Hepatitis B y D
¿Estamos haciendo lo necesario?

Maria Buti

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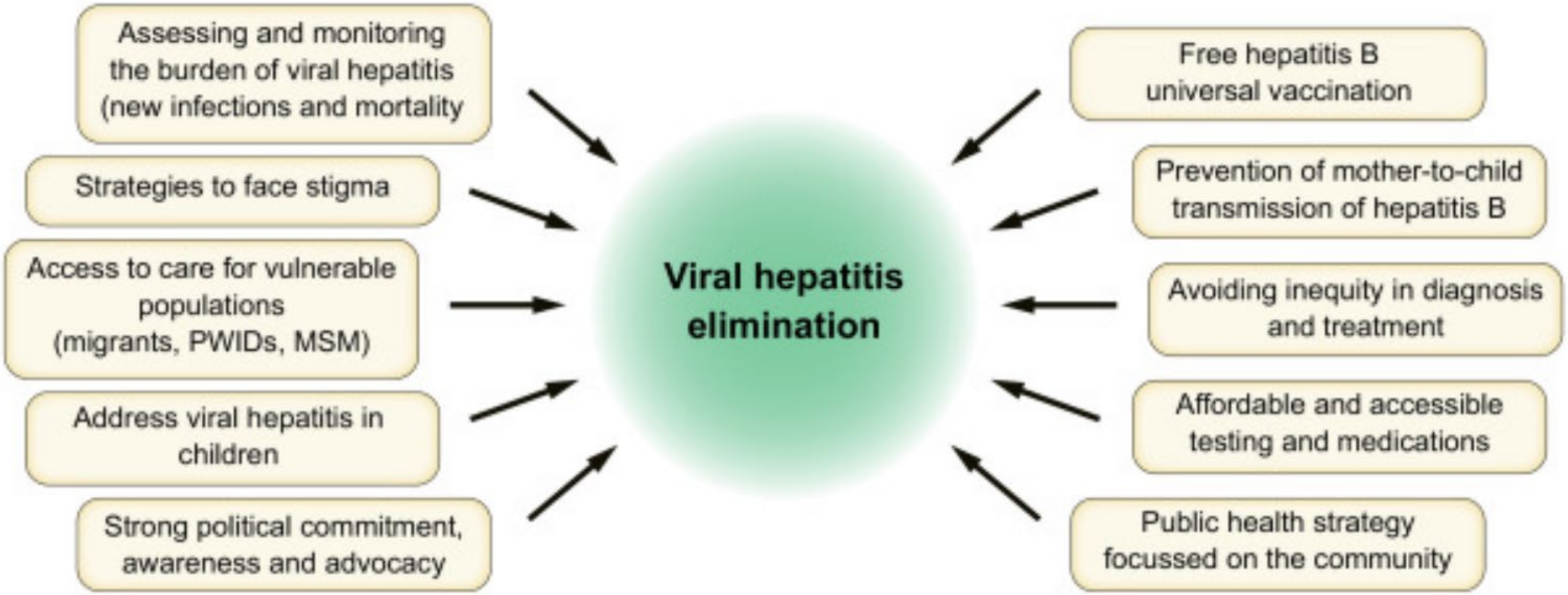
Barcelona.

Priorities in viral hepatitis elimination

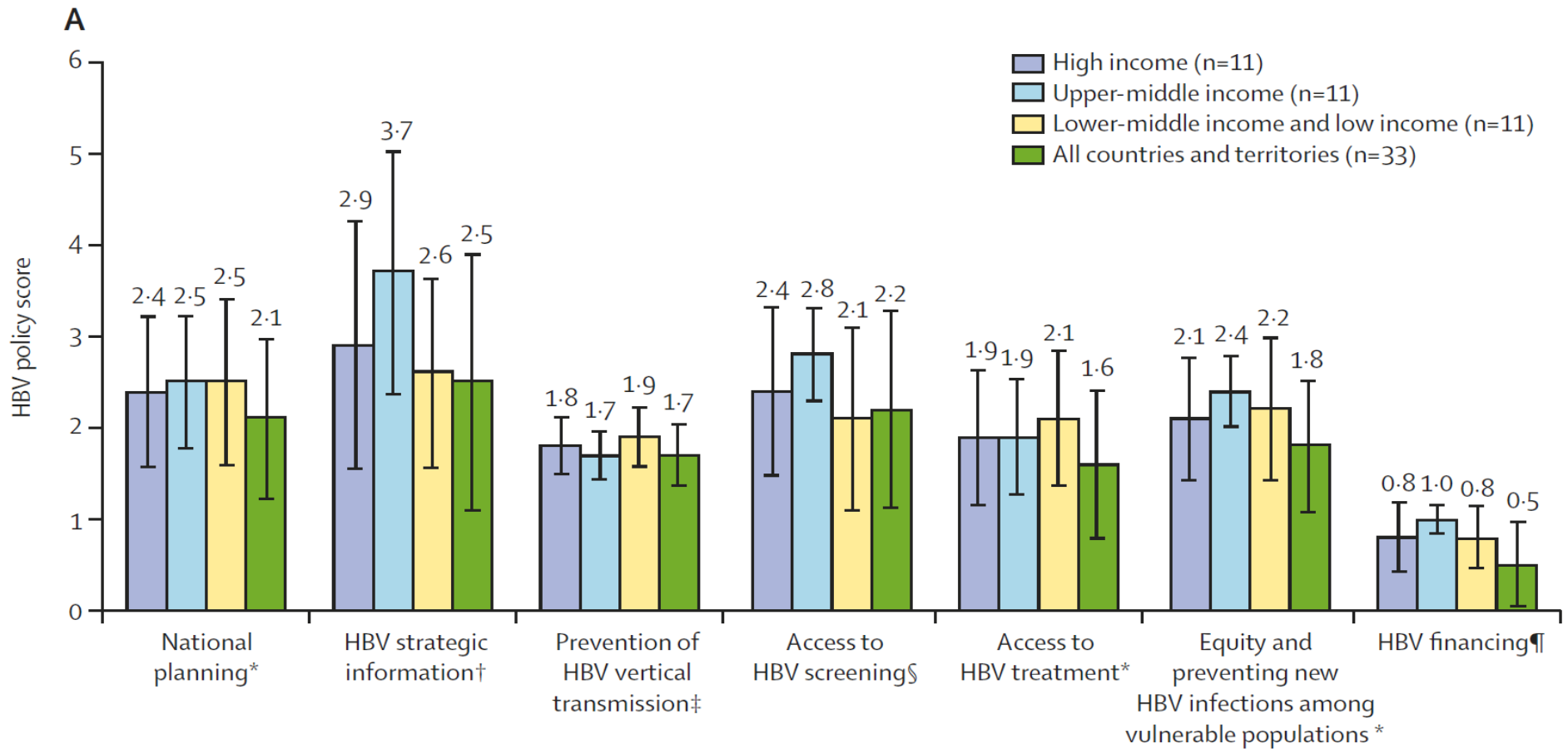


Buti M et al J Hepatol 2023

A 2024 global report on national policy, programmes, and progress towards hepatitis B elimination: findings from 33 hepatitis elimination profiles

