Hépatite Delta

SAHGE-SMMAD Tanger 2018

Pr Nabil DEBZI
Hépatologie
CHU MUSTAPHA
Alger

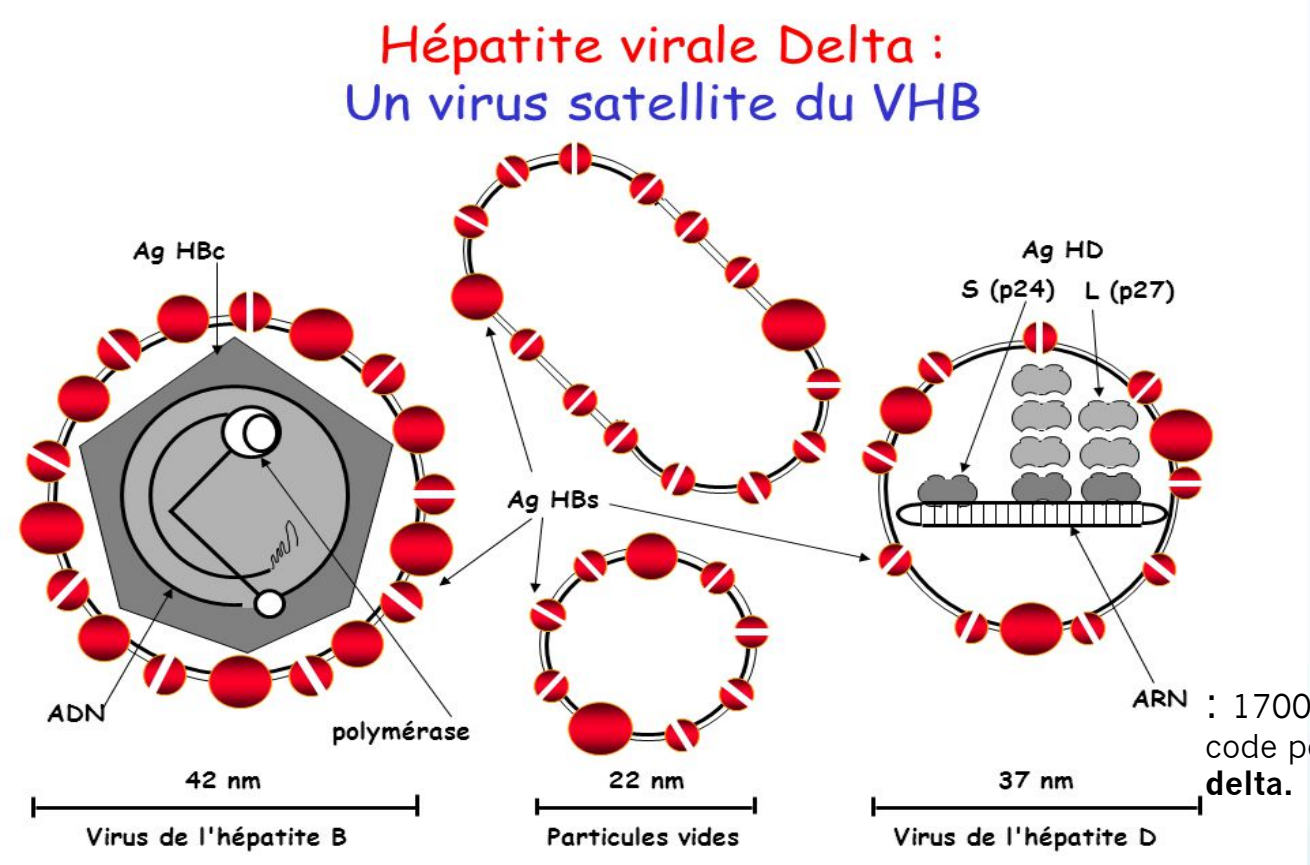
Reprinted from the Journal of the British Society of Gastroenterology—GUT
Volume 18, page 997, 1977.

Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

M. RIZZETTO, M. G. CANESE, S. ARICO, O. CRIVELLI, C. TREPO, F. BONINO AND G. VERME

Caractéristiques du VHD

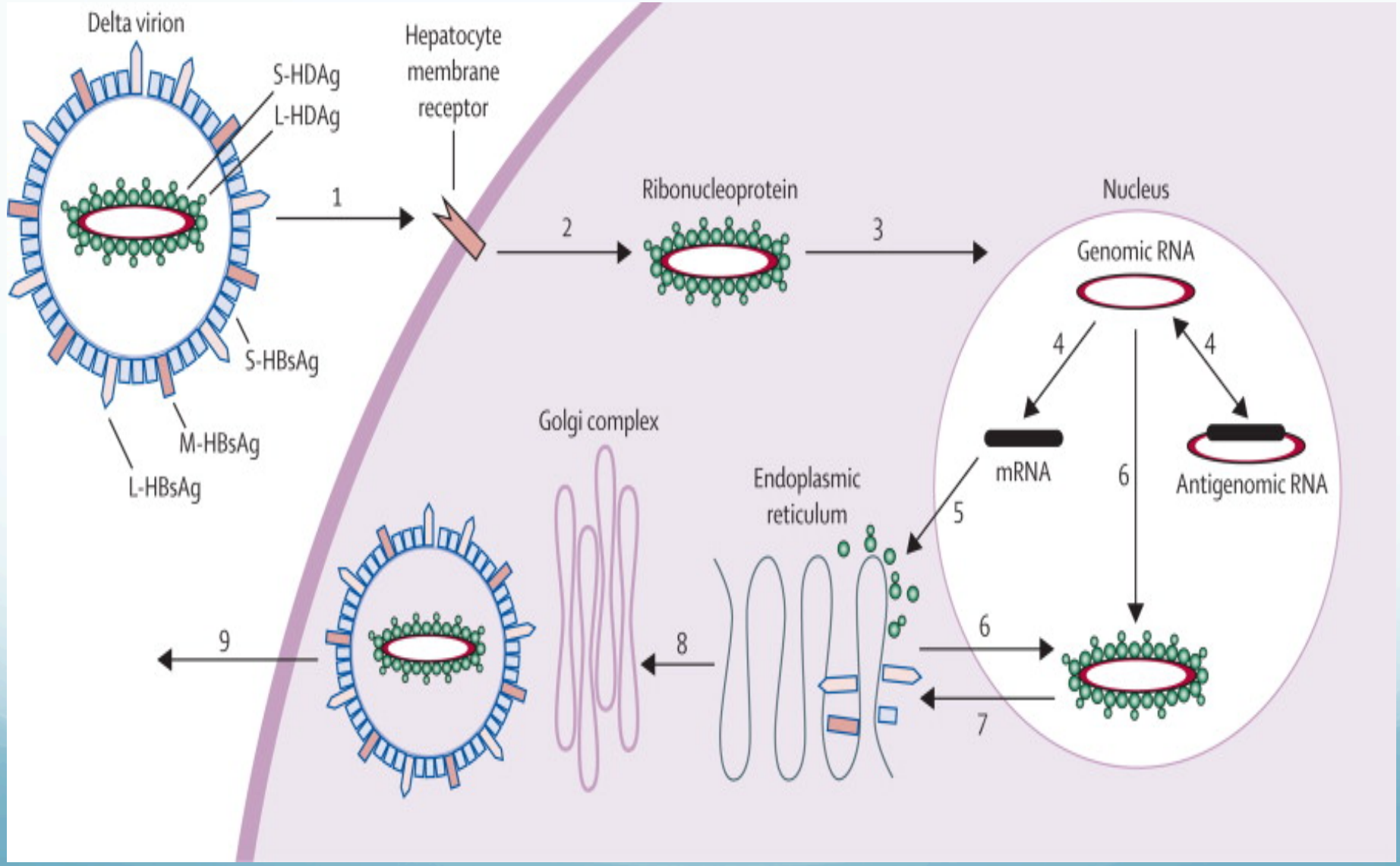
Structure



ARN : 1700 nucléotides, polarité négative, code pour une protéine: **l'antigène delta.**

L'ARN et la protéine delta sont contenus dans une enveloppe constituée d'AgHBs.
Pas d'enzyme virale , pas de cible des agents antiviraux directs
Le VHB est réprimé

Cycle de réplication du VHD



Devil hepatitis D: an orphan disease or largely underdiagnosed?

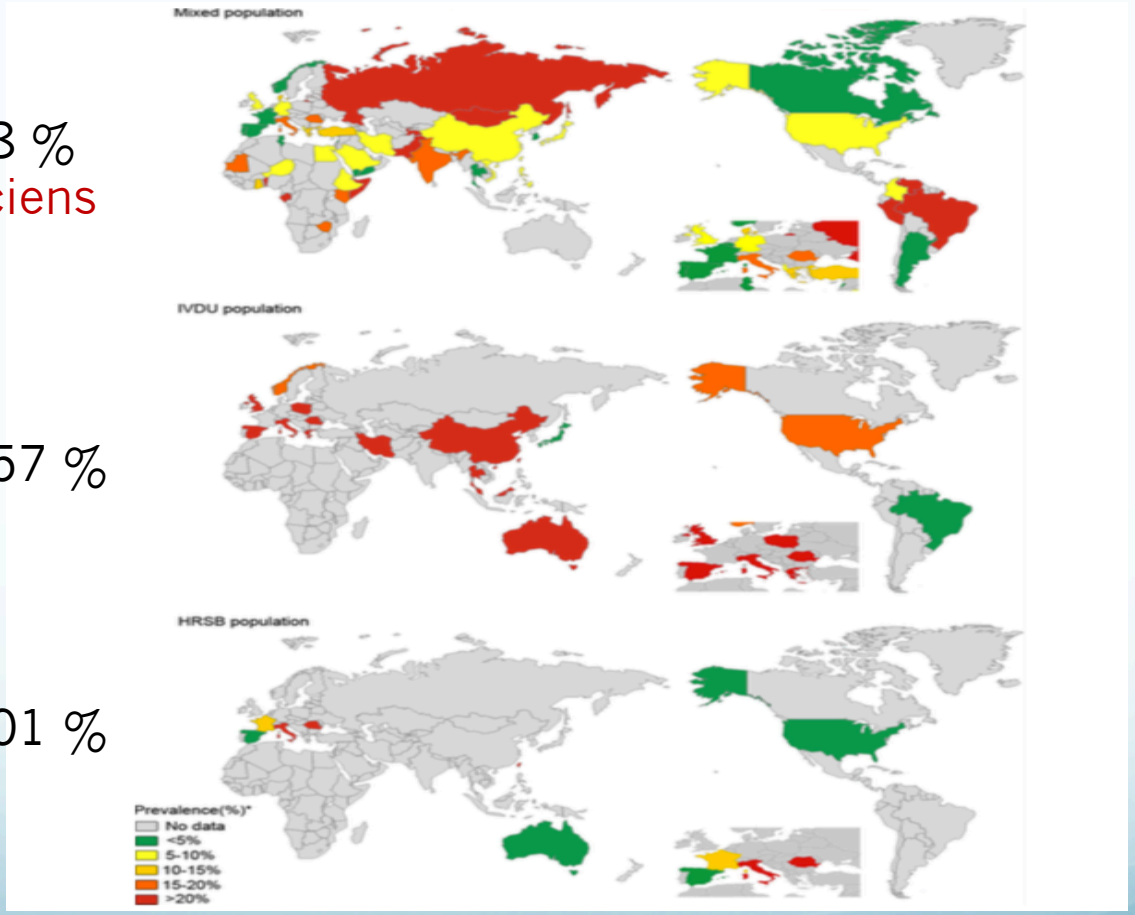
Heiner Wedemeyer,[1] Francesco Negro[2]

