Impact of HCV Polymorphisms in DAA Clinical Trials

Patrick Harrington, PhD
Division of Antiviral Products
FDA/CDER

Disclaimer

The views expressed in these slides are those of the presenter and do not necessarily represent official policy of the Food and Drug and Administration.

Presentation Outline

- Impact of HCV polymorphisms on treatment efficacy in DAA clinical trials
- Perspective on DAA-experienced patients
- Considerations for pre-treatment resistance testing

Boceprevir + P/R (GT1)

Table 27. SVR outcome for subjects with or without boceprevir resistance-associated substitutions detected at baseline, stratified by virologic response through Treatment Week 4 (end of Peg-IFNα-2b/RBV lead-in period). Analysis was conducted using as treated, non-VF-censored subject datasets. Baseline boceprevir resistance-associated substitutions considered in this analysis were V36M, T54A, T54S, V55A and R155K.

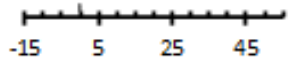
Subject Population Analyzed	SVR Rate According to HCV RNA Decline through Treatment Week 4		
	<1 $\log_{10}$ IU/mL	≥1 to <2 $\log_{10}$ IU/mL	≥2 $\log_{10}$ IU/mL
Boceprevir-Treated Subjects **with** Baseline Resistance Substitution(s)	0/7 (0%)	3/7 (43%)	25/26 (96%)
Boceprevir-Treated Subjects **without** Baseline Resistance Substitution(s)	90/235 (38%)	148/199 (74%)	376/408 (92%)
All Subjects in Control Arms	2/89 (2%)	26/100 (26%)	109/163 (67%)

P.Harrington, FDA Clinical Virology review of boceprevir

- Evidence of impact of baseline NS3 resistance-associated polymorphisms in those who respond poorly to background regimen
- Very small fraction of population (1-2%) with poor P/R lead-in response and baseline polymorphism

Simeprevir + P/R: GT1a NS3 Q80K

		SVR (n/N) (%)		SVR_{PI}-SVR_{PBO}			
		PI+P/R	PBO+P/R	Δ(%)	95%CI	Plot	pvalue
TMC435	GT1	415/521 (79.7)	132/264 (50)	29.7	(22.6 , 36.5)		<0.0001
	1a	188/252 (74.6)	61/129 (47.3)	27.3	(17 , 37.1)		<0.0001
	non-Q80K	137/164 (83.5)	36/83 (43.4)	40.2	(27.7 , 51.4)		<0.0001
	Q80K	48/84 (57.1)	24/44 (54.5)	2.6	(-14.8 , 20.2)		0.78
	1b	225/267 (84.3)	69/133 (51.9)	32.4	(22.8 , 41.7)		<0.0001
Boceprevir	GT1	468/734 (63.8)	133/363 (36.6)	27.1	(20.9 , 33)		<0.0001
	1a	221/366 (60.4)	59/177 (33.3)	27.0	(18.2 , 35.2)		<0.0001
	non-Q80K	110/193 (57)	39/106 (36.8)	20.2	(8.4 , 31.1)		0.00083
	Q80K	111/173 (64.2)	20/71 (28.2)	36.0	(22.4 , 47.4)		<0.0001
	1b	180/267 (67.4)	50/126 (39.7)	27.7	(17.2 , 37.4)		<0.0001
Telaprevir	GT1	270/359 (75.2)	158/359 (44)	31.2	(24.2 , 37.8)		<0.0001
	1a	158/217 (72.8)	87/210 (41.4)	31.4	(22.2 , 39.8)		<0.0001
	non-Q80K	88/128 (68.8)	53/129 (41.1)	27.7	(15.6 , 38.6)		<0.0001
	Q80K	70/89 (78.7)	34/81 (42)	36.7	(22.2 , 49.1)		<0.0001
	1b	112/142 (78.9)	71/149 (47.7)	31.2	(20.3 , 41.1)		<0.0001

