8th Paris Hepatitis Conference

How do I treat my HBeAg-positive patients?

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Je suis
CHARLIE

When do I treat my HBeAg-positive patients?

Antiviral therapy in HBeAg(+) patients with PNALT

- Maintenance of high HBV replication: increasing numbers of infected hepatocytes, risk of progression of liver lesions, increasing HCC risk
- High risk of HBV transmission

- Usually minimal histological lesions
- Immune tolerance – Low probability of anti-HBe seroconversion
- (Peg-)IFNa: not effective - NAs: inhibition of HBV replication
- Probably life-long therapy in young patients: long-term safety, family planning?

Indications for treatment in HBeAg+ patients

- ALT >2xULN & HBV DNA >20,000 IU/ml

  Treatment (Biopsy optional)

- ALT 1-2xULN and/or HBV DNA 2,000-20,000 IU/ml

  Biopsy – Treatment in patients with ≥moderate histol. lesions

- ALT <ULN regardless of HBV DNA levels

  Usually no treatment – Biopsy?

- *Indications for treatment may also take into account* ***age, health status, family history of HCC or cirrhosis and extrahepatic manifestations***

EASL HBV CPGs. J Hepatol 2012;57:167-85

Management of HBeAg-positive patients with high HBV DNA (>20,000 IU/mL) and PNALT

- Age >40 years: treatment
- Age 30-40 years: decisions individualised - liver biopsy
- Age <30 years: follow-up (ALT /3-6 mos, HBeAg/anti-HBe /6-12 mos)
- Positive family history for HCC: reduce the age limit for treatment initiation
- Clinical or laboratory indications of advanced liver lesions ***(eg low PLT, high gamma-globulins, splenomegaly, spiders, palmar erythema, advanced fibrosis by noninvasive markers etc):*** liver biopsy even in patients <30 years

Potential additional treatment indications

- Immunosuppression/Chemotherapy
- Professional reasons
- Last trimester of pregnancy

EASL HBV CPGs. J Hepatol 2012;57:167-85

TDF vs TDF+FTC x192 wks in HBeAg+ patients with normal ALT and high HBV DNA

Mean age: 33 years; 89% Asians, 93% gen. B/C, mean HBV DNA: 8.4 $\log_{10}$ IU/mL

Outcome at week-192	TDF (N=64)	TDF+FTC (N=62)	P
HBV DNA <69 IU/ml	55%	76%	0.016

HL Chan et al. Gastroenterology 2014;146:1240-8

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Outcome at week-192	TDF (N=64)	TDF+FTC (N=62)	P
HBV DNA <69 IU/ml	55%	76%	0.0 16
HBV resistance	0%	0%	NS
HBeAg seroconversion	5% 29%	0%	NS
HBsAg loss	0% 11%	0%	NS

TDF x192 wks in HBeAg+ CHB: Heathcote EJ et al. AASLD 2010, Abstr. 477

HL Chan et al. Gastroenterology 2014;146:1240-8

How do I treat my HBeAg-positive CHB patients?

HBV-RELATED CHRONIC LIVER DISEASE
Groups of treatment options

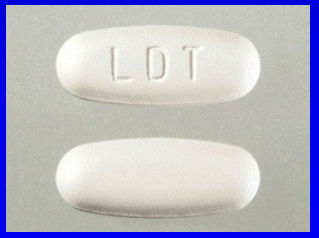
(Peg)-IFNa

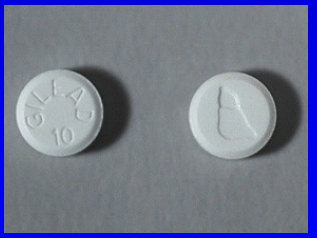
(antiviral+ immunomodulator)

ETV, TDF

TBV, LAM, ADV

(pure antivirals)





HBV-RELATED CHRONIC LIVER DISEASE THERAPEUTIC INDICATIONS

(Peg-)IFNa or Nucleos(t)ide analogue(s) [NA(s)]

- Chronic hepatitis B (including compensated cirrhosis)

Only NA(s)

- Decompensated HBV cirrhosis
- Prophylaxis in HBV transplant cases
- Pre-emptive therapy in inactive HBV carriers receiving immunosuppressive/chemo-therapy
- Pregnant women with high HBV viremia
- Health care workers in the HBV immunotolerant phase

Peg-IFNa for HBeAg+ CHB

- 48 weeks of therapy
- 30-32% HBeAg seroconversion
- 80-90% long-term durability of response off-therapy
- 12-15% (~50% of responders) HBsAg clearance after 5 years
- Improved histology & long-term outcomes in sust. responders

Baseline and/or on-therapy predictors of response
(HBeAg seroconversion & low HBV DNA)?

