AASLD Nov. 4-8, 2022

The Liver Meeting®

WASHINGTON D.C.

The Best of The Liver Meeting®

VIRAL HEPATITIS

About the program:

Best of The Liver Meeting 2022 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

Use of these slides:

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Tenofovir-DF therapy prevents hepatitis B vertical transmission in highly viremic mothers without HBV immunoglobulin (HBIG) for infants

Objective

Maternal tenofovir disoproxil fumarate (TDF) therapy with an infant's immunoprophylaxis is recommended for highly viremic mothers with CHB, but HBIG is not widely available in most countries.

Methods

- We randomized 280 HBeAg+ CHB mothers (HBV DNA levels >200,000 IU/ml) at a multicenter RCT (1:1 ratio) in China, to receive TDF 300mg QD at the gestational week 16 (experimental group) or week 28 (comparator group) until delivery.
- All infants received a series of HBV vaccines (0, 1, and 6 months), but birth-dose HBIG was only administered to those in the comparator group.
- We assessed HBV transmission rates (percentage of infants with HBsAg+ or HBV DNA >20 IU/mL) at the age of 28 weeks (primary outcome) and safety.

Main Findings

A total of 265/280 mothers (Table 1) and 269/273 infants completed the trial (95% retention). The median duration of the TDF treatment was 23 weeks and 11 weeks for mothers in the experimental and comparator groups (p <0.001), respectively. At delivery, the maternal median [IQR] HBV-DNA level (log_{10} IU/ml) was significantly lower in the experimental group (2.4 [1.9, 3.0] vs 3.6 [2.9, 4.6]; p <0.001).

- The per-protocol, last observation carried forward, and sensitivity analyses showed that transmission rates did not differ significantly between groups (Figure 1).
- The congenital defect rates were similar between groups (Experimental-2.3% [3/131] vs Comparator-6.3% [9/142; p=0.10).
- Other maternal and infant safety parameters were also comparable between the two groups.

Conclusions

Maternal TDF therapy from gestational week 16 in combination with infants' HBV vaccinations reduced HBV vertical transmission to 2%, which had similar efficacy and safety outcomes compared to the current standard of care.

Table 1. Maternal variables at baseline and infant characteristics at birth

Maternal Variables, median [IQR] #	*Entire cohort (n=280)*	*Experimental (n=140)*	*Comparator (n=140)*
Age at enrollment – year	28.22 ± 3.09	28.41 ± 3.15	28.02 ± 3.03
Gravidity – No.	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
HBV DNA – log_{10} IU/ml	8.23 (7.98, 8.42)	8.23 (7.92, 8.42)	8.23 (8.02, 8.40)
Alanine aminotransferase – U/l	20.15 (16.00, 28.90)	20.40 (16.00,31.68)	20.00 (15.05, 28.00)
eGFR – ml/min	189.55 (166.14, 214.45)	188.81 (165.21, 213.95)	190.73 (166.47, 216.53)
Infant Characteristics at Birth #	*n=273*	*n=131*	*n=142*
Male sex – No. (%)	133/273 (48.7)	59/131 (45.0)	74/142 (52.1)
Body weight <2500 g – No. (%)	9/273 (3.3)	4/131 (3.1)	5/142 (3.5)
Body length – cm	50.00 (49.00, 50)	50.00 (49.00, 50.00)	50.00 (48.38, 50.00)
Head circumference – cm	34.00 (32.00, 34.50)	34.00 (32.00, 34.50)	34.00 (32.50, 34.00)
APGAR score at 1 min	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)
Detectable HBV DNA at birth – No. (%) ¶	0 / 273 (0)	0 / 131 (0)	0 / 142 (0)

When comparing variables between the experimental group and comparison group, p values were all >0.05.
¶ LLOQ = 20 IU/ml.

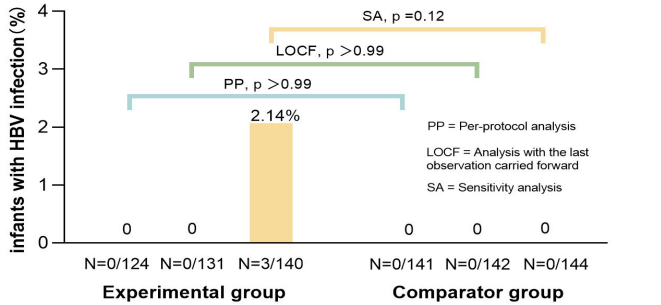

Figure 1. Mother-to-child transmission rates at the age of 28 weeks

Pan C, et al., Abstract 1.

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Short duration combination regimens of VIR-2218 plus VIR-3434 achieve mean HBsAg reductions >2.5 log_{10} IU/mL

Objective

Evaluate the safety, tolerability, and antiviral activity of VIR-2218 in combination with VIR-3434 in virally suppressed participants with chronic HBV infection.

Methods

Open-label, phase 2 study of combination regimens (Figure) of the siRNA VIR-2218 and the monoclonal antibody VIR-3434 in virally suppressed adults with chronic HBV infection.

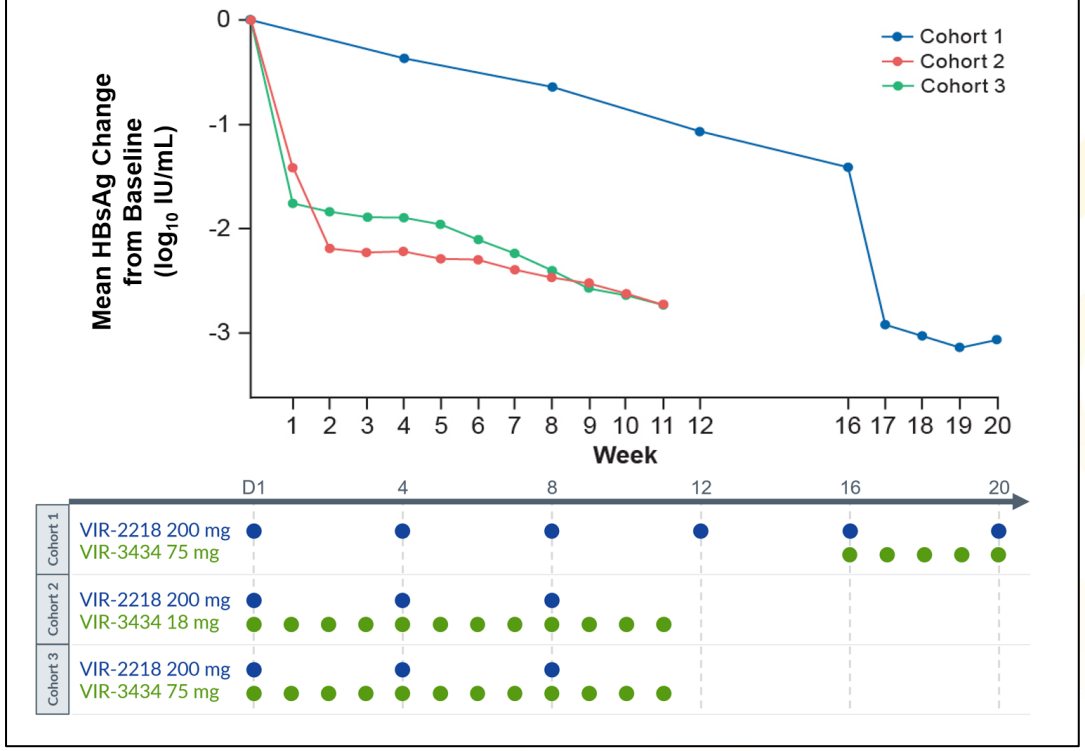
Main Findings

- The majority of participants were HBeAg-negative at baseline, and median age was 48-51 years
- Mean HBsAg reductions from baseline at end of treatment were >2.5 log_{10} IU/mL in all cohorts (Figure)
- All participants achieved HBsAg reductions > 1.5 log_{10} IU/mL from baseline and absolute HBsAg levels < 100 IU/mL at end of treatment
- Most adverse events were mild or moderate and unrelated to study treatment, and no serious adverse events were reported

Conclusions

Based on these preliminary data, short duration regimens of VIR-2218 plus VIR-3434 were generally well tolerated and associated with substantial reductions in HBsAg; longer durations of treatment are being evaluated in this ongoing trial

Figure. HBsAg Change from Baseline by Cohort



Gane E, et al., Abstract 18.

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Preliminary 48-week safety and efficacy data of VIR-2218 alone and in combination with pegylated interferon alfa in participants with chronic HBV infection

Objective

Evaluate the safety and efficacy of multiple doses of VIR-2218 with or without PEG-IFNα in virally-suppressed participants with chronic HBV infection

Methods

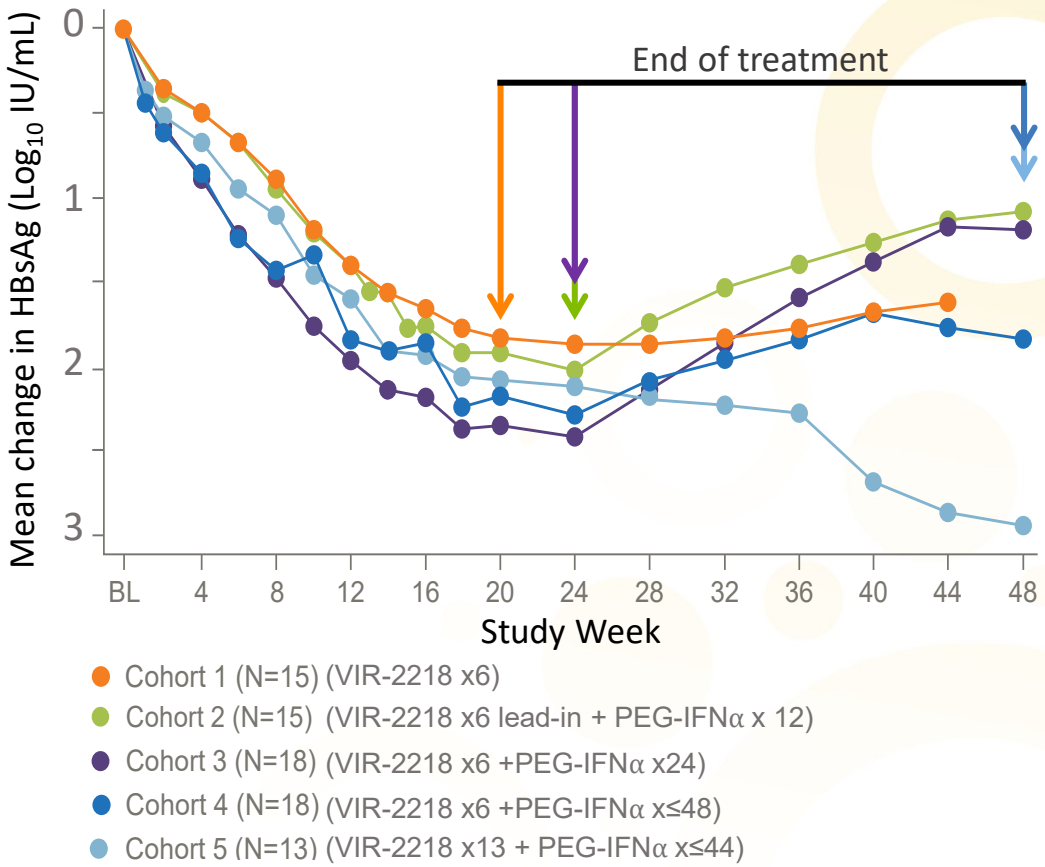
Non-cirrhotic participants with chronic HBV infection on NRTIs were enrolled into 1 of 5 cohorts (C) to receive 200 mg VIR-2218 subcutaneous (SC) every 4 weeks ± PEG-IFNα 180 µg SC weekly (figure)

Main Findings

- Participants receiving longer duration of VIR-2218 + PEG-IFNα had greatest declines from baseline HBsAg (log_{10} IU/mL) levels at Week 48 (C5 -2.9 ± 1.36)
- To date, 10 participants receiving VIR-2218+PEG-IFNα achieved HBsAg seroclearance, 9 accompanied by anti-HBs
  - 30.8% (4/13) participants in Cohort 5 achieved HBsAg seroclearance
- Most adverse events (AEs) reported were grade ≤ 2

Conclusions

- Longer duration (48 weeks) of VIR-2218 + PEG-IFNα treatment achieved higher rates of HBsAg seroclearance with anti-HBs seroconversion by end of treatment (30.8%).
- Antiviral activity of VIR-2218 may be potentiated by PEG-IFNα, supporting future evaluation of combination with immunomodulators



Yuen M-F, et al., Abstract 19.

