Hépatite Delta : ça secoue

DES d'infectiologie sur les hépatites virales
Année 2025/2026

Tarik Asselah

Université de Paris-Cité, INSERM UMR 1149,
Service d'Hépatologie, Hôpital Beaujon, AP-HP,
Clichy, France.

Liens d’intérêts

- Employé (AP-HP, Hôpital Beaujon) et Université de Paris-Cité.
- Investigateur Principal : financements à l’hôpital (AP-HP)
- Consultant, Expert et Orateur: Abbvie, Antios, Bristol-Myers Squibb, Eiger, Enyo, Gilead, Janssen, Merck Sharp Dohme, Roche.
- Projets de recherche: ANR, CNRS , INSERM , Université de Paris-Cité, ANRS.

Hépatite Delta : ça secoue

1- Épidémiologie

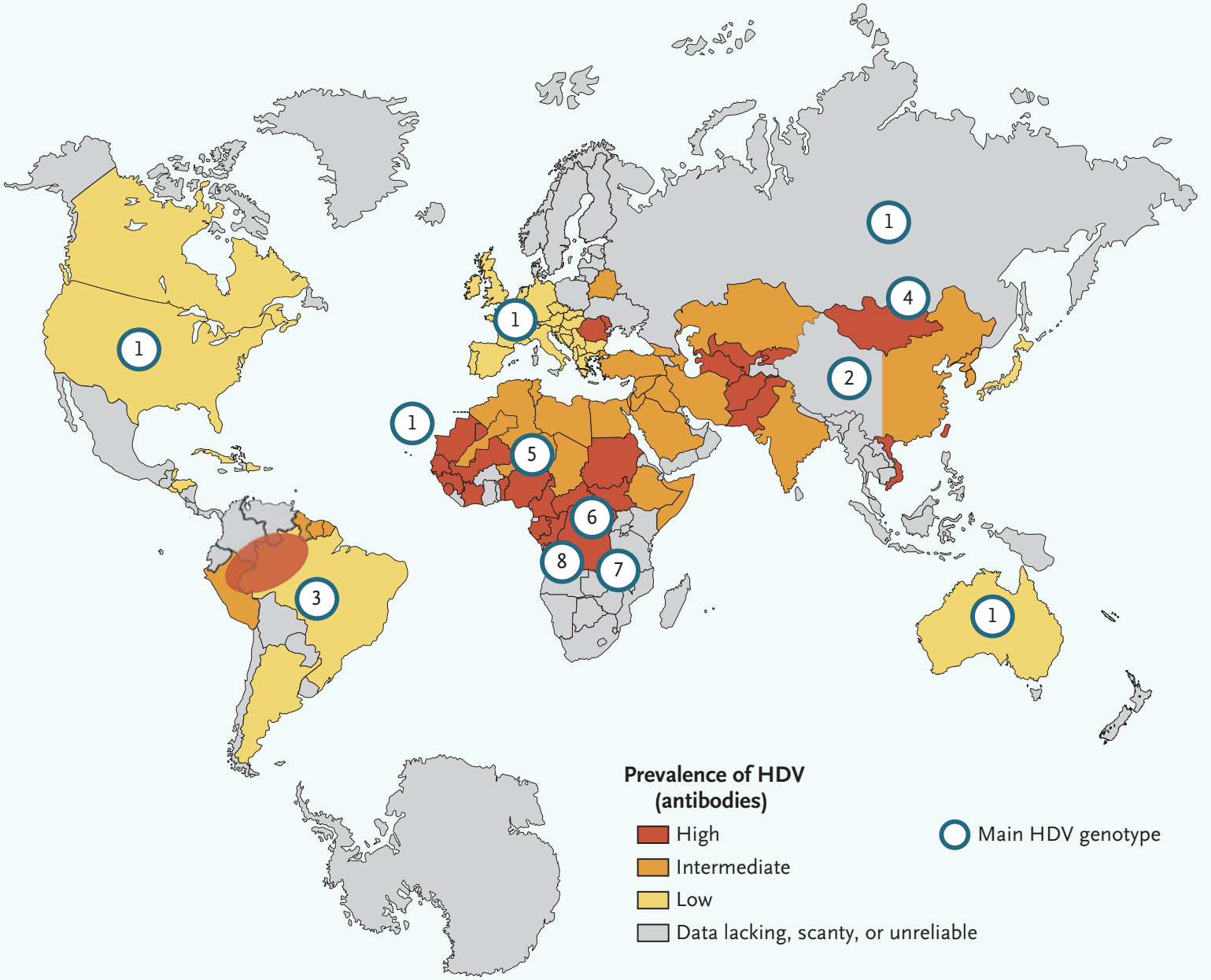
2- Histoire naturelle

3- Principes du traitement : Bulevirtide +/- Interferon-Pegylé ?

4- Perspectives

5 - Conclusion

Prévalence du VHD (sérologie) dans le Monde (10 dernières années)



Data are limited

- Poor epidemiologic study
- Diagnostic Tests not available

African countries with high prevalence:

- Cameroon
- Gabon
- Central African Republic

Asian countries with high prevalence

- Mongolia
- Uzbekistan
- Tajikistan
- Kyrgyzstan
- Pakistan

Eight HDV genotypes identified

Asselah Tarik-2024-1/20

Asselah T, Rizzetto M. Hepatitis D Virus Infection. N Engl J Med. 2023; 389 (1):58-70.

Table 1. Anti-HDV and HDV RNA prevalence in 25 countries and territories.

Country/Territory	2023 HBsAg+	Literature % anti-HDV+	Adjusted % anti-HDV+	RNA+ cases	Adjusted HDV RNA+ prevalence	Adjusted HDV RNA+ cases
Albania	183,000	9.0%	2.4%	4,400	62.5%	2,800
Brazil	1,025,000	3.2%	1.7%	17,400	75.3%	13,100
Bulgaria	169,000	8.6%	3.2%	5,400	80.0%	4,300
Canada	214,000	1.6%	3.0%	6,400	64.8%	4,100
China Mainland	78,548,000	1.2%	1.2%	942,600	66.6%	627,800
Colombia	302,000	5.2%	1.0%	3,000	69.9%	2,100
England	418,400	2.9%	1.0%	4,200	50.0%	2,100
France	142,000	1.8%	3.5%	5,000	75.0%	3,800
Germany	215,000	5.5%	3.0%	6,500	60.0%	3,900
Hong Kong	332,000	0.2%	0.2%	500	60.0%	300
Israel	129,000	6.5%	5.4%	7,000	47.0%	3,300
Italy	336,400	8.3%	3.4%	11,300	60.5%	6,800
Japan	926,000	8.5%	0.5%	4,600	40.8%	1,900
Korea, Republic of	1,360,000	0.3%	0.3%	4,100	54.0%	2,200
Mexico	116,000	2.4%	0.2%	300	69.9%	200
Mongolia	191,000	61.0%	61.0%	116,500	61.5%	71,600
Pakistan	3,762,000	16.6%	16.6%	624,500	85.0%	530,800
Portugal	110,000	12.6%	1.5%	1,700	72.9%	1,200
Romania	568,000	23.1%	2.9%	16,500	80.0%	13,200
Saudi Arabia	570,000	5.3%	4.0%	22,800	60.0%	13,700
Spain	208,000	5.2%	2.3%	4,800	72.9%	3,500
Sweden	31,000	3.8%	2.8%	900	75.0%	650
Taiwan	1,864,000	3.3%	0.9%	16,800	60.0%	10,100
Türkiye	1,962,000	2.8%	2.8%	54,900	68.0%	37,300
United States	1,650,000	6.0%	3.0%	49,500	66.0%	32,700

Asselah Tarik-2025-2/20

Polaris. J Hepatol. 2024 Feb;80(2):232-242.

