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The Liver Meeting®
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THE BEST OF THE LIVER MEETING® 2020

Viral Hepatitis

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

About the program:

Best of The Liver Meeting 2020 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.

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Use of these slides:

Tenofovir disoproxil fumarate lowers transcriptionally active viral integrations of hepatitis B virus infection

Aim

To investigate the effect of viral suppression with TDF on the number of expressed viral integrations in patients with CHB

Methods

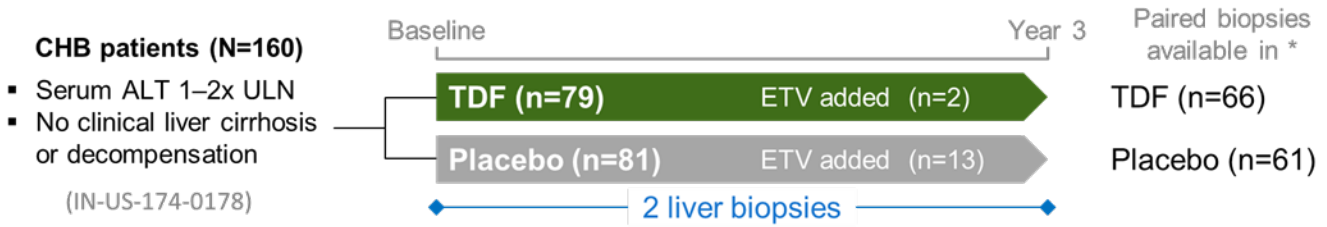
- CHB patients with viremia >2000 IU/mL and minimal ALT elevation (1~2 folds ULN) were randomized to receive either TDF or placebo for 3 years (IN-US-174-0178).
- RNA sequencing was generated from paired liver biopsies, taken at baseline and at 3 years after randomization.
- Expressed viral integrations were quantified and normalized by the sequencing depth and by the fraction of hepatocytes.

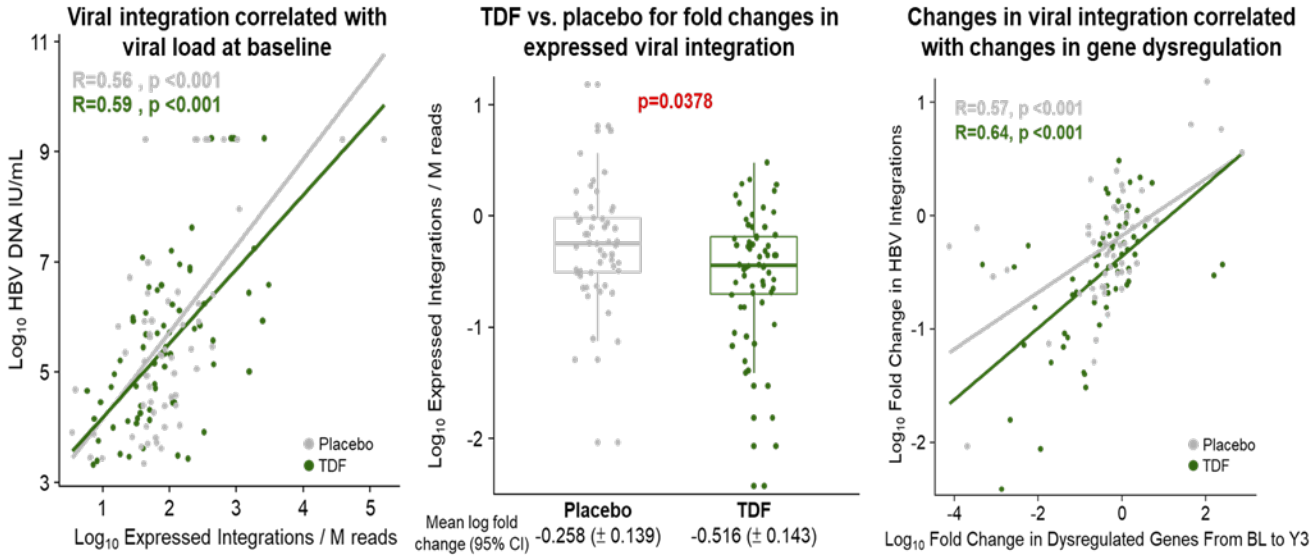
Main Findings

- The unique expressed viral integrations were significantly correlated with viral load and numbers of dysregulated genes.
- TDF vs placebo achieved a greater reduction in expressed viral integrations (mean $\log_{10}$fold-change i_{Mr} -0.516 vs -0.258; P=0.0378).

Conclusion

Viral suppression using TDF for 3 years reduced expressed viral integrations that were implicated in dysregulation of human genes.





Hsu YC, et al., Abstract 16

i_{Mr}: integrations per million sequenced reads

Machine learning reveals NASH/NAFLD may explain lack of ALT normalization after TDF treatment in HBV subjects

Objective

To apply machine learning (ML) models to investigate the basis for persistent elevated ALT in some clinical trial subjects after treatment with tenofovir disoproxil fumarate (TDF) for chronic HBV (CHB)

Methods

ML models detected and quantified cell- and tissue-level histology features from hematoxylin and eosin-stained liver biopsies collected at baseline, Year 1, and Year 5.

