Management of HDV infection in 2020

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International Conference on the Management of Liver Diseases

Tarik Asselah (MD, PhD)

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Professor of Medicine
Hepatology, Chief INSERM UMR 1149,
Hôpital Beaujon, Clichy, France.

Inserm · Assistance Publique Hôpitaux de Paris · anrs French National Agency for Research on AIDS and Viral Hepatitis | An autonomous agency at Inserm | · Université Paris Diderot Paris 7 · CRI Centre de Recherche sur l'Inflammation · unity Addressing Unmet Needs through Innovation in hepatology and gastroenterology

Disclosures

- Employee of Paris Public University Hospitals (AP-HP, Beaujon's Hospital) and University of Paris.

- Principal investigator for research grants : Funds paid to Hospital (AP-HP)

- Consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, Roche. Clinical Investigator: Abbvie,Gilead, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, Eiger pharmaceutical.

- Grants from : ANR, CNRS , INSERM , University of Paris, ANRS.

HDV infection: Clinical Case

43 years old man

From Moldavie, in France since 2005

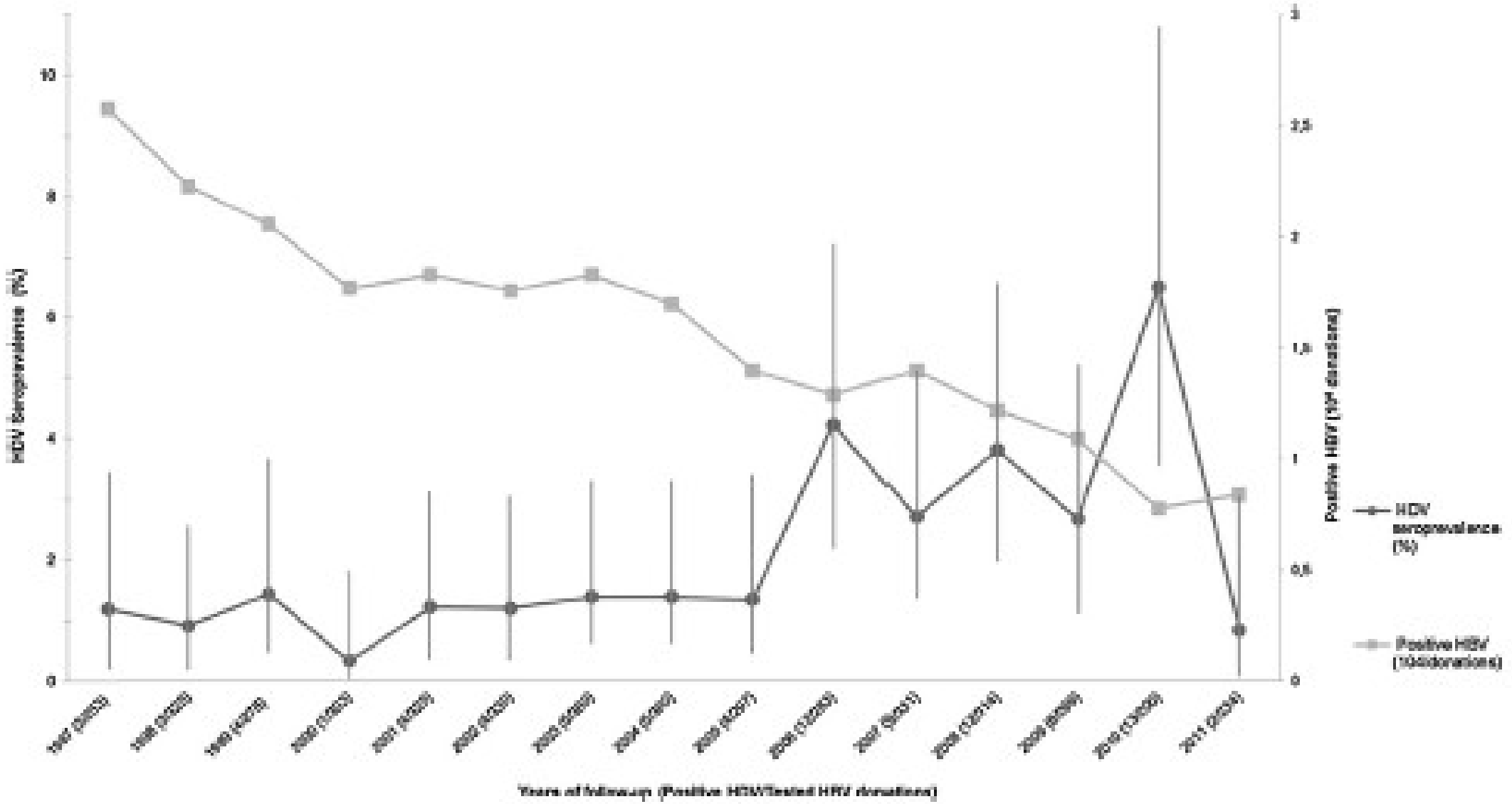
Diagnostic of HBV infection (HBsAg + since 1991)

