Take-home messages
from Tuesday 12th January 2016

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ary 2016

France
REcherche
Nord & sud
Sida-hiv
Hépatites

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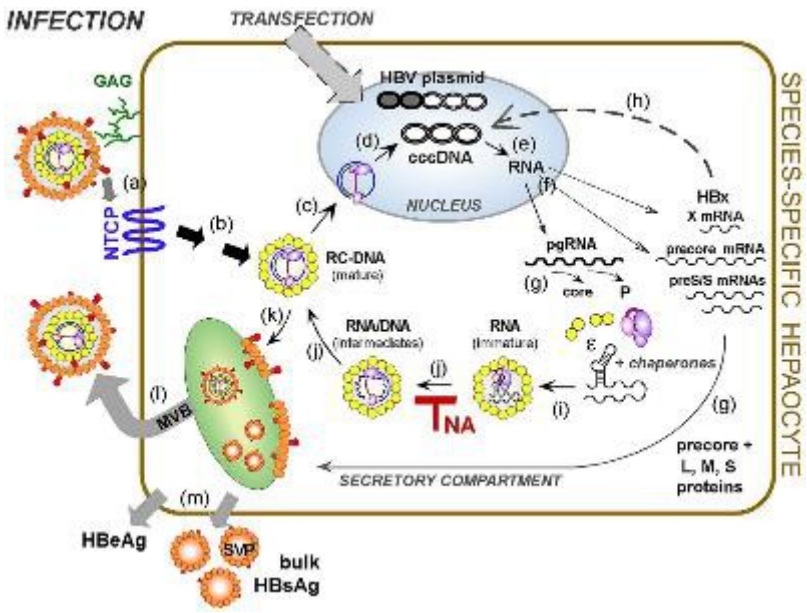
Disclosures

- Board member for : Schering-Plough, Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix
- Speaker for : Roche, Schering-Plough, Merck, Janssen, Gilead, BMS, Abbvie

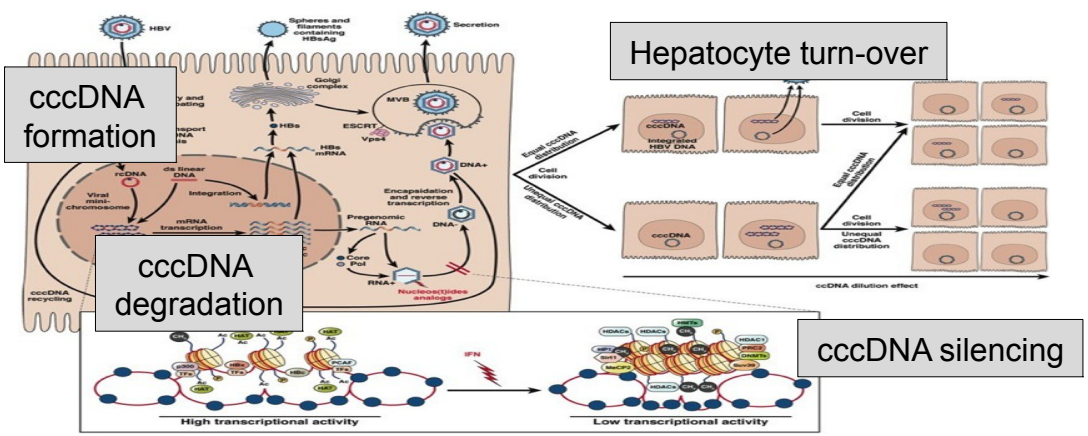
What’s new in hepatitis B

Clinical relevance of HBV cccDNA



- Covalently closed circular DNA
- « viral minichromosome »
- Template for viral gene expression
- Genetic archiving of mutations
- Responsible for viral persistence at the single cell level
- Long half-life

