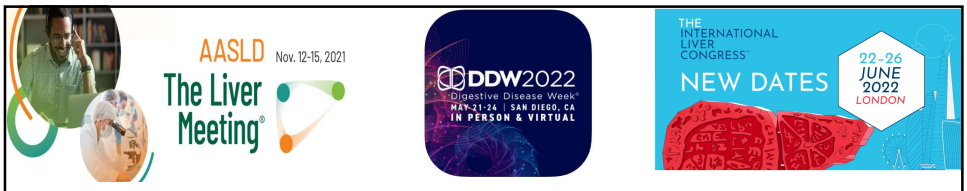
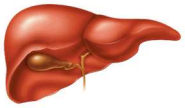


QUAN ĐIỂM MỚI VỀ VIÊM GAN VIRUS

TỪ AASLD 2021- DDW 2022 - EASL 2022



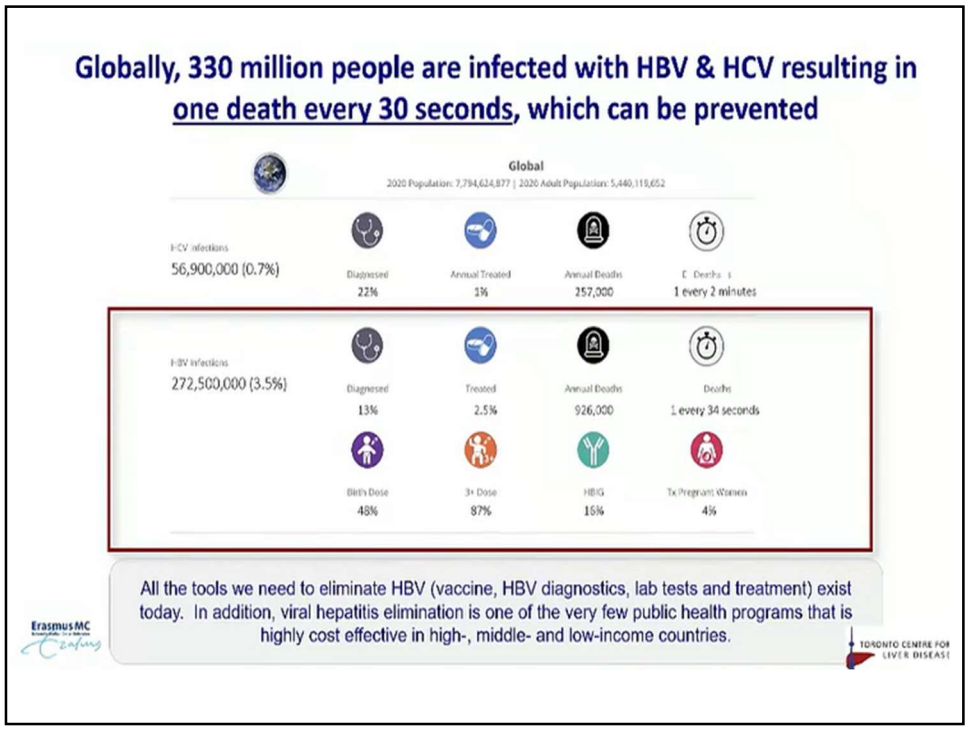
PGS. TS. BS. Phạm Thị Thu Thủy
Trung Tâm Y Khoa MEDIC, TP. Hồ Chí Minh

1

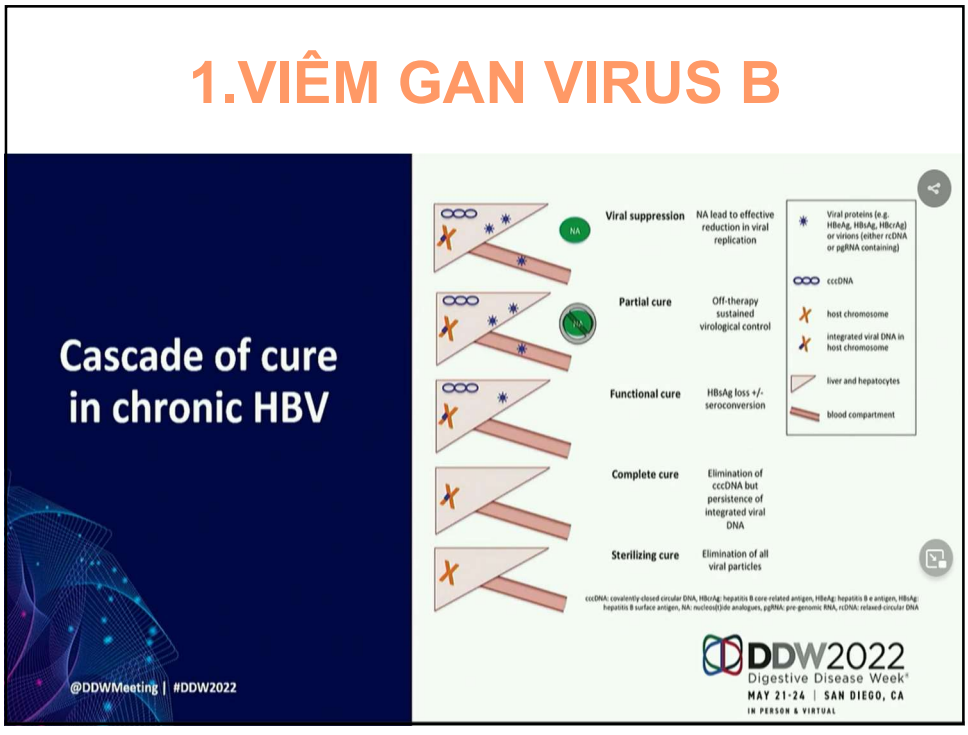
THÔNG TIN MỚI VỀ VIÊM GAN VIRUS AASLD 2021- DDW 2022 - EASL 2022.

1. Viêm gan virus B & D
2. Viêm gan virus C.
3. Ung thư gan và ung thư đường mật.
4. Covid-19 và bệnh gan.

2


Globally, 330 million people are infected with HBV & HCV resulting in one death every 30 seconds, which can be prevented
Global
HCV infections
56,900,000 (0.7%)
Diagnosed
22%
Annual Treated
1%
Annual Deaths
257,000
1 every 2 minutes
HBV infections
272,500,000 (3.5%)
Diagnosed
13%
Treated
2.5%
Annual Deaths
926,000
1 every 34 seconds
Birth Dose
48%
3+ Dose
87%
HBIG
15%
4%
All the tools we need to eliminate HBV (vaccine, HBV diagnostics, lab tests and treatment) exist today. In addition, viral hepatitis elimination is one of the very few public health programs that is highly cost effective in high-, middle- and low-income countries.
Erasmus MC
TORONTO CENTRE FOR LIVER DISEASE

3


1.VIÊM GAN VIRUS B
Cascade of cure in chronic HBV
@DDWMeeting | #DDW2022
Viral suppression
NA lead to effective reduction in viral replication
Partial cure
Off-therapy sustained virological control
Functional cure
HBsAg loss +/- seroconversion
Complete cure
Elimination of cccDNA but persistence of integrated viral DNA
Sterilizing cure
Elimination of all viral particles
Viral proteins (e.g. HBeAg, HBsAg, HBcrAg) or virions (either rcDNA or pgRNA containing)
cccDNA
host chromosome
integrated viral DNA in host chromosome
liver and hepatocytes
blood compartment
DDW2022
Digestive Disease Week®
MAY 21-24 | SAN DIEGO, CA
IN PERSON & VIRTUAL

4

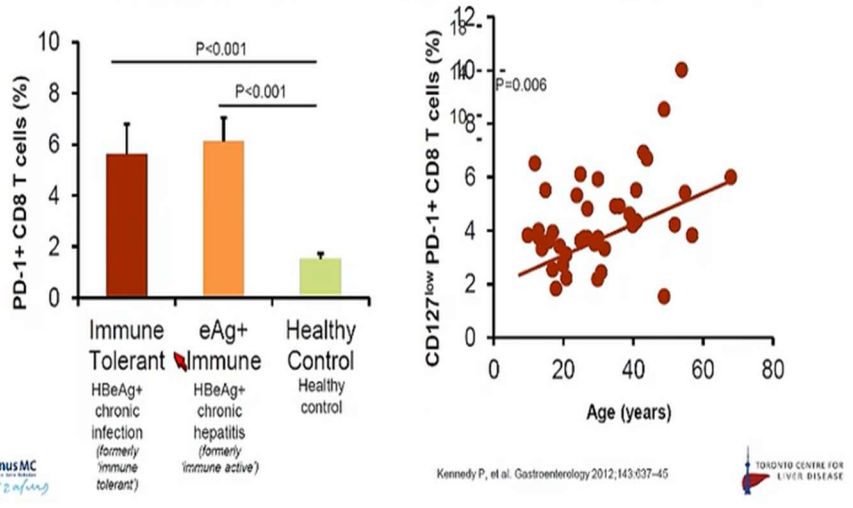
Quan điểm mới trong quyết định điều trị viêm gan virus B

- In this cohort of U.S. indeterminate phase HBV patients, ~5% patients progressed to cirrhosis or HCC within 6 years of follow up
- The risk of progression in the indeterminate phase was 5.0- fold higher compared to those in immune-inactive phase
- The risk of progression was the highest in older HBeAg positive patients with baseline HBV DNA of >2000 IU/ml
- These patients may benefit from close monitoring and risk reduction strategies, including antiviral treatment
- Further studies with larger sample size are warranted to describe the natural history of intermediate phase CHB patients

5

T cell response in immune tolerant chronic hepatitis B

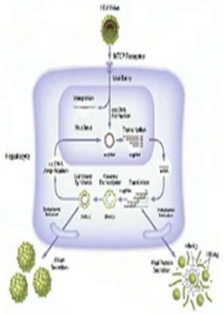
Evidence of immune activity in the 'immune-tolerant' disease phase



6

HBV-DNA integration?

