



Treatment emergent variants to combined direct antiviral agents against hepatitis C virus

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Background

- Most data on HCV resistance come from controlled clinical trials
- “Real life” data are being presented but are still lacking
- HCVRESp is a Spanish HCV Resistance Cohort including patients treated with DAA IFN-free regimens, endorsed by GEHEP
- Our main goal is to study the impact of resistance testing on the selection of the regimen used for retreatment and SVR rates



HCVRESp

- Open, prospective COHORT
- Adult (>18 y.o.), Chronic HCV hepatitis
- Naïve to IFN-free DAA

HCVRESp	n=4348
SOF-SIM	n=655 (15%)
SOF-DCV	n=765 (18%)
SOF-LPV	n=1838 (42%)
2D/3D	n=1069 (25%)
Others	n=21 (0,4%)

Failing patients

- Patients failing DAA combinations, n=138

Sex	83% males	
Age (years, median)	53 (IQR 48-58)	
Viral load (Log IU/ml)	6,02 (IQR 5,58-6,47)	
Genotyping (baseline)	GT-1 (6) GT-1a (39) GT-1b (41)	62%
	GT-3 (14) GT-3a (12)	22%
	GT 4 or 4a/c/d (20)	15%
	Others (6)	1%

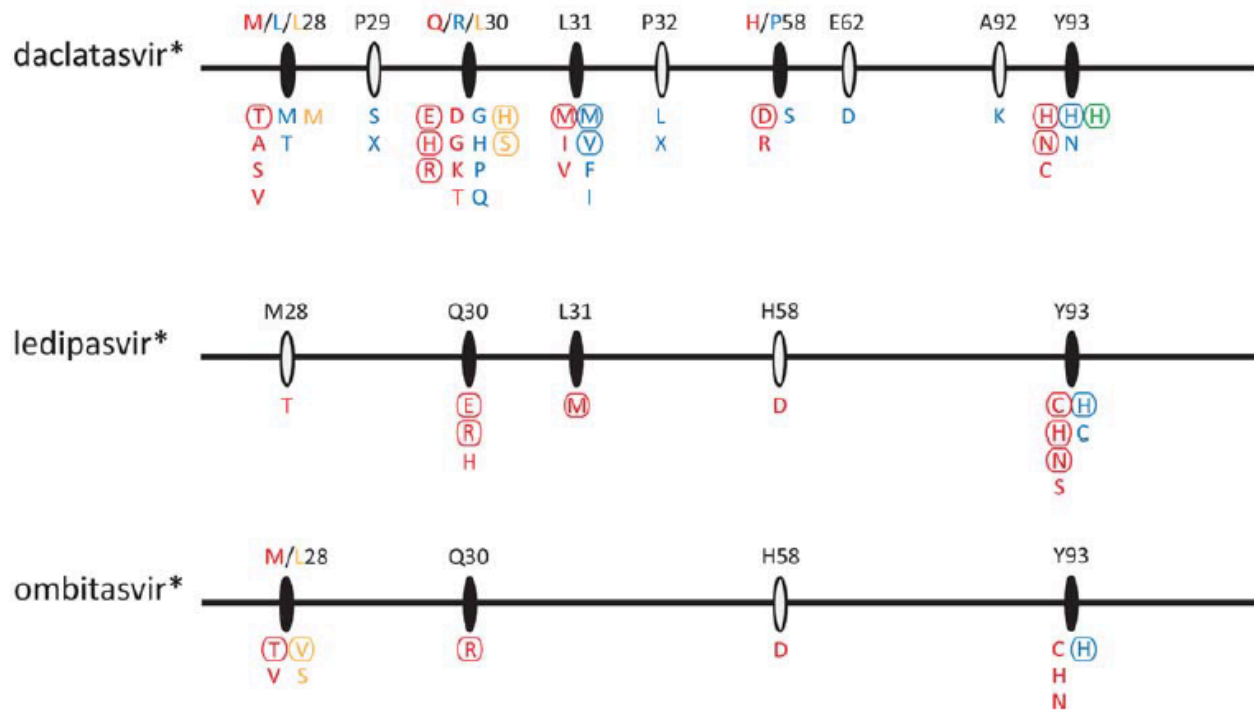
Methods

- **Sanger Sequencing:**
 - **NS5B:** re-genotyping & S282T; if Dasabuvir: 316, 414, 448, 553, 554, 556 y 559
 - **NS5A:** 28, 29, 30, 31, 32, 58, 62, 92 y 93
 - **NS3:** 36, 55, 56, 80, 122, 155, 168 y 170
- **Deep Sequencing of NS5B**
 - Mixed infection vs reinfection; S282T confirmation

