MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Hepatitis virales I

“Hepatitis Delta”

Sabela Lens

Hospital Clínic de Barcelona, IDIBAPS, Universidad de BARCELONA, CIBERehd

Clinical Case

- Woman 57 years old
- No toxics
- No other medications
- ER: Mild Traumatism

AST (UI/L)	**316**
ALT (UI/L)	**420**
GGT (UI/L)	365
AP (UI/L)	196
Bilirubin (mg/dL)	2.8
Platelets (x10^9/L)	150
PT (%)	**64**

HBsAg	**Positive**
IgM-HAV	Negative
IgG-HAV	**Positive**
IgG HCV	Negative

Acute Hepatitis B → discharged

Clinical Case

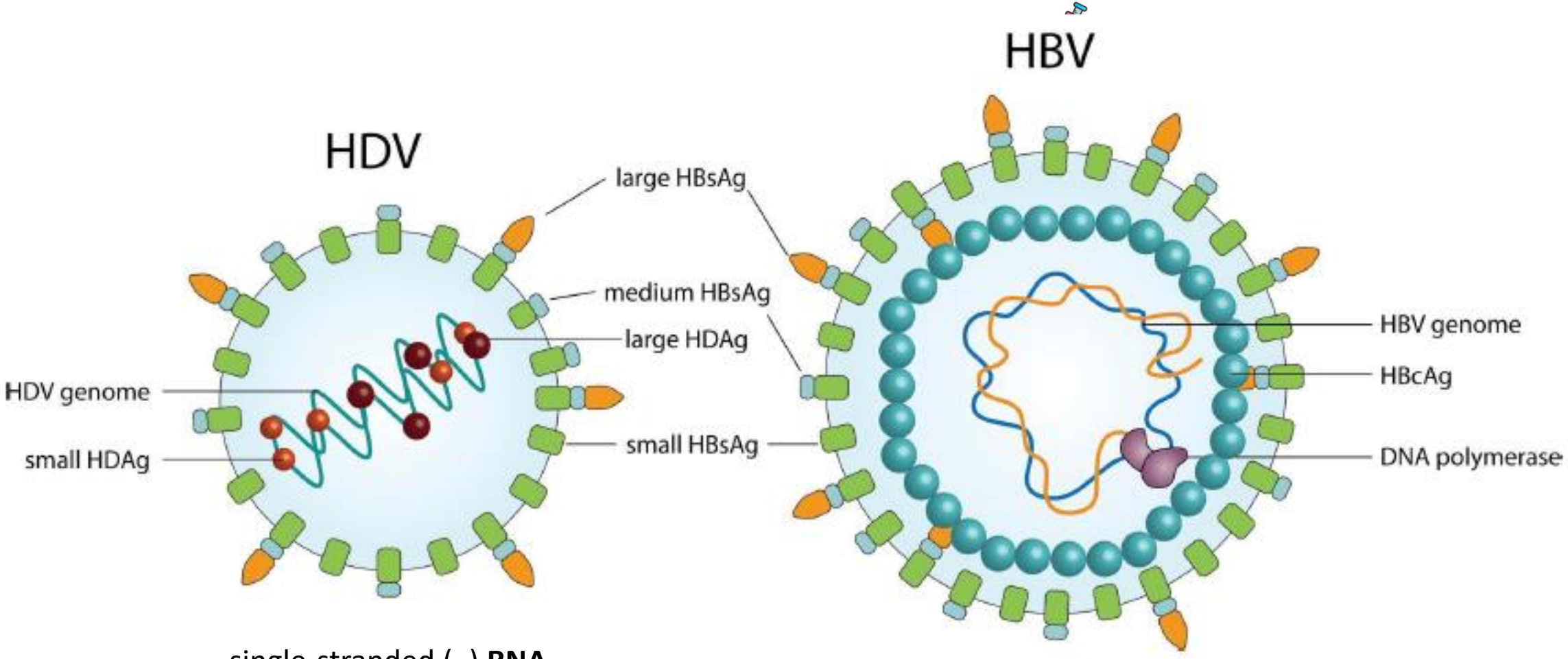
Visit at outpatient clinics 2 weeks later:

AST/ALT 180/200
GGT/AP 140/ 150,
Bi 1.5,
Albumin 35,
Platelets 150000,
PT 76%
HBsAg+ 7 years before (normal liver tests)

IgM anti-HBc	Negative
IgG anti-HBc	Positive
HBeAg Anti-HBe	Negative Positive
DNA-VHB (UI/ml)	1304

Hepatitis crónica HBeAg-negativo con criterio de tratamiento antiviral por ALT y sospecha fibrosis significativa?

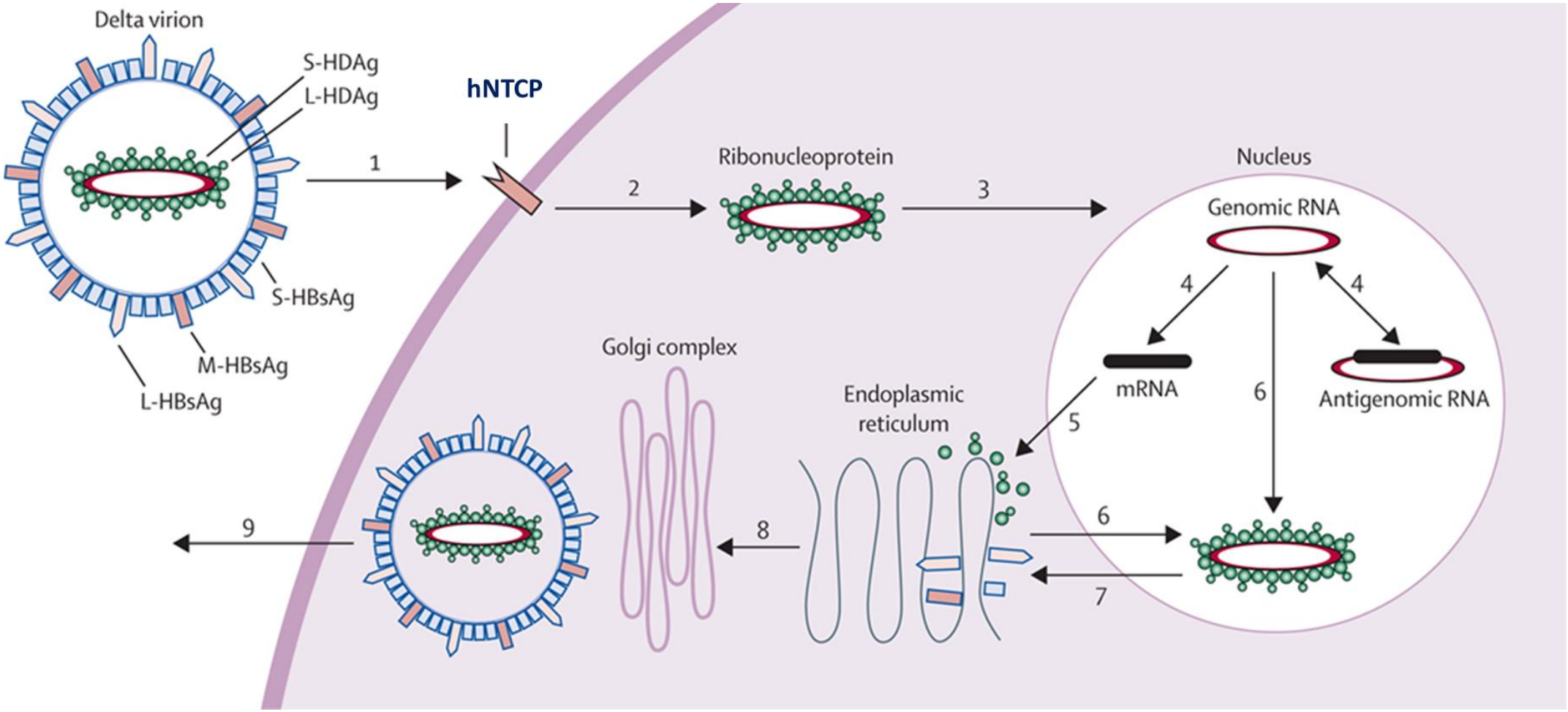
El virus Hepatitis Delta (VHD)



