CLINICAL APPLICATIONS of HBsAg QUANTIFICATION

Rami MOUCARI, MD, PhD

Paris Hepatitis Conference 2015

CASE - 1

- 25 Years Old Patient
- HBsAg (+) HBeAg (-) HBeAb (+)
- HBV DNA = 380 U/mL HBsAg = 260 U/mL
- ALT = 26 U
- Abdominal US Normal

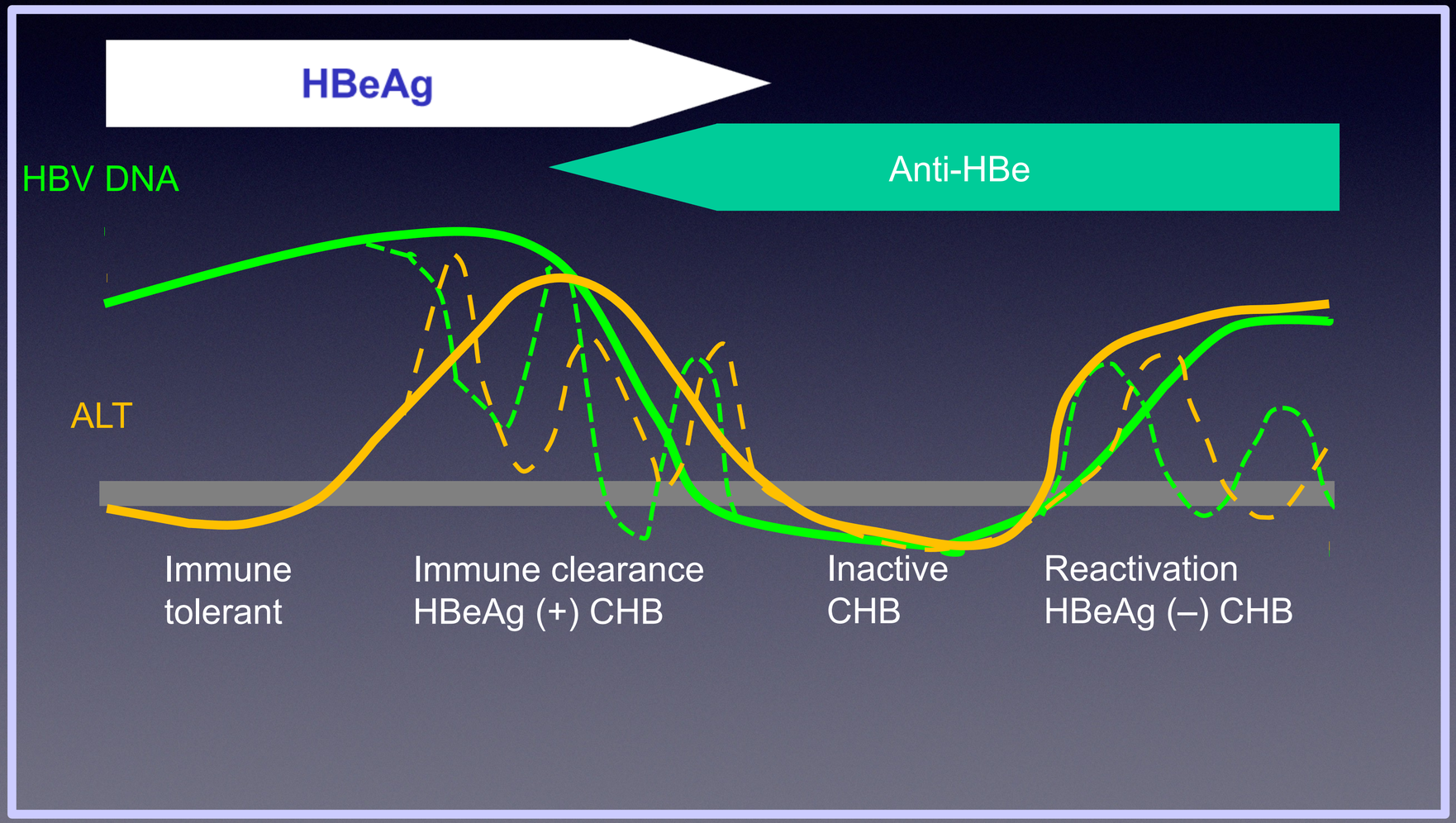
Diagnosis ?

1. HBV Inactive Carrier
2. Mutant - Type Chronic HBV Infection
3. Immune Clearance Phase of HBV Infection
4. Immune Tolerance Phase of HBV Infection

Management?

1. Start PEG-IFN Injections
2. Start Oral Treatment (TDF or ETV)
3. Follow-up Every 3 - 6 Months
4. No Need for Follow-up

HBV Infection: Natural History



Inactive Carrier Status: Dynamic

After spontaneous HBeAg seroconversion,
67% to 80% of carriers remain in inactive carrier phase

Immunotolerant ⟷ Inactive Carrier ⟷ HBeAg-Negative Hepatitis B

4% to 20% of inactive carriers have reversion back to HBeAg positive

10% to 20% have reactivation after years of quiescence disease

Serial testing is necessary during the “inactive carrier state”

Lok AS et al. Hepatology 2009

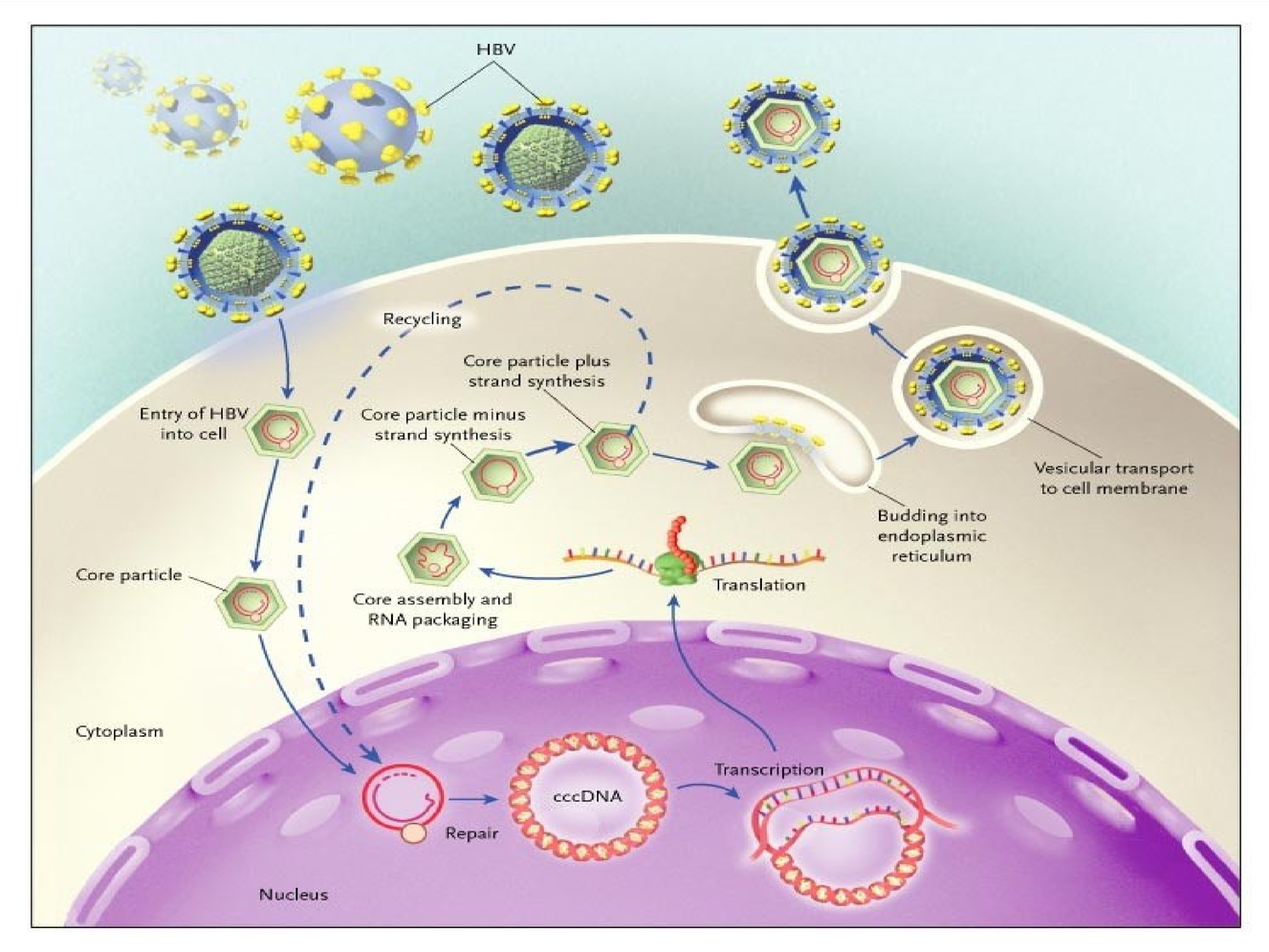
Inactive Carrier: Monitoring

- A minimum follow-up of 1 year with ALT levels at least every 3-4 months and HBV DNA levels is required before classifying a patient as inactive carrier

- Inactive carriers should be followed up for life with ALT determinations at least every 6 months after the first year and periodical measurement of HBV DNA levels

EASL Guidelines. J Hepatol 2012

HBV Life Cycle



HBV DNA & HBsAg: Different Meanings

	HBV DNA	HBsAg
Virology	Dane particle	Dane particle and subviral particles
Natural history	Reduced after HBeAg seroconversion but relapse on immune escape	Very slow reduction over time regardless of HBV DNA levels or disease activity
Implication	Viral replication	Immune clearance of infected hepatocytes

Moucari et al. Liver Int. 2011

Role of qHBsAg in Inactive Carrier Status

- Single Point Quantification of
  - HBsAg (< 1000 IU/mL) &
  - HBV DNA (< 2000 IU/mL)
- Negative Predictive Value: > 96%
- Positive Predictive Value: > 88%
- Accuracy > 90 %

Brunetto et al. Gastroenterology 2010 - Martinot-Peignoux et al. J Clin Virol. 2013 - Larsson SB et al. Liver Int 2013

CASE - 2

- 40 Years Old Patient
- HBsAg (+) HBeAg (-) HBeAb (+)
- HBV DNA = 145 000 U/mL HBsAg = 3460 U/mL
- Genotype D
- ALT = 118 U
- Abdominal US Normal
- Liver Biopsy: A2F1

Management?