NA(s) for HBeAg+ CHB

- HBeAg seroconversion: 20% at year 1, 40-50% at year 5
- On-therapy HBV DNA undetectability in >95% of compliant patients under ETV or TDF (first-line options)
- No/negligible risk of resistance with ETV (1%) or TDF (0%)
- 10-12% HBsAg loss at year 5 – no major increase until year 8
- Improved histology & long-term outcomes

Durability of off-NA response (anti-HBe seroconv. & low HBV DNA)?

Baseline and/or on-therapy predictors of response?

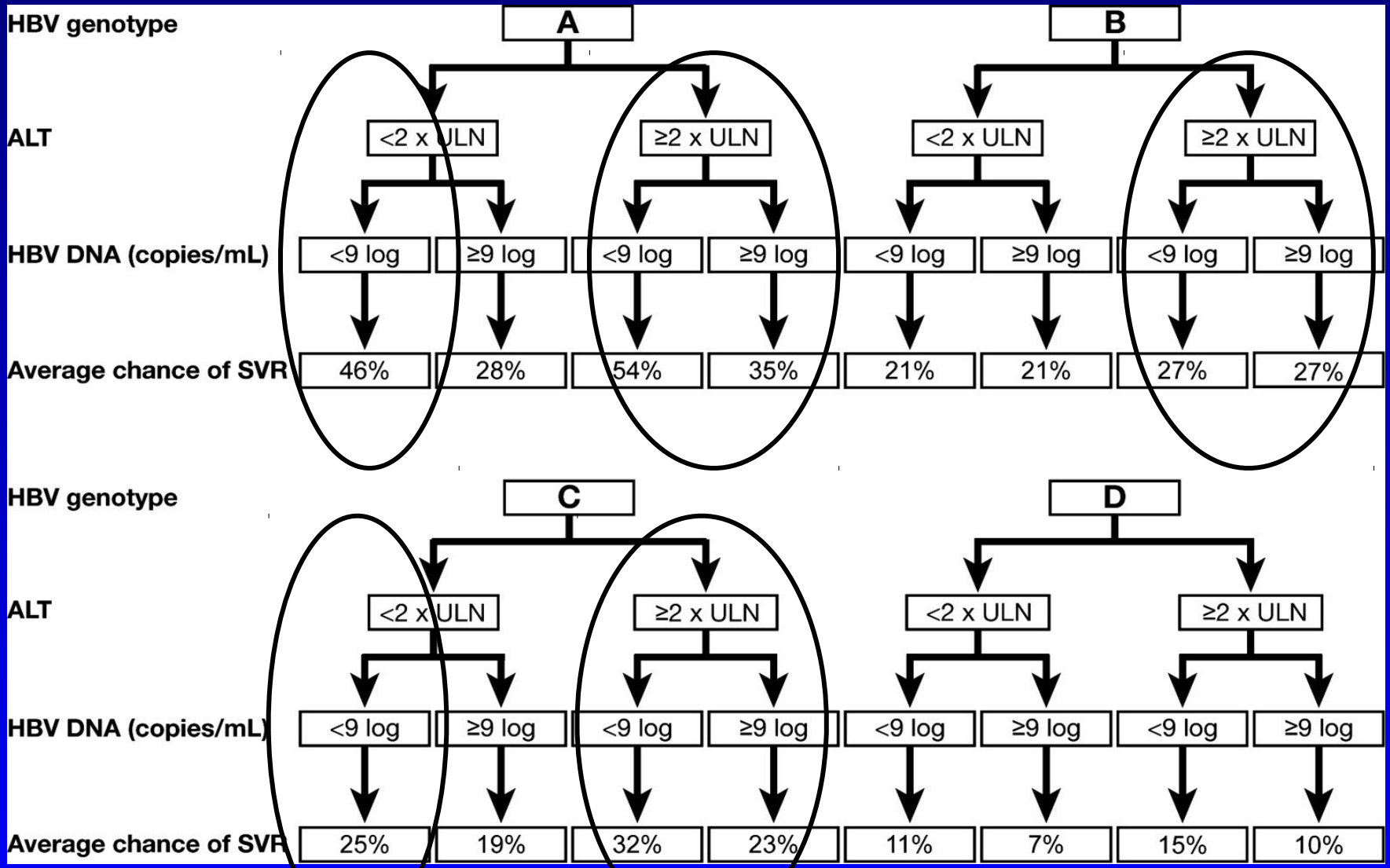
Baseline predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients

Baseline predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients

Similar for Peg-IFNa and NAs

- Higher ALT
- Lower HBV DNA
- Higher histological activity
- HBV genotype A > D & B > C
  (better predictors for Peg-IFNa)

Baseline predictors of response to Peg-IFNa (HBeAg loss & HBV DNA<10,000 cp/ml) in HBeAg+ CHB