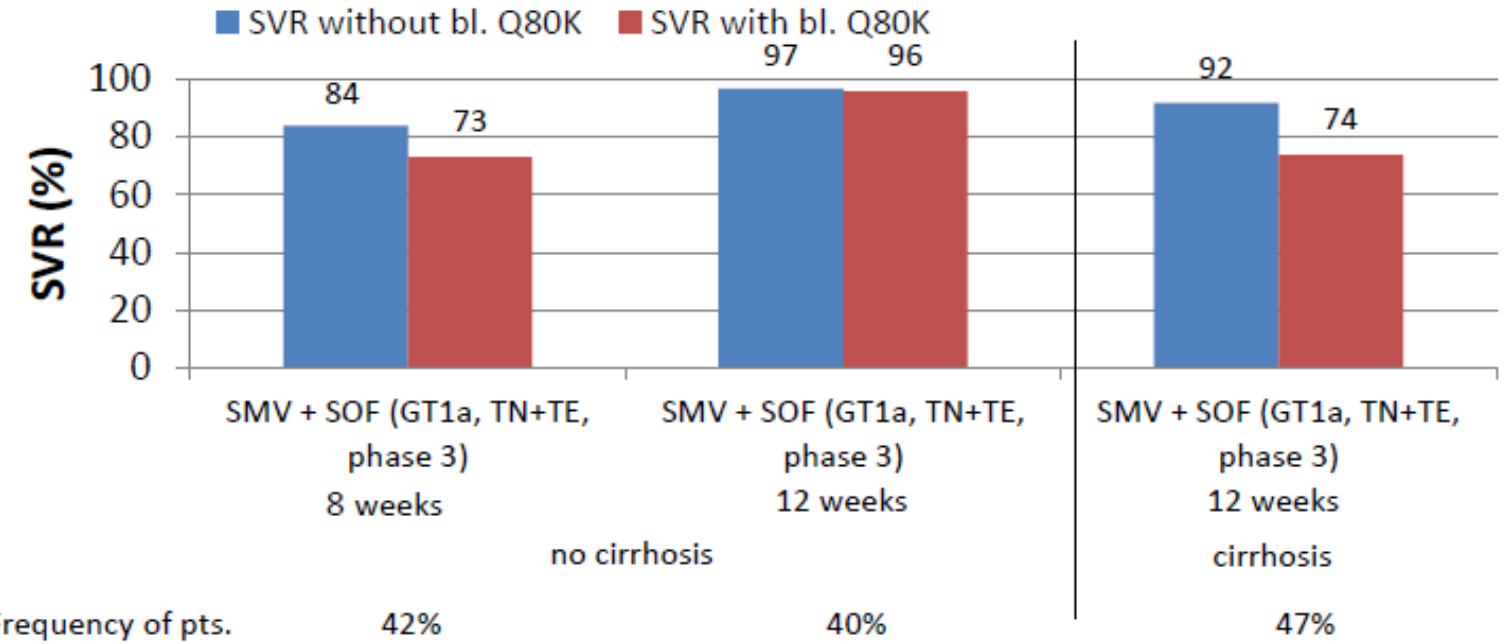


D.Deming, FDA Clinical Virology review of simeprevir

Key factors that contributed to label <u>recommending screening for Q80K</u>

- GT1a Q80K polymorphism substantially reduces efficacy of SMV + P/R
- High prevalence of Q80K in U.S. (48% of GT1a)
- Resistance consequences of failure in this population: Emergence or R155K (or others)
- Boceprevir and telaprevir not impacted and represented alternative treatment options

SMV/SOF Q80K?



Sarrazin C., 2015. Review: The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol. In press.

- No impact of Q80K w/12-week duration in non-cirrhotic patients
- Reduced efficacy in patients with Q80K: 8-week duration or patients with cirrhosis