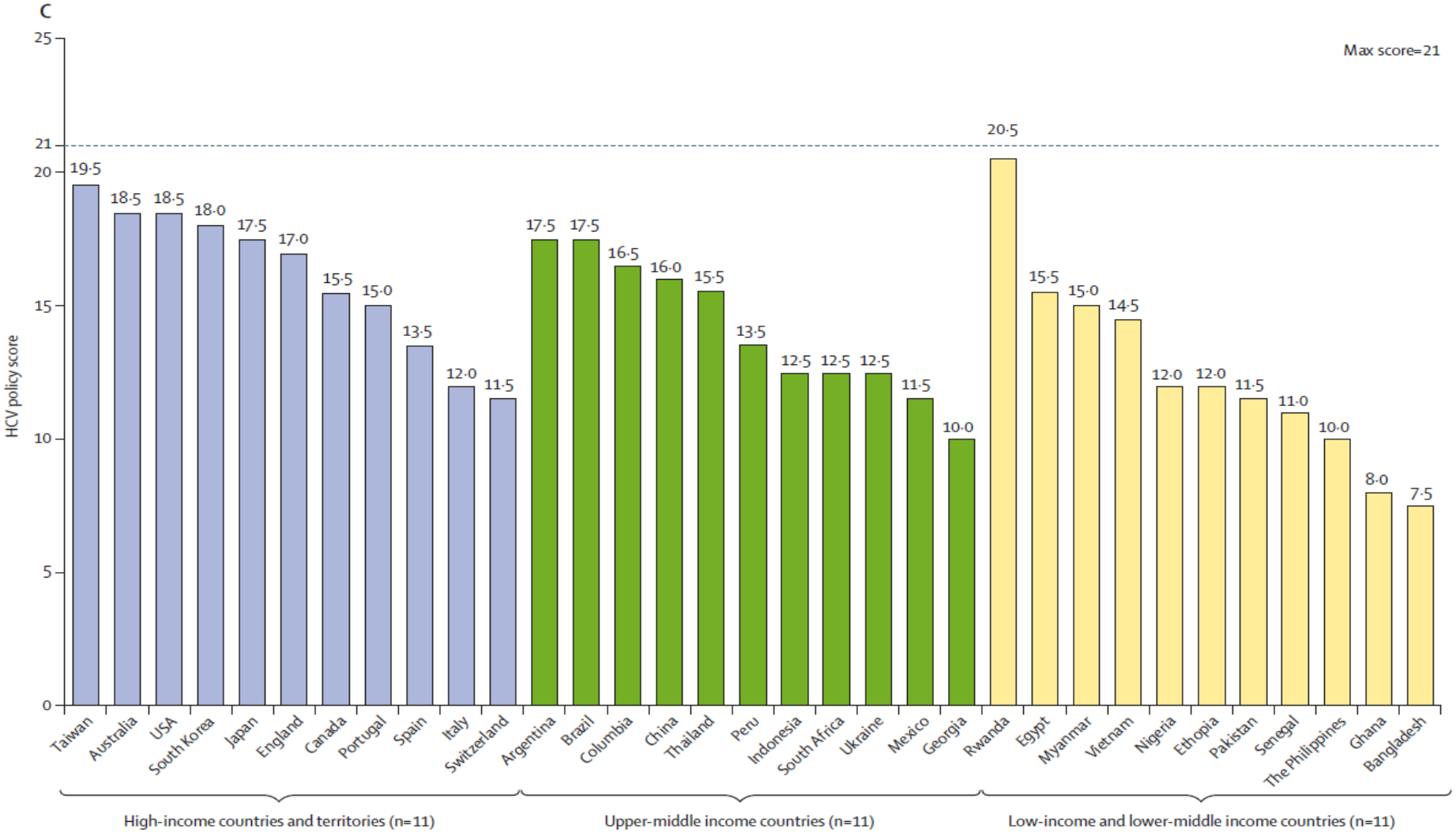
Hiebert-Suwondo L et al. Lancet GastroHep 2025

Hepatitis B mean policy scores across country and territory income classifications



Hiebert-Suwondo L et al. Lancet GastroHep 2025

Hepatitis B policy scores by Country and territory hepatitis B policy scores, by income classification



Hiebert-Suwondo L et al. Lancet GastroHep 2025

Results from Spain

HBV elimination goal	Yes
Year of HBV elimination goal	No data
HBV Action Plan	No
HBV screening recommendations for pregnant women	Adopted

Diagnosed & treated

Proportion of persons living with HBV diagnosed (%)	No data
Proportion of diagnosed persons receiving appropriate HBV treatment (%) (among those eligible)	No data

Prevalence of chronic HBV (HBsAg+) (%) 2019 , Modelled	0.51 (0 - 0)
Prevalence of chronic HBV (HBsAg+), Children < 5 yrs	No data

Mortality

HBV-related death rate (per 100,000) 2021 , Modelled	1.74 (1 - 2)

HBV Recommendations: Shift From Testing to Screening

Out with the old... ...in with the new

Guideline	Whom to Test	How to Test
AASLD 2018[1]	▪ Risk-based testing	▪ HBsAg ▪ Anti-HBs
APASL 2016[2]	▪ Risk-based testing	▪ HBsAg ▪ Anti-HBs ▪ Anti-HBc
EASL 2025[3]	▪ Not specified	▪ Not specified
ECDC 2018[4]	▪ Risk-based testing	▪ HBsAg
WHO 2015[5]	▪ Risk-based testing	▪ HBsAg

Only includes recommendations to screen **pregnant persons** and **candidates for chemotherapy/immunosuppressive therapy**

2023 CDC Recommendations[6]

- **Universal screening for all adults at least once in their lifetime**
  - HBsAg
  - Anti-HBs
  - Total anti-HBc
- Pregnant persons: screen in first trimester
- Continued periodic risk-based testing:
  - Incarcerated
  - History of STI or multiple sex partners
  - History of HCV

1. AASLD HBV Guidelines. April 2018. 2. APASL HBV Guidelines. November 2015. 3. EASL HBV Guidelines. May 2025. 3. ECDC HBV Guidelines. February 2018. 5. WHO HBV Guidelines. March 2015. 6. cdc.gov/mmwr/volumes/72/rr/rr7201a1.htm?s_cid=rr7201a1_w.

