CLINICAL CARE OPTIONS®
HEPATITIS

CCO Independent Conference Coverage: Clinical Impact of New Data From EASL 2020*

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Stefan Zeuzem, MD, has disclosed that he has received consulting fees from AbbVie, Gilead Sciences, Intercept, and Janssen, and fees for non-CME/CE services from AbbVie, Gilead Sciences, Janssen, and Merck.

Outline

- HCV Elimination: Progress Update and Implementation Strategies
- Treatment of HCV Infection
- Treatment of HBV Infection

HCV Elimination: Progress Update and Implementation Strategies

HCV Elimination: Updating Markov Models

- Updated evaluation of progress toward HCV elimination in high-income populations using published Markov disease progression models[1]
  - Demographic/epidemiologic inputs sourced from the UN World Population Prospects and the Polaris Observatory
  - Added annual new diagnoses (2017-18), treatment data (2017-19)
- Pinpointed timeframe each country likely to achieve WHO targets[2]
  - 80% reduced incidence, 65% reduced mortality vs 2015
  - 90% of patients diagnosed, 80% of patients treated

1. Razavi. EASL 2020. Abstr THU365. 2. WHO. Global Health Sector Strategy on Viral Hepatitis, 2016-2021.

HCV Elimination: Timing Across High-Income Countries

Elimination by 2030
Australia
Canada
France
Germany
Iceland
Italy
Japan
Spain
Sweden
Switzerland
United Kingdom

Elimination by 2040
Austria
Malta
Netherlands
New Zealand
South Korea

Elimination by 2050
Saudi Arabia

Elimination After 2050		
Bahrain	Hungary	Portugal
Belgium	Ireland	Qatar
Chile	Israel	Singapore
Cyprus	Kuwait	Slovakia
Czechia	Latvia	Slovenia
Denmark	Lithuania	Taiwan
Estonia	Luxembourg	UAE
Finland	Norway	United States
Greece	Oman	
Hong Kong	Poland	

Razavi. EASL 2020. Abstr THU365.

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HCV Elimination: Progress and Implications

- **Among 45 high-income countries,** WHO elimination targets for HCV estimated to be met by 2030 in 24%, by 2040 in an additional 11%, and by 2050 in an additional 2%
  - **Remaining 28 countries (62%) off track by ≥ 20 yrs;** 11 of 28 still endorse treatment restrictions related to fibrosis level
  - Analyses assume HCV diagnosis and treatment rates maintained at current thresholds; service expansion will be critical to reaching targets
- Of note, 3 countries previously off track for 2030 have course corrected and 1 country previously on track for 2030 has slipped to the "by 2040" stratum
  - Canada focused elimination efforts in populous provinces, Germany improved diagnosis tactics, and Sweden removed fibrosis-related restrictions on HCV therapy
  - South Korea has experienced declining treatment rates and lacks comprehensive screening initiatives

Razavi. EASL 2020. Abstr THU365.

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SToP-C: HCV TasP in Australian Prisons

- Interventional clinical trial enrolling incarcerated persons across New South Wales, Australia, into open, prospective cohort beginning October 2014
  - Max security: Goulburn and Lithgow (both male)
  - Medium security: OMMPCC (male), Dillwynia (female)
- HCV status and risk behavior assessed at baseline and every 6 mos thereafter
  - If uninfected or previously infected, followed for primary infection or reinfection; if infected, evaluated for HCV therapy
- Intensive DAA scale-up begun mid-2017 with 12-wk SOF/VEL offered to HCV RNA positive individuals
  - HCV incidence compared for periods **before (2014-17)** vs **after (2018-19)** treatment scale-up

Baseline Characteristic, n (%)	Prisoners
Use of injected drugs (N = 3691)	
▪ Never	1654 (45)
▪ Before current imprisonment	792 (21)
▪ During current imprisonment	
• More than 6 mos ago	139 (4)
• Within 2-6 mos	198 (5)
• Within 1 mo	797 (22)
Current OAT*	315 (28)
Used shared injecting equipment†	722 (91)

Among persons injecting *any time during current imprisonment or †in prior mo of current imprisonment.

Dore. EASL 2020. Abstr LBP07.