Diagnostic of HDV Delta since 2008

HIV - HCV –

Prevalence of HDV infection in France (1997-2011)

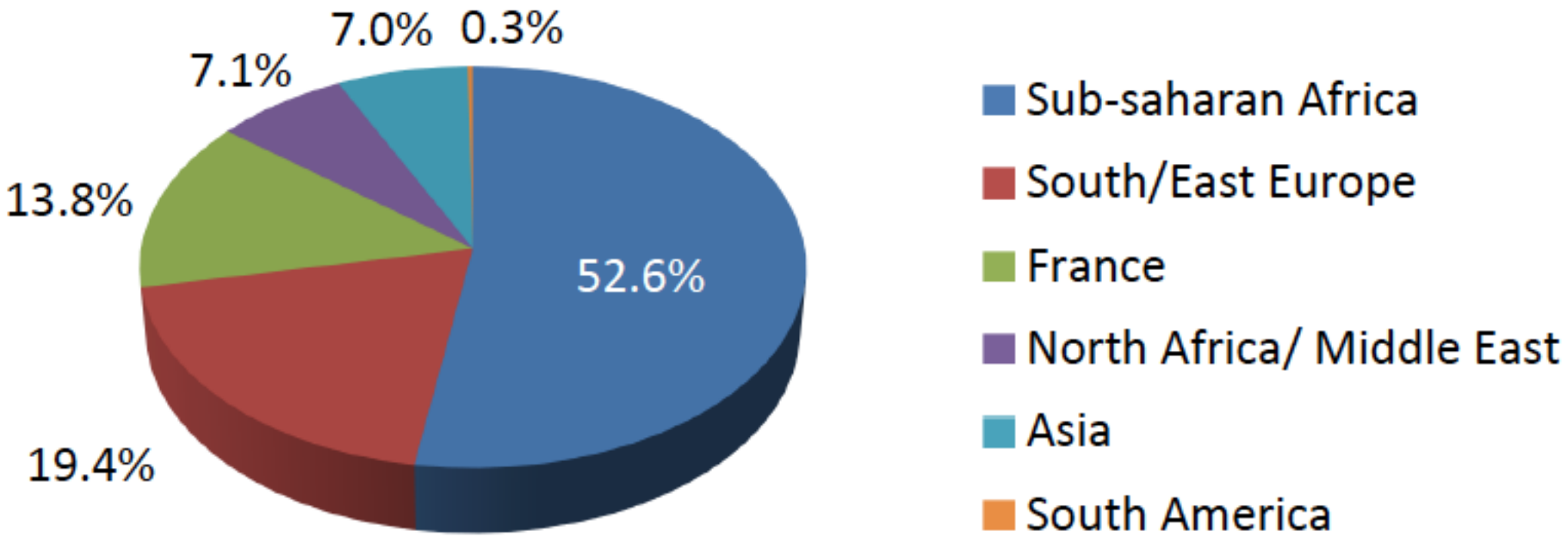
Prevalence of HBV per 100,000 donations and of HDV on HBV positive donations

