Delta hepatitis:
How to manage and optimize therapy?

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Delta hepatitis treatment in 2018

- Currently, **Peg-IFNα 180 µg/wk** is the only effective treatment for inhibiting HDV replication

- With disappointing outcome 6 months after the end of treatment :
  - HDV RNA is undetectable in only 25-30%,
  - HBsAg loss in less than 10%

- With missing informations:
  - appropriate predictive response factors
  - criteria for treatment interruption

Mr. K, 30 yrs old

- Born in Mali, lives in France since 2015
  No previous medical or surgical history
  No alcohol or tobacco consumption
  No comorbidity, normal BMI of 24 kg/m2

- Admission for fever and vesicular cutaneous eruption caused by varicella infection. No other clinical anomalies

- **Laboratory tests**:
  ALT 3xN, AST 2xN ; platelet count 135 000/mm3 ; PT 60%
  No HIV or HCV antibodies
  HBsAg positive (3.2 log IU/ml); HBV genotype E, HBV DNA 4.4 log IU/ml Anti-HDV antibodies including IgM; HDV genotype 5; HDV RNA 8.6 log IU/ml

- **Fibroscan** 14kPa, **Fibrotest** score 0.76

In this African patient with HDV infection…

Which are the baseline predictive factors of response to treatment?

1. Age
2. Ethnic origin
3. HDV genotype
4. HDV RNA levels
5. HBsAg levels
6. Fibrosis score

Better prognosis and response in African HDV co-infected patients

	African	Non-African	*p*-value
Number	74	39	
Male (%)	54.1	46.2	0.437
Cirrhosis (%)	17.7	41.0	**0.012**

- Lower incidence of cirrhosis and decompensation

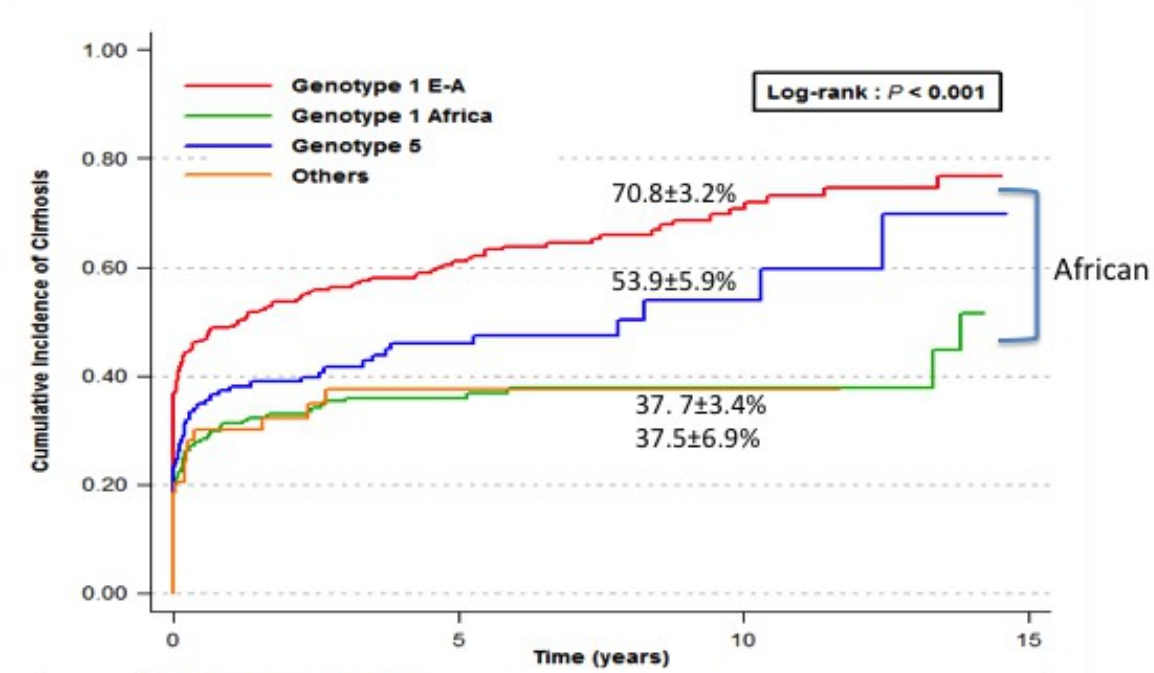
	Response *	Non-Response	*p*-value
Number	11	19	
Cirrhosis (%)	36.4	73.7	0.063
Origin (n)	10 African 1 non-African	6 African 11 non-African	**0.006**
Peg-IFN-Tx (weeks)	48.0	48.0	1

