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Update of Viral Hepatitis (HBV, HCV, HDV)

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Hepatitis B
Approved Therapies

Immediate vs Late Cessation of Tenofovir in Highly Viremic Pregnant Patients With Chronic Hepatitis B

Background: Antiviral therapy in pregnant patients with high HBV viral load is a cornerstone to preventing HBV vertical transmission, yet optimal timing of treatment discontinuation is unclear.

Aim: To compare the risk of maternal HBV virologic relapse after early vs late cessation of prophylactic TDF

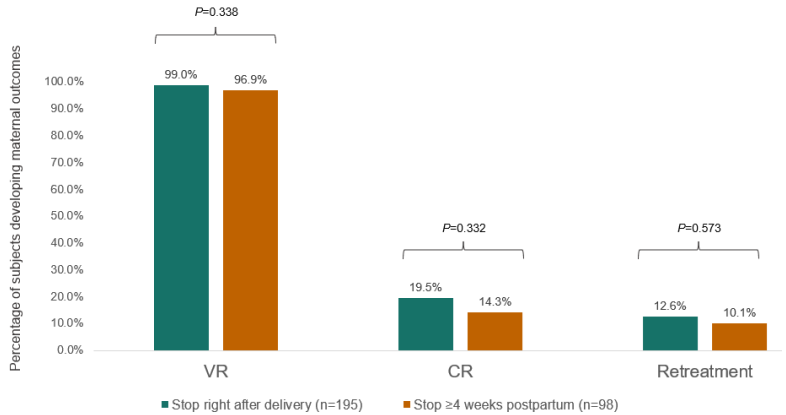
Methods: Single-center prospective study in a tertiary hospital in Shenzhen, China

- TDF withdrawal early (immediate) vs late (≥4 weeks)

Results: 330 participants, median 30 y/o, 83% HBeAg+, median HBV DNA 7.8 $\log_{10}$ IU/mL, 66% early cessation

- Virologic relapse was nearly universal
- No significant difference in maximum ALT changes, clinical relapse, or retreatment
- No MTCT occurred

Conclusions: Early compared to late post-partum TDF withdrawal did not adversely impact maternal outcomes.



Mak L et al. Abstract 59.

Tenofovir for Chronic Hepatitis B With High Viral Load but Mildly Elevated ALT

Background: Uncertainty exists regarding antiviral therapy indications for CHB with minimally (1-2x ULN) ALT elevations.

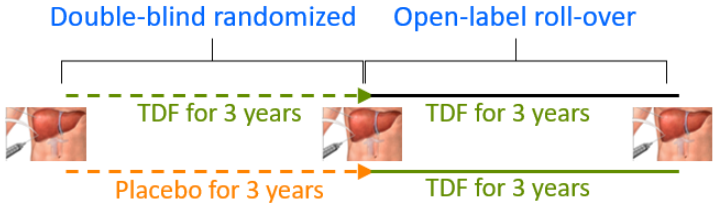
Aim: Assess changes in liver histology after 3 years of TDF

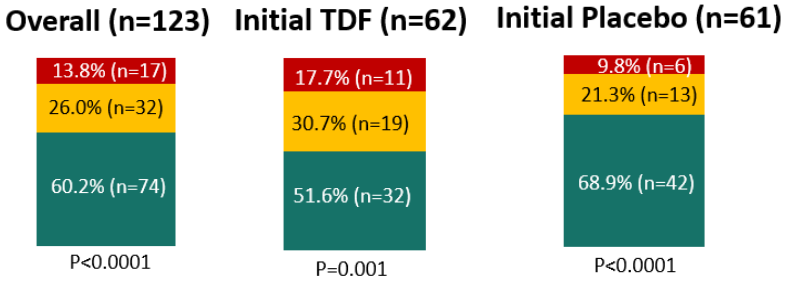
Methods: Open-label rollover study following RCT (TORCH-B) with paired liver biopsies

Results: N=123, median 47 y/o, 80% male, 19% HBeAg+

- Ishak score ≥ 3 points decreased from 27% to 10%
- Knodell improved in 47%: 34% TDF, 61% Placebo
- 5 incident HCC's

Conclusions: Liver pathology improved with 3-year TDF. Changes were more pronounced in placebo switchers, but continued TDF was associated with further improvement.