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High prevalence of Hepatitis Delta Virus infection among ethnically diverse, urban, safety-net populations with Chronic Hepatitis B

Aim

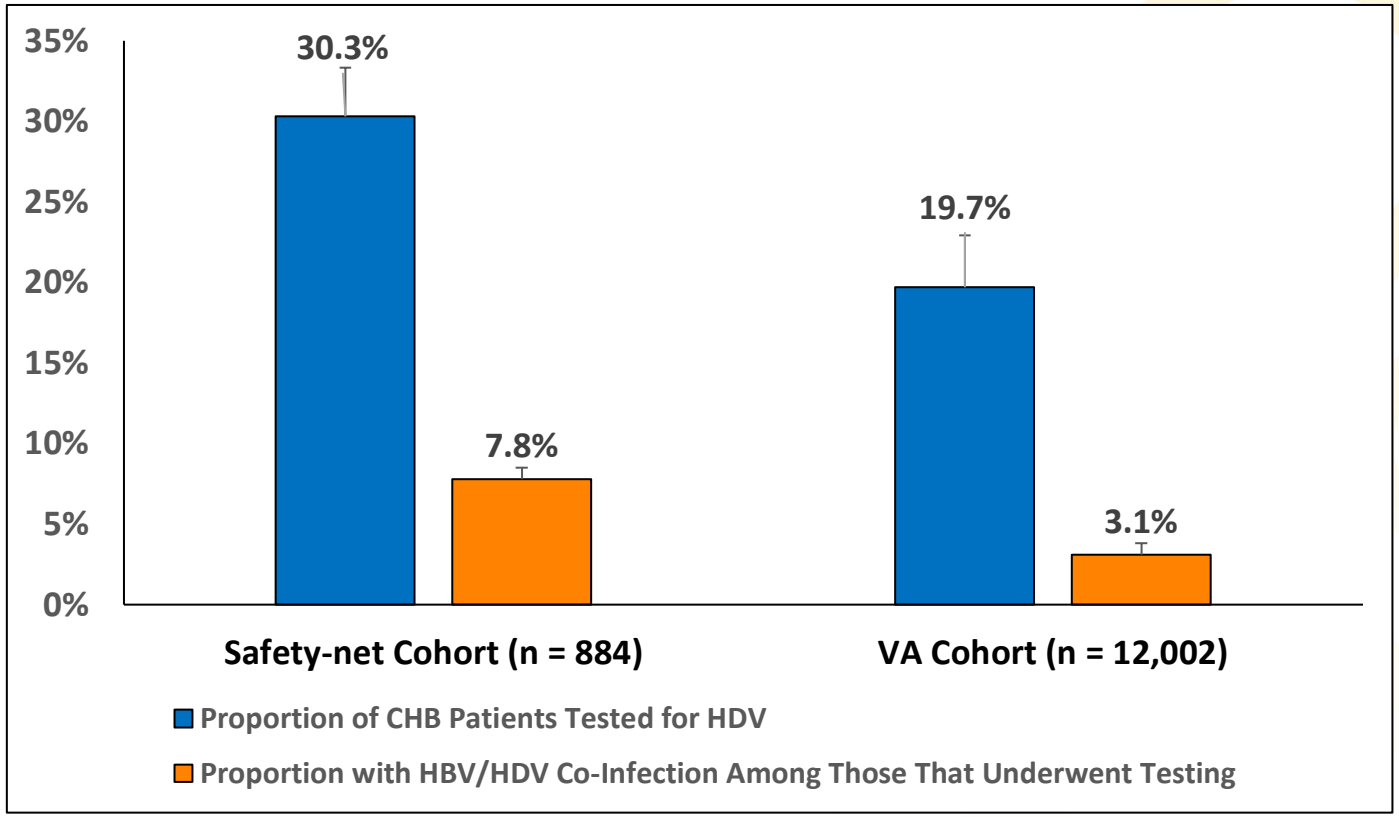
To evaluate HDV testing practices and HDV prevalence among a large, urban safety-net cohort of chronic hepatitis B (CHB) patients and a national Veterans Affairs (VA) cohort of CHB patients.

Methods

Retrospective cohort study of two unique populations of adults with CHB from 2010 to 2021 to evaluate the proportion of patients that have been tested for HDV (HDV Ab or PCR), and among those that were tested, the proportion with concurrent HDV infection (positive for either HDV Ab or PCR).

Conclusions

Among two distinct U.S. CHB cohorts, HDV testing ranged from 19.7% to 30.3%, and among those that underwent testing, HBV/HDV prevalence ranged from 3.1% to 7.8%.



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Wong R, et al., Abstract 20.

GS-2829 and GS-6779 HBV therapeutic vaccine generates robust CD8 T cell responses and anti-HBsAg antibodies

Objective

Generate an HBV therapeutic vaccine that induces both anti-HBsAg antibodies and strong genotype cross-reactive CD8 T cell responses.

Methods

Variants of HBV core, polymerase, and HBsAg were expressed in arenavirus vectors and screened for magnitude and genotype cross-reactivity of response.

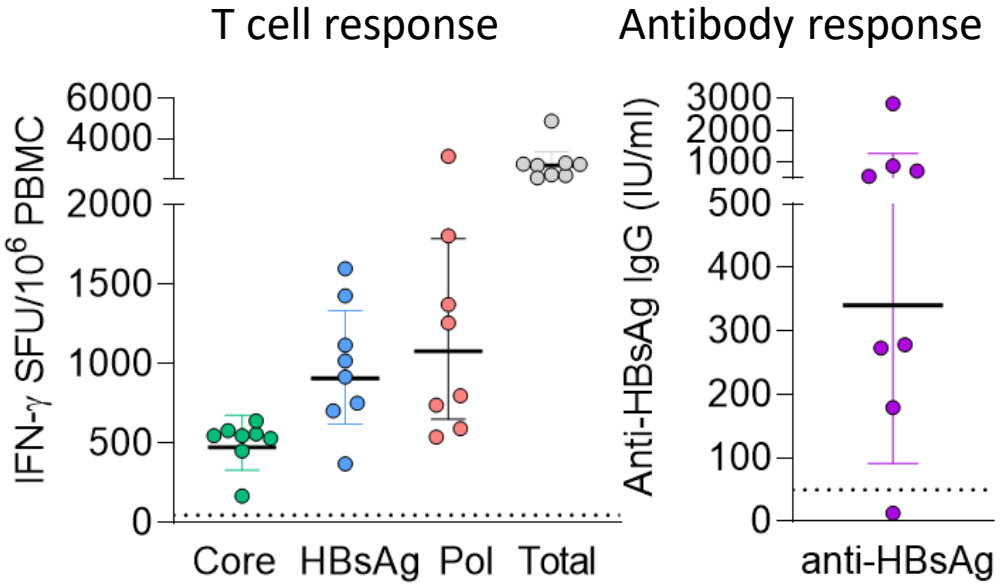
Main Findings

Immunization with both Pichinde (GS-2829) and LCMV (GS-6779) vectors encoding core, HBsAg, and an inactivated polymerase achieved consistent high-magnitude, genotype cross-reactive immune responses in preclinical studies.

Conclusions

Due to its promising preclinical profile, GS-2829 + GS-6779 immunization has the potential to serve as a backbone component of an HBV cure combination regimen.

Immunogenicity in cynomolgus macaques



Balsitis S, et al., Abstract 23.

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Low level of hepatitis B viremia increases the risk of hepatocellular carcinoma in patients with untreated compensated cirrhosis

Objective

To evaluate long-term outcomes of untreated chronic hepatitis B (CHB) patients with compensated cirrhosis and low-level viremia (LLV; HBV DNA 15–2,000 IU/mL)

Methods

- Historical cohort study of 627 CHB untreated patients with compensated cirrhosis in Korea between 2007 and 2021
- The **risk of hepatocellular carcinoma (HCC)** was compared **between patients with LLV and undetectable HBV DNA**.

Main Findings

- Patients with LLV had a significantly higher risk of developing HCC than those with undetectable HBV DNA.
- More frequent episodes of LLV, a greater median HBV DNA level, and a higher peak HBV DNA level during the observational period were associated with an increased risk of HCC.

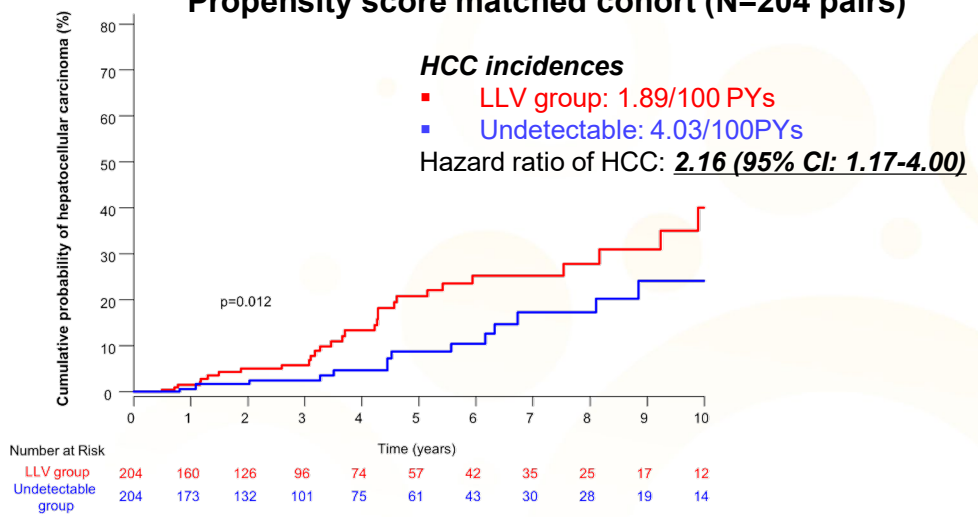
Conclusions

- Compared with patients with undetectable HBV DNA, those with compensated cirrhosis and ***LLV had a significantly higher risk of HCC***.
- Antiviral treatment should be advised for CHB patients with compensated cirrhosis and LLV.

