Screening, diagnosis and management of hepatitis B

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Global Burden of Hepatitis B

- 250 million (3.5%) persons in the world have chronic HBV
  - Born before HBV vaccine was available
  - Acquired during prenatal period or early childhood

- 2.2 million infected in the United Sates.
  - Foreign born or from endemic regions

- Hepatitis B infections have increased up to 114% from 2006 to 2013 in some states affected by the opioid and heroin epidemics

- Hepatitis B and C could be eliminated as a public health threat (i.e. 90% reduction in new chronic infections, 65% reduction in mortality)

WHO, Global hepatitis report, 2017

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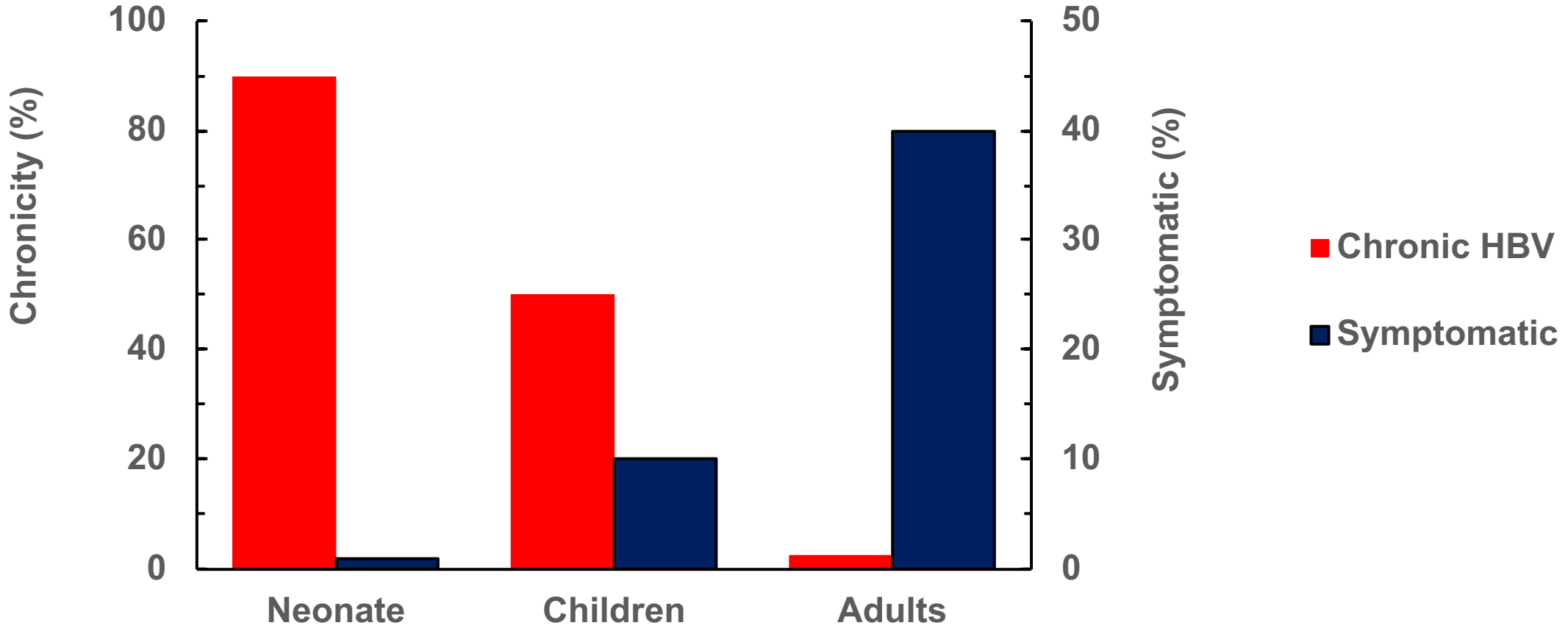
Risk of Developing Chronic HBV: Age and Symptoms



ML Shiffman *Clin Liv Dis.* 2010; 14:75-91.

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Screening for Hepatitis B

- HBsAg and Anti-HBs is recommended
- Screening for Anti-HBc is ***not*** routinely recommended except if
  - HIV infected
  - Undergoing HCV or immunosuppressive therapy
  - Donating Blood or organs
  - Renal dialysis
- Anti-HBs - negative screened persons should be vaccinated

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HBV Serologies

HBsAg	IgG Anti-HBc	IgM Anti- HBc	Anti-HBs	Interpretation	Action
-	-	-	-	Never infected and absence of immunity	Vaccinate
+	+	-	-	Chronic Infection	Link to HBV directed care
+	+	+	-	Acute Infection or disease flare in chronic carrier	Link to HBV directed care
-	+	-	+	Recovered from past infection with immunity	Reassurance
-	-	-	+	Immunity from vaccination	Vaccinate for HAV if indicated
-	+	-	-	* Isolated HB core Ab	Vaccinate if indicated

*False positive: Repeat testing required

[2] Past infection: No action needed

[3] Occult HBV infection: Needs to be known if patient ever becomes immunosuppressed or given chemotherapy or treated with antiviral therapy for hepatitis C virus infection. Consider monitoring HBV DNA.