Hépatite Delta : ça secoue

1- Épidémiologie

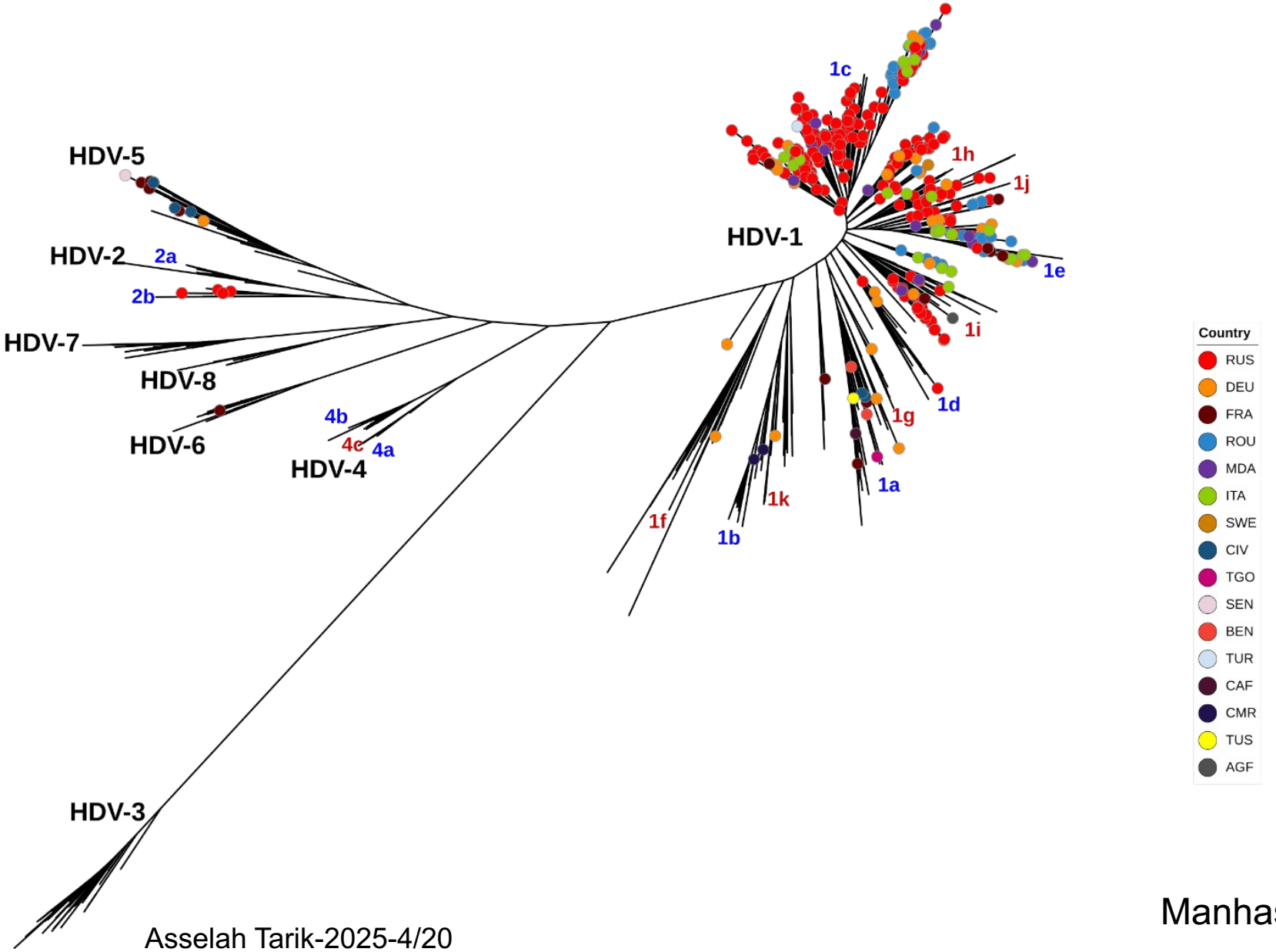
2- Histoire naturelle

3- Principes du traitement : Bulevirtide +/- Interferon-Pegylé ?

