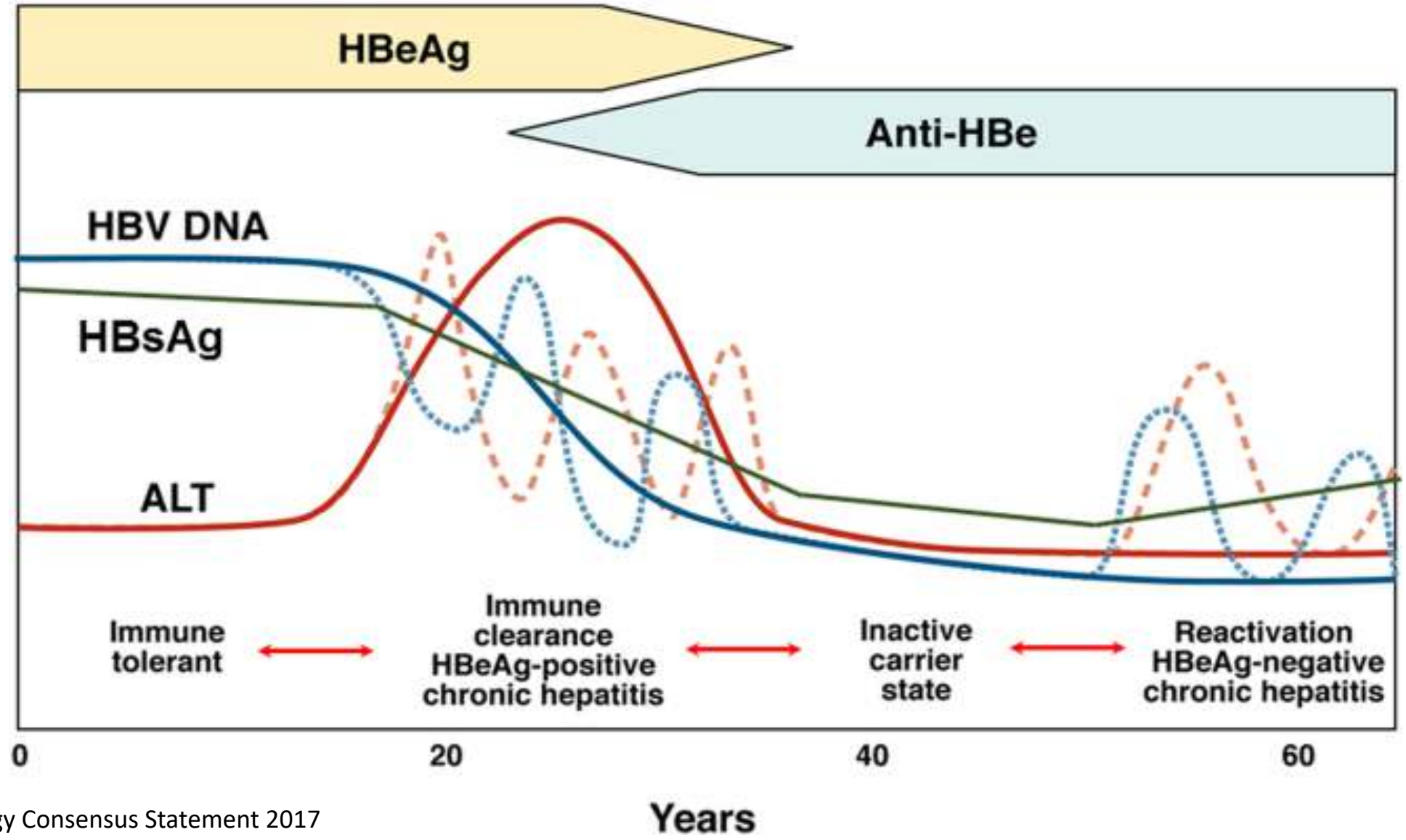
When to initiate HBV Treatment/Choosing Initial Treatment Regimen