[4] Passive transfer to infant born to HBsAg-positive mother No specific action needed

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Vaccines

	Engerix- B	Recombivax - HB	HEPlisav-B	TwinRix
Doses	3	3	2	3-4
Viral antigen mimicked	HBsAg	HBsAg	HBsAg	HBsAg? HAVA g
Adjuvant Used	Aluminum hydroxide	Aluminum hydroxide	Toll like receptor	Aluminum Hydroxide
Derivation source	rDNA yeast	rDNA yeast	rDNA yeast. Adjuvant from bacterial DNA	rDNA yeast
Manufacturer	GSK	Merck	Dynavax	GSK
Cost	$170	$180	$230	$298

JAMA February 2018

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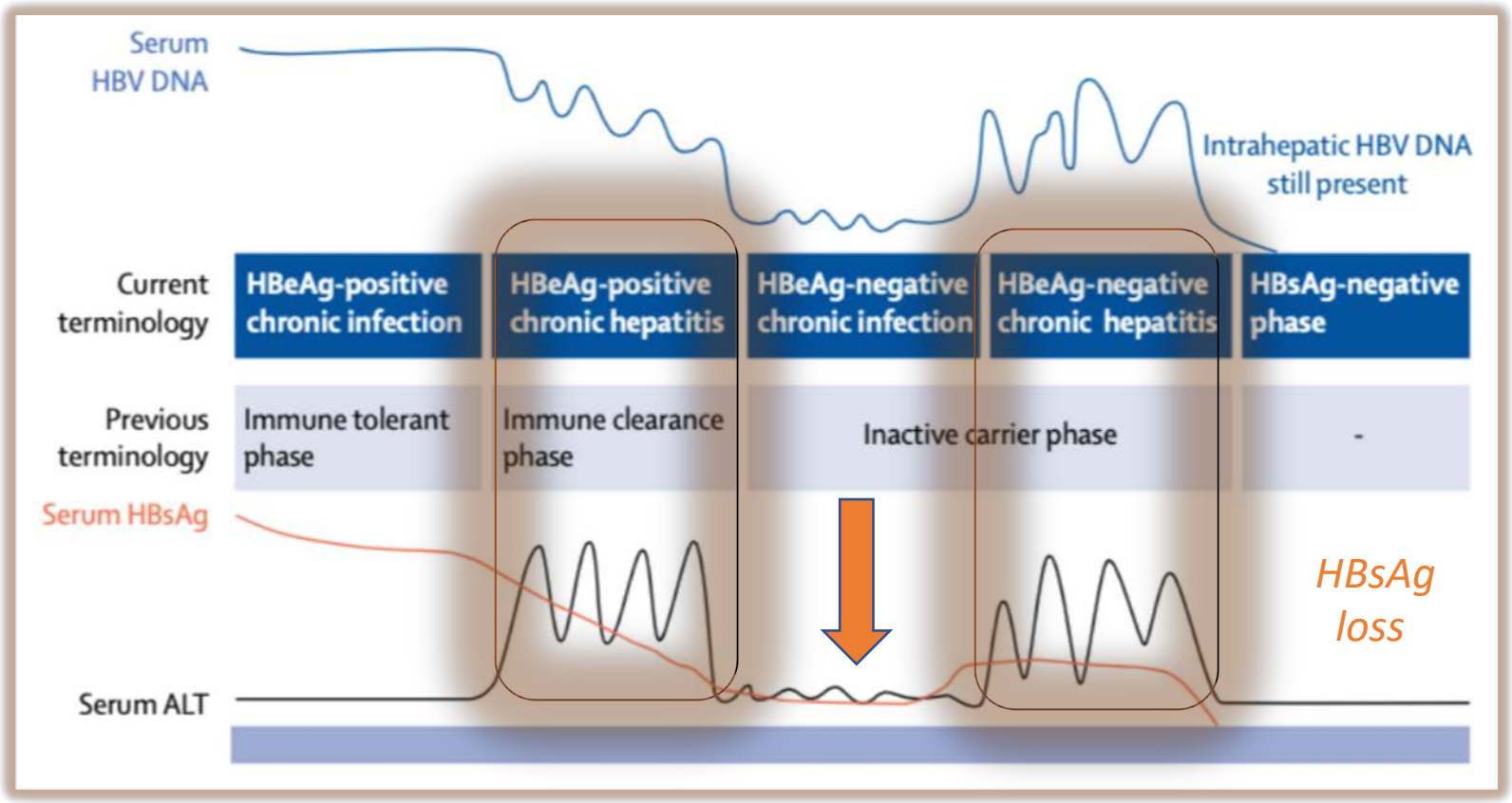
Natural History- *e antigen status*