- A large, transcriptionally active intrahepatic HBV reservoir increases risk of liver inflammation & disease progression
- Integration is known to contribute to HBV-driven tumourigenesis



cccDNA
pgRNA

Inflammation

Cirrhosis

HBV DNA integration

HBV DNA

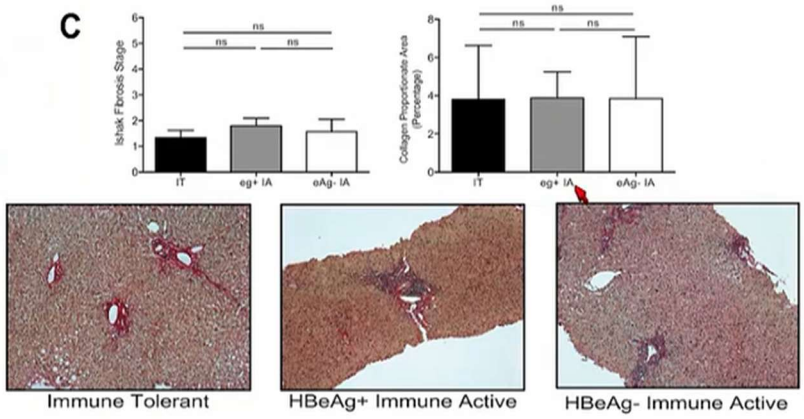
Hepatocellular Carcinom… (HCC)

Liang LB, IJID 2016
Larsson SB wt al., Liver Int. 2014
Jiana Z et al., Genome Res. 2013
et al., J Virol. 2015
LH et al., Nat Comm, 2016

Erasmus MC

7

Liver damage in 'Immune Tolerant' patients



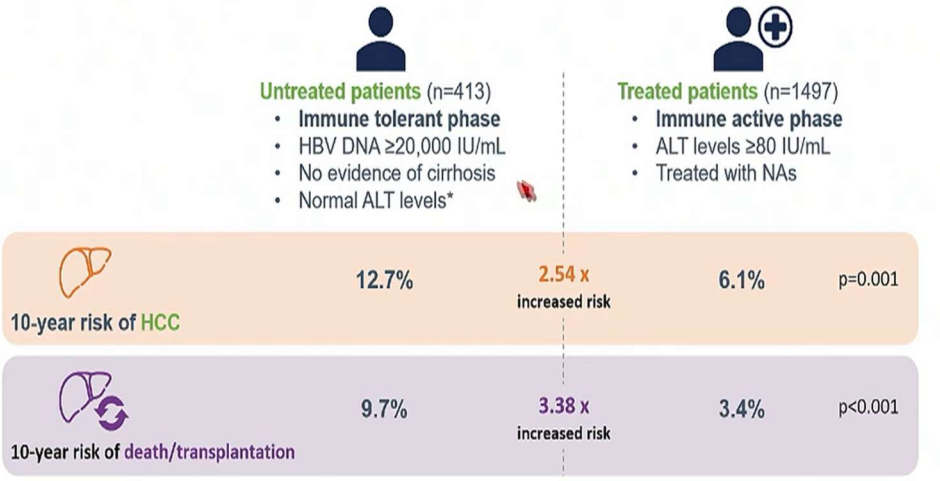
Erasmus MC

Mason et al., Gastroenterology 2016

TORONTO CENTRE FOR LIVER DISEASE

8

Untreated 'Immune-Tolerant' patients have a significant risk for morbidity and mortality



Percentages represent estimated cumulative incidence. *Normal ALT females, <19 IU/mL and males, <30 IU/mL

Kim GA, et al. Gut 2018;67:945–52

9

Why treat patients in immune tolerant phase?

- Reduce HBV integration by treating early, hence reduce HCC risk
- By suppressing HBV DNA not only risk reduction of HCC but also of potential liver damage
- IT patients will later develop immune active disease where the risk is highest. Why not short circuit through treatment which is safe and without resistance?
- Reduce the rate of horizontal and vertical transmission
- Simplified treatment strategy to drive HBV elimination goal

Erasmus MC

TORONTO CENTRE FOR LIVER DISEASE

10

TAF hiệu quả & an toàn cho phụ nữ mang thai trong nhiều nghiên cứu.

Multicenter, prospective study of 60 pregnant women who were receiving TAF or switched to TAF were followed until at least post-partum Month 7

Maternal Characteristics	n=60
Mean age, years ± SD	30±5
Mean gestational age at TAF initiation, weeks ± SD	1.0 ±13.7
Mean ALT, U/L ± SD	113±93
Mean HBV DNA, log_{10} IU/mL ± SD	4.6±3.5
Mean TAF treatment duration, weeks ± SD	82±20
Maternal Outcomes	**n=60**
Virologic breakthrough, n (%)	2 (3)

Infant Outcomes	n=59*
MTCT at month 7, n (%)	0
Breast fed, n (%)	43 (73)
Congenital defects or malformations, n (%)	0

*One mother who initiated TAF at 12 weeks of pregnancy underwent induced abortion at 23 weeks of gestation due to the diagnosis of cleft lip and palate for the fetus.

Physical and neurological development of infants was normal at birth, 7 months, and 12 months

TAF administered throughout pregnancy in women with active CHB was generally safe for both mothers and infants, and reduced the MTCT rate to 0%

Infants received standard immunoprophylaxis and were followed until at least postpartum Month 7.
Zeng Q-L, et al. EASL 2021. #990

11

TAF được dung an toàn cho phụ nữ mang thai ở nhiều nghiên cứu ở TQ

Tenofovir alafenamide used throughout pregnancy in Chinese active chronic hepatitis B mothers: a multicenter prospective study

Aim

To investigate safety and effectiveness of tenofovir alafenamide (TAF) in active chronic hepatitis B (CHB) mothers and their infants

Methods

In this multicenter, prospective study, active CHB mothers treated with TAF and tenofovir (TDF) were enrolled, infants received standard immunoprophylaxis, and the mothers' and infants' safety and effectiveness profiles were observed.

Main Findings

The TAF was well tolerated, safe, and effective during a mean of nearly two years of treatment for active CHB mothers and their infants.

A mean of about two years of TAF and TDF therapy had comparable safety and effectiveness profiles for active CHB mothers and infants.

Conclusions

TAF administered throughout or from early pregnancy are safe and effective for active CHB mothers and their infants.

Characteristics of the mothers at baseline	TAF group (n=103)	TDF group (n=104)
Age, years	29.3 ± 4.7	29.4 ± 4.4
Gestational age, weeks	1.4 ± 14.6	1.0 ± 12.1
HBeAg positivity	82 (79.6)	88 (84.6)
HBV DNA, log_{10} IU/ml	5.1 ± 3.4	4.6 ± 3.4
ALT, U/L	122.2 ± 97.5	94.6 ± 78.3
Treatment duration, weeks	92.1 ± 24.2	94.7 ± 21.9
Most common adverse events-nausea	30 (29.1)	33 (31.7)
Characteristics of the infants at birth	n=102*	n=104
Gestational age, weeks	39.2 ± 1.1	39.3 ± 1.2
Apgar score at 1 minute	9.7 ± 0.5	9.5 ± 0.5
Congenital defects or malformations	0 (0)	0 (0)
Anthropometric indexes	Normal	Normal
At postpartum month 6 for mothers	n=102	n=104
HBV DNA undetectable	101 (99.0)	103 (99.0)
ALT normalization	93 (91.2)	97 (92.3)
HBeAg seroconversion	17/82 (20.7)	15/88 (17.0)
At 7 months of age for infants	n=102	n=104
Anthropometric indexes	Normal	Normal
HBsAg positive infants	0 (0)	0 (0)
At postpartum month 18 for mothers	n=30	n=32
Cumulative HBeAg seroconversion	20/82 (24.4)	21/88 (23.9)
At 18 months of age for infants	n=30	n=32
Anthropometric indexes	Normal	Normal

*One fetus suffered induced abortion unrelated to TAF.

Zeng Q-L, et al., Pub Number 19.

