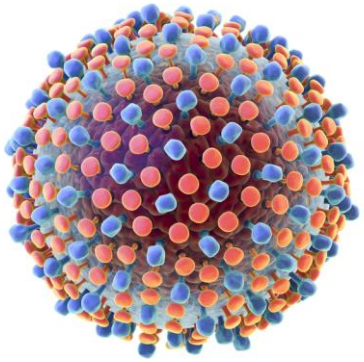

Why Hepatitis B Antiviral Treatment is So Confusing
(it doesn't have to be!)

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Disclosure

- None for hepatitis B
- Author, UpToDate, Hepatitis C

WHO Guidelines for the Prevention, Care, and Treatment of Persons with Chronic Hepatitis B Infection

"Ensuring the human rights and ethical principles of fairness, equity, and urgency guide the development of national treatment policies so that barriers in access to testing, prevention, and treatment services, particularly among certain populations, are addressed."

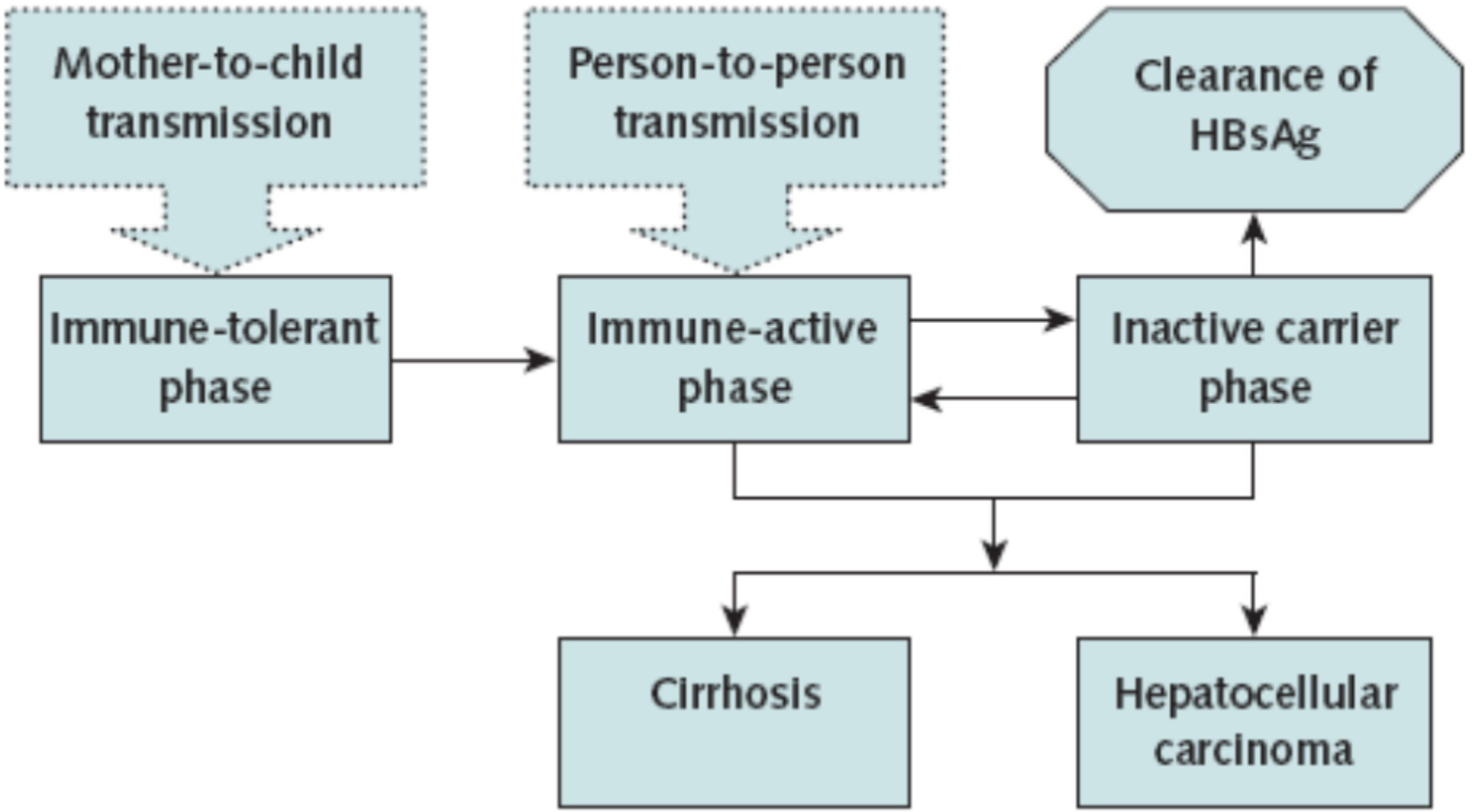
Cited in Wang et al. Hepatitis B Virus Elimination in the US: Time to Dismantle Barriers and Implement Solutions. *Current Hepatology Reports* 2021; 20:34 – 42.