Pts, n

Gen. A=115

Gen. B=166

Gen. C=333

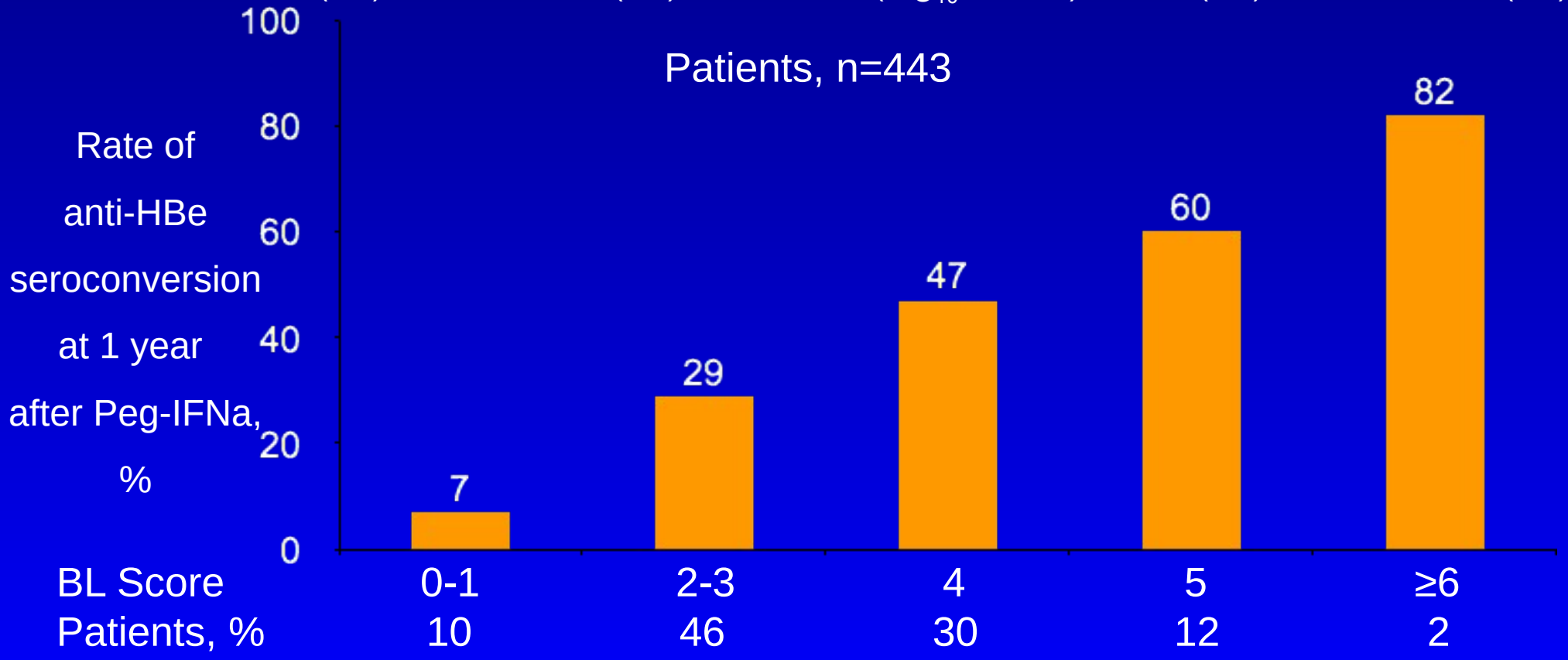
Gen. D=107

Buster EHCJ et al. Gastroenterology 2009;137:2002-9

Baseline predictors of response to Peg-IFNa-2a (anti-HBe seroconversion) in HBeAg+ CHB

Baseline (BL) Score: Female (+1); HBsAg<20,000 IU/mL (+1); HBV genotype A (+2);

ALT 1.5-<4xULN (+1), ALT≥4xULN (+2); HBV DNA (log_{10} IU/mL) 8-<10 (+1), HBV DNA<8 (+2)



HLY Chan et al. AASLD 2014, Abstr. 1886

On-treatment predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients

On-treatment predictors of response (anti-HBe seroconversion) in HBeAg+ CHB patients

Clinically meaningful

- Only for Peg-IFNa
- Not for NAs (used as both finite duration and maintenance therapy)

  Meaningful for NAs:
  on-treatment predictors of HBsAg loss

Peg-IFNa stopping rules

- HBeAg+ve: HBsAg levels ≥20,000 IU/mL or no decline in HBsAg levels by month 3 (C2)

Piratvisuth et al. APASL 2010; Gane et al. EASL 2011; Sonneveld et al. Hepatology 2010

EASL HBV CPGs. J Hepatol 2012;57:167-85

HBsAg levels as a positive predictor of response to Peg-IFNa

- HBeAg+ve: HBsAg levels <1,500 IU/mL at 12 or 24 wks = probability of anti-HBe seroconversion >50%