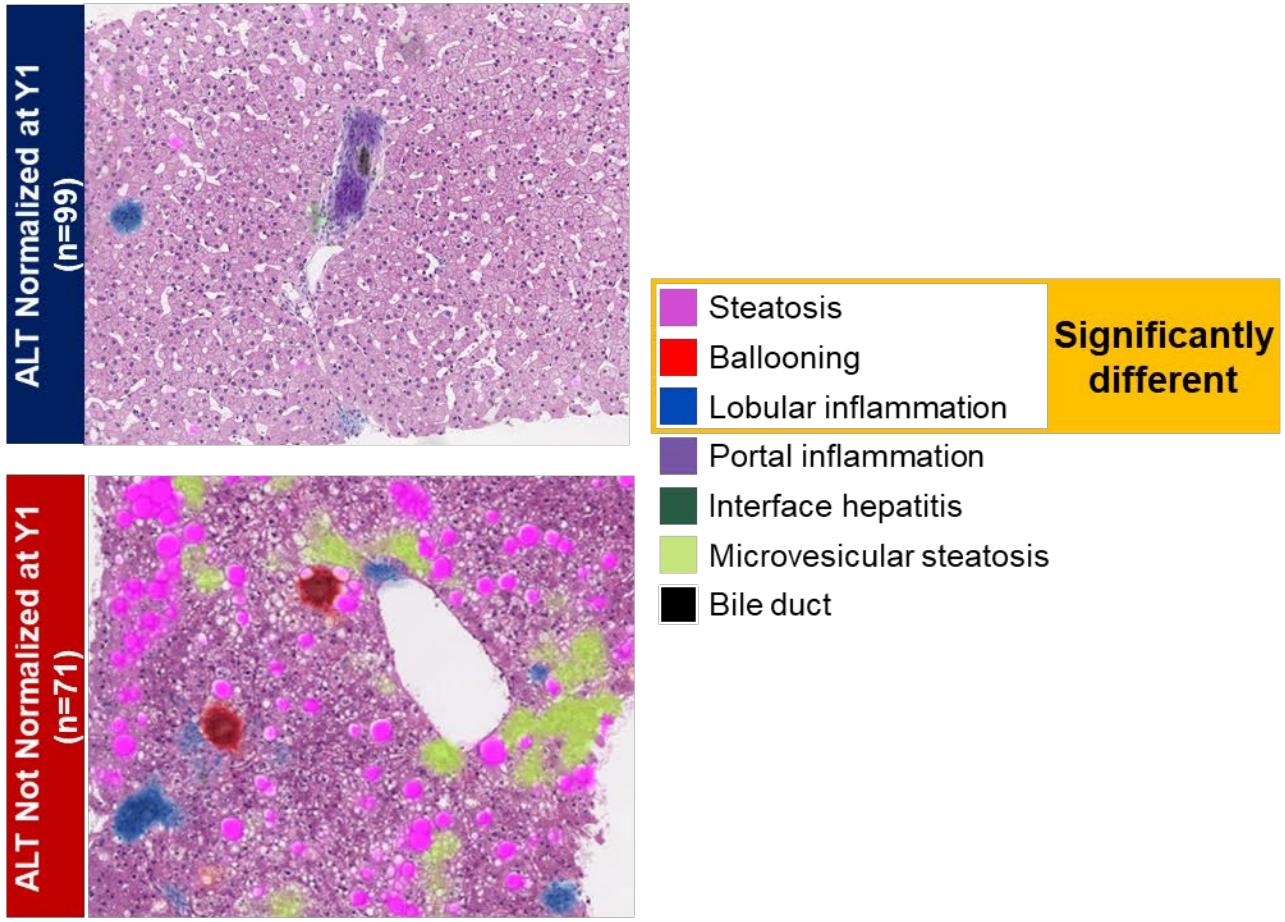
Main Findings

ML-based quantitation demonstrated lobular inflammation, steatosis and hepatocellular ballooning were significantly greater in CHB subjects who lacked ALT normalization (Figure). Furthermore, in an analysis of subjects who had suppressed virus at Y1 (HBV DNA ≦ 69 IU/mL and HBeAg negative), steatosis and hepatocellular ballooning worsen over time in subjects with lack of ALT normalization.

Conclusions

Liver histology signatures consistent with NAFLD/NASH were found in subjects that do not normalize ALT after TDF treatment.

Shukla C, et al., Abstract 18



Randomized trial of 192 weeks of tenofovir with or without peginterferon alfa for the first 24 weeks followed by protocolized withdrawal in adults with chronic hepatitis B

Aim

To evaluate the safety and efficacy of 192 weeks of tenofovir (TDF) alone or in combination with 24 weeks Peg-IFN alfa-2a (pIFN) followed by *protocolized treatment withdrawal* in adults with immune active CHB

Methods

Randomized 1:1 to TDF + pIFN or TDF for 192 weeks, then TDF was discontinued if eligible (=HBeAg negative, anti-HBe positive, HBV DNA <1000 IU/mL for 24 weeks) and outcomes assessed at Week 240

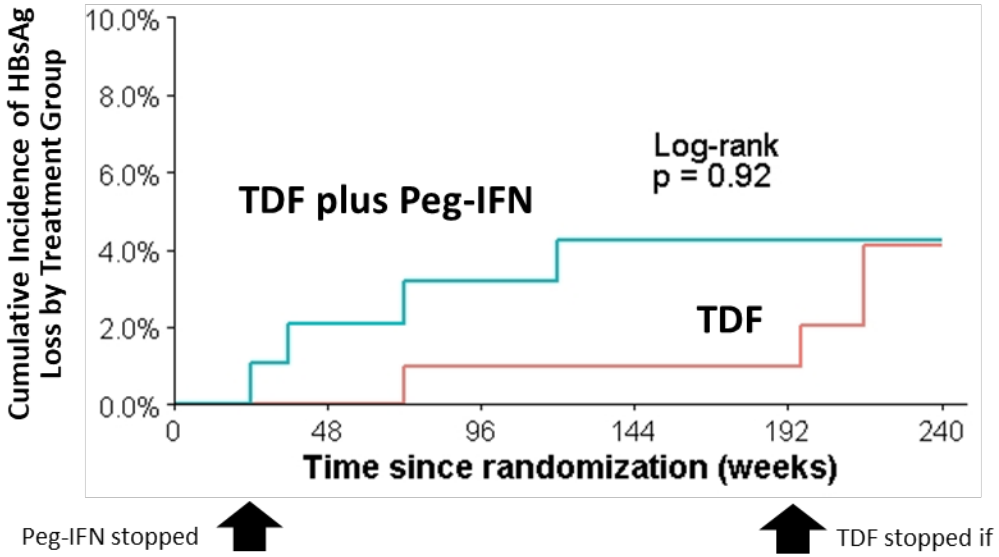
Main Findings

- TDF/TDF + pIFN at baseline: median age 41 years; cirrhosis 7%; HBeAg+ 53%/49%; genotype A 15%/7%; HBV DNA 6.7/6.3 log IU/mL; qHBsAg 3.1/3.6 log IU/mL
- % eligible for stopping TDF: 61% TDF/pIFN, 50% TDF

Conclusions

- Withdrawal of TDF after 4 years can be safely achieved in most patients meeting protocolized criteria.
- HBsAg loss not significantly enhanced by combination TDF + pIFN followed by TDF withdrawal.

Outcomes at Week 240	TDF N=102	TDF Plus Peg-IFN N=99	*P* value
HBsAg Loss	4 (4.5%)	5 (5.7%)	0.74
HBeAg Loss (N=93)	20 (41%)	27 (61%)	0.06
HBV DNA <1000 IU/mL + Normal ALT*	39 (45%)	41 (49%)	0.64



Terrault NA, et al., Abstract 19

Efficacy and safety of TAF for preventing mother-to-child transmission of hepatitis B

Aim

To investigate if TAF therapy during the 2nd or 3rd trimester is effective and safe for preventing HBV transmission

Methods

- Multicenter, single-arm, retrospective national cohort study
- HBV mono-infected HBeAg (+) mother with HBV DNA >200,000 IU/mL received TAF during late trimester. Infant received immunoprophylaxis (HBIg at birth, vaccine 0/1/6).

Main Findings

- TAF reduced maternal viremia by 3.7 log IU/mL at delivery, 86% of mothers achieved HBV DNA levels <200,000 IU/mL.
- At the age of 24-28 weeks, none of the infants had HBsAg (+) or detectable levels of HBV DNA. No congenital malformation was reported.

Conclusions

TAF is effective for preventing HBV transmission.

