 = $(dAdC)_{20}$ PS-ON

REP 2139 = $(A,5'MeC)_{20}$ PS-ON, fully 2'O-methylated

REP 2139-Ca = calcium chelate complex of REP 2139

(improved administration tolerability)

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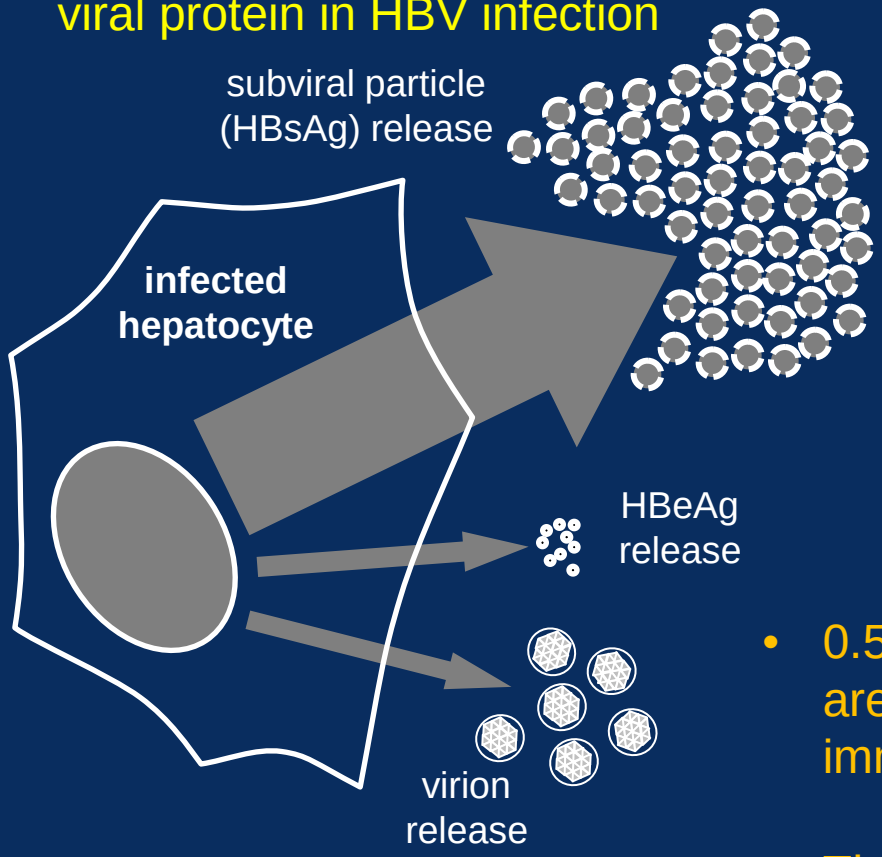
Chronic HBV infection is an immunological disorder

SVP-associated HBsAg is the most abundant viral protein in HBV infection



sequestration of anti-HBs
suppresses innate immunity
suppresses T-cell proliferation
suppresses cytokine signaling

dominant immunosuppressive effect in HBV infection

- 0.5 – 1 log reductions in serum HBsAg are routinely achieved during immunotherapy with no impact on SVR
- Thousands of quasi-species of HBV (and HBsAg) exist in all patients

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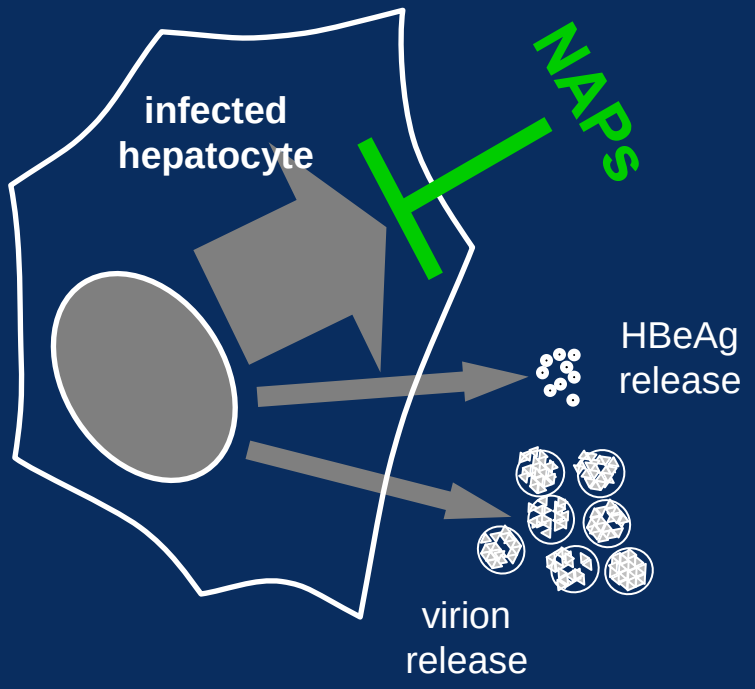
NAPs block the release of subviral particles



HBsAg-mediated immunosuppression is removed

Restoration of host immune response?

NAP Proof of concept studies in human patients

(Dr. Mamun Al-Mahtab, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh)

All patients have stable, chronic HBV infection at the start of treatment:

- HBeAg+
- HBV DNA 10^6 – 10^{12} copies / ml
- compensated liver disease
- mild to moderate fibrosis

Treatment naive

Virema monitored by IMPACT*, Cobas™ and Architect™ platforms.

Dosing: REP 2055 (REP 9AC) – 400mg qW IV infusion

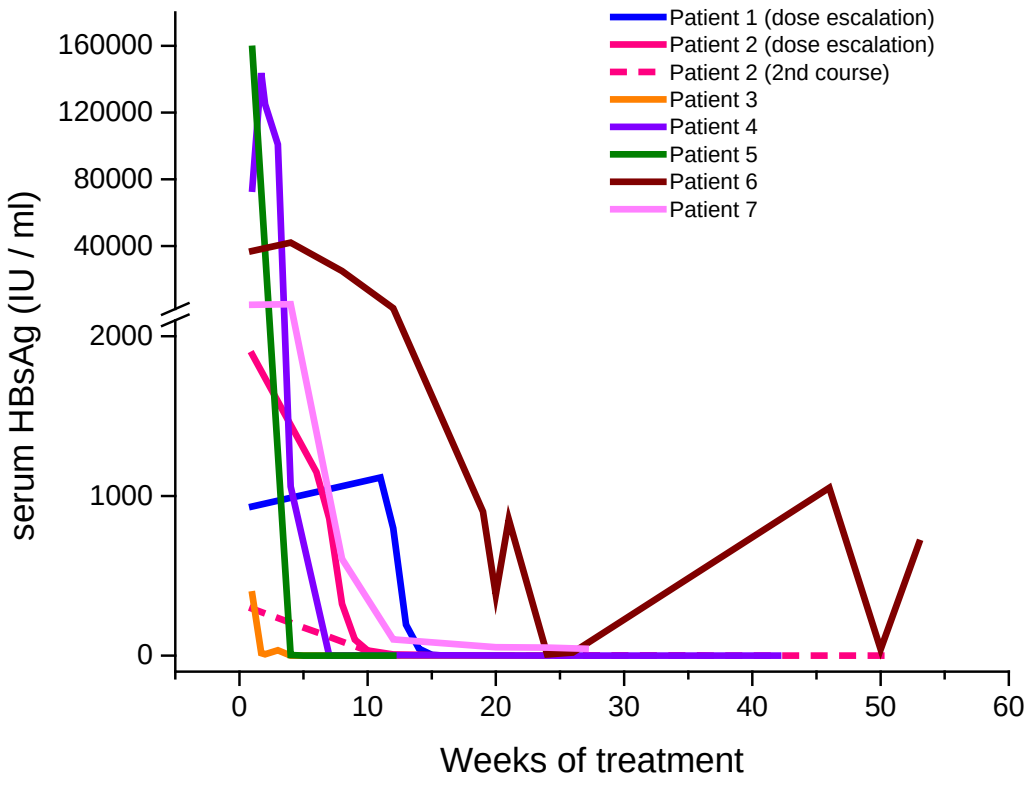
REP 2139-Ca (REP 9AC') – 500mg qW IV infusion