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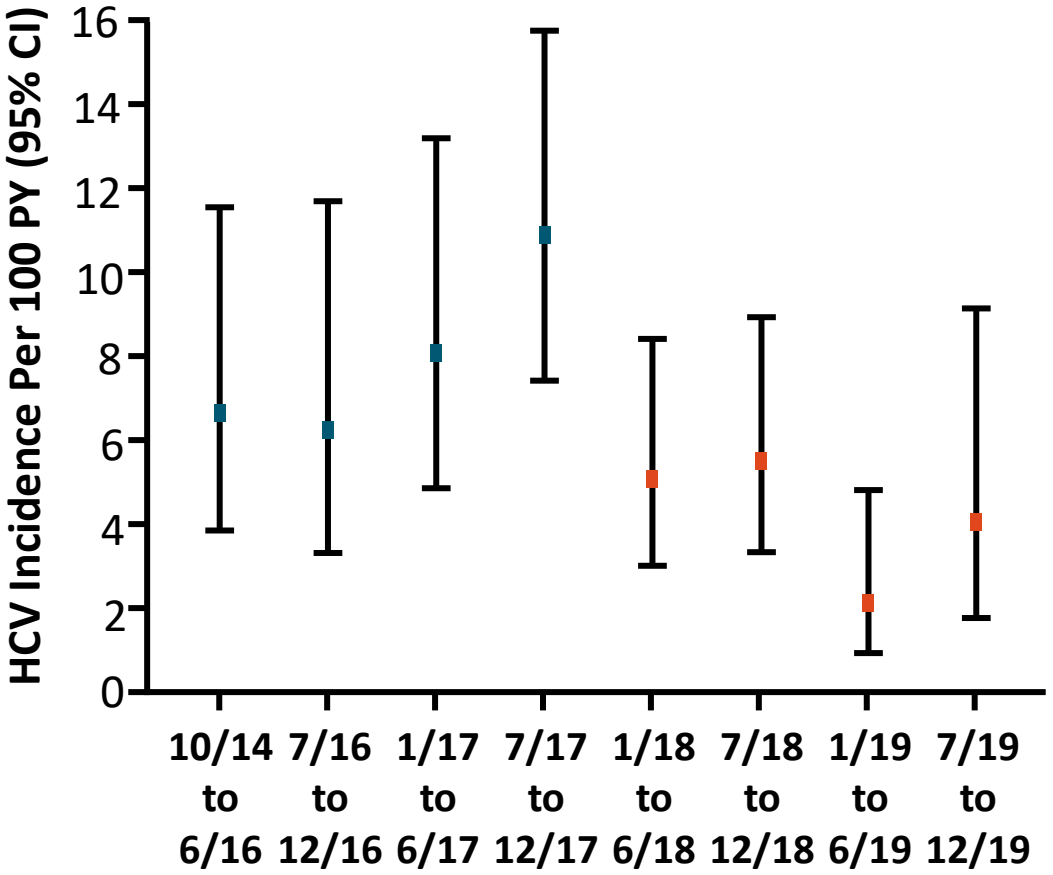
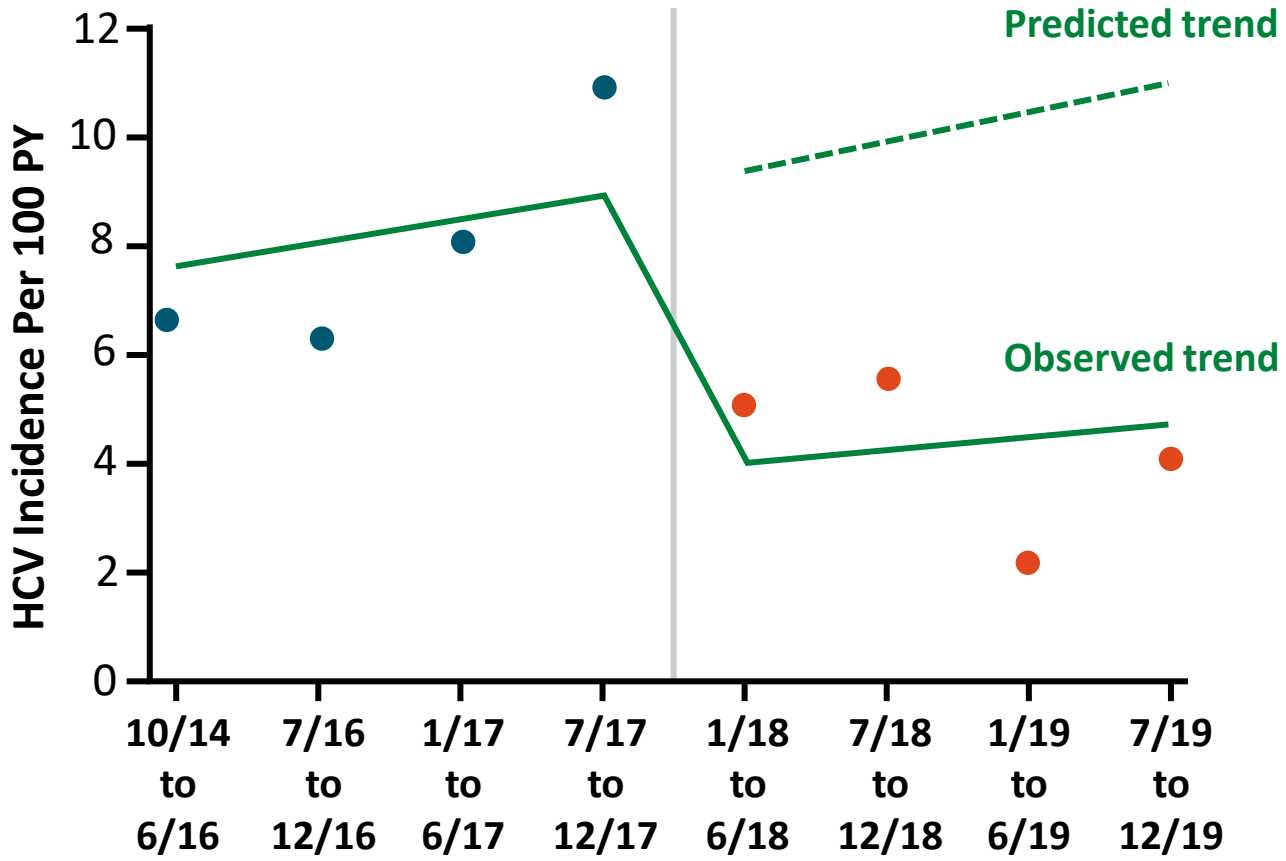
SToP-C: Overall Biannual HCV Incidence Before vs After DAA Scale-Up

- Similar trends observed when data stratified by primary HCV infection or HCV reinfection





Dore. EASL 2020. Abstr LBP07.