Mothers (mean ± SD, specified)	n=71
Age (years)	30.3 ± 2.2
HBV DNA-Log_{10} (IU/mL)	7.78 ± 0.72
ALT, U/L (normal ≤40)	32.64 ± 68.86
HBeAg Positivity, n (%)	71/71 (100)
Duration of TAF (weeks)	13 ± 4

Infants at Birth	n=73
Gestational Age (weeks)	38.22 ± 2.94
Infant Height (cm)	50.55 ± 2.03
Infant Weight (kg)	3.32 ± 0.41
APGAR Score at 1 Minute	9.70 ± 1.11
Detectable HBV-DNA at Birth, n (%)	0/52 (0)

Ding Y, et al., Abstract 20

HBsAg loss is higher among Caucasians compared to Asians after stopping nucleos(t)ide analogue therapy (RETRACT-B study)

Main Aim

To evaluate HBsAg loss following cessation of NA therapy in a large, global, multi-center, multi-ethnic cohort of CHB patients

Methods

- Retrospective cohort study of 1541 CHB patients who stopped NA therapy
- Patients were HBeAg negative with undetectable HBV DNA at the time of cessation without coinfection (HCV, HDV, HIV) or (peg)interferon treatment within a year prior to cessation of NA therapy.

Main Findings

Cumulative rates of HBsAg loss were 3% and 14% at 1 year and 4 years, respectively.

Conclusions

Caucasians had almost a 6-fold higher rate of HBsAg loss compared to Asians.

Hirode G, et al., Abstract 23

	Univariate Cox Models Hazard Ratio (95% CI)	*p*	Multivariable Cox Model Hazard Ratio (95% CI)	*p*
Age at Cessation				
< 50 y	1.0 (Reference)		1.0 (Reference)	
≥ 50 y	**1.7 (1.1 - 2.5)**	**0.01**	1.4 (0.9 – 2.3)	0.12
Sex				
Female	1.0 (Reference)		1.0 (Reference)	
Male	1.4 (0.9 – 2.2)	0.17	1.4 (0.8 – 2.3)	0.20
Race				
Asian	1.0 (Reference)		1.0 (Reference)	
Caucasian	**5.5 (3.5 – 8.4)**	**<0.001**	**5.8 (3.6 – 9.5)**	**<0.001**
NA Type				
ETV	1.0 (Reference)		1.0 (Reference)	
TDF	**2.0 (1.3 – 3.0)**	**0.001**	1.4 (0.9 – 2.2)	0.18
Start-of-therapy HBeAg Status				
Negative	1.0 (Reference)		1.0 (Reference)	
Positive	0.7 (0.4 – 1.2)	0.21	1.0 (0.5 – 2.0)	0.98

Determining feasibility of hepatitis C elimination in the United States using a simulation model

Objective

To determine what levels of hepatitis C screening and treatment are needed in each state in the U.S. to meet the WHO elimination goals by 2030

Methods

We used a previously validated microsimulation model that simulates disease progression in hepatitis C patients in the U.S., and estimated state-level HCV prevalence by insurance coverage and incarceration status.

Main Findings

- We need to implement *universal* screening of all adults in all subpopulations to meet goal of 90% diagnosis coverage by 2030.
- If universal screening is implemented at rate needed to meet diagnosis goal, all treatment strategies tested resulted in the treatment coverage goal also being met in 2030. No screening and treatment policy will be able to achieve 65% reduction in liver-related deaths, but higher treatment rates reduce mortality.

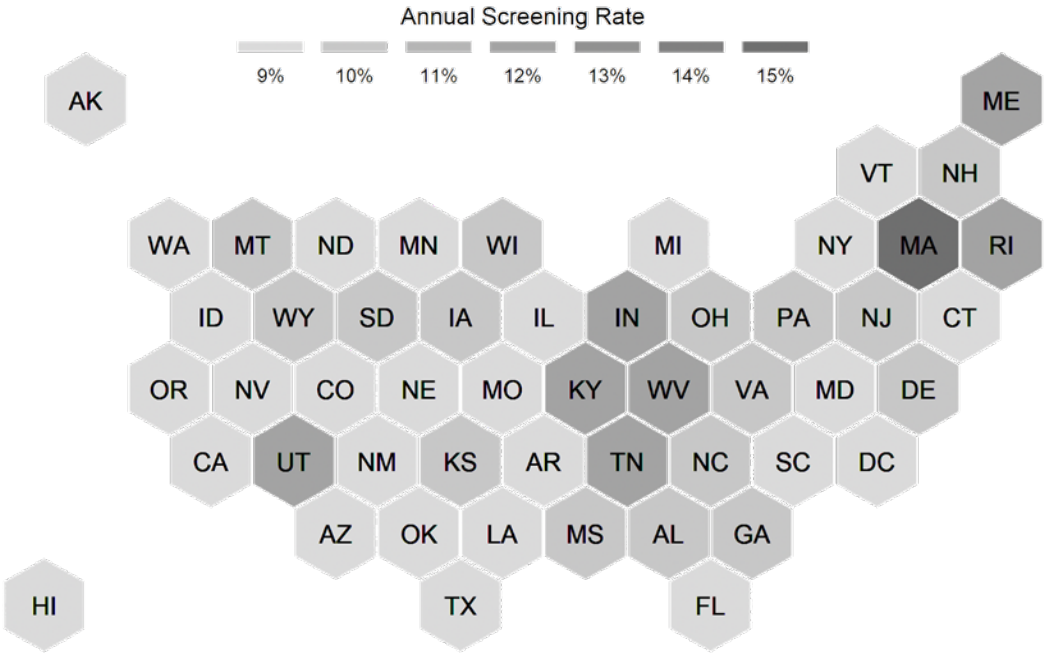


Figure. The annual universal screening rate needed in each state to meet 90% diagnosis coverage in 2030. Range: 9% - 15%. National mean: 9.8%.

Conclusions

WHO diagnosis and treatment coverage targets can be met in the U.S. with universal screening; mortality reduction target cannot be met but mortality can be substantially reduced with aggressive treatment.

Adee M, et al., Abstract 43

Can hepatitis C treatment with direct-acting antivirals be cost saving? A global modeling study of 158 countries

Objective

To determine at what price and timeframe DAA treatment becomes cost-saving

Methods

Previously validated microsimulation model used to simulate disease progression in a cohort of hepatitis C patients in 158 countries. Model adapted to costs and epidemiology of each country. Compared DAA treatment vs no treatment.

Main Findings

- Median threshold prices for income groups to achieve cost-savings in 5 years: Low - $64, Lower middle - $156, Upper middle - $665, High - $3,682. Some countries have already achieved a DAA price that makes treatment cost-saving in 5 years or in 10 years.
- The percentage of healthcare budget needed to treat HCV (at 5-year cost-saving price) is lower in lower income countries and higher in higher income countries (see Figure).

Conclusions

Treating hepatitis C with DAAs can be cost-saving and prevent many premature deaths.