Gut 2018;**0**:1–2. doi:10.1136/gutjnl-2018-317403

Prevalence 10.58 %
X 2 /Travaux anciens

Prevalence 37.57 %

Prevalence 17.01 %

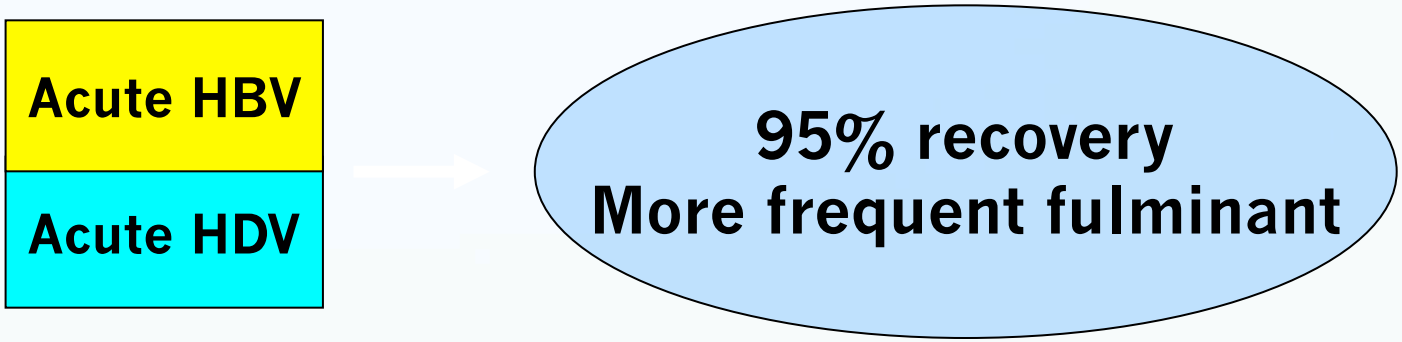


chen H-Y, *et al*. *Gut* 2018;**0**:1–10. doi:10.1136/gutjnl-2018-316601

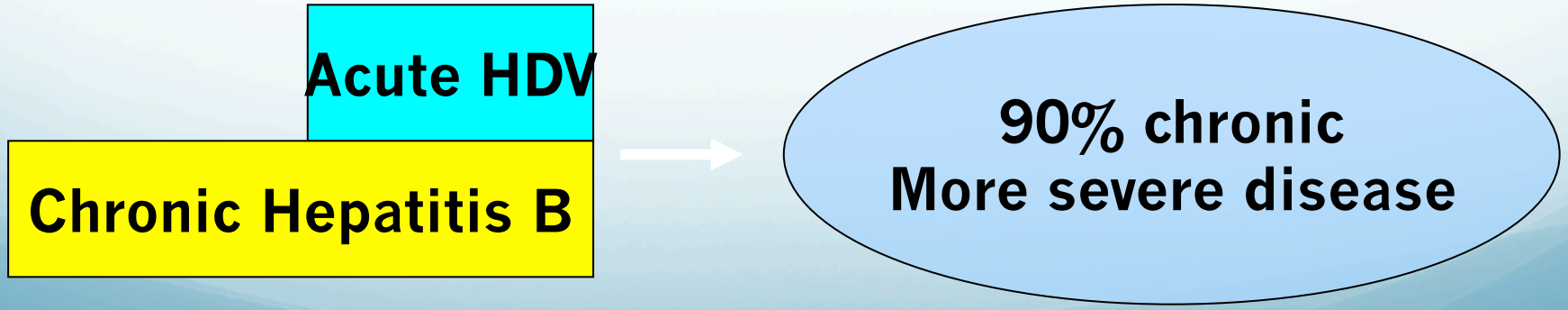
HDV and HBV Genotypes

Region	HDV genotype	HBV genotype
Europe	1	D / A
Brazil	1 / 3	F / A / D
China, Taiwan, Japan	1 / 2 / 4	B / C
Turkey, Iran, Pakistan, India	1	D
Western Pacific	1 / 2	B / C / D
Africa	1, 5-8	D / A / E

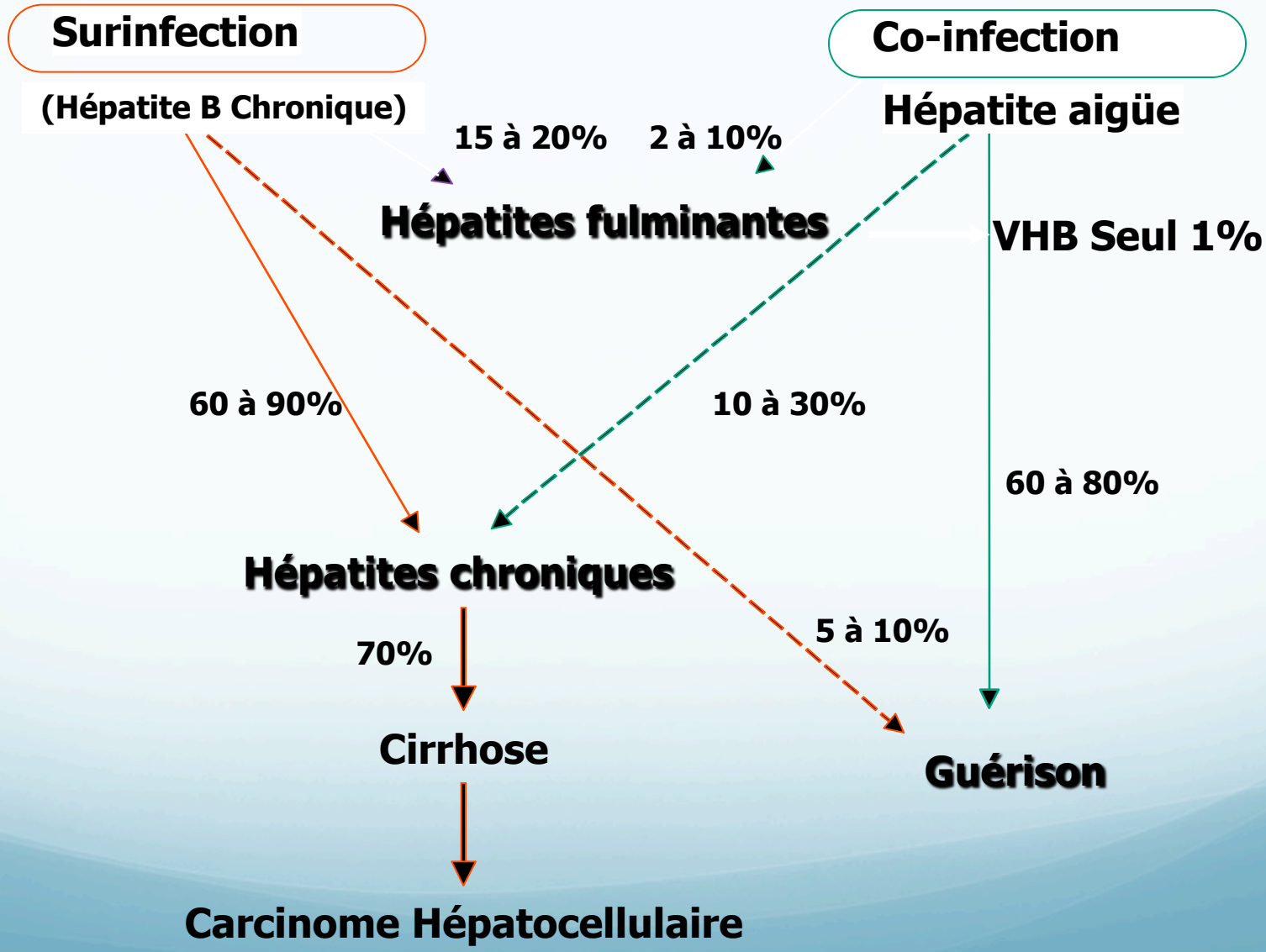
Simultaneous Co-Infection



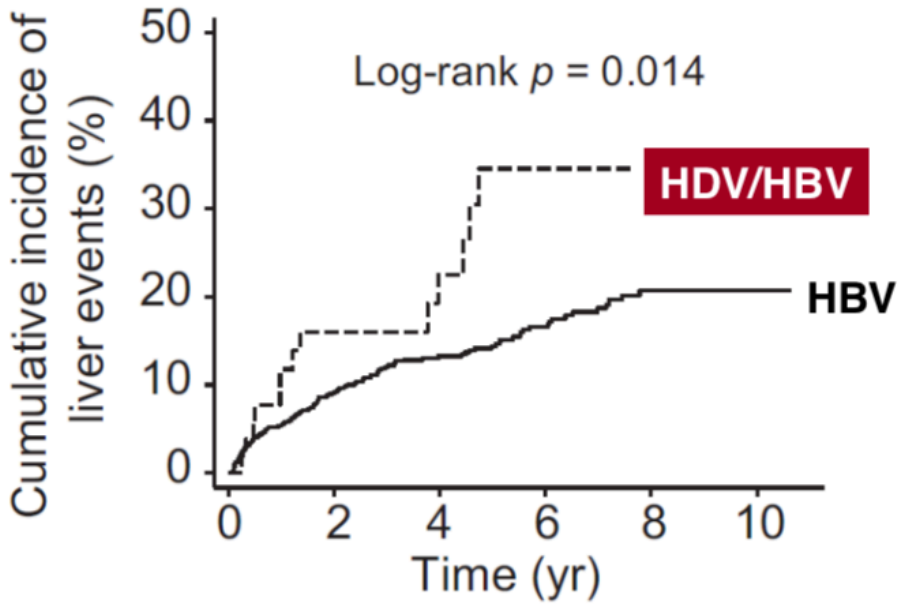
HDV Super-Infection



Histoire Naturelle de l'infection



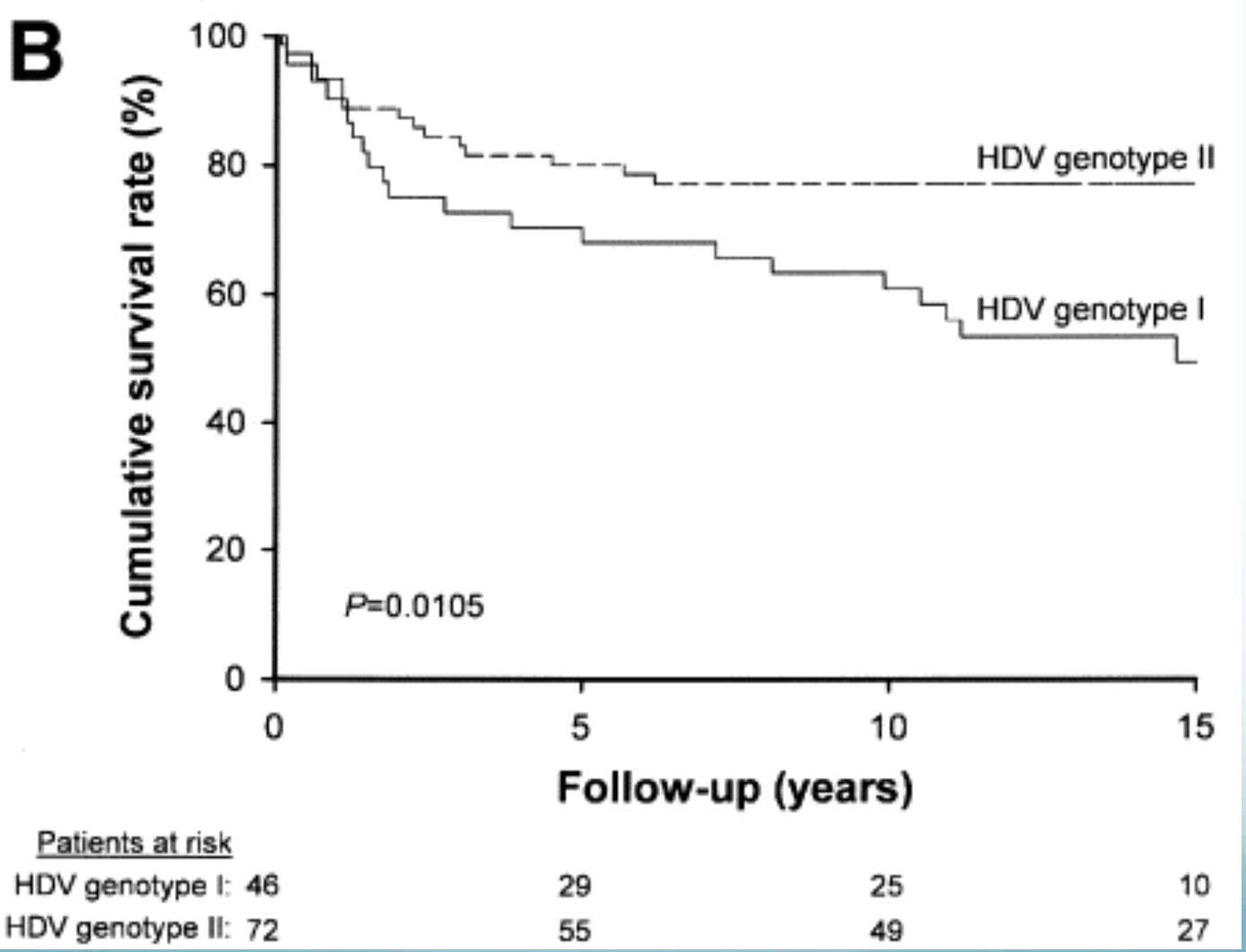
Sévérité plus importante de l'hépatite Delta par rapport à la mono-infection VHB