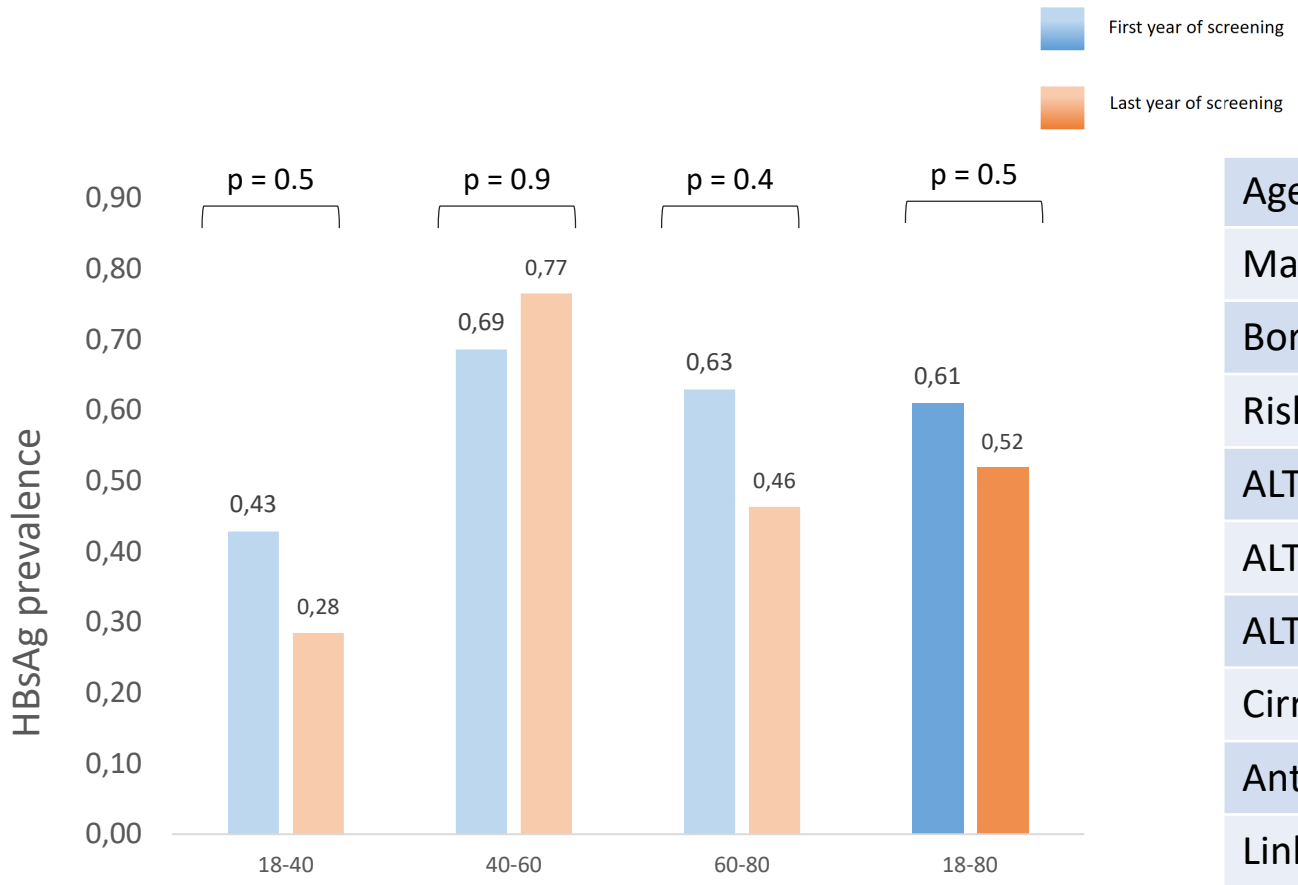
Prevalencia de hepatitis B y C en el Servicio de Urgencias del Hospital Vall d´Hebron

	01/2020-07/2024	01/2020-12/2022	
Pacientes cribados	36.307	17560	
Anti-VHC detectable	**1.297 (3,6%)**	684 (3,8%)	0.85%[1]
RNA VHC detectable	**200 (0,55%)**	128 (0,7%)	0.22%[1]
HBsAg detectable	**215 (0,59%)**	91(0.52%)	0.22%[2]

Ruiz-Cobo JC et al. AEEH 2025

1. Resultados del 2º Estudio de Seroprevalencia en España (2017-2018). Ministerio de Sanidad, Consumo y Bienestar Social; 2019.
2. Centro Nacional de Epidemiología, Instituto de Salud Carlos III. Vigilancia epidemiológica de la Hepatitis B en España, 2019. Madrid; octubre 2020

Impacto del cribado sobre la prevalencia de hepatitis virales en el Servicio de Urgencias



	Total (n = 215)
Age, years (IQR)	58 (46-71.5)
Male sex, n (%)	138 (64.2)
Born in spain, n (%)	122 (56.7)
Risk factors, n (%)	30 (14)
ALT, IU/mL	23 (15.3-35.8)
ALT high, n (%)	35 (16.3%)
ALT high or risk factors, n (%)	59 (27.4)
Cirrhosis, n (%)	25 (12.1)
Anti-HDV, n (%)	9 (4.4)
Linked to care before, n (%)	70 (32.6)

Ruiz-Cobo JC et al. AEEH 2025

Migrants: HBV-COMSAVA and COMSAVAC

VIRAL HEPATITIS COMSAVAC
Multi-Country Community Screening, Vaccination, and Care

Hepatitis B Virus Community Screening and Vaccination in Africans study aims to use point-of-care testing and simplifed diagnostic tools to identify, link to care, or vaccinate African migrants initially in Barcelona and after in 4 European cities

HBV COMSAVA
Hepatitis B Community Screening and Vaccination in Africans

Program	People screened	Age	Recently arrived (< 5yrs)	HBsAg+	Anti-HCV+	Linkage to care
Barcelona	**624** (79.8% Ghana 16.2% Senegal)	**41,93 yrs**	**23,7%**	**10,1%**	**0%**	**70%**
Europe	**335** (54. Ghana 11% Guinea 7.5% Morocco 5. Philippines 5.1% Senegal)	**40,36 yrs**	**34,8%**	**5,37%**	**0,6%**	

Picchio CA, et al. Commun Med (Lond). 2023 Dec 14;3(1):182.

Very few Point of Care Testing for Hepatitis B. No saliva test

B. Point-of-care HCV test and treat

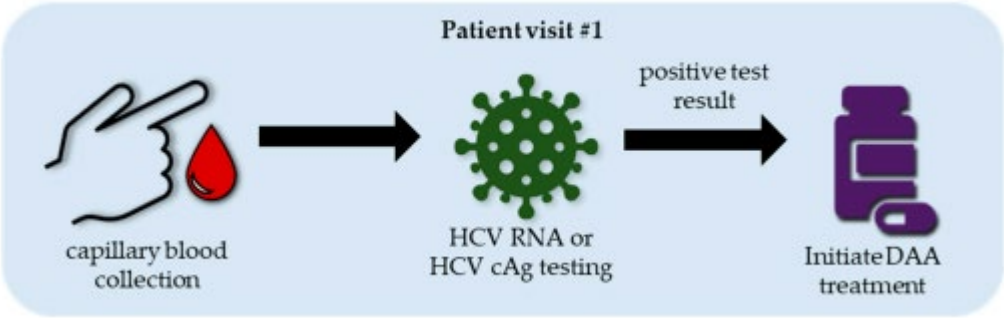
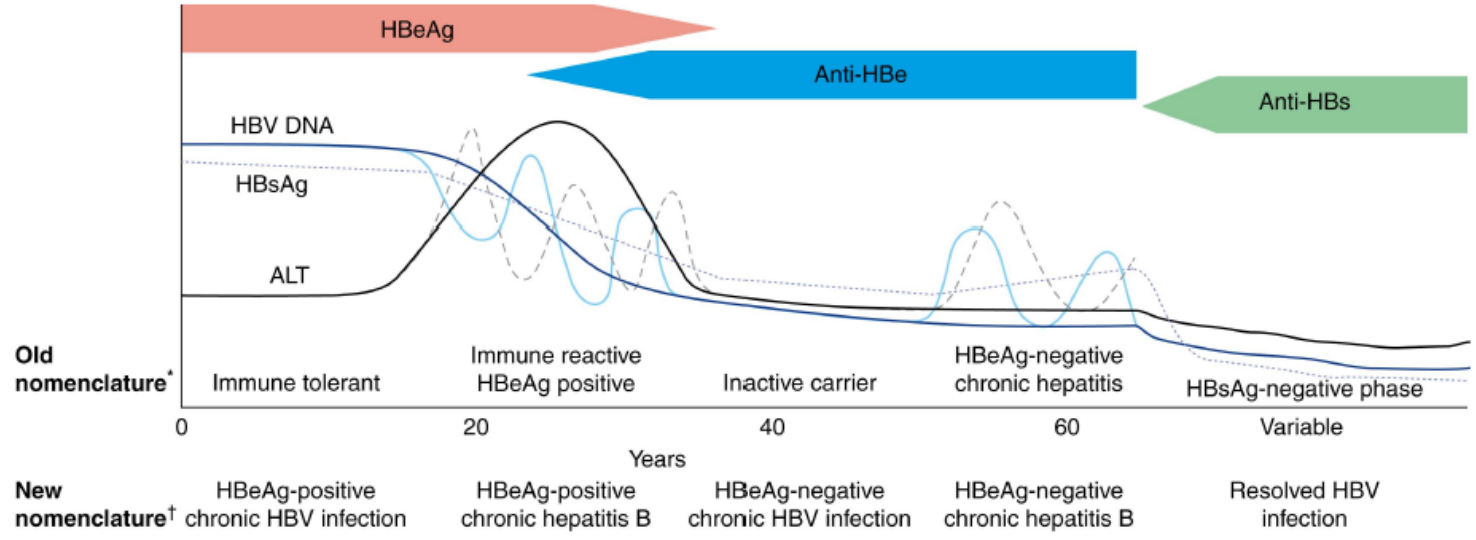


Table 2. WHO-prequalified point-of-care tests for hepatitis virus markers.

