

Evolving understanding of HBV infection and reframing stages

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Professor of Medicine

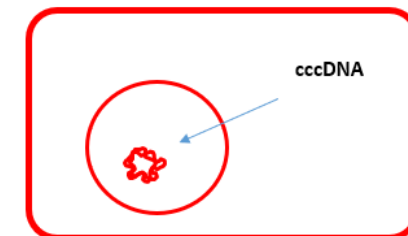
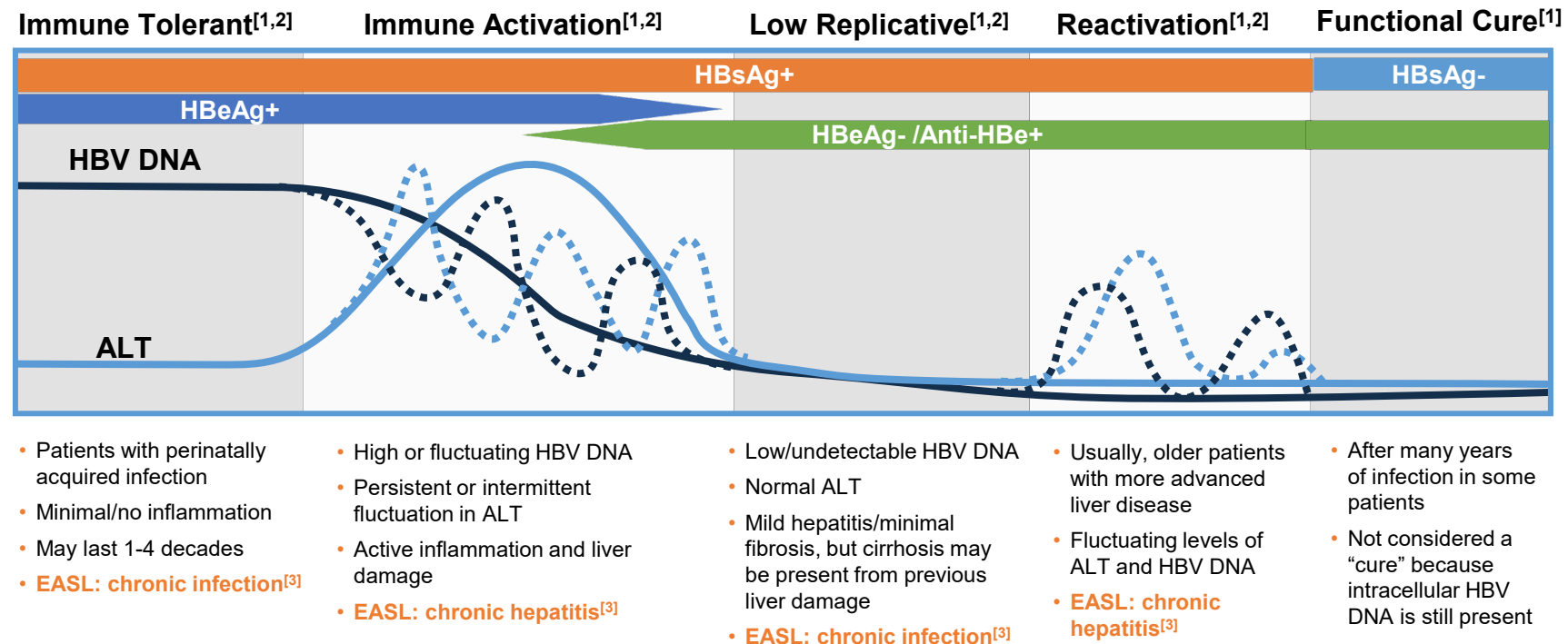
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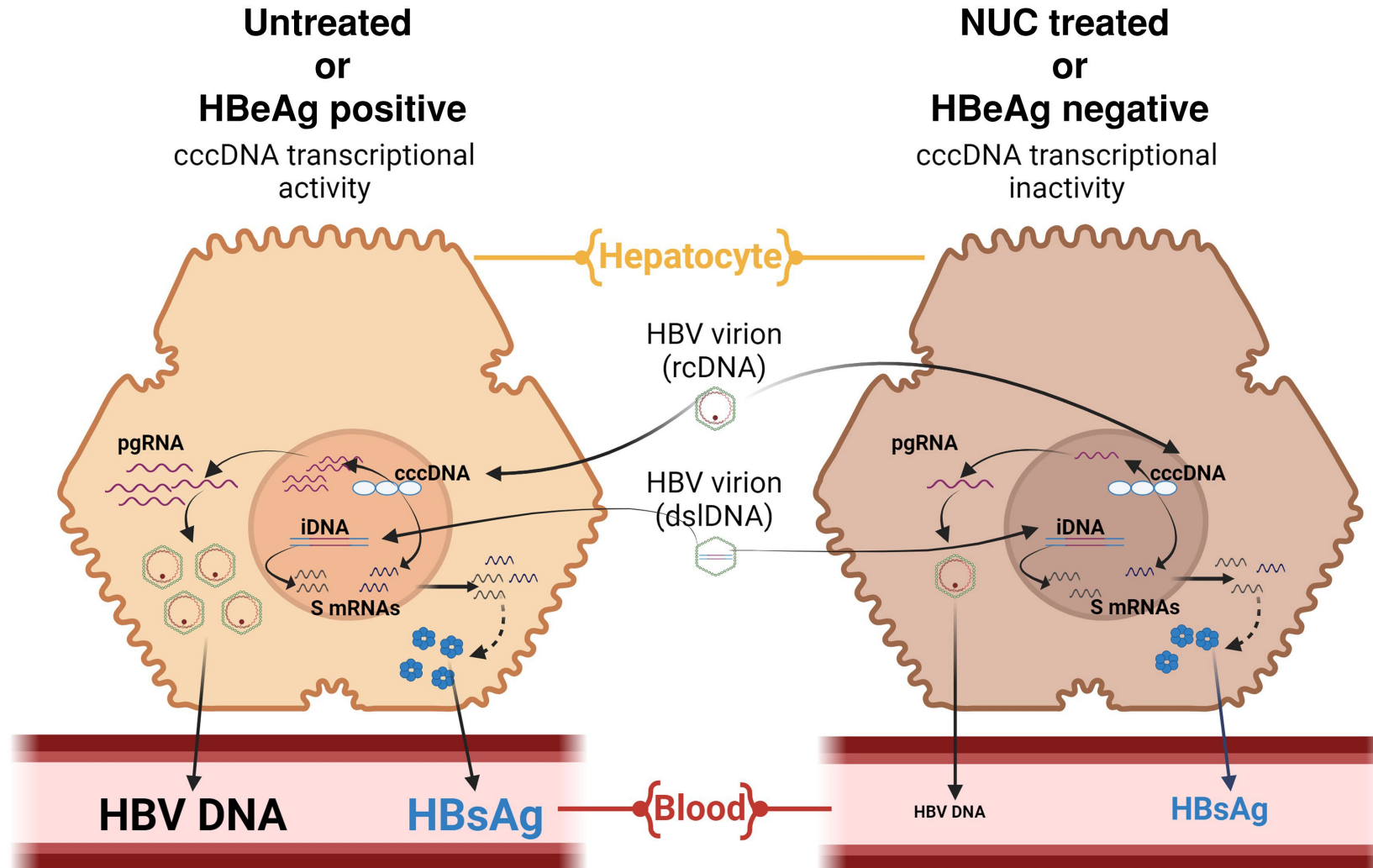
Baltimore Maryland