12

Không nên dừng đột ngột Nas khi điều trị viêm gan B

Nucleos(t)ide analogue withdrawal in chronic hepatitis B patients leads to limited sustained remission in the absence of HBsAg loss: results from the RETRACT-B study

Study Aim

- To examine the long-term virological and biochemical response after NA withdrawal, particularly in patients who did not achieve HBsAg loss

Methods

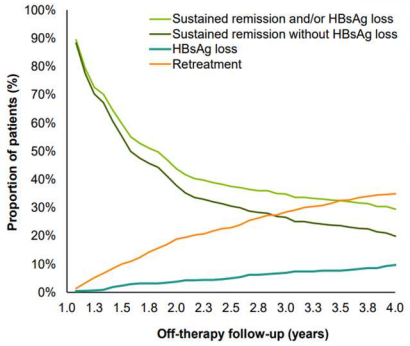
- CHB patients who were virally suppressed and HBeAg negative at NA withdrawal who remained off-therapy, were not lost to follow-up, and did not experience HBsAg loss, hepatic decompensation, HCC, HBeAg seroreversion, or death within 1 year off-therapy (n = 945).
- Sustained remission was defined by persistent HBV DNA ≤2000 IU/mL and ALT ≤1.5x ULN after 1 year off-therapy.

Main Findings

- At 4 years off-therapy, 30% of patients achieved sustained remission and/or HBsAg loss, 20% achieved sustained remission in the absence of HBsAg loss, 10% had achieved HBsAg loss, and 35% had started retreatment.

Conclusions

- Despite allowing for any HBV DNA and ALT fluctuations within the first year after NA withdrawal, most patients continued to experience virological and biochemical relapses beyond 1 year and the majority did not remain in sustained remission at 4 years off-therapy.



Hirode G, et al., Abstract 22.

13

Viêm gan virus B trở nên trầm trọng hay gây tử vong khi ngưng NAs

Severe hepatitis flare & subsequent mortality after discontinuation of antiviral treatment for chronic hepatitis B: a population-based study

Aim To quantify the incidences of severe hepatitis flare and related morality in chronic hepatitis B patients who discontinued antiviral therapy as part of the routine care

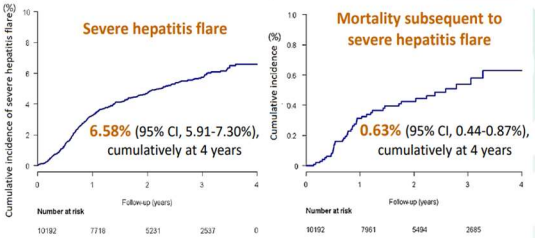
Methods

- A nationwide population-based cohort study of 10,192 treatment-naïve adults who initiated entecavir or tenofovir and stopped the treatment per routine care standard and local reimbursement policy
- Severe hepatitis flare defined as serum ALT above 5 times the upper limit of normal plus elevation of serum bilirubin, and subsequent mortality as occurrence of death within 6 months of severe flare

Main Findings

Patient characteristics	All (N =10,192)
Male sex, n (%)	7,308 (71.70)
Age, years (median and IQR)	50.87 (41.51, 59.30)
Cirrhosis, n (%)	1,092 (10.71)
History of hepatic decompensation, n (%)	465 (4.56)
Use of entecavir, n (%)	6,921 (67.91)
Treatment duration, years (median and IQR)	3.0 (3.0, 3.0)

IQR, interquartile range



Age (adjusted sub-distributional hazard ratio [aSHR], 1.19 per 10 years; 95% CI, 1.09-1.29), **male sex** (aSHR, 1.76; 95% CI, 1.41-2.22), **cirrhosis** (aSHR, 1.84; 95% CI, 1.45-2.33), and **history of hepatic decompensation** (aSHR, 1.45; 95% CI, 1.01-2.09) were significant risk factors for severe hepatitis flare

Conclusions The risks of severe hepatitis flare and subsequent mortality were substantial after discontinuation of oral antiviral treatment in patients with chronic hepatitis B.

Hsu Y-C, et al., Abstract 23.

14

Nguy cơ HCC khi dùng TDF so với Entecavir

The risk of hepatocellular carcinoma in tenofovir versus entecavir-treated U.S. cohort with chronic HBV virus

Objective

Analyze a cohort of patients treated with ETV or TDF in the VA with an extended follow up to examine the association between TDF vs. ETV and HCC risk

Methods

Retrospective cohort study analyzing the incidence of HCC in veteran patients with a positive HBV surface antigen test and TDF or ETV use

Main Findings

During a mean follow-up of 4.1 years, 84 in ETV and 102 in TDF patients developed HCC for an incidence rate of 12.5/1000 PY in ETV vs. 11.6/1000 PY in TDF.

Conclusions

In this cohort of US veterans with chronic HBV treated with TDF or ETV, there was a significant trend toward a slightly lower HCC risk developing in patients treated with TDF.

Antiviral Therapy	# HCC	Person years	IR (%) (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
HCC any time after index					
Overall	186	15366.9	1.21 (1.04 - 1.40)	N/A	N/A
Duration					
Tenofovir	59	4396.37	1.34 (1.02 - 1.73)	0.91 (0.81 - 1.01)	0.89 (0.79 - 0.99)
Entecavir	72	4647.24	1.55 (1.21 - 1.95)	1.0	
Current use					
Tenofovir	84	7230.01	1.16 (0.93 - 1.44)	0.87 (0.62 - 1.23)	0.86 (0.60 - 1.21)
Entecavir	102	8136.85	1.25 (1.02 - 1.52)	1.0	

El-Serag H, et al., Abstract 61.

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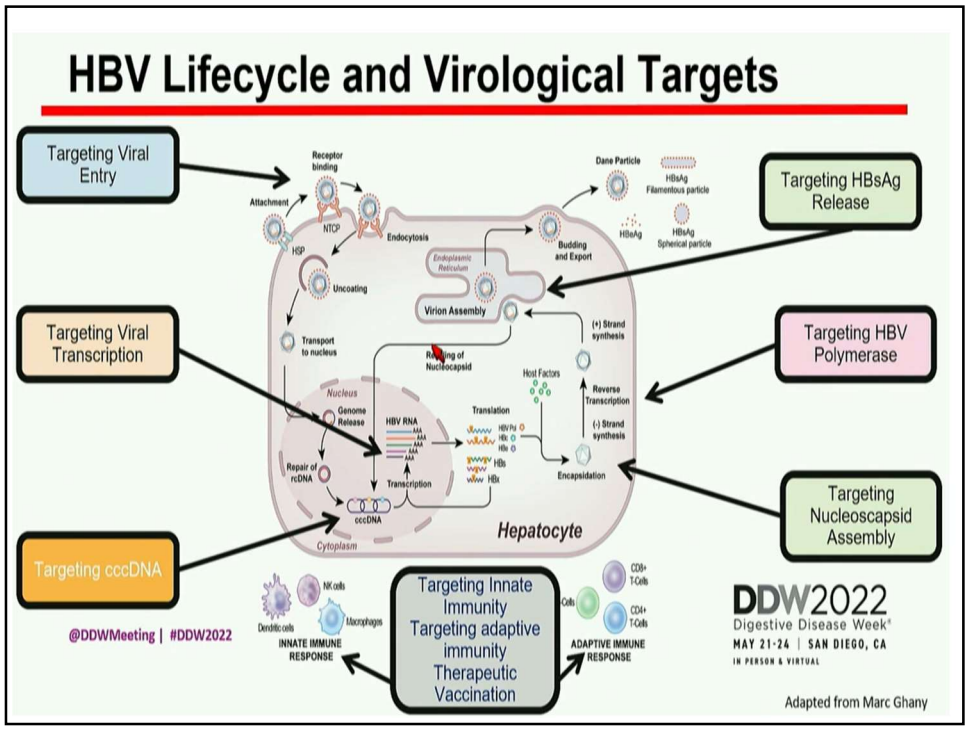
15

16



17

Novel therapies (CAM, siRNA and ASO)

Core or Capsid Inhibitors	Vebivorvir (ABI-H0731), ABI-4334 *Assembly Biosience*	ILC 2022; SAT366 & SAT383
	JNJ-6379 *Johnson & Johnson*	ILC 2022; SAT422 & GS010
	EDP-514 *Enanta*	ILC 2022; SAT390 & SAT393
	Canocapavir (ZM-H1505R) *Zhimeng Biopharma*	ILC 2022; SAT367
	ALG-000184 Aligos Therapeutics	ILC 2022; SAT365
	AB-836 *Arbutus*	ILC 2022; SAT392
	RG-7907 *Roche … and others*	
Inhibition of HBV gene expression (ASO, siRNA).	JNJ-3989 *Johnson & Johnson*	ILC 2022; GS010 & SAT422
	VIR-2218 *Vir Biotech*	ILC 2022; SAT434
	AB-792 *Arbutus*	ILC 2022; SAT397
	Bepirovirsen *GSK & Ionis*	ILC 2022; LB004B

18

A Phase IIa trial of subcutaneously administered PD-L1 antibody ASC22 (Envafolimab) in patients with chronic hepatitis B

Objectives

To evaluate the safety and preliminary efficacy of ASC22 in patients with chronic hepatitis B (CHB) after a single subcutaneous injection

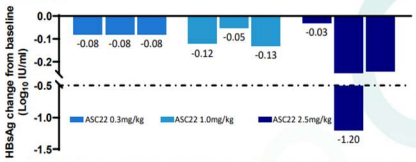
Methods

This Phase IIa clinical trial was a single-ascending dose study of three subcutaneously administered doses (0.3, 1.0, and 2.5 mg/kg, three patients per dose) with 12-week follow-up. Enrolled CHB patients were HBeAg negative, HBsAg ≤ 10000 IU/mL, and HBV DNA <20 IU/mL.

