



Treatment of Chronic Hepatitis B in an HBeAg Positive Patient

Adrián Gadano, MD

Chief, Liver Unit - Hospital Italiano

President, Fundación Icalma

Buenos Aires - Argentina

ICALMA
FUNDACION DE CUIDADOS INTEGRALES



Case 1: History

- 52-year-old man.
- Referred from a gastroenterologist for HBeAg + CHB.
- Diagnosis established 3 years before, when donating blood (HBsAg positive).
- Possible route of transmission: high-risk sexual contacts during adolescence.
- No family history of HBV. Alcohol use occasional.
- Asymptomatic. Physical exam unremarkable.
- He had received 2-year therapy with lamivudine after diagnosis with unknown outcome...



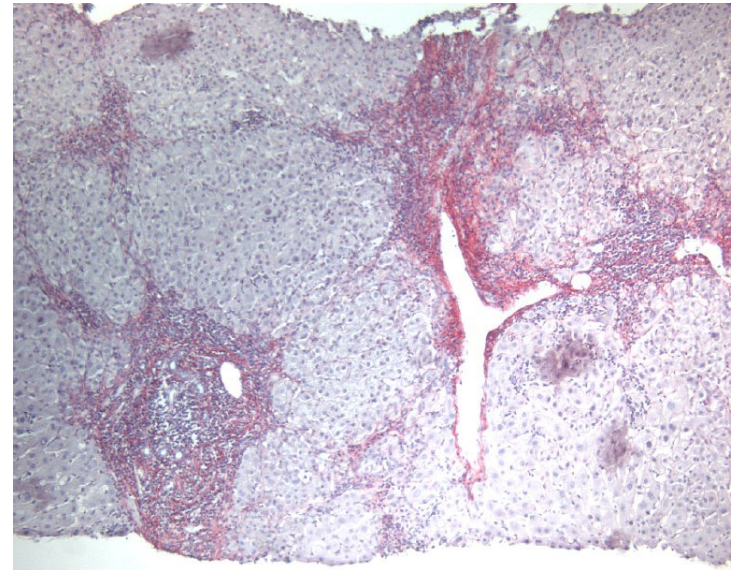
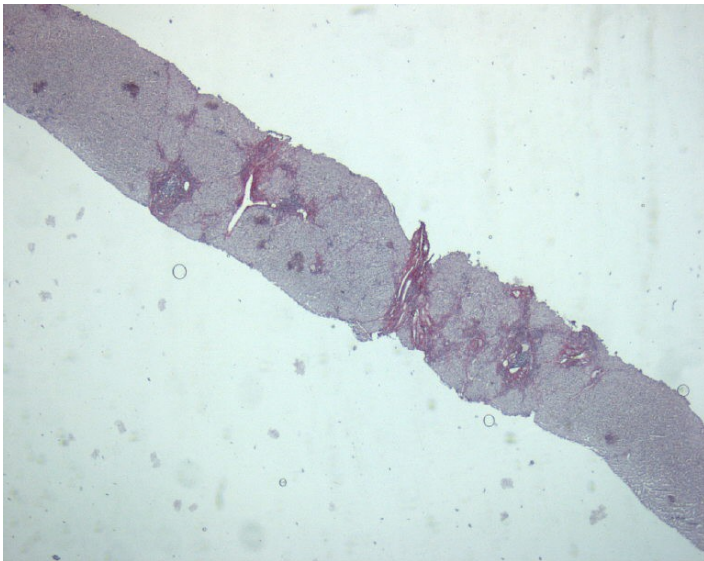
Current presentation

- Serological and biochemical status at baseline:
 - ALT level: 112 IU/L (ULN: 40 IU/L).
 - AST level: 87 IU/L (ULN: 40 IU/L).
 - HBsAg: positive.
 - HBeAg: positive / anti-HBe: negative.
 - HBV DNA level was 7.8 log₁₀ copies/mL.
 - Albumin 3.7 mg/dL, total bilirubin 1.0 mg/dL, platelet count 198.000/mm³, INR 1 and serum creatinine 1.0 mg/dL.
 - HCV and HIV were negative.
- Ultrasound: mild heterogeneous liver architecture with no focal lesions.



Current presentation

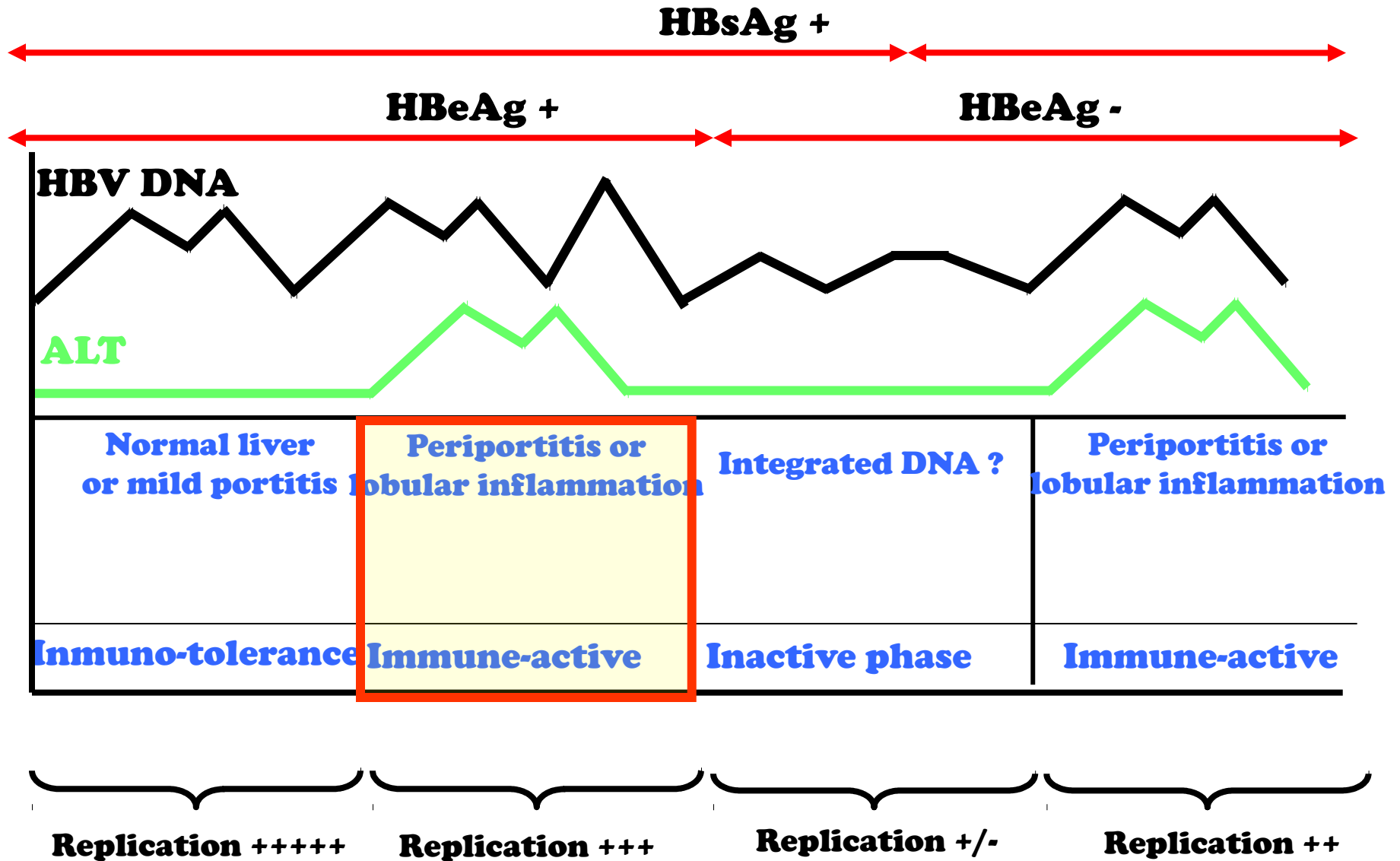
- Liver biopsy (3 years before): moderate inflammation and fibrosis extending outside the portal tracts (Metavir A2, F3).