Resistance Interpretation

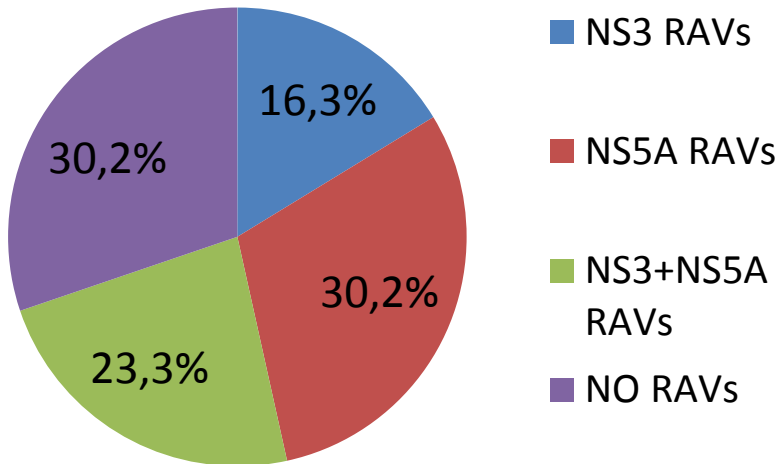
Hepatitis C Virus Drug Resistance–Associated Substitutions: State of the Art Summary

NS5A Domain 1 (213 aa)



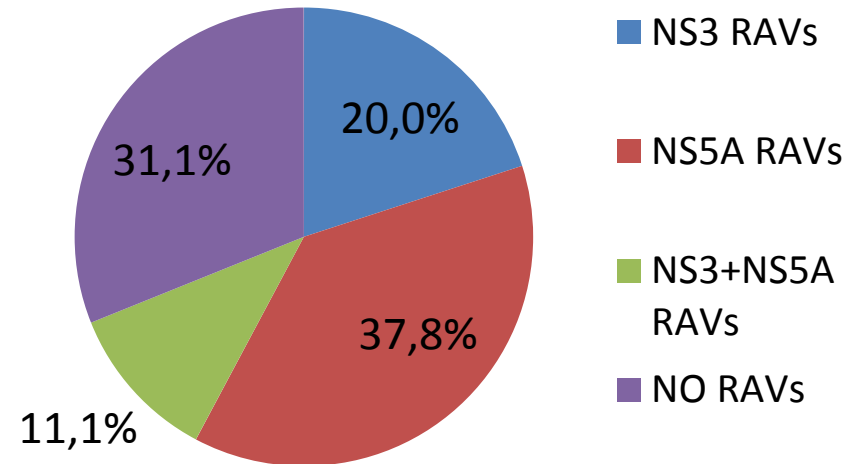
RAS by Genotype

Genotype 1a (n=43)



RAVs in 70% of GT-1a

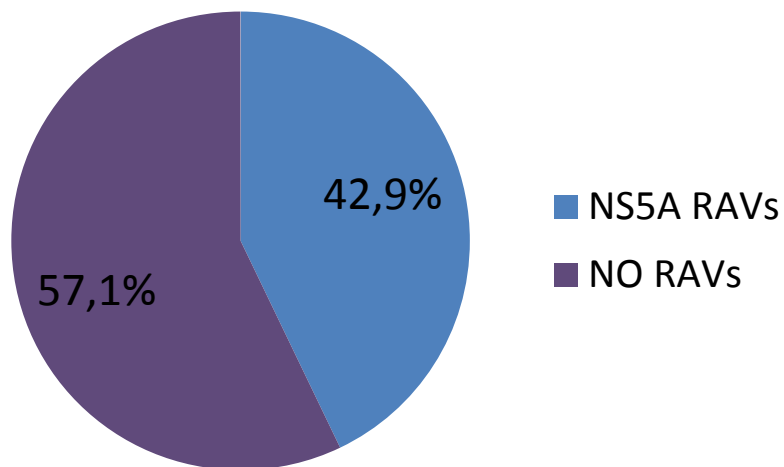
Genotype 1b (n=45)