* Roche Diagnostics, Penzburg, German

Effect of REP 2055 (REP 9AC) on serum HBsAg

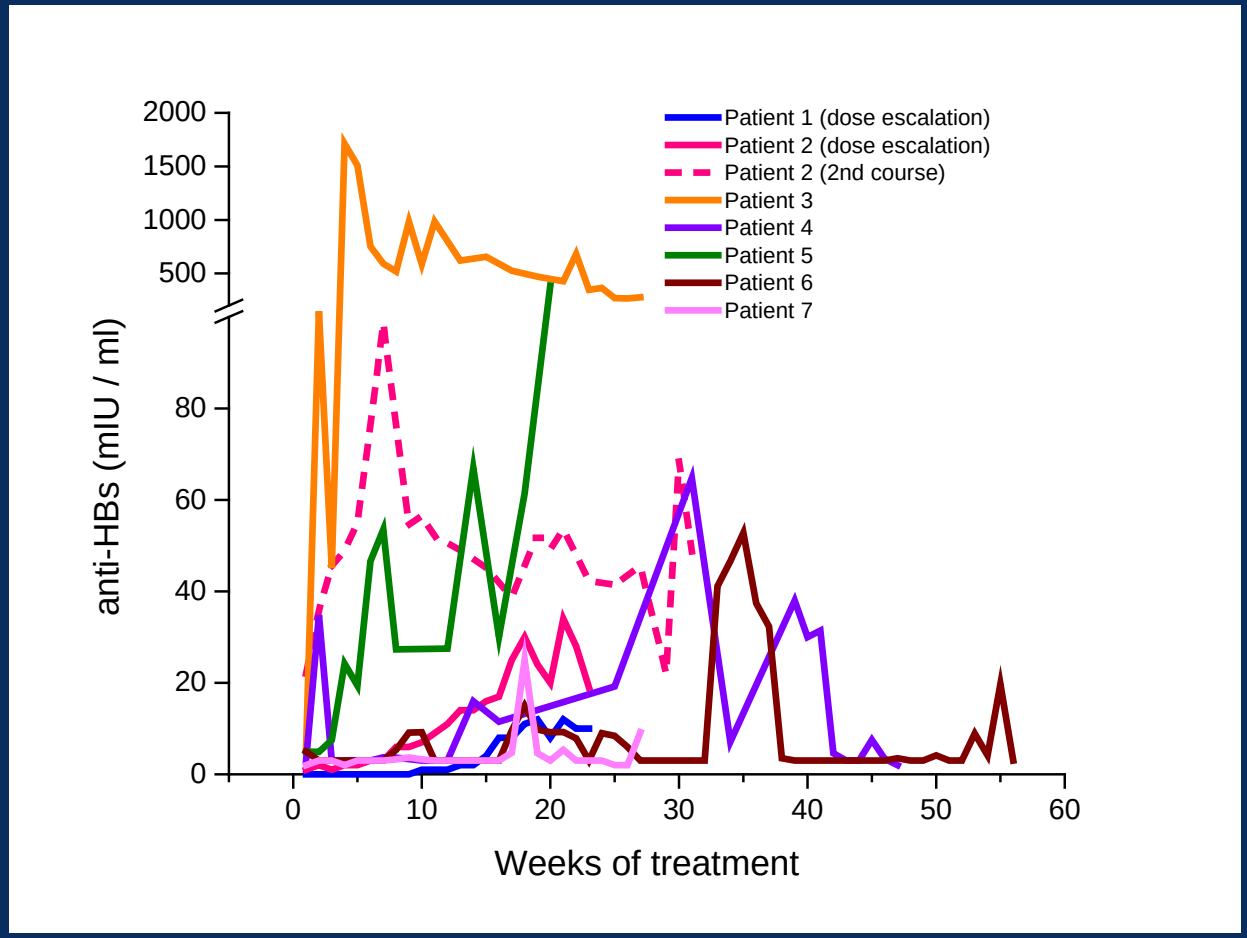
8 patients treated, 1 non responder

7 patients with HBsAg clearance



Patient	Serum HBsAg (IU / ml)		Log reduction
	Start	Lowest observed	
1	934	0.14	3.82
2	1885	0.38	3.70
2 (2)	294	0.30	2.99
3	384	0.01	4.58
4	74330	0.03	6.39
5	158180	0.01	7.20
6	36996	7.00	3.72
7	4673	43.70	2.03

HBsAg clearance unmasks existing anti-HBs response in all patients



Anti-HBs response is heterogenous but is a good indicator of complete serum HBsAg clearance

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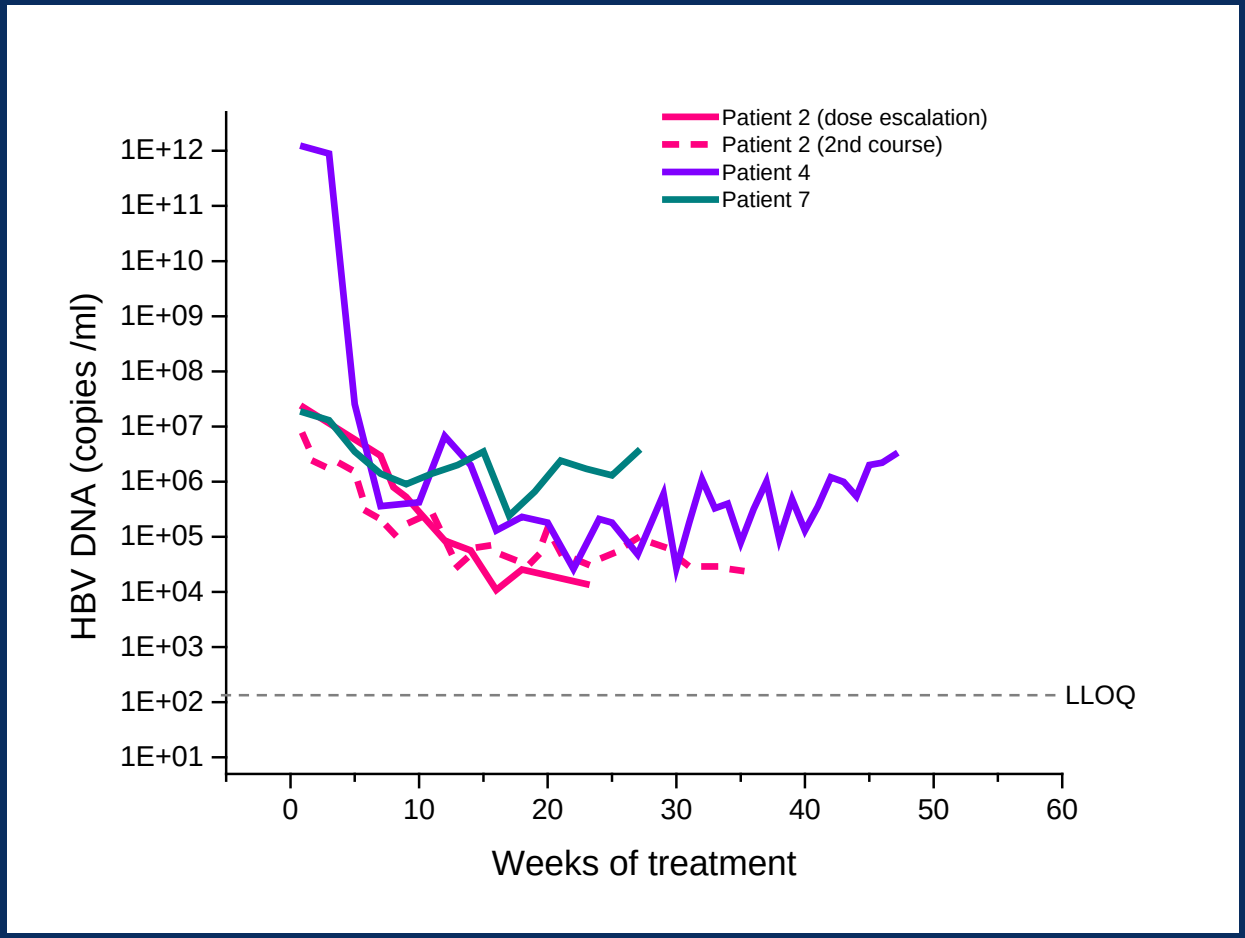
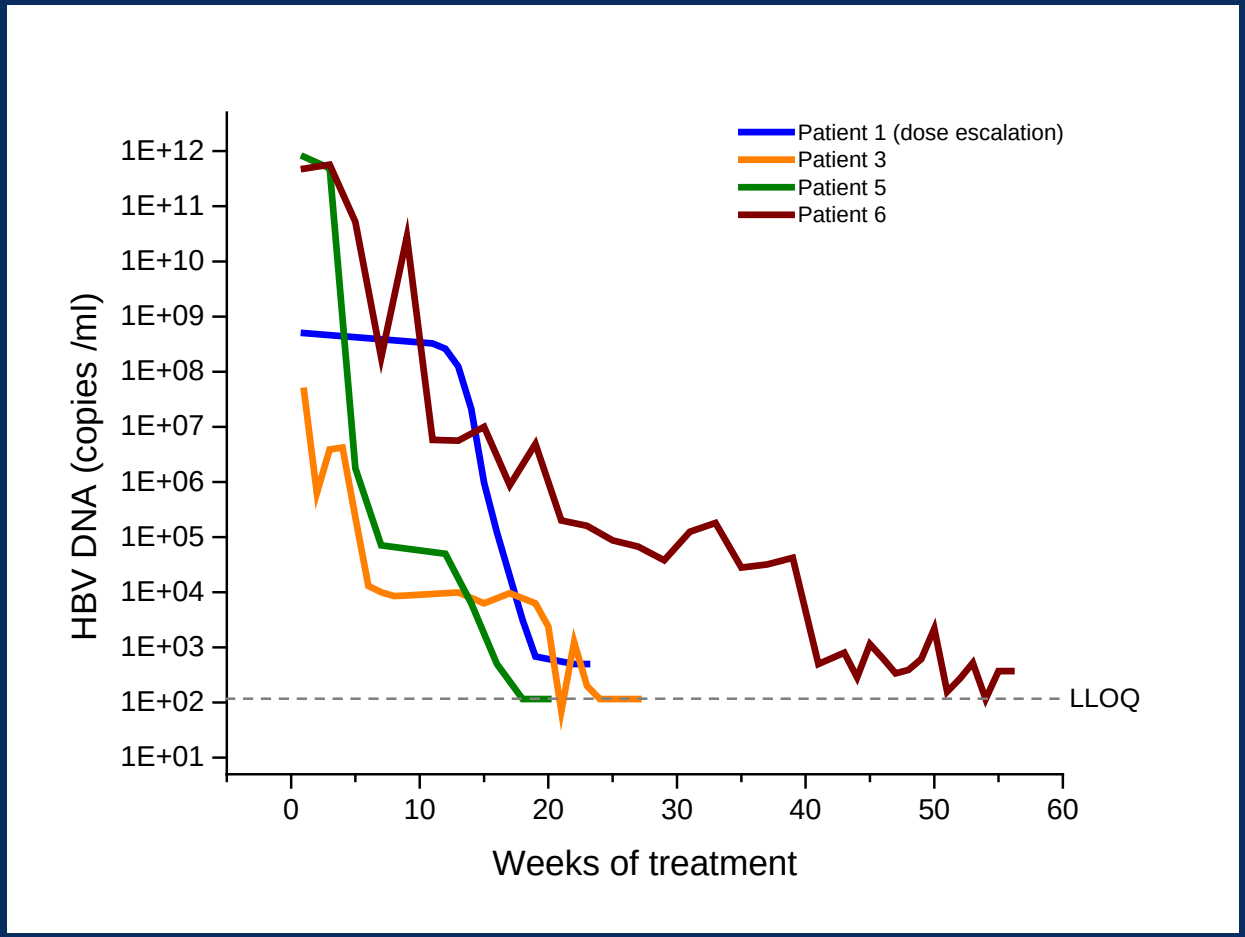
Some patients do not achieve control of infection after HBsAg clearance