Piratvisuth et al. APASL 2010; Gane et al. EASL 2011

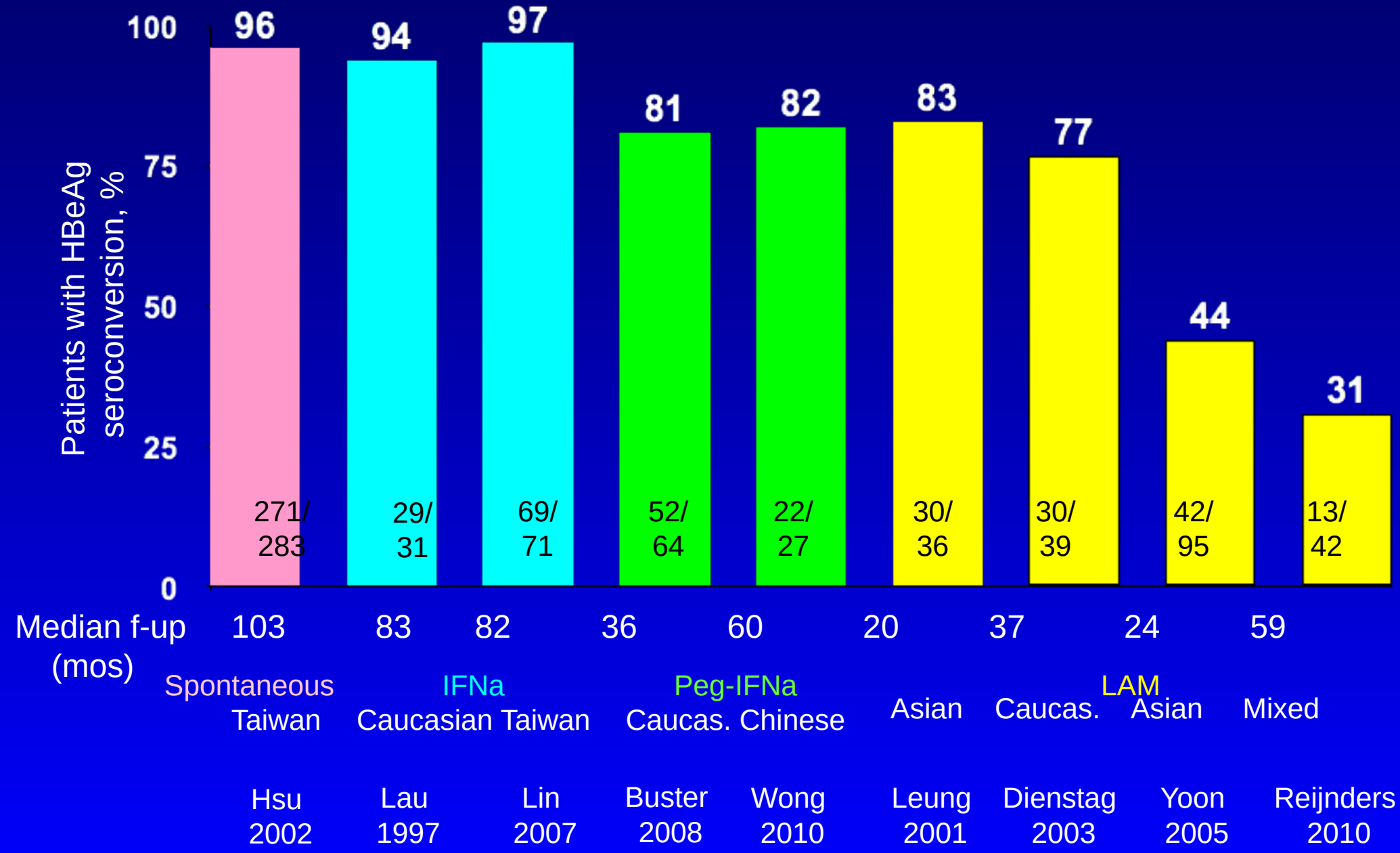
Peg-IFNa stopping rules

- HBeAg+ve: HBsAg levels ≥20,000 IU/mL (better predictability in genotype B or C*) or no decline in HBsAg levels by month 3 (better predictability in genotype A or D*) (C2)

EASL HBV CPGs. J Hepatol 2012;57:167-85. *Sonneveld MJ et al. Hepatology 2013; 58:872-80

Post-NA(s) durability of anti-HBe seroconversion

Post-therapy durability of HBeAg seroconversion



Variability in the rates of durable anti-HBe seroconversion induced by NAs

- Anti-HBe seroconversion not always accompanied by HBV DNA undetectability at NA(s) discontinuation
- Variable durations of consolidation therapy after anti-HBe seroconversion
- Variable definitions of post-NA(s) response

Clinical significance of relapse following NA(s) discontinuation in initially HBeAg+ CHB patients

- NO DATA for dramatic events in non-cirrhotic patients who discontinued NA(s)
- Patients who fulfill the standard treatment indications can be always retreated

When can we consider stopping NA therapy in HBeAg+ CHB?

