CLINICAL CARE OPTIONS®
HEPATITIS

The Toolkit to Achieve Cure

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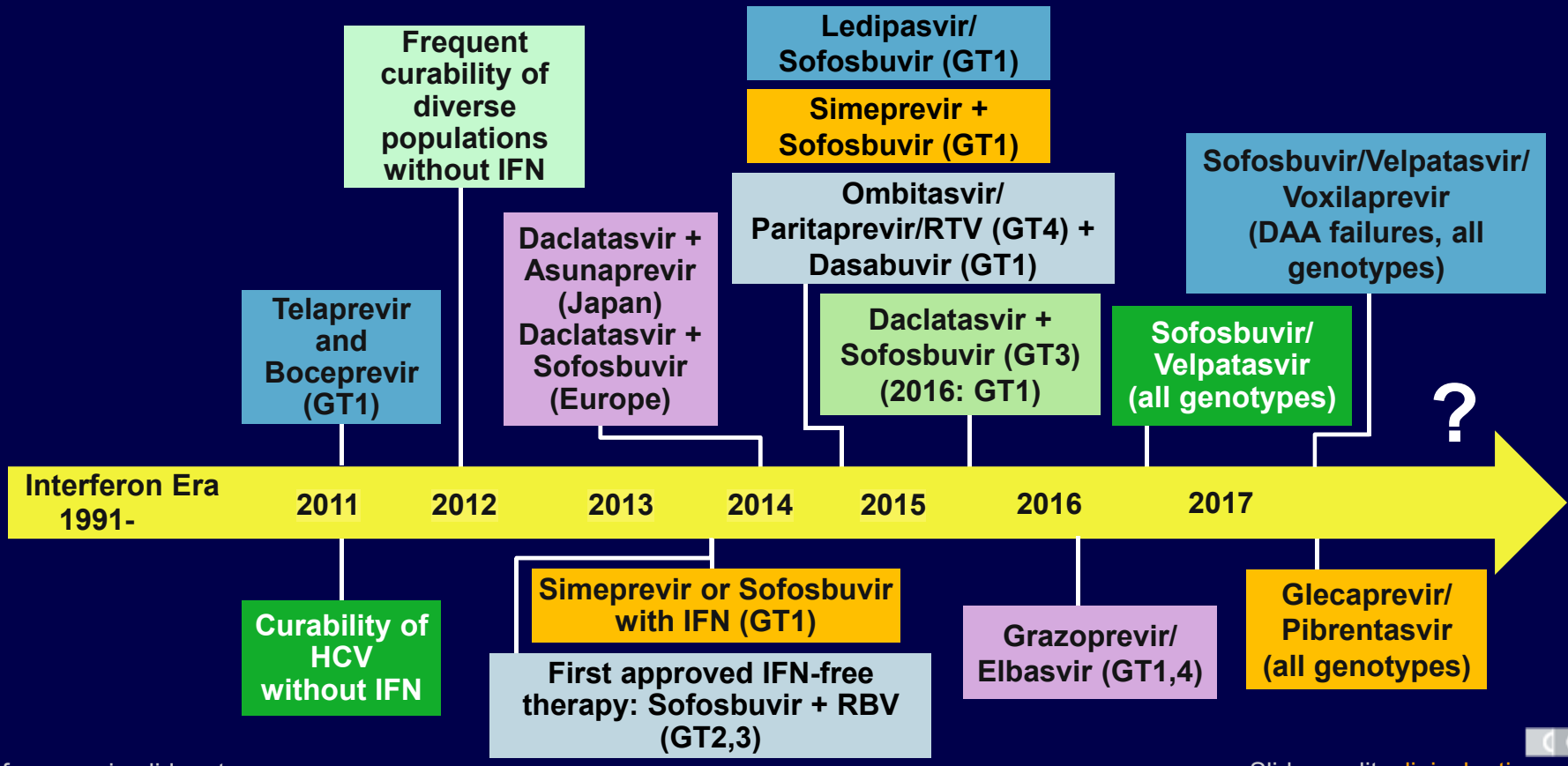
What Are the Tools in the Toolkit?

The Evolution of HCV Therapy



References in slidenotes.

Slide credit: clinicaloptions.com

Pangenotypic Regimens

Pangenotypic, RBV-Free, Oral HCV Therapy for 8-12 Wks Now an Option for Many Pts

Setting	FDA Indications for Pangenotypic HCV Regimens in Non-DAA Experienced Pts (Except as Noted)	
	SOF/VEL	GLE/PIB
Treatment naive	GT1-6 § No cirrhosis or compensated cirrhosis: 12 wks	GT1-6 § No cirrhosis: 8 wks § Compensated cirrhosis: 12 wks
IFN/RBV experienced*	GT1-6 § No cirrhosis or compensated cirrhosis: 12 wks	GT1, 2, 4, 5, 6 § No cirrhosis: 8 wks § Compensated cirrhosis: 12 wks GT3 § No cirrhosis or compensated cirrhosis: 16 wks

*Includes PR ± SOF for GLE/PIB and PR ± BOC, SMV, or TVR for SOF/VEL.

FDA GLE/PIB 2017. FDA SOF/VEL 2017.

Slide credit: clinicaloptions.com

HCV NS5A Inhibitor Activity by HCV Genotype/Subtype

NS5A Inhibitor	Stable/Transient HCV Replicon EC_{50}, pM							
	GT1a	GT1b	GT2a	GT2b	GT3a	GT4a	GT5a	GT6a
Ledipasvir[1-3]	34	4	21000	NA	35000	110	150	120
Daclatasvir[4]	50	9	71	NA	146	12	33	NA
Ombitasvir[1]	14	5	12	4	19	2	3	370
Elbasvir[1,5]	4	3	3	3000	20	3	NA	NA
Velpatasvir[6]	12	15	9	8	12	9	75	6
Pibrentasvir[1,7]	2	4	2	2	2	2	1	3

1. Poordad F, et al. AASLD 2015. Abstract 41. 2. Cheng G, et al. EASL 2012. Abstract 1172. 3. FDA LDV/SOF. 2017. 4. Wang C, et al. Antimicrob Agents Chemother. 2014;58:5155-5163. 5. Liu R, et al. EASL 2012. Abstract 858. 6. Cheng G, et al. EASL 2013. Abstract 1191. 7. Ng TI, et al. Antimicrob Agents Chemother. 2017;61:e02558-16.