single-stranded (−) **RNA**
~1.7kb

relaxed circular partially double-stranded **DNA**, ~3.2kb

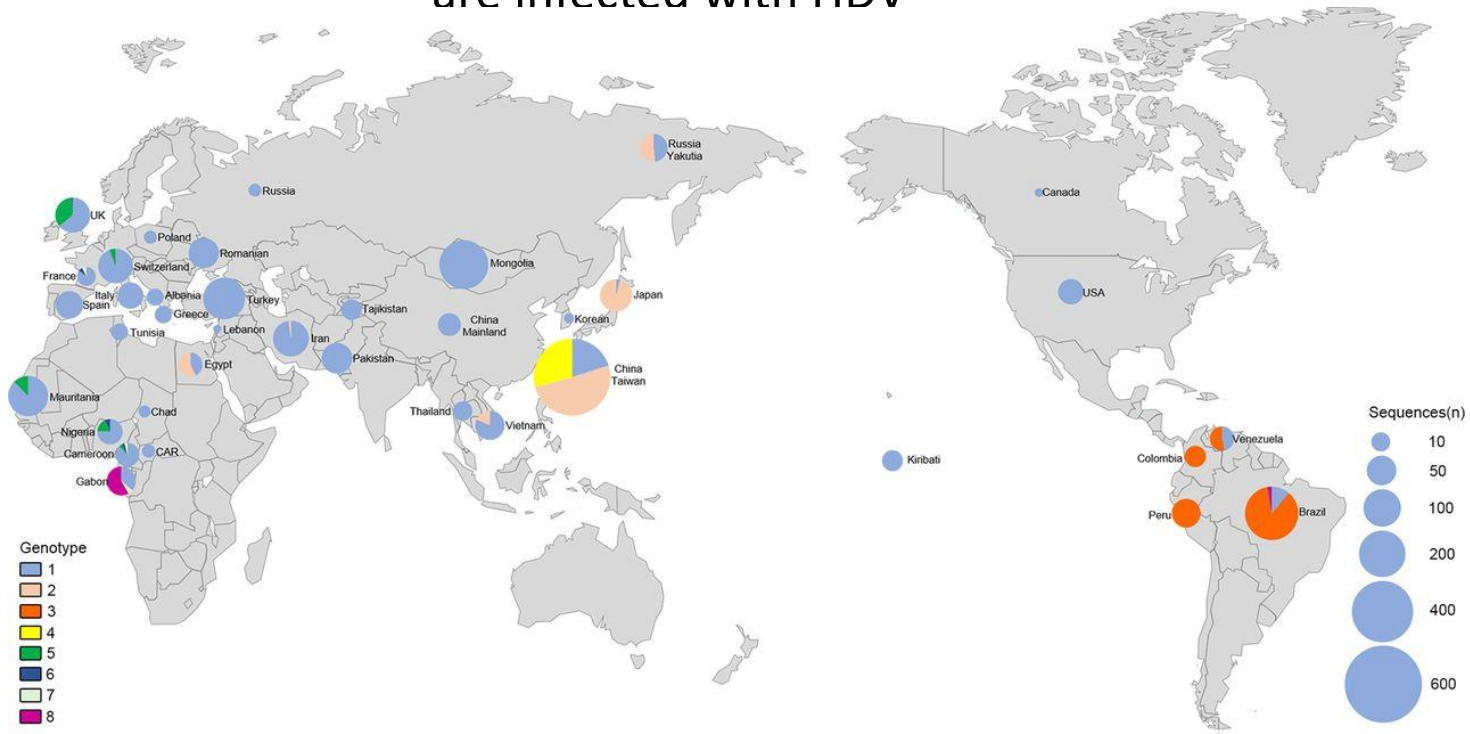
HDV replication cycle



Adapted from Hughes SA et al., The Lancet 2011

Epidemiología Hepatitis Delta

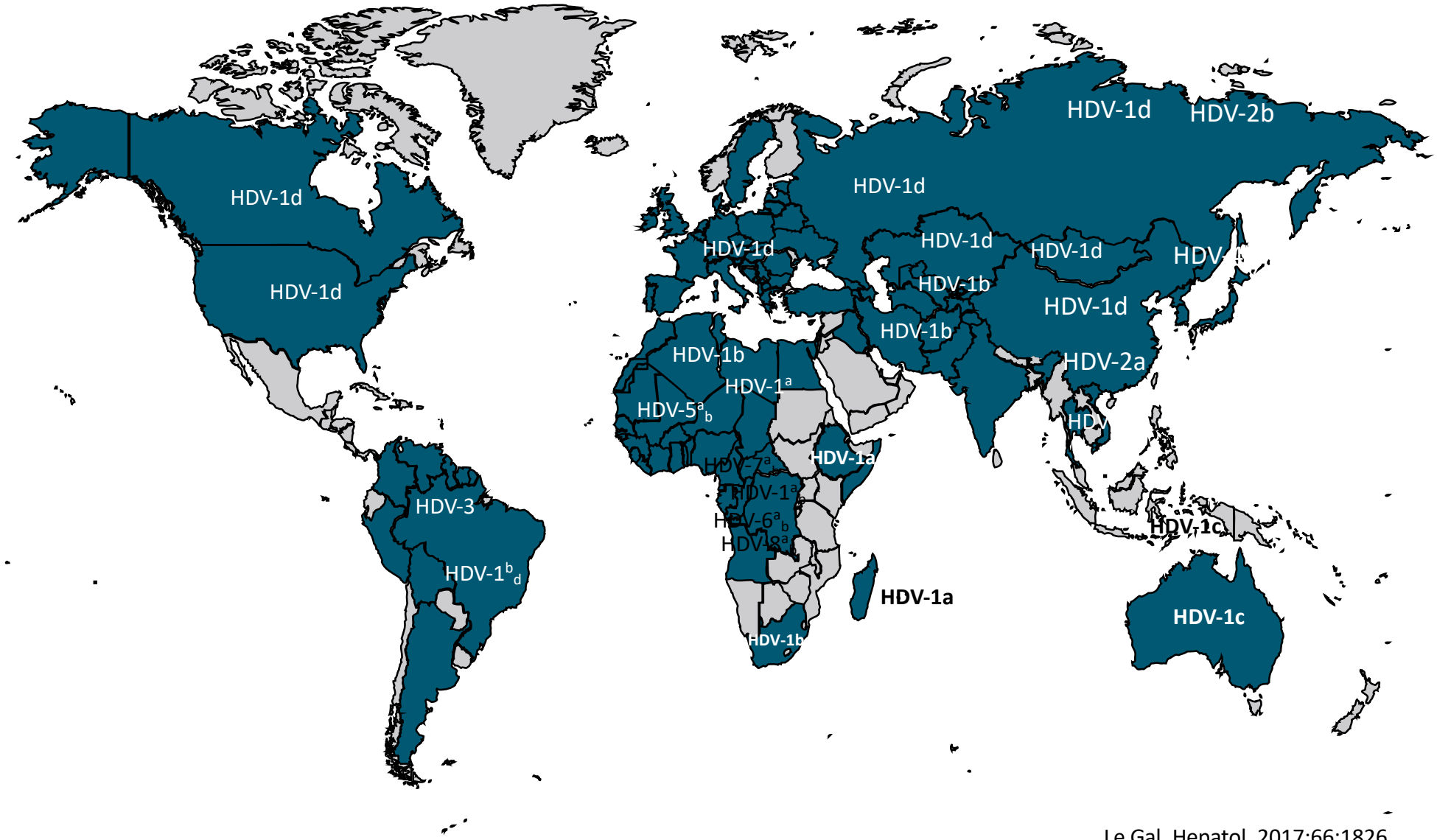
The WHO estimates 4.5% of patients with chronic Hepatitis B (240 mill) are infected with HDV



HDV ascertainment has been suboptimal, even in high-income settings. HDV may therefore have an under-recognised role in the causation of liver disease and liver-related deaths.

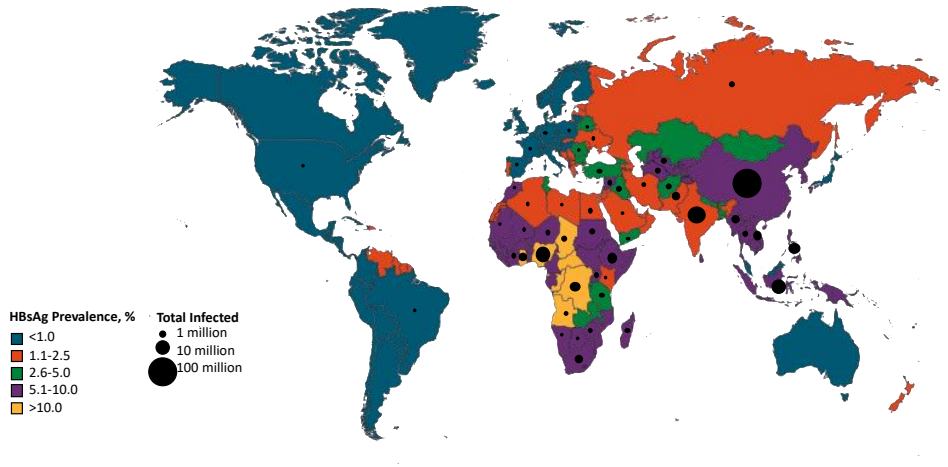
Always screen for HDV if HBsAg+

Genotipos Hepatitis Delta



Le Gal. Hepatol. 2017;66:1826.

Reducción en la prevalencia de VHD



- Introduction of universal HBV **vaccination** at an early age
  - Significant improvements in **public health**
  - Modifications in sexual behaviors (due to HIV)
  - Widespread availability of single-use syringes

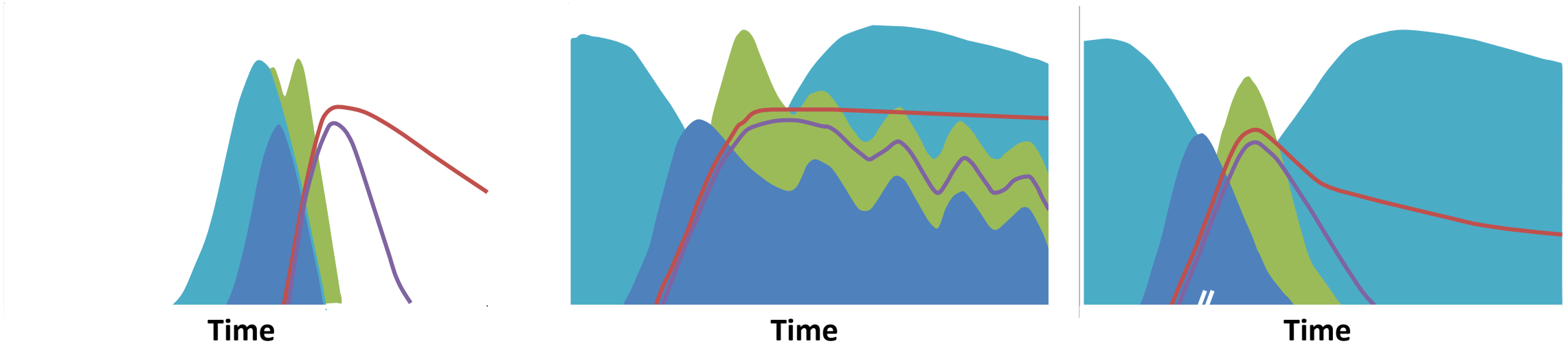
Historia natural hepatitis delta

Simultaneous Coinfection With HBV and HDV
Usually results in spontaneous clearance of both viruses