- All international guidelines: stop NAs after HBeAg seroconversion & undetectable HBV DNA & 6–12 months consolidation[1–3]

- EASL: perhaps continue until HBsAg loss (i.e. potentially indefinitely) particularly in severe fibrosis/cirrhosis due to high risk of relapse[1]

1. EASL. J Hepatol 2012;57:167–85. 2. Lok AS et al. J Hepatol 2009;50:661–2. 3. Liaw YF et al. Hepatol Int 2012;6:531–61

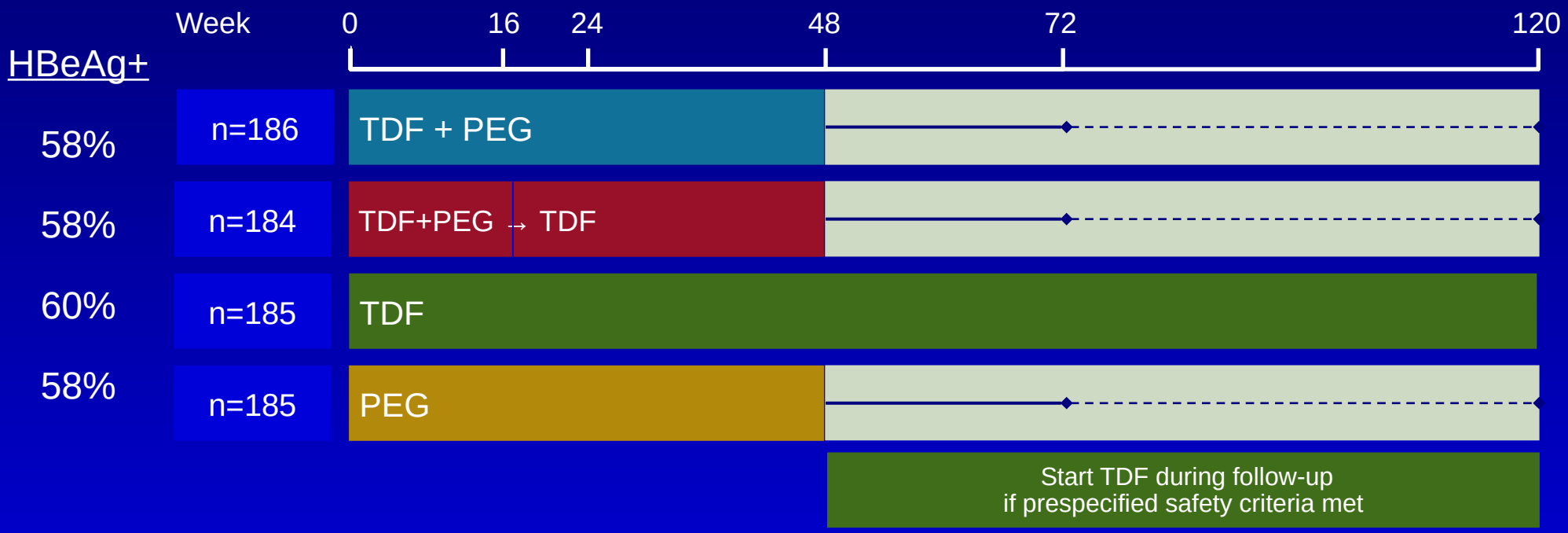
Main predictors of HBsAg loss after 3 years of TDF in HBeAg+ CHB patients

- Non-Asian race
- Genotype A
- Higher baseline necroinflammatory activity
- Higher baseline HBsAg levels
  (median: 5.11 vs 4.50 log IU/ml)
- Greater change in HBsAg levels at week 24
  (median: 2.41 vs 0.20 log IU/mL)

EJ Heathcote et al. Gastroenterology 2011; 140: 132-43

Is there a role for Peg-IFNa and NA(s) combination for HBeAg+ CHB?