- Fibroscan: 9.1 KPa



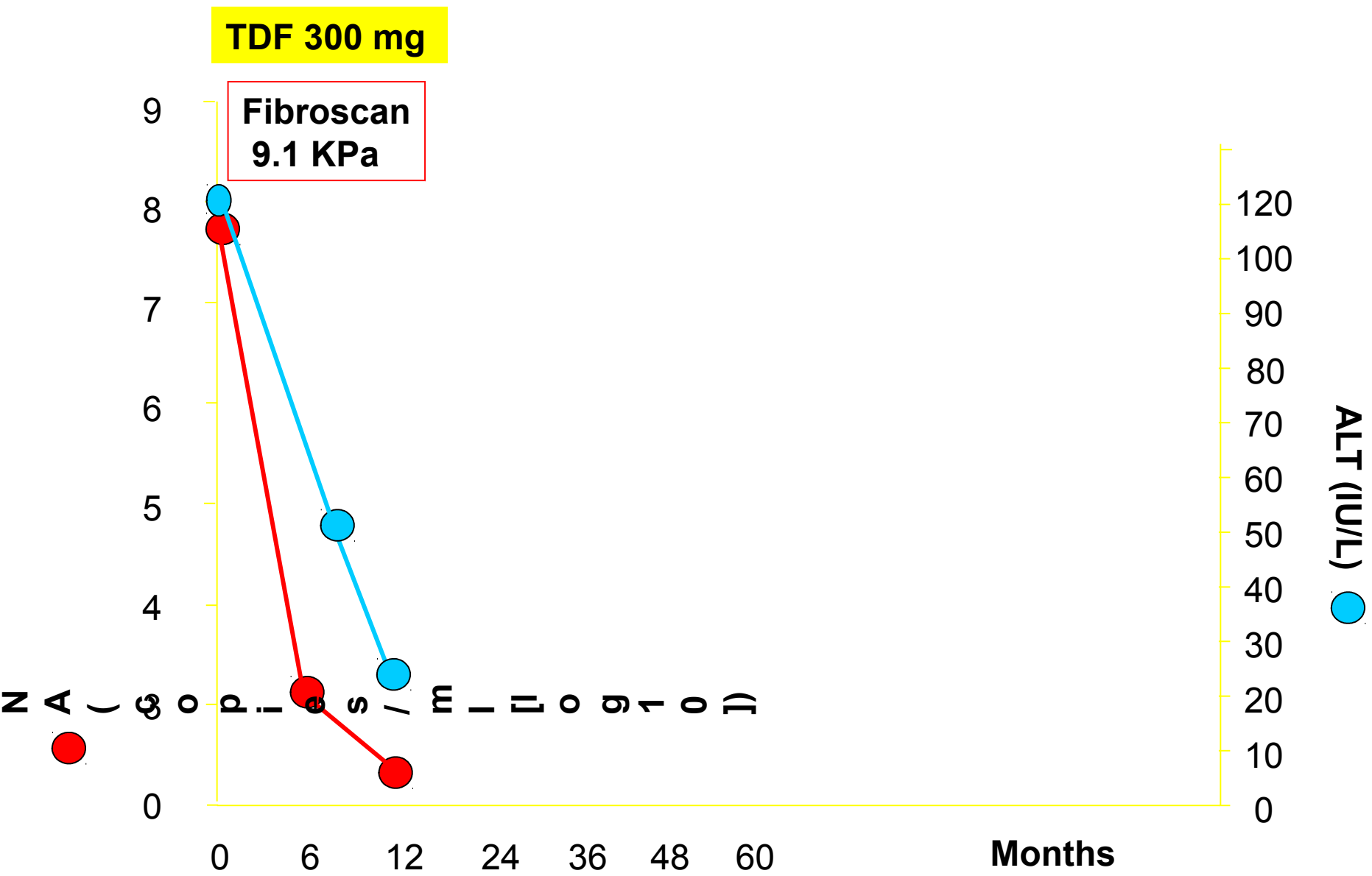
Natural History of Chronic Hepatitis B



Decision-making process and outcome

- Treatment with tenofovir was started at the dose of 300 mg/day.
- TDF was well-tolerated.
- After 12 months of therapy, HBV DNA level was undetectable and ALT was normal. HBsAg and HBeAg remained positive.





N A (S o p r e s / m - u o g 1 0)

