Project ECHO®

Chronic Liver Disease Foundation
New Jersey

HBV Alliance:

Expert Recommendations on Managing Patients with Chronic Hepatitis B

Accredited by

Rehoboth McKinley Christian Health Care Services

This program is supported by an educational grant from Gilead Sciences.

Provided by

CLDF
Chronic Liver Disease Foundation

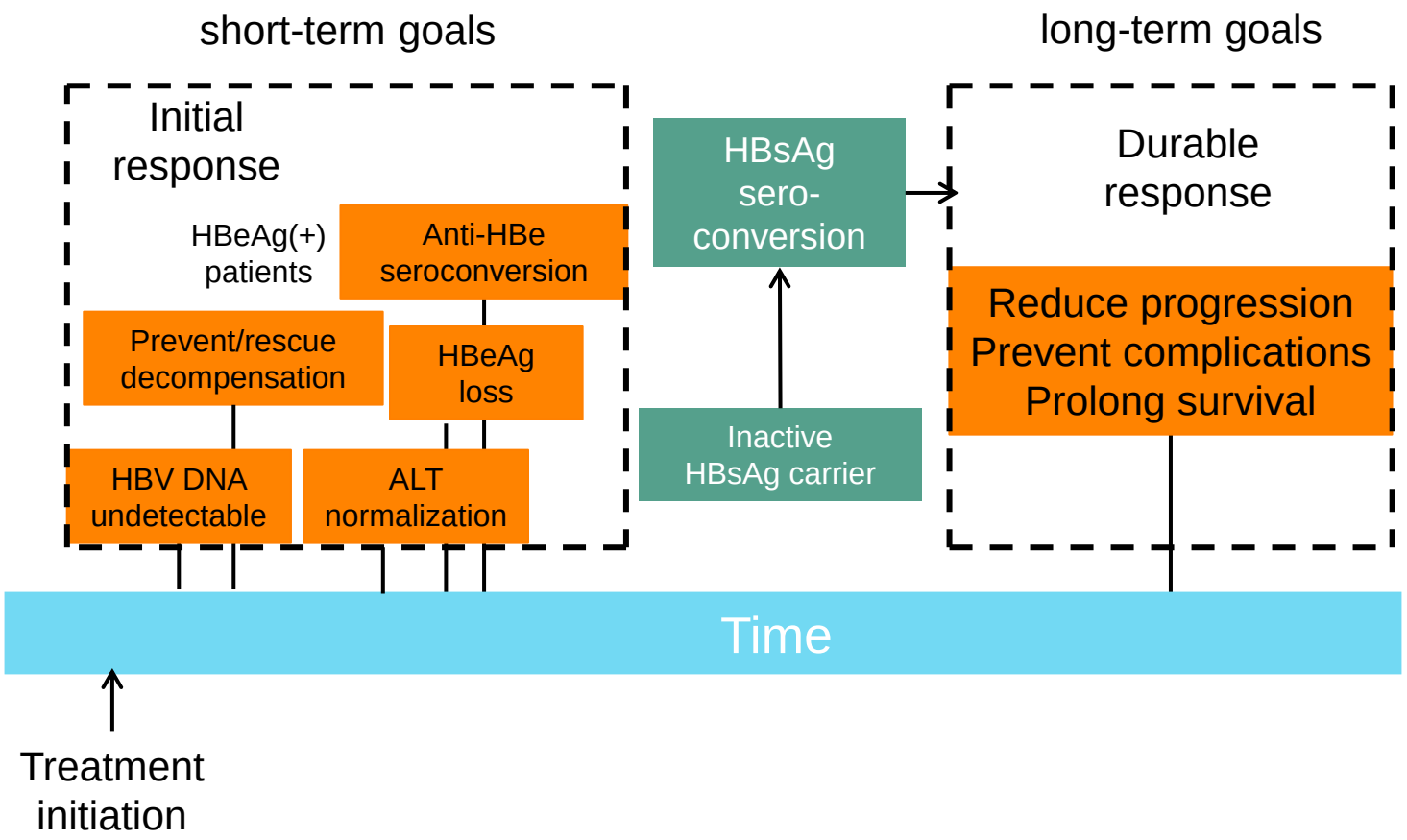
Management of HBV: New Data

Learning Objectives HBV ECHO Series

Upon completion of this activity, participants should be able to:

- Review data on the prevalence and transmission of HBV
- Define the risk of HBV among different patient populations, highlighting high-risk settings
- Describe the detrimental effects of untreated, chronic HBV to emphasize the need for diagnosis and treatment
- Demonstrate strategies to incorporate various diagnostic and treatment guidelines into clinical practice
- Analyze approved and emerging treatment options for HBV
- Identify patients that are likely to benefit from emerging treatment options versus currently available therapies