LDV/SOF: NS5A PMs and Relapse Rates

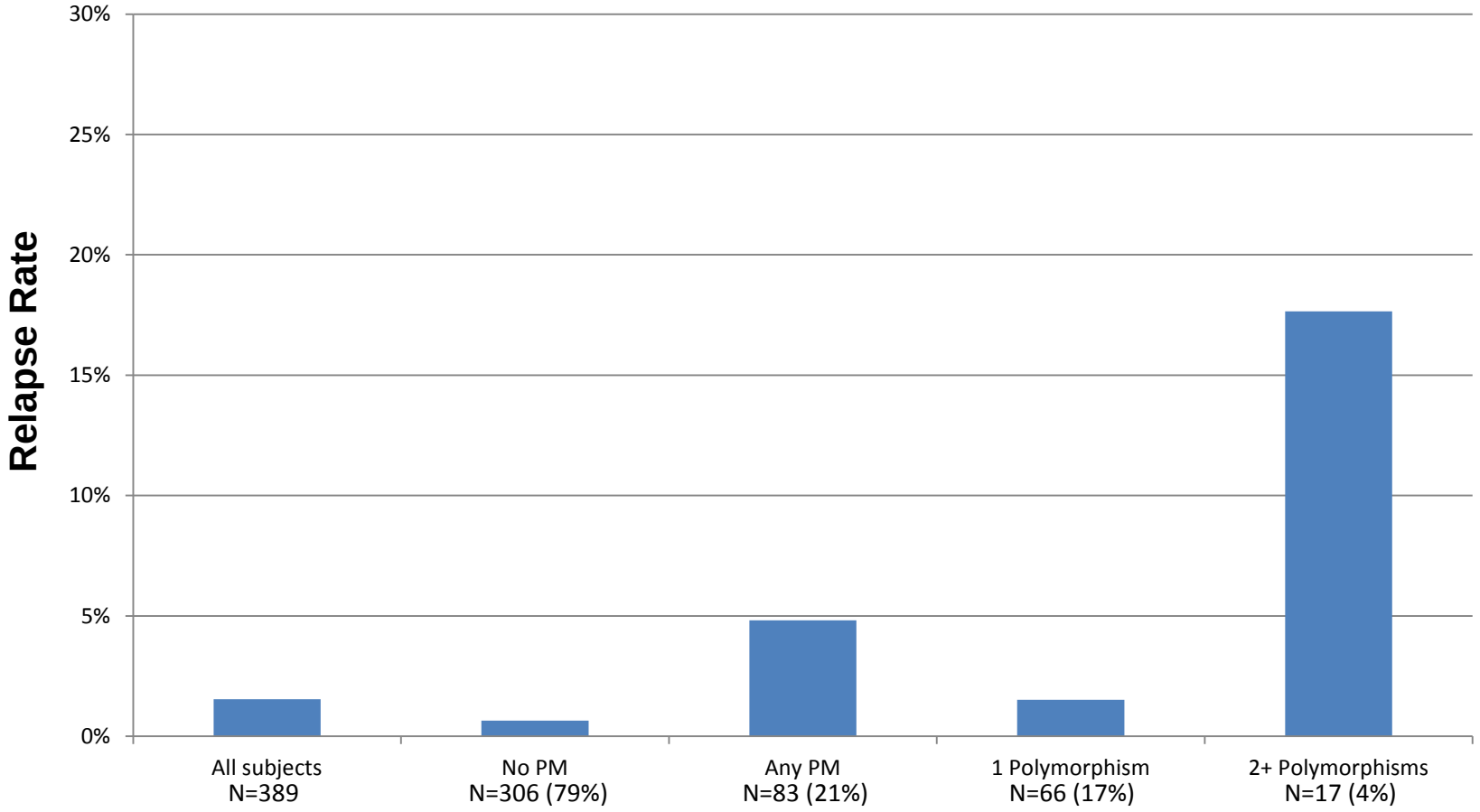
	GT1 (NS5A)	ALL	No BL NS5A	BL NS5A
ION-3	**Study 108 naïve**	3.6% (23/645)	3.3% (16/492)	4.6% (7/153)
	LDV/SOF 8 WK	5.1% (11/215)	4.8% (8/167)	6.3% (3/48)
	LDV/SOF 12WK	1.4% (3/214)	1.9% (3/158)	0% (0/56)
	LDV/SOF+RBV 8WK	4.2% (9/216)	3% (5/167)	8.2% (4/49)
ION-2	**Study 109**	2.5% (11/440)	1.4% (5/356)	7.2% (6/83)
	LDV/SOF 12 WK	6.4% (7/109)	2.3% (2/86)	22% (5/23)
	LDV/SOF 24 WK	0% (0/109)	0% (0/90)	0% (0/19)
	LDV/SOF+RBV 12WK	3.6% (4/111)	3.4% (3/89)	4.5% (1/22)
	LDV/SOF+RBV 24WK	0% (0/111) Note: 1 BT	0% (0/91)	0% (0/19)