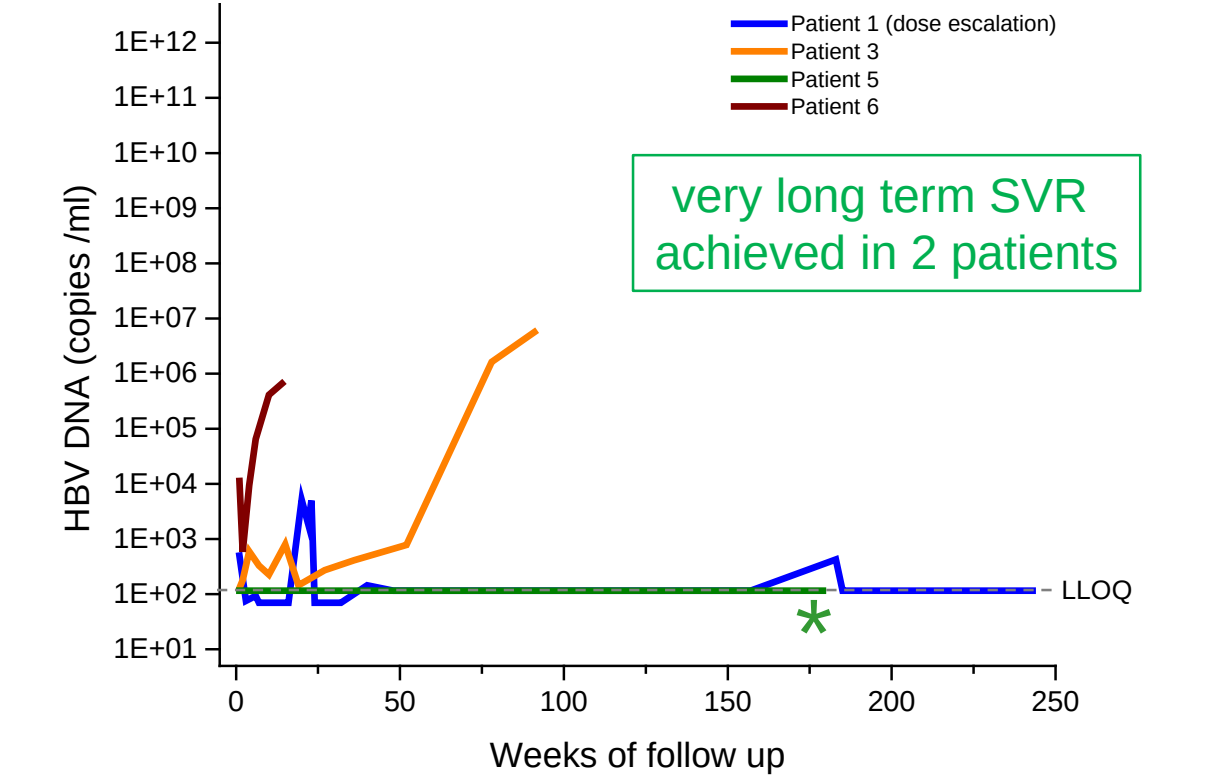


Serum HBsAg clearance is insufficient to restore immunological control of infection in many patients

Some patients can achieve control of infection after HBsAg clearance



SVR off treatment in patients achieving control of infection after HBsAg clearance