HCV NS3/4A Inhibitor Activity by HCV Genotype/Subtype

NS3/4A Inhibitor	Stable/Transient HCV Replicon EC_{50}, nM					
	GT1a	GT1b	GT2a	GT3a	GT4a	GT6a
Simeprevir[1,2]	4.0	9.0	15.0	472.0	--	--
Paritaprevir[3]	1.0	0.2	5.3*	19.0	0.1	0.7
Grazoprevir[3]	0.4	0.9	1.3	36.0	1.2	0.9
Glecaprevir[3]	0.8	0.9	2.7*	1.6	2.8	0.9
Voxilaprevir[4]	3.9	3.3	3.7	6.1	2.9	1.5

*Study conducted at Southern Research Institute.

1. FDA Simeprevir. 2017. 2. Chase R, et al. IAPAC 2013. Abstract OA25.
3. Poordad F, et al. AASLD 2015. Abstract 41. 4. Taylor JG, et al. EASL 2015. Abstract P0899.

Most Common, Clinically Important RASs to DAAs

DAA	GT1a				GT1b		GT3a
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N	Y93H
Ledipasvir	20x	> 100x	> 100x / > 100x	> 1000x / > 10,000x	> 100x > 50x	> 100x / --	NR
Ombitasvir	> 1000x	> 100x	< 3x > 100x	> 10,000x / > 10,000x	< 10 x	20x / 50x	NR
Daclatasvir	> 100x	> 1000x	> 100x / > 1000x	> 1000x / > 10,000x	< 10 x	20x / 50x	> 1000x
Elbasvir	20x	> 100x	> 10x > 100x	> 1000x / > 1000x	< 10 x	> 100x / --	NR
Velpatasvir	< 10x	< 3x	20x / 50x	> 100x / > 1000x	< 3x	< 3x / --	> 100x
Pibrentasvir	< 3x	< 3x	< 3x	< 10 x	< 3x	< 3x / --	< 3x

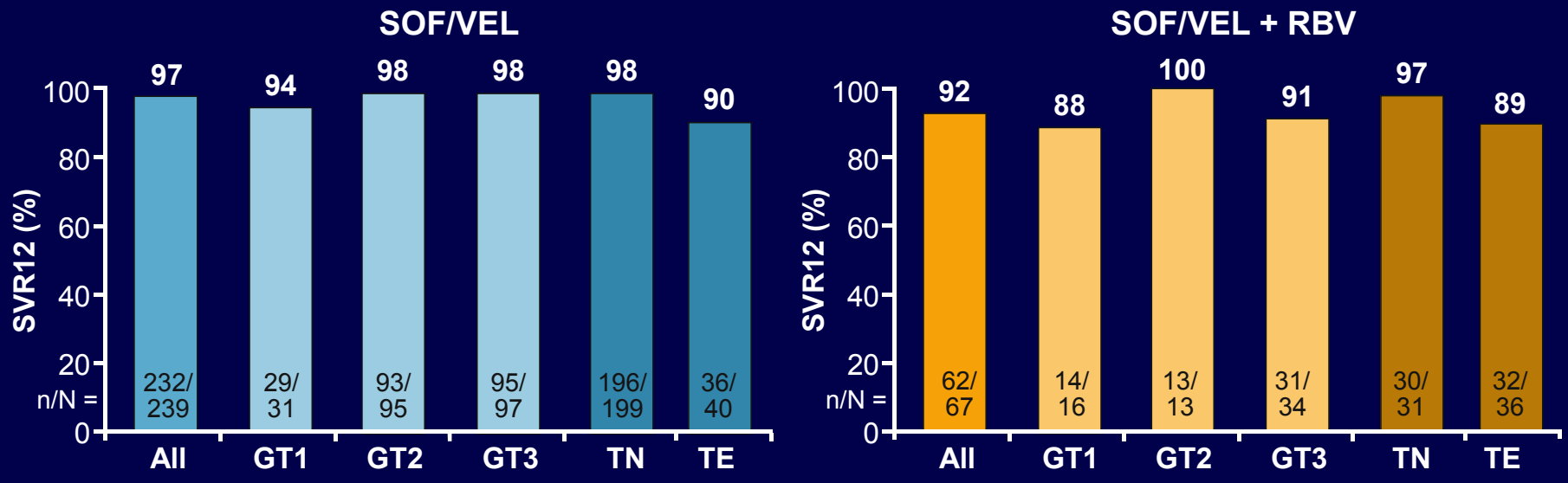
< 3-fold change < 10-fold change < 10- to 100-fold change > 100-fold change

AASLD/IDSA. HCV guidance. September 2017. Ng TI, et al. Antimicrob Agents Chemother. 2017;61:e02558-16. FDA Sofosbuvir/velpatasvir. FDA Daclatasvir.