Naoky Tsai MD

Clinical Course of Chronic Hepatitis B

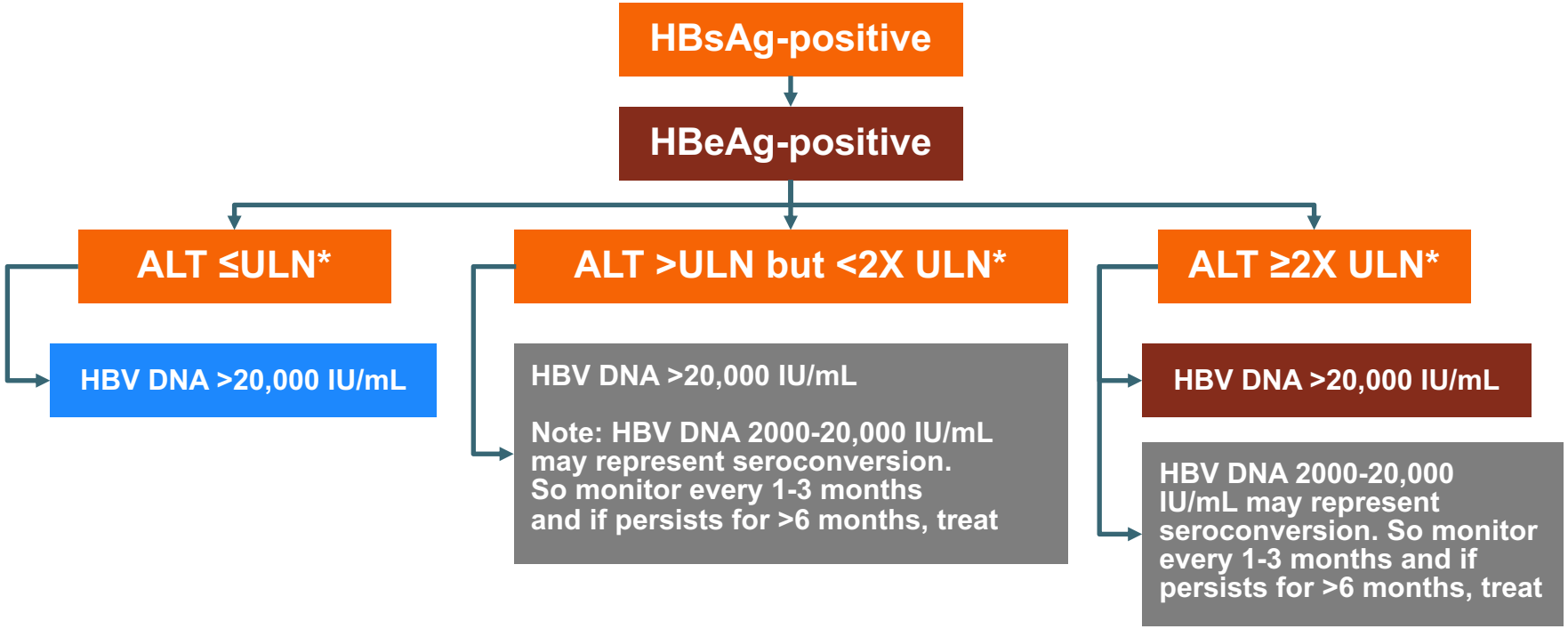


Hepatology Consensus Statement 2017

Conditions with Consensus to Initiate Treatment (Based on Multiple Guidelines)

- HBeAg (+) with HBV DNA > 20,000 IU/ml and ALT 2x ULN.
- HBeAg (-) with HBV DNA >2000 IU/ml and ALT $\geq$2 x ULN
- Cirrhosis with detectable HBV DNA regardless of ALT level or HBeAg status.
- Immune suppressive therapy for those with evidence of previous exposure regardless of serology or HBV DNA status.
- Direct Anti-Viral Agent (DAA)HCV therapy for those with HBV DNA (+) patient.
- HIV co-infected patients.

AASLD 2018: Monitoring Patients with HBV



Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.

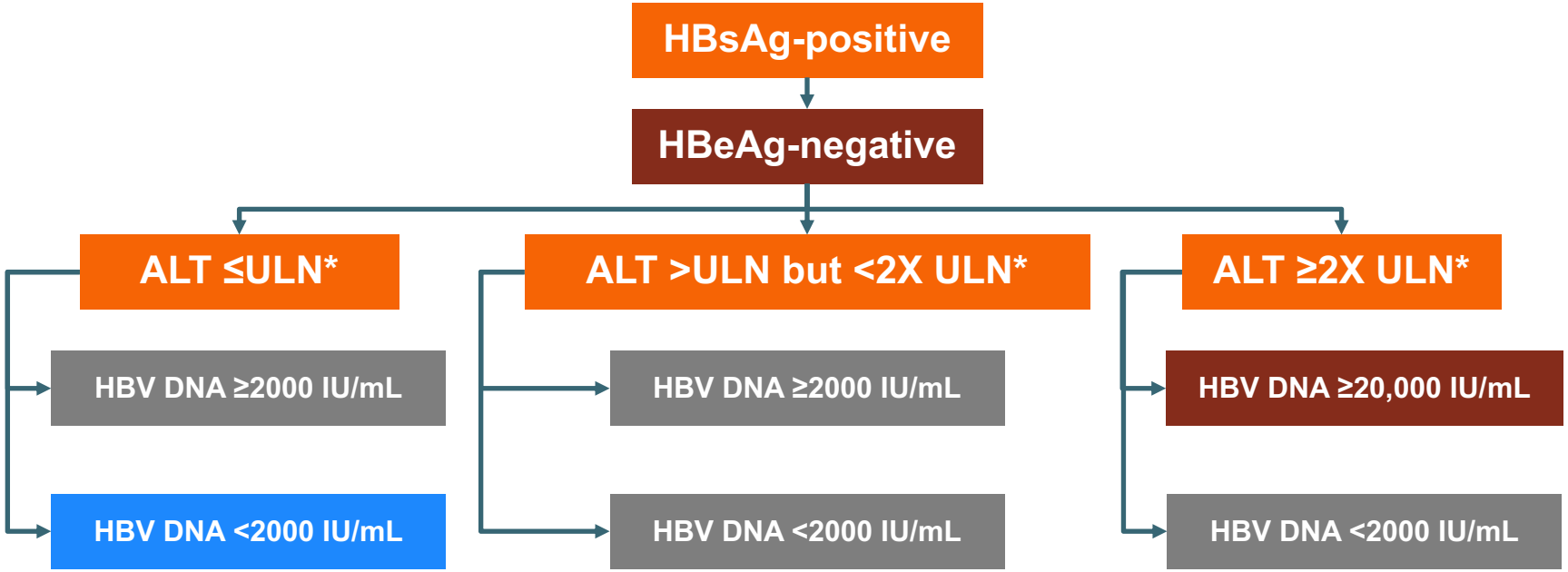
Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age >40.