Test Analyte	Test Name (Company)	Sample Types	Time (min.)
HBsAg	Determine HBsAg 2 (Alere Medical, Waltham, MA, USA)	venous or capillary blood, plasma, or serum	15–30
HBsAg	Bioline HBsAg (Abbott Diagnostics, Abbott Park, Il, USA)	venous blood, plasma, or serum	20

Phases of infection with multiple names



A

	HBeAg-positive		HBeAg-negative		HBsAg-negative
	Chronic HBV infection	**Chronic hepatitis B**	**Chronic HBV infection**	**Chronic hepatitis B**	**Resolved HBV infection**
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBV DNA	$\geq 10^7$ IU/mL	10^4-10^7 IU/mL	<2000 IU/mL‡	≥2000 IU/mL	Undetectable
ALT	Normal	Elevated	Normal	Elevated§	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg-negative chronic hepatitis	HBsAg-negative phase

B

EASL Guidelines Hepatitis B 2017

Phases of Infection – Natural History

AASLD	EASL
	APASL/WHO/Others
• Immunotolerant (IT)	• HBeAg+ chronic HBV infection
• HBeAg+ Immune Active (IA)	• HBeAg+ chronic hepatitis B
• Inactive Carrier/Immune Control (IC)	• HBeAg- chronic HBV infection
• HBeAg- Immune Reactivation Phase	• HBeAg- chronic hepatitis B
• Resolved HBV/Functional Cure	• Occult Infection
• Gray zone/indeterminate	• Grey zone/indeterminate

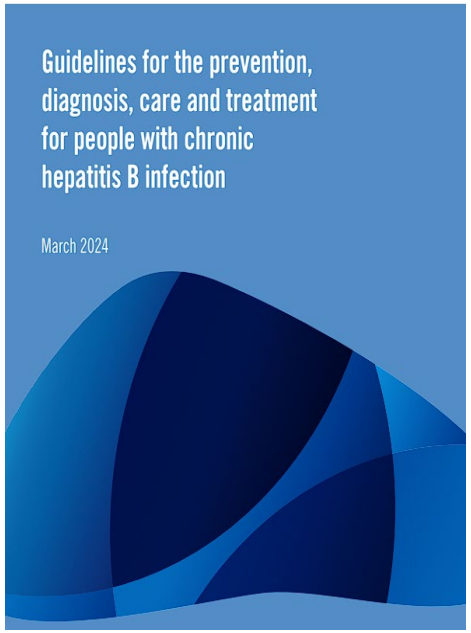
Different names cause MUCH unnecessary confusion

Population	ALT	HBV DNA	HBsAg	Specifics	Serum HBcrAg	Serum HBV RNA
HBeAg positive						
HBeAg-positive infection, high replicative	Normal (low normal)	Very high, usually $\geq 10^8$	Very high, (usually ≥25,000 IU/ml)	Young age, no/mild fibrosis, no disease progression if stable	Positive ++++	Positive ++++
HBeAg-positive infection, impending phase transition	Normal (high normal)	High, usually $\geq 10^6$	Intermediate to high (usually <25,000 IU/ml)	Age usually ≥30 years, fibrosis can be present	Positive ++++	Positive ++++
HBeAg-positive hepatitis	Elevated	High, usually $\geq 10^4$	Intermediate to high (usually <25,000 IU/ml)	Any age, high risk for disease progression	Positive ++++	Positive ++++
HBeAg-positive cACLD	Normal or elevated	Usually high, but any HBV DNA is possible	Usually high, but any HBsAg is possible	cACLD according to BAVENO VI [80]	Positive + to +++	Positive Any value is possible
HBeAg negative						
HBeAg-negative cACLD	Normal or elevated	Usually high, but any HBV DNA is possible	Usually high, but any HBsAg is possible	cACLD according to BAVENO VI [80]	Positive +++ or negative	Positive Any value is possible
HBeAg-negative hepatitis	Elevated	Usually ≥2,000 IU/ml	Low to high	High risk for disease progression	Positive ++	Positive or negative Any value is possible
HBeAg-negative infection, high replicative, high-risk infection	Normal	Usually >20,000 IU/ml	Low to high	Usually older age, fibrosis	Positive ++	Positive Any value is possible
HBeAg-negative infection, high replicative, low-risk infection	Normal	Usually >2,000-20,000 IU/ml	Low to high	No disease progression if stable for ≥3 years	Positive ++	Positive or negative Any value is possible
HBeAg-negative infection, low replicative	Normal (low normal)	<2,000 IU/ml	Usually <1,000 IU/ml	No/mild fibrosis, no disease progression if stable	Negative or +	Negative or +
HBeAg-negative infection, partial cure	Normal (low normal)	Not detectable	<100 IU/ml	High chance to achieve HBsAg loss	Negative or +	Negative
HBsAg-negative (functional cure)	Normal	Not detectable	<0.05 IU/ml	Associated with best prognosis	Negative or +	Negative

*Compensated chronic liver disease, cACLD, compensated advanced chronic liver disease

EASL Guidelines Hepatitis B 2025

TREATMENT ELIGIBILITY



TREAT ALL ADULTS and ADOLESCENTS (aged ≥12 years[c]) (including pregnant and non-pregnant women and girls of reproductive age) **WITH:**

1. **SIGNIFICANT FIBROSIS (≥F2) or CIRRHOSIS (F4)** (regardless of HBV DNA or ALT levels
   - Clinical criteria for cirrhosis[d]
   - Non-invasive tests: **APRI >0.5** or **transient elastography>7 kPa** (adults)[e]

OR

2. **HBV DNA>2000 IU/mL AND ALT level > ULN**[e]

OR

3. **PRESENCE OF of any of following** (regardless of APRI score, HBV DNA or ALT level)
   - **Coinfection** (eg. HIV, HDV, HCV)
   - **Family history** of liver cancer or cirrhosis
   - **Immune suppression**
   - **Comorbidities** (eg. diabetes, metabolic dysfunction-associated steatotic liver disease)
   - **Extrahepatic manifestations** (eg. glomerulonephritis or vasculitis)

OR

In absence of access to HBV DNA assay

4. **PERSISTENTLY ABNORMAL ALT LEVELS ALONE**[f,g]

ALT
Persistently normal[f,g]

AND

HBV DNA
<2000 IU/mL

AND

Absence of
coinfections,
comorbidities,
immune suppression,
extrahepatic
manifestations
family history of liver
cancer or cirrhosis

INITIATE ANTIVIRAL THERAPY AND MONITOR[h]
- **TDF or ETV**
- **TDF + 3TC or TDF + FTC** (if no access to TDF monotherapy)
- **ETV or TAF** in persons with osteoporosis or impaired kidney function or in children and adolescents