4- Perspectives

5 - Conclusion

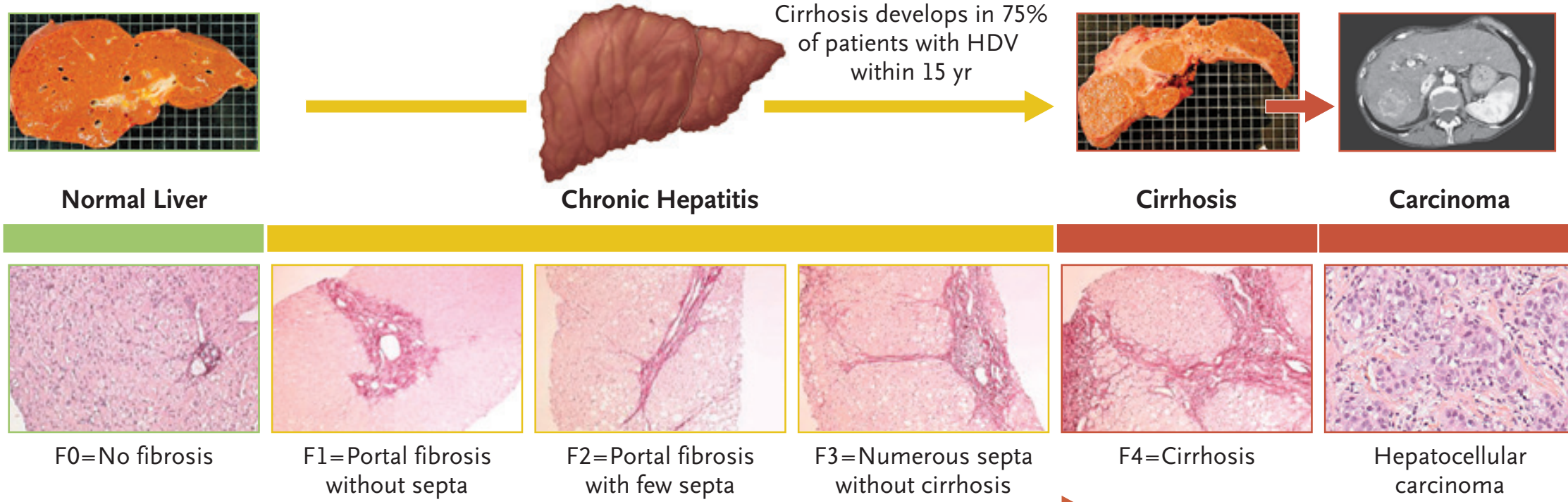
VHD: une grande diversité génétique



Asselah Tarik-2025-4/20

Manhas (Asselah) in press 2025

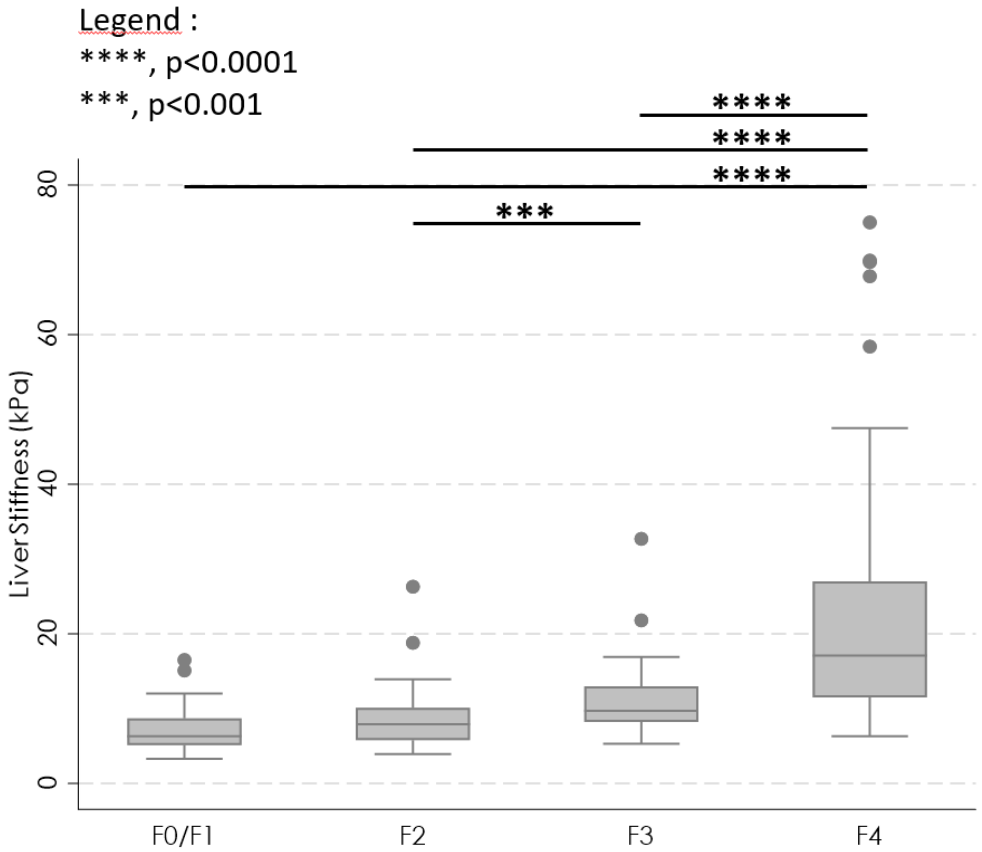
Une maladie sévère

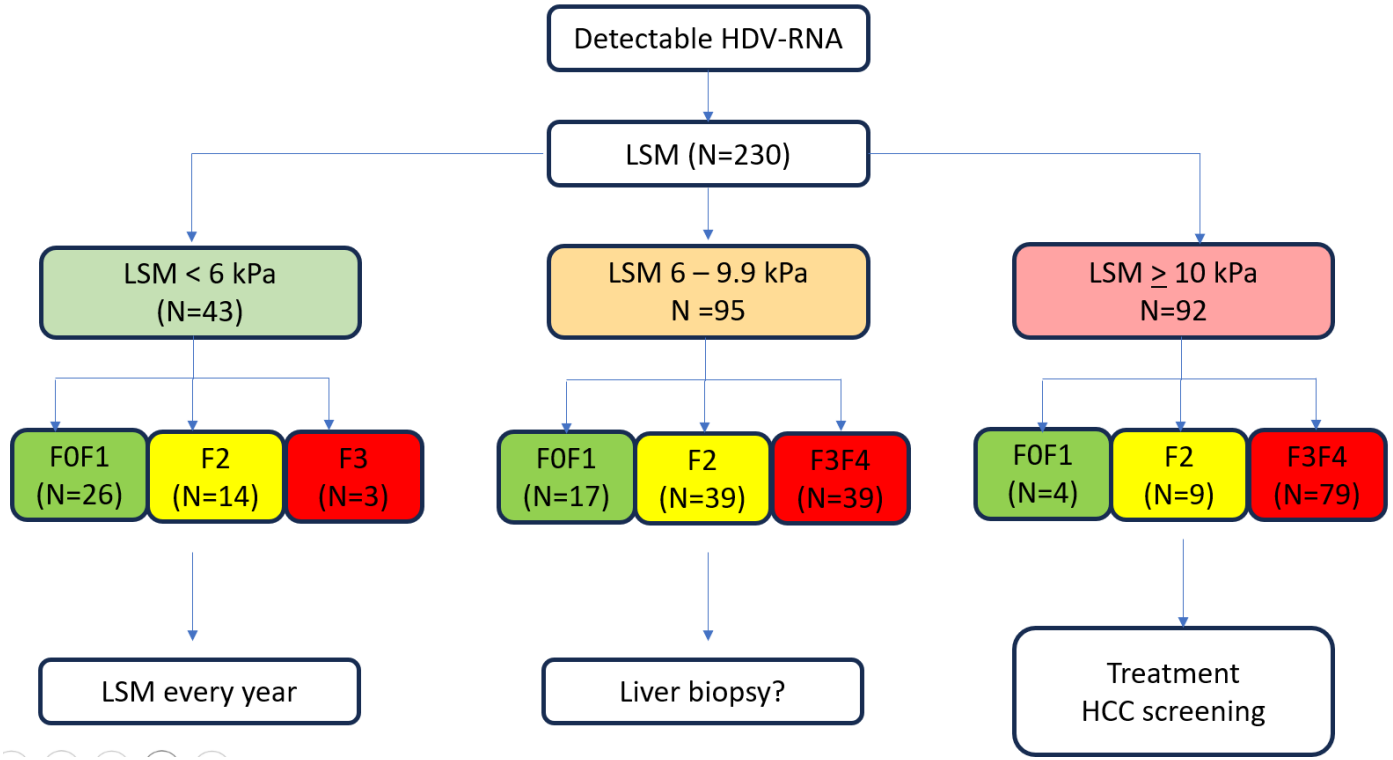


Asselah Tarik-2025-5/20

Asselah T, Rizzetto M. N Engl J Med. 2023; 389(1):58-70.

Hépatite chronique Delta: évaluation de la fibrose





Roulot et al. CGH 2024.

Asselah Tarik-2025-6/20

Hépatite Delta : ça secoue

1- Épidémiologie

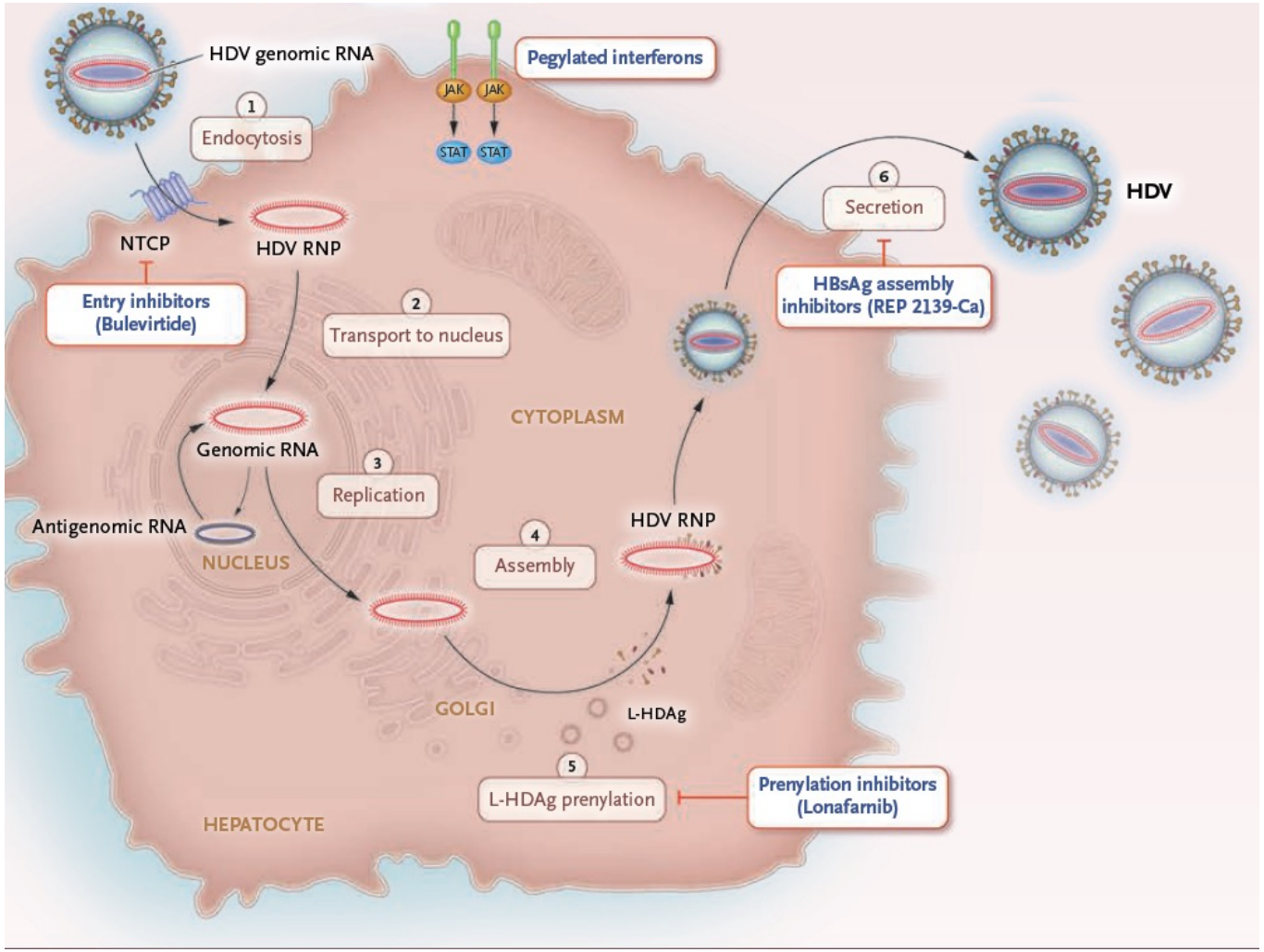
2- Histoire naturelle

3- Principes du traitement : Bulevirtide +/- Interferon-Pegylé ?

4- Perspectives

5 - Conclusion

Cycle de réplication du VHD et cibles thérapeutiques



1. Endocytosis: HDV binds to NTCP,
2. Transport to the nucleus.
3. Replication of HDV genomic RNA into the HDV antigenome in the nucleus.
4. Assembly of the neosynthetized HDV ribonucleoprotein (RNP) in cytoplasm.
5. Farnesylation of the C terminal in L-HDAg;
6. Secretion

Asselah Tarik-2025-7/20

Asselah & Rizzetto; N Engl J Med. 2023; 389 (1):58-70.

Place du Bulévirtide dans la stratégie thérapeutique

- **Bulevirtide** 2mg est une **option thérapeutique de 1ère ou 2ème intention** dans la prise en charge de **l'infection chronique par le VHD** chez des **patients adultes** ayant une **maladie hépatique compensée** testés positifs pour la présence d'ARN du VHD dans le plasma (ou le sérum)

- **En association à un traitement de fond contre le VHB** (analogue nucléotidique ou nucléosidique)

- En cas **d'échec, d'intolérance** ou de **contre-indication** au **Peg-IFN alpha**

Asselah Tarik-2025-8/20

Source : HAS, Avis de la commission de la transparence du 16 décembre 2020

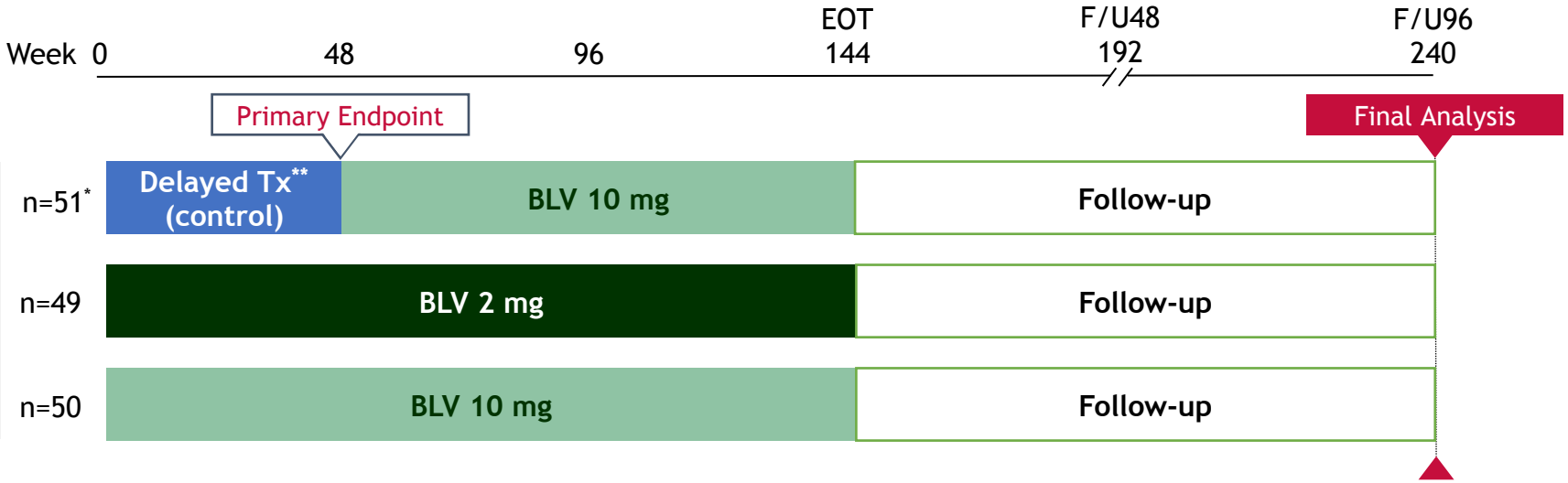
MYR301 Schéma de l'étude

Multicenter, open-label, randomized, Phase 3 study

Key Inclusion Criteria:

- Adults with chronic hepatitis delta with or without compensated cirrhosis
- CTP score ≤7
- ALT >1× to <10× ULN
- Platelets ≥60,000 cells/mm^3
- Controlled HIV coinfection allowed

MYR301:
N=150
Randomized
1:1:1



Endpoints reported at F/U96	
Virologic response	HDV RNA undetectable or decreased by ≥2 $\log_{10}$ IU/mL from baseline
ALT normalization	• ≤34 U/L for female patients and ≤49 U/L for male patients (all other sites)
Undetectable HDV RNA	HDV RNA levels by RT-PCR using RoboGene® 2.0 (limit of detection 6 IU/mL)
Combined response	Virologic response + ALT normalization

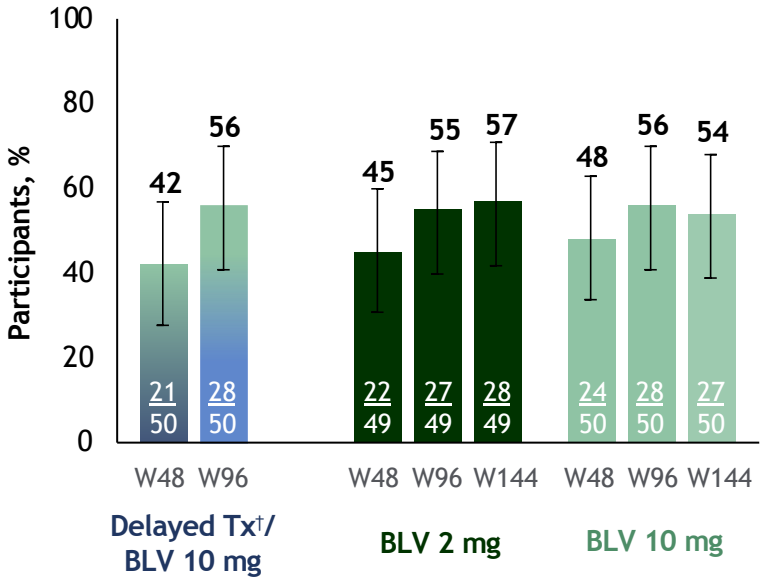
*One patient discontinued the study prior to receiving BLV; therefore, n=50 was used for all Arm A efficacy results, with baseline reset at the Week 48 visit, and efficacy presented by BLV duration (not including the delayed treatment period); **Delayed treatment arm did not receive any BLV through Week 48.
ALT, alanine aminotransferase; BLV, bulevirtide; CTP, Child-Turcotte-Pugh; EOT, end of treatment; F/U48, follow-up at 48 weeks after EOT; F/U96; follow-up at 96 weeks after EOT; HIV, human immunodeficiency virus; RT-PCR, reverse transcription polymerase chain reaction; Tx, treatment; ULN, upper limit of normal.

Wedemeyer H and Aleman S, et al. EASL 2025. Oral LBO-004

BLV Efficacité à la semaine 144

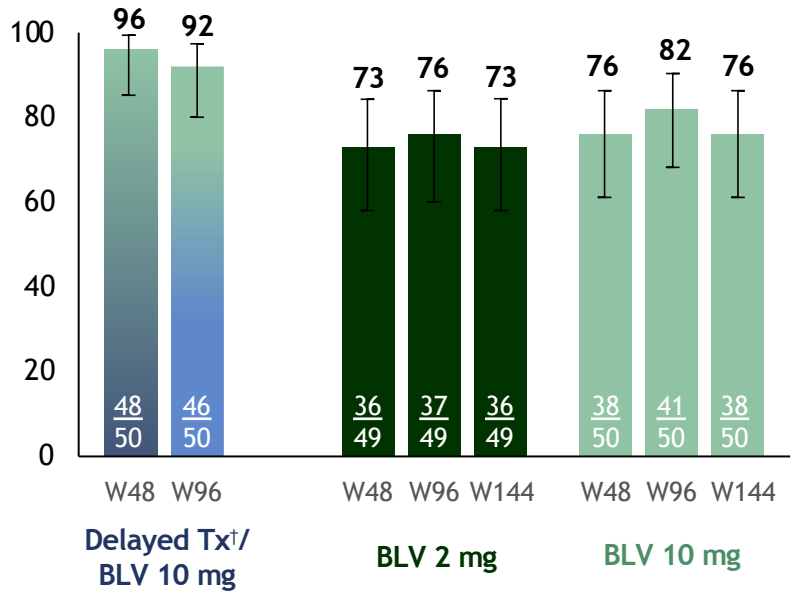
Combined Response

Undetectable HDV RNA* or ≥2 log_{10} IU/mL decline from BL and ALT normalization**



Virologic Response

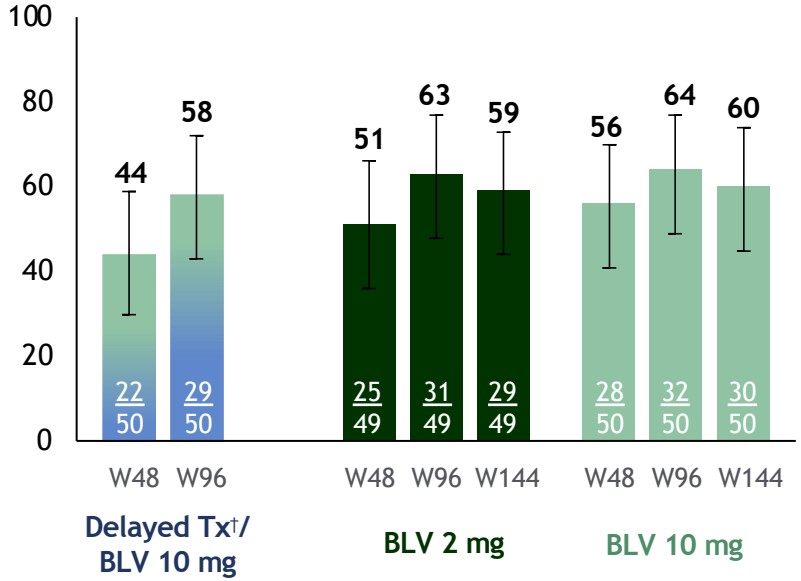
Undetectable HDV RNA* or ≥2 log_{10} IU/mL decrease from BL



Undetectable HDV RNA, %

Delayed Tx†/ BLV 10 mg		BLV 2 mg			BLV 10 mg		
24	52	12	20	29	20	36	50

ALT Normalization**



Long-term BLV therapy demonstrated improved virologic and ALT responses through 144 weeks