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SToP-C: Factors Associated With HCV Acquisition Risk

Characteristic		Adjusted HR (95% CI)	*P* Value
Study period	▪ 2014-17 ▪ 2018-19	1.00 0.50 (0.33-0.76)	 .001
Age at enrollment, yrs		0.92 (0.89-0.95)	< .001
Previous imprisonment	▪ No ▪ Yes	1.00 2.27 (1.21-4.26)	 .011
Injecting drugs status in current imprisonment	▪ None ▪ More than 6 mos ago ▪ Within last 6 mos	1.00 3.32 (1.04-10.59) 6.14 (3.16-11.92)	 .043 < .001
Prison site at last visit	▪ Lithgow ▪ Dillwynia ▪ Goulburn ▪ OMMPCC	1.00 2.10 (1.06-4.15) 1.97 (1.18-3.29) 1.18 (0.53-2.63)	 .034 .009 .690

Dore. EASL 2020. Abstr LBP07.

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Treatment of HCV Infection

SHARED Cohort: Correlates of Treatment Failure With GLE/PIB or SOF/VEL/VOX

- SHARED: International cohort of patient data on treatment histories, HCV RNA sequences, and health outcomes
- Current analysis included 130 patients from leading centers in Germany, Italy, France, Spain, Australia: 54% GT3a, 34% GT1a, 19% GT1b, 17% GT2c, 3% GT2a, 2% GT4d, and 1% GT3b
  - NS3, NS5A, NS5B sequenced to identify relevant RASs (those that occur in association with treatment failure or confer > 2-fold change in drug susceptibility in vitro)

Patients with GLE/PIB failure

- 92.9% (52/56) retreated with SOF/VEL/VOX: **97.8% (45/46) of evaluable patients achieved SVR12 across all GTs**
- 4 patients retreated with SOF/VEL: 75% achieved SVR12

RASs, n/N (%)	GT 1a	GT 1b	GT 2a/2c	GT 3a	*P* Value
Any NS5A or NS3	21/23 (91.3)	5/10 (50.0)	4/18 (22.2)	27/34 (79.4)	< .05
NS5A	20/23 (87.0)	4/10 (40.0)	4/18 (22.2)	25/33 (75.8)	< .05
NS3	5/21 (23.8)	1/10 (10.0)	0	7/33 (21.2)	NS
None	2/23 (8.7)	5/10 (50.0)	14/18 (77.8)	6/34 (17.6)	--

De Salazar. EASL 2020. Abstr AS156.

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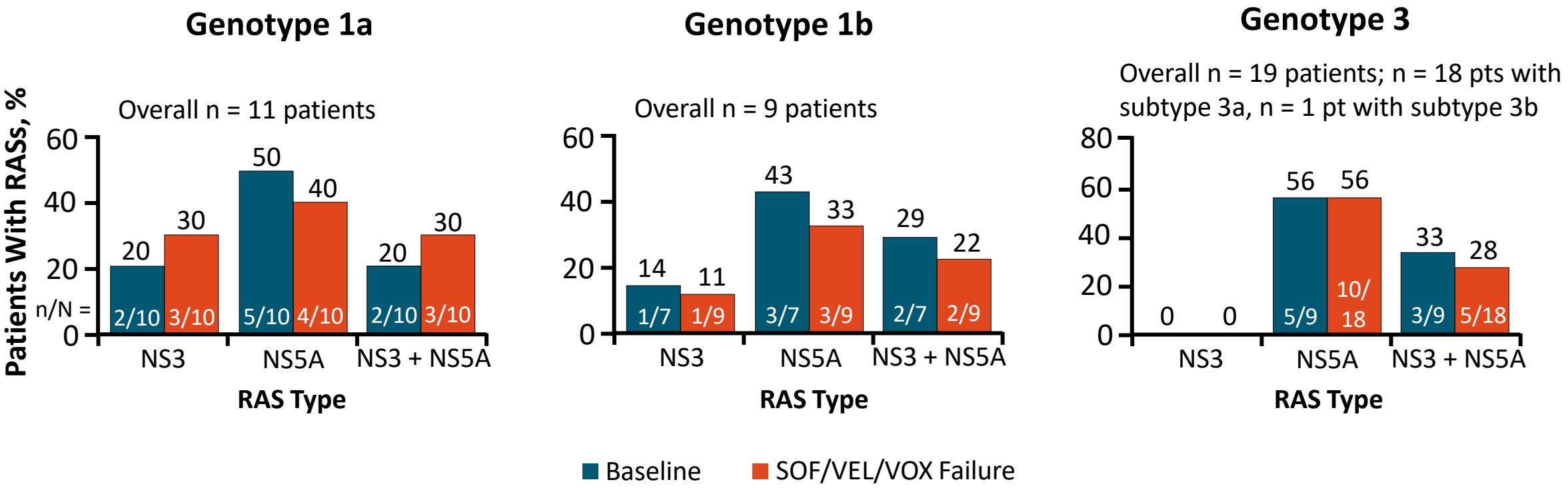
SHARED Cohort: RASs With SOF/VEL/VOX Failure