People Living with HBV Are at High Risk of Not Being Appropriately Treated

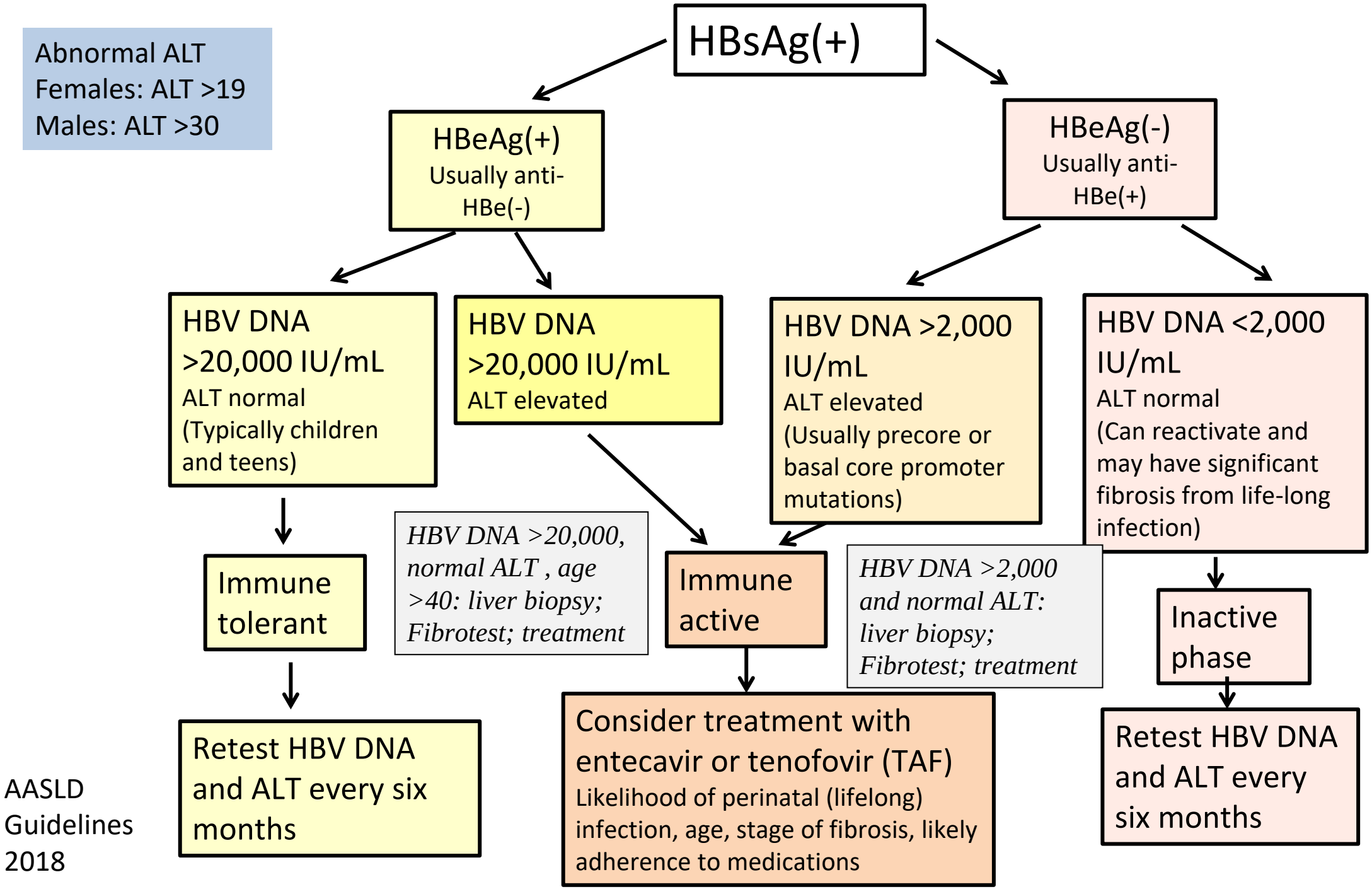
- 66% of people with chronic HBV infection have not been diagnosed
  - no diagnosis = no treatment
- 2338 patients enrolled in CHeCS-HBV from 2006 to 2013
  - 37% had ≥1 HBV DNA test annually
  - 14% with cirrhosis had ≥1 annual liver imaging study
  - 56% with cirrhosis were prescribed antiviral therapy

Spradling. Infrequent Clinical Assessment of Chronic Hepatitis B Patients in United States General Healthcare Settings. CID 2016; 63(9):1205-1208.

