# What is the HBV cure rate with current therapy

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# Treatment of Hepatitis B

**1978**
**No Treatment**

**1991**
**Challenge**

**2018**
**Easy**

***40 years***

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# Antiviral therapy for Hepatitis B
# Primary aims achieved

- Past three decades
  - Conventional interferon
  - PEG interferon
  - Nucleotide analogues (seven)
    - Lamivudine, adefovir, entecavir, telbivudine, tenofovir, emtricitabine, TAF
- Have been shown to delay progression of cirrhosis
- Reduce (but not eliminate) the risk of HCC
- Improve survival
- Reduce the need for liver transplantation
- A cure is seldom achieved; cessation of treatment is possible in some

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# Current treatment options for hepatitis B

| | Peg-interferon | NAs |
|---|---|---|
| **Pros** | • Finite duration<br>• Higher sustained off-treatment response<br>• No resistance | • Potent viral inhibition<br>• Well tolerated<br>• Oral administration |
| **Cons** | • Side effects<br>• Injection<br>• Contraindications<br>• Sustained off-treatment responses in minority | • Long/indefinite treatment<br>• Long-term toxicity unknown<br>• Potential for resistance |

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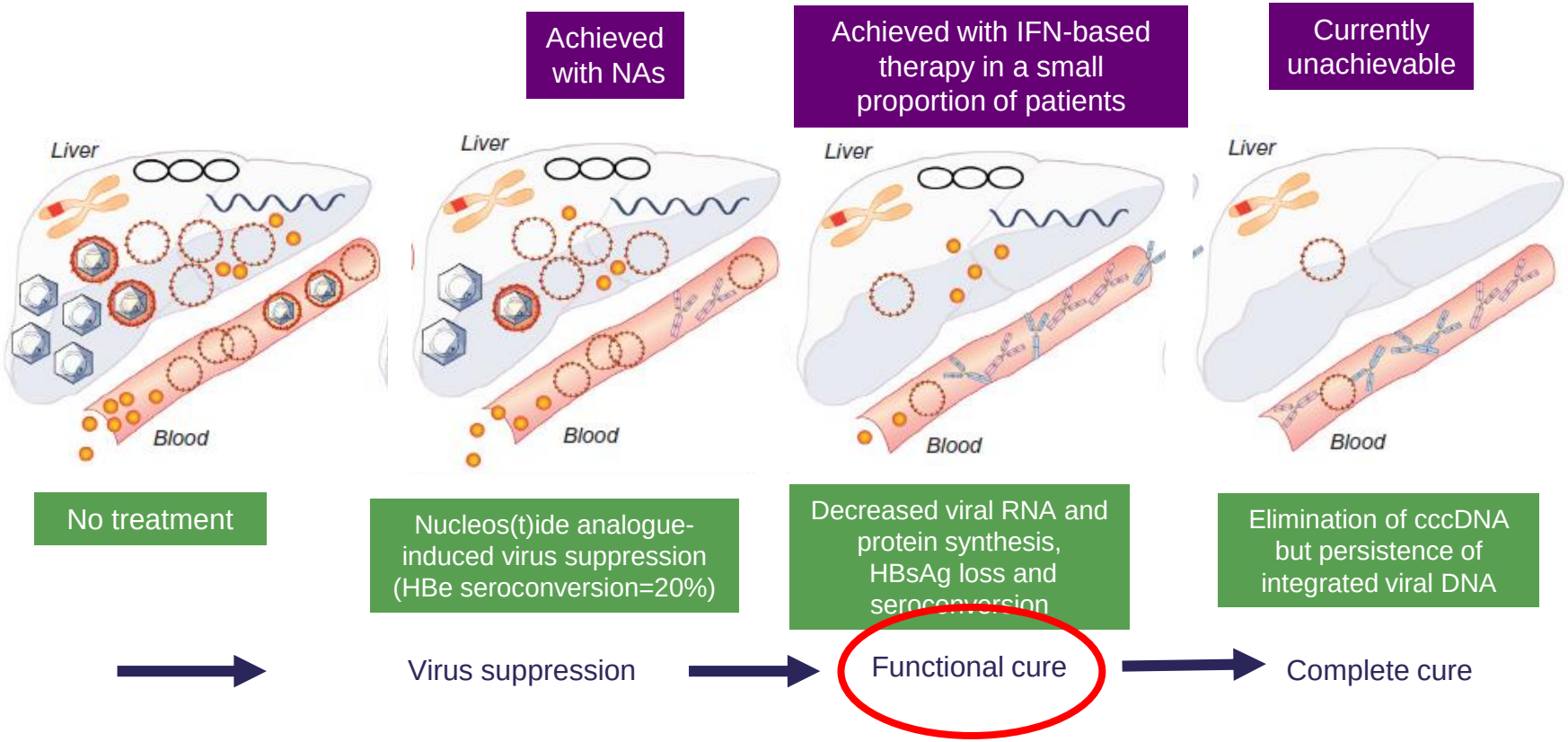
# What does cure of HBV mean? Several definitions are used




cccDNA: covalently closed circular DNA; HBeAg: hepatitis B 'e' antigen; HBsAg: hepatitis B surface antigen; IFN: interferon; NA: nucleos(t)ide analogue