L.Naeger, FDA Clinical Virology review of ledipasvir/sofosbuvir

- Relapse rates -2% to +20% in those with baseline PMs versus those without
- Consistent trend of higher relapse rates for “less intense” regimens
- Presence of multiple key NS5A polymorphisms (rare) had greatest impact
- Impact of PMs minimized with regimens recommended in labeling: 12 weeks for most patients, 24 weeks for cirrhotic tx-exp.; 8-weeks can be considered but only for non-cirrhotic with low baseline HCV RNA

Pooled LDV/SOF Relapse Rate for Recommended Regimens

GT1a, any change at NS5A positions 28, 30, 31, 58, or 93



OBV/PTV/r + DSV (GT1a)

Baseline Polymorphism	M11-652 3-DAA +/- RBV (8-24W)	M11-652 3-DAA +/- RBV (12-24W)	Estimated Phase 3 3-DAA +/- RBV (12-24W)*
NS3 K80	79/90 (88%)	65/71 (92%)	89%
w/o NS3 K80	121/130 (93%)	95/100 (95%)	97%
NS5A Polymorphism	39/43 (91%)	28/30 (93%)	91%
w/o NS5A Polymorphism	165/181 (91%)	140/149 (94%)	96%
NS3 K80 or NS5A Polymorphism	103/116 (89%)	84/91 (92%)	92%
NS3 K80 and NS5A Polymorphism	15/17 (88%)	9/10 (90%)	Not Determined
No NS3 K80 or NS5A Polymorphism	86/93 (92%)	70/74 (95%)	98%
NS5B Polymorphism	17/18 (94%)	11/12 (92%)	97%
w/o NS5B Polymorphism	210/229 (92%)	172/182 (95%)	95%

P.Harrington, FDA Clin. Virology review of OBV/PTV/r+DSV

- Low impact (~0-8%) of NS3 Q80K or NS5A polymorphisms in Phase 2b/3 trials
- Label recommendations maximize efficacy (and minimize tx-emergent resistance) for all subjects regardless of baseline polymorphisms
- 2-3% GT1a failure rate for recommended regimens indicates polymorphisms (present in most GT1a patients) did not have a substantial impact on efficacy

Daclatasvir/Asunaprevir (GT1b)

Kumada et al., Hepatology 2014 Jun;59(6):2083-91 (Supp. Table 1)

Treatment Group	Baseline		After Virologic Failure	
	NS5A[a]	NS3[b]	NS5A	NS3
Interferon-Ineligible/Intolerant	L31M (n=1) Y93Y/H (n=6) Y93H (n=5)	D168E (n=1)	L28M-R30Q-L31I-Y93H (n=1) L28M-R30Q-Y93H (n=1) L28M-R30Q (n=1)[c] R30Q-L31M-P58S-Y93H (n=1) L31M/V (n=1)[d] L31I-Y93H (n=1) L31M-Y93H (n=1) L31M-Q54H-Y93H (n=5) L31V-Y93H (n=5)[e]	V36G, T54S, Q80L, D168E (n=1) T54S (n=1)[d] N77S, Q80L, D168E (n=1) S122G (n=2)[c] D168E/T/V/Y[f] (n=8) Q80L, D168V (n=1) S122G, D168E (n=1) No variant (n=2)
Subtotal	**n=12**	**n=1**	**n=17**	**n=17**
Nonresponder	L31M (n=4) Y93Y/H (n=3) Y93H (n=2) L31V,Y93H (n=1)		L28M-R30H-Q54H-Y93H (n=1) L28M-R30Q-Y93H (n=1) L31M-Y93H (n=3) L31M-Y93N (n=1) L31M-Q54H-Y93H (n=1) L31M-Q54Y-Y93H (n=1) L31V-Y93H (n=3)[g] L31V-Q54H-Y93H (n=5) ΔP32 (n=1)	N77S, S122G, R155Q (n=1) V78A, D168T (n=1) D168E/V/Y (n=9) Q80L, D168V (n=1) Q80L,S122G, D168A (n=1) S122G, D168E/T/V/Y (n=4)
Subtotal	**n=10**	**n=0**	**n=17**	**n=17**
TOTAL	**n=22[e]**	**n=1**	**n=34**	**n=34**