HDV Superinfection in HBV Carrier

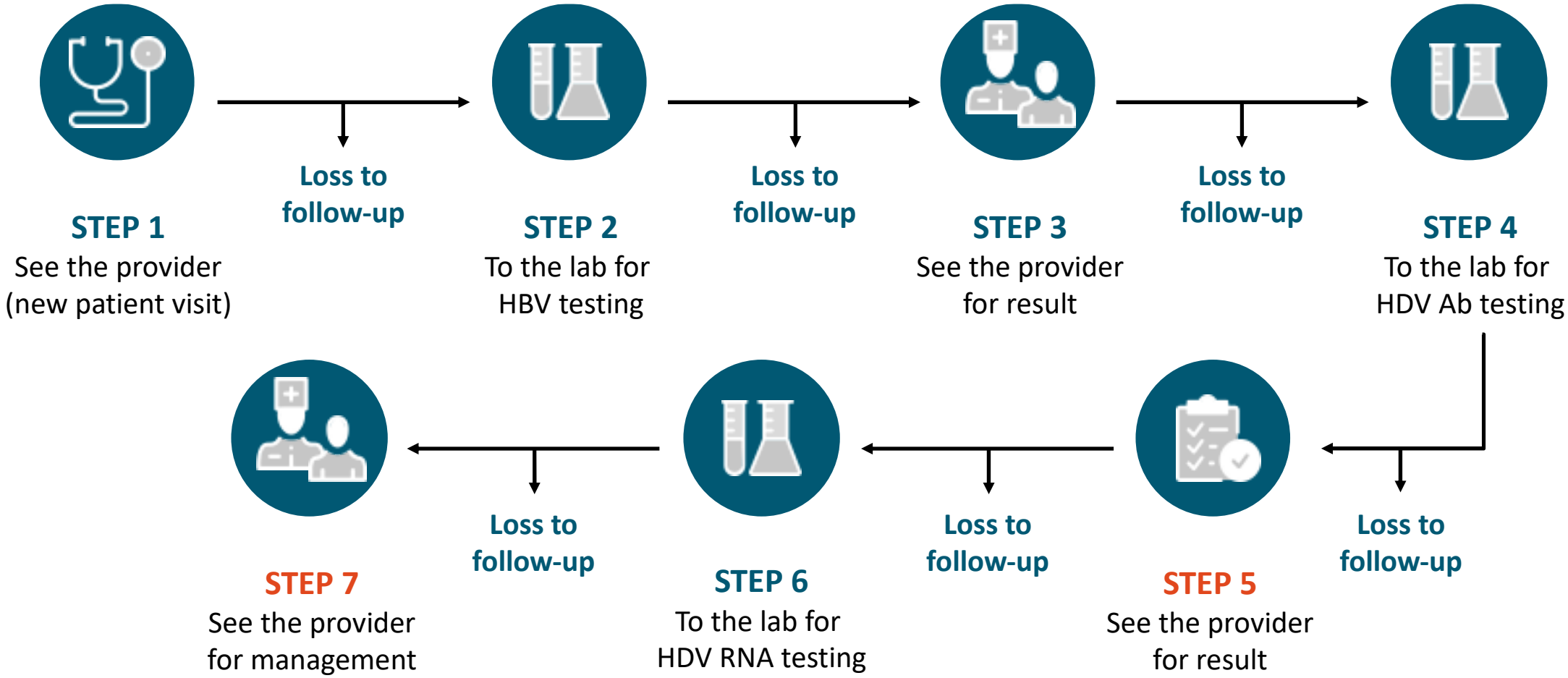
Usually results in persistent viral replication

May occasionally result in HDV RNA clearance after many yr



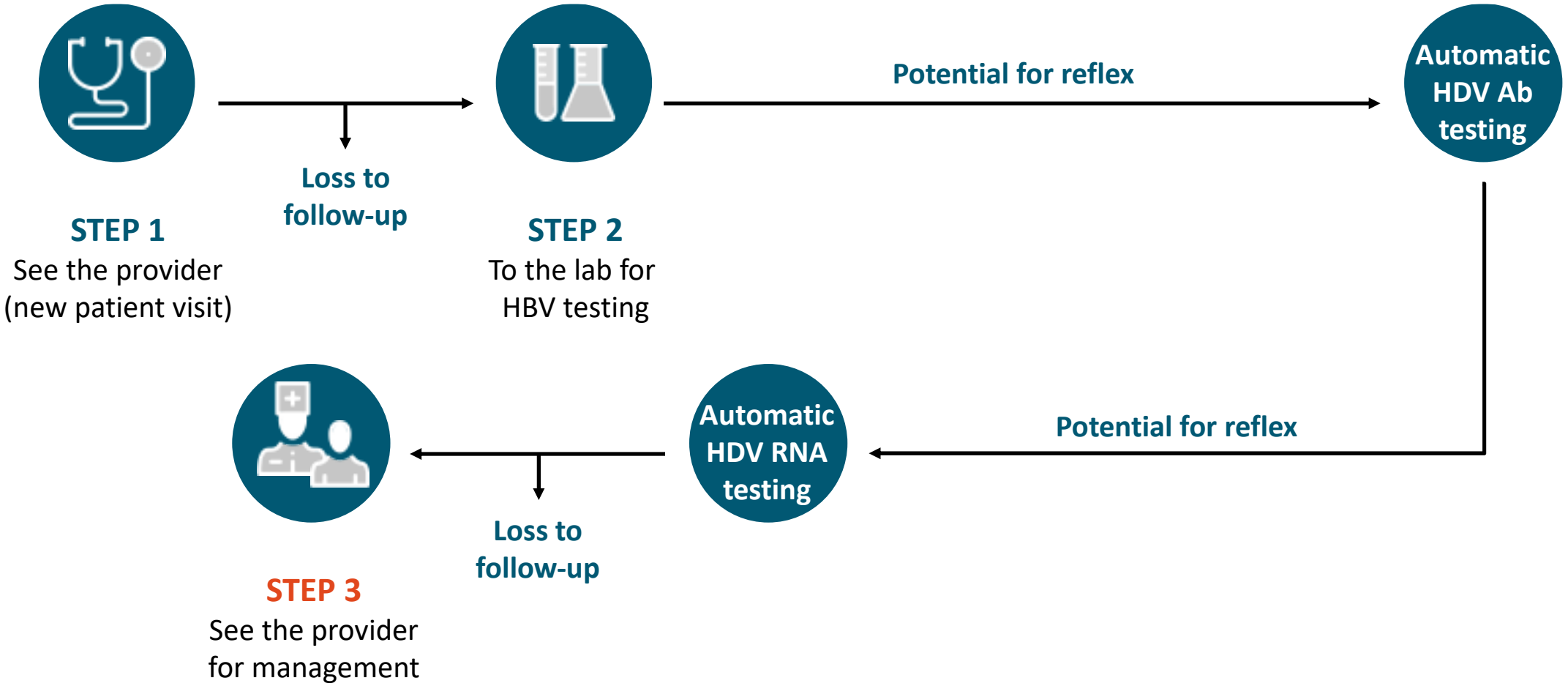
Hughes. Lancet. 2011;378:73.

Optimizando Diagnóstico



Adapted from: Feld. Clin Liv Dis. 2018;12:125.

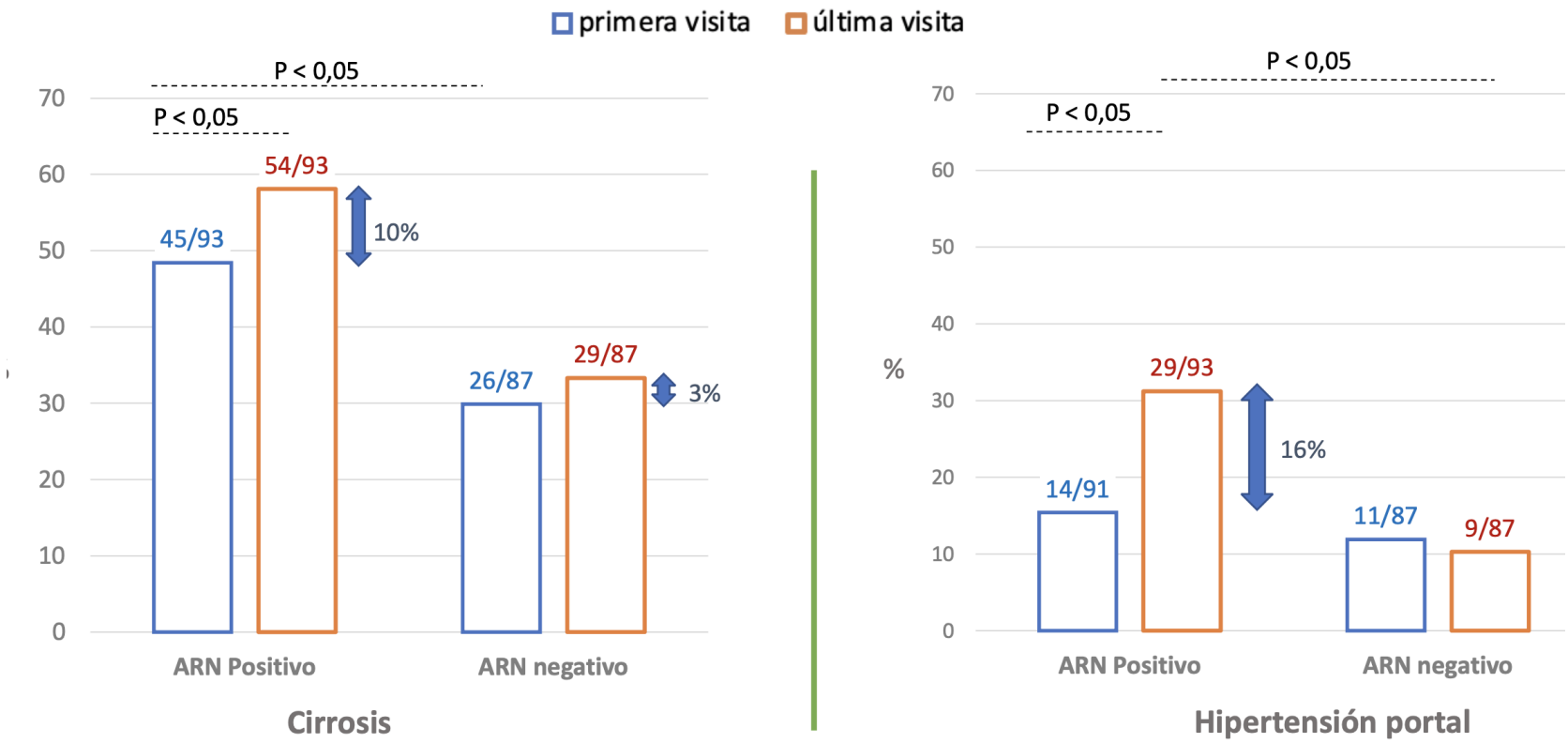
Optimizando Diagnóstico



Adapted from: Feld. Clin Liv Dis. 2018;12:125.