Goals of Treatment in Chronic HBV Infection

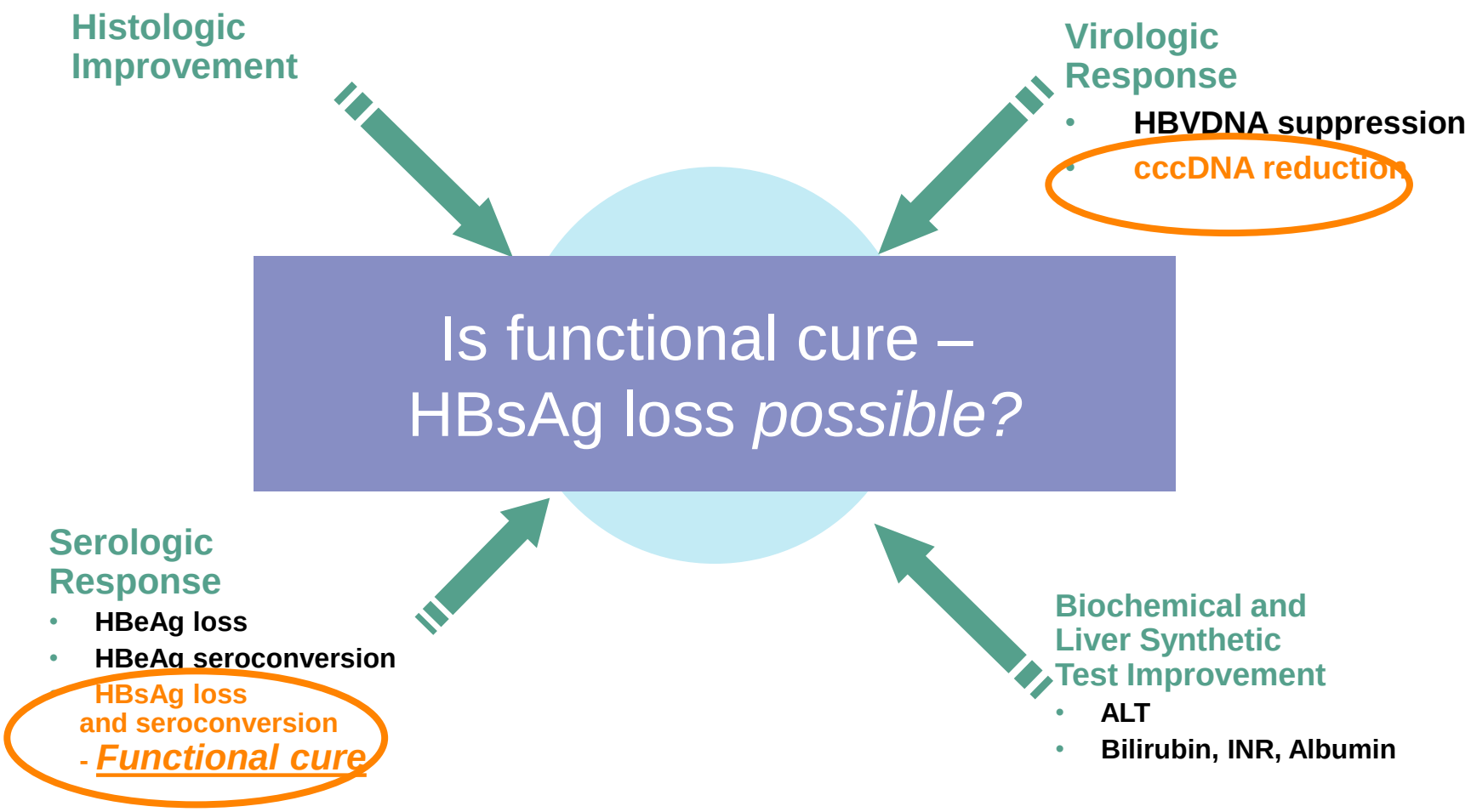


Liaw. *Clin Liver Dis*. 2013.