DEFER TREATMENT AND MONITOR

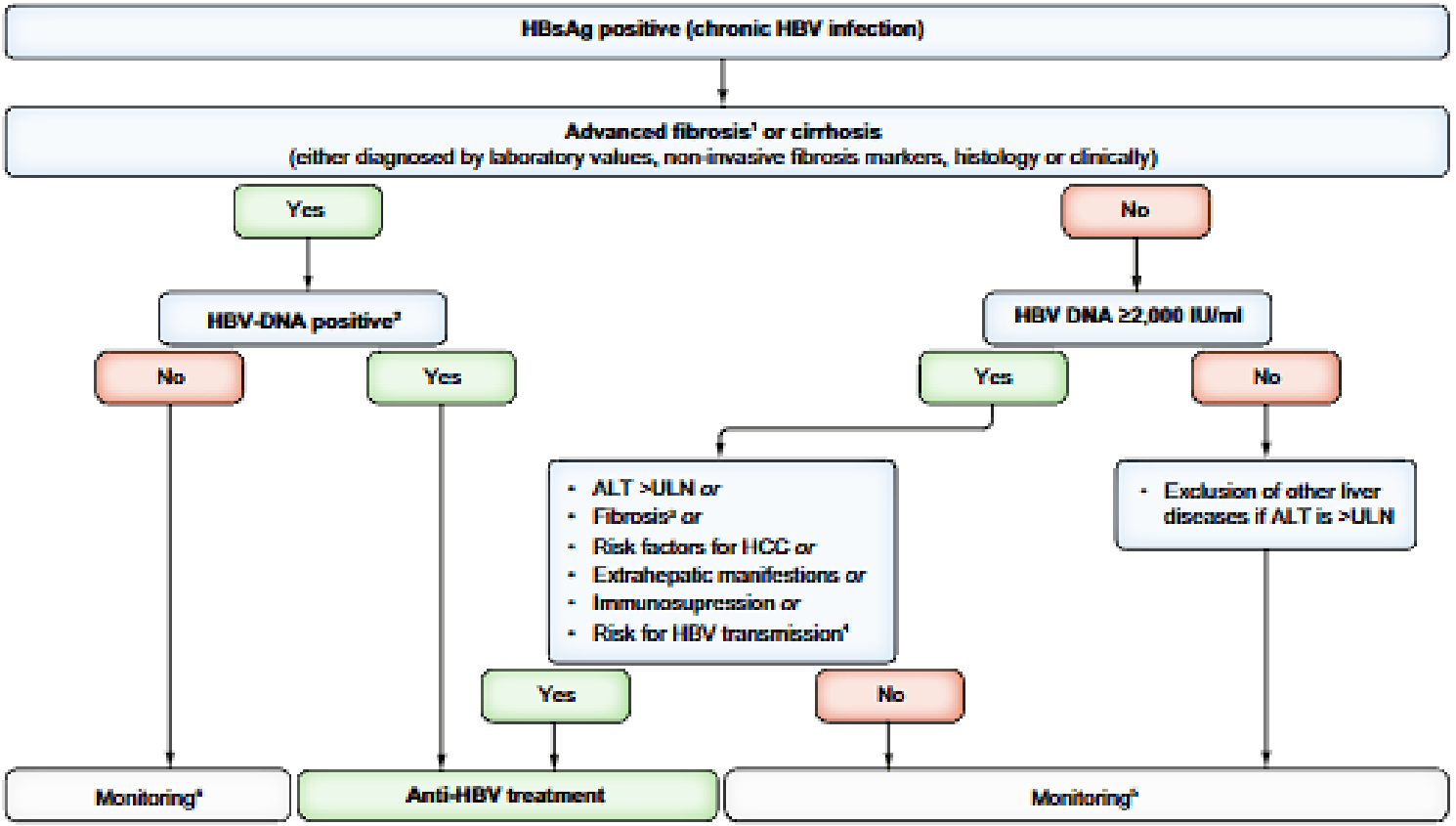
https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf

Clinical Practice Guidelines

JOURNAL
OF HEPATOLOGY

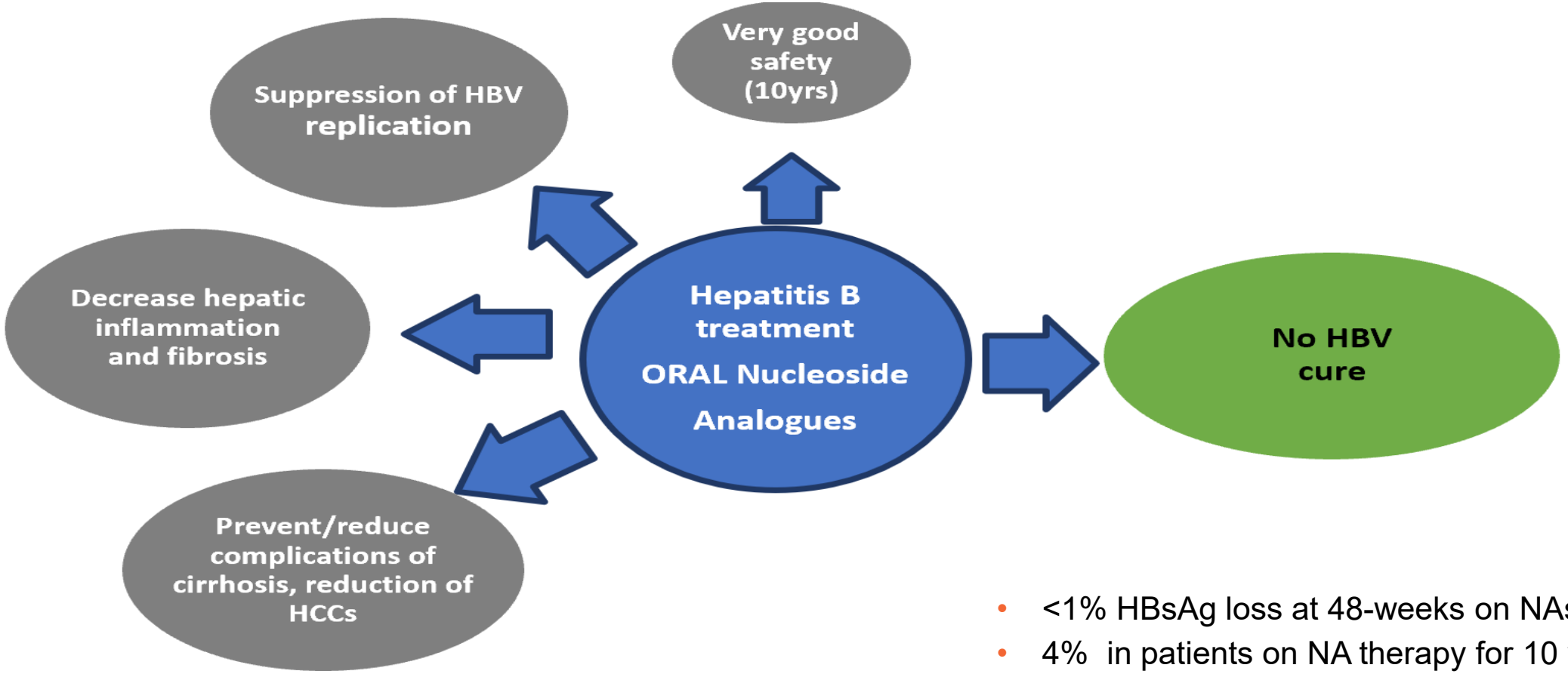
EASL Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*