Historia natural VHD, datos del registro Español

213 HBV/HDV patients with active follow-up in Hepatology units in Spain (45% migrants), median FU 6 years



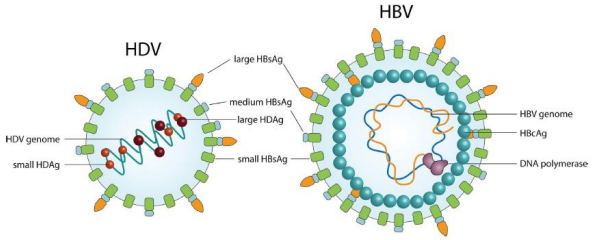
HEPATITIS DELTA REGISTRO

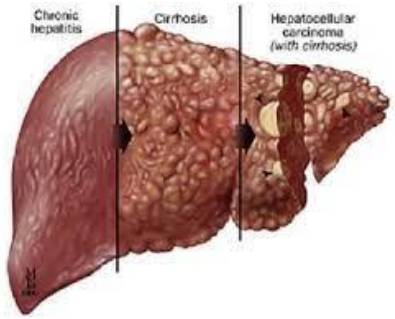
AEEH

https://aeeh.es/proyectos/registros/

Rodríguez-Tajes et al Presented at AEEH 2022

Historia natural VHB/VHD con respecto a VHB





Cirrosis
x 2

Carcinoma Hepatocelular
x 2

Descompensación
x 2

Trasplante
x 2

Screen for HCC every 6 months if HDV-RNA positive

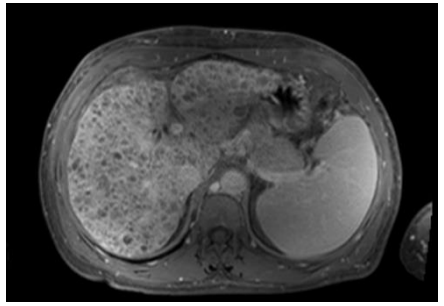
Kamal H et al. J Viral Hep 2021;28:1431–1442.

Clinical Case

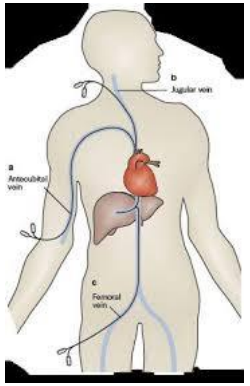
Does the patient have advanced liver fibrosis?

TE 10.5 KPa

US: liver cirrhosis,
mild esplenomegaly



HVPG: 16 mmHg
UGE: large esophageal varices



Are noninvasive markers useful in
HDV/HBV coinfection?

Clinical Case

Non-invasive fibrosis tests used in Hepatitis B and C perform poorly in HDV

Goal AUROC was > 0.8, sensitivity > 80% and positive predictive value (PPV) > 90%. None of the scores met criteria even after adapting cut-off values to optimize for chronic HDV infection.

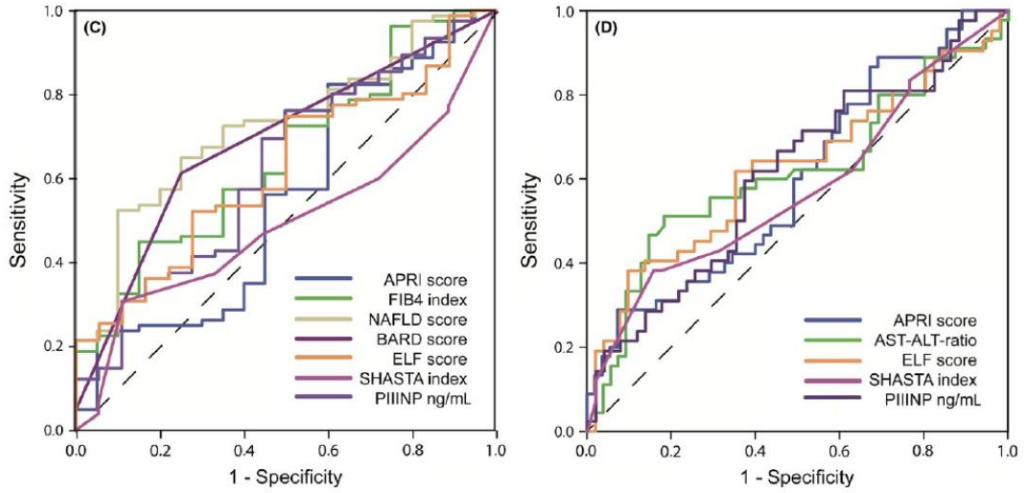


FIGURE 1 Boxplot of the Delta Fibrosis Score comparing ISHAK F0-2 vs ISHAK F3-6 (A); ROCs of the novel DFS (B), already existing non-invasive fibrosis scores (C) and already existing non-invasive cirrhosis scores (D)

Liver Int 2017

ELF score Se >80% PPV 81%

DFS score Se 85% PPV 95% AUROC 0.87

Delta Fibrosis Score (DFS) = 1(if albumin < 1.19[*LLN]) + 1(if gGT > 0.5[*ULN]) + 1(if CHE < 1.46[*LLN]) + 1(if age >42)

AUROC 0,94

$$\mathrm{D4FS} = \frac{\mathrm{LSM}(kPa)\ x\ \mathrm{GGT}(IU/L)}{\mathrm{PLT}(K/\mu L)\ x\ \sqrt{(\mathrm{ALT}(IU/L))}}$$

Antiviral Res 2020

Clinical Case

How would you treat this patient?

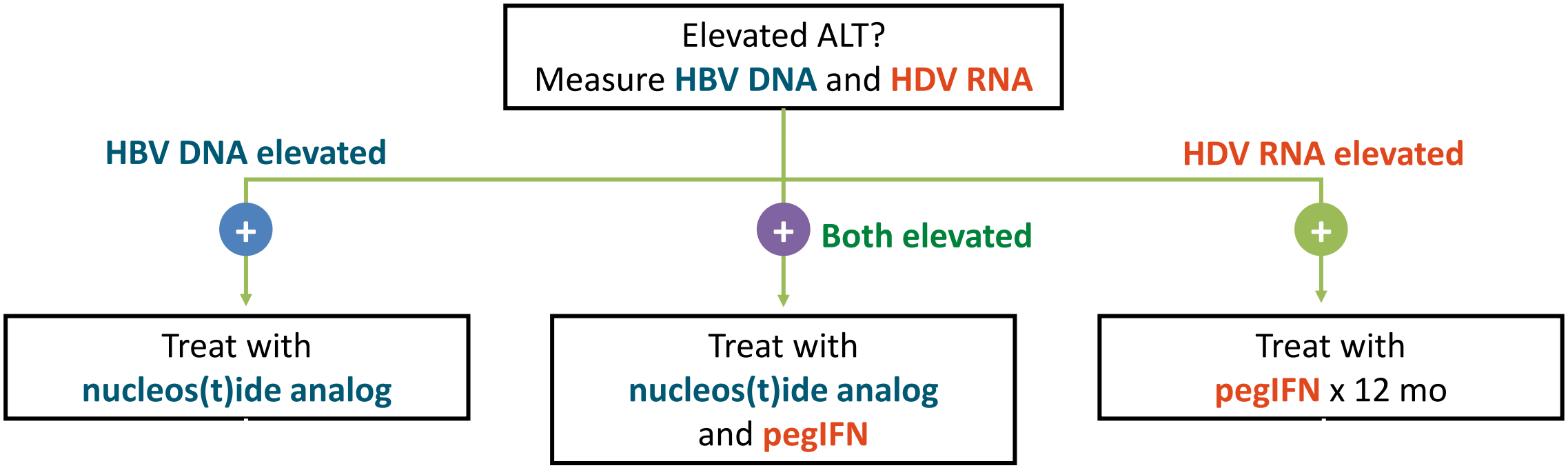
a) Peg-Interferon both to treat HBV and HDV

b) Combination therapy Peg-IFN and Nucleos(t)ide analogs (NAs)

c) PegIFN is contraindicated due to the presence of portal hypertension

d) Nucleos(t)ide analogs (NAs) only if HBV-DNA > 2000 IU/mL

Manejo infección crónica VHD



- Nucleos(t)ide analogs have no efficacy against HDV infection

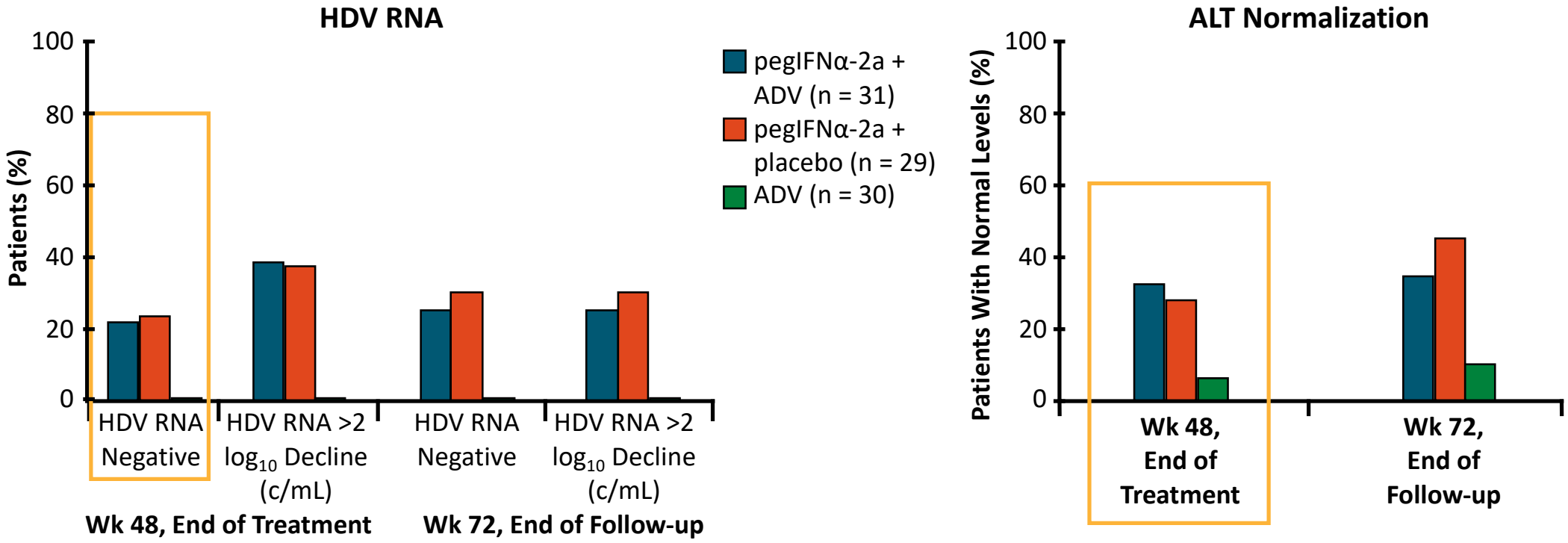
- Treatment success with pegIFN at Wk 24 ranges from 23% to 57%
- PegIFN contraindicated in decompensated cirrhosis

- PegIFN contraindicated in decompensated cirrhosis

Terrault. Hepatology. 2018;67:1560.