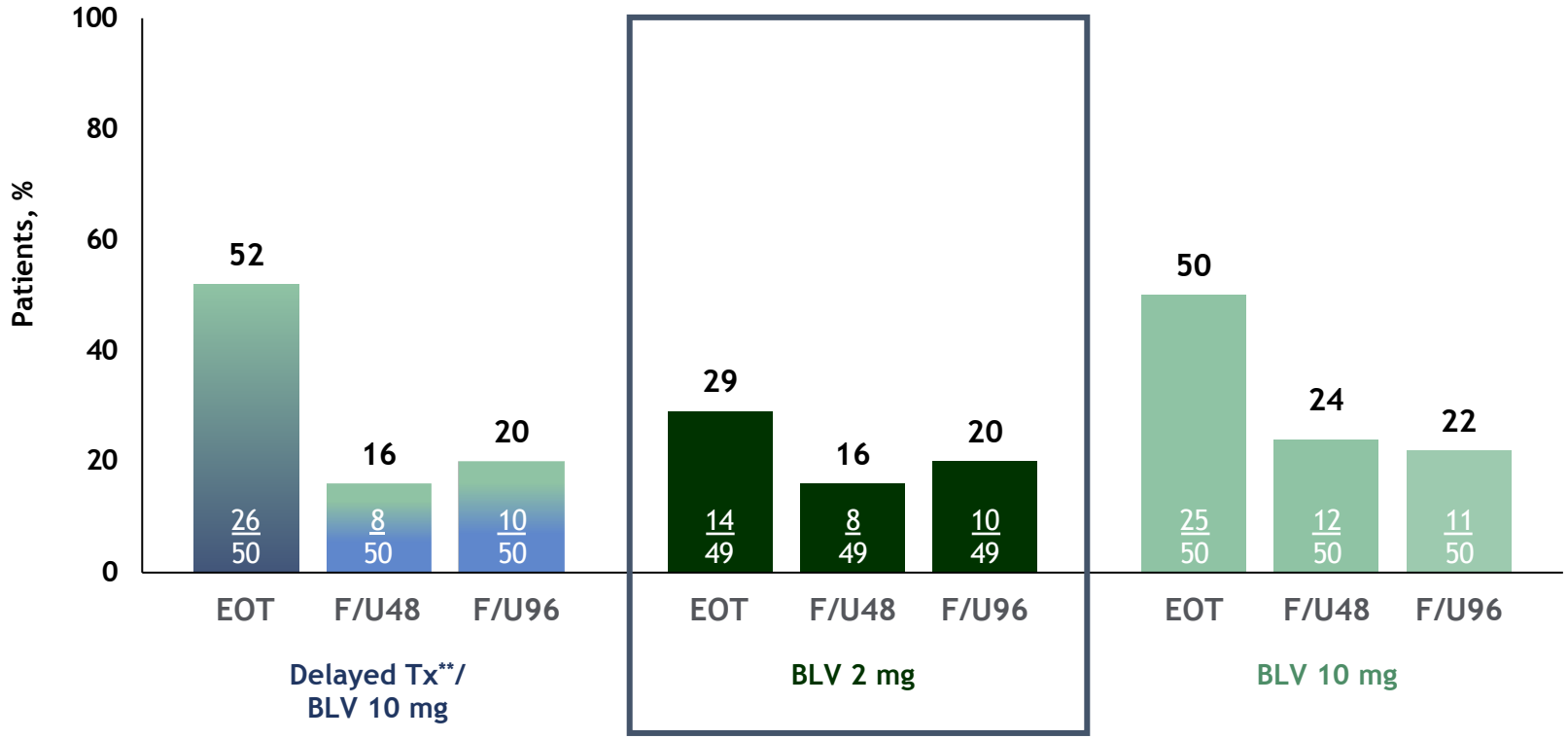
Asselah Tarik-2025-10/20

Data shown here are BLV treatment by duration. *Undetectable HDV RNA was defined as <LLOQ (50 IU/ml) and target not detected; **ALT normalization: ≤31 U/L for females and ≤41 U/L for males (Russian sites) or ≤34 U/L for females and ≤49 U/L for males (all other sites);
†Delayed treatment arm did not receive any BLV in the first 48 weeks of the trial. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; LLOQ, lower limit of quantification; LOD, limit of detection;
Tx, treatment; W, week

Lampertico P, et al. EASL 2024. Poster #LBP-029

BLV Efficaccité en fin de traitement et après le suivi

Undetectable HDV RNA* at EOT, F/U48, or F/U96



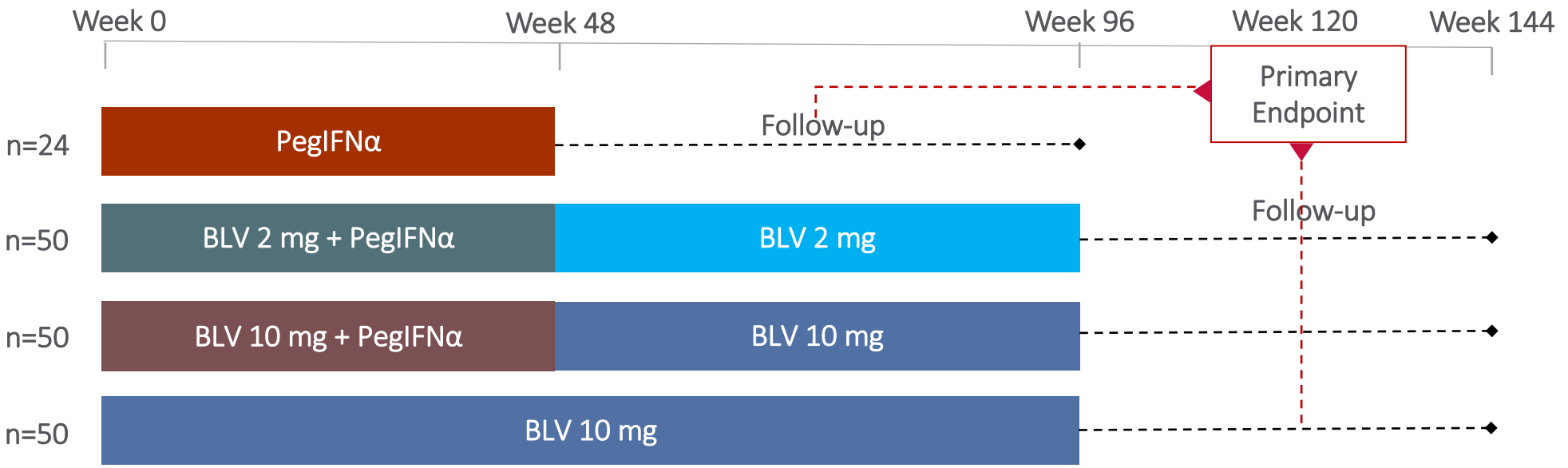
Approximately 1 out of 5 patients maintained undetectable HDV RNA at F/U96

Data shown here are BLV treatment by duration. *HDV RNA was quantified using the RoboGene®, version 2.0, with limit of detection 6 IU/ml; **Delayed treatment arm did not receive any BLV in the first 48 weeks of the trial.

BLV, bulevirtide; EOT, end of treatment; F/U48, follow-up at 48 weeks after EOT; F/U96, follow-up at 96 weeks after EOT; Tx, treatment.

Wedemeyer H and Aleman S, et al. EASL 2025. Oral LBO-004

MYR 204: Schéma de l'étude



- Open-label, randomized, multicenter, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Key Inclusion Criteria

- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh (CTP) ≤6
- ALT >1× - <10× ULN; Platelets ≥90,000 cells/mm^3
- No IFN within 6 months before enrollment

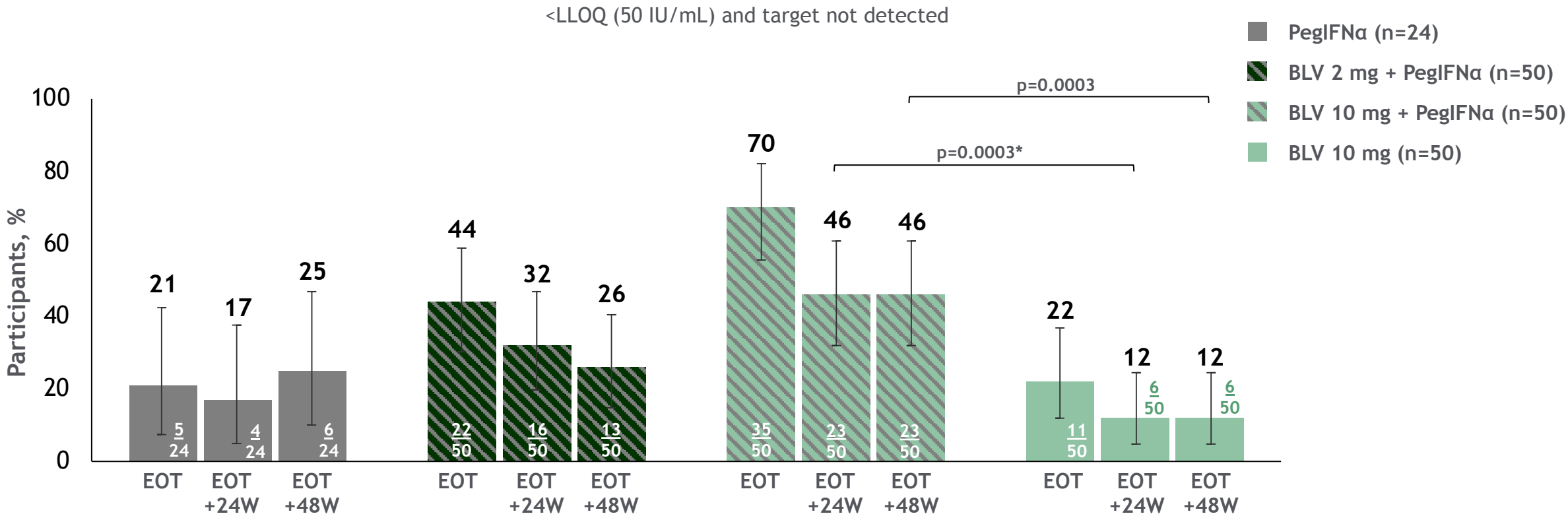
Asselah et al. N Engl J Med. 2024 Jul 11;391(2):133-143.

Asselah Tarik-2025-12/20

ALT, alanine transaminase; **BLV**, bulevirtide; **CHD**, chronic hepatitis D; **IFN**, interferon; **PegIFNα**, pegylated interferon alpha; **ULN**, upper limit of normal.