*HDV RNA undetectable 24wks post-treatment

- Better response to treatment compared to patients of non-African origin

Spaan M, abs 152; AASLD 201

Less cirrhosis and better response to treatment in African HDV co-infected patients



Twice less cirrhosis

	Response	Non-Response	P-value
Number	166	158	
Cirrhosis (%)	38.5	46.8	NS
Origin n (%)	107 African (57.5) 59 non-Afr. (42.7)	79 African 79 non-African	p < 0.01

Roulot D et al. J Hepatol 2015; 62:S541

Baseline predictors of response to treatment in HDV-coinfected patients

1. Age — *No impact*
2. Ethnic origin: — *Superior response in African patients*
3. HDV genotype: — *Possibly*
4. HDV RNA levels: — *Better if low RNA*
5. HBsAg levels: — *Better if low HBsAg*
6. Fibrosis score: — *Paradoxical better response in cirrhotic patients*

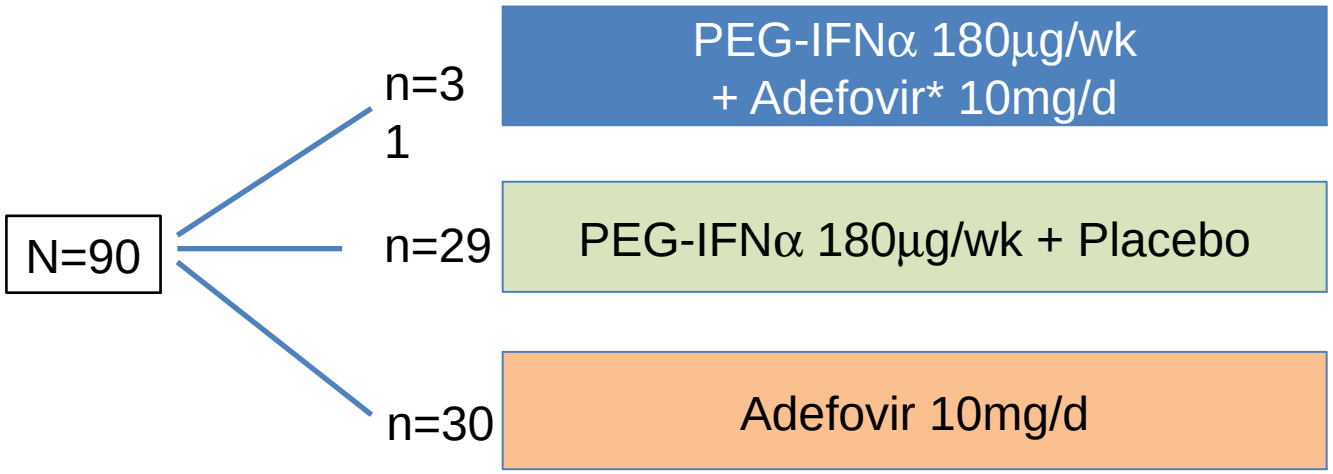
Wedemeyer H et al. J Hepatol 2014;60:S2-S3
Keskin O et al. Clin Gastroenterol Hepatol 2015
Niro GA et al.Aliment Pharmacol Ther 2016

Therapeutic options for this cirrhotic HDV co-infected patient

Among the following, what treatment would you choose?

1. Peg-IFNα 180 µg/wk for 48 weeks
2. Peg-IFNα 180 µg/wk for 96 weeks
3. Peg-IFNα 180 µg/wk plus a nucleos(t)ide analogue for 48 wks
4. Peg-IFNα 180 µg/wk plus a nucleos(t)ide analogue for 96 wks

Peg-IFNα plus Adefovir vs either drug alone (the HIDIT-1 study)