Slide credit: clinicaloptions.com

HCV-TARGET: Real-World Efficacy and Safety of SOF/VEL for GT1-6 HCV

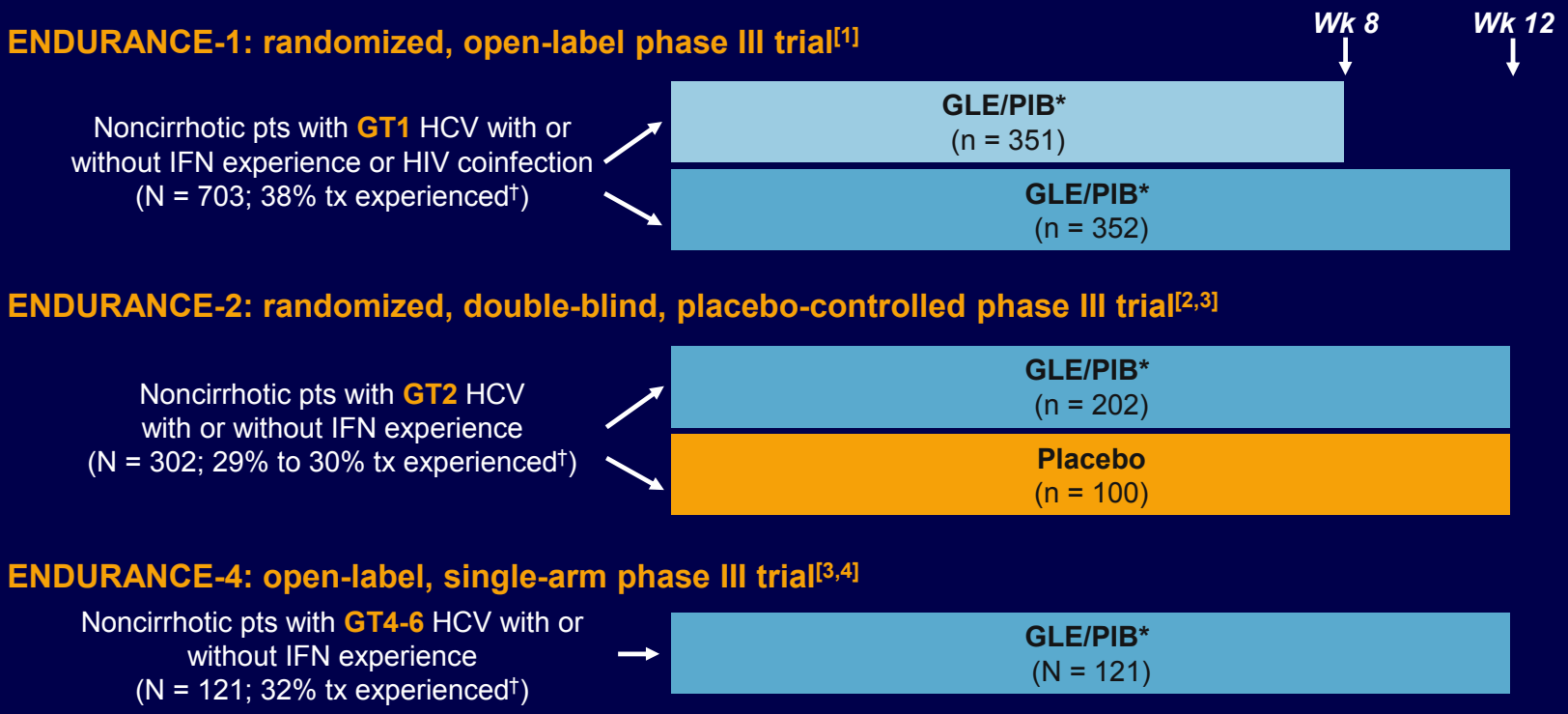
- Pts treated per local standard of care at academic (n = 45) and community medical centers (n = 19) in North America (n = 60) and Europe (n = 4)
  - N = 451 for SOF/VEL; N = 119 for SOF/VEL + RBV



Landis CS, et al. AASLD 2017. Abstract 1096.

Slide credit: clinicaloptions.com

ENDURANCE-1, -2, -4: GLE/PIB for Treatment of GT1, 2, 4, 5, 6 HCV Without Cirrhosis

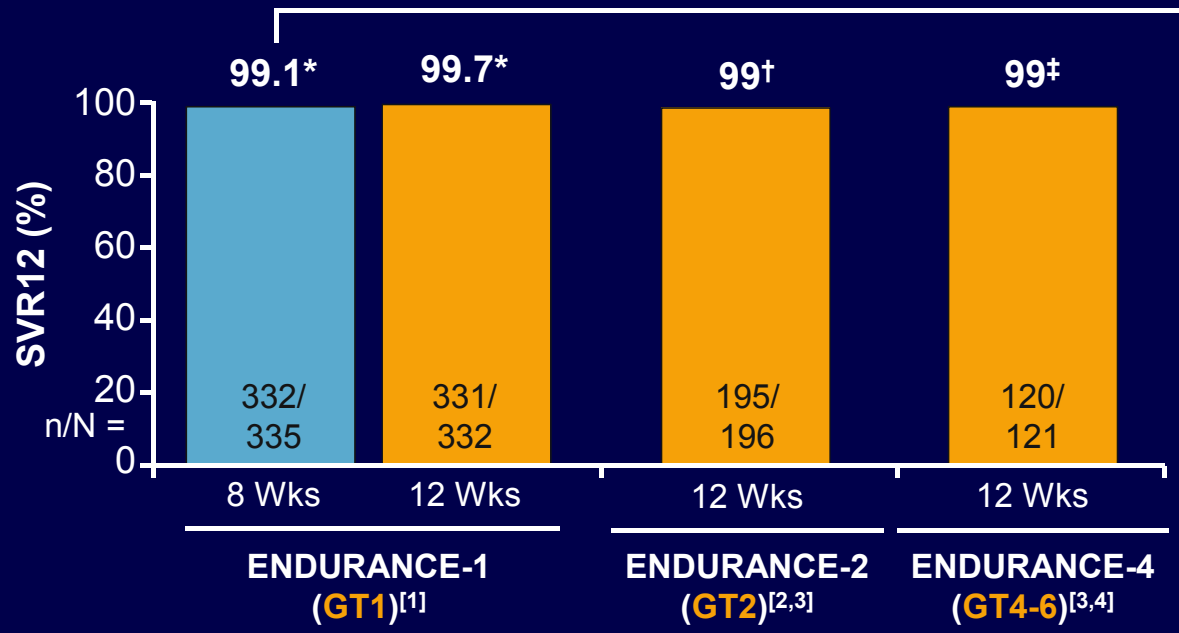


*Dosing: GLE/PIB given as 3 coformulated 100/40-mg tablets QD for a total dose of 300/120 mg.
†Tx experience permitted: IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.

References in slidenotes.

Slide credit: clinicaloptions.com

ENDURANCE-1, -2, -4 Studies: Efficacy of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV



1 case of on-treatment virologic failure at Day 29 in pt with GT1a HCV infection

*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience.
†ITT analysis: excluded pts with SOF experience. ‡ITT analysis.