1. Start PEG-IFN Injections
2. Start NUCs (TDF or ETV)
3. No Treatment - Mild Fibrosis (F1)
4. No Treatment - Difficult Genotype

Treatment Indications in HBeAg (-) Patients

- Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy showing moderate to severe active necro-inflammation and/or at least moderate fibrosis

- Patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy

EASL Guidelines. J Hepatol 2012

Treatment Endpoints in HBeAg (-) Patients

- The ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs
- Induction of sustained off-therapy virological (HBV DNA < 2000 U/mL) and bio- chemical response (Normal ALT) is a satisfactory end point
- A maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy is the next desirable endpoint

EASL Guidelines J Hepatol 2012

Treatment Modalities in HBeAg (-) Patients

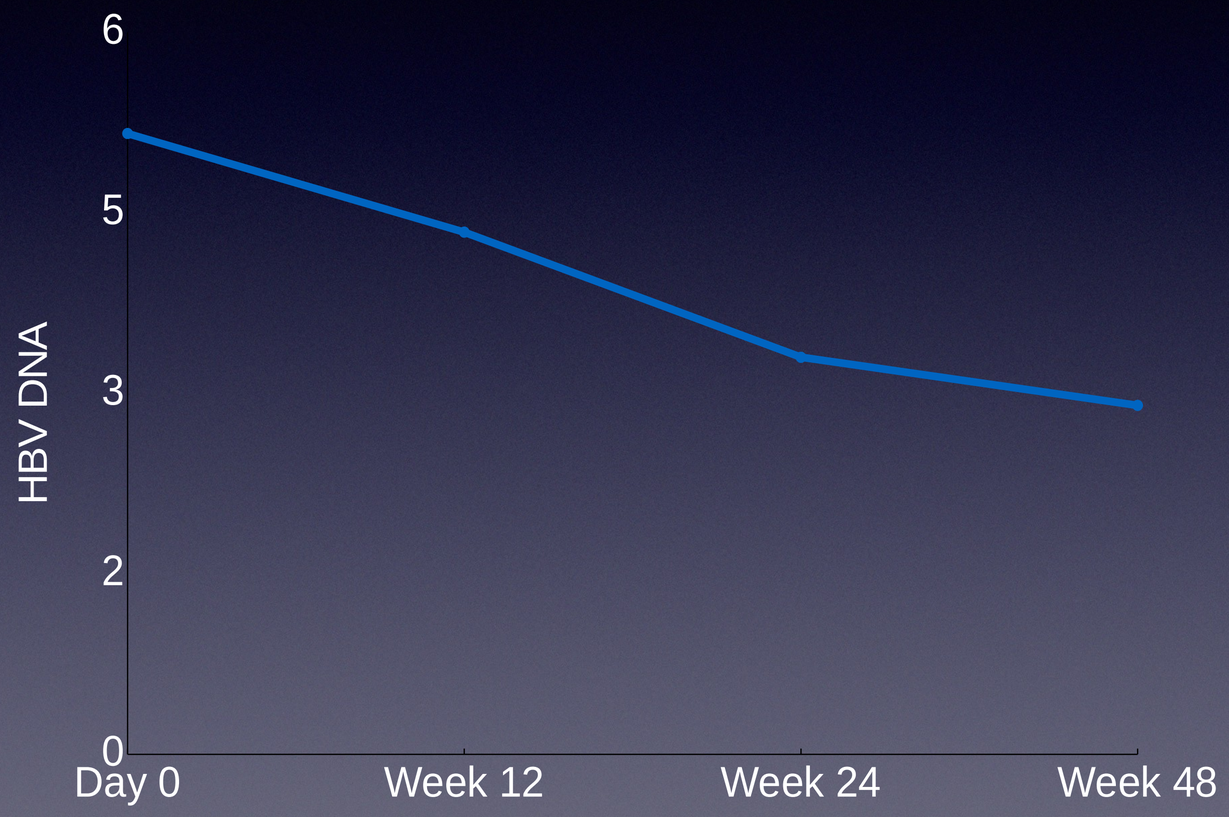
- A finite duration treatment with of PEG-IFN can be used: the only option that may offer a chance for sustained off-treatment response

