Working Group 1: HCV Resistance Reporting and Analysis Standardization

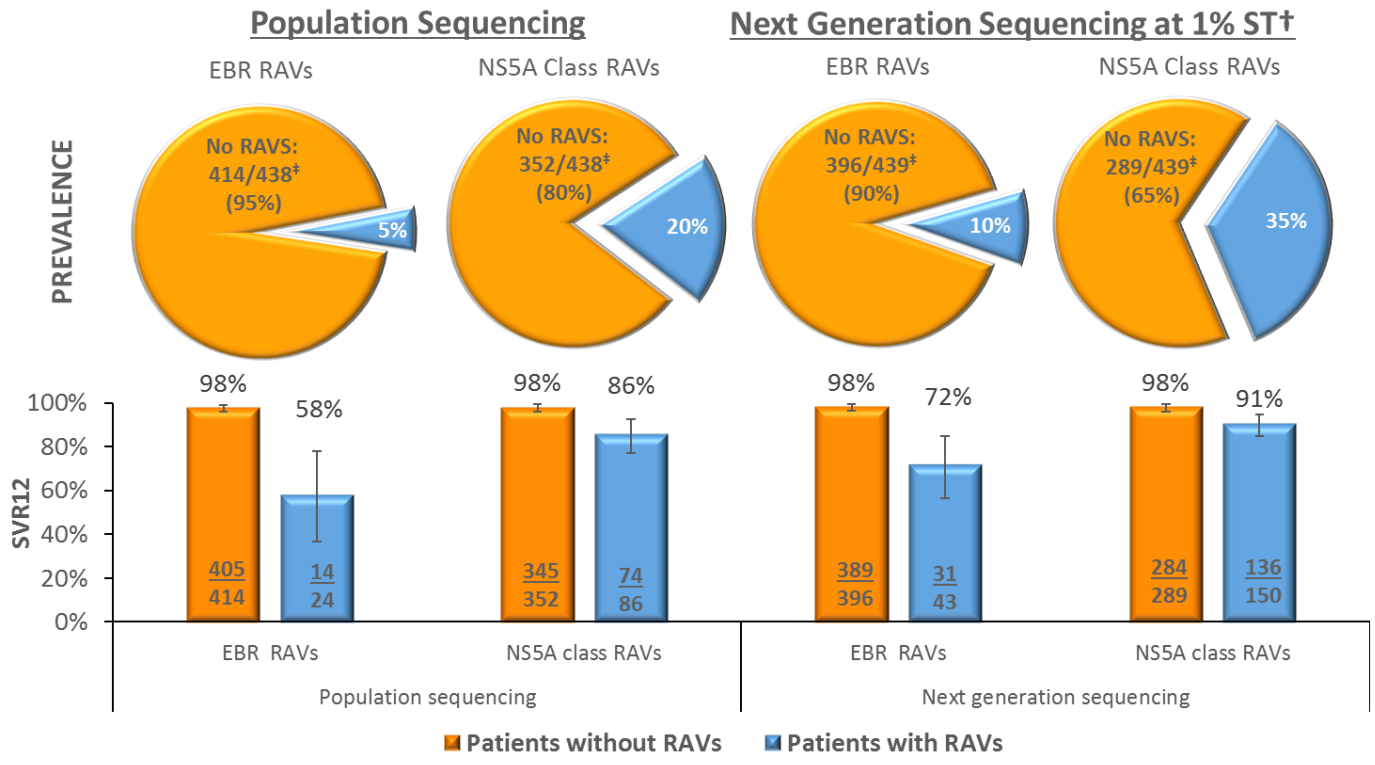
15th HCV DrAG Meeting

April 14th, 2016

Background

- Impact of RAVs on SVR rates can vary dependent upon analysis/reporting criteria; including the method used to detect RAVs and the substitutions considered RAVs
  - Exemplified by elbasvir/grazoprevir data presented by Todd Black, HCV DrAG 2015

AMONG GT1a TREATMENT-NAÏVE/PRIOR RELAPSERS WITH BASELINE NS5A RAVS - SVR WITH EBR/GZR (12 WKS, NO RBV) VARIED FROM 58% TO 91%, DEPENDING ON METHODOLOGY



- With population sequencing and a focus on EBR RAVs, the efficacy of EBR/GZR is reduced in the presence of NS5A RAVs at baseline
- With 1% NGS and a broad definition of NS5A RAVs, the impact of baseline NS5A RAVs on the efficacy of EBR/GZR is minimal

†NGS with 1% ST supplemented by Population Sequencing when NGS not available. ‡ One GT1a was missing baseline population sequencing data but had baseline NGS data
EBR RAV List = For GT1a: M/L28T/A/G, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, or Y93C/H/N/S
NS5A Class RAV List = Any variant from reference strain at NS5A position 24, 28, 30, 31, 32, 38, 58, 92 or 93

Objectives

- Develop guidelines for the standardization of resistance analysis and reporting of resistance-associated variants (RAVs) variants
  - Variants present at treatment baseline
  - Treatment-emergent variants
  - Variants that persist post-treatment
  - Incorporating analysis and reporting of variants relative to variables that may impact treatment responses
- ➢ Report outcome to WG#2
- ➢ Facilitate comparison of the impact of RAVs across different regimens to help inform treatment decisions