Number at risk						
HBV monoinfected	1091	685	434	266	123	36
HBV/HDV co-infected	53	33	24	7	2	2

Manesis et al., J Hepatol 2013

Different HDV Genotypes Are Associated With Different Clinical Outcomes



Su, Wu et al., Gastroenterology 2006

Le diagnostic

Diagnostic indirect: Tests immuno-enzymatiques (ELISA)

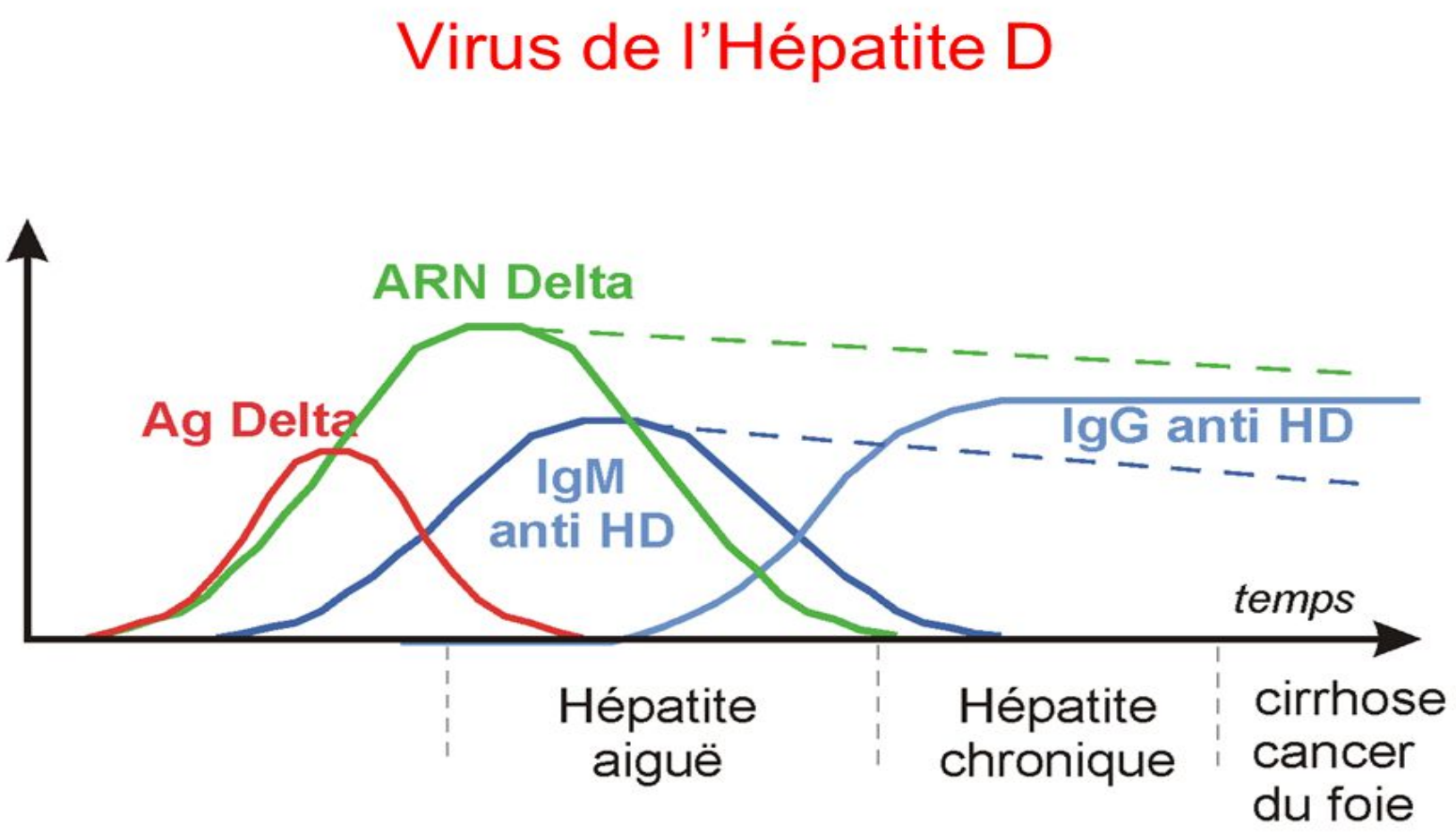
- **les anticorps anti-VHD totaux** le premier marqueur recherché en 1ère intention.

- **Les IgM anti-VHD** ont la particularité de persister en cas d'hépatite D chronique, elles peuvent manquer chez certains patients africains.

Diagnostic direct :

- Ag delta : fugace+++ peu d'intérêt en pratique.
- **ARN delta** : RT-PCR en temps réel
  Quantification de l'Ag Hbs q + (Titre= Traitement)
- Génotypes VHD

Cinétique des marqueurs



Algorithme Diagnostic

Ac anti VHD Totaux (IgG) : Pos

↓

Ac anti VHD IgM

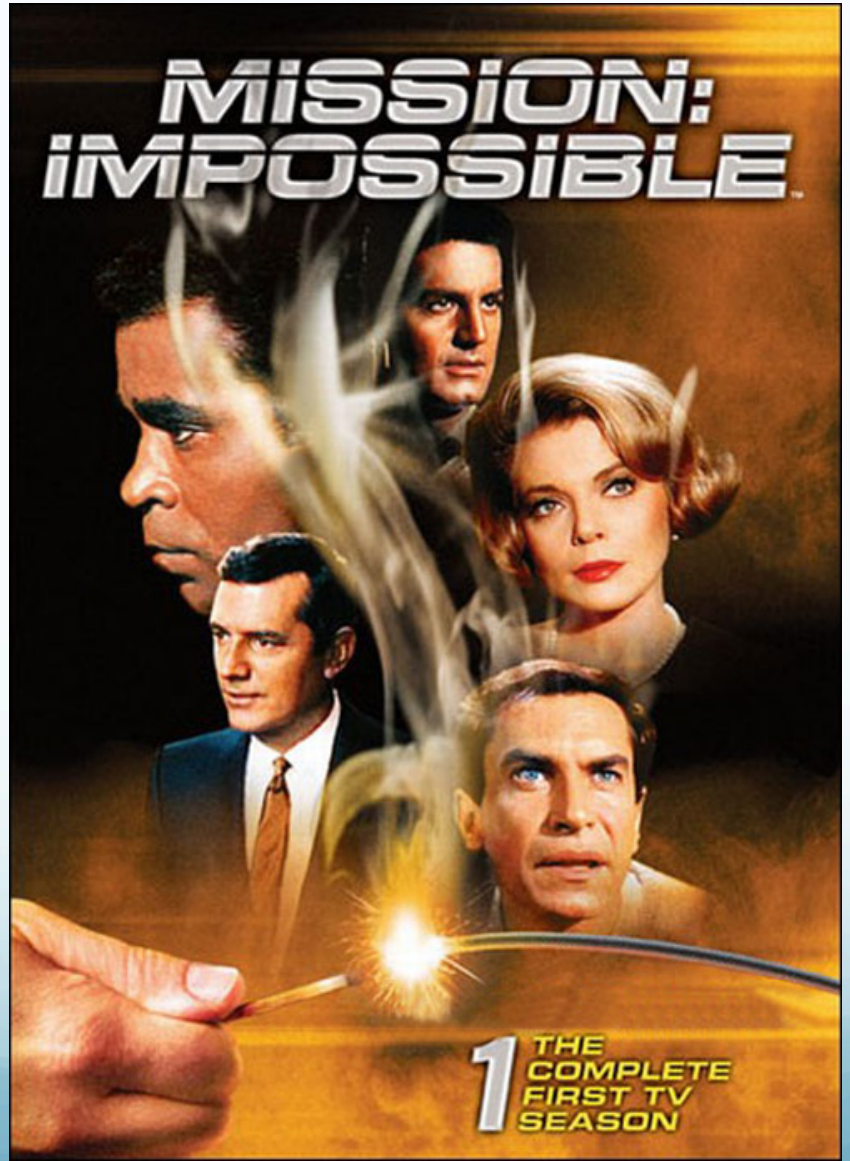
ARN VHD

(PCR)

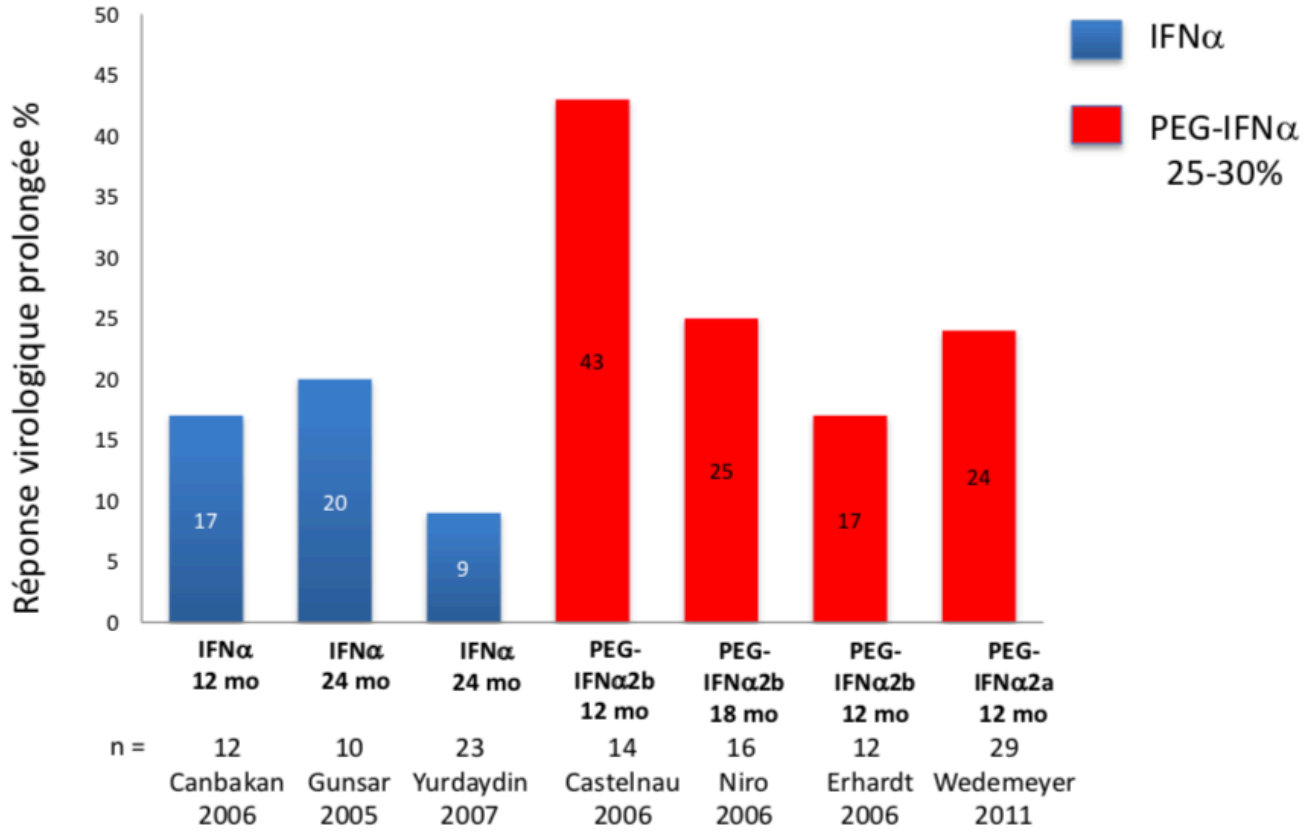
↙ ↓ ↘

IgM (-) et ARN(-)	IgM (-) et ARN(+)	IgM (+) et ARN(+)
Infection Ancienne et Résolue	Infection Aiguë ou Chronique	Infection Aiguë ou Chronique