Peg-IFN in chronic Hepatitis Delta

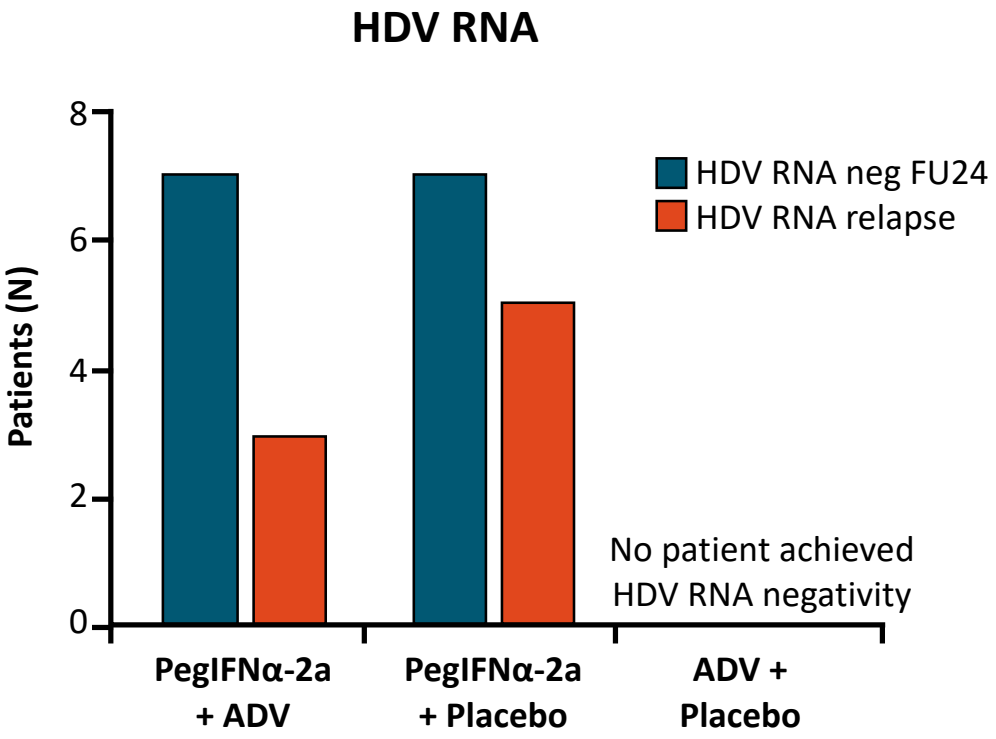
- Multicenter, randomized trial of treatment in patients with chronic HDV for 48 wk
  - **Primary endpoint:** undetectable HDV RNA and ALT normalization at Wk 48
  - ADV had **no** beneficial effect on HDV RNA

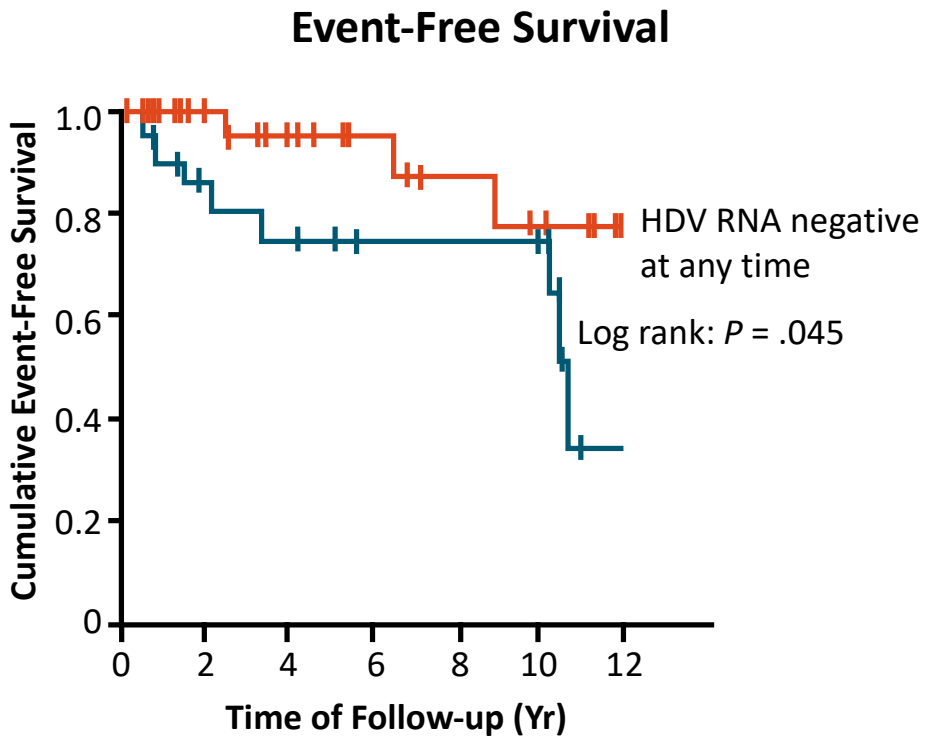


Wedermeyer. NEJM. 2011;364:322.

Peg-IFN in chronic Hepatitis Delta

- Follow-up of 60 patients from HIDIT-I: pegIFNα-2a 180 µg/kg SC QW + ADV 10 mg QD (n = 19) vs pegIFNα-2a 180 µg/kg SC QW + placebo (n = 20) vs ADV 10 mg QD (n = 21), each for 48 wk

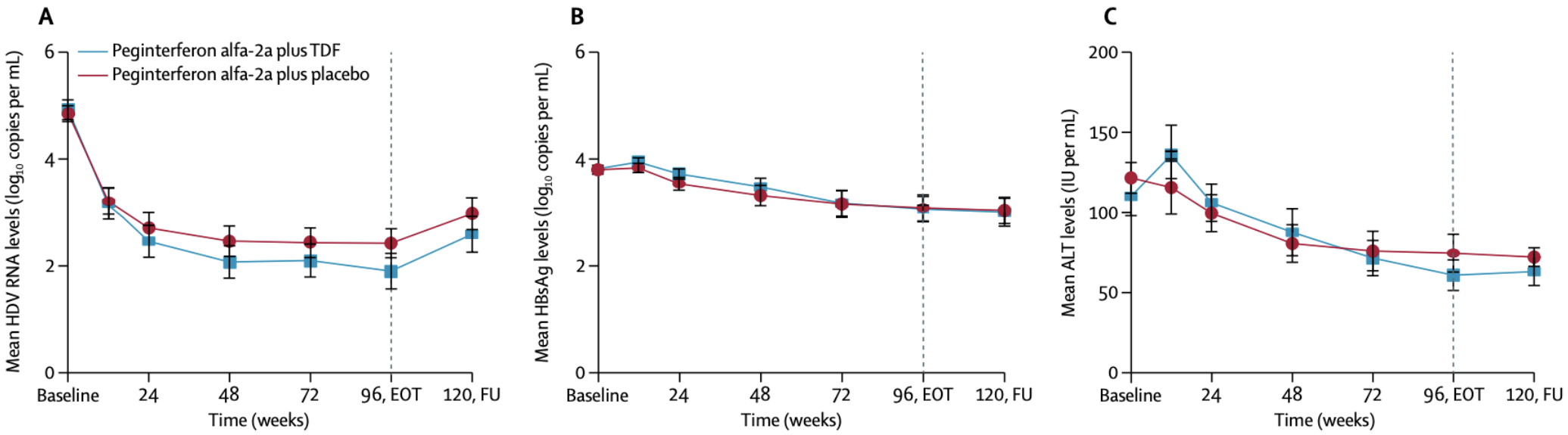




Wranke. J Viral Hepat. 2020;27:1359.

Peg-IFN in chronic Hepatitis Delta

HIDIT-II study PegIFN 96 weeks +/- TDF
on-treatment HDV RNA suppression rates of about 40% **BUT** 1/3 post-treatment relapse



Lancet Gastroent Hepatol 2019

Using high sensitive HDV-RNA→ (+) in 1/3 of samples previously classified as undetectable at wk 48 or 96 → higher (60-70%) risk of HDV-RNA relapse at week 120

Liver International 2020

Clinical Case

The patient declined Peg-IFN therapy, Tenofovir was initiated

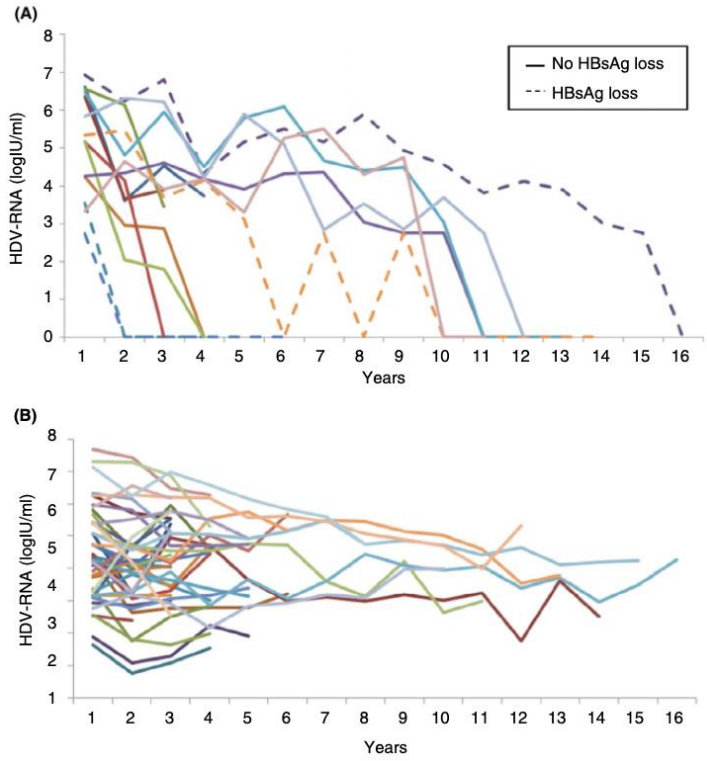
'NA treatment is recommended for those patients with HBV DNA levels being persistently above 2,000 IU/ml, and might be considered in order to block residual HBV replication in those with advanced liver disease' (EASL guidelines 2017)