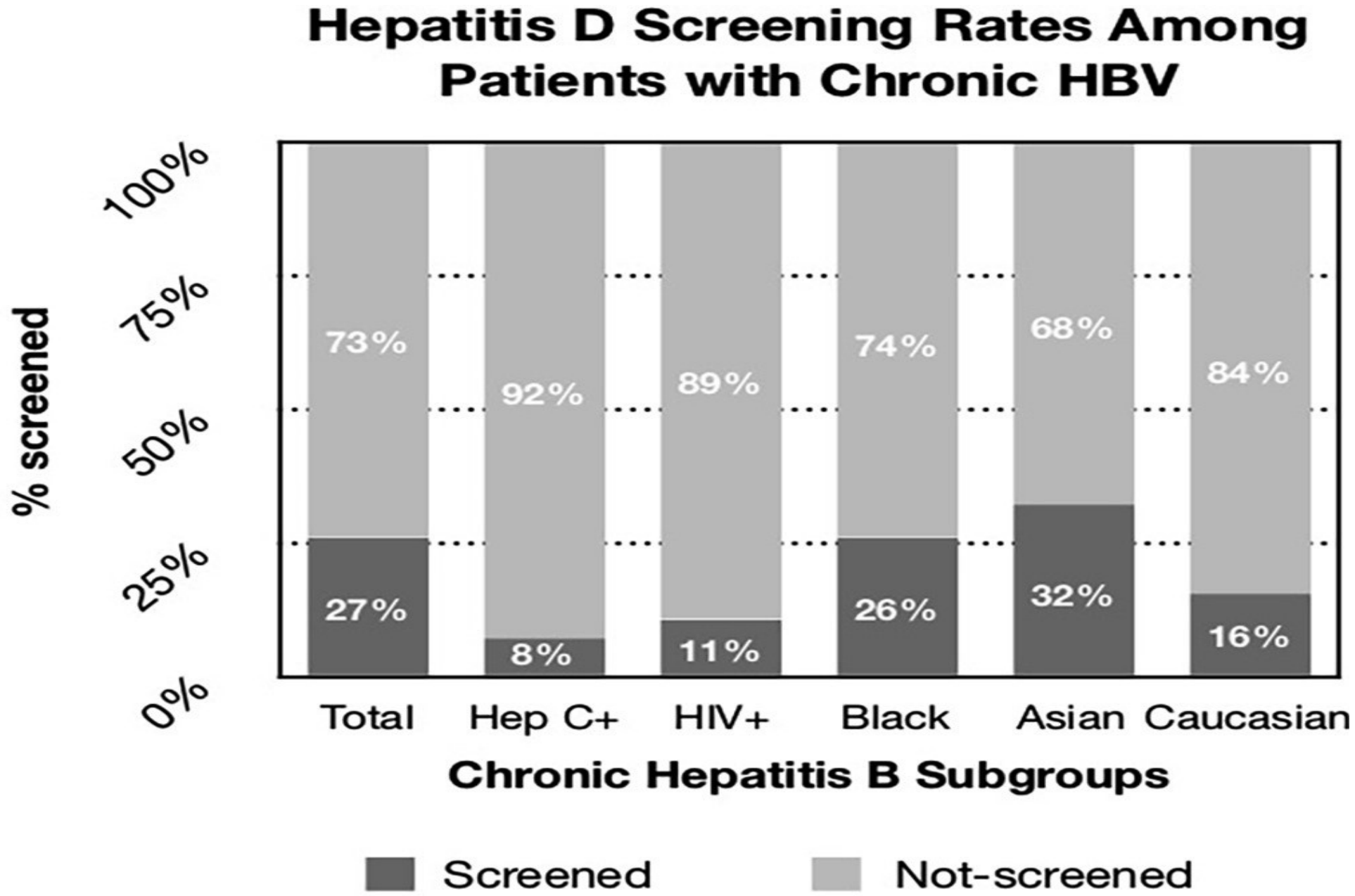


Servant-Delmas A et al. J Clin Virol 2014; 59: 126-8.

HDV infection in France

Patient's Origin





Moore A et al. Hepatology 2019; 70(Suppl.): 585A-586A

HDV infection: Clinical Case

43 years old man

From Moldavie, in France since 2005

Diagnostic of HBV infection (HBsAg + since 1991)

Diagnostic of HDV Delta since 2008

HIV - HCV –

Treated with PEG-IFN from 2009 to 2010 (48 weeks)