- Clear impact of baseline NS5A L31M/V and Y93H polymorphisms: "11/23 interferon-ineligible/intolerant patients and 4/14 nonresponder patients achieved SVR."
- Clear resistance consequences with failure in those with pre-existing polymorphisms
- Lack of phenotypic impact does not preclude clinical relevance:
  - L31M, L31V and Y93H alone cause 3- to 15-fold reduction in DCV anti-HCV activity in GT1b replicon (minimal for an NS5A inhibitor) (Lontok et al., Hepatology 2015)

Daclatasvir + Sofosbuvir (GT3)

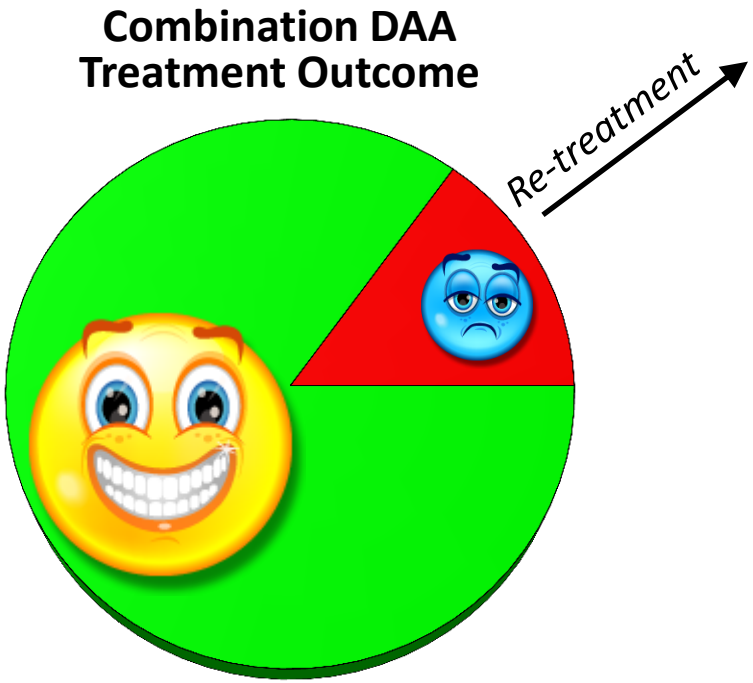
Table 8. SVR12 rate according to detection of Y93H polymorphism and cirrhosis status.

	n	# Failure	#SVR	SVR rate
All subjects:				
Y93H	13	6	7	54%
No Y93H	135	11	124	92%
Cirrhotic subjects:				
Y93H	4	3	1	25%
No Y93H	28	9	19	68%
Noncirrhotic subjects:				
Y93H	8	3	5	63%
No Y93H	97	1	96	99%

P.Harrington, FDA Clin. Virology review of daclatasvir

- Clear impact of Y93H polymorphism
- Low or no NS5A inhibitor resistance consequence of failure
  - Y93H alone confers >3,000-fold further reduction in DCV activity
  - No other major NS5A resistance-associated substitutions emerged in failures who already had the Y93H polymorphism
- Assay for screening was not commercially available

Re-Treatment Following DAA Failure



Must Address These Challenges:

1. <u>Baseline characteristics that reduced efficacy of 1st line DAA regimen, such as:</u>
   - Poor IFN/immune status and IL28B unfavorable GT
   - HCV GT 1a or GT3
   - High HCV RNA levels
   - Natural drug resistance polymorphisms
   - Advanced disease
   - Poor drug PK
   - Poor adherence or tolerability
2. <u>AND…</u>
   - Treatment-emergent DAA resistance (possibly across multiple classes)
   - Any further disease progression or other comorbidities

To screen or not to screen for polymorphisms...