Hsu YC et al. Abstract 61.

Tenofovir vs Entecavir in Preventing HCC

Background: HBV antiviral therapy reduces risk of HCC, but controversy exists regarding whether choice of agent impacts outcomes.

Aim: Compare HCC incidence in adults with CHB on suppressive TDF or ETV.

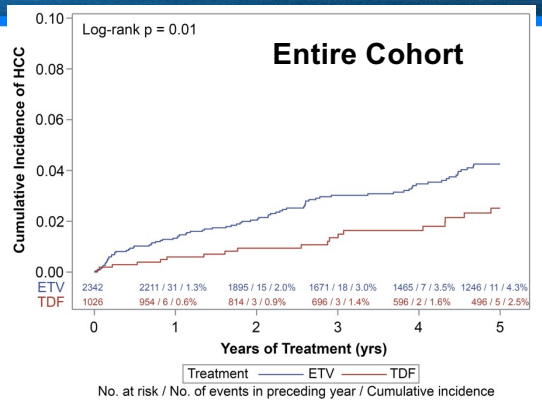
Methods: Retrospective cohort study of all Kaiser Permanente N. California adults with CHB treated with TDF or ETV for ≥1 year 2006-2021.

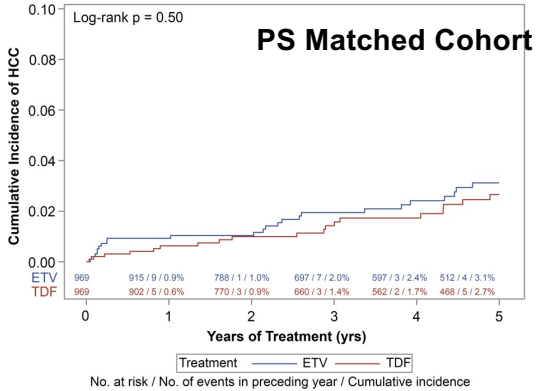
- Pts with >90% adherence by prescription refill data included
- TDF pts 1:1 propensity score (PS) matched to ETV pts on multiple demographic and clinical factors

Results: 3368 pts: 30% on TDF, 70% on ETV

- TDF pts had more favorable clinical characteristics and lower risk of HCC
- 969 TDF pts PS matched to ETV pts: differences in HCC resolved

Conclusions: When PS matching is used, there is no distinguishable advantage by agent. Supports keeping TDF and ETV as front-line CHB treatment.





Saxena V et al. Abstract 64.

Hepatitis B
Novel Therapies

PEG-IFN Following Bepirovirsen in Participants With CHB on Nucleos(t)ide Analogs: End of Study Results From the Phase 2b B-Together study

Background: Bepirovirsen (BPV) is an antisense oligonucleotide targeting all HBV RNAs; given with NA for 12 or 24 weeks, 3-9% achieved HBsAg and HBV DNA loss sustained for 24 weeks after EOT (B-Clear Trial).

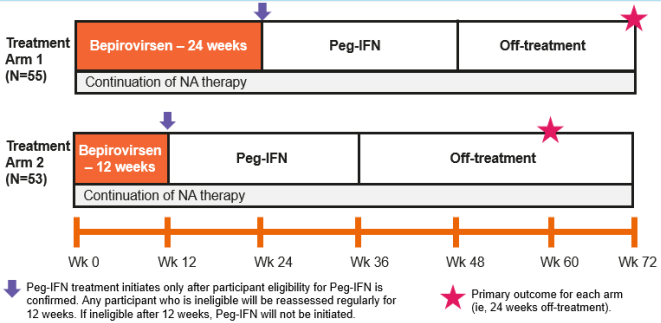
Aim: To examine whether sequential treatment with BPV followed by Peg-IFN could reduce relapse rates and improve responses observed in the B-Clear trial