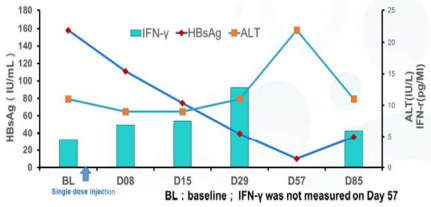
Conclusion

- A single subcutaneous dose of ASC22 up to 2.5 mg/kg is safe and well-tolerated with only grade 1 adverse effects observed during 12-week study.
- The single subcutaneous dose of ASC22 induced a dose-dependent reduction of HBsAg.
- ASC22 treatment increased serum level of IFN-g.
- ASC22 has potential to cure CHB patients in combination with other therapies.

Main Findings



▪ ASC22 induced a dose-dependent reduction of HBsAg (n = 3 for each dose).



▪ In the patient with HBsAg reduction of 1.2 log_{10} IU/mL, elevation of IFN-γ and ALT were accompanied with reduced HBsAg.

Wang GQ, et al., Abstract 91.

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19

Co-administration of VIR-2218 and PEG-IFNα achieves deeper HBsAg reduction compared to VIR-2218 alone

Objective

- Evaluate the safety and efficacy of VIR-2218, an siRNA, alone and in combination with PEG-IFNα for the treatment of chronic hepatitis B virus infection

Methods

- Virally-suppressed participants received 200 mg SC VIR-2218 every 4 weeks for 6 doses, alone or in combination with various durations of PEG-IFNα (see figure).

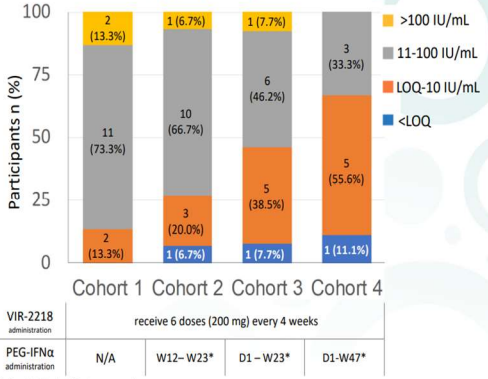
Main Findings

- Mean HBsAg reduction at Week 24 in Cohorts 1, 2, 3, and 4 was -1.89, -2.03, -2.55, and -2.3 log_{10}IU/mL, respectively.
- Three participants achieved HBsAg <LOQ** by Week 24 (HBsAg levels at Week 24 presented in figure).
  - Two of three also had anti-HBs seroconversion.

Conclusions

- Co-administration of VIR-2218 and PEG-IFNα resulted in substantial HBsAg reduction by Week 24; reported AEs have been generally consistent with the known safety profile of PEG-IFNα.

HBsAg (IU/mL) at Study Week 24



VIR-2218 administration	receive 6 doses (200 mg) every 4 weeks			
PEG-IFNα administration	N/A	W12– W23*	D1 – W23*	D1-W47*

PEG-IFNα: pegylated interferon alfa 2a, SC: subcutaneous, HBsAg: Hepatitis B surface antigen, N/A: Not applicable, D: Day, W: Week, AE: adverse event
**180 mcg SC PEG-IFNα was administered weekly during the specified study period*
*** LOQ is <0.05 and the same as the limit of detection for the HBsAg assay*

Yuen M-F, et al., Abstract 93.

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20

Efficacy and safety of the siRNA JNJ-3989 and/or the capsid assembly modulator (CAM-N) JNJ-6379 for the treatment of chronic hepatitis B virus infection (CHB): results from the Phase 2b REEF-1 study

Objective

- To assess the efficacy and safety of 12 Q4W SC doses of the siRNA JNJ-3989 (40, 100, and 200 mg) and/or QD oral doses of the CAM-N JNJ-6379 (250 mg) in combination with nucleos(t)ide analog (NA) in patients with CHB

Methods

- In this Phase 2b, multicenter, active-controlled study, 470 CHB patients were randomized to 6 arms and dosed for a 48-week double-blind placebo (PBO)-controlled treatment period and 48 weeks of follow up.

Main Findings

- 19.1% of patients in the JNJ-3989 200 mg + NA group met the primary endpoint (proportion of patients meeting NA stopping criteria) at Week 48 compared to 0% in the JNJ-6379 + NA and 2.2% in the PBO + NA arm.
- Reduction of HBsAg levels was greatest with JNJ-3989 200 mg + NA (**Figure**; -2.58 $\log_{10}$ IU/mL at Week 48), with 3.3% of patients achieving HBsAg seroclearance at this time (**Table**).

Conclusions

- JNJ-3989 showed dose-dependent reductions in HBsAg levels; addition of JNJ-6379 did not provide additional HBsAg suppression.
- All JNJ-3989-based regimens were well tolerated.

Figure. Mean change from baseline in HBsAg

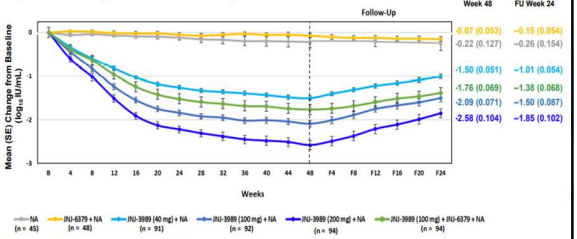

Table. HBsAg cutoff values for JNJ-3989 200 mg

	N	HBsAg, $\log_{10}$ IU/mL	HBsAg cut-off reached (%)											
			<100 IU/mL			<10 IU/mL			<1 IU/mL			<0.05 IU/mL (LLOQ)		
			Treatment week			Treatment week			Treatment week			Treatment week		
	BL	BL	24	48	F24	24	48	F24	24	48	F24	24	48	F24
JNJ-3989 200 mg	94	3.82 (0.718)	65.2%	74.7%	47.0%	19.6%	37.4%	14.5%	5.4%	13.2%	4.8%	1.1%	3.3%	1.2%

BL, baseline; HBsAg, hepatitis B s antigen; LLOQ, lower limit of quantitation; SE, standard error.

Yuen MF, et al., Abstract LO10.

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21

HBsAg loss in chronic hepatitis B patients with subcutaneous PD-L1 antibody ASC22 (envafolimab) plus nucleos(t)ide analogs treatment: interim results from a Phase IIb clinical trial

Objectives

To assess the efficacy and safety of ASC22 in patients with chronic hepatitis B (CHB)

Methods

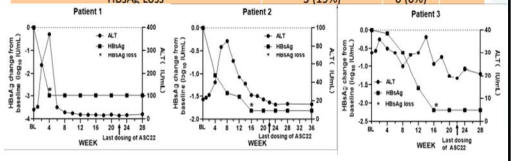
This randomized, single-blind multi-center Phase IIb trial enrolled a total of 149 CHB patients (negative HBeAg, HBsAg ≤ 10000 IU/mL and HBV DNA < 20 IU/ml) in two cohorts for 24 weeks treatment of different doses of ASC22 and a 24-week follow-up (NCT04465890). In cohort 1, 75 patients were treated with 1 mg/kg ASC22 Q2W (n=60) or placebo (PBO) Q2W (n=15) + Nucleos(t)ide Analogs (NAs). This interim analysis reported the efficacy and safety from 44 patients who completed 24-week treatment of 1 mg/kg ASC22 (n=33) or PBO (n=11) + NAs.

Conclusion

Subcutaneous administration of ASC22 Q2W for 24 weeks can induce HBsAg decline, even HBsAg loss, in CHB patients, especially in those with baseline HBsAg ≤ 500 IU/mL. Patients treated with ASC22 + NAs had a similar AE profile with those treated with PBO + NAs. All three patients who obtained HBsAg loss during ASC22 treatment still maintained HBsAg negative 6-14 weeks after last dosing of ASC22.

Main Findings

Outcomes after 24 weeks treatment of ASC22	ASC22 + NAs (Baseline HBsAg ≤ 10000 IU/mL , N =33)	PBO + NAs (N = 11)	*P* value
Mean HBsAg change from baseline ($\log_{10}$ IU/mL)	-0.38	0	0.0639
HBsAg reduction ≥ 0.5 $\log_{10}$ IU/mL	7 (21%)	0 (0%)	
HBsAg Loss	3 (9%)	0 (0%)	
Outcomes after 24 weeks treatment of ASC22	**ASC22 + NAs (Baseline HBsAg ≤ 500 IU/mL , N =16)**	**PBO + NAs (N = 11)**	***P* value**
Mean HBsAg from change baseline ($\log_{10}$ IU/mL)	-0.7	0	**0.0084**
HBsAg reduction ≥ 0.5 $\log_{10}$ IU/mL	7 (44%)	0 (0%)	
HBsAg Loss	3 (19%)	0 (0%)	



Wang GQ, et al., Abstract LO12.