Treatment Criteria for Chronic HBV

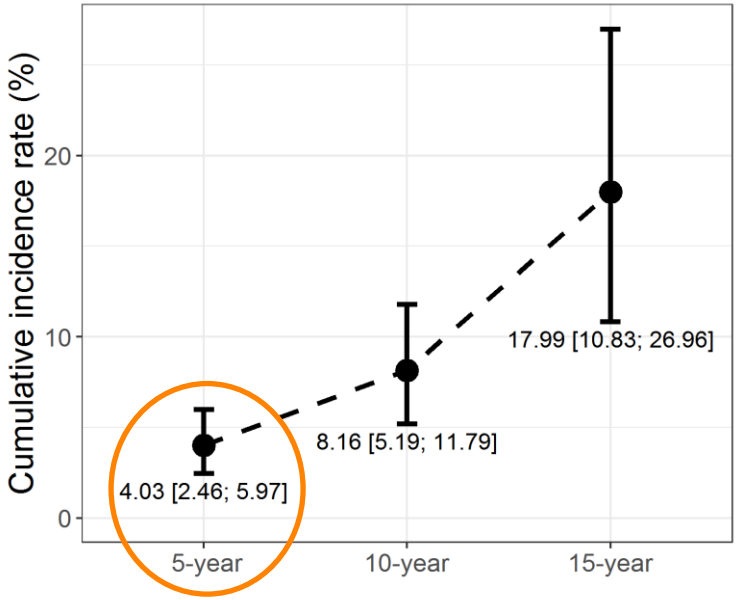
Guideline	HBeAg+		HBeAg-	
	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L
EASL 2009	>2,000	>ULN	>2,000	>ULN
US Algorithm 2015	≥2,000	>ULN or (+) biopsy	≥2,000	>ULN or (+) biopsy
APASL 2008-12	≥20,000	>2x ULN	≥2,000	>2x ULN
AASLD	>20,000	>2x ULN or (+) biopsy	>20,000 or >2,000	≥2x ULN or (+) biopsy

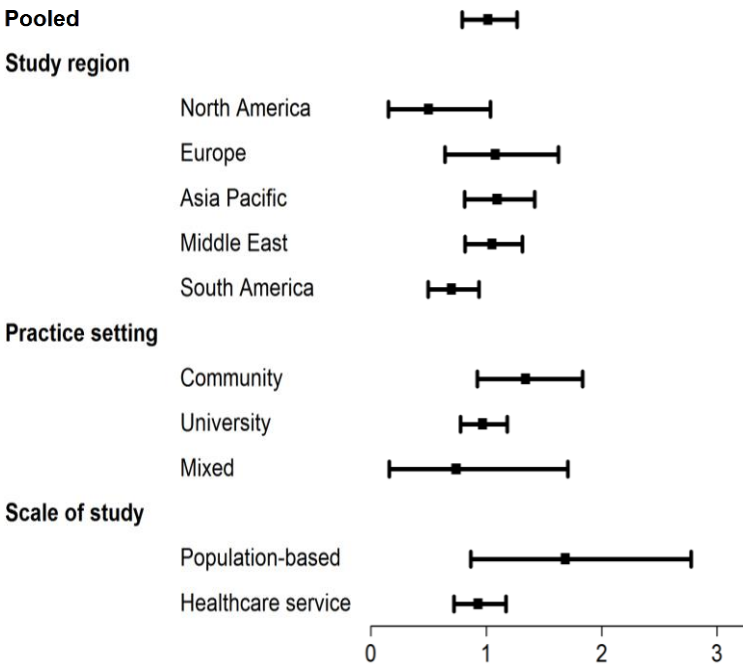
Current Goals of Treatment – Viral Suppression



Low HBsAg Seroclearance in Both Treated & Untreated Real-World Patients

Factors Associated with Rates of HBsAg Seroclearance in Adults with Chronic HBV Infection: A systematic review and meta-analysis





***Meta-analysis with additional aggregated data**, ~40,000 patients, ~40 studies , additional data from 19 cohorts: US, Europe (Spain, Romania), Asia Pacific (HK, TW, JP, China, Thai, KR).

Yeo YH[1], Ho HJ[2], Yang HI[3], Tseng TC[4], Hosaka T[5], Trinh HN[6], Kwak MS[7], Park YM[8], Fung JYY[9], Buti M[10], Rodriguez M[11], Treeprasertsuk S[12], Preda CM[13], Ungtrakul T[14], Charatchareonwitthaya P[15], Li X[16], Li J[17], Zhang J[18], Le MH[1], Wei B[1], Zou B[1], Le A[1], Jeong D[1], Chien N[19], Kam L[19], Lee CC[20], Riveiro-Barciela M[10], Istratescu D[13], Sriprayoon T[15], Chong Y[16], Tanwandee T[15], Kobayashi M[21], Suzuki F[5], Yuen MF[9], Lee HS[7], Kao JH[22], Lok AS[23], Wu CY[24], Nguyen MH[25]. *Gastroenterology*. 2018 Oct 17. pii: S0016-5085(18)35158-8.doi: 10.1053/j.gastro.2018.10.027. [Epub ahead of print].

Can We Ever Stop Therapy in eAg Negative Chronic Hepatitis B?