W Seto, *The Lancet*, 2018

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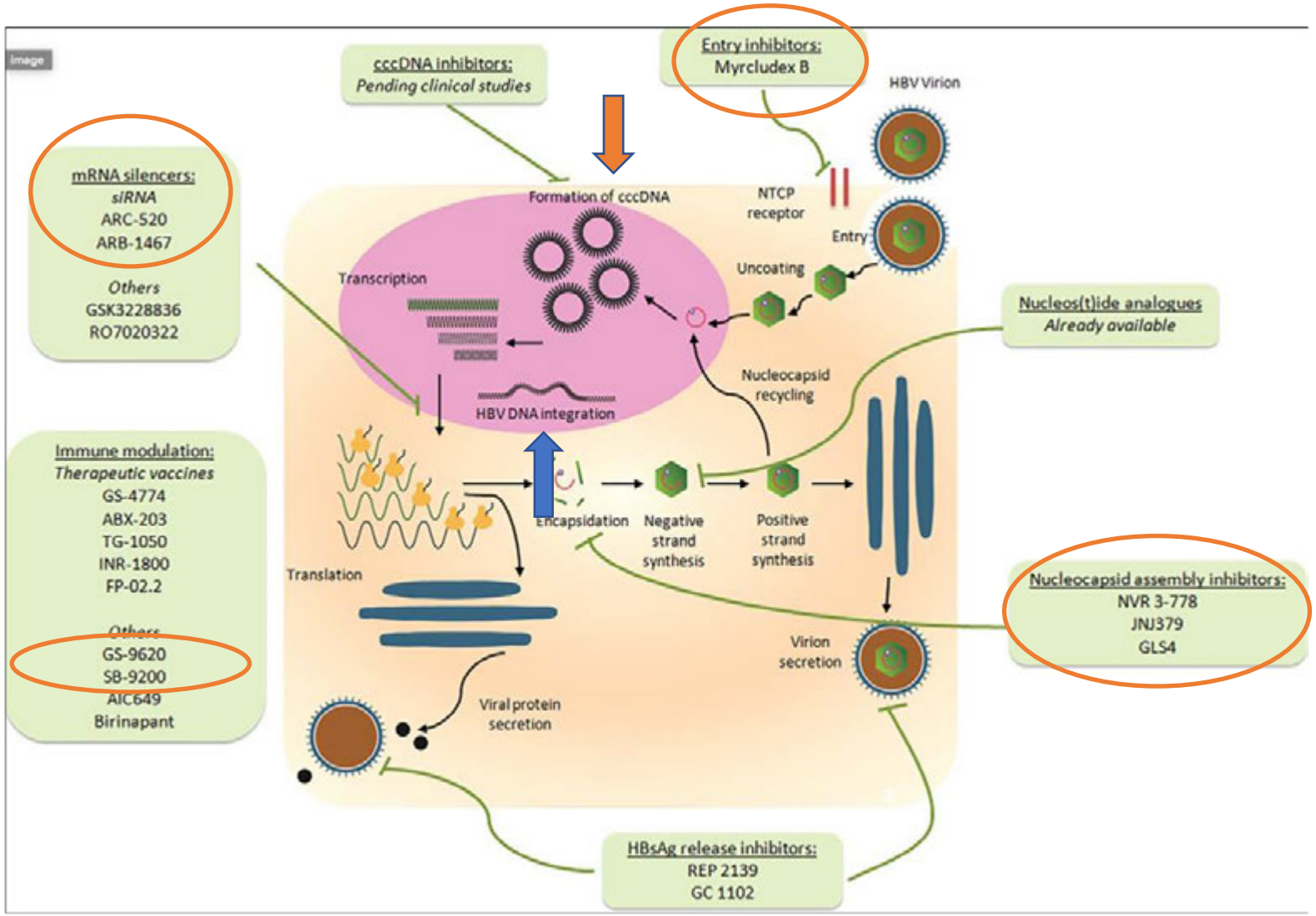
Goals of Therapy

- HBV DNA undetectable in the serum
- HB e seroconversion, HBsAg loss highly desirable,
- Decrease morbidity and mortality
- Decrease liver inflammation and progression to fibrosis
- Prevention of cirrhosis, hepatic failure and cancer

CURE is <u>not</u> a term typically discussed with patients regarding treatment for Chronic Hepatitis B infection

Why HBV is difficult to eradicate?