- No specific RAS patterns among patients with SOF/VEL/VOX retreatment failure



SHARED Cohort: RASs and Retreatment Outcomes After SOF/VEL/VOX Failure

GT	RASs at Failure		Retreatment		
	NS3	NS5A	Regimen	Duration (Wks)	Response
1a	Q80K	L31M	GLE/PIB + SOF	12	SVR12
1a	None	M28V	GLE/PIB + SOF	16	Exitus
1b	Y56H, D168V	L31V, Y93H	GLE/PIB + SOF + RBV	24	SVR12
3a	None	Y93H	GLE/PIB + SOF + RBV	12	SVR12
3a	Q168K	Y93H	GLE/PIB + SOF + RBV	24	SVR12
3a	None	Y93H	GLE/PIB + SOF	12	SVR12
3a	None	ND	GLE/PIB + SOF + RBV	16	Failure
3a	Q168K	Y93H	GLE/PIB + SOF + RBV	16	SVR12

GT	RASs at Failure		Retreatment		
	NS3	NS5A	Regimen	Duration (Wks)	Response
1a	None	Q30R, L31V, Y93H	GLE/PIB + SOF	24	Pending
1a	None	Q30R, L31M	GLE/PIB + SOF + RBV	16	Pending
1b	Q80R	L31M, Y93H	GLE/PIB + SOF + RBV	24	Pending
3a	Q168R	Y93H	GLE/PIB + SOF	12	Pending
1b	None	Y93H	GLE/PIB	12	SVR12
1b	None	L31I	SOF/VEL/VOX	24	Pending
3a	Q168R	A30K, Y93H	SOF/VEL/VOX + RBV	24	SVR12
3a	None	None	SOF/VEL/VOX	24	Pending
3a	None	Y93H	SOF/VEL + RBV	24	Failure

De Salazar. EASL 2020. Abstr AS156.

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Retreating HCV Infection With GLE/PIB or SOF/VEL/VOX After DAA Failure

- Evaluated efficacy of GLE/PIB (n = 55) or SOF/VEL/VOX (n = 176) among patients experiencing prior failure/relapse with IFN-sparing DAAs
  - Data sourced from Trio Health's disease management program for patients receiving therapy between July 2017 and December 2018
- Variables differing significantly between treatment groups fed into logistic regression to produce propensity scores

Flamm. EASL 2020. Abstr SAT387.

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GLE/PIB vs SOF/VEL/VOX: Baseline Characteristics
Before and After Propensity Score Matching

Baseline Characteristic, n/N (%)		Before Matching			After Matching		
		SOF/VEL/VOX (n = 176)	GLE/PIB (n = 55)	*P* Value	SOF/VEL/VOX (n = 39)	GLE/PIB (n = 39)	*P* Value
Regimen duration	▪ 8 wks ▪ 12 wks ▪ 16 wks ▪ 24 wks	1/176 (1) 174/176 (99) 0 1/176 (1)	8/55 (15) 9/55 (16) 38/55 (69) 0	< .001	0 39/39 (100) 0 0	6/39 (15) 6/39 (15) 27/39 (69) 0	< .001
Disease severity	▪ eGFR < 30 mL/min ▪ FIB-4 < 1.45 ▪ FIB-4 = 1.45-3.25 ▪ FIB-4 > 3.25	2/163 (1) 34/162 (21) 67/162 (41) 61/162 (38)	4/53 (8) 14/52 (27) 19/52 (37) 19/52 (37)	*eGFR:* .015 *FIB-4:* .651	0 10/39 (26) 15/39 (38) 14/39 (36)	0 11/39 (28) 15/39 (38) 13/39 (33)	*FIB-4:* .959
HCV genotype	▪ GT1 ▪ GT2 ▪ GT3 ▪ GT4-6	138/176 (78) 4/176 (2) 28/176 (16) 6/176 (3)	45/55 (82) 5/55 (9) 5/55 (9) 0	.040	37/39 (95) 0 2/39 (5) 0	37/39 (95) 0 2/39 (5) 0	1.000
Previous regimen	▪ DCV + SOF ▪ EBR/GZR ▪ GLE/PIB ▪ LDV/SOF ▪ PrOD ▪ SMV + SOF ▪ SOF + RBV ▪ SOF/VEL	11/176 (6) 20/176 (11) 4/176 (2) 102/176 (58) 12/176 (7) 1/176 (1) 5/176 (3) 21/176 (12)	1/55 (2) 1/55 (2) 0 35/55 (64) 2/55 (4) 1/55 (2) 8/55 (15) 7/55 (13)	.008	0 0 0 31/39 (79) 2/39 (5) 0 1/39 (3) 5/39 (13)	0 0 0 31/39 (79) 2/39 (5) 0 1/39 (3) 5/39 (13)	1.000

Flamm. EASL 2020. Abstr SAT387.

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GLE/PIB vs SOF/VEL/VOX: SVR by Previous Regimen *Before Propensity Score Matching*

SVR by Previous Regimen, n/N (%)	ITT			PP		
	SOF/VEL/VOX	GLE/PIB	*P* Value	SOF/VEL/VOX	GLE/PIB	*P* Value
DCV + SOF	11/11 (100)	1/1 (100)		11/11 (100)	1/1 (100)	
EBR/GZR	18/20 (90)	1/1 (100)	.905	18/18 (100)	1/1 (100)	
GLE/PIB	3/4 (75)			3/4 (75)		
LDV/SOF	97/102 (95)	29/35 (83)	.021	97/98 (99)	29/35 (83)	< .001
PrOD	11/12 (92)	2/2 (100)	.857	11/11 (100)	2/2 (100)	
SMV + SOF	1/1 (100)	1/1 (100)		1/1 (100)	1/1 (100)	
SOF + RBV	5/5 (100)	7/8 (88)	.411	5/5 (100)	7/7 (100)	
SOF/VEL	20/21 (95)	5/7 (71)	.078	20/21 (95)	5/7 (71)	.145
Total	**166/176 (94)**	**46/55 (84)**	**.017**	**166/169 (98)**	**46/54 (85)**	**< .001**

Flamm. EASL 2020. Abstr SAT387.