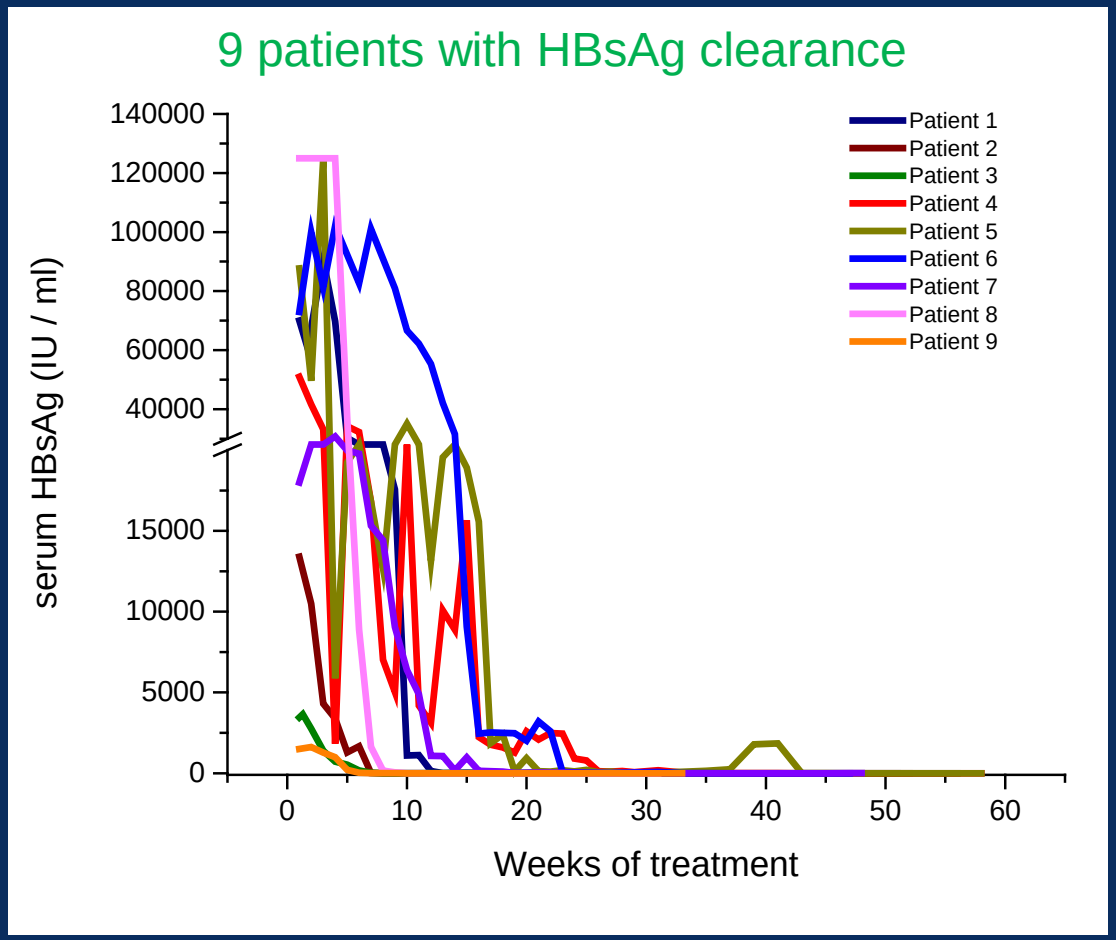


* lost contact with patient 5 after follow up week 179

Adding immunotherapy after HBsAg clearance

Effect of REP 2139-Ca on serum HBsAg levels

12 patients treated, 2 non responders, 1 with 1.1 log reduction in HBsAg



Patient	Serum HBsAg (IU / ml)		Log reduction
	Start	Lowest observed	
1	70050	0.03	6.37
2	13400	0.01	6.13
3	3450	0.03	5.06
4	50994	0.03	6.23
5	87690	0.01	6.94
6	72968	0.02	6.56
7	17988	0.03	5.78
8	125000	0.02	6.80
9	1504	0.02	4.88

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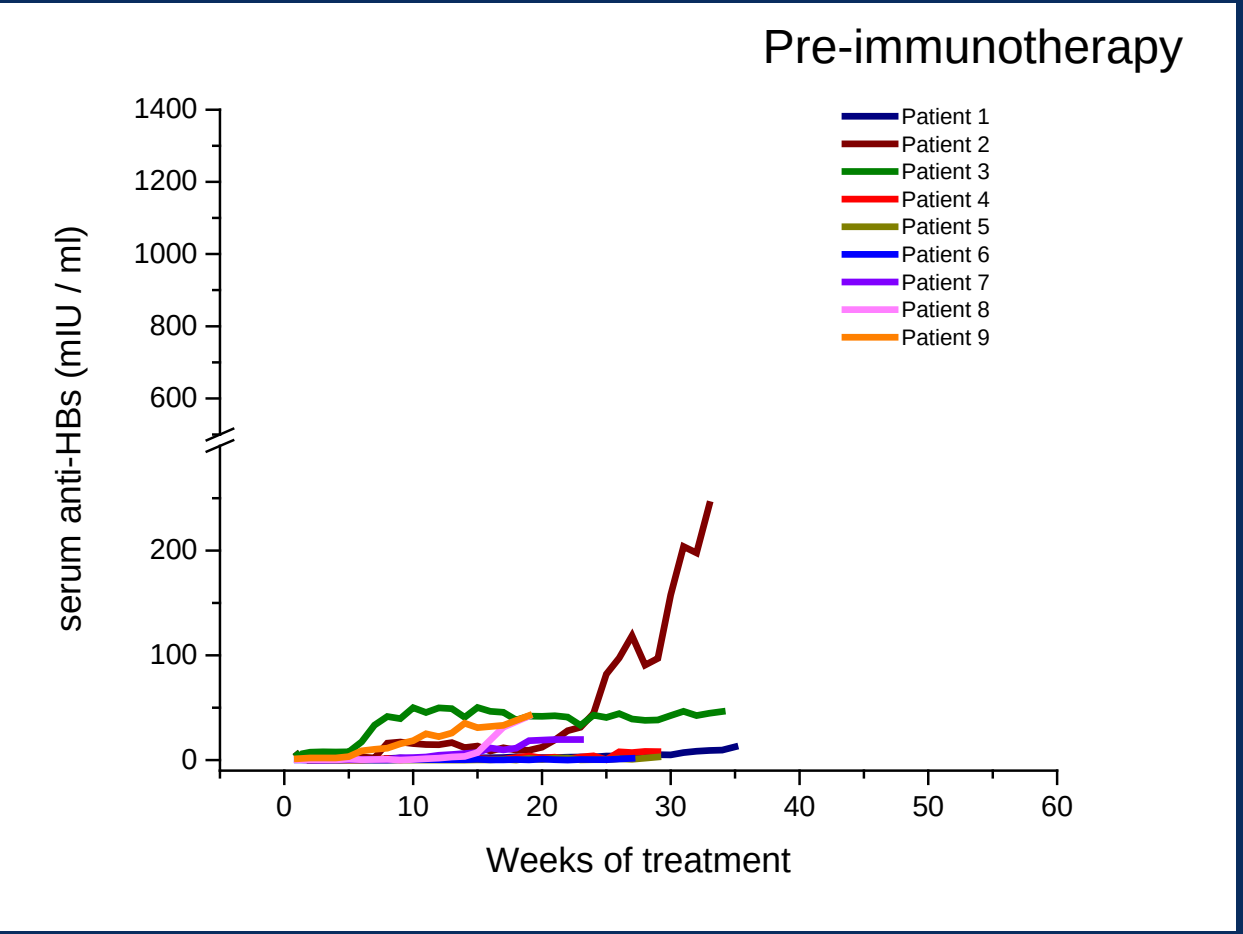
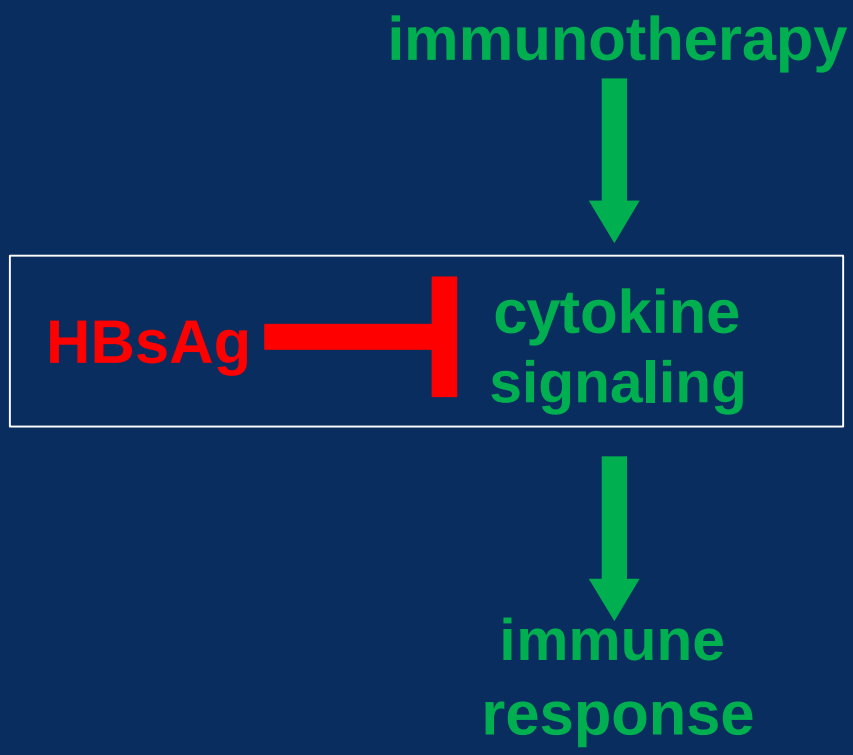
Efficacy of immunotherapy in the absence of HBsAg



Can HBsAg removal potentiate the response to immunotherapy in patients with HBV infection?



