Clearance of serum HBsAg by nucleic acid polymers suggests a critical role for HBsAg loss in establishing functional control of HBV and HDV infection

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BACKGROUND & AIMS

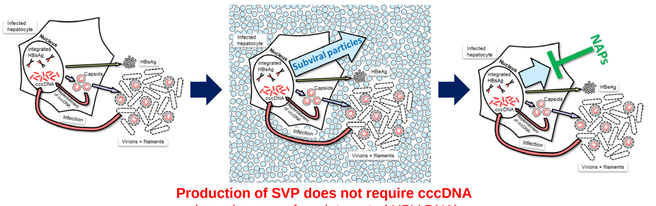
- The hepatitis B surface antigen (HBsAg) is the most abundant circulating viral protein.
- HBsAg is primarily derived from subviral particles and inhibits not only the host immune response to HBV infection but its ability to response to immunotherapy.
- Removing HBsAg from the circulation is a critical therapeutic effect which is required for the establishment of functional control that persists after the end of therapy.
- A critical question in developing an effective therapeutic regimen is: what level of HBsAg reduction will be required to achieve high rates of functional control?
- Nucleic acid polymers have the unique ability to clear serum HBsAg in a high proportion of patients.
- **An examination of the clinical effects of NAPs may provide clues to the extent of HBsAg clearance required to restore immune function and functional control of infection.**

UNDERSTANDING THE ANTIVIRAL MECHANISM OF NAPS

Classic antiviral targets:
(HBV RT, core antigen, cccDNA)

The reality of HBV infection:
Almost all HBsAg is derived from SVPs

NAPs block release of SVPs



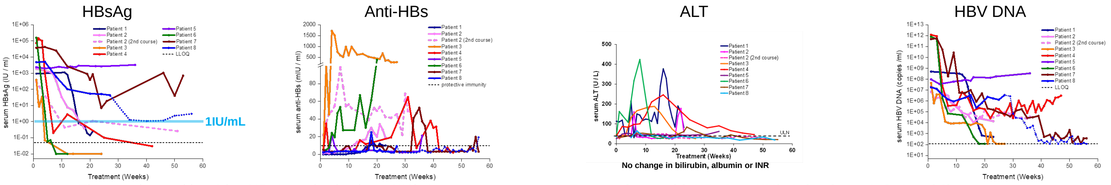
Production of SVP does not require cccDNA
(can also occur from integrated HBV DNA)

What do we currently know about NAPs?

- NAPs do not target HBsAg.
- NAP do not stimulate an antiviral immune response.
- Inhibition of HBsAg release does not lead to increased intracellular HBsAg levels.
- NAPs target a host protein(s) involved in the assembly of SVPs, leading to loss of SVP secretion.
- NAP effects (and SVP assembly) may be related to apolipoprotein metabolism.

REP 101 AND REP 102 STUDIES (HBeAg positive chronic HBV)

NAP monotherapy (REP 2055)



Three patients with > 1 log HBsAg reduction but >1IU/mL:

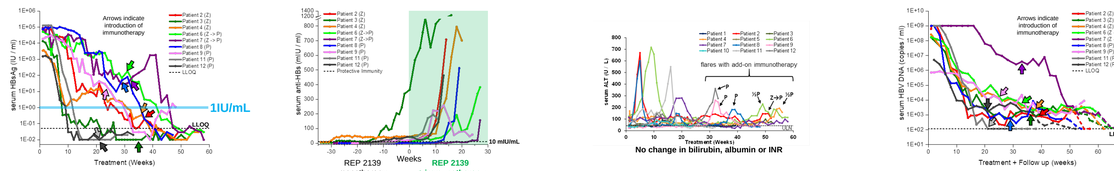
- no ALT flare
- no functional control after the end of therapy

Four patients with HBsAg <1IU/mL (Patients 1, 3, 4 and 6):

- **4/4 had ALT flare,**
- **3/4 with functional control* of infection persisting after the end of therapy up to 5 years**

*HBsAg <1IU/mL, HBV DNA < 1000 copies/mL

NAP + immunotherapy (REP 2139)

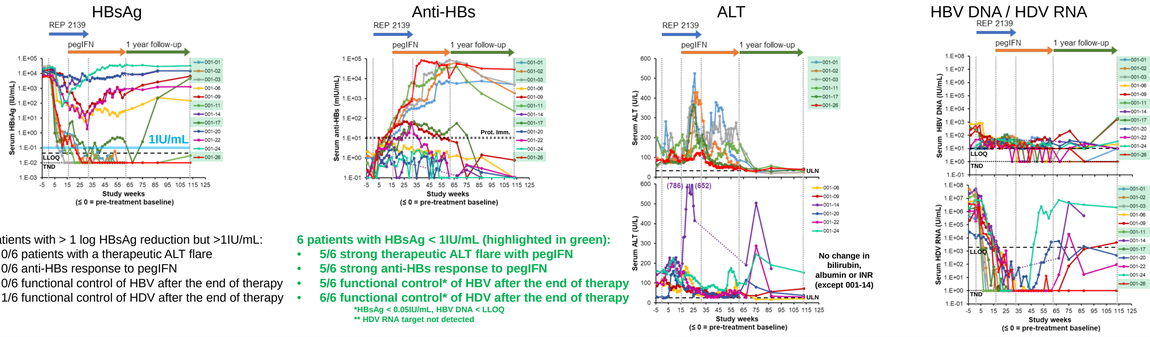


Nine patients with substantial HBsAg clearance received add-on immunotherapy
HBsAg <0.01 -180.44 IU/mL (2.45 – 7.09 log reduction from baseline)