HBeAg pos

HBsAg pos



TDF 300 mg

**Fibroscan
9.1 KPa**

**Fibroscan
7.1 KPa**

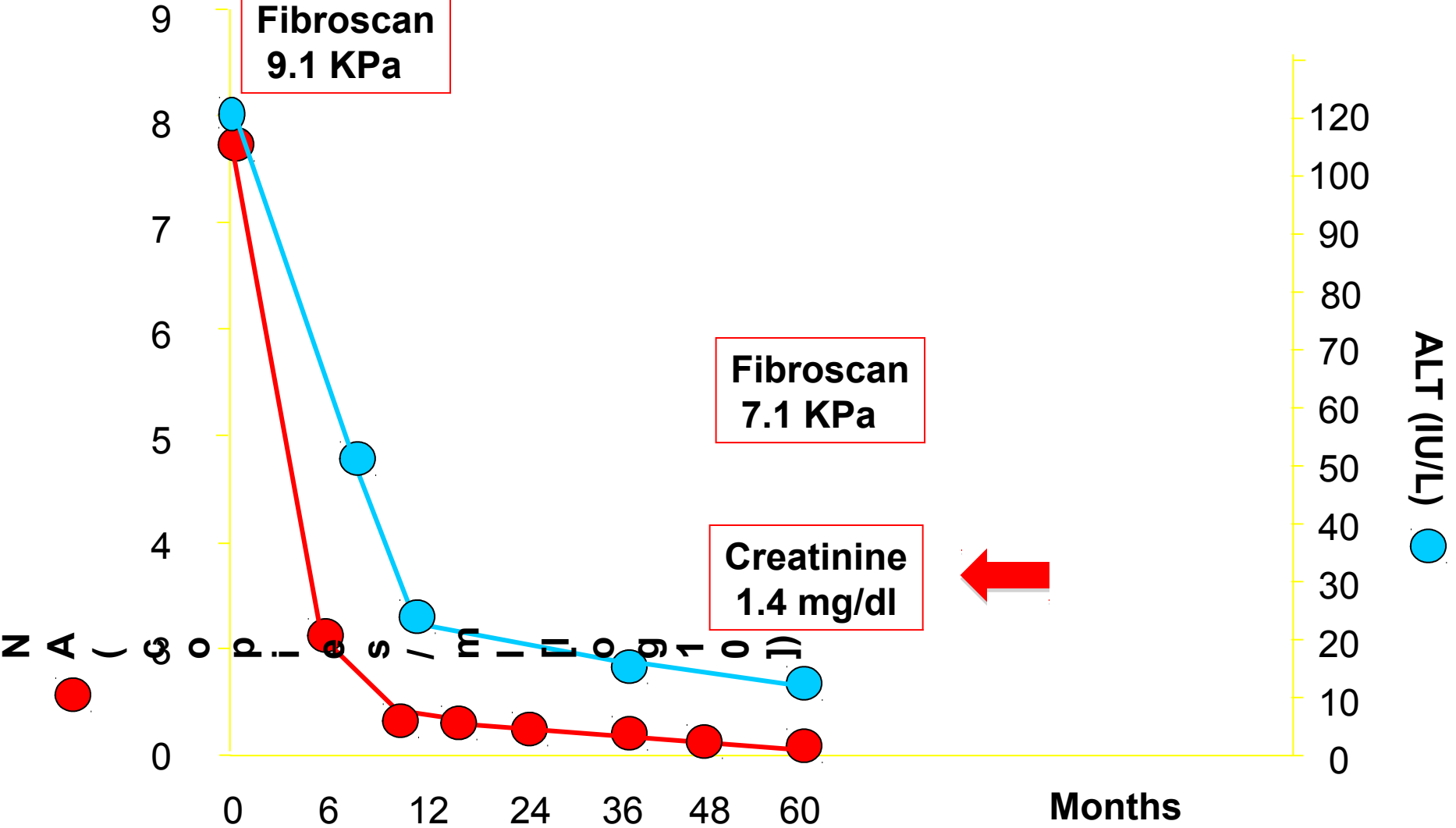
**Creatinine
1.4 mg/dl**

ALT (IU/L)

HBsAg pos

HBeAg pos

HBsAg pos



What would you recommend at this time?

- a. Stop tenofovir and start entecavir
- b. Stop tenofovir and start PEG IFN alfa 2a
- c. Add PEG IFN alfa 2a
- d. Continue with tenofovir





Treatment of Chronic Hepatitis B in an HBeAg Negative Patient

Adrián Gadano, MD

Chief, Liver Unit - Hospital Italiano

President, Fundación Icalma

Buenos Aires - Argentina

ICALMA
FUNDACION DE CUIDADOS INTEGRALES



Case 2: History

- 56-year-old woman.
- Diagnosis established 6 months before.
- Possible route of transmission: Family history of HBV (husband).
- Asymptomatic.

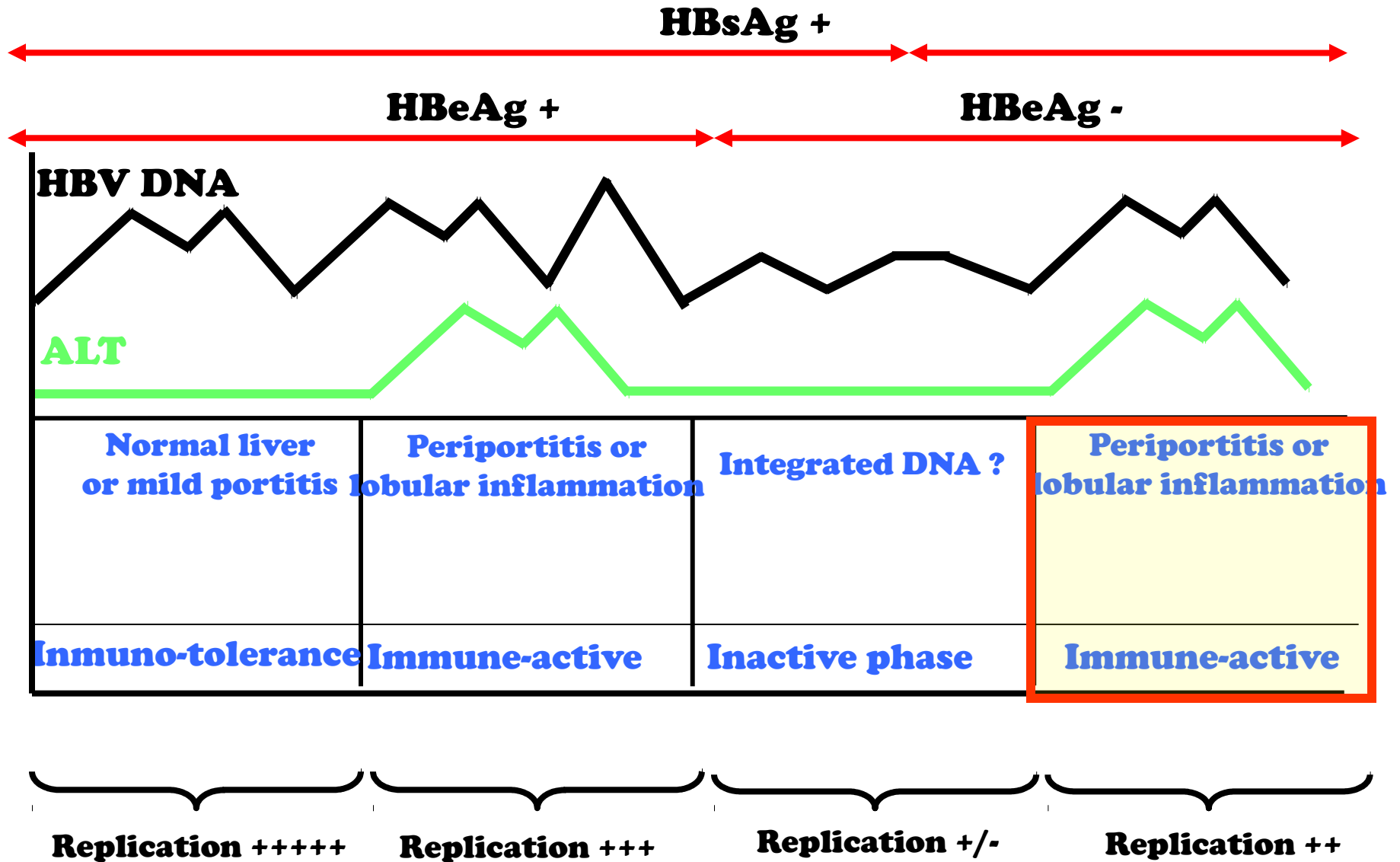


Current presentation

- ALT level: 86 IU/L (ULN: 40 IU/L).
- AST level: 77 IU/L (ULN: 40 IU/L).
- HBsAg: positive.
- HBeAg: negative / anti-HBe: negative.
- HBV DNA level: 6.8 log₁₀ copies/mL.
- HBV genotype: A
- Albumin 3.8 mg/dL, total bilirubin 1.1 mg/dL, platelet count 144.000/mm³, INR 1.1 and serum creatinine 0.8 mg/dL.
- HCV and HIV were negative.
- Ultrasound revealed heterogeneous liver architecture with no focal lesions.