EASL Guidelines Hepatitis B 2025

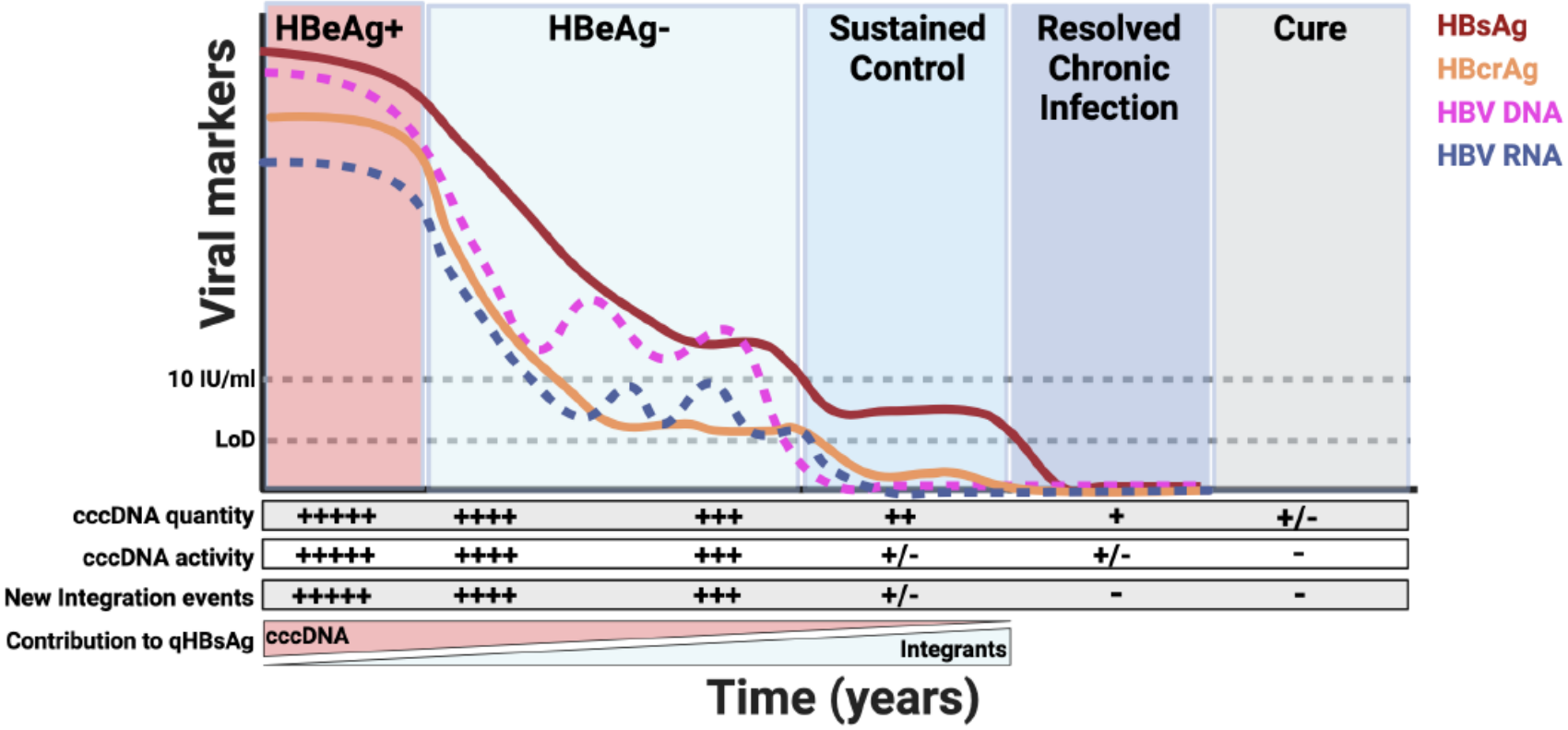
Achievements with NAs in the Treatment of Hepatitis B



- <1% HBsAg loss at 48-weeks on NAs therapy[1]
- 4% in patients on NA therapy for 10 years[2]

1. Marcellin P, et al. *Liver Int*. 2019;39(10):1868–1875; 2 Slaets L, et al. *Gastroenterol Hepatol.* 2020;2(3):106–116

Some options for consideration



New Nomenclature for consideration…

Sustained Control

- HBsAg+ but < 10 IU/mL
- HBV DNA negative
- HBcrAg/HBV RNA negative
- Durable off therapy
- ***Replaces 'partial cure'***

Resolved Chronic Infection

- HBsAg-
- HBV DNA negative
- HBcrAg/HBV RNA negative
- Durable off therapy
- ***Replaces 'functional cure'***

Cure

- HBsAg –
- No or silenced cccDNA and integrated DNA
- ***Replaces 'sterilizing cure'***

Feld, Gehring, Zoulim. Hepatology *In Press*

TORONTO CENTRE FOR LIVER DISEASE

Novel Classes of Drugs Being Investigated

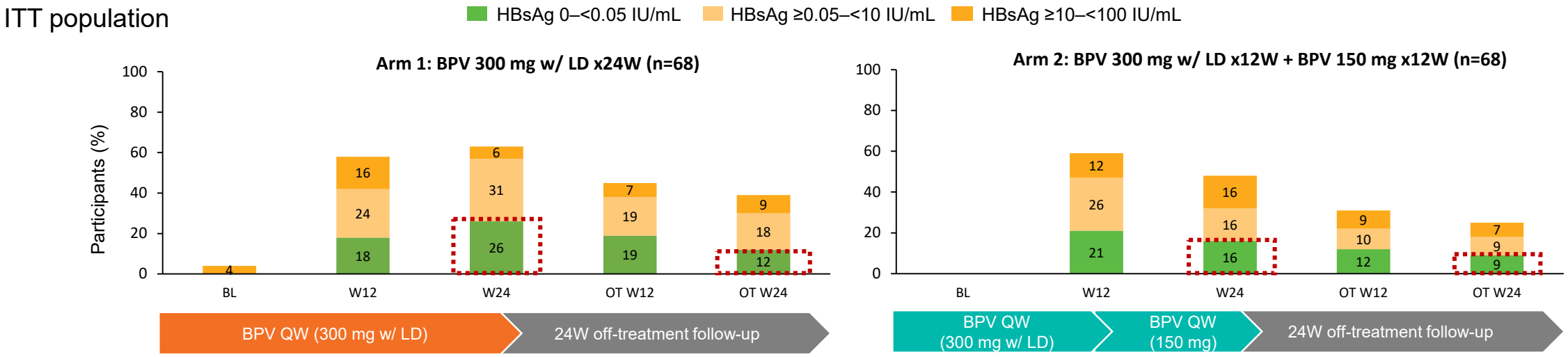
Antiviral
ASO
siRNA
CAMs
Entry inhibitors
Nucleic acid polymers (NAPs)

Immunological
PEG IFN
TLR agonists
Therapeutic vaccines
PD-1/PD-L1 inhibitors
Monoclonal antibodies

Many potential combinations: Antiviral + antiviral
Antiviral + immune modulator
Immune modulators combined

2025 Pipeline >100 drugs in preclinical, phase 1-2 clinical study and 1 in phase 3

B-Clear study –Bepirovirsen in patients with CHB: Results from the randomized Phase 2b in NAs suppressed



Approximately half of participants who achieved HBsAg loss after 24 weeks of treatment maintained the response at week 24 oof therapy

Baseline HBsAg levels predicts HBsAg loss

Low HBsAg level (≤3 log10 IU/ml), HBsAg loss 16% of the participants on NAs and 25% on non-NAs at the end of follow-up

High HBsAg level (>3 log10 IU/ml), HBsAg loss 6% of the participants on NUCs and 7% on non-NUCs

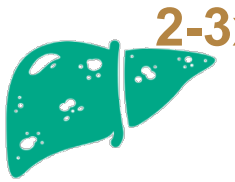
Percentages calculated based on the total number of participants in the ITT population, therefore totals may not add up to 100% due to missing data.
BPV, bepirovirsen; BL, baseline; HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; OT, off treatment; PBO, placebo; QW, once a week; W, week; w/=with; w/o=without.