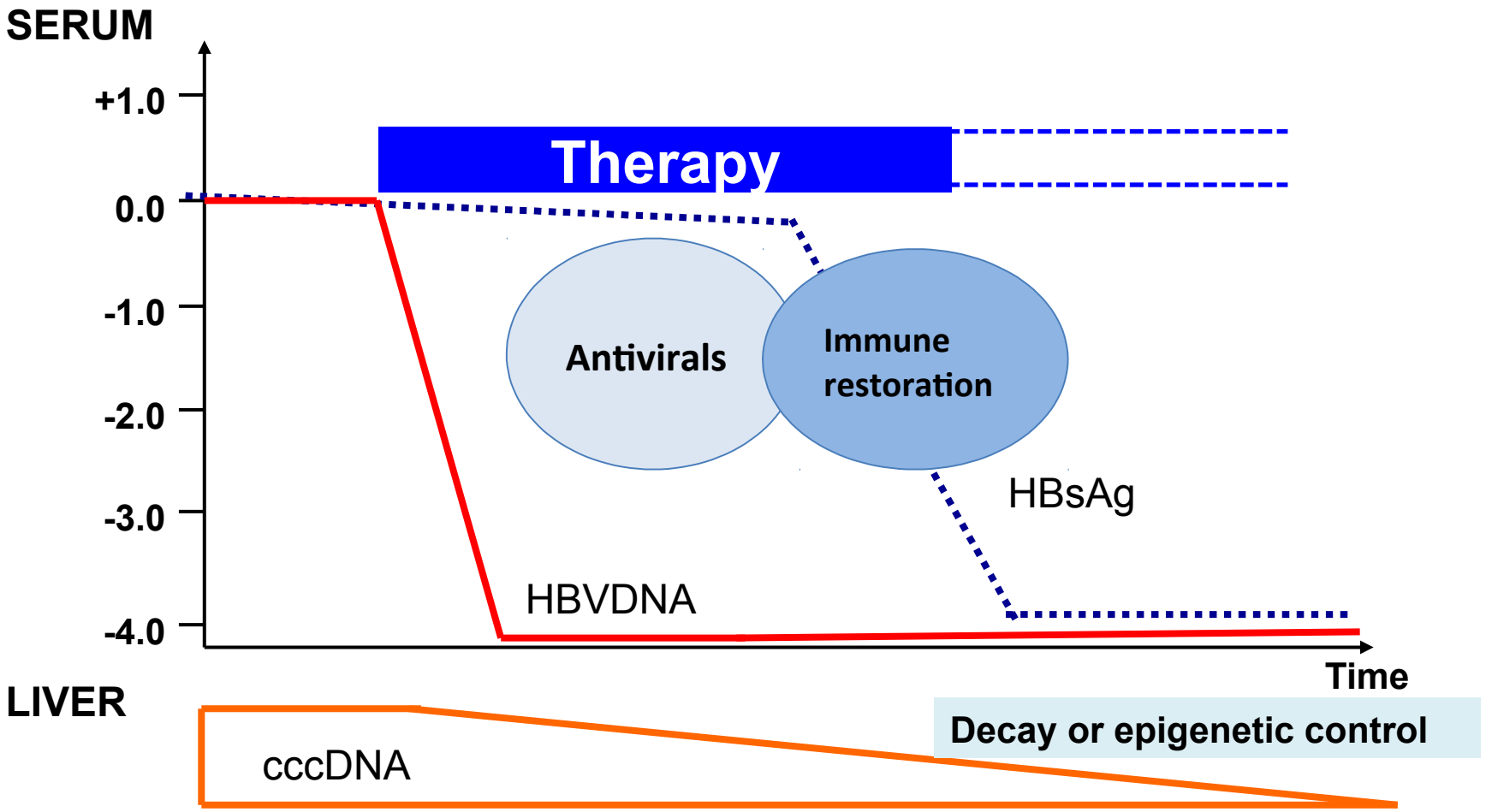
- **Can we target cccDNA to improve the rate of functional cure with antiviral therapy ?**



Fabien Zoulim PHC 2016

Clinical relevance of HBV cccDNA

New treatment concepts for a functional cure of HBV infection



Virological markers for the management of patients

Natural History

- ✓ Combination HBV DNA (< 2000 IU/ml) and HBsAg (<100 IU/ml) prediction of HBs loss at 5 years.
- ✓ High viral load (> 2000 IU/ml) and BCP mutant associated with higher risk of HCC development independently from HBsAg titer.
- ✓ Genotype C associated with higher risk of HCC development.
- ✓ Combination of HBV DNA <2000 IU/mL and HBsAg <1000 IU/mL robust predictor of inactive carrier status.

Virological markers for the management of patients

Patients treated with PegIFN

- ✓ Genotypes A and B respond better than C and D
- ✓ Treatment should be discontinued at week 12:

HBeAg positive: HBsAg > 20 000 IU/ml genotypes B and C

HBeAg negative: no HBsAg decline or < 2 log HBV DNA decrease.

