Phenotype Analysis Working Group

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Points of discussion

- Clinical relevance of minority variants phenotypic data?
- Generation of a table with known resistance mutations and phenotypic effect

Clinical relevance of minority variants phenotypic data

- Information largely driven by enhancements and evolution of sequencing technology
- This topic willl be driven by SAWG is currently working on
- Sequence information on minor variants would have to be translated to phenotypic susceptibility data.
- To avoid bias from individual clonal variants (perhaps RT-PCR errors), especially as it relates to replication capacity, testing of multiple clones or pools of clones will be required.

Table drug resistance mutations & phenotypic data

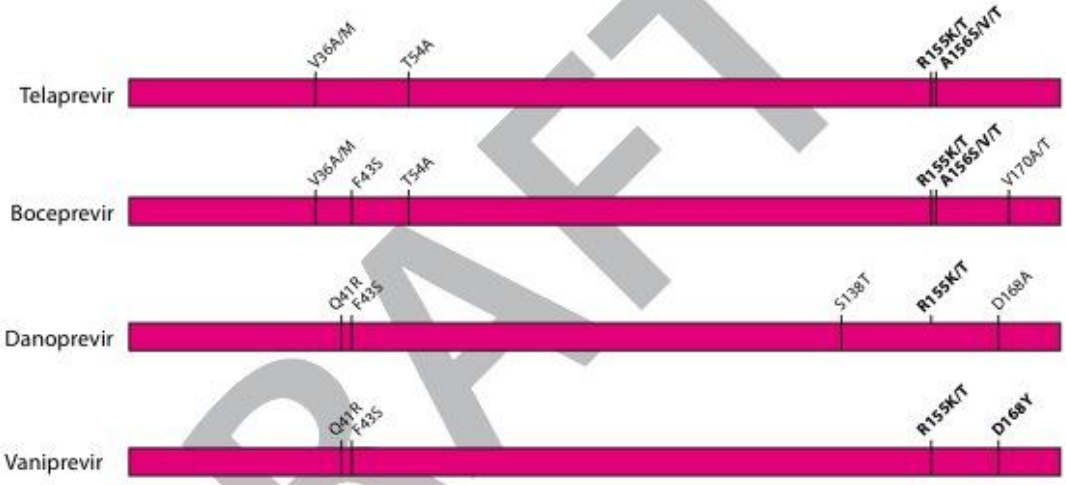
- **Objective:** Generation of a table, which will be updated periodically, with key HCV resistance mutations including phenotypic susceptibility data, based on published findings

- **Posting**: Potential for publishing in:
  - Forum's online publication "Annals of the Forum for Collaborative HIV Research"
  - At the Forum's website: high level overview with the ability to have an in- depth look at the data.

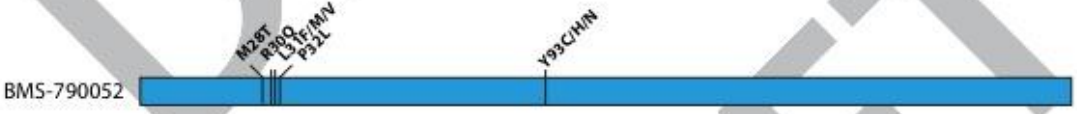
- **Data to include**: data on NS3, NS5A and NS5B mutations for compounds that are:
  - Phase 3 trials. Include phase 2 at this point?
  - From In vitro and/or in vivo ?
  - To include linkage information ?
  - Fitness ?

- **Phenotypic effect to be defined:**
  - Clinical impact
  - Order of appearance
  - Format: $EC_{50/90}$ values or fold vs control
  - Format for aa substitutions: proposal and example prepared by Neil Parkin

NS3 protease (180 aa)

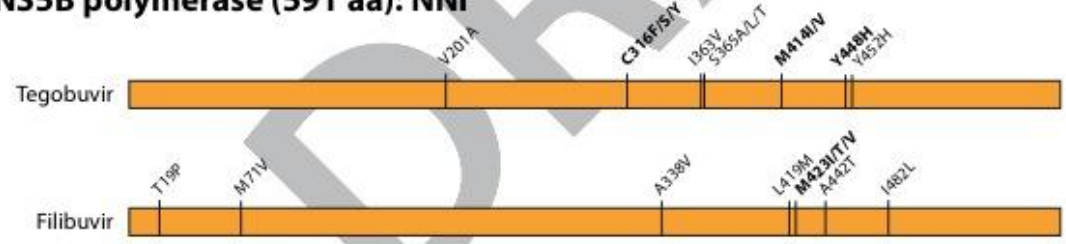


NS5A Domain I (213 aa)



NS5B polymerase (591 aa): NI

NS5B polymerase (591 aa): NNI



Next steps

- Discussion of the specifics for the Table
  - Discussion at meeting
  - Sign up for subgroup to agree on:
    - Definitions for phenotypic changes
    - Particulars on format for data to be included
    - Process for reviewing and updating the data periodically (annually)

- The Forum has put together a draft of the proposal for companies and academic groups to provide phenotypic data to include in the table
  - Encourage groups to agree to provide data
  - Data can already be sent to Nina Mani at nmani@hivforum.org

Proposal of data to provide for Table

- Drug manufacturer
- Compound generic name
- Compound aka
- Target enzyme
- Compound class
- Resistance mutation
- Replicon vector (name, subtype)
- Cell type
- Replicates (N)
- Mean EC50 (uM)
- EC50 SD
- Mean fold-resistance:
- FR SD
- Citation
- Key assay parameters (duration, read out etc.)
- Data submitted by
- Date submitted