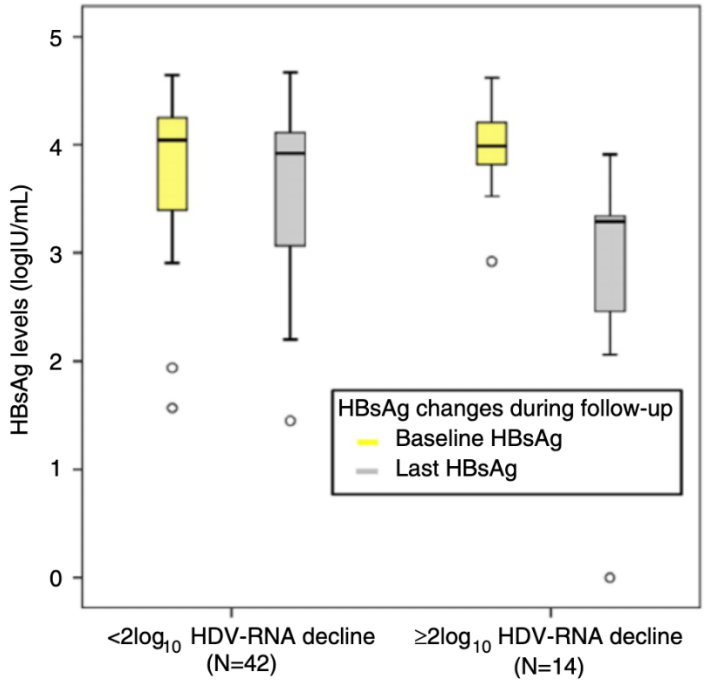
Undetectable HBV-DNA but HDV-RNA +

Clinical Case scenario a)

Spontaneus HDV-RNA fluctuations / decline

300 samples from 56 CHD patients, during a mean follow-up of 5 ys: **25% of chronic hepatitis D patients reach HDV- RNA decline (2 log HDV-RNA) or undetectability (20%) during the natural course of the disease**





Alimentary Pharmacol and Ther 2021

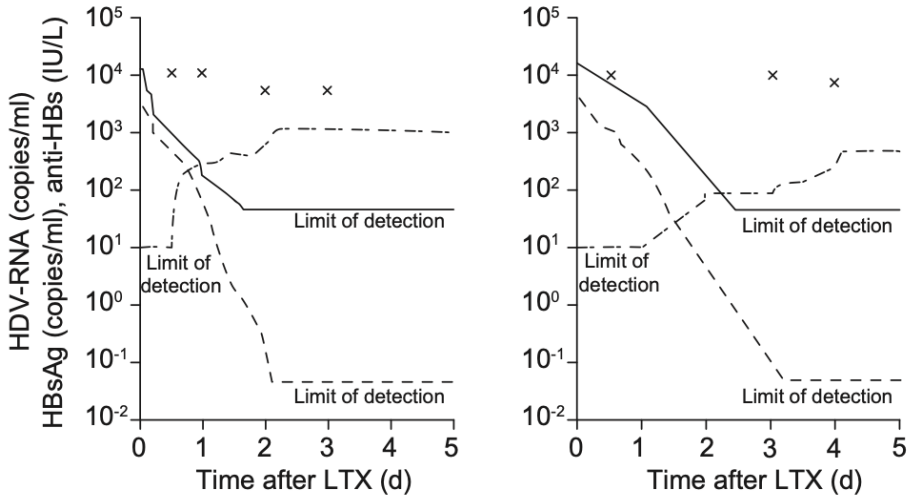
Check periodically HDV-RNA (quantify if posible)

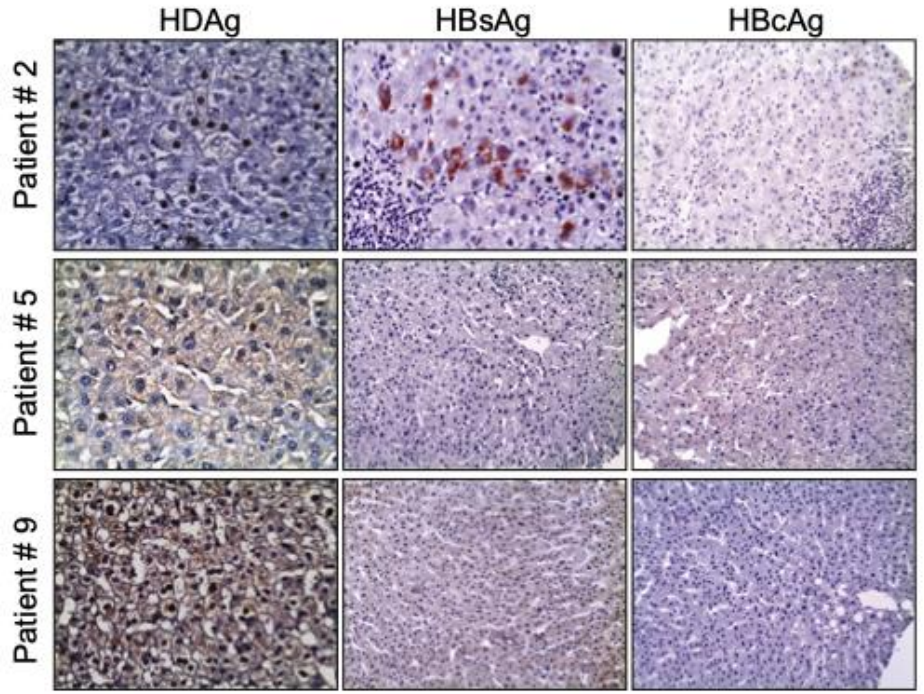
Clinical Case scenario b)

Hepatitis Delta post-trasplante

Theoretically, higher risk as HBsAg+ → HDV entrance → life-long HBIG?

N=26 HBV/HDV LT, sampling every 1-3 days after LT until 14 d





Mathematical model: HBsAg and HDV RNA became negative after a median of 5 days (range 1–13) and 4 days (range 1–10), respectively

HDAg+ in transplanted livers in 6 patients in the absence of liver HBV DNA/cccDNA, serum-HBsAg, and HDV RNA for up to 19 months after LT

Medereacke et al. J Hepatol 2012

Hepatitis Delta post-trasplante

Theoretically, higher risk as HBsAg+ → HDV entrance → life-long HBIG?

TABLE 1. HDV Liver Transplants on Long-Term Prophylaxis With Antivirals Only

Study	HDV pts	NA After HBIG Discontinuation	NA Duration Median (Range)	HBV/HDV Recurrence
Manini MA, Dig Liv Dis 2017;49S:e11	8	ETV or TDF	61 mo (31-78)	0
Caccamo L, Transpl Infect Dis 2017;19:e12641	5	LAM	20 y (18-20)	0
Cholongitas E, Transplant Infect Dis 2016;18:667-673	33*	LAM or ADF or ETV or TDF or LAM + ADF or LAM + TDF	28 mo (12-58)	1 pt†
Öcal S, Exp Clin Transplant 2015;13(Suppl 1):133-138	25	LAM or ADF or ETV	59 mo (3-120 mo)	6 pts HBsAg+
Fernández I, Transpl Infect Dis 2015;17:695-701	10	ETV or TDF	mean 28 ± 5 mo (13-36)	0

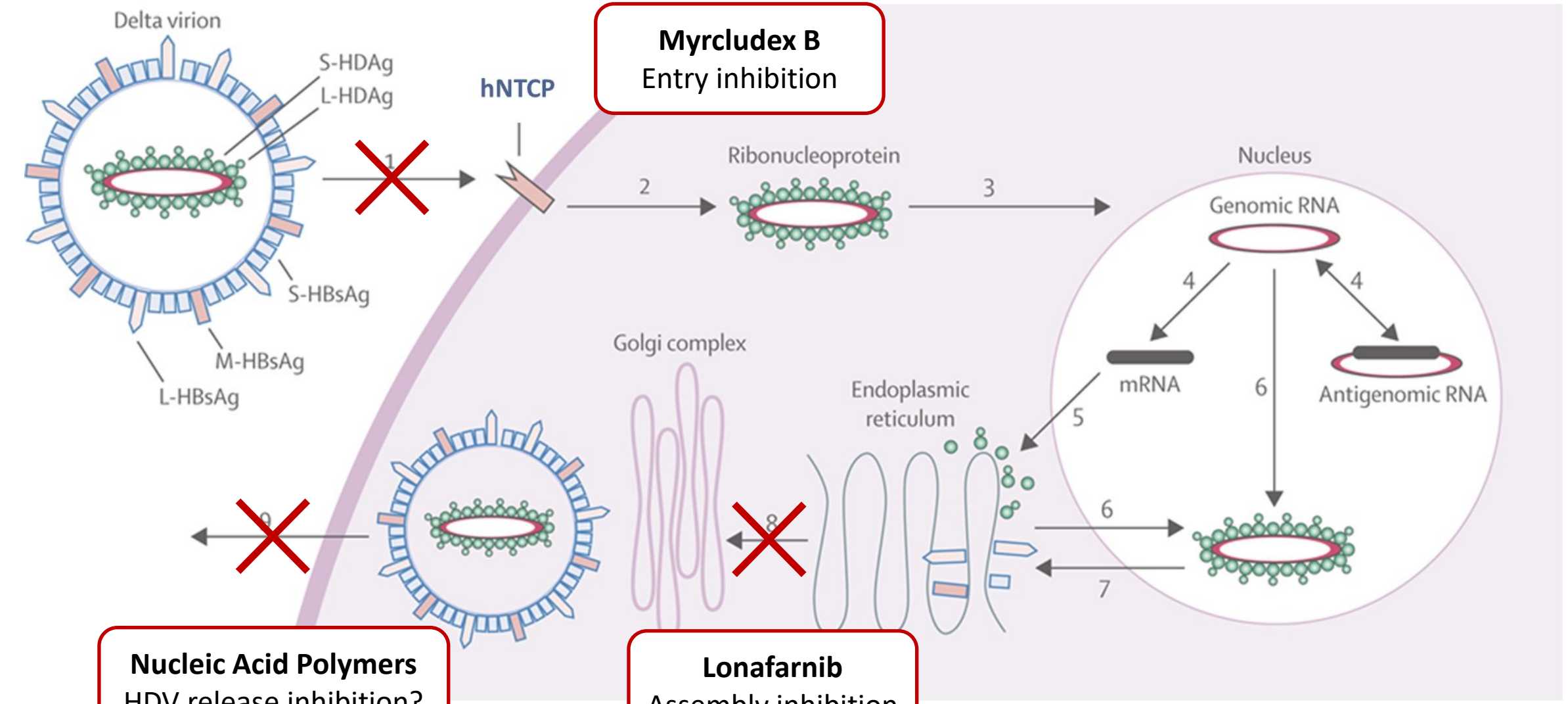
*One patient who received an HBsAg-positive liver graft was disregarded.
†The patient was rescued with HBIG for 12 months and LAM/ADF was changed to TDF.
Abbreviations: ADF, adefovir; ETV, entecavir; LAM, lamivudine; mo, months; NA, nucleos(t)ide; pt, patient; TDF, tenofovir; y, years.