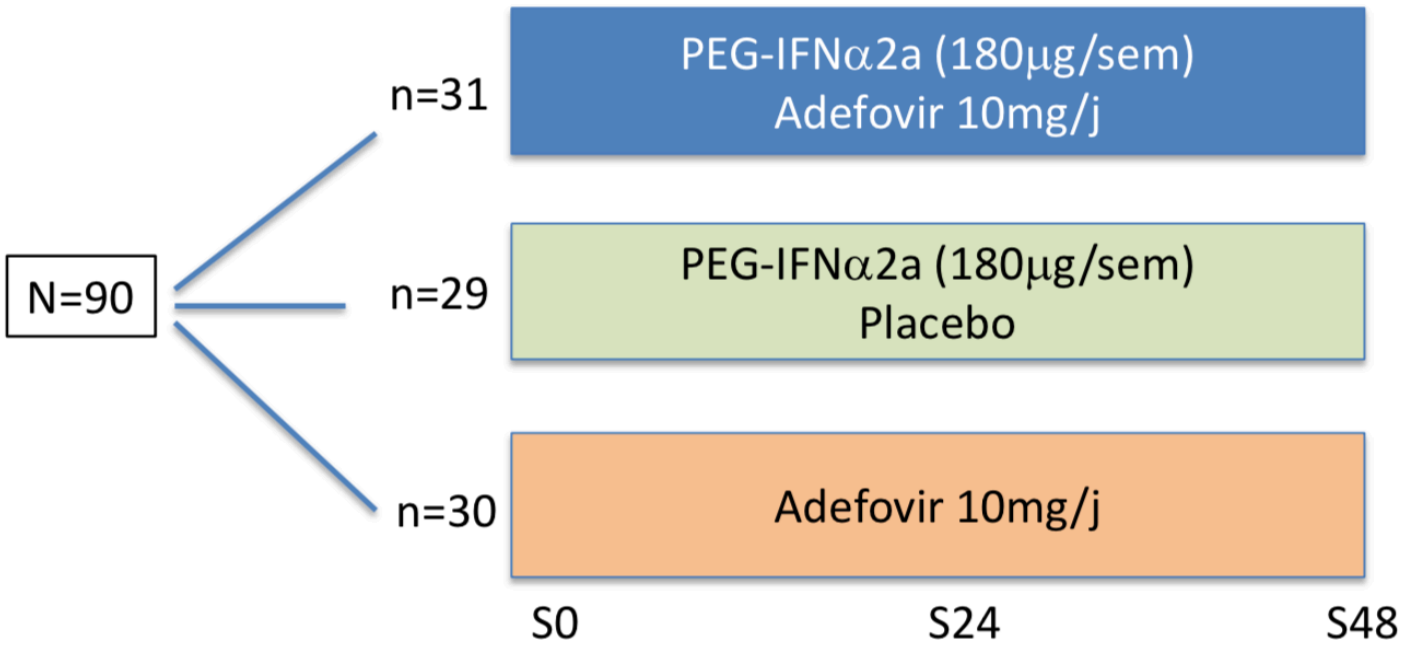
Prise en charge Thérapeutique



Traitement de l'hépatite Delta par Peg-IFNα



HIDIT 1: Peg-IFNα2a et Adéfovir



Etude HIDIT-1 randomisée contrôlée, multicentrique internationale (Allemagne, Turquie, Roumanie, Grèce)

Wedemeyer H, NEJM 2011

Treatment of Hepatitis Delta With PEG-IFN α 2a: ~25% Sustained HDV RNA Clearance

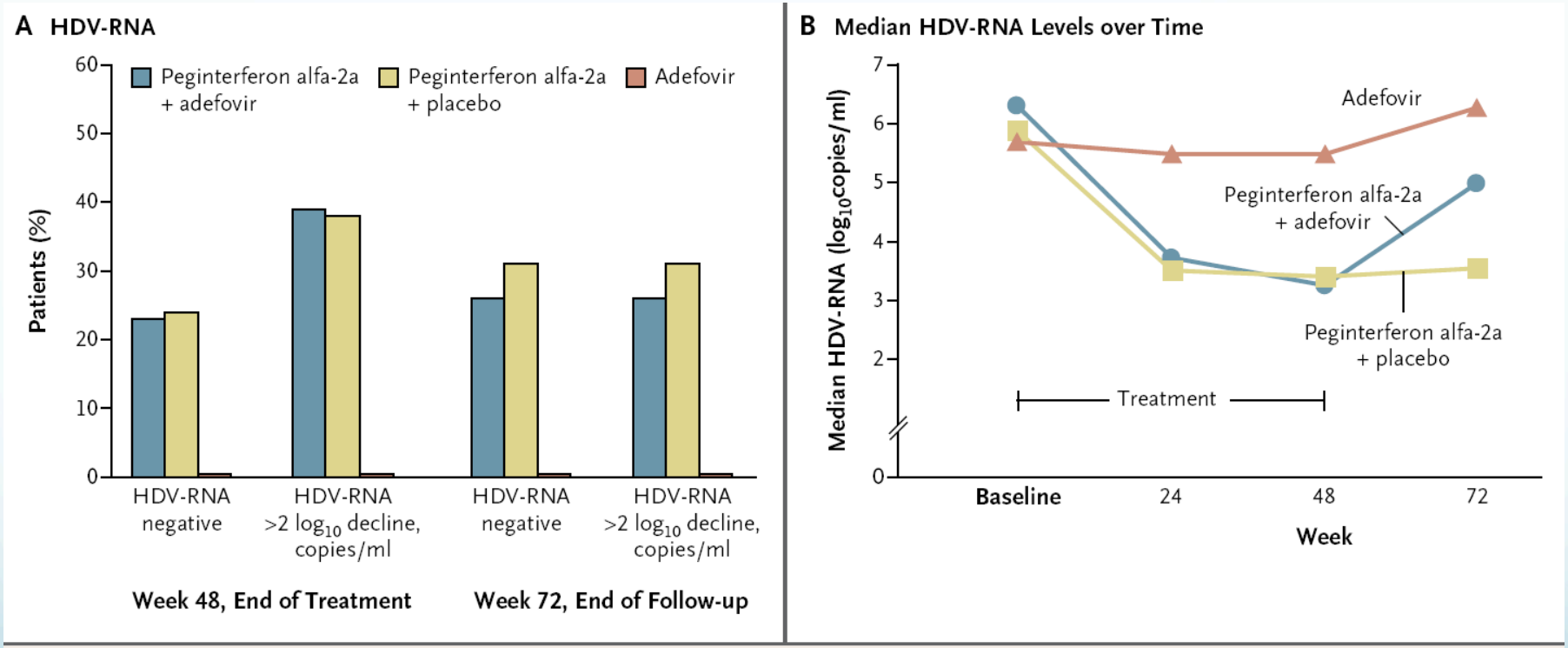
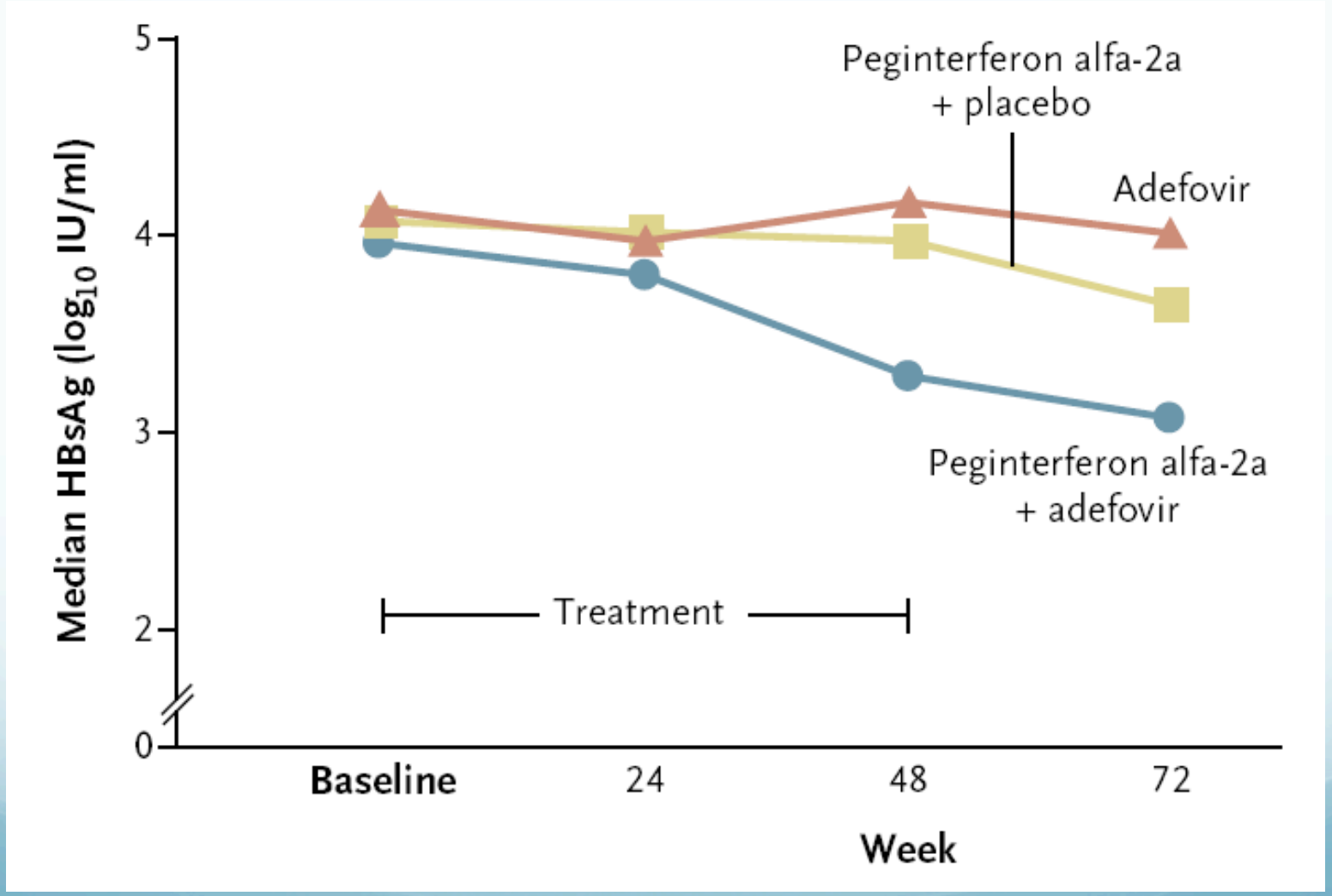