Terrault N, et al. Hepatology. 2018 Apr;67(4):1560-1599.

My Viewpoints: HBeAg(+)

- ALT≤ULN,HBV ≥20,000 IU/ml
  - Age<30, No treatment ,Monitor ALT and HBV DNA Q 3 M for the first year, then Q6-12M. Treat if guideline criteria met.
  - Age between 30-40:
    - Treat:
      - FH of HCC/Cirrhosis due to chronic hepatitis B.
      - Evidence of stage 2 (F2) or above by Biopsy, or non-invasive methods.
      - Fluctuating ALT above ULN without other causes.
  - Age >40:
    - Treat:
      - F2 and above.
      - Fluctuating ALT above ULN without other causes.
- ALT >2xULN:
  - Treat:
    - Age<30: HBV DNA 2000-20,000 and persist for 6 months.(No other causes of increased ALT)
    - Age>30: HBV DNA 2000-20,000IU/ml.
  - No treatment if HBV DNA <2000 IU/ml.(May be HBeAg seroconverting.)

AASLD 2018: Monitoring Patients with HBV



Recommendations:

Treat

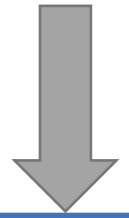
Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, excluded other causes of ALT elevation and assess disease severity with non-invasive test and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT>ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

*The upper limits of normal ALT in healthy adults is reported to be 29 to 33 U/L for males and 19 to 25 U/L for females. An upper limit of normal for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.

Terrault N, et al. Hepatology. 2018 Apr;67(4):1560-1599.

Flow sheet



	12/4/2017	3/25/2019	7/1/2020	3/9/2021	7/5/2021
ALT	30	27	46	64	29
DNA	9872	8242	22577	55902	<10
Bili	0.9	0.9		0.8	0.9

55 y/o Asian man, HBeAg (-), no cirrhosis or advanced fibrosis.

1. When to initiate anti-viral therapy?
2. How to differentiate ALT elevation deriving from NAFLD or HBV?
   -If HBV DNA elevated, treat HBV.
   (Xuemei Tao et al. March 23 2022. Frontiers in Medicine)
3. Can NAFLD cause HBV reactivation and vice versa?
   Not likely
4. What are the predictive factors for CHB reactivation?
   -Immune suppression
   -HCV DAA treatment
   -Persistent HBV DNA
   -HBsAg titer>1000IU/ml?

My Viewpoints: HBeAg (-)

- ALT ≥ 2xULN HBV DNA <2000IU/ml
  - <30: Monitor,Q3m x 1 year then Q 6-12 m. Treat if HBV DNA fluctuate between 2000-20,000 during observation.
  - >30 but <40: Treat if
    - ≥F2
    - FH of HCC/Cirrhosis due to HBV
  - >40: Treat if no other causes of increased ALT.
- ALT>ULN but <2xULN:
  - HBV DNA 2000-20,000:
    - <30 : Monitor : Treat if HBV DNA trend up rather than down.
    - >30 Treat
  - HBV DNA <2000 IU/ml:
    - <30: Monitor: Treat if HBV DNA trend up.
    - 30-40:
      - Treat
        - FH of HCC/Cirrhosis due to HBV
        - ≥ F2.
    - >40: Treat.