RAVs in 69% of GT-1b

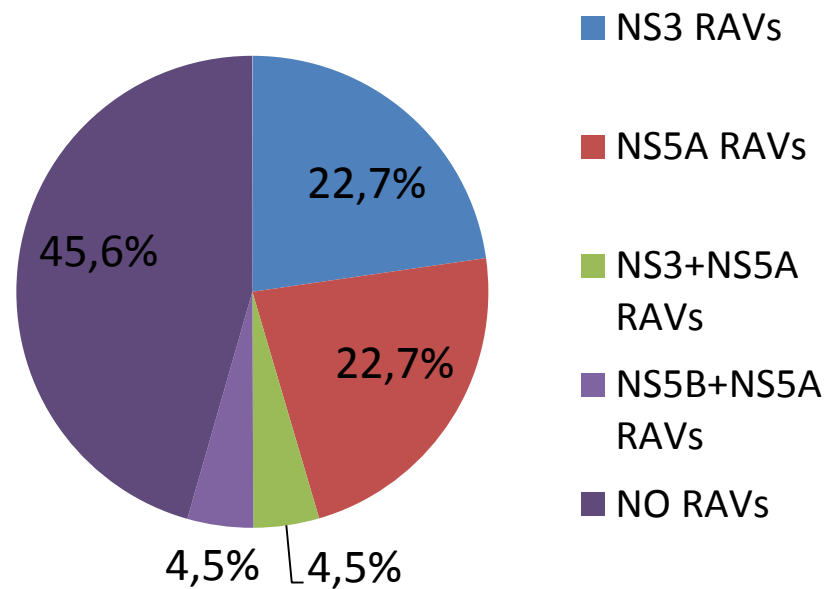
RAS by Genotype

Genotype 3 (n=28)



RAVs in 43% of GT-3

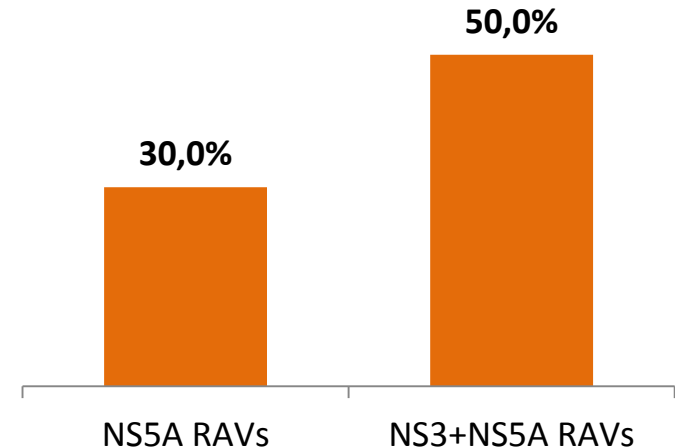
Genotype 4 (n=22)



RAVs in 55% of GT-4

Paritaprevir_r/Ombitasvir/Dasabuvir

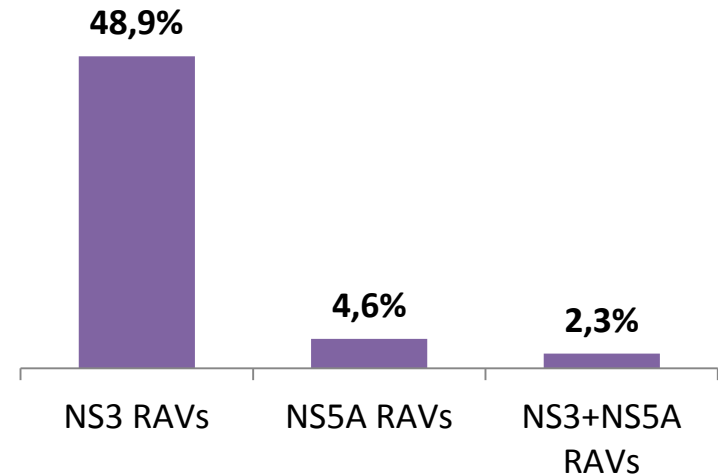
- 8/10 (80%) with RAS
- 30% only NS5A RAS
- 50% NS5A+NS3+NS5B RAS