Stop-NUC: Discontinuation of Long-Term NA Therapy in Patients With HBeAg Negative CHB

- Multicenter, prospective, randomized phase IV trial

Adult patients with HBeAg negative CHB and normal ALT receiving NA therapy* with HBV DNA < 1000 IU/mL for ≥ 4 yrs; no advanced fibrosis or cirrhosis, HCC, or HCV, HDV, HIV coinfection
(N = 158)

Discontinue NA Therapy† (n = 79)

Continue NA Therapy (n = 79)

Enrolled patients had HBeAg status and ALT data available for period before NA therapy, were known to have pre-treatment HBV DNA > 2000 IU/mL. Liver function, HBV virology and serology regularly evaluated on study for all patients. *TDF (51%), ETV (39%), telbivudine (6%), or lamivudine (4%). †Patients retreated upon severe acute or chronic hepatitis reactivation (ie, confirmed ALT > 0 x ULN, ALT > 5 x ULN and ≤ 0 x ULN for ≥28 days, ALT >2 x ULN and ≤ 5 x ULN for ≥112 days with HBV DNA >20,000 IU/mL, or total bilirubin increase >1.5 x ULN at 2 consecutive measurements within 1 wk).

- Primary endpoint: HBsAg loss up to Wk 96

- Secondary endpoints: time to HBsAg loss, time to HBsAg seroconversion, virologic response (HBV DNA <12 IU/mL), biochemical response (ALT ≤ULN), time to fulfill retreatment criteria, sustained remission (HBV DNA <2000 IU/mL and normal ALT)

Slide credit: clinicaloptions.com

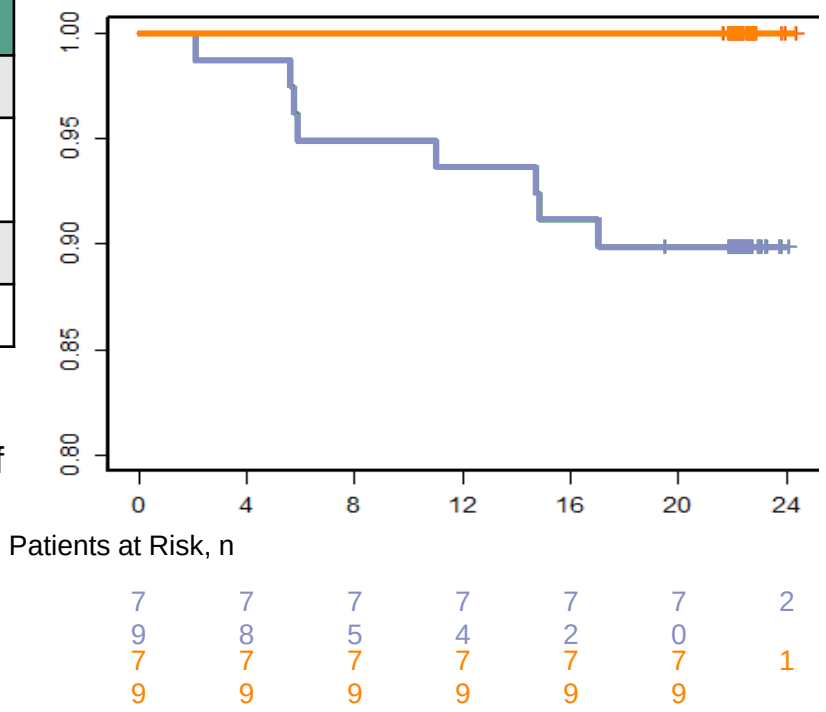
Van Bömmel. *EASL*. 2020. Abstr LBO06. EudraCT 2013-004882-15.

Stop-NUC: Retreatment and Time to HBsAg Loss

Outcome at Wk 96, n (%)	Discontinue NA (n = 78)
HBsAg loss	8 (10.3)*
No retreatment indicated	53 (67.9)
Retreatment indicated	6 (7.7)
Retreatment initiated	11 (14.1)†

NA

*Continuation arm (*P* = .006).
†Per predetermined criteria, n = 9; by decision of treating physician, n = 3.



Slide credit: clinicaloptions.com
Van Bömmel. *EASL*. 2020. Abstr LBO06.