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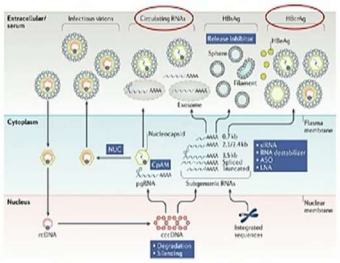
22

Novel biomarkers: HBV RNA and HBcrAg to assess target engagement and treatment endpoints

- Limited value to differentiate between phases of HBV disease (HBRN)
- Associated with risk of HCC like most other HBV markers (HBsAg quant)
- More directly reflect active ccc-DNA: target engagement of new compounds
- Standardisation and validation is needed
- Need to optimize sensitvity of tests
- Not yet licensed



Testoni et al, Sem Liver Dis, 2017; Ghany M, et al. Hepatology 2021

23

Therapies to cure HBV infection Consideration for clinical trial design

Replication inhibition ± **Antigen reduction** ± **Immune stimulation**

Entry inhibitors: bulevirtide

NUC: ETV, TDF, TAF

CAM: ABI-H0731, JNJ-56136379, RO7049389,

NAPs: REP 2139 or REP 2165

siRNA: JNJ-3989, VIR-2218, AB-729, RG6346

ASO: GSK3228836

LNA: RO7062931

Invigorate immune responses

PEG-IFN

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

Anti-PD1: nivolumab, GS4224, Oral PDL1

Therapeutic Vaccines GS4774, TG1050,T101, SCI-B-VAC

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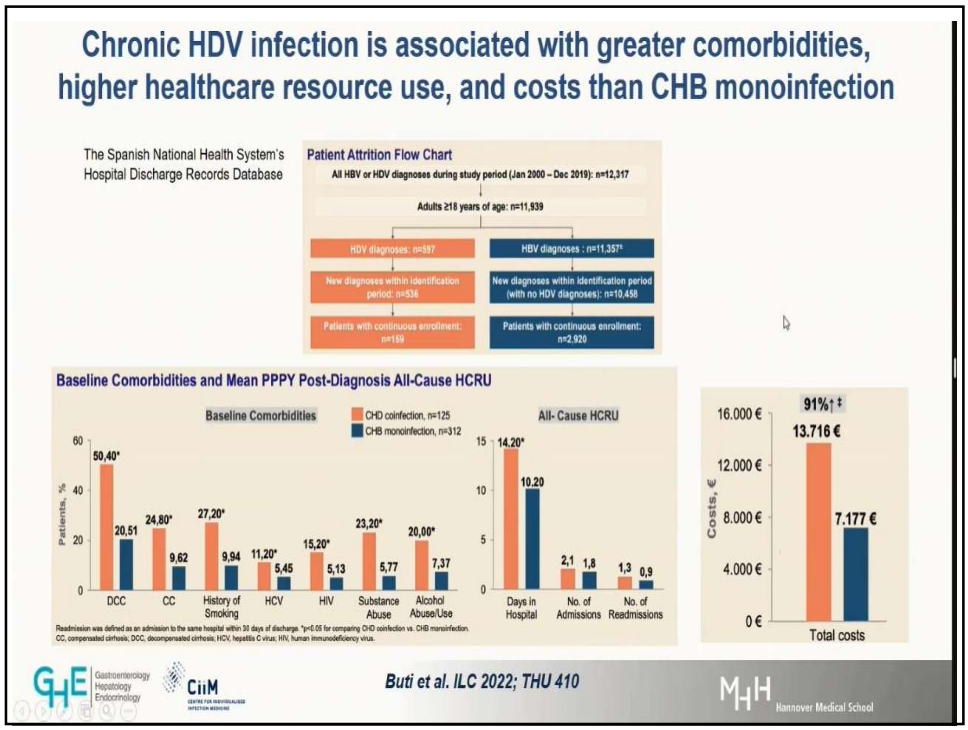
Chronic HDV infection is associated with greater comorbidities, higher healthcare resource use, and costs than CHB monoinfection
The Spanish National Health System's Hospital Discharge Records Database
Patient Attrition Flow Chart
All HBV or HDV diagnoses during study period (Jan 2000 – Dec 2019): n=12,317
Adults ≥18 years of age: n=11,939
HDV diagnoses: n=597
HBV diagnoses : n=11,357
New diagnoses within identification period: n=536
New diagnoses within identification period (with no HDV diagnoses): n=10,458
Patients with continuous enrollment: n=159
Patients with continuous enrollment: n=2,920
Baseline Comorbidities and Mean PPPY Post-Diagnosis All-Cause HCRU
Baseline Comorbidities
CHD coinfection, n=125
CHB monoinfection, n=312
Patients, %
50,40*
20,51
24,80*
9,62
27,20*
9,94
11,20*
5,45
15,20*
5,13
23,20*
5,77
20,00*
7,37
DCC
CC
History of Smoking
HCV
HIV
Substance Abuse
Alcohol Abuse/Use
All- Cause HCRU
14,20*
10,20
2,1
1,8
1,3
0,9
Days in Hospital
No. of Admissions
No. of Readmissions
Costs, €
91%↑‡
13.716 €
7.177 €
Total costs
Buti et al. ILC 2022; THU 410
Hannover Medical School

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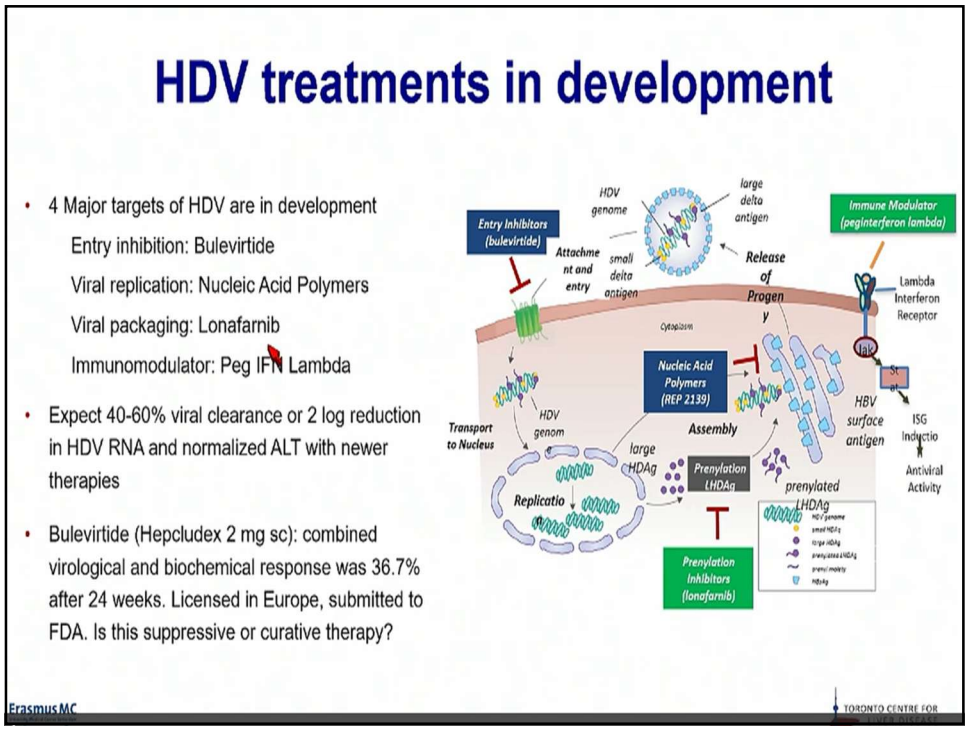
HDV treatments in development
4 Major targets of HDV are in development
Entry inhibition: Bulevirtide
Viral replication: Nucleic Acid Polymers
Viral packaging: Lonafarnib
Immunomodulator: Peg IFN Lambda
Expect 40-60% viral clearance or 2 log reduction in HDV RNA and normalized ALT with newer therapies
Bulevirtide (Hepcludex 2 mg sc): combined virological and biochemical response was 36.7% after 24 weeks. Licensed in Europe, submitted to FDA. Is this suppressive or curative therapy?
HDV genome
large delta antigen
Entry Inhibitors (bulevirtide)
Attachment and entry
small delta antigen
Release of Progeny
Immune Modulator (peginterferon lambda)
Lambda Interferon Receptor
Cytoplasm
Nucleic Acid Polymers (REP 2139)
Transport to Nucleus
HDV genom
Assembly
HBV surface antigen
ISG Induction
Antiviral Activity
large HDAg
Prenylation LHDAg
prenylated LHDAg
Replicatio
Prenylation Inhibitors (lonafarnib)
ErasmusMC

