CLINICAL CARE OPTIONS®
HEPATITIS

Curing the 10%: Evolving Options for DAA-Experienced Patients

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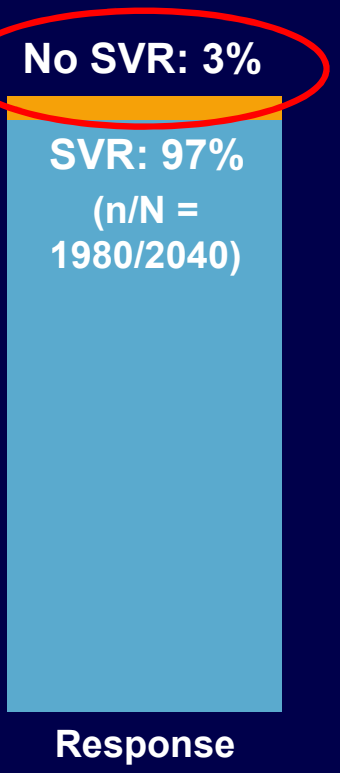
Overview of DAA Failure in GT1 and 3: General Principles

GT1 HCV: Low VF Rate With DAA Regimens in Clinical Trials, but Not 0%

IFN-Free Regimens for GT1*	Duration, Wks	Trials (Pre-2017)
Ledipasvir/sofosbuvir	12	ION-1,[1] ION-2,[2] ION-3[3]
Sofosbuvir/velpatasvir	12	ASTRAL-1[4]
Elbasvir/grazoprevir 1a (± NS5A RAS) and 1b	12	C-EDGE[5]
Ombitasvir/ritonavir/paritaprevir + dasabuvir 1b	12	PEARL-III,[6] TURQUOISE-III[7]
Ombitasvir/ritonavir/paritaprevir + dasabuvir + RBV 1a	24	PEARL-IV,[6] TUROQUOISE-II[8]
Simeprevir + sofosbuvir ± RBV	12-24	OPTIMIST-1,[9] COSMOS[10]
Daclatasvir + sofosbuvir	12	ALLY-2 (HIV coinfected)[11]

*Includes treatment-naive and treatment-experienced pts ± cirrhosis. Does not include nonresponders to SOF + RBV.



References in slidenotes.

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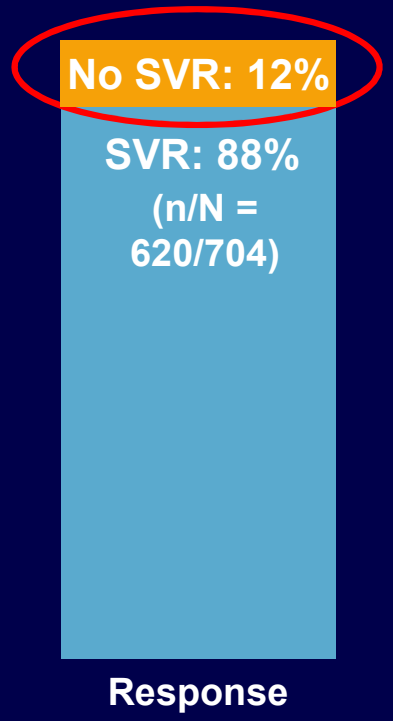
GT3 HCV: VF Rate With DAA Regimens in Clinical Trials Slightly Higher Than for GT 1

IFN-Free Regimens for GT 3*	Duration, Wks	Trials (Pre-2017)
DCV + SOF	12	ALLY-3[1]
SOF/VEL or SOF + RBV	12-24	ASTRAL-3[2]

*Included treatment-naive and treatment-experienced patients ± cirrhosis

GT1 and 3 remain the most challenging when it comes to retreatment after DAA failure



1. Nelson DR, et al. Hepatology. 2015;61:1127-1135.
2. Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

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DAA Drug Classes Are Important in Planning Retreatment Strategies

Inhibitor Class	Reminder	Examples
Targeting HCV Protein Processing		
NS3/4A protease	PREVIR	§ Glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir
Targeting HCV Replication		
NS5B polymerase	BUVIR	§ Nucleos(t)ide: sofosbuvir § Non-nucleos(t)ide: dasabuvir
NS5A	ASVIR	§ Daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir

- § Resistance is shared within classes
  - – New-generation drugs may overcome single-site polymorphisms associated with in-class resistance
- § Resistance mutants are sensitive to drugs from other classes
  - – Basis for combination DAA therapies

Ahmed A, et al. Viruses. 2015;7:6716-6729.

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Most Common, Clinically Important RASs to DAAs

DAA	GT1a				GT 1b		GT 3a
	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.

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