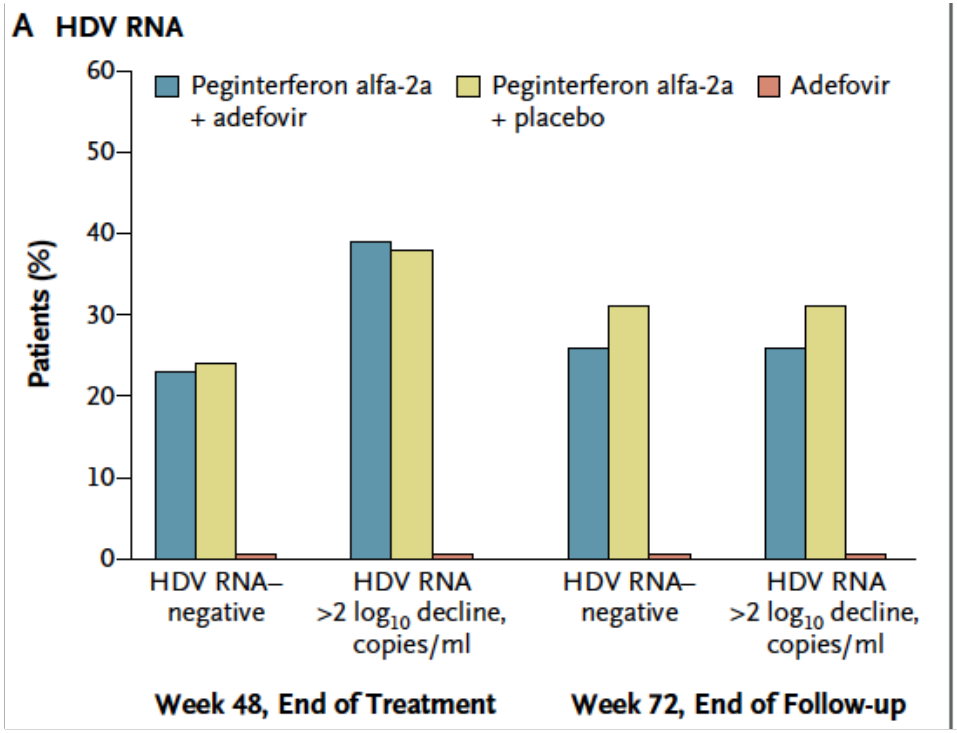


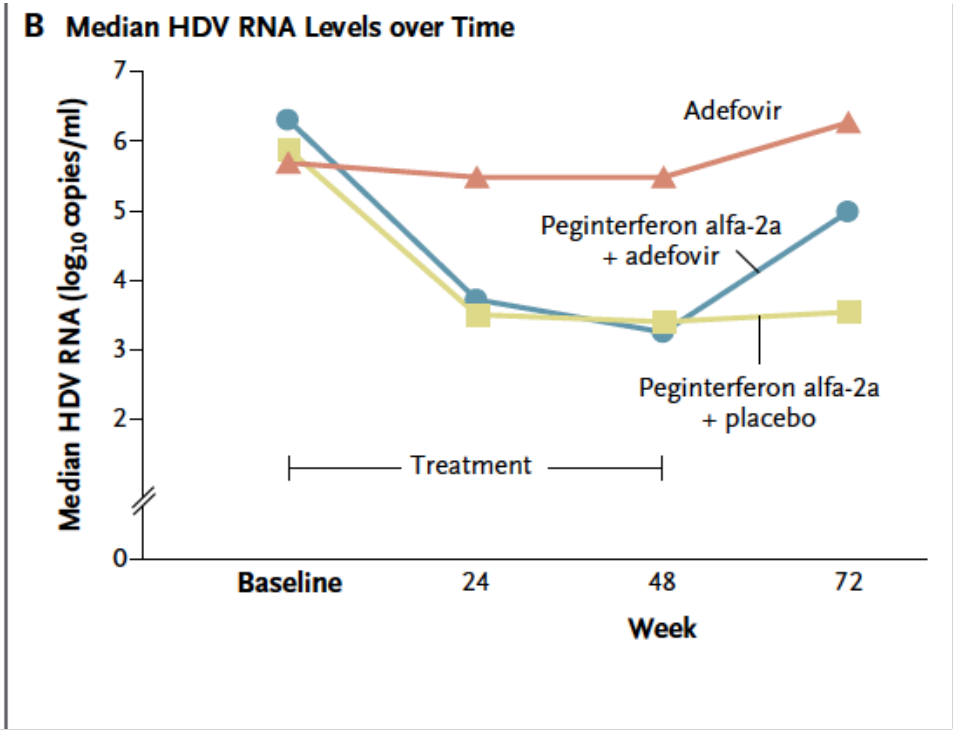
Treatment duration: 48 weeks
Follow-up: 5 years

(* To simultaneously target HBV)