GLE/PIB vs SOF/VEL/VOX: SVR by Previous Regimen *After Propensity Score Matching*

SVR by Previous Regimen, n/N (%)	ITT			PP		
	SOF/VEL/VOX	GLE/PIB	*P* Value	SOF/VEL/VOX	GLE/PIB	*P* Value
LDV/SOF	30/31 (97)	26/31 (84)	.086	30/30 (100)	26/31 (84)	.022
PrOD	2/2 (100)	2/2 (100)		2/2 (100)	2/2 (100)	
SOF + RBV	1/1 (100)	1/1 (100)		1/1 (100)	1/1 (100)	
SOF/VEL	5/5 (100)	4/5 (80)	.292	5/5 (100)	4/5 (80)	.292
Total	**38/39 (97)**	**33/39 (85)**	**.048**	**38/38 (100)**	**33/39 (85)**	**.012**

- Reasons for failure to achieve SVR in total unmatched ITT population
  - **SOF/VEL/VOX (n = 10)**: discontinuation, n = 4 (1/4 in a matched pair); LTFU, n = 1; death, n = 2; virologic failure, n = 3
  - **GLE/PIB (n = 9)**: discontinuation, n = 1; virologic failure, n = 8 (6/8 in matched pairs)

Flamm. EASL 2020. Abstr SAT387.

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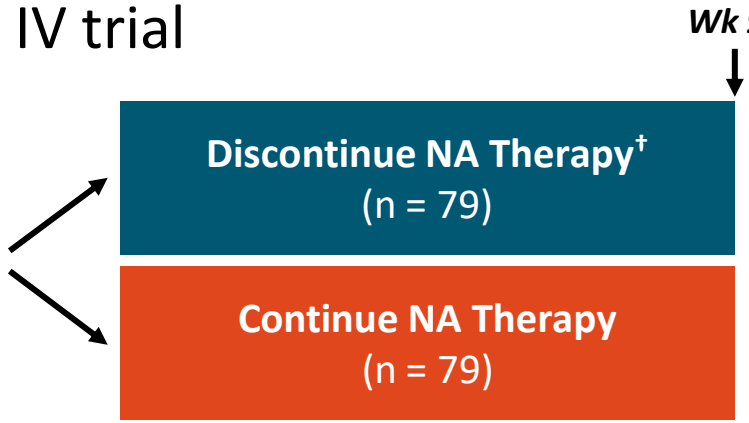
Treatment of HBV Infection

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)



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 > 10 x ULN, ALT > 5 x ULN and ≤ 10 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)

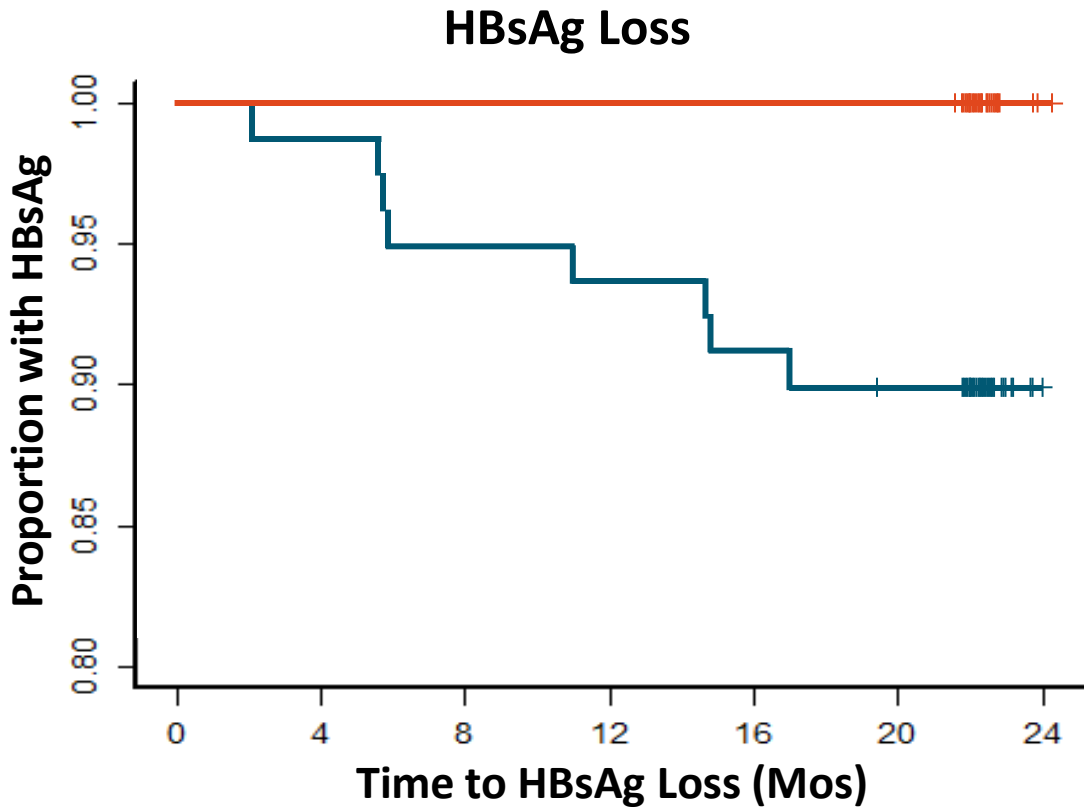
van Bömmel. EASL 2020. Abstr LBO06. EudraCT 2013-004882-15.