cccDNA: replicate intermediate not affected by NA

1-50 cccDNA particles per hepatocyte

Integrated subgenomic HBV DNA fragments into multiple locations within host DNA

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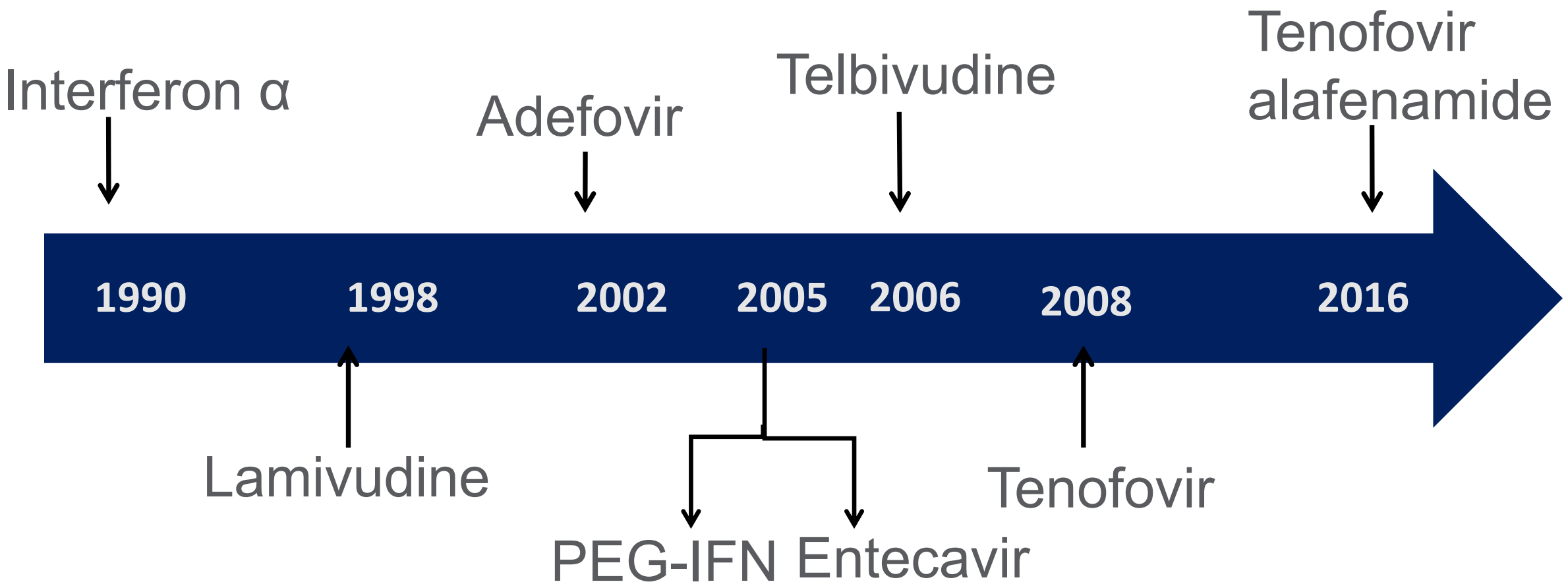
DEFINING CURE

- Partial cure
  - HBsAg positive, HBV DNA persistently undetectable off treatment
    - Subgroup of those within inactive carrier
- Functional cure
  - Sustained loss of hepatitis B surface antigen (HBsAg) with or without hepatitis B surface antibody seroconversion
- Sterilizing cure
  - Eradication of detectable HBsAg and all HBV DNA including covalently closed circular (ccc) and integrated DNA
    - No risk for reactivation and elimination of HCC risk
- HBV e antigen seroconversion
  - The loss of serum hepatitis B e antigen (HBeAg) and the development of anti-HBe antibodies (HBeAg seroconversion) mark a transition from the immune-active phase of disease to the inactive carrier state.

Evolution of HBV Therapies



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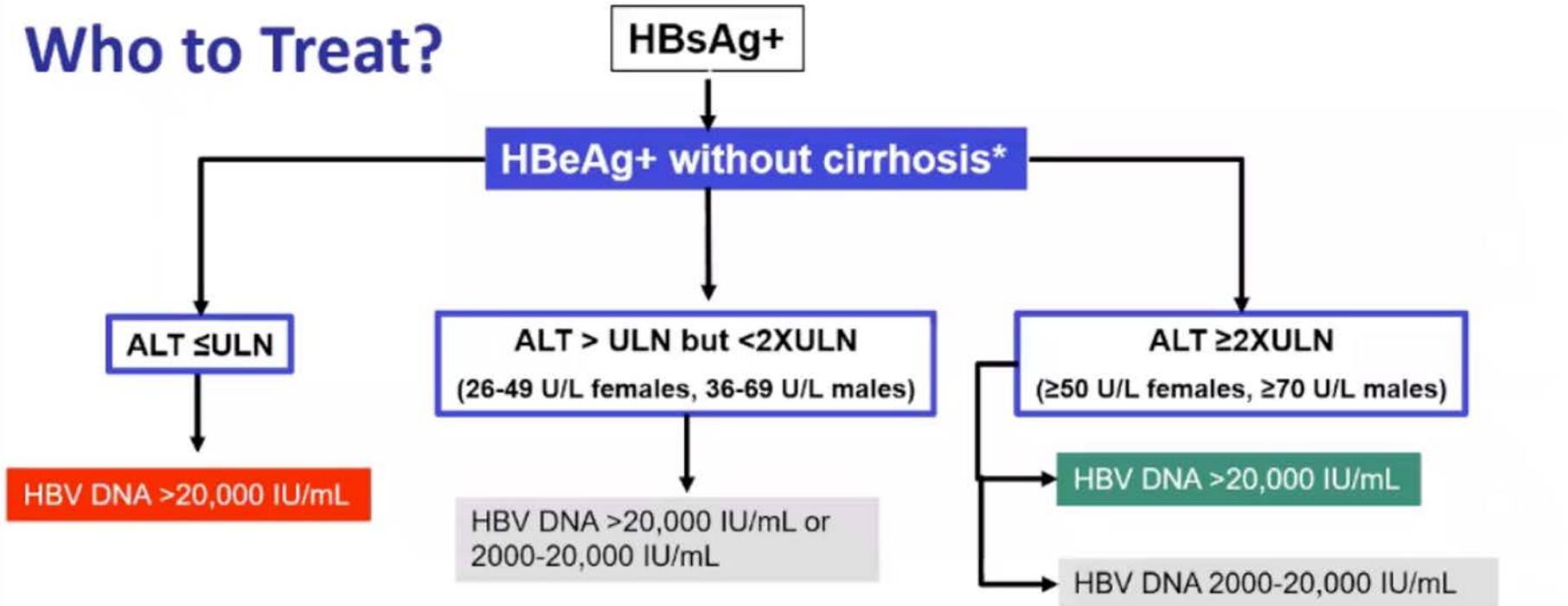
Who to Treat?