Entire population (N=627)

	Multivariable analysis	
Variable	**AHR (95% CI)**	**P–value**
Based on baseline HBV DNA		
Undetectable HBV DNA	1 (reference)	***0.002***
Low-level viremia	***2.36 (1.36–4.11)***	
Age, per 1 year increase	1.05 (1.02–1.08)	<0.001
Sex, male	2.13 (1.14–3.97)	0.01
Family history of HCC	1.83 (0.83–4.01)	0.13
Diabetes	0.93 (0.50–1.72)	0.82
Hypertension	1.42 (0.82–2.45)	0.21
Alcohol drinking, current	0.97 (0.55–1.70)	0.91
Fatty liver	1.26 (0.62–2.53)	0.52

Propensity score matched cohort (N=204 pairs)



Yang J, et al., Abstract 24.

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Functional cure based on pegylated interferon α-2b therapy in nucleoside analog-suppressed HBeAg negative chronic hepatitis B: A multicenter real-world study (Everest Project in China)–4 years data update

Aim

To investigate the efficacy and safety of this “add-on” or “switch to” therapy in a large-scale real-world setting and investigate the predictors for HBsAg loss by pegIFNα.

Methods

- The Everest Project is a multicenter real-world study cohort in China, focusing on functional cure of CHB
- Patients who were treated with NA for more than one year and achieved HBV DNA<100 IU/ml, HBeAg negative and HBsAg ≤1500 IU/mL would receive monotherapy of pegIFNα-2b or combination therapy of NA and pegIFNα-2b.

Conclusions

Functional cure could be well achieved in NA-suppressed HBeAg negative CHB patients by pegIFNα-2b strategy.

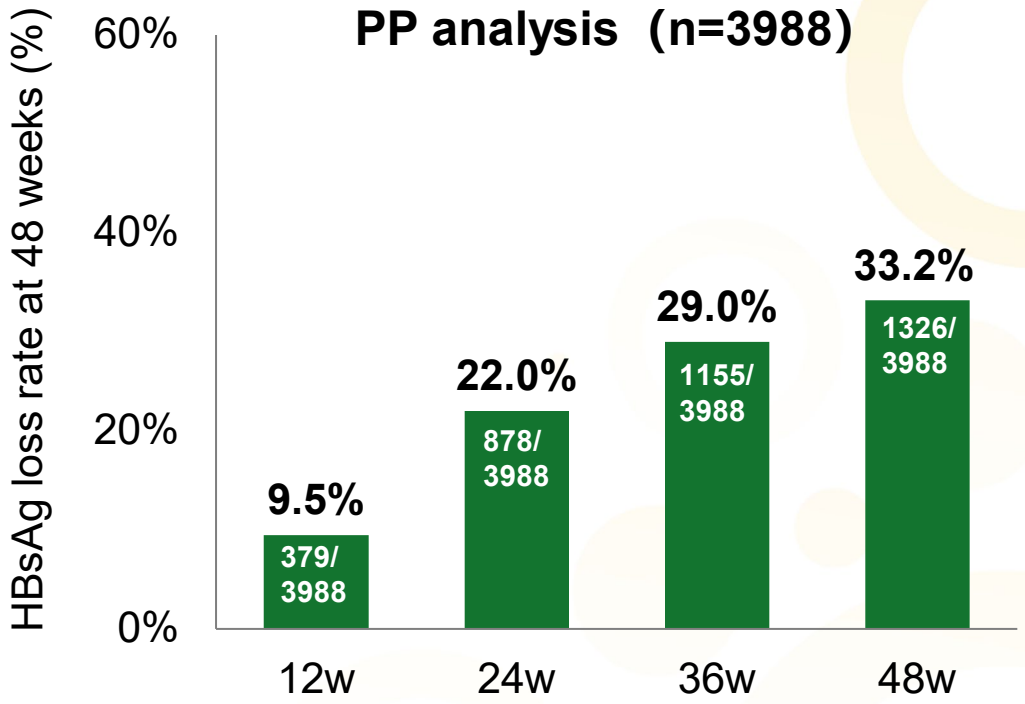

Figure. HBsAg loss rate at different time points in PP analysis.

Mo Z, et al., Abstract 25.

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Treatment with Bulevirtide in HDV-infected patients in a real-life setting: Two-year results

Objective

To evaluate the efficacy and safety of bulevirtide (BLV) 2 mg daily with or without PEG-IFN for 18 and 24 months in HBV/HDV patients.

Methods

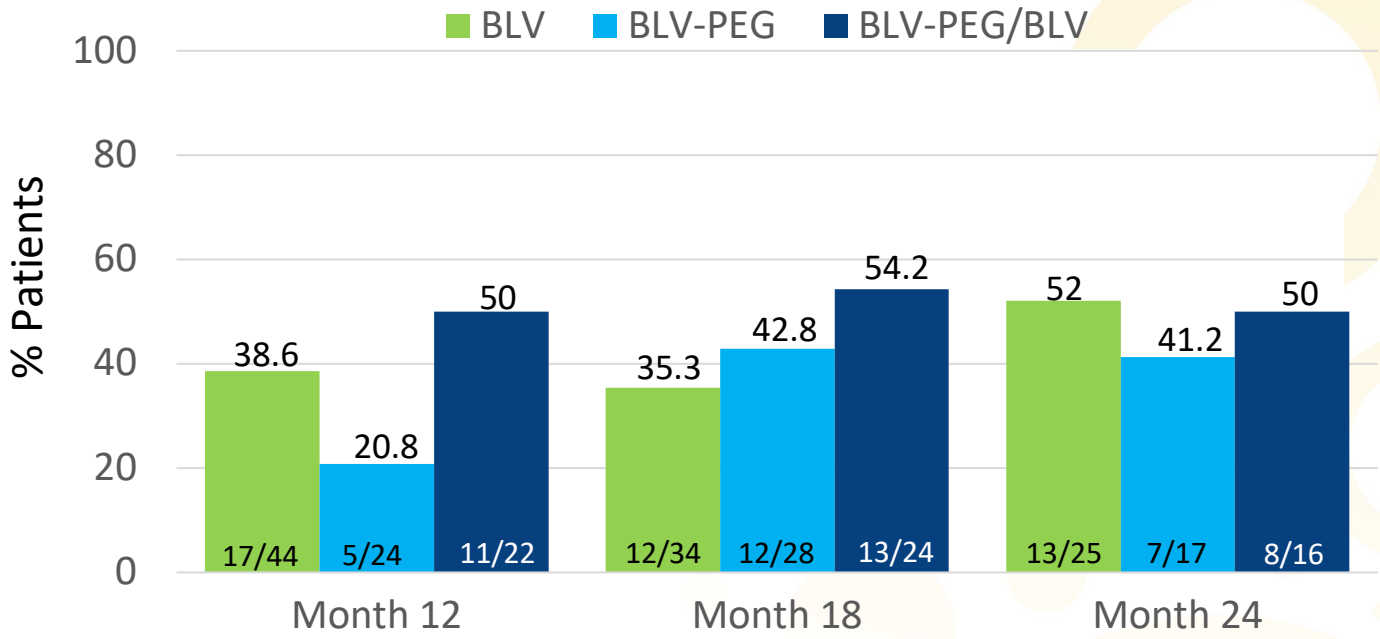
- Multicenter, open-label, observational, prospective study without randomization.
- HDV patients (mean age 40 years, male 68%) with severe disease (cirrhosis 62%, median HDV RNA 6.5 log10 UI/ml)

Main Findings

At month 18 and 24, 35.3% and 52% of HDV patients treated with BLV have undetectable HDV RNA or >2 log_{10} IU/mL decrease from baseline and normal ALT (FDA criteria), respectively (Figure).

Conclusions

In this real-life study, BLV 2 mg shows a favorable safety and efficacy profile.



de Lédinghen V, et al., Abstract 28.

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The incidence of chronic hepatitis B by age at the global and regional level, 2022

Objective

To estimate the incidence of chronic hepatitis B virus (HBV) infections by region and age group.

Methods

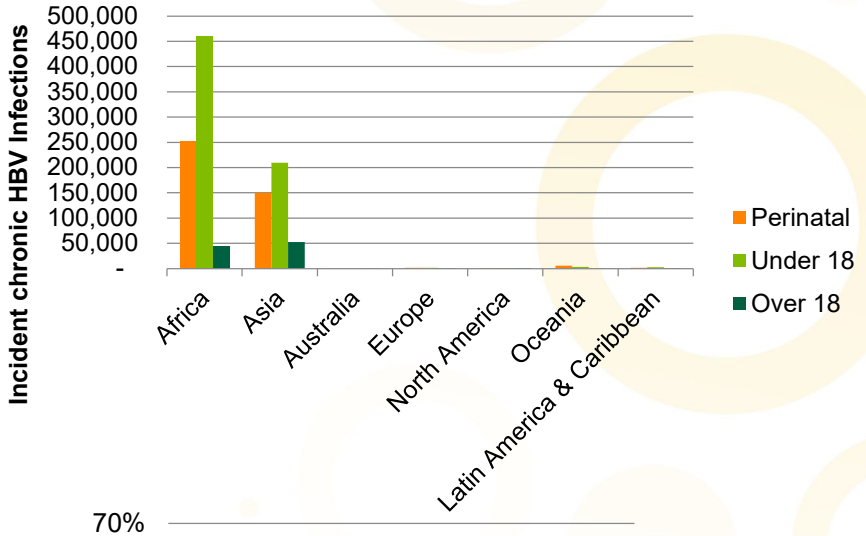
The Polaris Observatory maintains and annually updates 166-country specific fully dynamic PRoGReSs models that were used to estimate incidence by age and region.

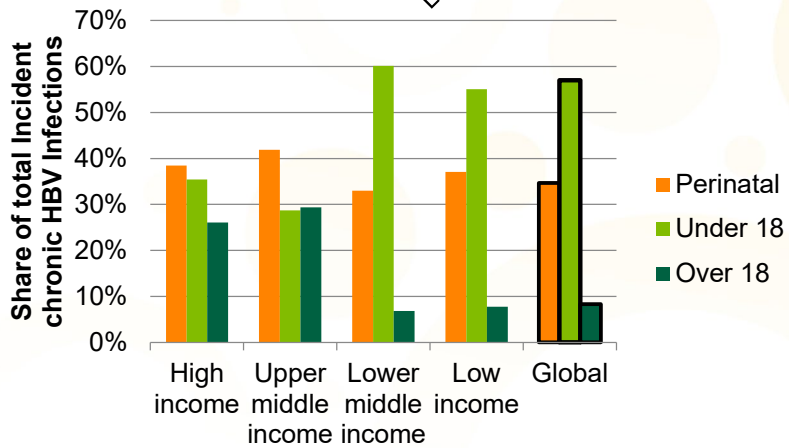
Main Findings

- The global chronic HBV incidence was estimated to be 1,194,300 in 2022, which were concentrated in lower-middle and low-income countries (65% and 30% of total, respectively). Africa accounted for 64% of new chronic cases and 35% were in Asia.
- Globally, 35% of chronic incidence occurred perinatally, 57% ages 1-18, and 8% occurred in those aged 18 and older. The share of incident chronic infections in adults is highest in upper middle income, high income, and countries in Europe with rates of 29%, 26%, and 22%, respectively.

Conclusions

The largest impact in reducing incidence in most of the world would be through strengthening prevention of mother-to-child transmission interventions and implementing high coverage of catch-up vaccination in the pediatric population.





Razavi-Shearer D, et al., Abstract 30.

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Profile of HBV DNA integration in the natural history of chronic hepatitis B

Objective

To study the profile of HBV DNA integration in CHB and occult hepatitis B virus infection (OBI) patients.