Natural History of Chronic Hepatitis B



Decision-making process and outcome

- Treatment with entecavir was started at the dose of 0.5 mg/day.
- ETV was well-tolerated.
- After 12 months of therapy, HBV DNA level was undetectable and ALT was normal. HBeAg remained negative and HBsAg remained positive.
- After 60 months of therapy, ETV was discontinued.



Hepatitis B: CASE 2

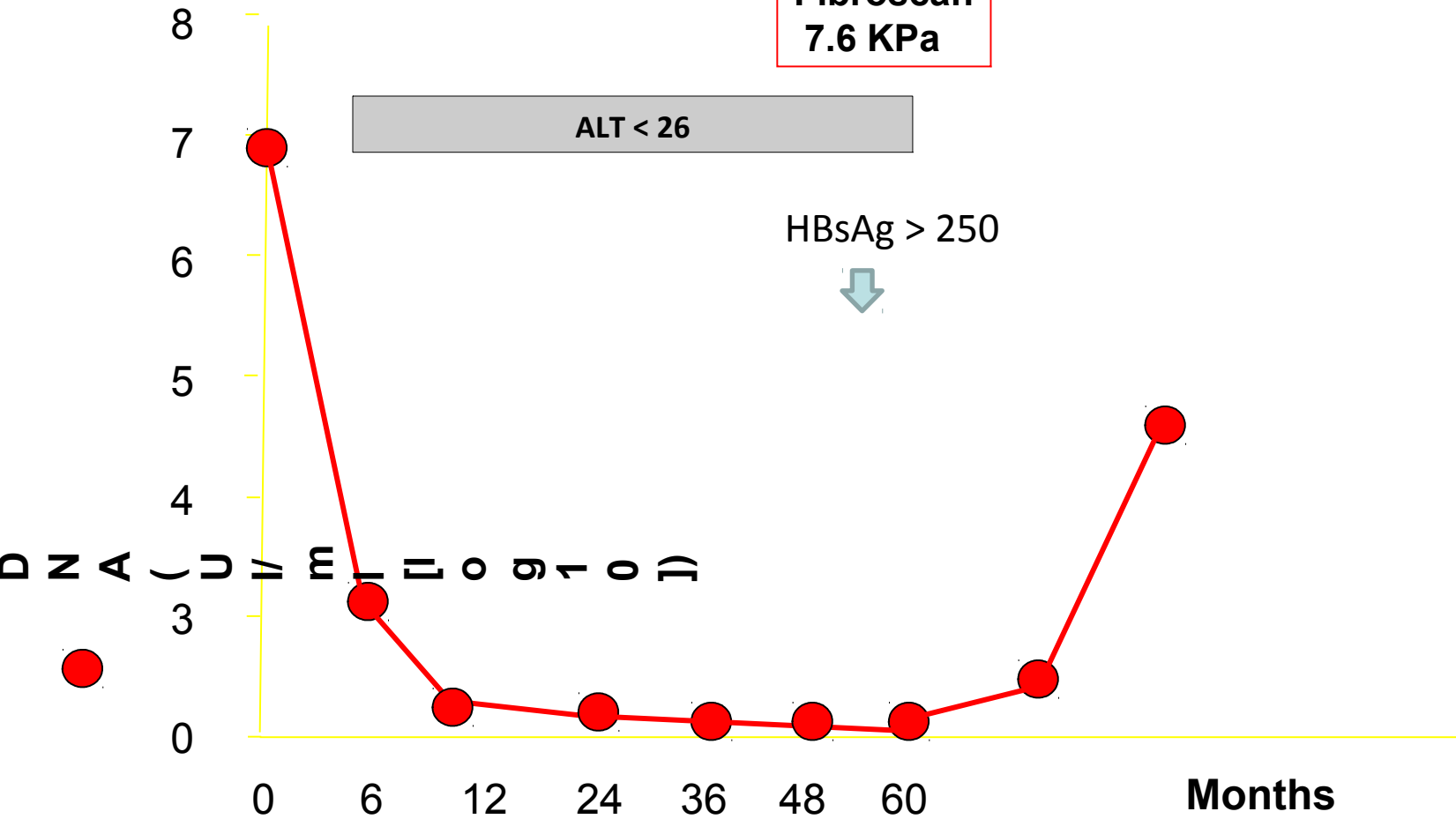
Fibroscan
10.2 KPa

Entecavir 0.5 mg

Fibroscan
7.6 KPa

ALT < 26

HBsAg > 250



HBeAg neg

HBsAg pos



Hepatitis B: CASE 2

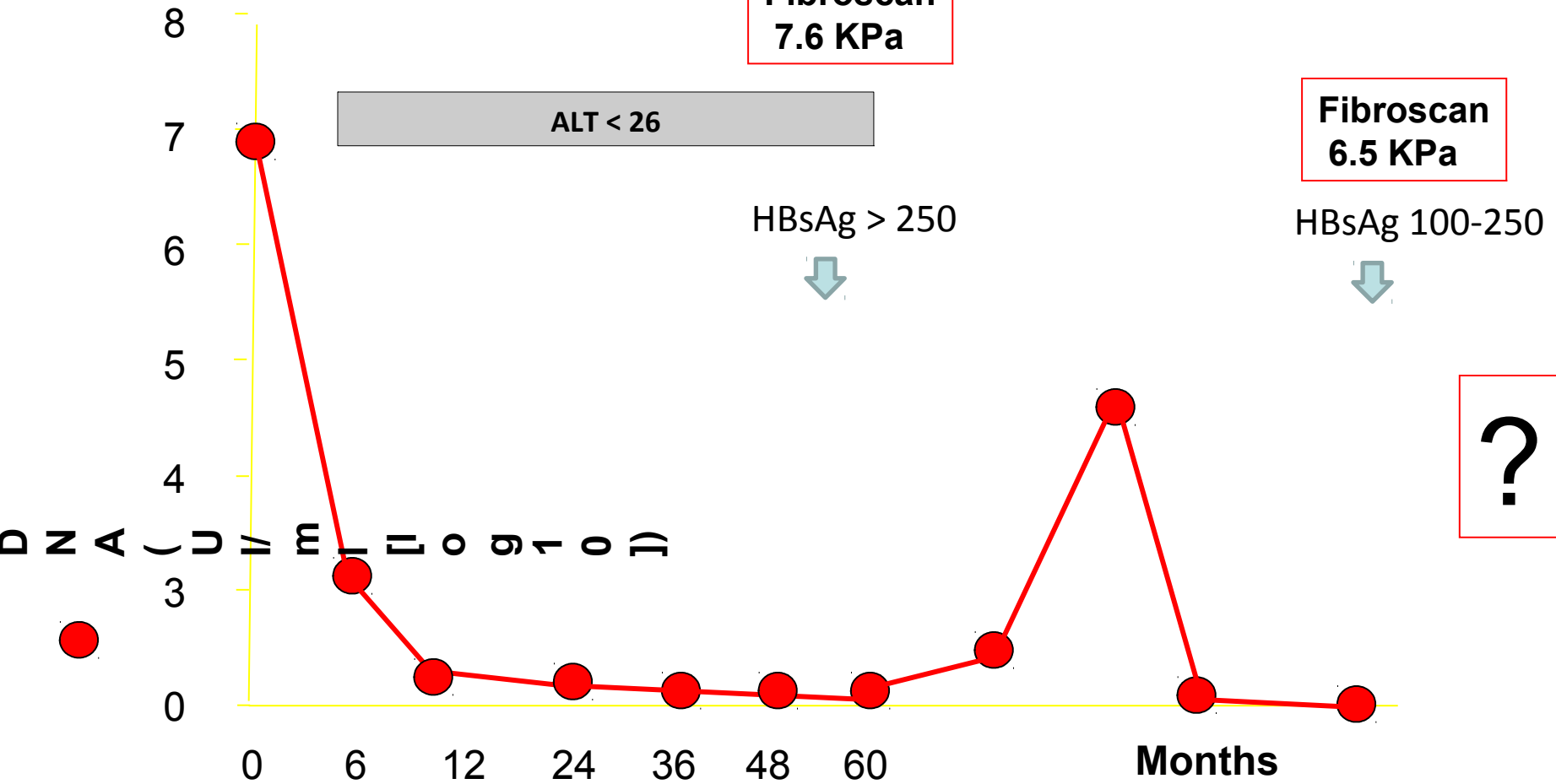
Fibroscan
10.2 KPa

Entecavir 0.5 mg

Entecavir 0.5 mg

Fibroscan
7.6 KPa

Fibroscan
6.5 KPa



HBeAg neg

HBsAg pos



What would you recommend at this time?

a. Stop entecavir ?

- According to HBsAg levels ? Below which threshold ?
- According to fibrosis stage ?

b. Start PEG IFN alfa 2a ?

- Taking into account HBsAg levels ?
- Taking into account fibrosis stage ?