Stop-NUC: HBsAg Loss by Baseline Characteristics

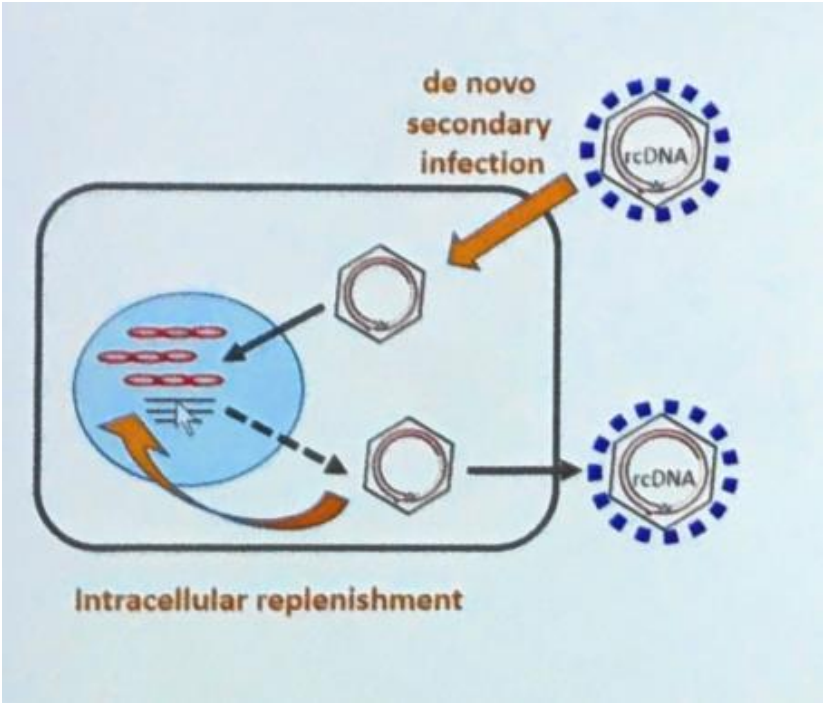
Baseline Characteristic, n (%)	HBsAg Loss	No HBsAg Loss	*P* Value
HBsAg <1000 U/mL • Yes • No	7 (28) 1 (1.9)	18 (72) 53 (98.1)	.001
Previous NA therapy • ETV or TDF • Lamivudine or telbivudine	7 (10) 1 (11.1)	63 (90) 8 (88.9)	1

Slide credit: clinicaloptions.com

Van Bömmel. *EASL*. 2020. Abstr LBO06.

Why Is Hepatitis B So Hard to Cure?

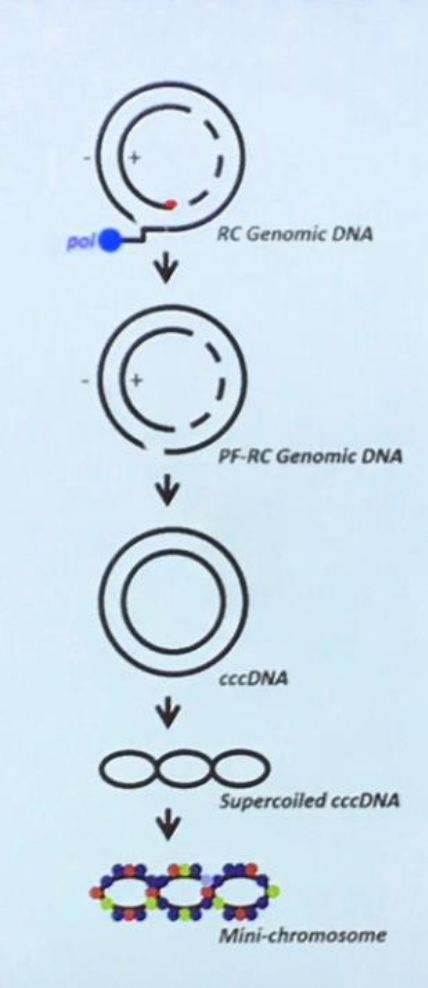
cccDNA: The Key Molecule in HBV Life-Cycle and Persistence in CHB



- The ccDNA is first generated from incoming virions
- It serves as transcriptional template for all HBV RNAs and progeny formation
- It forms a stable minichromosome in nondividing hepatocytes
- A cccDNA pool is determined in infected cells

Zoulim F, AASLD-EASL HBV Conference, London. 2019.

HBV cccDNA



- Long half-line, stable in quiescent cells; mechanism of turn-over unknown
- Loss of cccDNA controlled by
  - Cell death: immune cytolytic mechanism
  - Dilution by cell proliferation: liver regeneration
  - Cell cure: immune non-cytolytic mechanism, IFNs & other cytokines