81 HDV LT, long-term follow-up, only 1 HDV recurrence

Rizzetto et al. Hepatol 2018

Clinical Case scenario c)

Opciones terapéuticas en Hepatitis Delta

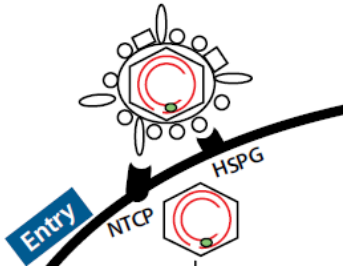


Myrcludex B
Entry inhibition

Nucleic Acid Polymers
HDV release inhibition?

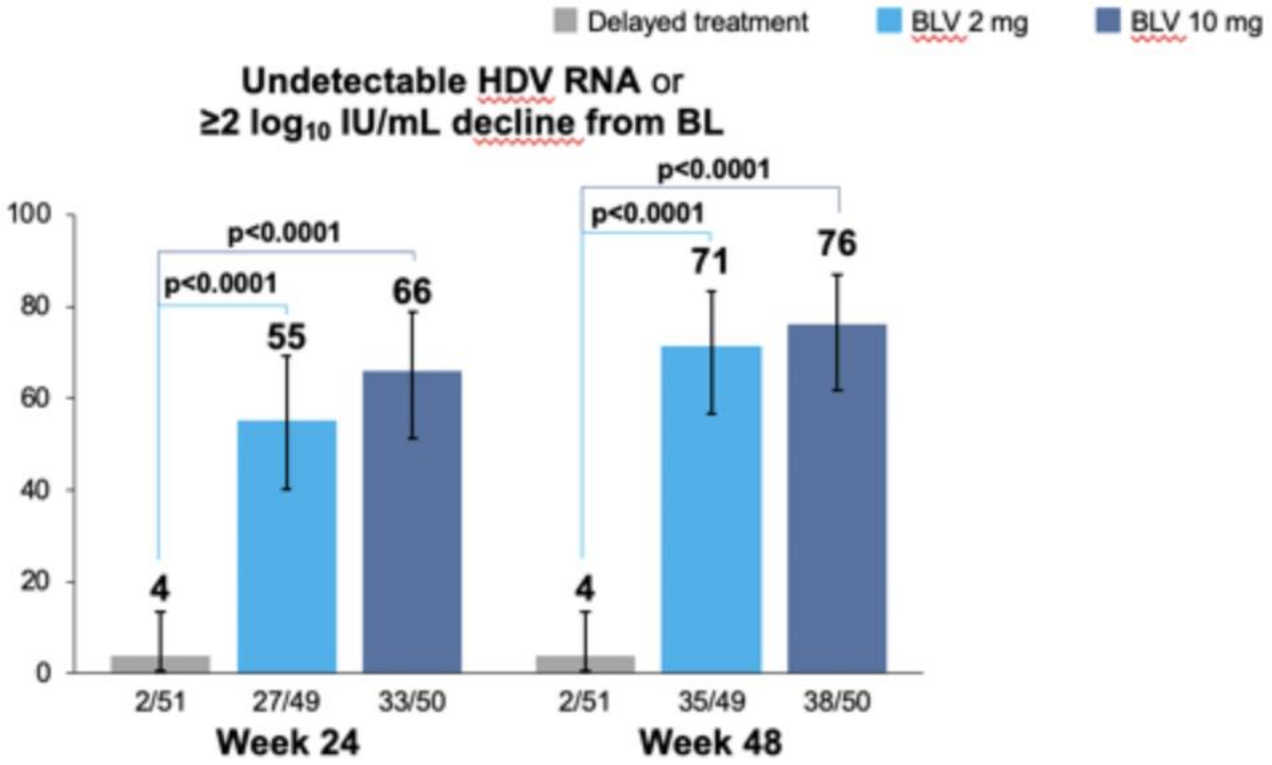
Lonafarnib
Assembly inhibition

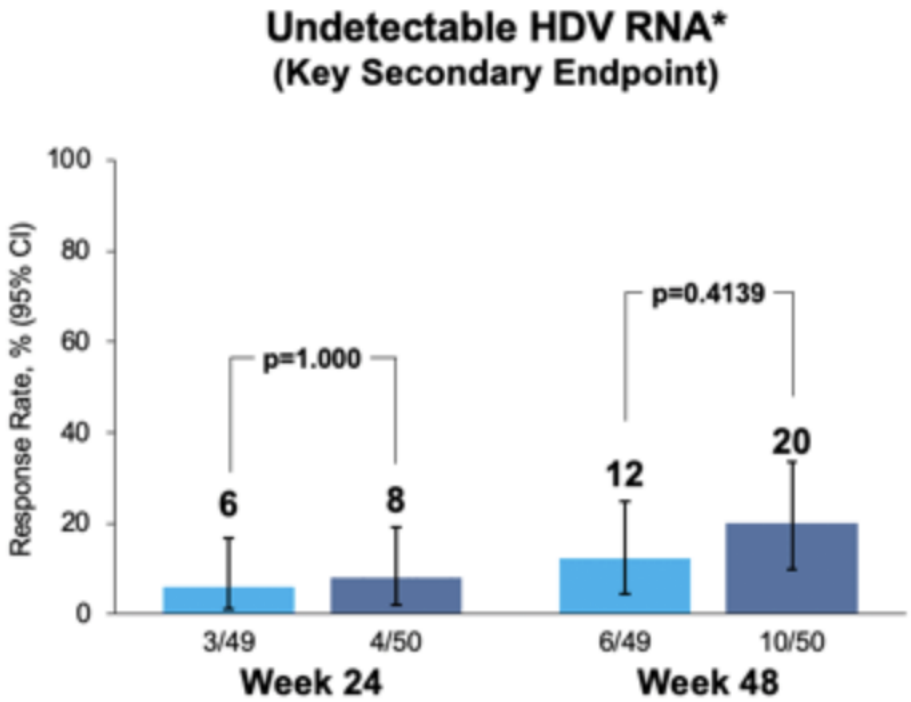
Adapted from Hughes SA et al., The Lancet 2011



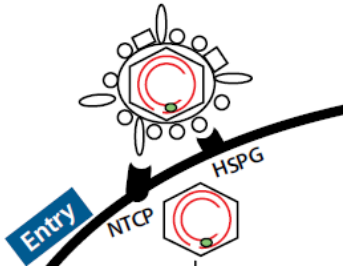
Bulevertide en Hepatitis Delta (estudio MYR301)

Myrcludex (Bulevirtide) bloquea NTCP





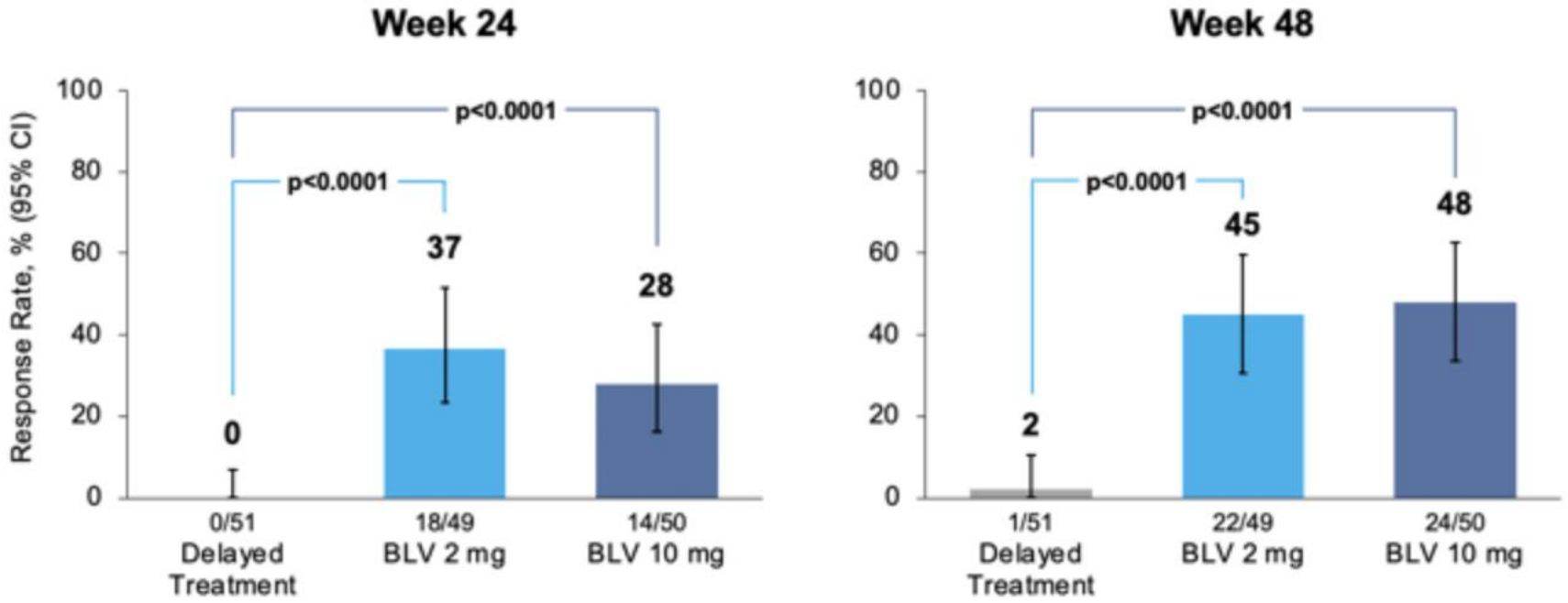
Wedemeyer et al. ILC 2022



Bulevertide en Hepatitis Delta (estudio MYR301)