1. Zeuzem S, et al. AASLD 2016. Abstract 253. 2. Kowdley KV, et al. AASLD 2016. Abstract 73. 3. Asselah T, et al. Clin Gastroenterol Hepatol. 2017;[Epub ahead of print]. 4. Asselah T, et al. AASLD 2016. Abstract 114.

ENDURANCE-1, -2, -4 Studies: Safety of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV

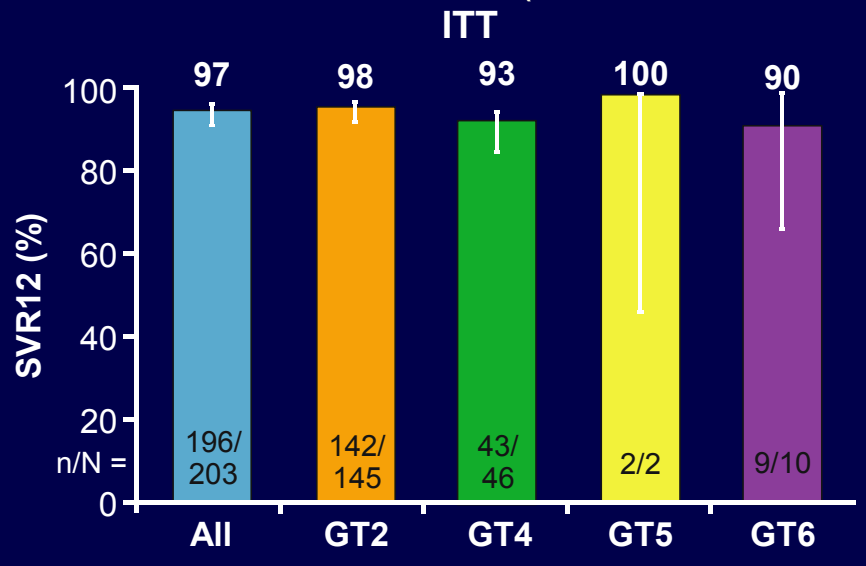
Outcome, %	ENDURANCE-1 (GT1)[1]		ENDURANCE-2 (GT2)[2,3]		ENDURANCE-4 (GT4-6)[3,4]
	GLE/PIB 8 Wks (n = 351)	GLE/PIB 12 Wks (n = 352)	GLE/PIB 12 Wks (n = 202)	PBO 12 Wks (n = 100)	GLE/PIB 12 Wks (n = 121)
Any AE	62	66	65	58	69
D/c for AE	0	< 1	0	0	2
Serious AE	1	1	1	1	< 1
Death	0	< 1	0	0	0
AE in ≥ 10% of pts					
§ Fatigue	9	12	11	10	17
§ Headache	19	18	12	12	21
AST grade ≥ 3*	0	< 1	1	1	0
ALT grade ≥ 3*	0	0	< 1	2	0
Tot. bilirubin grade 3†	< 1	< 1	< 1	0	0

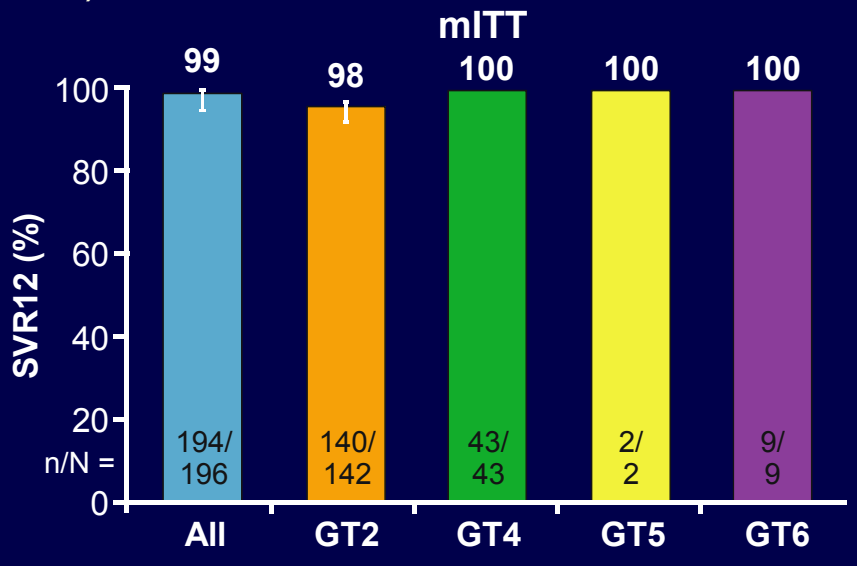
*> 5 times ULN. †3-10 times ULN.

1. Zeuzem S, et al. AASLD 2016. Abstract 253. 2. Kowdley KV, et al. AASLD 2016. Abstract 73. 3. Asselah T, et al. Clin Gastroenterol Hepatol. 2017;[Epub ahead of print]. 4. Asselah T, et al. AASLD 2016. Abstract 114.

SURVEYOR 2, Part 4: 8-Wk GLE/PIB for Pts With GT2, 4, 5, 6 HCV Without Cirrhosis

- 99% SVR12 rate with 8-wk regimen in DAA-naive pts with GT2 HCV—noninferior to 95% historical control (SOF + RBV for 12 wks)