Versus

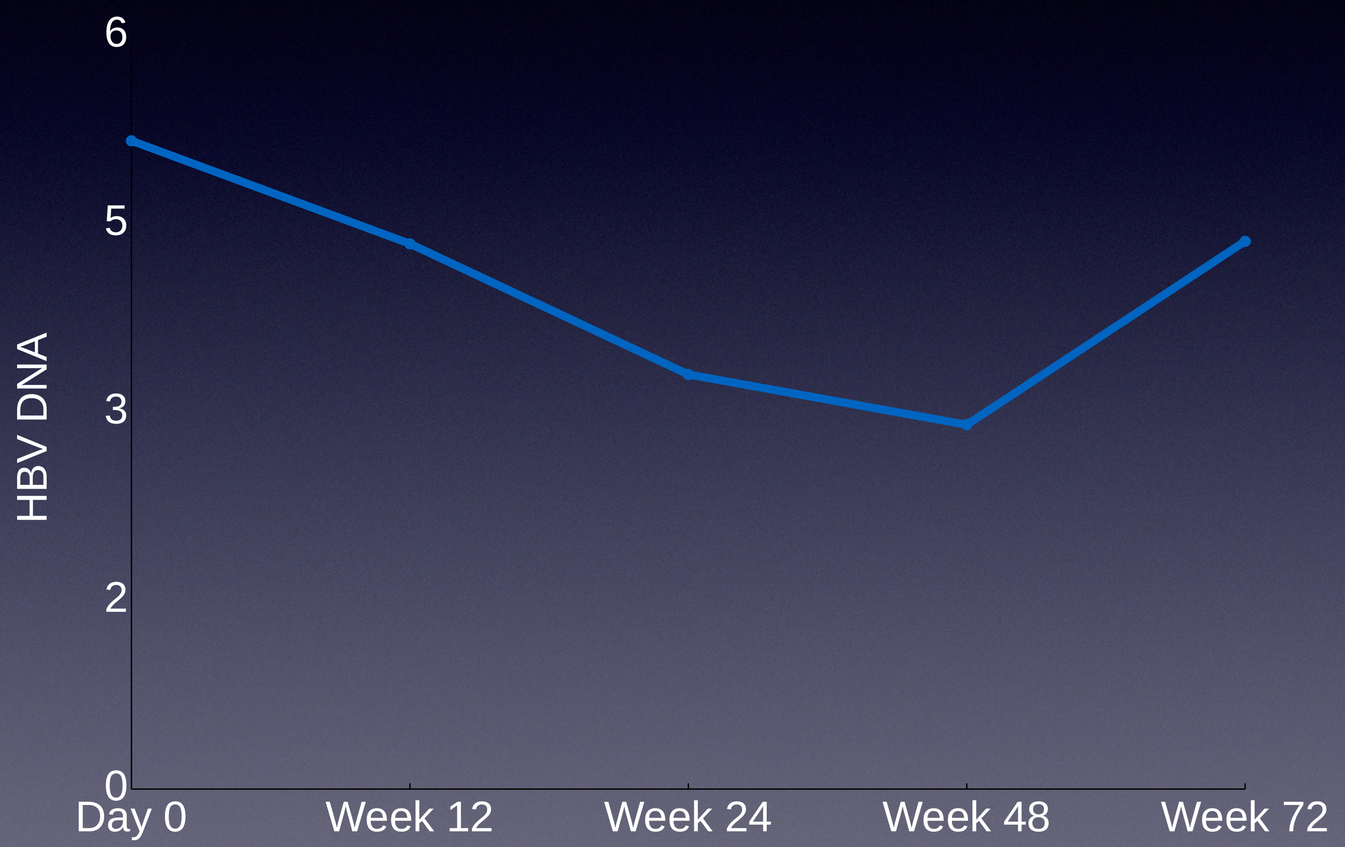
- A long term treatment with NUCs

EASL Guidelines. J Hepatol 2012

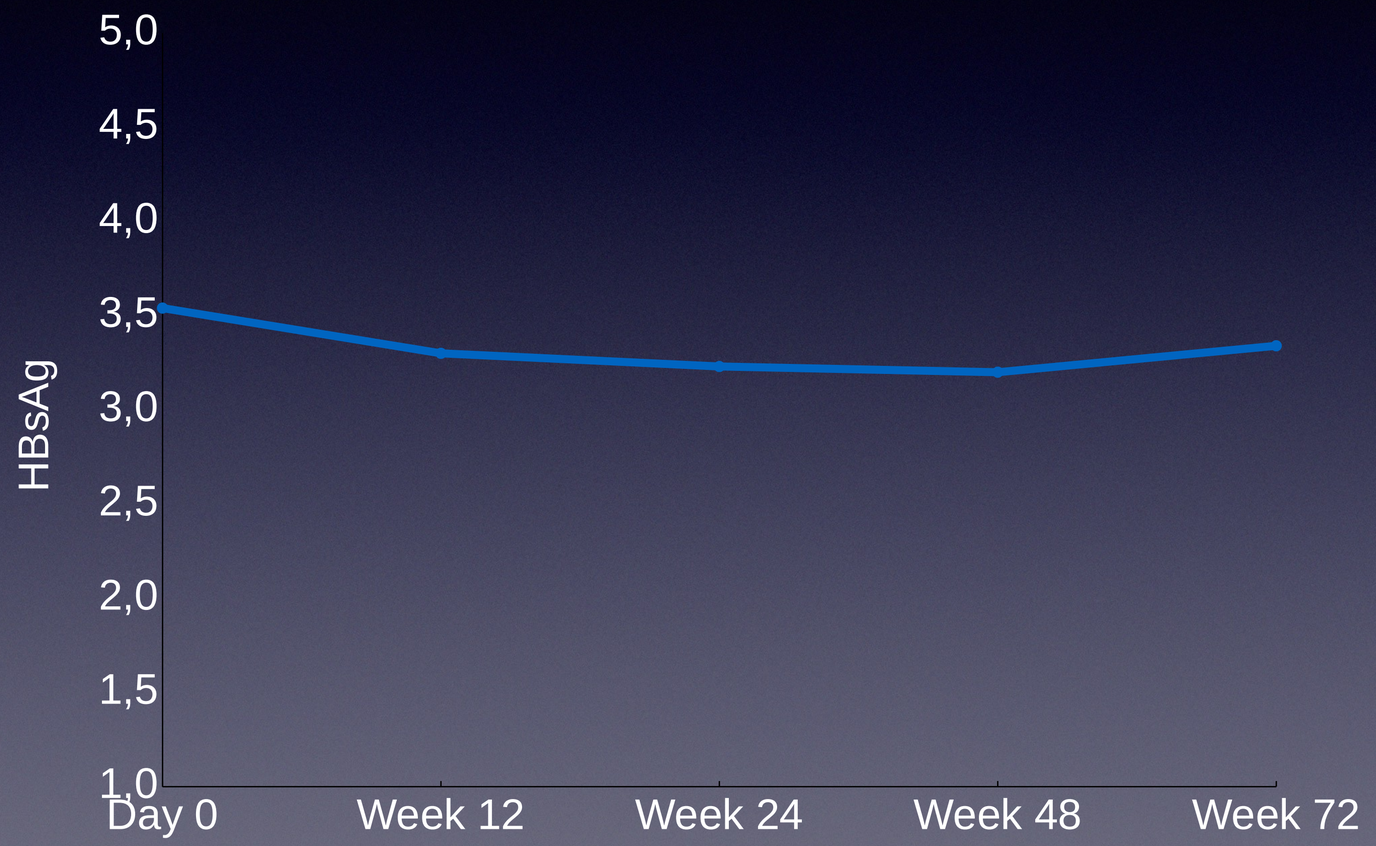
Case - 2: On-Treatment (PEG-IFN)
HBV DNA Pattern



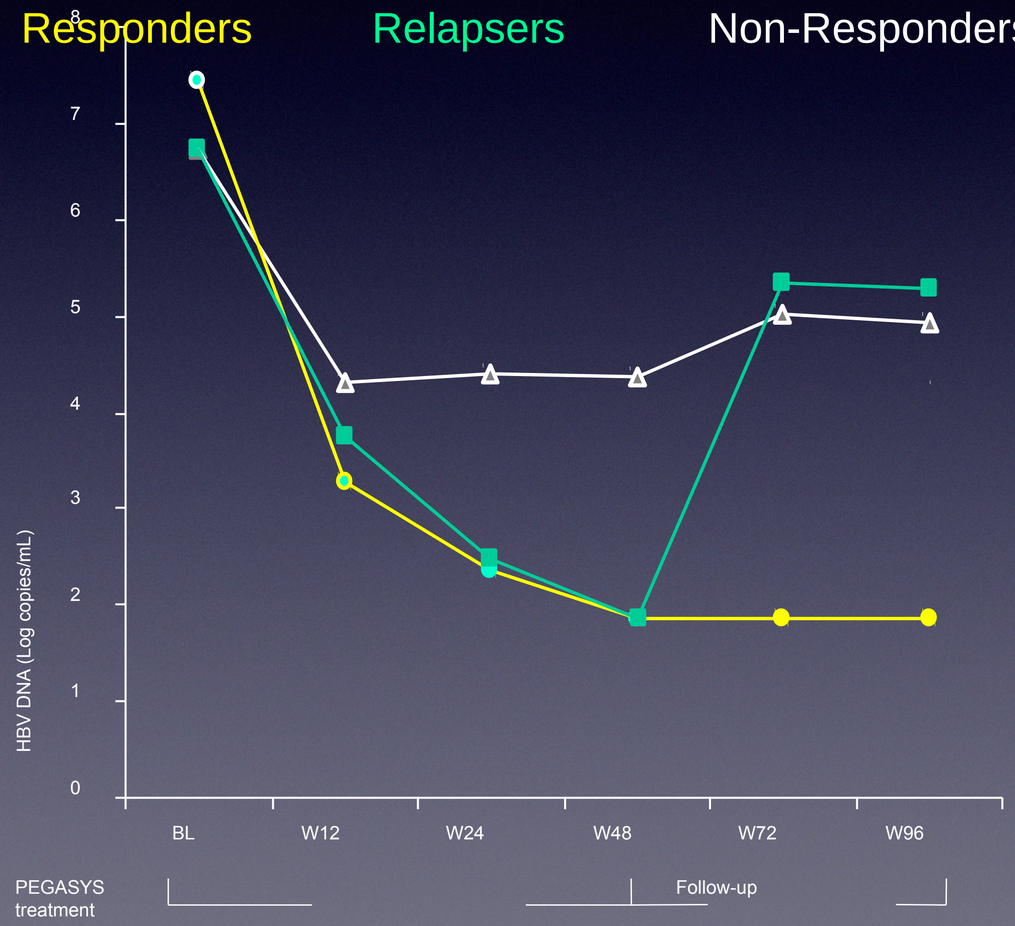
Case - 2: On-Treatment (PEG-IFN)
HBV DNA Pattern