Methods: Phase 2b, randomized, proof-of-concept trial

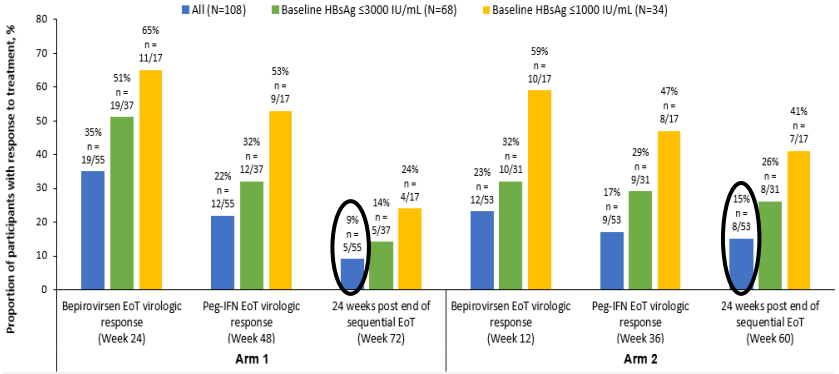
Results: 71% male, 52% Asian, 74% HBeAg neg, 69% HBsAg>1000 IU/mL

- 9-15% achieved sustained HBsAg and HBV DNA <LLOQ
- Low baseline HBsAg predicted response
- Most BPV EOT responders did not relapse on Peg-IFN (58%)
- Only 2 BPV EOT partial responders had Peg-IFN EOT response
- 1 study-related SAE- ALT increase on bepirovirsen

Conclusion: Adding Peg-IFN to BPV regimen does not appear to further reduce HBsAg levels but may prevent relapse in a subset of BPV responders.



Primary outcome: sustained HBsAg and HBV DNA <LLOQ for 24 wks from planned end of PEG-IFN in absence of retreatment



Buti M et al. Abstract 49.

Preliminary Pharmacodynamics & Safety of Imdusiran (AB-729) Followed by VTP-300 or Placebo in Virally-Suppressed CHB

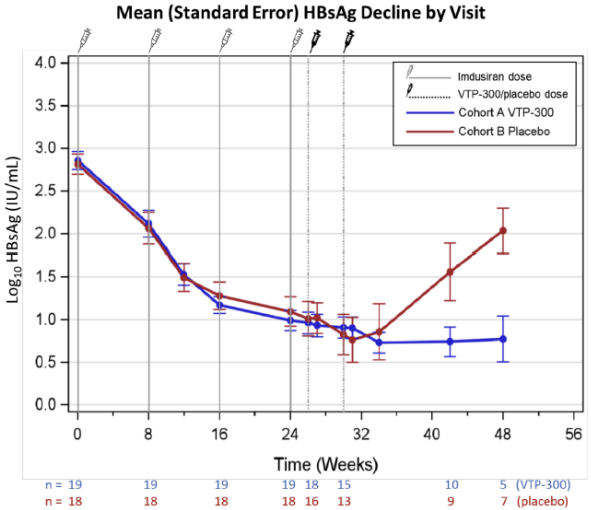
Background: AB-729 is a Gal-NAC conjugated siRNA; VTP-300 is a targeted immunotherapy sequentially combining ChAdOx1/MVA.

Aim: Assess safety, tolerability, immunologic and antiviral activity of AB-729 (to reduce HBsAg) followed by VTP-300 (to enhance HBV-specific T cell response).

Methods: Phase 2a is a randomized, placebo-controlled, multicenter study (AB-729-202).

Results:

- Robust HBsAg declines after 4 doses of AB-729
- Mean HBsAg levels in the placebo group begin to rebound ~12 weeks after the last dose of AB-729
- All VTP-300 treated subjects maintained HBsAg <100 IU/mL through Week 48.
- No Grade 3 or 4 adverse events, no treatment d/c's
- Few treatment-related TEAEs (Grade 1 injection site redness, bruising, and/or pain and mild ALT elevations)



Conclusions: VTP-300 treatment appears to contribute to maintaining low HBsAg levels after AB-729. Follow-up ongoing, and addition of low dose nivolumab to the MVA-HBV dose is enrolling.