Methods

- 53 treatment naïve patients:
  - HBeAg-positive infection (EPI)
  - HBeAg-positive hepatitis (EPH)
  - HBeAg-negative infection (ENI)
  - HBeAg-negative hepatitis (EPH)
  - Patients with HBsAg-seroclearance (Sloss)
  - HBsAg-negative, NAT-positive subjects without previous HBsAg data (NAT+)
- HBV integration was detected using a HBV probe-capture NGS approach.

Main Findings

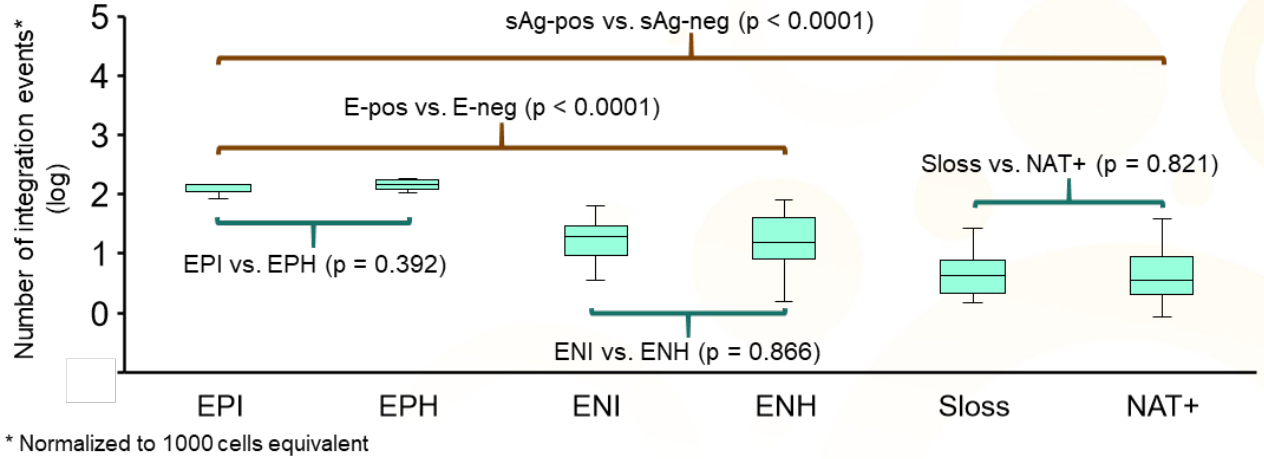
HBV integration was detectable in all 53 patients. HBsAg-negative patients/ subjects also had detectable HBV DNA integration, albeit the levels were lower.

Conclusions

We observed a decreasing trend in the degree of HBV integration upon transition from HBeAg-positive to HBeAg-negative to HBsAg-negative phases.

	EPI (n=3)	EPH (n=11)	ENI (n=7)	ENH (n=12)	Sloss (n=10)	NAT+ (n=10)
Mean age (year)	34	34	46	44	49	45
ALT (U/L)	37	103	32	103	29	26
Serum HBV DNA (log IU/mL)	6.5	7.3	4.1	5.8	<1.3	<1.3
Serum HBsAg (IU/mL)	2690	12538	1564	1064	<0.05	<0.05
HBcrAg (log U/mL)	7.3	8.4	3.4	4.7	ND	ND
Intrahepatic HBV DNA (copies/cell)	48	3026	98	74	3.6	0.06
cccDNA (copies/cell)	1.6	57	1.5	5.9	0.09	<0.005

Median values (except otherwise specified); ND: not determined; cutoff for normal ALT is 40 U/L



* Normalized to 1000 cells equivalent

Wong D, et al., Abstract 33.

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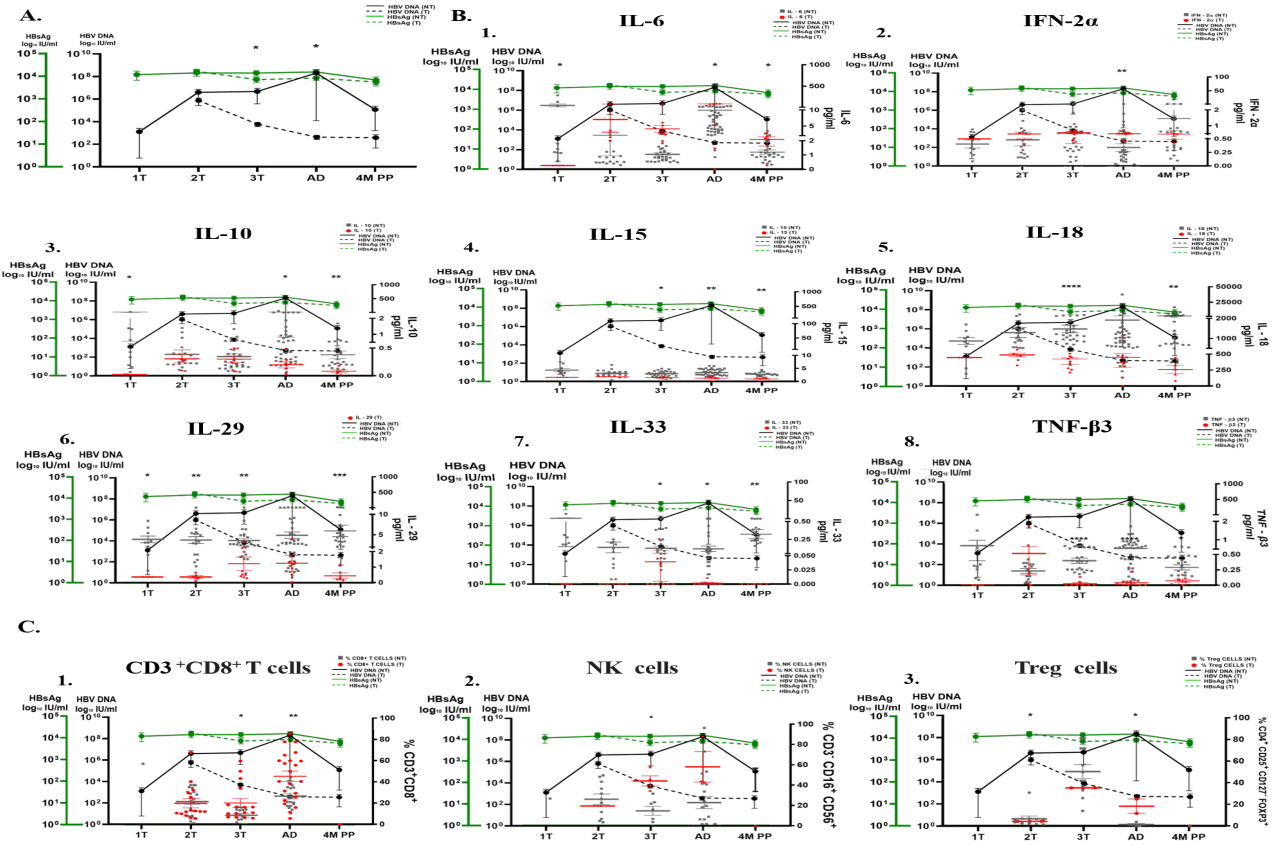
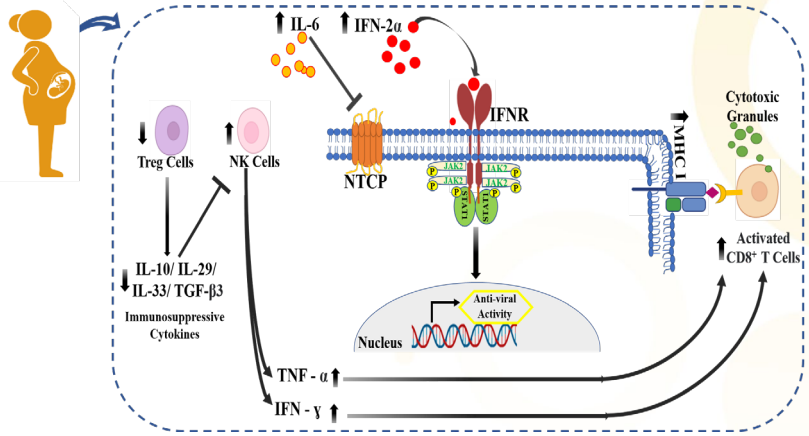
Decline in viral load induces CD8+T cells, natural killer cells, and Th1 cytokine profile in chronic hepatitis B-infected pregnant women treated with tenofovir disoproxil from second trimester

Aim: To understand cytokine and immune kinetics in pregnant women who started TDF treatment at early gestational stage compared to those without therapy.

Methods: Immune cell profiling and plasma cytokines were done using flow cytometry and multiplex cytokine bead array.





Conclusions: Anti-viral treatment during early gestational phase showed an inverse correlation of decline in HBV DNA and enhanced Th1-mediated than Th2-mediated immune response.

- On viral decline, IFN-2α and IL-6 induce the phosphorylation of JAK/STAT and activate TNFα and IFN-γ secreting CD8 T and NK cells.
- IL-6 reduces the IL-10, IL-29, IL-33, TGF-β3 secreting Treg cells and promotes anti-viral immunity in treated patients.

A. Reduction in HBV viral load after TDF treatment. **B.** Treated patients showed increased levels of pro-inflammatory IL-6 and IFN-2α, and decrease in immune suppressive cytokines after early treatment with TDF. **C.** Increased cytotoxic CD8⁺ T cells and NK cells, Decreased Treg cells population

Pahwa P, et al., Abstract 34.

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Antiviral therapy substantially reduces hepatocellular carcinoma risk in chronic hepatitis B patients in the indeterminate phase (a REAL-B study)

Objective

- HCC risk in CHB is higher in the indeterminate phase compared to the inactive phase, but it is unclear if antiviral therapy reduces HCC risk in this population.
- We aimed to evaluate the association between antiviral therapy and HCC risk in the indeterminate phase.

Methods

- We analyzed 855 adult, treatment-naïve CHB patients without advanced fibrosis in the indeterminate phase at 14 centers (U.S., Europe and Asia).
- Inverse probability of treatment weighting analysis (IPTW) was used to balance the treated (n=405) and untreated (n=450) groups.