Adee M, et al., Abstract 45

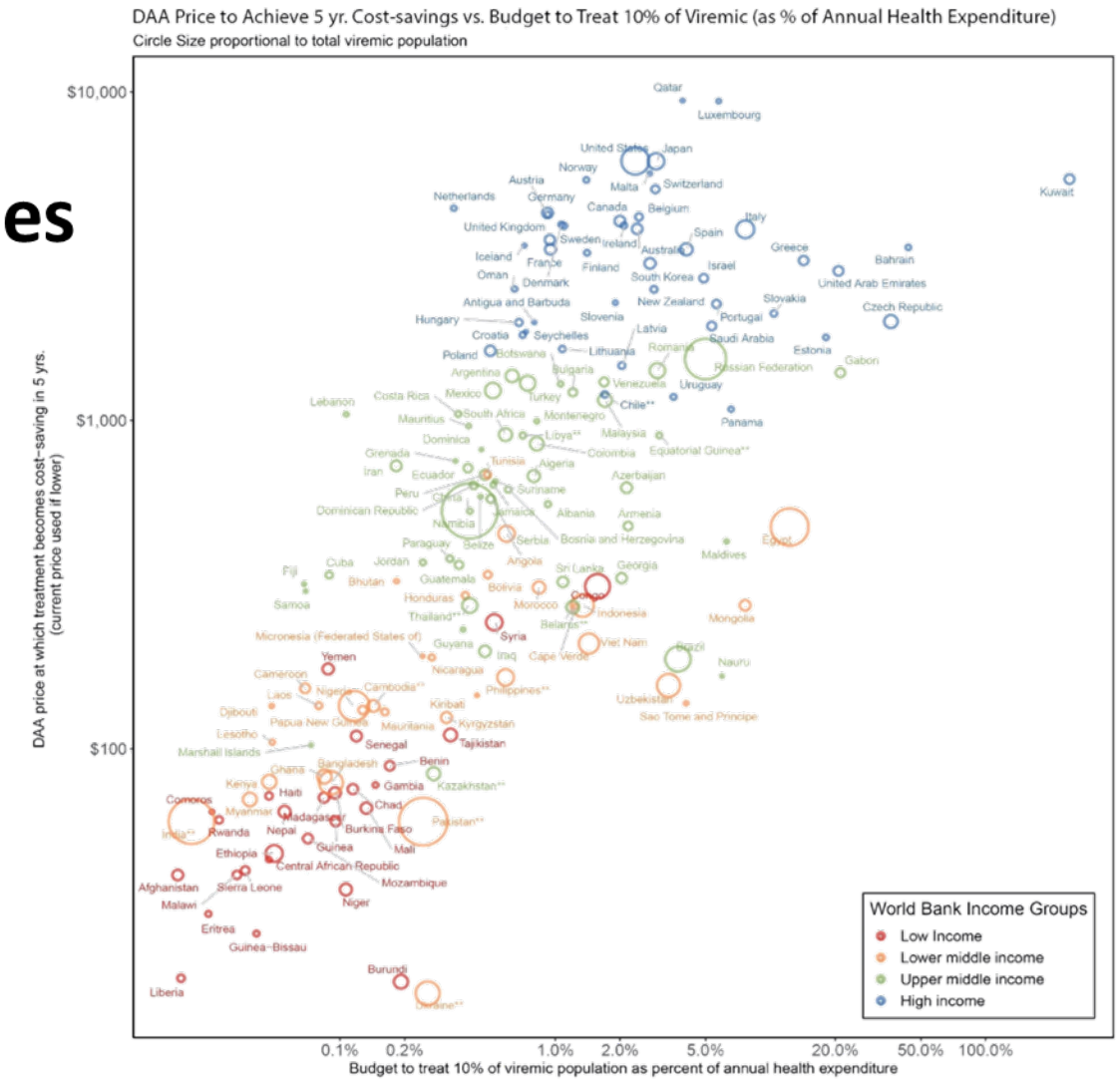


Figure. DAA price to achieve cost-savings in 5 years vs budget to treat 10% of viremic population (as % of annual health expenditure)

Country and WHO regional trends for HCV mortality, 1990-2019: an analysis of the GBD study

Objective

Estimate trends in country level HCV-related deaths and mortality rate from 1990-2019 and 2015-2019 to monitor progress towards WHO elimination targets

Methods

With Global Burden of Disease Study 2019 results, estimate percent change in national HCV death counts and mortality rates for the years 1990-2019 and 2015-2019

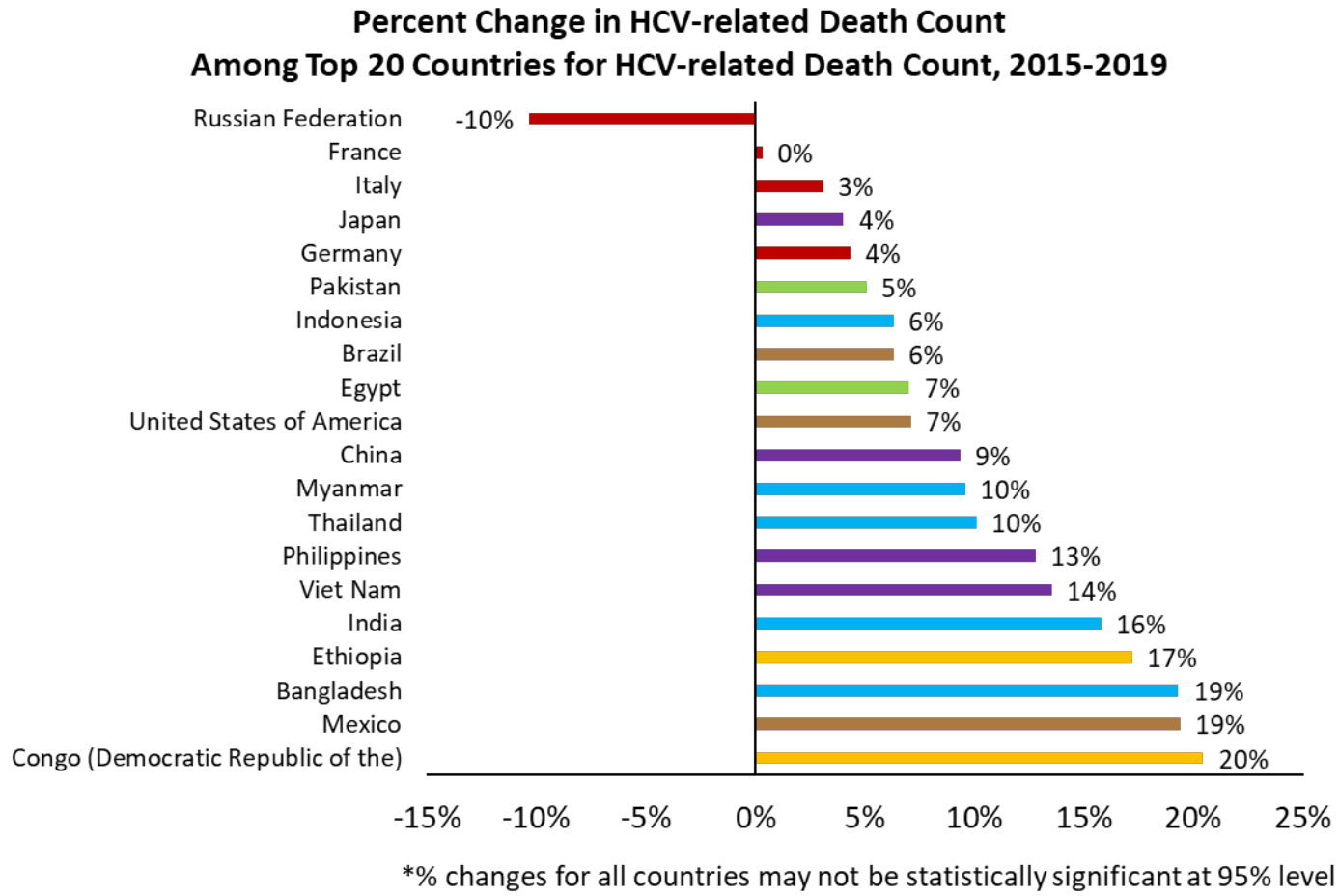
Main Findings

- In 2019, an estimated 542,326 deaths were attributed to HCV infection.
- From 2015-2019, HCV-related mortality increased in a majority of the top 20 countries for HCV mortality burden (see Figure).