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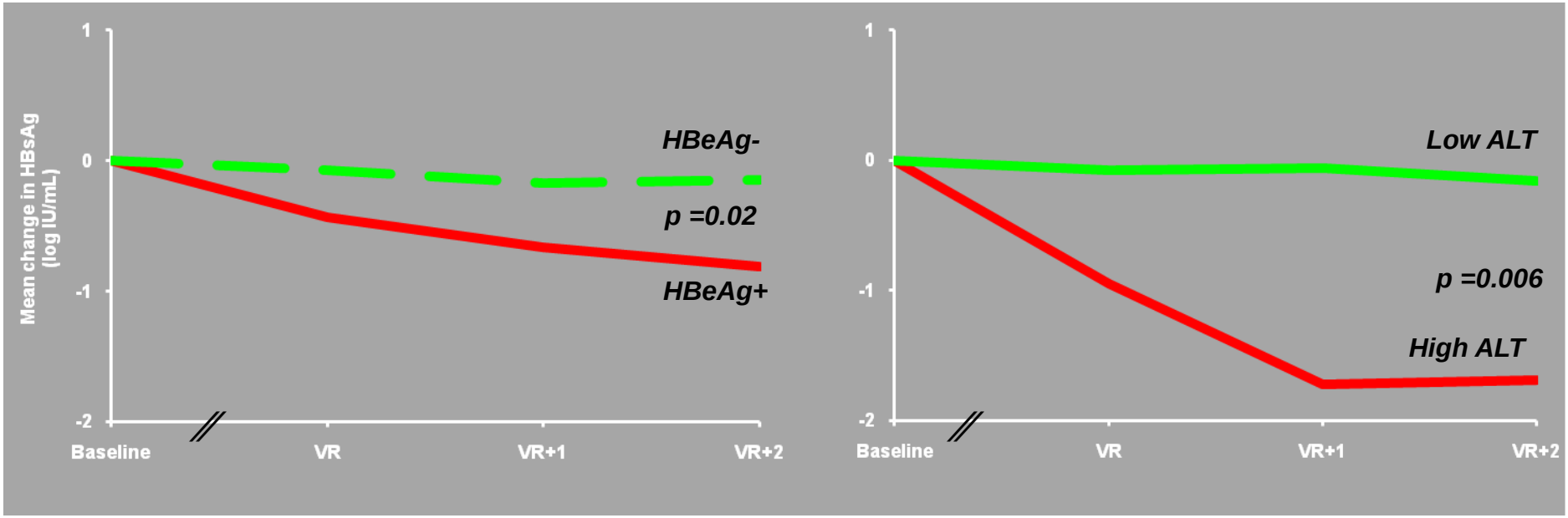
Durantel D, et al. J Hepatol 2016;64:S117–31

# HBsAg decline in patients treated with ETV or TDF need for host immune response

- *Patients treated with ETV or TDF who achieved a Virologic Response (VR)*
- *No difference in HBsAg decline between treatment regimens*




| | HBeAg-positive | HBeAg-negative | HBeAg-positive High ALT |
|---|---|---|---|
| Years to 1log decline* | 6.6 [1.7; 17.5] | 8.0 [0.5; 14.9] | 3.6 [1.3; 16.7] |
| Years to HBsAg loss* | 36.4 [9.6; 98.3] | 38.9 [1.3; 80.5] | 19.5 [7.3; 99.9] |

*Zoutendijk et al. J Inf Dis 2011*

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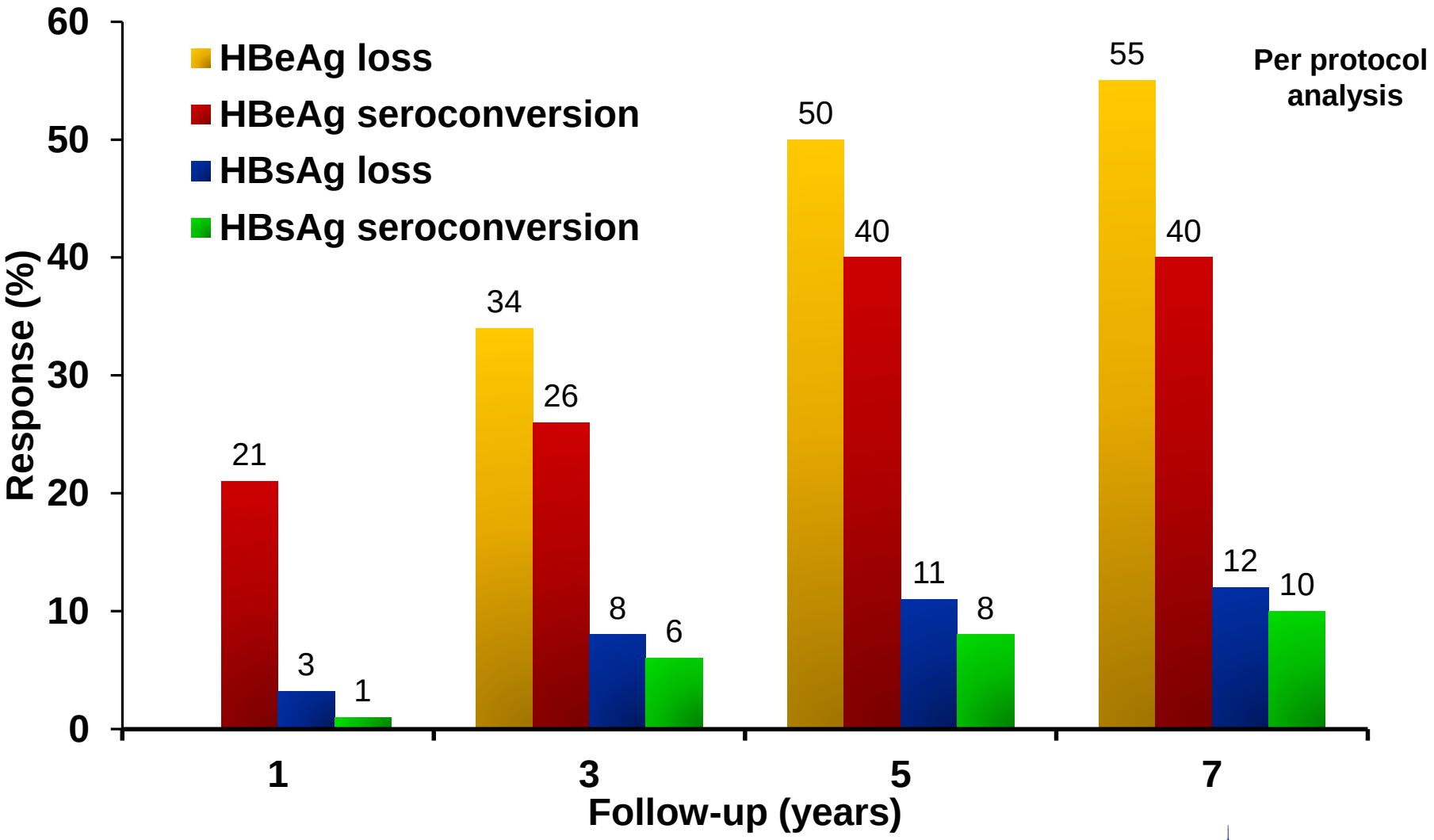
# Serological response to TDF therapy in HBeAg positive patients: 8 year follow-up