Classic View of Natural History of HBV



Slide courtesy of Marion Peters, MD


Abnormal ALT
Females: ALT >19
Males: ALT >30
HBsAg(+)
HBeAg(+)
Usually anti-HBe(-)
HBeAg(-)
Usually anti-HBe(+)
HBV DNA >20,000 IU/mL
ALT normal
(Typically children and teens)
HBV DNA >20,000 IU/mL
ALT elevated
HBV DNA >2,000 IU/mL
ALT elevated
(Usually precore or basal core promoter mutations)
HBV DNA <2,000 IU/mL
ALT normal
(Can reactivate and may have significant fibrosis from life-long infection)
Immune tolerant
HBV DNA >20,000, normal ALT , age >40: liver biopsy; Fibrotest; treatment
Immune active
HBV DNA >2,000 and normal ALT: liver biopsy; Fibrotest; treatment
Inactive phase
Retest HBV DNA and ALT every six months
Consider treatment with entecavir or tenofovir (TAF)
Likelihood of perinatal (lifelong) infection, age, stage of fibrosis, likely adherence to medications
Retest HBV DNA and ALT every six months
AASLD Guidelines 2018

HBV AASLD Guidelines Leave Many People in a "Grey Area"

		ALT < ULN M<35, F <25	ULN < ALT < 2x ULN	ALT > 2x ULN
HBeAg+	HBV DNA >20,000	Monitor	Monitor*	Treat
	HBV DNA <20,000	Monitor	Monitor*	Monitor*
HBeAg-	HBV DNA >2,000	Monitor*	Monitor*	Treat
	HBV DNA <2,000	Monitor	Monitor*	Monitor*

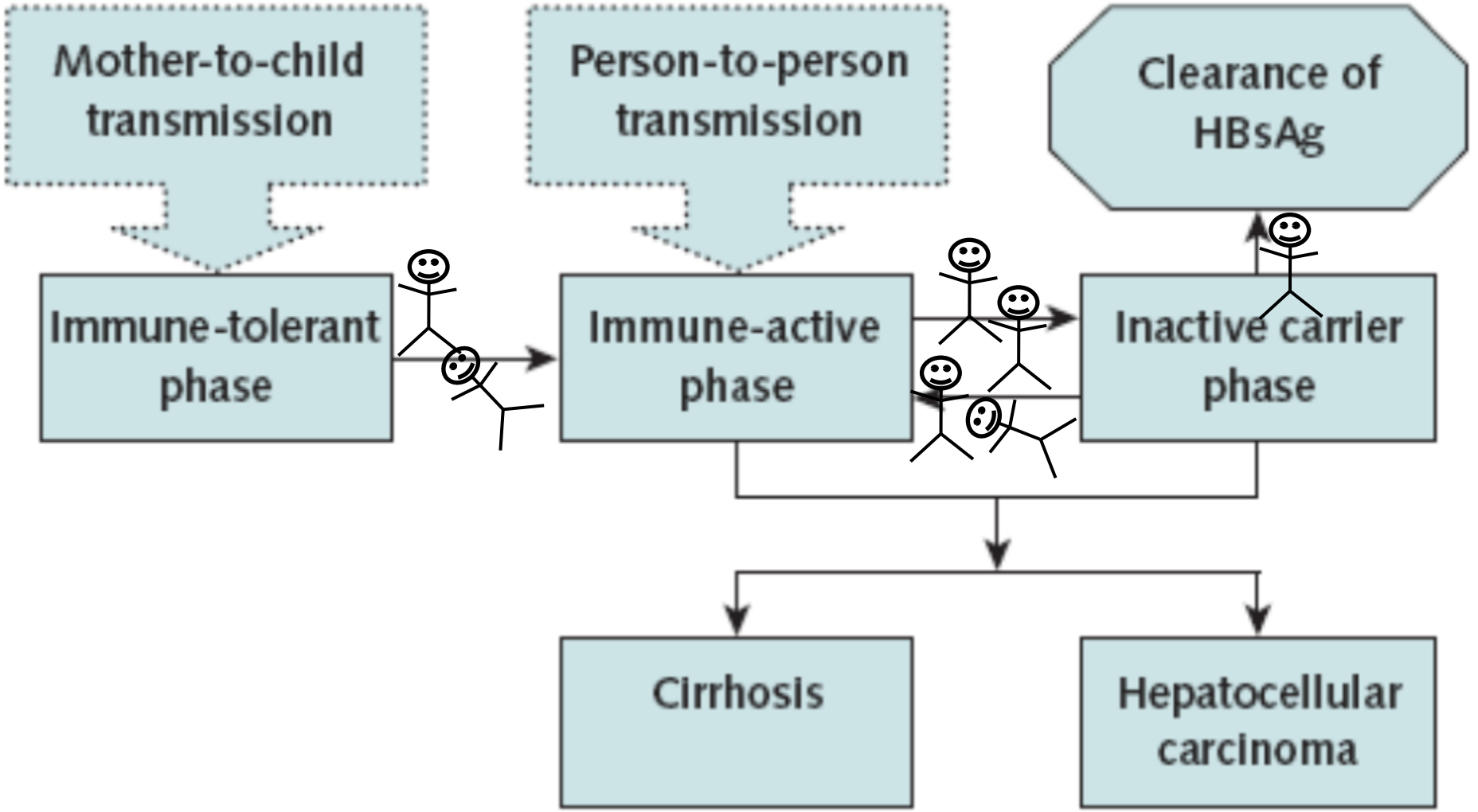
*Values, alone or in combination, that would shift decision making towards antiviral therapy:

- -Inflammation >A3 (requires liver biopsy)
- -Fibrosis >=F2 (elastography, noninvasive serum markers, biopsy)
- -Age >40
- -Persistent ALT >ULN >6 months
- -Other causes elevated ALT excluded (alcohol, fatty liver, autoimmune, etc)