Yuen MF et al. LB-Abstract 5036-C.

Hepatitis C Epidemiology

Estimating Prevalence of Hepatitis C Virus Infection in the US, 2017-2020

Background: An estimated 2.4 million people living in the US with HCV RNA positivity based on 2013-2016 data.

Aim: To estimate the national prevalence of HCV in the US during 2017-2020.

Methods: Prevalence models were creating using 2 approaches:

1) NHANES + literature review for estimates among non-NHANES population
2) Above + accounting for under-representation of PWID in NHANES

Results:

- Model 1: estimated 2.46 million HCV RNA+ (95%CI 1.32-3.63 million)
- Model 2: estimated 4.04 million HCV RNA+ (95%CI 2.40-5.61 million)

Conclusions: Despite years of effective cure, estimate prevalence of HCV in 2017-2020 remains unchanged from 2013-2016 when using comparable methodology. It is substantially higher when accounting for increased IDU in the US.

Hall E et al. Abstract LB-5030C.

Hepatitis C
Special Populations

Sofosbuvir/Velpatasvir in Treatment of HCV During Pregnancy: Interim STORC Study Results

Background: HCV treatment during pregnancy has several potential benefits but safety and efficacy data on DAAs during pregnancy are lacking.

Aim: Evaluate the safety and efficacy of SOF/VEL for HCV treatment in pregnancy.

Methods: Multicenter, phase 4, open-label, single-arm study enrolling participants between 20-30 weeks gestation.

Results:

- 17/17 (100%) with SVR assessment achieved SVR12
- 3 preterm births (12.5%); 22 AEs related to SOF/VEL (all maternal); no SAEs related to SOF/VEL
- 16/16 (100%) infants tested had undetectable HCV RNA

Conclusions: Interim data provide preliminary reassurance regarding safety and efficacy of SOF/VEL administered after 20 weeks gestation.

July 2022-Sep 2023

Figure 2. Maternal Participant Flow

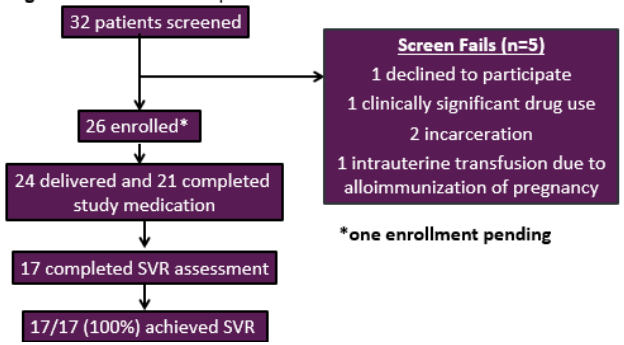
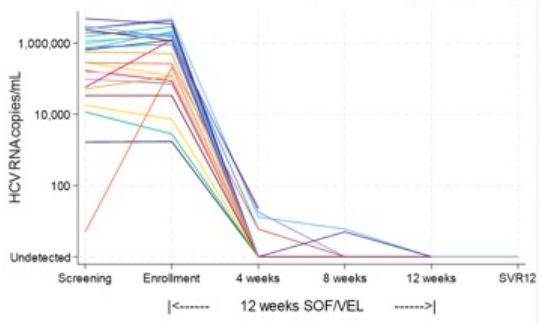


Figure 3. HCV viral response to SOF/VEL during pregnancy



15 participants had HCV RNAs assessed at delivery and all (100%) were undetectable.

Chappell C et al. Abstract LB-5018C.

Ultrashort GLE/PIB and Ezetimibe for HCV D+/R- Solid Organ Transplant: "Toronto Protocol"

Background: G/P and ezetimibe (E) given 1d pre and 7d post-SOT prevented chronic HCV in a clinical trial of 30 D+/R- organ recipients.