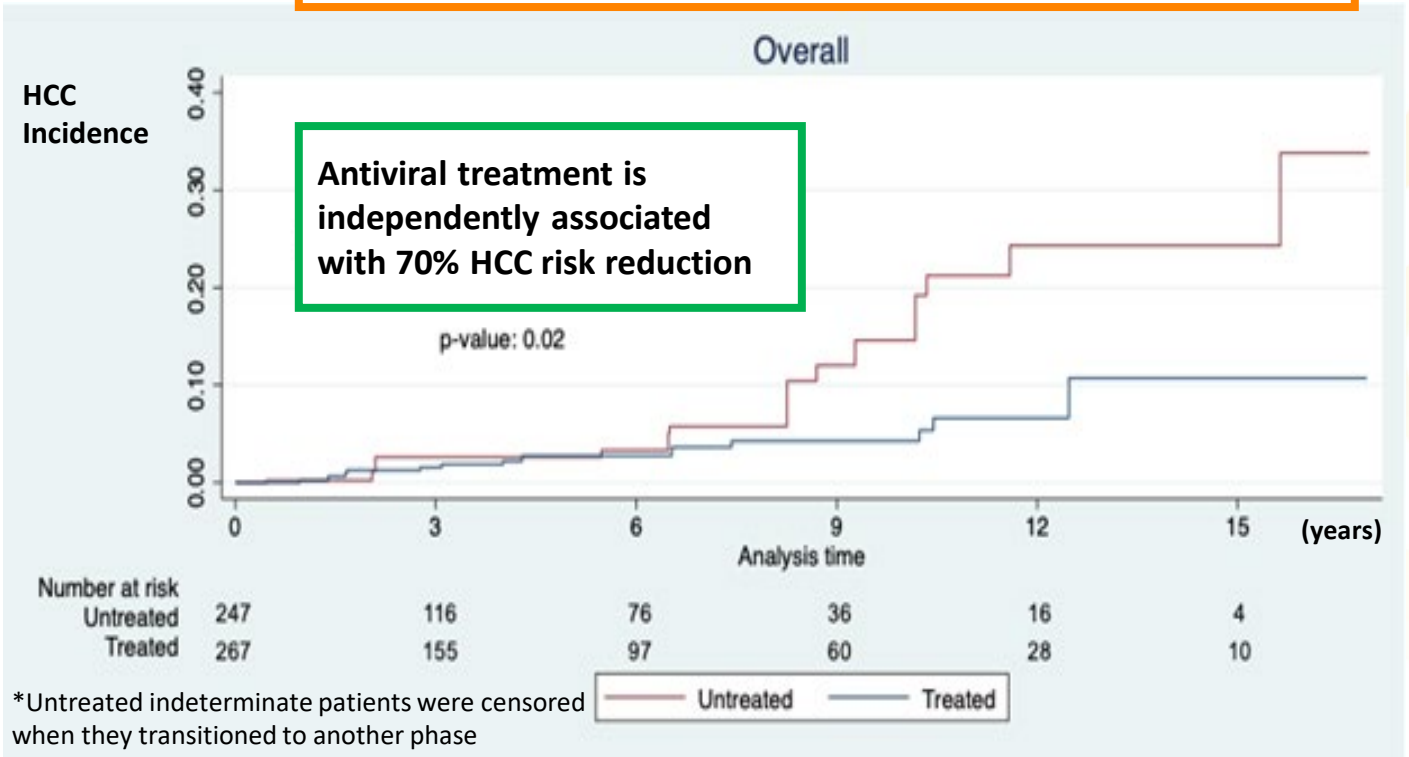
Main Findings

- In multivariable Cox proportional hazards model adjusted for age, sex, HBeAg, HBV DNA, ALT, diabetes, and platelet count, antiviral therapy was an independent predictor of lower HCC risk (adjusted HR 0.3, 95% CI 0.1 – 0.6, *P*=0.001).

Conclusions

- Antiviral therapy reduces HCC risk by 70% among CHB patients in the indeterminate phase.
- These data have important implications for the potential expansion of CHB treatment criteria.

15-year HCC incidence: 34% (untreated) vs. 11% (treated), *P*=0.02



*Untreated indeterminate patients were censored when they transitioned to another phase

Huang D, et al., Abstract 36.

Funding: No external funding to disclose

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Transcriptionally active HBV integration contribute to residual intrahepatic HBsAg in patients with functional cure

Objective

Explore the potential of HBV integration in patients with functional cure.

Methods

HBV capture sequencing and transcriptome sequencing were performed for HBV integration analysis and immunohistochemis-try of intrahepatic HBsAg was performed in patients with functional cure.

Main Findings

The positive HBsAg hepatocytes existed in 21.1% of patients with functional cure and we found that intrahepatic residual HBsAg was mainly derived from transcriptionally active HBV integration in five patients with functional cure (Figure 1).

Conclusions

Transcriptionally active HBV integration contribute to the residual intrahepatic HBsAg in patients with functional cure.

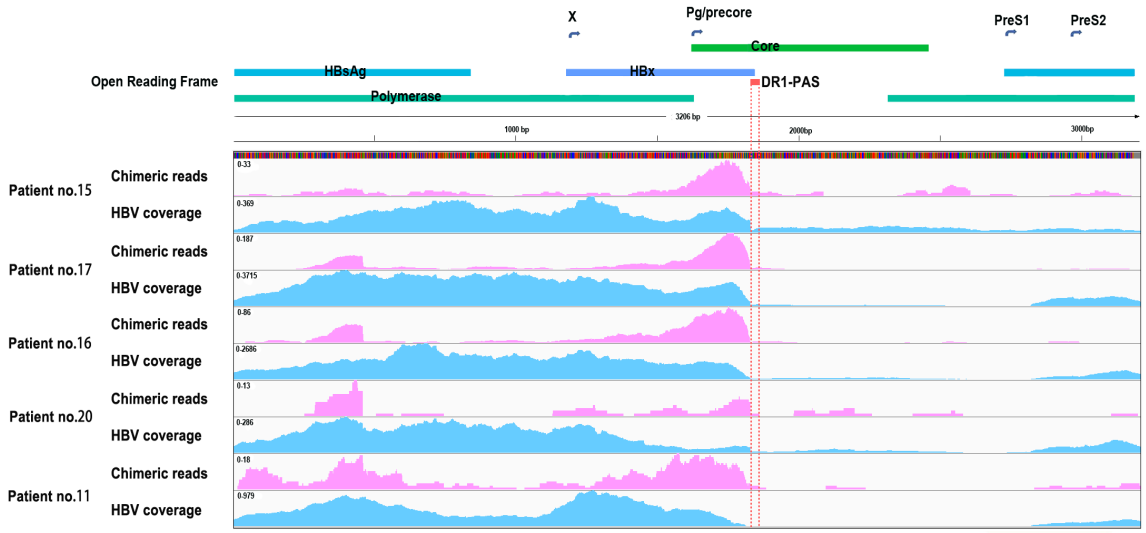

Figure 1. Five profiles of functionally-cured patients with immunohistochemical HBsAg positivity mapped to the HBV reference genome.

The profiles in pink show the coverage of chimeric reads, which represent the HBV integration events. The profiles in blue show the HBV RNA reads coverage. The location of the direct repeats 1 (DR1) to polyadenylation signal (PAS) (orange dashed line) is indicated.

Gao N, et al., Abstract 37.

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HBsAg/Anti-HBs complex levels persists up to 13 years after HBsAg loss

Objective

To examine the immune complex (IC) kinetics prior to and after spontaneous and treatment-induced HBsAg loss using a novel assay.

Methods

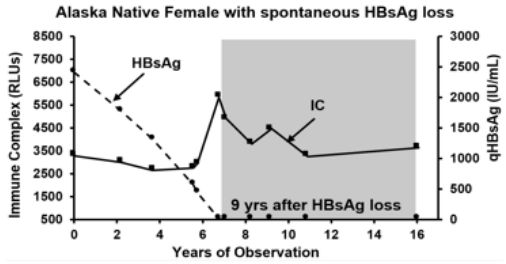
Retrospective study: 31 HBeAg (-) CHB subjects (13 Alaska natives, 18 US tertiary center patients) with spontaneous or nucleos(t)ide analog (NA)-induced HBsAg loss.

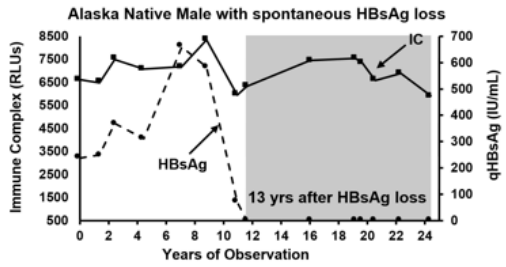
Main Findings (see Figure for representative patients)

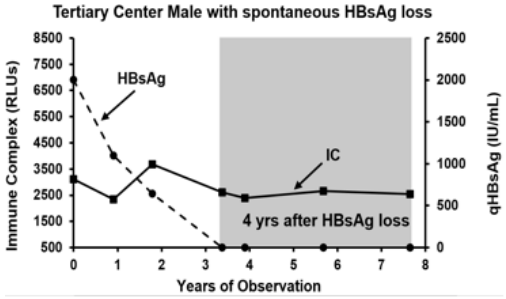
17 (55%) achieved HBsAg seroconversion with anti-HBs (+). Regardless of the anti-HBs status, IC continued to be detectable after HBsAg loss.

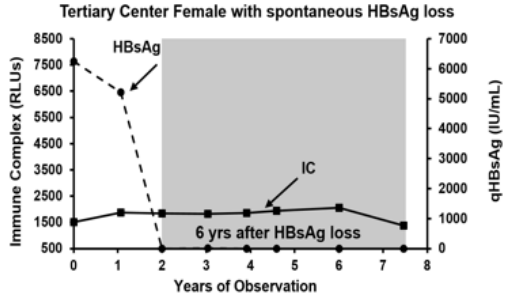
Conclusions

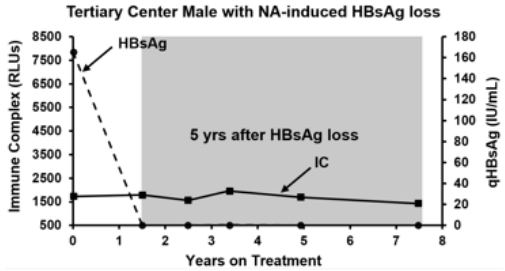
- Immune complexes are present for prolonged periods after both spontaneous and NA-induced functional cure.
- It is possible that HBsAg continues to be generated from integrated HBV DNA to extend HBsAg/anti-HBs immune complex production over time.

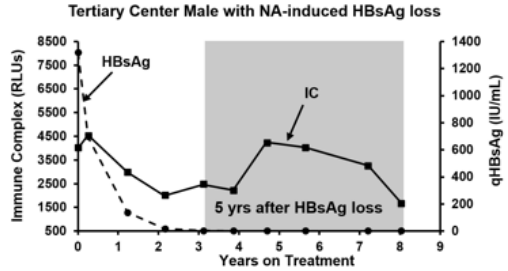












Ali MJ, et al., Abstract 38.

AASLD The Liver Meeting®

High levels of intrahepatic integrated HBV DNA that correlated with serum quantitative HBsAg level in HBeAg negative chronic hepatitis B

Aim

To correlate cccDNA and integrated DNA from liver tissues of HBeAg(+) and (-) CHB participants with serum virological parameters.

Methods

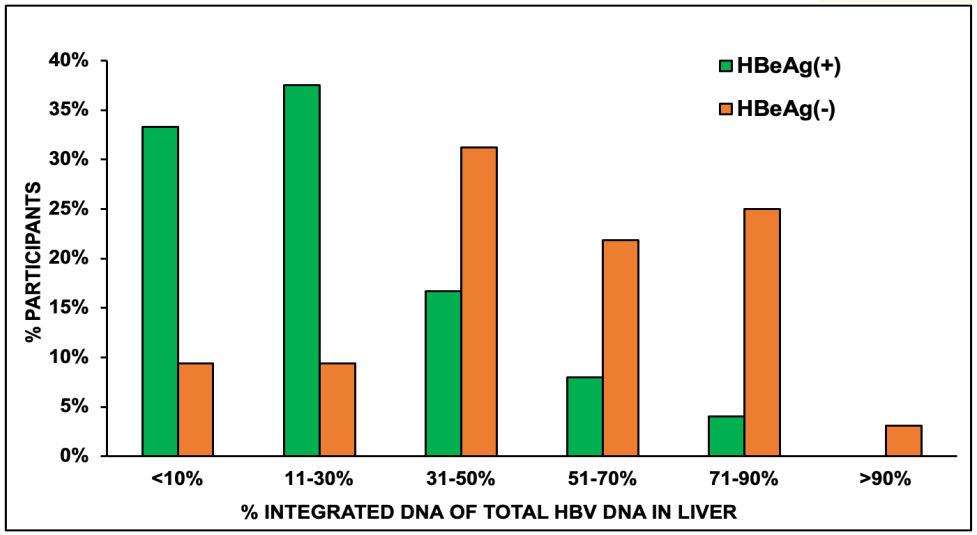
Liver tissues from 56 untreated CHB participants of the North American Hepatitis B Research Network (HBRN) were evaluated for cccDNA and integrated DNA.