Failure HDV RNA undetectable, Tolerability correct

Adressed to Beaujon Hospital

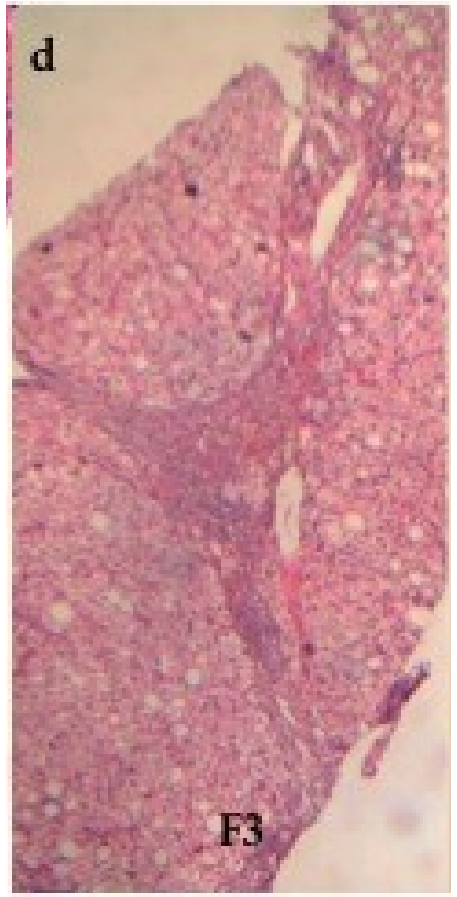
IFN treatment for HDV

References	Type/dose	No. of patients	Duration of therapy	Duration of follow-up	Overall virological response at EOT (%)	SVR (%)
[28]	Peg-IFNα2b 1.5 μg/kg	14	12 months	16 months	57	43
[29]	Peg-IFNα2b 1.5 μg/kg	16	18 months	6 months	19	25
	Peg-IFNα2b 1.5 μg/kg + RBV	22	12 months	6 months	9	18
[30]	Peg-IFNα2b 1.5 μg/kg	12	12 months	12 months	–	17
[31]	Peg-IFNα2b 1.5 μg/kg	49	13 months	26 months	33	25
[32]	Peg-IFNα2b 1.5 μg/kg	11	24 months	6 months	56	–
		7	12 months	6 months	57	
[33]	Peg-IFNα2a 180 μg	29	12 months	6 months	24	31
	Peg-IFNα2a 180 μg + adefovir 10 mg/day	31	12 months	6 months	23	24
	Adefovir 10 mg/day	30	12 months	6 months	0	0
[34]	Peg-IFNα2b	277 enrolled (238 evaluated)	48 weeks	24 weeks	29.8	29.4
[35]	Peg-IFNα2a 180 μg or peg-IFNα2b 1.5 μg/kg	32	24 months	6 months	50	47
[36]	Peg-IFNα2a + tenofovir	59	96 weeks	24 weeks	48	29
	Peg-IFNα2a + placebo	61	96 weeks	24 weeks	33	21
[37]	Peg-IFNα2a 90–270 μg/week	13	6–240 weeks (median, 140 weeks)	–	–	39 (3 lost HBsAg)
[38] [a]	Peg-IFNα2a 180 μg + entecavir 0.5 mg/day	22	48 weeks	48 weeks	95	95
[39]	Peg-IFNα2a	41	12 months		39	37
	Peg-IFNα2b	15	12 months		13	13
[40]	IFN or peg-IFN	99	6–126 months (median, 24 months)	24–225 months (median, 55 months)	–	35.3

EOT, end of treatment; SVR, sustained virological response; RBV, ribavirin; HBsAg, hepatitis B surface antigen.
[a] South American study enrolling patients with HDV genotype 3.

Brancaccio G and Gaeta G. IJAA 2019;54:697–701

HDV infection: Clinical Case



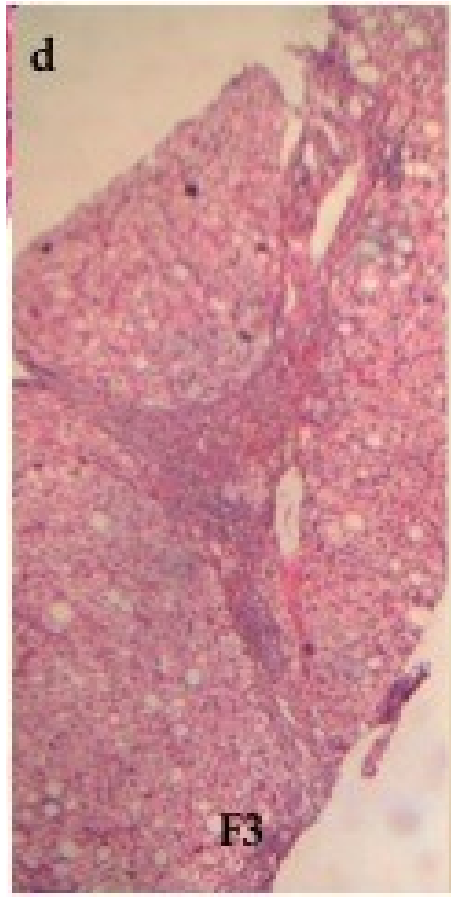
2010 : Liver biopsy : A2, F3 fibrosis stage

Delta RNA PCR

Viral load 8 log (copies/ml)