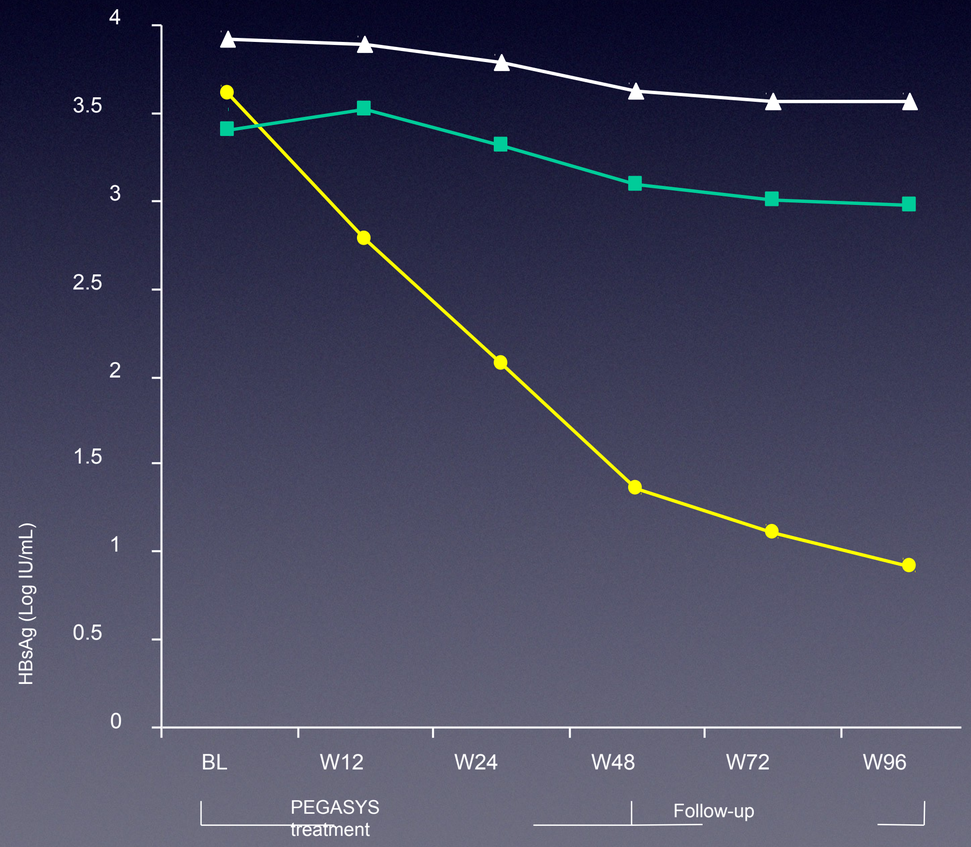


Case - 2: On-Treatment (PEG-IFN)
HBsAg Pattern



qHBsAg in HBeAg (-) Patients Treated with PEG-IFN: Responders Vs. Relapsers & NR

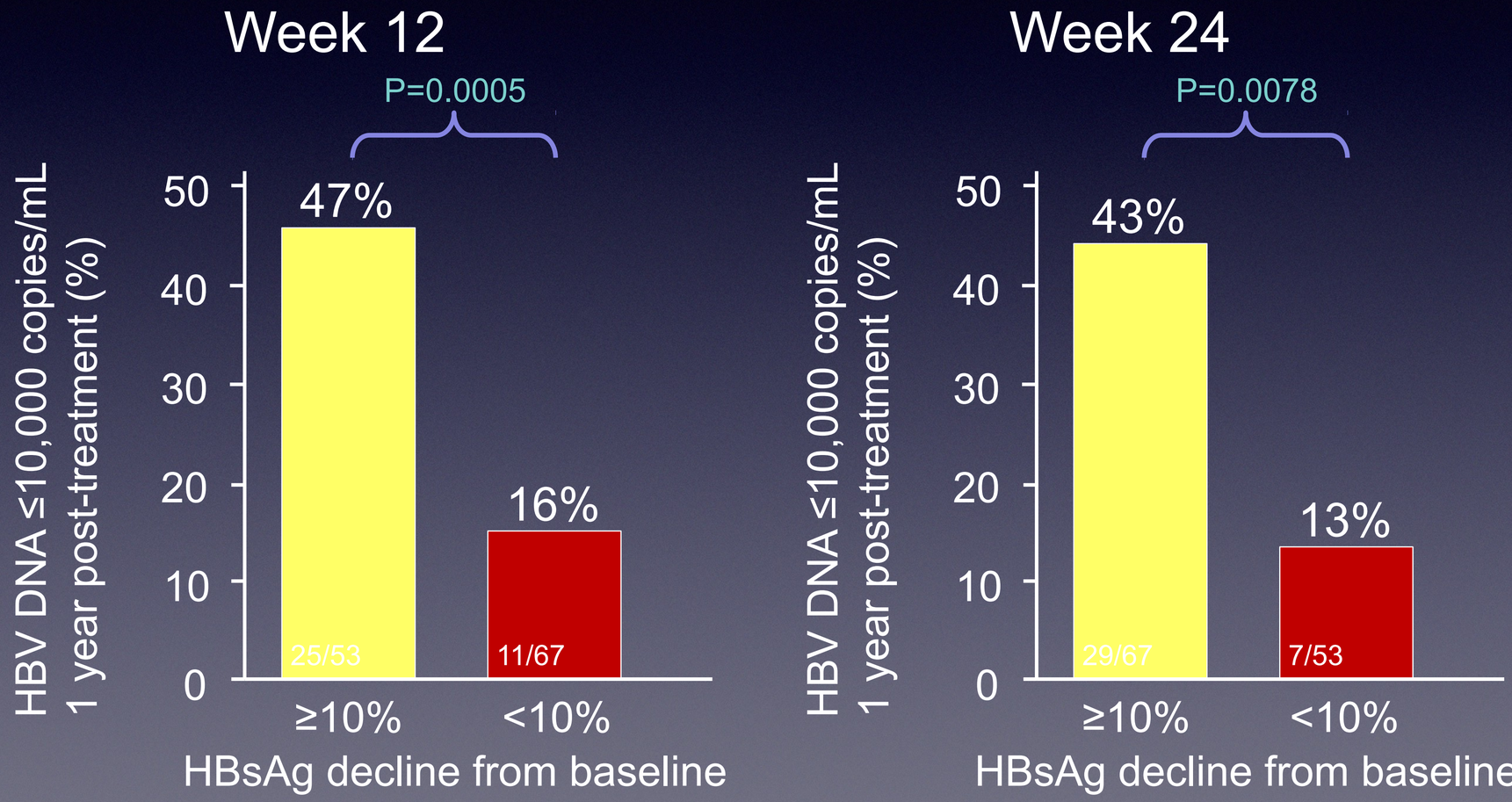




Moucari et al. Hepatology 2009

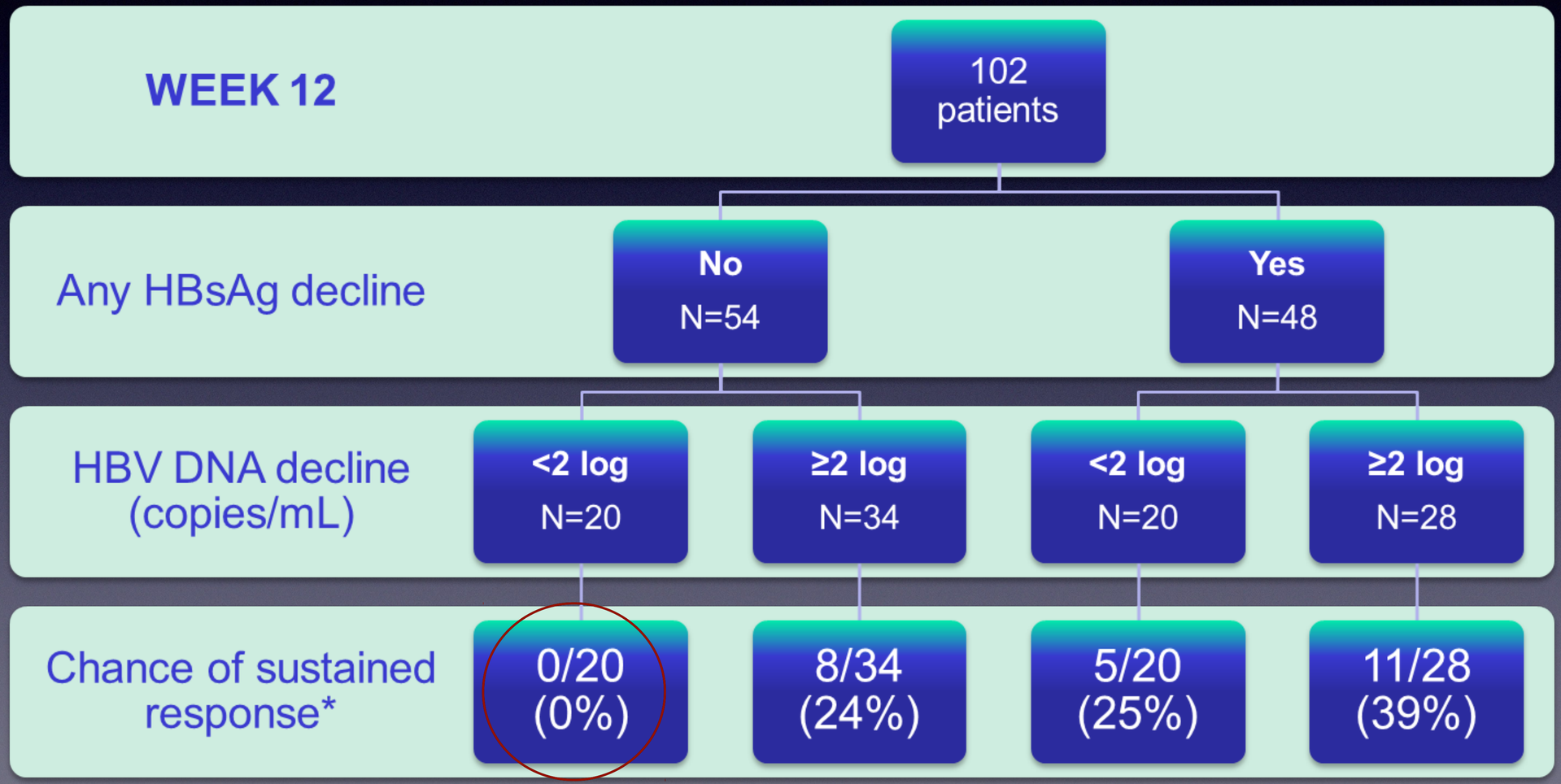
qHBsAg: Predictor of Response in HBeAg (-) Patients Treated with PEG-IFN

230 patients with HBeAg-negative CHB treated with peg-IFN alfa 2a ± lamivudine*



Marcellin et al. Hepatol Int. 2013

qHBsAg: Predictor of Response in HBeAg (-) Patients Treated with PEG-IFN



Rijckborst et al. Hepatology 2010 – Rijckborst et al. J Hepatol 2012 – EASL Guidelines J Hepatol 2012

CASE - 2

- Patient Decide to Start Oral Therapy with ETV 0.5 mg / day
- At Treatment Week 24: HBV DNA < LLD
- At Treatment Week 48: HBV DNA < LLD
- At Treatment Week 96: HBV DNA < LLD

Treatment Duration?