Recommendations

Treat

Don't treat, monitor only

Assess disease severity using non-invasive tests and/or liver biopsy; consider other causes of liver disease if elevated ALT. If staging indicates ≥F2 or ≥A3, or if other causes of ALT excluded and persistent, treat, **especially if ≥40 years of age**.

***If cirrhosis, treat regardless of ALT or HBV DNA level.**

Terrault, N. *Hepatology*, Nov 2018

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Chronic Hepatitis HBeAg – *Positive* on NA

<40 years seroconversion

HBeAg ⟶ Anti - HBeAb

- Consolidate tx for 12 months
- Monitor for relapse and need of retreatment

> 40 years seroconversion

HBeAg ⟶ Anti - HBeAb

- Longer consolidation period ideal
- Monitor for relapse and expect in 50%
- Treating to HBsAg loss may be preferred.

* Treat indefinitely if cirrhosis or advanced fibrosis
* Unclear if therapy withdrawal enhances HBsAg loss

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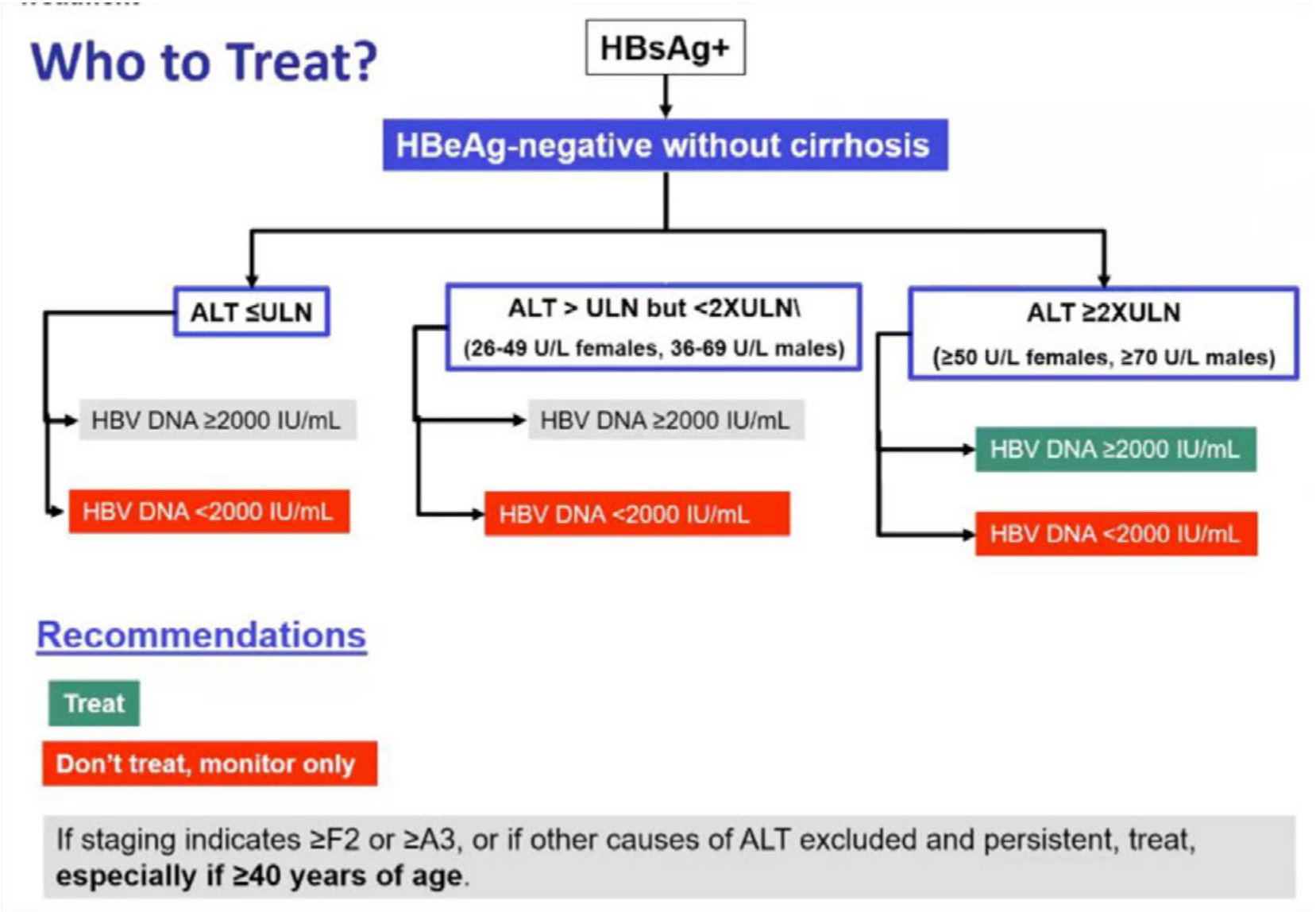

Terrault, N. Hepatology, Nov 2018

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Chronic Hepatitis HBeAg – *NEGATIVE* on NA

- Treat until HBsAg loss = *functional cure*
  - Unlikely to be achieved with NAs alone
- NA withdrawal strategies_ appear promising
  - Achieves *functional cure* in up to 20% (with 3 years follow up)
  - Achieves *partial cure (*inactive CHB) in additional proportion (at maximum 30%)
  - Close monitoring needed as flare can be severe
  - Predictors: duration of NA therapy: qHBsAg but more studies needed.