Figure 1. Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

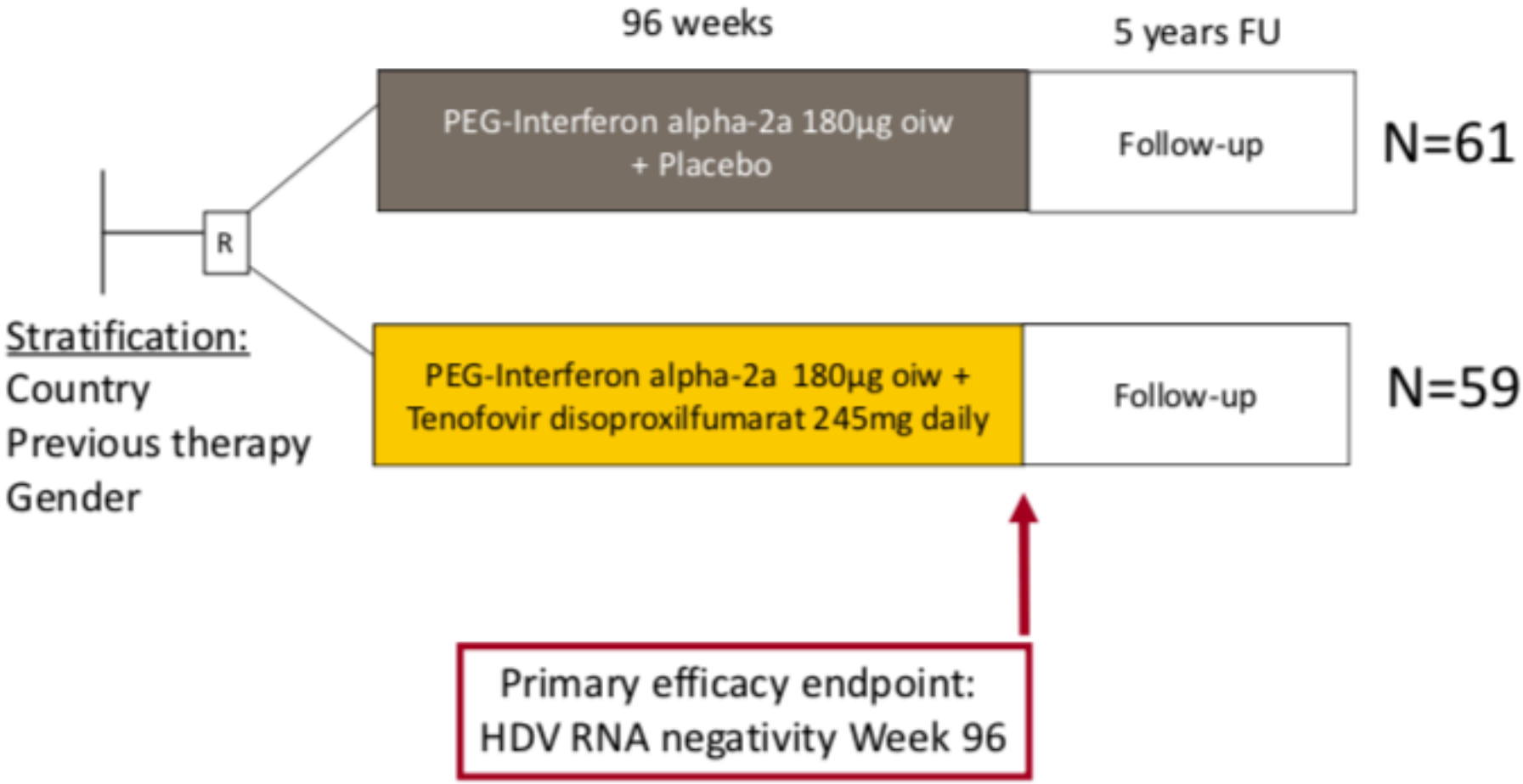
Wedemeyer H, et al. *N Engl J Med.* 2011 Jan 27;364(4):322-331.

PEG-IFN α 2a – Adefovir Combination Resulted in a More Pronounced HBsAg Suppression



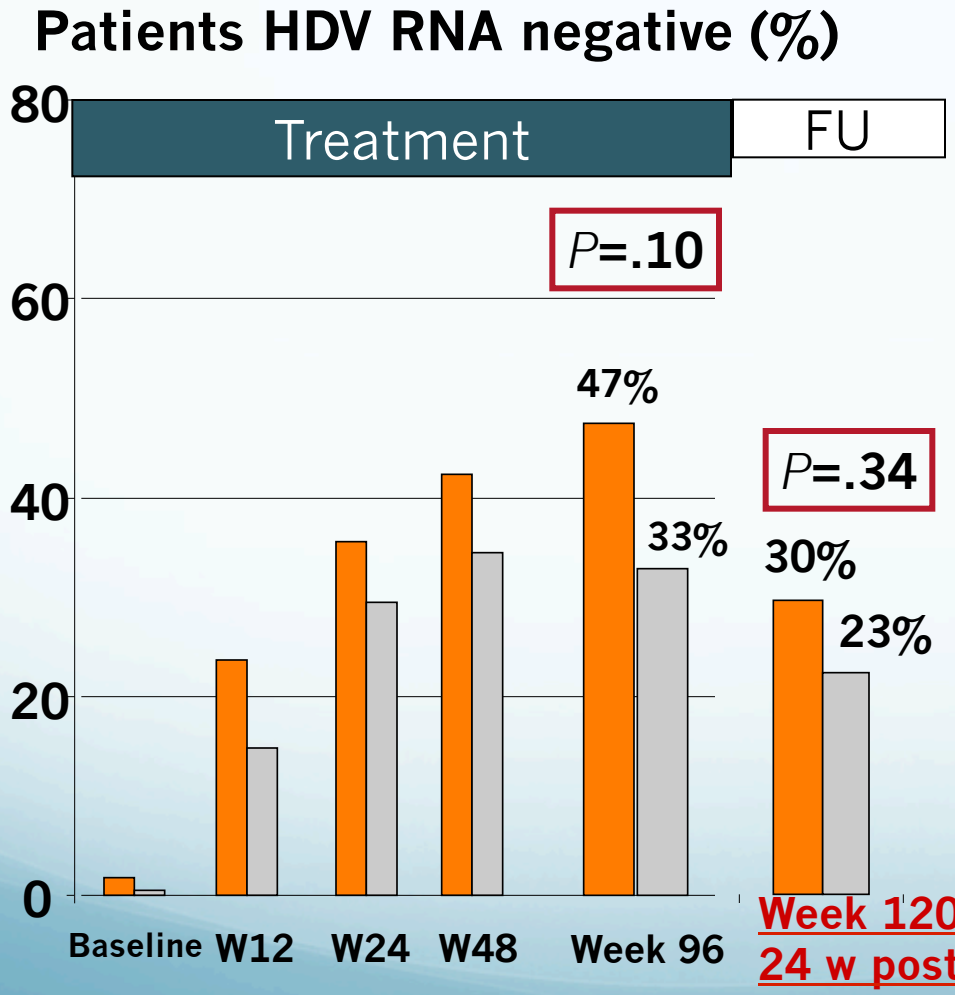
Wedemeyer, Yurdaydin, et al. *N Engl J Med.* 2011 Jan 27;364(4):322-331.

The Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2



HDV RNA Response Until Week 120

Intent-to-Treat Analysis



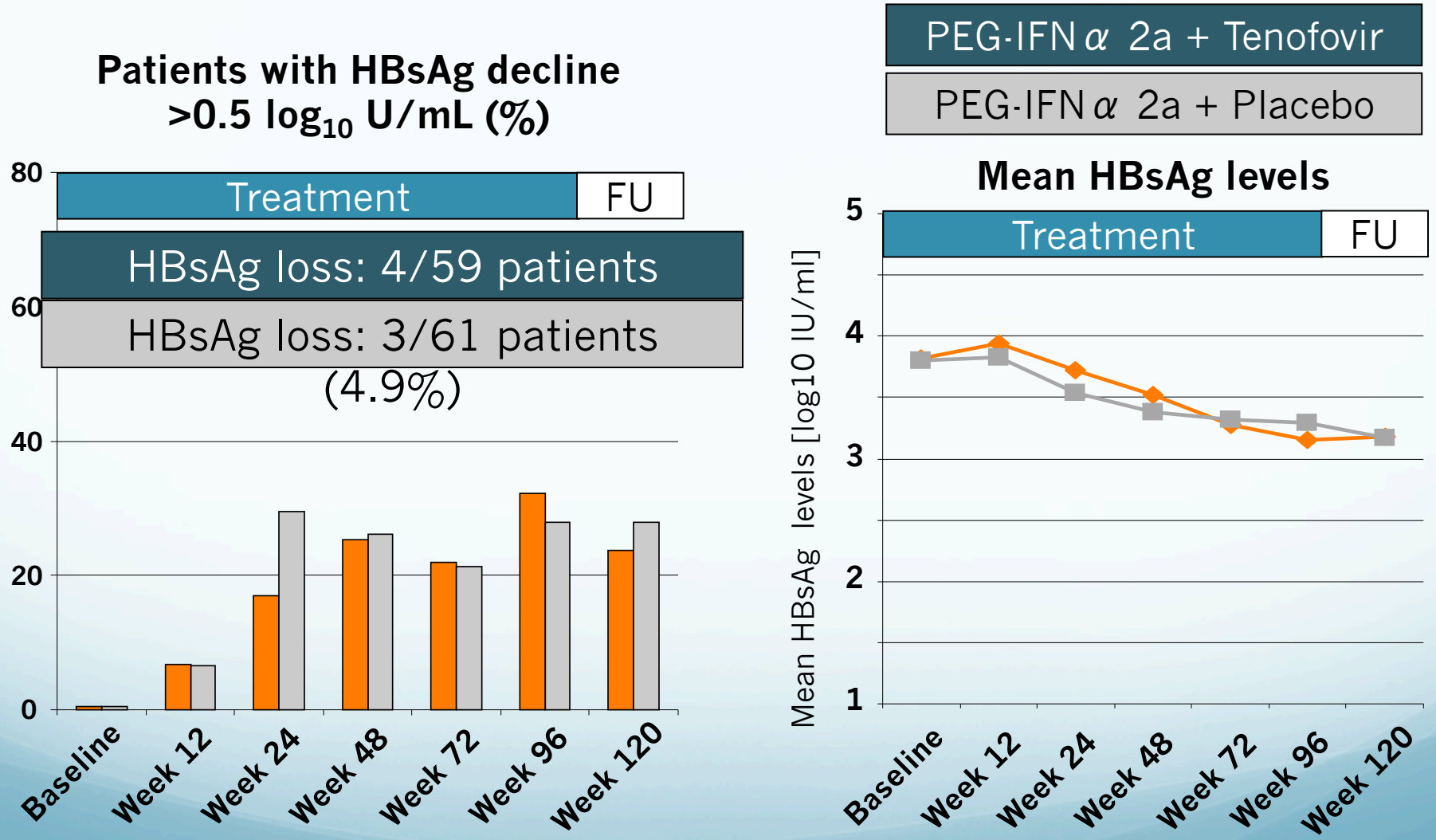
PEG-IFN α 2a + Tenofovir
PEG-IFN α 2a + Placebo

Relapse 11/25 (44%)
Relapse 8/20 (40%)

HDV RNA Clearance after Therapy
Neg post Tx, 1 patient
Neg post Tx, 3 patients

Wedemeyer, Yurdaydin, et al. EASL 2014.

