Hepatitis C Resistance-Associated Variants Among People Who Inject Drugs Treated With Direct-Acting Antiviral-Containing Regimens

Albert Einstein College of Medicine OF YESHIVA UNIVERSITY
Science at the heart of medicine

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BACKGROUND

- Resistance-associated variants (RAVs) to HCV direct-acting antivirals (DAAs) have been associated with virologic failure and may limit retreatment options.
- Approximately 10-15% of HCV genotype (GT) 1 infected patients without prior exposure to NS5A inhibitors will have detectable NS5A RAVs prior to treatment.[1]
- People who inject drugs (PWID) are the main driver of the HCV epidemic and are at highest risk for HCV transmission and reinfection.
- In this study, we report on RAVs at baseline (BL) and following virologic failure in treatment-naïve (TN) and -experienced (TE) methadone-maintained PWID with HCV GT1a/b.

OBJECTIVE

- To determine prevalence of HCV RAVs among a cohort of methadone maintained PWID.

METHODS

- NS3/4A, NS5A and NS5B regions from the first 69 of 150 GT1a/b viruses from PWID in a trial examining 3 models of care for HCV treatment between 11/2013 and 11/2015 were sequenced based on anticipated DAA regimen.
- 65/69 participants were treatment naïve.
- Regimens included SMV/SOF N=12, SOF/RBV ± IFN N=33, and SOF/LDV N=24.
- Variants relative to genotype/subtype specific H77 (GT1a) and Con1 (GT1b) reference sequences were reported.
- Phylogenetic analyses of NS3 sequences obtained at baseline and failure from a patient with suspected reinfection, along with 10 unrelated NS3 sequences, were performed using neighbor-joining methods (MEGA).

RESULTS

Figure 1. HCV RAVs Among Treatment-Naïve PWID

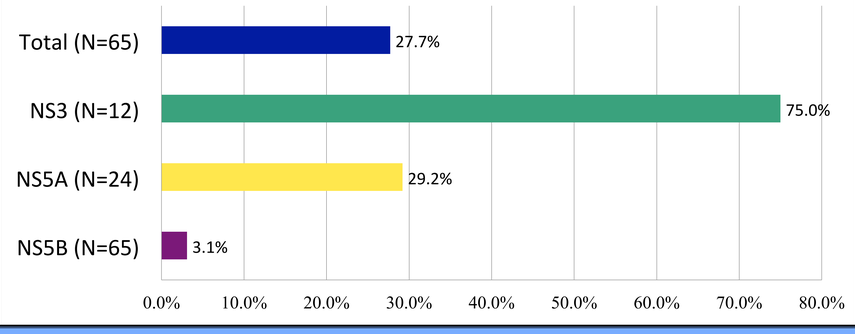
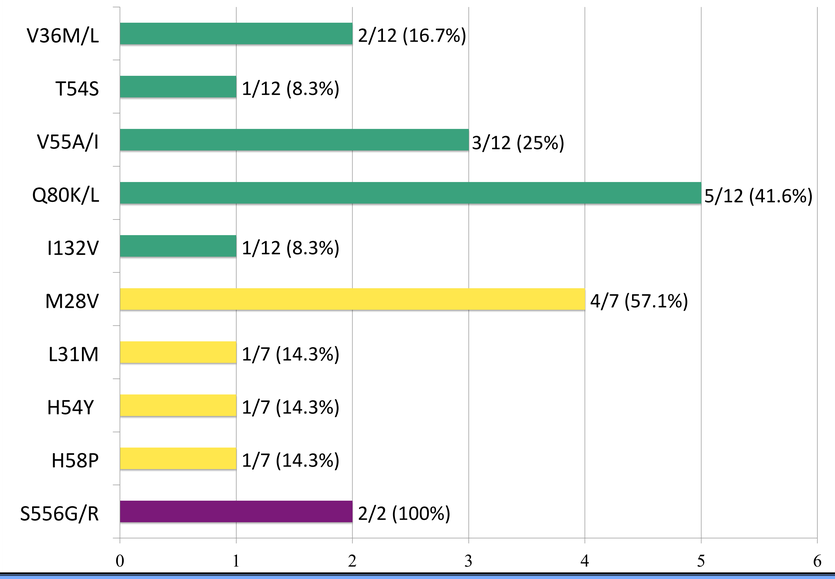


Figure 2. Specific RAVs Among Treatment-Naïve PWID



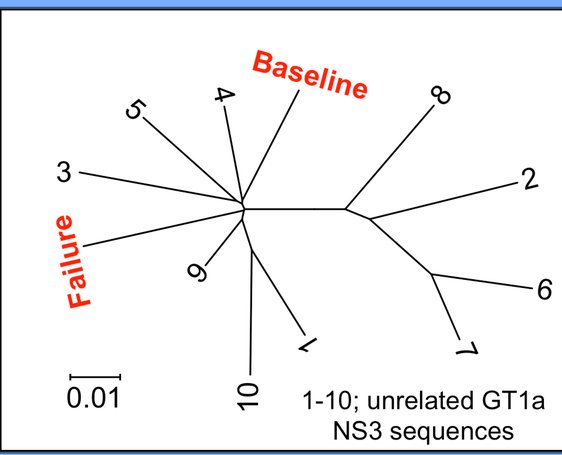


Figure 3. Phylogenetic tree of GT1a NS3 sequences at baseline and following SMV/SOF treatment failure as well as from 10 unrelated individuals (not from this study)

RESULTS

- Of the 65 (94.2%) TN PWID, 18/65 (27.7%) had RAVs at baseline – 9/12 (75%) NS3, 7/24 (29.2%) NS5A, 2/65 (3.1%) NS5B (Figure 1). The prevalence of specific RAVs is shown in Figure 2.
- No RAVs were observed among 4 GT1b patients.
- Of the 4 TE patients, 1 had a BL Q80K.
- 6 (8.7%) failed therapy – 1 SMV/SOF, 3 SOF/RBV, 2 SOF/LDV. All had GT1a virus, 5 were TN, and 1 a prior SOF/RBV failure.
- Only the SMV/SOF failure had a BL RAV (Q80K). This patient became HCV RNA positive at 24 weeks. A different set of viral variants were observed, and the Q80K was no longer present. The baseline and failure sequences were phylogenetically distinct (Figure 3).
- RAVs were not detected following SOF/RBV failure.
- Both SOF/LDV failures had NS5A mutations (Q30H/R, Y93H) post-baseline.

CONCLUSIONS

- RAVs were present among a subset of TN PWID, particularly in NS3 due to the Q80K polymorphism.
- Some RAVs appeared enriched compared to expected prevalence in DAA-naïve individuals.
- BL RAVs did not affect treatment outcomes.
- Phylogenetic analysis was supportive of reinfection or selective outgrowth of a coinfecting minor variant following treatment failure in one individual.
- Re-treatment options may be limited among patients who fail SOF/LDV given selection of NS5A RAVs.
- The potential for transmitted NS5A RAVs could pose a particular concern for treatment of PWID.

REFERENCES & ACKNOWLEGMENTS

1. Zeuzem S, et al. Prevalence of Pre-Treatment NS5A Resistance Associated Variants in Genotype 1 Patients Across Different Regions Using Deep Sequencing and Effect on Treatment Outcome with LDV/SOF. AASLD. November 13-17, 2015b; San Francisco, CA.

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