Genotype 1

HDV infection: Clinical Case



2010 : Liver biopsy : A2, F3 fibrosis stage

Delta RNA PCR

Viral load 8 log (copies/ml)

Genotype 1

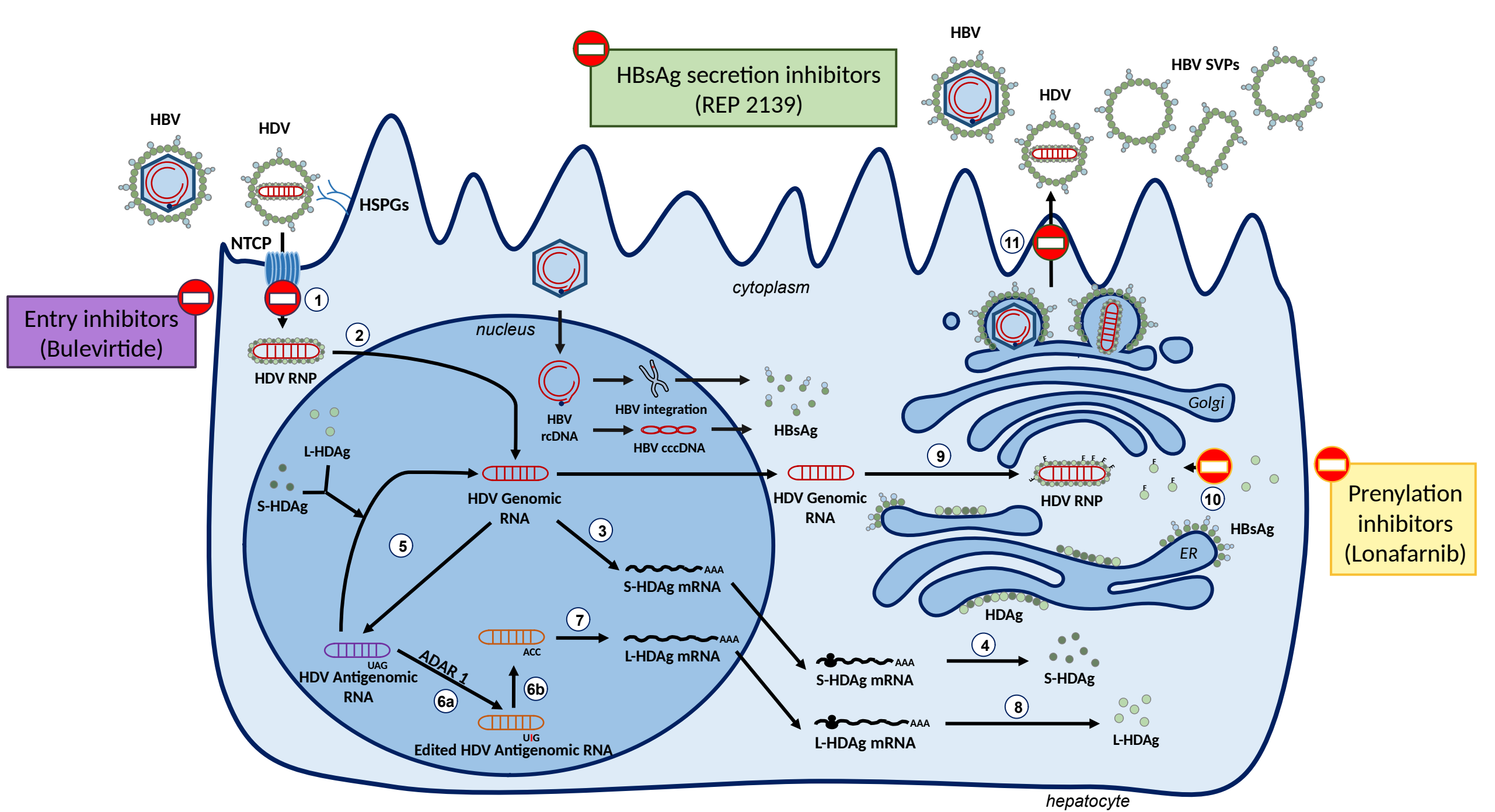
Follow-up without treatment

Screening for HCC (ultrasound each 6 months)

Lifestyle recommendations (soprt & diet & reduced alcohol)

HDV infection: Clinical Case

2019 : New proposals for the Patient



Asselah et al. Liver International, in press, 2020.

Cohort ATU in France

Bulevirtide 2mg, self administered by patients once daily s.c.