Wedemeyer H et al , NEJM 2011

HIDIT-1 results: HDV RNA

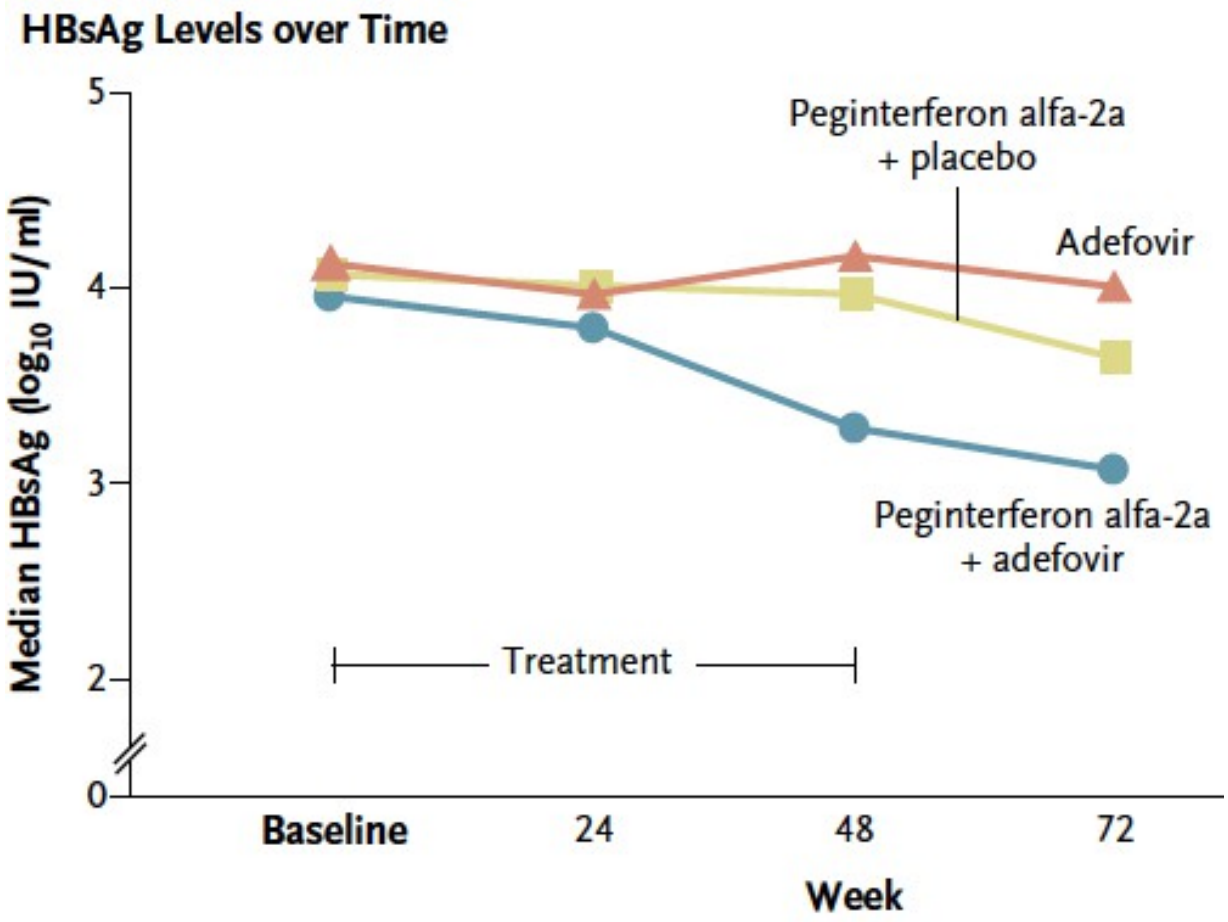




- ~**25%** of RNA HDV clearance whether or not Adefovir is present
- **Late HDV RNA clearance** 24wk after the end of Peg-IFNα treatment
- **No effect** of Adefovir on HDV RNA levels