- **HBsAg loss (<0.01-0.03 IU/ml) in 9/9 patients**
- **Rapid increase in production of anti-HBs (242-1302 IU/ml) in 9/9 patients**
- **HBV DNA became LLOQ-2400 copies/mL in 9/9 patients**
- **Functional control* established in 8/9 patients after the end of therapy (4/9 persisting to 2 years)**

*HBsAg <1IU/mL, HBV DNA < 1000 copies/mL

REP 301 STUDY (HBeAg negative chronic co-infection with HDV)



6 patients with > 1 log HBsAg reduction but >1IU/mL:

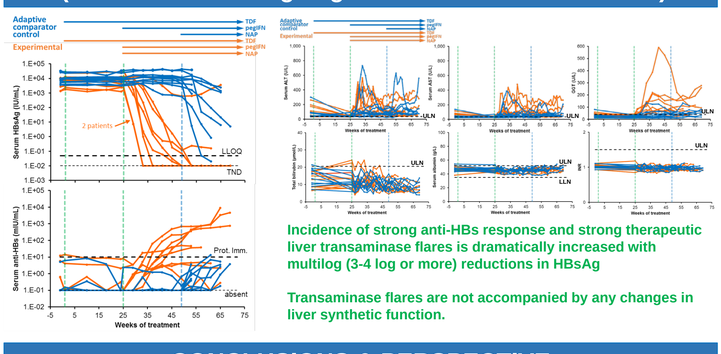
- 0/6 patients with a therapeutic ALT flare
- 0/6 anti-HBs response to pegIFN
- 0/6 functional control of HBV after the end of therapy
- 1/6 functional control of HDV after the end of therapy

6 patients with HBsAg < 1IU/mL (highlighted in green):

- **5/6 strong therapeutic ALT flare with pegIFN**
- **5/6 strong anti-HBs response to pegIFN**
- **5/6 functional control* of HBV after the end of therapy**
- **6/6 functional control* of HDV after the end of therapy**

*HBsAg < 0.05IU/mL, HBV DNA < LLOQ
** HDV RNA target not detected

REP 401 STUDY (REP 2139 in HBeAg negative chronic HBV infection)

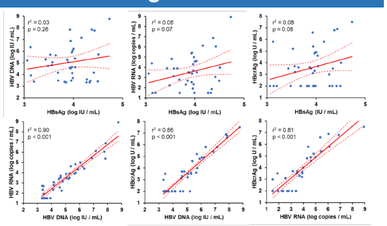


Incidence of strong anti-HBs response and strong therapeutic liver transaminase flares is dramatically increased with multilog (3-4 log or more) reductions in HBsAg

Transaminase flares are not accompanied by any changes in liver synthetic function.

REP 401 STUDY HBV RNA / HBcrAg ANALYSIS

Pre-treatment regression analysis on all 40 patients in the REP 401 demonstrated no relationship between serum HBsAg and HBV DNA, HBV RNA or HBcrAg (right, top row). HBV DNA, HBV RNA or HBcrAg levels were all highly related to each other (right, bottom row).



Response after completion of 24 weeks of TDF followed by 24 weeks of TDF + pegIFN in 20 control patients.

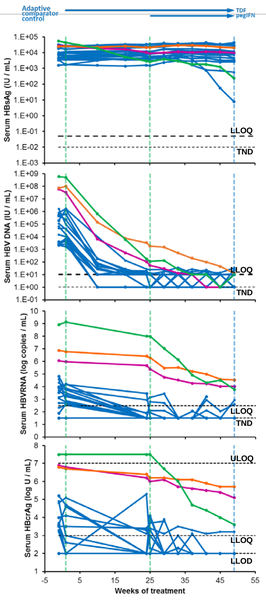
- HBV RNA and HBcrAg levels continually decline with the introduction of peg-IFN

  HBV RNA becomes TND in 14/20 patients
  HBcrAg becomes < LLOD in 15/20 patients
  HBsAg reduction > 1 log in only 3/20 patients

- weak or absent HBsAg response even in patients with continuous declines from high pre-treatment HBV RNA and HBcrAg (green, pink and orange lines)

With the introduction of pegIFN, continuous HBV RNA and HBcrAg declines are observed with little change in HBsAg. These effects suggest that pegIFN is inactivating cccDNA but this inactivation is not affecting HBsAg levels.

These observations are consistent with the bulk of HBsAg being derived from integrated HBV DNA, which is cccDNA independent.



CONCLUSIONS & PERSPECTIVE

- NAPs reliably eliminate HBsAg in HBV monoinfection (HBeAg+ and HBeAg-) and HBV/HDV coinfection.
- HBsAg reductions ≤ 1 log from baseline are not accompanied by any other antiviral response.
- Multilog HBsAg reductions > 1log but still >1IU/mL are accompanied by unmaksing of anti-HBs and reductions in HBV DNA but appear insufficient to create a permissive environment for immunotherapy to function efficiently.
- HBsAg reduction to ~1IU/mL appears required for efficient functioning of immunotherapy:
  - ✓ Multilog increases in circulating anti-HBs
  - ✓ Onset of strong, therapeutic transaminase flares
  - ✓ Establishment of functional control of HBV and HDV infection persisting after the end of therapy.
- In HBeAg- chronic HBV infection, most HBsAg may derive from integrated HBV DNA.
- Immunotherapies or agents directly or indirectly targeting cccDNA or virion production may have limited impact on HBsAg derived from integrated HBV DNA.