Réponse virologique 48 semaines après la fin du traitement

Undetectable HDV RNA[1,2]



BLV 10 mg + PegIFNα resulted in the highest rates of undetectable HDV RNA, which were sustained between 24 and 48 weeks off treatment

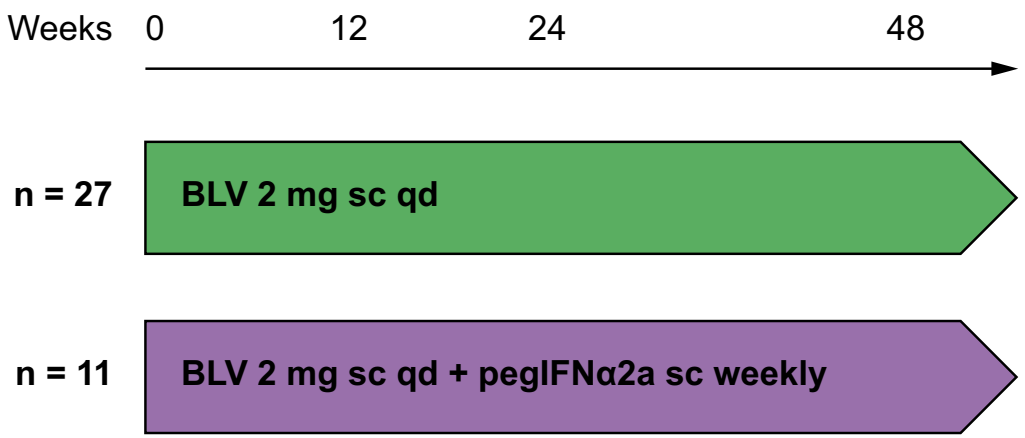
Asselah Tarik-2025-12/20

*Primary endpoint. BLV, bulevirtide; EOT, end of treatment; LLOQ, lower limit of quantification; PegIFNα, pegylated interferon alpha; W, week.

1. Asselah T, et al. EASL 2024. Oral #GS-002; 2. Asselah T, et al. N Engl J Med. 2024. DOI: 10.1056/NEJMoa2314134

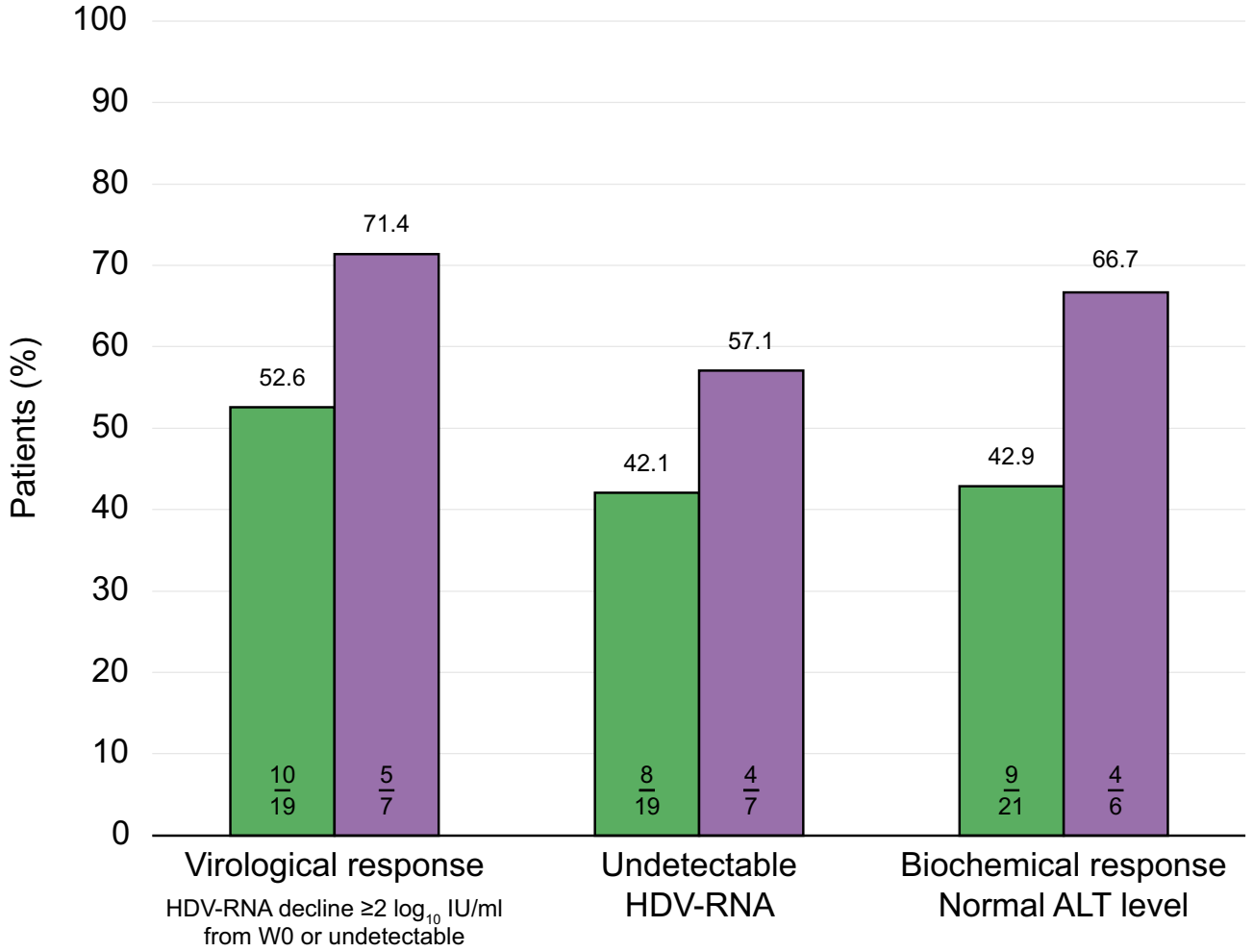
BLV +/- IFN-PEG : VIH-VHD

Study design



- Multicenter, prospective and retrospective observational study
- No randomization
- HIV infected patients with HBV/HDV infection
- Treatment regimen, duration and modifications were at the discretion of the physician

Week 48 responses



De Ledinghen et al. JHEP reports 2024

Bulevirtide, side effects (integrated analysis)

Data from MYR203, MYR204, and MYR301 are included. AEs, discontinuations, and laboratory abnormalities by week 48.

	Control (n = 51) n (%)	BLV 2 mg (n = 64) n (%)	BLV 10 mg (n = 115) n (%)	Peg-IFNα (n = 39) n (%)
Any AE	39 (77)	55 (86)	99 (86)	35 (90)
Grade ≥3 AE	3 (6)	7 (11)	13 (11)	20 (51)
Serious AE	1 (2)	2 (3)	2 (2)	3 (8)
Related to study drug	-	38 (59)	72 (63)	34 (87)
AE related to study drug Grade ≥3	-	2 (3)	5 (4)	20 (51)
Discontinuations of study drug due to AE	-	0	0	3 (8)
Death	0	0	0	0
Common AEs[†]				
Total bile acids increased	0	13 (20)[‡]	19 (17)[‡]	6 (15)[‡]
Injection-site reaction[§]	0	10 (16)	23 (20)	1 (3)
Pruritus	0	7 (11)	11 (10)	2 (5)
ALT increased	3 (6)	5 (8)	9 (8)	14 (36)
Fatigue	1 (2)	6 (9)	8 (7)	2 (5)
Laboratory abnormality	42 (82)	58 (91)	100 (87)	37 (100)
Grade ≥3	6 (12)	13 (20)	16 (14)	25 (68)

Asselah et al. Liver International, 2024

Quelle experience du Bulévirtide en France ?

Barodelta : données VHD du SNDS
Sept 2019 à déc 2022 : 498 patients VHD sous bulévirtide

	Patients sous BLV
Age	42,5 ans
Sexe masculin	69,5 %
Patients aux revenus et ressources limités	76,7 %
Pathologies associées (%)	
Syndrome métabolique	21,3 %
Co-infection VIH	11,6 %
Usage actif ou passé de drogue	7,8 %
Co-médication (%)	
NUC	60 %
Sans NUC, ni IFN	22 %
IFN avant BLV	26 %
Bithérapie BLV+IFN	46 %

62%
Patients autonomes pour l'injection à J15

87%
Observance à 24 mois

-population majoritairement masculine
-précarisée
-rapidement autonome
-et adhérant au traitement

Asselah T, Clichy, AASLD 2024, Abs. 1152 actualisé

Hépatite Delta : ça secoue

1- Épidémiologie

2- Histoire naturelle

3- Principes du traitement : Bulevirtide +/- Interferon-Pegylé ?