Conclusions

Over 75% of global HCV deaths occurred in top 20 burden countries in 2019, and only one of these countries is on track to meet 2020 targets (Russian Federation).

Adams A, et al., Abstract 48



HBsAg reduction by nasal administration of a therapeutic vaccine containing HBsAg and HBcAg (NASVAC) in patients with chronic HBV infection: the results of 18 months follow up

Hypothesis/Aim/Objective

To evaluate the HBsAg reduction during 18-months follow-up after a nasal administrative therapeutic vaccine (NASVAC) treatment

Methods

Open-label study of NASVAC in HBV carrier with/without NAs treatment

Main Findings

- HBs reduction at 18 months was -0.1546 Log IU/mL in CHB under NAs and -0.2965 Log IU/mL in CHB w/o NAs
- About 50% of participants maintained anti-HBs until 18 months
- Total 6 patients achieved functional cure at 18 months.

Conclusions

Further HBsAg reduction and more HBsAg loss were observed during longer follow up after NASVAC treatment.

	Under NAs treatment				Without NAs treatment			
	baseline	EOT	6mo after EOT	18mo after EOT	baseline	EOT	6mo after EOT	18mo after EOT
Patient numbers reach to each time point	n=29	n=29	n=29	n=22	n=42	n=42	n=42	n=33
ALT (meam, U/L)	22.6	22.6	23.3	22.8	24.3	22.4	22.4	23.1
HBsAg reduction (LogIU/mL)		-0.0466	-0.1003	-0.1546		-0.1630	-0.1902	-0.2965
Percent of patients lower than the baseline (HBsAg)		69.0% (20/29)	75.9% (22/29)	72.3% (16/22)		73.8% (31/42)	76.2% (32/42)	78.9% (26/33)
HBsAg negativity	0% (0/25)	3.4% (1/29)	6.9% (2/29)	9.1% (2/22)	0% (0/33)	0% (0/38)	4.8% (2/42)	12.1% (4/33)
Anti-HBs positivity	3.4% (1/29)	37.9% (11/29)	34.5% (10/29)	31.8% (7/22)	21.4% (9/42)	61.9% (26/42)	59.5% (25/42)	57.6% (20/33)
HBeAg positivity	24.1% (7/29)	24.1% (7/29)	24.1% (7/29)	27.3% (6/22)	4.8% (2/42)	4.8% (2/42)	2.4% (1/42)	3.0% (1/33)
Anti-HBe positivity	48.3% (14/29)	62.1% (18/29)	62.1% (18/29)	68.1% (15/22)	97.6% (41/42)	97.6% (41/42)	97.6% (41/42)	96.7% (1/33)
HBV-DNA (mean, Log IU/mL)	0	0	0	0	2.48	2.43	2.51	2.19
Percent of patients lower than the baseline(HBV-DNA)						54.8% (33/42)	59.5% (25/42)	51.5% (17/33)
HBV-DNA negativity	93.1% (27/29)	96.6% (28/29)	100% (29/29)	100% (22/22)	7.1% (3/42)	14.3% (6/42)	7.1% (3/42)	12.1% (4/33)
HBcrAg (mean, Log U/mL)	4.16	3.99	3.9	3.78	3.24	3.21	3.11	3.1
Functional Cure Achievement		3.4% (1/29)	6.9% (2/29)	9.1% (2/22)		0% (0/42)	4.8% (2/42)	12.1% (4/33)

Yoshida O, et al., Abstract 80

Association of aspirin with hepatocellular carcinoma in patients with chronic hepatitis B with or without cirrhosis

Objective

To investigate the association of aspirin use with the risk of HCC development, liver-related mortality, and major bleeding in patients with chronic hepatitis B (CHB) with or without cirrhosis

Methods

A Korean population-based study, including 38,006 CHB patients

Main Findings

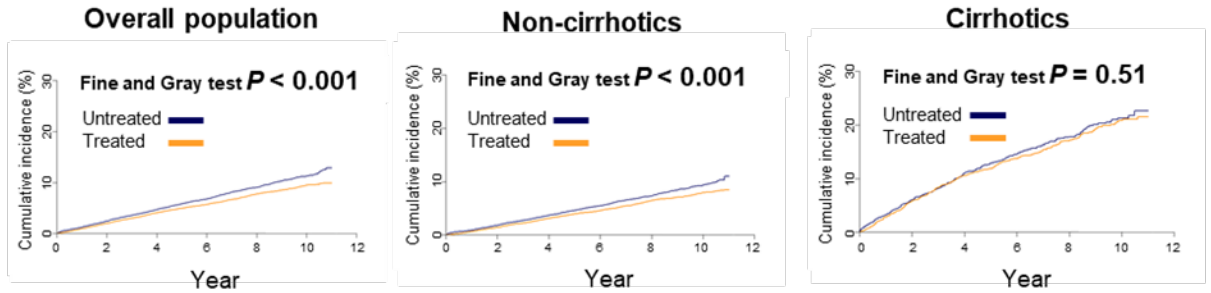
- Use of aspirin had a significant association with reduced risk of HCC and liver-related mortality in overall population. However, the association was not evident among cirrhotic patients (n=4958).
- Aspirin use was not associated with the risk of major bleeding in overall population, but it showed an association with higher risk of major bleeding among non-cirrhotic patients (n=33,014).

Conclusions

Aspirin use was associated with lower risk of HCC and liver-related mortality in CHB patients, but its chemopreventive effect was limited in cirrhotics.

Jang H, et al., Abstract 159

Risk of HCC Development According to Aspirin-Use Status



Outcomes	No. of patients	Adjusted HR (95% CI)	*P* value
Hepatocellular carcinoma			
Overall population	**38,006**	**0.85 (0.78-0.92)**	**<0.001**
Non-cirrhotics	**33,014**	**0.87 (0.79-0.95)**	**0.002**
Cirrhotics	**4,958**	**1.00 (0.85-1.18)**	**0.99**
Liver-related mortality			
Overall population	38,006	0.80 (0.71-0.90)	<0.001
Non-cirrhotics	33,014	0.84 (0.73-0.97)	0.016
Cirrhotics	4,958	0.91 (0.72-1.14)	0.40
Major bleeding			
Overall population	38,006	1.09 (0.99-1.21)	0.07
Non-cirrhotics	33,014	1.15 (1.03-1.28)	0.014
Cirrhotics	4,958	1.05 (0.84-1.31)	0.68

Tenofovir alafenamide to prevent perinatal hepatitis B transmission: a multicenter, prospective, observational study

Hypothesis/Aim/Objective

To investigate the safety and effectiveness of tenofovir alafenamide fumarate (TAF) during pregnancy for the prevention of mother-to-child transmission (MTCT) of hepatitis B virus (HBV)

Methods

Pregnant women with HBV DNA levels higher than 200,000 IU/ml were treated with TAF from gestational weeks 24-35 to delivery and their infants were received immunoprophylaxis at birth and were tested for the hepatitis B surface antigen (HBsAg) status at 7 months.