* Treat indefinitely if cirrhosis or advanced fibrosis

Indications for selecting ETV or TAF over TDF*

- In some circumstances ETV or TAF may be a more appropriate treatment choice than TDF

Age	• >60 years
Bone disease	• Chronic steroid use or use of other medications that worsen bone density • History of fragility fracture • Osteoporosis
Renal alteration†	• eGFR <60 ml/min/1.73 m^2 • Albuminuria >30 mg/24 h or moderate dipstick proteinuria • Low phosphate (<2.5 mg/dl) • Haemodialysis

TAF over ETV	ETV over TAF
Previous nucleoside exposure	Less expensive(generic available)
Lamivudine with and without adefovir resistance	No prior nucleoside exposure and HIV uninfected
HIV/HBV coinfection	CrCl <15 mL/min(with dose adjustment)
No dose adjustment if CrCl > 15 mL/min	

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis

EASL CPG HBV. J Hepatol 2017;67:370–98

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Special Populations

Population	Entecavir	TDF	TAF
Prophylaxis in the setting of immunosuppression	X	X	X
Acute HBV, with severe protracted course	X	X	X
Decompensated Cirrhosis	X	X	(X) Good option, Not studied
Liver transplant patients	X	X	X
Other Solid organ transplant	X	X	X
Pregnancy	X	X	*
Children	X (>2 yrs, 30 kg)	X (>12 years)	*

* Insufficient Data to recommend

AASLD HBV Guidance, Hepatology 2018, Adapted with permission.

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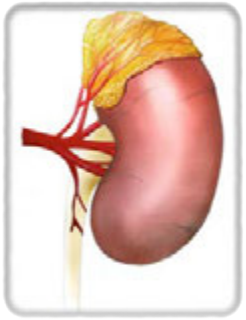
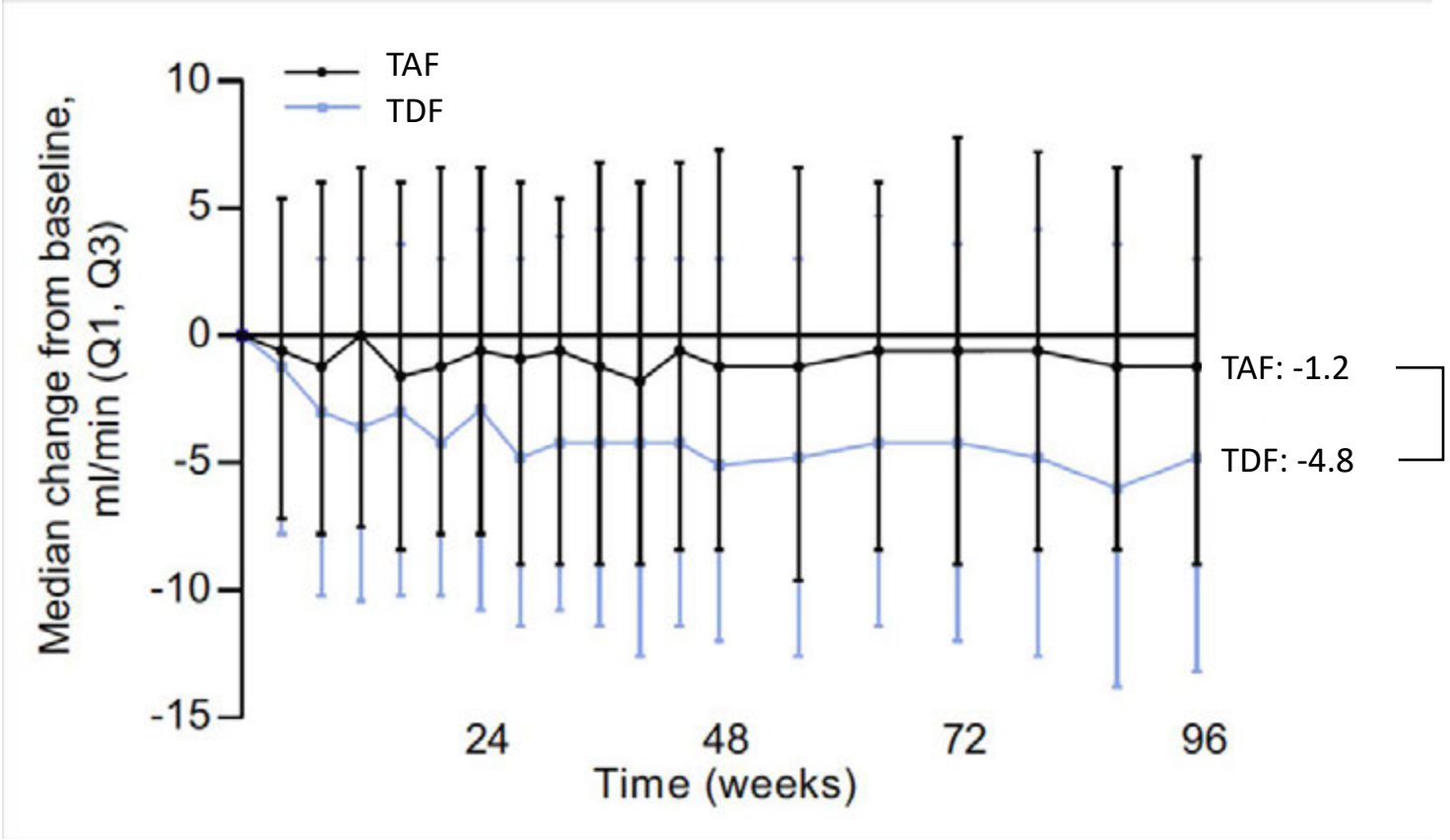
TAF vs TDF for HBV: Change in eGFR