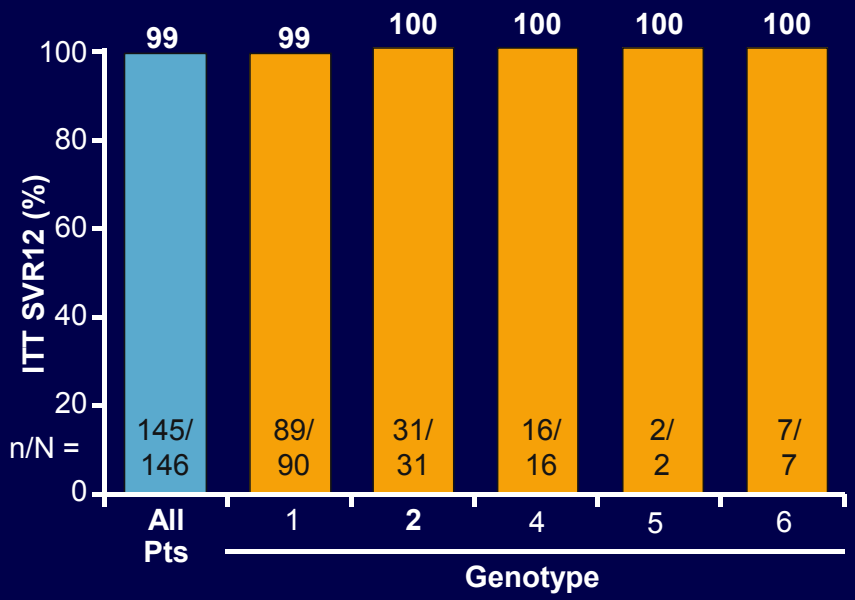
	All	GT2	GT4	GT5	GT6
Relapse	2	2	0	0	0
D/c	2	1	1	0	0
No SVR12 data	3	0	2	0	1

Hassanein TI, et al. AASLD 2016. Abstract LB-15. Kwo PY, et al. J Hepatology 2017;67:263-271.

Slide credit: clinicaloptions.com

EXPEDITION-1: Glecaprevir/Pibrentasvir in GT1, 2, 4, 5, or 6 HCV and Compensated Cirrhosis

- Tx-naive and tx-exp'd pts enrolled
  - 1 relapse in pt with GT1a HCV with new NS5A mutations (Q30R, H58D)



- No AE-related discontinuations or DAA-related serious AEs
  - 1 death deemed unrelated to study drug
- Rare grade 3 laboratory abnormalities

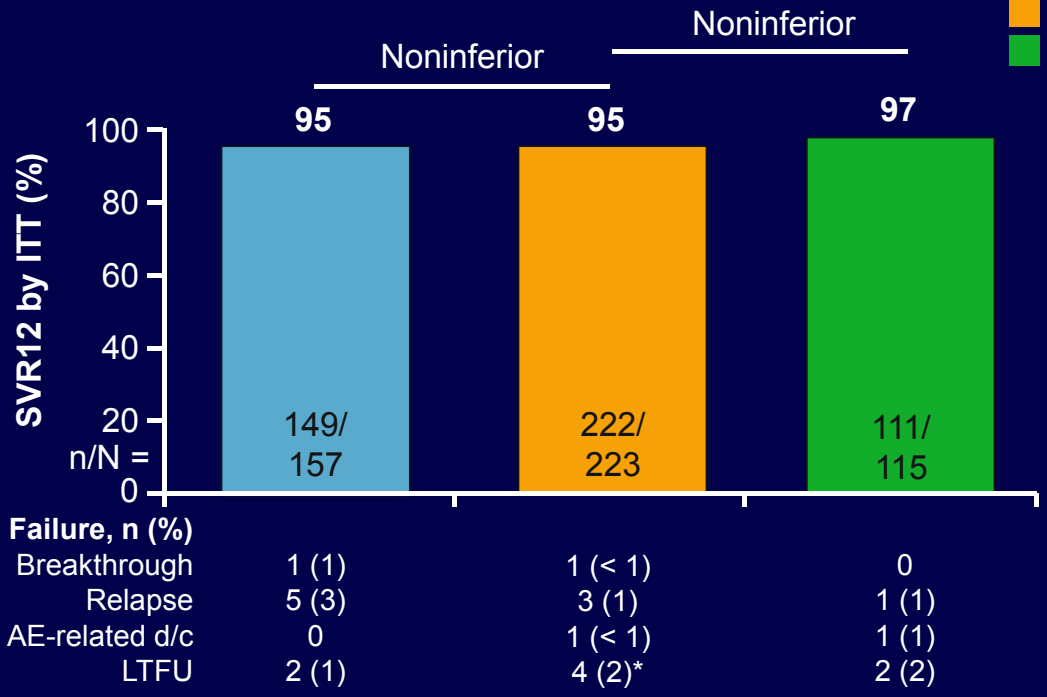
AE, n (%)	Pts (N = 146)
Any AE	101 (69)
Any serious AE	11 (8)
AEs occurring in ≥ 10% of pts	
§ Fatigue	28 (19)
§ Headache	20 (14)
§ Pruritus	14 (10)
HCC	2 (1)

Forns X, et al. Lancet Infect Dis. 2017;17:1062-1068.

Slide credit: clinicaloptions.com

ENDURANCE-3: Glecaprevir/Pibrentasvir in GT3 HCV Without Cirrhosis

§ Majority of pts had history of IDU (63% to 66%)



Failure, n (%)			
Breakthrough	1 (1)	1 (< 1)	0
Relapse	5 (3)	3 (1)	1 (1)
AE-related d/c	0	1 (< 1)	1 (1)
LTFU	2 (1)	4 (2)*	2 (2)

*2 other failures due to consent withdrawal and noncompliance.