Main Findings

Integrated DNA was present in various quantities in all patients. HBeAg(-) participants had larger proportion of integrated HBV DNA in liver based on HBV-host junctional read compared to the HBeAg(+) ones (Figure).

Conclusions

There was a positive relationship between the levels of integrated HBV DNA and serum qHBsAg in HBeAg(-) participants only. The HBsAg derived from the integrated DNA likely contributed to the discordant serum DNA and RNA correlations to qHBsAg.



	HBeAg(+)	HBeAg(-)
Serum RNA and serum DNA	***r* = .93** ***P*= .00001**	***r* = .87** ***P*= .000001**
Serum RNA and serum qHBsAg	*r* = .45 ***P*= .03**	*r* = .27 *P*= .14
Serum DNA and serum qHBsAg	*r* = .55 ***P*= .005**	*r* = .33 *P* = .06
HBV-Host Junctional read (%) and serum qHBsAg	*r* = .23 *P*=0.27	*r* = .46 ***P*= .008**

Lau D, et al., Abstract 39.

AASLD The Liver Meeting®

Predictors of achieving HBV surface antigen level <100 IU/mL at end of finite NUC treatment in hepatitis B e antigen-negative patients

Hypothesis/Aim/Objective

- Quantitative HBsAg (qHBsAg) level at end-of-treatment (EOT) <100 IU/mL is an independent predictor for off-therapy sustained response or HBsAg loss in chronic hepatitis B (CHB) patients stopping nucleos(t)ide analogue (NUC).
- The study aims to investigate the contributory factors to the achievement of EOT qHBsAg <100 IU/mL.

Methods

The 1188 HBeAg-negative CHB patients who stopped Entecavir or Tenofovir after consecutive undetectable HBV DNA ≥1 year were enrolled.

Conclusions

HBeAg negative CHB patients with pretherapy ALT <5X ULN and HBsAg ≥3 $\log_{10}$ IU/mL were **least** likely to achieve EOT qHBsAg <100 IU/mL. Starting therapy in CHB patients with **hepatitis flare** is more likely to achieve the goal of EOT qHBsAg <100 IU/mL.

All patients (N=1188)	aOR (95%CI)	P value
ALT <5X ULN and HBsAg ≥3 $\log_{10}$	Referent	
ALT <5X ULN and HBsAg <3 $\log_{10}$	6.64 (3.48-12.66)	<0.01
ALT ≥5X ULN and HBsAg ≥3 $\log_{10}$	5.33 (2.86-9.96)	<0.01
ALT ≥5X ULN and HBsAg <3 $\log_{10}$	9.22 (4.67-18.20)	<0.01
Adjusted by age, genotype, Nuc type, time to HBV DNA undetectable, ALT normalized duration, consolidation duration and HBsAg reduction from baseline		

Non-cirrhosis (N=711)	aOR (95%CI)	P value
ALT <5X ULN and HBsAg ≥3 $\log_{10}$	Referent	
ALT <5X ULN and HBsAg <3 $\log_{10}$	4.04 (1.92-8.51)	<0.01
ALT ≥5X ULN and HBsAg ≥3 $\log_{10}$	3.98 (1.92-8.28)	<0.01
ALT ≥5X ULN and HBsAg <3 $\log_{10}$	4.75 (2.15-10.46)	<0.01
Adjusted by age, genotype, and time to HBV DNA undetectable		

Cirrhosis (N=477)	aOR (95%CI)	P value
ALT <5X ULN and HBsAg ≥3 $\log_{10}$	Referent	
ALT <5X ULN and HBsAg <3 $\log_{10}$	8.75 (2.47-31.01)	<0.01
ALT ≥5X ULN and HBsAg ≥3 $\log_{10}$	9.80 (2.84-33.86)	<0.01
ALT ≥5X ULN and HBsAg <3 $\log_{10}$	17.44 (4.71-64.62)	<0.01
Adjusted by age, anti-HBV treatment experienced, Nuc type, and HBsAg reduction from baseline		

Liu Y-C, et al., Abstract 40.

AASLD The Liver Meeting®

Finite therapy decreases HCC incidence greater than long-term treated Nuc suppressed HBeAg negative CHB patients with cirrhosis

Objective

- Long-term Nuc treatment decreases HCC incidence in CHB patients with cirrhosis (HBV-LC).[1]
- Two hospital-based cohorts of patients with cirrhosis showed that a 5-6 year cumulative incidence of HCC is not higher in patients receiving finite therapy compared with those under continued treatment.[2,3]
- Objective: To investigate the above finding using a large-scale multicenter cohort with longer follow-up.

Methods

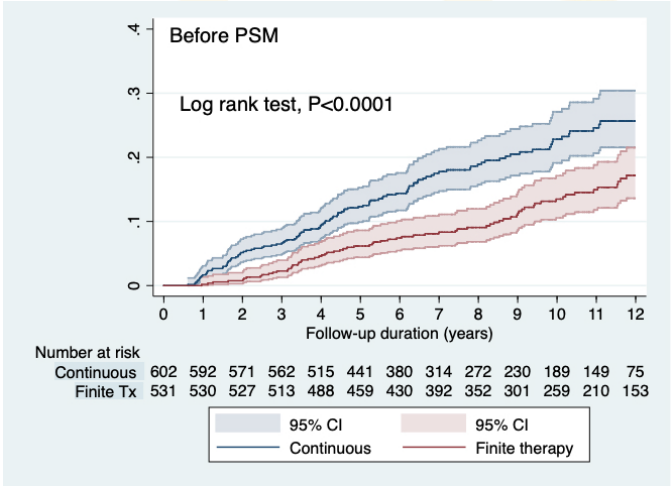
- HBeAg negative HBV-LC patients from two medical centers were recruited and categorized into two arms: finite (interrupted) and continuous arms.
- Patients in continuous arm were treated >=3 years and those in finite arm >=2 years. Those with HCC occurrence prior to antiviral treatment or occurence within 6 months from start of treatment were censored. Propensity score matching of age, gender, Nuc pretreatment, HBV DNA, HBsAg, AST, ALT, and platelets were done at 1:1 ratio between the two arms for sensitivity analysis. Kaplan Meier and Log rank tests were applied to compare cumulative incidence of HCC.

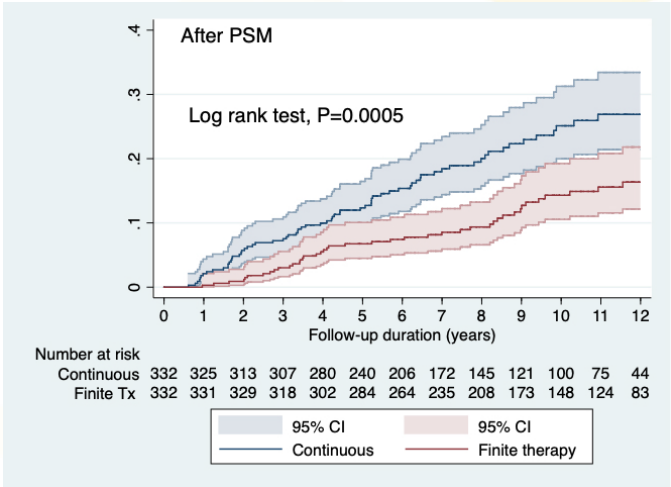
Main Findings

- During a median of 9.3 (IQR: 6.4-11.9) years follow-up, the 10-year cumulative incidence of HCC and HBsAg loss in finite and continuous arms were 23% vs.14% (Log rank test, P=0.0005) and 3% vs. 16% (P<0.0001); no difference in liver-related mortality/transplantation between these two arms (P=0.94).
- Multivariate cox regression analysis showed older age [aHR: 1.05 (1.03-1.06), P<0.001], FIB-4 [aHR: 1.02 (1.0-1.05), P=0.04] and finite therapy [aHR: 0.48 (0.34-0.67), P<0.001] were independent factors for HCC.

Conclusions

Finite therapy further reduces HCC risk in HBeAg negative CHB patients with cirrhosis.





1. Su TH et al, Liver Int. 2016 Dec;36(12):1755-1764; 2. Hung CH et al J Viral Hepat. 2017 Jul;24(7):599-607; 3. Chen YC et al Aliment Pharmacol Ther. 2015 Nov;42(10):1182-91

Jeng, W, et al., Abstract 41.

AASLD The Liver Meeting®

Risk factor of hepatocellular carcinoma occurrence after sustained virologic responses in hepatitis C virus patients without advanced liver fibrosis

Aim

To develop a scoring system to predict HCC occurrence after SVR in HCV patients without advanced liver fibrosis.

Methods

A total of 1,682 HCV patients without advanced liver fibrosis (FIB-4 index less than 3.25) without history of previous HCC who started DAA therapy and achieved SVR were included.

Main Findings

- HCC occurrence was observed in 28 patients during 42.5 months from SVR, and the cumulative HCC occurrence rates at 3 and 5 years were 1.8% and 2.5%, respectively.
- In the multivariate analysis, age ≥65 years, ALT levels at SVR ≥30 U/l, and AFP levels at SVR ≥5.0 ng/ml were significantly associated with HCC occurrence.
- We developed a new scoring system to predict HCC occurrence after SVR using these three factors (1 point was added for each factor).
- The cumulative HCC incidence rates at 3 and 5 years were 6.0% and 7.9% in patients with score of 2 or 3, respectively, and no patients developed HCC in those with score of 0.

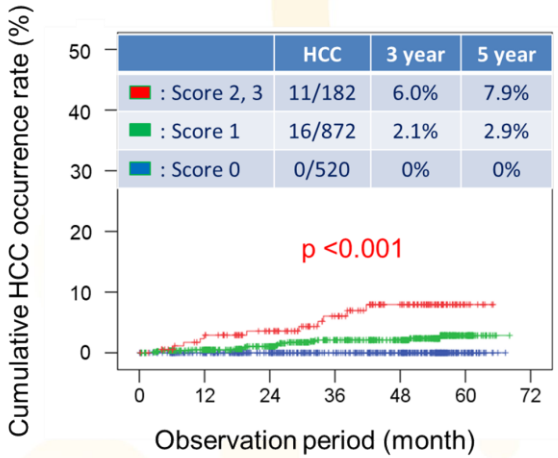
Predictors for HCC occurrence after SVR

		Multivariate analysis		
Factor	Category	HR	95% CI	P value
Age (years)	<65 ≥65	1 3.380	1.342 – 8.510	0.010
ALT at SVR (U/l)	<30 ≥30	1 5.973	2.461 – 14.497	< 0.001
Total bilirubin at SVR (mg/dl)	<0.8 ≥0.8	1 0.388	0.145 – 1.043	0.060
Albumin at SVR (g/dl)	≥4.0 <4.0	1 1.767	0.653 – 4.786	0.263
AFP at SVR (ng/ml)	<5.0 ≥5.0	1 4.060	1.823 – 9.039	0.001

3A scoring system for HCC occurrence

Factor	Category	Score
Age	≥65 years	1
ALT at SVR	≥30 U/L	1
AFP at SVR	≥5.0 ng/mL	1

Cumulative HCC occurrence rate according to 3A score



Conclusions

This 3A score (Age, ALT at SVR, and AFP at SVR) may be useful for stratification of HCC risk in patients without advanced liver fibrosis.