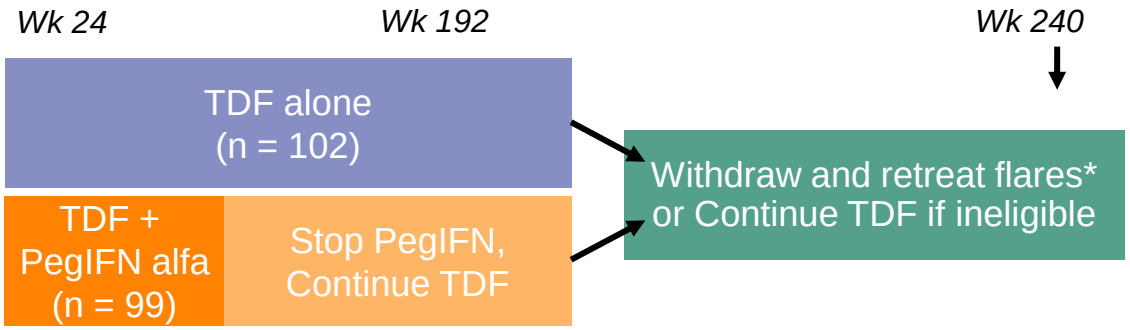
Guidotti et al. *Science*. 1999; Summers et al. PNAS. 2003; Mason et al. *J Virol*. 2009;
Zoulim F, AASLD-EASL HBV Conference, London. 2019.

- Can we boost HBsAg loss with combination regimens?

192 Wks TDF +/- PegIFN Alfa in First 24 Wks, Followed by Protocolized TDF Withdrawal in Patients With CHB

Hepatitis B Research Network

HBeAg +/- patients, ≥18 yo, no prior antiviral tx ≥24 wks, ALT >1.5 x ULN, HBV DNA ≥1000 IU/mL, compensated liver disease
(N = 201 randomized)

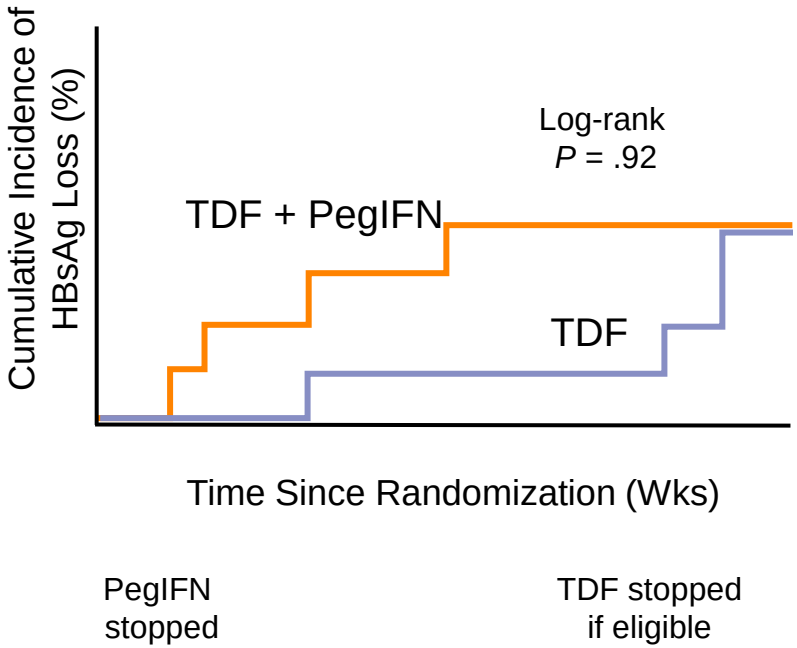


*TDF Withdrawal Criteria: HBV DNA <1000 IU/mL for 24 wks, absence of cirrhosis, HBeAg negative, anti-HBe positive;
TDF Retreatment Criteria: any clinical decompensation, total bilirubin ≥3.0 mg/dL or direct bilirubin ≥1.0 mg/dL, HBV DNA ≥10,000 IU/mL with ALT either >1000 U/L for 1 wk, ≥300/200 U/L (M/F) for ≥4 wks or ≥150 U/L for ≥12 wks

- Primary endpoint: HBsAg loss
- Participants 65% male, 17% non-Asian, median age 41 yrs, 52% HBeAg positive, 12% genotype A, 7% with cirrhosis, median ALT 71 U/L, HBV DNA: 6.5 log IU/mL

Slide credit: clinicaloptions.com
Terrault. *AASLD*. 2020. Abstr 19.

TDF +/- PegIFN Alfa: HBsAg Loss at Wk 240



HBsAg Loss, n (%)	TDF (n = 102)	TDF + PegIFN (n = 99)	*P* Value
Wk 192 (EOT, ITT)	1 (1.0)	4 (4.3)	.21
Week 240 (End of follow-up, ITT)	4 (4.5)	5 (5.7)	.74