- Switch or add-on ?
- For how long ?

...



Realistic goal → a “functional cure”:

- HBV DNA not detectable after a finite treatment
- Loss of HBsAg
- Regression of fibrosis
- Minimization of hepatocellular carcinoma risk

To accomplish this goal, a combination of antiviral drugs that target different steps in the HBV life cycle or immunomodulatory therapies to restore host immune response to HBV might be needed...



HBV: Improving therapeutic options...

Cure of HBV infection:
Is it possible ?



New strategies with
known drugs



New drugs with
different targets

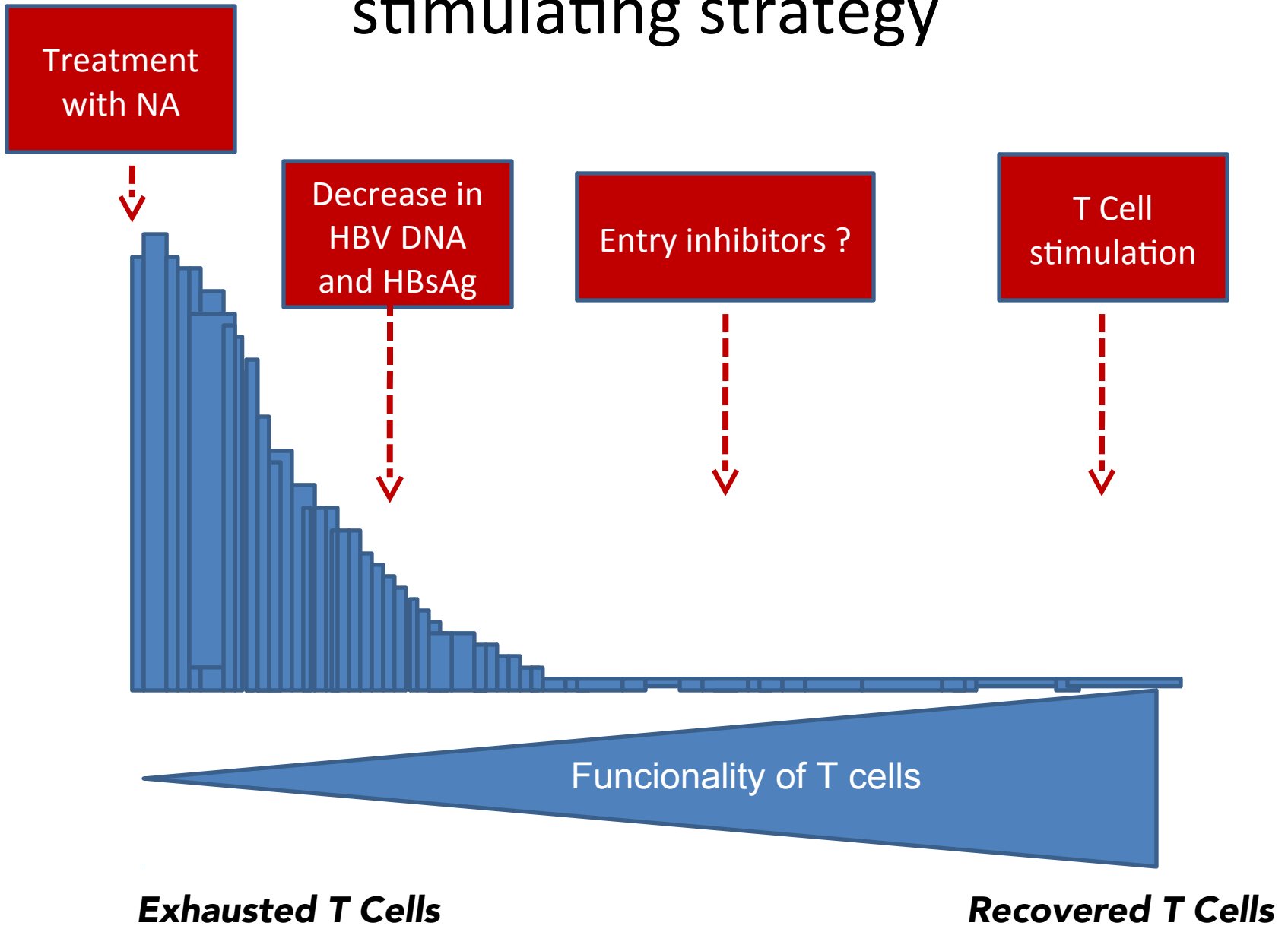


New Strategies with Known Drugs...

- Given the two classes of anti-HBV agents that are currently available, combination therapy consist of an NRTI (TDF or ETV) plus PEG-IFN.
- NRTI and PEG-IFN may be combined simultaneously, sequentially, starting with either drug first, or as an add-on strategy with either drug first.