1. Life - Time Treatment
2. 5 Years of HBV DNA Undetectability
3. HBsAg Loss
4. HBsAg Decline < 200 U/mL

Treatment Duration with NUCs

Long-term treatment with ETV / TDF is necessary for patients who are not expected to achieve a sustained off-treatment virological response

- HBeAg-positive patients who do not develop anti-HBe seroconversion

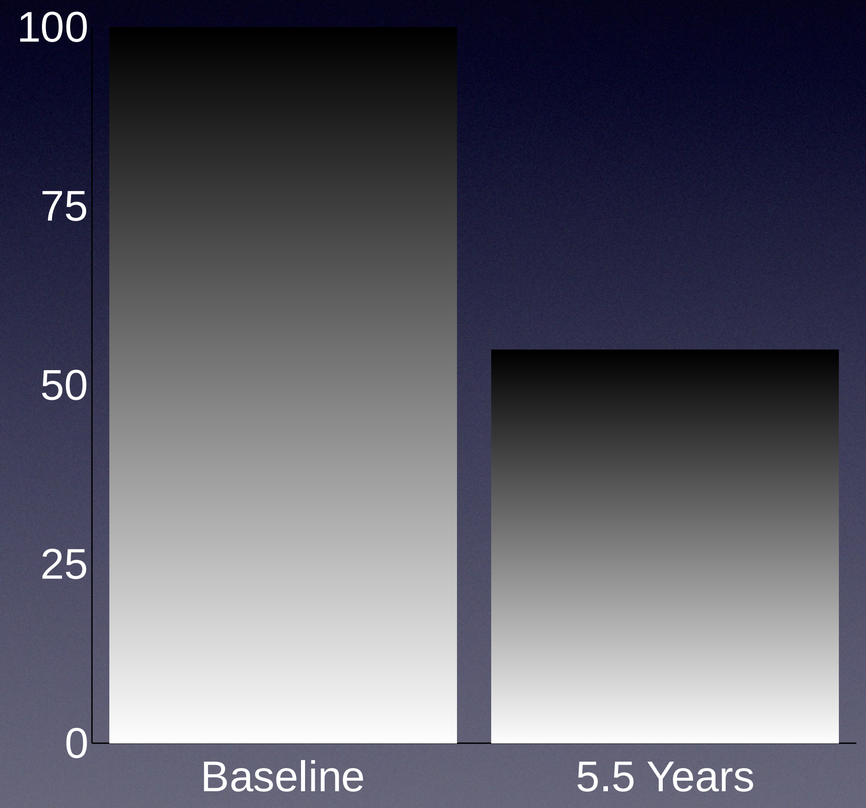
&

- HBeAg-negative patients

EASL Guidelines J Hepatol 2012

Sustained Response in HBeAg (-) Patients Treated with NUCs

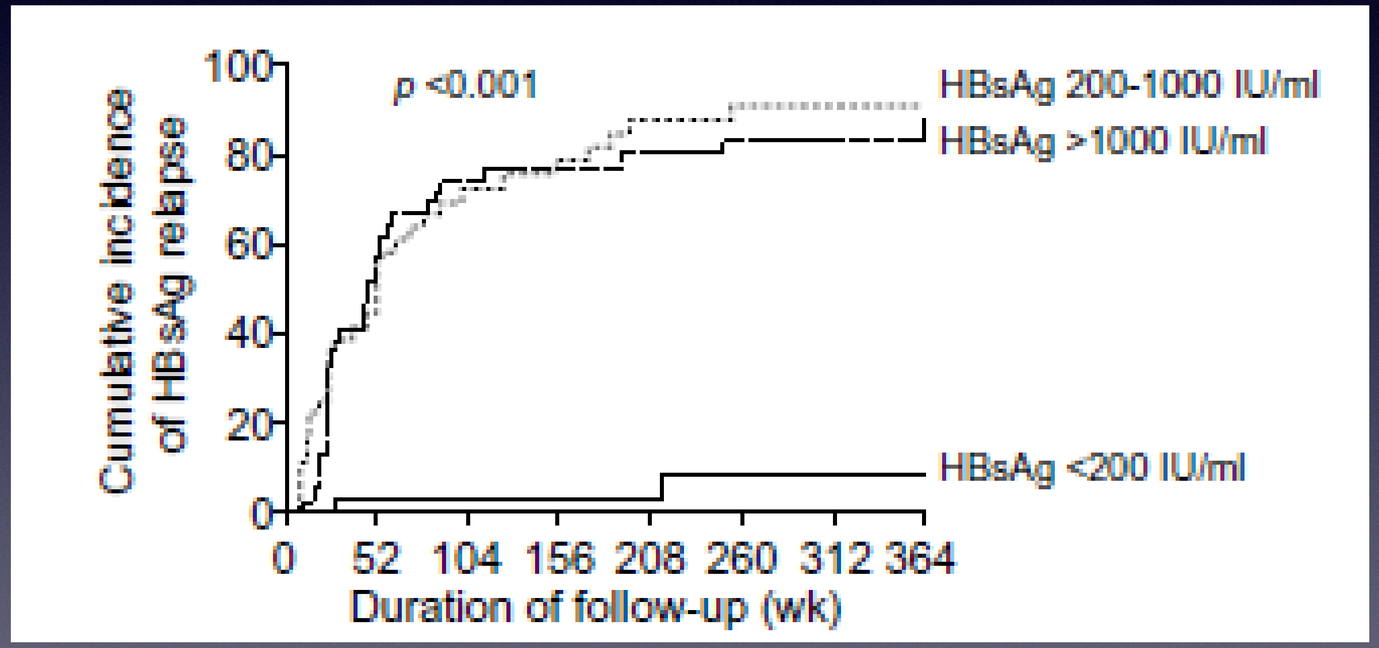
- 33 HBeAg (-) Patients
- ADV for 5 Years
- 55% SVR
- Lower HBsAg Level



Hadziyannis et al. Gastroenterology 2012

qHBsAg Predictor of SVR in HBeAg (-) Patients Treated with NUCs

- 105 HBeAg (-) Patients
- Lamivudine for 52 - 243 weeks
- FUP: 12 - 157 months
- Relapse Rate: 43.4%, 60.1% & 68.4% at years 1, 3 & 6
- HBsAg < 200 U/mL had a PPV 93.3% for SVR



Chen et al, J. Hepatol 2014

CASE - 3

- 32 Years Old Patient
- HBsAg (+) HBeAg (+) HBeAb (-)
- HBV DNA = 12 650 000 U/mL HBsAg = 11 460 U/mL
- Genotype A
- ALT = 142 U
- Abdominal US Normal

Management?

1. Start PEG-IFN Injections - Good Genotype
2. Start NUCs (TDF or ETV) - High HBV DNA
3. Combination PEG-IFN + NUC

Treatment Indications in HBeAg (+) Patients

- Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy showing moderate to severe active necro-inflammation and/or at least moderate fibrosis

- Patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy

EASL Guidelines. J Hepatol 2012

Treatment Endpoints in HBeAg (+) Patients

- The ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs
- Induction of sustained off-therapy virological (sustained HBe seroconversion, HBV DNA < 2000 U/mL) and bio- chemical response (Normal ALT) is a satisfactory end point
- A maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy in patients who do not achieve anti-HBe seroconversion is the next desirable endpoint

EASL Guidelines J Hepatol 2012

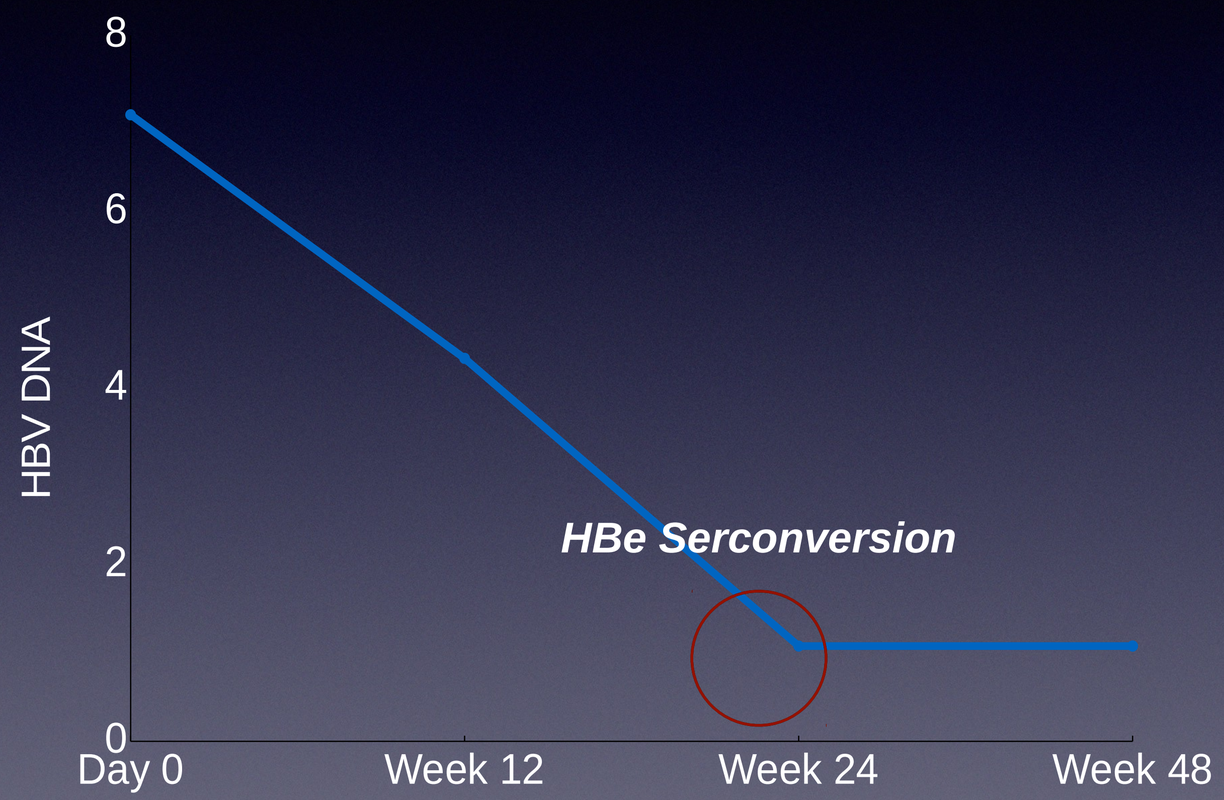
Treatment Modalities in HBeAg (+) Patients