4- **Recommendations EASL et Perspectives**

5 - Conclusion

Résumé EASL

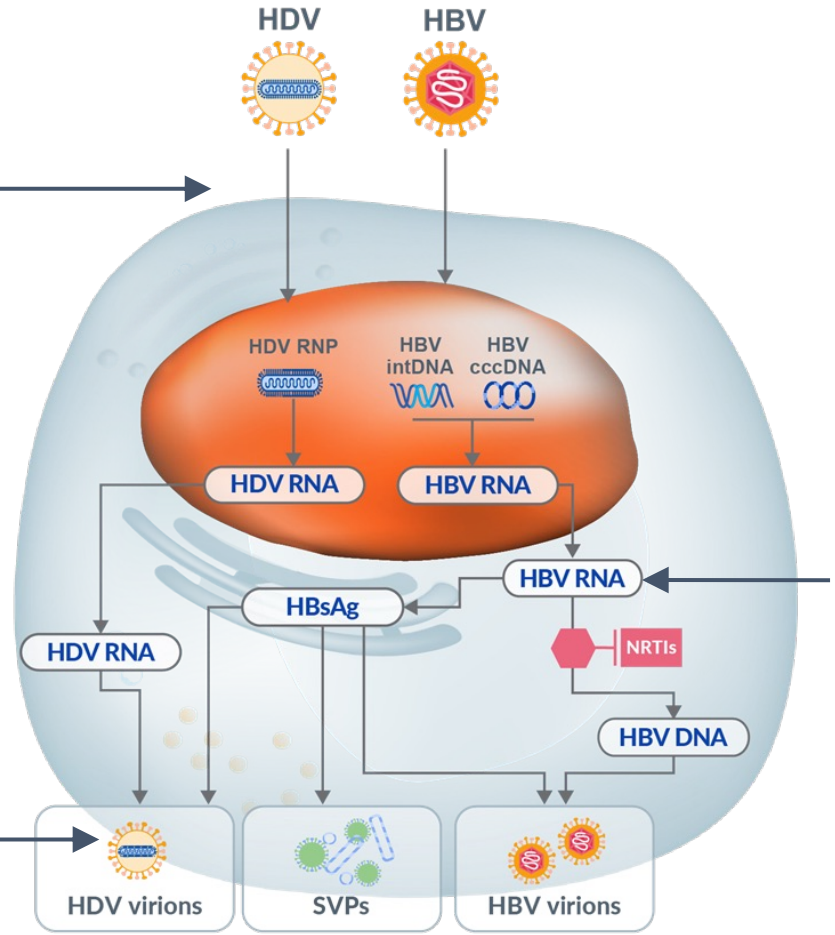
Screening	Screening for anti-HDV antibodies should be performed with a validated assay at least once **in all HBsAg+ individuals** (and retested as indicated)
	HDV RNA should be tested **in all anti-HDV positive individuals** using a standardized and sensitive reverse transcription PCR assay to diagnose active HDV infection
Treatment	**All patients with CHD should be considered for antiviral treatment**
	Finite or prolonged treatments are the two approaches used in CHD aimed to cure or control the infection and disease
	All patients with CHD and compensated liver disease should be considered for treatment with BLV • The optimal dose and duration of treatment have not yet been defined
	All patients with CHD and compensated liver disease, irrespective of cirrhosis, should be considered for treatment with PegIFNα
	The combination of PegIFNα and BLV may be considered in patients without PegIFNα intolerance or contraindications
Monitoring	Patients with CHD should be monitored during and after treatment using virological markers, biochemical markers, liver imaging, histology, and clinical events

CHD, chronic hepatitis delta; PegIFNα, pegylated interferon alpha.
EASL, J Hepatol. 2023

Tobevibart et Elebsiran: Mode d’actions

Tobevibart (VIR-3434, mAb)

Inhibition of viral entry (neutralization)



Elebsiran (VIR-2218, siRNA)

Reduction of HBsAg RNA (silencing HBV RNA)

Tobevibart

Clearance of free virions (opsonization)

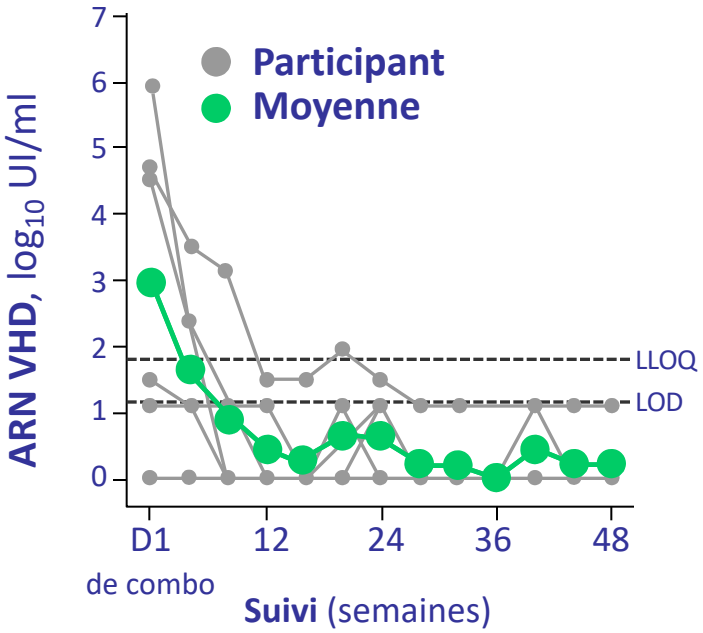
cccDNA, covalently closed circular DNA; CHD, chronic hepatitis delta; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; intDNA, integrated DNA; mAb, monoclonal antibody; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; RNP, ribonucleoprotein; siRNA, small interfering RNA; SVP, subviral particle.

Asselah Tarik-2025-16/20

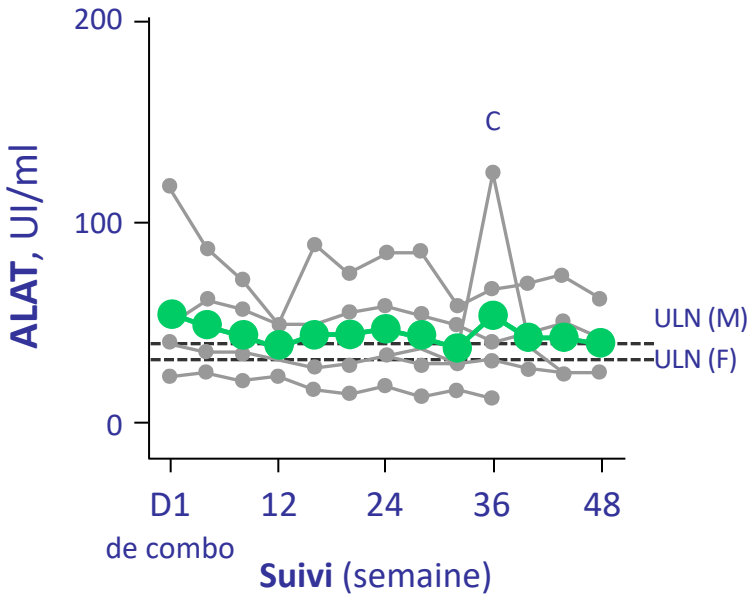
VIR-2218 (ARNi) et VIR-3434 (Ac monoclonal) chez les patients VHD *(2)*

Réponse combinée de la combo Rollover

Réponse virologique



Réponse ALAT



Réponse virologique et réponse ALAT

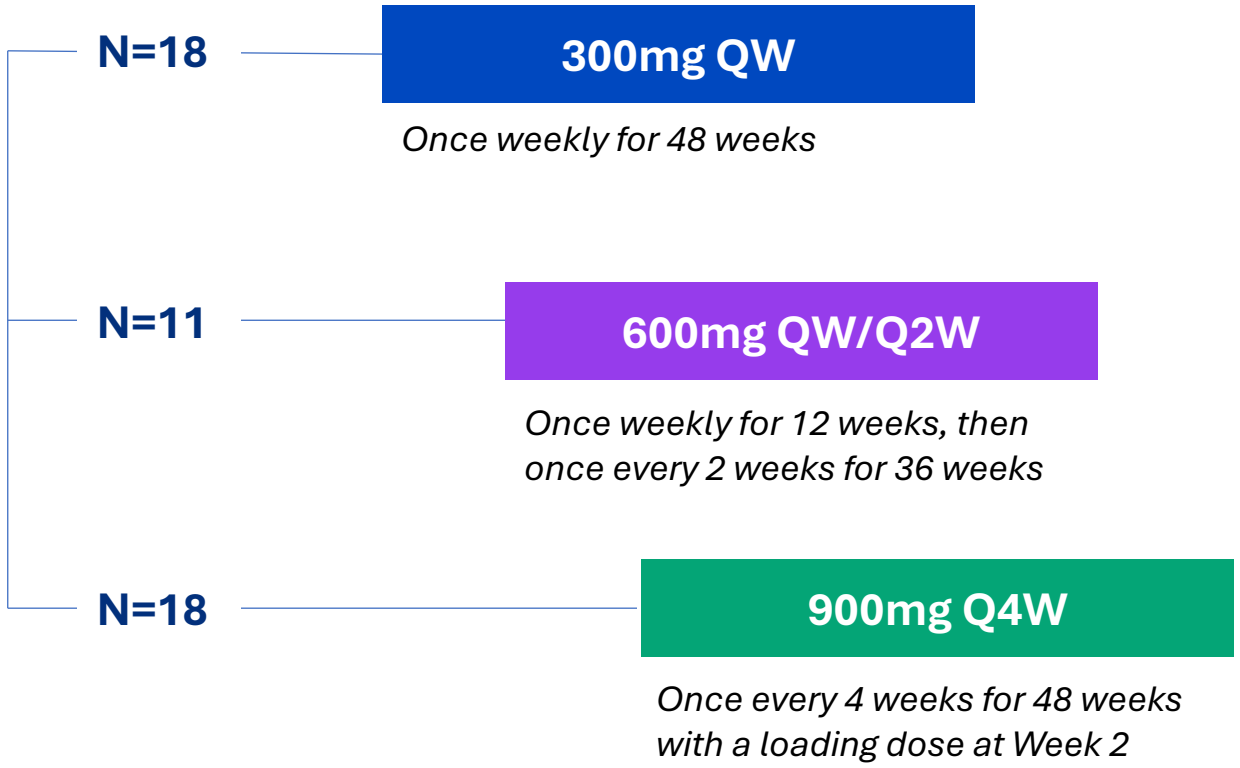
	Combo/4 sem rollover		
	S12 (n = 6)	**S24** (n = 6)	**S48** (n = 5)
ARN VHD < LLOQ, n (%)	6 (100)	6 (100)	5 (100)
ARN VHD< LOD, n (%)	5 (83,3)	5 (83,3)	5 (100)
ARN VHD TND, n (%)	4 (66,7)	3 (50)	4 (80)
Normalisation ALAT, n (%)	2 (33,3)	2 (33,3)	2 (40)