Yuen MF, et al. N Engl J Med. 2022;387:1957-1968

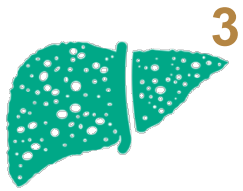
HDV

Chronic hepatitis D

- Chronic hepatitis D (CHD) presents a more rapid progression than chronic hepatitis B monoinfection.



Liver cirrhosis



Hepatocelular carcinoma

Liver transplantation

Hepatic decompensation

Liver-related death

CHD patient will develop a liver cirrhosis 15 years before than those with HBV monoinfection

CHD is often diagnosed in advanced stages of fibrosis

Da *et al. Gastroenterol Rep*. 2019
Miao *et al. J Infect Dis*. 2020
Hercun *et al. Gastroenterol Clin North Am*. 2020

Hepatitis D screening recommendations

Organization	Guidelines, year	Screening recommendation
EASL	Hepatitis D, 2023	All HBsAg+ve
AASLD	Hepatitis B, 2018	HBsAg+ve with risk factors
APASL	Hepatitis B, 2021	All HBsAg+ve
WHO	Hepatitis B, 2024	All HBsAg+ve

Screening: Determination of anti-HDV antibodies and, if positive, quantification of HDV RNA.

Hepatitis Delta Global Landscape Survey Report

The Hepatitis Delta Global Landscape Survey

World Hepatitis Alliance

A total of 583 individuals from 102 countries completed the survey.

45.2% - healthcare professionals
29.5% - community-based organisations
4.7% - policymakers
20.3% - other

One in six healthcare professionals
NOT AT ALL FAMILIAR
16.8%

More than one in three policymakers
SLIGHTLY OR NOT AT ALL FAMILIAR
38.9%

Half of community based organisations
SLIGHTLY OR NOT AT ALL FAMILIAR
49.1%

AVAILABILITY AND ACCESSIBILITY INEQUITY BY REGION

The Hepatitis Delta Global Landscape Survey

World Hepatitis Alliance

Europe and Central Asia
55.7%

East Asia and the Pacific
38.7%

North America
35.5%

South Asia
35.1%

Latin America and the Caribbean
28.5%

Africa and the Middle East
21.5%

La implementación del cribado en un solo paso incrementa la detección del número de casos de Hepatitis D activa[2]

Cascadas de cribado del VHD

Estudio de Barcelona[1]

2018-2020

Antes de la implementación del cribado en un solo paso

- **HBsAg+** N=1492
- **Anti-VHD cribados** N=114 **(7,6%)**
- **Anti-VHD+** N=11
- **Anti-VHD+** N=8

2021

Después de la implementación del cribado en un solo paso

- **HBsAg+** N=744
- **Anti-VHD cribados** N=691 **(93%)**
- **Anti-VHD+** N=56
- **ARN-VHD+** N=27

Estudio de Andalucía [2]

2018 (enero)-2022 (junio)

Antes de la implementación del cribado en un solo paso

- **HBsAg+** N=18583
- **Anti-VHD cribados** N=3436 **(18%)**
- **Anti-VHD+** N=205 **(6%)**
- **ARN-VHD +** N=69 **(1,9%)**

2022 (octubre) - 2023 (abril)

Después de la implementación del cribado en un solo paso

- **HBsAg+** N=3370
- **Anti-VHD cribados** N=2293 **(96%)**
- **Anti-VHD+** N=109 **(4,7%)**
- **ARN-VHD +** N=30/97 **(1,3%)**

Incremento anual x2-5 de casos de pacientes diagnosticados dehepatitis D (ARN-VHD)+

GILEAD | Liver

VHD: virus de la hepatitis delta; **HBsAg:** antígeno de superficie del virus de la hepatitis B; **ARN:** ácido ribonucleico. **1.** Palom A, *et al*. Implementation of anti-HDV reflex testing among HBsAg-positive individuals increases testing for hepatitis D. JHEP Rep. 2022;4(10):100547; **2.** Fuentes A, et al. Enhancing Hepatitis Delta Diagnosis in Southern Spain: Efficacy and Cost-Effectiveness of Double Reflex Testing. EASL congress. 5-8 junio 2024. FRI-409

OPTI-HEP-D

An innovative approach to test and treat hepatitis D: filling the gaps in the cascade of care of hepatitis D in Catalonia

7 centralized laboratories that attend 7 tertiary hospitals,

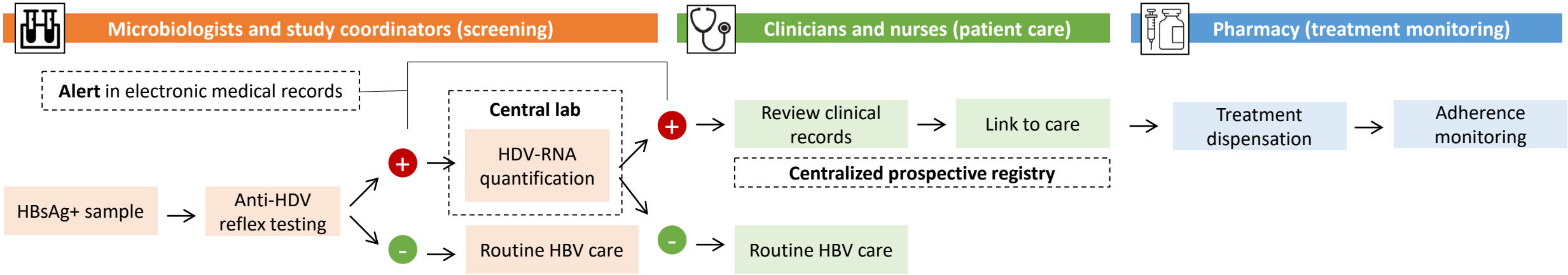
362 primary care centers,

26 addiction centers and 11 prisons

Covers 95% of Catalonia Population

Participating centers*

*



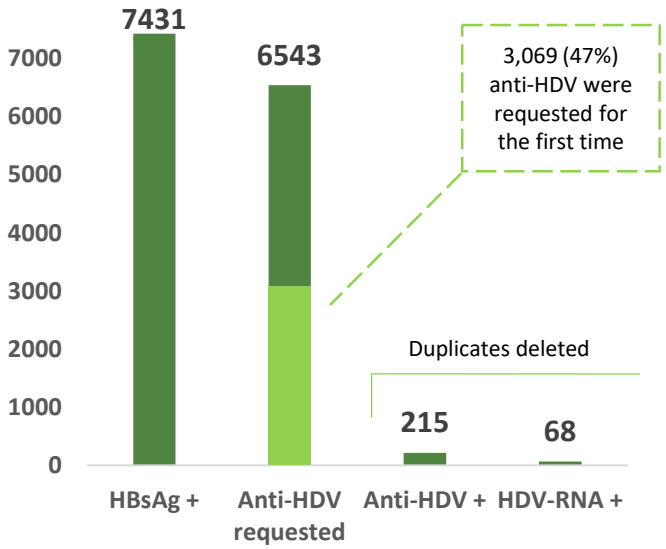
Competitive grant awarded by Gilead Sciences, IN-ES-980-7058

OPTI-HEP-D

An innovative approach to test and treat hepatitis D: filling the gaps in the cascade of care of hepatitis D in Catalonia