Combined Antiviral and Immune-stimulating strategy



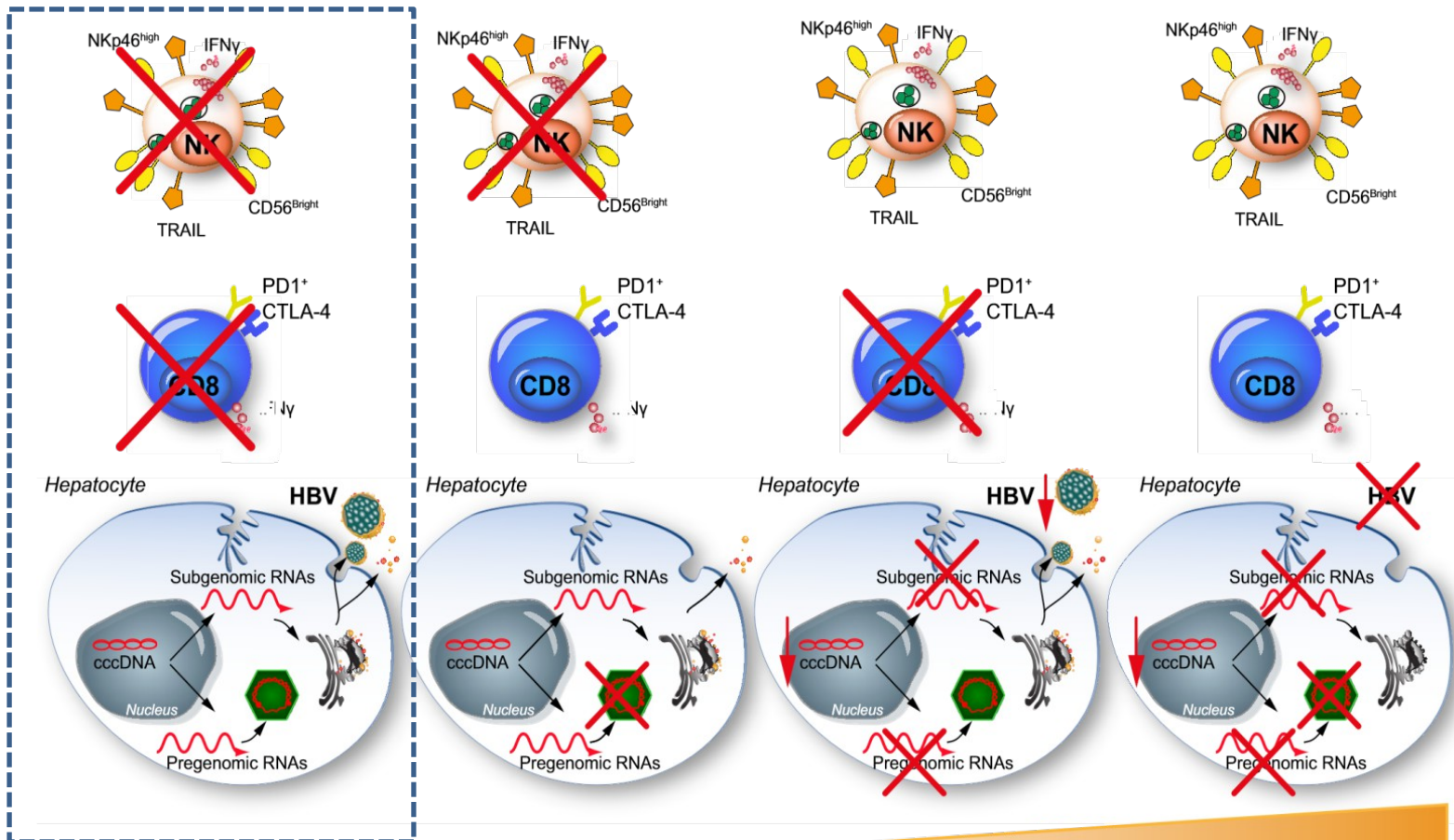
Combined Antiviral and Immune-stimulating strategy

Chronic HBV infection

ETV-TDF

Peg IFN

Peg IFN + AN



Restoration of immune response

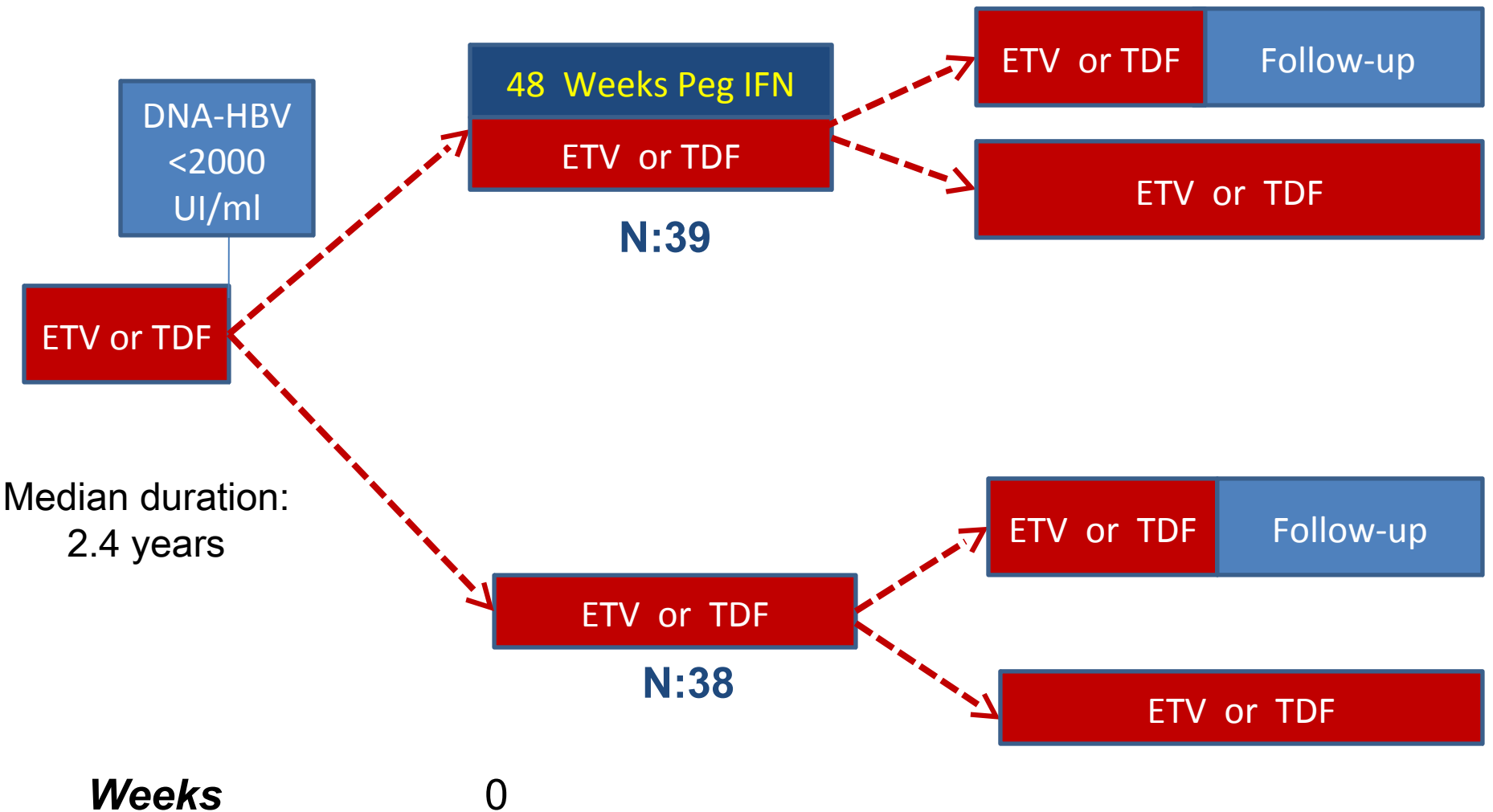
Combined Antiviral and Immune-stimulating strategy