If persistent ALT >ULN > 6 months and HBV DNA >2,000 and age >40, consider antiviral treatment

HBV Guidelines AASLD 2018; table adapted from Dr. Hawra Al Lawati

Classic View of Natural History of HBV

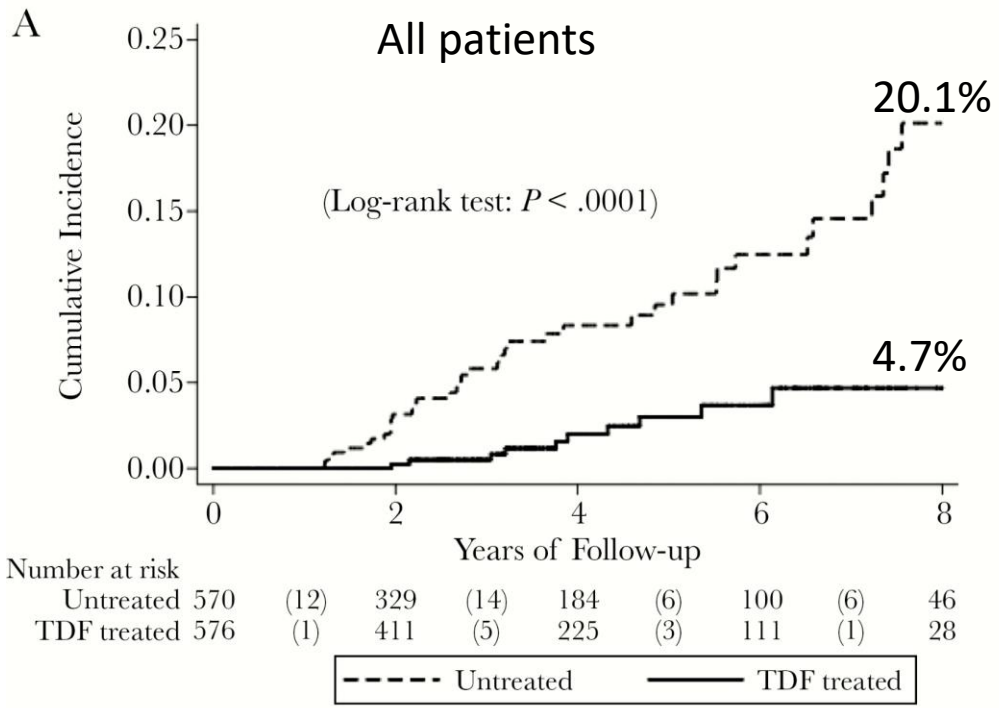


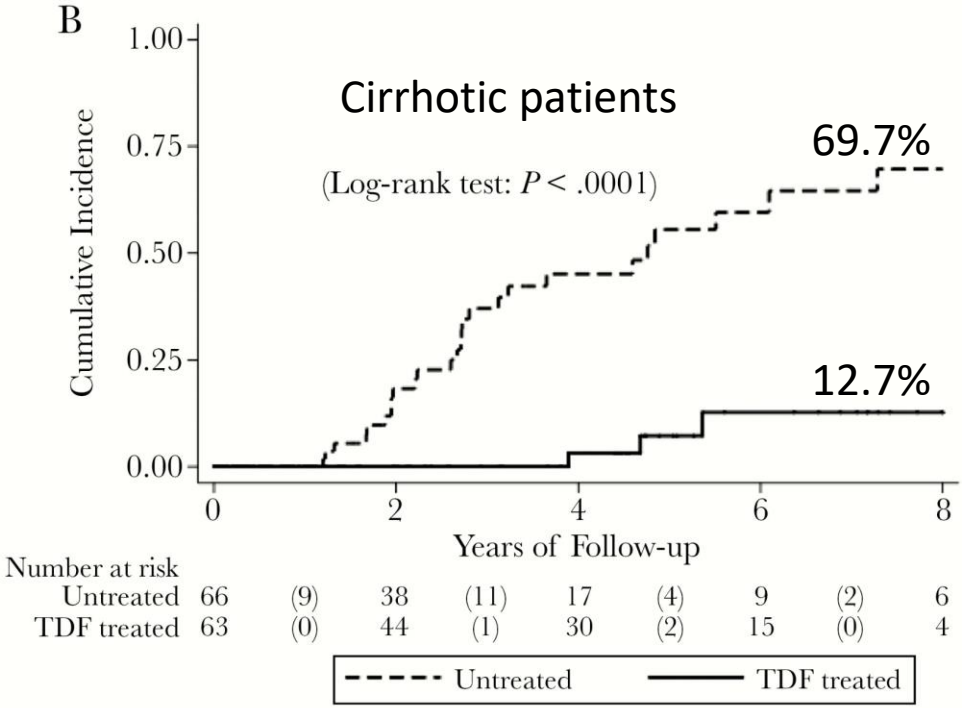
Adapted from slide courtesy of Marion Peters, MD