- A 48-week course of PEG-IFN is mainly recommended for patients with the best chance of anti-HBe seroconversion (Genotypes A & B, Low HBV DNA and High ALT)

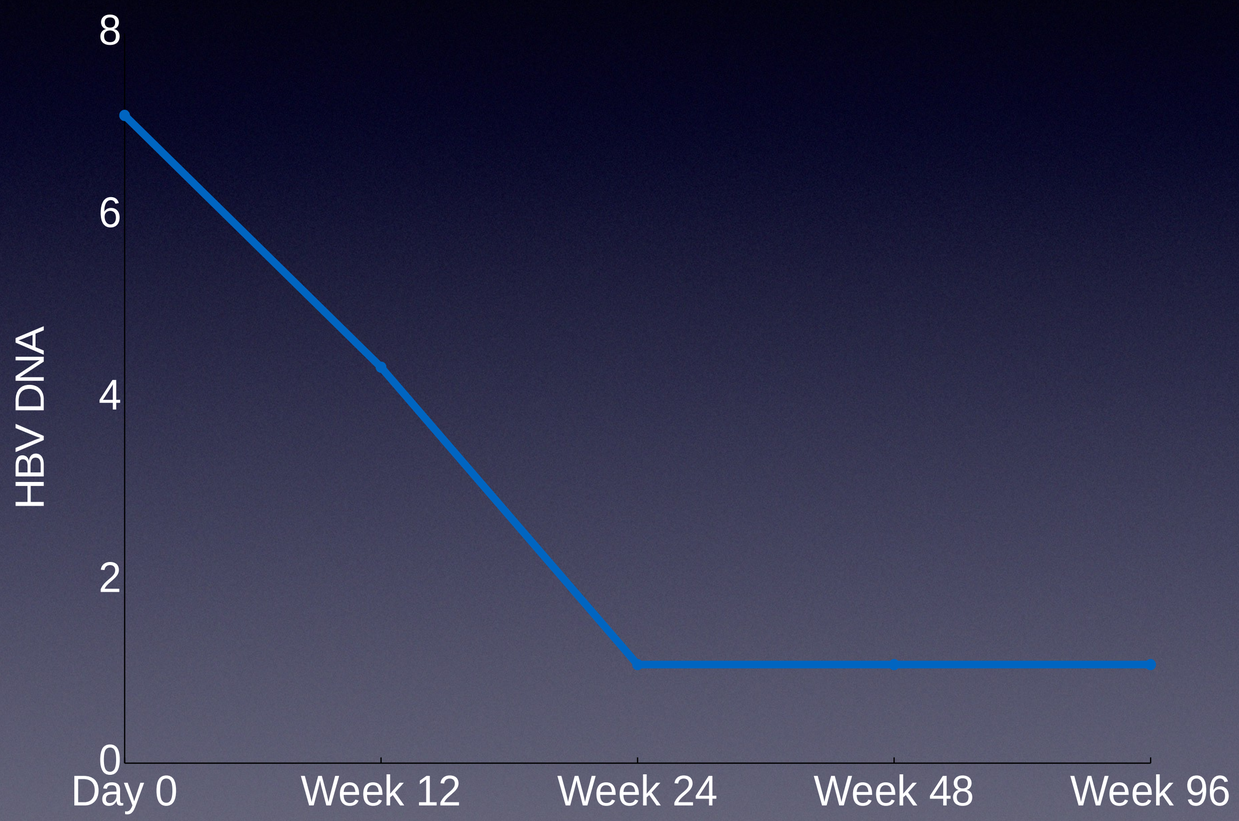
- A Finite-duration treatment with a NA is achievable for HBeAg-positive patients who seroconvert to anti-HBe on treatment. Once anti-HBe seroconversion occurs during NA administration, treatment should be prolonged for an additional 12 months

EASL Guidelines. J Hepatol 2012

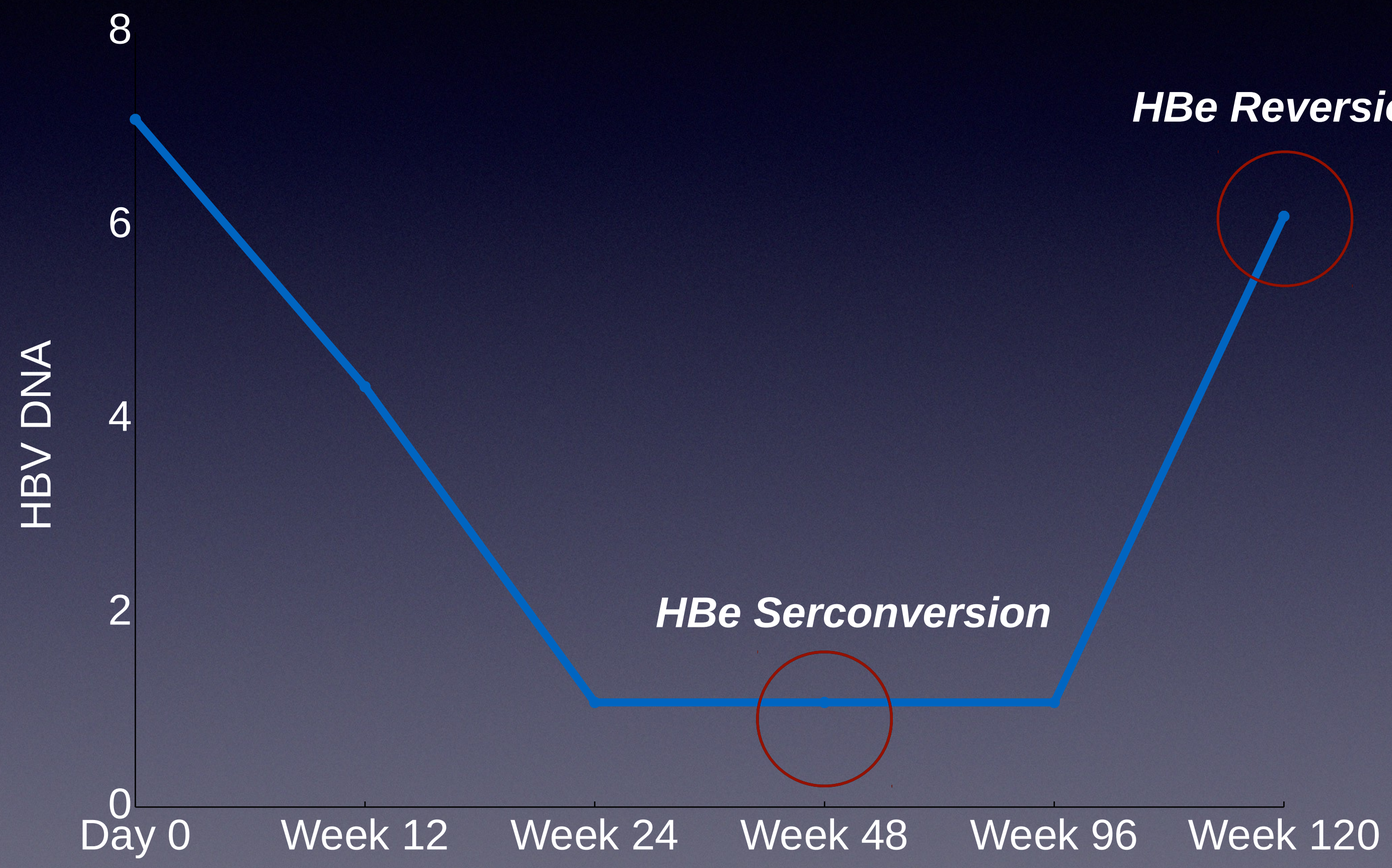
Case - 3: On-Treatment (TDF) HBV DNA Pattern