Tahata Y, et al., Abstract 42.

Updated evaluation of global progress towards HBV and HCV elimination, preliminary data through 2021

Objectives

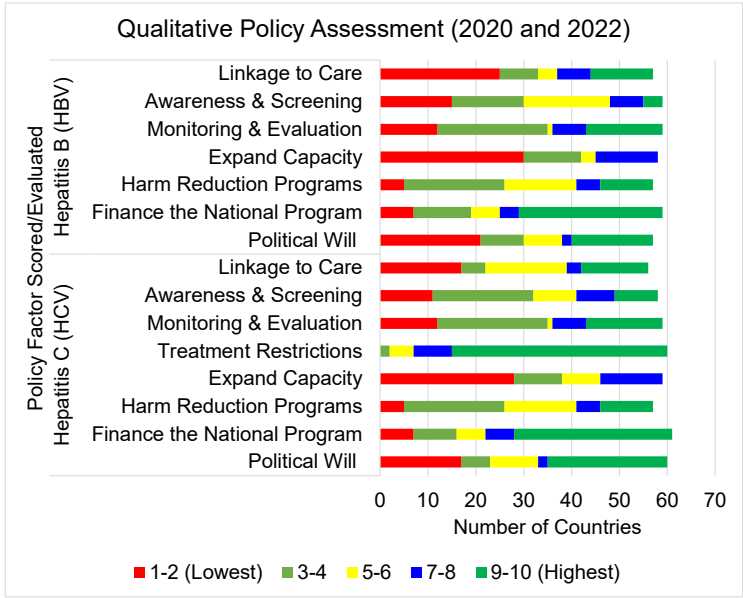
Evaluate recent (2020/2021) country data (prophylaxes, diagnosis, treatment) to assess progress towards HBV/HCV elimination, and report on updated (2022) policy assessment surveys.

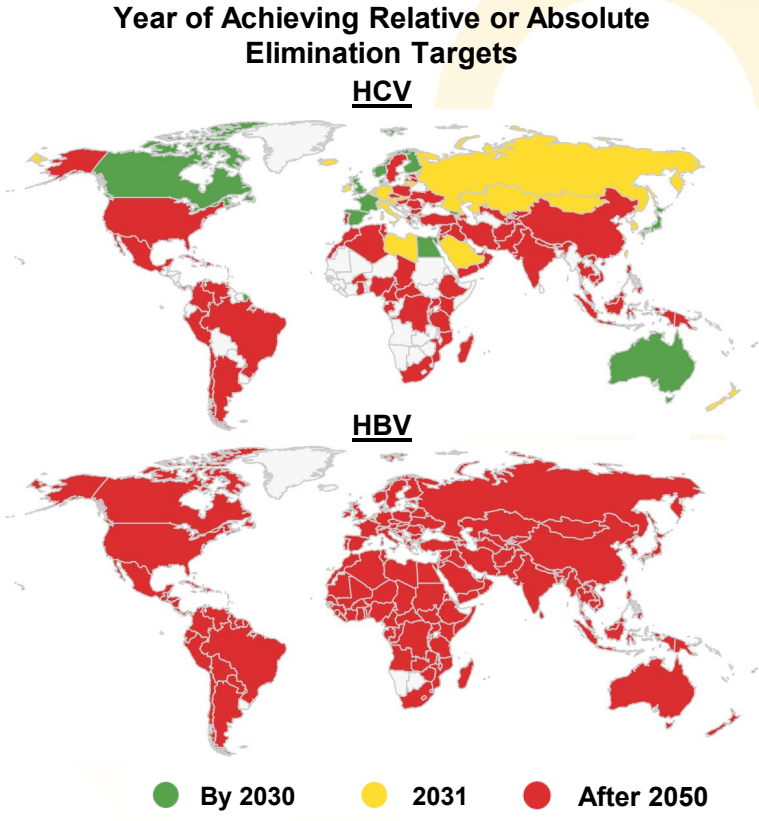
Methods

Years of elimination (by target) were extracted from models maintained by the CDA Foundation; results from a policy assessment survey were used to score national viral hepatitis elimination policies.

Main Findings

- Considering 2020 and 2022 survey data, top scores (9 or 10) for "political will" were seen in 17 countries (30%) for HBV and 25 countries (42%) for HCV. Top scores for "financing of the national program" were seen in 30 countries (51%) for HBV and 33 countries (54%) for HCV.
- 11 countries were on track to achieve all absolute or relative targets for HCV; no countries were on track to achieve all targets for HBV by 2030. More than 80 countries were on track to achieve the HBsAg prevalence target for children ≤5 years of age by 2030.





Conclusions

As countries progress toward eliminating HCV and HBV, more work is needed to enhance political will and financing of national elimination programs; in particular, expanded screening and treatment for HBV is needed.

Blach S, et al., Abstract 45.

The Liver Meeting®

Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in Canada

Aim

We estimated HCV reinfection rates among all DAA-treated individuals in a population-based cohort study in British Columbia (BC), Canada.

Methods

We analyzed data from the BC Hepatitis Testers Cohort. We followed individuals with HCV infection treated with DAAs who achieved sustained virologic response (SVR) and had ≥1 subsequent HCV RNA measurement until Oct 31, 2021. Reinfection was defined as a positive RNA measurement after SVR. Injection drug use (IDU) was categorized as none, recent (IDU visits <3 years), and past. Cox proportional hazards modelling was performed to identify factors associated with reinfection.

Results

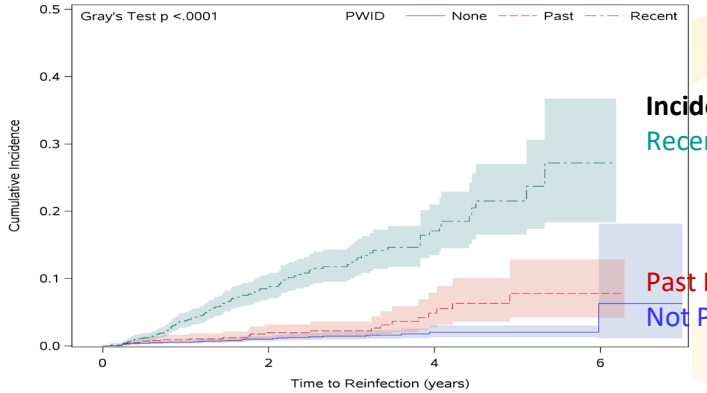
- Among 8,423 eligible individuals achieving SVR, 20% persons with recent IDU (n=1,658), and 17% persons with past IDU (n=1,437). We identified 176 HCV reinfections during 11,807.6 PY of follow-up, yielding a reinfection rate of 1.49/100 PY. Reinfection rates were higher among persons with recent IDU (n=115, 4.39/100 PY) than persons with past IDU (n=24, 1.04/100 PY) and persons with no IDU (n=37, 0.54/100 PY).
- In a multivariable model for persons with recent IDU, younger age (age <30 yrs adjusted hazards ratio (AHR): 3.26, 95%CI:1.55-6.78, and opioid use (AHR: 2.03, 95%CI:1.11-3.72) were associated with higher reinfection risk, while receiving antipsychotic drugs was associated with lower reinfection risk (AHR:0.44, 95%CI:0.29-0.64).

Conclusions

HCV reinfection rates after DAA therapy were highest among persons with recent IDU, especially among younger PWID. Treatment with antipsychotic drugs was associated with lower reinfection risk.

Janjua NZ, et al, Abstract 47.

Cumulative incidence curve by IDU history



Factors associated with HCV reinfection among recent PWID

	PWID (N= 1,613)
	AdjHR (95% CI)
Age, 30 yrs (Ref: 50-59 yrs)	**3.26(1.56-6.78)**
30-39	2.06(1.22-3.46)
40-49	1.73(1.09-2.75)
≥60	0.67(0.29-1.52)
Male (Ref: Female)	**1.38(0.91-2.11)**
Illicit opioid use history (Ref: No)	**2.03(1.11-3.72)**
Antipsychotic treatment (Ref: No)	**0.44(0.29-0.64)**

AASLD The Liver Meeting®

Efficacy and safety of combination treatment with siRNA JNJ-73763989 and capsid assembly modulator JNJ-56136379 (bersacapavir) in HBeAg-negative virologically suppressed chronic hepatitis B patients: Follow-up week 48 end of study results from REEF-2

Objective

To assess the efficacy and safety of 48 weeks of combination treatment with JNJ-3989, JNJ-6379, and NA in VS HBeAg-negative CHB patients.

Methods

In this phase 2b, double-blind, multicenter, placebo-controlled study, 130 VS HBeAg-negative CHB patients with HBsAg >100 IU/mL on NA treatment for ≥2 years were randomized (2:1) to receive add-on JNJ-3989 + JNJ-6379 or placebos for 48 weeks, followed by 48 weeks of off-treatment follow-up, during which all treatment including NA was discontinued.

Main Findings

- JNJ-3989 + JNJ-6379 + NA showed a sustained off-treatment reduction in HBsAg (**Figure 1**).
- 46.9% of patients in the JNJ-3989 + JNJ-6379 + NA group achieved HBsAg <100 IU/mL at the end of the 48-week follow-up versus 15.0% in the Placebos + NA group (**Figure 2**).
- No patients achieved HBsAg seroclearance (<0.05 IU/mL) without restarting NA at Follow-up Week 24 (primary endpoint) or Follow-up Week 48.
- JNJ-3989 + JNJ-6379 + NA showed pronounced off-treatment HBV DNA suppression with 87.3% of patients achieving HBV DNA <2000 IU/mL and rarely resulted in ALT flares (3.6% versus 28.6% in the Placebos + NA group) or NA retreatment (7.1% versus 27.3% in the Placebos + NA group).
- All treatments were well tolerated.

Conclusions

Treatment with JNJ-3989 + JNJ-6379 + NA for 48 weeks led to lower HBsAg levels, greater HBV DNA suppression, and a lower frequency of ALT flares and NA retreatment, versus placebos + NA at the end of the 48-week off-treatment follow-up.