3. RESULTS

Laboratory results from Jan/2024 – Mar/2025

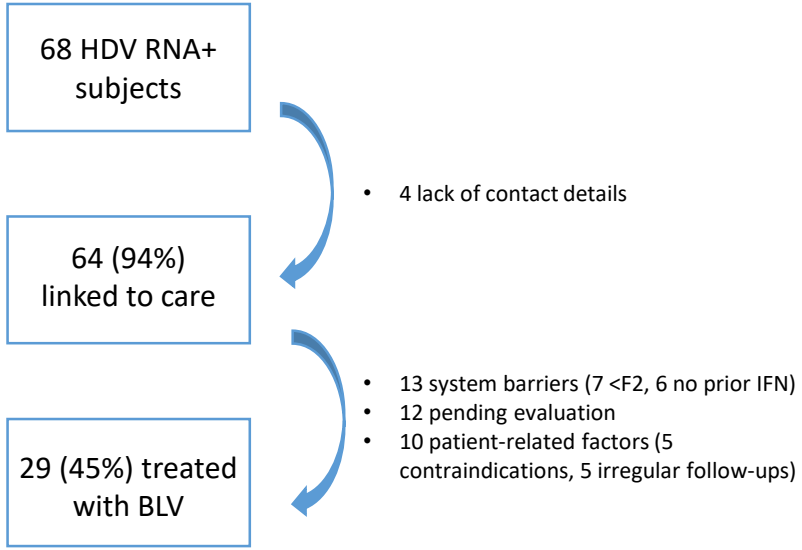


Baseline characteristics of anti-HDV+ subjects

Medical records accessible for 195 anti-HDV+ subjects.

	Total anti-HDV + (N=195)	HDV RNA + (n=68)	HDV RNA – (n=127)	p
Age	52 (41-59)	46 (37-53)	56 (44-61)	0.358
Male	131 (67%)	48 (71%)	83 (65%)	0.458
Eastern European	43 (22%)	30 (44%)	13 (10%)	<0.001
Parenteral	40 (21%)	17 (25%)	23 (18%)	0.256
Normal ALT	116 (59%)	16 (24%)	100 (78%)	<0.001
Liver cirrhosis	49 (25%)	30 (44%)	19 (15%)	<0.001
HCC	7 (4%)	3 (4%)	4 (3%)	0.696
Decompensation	12 (6%)	6 (9%)	6 (5%)	0.348
Previous pegIFN	41 (21%)	25 (38%)	16 (13%)	<0.001

Linkage to care



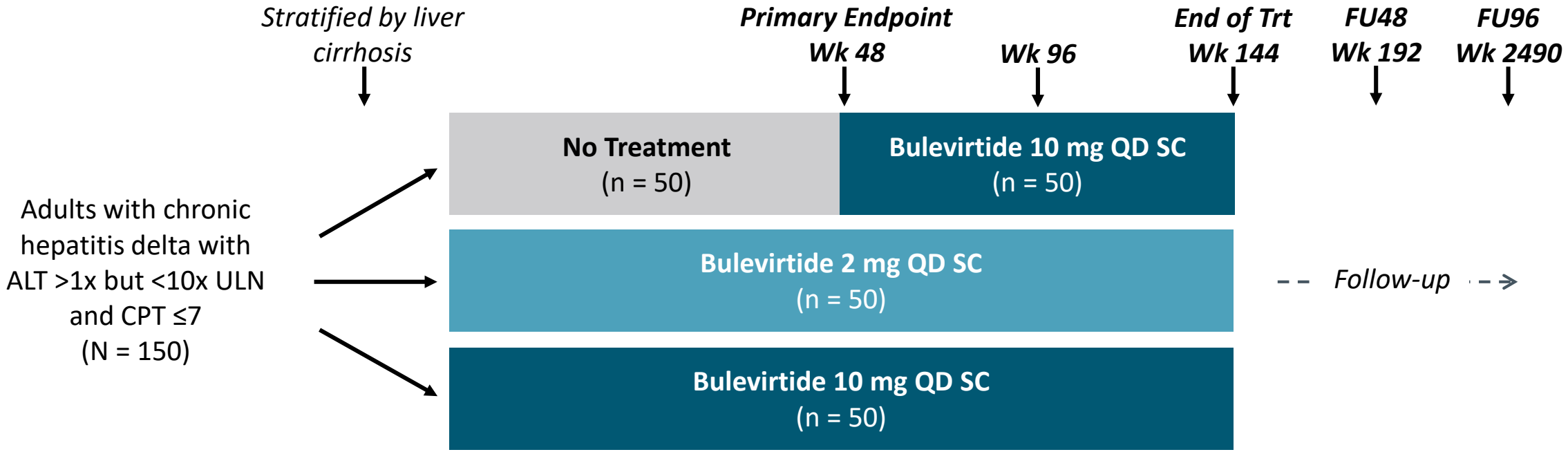
4. CONCLUSIONS

- This multidisciplinary program successfully implemented reflex testing and linkage to care for hepatitis D in Catalonia.
- While the majority of patients were correctly linked to care, treatment initiation is ongoing, still limited by some factors.
- This ongoing program shows the need to address these obstacles to improve treatment access and reduce the impact of hepatitis D.

Competitive grant awarded by Gilead Sciences, IN-ES-980-7058

MYR301: Bulevirtide Monotherapy for Chronic HDV

- Randomized, multicenter, open-label phase III trial[1]



- **Primary endpoint**: Combined response at wk 48
- Previously reports found superiority of BLV 2 mg or 10 mg SC QD for 48 wk over delayed BLV treatment[2] but that was lost at 96 wk[3]
- Current analysis reports safety and efficacy endpoints at follow-up wk 96 (wk 240)

1. Wedermeyer. EASL 2025. Abstr LB25221. 2. Wedemeyer. EASL 2022. Abstr GS-006. 3. Wedemeyer EASL 2023. Abstr OS-068.

MYR301: Efficacy Endpoints at FU96

Parameter, n (%)	BLV 2 mg (n = 49)			BLV 10 mg (n = 50)			Delayed Tx (n = 50)		
	EOT	FU48	FU96	EOT	FU48	FU96	EOT	FU48	FU96
CR	28 (57)	11 (22)	12 (24)*	27 (54)	10 (20)	12 (24)*	28 (56)	9 (18)	12 (24)*
VR	36 (73)	14 (29)	16 (33)*	38 (76)	20 (40)*	15 (30)*	46 (92)	14 (28)	16 (32)†
ALT normalization	29 (59)	13 (27)	12 (24)*	30 (60)	14 (28)	16 (32)†	29 (58)	12 (24)	14 (28)*
Undetectable HDV RNA ▪ Sustained from EOT, n/N (%)	14 (29)	8 (16) 7/14 (54)	10 (20) 7/14 (54)	25 (50)	12 (24) 10/25 (40)	11 (22) 10/25 (40)	26 (52)	8 (16) 6/26 (23)	10 (20) 6/26 (23)

*Includes 1 responder who restarted BLV prior to FU96; †Includes 2 responders who restarted BLV prior to FU96

- **90% of people with ≥96 weeks of continuously undetectable HDV RNA at therapy's end sustained HDV RNA undetectability off treatment until FU96**
- All relapses occurred by FU48, with 38/41 (93%) occurring by FU24
- Some people who achieved undetectable HDV RNA at FU96 had transient low-level viremia during earlier follow-up
- **HBsAg loss occurred in 4 people**: n = 2 in the delayed tx arm and n = 1 in each of the other 2 arms

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Hepatitis B y D
¿Estamos haciendo lo necesario?

- ¡¡¡¡¡¡¡¡No lo sabemos !!!!!!!!
- Se necesitan datos registrados y disponibles para todos
- Tenemos buenas intenciones.
- Múltiples programas de microeliminación que es necesario que persistan
- Fármacos que suprimen la replicación viral pero raramente curativos
- Debemos ser mas activos para conseguir la eliminación