Median change from baseline in eGFR over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)



Agarwal K, et al. J Hepatol 2018;68:672–81

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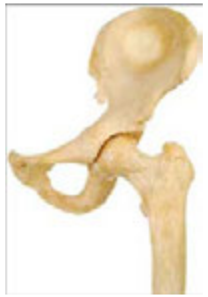
TAF vs TDF for HBV: Change in BMD



Median change from baseline in BMD over 96 weeks
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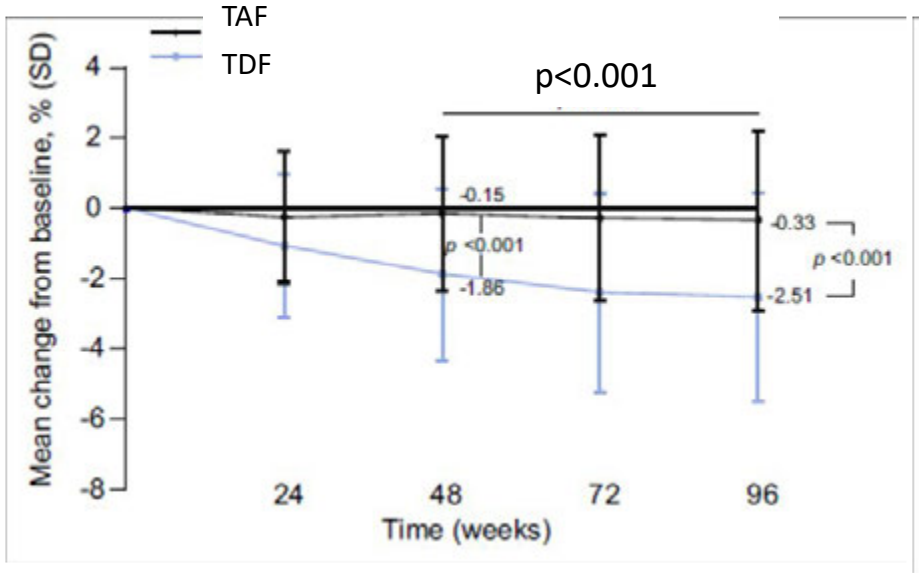
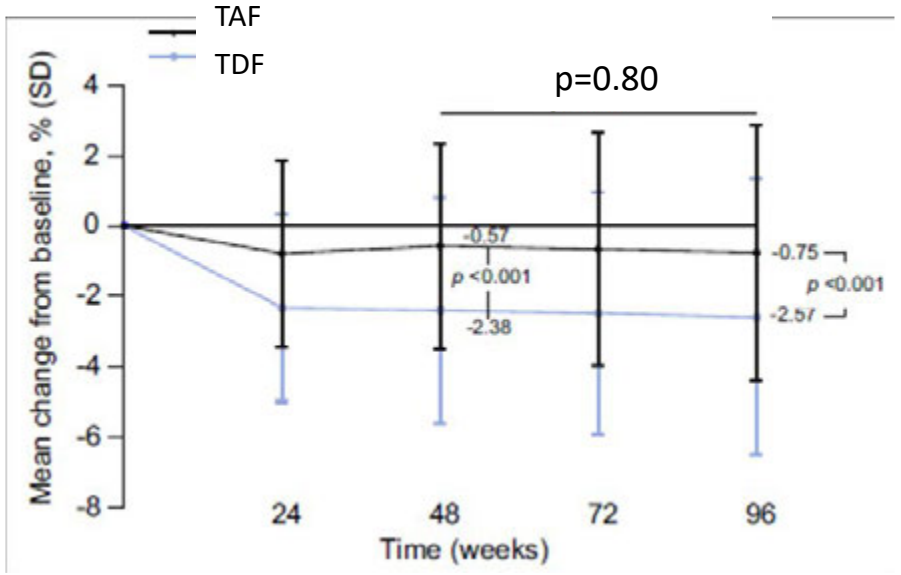
Hip