Figure 1. Mean (SE) change from baseline in HBsAg

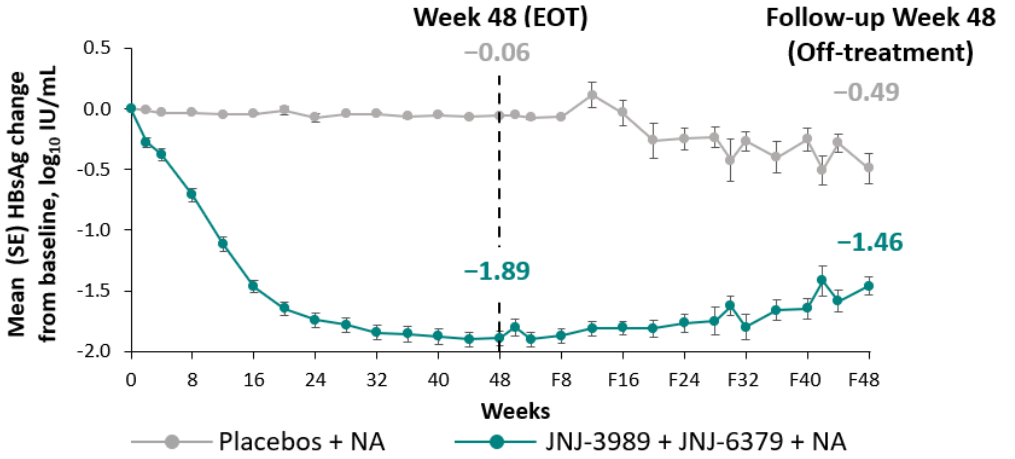
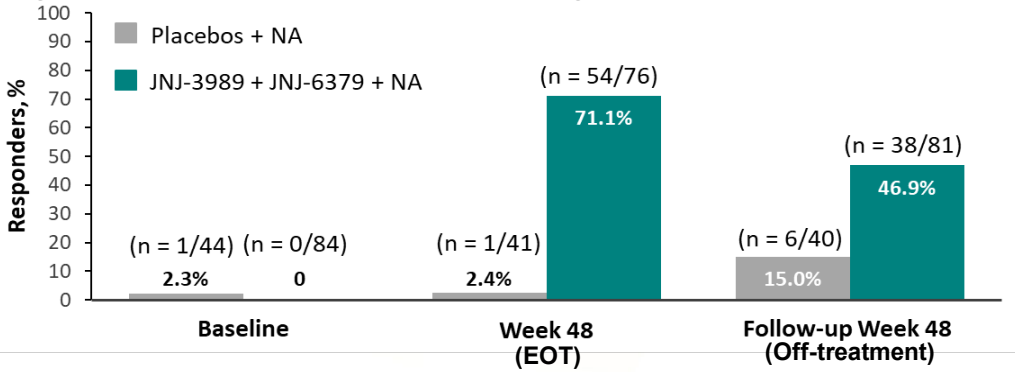


Figure 2. Proportion of patients with HBsAg <100 IU/mL



ALT, Balanine transaminase; CHB, chronic hepatitis B; EOT, end of treatment; F, follow-up; HBeAg, hepatitis B e antigen; HBsAg, hepatitis surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogs; VS, virologically suppressed.

Agarwal K, et al., Abstract LO12.

AASLD The Liver Meeting®

Extension of Bulevirtide Monotherapy to 72 Weeks in HDV Patients with Compensated Cirrhosis: Efficacy and Safety from the Italian Multicenter Study HEP4Di

Background and Aim

Real-world data on efficacy and safety of BLV 2mg monotherapy in compensated cirrhosis beyond week 48 are limited

Methods

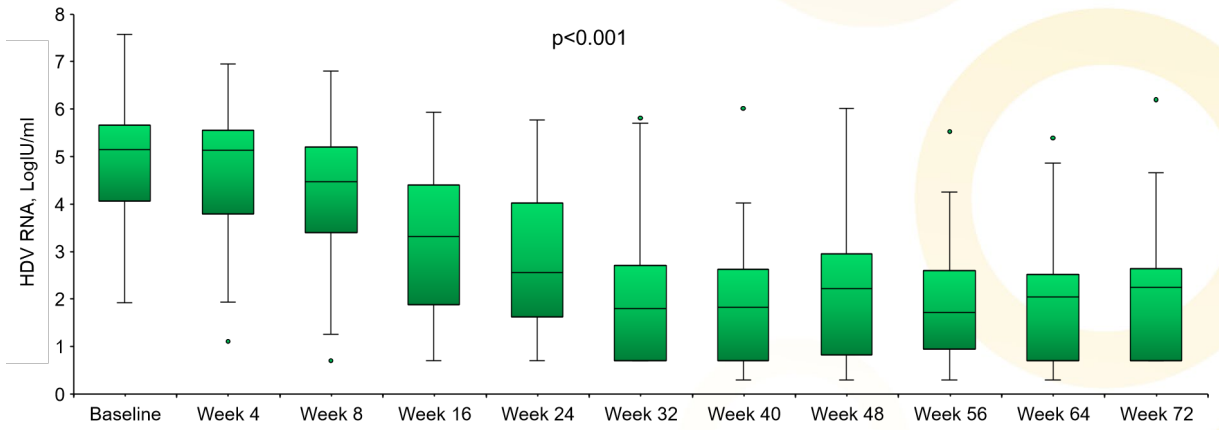
- Multicenter, real-life, investigator-driven, retrospective study
- December 2020-May 2022; 16 Italian Centers
- Consecutive HDV cirrhotic patients starting BLV 2 mg monotherapy up to 72 weeks

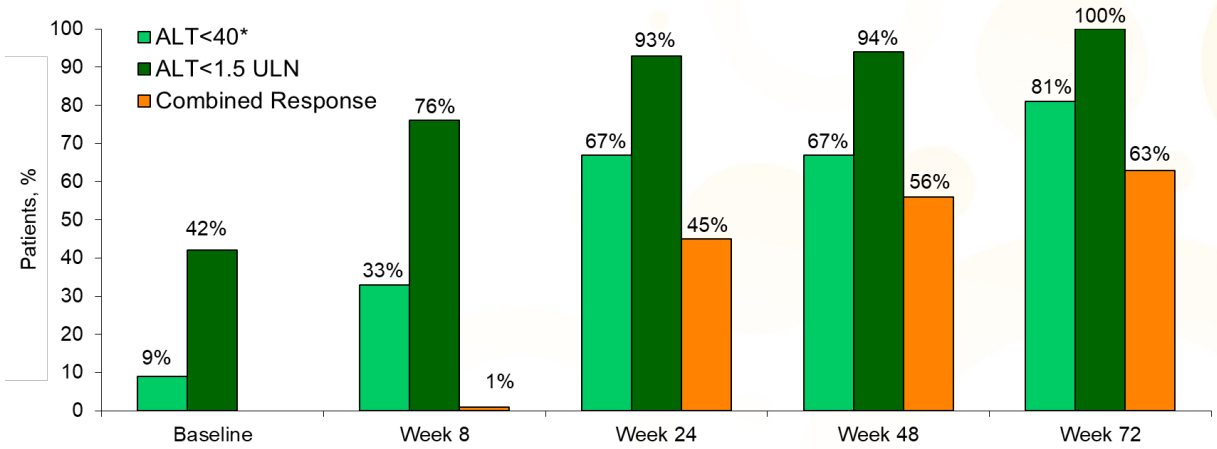
Main Findings (Week 72)

- Virological response (HDV RNA ≥2 Log decline): 75%
- Biochemical response: 81%
- Combined Response: 63%
- Improvement of biochemical parameters and serological NITs
- Asymptomatic increase in biliary acids, no major safety issues

Conclusions

Extension of BLV monotherapy to 72 weeks is safe and effective in patients with HDV-related compensated cirrhosis. Virological and clinical responses increase over time





Anolli, MP. et al., Abstract LO13.

AASLD The Liver Meeting®

Bepirovirsen (BPV) in patients with chronic hepatitis B virus (HBV) infection controlled by nucleos(t)ide analogue therapy: HBV DNA and HBsAg loss 6 months after end of BPV treatment (B-Clear study)

Objective

- Efficacy and safety of bepirovirsen in participants with chronic HBV infection: B-Clear end-of-study results

Methods

- Phase 2b randomized, partial-blind*, parallel cohort trial (NCT04449029) in participants with chronic hepatitis B virus infection on stable nucleos(t)ide analogue therapy†

Main Findings

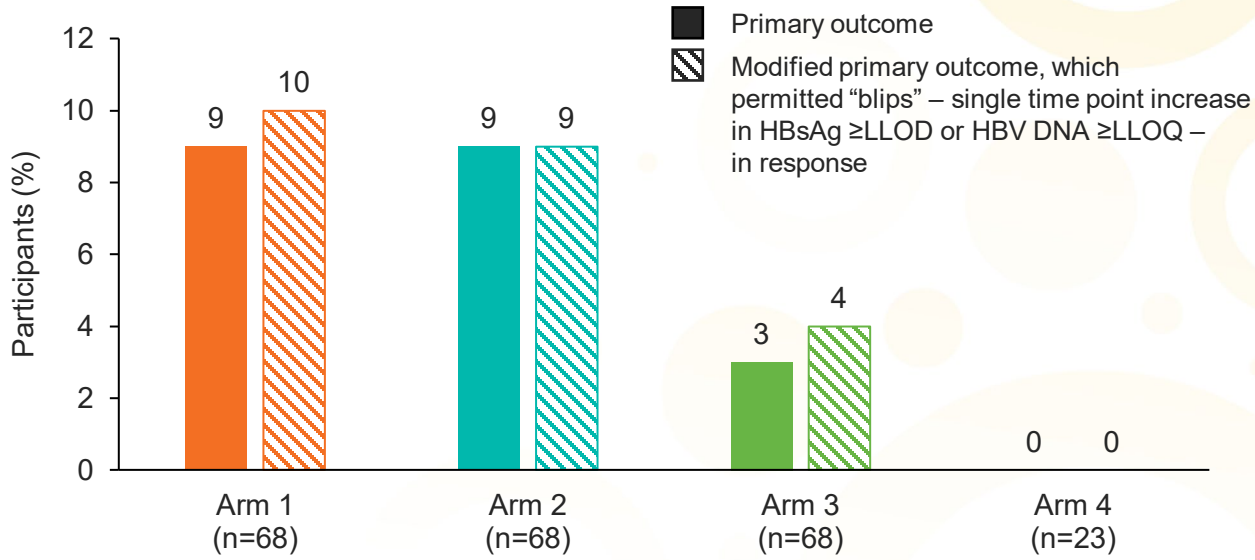
- At end of study, up to 9% of participants (Arms 1 and 2) achieved the primary outcome. The proportions of participants who met the modified primary outcome (allowing unconfirmed increases in HBsAg and/or HBV DNA) were similar (Figure)
- The proportion of participants achieving HBsAg and HBV DNA loss at end of study was higher in the low vs high baseline HBsAg subgroup (≤3 vs >3 log10 IU/mL; Arm 1: 16% vs 6%) and similar in the HBeAg negative and positive subgroups (Arm 1: 10% vs 6%)

Conclusions

- Arm 1 and Arm 2 were the most efficacious treatment regimens and overall study results identified low HBsAg and negative HBeAg as predictors of response; there were no safety signals to preclude further development

Arm 1: BPV 300 mg w/ LD x24W
Arm 2: BPV 300 mg w/ LD x12W + BPV 150 mg x12W
Arm 3: BPV 300 mg w/ LD x12W + PBO x12W
Arm 4: PBO x12W + BPV 300 mg w/o LD x12W

Participants achieving HBsAg <LLOD and HBV DNA <LLOQ maintained for 24 weeks post bepirovirsen end of treatment in the absence of newly initiated antiviral treatment‡



*Investigator unblinded; †Stratified by baseline HBeAg (positive/negative) and HBsAg (≤3/>3 log10 IU/mL) levels; ‡New NA therapy was started in 4 participants: 3 during the on-treatment period and 1 during the off-treatment period
HBsAg lower limit of detection (LLOD) = 0.05 IU/mL; HBV DNA lower limit of quantification (LLOQ) = 20 IU/mL
HBsAg, hepatitis B surface antigen; LD, loading dose (Days 4 and 11); PBO, placebo; W, week; w/ with; w/o, without

Yuen, M-F, et al., LO15

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