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)†

*Compared with 0 patients achieving HBsAg loss in **NA continuation arm** (*P* = .006).

†Per predetermined criteria, n = 9; by decision of treating physician, n = 3.



van Bömmel. EASL 2020. Abstr LBO06.

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Stop-NUC: HBsAg Loss by Baseline Characteristics

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

van Bömmel. EASL 2020. Abstr LBO06.

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Stop-NUC: Response and Safety

Outcome at Wk 96 in Patients Without Retreatment, n (%)	Discontinue NA (n = 79)
Virologic response	
▪ HBV DNA > 20 IU/mL	53 (67.1)
▪ HBV DNA ≤ 20 IU/mL	14 (17.7)
Biochemical response	
▪ ALT > ULN	7 (8.8)
▪ ALT ≤ ULN	61 (77.2)
Sustained remission*	
▪ No	36 (45.6)
▪ Yes	32 (40.5)

*HBV DNA < 2000 IU/mL and normal ALT.

- Mean AEs per patient: **3.19** vs **2.06**
- Severe AEs: **8** vs **2**
  - Bone fractures, abortion, ventricular tachycardia, artrial fibrillation, acute myocardial infarction, subileus and gastritis influenca
  - Gastritis, cerebrovascular accident
  - No severe AE related to study intervention

van Bömmel. EASL 2020. Abstr LBO06.

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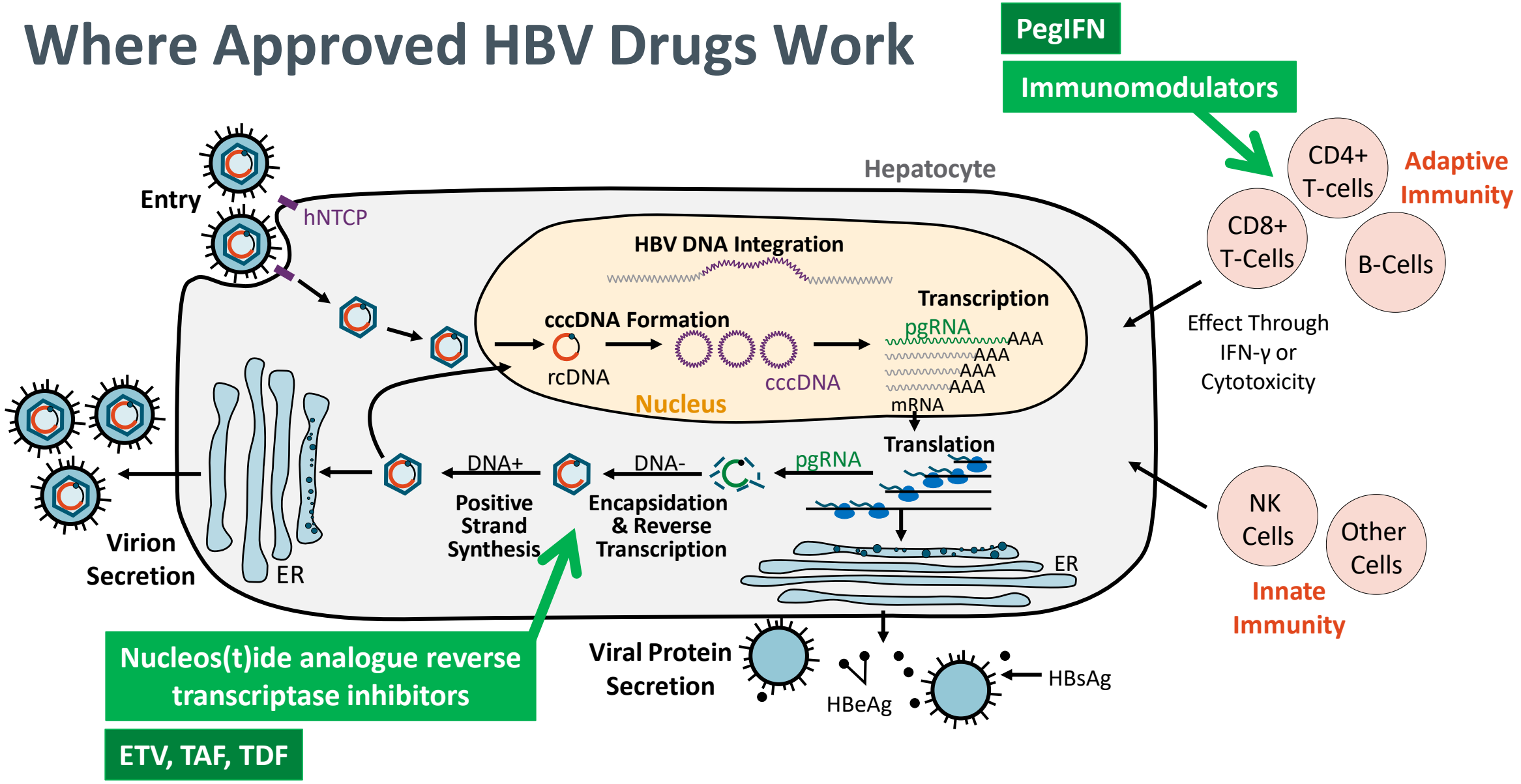
Where Approved HBV Drugs Work



