**WHOLE GENOME SEQUENCING AND DRUG RESISTANCE ANALYSIS OF 'UNUSUAL' HEPATITIS C SUBTYPES 6XA AND A 3B RELAPSE CASE: A STUDY ON INTRAVENOUS DRUG-USERS ON DIRECT-ACTING ANTIVIRAL (DAA) TREATMENT, INDIA**

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**Background:** Pangenotypic DAAs are effective against highly prevalent HCV subtypes; but clinically validated almost exclusively in high-income countries. However, 'unusual' HCV subtypes common in Asian and African countries are known to carry natural NS3 and/or NS5A polymorphisms, reducing DAA susceptibility. We conducted full-genome characterization and drug-resistance analysis of unusual HCV subtypes 6xa and a relapse case with subtype 3b, in IVDU on DAA treatment.
**Methods**: A prospective hospital-based study was conducted, where eligible patients were screened for anti-HCV antibodies. Active infection was confirmed by HCV RNA detection. Genotype was determined by virus core region sequence analysis and viral load quantified by real-time PCR. Whole genome sequencing was done by overlapping multiplex PCR followed by sequencing on Oxford Nanopore Technology platform. Phylogenetic analysis was done by alignment of globally available HCV reference sequences. HCV-GLUE online data resource was used for conducting resistance associated substitutions (RAS) analysis.
**Results:** A total of 42 IVDUs with confirmed HCV infection were enrolled, with predominant genotype 3 (n=30, 71.4%), followed by 6 (n=9, 21.4%) and 1 (n=3, 7.1%). Unusual HCV subtype 6xa was obtained from two patients and one subtype 3b patient relapsed at 24 weeks post-DAA treatment completion. HCV 6xa sequences did not show any RAS against NS3/4A protease inhibitors, but showed 28V category II mutation, for NS5A inhibitors. HCV 3b relapse case showed 30K and 31M RAS against NS5A inhibitors, in both baseline and relapse sequences.
**Conclusion:** For the first time in India, whole genome sequencing of HCV subtype 6xa was conducted. Drug resistance analysis of relapse subtype 3b case showed 30K+31M RAS combination, known to confer high level of resistance to NS5A inhibitors, reported in patients with unusual subtypes 3b and 3g. Our study highlights a critical challenge remaining for global HCV elimination, where DAA efficacy in unusual nonepidemic genotypes circulating in low-and middle-income countries needs to be determined, warranting prompt and robust action.

**Disclosure of Interest Statement:** ***See example below:***
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