Genotype	All	NS5A	NS3+NS5A+NS5B
	80,0% (8/10)	30,0% (3/10)	50,0% (5/10)
1a	85,7%	2/7 Q30R,H58D	4/7 Q80K,1R55K,D168V M28T,Q30R S556G
1b	66,7%	1/3 Y93H	1/3 Q80K,S122T L31M

Sofosbuvir/Simeprevir

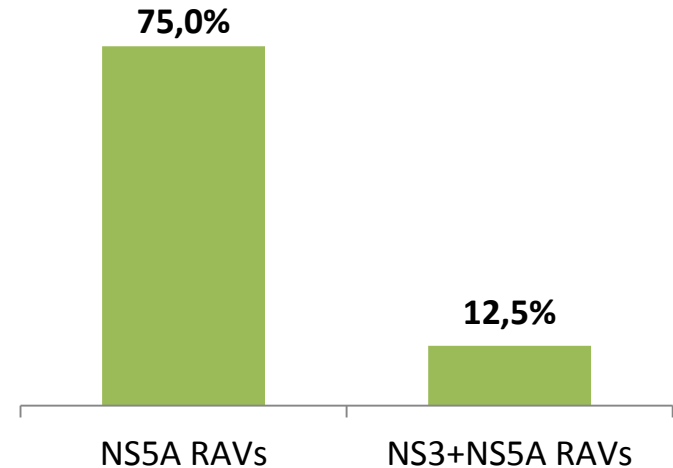
- No Sofosbuvir RAS
- 22/43 (51%) with PI RAs
- Most prevalent RAS:
168>155>80=122



Genotype	All	NS3	NS5A	NS3+NS5A
All	55,8% (24/43)	48,9% (21/43)	4,6% (2/43)	2,3% (1/43)
1a	66,6%	7/12 Q80K,R155K,D168E	1/12 L31M	-
1b	57,1%	10/21 R155Q, D168AHV, S122T	1/21 P58S	1/21 D168V & L31M
4	44,4%	4/9 (D168HV)	-	-

Sofosbuvir/Daclatasvir

- No Sofosbuvir RAS
- 21/24 (87,5%) with NS5A RAS
- Most prevalent RAS:
93>>30>31

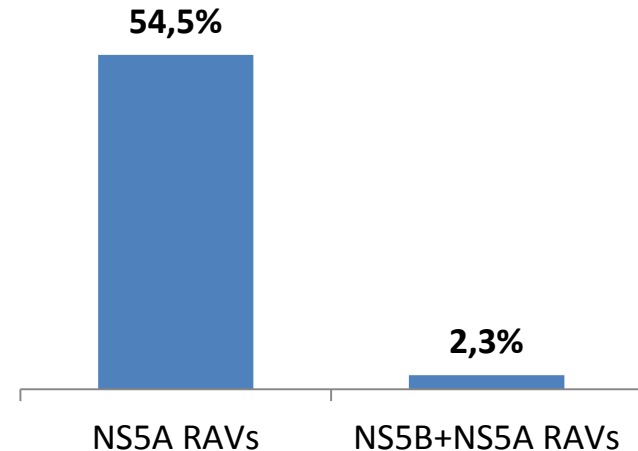


Genotype	All	NS5A	NS3+NS5A
All	87,5% (21/24)	75,0% (18/24)	12,5% (3/24)
1a	83,3%	2/6 (Q30H)	3/6 80K,122G,155K (NS3) 30EHR,31M (NS5A)
1b	100%	4/4 (L31MV,Y93H)	-
3	85,7%	12/14 Y93H 1/14 A30K	-