Marcellin et al, NEJM 2008; Heathcote et al, Gastro 2011 Snow-Lampart et al, Hepatology 2011; Marcellin et al, Lancet 2013; Buti et al, Dig Dis Sci 2015

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# TDF Treatment at Year 8: Primary and Secondary Endpoints

| % | HBeAg- n=375 | | HBeAg+ n=266 | |
|---|---|---|---|---|
| **HBV DNA** | **ITT[1]** | **Observed[2]** | **ITT** | **Observed** |
| <69 IU/mL | 75 | 99.6 | 58 | 98 |
| <29 IU/mL | 74 | 99 | 58 | 97 |
| **HBeAg** | | | | |
| Loss / seroconversion | NA | NA | 32 / 21 | 47 / 31 |
| HBsAg loss / seroconversion | 1.1 / 0.7 | 1.1 / 0.7 | 12.9 / 10.3 | 11.5 / 8.5 |

[1]Missing/addition of FTC = failure [LTE-TDF]); [2]Missing=excluded/addition of FTC = included.; [3]Kaplan-Meier (KM-ITT); NA = not applicable

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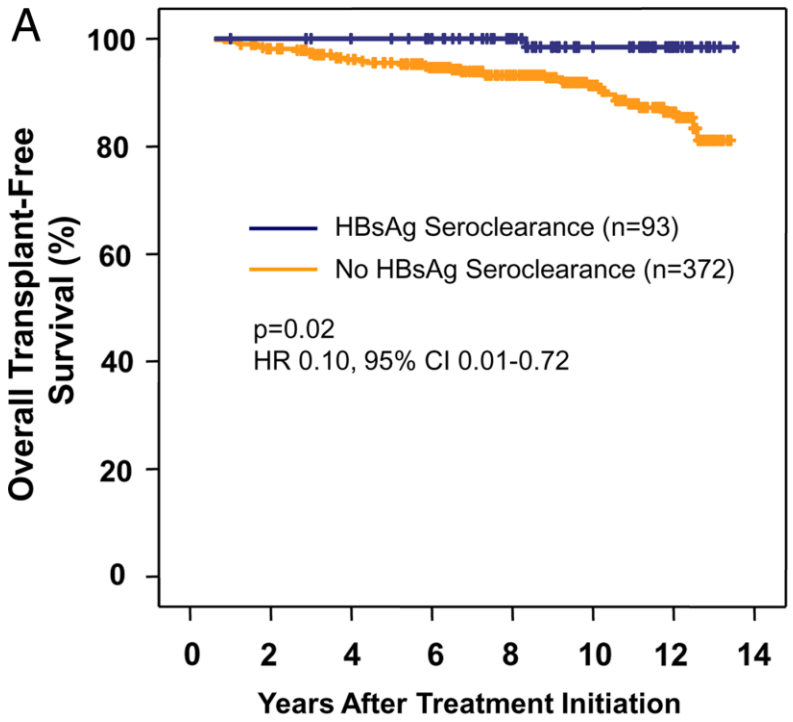
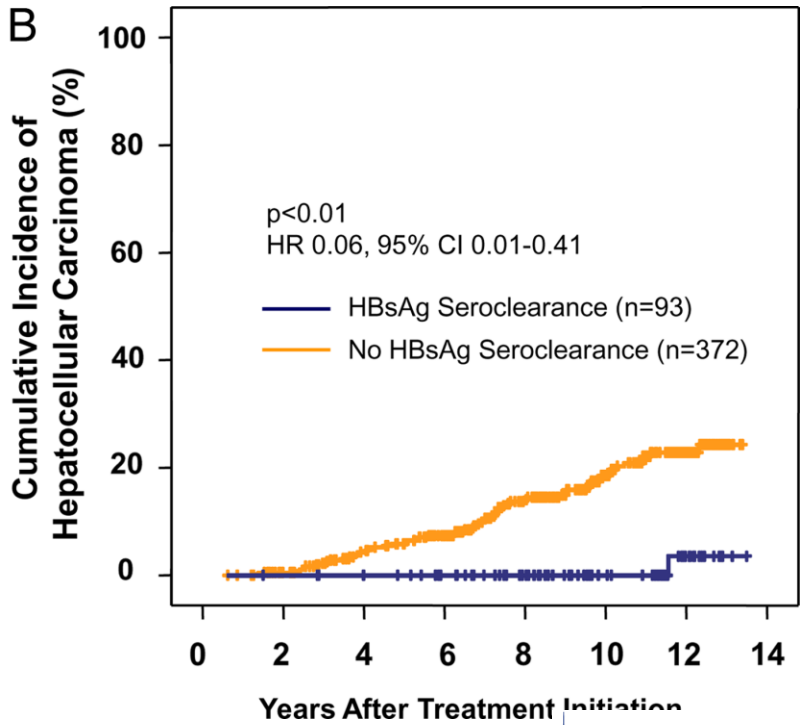
*Marcellin et al. J Hep 2014*

# NA-induced HBsAg seroclearance in Relation to Outcome

- **110/5409 patients had NA-induced HBsAg loss (0.33 annual clearance rate) and discontinued NA (LAM,ETV)**
- **Of these 110 patients, 1 developed HCC and 1 died**