- ✓ Treatment should be discontinued at week 24

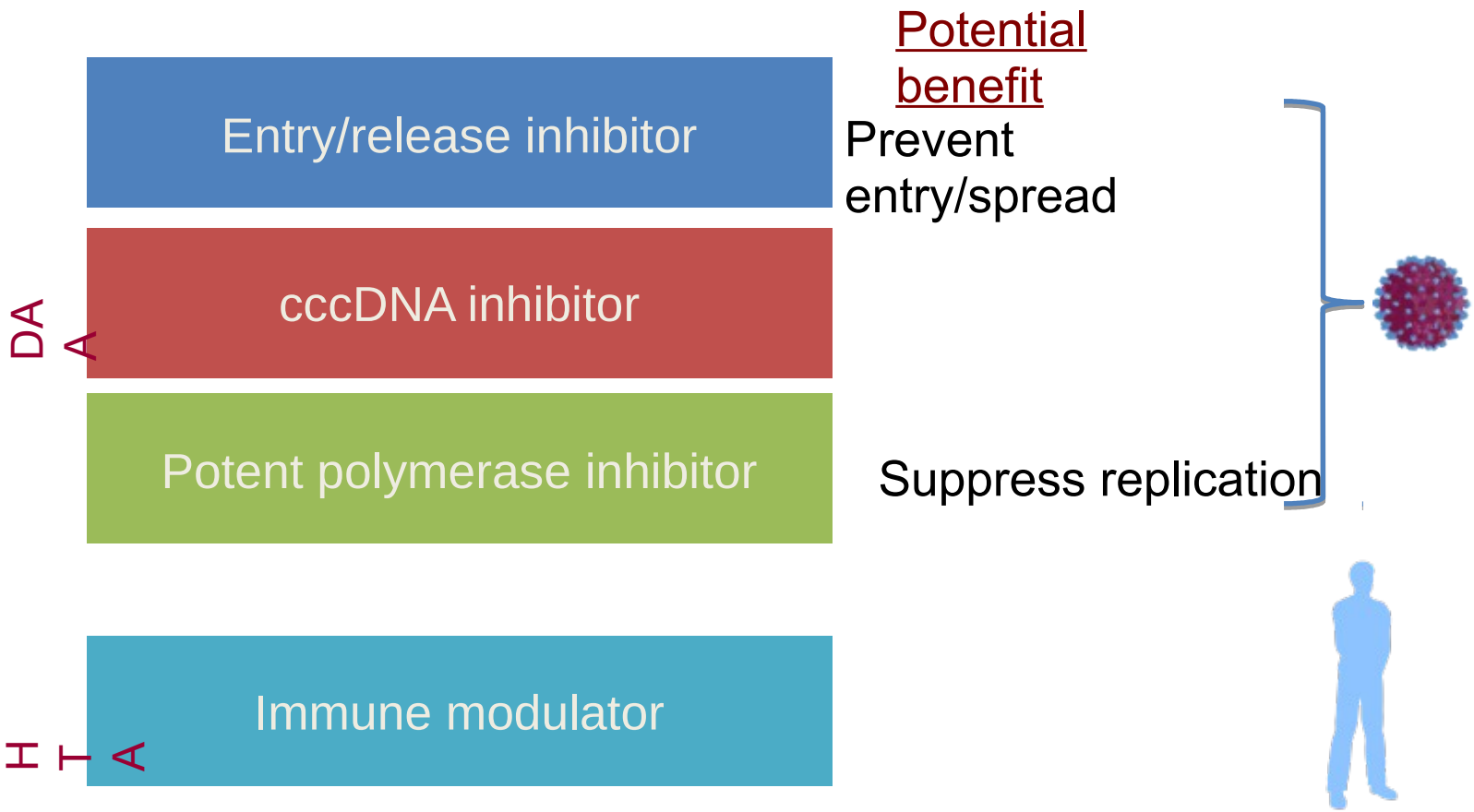
HBeAg positive HBsAg > 20 000 IU/ml all genotypes

Patients treated with NAs

- ✓ With an appropriate stopping rule (undetectable HBV DNA and HBsAg <200 IU/ml) and proper off-therapy monitoring cessation of therapy is a feasible alternative to indefinite treatment strategy.

New therapeutic perspectives ?

a combination approach is most likely ?



New therapeutic perspectives ?

- **The new goal of HBV therapy is to achieve "functional cure" or even "absolute cure"**
  - **HBsAg loss/seroconversion with clearance of cccDNA**
- **New agents (DAA and HTA) for CHB are starting to emerge**
  - **HBV entry inhibitors, small interfering RNA, capsid inhibitors promising but early in development**
  - **Direct cccDNA inhibition may be needed but is difficult to reach**
  - **Immune modification: TLR agonist, therapeutic**

Optimal therapy of chronic hepatitis B

Do I treat my immunotolerant patients ?