HBsAg Response Until Week 120
Intent-to-Treat Analysis



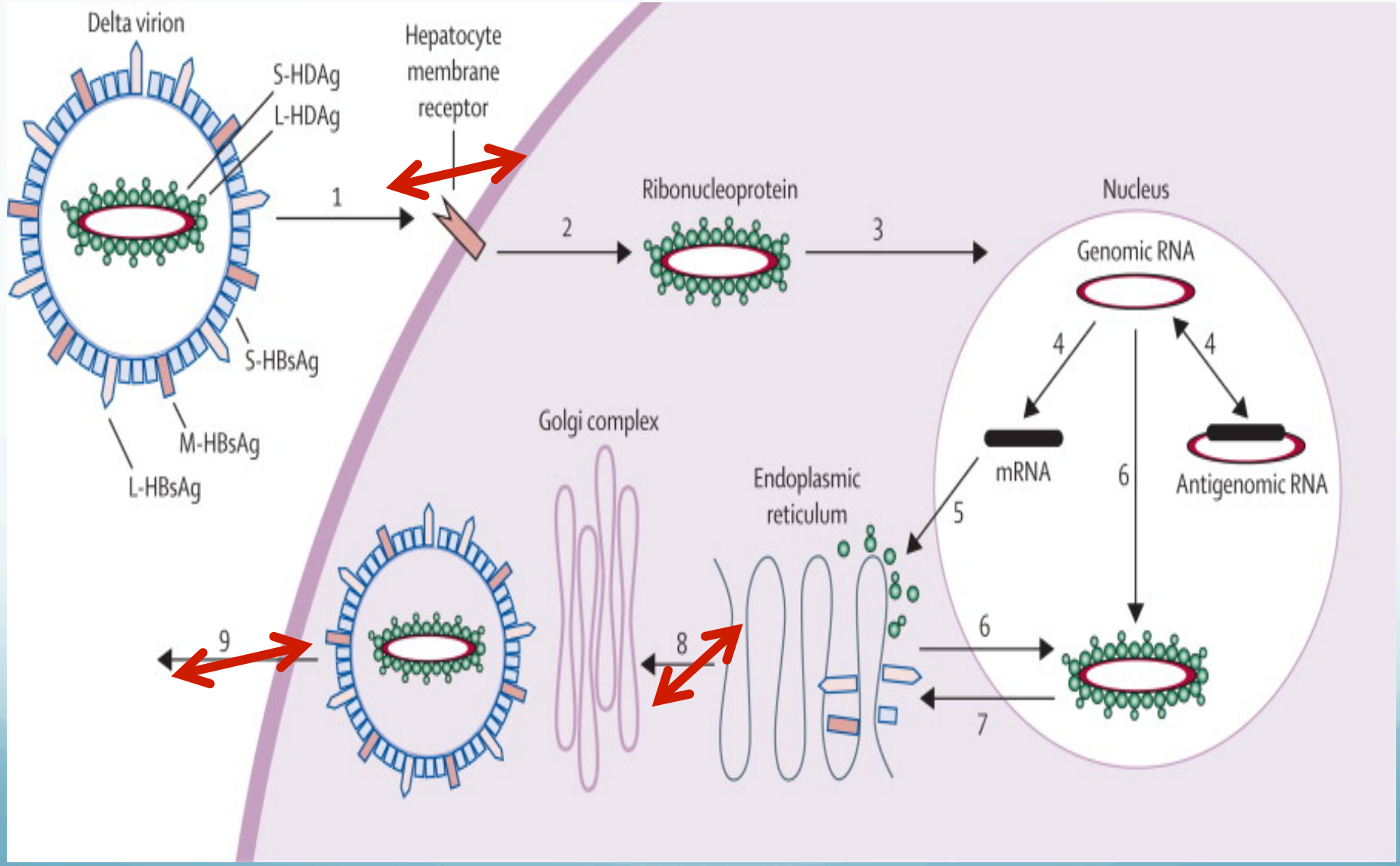
Wedemeyer, Yurdaydin, et al. EASL 2014.

Eiger Announces Positive Phase 2 Interim 24-Week Data with Pegylated Interferon Lambda in Hepatitis Delta Virus (HDV) Infection at the American Association for the Study of Liver Diseases (AASLD) Meeting

A PHASE 2 RANDOMIZED CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF PEGYLATED INTERFERON LAMBDA MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION: INTERIM RESULTS FROM THE LIMT HDV STUDY

interim analysis indicates that weekly Lambda-120 μg or 180 μg-has antiviral activity against HDV, with some patients already becoming PCR-negative by Week 8 of therapy. Overall, Lambda was well-tolerated, and hyperbilirubinemia events in three patients responded to dose reduction or discontinuation. Week 24 data is presented.

Cycle de réplication du VHD

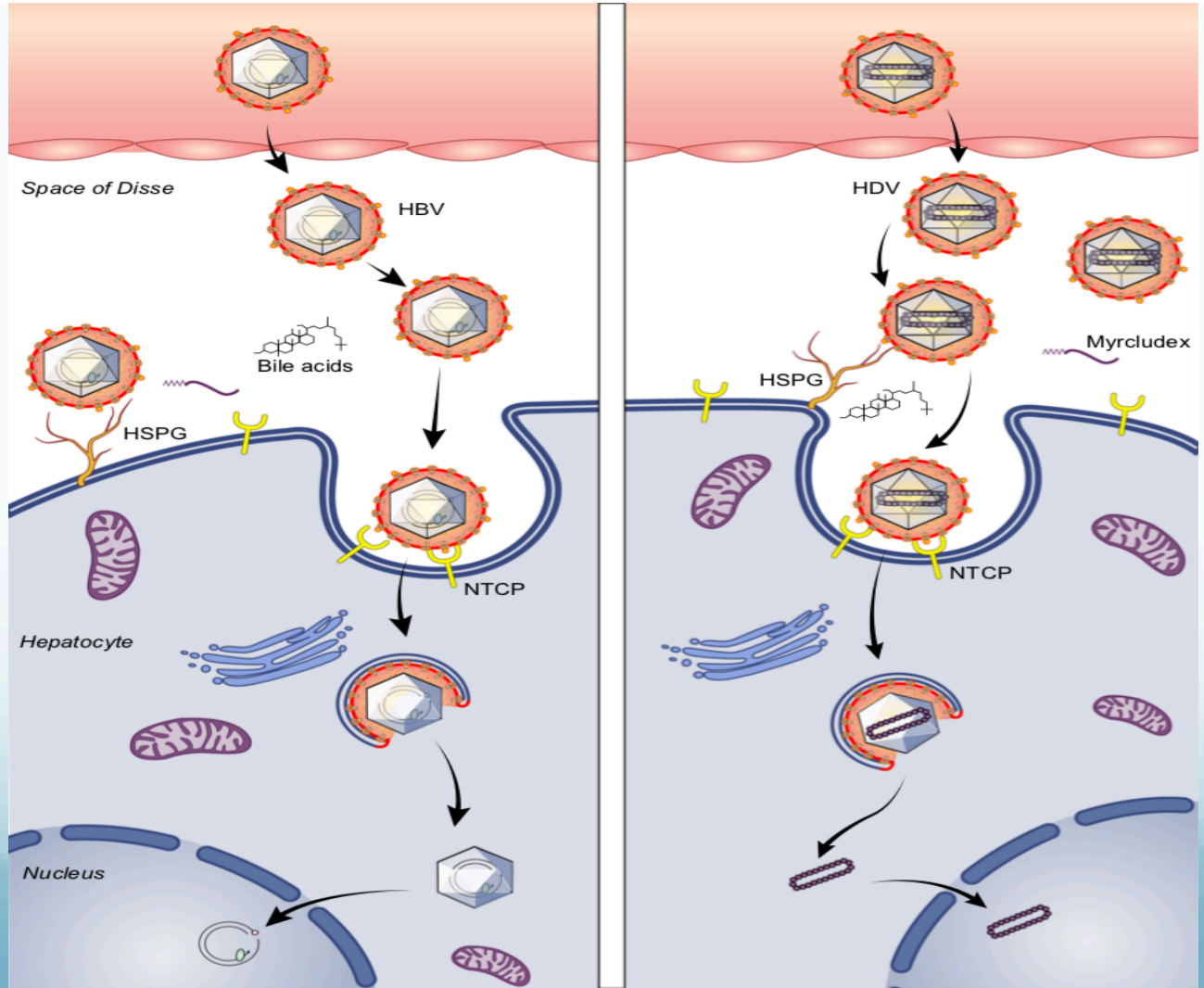


EASL | JOURNAL OF HEPATOLOGY

Journal of Hepatology **2016** vol. 64 | S32–S40

Entry of hepatitis B and hepatitis D virus into hepatocytes: Basic insights and clinical implications

Wenhui Li[1,*], Stephan Urban[2,3,*]

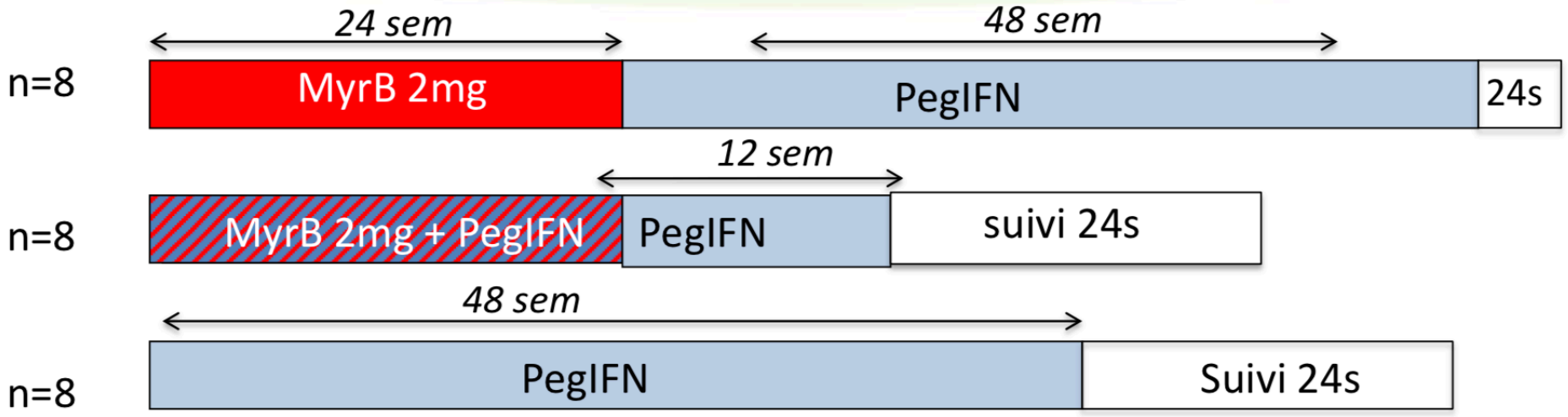


A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B

Patient Population	Treatment Arms	Endpoints
Cohort A Chronic HBV HBeAg negative HBV DNA > 2000 IU/mL No Cirrhosis • N=40	• Myr B, daily SC at 0.5, 1, 2, 5&10 mg • 12 wk treatment, with 12 wk follow-up (10 mg received 24 wk of treatment)	• Safety and tolerability • Efficacy (ALT, HBV DNA, HBsAg) • PK • Immunogenicity • Bile salt elevations
Cohort B Chronic HDV 12.5% cirrhosis • N=24	• 24 wk of Myr B, daily SC at 2 mg, followed by 48 wk Peg-IFN • 24 wk of Myr B added to 48 wk Peg-IFN • 48 wk Peg-IFN alone	• Safety and tolerability • Efficacy (ALT, HDV DNA) • PK • Immunogenicity • Bile salt elevations