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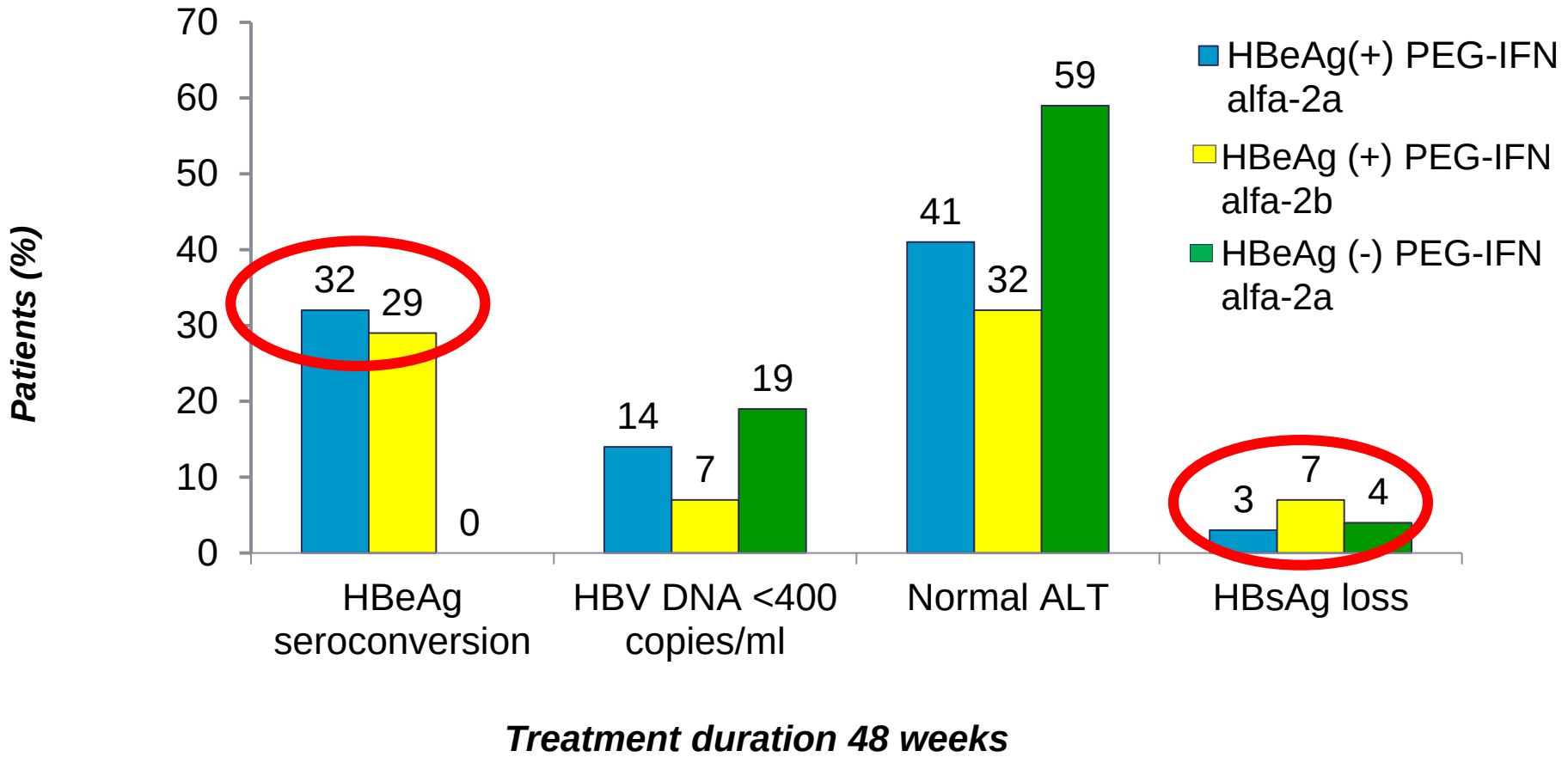
Kim et al, Gut 2013

# Response to PEG-IFN 6 months post treatment




***Treatment duration 48 weeks***

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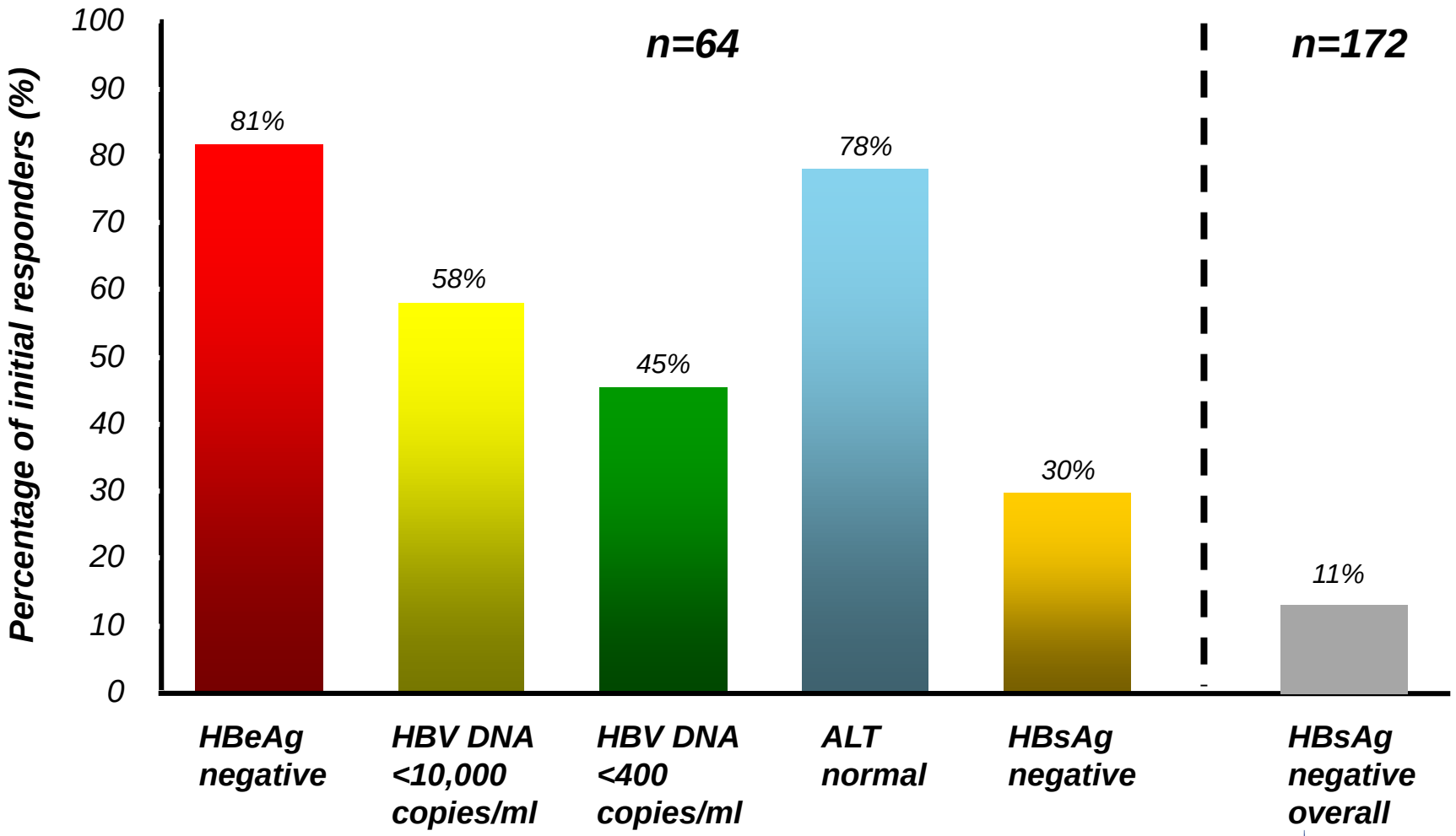
***Lau, NEJM 2005; Janssen, Lancet 2005; Marcellin, NEJM 2004.***