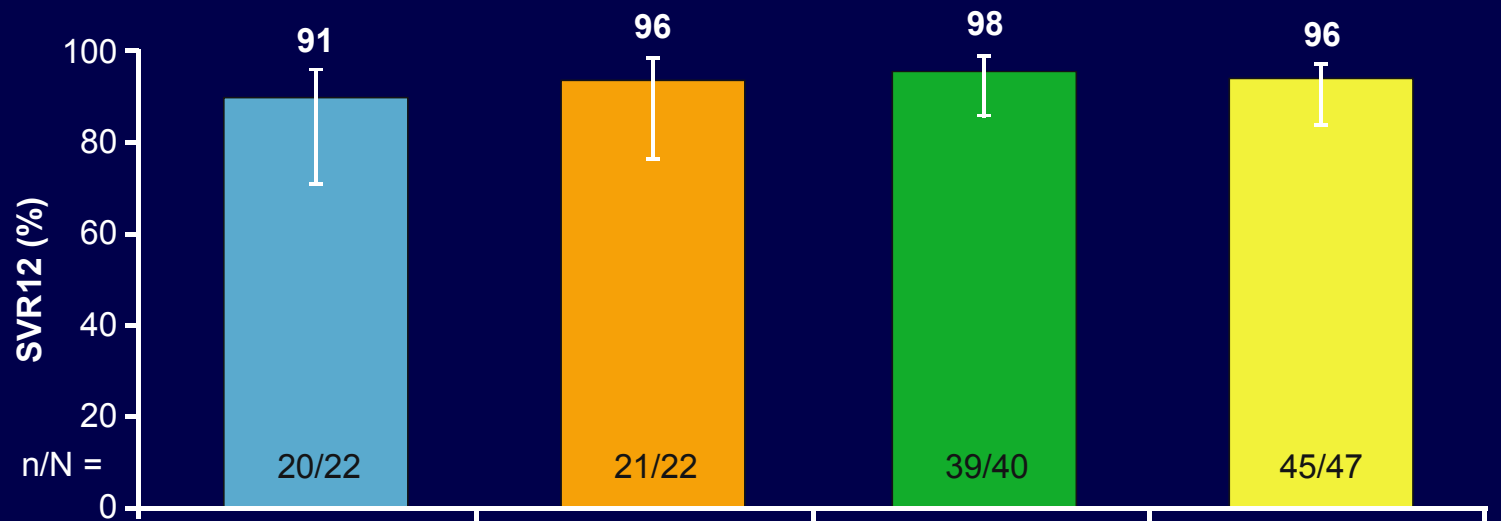
§ No serious AEs deemed related to study drug

§ No clinically relevant ALT increases, 1 isolated bilirubin increase (GLE/PIB 8 wks), 1 isolated neutrophil count decrease (GLE/PIB 12 wks)

Foster GR, et al. EASL 2017. Abstract GS-007.

Slide credit: clinicaloptions.com

SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis



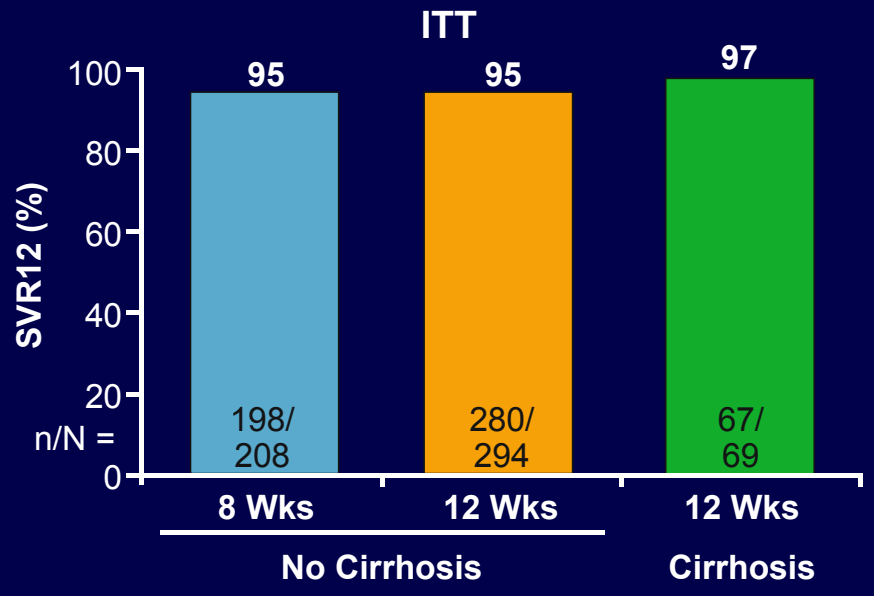
Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

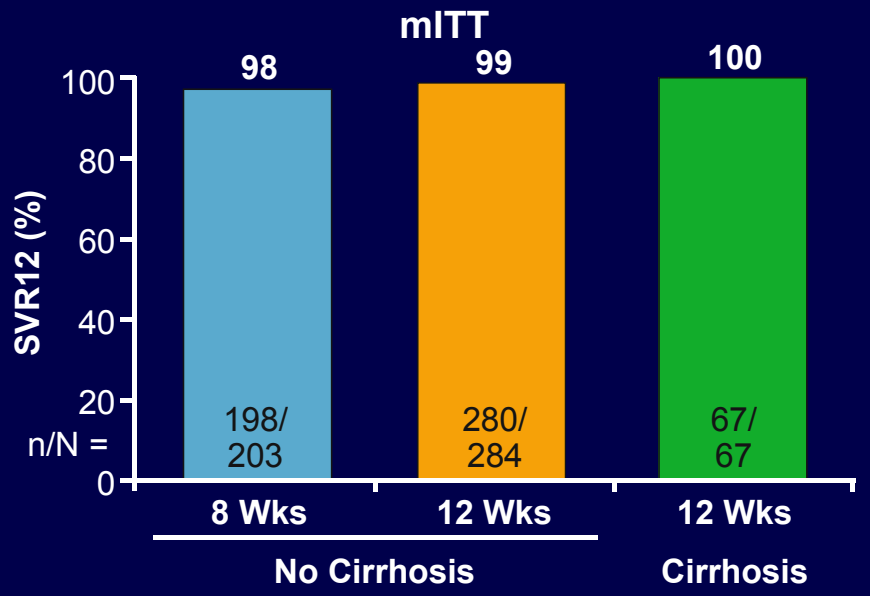
Wyles DL, et al. Hepatology. 2017;[Epub ahead of print].