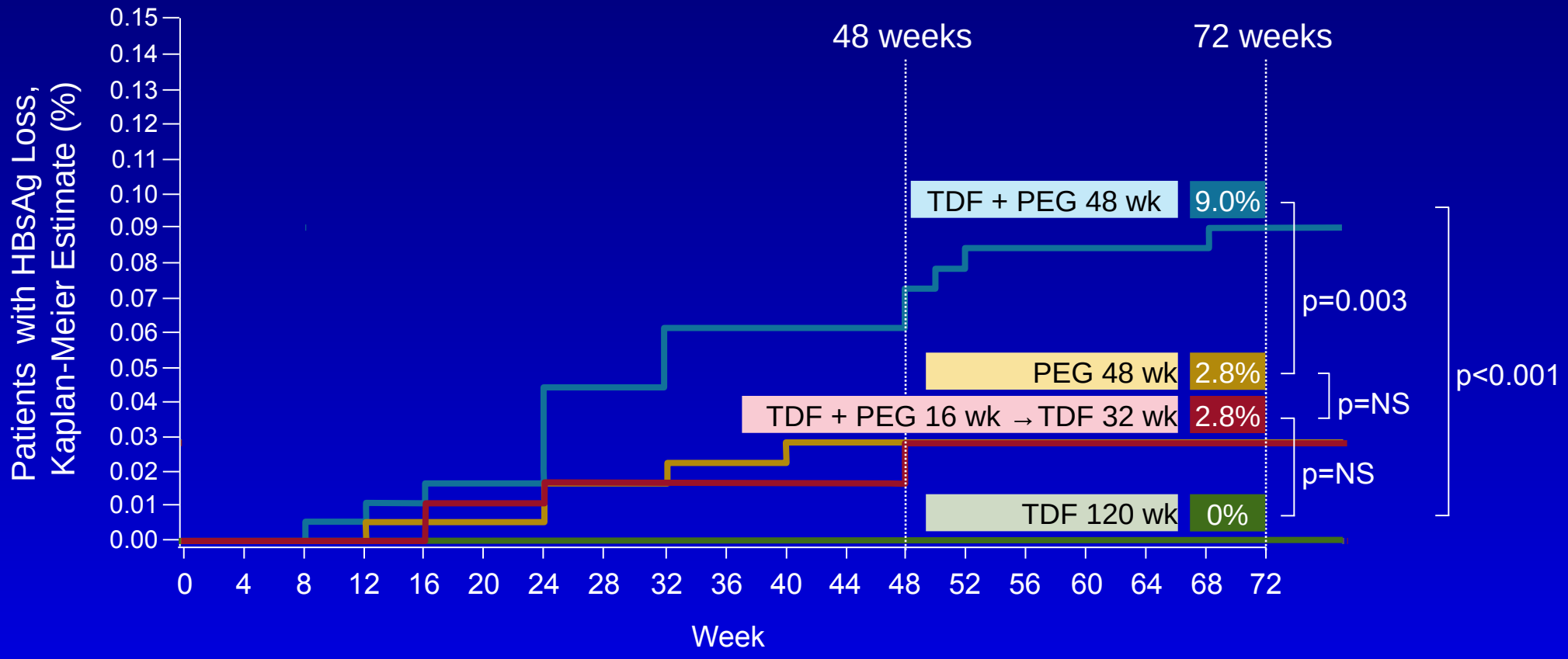
TDF +/- Peg-IFNa-2a in CHB



- 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

P Marcellin et al. AASLD 2014

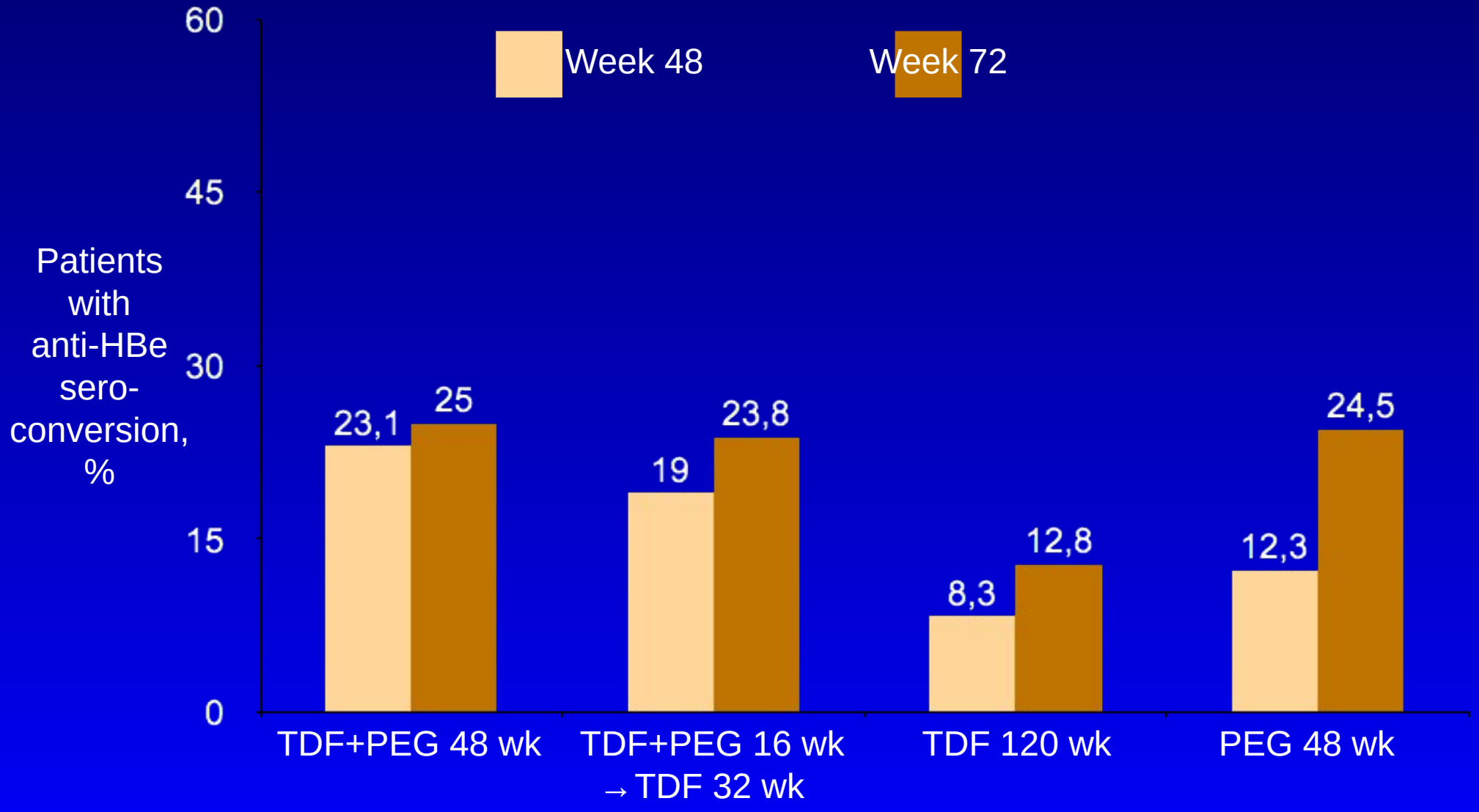
HBsAg Loss Over Time (Week 72)