# 3-year follow up of HBeAg responders to PEG-IFNα-2b: HBeAg-positive CHB




*Buster et al. Gastroenterology 2008*

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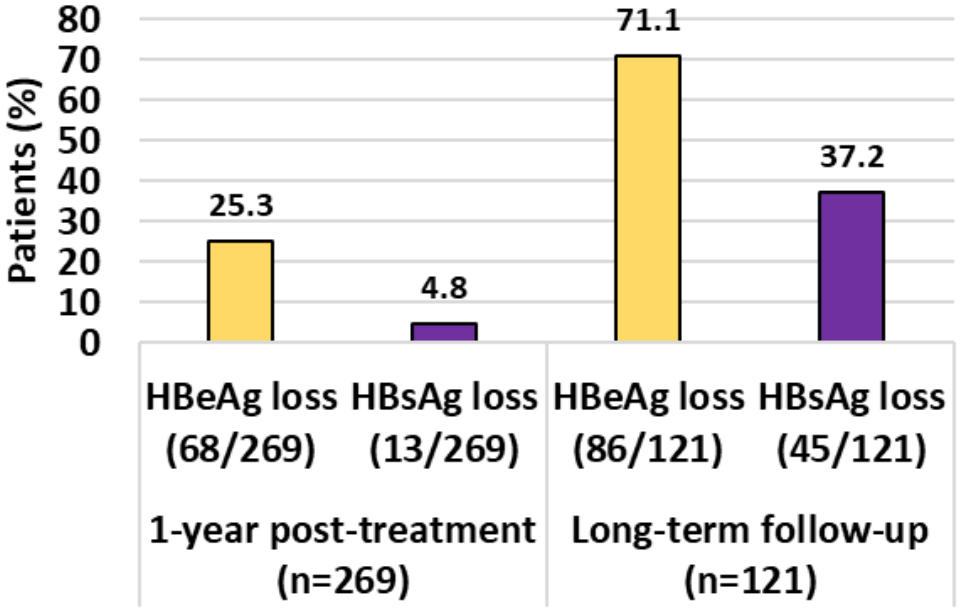
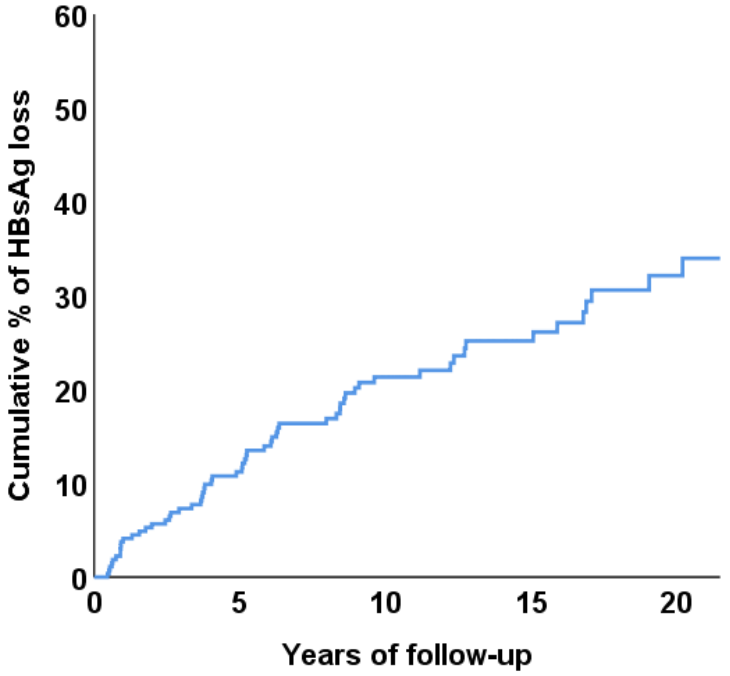
# HBsAg Loss after 13 Years of Follow-Up of Interferon-Alpha Treatment for HBeAg-positive CHB: ELITE-B Study