My Viewpoints: HBeAg (-)

- ALT ≤ULN:
  - HBV DNA 2000-20,000IU/ml:
    - <30: Monitor, treat if ALT fluctuate or HBV DNA trended up rather down.
    - 30-40:
      - Monitor: if HBV DNA trend down.
      - Treat:
        - If HBV DNA trend up.
        - >F2.
        - FH of HCC/Cirrhosis
    - >40: Treat.

Choosing antiviral therapy

- Who?
- What?
- Duration?
- Pros and Cons.
- Accessibility: Formulary and Cost.

First Line Therapies:

- Pegylated Interferon: Age ≥18.
- Interferon 2b: Children ≥ 1 year
- Nucleotide Analogue:
    - Tenofovir Disoproxil Fumarate:
        - 300 mg daily for 12 years and older/Body weight ≥ 35 Kg.
        - ≥ 2 years + ≥17 Kg, 8 mg/Kg up to 300mg.
- Nucleoside analogues:
    - Entecavir:
        - Age ≥ 16: 0.5 mg-1 mg daily.
        - Age ≥2 + >10 Kg: 0.15 mg/10 Kg up to 0.5 mg daily.
    - Tenofovir AF: ≥ 18, 25 mg daily.

Pegylated Interferon

- Immune modulator.
- Mechanism: Anti-viral effects through cytokine inducement.
- Pros:
  - Finite duration of treatment : Young people may prefer.
  - Sustained viral response: HBsAg seroconversion up to 5 %
- Cons:
  - Side effects: Plenty
  - Subcutaneous Injection once a week for 48 weeks.
  - Best for Genotype A, adult acquired infection, Higher ALT level, Lower HBsAg level.
  - May cause flare due to enhanced immune clearance in up to 18% of patients treated.
  - Contra-indication for cirrhosis patients, pregnancy, breast feeding.
- Cost: $$

Nucleotide Analogue: TDF

- Direct Anti-viral Agent.
- Mechanism: Reverse transcriptase inhibition terminating viral genetic replication.
- Pros:
  - Potent activity against HBV virus. Effective against all genotypes.
  - Low side effects profile: Long term experience. But rare cases of lactic acidosis especially in decompensated cirrhotic were reported.
  - Oral route. Does not need fasting.
  - No drug resistance has been reported.
  - Cirrhosis reversal is possible with long term therapy. (5 years)
  - Can be used in pregnancy, particularly in the third trimester.
- Cons:
  - Side effects: Renal tubular dysfunction, Fanconi Syndrome, Bone density loss.
  - Long term therapy needed and can be life long.
  - Renal dosing adjustment needed.
  - Danger of severe flare if discontinued abruptly.
- Cost: $$$

Nucleoside Analogues : TAF

- Direct Anti-viral Agent.
- Mechanism: Reverse transcriptase inhibition terminating viral genetic replication.
- Pros:
  - Potent activity against HBV virus. Effective against all genotypes.
  - Low side effects profile: Long term experience. But rare cases of lactic acidosis especially in decompensated cirrhotic were reported.
  - Oral route. Does not need fasting.
  - No drug resistance has been reported.
  - No renal dosing adjustment needed (but not approved for patients with GFR≤ 15 and not on dialysis)
- Cons:
  - Side effects: Renal tubular dysfunction, Fanconi Syndrome, Bone density loss. Less than TDF.
  - Long term therapy needed and can be life long.
  - Danger of severe flare if discontinued abruptly.
  - Not indicated in decompensated cirrhotic patients.
- Cost: $$$$

Nucleoside Analogue: Entecavir

- Direct Anti-viral Agent.
- Mechanism: Reverse transcriptase inhibition terminating viral genetic replication.
- Pros:
  - Potent activity against HBV virus. Effective against all genotypes.
  - Low side effects profile: Long term experience. But rare cases of lactic acidosis especially in decompensated cirrhotic were reported.
  - Oral route. “Need fasting”.
- Cons:
  - Drug resistance in treatment naïve patient: 1.2% after 5 years of therapy.
  - Drug resistance increased to 50 % after one year for patients with Lamivudine resistance.
  - Not indicated in treatment in patient with HIV co-infection or in pregnancy.
  - Renal dosing adjustment needed.
  - Long term therapy needed and can be life long.
  - Danger of severe flare if discontinued abruptly.
- Cost: $$$

Summary:

- Chronic hepatitis B is a clinically complex and dynamic, rendering decision to initiate anti-viral therapy complicated.
- Careful observation and trending clinical course is the way to approach this decision.
- Efficacy of Interferon is limited particularly in Asian population. And side effects is significant.
- All direct anti-viral agents are safe and effective but with its own pros and cons.
- Decision to chose which agents to use is based on several factors such as side effects, resistance, and cost.
- ***I have tried to simplify the message. But there will be questions!***