SHARED *An international collaboration of viral sequences, treatment histories, and health outcomes related to the hepatitis C virus*

Surveillance of Hepatitis-C Antiviral Resistance, Epidemiology and methoDologies

Resistance associated substitutions (RAS) in "unusual" HCV subtypes

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on behalf of the contributing members of the SHARED database (*Equally contributing authors)

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INTRODUCTION

- "Unusual" subtypes, defined as GT1 non 1a/b, GT2 non 2a/b, GT3 non 3a, GT4 non 4a/d, GT5, and GT6, have been associated with a lower SVR rate to direct-acting antiviral (DAA) therapy
- This can be ascribed to polymorphisms at relevant amino-acid positions compared to the most sensitive subtype in the same genotype

AIM

Using the global **SHARED network**, we aimed to describe the prevalence of resistance associated substitutions (RAS) and RAS patterns after failing an NS5A inhibitor containing regimen among HCV "unusual" subtypes.

MATERIAL & METHODS

- We extracted data from the SHARED database of patients who did not achieve SVR on an NS5A-inhibitor containing regimen
- Only DAA regimens recommended by the EASL guidelines were included
- Geno- and subtypes were sequences-derived based on BLAST and phylogenetic analysis with reference sequences obtained by GenBank
- RAS were evaluated at positions according to the 2018 EASL guidelines

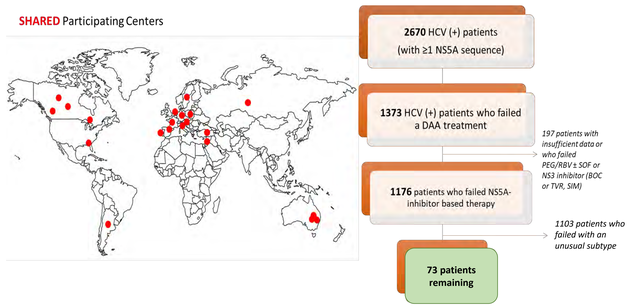


Figure 1 (left): SHARED participating centers. 6% of all failures containing an NS5A inhibitor were infected with an "unusual" subtype

Baseline characteristics	N=73 patients
Gender	
Male	45 (62%)
Female	28 (38%)
Age	
Median (range)	59 (25-86)
Cirrhosis	
Yes	20 (27%)
No	19 (26%)
Unknown	35 (47%)
Prior treatment History	
Treatment-naïve	37 (51%)
Treatment-experienced	20 (27%)
Unknown	16 (22%)
DAA regimen that failed	
SOF/LDV +/- RBV	18 (24%)
SOF + DCV +/- RBV	15 (20%)
SOF/VEL +/- RBV	13 (14%)
GZR+EBR	10 (15%)
2D/3D +/- RBV	11 (15%)
GLP/PIB	5 (7%)
Other (SIM+DCV+RBV)	1 (1%)

Table 1

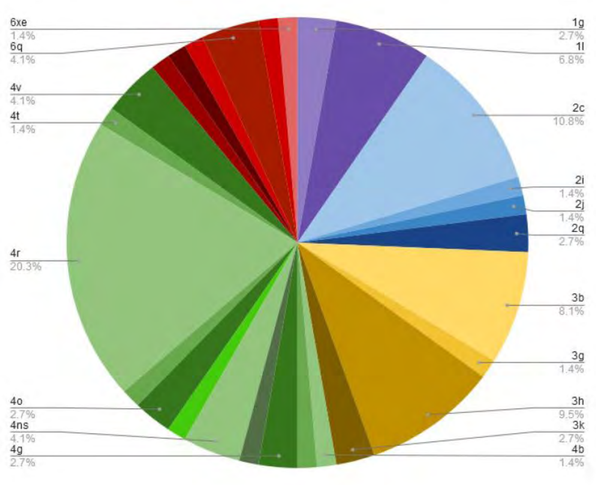


Figure 2 (Up): Geno- and subtype distribution of the unusual genotypes that failed an NS5A inhibitor. GT4r is largely overrepresented among GT4 non 4a/d. Additionally, large numbers of GT2c, GT3b, and GT3h were identified globally

