Analysis of HBsAg levels, HBsAg immune complexes, HBV pregenomic RNA and HBcrAg dynamics during and after NAP-based combination therapy in the REP 301-LTF and REP 401 studies.

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INTRODUCTION

In HBeAg negative HBV mono-infection, NAP combination therapy achieved 78% virologic control (HBV DNA ≤ 2000 IU/mL, normal ALT [VC]) with 39% further achieving functional cure (HBsAg < 0.05 IU/mL, HBV DNA target not detected, normal ALT [FC]) (REP 401 study, NCT02565719). Retrospective inclusion of participants with HBeAg negative HBV / HDV co-infection receiving suboptimal NAP-based combination therapy (REP 301 study, NCT02233075 and REP 301-LTF study, NCT02876419) yielded combined HBV outcomes of 18/52 (35%) FC, 19/52 (36%) VC and 15/52 (29%) rebound (R). The goal of this study was to analyze the dynamics of S-HBsAg, M-HBsAg and L-HBsAg during and after NAP therapy in the REP 301 / 301-LTF and 401 studies.

AIM

The goal of this study was to analyze the relationship between HBV outcome and experimental virologic markers of HBV infection.

METHODS

Frozen serum samples (n=1153) from all 52 participants in the REP 301 / REP 301-LTF and REP 401 studies were analyzed by the following:

1. Abbott ARCHITECT HBsAg NEXT (analytical sensitivity 0.005 IU/mL)
2. Abbott RUO assay for HBsAg/anti-HBs immune complexes (HBsAg IC)
3. Abbott RUO assay for pregenomic HBV RNA (pgRNA)
4. Fujirebio HBcrAg (LLOQ 3log$_{10}$ U/mL)

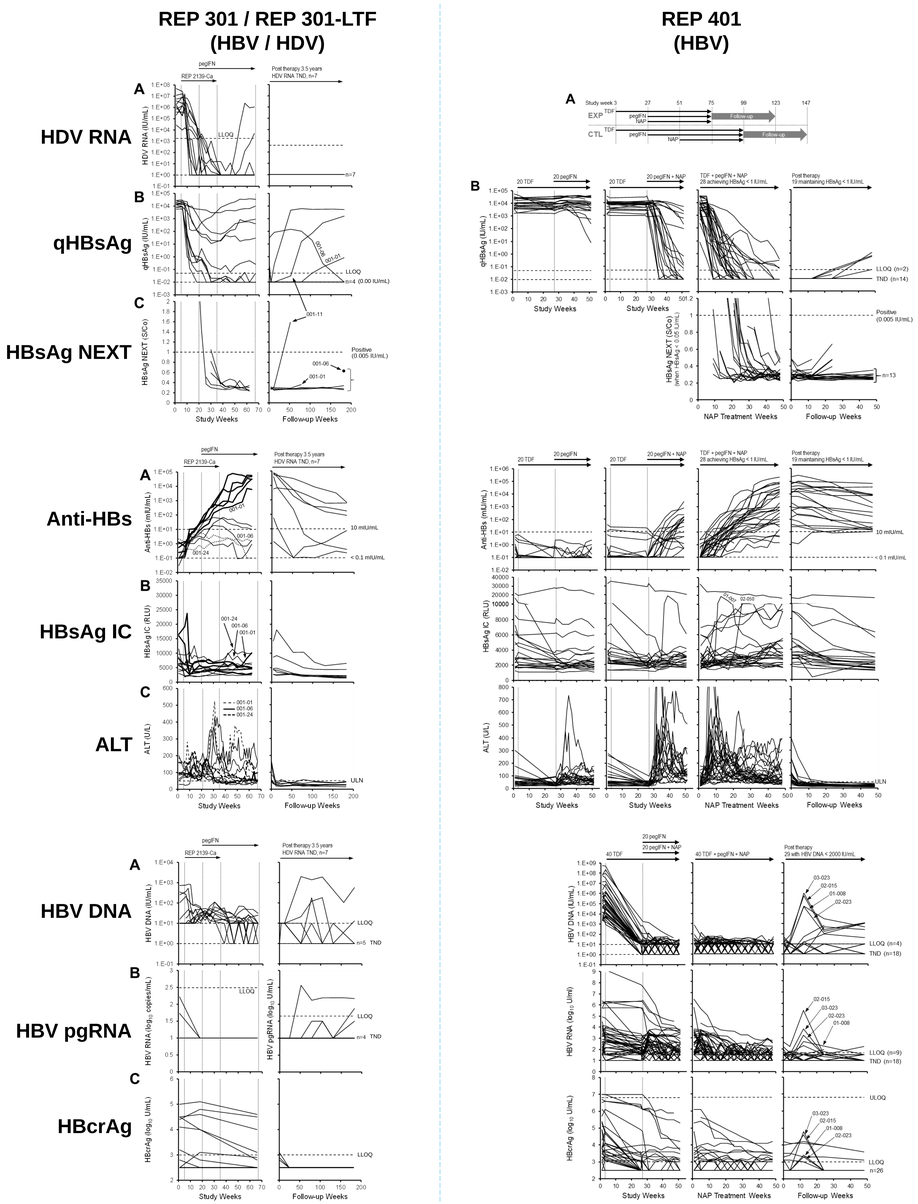

Figure 1. Individual patient responses during treatment and follow-up for HDV RNA (REP 301/REP 301-LTF only), qHBsAg, HBsAg NEXT, anti-HBs, HBsAg IC, ALT, HBV DNA, HBV pgRNA and HBcrAg are provided for the REP 301/REP 301-LTF trials (left group) and REP 401 trial (right group). Response data for rebound participants (not shown) indicated rebound or persistent levels for all viral parameters. Treatment paradigms are indicated at the top of each group.

Figure 1 Summary

- In all participants with HBsAg clearance during therapy < 0.05 IU/mL, HBsAg becomes < 0.005 IU/mL.
- HBsAg IC generally decline therapy and are not correlated with anti-HBs or ALT
- HBV pgRNA and HBcrAg universally decline during therapy

At the end of follow-up, all participants with functional cure of HBV display the following characteristics:

- HBsAg < 0.005 IU/mL
- HBsAg seroconversion
- No apparent HBsAg IC
- HBV DNA TND
- HBV pgRNA TND
- HBcrAg < LLOQ
- Normal ALT

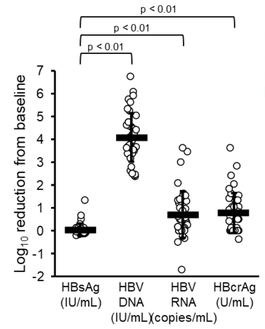

Figure 2. Antiviral responses during 24 weeks of TDF monotherapy in the REP 401 study.

CONCLUSIONS

Functional cure of HBV infection following NAP-based combination therapy is profound, with HBsAg < 0.005 IU/mL and both HBV RNA and HBcrAg < LLOQ. NEXT negativity and the absence of HBsAg IC RLUs in the positive range at the end of follow-up in participants with functional cure suggests efficient reduction in integrated HBV DNA.

TDF monotherapy is accompanied by inactivation / clearance of cccDNA, consistent with the effects of NUC monotherapy in other studies[5]. These effects may be driven by the immunostimulatory properties of NUCs[6-13].

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