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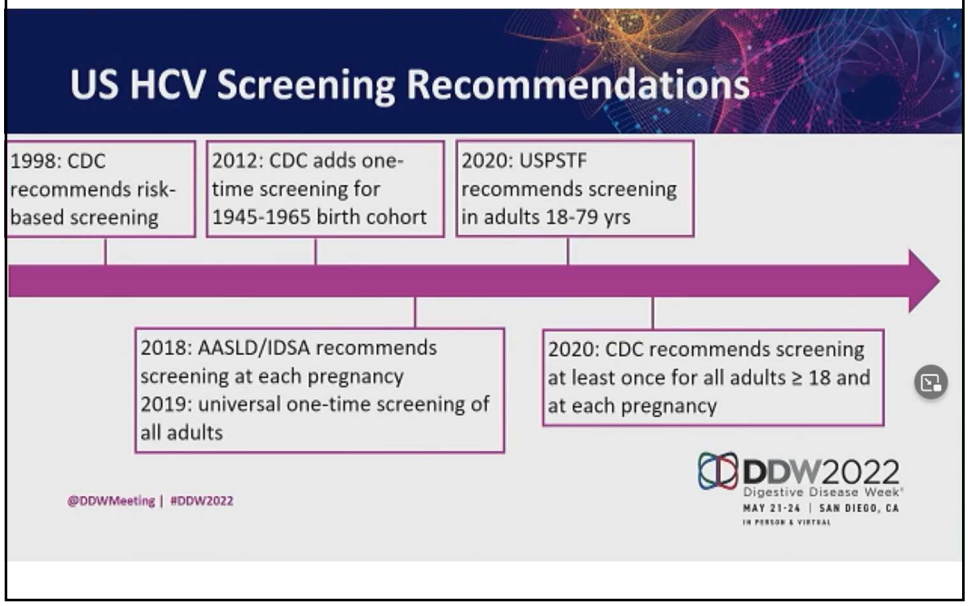
2.VIÊM GAN VIRUS C



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Rapid hepatitis C treatment initiation in young people who inject drugs: HCV-seek, test & rapid treatment (ST&RT) randomized pilot clinical trial

Objective

- To evaluate the effectiveness of a simplified, rapid treatment initiation (goal of initiation of treatment the same day as HCV confirmation result) approach to delivery HCV treatment to young PWID

Methods

- Open-labeled, randomized controlled pilot clinical trial comparing the efficacy (1) simplified & **Rapid Treatment** approach to (2) **Usual Care** (facilitated referral) in curing HCV in young PWID
- 18-29 year old who are HCV Ab+, HCV treatment naïve, and have injected illicit drugs in the prior 30 days

Main Findings

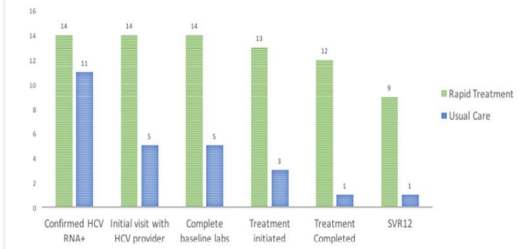
- 64% of participants in **Rapid Treatment** arm achieved SVR12 compared to 9% in **Usual Care** arm (p=0.01).

Conclusions

- Higher cure rates were achieved using the **Rapid Treatment** model with same day, low-threshold, simplified HCV care compared to facilitated referral.

	Rapid Treatment (n=14)	Usual Care (n=11)	p-value
SVR achieved during study by 12 months (Intention-to-treat)			
Yes	9 (64.3%)	1 (9.1%)	0.01
No	5 (35.7%)	10 (90.9%)	
Continued viremia	2	10	
Missing viral load testing	3*	0	
Clinical Outcome of those who Initiated DAA therapy	*(n=13)*	*(n=3)*	
SVR	9/13 (69.2%)	1/3 (33.3%)	0.52
Treatment failure	1/13 (7.7%)	2/3 (66.7%)	0.07
Unknown	3/13 (23.1%)	0/3 (0.0%)	

*One patient incarcerated within 7 days of initiating DAA therapy (remained incarcerated through remainder of study window); two patients without SVR testing, both of whom had undetectable viral load on treatment and confirmed treatment completion



Eckhardt B, et al., Abstract 97.

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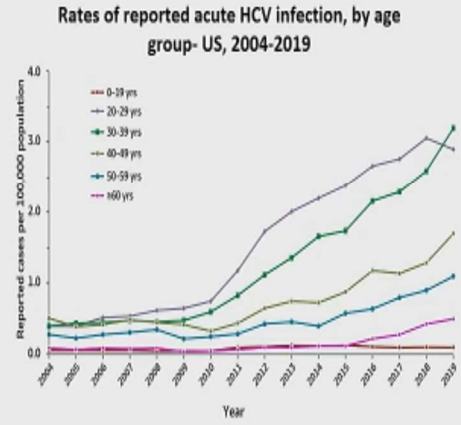
Acute HCV Infections in the US are Rising



- New acute HCV infections in 2019
  - Reported cases (n=4,136)
  - Estimated cases(n=57,500)
- >3-fold increase in new cases since 2009
- Highest rate among people **aged 20-39 years**

@DDWMeeting | #DDW2022

DDW2022 Digestive Disease Week® MAY 21-24 | SAN DIEGO, CA IN PERSON & VIRTUAL

Source: CDC, National Notifiable Diseases Surveillance System.

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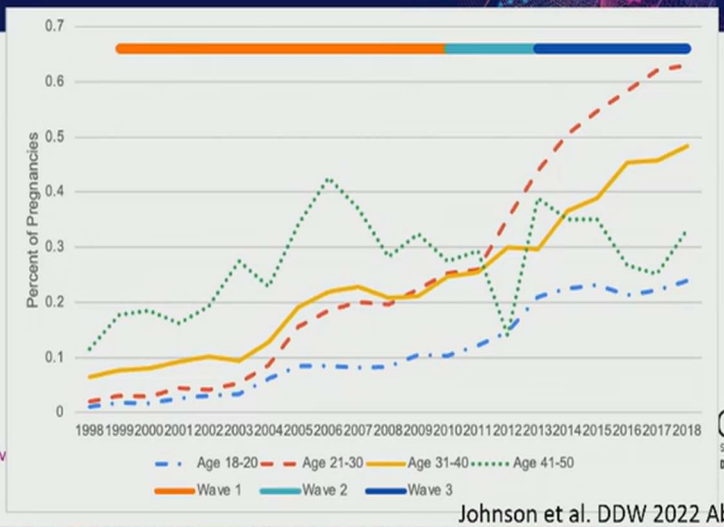
Prevalence of Maternal HCV (+) Pregnancies in U.S. during Opioid Epidemic, Stratified by Maternal Age



Johnson et al. DDW 2022 Abstract 154

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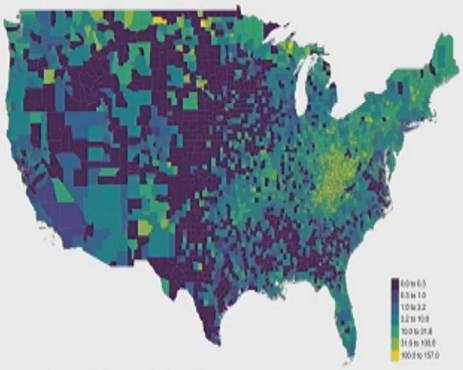
Reported Prevalence of Maternal HCV Infection is Rising

HCV prevalence (per 1,000 live births) at the county level in the US, 2017



Reported prevalence of maternal HCV infection **increased 161%** from 2009 to 2017.

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Rossi RM, et al. Obstet Gynecol 2020.

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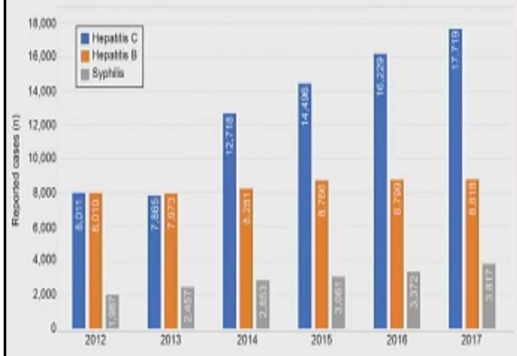
Maternal HCV Infection was the Second Most Prevalent and Most Rapidly Rising Infection in the US

Number of reported maternal infections by birth year



- The total reported number of maternal HCV cases exceeded the number of reported HBV and syphilis cases combined.
- HCV was the only infection not universally screened for in pregnancy during this time.