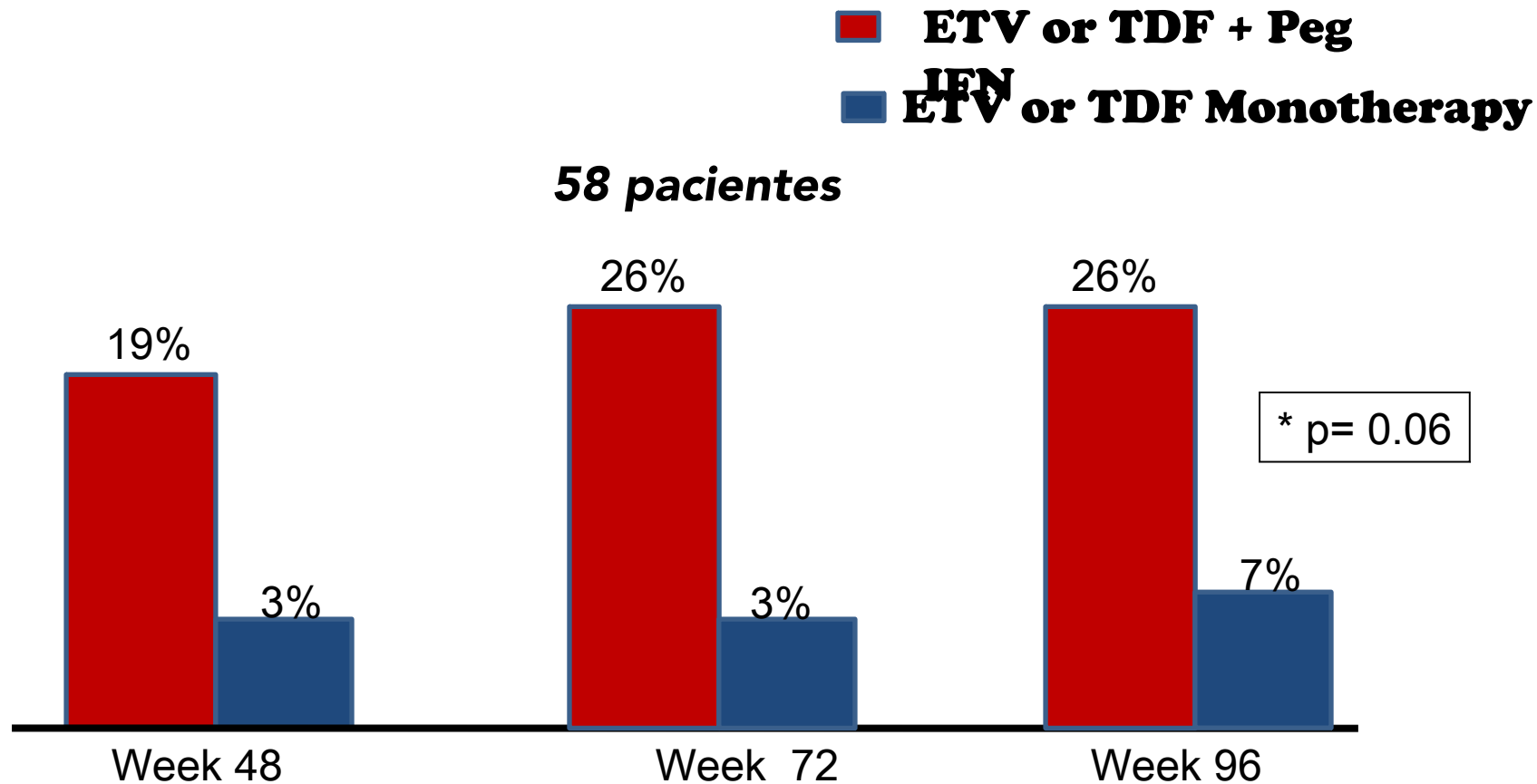
Peg-INF in patients previously treated with NA

PEGON study

HBeAg +



Seroconversion of HbeAg to anti-Hbe in patients with HBV DNA < 200 U/ml



HBV: Improving therapeutic options...

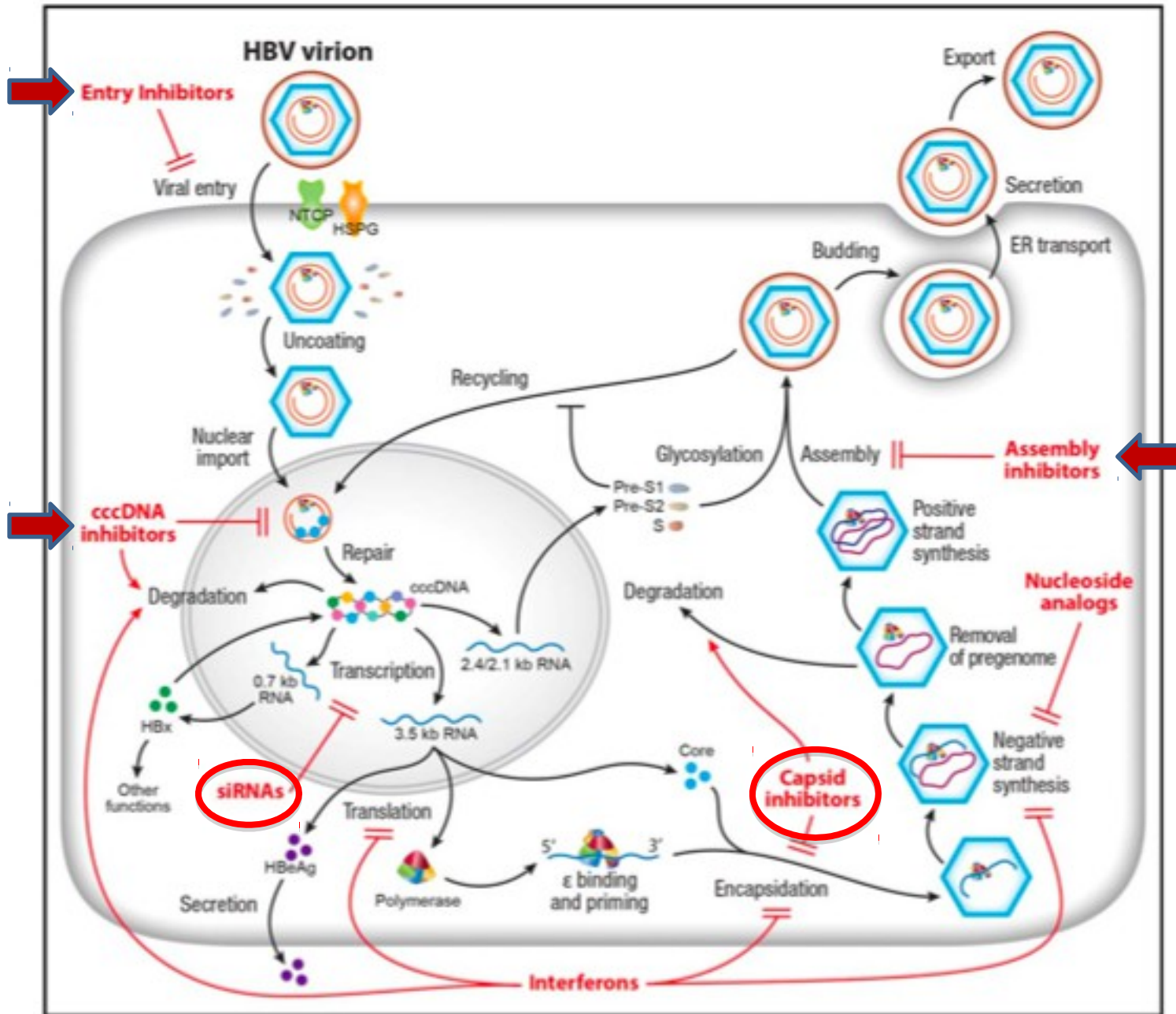
Cure of HBV infection:
Is it possible ?