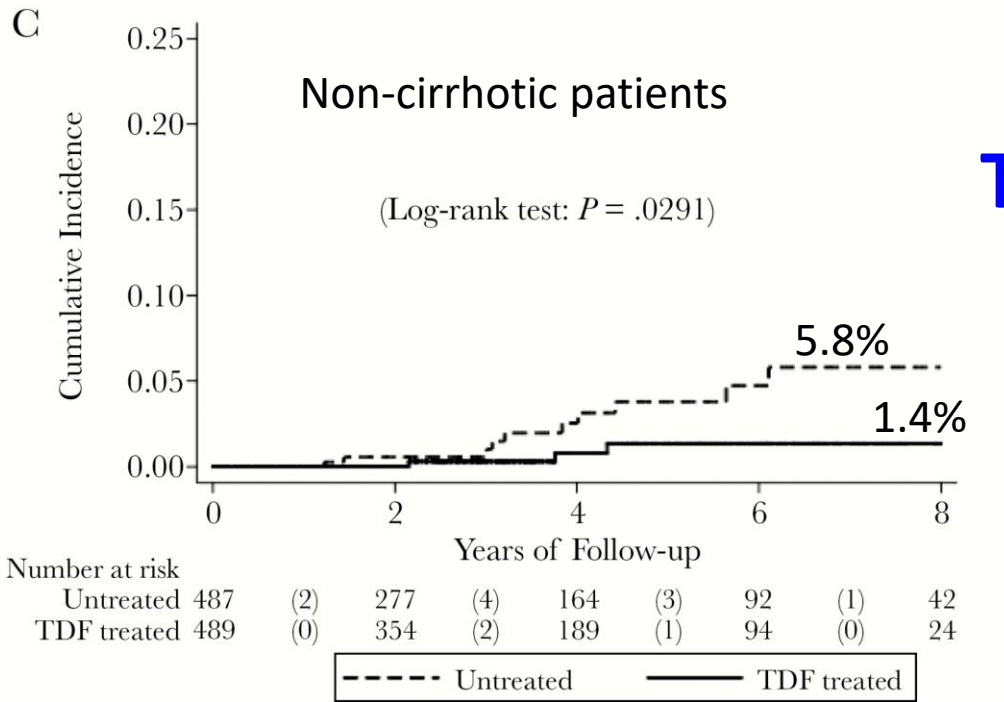
Need for a Simplified Approach to HBV Treatment

- “Grey area” guidelines are confusing and hard to implement
- HBV experts often don’t actually follow these guidelines
- Guidelines should be straightforward enough that community practitioners are able to follow them

Dieterich, D, Graham, C, Wang, S et al. It Is Time for a Simplified Approach to Hepatitis B Elimination. Gastro Hep Advances, 2023; 2(2):209-218