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

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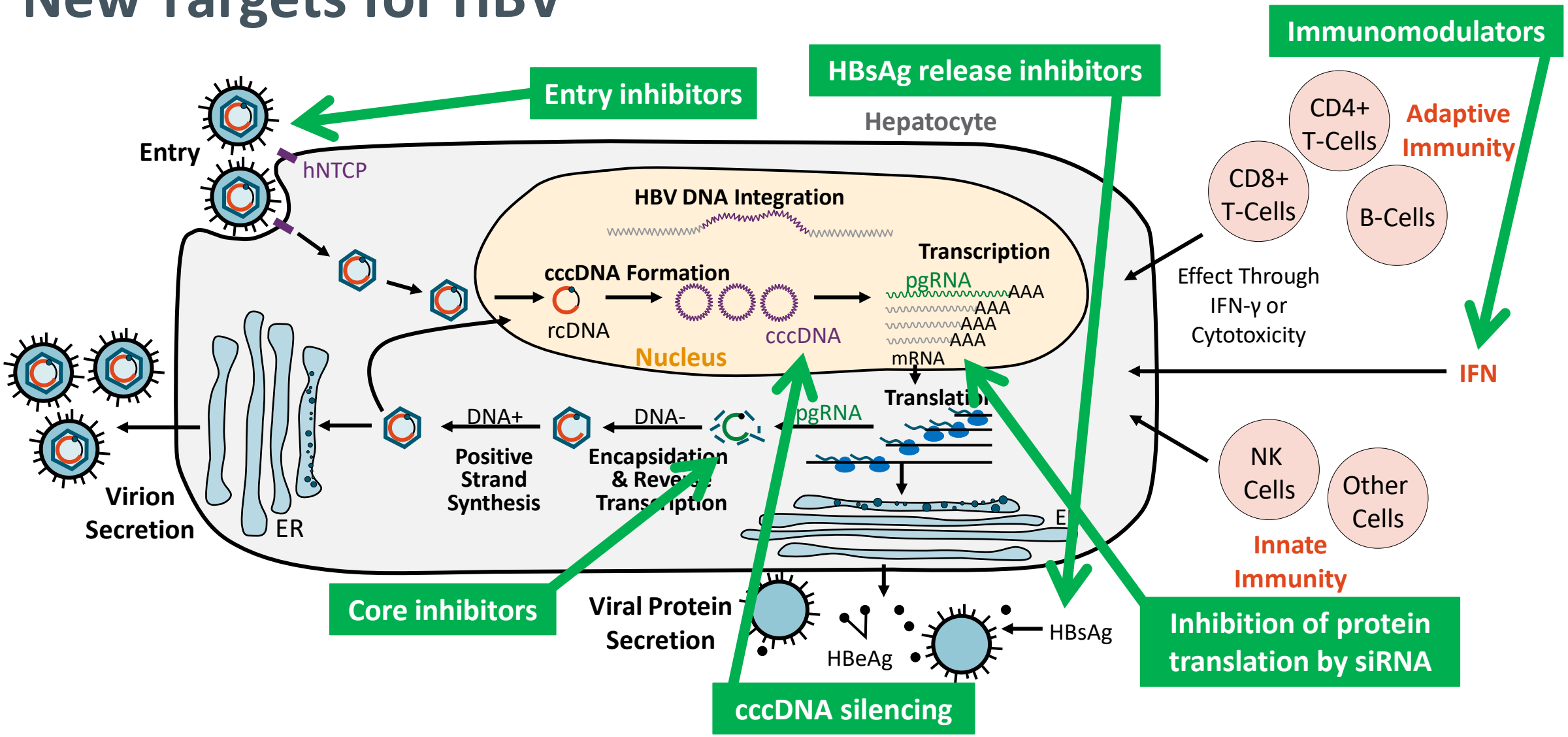
New Targets for HBV