New strategies with
known drugs



New drugs with
different targets





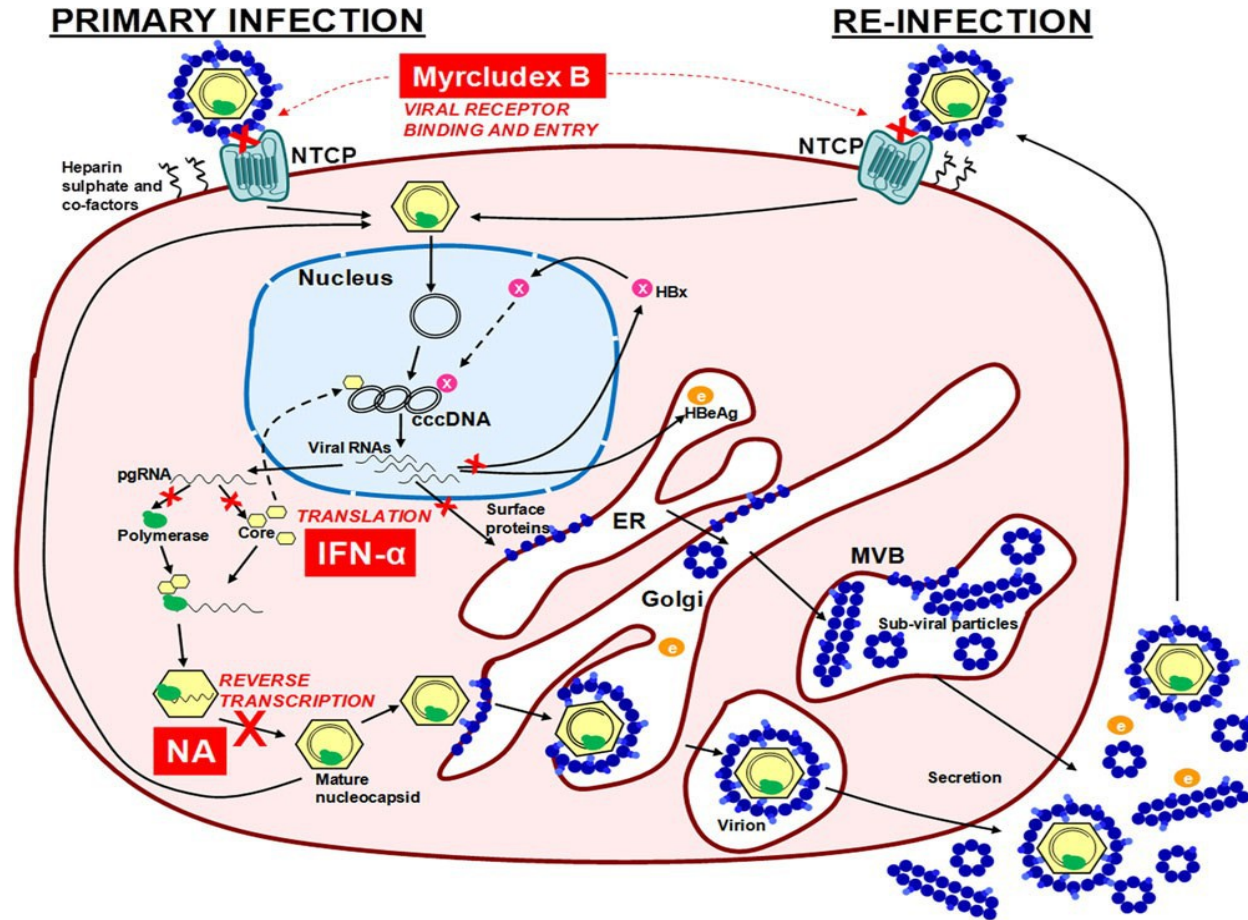
Experimental HBV Therapeutics in late preclinical or clinical phase

- Entry inhibitors: Myrcludex B, cyclosporine A...
- HBV capsid inhibitors: AT-130, Bay 41-4109...
- Inhibition of HBV gene expression.
- Inhibitors of HBV cccDNA formation and stability.
- Immune mechanisms of HBV control:
 - TLR agonists
 - PD-1 and other coinhibitory blockers
- Engineered T cells.
- Therapeutic vaccines...



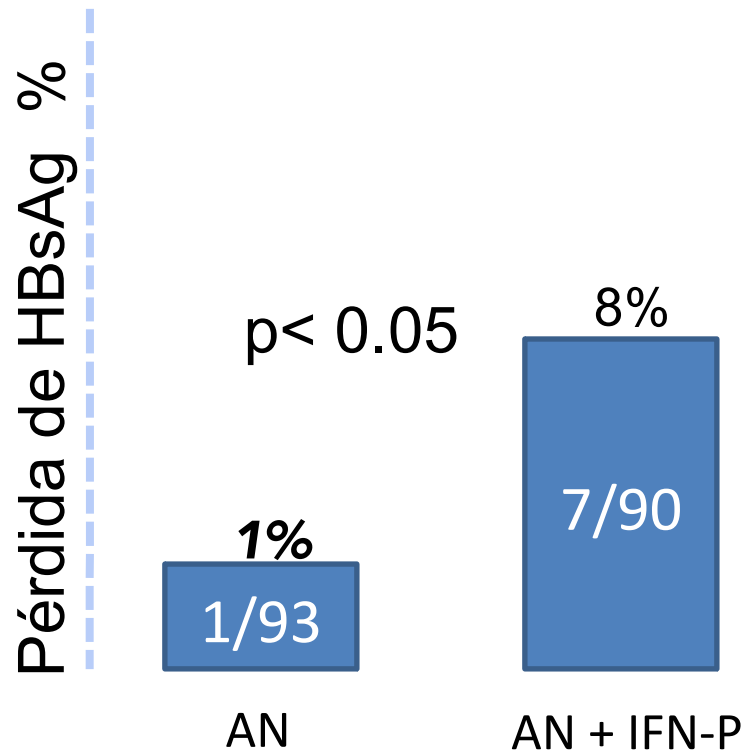
Back-up slides

Myrcludex B pre S1 Tratamiento contra HBV y HDV



Asociación de IFN más AN

85% ETV-TDF



N: 183 ptes

86% : Hombres

HBsAg @ 3520 UI/ml

DNA-HBV: ND

Duración : 48 semanas