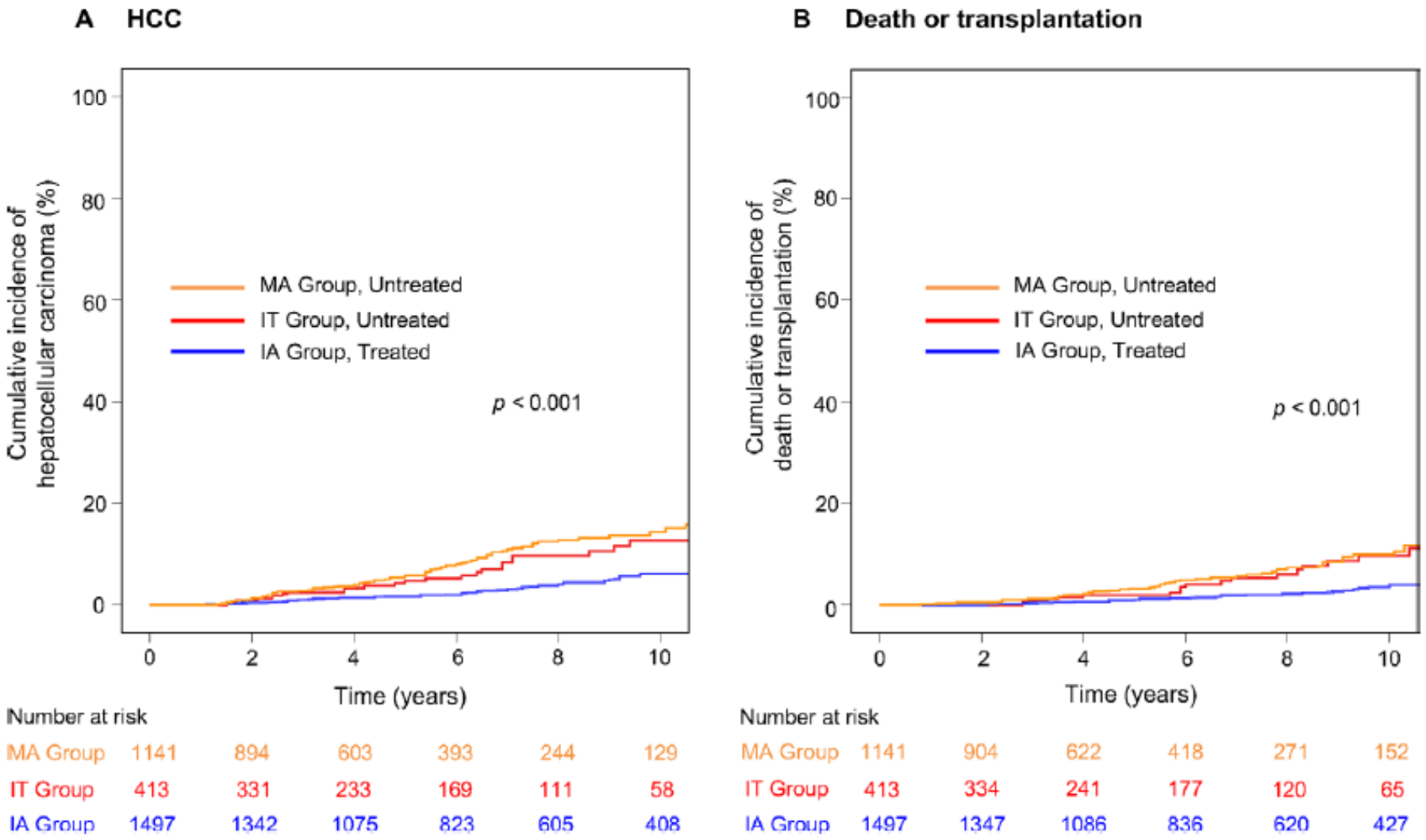
Tenofovir reduces HCC Incidence by ~70%

Propensity matched cohort of patients in US and Taiwan (95% Asian) with TDF vs no antiviral treatment

Nguyen. JID 2019; 291(1):10-18

Cumulative Incidence HCC, Tx or Death in Patients with Immune Tolerant, Immune Active, and Minimally Active HBV

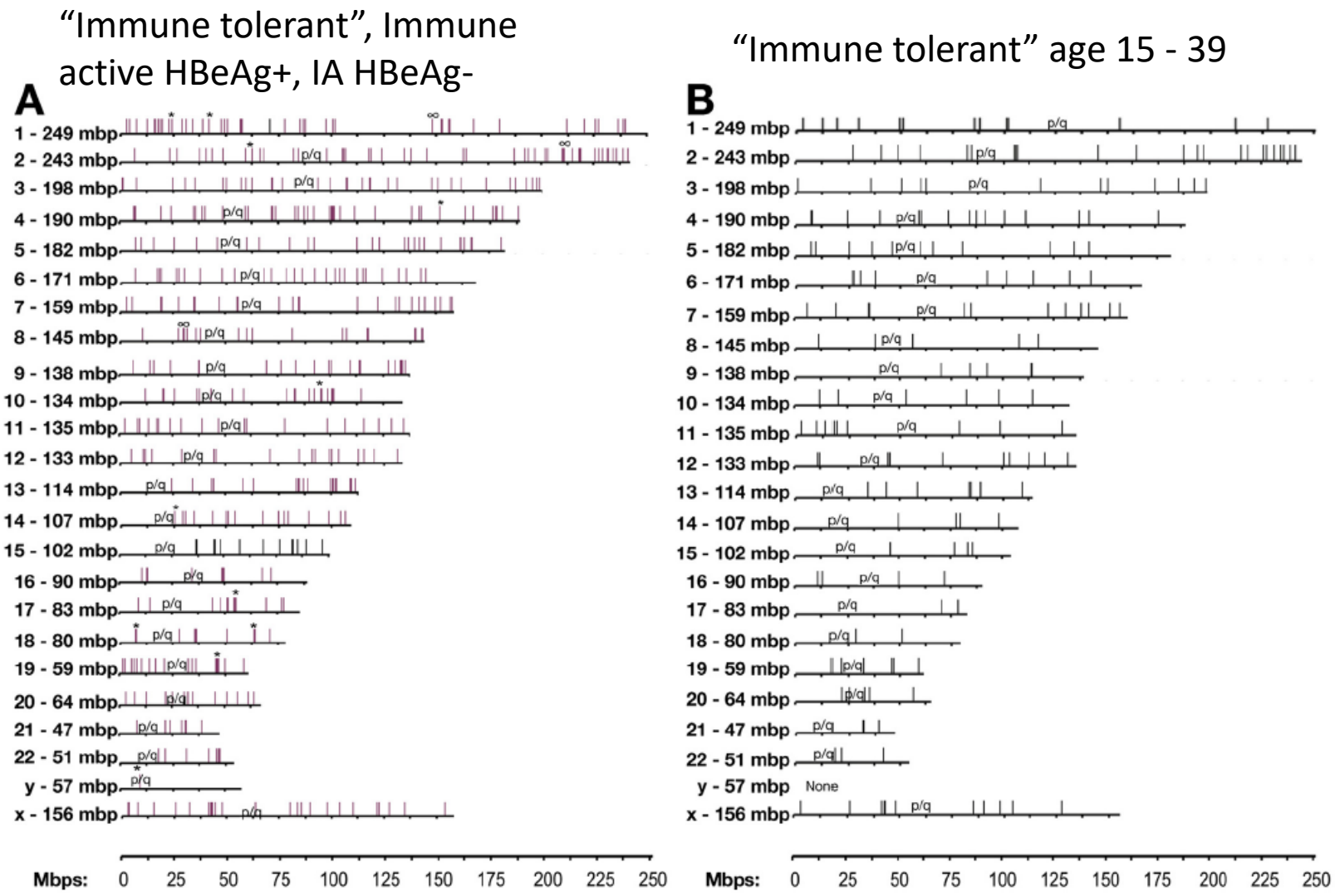
Immune tolerant (ALT <19 for women and <30 for men) and Minimally Active (ALT 1 -2 X ULN) patients were not treated with antivirals; Immune Active (ALT 2x ULN) patients were on antivirals (58% lamivudine)