Conclusions

Antiviral prophylaxis with TAF was generally safe for both mothers and infants and reduced the MTCT rate to 0%.

Characteristics of the Mothers	n=116
Age, years	29.6 ± 4.5
Gestational Age, weeks	28.2 ± 2.1
Most Common Maternal Adverse Events	
Nausea	22 (19.0)
Anorexia	18 (15.5)
Fatigue	14 (12.1)
Most Common Maternal Complications	
Premature Rupture of Membranes	15 (12.9)
Preterm Labor	4 (3.4)
Gestational Hypertension	2 (1.7)
Characteristics of the Infants at Birth	n=117
Gestational Age, weeks	39.2 ± 1.4
Apgar Score at 1 Minute	9.6 ± 0.5
Congenital Defects or Malformations	0 (0)
Anthropometric Indexes at Birth and 7 Months	Normal
HBsAg-positive Infants at 7 Months	0 (0)

Zeng QL, et al., Abstract 160

Country and WHO regional trends for HBV mortality, 1990-2019: an analysis of the GBD study

Objective

Monitor progress towards the interim WHO target for HBV elimination of a 10% reduction in HBV mortality from 2015-2020

Methods

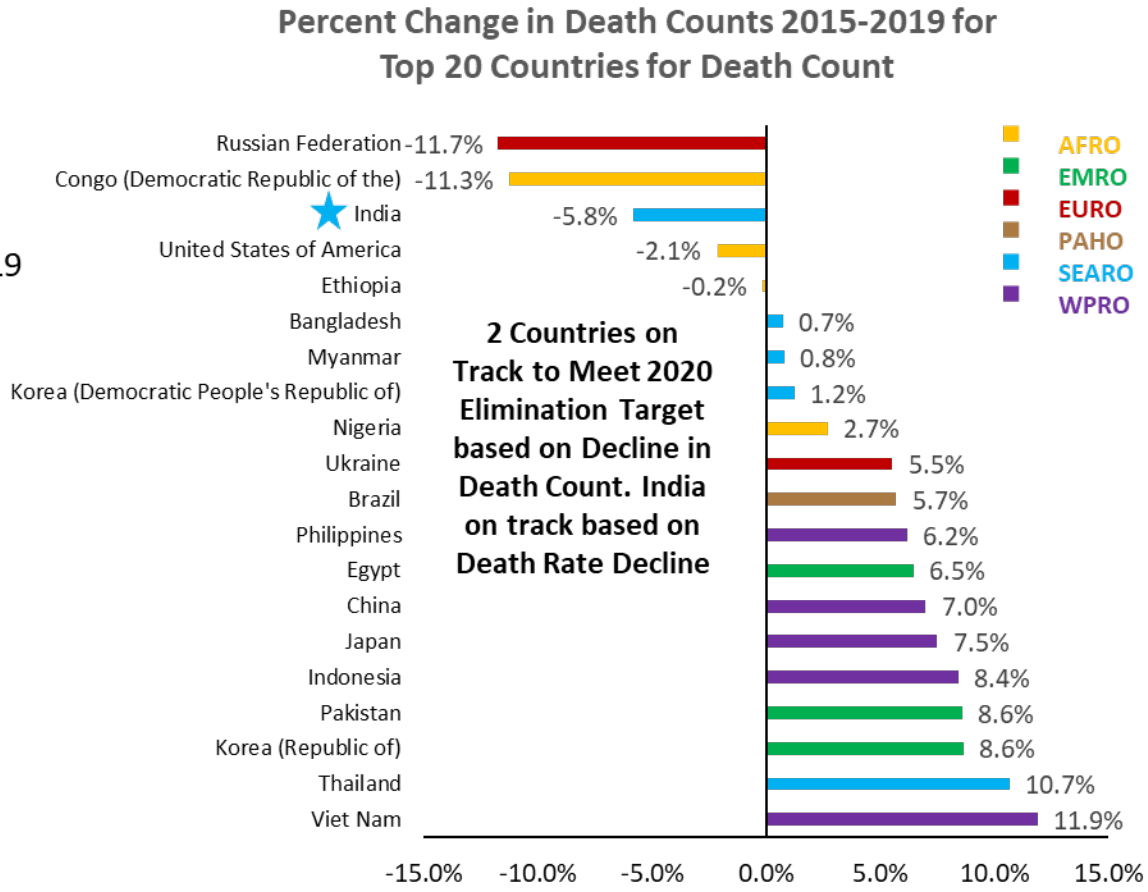
With Global Burden of Disease Study 2019 results, estimate percent change in national HBV death counts and mortality rates for the years 1990-2019 and 2015-2019

Main Findings

- In 2019, an estimated 555,487 deaths were related to HBV infection.
- From 2015-2019, HBV-related mortality increased globally (3%) and among the 20 countries with 81% of global HBV mortality burden (figure)

Conclusions

- HBV continues to be a major cause of death globally.
- Data suggests 25 countries are on track to meet the 2020 target of a 10% reduction in HBV mortality.
- 20 countries represent 81% of global HBV deaths; only 3 appear to be on track to meet the 2020 goals.
- Global HBV elimination requires scale up of birth-dose, testing, and treatment in high-burden countries.



*% changes for all countries may not be statistically significant at 95% level

Obiekwe R, et al., Abstract 162

The “keep it simple and safe” approach to HCV treatment: primary outcomes from the ACTG A5360 (MINMON) study

Objective

To evaluate the efficacy and safety of a minimal monitoring (MINMON) approach to deliver HCV therapy globally

Methods

- Phase 4, open-label, multi-country trial in 400 treatment-naïve participants with active HCV infection
- MINMON included: (1) no pre-treatment genotyping; (2) all 84 tablets dispensed at baseline; (3) no scheduled on treatment clinic/lab visits; (4) two remote contacts at Weeks 4 and 22