Urban S et al. AASLD 2014;LB20

Etude pilote Myrcludex B (n=24 VHD+)

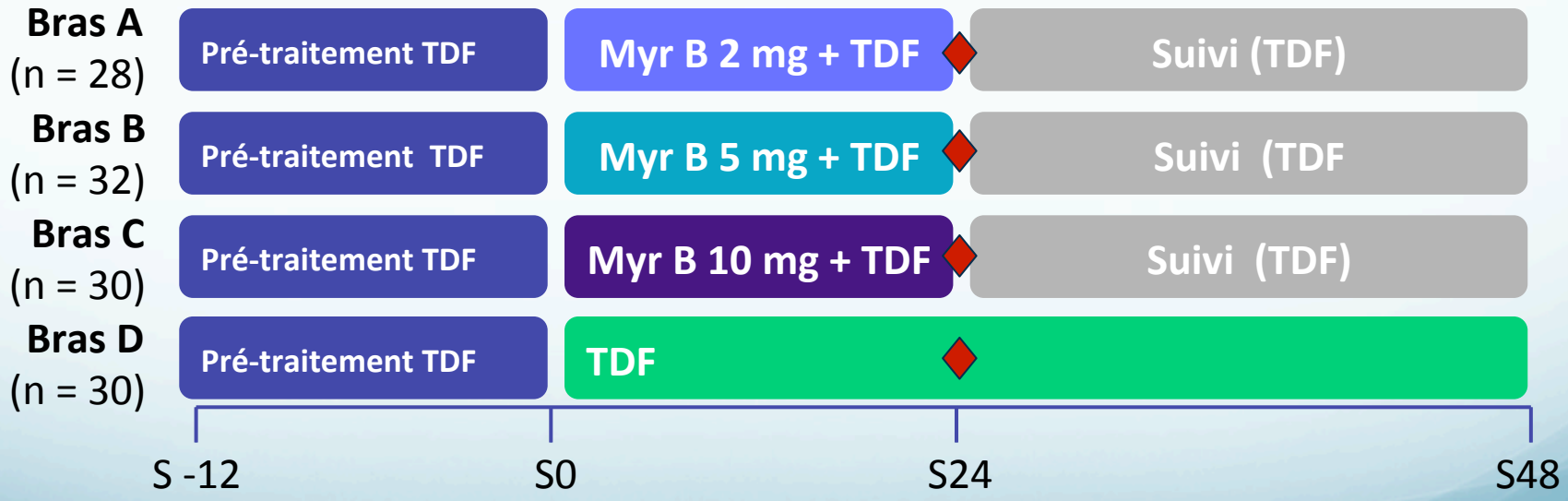


- Bonne tolérance Myrcludex 2mg seul ou avec IFNα
- ↓ ARN VHD > 1log chez 6/7 patients sous mono et 7/7 sous Myrcludex/IFNα
- Négativation ARN VHD chez 5 patients sous Myrcludex/IFN
- Pas d'effet sur taux d'AgHBs

Traitement prolongé par Myrcludex seul ou avec Peg-IFNα peut éliminer hépatocytes infectés par VHD chez les coinfectés VHB-VHD

Hépatite Delta : Myrcludex B + TDF *(1)*

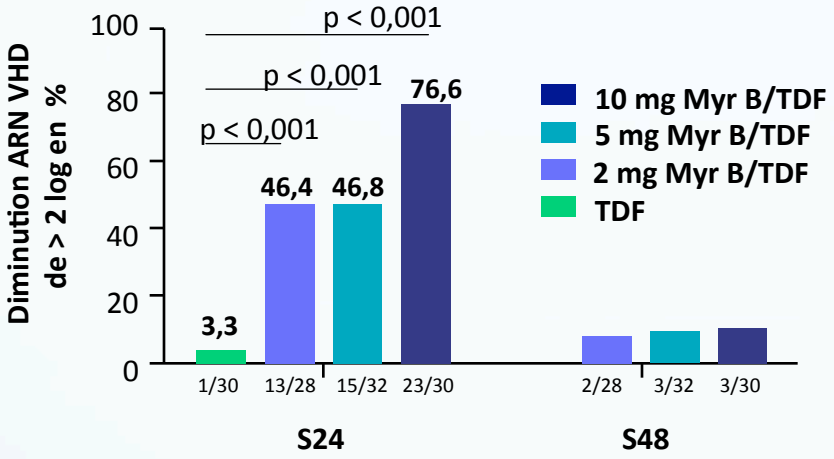
- Myrcludex B : inhibiteur d'entrée du VHB
- Etude phase 2b : 120 patients, 50 % : F4



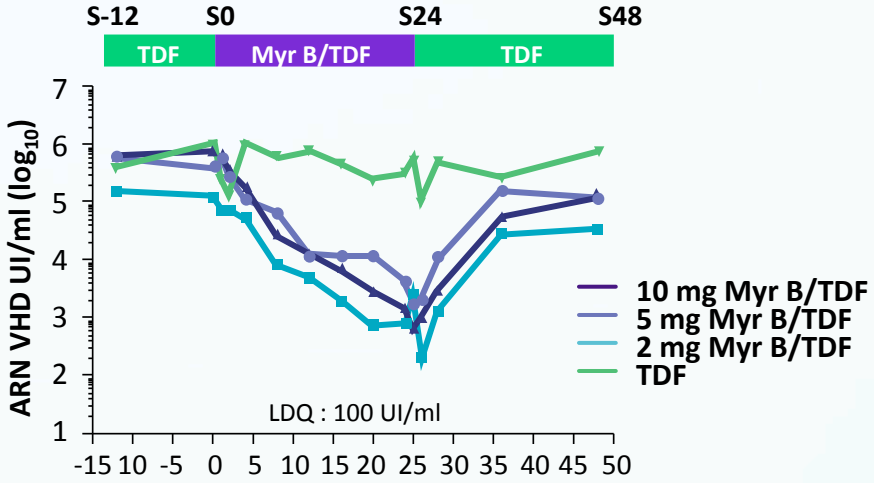
Wedemeyer H, Allemagne, EASL 2018, Abs. GS-005 actualisé

Hépatite Delta : Myrcludex B + TDF (2)

Objectif principal : diminution de 2 log ARN VHD ou négativation ARN VHD à S24 et S48



ARN VHD médian en fonction du temps



Modification ARN VHD en log_{10} UI/ml vs JO

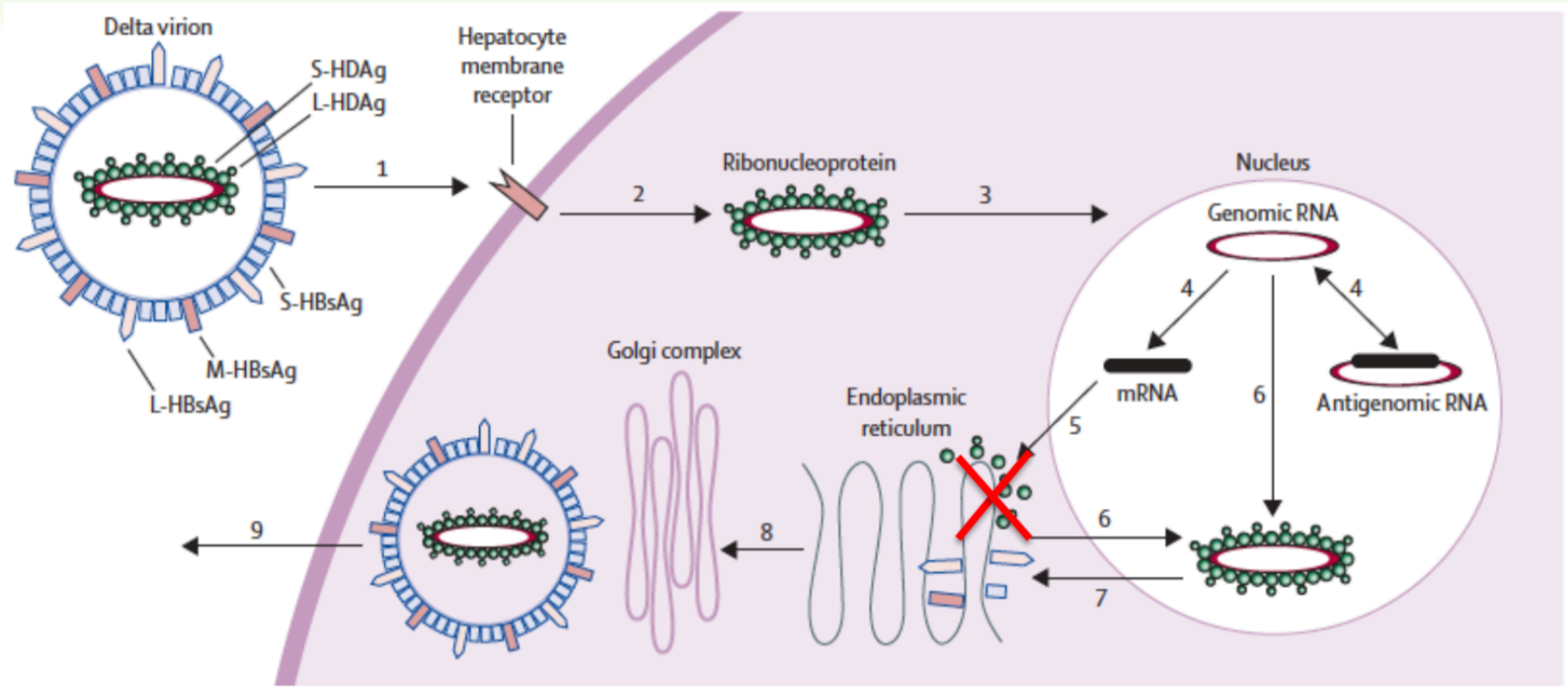
Myr B 2 mg : -1,75	Myr B 10 mg : -2,70
Myr B 5 mg : -1,60	TDF : -0,18

- Amélioration des ALAT
- Pas de modification titre AgHBs
- Augmentation des acides biliaires sans prurit
- Un patient avec ARN VHD indétectable

➔ **Résultats encourageants mais les modélisations suggèrent qu'une durée de 2-3 ans est nécessaire pour négativer le VHD**

Wedemeyer H, Allemagne, EASL 2018, Abs. GS-005 actualisé

Inhibiteur d'assemblage du VHD: Lonafarnib



Hughes SA, Lancet 2011

- Inhibe farnesylation de grande protéine Delta
- bloque assemblage et empaquetage particules virales

Bordier B, JCI 2003

Etude Lonafarnib et VHD (NIH)

Etude phase 2a, double aveugle, randomisée contre placebo

Groupe 1: Lonafarnib 100mg BID, traités(n=6); placebo(n=2)