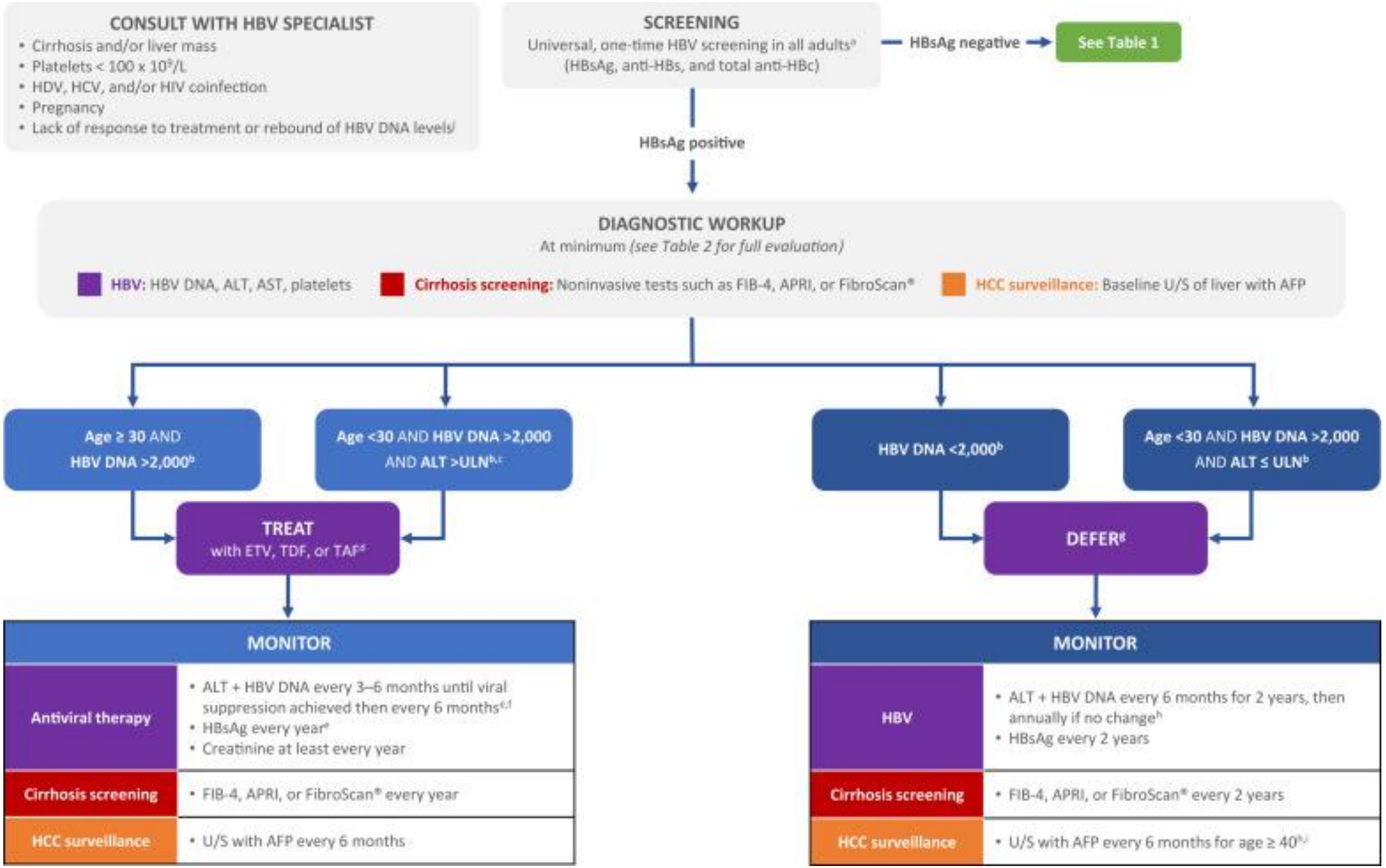
Kim, *Gut*, 2017

HBV DNA Integrations are Found in All Human Chromosomes

Potential Initiating Event for HCC Development



Mason, Gastro 2016



Dieterich, D, Graham, C, Wang, S et al. It Is Time for a Simplified Approach to Hepatitis B Elimination. Gastro Hep Advances, 2023; 2(2):209-218

Simplified Approach Eliminates “Grey Area”

		ALT < ULN	ALT > ULN
HBV DNA >2,000	Age ≥ 30	Treat	Treat
	Age < 30	Monitor	Treat
HBV DNA <2,000	Age ≥ 30	Monitor	Monitor
	Age < 30	Monitor	Monitor