Cheng et al., 2005. Journal of Hepatology, 43:4 65-471
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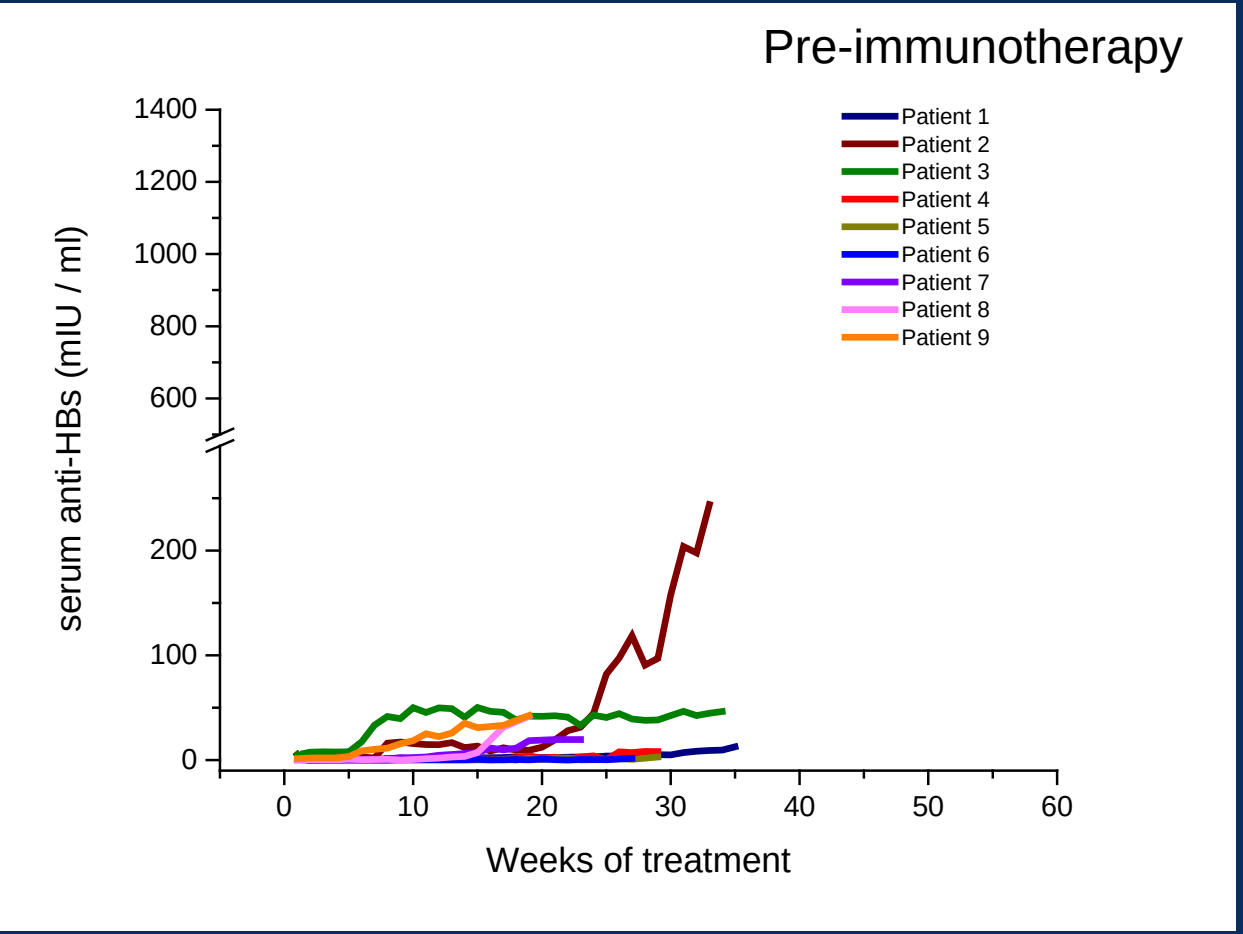
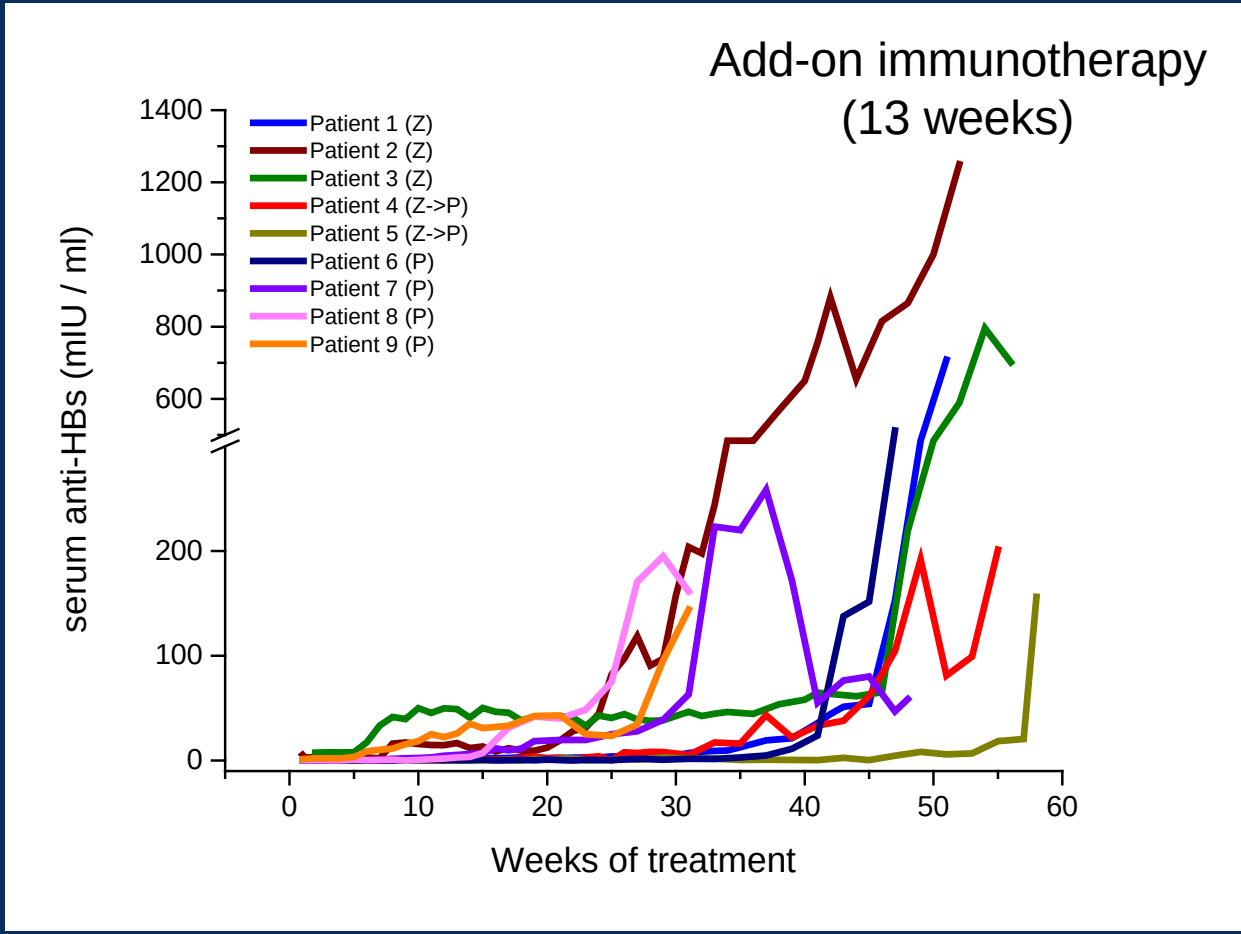
Xu et al., 2009. Molecular immunology, 46: 2640-2646