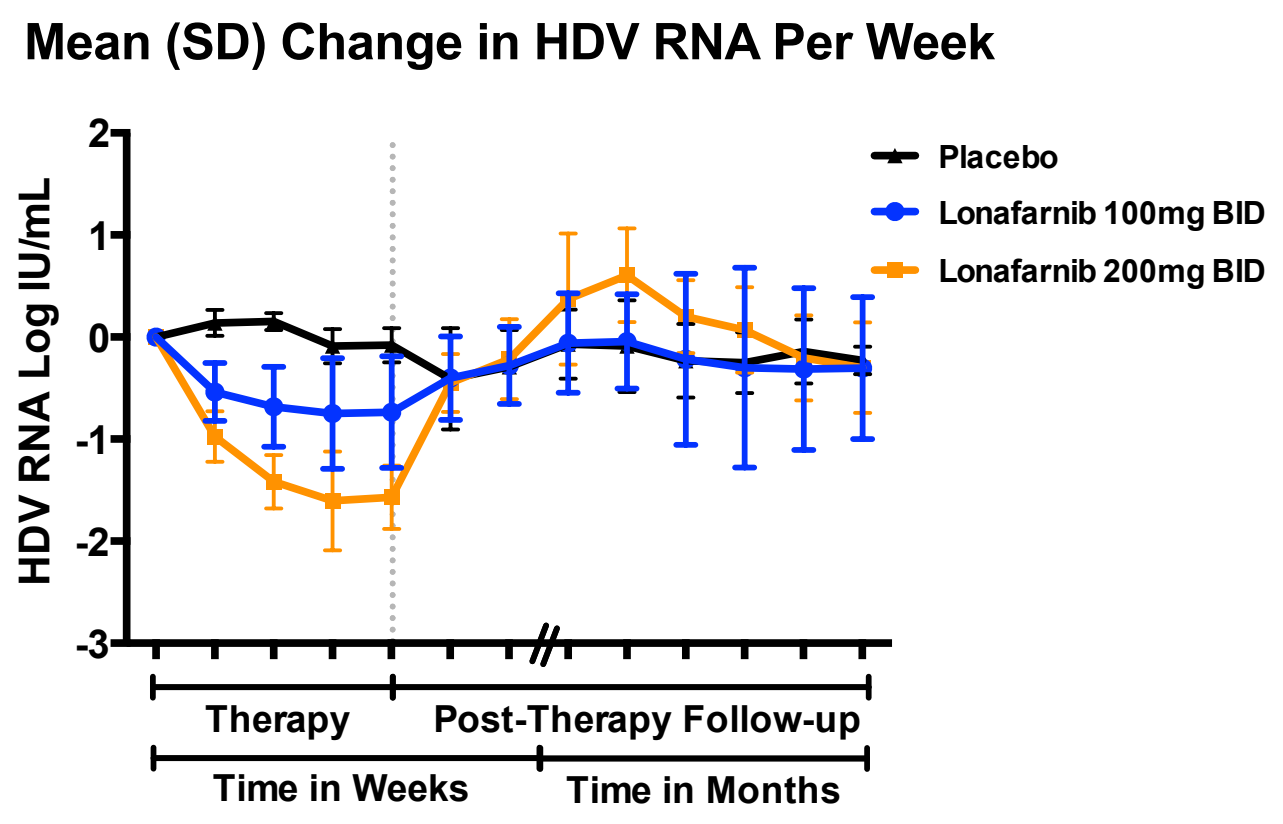
28j traitement; 6 mois de suivi

Groupe 2: Lonafarnib 200mg BID, traités(n=6); placebo(n=2)

28j traitement; 6 mois de suivi

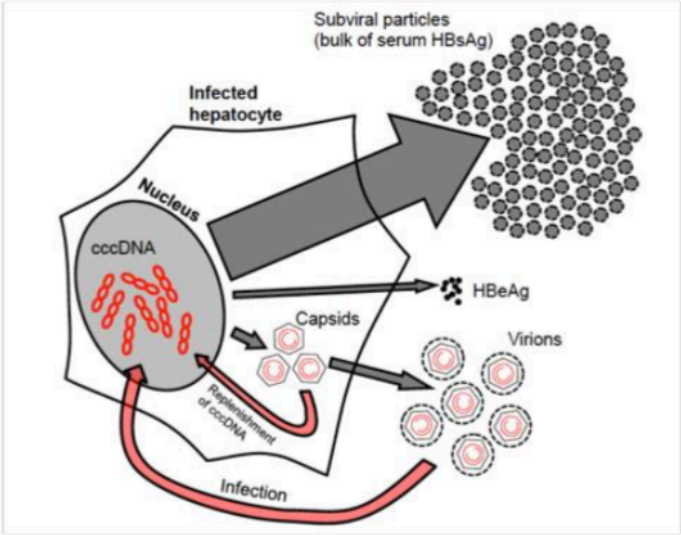
Koh C et al, Lancet Infect Dis 2015

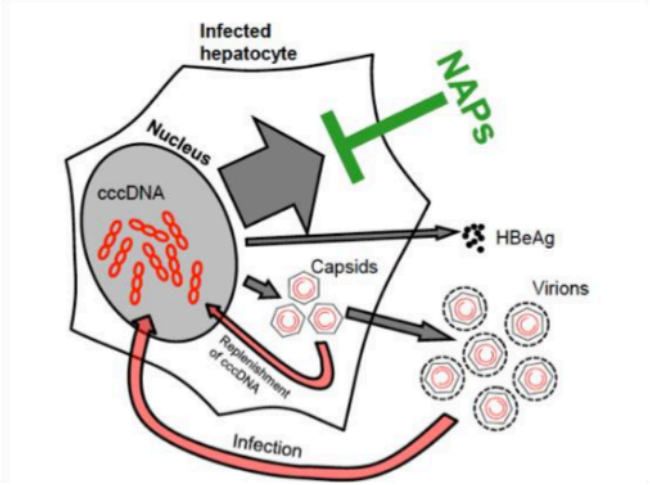
Treatment of CDH with Lonafarnib



Koh C et al, Lancet Infect Dis 2015

Polymères d'acides nucléiques (NAPs)





2 mécanismes anti-VHB et anti-VHD:

- bloque l'entrée VHB-VHD
- bloque formation particules sous-virales (PSV)

d'ou ↓ production de VHD derivée de l'assemblage PSV

d'ou ↓ AgHBs sérique d'ou restauration immune et ↑ anti-HBs

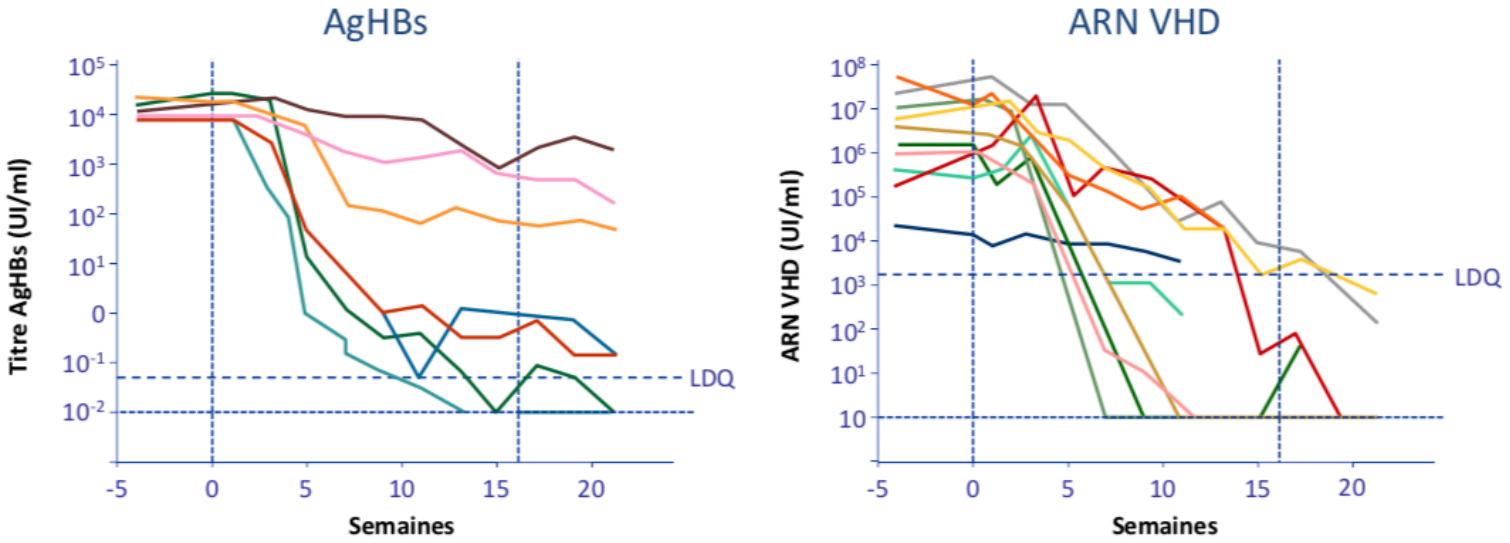
Réduction AgHBS et ARN HDV par le NAP REP 2139 chez patients caucasiens VHD+ (n=12)

REP 2139-Ca
500 mg i.v. 1x/s 15 sem.

REP 2139-Ca
250 mg i.v. 1x/s 15 sem.

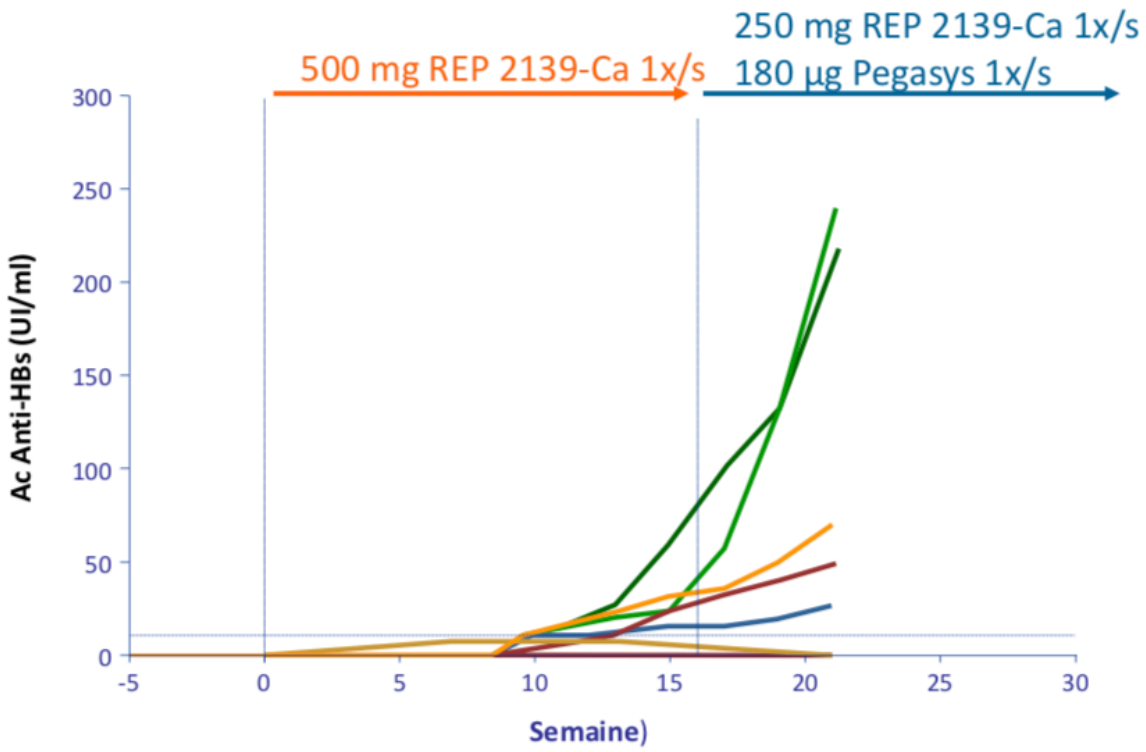
PEG IFN-α-2a (Pegasys)
180 µg 1x/s SC 48 sem.

suivi
4, 12 et 24 semaines



Bazinet M et al, abs LO2,EASL 2015et AASLD 2015; Replicor Inc Montréal,

NAP REP 2139:apparition des anticorps anti-HBs



Bazinet M et al, abs LO2,EASL 2015

CONCLUSION

- **Dépister VHD chez tout patient AgHBs+**
- Un seul traitement en 2018-2019: Peg-IFN, décevant
- Plusieurs essais cliniques encourageants:
  - Inhibiteur d'entrée: Myrcludex B
  - Inhibiteur d'assemblage: Lonafarnib
  - Polymères Acides nucléiques: NAPs
- **Meilleur traitement: Vaccination anti-VHB**