> 90 patients are included

Inclusion criteria:

Adult patients (>18 years) with chronic HDV infection since at least 6 months assessed by positive HDV RNA and/or HDV antibody testing and

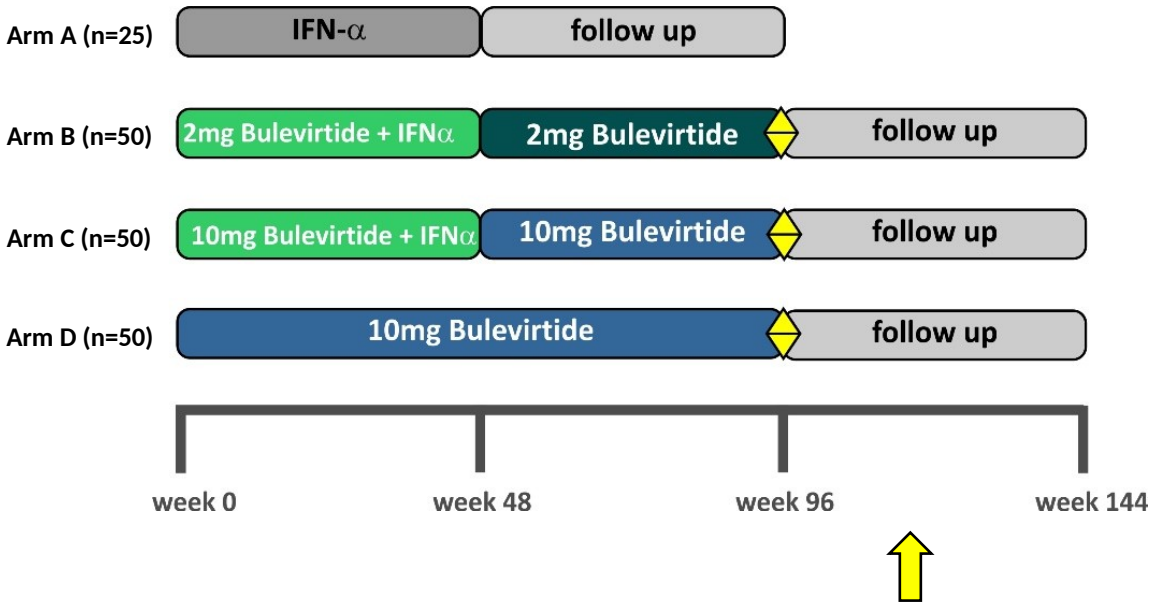
- **compensated liver cirrhosis or severe fibrosis grade 3** (evaluated by liver biopsy or Fibroscan) or
- **Fibrosis grade 2** (evaluated by liver biopsy or Fibroscan) **with persistent ALT elevation** (ALT > or = 2N since at least 6 months)

Exclusion criteria:

Presence of decompensated liver disease, creatinine clearance < 60 ml/min, pregnancy