**HBeAg loss* and HBsAg loss cross-sectional data**




**HBsAg loss Kaplan Meier Curve**




** Partly have HBeAg negative active CHB*

*Mainly Caucasian patients*

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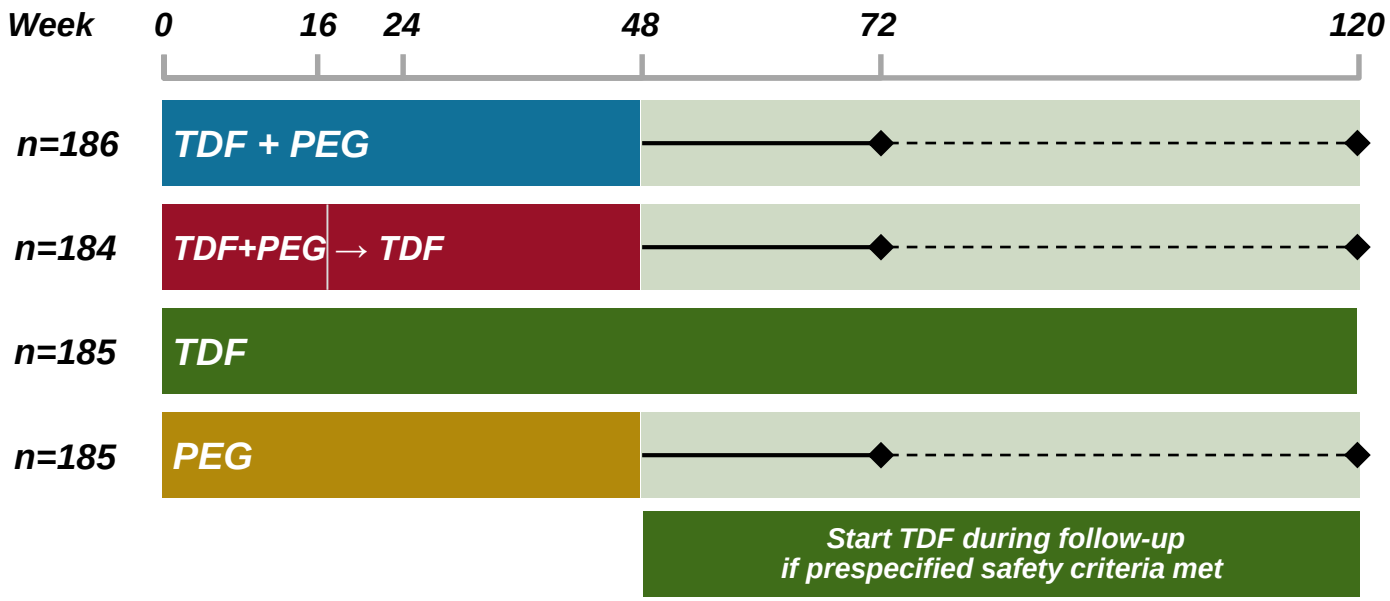
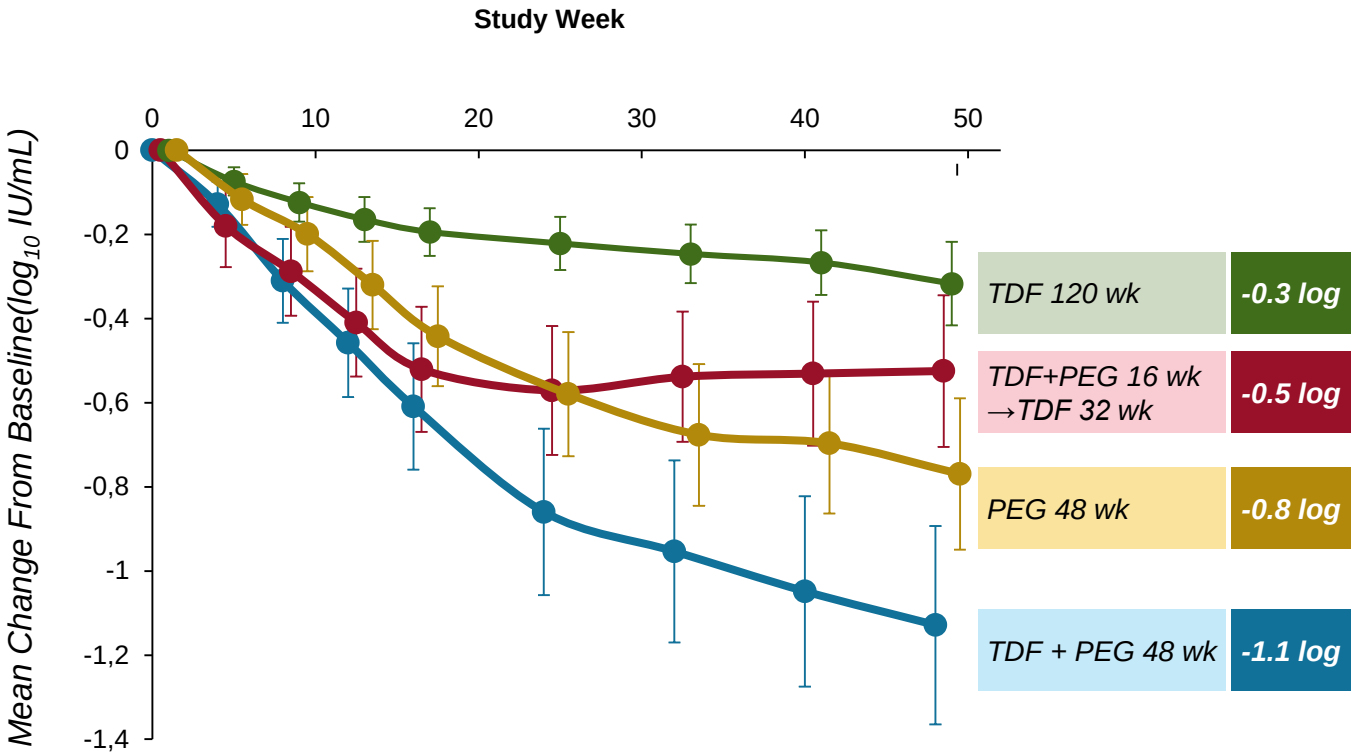
***H Choi et al. AASLD 2018***

# TDF vs PEG IFN vs Combination




- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
  - ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

# TDF vs PEG IFN vs Combination
# Change in Serum HBsAg Levels




3 patients who were re-treated at Week 48 were excluded from Week 48 calculations.
Error bars represent 95% confidence intervals.