RESULTS

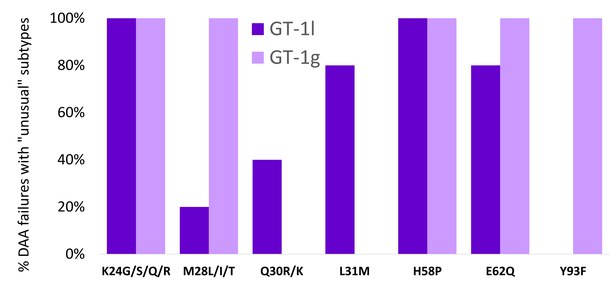


Figure 3 (Up): GT1 non 1a/b failures selected on average 4-5 RAS

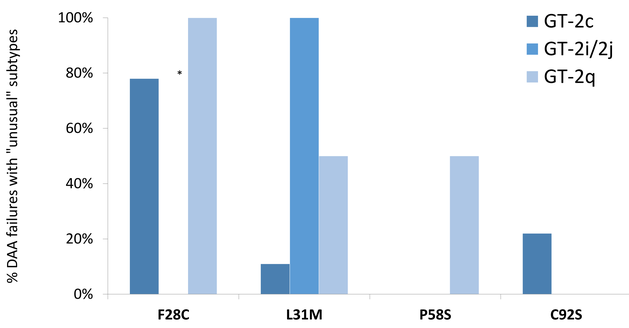


Figure 4 (Up): GT2 non 2a/b failures had signature F28C and/or L31M RAS after failure

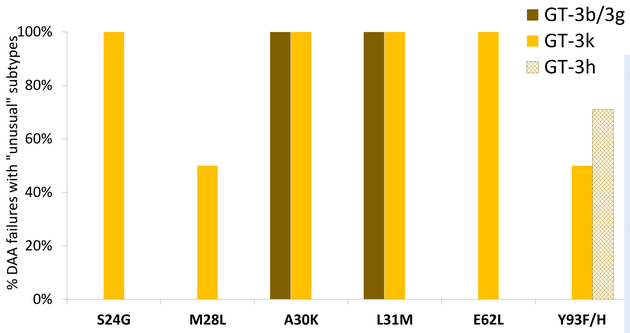


Figure 5 (Up): Each GT3 non 3a subtype had a distinct RAS pattern

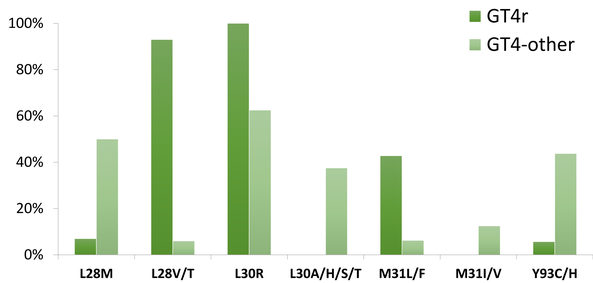


Figure 6 (Up): GT4 non 4a/d had a high occurrence of the L28V+L30R variant at failure

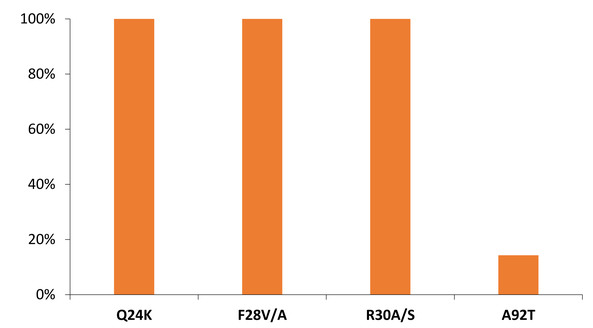


Figure 7 (Below): GT6 failures selected highly resistant triple mutations, Q24K+F28V/A+R30A/S

CONCLUSIONS

- "Unusual subtypes" (mainly GT3b, GT3h, and GT4r) may be overrepresented among DAA failures suggesting lower SVR rates due to multiple polymorphisms
- Indeed many unusual subtypes harbored 3-5 RAS with high level of resistance after treatment failure
- In-depth characterization of these subtypes is crucial in regions as Asia and Africa, were they are most common, as well as locations of immigration
- Our results emphasize the need for identification of these RAS in their subtypes and analyzes of *in vitro* drug susceptibilities

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