Slide credit: clinicaloptions.com

GLE/PIB for 8 or 12 Wks in Treatment-Naive GT3 HCV: Integrated Analysis of Phase II/III Data

§ Pooled data from treatment-naive pts with GT3 HCV infection, without cirrhosis or with compensated cirrhosis, across 7 phase II and III studies of 8 or 12 wks
GLE/PIB QD: N = 571 (22% had BL NS5A polymorphisms; 66% had IDU history)



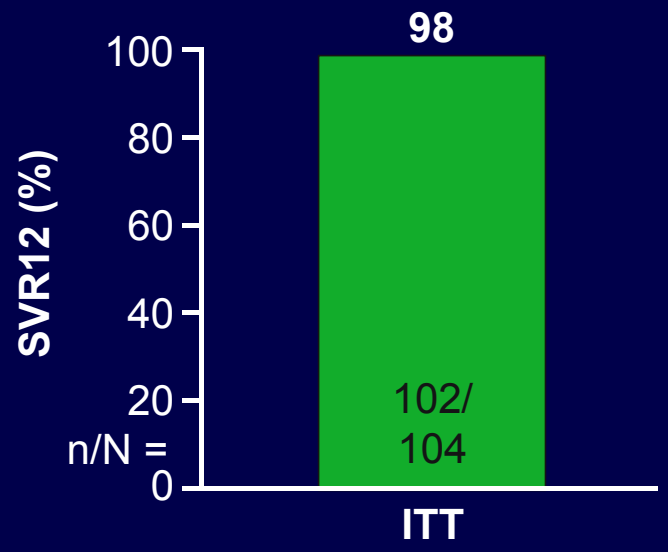


Flamm SL, et al. AASLD 2017. Abstract 62.

Slide credit: clinicaloptions.com

EXPEDITION-4: Glecaprevir/Pibrentasvir in Pts With GT1-6 HCV and Renal Impairment

- Pts with GT1-6 HCV and stage 4 or 5 CKD, with or without compensated cirrhosis, and with or without treatment experience (N = 104)
  - All treated with GLE/PIB for 12 wks



mITT SVR12 = 100%
(no virologic failure or relapse)

Gane EJ, et al. N Engl J Med. 2017;377:1448-1455.

Slide credit: clinicaloptions.com

AASLD/IDSA HCV Guidance: Genotype 1

Recommended for GT1 Treatment-Naive or IFN-Experienced Pts, ± Compensated Cirrhosis

Treatment Experience	Recommended Regimens for GT1
Treatment naive	§ EBR/GZR* 12 wks § GLE/PIB ***8 wks*** *if no cirrhosis,* ***12 wks*** *if compensated cirrhosis* § LDV/SOF 12 wks § LDV/SOF ***8 wks*** *if no cirrhosis, nonblack, no HIV, HCV RNA < 6 million IU/mL* § SOF/VEL 12 wks
PegIFN/RBV experienced	§ EBR/GZR* 12 wks § GLE/PIB ***8 wks*** *(****only*** *if no cirrhosis)* § LDV/SOF 12 wks *(****only*** *if no cirrhosis*) § SOF/VEL 12 wks § GLE/PIB ***12 wks*** *(compensated cirrhosis)*

*For GT1a, only if no baseline NS5A elbasvir RASs detected.

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA HCV Guidance: Genotype 3

Recommended for Treatment-Naive or PegIFN/RBV-Experienced Pts With GT3 HCV

Population	Cirrhosis?	Recommended Regimens for GT3
Treatment naive	No	§ GLE/PIB 8 wks § SOF/VEL 12 wks
	Yes	§ GLE/PIB 12 wks § SOF/VEL 12 wks*
PegIFN/RBV Experienced	No	§ SOF/VEL 12 wks†
	Yes	§ EBR/GZR + SOF 12 wks § SOF/VEL/VOX 12 wks

*NS5A RAS testing recommended if considering this regimen in treatment-naive pts with cirrhosis; if Y93H present, add RBV.
†NS5A RAS testing recommended; if Y93H present, use SOF/VEL/VOX 12 wks or add RBV to SOF/VEL 12 wks.

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA HCV Guidance: Genotypes 2, 4, 5, 6

Recommended Regimens for Treatment-Naive or PegIFN/RBV-Experienced Pts With GT2 HCV

No Cirrhosis	Compensated Cirrhosis
§ GLE/PIB **8 wks** § SOF/VEL 12 wks	§ SOF/VEL 12 wks § GLE/PIB 12 wks

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Recommended Regimens for Treatment-Naive Pts With GT4, 5, 6 HCV

HCV GT	No Cirrhosis	Compensated Cirrhosis
4	§ GLE/PIB **8 wks** § SOF/VEL 12 wks § EBR/GZR 12 wks § LDV/SOF 12 wks	§ SOF/VEL 12 wks § GLE/PIB 12 wks § EBR/GZR 12 wks § LDV/SOF 12 wks
5 or 6	§ GLE/PIB **8 wks** § SOF/VEL 12 wks § LDV/SOF 12 wks	§ GLE/PIB 12 wks § SOF/VEL 12 wks § LDV/SOF 12 wks

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Recommended Regimens for PegIFN/RBV-Experienced Pts With GT 4, 5, 6 HCV

HCV GT	No Cirrhosis	Compensated Cirrhosis
4	§ SOF/VEL 12 wks § GLE/PIB **8 wks** § EBR/GZR* 12 wks § LDV/SOF 12 wks	§ SOF/VEL 12 wks § EBR/GZR* 12 wks § GLE/PIB 12 wks
5 or 6	§ GLE/PIB **8 wks** § LDV/SOF 12 wks § SOF/VEL 12 wks	§ GLE/PIB 12 wks § LDV/SOF 12 wks § SOF/VEL 12 wks

*Previous relapse only; pts with previous virologic failure or breakthrough should be treated for 16 wks with addition of RBV.

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Considerations for Careful Use of the Tools

AASLD/IDSA HCV Guidance for Stage 4 or 5 Chronic Kidney Disease

- Stage 4 (severe) CKD: eGFR 15-29 mL/min
- Stage 5 (end-stage) CKD: eGFR <15 mL/min

HCV GT	Recommended Regimens for Stage 4 or 5 CKD
1a, 1b, 4	§ EBR/GZR 12 wks
1, 2, 3, 4, 5, 6	§ GLE/PIB 8-16 wks*

*Use durations recommended for pts without CKD - based on cirrhosis, previous treatment experience.