Asselah et al. EASL 2024, AOS-124

BJT-778, anti-HBsAg monoclonal antibody, achieved 100% virologic response in subjects with chronic hepatitis D (CHD): phase 2 study results

Kosh Agarwal, Marta Dobryanska , Alina Jucov, Patrick Kennedy, Edward J. Gane, Man-Fung Yuen, Grace Lai-Hung Wong, Simone Strasser, Jacinta Holmes, Stuart Roberts, Hassan Javanbakht, Nancy Shulman, Jenny C. Stanton

BJT-778-001 Phase 2 in CHD: Study Design



*HDV RNA Quantification performed at VIDRL, Melbourne, AUS
LLOQ <10 IU/mL
LLOD <5 IU/mL – 'Target not detected'

Key Entry Criteria

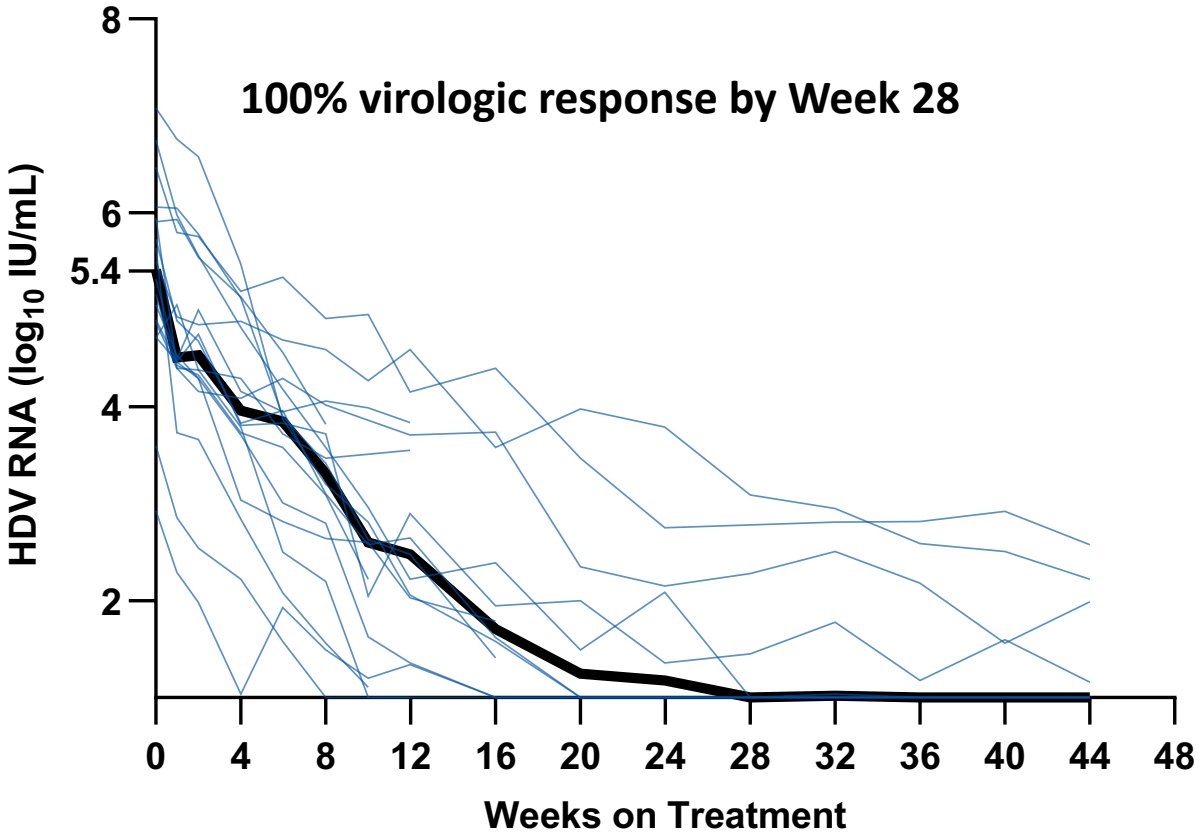
- Adults with chronic HDV
- Quantifiable HDV RNA
- HBV DNA <100 IU/mL on NUCs
- Compensated liver disease
- PLT >100 K/mm^3
- ALT ≤ 10x ULN
- Well-controlled HIV allowed

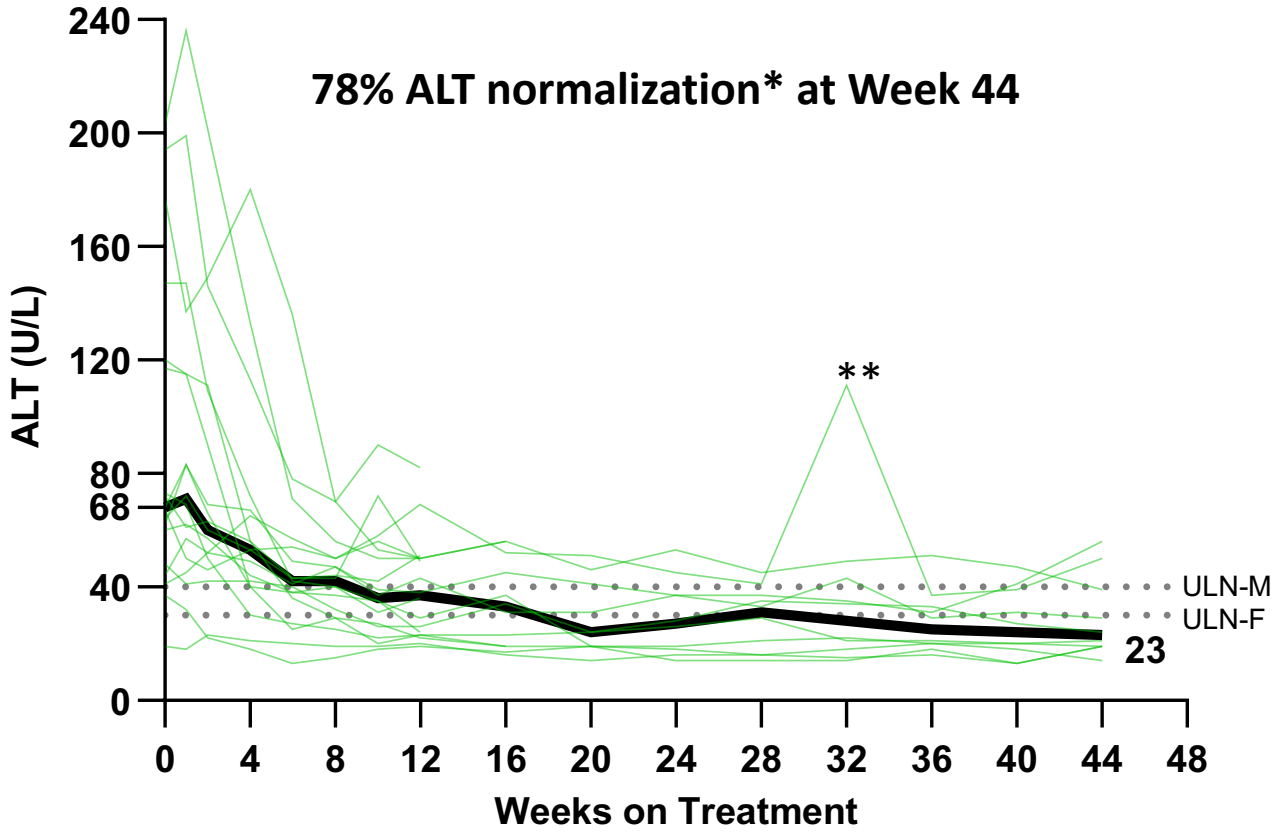
Key Endpoints

- **Safety** and tolerability
- **Virologic response:** ≥2 log10 HDV RNA IU/ml reduction from baseline or HDV RNA TND*
- **ALT normalization** in subjects with abnormal at baseline
- **Combined response:** virologic + ALT normalization

Bluejay THERAPEUTICS

BJT-778 300 mg Once Weekly: 100% Virologic Response and Parallel Declines in ALT





Bold lines are median values

*In subjects with abnormal ALT at baseline

**Isolated asymptomatic G2 ALT increase during holiday festivities with ↑↑ alcohol consumption

Virologic response = ≥2 log10 HDV RNA IU/ml reduction from baseline or HDV RNA TND; Upper Limit Normal

Hépatite chronique delta: Conclusion

1. **Dépister**: Chez tout patient VHB, dépister le VHD (sérologie VHD): Reflex testing
2. Répéter tous les 6 mois le dépistage sur facteurs de risques
3. **Evaluer la fibrose**: l'hépatite delta se complique souvent de cirrhose et de CHC.
4. **Instaurer le traitement**: Bulevirtide +/- IFN-PEG. Importance d'un bon suivi.
5. **La vaccination du VHB** reste le meilleur traitement préventif du VHD