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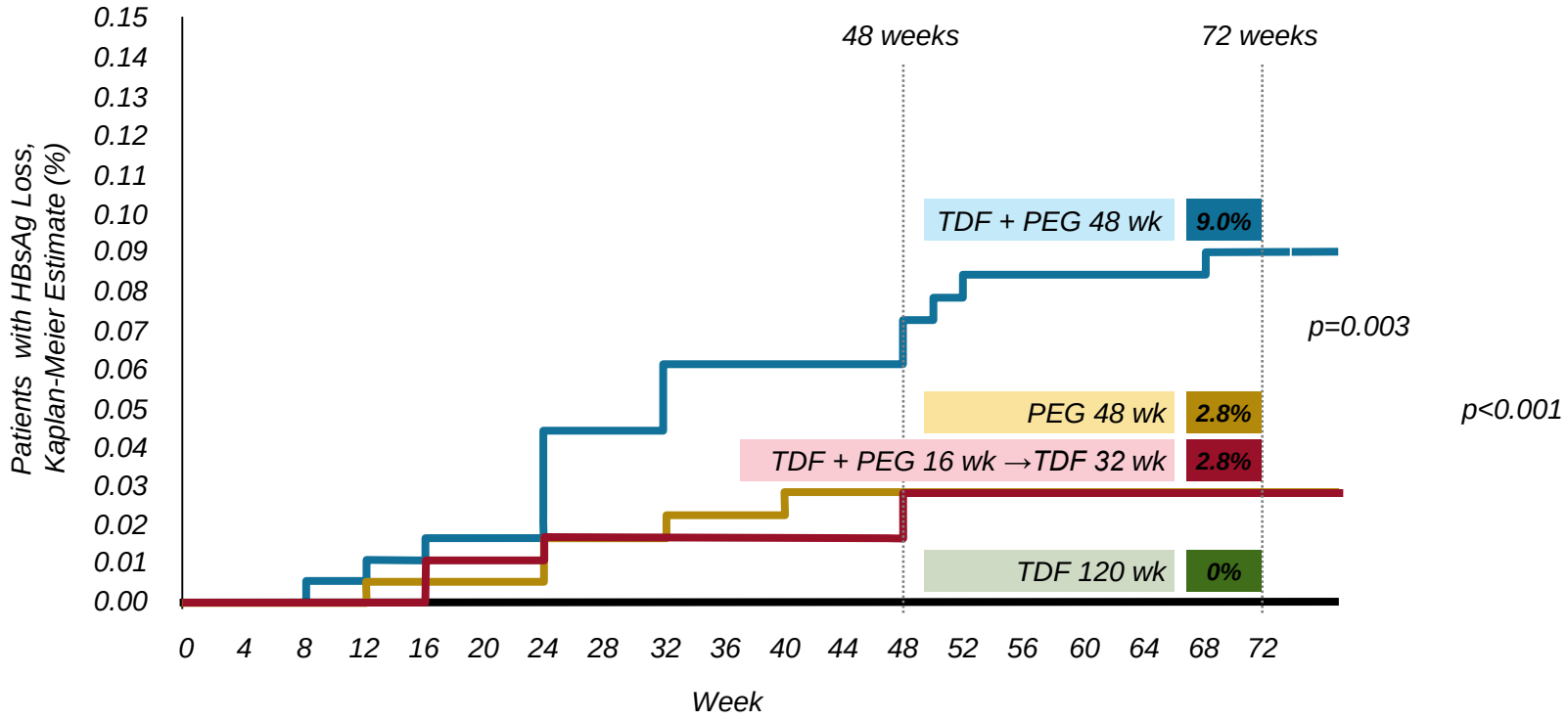
Marcellin et al. Lancet 2015

# TDF vs PEG IFN vs Combination
# HBsAg Loss through week 72




- *7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk →TDF 32 wk])*
  - *5/7 had ≤1 week of therapy after HBsAg loss*

*Marcellin et al. Lancet 2015*

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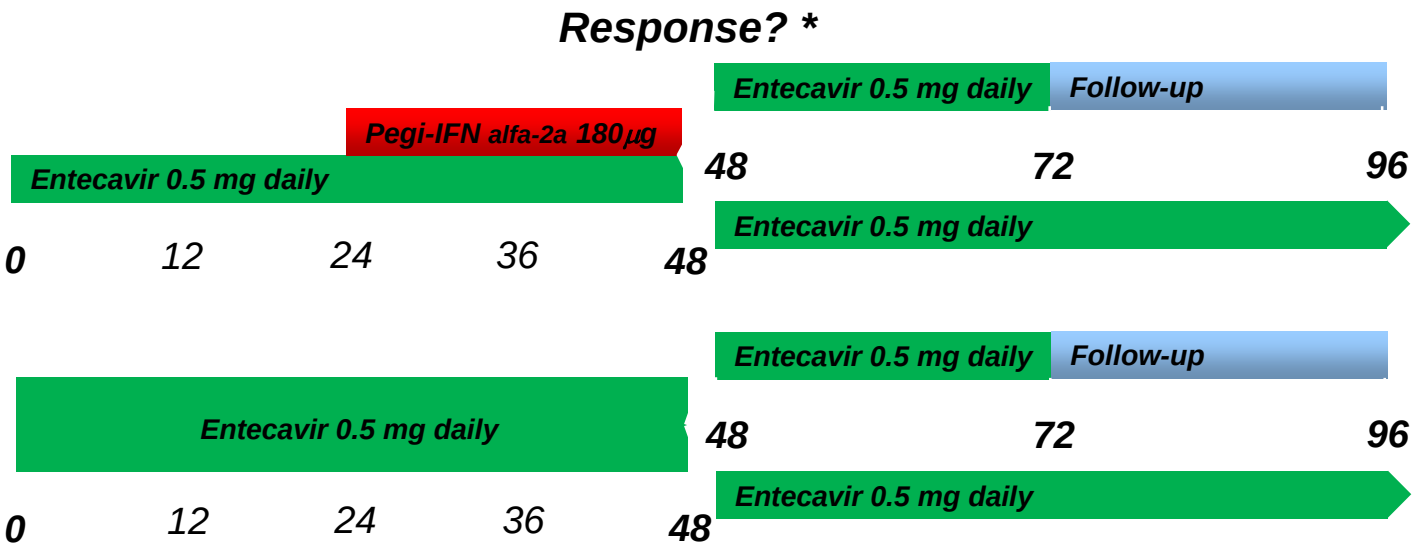
# ETV and PEG-IFN (ARES Study)