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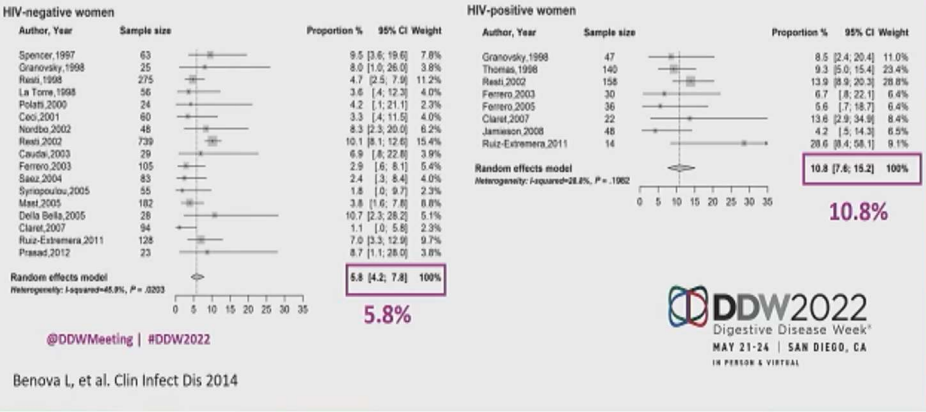
Maternal to Child Transmission of HCV

- Meta-analysis of 25 studies evaluating risk of vertical HCV transmission



Benova L, et al. Clin Infect Dis 2014

33

3. Ung thư gan và ung thư đường mật

Incidence and clinical characteristics of hepatocellular carcinoma associated with non-alcoholic fatty liver disease without cirrhosis or advanced liver fibrosis

Aim

- Hepatocellular carcinoma (HCC) usually occurs in cirrhotic livers but can develop in the absence of cirrhosis in NAFLD patients
- We aimed to estimate the incidence of HCC in NAFLD with and without cirrhosis or advanced liver fibrosis

Methods

- Retrospective case-control analysis of 47,970 NAFLD patients between 40-89 years of age, stratified by cirrhosis and by Fibrosis-4 index (FIB-4)

Main Findings

- 755 (1.6%) of 47,970 NAFLD patients developed HCC with an average 3.5 years of follow-up, resulting in annual rate at 0.46% (Table 1).
- Incidence rate of HCC in patients with cirrhosis was 1.94% and 0.16% in those without cirrhosis.
- Among patients without cirrhosis, HCC incidence rate was 0.6% for FIB-4 > 2.67 and 0.09% for FIB-4 < 1.3.
- HCC-NAFLD patients without cirrhosis had different characteristics (Table 2).

Conclusions

- NAFLD patients without cirrhosis or advanced fibrosis have low incidence of HCC but exhibit different clinical characteristics.

Behari J, et al., Abstract 134.

Table 1. Distribution of cirrhosis and FIB-4 scores among NAFLD patients with or without HCC and corresponding annual incidence rate of HCC.

	HCC N (%)	Non-HCC N (%)	Annual incidence rate of HCC (%)
All subjects	755 (100)	47,215 (100)	0.46%
Diagnosis of cirrhosis			
Yes	528 (69.9)	7,009 (14.8)	1.94%
No	227 (30.1)	40,206 (85.2)	0.16%
FIB-4 score among subjects without cirrhosis			
<1.30	55 (7.3)	18,760 (39.7)	0.09%
1.30-2.67	67 (8.8)	11,812 (25.0)	0.15%
>2.67	68 (9.0)	3,529 (7.5)	0.60%
Unknown	37 (4.9)	6,105 (12.9)	0.22%

Table 2. Characteristics of HCC patients with and without cirrhosis by FIB-4

	HCC with cirrhosis	HCC without cirrhosis			
		All	FIB-4<1.30	1.30-	>2.67
N	528	227#	55	67	68
Age (year)*	68.5	66.7	59.1	68.3	71.2
BMI (kg/m²)	31.1	31.9	31.6	32.3	31.3
AST (U/L)*	88.0	57.7	26.4	44.3	97.7
ALP (U/L)*	188.2	159.6	133.9	160.1	182.3
Albumin (g/dL)*	3.28	3.57	3.69	3.60	3.42
Platelet (x10⁴/ μL)*	173.0	227.7	324.7	222.1	154.8
Total bilirubin (mg/dL)*	2.21	1.10	0.89	0.88	1.55
Hyperlipidemia (%)*	28.3	36.6	45.5	47.8	36.8

*P<0.05 for difference between HCC with cirrhosis and without cirrhosis. ^P<0.05 for difference between FIB-4 groups among HCC without cirrhosis; # 37 cases with missing FIB-4 data were excluded from the analysis.

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GALAD score improves early detection of HCC prior to the diagnosis of HCC: a phase 3 biomarker validation study

Aims

- To compare the performance of AFP and GALAD for the detection of HCC
- To determine the performance of AFP and GALAD in those who underwent surveillance by US or CT/MRI

Methods

- A phase 3 biomarker validation study-HEDS study.
- Prospective cirrhosis cohort study of 1559 patients
- GALAD tested blindly at diagnosis and 6 months prior to HCC diagnosis.

Main Findings

- GALAD had the best performance of any biomarker at HCC diagnosis and 6 months prior to HCC diagnosis.
- GALAD can potentially limit unnecessary diagnostic CT or MRI.

Conclusions

- GALAD has better performance characteristics 6 months prior to HCC diagnosis and at the time of HCC diagnosis.

Marrero J, et al., Abstract 138.

	DCP	AFP-L3	AFP	GALAD
Threshold	2.82	6.35%	9.12	- 0.76 score
AUC	0.79	0.66	0.68	0.81
Sensitivity	44%	38%	33%	54%
Specificity (fixed 90%)	90%	90%	90%	90%

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A blood-based prognostic liver secretome signature for long-term HCC risk prediction and chemopreventive intervention

Aim

To identify a blood-based secretome signature to predict long-term HCC risk and to monitor chemopreventive intervention in patients with advanced liver fibrosis

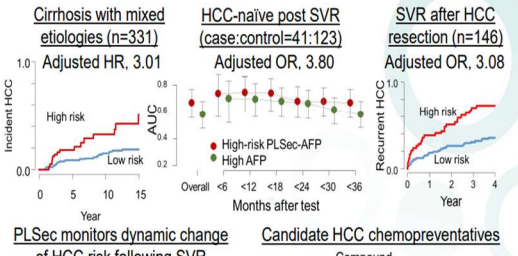
Methods

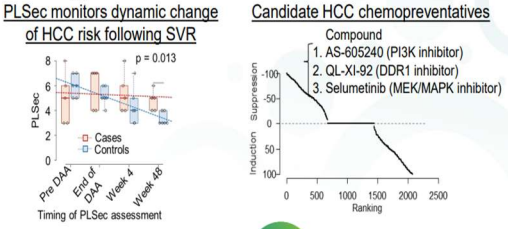
A serum protein-based signature, PLSec, was identified from previously validated hepatic transcriptome signature using our bioinformatic pipeline, TexSEC, and independently validated for its association with long-term HCC risk in three clinical scenarios (cirrhosis patients from mixed etiologies, HCC-naïve patients post sustained virologic response [SVR] by direct-acting agents [DAA], and HCC-experienced patients post SVR by DAA) as well as monitoring chemopreventive intervention.

Conclusions

The 8-protein PLSec, including IL-6, gp130, CCL-21, IGFBP-7, MMP-7, VCAM-1, Angiogenin, and Protein S, can stratify patients with advanced liver fibrosis for long-term HCC risk and may serve as a companion biomarker for chemopreventive intervention.

Fujiwara N, et al., Abstract 196.





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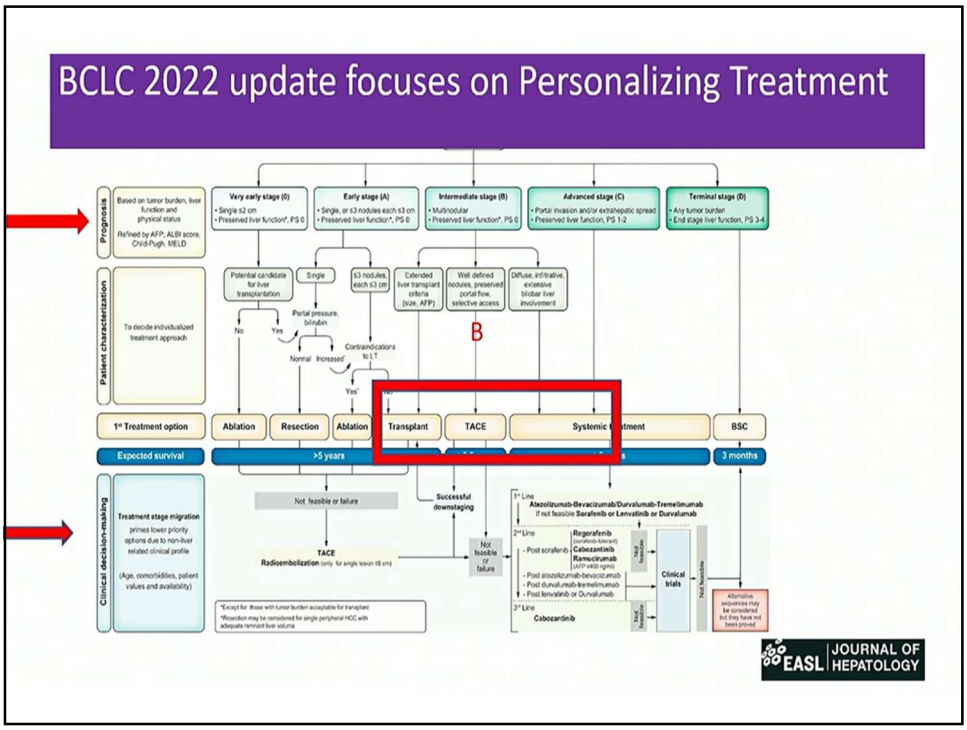
BCLC 2022 update focuses on Personalizing Treatment
Prognosis
Patient characterization
Clinical decision-making
Very early stage (0)
Early stage (A)
Intermediate stage (B)
Advanced stage (C)
Terminal stage (D)
B
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
BSC
Expected survival
>5 years
3 months
Not feasible or failure
Successful downstaging
TACE
Radioembolization
Clinical trials
EASL JOURNAL OF HEPATOLOGY