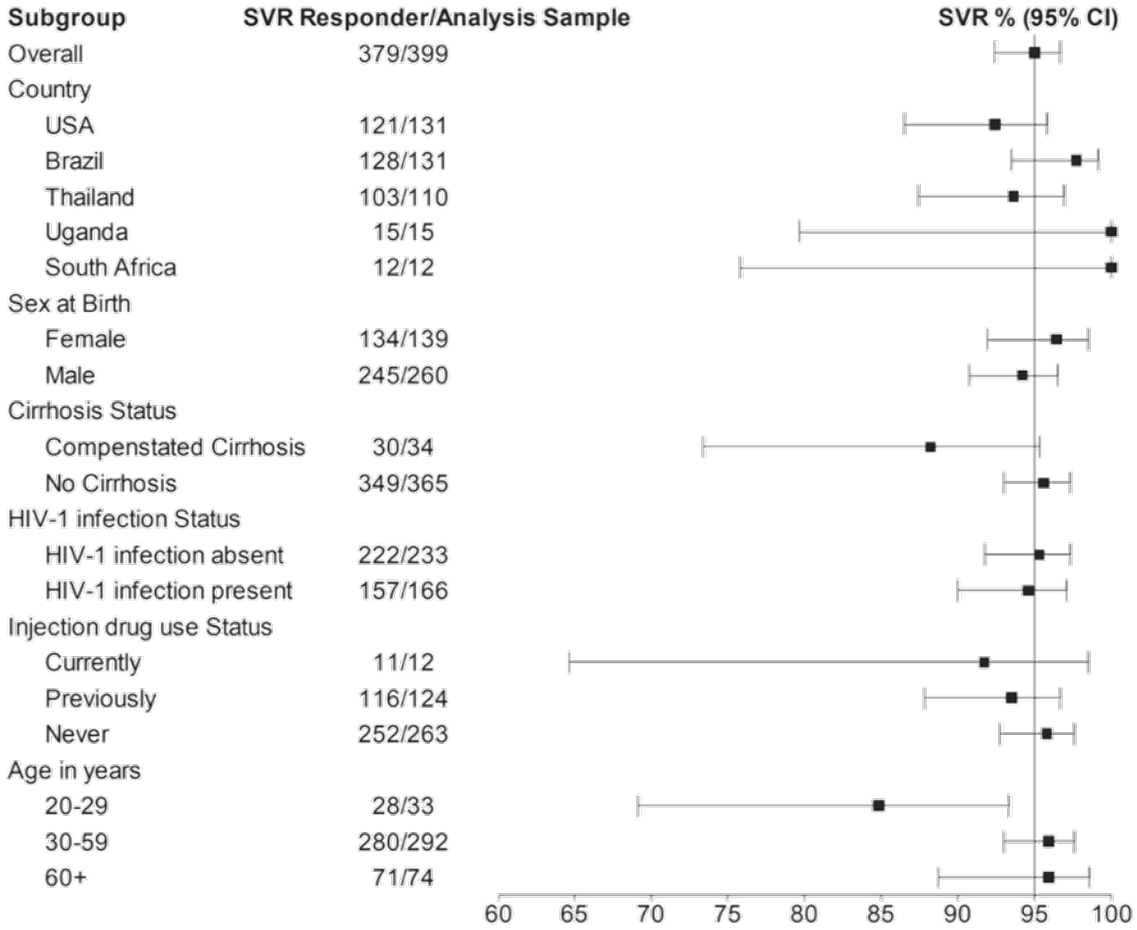
Main Findings

- 379/399 who initiated Rx achieved SVR (Overall SVR: 95%; see Figure).
- 14 (3.5%) SAEs were reported thru Week 28; none were treatment related or resulted in treatment discontinuation/death.

Conclusions

MINMON approach to HCV treatment delivery with SOF/VEL was simple, safe, and achieved SVR comparable to current clinical standards in treatment-naïve persons without decompensated cirrhosis.

Solomon SS, et al., Abstract L07



Peginterferon lambda, lonafarnib, and ritonavir for 24 weeks: results from the LIFT HDV study

Aim

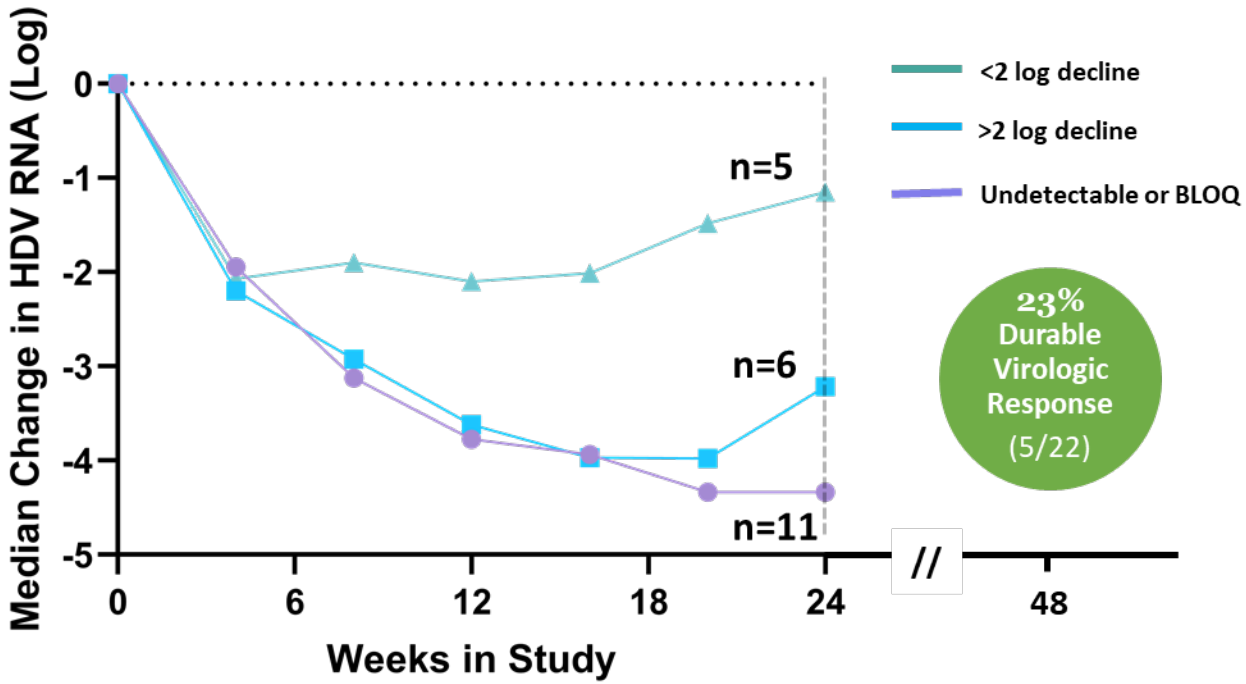
To evaluate the safety and antiviral effects of combination therapy with peginterferon lambda (LMD), lonafarnib (LNF), and ritonavir (RTV) in chronic HDV-infected patients

Methods

Phase 2 open-label prospective trial evaluating LMD/LNF/RTV in 26 patients for 24 weeks of therapy followed by 24 weeks of post-therapy follow-up

Conclusions

After 24 weeks of therapy, >75% of subjects achieve >2 log decline in HDV RNA with 50% achieving undetectable or below the lower limit of quantification HDV RNA levels.