Sofosbuvir/Ledipasvir

- S282T n=1 (UDS confirmed)
- 25/44 (57%) with NS5A RAS
- Most prevalent RAS

93>>31>30

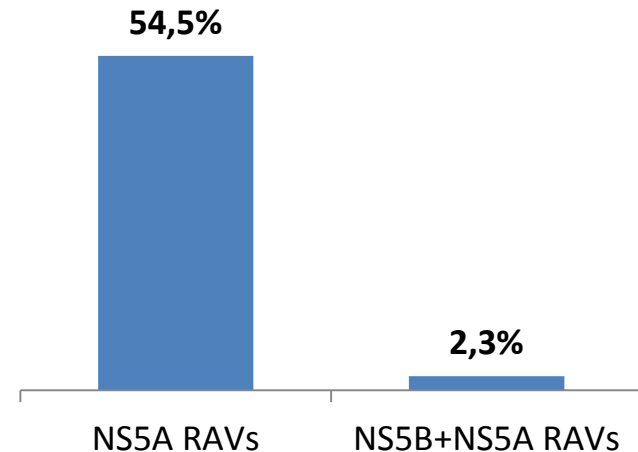


Genotype	N	NS5A	NS5B+NS5A
	56,8% (25/44)	54,5% (24/44)	2,3% (1/44)
1a	69,2%	9/13 (28A,30HR,31M)	-
1b	85,7%	12/14 (30Q,31MV,58S,93H)	-
3	0,0%	0/8 Y93H	-
4	44,4%	4/9 28M,93H 1/9 30F	1/9 S282T & Y93H

Sofosbuvir/Ledipasvir

- S282T n=1 (UDS confirmed)
- 25/44 (57%) with NS5A RAS
- Most prevalent RAS

93>>31>30



Genotype	N	NS5A	NS5B+NS5A
	56,8% (25/44)	54,5% (24/44)	2,3% (1/44)
1a	69,2%	9/13 (28A,30HR,31M)	-
1b	85,7%	12/14 (30Q,31MV,58S,93H)	-
3	0,0%	0/8 Y93H 3/8 A30K*V, L31I	-
4	44,4%	4/9 28M,93H 1/9 30F	1/9 S282T & Y93H

Frequency, characteristics of RAVs, and options for retreatment

	(n=138)	RAVs Detected	RAVS Detected (Clinically relevant)	Re Tx RAVs Possible in*
SOF/SIM	43	22 (51.2 %)	NS3: 22(51.2%)	SOF/NS5A: 89% (31/35) 3D/2D: 55% (23/42)
SOF/DCV	24	22 (91.7 %)	NS5A: 21(87.5 %)	SOF/LPV 24W RBV 13% (3/24) SOF/SIM: GT1 84% (5/6) 3D: (10%) 1/10
SOF/LED	44	32 (72,7 %)	NS5A/B: 25(56.8 %)	SOF/SIM: GT1/GT4 100% (30/30) SOF/NS5A 24W RBV: 43% (19/44) 3D/2D: 27% (8/30)
PTV/OMS/DSV	10	8 (80 %)	NS3/NS5A/NS5B: 8 (80%)	SOF/SIM 5/10 (50%) SOF/NS5A 2/10 (20%)

* With currently approved regimens in Europe

Genotype discordance

- 14/138 (10%) discordant genotype calls

Reported Genotype before AAD	NS5B Genotype at relapse
<p><u>Genotype (6)</u></p> <p>1 GT 1</p> <p>2 GT 4</p> <p>3 GT 1b</p>	
<p><u>GT 1 subtype (8)</u></p> <p>4 GT 1b</p> <p>4 GT 1a</p>	
	<p>GT 3a</p> <p>GT 1a</p> <p>GT 4d</p> <p>GT 3a</p> <p>GT 4a</p> <p>GT 1a</p> <p>GT 1b</p>