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

DDIs Between Recommended DAAs and Selected Medications

Concomitant Medication	DCV	LDV	SOF	EBR/GZR	GLE/PIB	SOF/VEL	SOF/VEL/VOX
Acid-reducing agents*		X				X	X
Amiodarone	X	X	X			X	X
Anticonvulsants*	X	X	X	X	X	X	X
Azole antifungals*	X†			X			
Calcineurin inhibitors,* cisapride, PDE inhibitors,* other antiarrhythmics* or sedatives*				X			
Calcium channel blockers*	X			X			
Cyclosporine					X		
Digoxin	X	X		X	X		X
Ethinyl estradiol–containing products					X		
Glucocorticoids*	X			X			
Herbals, St John's wort, milk thistle	X	X	X	X	X	X	X
Statins*	X	X		X	X		X
Macrolide antimicrobials*	X†			X			
Rifamycin antimicrobials*	X	X	X	X	X	X	X

*Some DDIs not class specific; see prescribing information for specific drugs within a class. †Requires DCV dose adjustment.

AASLD/IDSA. HCV guidance. September 2017. FDA GLE/PIB. FDA SOF/VEL/VOX.

Slide credit: clinicaloptions.com

HCC Occurrence or Recurrence Equivalent in Pts With SVR to DAAs vs IFN

- Meta-analysis and meta-regression analysis of 41 studies (N = 13,875)
  - HCC occurrence in cirrhotic pts who achieved SVR with DAAs or IFN
  - HCC recurrence in pts who had had curative treatment for liver cancer

HCC and Risk Factor	Adjusted RR (95% CI)	*P* Value
HCC occurrence		
§ Average follow-up	0.77 (0.62-0.97)	.03
§ Average age	1.06 (0.99-1.14)	.08
§ Treatment (DAA vs IFN)	0.75 (0.22-2.52)	.62
HCC recurrence		
§ Average follow-up	0.79 (0.55-1.15)	.19
§ Average age	1.11 (0.96-1.27)	.14
§ Treatment (DAA vs IFN)	0.62 (0.11-3.45)	.56

Dore G, et al. EASL 2017. Abstract PS-160.

Slide credit: clinicaloptions.com

HBV Reactivation in Pts Receiving HCV DAAs

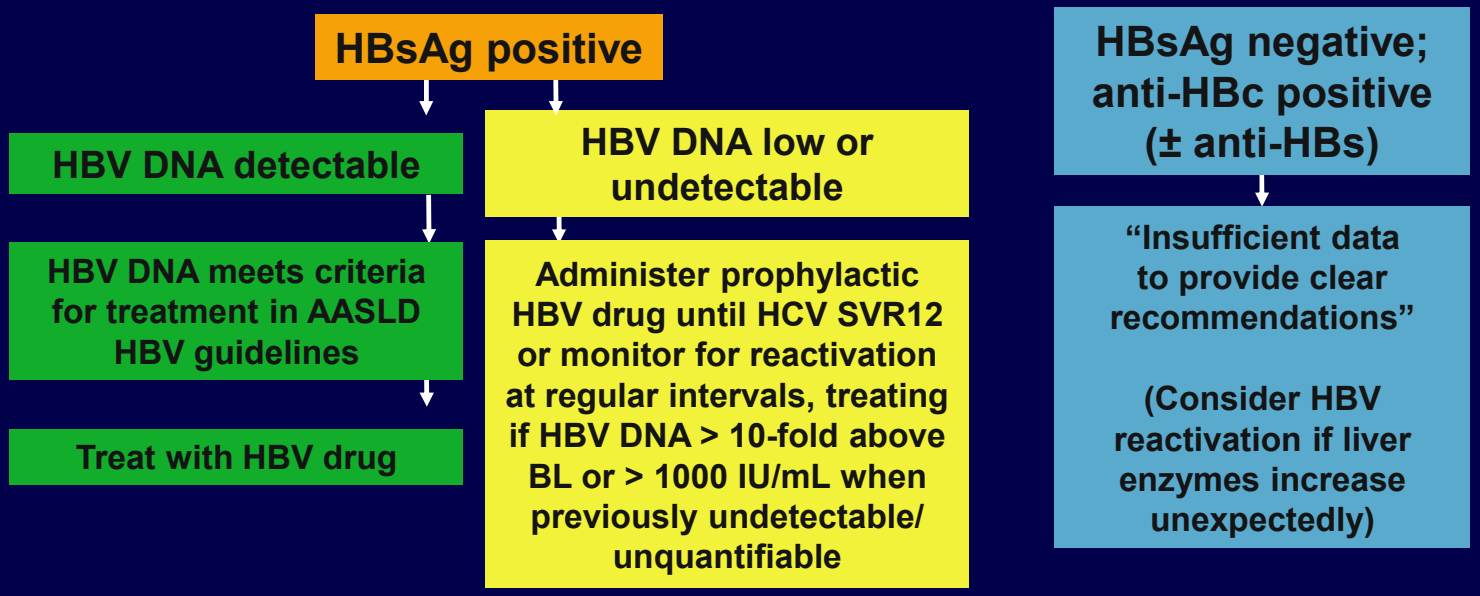
- Case reports of HBV reactivation in pts treated with SMV + SOF ± RBV,[1,2] DCV + ASV,[3,4] and LDV/SOF[5]
  - Possibly due to loss of host immune response to HBV[6]
- 29 confirmed cases of HBV reactivation in HCV DAA recipients in ~ 3 yrs (most from Japan, November 2013 to October 2016)[7]
  - Most cases occurred within 4-8 wks of HCV DAA initiation
  - 2 deaths, 1 liver transplant
  - 3 reactivations in pts with anti-HBc alone (one receiving rituximab)
- October 2016 FDA issued boxed warning[8]

References in slidenotes.

Slide credit: clinicaloptions.com

HBV Testing/Monitoring During HCV DAA Therapy

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Conclusions

- Multiple current regimens highly effective and safe across genotypes
  - 8-12 wks without RBV for vast majority of pts
- SOF/VEL and GLE/PIB provide 12-wk or 8-wk pangenotypic regimens for DAA-naive noncirrhotic pts; other regimens remain first-line for specific genotypes, especially GT1
- No convincing evidence of increased risk of de novo HCC after DAA-induced SVR
  - Controversy persists regarding potential increased risk for HCC recurrence after SVR with DAAs
- HBV reactivation very rare in anti-HBc–positive pts; precautions in HBsAg-positive pts especially with HBV viremia

Slide credit: clinicaloptions.com