BACKGROUND:
Attributes of the first 500 patient and telaprevir (TVR) resistance study compares boceprevir (BOC) resistance to BOC or TVR, but are not associated with resistance to BOC or TVR, but are associated with resistance to simeprevir (SMV), a second generation HCV PI. During clinical trials with SMV, mutations at amino acid positions 80, 155, 168 and/or 170 were associated with virologic failure2,3.

METHODS
HCV GT1a or GT1b patient samples with viral loads ≥ 2000 IU/mL were sent to Monogram Biosciences, Inc. for PI resistance analysis using the HCV GenoSure® NS3/4A resistance assay4. Briefly, the entire nonstructural protein 3 (NS3) and 4A (NS4A) region of HCV was amplified by RT-PCR using GT1a or GT1b subtype-specific primers. The nucleotide and derived amino acid sequences were determined and compared to either the H77 (GT1a) or Con 1 (GT1b) reference sequences. Resistance-associated variants (RAVs) were identified and a prediction of drug susceptibility was derived using a rules-based algorithm. The HCV genotype of the NS3/4A region was also determined (Figure 1). For this analysis, we assembled the results of the first 1500 reported samples.

RESULTS
• 77% of samples received for resistance testing were GT1a and 23% were GT1b (Figure 2).
• The overall predicted resistance to both BOC and TVR among all samples was 22%; 20% were GT1a and 2% were GT1b (Figure 3A). Resistance to BOC and TVR among GT1a patient samples was 28% and 27%, respectively, but only 13% and 16%, respectively, among GT1b samples (Figure 3B).
• The most commonly observed RAVs for both drugs were R155K (14.9%), V36M (13.5%) and T54S (2.9%). These were often present in combinations, with V36M+H152A (16.3%), V36M+T54S+R155K (2.3%) and V36M+T54S+R155K+T54S (1.3%) occurring most often. The combination of V36M+T54S was seen only in the triple variant, with V36M+T54S+R155K (Figure 4).
• Q80 substitutions were seen in 35.9% of patients: 34.6% were GT1a, 1.3% were GT1b. Of patient samples with Q80K, the most frequent substitution, 32.5% were GT1a but only 0.1% were GT1b. The most common SMV RAV2,3 combination, Q80K+R155K, was seen in GT1a samples only, at a frequency of 6.1% (Figures 4, 5).

SUMMARY & CONCLUSIONS
• The analysis of BOC and TVR RAVs and the trends observed among the first 1500 samples tested and reported was consistent with that of the first 500!
• Our findings demonstrated a higher prevalence of HCV PI RAVs among GT1a versus GT1b samples. For BOC and TPV RAVs, this was consistent with a higher genetic barrier to resistance for GT1b viruses.

REFERENCES

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Figure 1: HCV GenoSure® NS3/4A assay

Figure 3: Genotypic Susceptibility Assessments for Telaprevir and Boceprevir

Figure 4: Percent of NS3 Resistance-associated Variants among all Patient Samples

Figure 5: Subtype Distribution (A) and Percent (B) of Q80K-containing Variants among all Patient Samples

Figure 6: Percent of Patient Samples Classified as Resistant or Resistance Possible Over Time