No
Except
for a few

- **Age >40 years**: treatment
- **Age 30-40 years**: decisions individualised - liver biopsy
- **Age <30 years**: follow-up (ALT /3-6 months, HBeAg/anti-HBe /6-12 months)
- **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

Prognosis and management of inactive carriers

- ✓ Most of HBV carriers are inactive carriers
- ✓ Diagnosis and follow up of inactive carriers have been outline
- ✓ Minimal criteria : PNALT, HBV DNA <2000 IU/ml for at least 12 months (check for fibrosis, qHBsAg)
- ✓ Favorable prognosis , long term monitoring (no treatment)
- ✓ During immunosuppression , high risk of reactivation , universal prophylaxis with NUC is mandatory
- ✓ Prophylaxis with Lam or ETV/TDF according to immunosuppression regimen, baseline viremia , compliance and so on .. Treatment should be done during immunosuppression and 12 -18 months thereafter
- ✓ Challenges :
  - Is life long monitoring necessary ?
  - How do we monitor over time?
  - HCC surveillance ?

Which pregnant women to treat

- **Women of childbearing age with CHB are more likely to have high HBV viral load and be HBeAg+**
- **Pregnant women with active liver could be safely initiated or switch to NA therapy (preferably TDF)**
- **MTCT risk is greatest in those with high maternal viremia: HBV DNA >6~8 log**
- **Third-trimester NA treatment (preferably TDF) could further reduce the risk of HBV MTCT**
- **Maternal, obstetric and fetal safety is acceptable**

Ji Dong Jia PHC 2016

Hepatitis E : the neglected one

1. HEV is the first cause of acute hepatitis worldwide

3. In Europe HEV infection is a locally acquired zoonosis and caused by genotypes 3 and 4

4. Patients are usually middle-aged/elderly males

6. HEV infection may be misdiagnosed as Drug Induced Liver Injury

8. HEV infection may be associated with neurologic sympoms in particular parsonage Turner syndrome and GBS

Hepatitis E : the neglected one

1. HEV infection can cause chronic liver disease and liver cirrhosis in immunocompromised patients

3. Chronic HEV infection in immunocompromised patients is treated by ribavirin

4. In immunocompetent patients diagnosis relies on the detection of anti-HEV IgM in the serum

5. In immunocompromised patients detection of the viral genome by PCR in the serum or stools is mandatory

The adventure of delta

- ✓ Message to the young clinical Hepatologists:
  - Develop your own interest
  - Pursue it on the bench
  - Be open mind

End-stage liver disease is a multifaceted condition

Management of uninfected and infected ascites in cirrhosis

- Management of ascites is currently based on the use of diuretics, large-volume paracentesis, and/or TIPS, while antibiotics are the mainstay for prevention and therapy of spontaneous bacterial peritonitis.

- No new effective therapies for ascites or bacterial infections have been introduced in clinical practice in the last 15 years. This indicates that a change of therapeutic paradigm should be introduced in cirrhosis.

Management of uninfected and infected ascites in cirrhosis

- Complications of cirrhosis should ideally not be targeted individually but as a whole and from a pathogenical perspective. Potential new therapies for prevention and treatment of complications of cirrhosis should target the systemic inflammatory state and marked splanchnic arterial vasodilatation characteristic of advanced cirrhosis.

- Potentially-effective drugs include new generation vasopressin V1 receptor agonists, statins, FXR agonists, and drugs that improve innate immune function.

Iron and the liver

- The liver is both the main storage site of iron and the central regulator of iron homeostasis through hepcidin
- A number of genetic and acquired diseases are associated with hepatic iron excess and toxicity when the storing and antioxidant capacity of the organ are overcome
- Genetic loss of hepcidin or hepatic proteins involved in hepcidin expression, such as HFE, cause hereditary hemochromatosis.
- Acquired loss of hepcidin-producing liver mass or the presence of disease factors that inhibit hepcidin expression can lead to iron overload and damage.
- Manipulating hepcidin synthesis/activity or hepcidin hormone-replacing strategies may represent in the future an etiologic cure for iron-related disorders

Treatment of HCC beyond international guidelines

Outline

1. Loss of survival benefits in patients treated outside recommendations.

2. Local ablation of early cancer is more cost effective than limited resection.

3. Can resection in patients with portal hypertension be facilitated by DAAs?

4. Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy ?

5. Reconsidering non transplant therapeutic options in the era of donor shortage.

Thank you for your attention