Slide credit: clinicaloptions.com

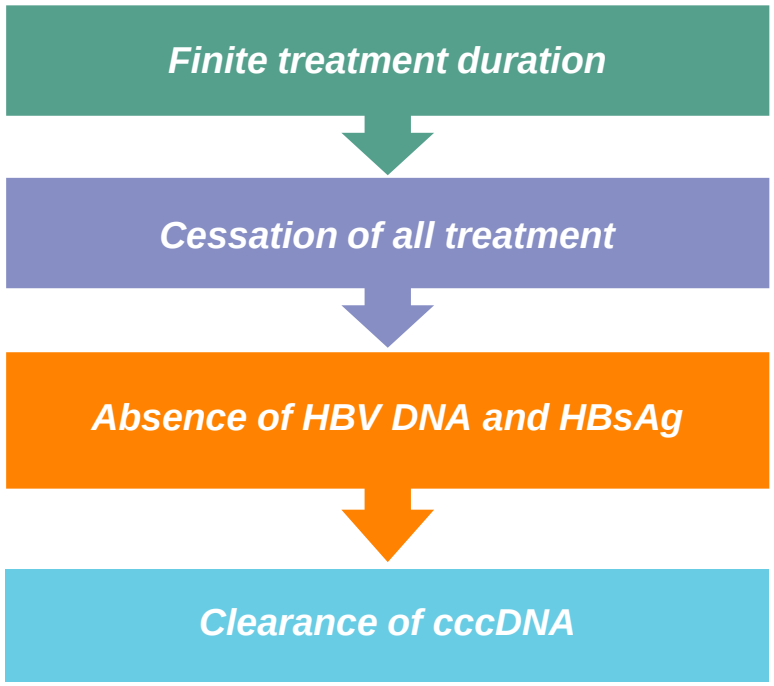
Terrault. *AASLD*. 2020. Abstr 19.

Disadvantages of Long-Term Oral Antiviral Therapy

- Treatment limited to those patients in immune active phase (high ALT, DNA, fibrosis)
- Cost limits access to long-term therapies in low-income countries and favours use of old therapies with high resistance
- No clear guidelines for stopping criteria
- No effect on cccDNA
- Viral breakthrough from nonadherence or resistance ➡ flares ➡ liver failure

Future Goal: Complete Cure

the CCH meeting
Clinical Cases in Hepatitis
HBV



No active liver disease

No viral replication

No risk of reactivation

➡ ***Still life-long risk of HCC***

Sterilizing cure - includes removal of integrated DNA and all viral particles

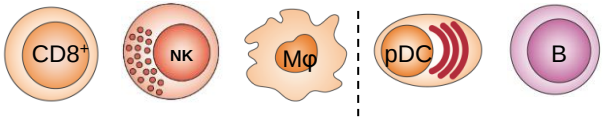
Virus-Directed Strategies

- **Target HBV entry:**
  1. **Entry receptor inhibitor**
- **Targeting cccDNA:**
  2. **RNA interference (RNAi)**
     - Promising efficacy with >1 log decrease in HBsAg
     - Not convenient (injection) and concern of off-target effects
  3. **Capsid assembly modifier (CAM)**
     - Effect on HBsAg level is modest, concern for drug resistance
  5. **Nucleic acid polymers (NAP)**
     - High rate of HBsAg loss
     - Complex study design, mechanism unclear (block viral assembly and release), safety concerns for fatal ALT flares or end-organ damage

Lok AS. *Hepatol Comm*. 2019; Blanchet et al. *Antiviral Res*. 2019; 164: 87-105.

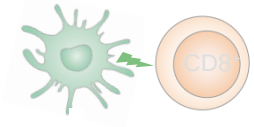
Host-Directed Therapies

1. Stimulate Antiviral Effector Cells



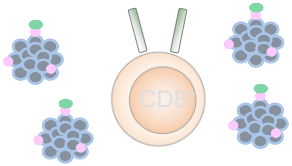
- TLR-7, TLR-8, RLRs, CLRs, NLRs
- DNA sensors

2. Generate New T cells



- Therapeutic vaccines

3. "Rescue" Exhausted T cells



- Reduce viral antigens
- Modulate immune receptors (PD-1)
- Relieve suppression of T cells
- Inhibit T regs

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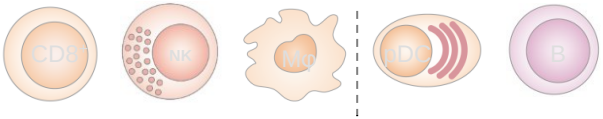

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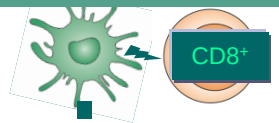

- Therapeutic vaccines (GS 4774)

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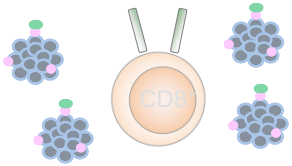