Phases of chronic hepatitis B virus infection

Should integrated HBV DNA be considered?



The primary source of HBsAg shifts from cccDNA to integrated DNA as the disease transitions for HBeAg positive to HBeAg negative



Patient from the clinic

A 3-year-old child diagnosed with chronic HBV infection after adoption and relocation to the US

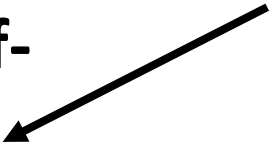
- HBeAg positive, HBV DNA 185 million IU/mL
- HBsAg level not available
- ALT normal
- Liver biopsy: Minimal inflammation, no fibrosis
- Enrolled in a clinical trial of Entecavir until about age 5 years – stopped after the trial ended and restarted at about age 9
 - HBeAg loss/Anti-HBe positive ~ age 10
- Continuous Entecavir for about 20 years
 - HBV DNA not detected, ALT normal, non-invasive testing – no fibrosis
 - HBsAg level = 0.12 (LLOQ 0.05)
 - Anti-HBs negative

FDA guidance for clinical trials of novel HBV therapies dosed for finite durations

- New finite duration therapies could be evaluated in clinical trials using any of the following endpoints:

- Sustained suppression (≥ 6 months) of HBV DNA off-treatment *without HBsAg loss (detectable HBsAg)*

Integrated
HBV DNA



or

- Sustained suppression (≥ 6 months) of HBV DNA off-treatment with HBsAg loss (< 0.05 IU/mL) with or without anti-HBs

Targeting HBV Therapeutics for Different Clinical Stages and Ages

- Phases of chronic hepatitis B virus infection differ with respect to the amount and ratio of cccDNA and iDNA derived HBsAg
 - Blood test to quantify circulating HBsAg by source is needed
 - Other markers of cccDNA transcription can be measured (HBV DNA, HBeAg, HBcrAg, HBV RNA)
- Tailor treatment to target each of the HBsAg sources
 - Predominately cccDNA – target HBV replication with antivirals
 - Predominately iDNA – target death of hepatocytes with iDNA or outcome of HBV DNA not detected off therapy
 - Mixed cccDNA + iDNA – target both or outcome of HBV DNA not detected of therapy