- 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

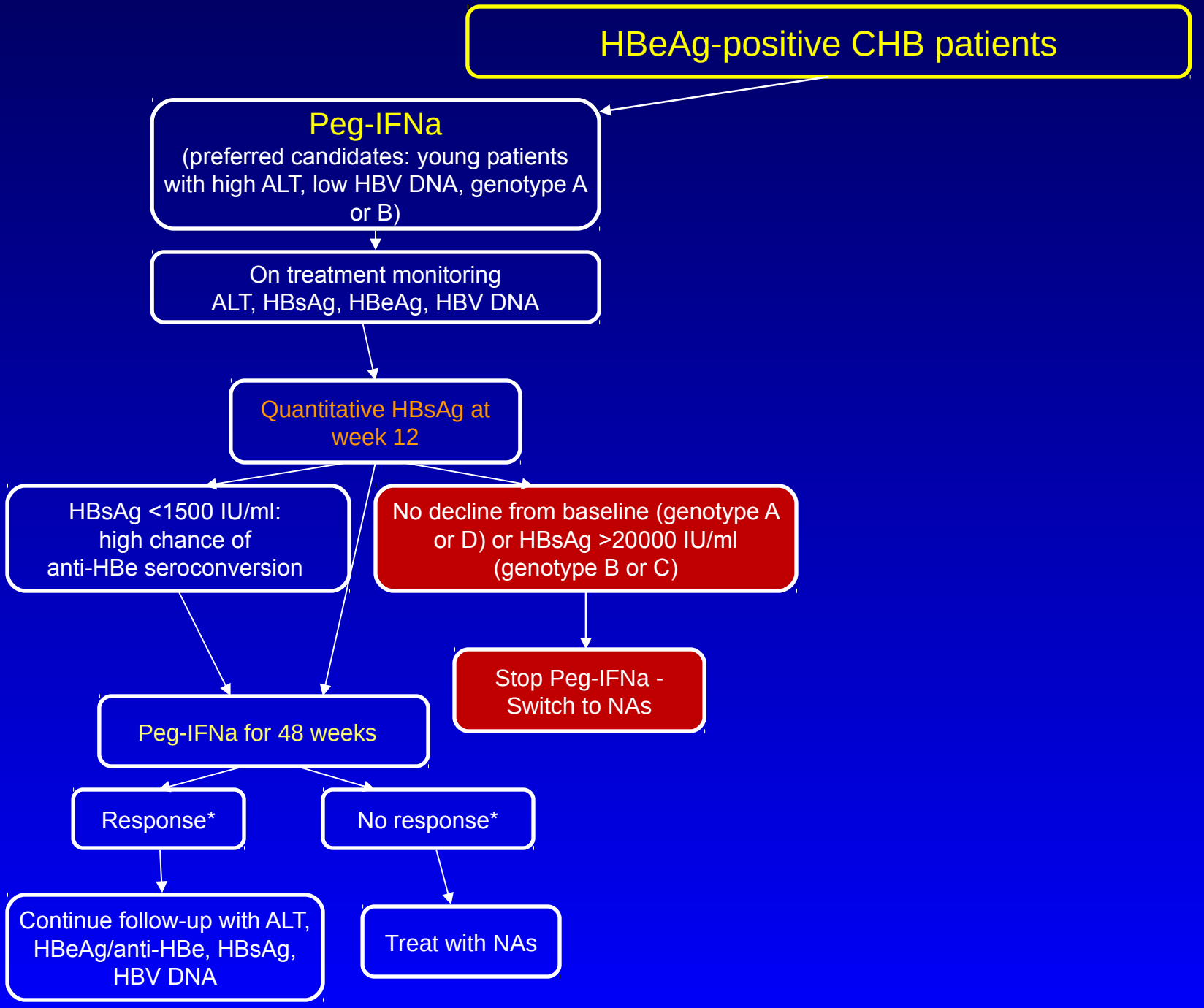
P Marcellin et al. AASLD 2014

HBeAg seroconversion rates (Weeks 48 & 72)