Monitor:

- Age ≥ 30 = If HBV DNA >2,000 then treat
- Age <30 = If HBV DNA >2,000 and ALT > ULN then treat

Slide adapted from Dr. Hawra Al Lawati

A Bit of Nuance

		ALT < ULN	ALT > ULN
HBV DNA >2,000	Age ≥ 30	Treat	Treat
	Age < 30	Monitor	Treat
HBV DNA <2,000	Age ≥ 30	Monitor*	Monitor*
	Age < 30	Monitor	Monitor

*Factors that make me lean towards antiviral treatment:

- Preference of person with HBV infection
- HBV DNA levels “near” 2,000
- Liver fibrosis tests that cannot exclude advanced fibrosis
- Family history of HCC
- Genotype with basal core promoter mutation

Slide adapted from Dr. Hawra Al Lawati

Reasons to Treat People Living with HBV Infection

- Reduce incidence of HCC
- Reduce the risk of progression to cirrhosis
- Reduce need for liver transplant
- Reduce perinatal transmission in pregnant people
- Allow people in certain professions to return to work
- May better position people for future curative strategies
- Reduce stigma
- Treatment as prevention?

Possible role of prior suppressive therapy in HBV treatment regimens under investigation

Company	Investigational Drug (s)	HBV status	Nuc Requirement (stable entecavir, TDF or TAF)	HBV DNA Requirement (duration time)
Arbutus Biopharma NCT04980482	AB-729 (plus Nucleos(t)Ide Analogue and Peg-IFN)	HBeAg-negative	≥12 months	<LLOQ at Screening (no duration)
Assembly Biosciences NCT04820686	vebicorvir (ABI-H0731) AB-729 (plus Nuc)	HBeAg negative for > 3 months	>12 months	<LLOQ for ≥6 months
Hoffmann-La Roche NCT04225715	CpAM (RO7049389); TLR7 (RO7020531); siRNA (RO7445482); PEG-IFN; PD-L1 LNA (RO7191863) (plus Nuc)	No mention	≥12 months	LLOQ or < 20 IU/mL for > 6 months
GlaxoSmithKline NCT05276297	GSK3228836; GSK3528869A (vaccine)	HBeAg positive or negative	> 6 months	"suppressed" <90 IU/mL (no duration)
Vir Biotech NCT04856085	VIR-2218; VIR-3434; +/- PEG-IFNα	HBeAg positive or negative	≥2 months	No mention
Altimmune Inc. NCT04684914	HepTcell (Adjuvanted FP-02.2)	HBeAg-negative	No mention	≥ 10 IU/mL at screening

Clinicaltrials.gov

Case 1

- 52 yo man from Albania with HBsAg(+) and HBeAg(-) infection diagnosed ten years ago

Months from first visit	ALT	AST	Total bilirubin	Platelets	HBV DNA (IU/mL)
0	25	20	0.4	327,000	80
3	23	22	0.3	310,000	120
6	28	24	0.4	280,000	100
9	22	25	0.4	305,000	60

- Keep checking labs every six months
- 15% chance of developing immune active disease (immune escape) at some point
- Due to age >40, screen for HCC every 6 - 12 months

Case 2

- 34 yo man from Cape Verde with HBsAg(+) infection diagnosed two years ago

Months from first visit	ALT	AST	Total bilirubin	Platelets	HBV DNA (IU/mL)	Hepascore
0	35	30	0.4	220,000	80	
3	44	38	0.3	260,000	60	0.40
6	48	40	0.4	280,000	120	
9	42	30	0.4	240,000	100	

- Keep checking labs every 3 - 4 months
- Look for other causes of elevated liver enzymes – alcohol, HCV, HDV, hemochromatosis, autoimmune, medications, hepatic steatosis/NASH
- Due to birth in West Africa, screen for HCC every six months

Case 3

- 44 yo woman from South Korea with HBsAg(+) and HBeAg(-) infection diagnosed twenty years ago. Mother has chronic HBV.

Months from first visit	ALT	AST	Total bilirubin	Platelets	HBV DNA (IU/mL)	Hepascore
0	21	19	0.4	220,000	80	
3	20	21	0.3	260,000	60	0.40
6	32	26	0.4	280,000	200	
9	42	36	0.4	240,000	6,000	

- Recheck HBV DNA level and if still >2,000 IU/mL, start antiviral treatment
- Most likely developing immune escape
- Screen for HCC every six months

Case 4

- 42 yo man from China with HBsAg(+) infection diagnosed in China years ago. Does not think he has been treated. Mother also with chronic HBV

Months from first visit	ALT	AST	Total bilirubin	Platelets	HBV DNA (IU/mL)	Hepascore
0	32	30	0.4	220,000	2,500	
3	40	38	0.3	180,000	6,000	
6	42	40	0.4	200,000	3,000	0.65
9	38	32	0.4	170,000	10,000	

- Most likely has precore or basal core promoter mutations
- Treat with tenofovir (not entecavir) since cannot exclude exposure to lamivudine
- Transient elastography to evaluate for advanced fibrosis
- Screen for HCC every six months