Aim: Report extended follow-up of clinical trial (n=30) and outcomes of standard of care (n=59) cohorts

Methods: Primary endpoint: establishment of chronic HCV

Results:

- **SOC cohort:** all but 5 kidney recipients completed full treatment before hospital discharge; none had HCV RNA breakthrough
- **Total cohort**: No virologic breakthrough, HCV complications, or retreatment

Conclusions: Ultrashort G/P + E protocol for HCV D+/R- prevents chronic HCV infection, is well-tolerated, and is feasible.

Aleyadeh W et al. Abstract 56.

Recipients

Variables	Recipients (n=59)
Age (years)	59 (23-80)
Male	35 (59%)
Organ Received	
Lung	14 (24%)
Heart	6 (10%)
Kidney	33 (56%)
Pancreas	3 (5%)
Kidney-Pancreas	3 (5%

Learning from implementation

1 • **Specified Protocol**
  - Notification of all NAT+ donors to:
    - Surgeon
2   - House-staff,
    - Transplant team
3   - Hepatology
  - Order sets for medications & HCV RNA/NAT testing post-op
  - Pre- and post-transplant infographics emailed to all involved staff
  - Follow-up visit with hepatology 3m post-transplant

4 • **Missed/late NAT/HCV RNA testing** in 19 (32%)
• **Regular (monthly) audit** of all charts

AASI

Low Antiviral Treatment Rate for Hepatitis C-Related HCC: A Real-World National U.S. Study

Background: Optimal timing of HCV treatment in patients with HCC is unclear, and practice patterns vary.

Aim: Determine proportion of patients with HCV-related HCC who received DAAs after 2014 and factors associated with treatment

Methods: Retrospective study of patients with HCV-related HCC from 2015-2021 using Optum's Clinformatics® Data Mart Database

Results: 3,922 HCC patients with HCV: 24% received DAA's

- Factors associated with treatment: younger age, cirrhosis, GI/ID specialty care,
- DAA treatment was associated with lower 5-year mortality (aHR 0.61) adjusted for age, sex, race/ethnicity, Charlson Comorbidity Index, and HCC treatment

Conclusions: DAA treatment receipt is associated with improved 5-year survival in patients with HCV-related HCC but is underutilized.

Kam L et al. Abstract 58.

Recompensation after DAA Therapy in Patients With Decompensation: Punjab Real World Data

We enrolled 1152 with decompensated cirrhosis with mean age: 53.2±11.5 years, 62.9% men. mean duration of follow up was 48.3 ± 8.9 months.

The median MELDNa was 16.5 and Child score was 12.7.

The decompensation events included ascites (1098, 95.3%), hepatic encephalopathy (191,16.6%), and history of variceal bleeding (284, 24.7%) at enrolment.

Overall SVR-12 was 81.8%. *Higher CPT and MELD associated with lower SVR*

Progression of PH was noted in 158 patients: with rebleed in 45 (3.9%) during a follow-up period of 48 months.

Recompensation was documented in 284(24.7%).

Predictors of failure to recompensated:
Higher LSM
Prior treatment failure
Presence of high-risk varices
Higher MELD-NA

Premkumar M. AASLD 2023.

Hepatitis D
Epidemiology

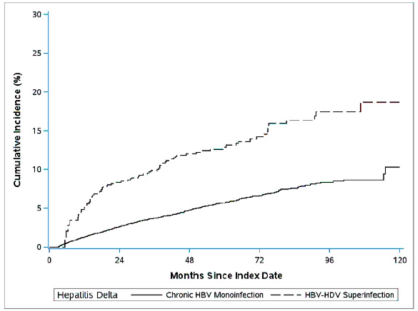
HDV Superinfection Doubles Risk of HCC Versus HBV Infection Alone

Background: HDV disease progression in U.S. population poorly characterized.