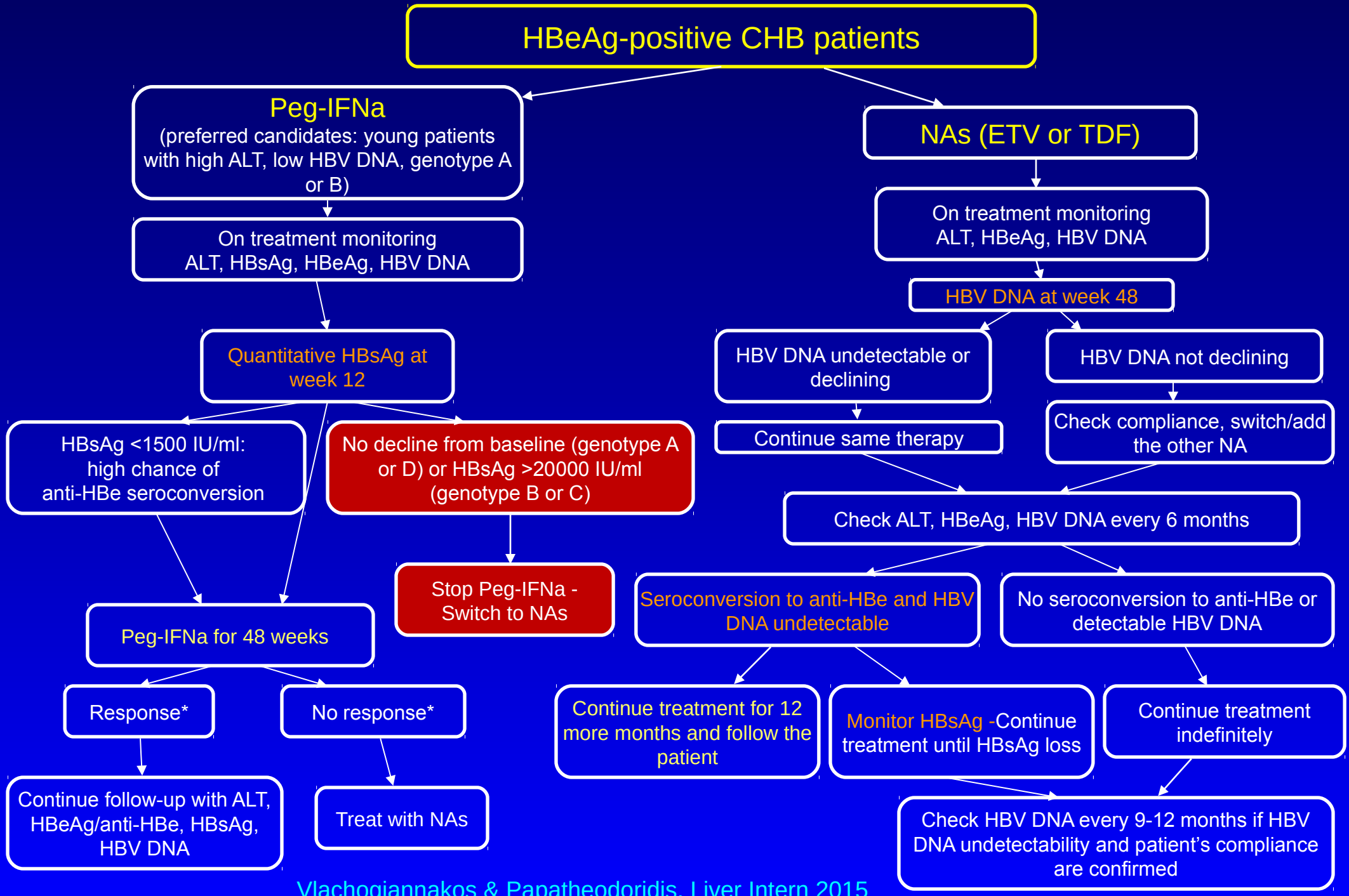


P Marcellin et al. AASLD 2014

No clear role for Peg-IFNa and NA(s) combination in the current management of HBeAg+ CHB



Vlachogiannakos & Papatheodoridis. Liver Intern 2015



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Thank you for your attention!