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

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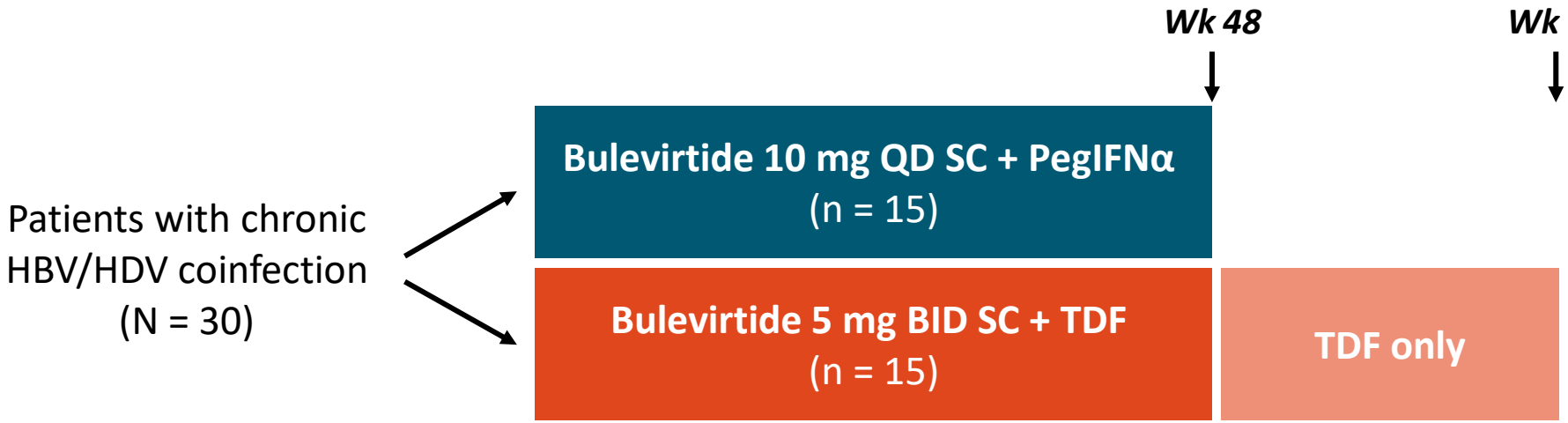
High-Dose Bulevirtide for Chronic HBV/HDV Coinfection

- **Bulevirtide**: investigational entry inhibitor targeting NTCP on hepatocytes with strong inhibitory potential against HBV/HDV coinfection[1]



- Primary endpoint: undetectable HDV RNA (LOD < 10 IU/mL) at Wk 72[2]
- Secondary endpoints: ALT normalization, combined treatment response (ie, ≥ 2 log serum HDV RNA decline + normal ALT levels), HBsAg response[2]

1. Koh. Clin Liver Dis. 2019;23:557. 2. Wedemeyer. EASL 2020. Abstr AS072.

Slide credit: clinicaloptions.com

High-Dose Bulevirtide: Efficacy and Safety

- Treatment-related AEs: n = 143 overall (none considered serious)
  - No treatment discontinuations for bulevirtide AEs

Wk 48 Outcome	Bulevirtide 10 mg QD SC + PegIFNα (n = 15)	Bulevirtide 5 mg BID SC + TDF (n = 15)
Median HDV RNA reduction, $\log_{10}$ IU/mL	-6.09	-4.58
HDV RNA undetectable, %	86.7	40
ALT normalization, %	26.7	40
HBsAg undetectable, n	1	0

Wk 72 Outcome	Bulevirtide 10 mg QD SC + PegIFNα (n = 15)	Bulevirtide 5 mg BID SC + TDF (n = 15)
HDV RNA undetectable, %	7	33
ALT normalization, %	33	33
HBsAg undetectable, n	2	0

Wedemeyer. EASL 2020. Abstr AS072.

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Select Agents Under Early-Phase Investigation For HBV

Agent	MOA	Phase	Key Findings
JNJ-3989[1]	RNA interference	IIa	▪ Population & Treatment: naive or experienced CHB; 3 JNJ-3989 injections (100-400 mg Q4W) given with oral ETV or TDF ▪ Efficacy: 39% (15/38) of patients maintained HBsAg decline ≥ 1 $\log_{10}$ IU/mL 48 wks after final JNJ-3989 injection ▪ HBV RNA, HBeAg, and HBcrAg declines most evident among these HBsAg sustained responders ▪ Safety: Well tolerated, no new drug-related AEs since last analysis
GSK836[2]	RNA interference	IIa	▪ Population & Treatment: naive or experienced CHB; 6 GSK836 injections (300 mg on Days 1, 4, 8, 11, 15, 22), then oral ETV or TDF ▪ Efficacy: 75% (3/4) of NA-experienced and 25% (3/12) of NA-naive patients experienced HBsAg reduction > 3 $\log_{10}$ IU/mL by Day 29 ▪ All 6 responders were HBeAg negative ▪ Safety: ALT flares observed but were asymptomatic/self-resolved; single case of treatment-related pyrexia led to early discontinuation

1. Gane. EASL 2020. Abstr GS10. 2. Yuen. EASL 2020. Abstr AS067.

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Select Agents Under Early-Phase Investigation For HBV

Agent	MOA	Phase	Key Findings
Vebicorvir[1]	HBV core protein inhibitor	II	▪ Population & Treatment: virologically suppressed HBeAg negative CHB; vebicorvir 300 mg PO QD given with oral ETV, TAF, or TDF ▪ Efficacy: 100% (18/18) of patients had composite DNA + pgRNA levels < 20 IU/mL after 48 wks of treatment ▪ Safety: No grade ≥ 3 treatment-emergent AEs, SAEs, or resistance; single discontinuation for grade 1 rash
Selgantolimod[2,3]	TLR8 agonist	II	▪ Population & Treatment: virologically suppressed CHB; selgantolimod 1.5 mg or 3 mg PO QD given with oral antiviral therapy (OAV)* for 24 wks, then OAV taken alone for 24 wks ▪ Efficacy: By Wk 48, 5% (2/39) of patients achieved HBsAg loss and 16% (3/19) of HBeAg-positive patients experienced HBeAg loss ▪ Safety: GI-related AEs common but mostly mild/transient; dose-dependent IFNγ elicited alongside temporary T-cell marginalization

*Could include one of the following: adefovir, ETV, lamivudine, TAF, TDF, or telbivudine.

1. Fung. EASL 2020. Abstr AS070. 2. Gane. EASL 2020. Abstr AS071. 3. NCT03491553.

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