Wedemeyer H, NEJM 2011

HIDIT-1 results: HBsAg

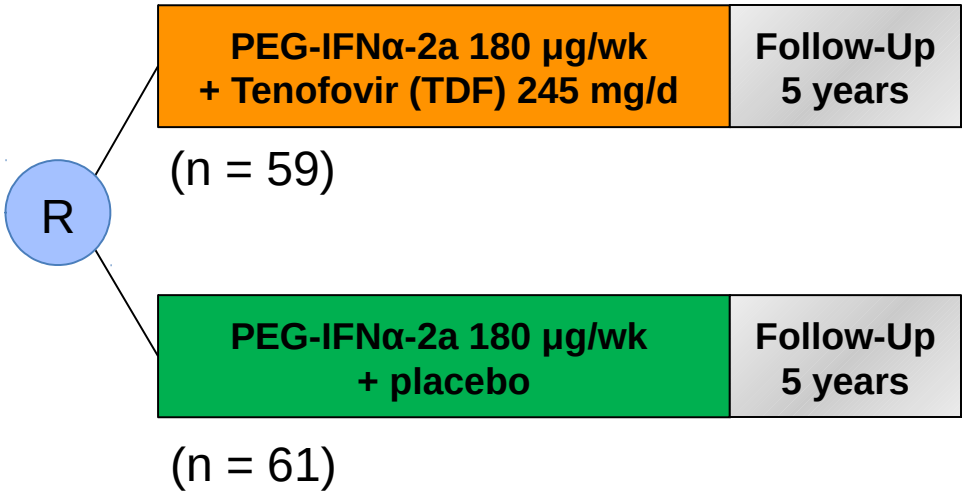


Larger decrease of HBsAg levels is observed for the Peg-IFNα and Adefovir combination compared to Peg-IFNα or Adefovir alone.

Wedemeyer H et al, NEJM 2011

Peg-IFNα + Tenofovir (TDF) compared to Peg-IFNα alone for 96 weeks (HIDIT-2 study)

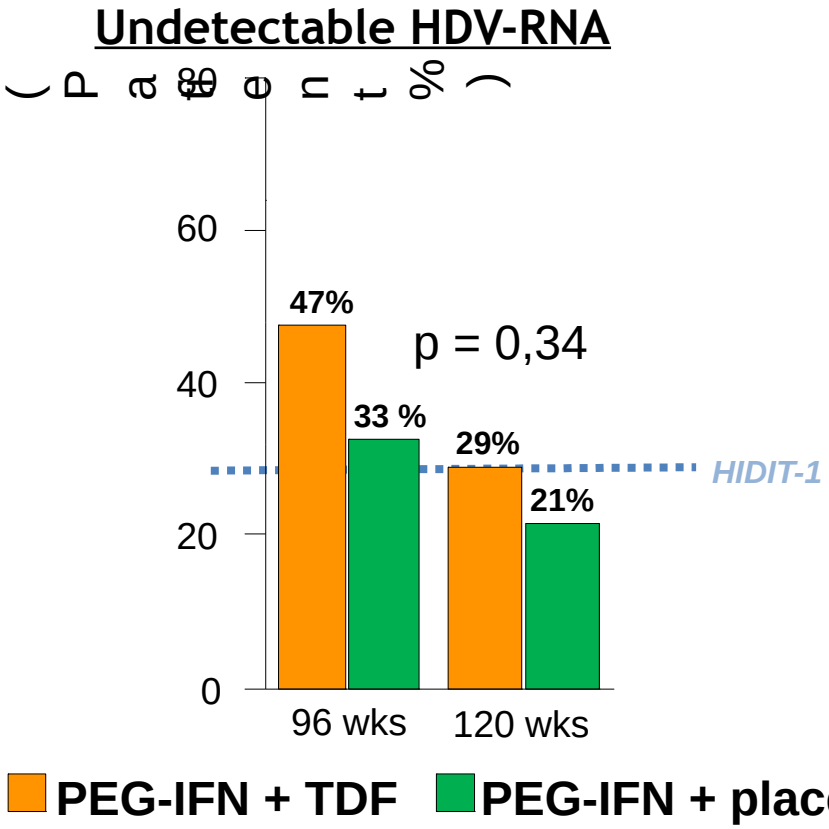
- 120 HDV co-infected patients (45% with cirrhosis) randomized in 2 arms



- A more potent antiviral drug and a longer duration (96 wks vs 48 wks)