➢ More information on ANSM website

Ongoing clinical trial MYR 204

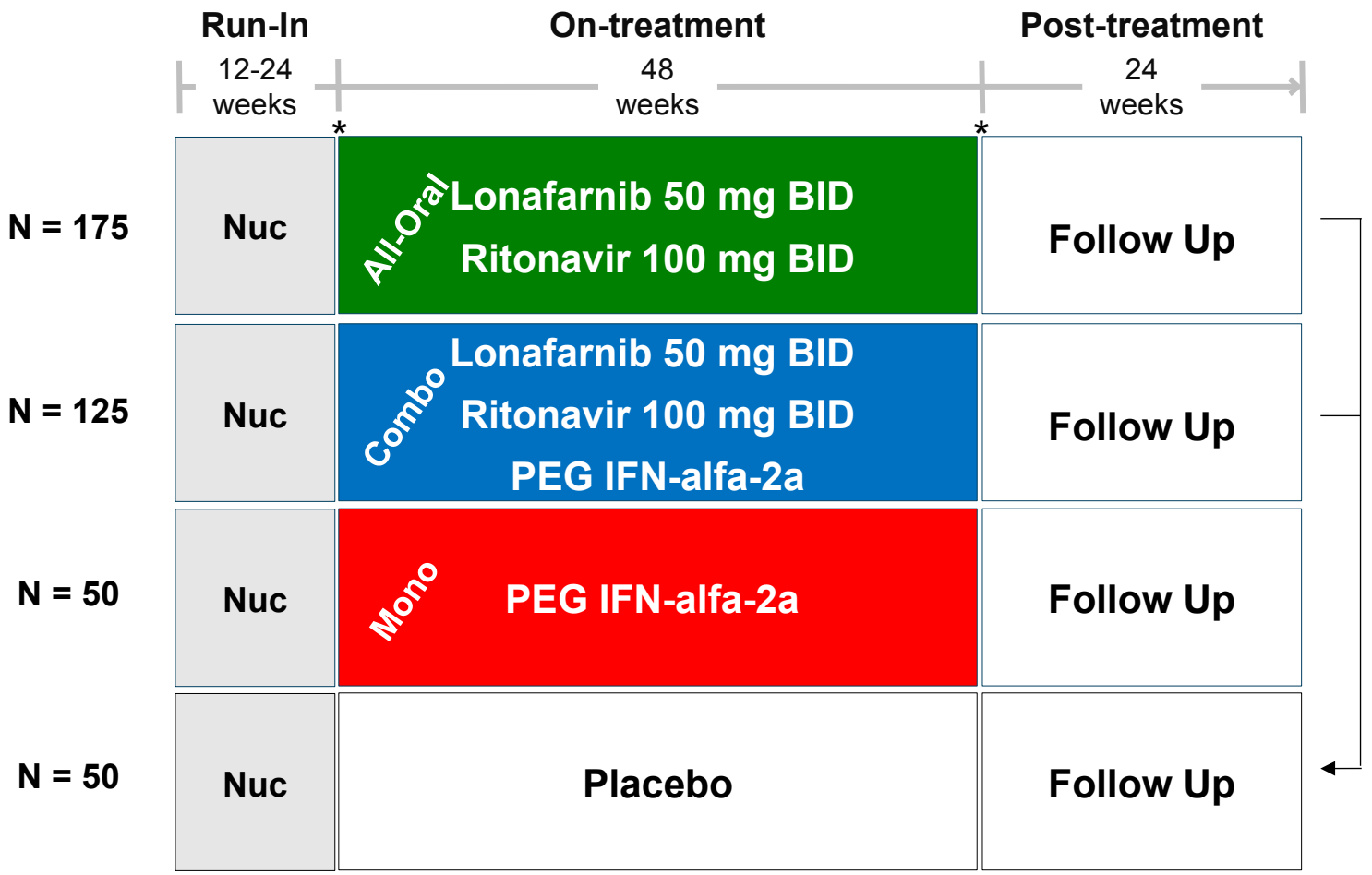


- 175 HDV patients, in combination with PEG-IFNα
- Enrolment completed December 2019
- Patients randomized in 4 treatment arms
- In 4 countries: **France**, Russia, Romania, Moldova

- Primary endpoint:
  Sustained virologic response defined as negative PCR result for HDV RNA at week 24 after end of treatment

D-LIVR: Phase 3 study

Delta-Liver Improvement and Virologic Response in HDV (400 patients)



All patients will be maintained on background HBV nucleoside therapy.
Superiority over PEG IFN-alfa-2a not required.

* biopsy

Primary Endpoint at Week 48

- ≥ 2 log decline in HDV RNA
  +
  Normalization of ALT

Secondary Endpoint at Week 48

- Histologic improvement
  - > 2-point improvement in HAI inflammatory score
  - No progression in fibrosis
- Improvement of fibrosis