Efficacy of immunotherapy in the absence of HBsAg



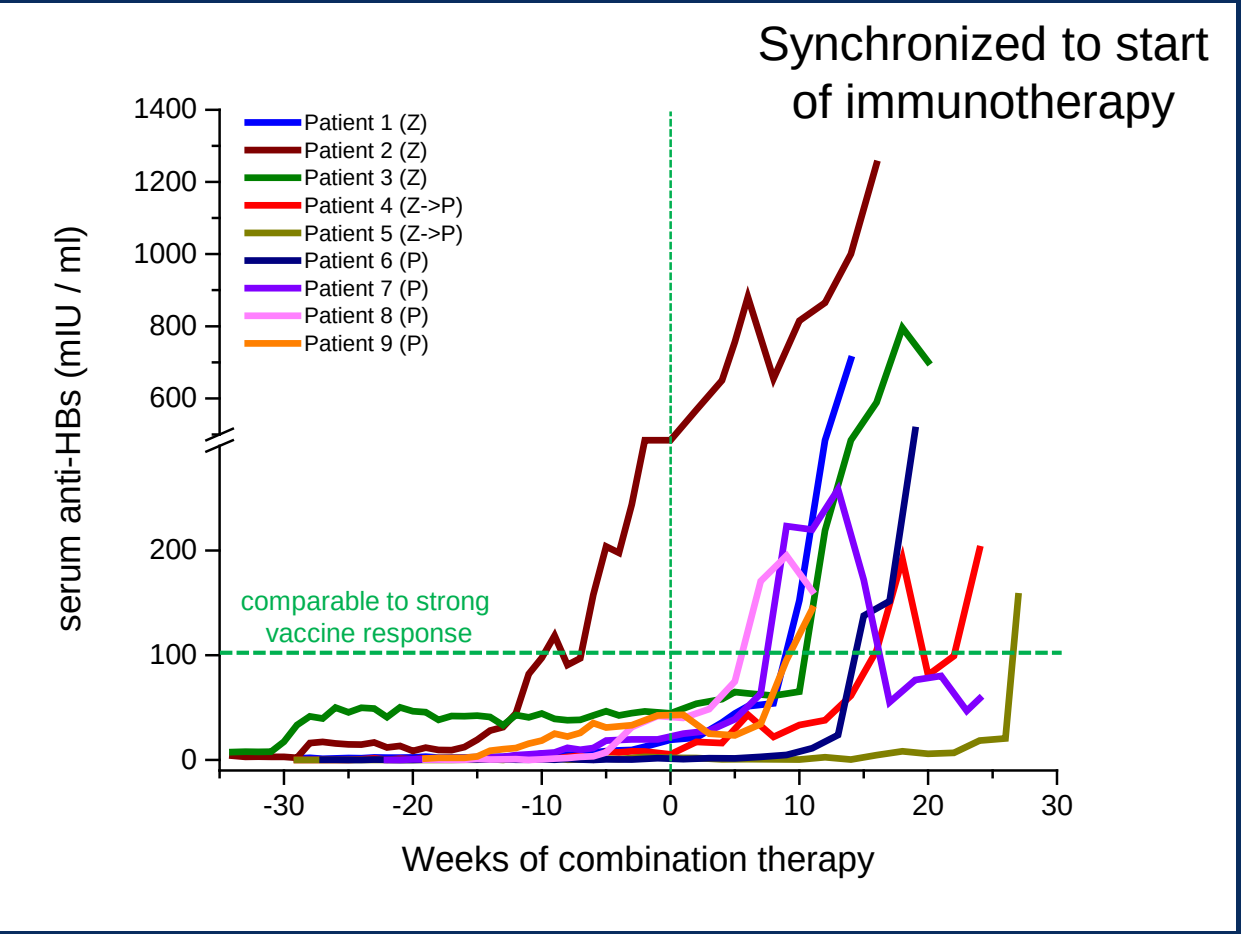
Efficacy of immunotherapy in the absence of HBsAg



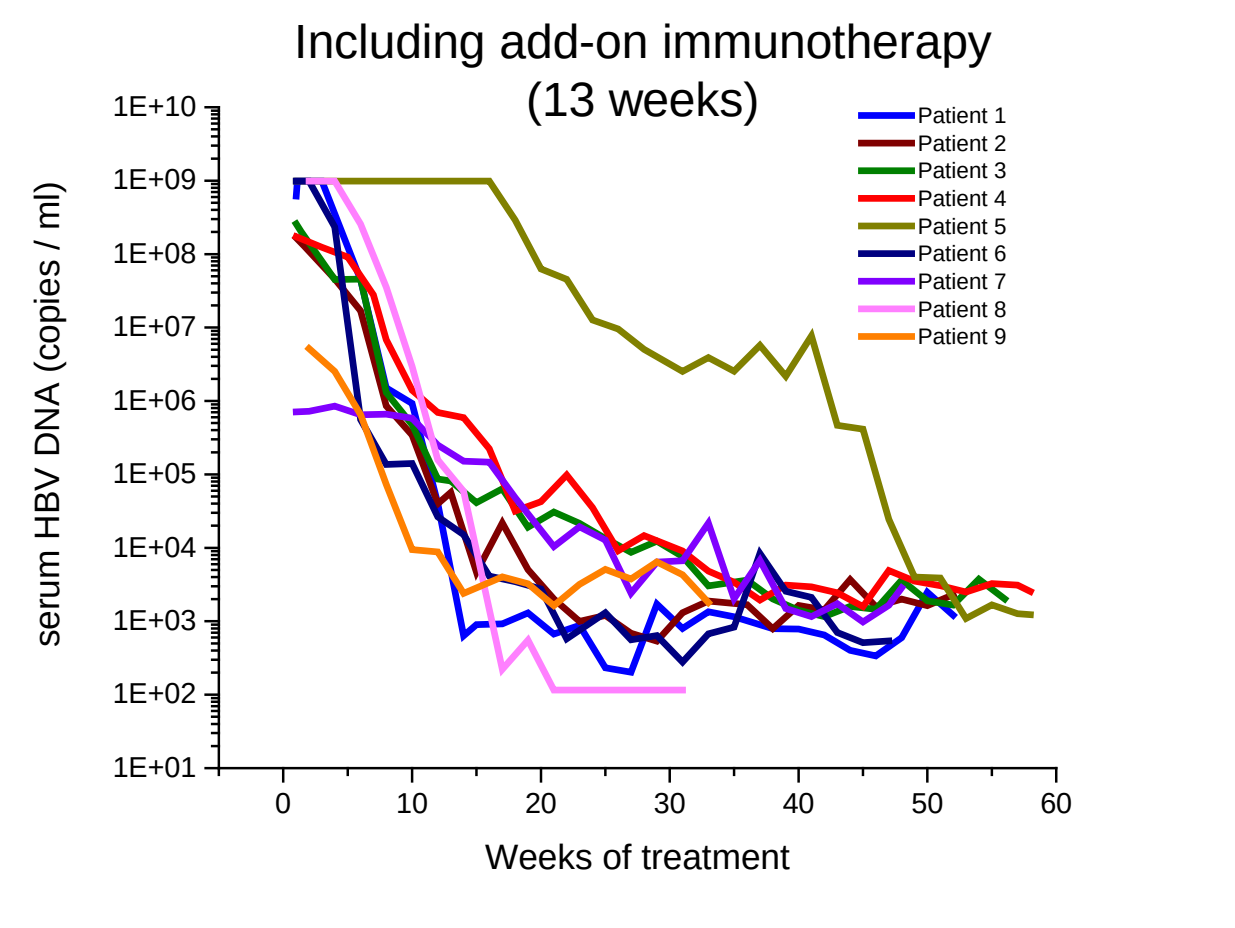
Z = Zadaxin® (thymosin α1), P = Pegasys®