HIDIT-2 main conclusions

Comparison of HDV-RNA at 96 and 120 weeks

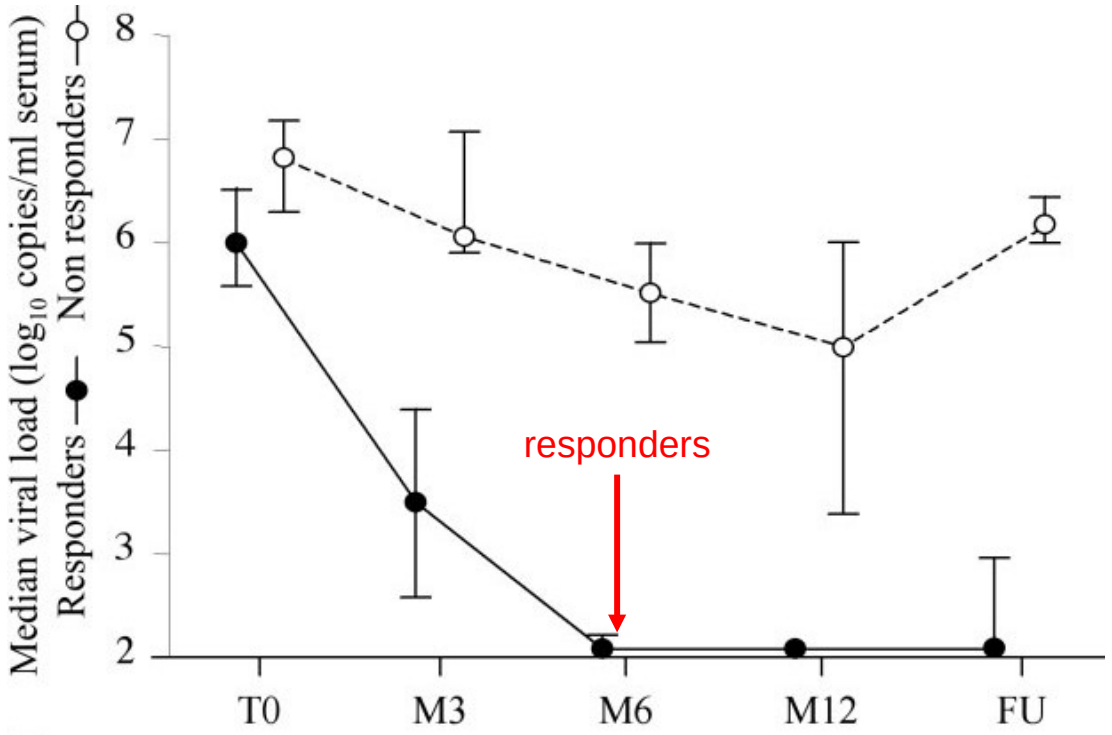


- Slightly better than HIDIT-1 (at 48 wk)
- The combination had no superior effect
- More than 1/3 of the patients **relapsed**
  6 months after the end of treatment

- A better response was observed in patients with cirrhosis.

Wedemeyer H et al. J Hepatol 2014;60:S2-S

1. Evolution of HDV RNA levels



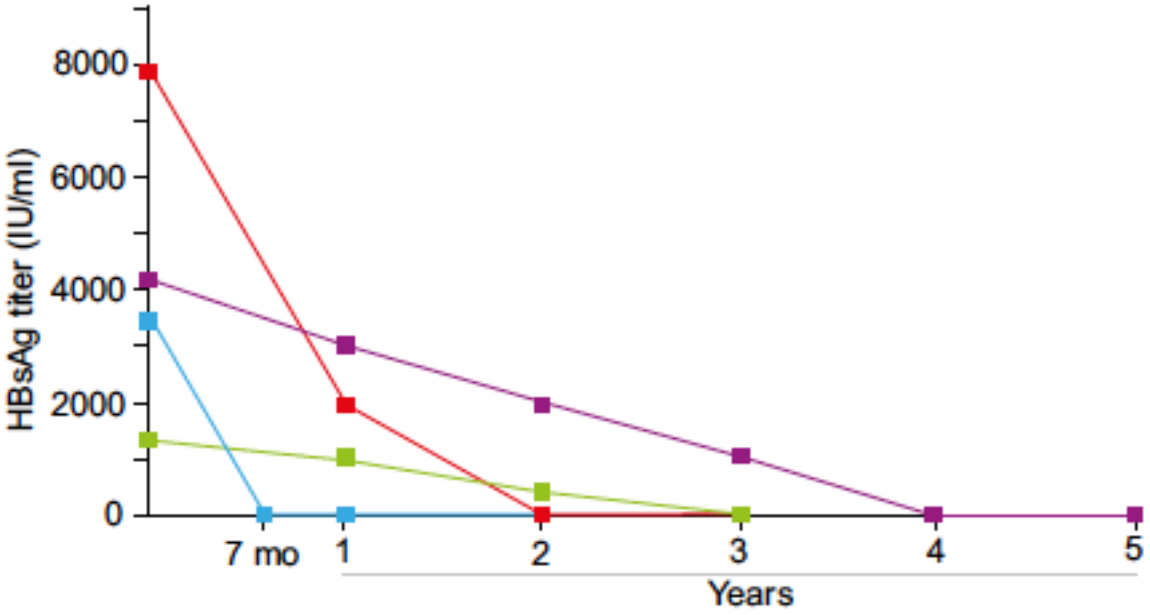
In patients treated for 48 weeks:

- Levels of HDV RNA was **the best** predictive factor for virologic response 6 months after treatment

Castelnau C et al. Hepatology 2006
Keskin O et al. Clin Gastroenterol Hepatol 2015

Predictive factors during treatment for sustained response (2)

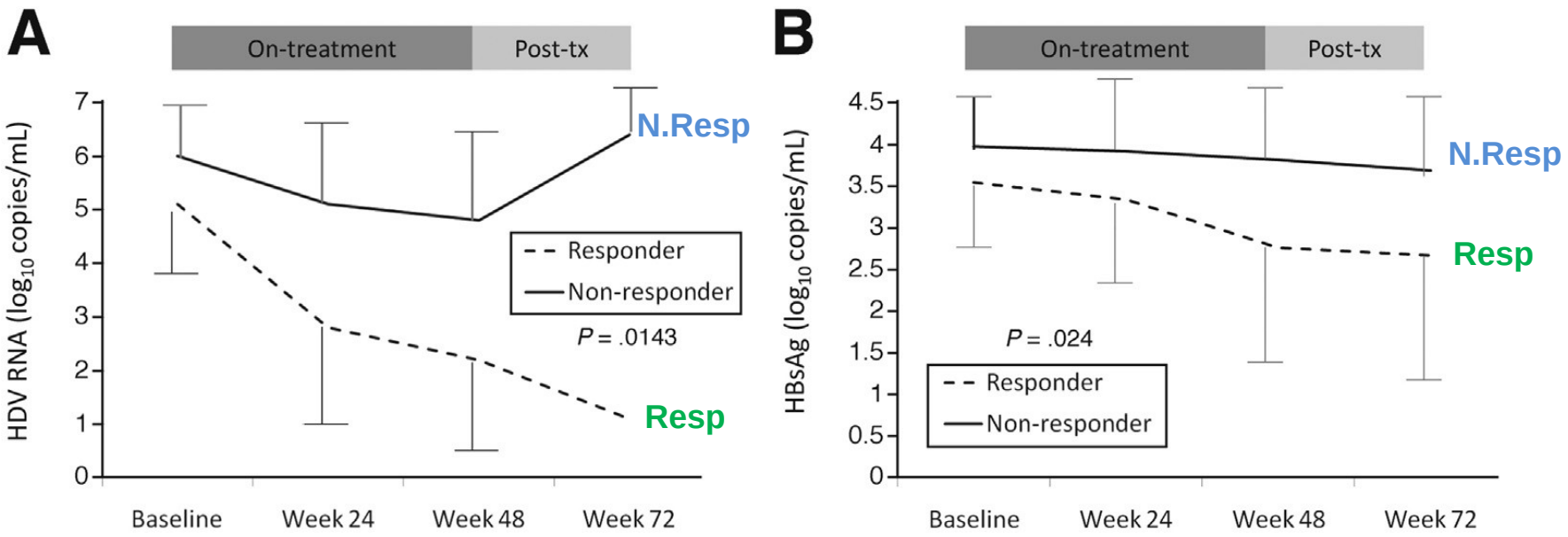
2. Evolution of HBsAg levels (n=4)



- The loss of HBs Ag was regarded as the optimal endpoint.
- Peg-IFNα was discontinued when HBsAg levels were undetectable
- HBsAg values remained stable 12 months after the end of the treatment

Ouzan D et al. J Hepatol 2013

Combination of HDV RNA and HBsAg decrease is the best predictor of response



- Significant difference in HDV RNA and HBsAg levels between **responders** and **non-responders**
- HBsAg <1000 IU at 6 months (M6) discriminates **responders** from **non-responders**
- Best predictor of response: combination of a reduction of HBsAg (0.105 log) and a reduction of HDV RNA (1.6log) from baseline to M6

Keskin O et al. Clin Gastroenterol Hepatol 2015
Niro GA et al.Aliment Pharmacol Ther 2016
Guedj J et al. Hepatology 2014

- **Starting treatment:**

  Peg IFNα (180 µg/wk) for at least 48 weeks
  Associate an analog only if active HBV DNA replication

  - **Monitoring every 3 months:**

    ALT, HDV RNA, HBV DNA, HBsAg

- **Discontinuation after 48 weeks if no response :**

  No decrease (or decrease < 2log) of HDV RNA
  No decrease (or decrease < 0.5 log) of HBsAg

  - **Continuation after 48 weeks**:

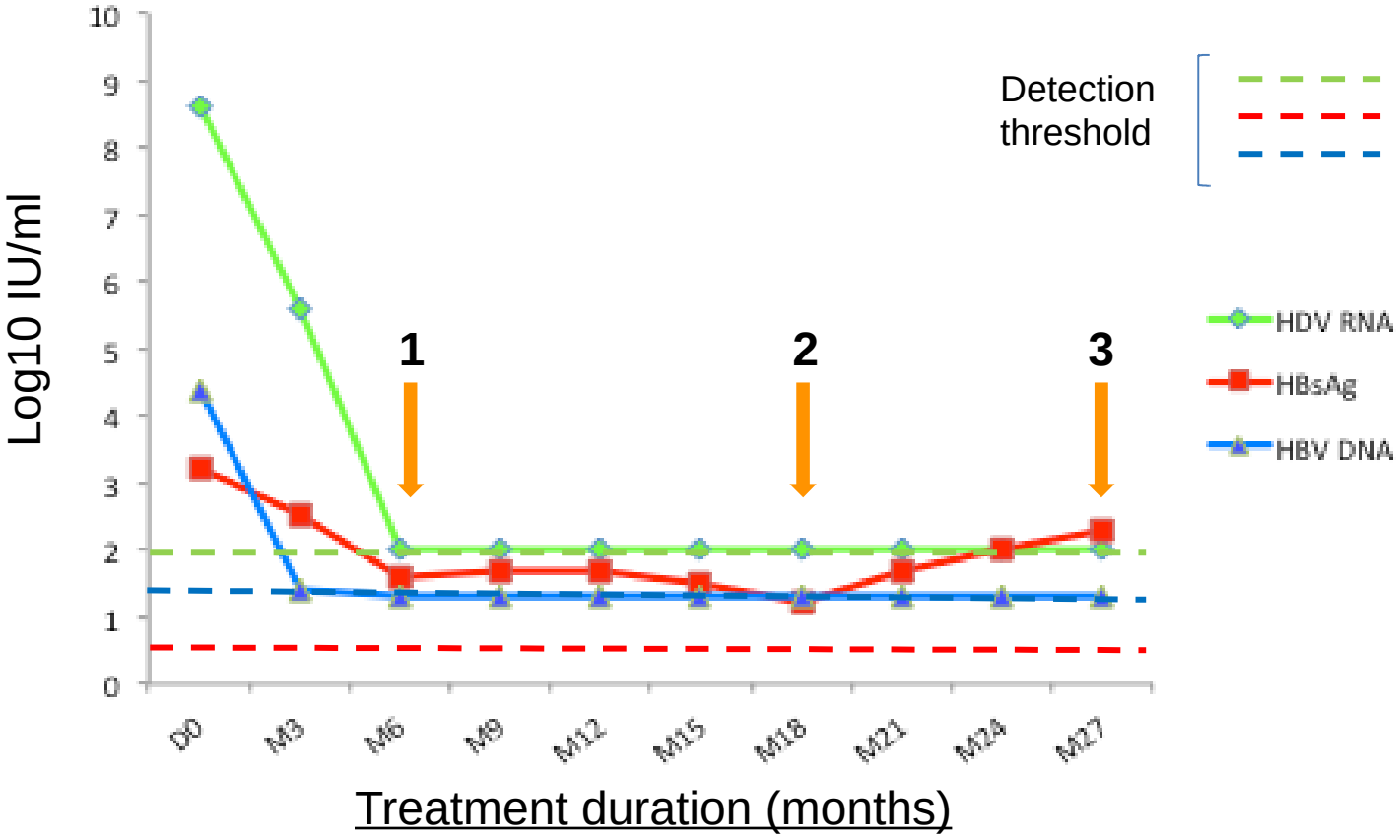
    Maintain as long as HDV RNA and/or HBsAg decrease
    Optimal endpoint: loss of HBsAg (rarely achieved!)

Therapeutic options for our cirrhotic HDV co-infected patient, Mr.K

1. Peg-IFNα 180 µg/wk for 48 weeks
2. Peg-IFNα 180 µg/wk for 96 weeks
3. Peg-IFNα 180 µg/wk plus a nucleos(t)ide analogue for 48 wks
4. Peg-IFNα 180 µg/wk plus a nucleos(t)ide analogue* for 96 wks

*Tenofovir

Evolution of Mr K. status under treatment with Peg-IFNα + Tenofovir*



1. Treatment continued because persistence AND slow decrease of HBsAg
2. Interruption was motivated by the occurrence of pulmonary tuberculosis
3. HDV RNA is still undetectable 9 months after the end of treatment