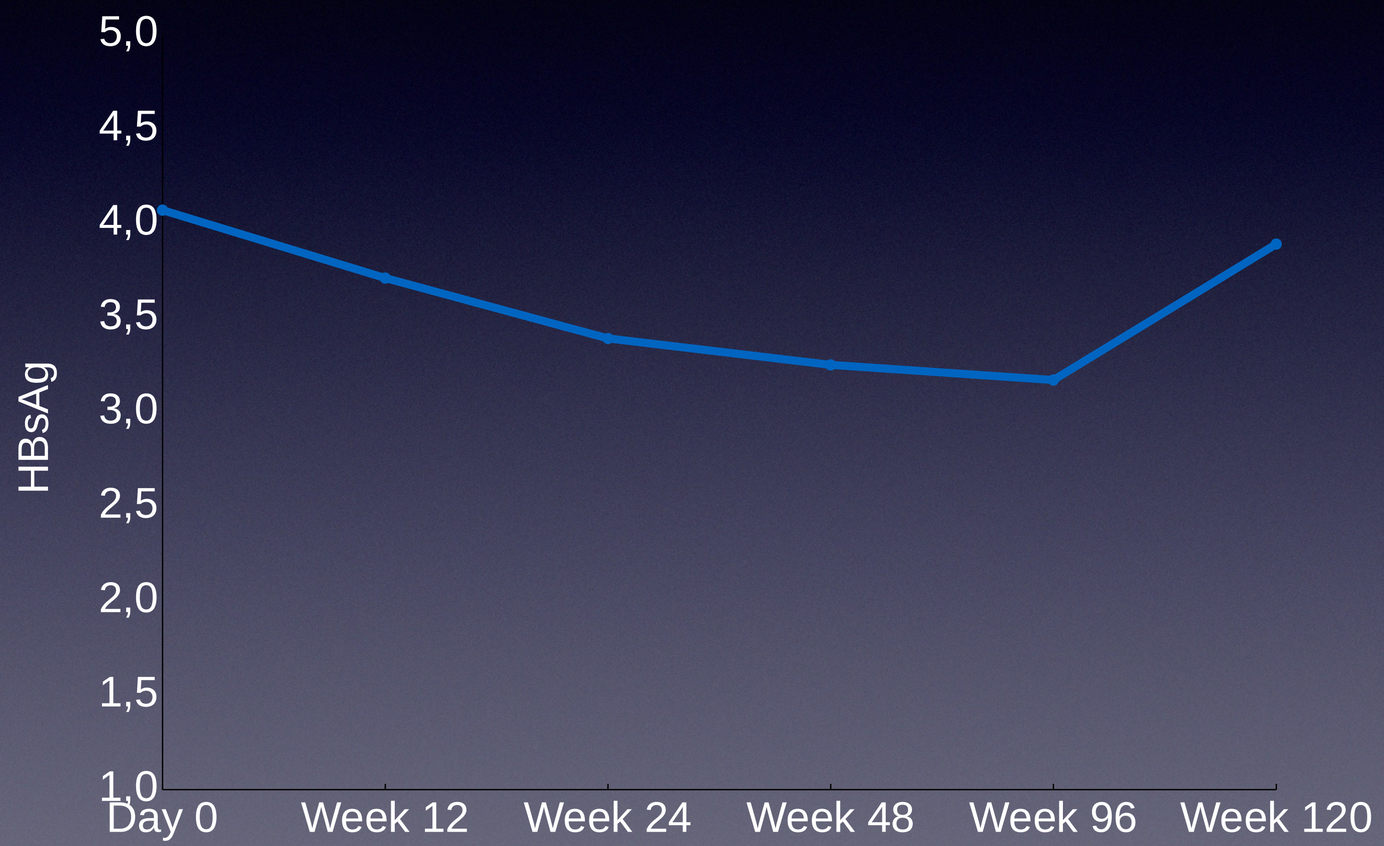
Case - 3: On-Treatment (TDF) HBV DNA Pattern



Case - 3: On-Treatment (TDF) HBV DNA Pattern

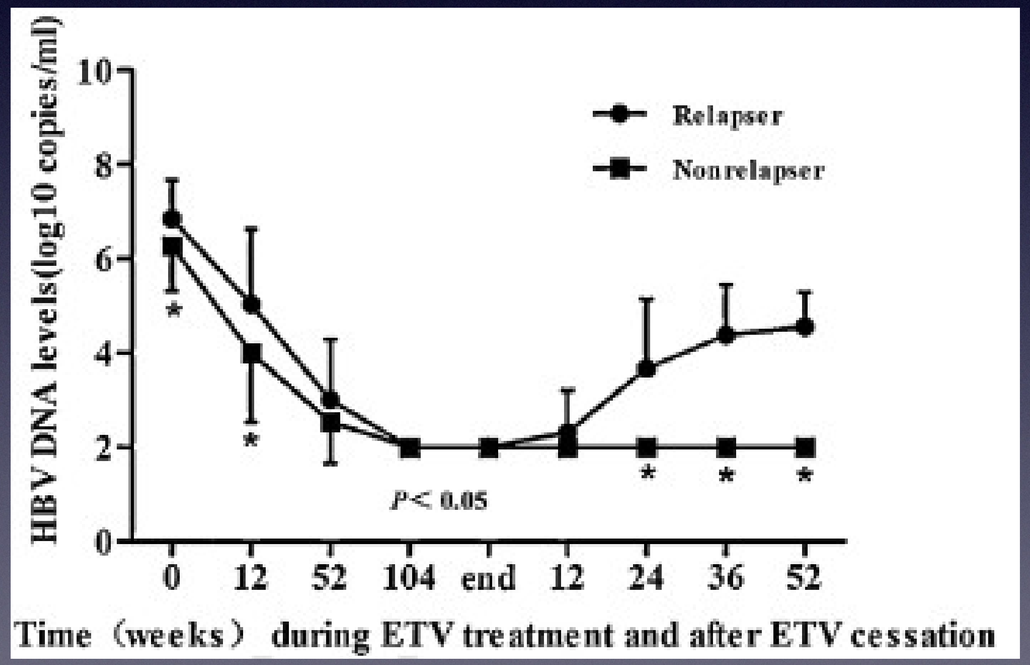


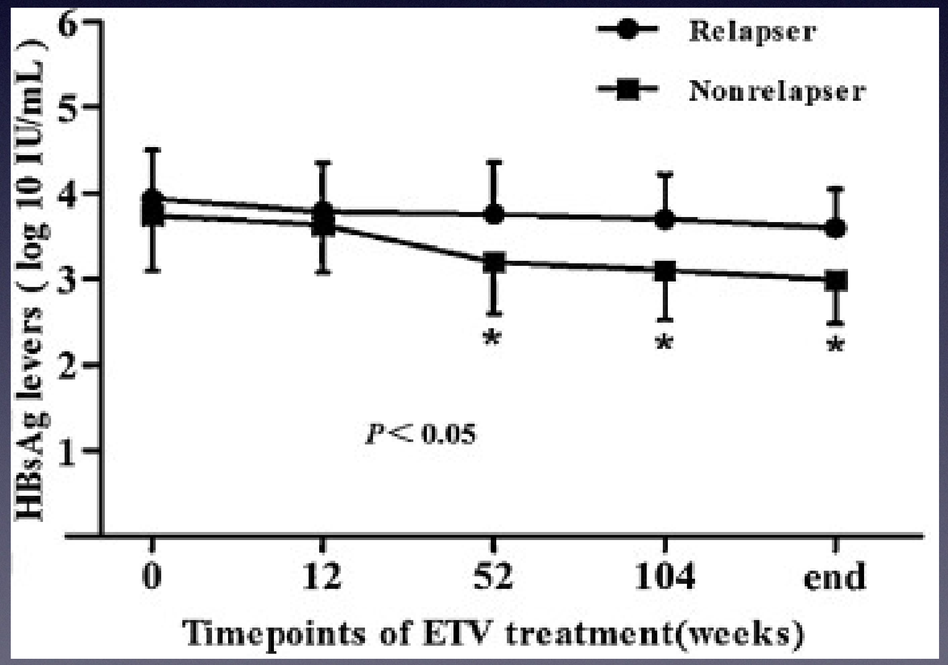
Case - 3: On-Treatment (TDF) HBsAg Pattern



qHBsAg: Predictor of SVR in HBeAg (+) Patients Treated with NUCS

112 HBeAg (+) Patients
ETV for 26 - 40 Months, including at Least 12 Months after HBe Seroconversion
ETV Was Stopped with Post-Treatment FUP of 52 Weeks

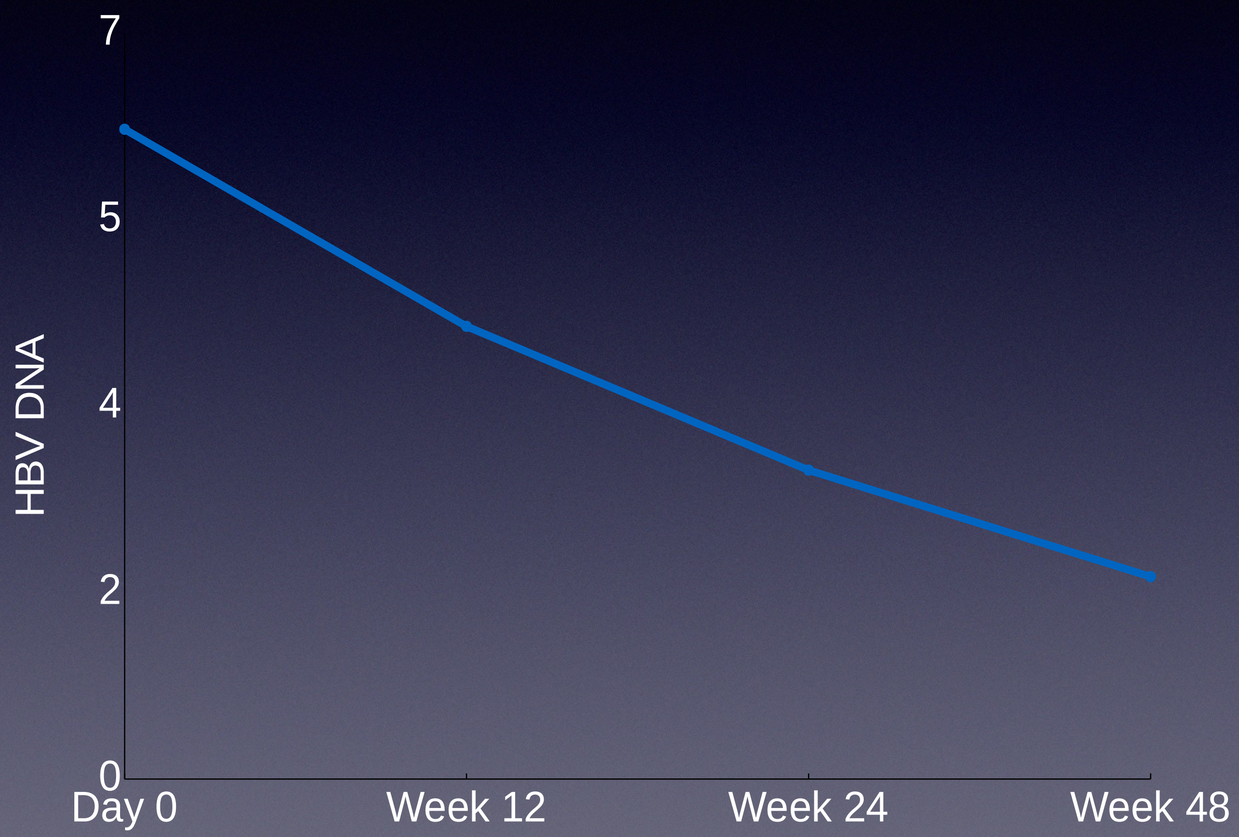




Relapse Rate = 48.2%. HBsAg level of 2.5 log10 IU/ml at HBeAg seroconversion had a PPV = 95 % for SVR