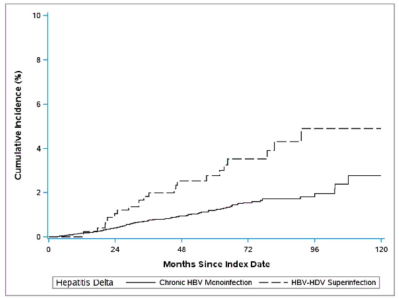
Methods: MarketScan data: CHB and CHB (using ICD-9 codes) from 2008-2017. Inverse probability of treatment weighing used to address differences in baseline characteristics

Results: 36,689 CHB adults; 1,633 CHD adults, median f/I 19 mos

Cirrhosis: aHR 2.94 for CHD vs CHB



HCC: aHR 1.93 for CHD vs CHB



Conclusions: Underscores importance of early diagnosis (need to screen!)

Elsaid MI. AASLD 2023.

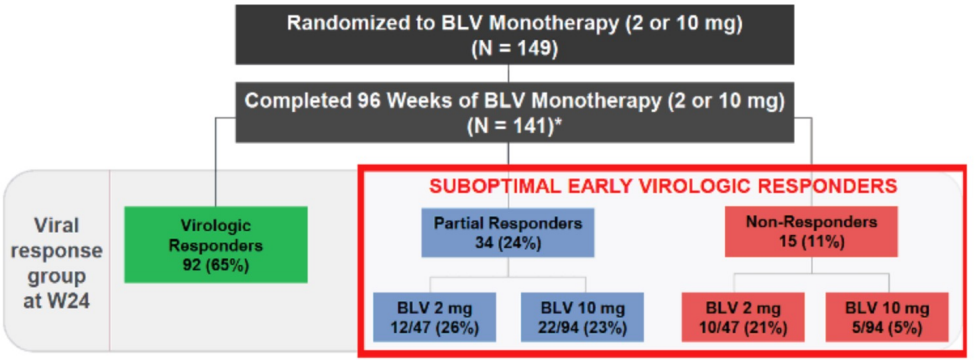
Hepatitis D
Novel Therapies

Continuation of Bulevirtide in Early Virologic Non-Responders or Partial Responders With Chronic Hepatitis D

Background: Bulevirtide (BLV), a novel HDV entry inhibitor, is approved in Europe. The optimal BLV monotherapy duration for CHD is unknown.

Methods: Integrated analysis of clinical trials of BLV 2 or 10 mg monotherapy for 96W (N=141, 43% cirrhosis)

- VR: Undetectable or >2 $\log_{10}$ decline in HDV RNA
- Nonresponse: <1 $\log_{10}$ decline HDV RNA
- Partial response: 1-2 $\log_{10}$ decline HDV RNA



Conclusion: Majority with early suboptimal virologic responses can achieve VR with continued BLV therapy

At W24: 35% had suboptimal response
At W96: 74% of partial responders had VR
At W96: 47% non-responders had VR

Lampertico P et al. Abstract 63.

Monoclonal Antibody VIR-3434 and siRNA VIR-2218 for the Treatment of Chronic Hepatitis D Virus

Background: VIR-3434 is monoclonal AB blocking viral entry and promoting viral clearance of free virions; VIR-2218 is siRNA targeting HBsAg production

Methods: Non-cirrhotic CHD with HDV RNA >500 IU/mL. Treatment endpoint = ≥2 log-decline or undetectable HDV RNA + ALT normalization at W24 (N=5-6 per group)

Results: ALT flares with siRNA monotherapy only (not VIR-3434 or combo)

At 12 weeks	VIR-2218 Q4W N=5	VIR-3434 Q4W N=6	Comb N=6
Mean HDV RNA decline (log)	-1.39	-1.98	-4.29
HDV RNA <LOD	1 (20)	1 (17)	4 (80)
HBsAg decline (log)	-1.35	-1.17	-3.88

Conclusion: Promising - potent and early HDV suppression possible with combination therapy

Asselah T, AASLD; LB5004.


Thank You