serum HBsAg clearance potentiates the effect of immunotherapy

Efficacy of immunotherapy in the absence of HBsAg

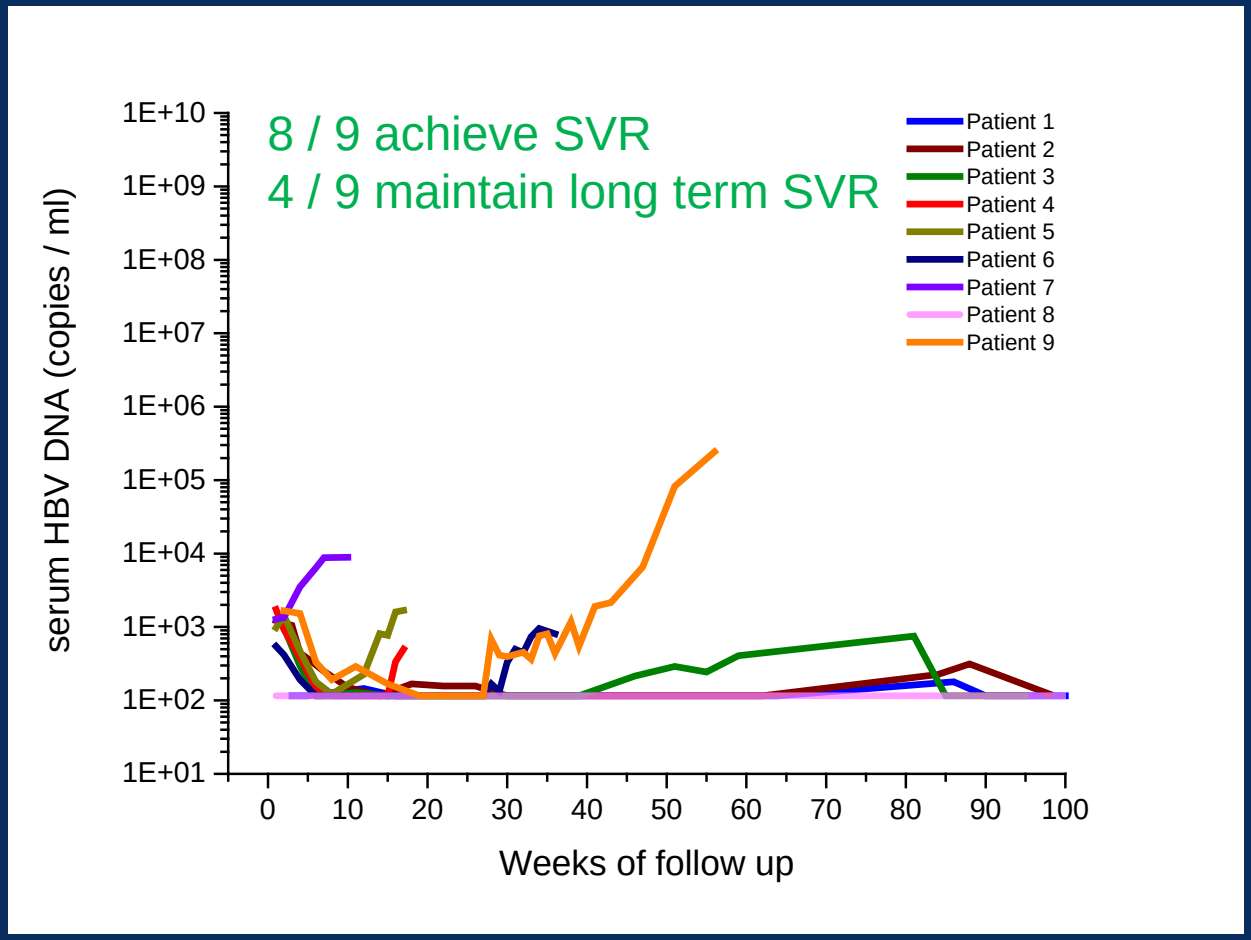


Control of HBV infection with combination therapy



replicor

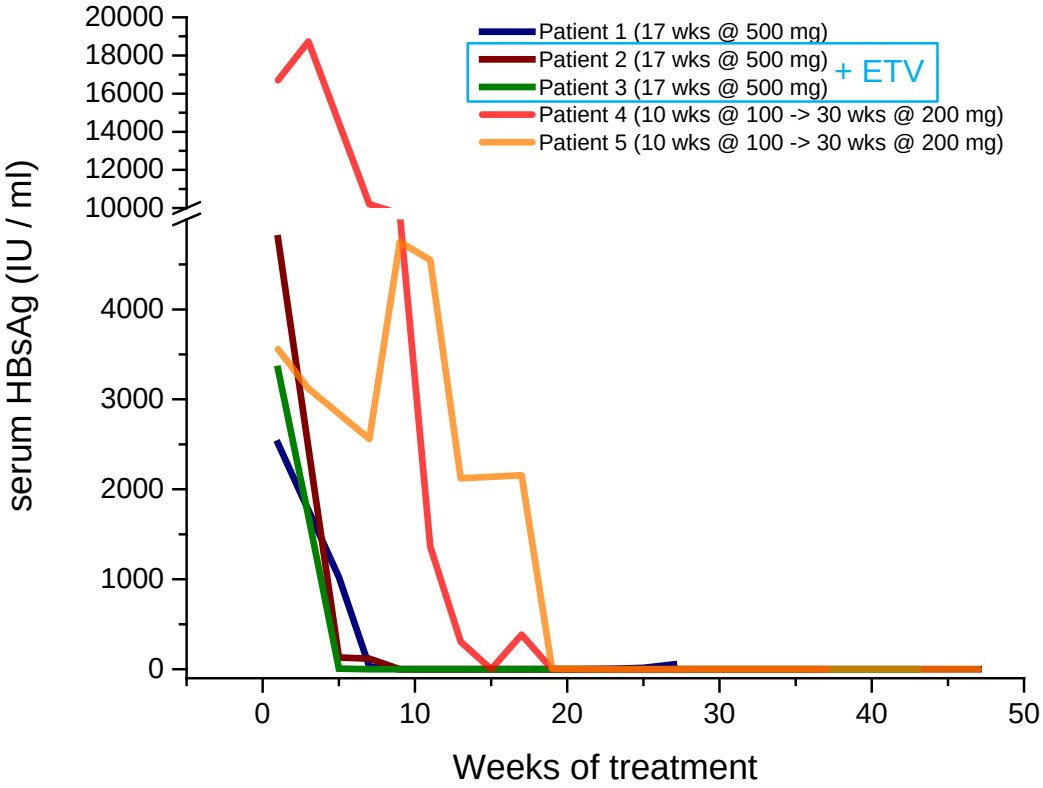
SVR off treatment in patients receiving REP 2139-Ca + short term immunotherapy



Combining REP 2139-Ca and Pegasys® at the start of treatment

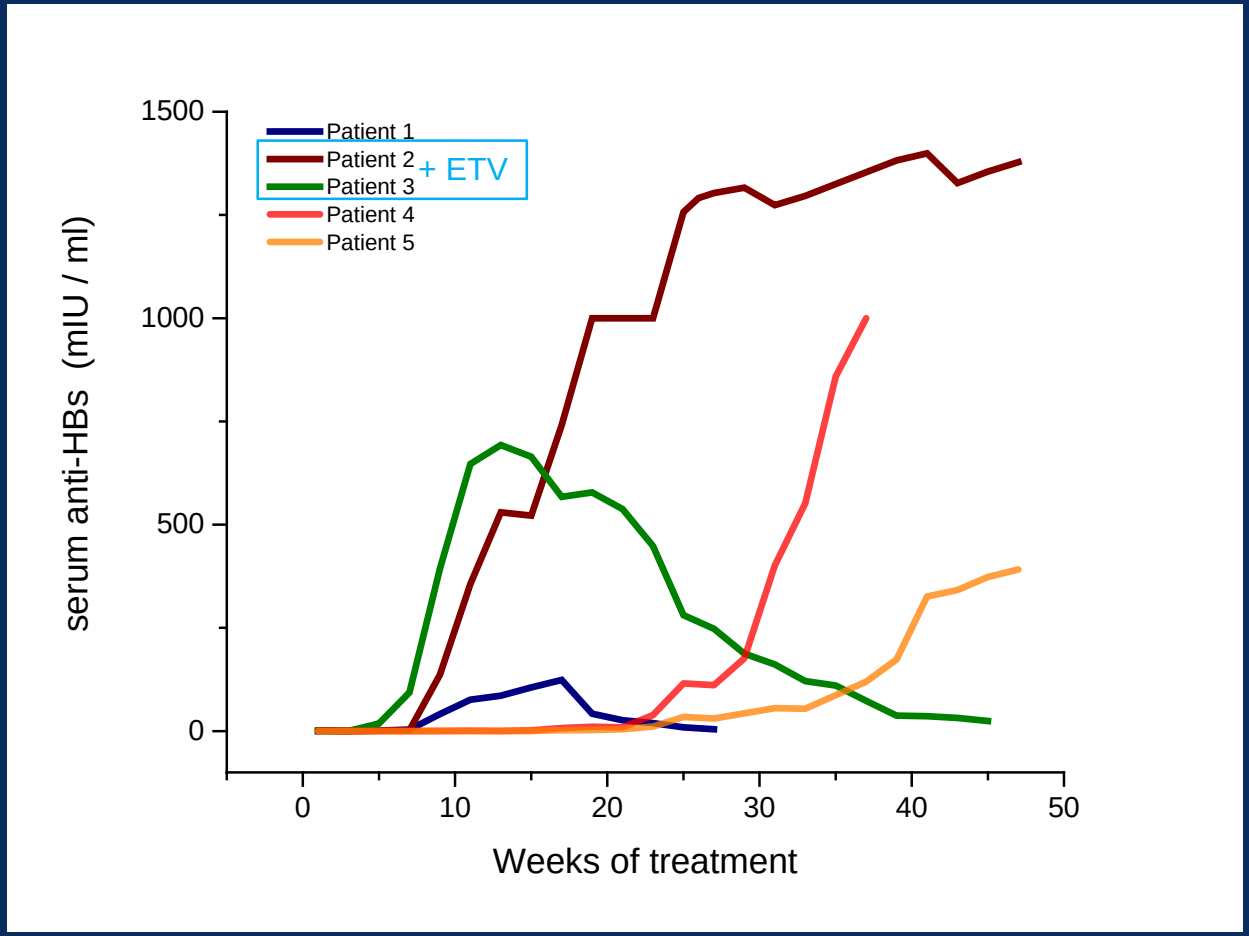
Serum HBsAg levels (up front combination therapy)