Myrcludex (Bulevirtide) bloquea NTCP

Datos respuesta combinada (HDV-RNA+ALT)

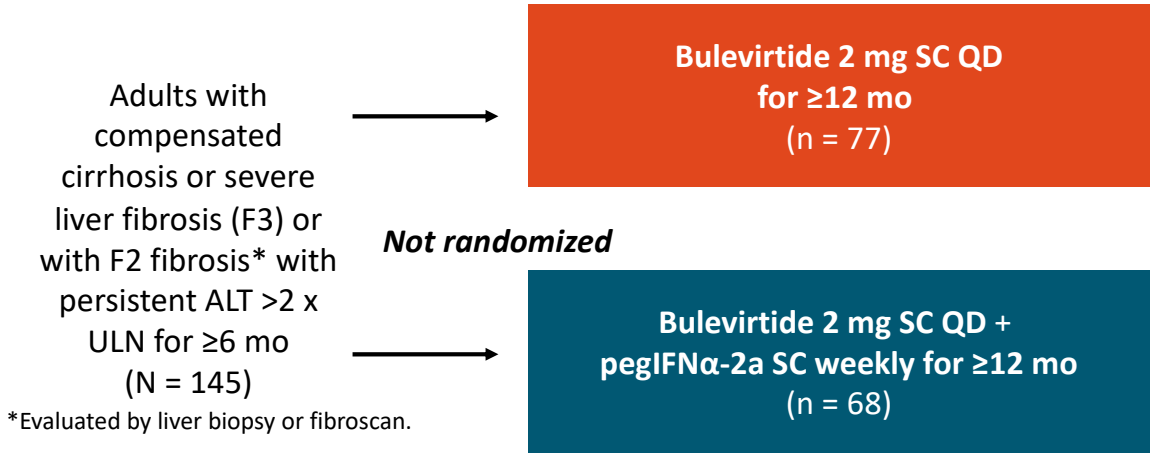


Wedemeyer et al. ILC 2022

Bulevertide: práctica clínica real

French Early Access Program: Bulevirtide 2 mg ± PegIFNα-2a for Chronic HDV Infection

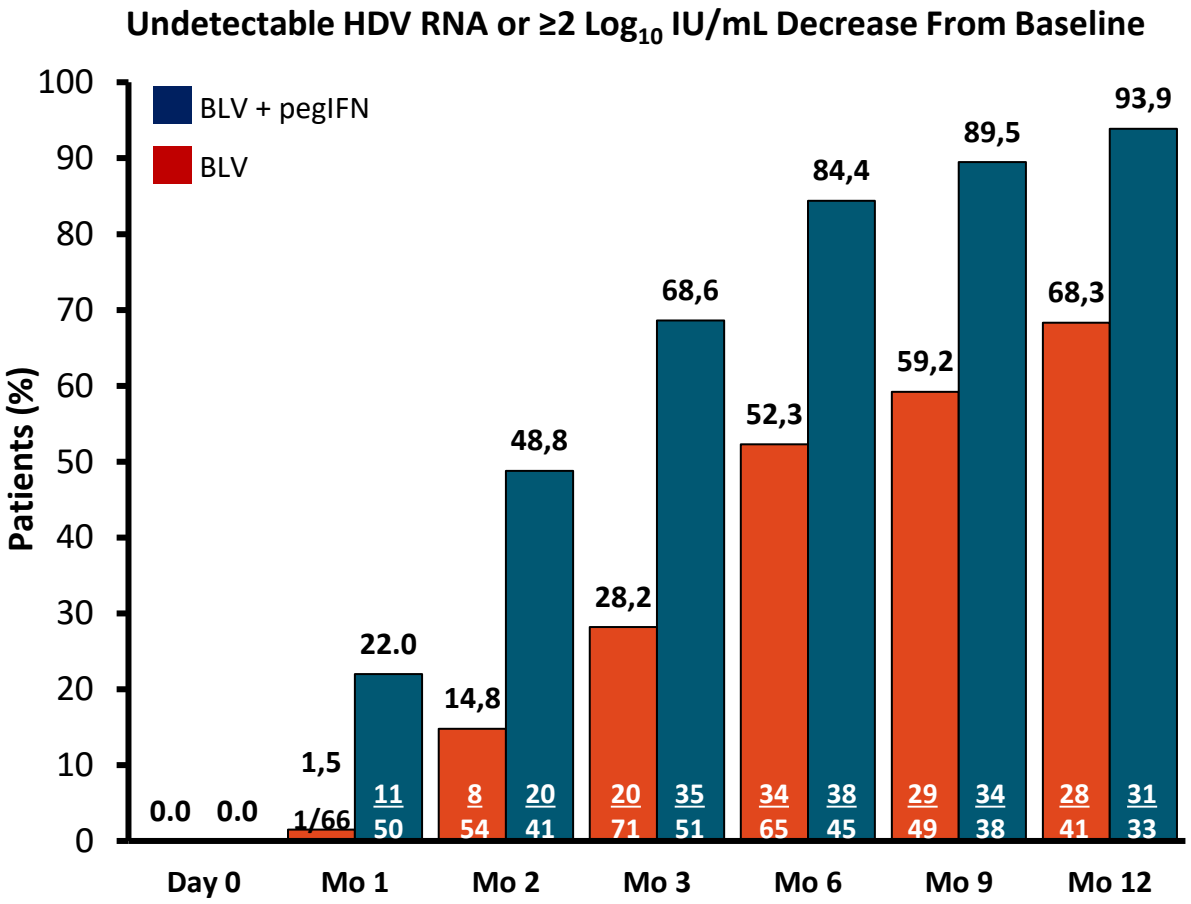
- Multicenter, prospective, retrospective, observational study in patients with chronic HDV infection from French Early Access Program (cATU)

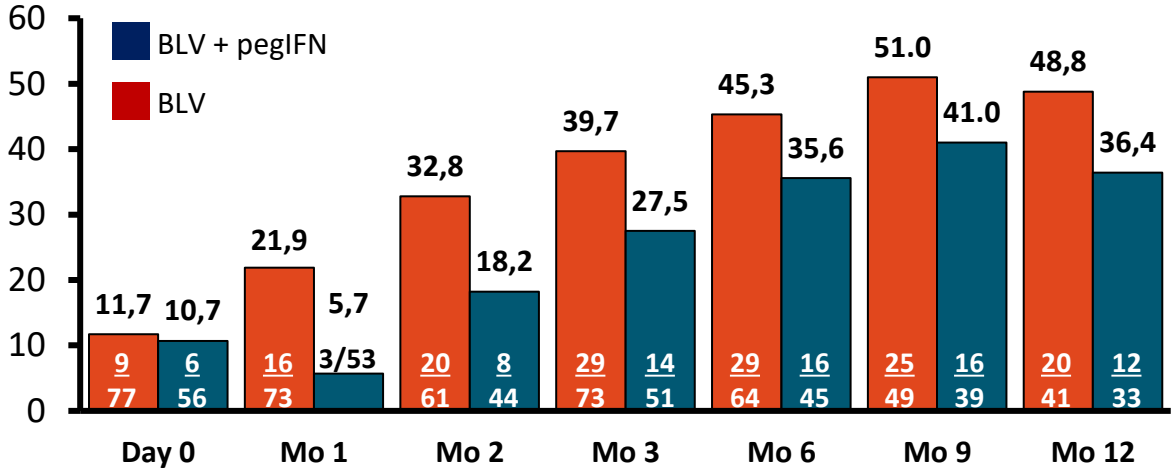


- Efficacy endpoints
  - **Virologic efficacy** defined as HDV RNA undetectable or decrease by ≥2 $\log_{10}$ from baseline
  - **Biochemical efficacy** defined as normal ALT levels (ALT <40 IU/L)

De Ledinghen. AASLD 2021. Abstr OA21.

Bulevertide: práctica clínica real





Combined response RNA+ALT

De Ledinghen. AASLD 2021. Abstr OA21.

‘Take-home messages’

- Debemos cribar a todos los pacientes HBsAg+ al menos una vez y más a menudo si factores de riesgo de transmisión o elevación transaminasas de causa no aclarada. En caso de anti-VHD positivo deberemos evaluar la presencia de RNA-VHD.

- La coinfección VHB/VHD (RNA+) se asocia a peor pronóstico con mayor desarrollo de cirrosis, descompensación y carcinoma hepatocelular.

- La eficacia del interferón es limitada y hay pacientes que tienen recidivas tardías

- Existen nuevos tratamientos en desarrollo clínico. **Bulevertide** ya ha sido aprobado (duración? Factores asociados a respuesta?).

PI15/00151
PI16/00111
PI18/00079
IFI18/00006

Viral Hepatitis Unit
Liver Unit
Hospital Clínic
Barcelona

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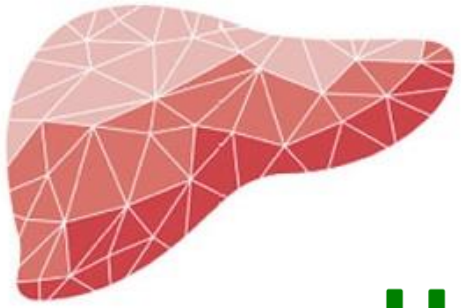

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