-1 case of mixed infection: 65% GT 1a + 35% genotipo 3

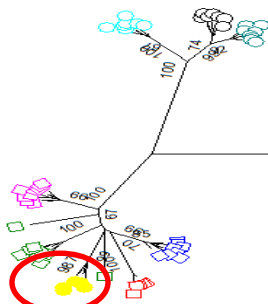
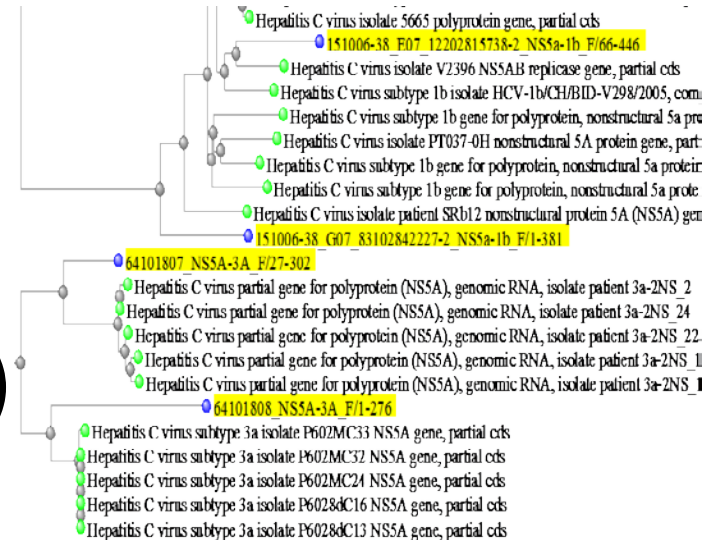
Relapse or Reinfection

31 Relapsers

3 undergoing confirmation (same genotype)

1 reinfection

35 paired samples



Baseline (1a)

Relapse (3a)

Conclusions

- We present the first “real life” data on genetic barrier and RAV prevalence at patients failing DAA regimens in Spain
- A high genetic barrier to resistance of Sofosbuvir, low to NS5A inhibitors, and low-moderate for PIs, has been confirmed.
- For NS5a inhibitors, special attention must be drawn to clinically significant RAVs
- Resistance testing offers important information for choosing the retreatment regimen, and for duration and the need to add ribavirine.
- Resistance testing brings additional information on accurate genotyping and reinfection episodes

Acknowledgments



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- ✓ Patients & their families
- ✓ HUSC molecular lab
- ✓ HCVRESp participants



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HCVRESp Cohort

- Complejo Hospitalario de Jaén: M Omar
- Complejo Hospitalario Santiago Compostela: A Aguilera
- CP Albolote: JJ Antón
- CP Castellón: C Mínguez
- EPHAG Andújar: C Delgado
- Hospital Arnau de Vilanova: J Flores
- Hospital de Baza: J Guilarte
- Hospital General de Alicante: S Reus, J Portilla, L Giner
- Hospital Carlos Haya: M Jiménez, M Delgado
- Hospital Cartagena: F Vera, O Martínez
- Hospital Costa del Sol: JM Rosales; N Montiel
- Hospital de Elche: M Masiá, F Gutierrez
- Hospital General de Valencia: M Diago, M Garcia-delToro, MD Ocete
- Hospital General JM Morales Meseguer: P Antequera
- Hospital Gregorio Marañón: T Aldamiz-Echevarría, H Reigadas
- Hospital Universitario Virgen de la Arrixaca: C Galera
- Hospital Infanta Elena: A de la Iglesia, D Merino
- Hospital de Jerez: JC Alados
- Hospital de la Línea: F Téllez
- Hospital de La Paz: J González, S G. Bujalance, V Hontanón, R Micán
- Hospital Melilla: A Fernández
- Hospital Miguel Servet: A Martínez-Sapiña, MA Simón
- Hospital de Poniente: M Álvarez, E Fuertes, A Lozano
- Hospital Puerta del Mar: Clotilde Fernández
- Hospital de Puerto Real: F Téllez, JM Montero
- Hospital Reina Sofía de Córdoba: A Poyatos, A Rivero
- Hospital Reina Sofía de Murcia: E Bernal
- Hospital San Cecilio: J Salmerón, A Gila, E Ruiz Escolano, J Hernández-Quero, R Quiles
- Hospital Torrecárdenas: A Collado, MC Galvez, M Gonzalez, M Casado
- Hospital de Valdepeñas: P Reales
- Hospital de Valme: JA Pineda, E Suarez, S Bernal
- Hospital de Vinalopó: V Navarro, L Giner
- Hospital Virgen Macarena: Felipe Fernández
- Hospital Virgen de las Nieves: F Nogueras, M.A. López Garrido, S Espinosa
- Hospital Virgen del Rocío: JM Pascasio, P Viciano
- Hospital Virgen de la Victoria: J Santos

UDS for 282 confirmation

Patient	Sanger		UDS
16051534	S282CT	WST	Not confirmed
64101810	S282T	ASC	Not confirmed
15254266	S282T	ACC	UDS 100%
16062034	S282R	AGM	Not confirmed