Koh C, et al., Abstract L08

HBV RNAi inhibitor RG6346 in phase 1b-2a trial was safe, well-tolerated, and resulted in substantial and durable reductions in serum HBsAg levels

Objective

To evaluate the safety and efficacy of RG6346 and long-term follow-up in a phase 1b-2a trial of chronic HBV patients (HBeAg pos/neg)

Methods

Double-blind, placebo-controlled trial including 4 monthly doses of RG6346 (1.5, 3.0, and 6.0 mg/kg) in NUC suppressed CHB patients (n=18; RG6346:placebo=2:1)

Main Findings

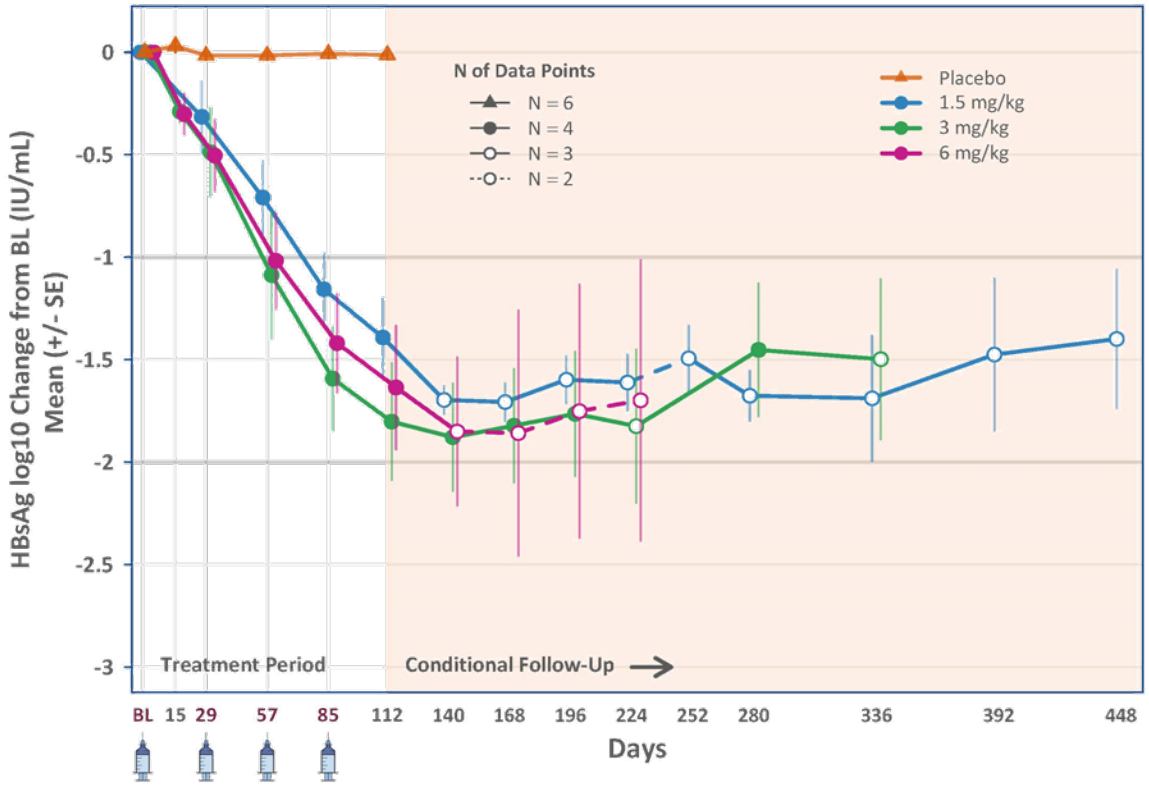
- RG6346 elicited a strong (>1 $\log_{10}$ IU/mL in all dose cohorts) and durable (observed up to D448) reduction in mean HBsAg levels compared with placebo, independent of HBeAg status.
- Max. individual HBsAg reduction is 2.66 $\log_{10}$ IU/mL, 7/12 (58%) achieved HBsAg <100 IU/mL.
- No SAEs, withdrawals due to AE, dose-limiting toxicities, or dose-exposure relationship with AEs/safety labs.

Conclusions

RG6346 was shown to be safe and well tolerated to date, while providing significant and durable reductions in HBsAg levels lasting up to one year after last dose, supporting the potential role of RG6346 as a backbone of a finite treatment regimen with the goal of functional cure in patients infected with CHB.

Yuen MF, et al., Abstract LO9

Mean HBsAg $\log_{10}$ IU/mL Change From Baseline in NUC sup CHB pts



A multisite randomized pragmatic trial of patient-centered models of hepatitis C treatment for people who inject drugs: the HERO study

Objective

To compare SVR rates in active people who inject drugs (PWID) among those who initiated treatment using *modified Directly Observed Therapy (mDOT)* compared to *Patient Navigation (PN)* at methadone programs and community-based clinics

Methods

We conducted a pragmatic randomized trial in 8 US states testing the effectiveness of mDOT vs mDOT on treatment initiation, adherence (measured by electronic packs), treatment completion, and SVR. Eligible PWID (injecting within prior 12 weeks) were randomized 1:1 to mDOT or PN and were treated with 12 weeks of sofosbuvir/velpatasvir.

Conclusions

SVR rates were similar with mDOT and PN models. More than 80% of PWID initiated and completed treatment; adherence was higher with mDOT but not PN.

Litwin AH, et al., Abstract LO10

Figure 1. Cascade of Care

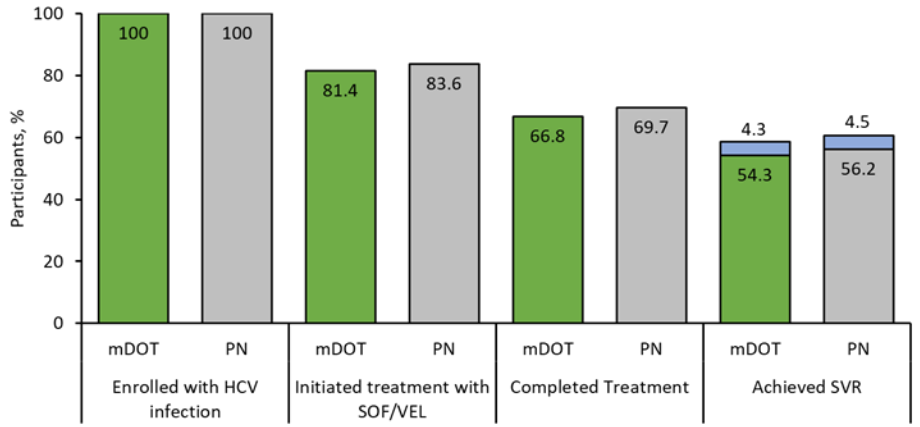
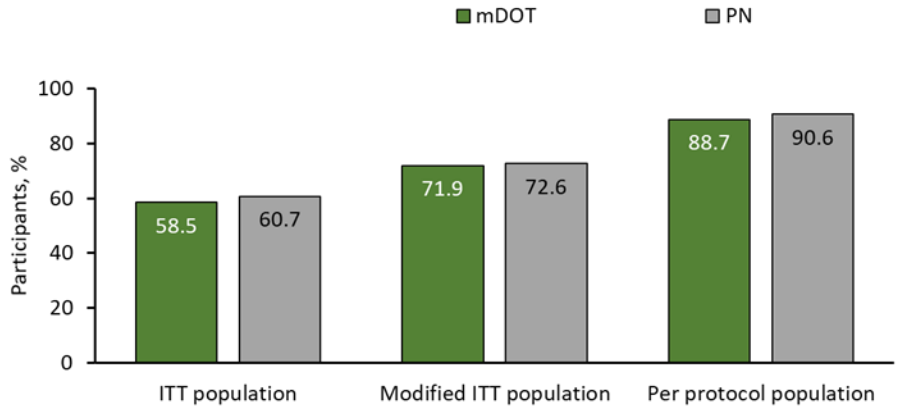


Figure 2. SVR



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