5 patients treated, all responded
(Pegasys®: 180ug qW SC for 48 weeks)

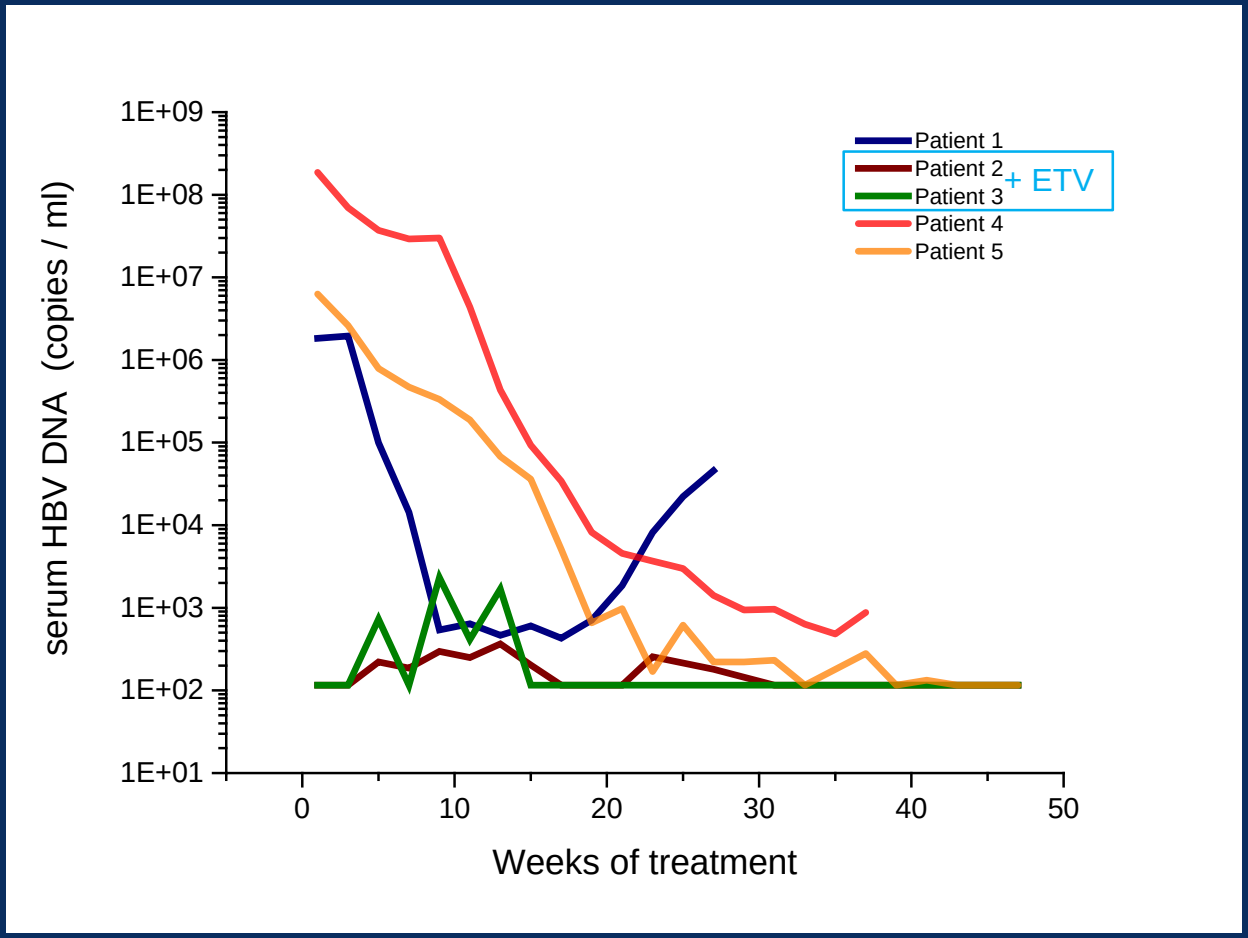


Patient	Serum HBsAg (IU / ml)		Log reduction
	Start	Lowest observed	
1	2510	0.08	4.50
2	4789	0.03	5.20
3	3338	0.01	5.52
4	16705	0.02	5.92
5	3558	0.01	5.55

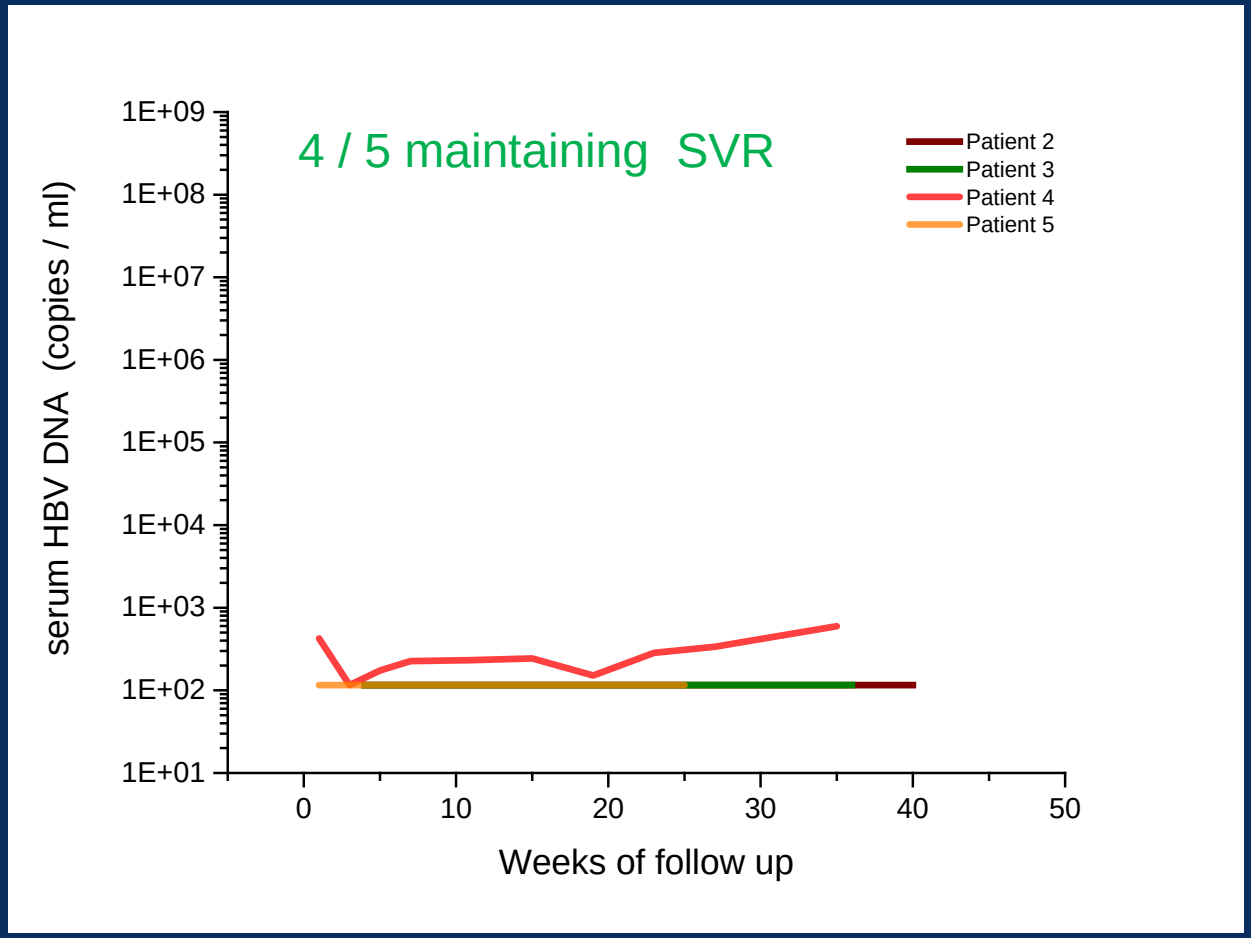
Serum anti-HBs levels (up front combination therapy)



Serum HBV DNA (up front combination therapy)



SVR off treatment
(up front combination therapy)



Summary

NAP treatment results in efficient clearance of serum HBsAg

- expected to be effective regardless of patient ethnicity, HBV genotype or infection status

HBsAg clearance is critical to achieve long term SVR

- allows for an enhanced response to immunotherapy in patients

Optimizing achievement of SVR will likely involve triple combination treatment

- triple combination NAP / immunotherapy / DAA will further accelerate cccDNA clearance by preventing cccDNA replenishment