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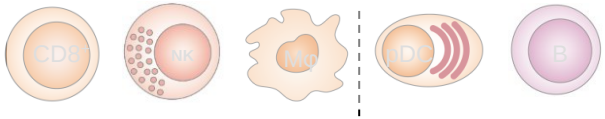

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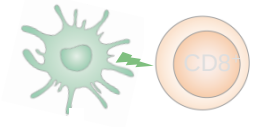

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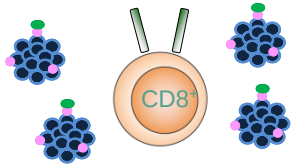

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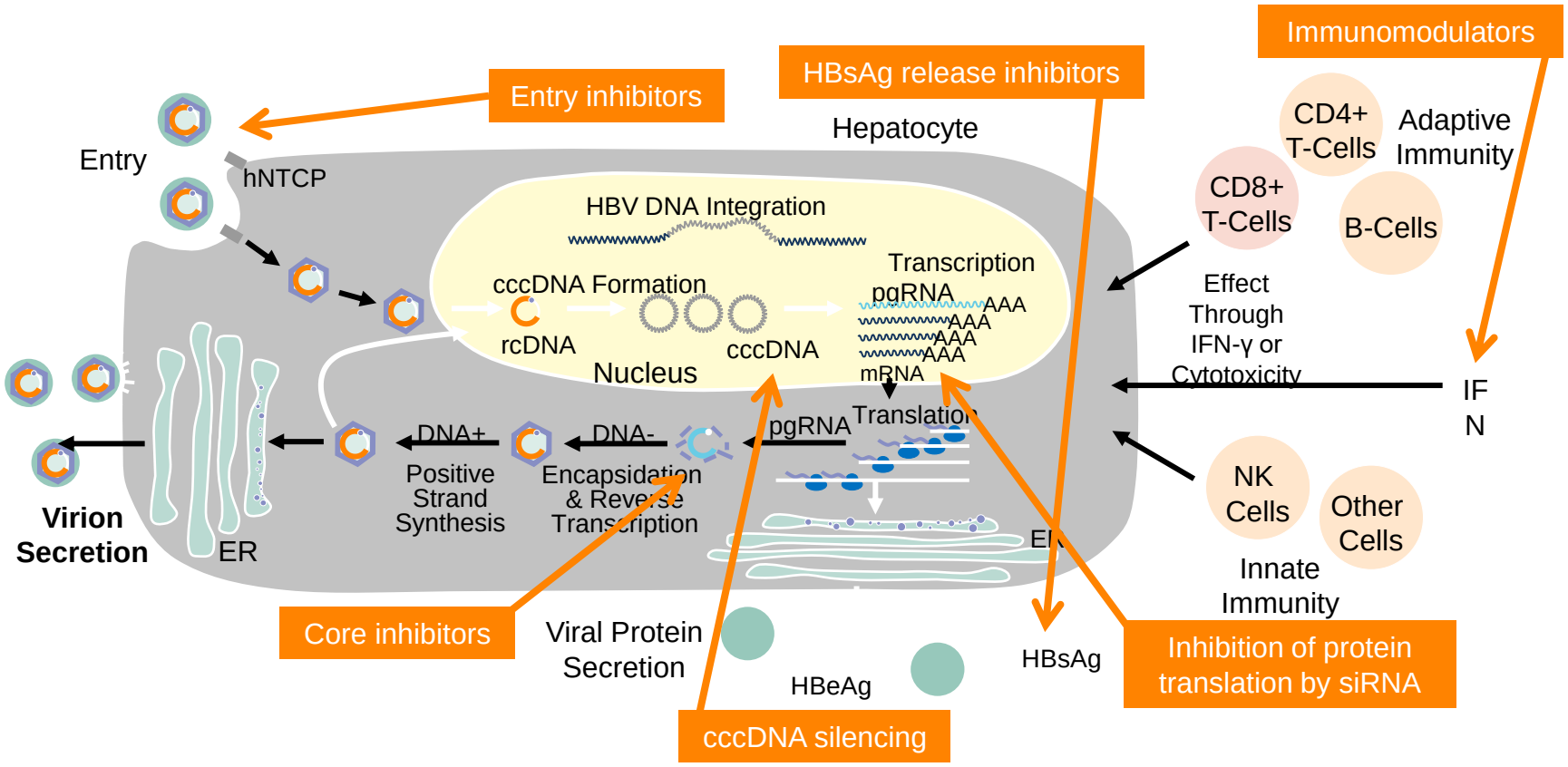
New Targets for HBV



Slide credit: clinicaloptions.com

Zoulim. *Cold Spring Harb Perspect Med*. 2015;5:a021501.

- HBV therapy remains suppressive not curative
- Variety of agents in clinical trials
- Role of new diagnostic tests under evaluation

Thank You!