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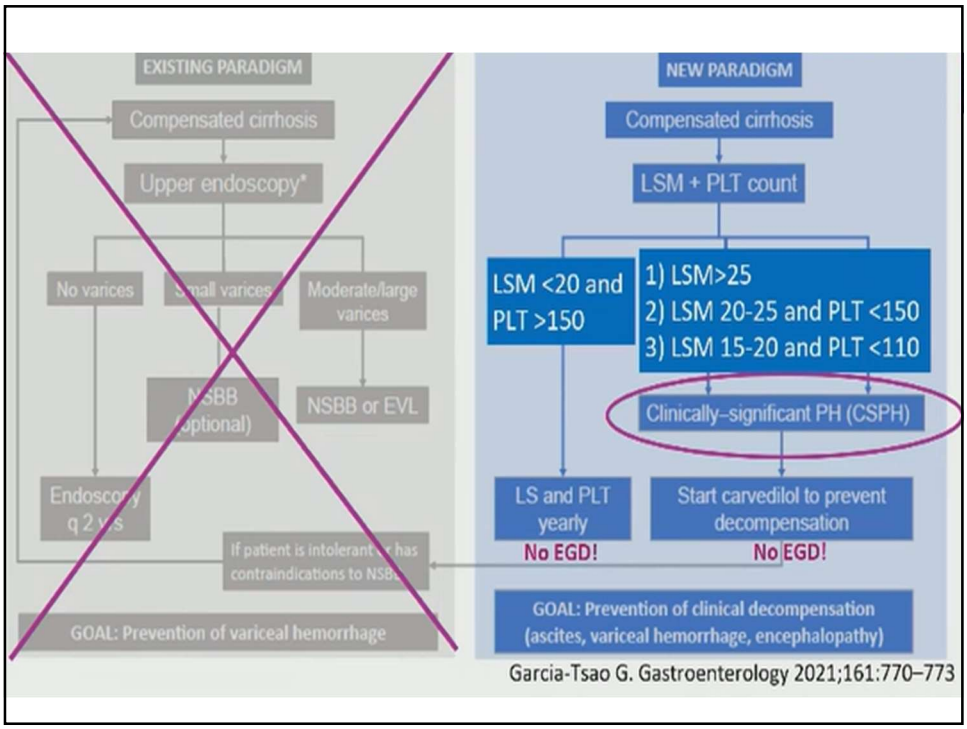
EXISTING PARADIGM
Compensated cirrhosis
Upper endoscopy*
No varices
Small varices
Moderate/large varices
NSBB (optional)
NSBB or EVL
Endoscopy q 2 yrs
If patient is intolerant or has contraindications to NSBB
GOAL: Prevention of variceal hemorrhage
NEW PARADIGM
Compensated cirrhosis
LSM + PLT count
LSM <20 and PLT >150
1) LSM>25
2) LSM 20-25 and PLT <150
3) LSM 15-20 and PLT <110
Clinically-significant PH (CSPH)
LS and PLT yearly
No EGD!
Start carvedilol to prevent decompensation
No EGD!
GOAL: Prevention of clinical decompensation (ascites, variceal hemorrhage, encephalopathy)
Garcia-Tsao G. Gastroenterology 2021;161:770–773

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4. Covid 19 và bệnh gan

Long-term clinical outcomes of patients with COVID-19 and chronic liver disease: US multicenter COLD study

Aim

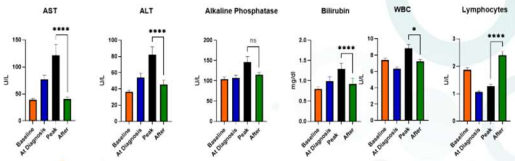
To understand the long-term consequences of coronavirus 2019 (COVID-19) in patients with chronic liver disease diseases (CLD)

Study Cohort

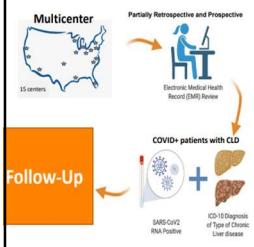
- 15 participating centers
- Median follow-up 364 days
- Total 321 patients

Lab Parameters

All the following lab parameters showed significant improvement after resolution of COVID-19.



Methods



Natural History

- Hospitalization rate during the follow up: 38.3% (n=123)
- Long COVID-19: 26.5% (n=85)
- Long-term mortality was 7.1% (n=23)

Sequelae

- Alcohol Use: 24.3% (n=78) patients reported moderate to heavy alcohol use
- Weight gain was noted in 32% (n=94) patients.

Vaccine Status: 70% had received COVID-19 vaccination

Implications

The acute liver injury and lymphopenia observed during COVID-19 resolved in most patients. However, we observed a high burden of morbidity with persistence of symptoms related to COVID-19, weight gain, and alcohol use.

Aby E, et al., Abstract 71.

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Vaccination against COVID-19 decreases hospitalizations in patients with cirrhosis: results from a nationwide analysis

Objective

- To assess the impact of vaccination against COVID-19 in Chilean patients with cirrhosis

Methods

- Quasi-experimental design from nationwide data, using regression discontinuity models to estimate the hospitalization rates (recorded as a continuous variable beyond 14 days following the second vaccination dose)

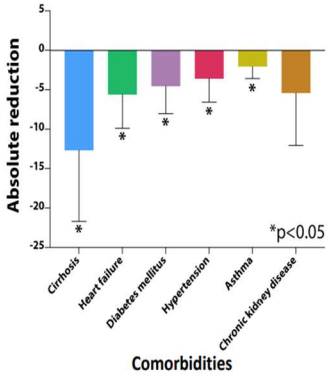
Main Findings

- 1,648,680 COVID-19 cases. A total of 0.1% COVID-19 cases had underlying cirrhosis, and 42.9% required hospitalization.
- We observed a substantial decline of absolute hospitalization rates among patients with cirrhosis who were vaccinated versus those not vaccinated (-12.69, 95%CI -21.71 to -3.68; p <0.01).

Conclusions

- Our nationwide study showed an association between vaccination against COVID-19 and a lower hospitalization risk in patients with cirrhosis.

Absolute reduction in hospitalization rates after administration of two vaccine doses in Chile



Diaz LA, et al., Abstract 39.

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Acute hepatitis after COVID-19 vaccine: case series by the International Autoimmune Hepatitis Group and the European Reference Network on Hepatological Diseases

RESULTS (CONT.)

Central histological review of the 59 cases

Predominantly lobular injury (n=45)	Predominantly portal injury (n=10)	Other (n=4)
Lobular hepatitis with confluent necrosis (n=33)	Portal hepatitis with more than mild interface hepatitis (n=8)	Bland cholestasis (n=2)
Paniobular hepatitis without confluent necrosis (n=7)	Portal hepatitis with mild interface hepatitis (n=2)	Steatohepatitis (n=1)
Isolated central perivenulitis (n=5)		Minor changes (n=1)

Codoni G, et al. ILC 2022; THU435

CONCLUSION

- Acute liver injury with autoimmune features after SARS-CoV-2 vaccination is a heterogeneous condition
- Long-term follow-up is necessary to differentiate between newly acquired classical AIH or AIH-like DILI
- Patients have a good short-term response to immunosuppression, though firm indications on when to start treatment are needed, to avoid adverse effects

EASL

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KẾT LUẬN.

- ☞ Hội nghị AASLD, DDW, EASL có rất nhiều thành tựu mới trong ngành Gan Mật.
- ☞ Có những quan điểm mới trong điều trị viêm gan B mạn.
- ☞ Trong lĩnh vực viêm gan virus, có nhiều thuốc điều trị khỏi viêm gan B mạn đang nghiên cứu và hứa hẹn tương lai tốt đẹp.
- ☞ Nhiều nghiên cứu chứng minh TAF an toàn cho phụ nữ mang thai.
- ☞ Nhiều nghiên cứu cho thấy dùng TDF điều trị viêm gan B mạn ít xảy ra HCC hơn khi dùng ETV.
- ☞ Quan điểm mới trong điều trị viêm gan C và chăm sóc phụ nữ mang thai nhiễm HCV.
- ☞ Nhiều thành tựu trong ung thư tế bào gan nguyên phát và ung thư đường mật.

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