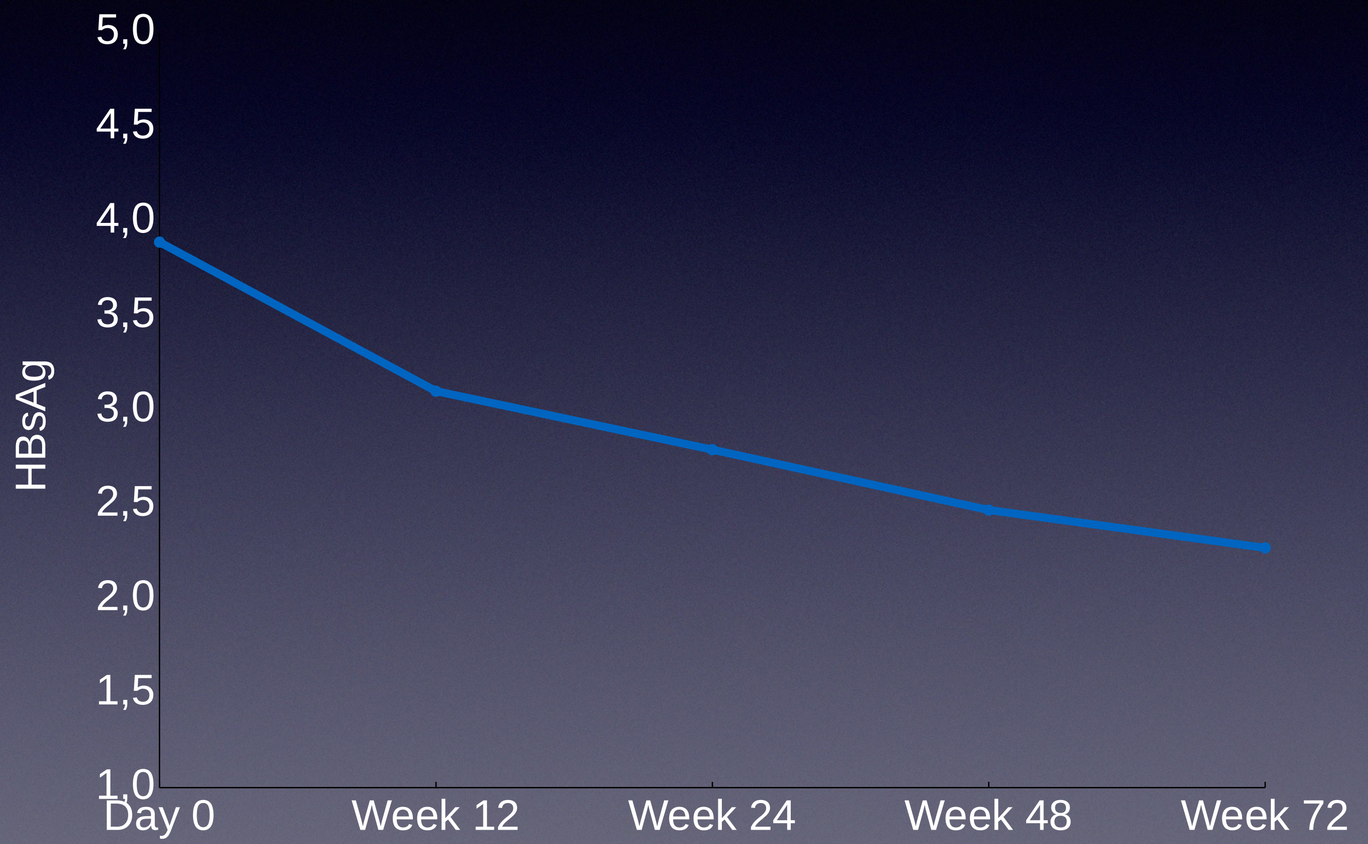
Qiu et al, JID 2014

Case - 3: On-Treatment (PEG-IFN)
HBV DNA Pattern

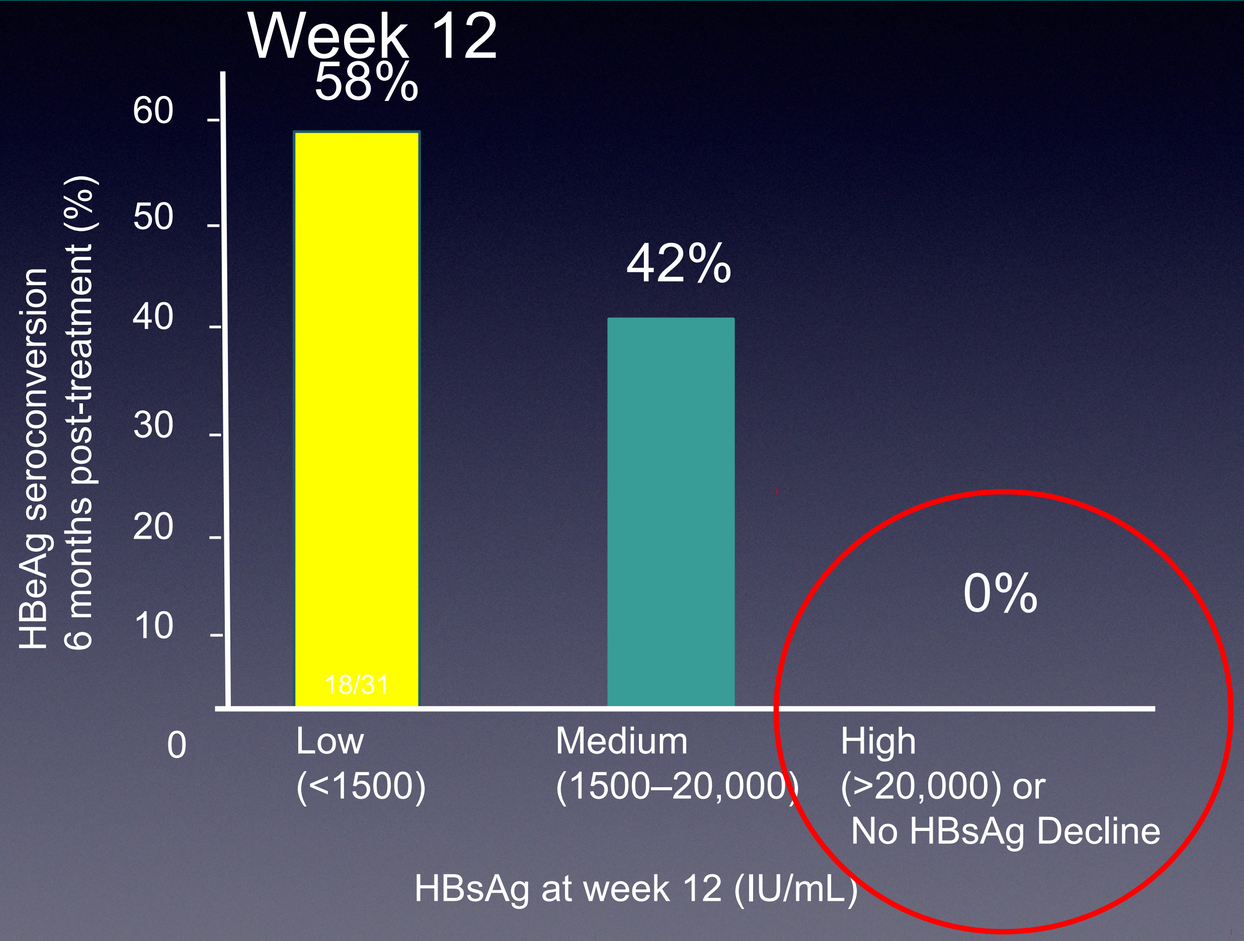


Case - 3: On-Treatment (PEG-IFN)
HBV DNA Pattern

Case - 3: On-Treatment (PEG-IFN)
HBsAg Pattern



qHBsAg: Predictor of SVR in HBeAg (+) Patients Treated with PEG-IFN



EASL Guidelines. J Hepatol 2012 – Liaw et al. Hepatology 2011 – Sonneveld et al. Hepatology 2013

Take Home Messages

HBsAg: Different then HBV DNA

qHBsAg: May Reflect the Number of Infected Hepatocytes

qHBsAg: Clinically Relevant Marker

in Combination with HBV DNA May Help to:
etermine the Stage of the Disease (Inactive Carrier Vs. Active Hepatitis)
redict Sustained Off-Treatment Response to PEG-IFN & NUCS
ailor the Treatment Duration & Generate Stopping Rules