Discussion Topics

- Preferred Terminologies and Abbreviations
- Target Audiences
- Scope and Format for Analysis and Reporting
- Analysis
  - What characteristics of the resistance analysis population should be captured?
  - Which variables should be included in standardized analysis?
- Reporting
  - *In vitro* resistance data
  - Baseline variants
  - Combined report of variants associated with failure?
  - Persistence of RAVs

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(~5 min)

- Analysis (~10 min)
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- Reporting (~10 min)
  - *In vitro* resistance data
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Preferred Terminologies and Abbreviations

- Resistance-associated variant (RAV) vs substitution (RAS) vs polymorphism (RAP)?
- Treatment-emergent RAV vs post-baseline RAV vs persistent baseline RAV (that causes VF)?
- Do we need a specific term to describe a persistent baseline variant that is sufficient to cause treatment failure?
- Class RAV (encompass polymorphisms?), drug RAV?
- RAV persistence: not detected vs return to wild-type / baseline vs disappearance vs undetectable”
- Others?

Which Variables should be Included in Standardized Analysis?

- Methodology
  - Sanger vs NGS
    - NGS reporting thresholds:
      1, 10, 15, 20%? (ref. WG#2)
- Evaluation by amino acid (aa) position and specific RAV (ref. WG#2)
  - All class RAV aa positions – should this differ by GT/subtype?
  - Drug RAV aa positions – individual and/or combined?
  - Evaluation of specific RAVs – individual and/or combined?
- # variants/target
- # targets with variants
- Challenges in rare/less studied genotypes/subtypes?
- Susceptibility fold-change conferred by variants
  - Numeric (e.g. 10, 100, 1000-fold RAV)?
  - Drug specific (range tailored based on range of variation seen)?
  - What are most reliable replicon assay methods (e.g., transient vs. stable replicon, readouts)?

Reporting: Baseline Variants

- Variants at aa position of interest as well as drug specific RAPs, RAVs, RASs? Individual and/or combined?
- Impact on SVR
  - Overall
  - By patient characteristics of interest (e.g. cirrhosis)?
  - By analysis variables of interest (e.g. NGS threshold)?
- Document BL prevalence of variants of interest in non-SVR as well as SVR samples?

Combined Report of Variants Associated with Treatment Failure?

- Summary of subjects with RAPs/RASs/RAVs at virologic failure (not just treatment-emergent RAVs)?
  - In each and all target regions?
  - By genotype/subtype?
  - In sub-group of interest?
- List of variants associated with virologic failure to include treatment-emergent variants and persistent BL RAPs/RAVs/RASs?

e.g. mock data

	No. of non-SVR subjects with RAVs at virologic failure		
	NS5A	NS5B	NS5A + NS5B
RAVs observed	124/208 (59.6%)	2/208 (1%)	2/208 (1%)
Treatment-emergent RAVs	67/208 (32.2%)	2/208 (1%)	2/208 (1%)
Persistent BL RAVs	30/208(14.4%)	0/208 (0%)	0/208 (0%)
Tx-emergent + Persistent BL RAVs	27/208 (13.0%)	0/208 (0%)	0/208 (0%)
No RAVs observed	84/208 (40.1%)	n/a	n/a

Reporting: Persistence of RAVs

- Summary of subjects in the analysis, studies, genotypes etc
- Appropriate nomenclature use: “not detected” versus “return to wild-type / baseline”, “disappearance”, “undetectable”?
- Duration of observation?
- % subjects with RAVs over X months (by what method / detection threshold)?
- % of viral population with RAVs at time of failure and follow-up time points?
- Absolute concentration of variant - perhaps more important clinically?
- Median time / rate for all / individual RAVs to become undetectable (in months, in 100 PY)?
- Sub-group analysis?

Target Audiences

- Should reporting be different for different target audiences? E.g. basic researcher vs clinician vs regulatory vs patient/general public
- Common objectives/scope for all audience?
- Target audience-specific objectives/scope?

Scope and Format for Analysis and Reporting

- How detailed should the working groups recommendations be?

What Characteristics of the Resistance Analysis Population should be Captured?

- # patients included in analysis
- Virologic failure response category:
  - Breakthrough (BT)
  - Relapse (RL), late relapse?
  - Incomplete virologic response (IVR)
  - Non-response (e.g., when someone clearly fails virologically but doesn't meet a definition of relapse or breakthrough)?
  - Include subjects lost-to-follow-up?
  - Include non-compliant subjects?
- Sustained virologic response (SVR) :
  - Overall
  - Regimen (dose, drug combinations)
  - Treatment duration
  - Prior treatment history/response
  - Genotypes and subtypes
  - Patient characteristics
    - Cirrhosis
    - High viral load
    - IL-28B CC/non-CC
    - Others?
  - Exclude those who didn't achieve SVR for non-virologic reasons (e.g. early discontinuation or missing SVR12 visit)?
  - Others?

Reporting: In vitro Resistance Data

- EC50 and EC50-fold change for SDMs?
- EC50, EC90/95 and EC50-, EC90/95-fold change for replicons containing populations of plasma derived sequences?
- Replication capacity?
- Include information on human serum/protein binding adjustment?
- Important assay details?

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