HDV infection: Clinical Case

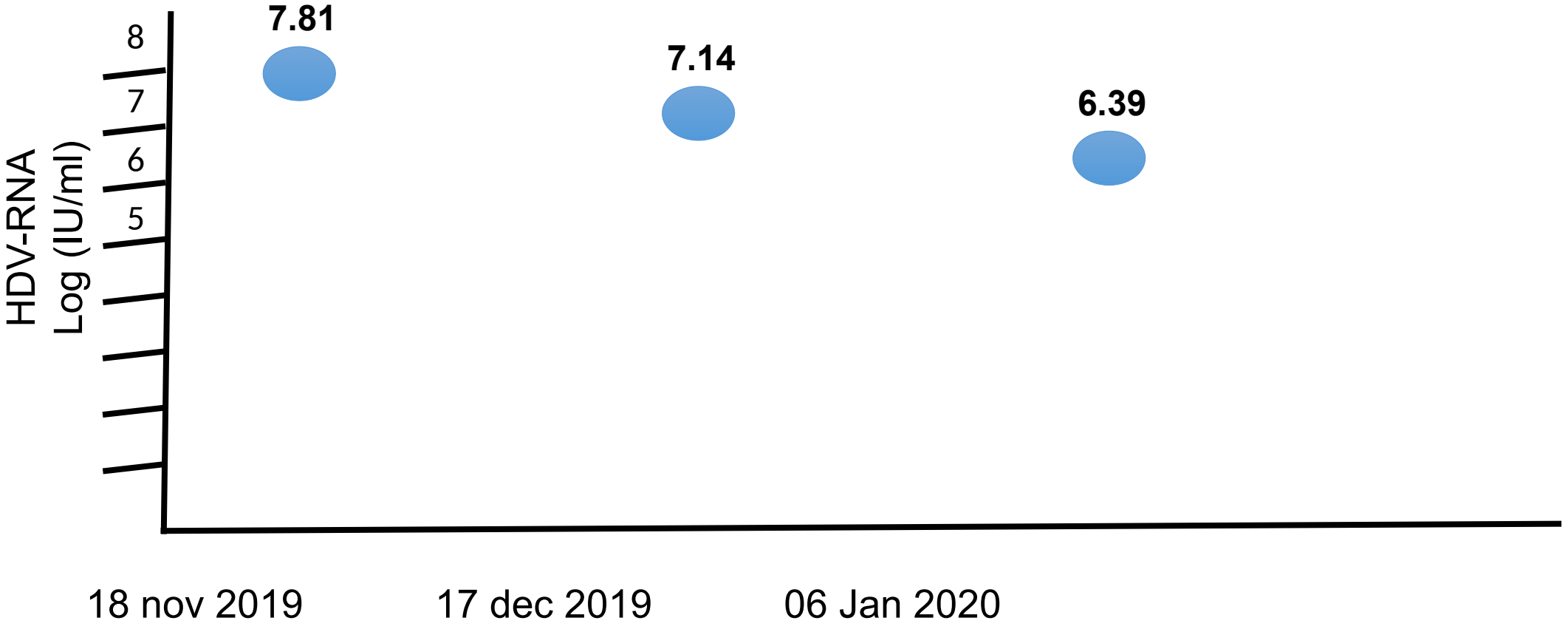
- 43 years old man
- HDV genotype 1
- Failure to PEG-IFN from 2009 to 2010 (48 weeks)
- Cirrhosis Child-Pugh A, no decompensation
- Platelets count 125 000/mm3, Prothrombin Time 65%
- Viral Load 7.81 log
- Decision for ATU (Agence nationale de sécurité du médicament et des produits de santé) https://www.ansm.sante.fr

Started treatment with PEG-IFN and Bulevirtide 2 mg/d (18 nov 2019)

Tolerability favorable, mild asthenia related to PEG-IFN

HDV infection: Clinical Case

Started treatment with PEG-IFN and Bulevirtide 2 mg/d
(decision to add or not PEG-IFN rely on the decision of the clinician)
(Virology performed in the HDV referral lab (E Gordien)



There is a need to cure HDV

- New propotions for patients
- 2 ongoing clinical trials in France
- ATU program
- We need an HDV Cure

Hepatitis Delta: ongoing trials

Mode of Action Compound Company	Official Title	Number (participants)	Stage of devlopment	Reference; Clinicaltrials.gov
Entry Inhibitor; Bulevirtide; MYR GmbH	Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients With Chronic Hepatitis Delta	150	3	NCT03852719
	A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination With Pegylated Interferon Alfa-2a in Patients With Chronic Hepatitis Delta	175	2b	NCT03852433
	A Multicenter, Open-label, Randomised, Comparative, Parallel-Arm, Phase II Study to Assess Efficacy and Safety of Myrcludex B in Combination With Peginterferon Alfa-2a Versus Peginterferon Alfa-2a Alone in Patients With Chronic Viral Hepatitis B With Delta-agent	60	2b	NCT02888106
Prenylation Inhibitor; Lonafarnib; Eiger BioPharmaceuticals	A Phase 3, Matrix Design, Partially Double-Blind, Randomized Study of the Efficacy and Safety of 50 mg Lonafarnib/100 mg Ritonavir BID With and Without 180 mcg PEG IFN-alfa-2a for 48 Weeks Compared With PEG IFN-alfa-2a Monotherapy and Placebo Treatment in Patients Chronically Infected With Hepatitis Delta Virus Being Maintained on Anti-HBV Nucleos(t)Ide Therapy (D-LIVR)	400	3	NCT03719313
	Treatment of Chronic Delta Hepatitis With Lonafarnib, Ritonavir and Lambda Interferon	32	2A	NCT03600714

Asselah T. PHC 2020-20/20.