Spine



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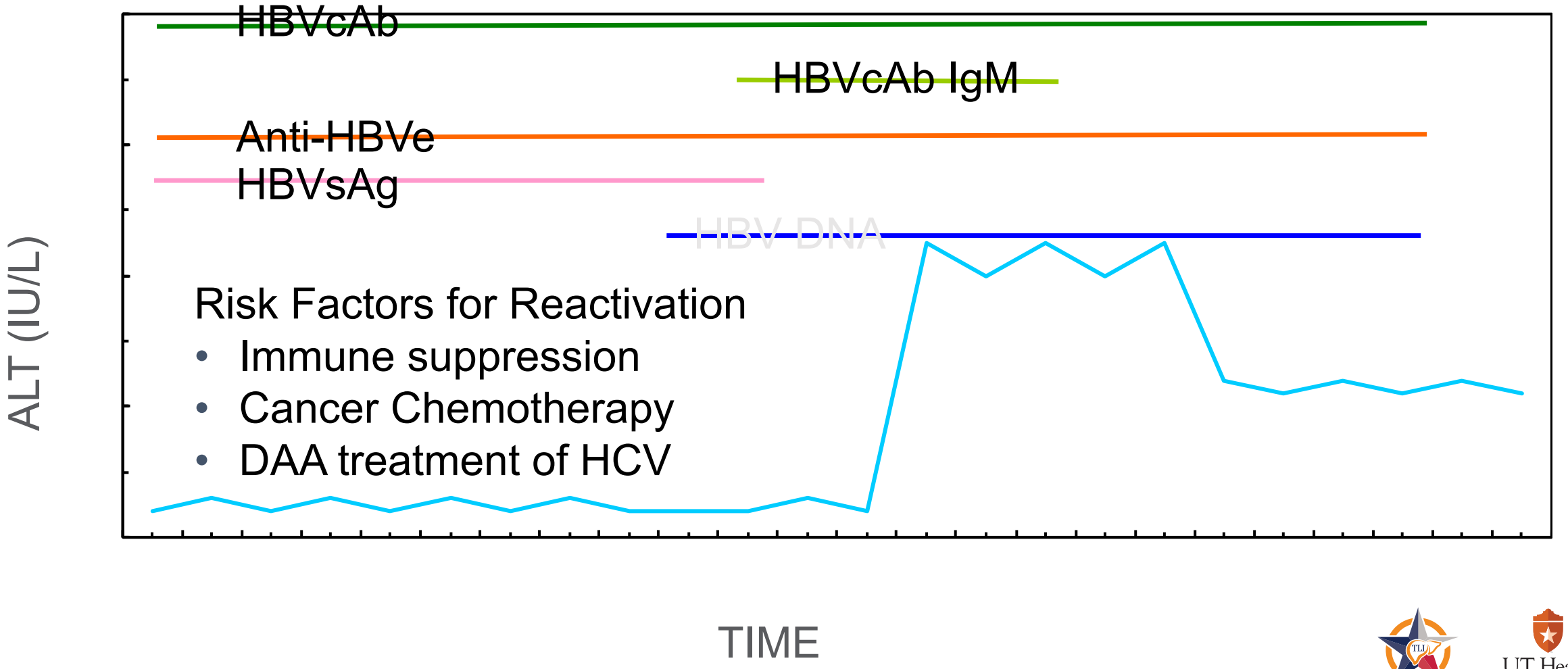
Chronic HBV: Reactivation of Inactive HBV



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FDA BLACK BOX on HCV DAA Therapies

- **Hepatitis B Reactivation**
  - Reported in HCV/HBV co-infected patients on or those who completed HCV DAA therapy who were not on anti-HBV therapy, including cases resulting in fulminant hepatitis, hepatic failure, and death.

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Monitoring of HBV During HCV DAA Therapy

- Identify HBV status in all patients prior to DAA therapy
- Monitor for elevations in ALT
- Obtain HBV DNA
- Initiate of suppression if indicated

Hepatitis B: Is it Curable?

- Sterilizing Cure: Remains elusive
- Functional Cure: Yes but rare
  - HBeAg positive > HBsAg negative patients on NAs
  - Peg-IFN offers more rapid route of HBsAg loss
  - Strategies to bolster rates of HBsAg are needed
- Partial Cure: Feasible and current goal
  - Close monitoring after discontinuation essential to monitor for relapse/flares

Case Study

- A 23-year-old, Asian-American male presents for ongoing care.
- History of chronic infection with hepatitis B virus (HBV), which was diagnosed at 21 years of age.
- Positive family history of HBV infection (sister and mother).
- No family history of cirrhosis or liver cancer.
- Findings from his physical examination are normal.
- Never received HBV treatment and takes no medications.
- Imaging: Ultrasound normal; liver stiffness by transient elastography is 3.7 kPa (normal).

Case Study (con't)

Laboratory Test	6 Months Prior	Current	Reference Range
ALT, SGPT	31 U/L	81 U/L	10-40 U/L
AST, SGOT	-	71 U/L	10-40 U/L
Bilirubin, Total	-	0.3 mg/dL	0.3-1.0 mg/dL
CBC	-	Normal	Normal
Creatinine, Serum	-	0.9 mg/dL	0.7-1.5 mg/dL
HBV DNA	20 million IU/mL	2.2 million IU/mL	Negative
Hepatitis B (HBeAg)	-	Positive	Negative
HCV	-	Negative	Negative
HDV	-	Negative	Negative
HIV	-	Negative	Negative

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Case Study (con't)

- What is the best approach for managing his chronic HBV infection?
  1. Monitor yearly as no treatment is necessary now
  2. Monitor for 2 years before starting treatment
  3. Treat with tenofovir alafenamide now
  4. Treat if ALT and HBV DNA are elevated in 6 months

Thank You

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