HBeAg positive study

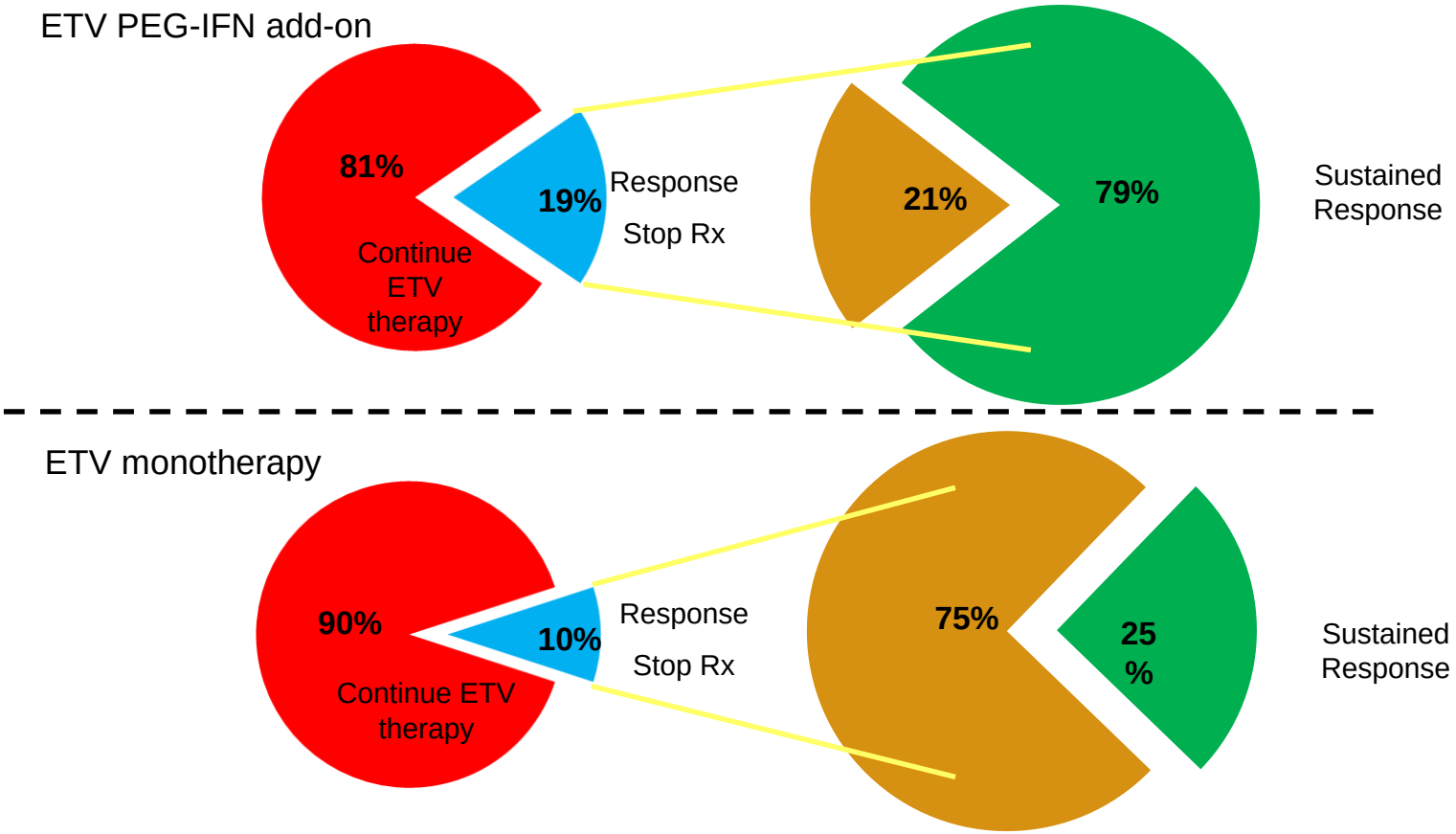
Multicenter, open-label, randomized controlled trial




***Response: combined presence of HBeAg loss and HBV DNA level < 200 IU/ml at week 48***

***Brouwer et al. Hepatology 2015***

# Sustained Response: ETV Peg-IFN add-on vs. ETV ARES Study




Response: HBeAg loss, normal serum ALT and HBV DNA <2000 IU/mL

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***Brouwer et al. Hepatology 2015***

# Combination of NA and PEG-IFN ?
## A systematic review

- NA to improve IFN response in <u>naive patients</u>
  - Sequential NA to IFN **(NO)**
  - *De-novo* NA + IFN combination **(few patients, GT A ?)**
- IFN to improve NA response in <u>naive patients</u>
  - ″Early″ add-on IFN for HBeAg pos pts **(limited benefit)**
  - *De-novo* NA + IFN combination **(limited benefit)**
- IFN to improve NUC response in <u>treated patients</u>
  - ″Add-on″ IFN to NA in HBeAg pos or HBeAg neg **(limited benefit)**

Limted benefit: 5-10 improvement

***Viganò M, Invernizzi F, Grossi G, Lampertico P. APT 2016;***
***Brouwer et al. Hepatology 2015, Chi et al. CID 2017***

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# Prediction of HBsAg loss for NA and PEG-IFN

| | |
|---|---|
| HBV genotype | **A>B>C>D** |
| HBV DNA | **Low** |
| ALT | **High** |
| Viral Genome | **Wildtype vs PC/BCP** |
| HBsAg | **Low** |

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# Conclusions

- Functional cure as indicated by HBsAg loss/seroconversion is very difficult to achieve in CHB with current therapy
- NA therapy is most probably indefinite because the majority of HBV patients relapse after stopping NA
- PEG-IFN whether or not in combination with NA has more potential for HBsAg seroconversion, particularly long-term
- HBV genotype, HBVDNA , AST and HBsAg levels pre-treatment may help to predict functional cure
- Monitoring HBsAg may help us identify patients who will reach functional cure
- New treatments targets are warranted to reach cure of HBV