Favoring Screening	Screening Not Necessary
Clear impact on efficacy	No clear impact on efficacy
Significantly impacts U.S. Population	Very low (<<5%) overall virologic failure rates in population
Assay commercially available	No commercially available assay
Reasonable alternative treatment options available (including waiting)	Alternative treatment options not available
Resistance consequences of failure	Minimal resistance consequences of failure
Limited or no re-treatment options	Reasonable re-treatment options available
Clinical consequences of failure	Minimal clinical consequences of failure

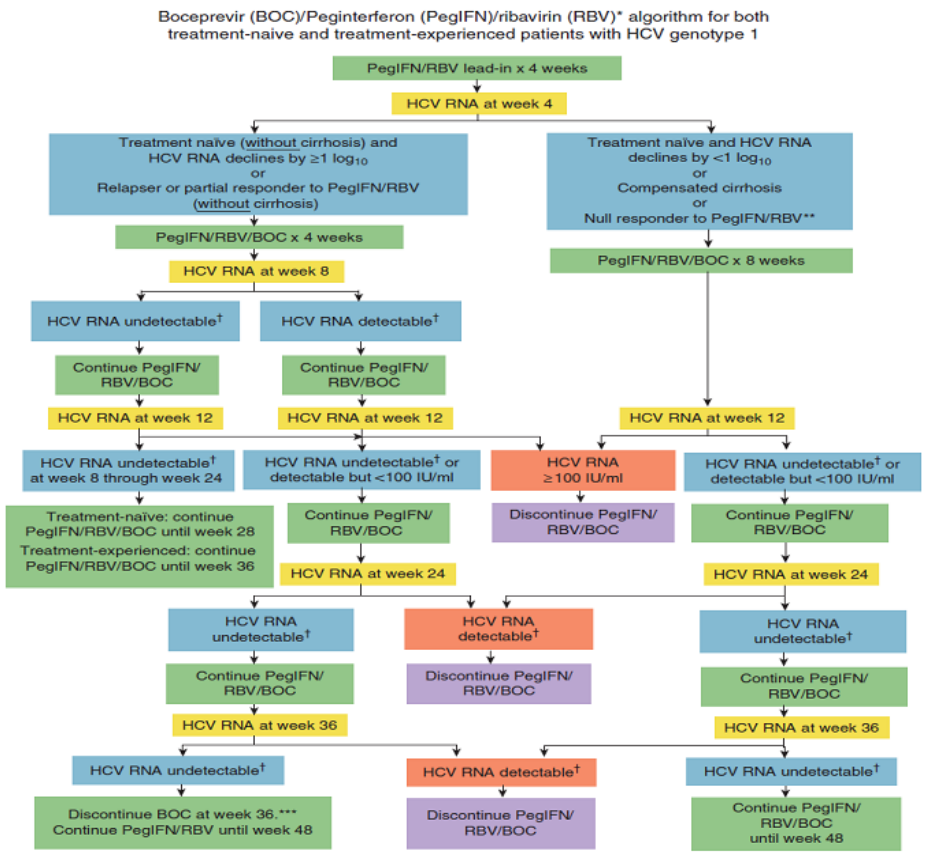
Factors Generally Not Considered

Cost

Complicating the treatment algorithm

Resistance testing is relatively simple...

Response-Guided Therapy



VA boceprevir treatment algorithm

Cirrhosis Determination in Trials (e.g.)

8) Cirrhosis determination [approximately 20% of study subjects may have cirrhosis]:

a) Cirrhosis is defined as any one of the following:

i) Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥ 5)

ii) FibroTest® score of > 0.75 AND an AST: platelet ratio index (APRI) of > 2 during Screening

b) Absence of cirrhosis is defined as any one of the following:

i) Liver biopsy within 2 years of Screening showing absence of cirrhosis

ii) FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 during Screening

c) In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required; liver biopsy results will supersede blood test results and be considered definitive.

Afdhal N, Reddy KR, Nelson DR, et al. N Engl J Med 2014;370:1483-93.

Resistance Test

Test: NS5A
Substitution Detected: Y93H

To screen or not to screen for polymorphisms...

Favoring Screening	Screening Not Necessary
Clear impact on efficacy	No clear impact on efficacy
Significantly impacts U.S. Population	Very low (<<5%) overall virologic failure rates in population
Assay commercially available	No commercially available assay
Reasonable alternative treatment options available (including waiting)	Alternative treatment options not available
Resistance consequences of failure	Minimal resistance consequences of failure
Limited or no re-treatment options	Reasonable re-treatment options available
Clinical consequences of failure	Minimal clinical consequences of failure

Factors Generally <u>Not</u> Considered

Cost

Complicating the treatment algorithm

Thanks to the following FDA/DAVP HCV DAA review team members...

Clinical Virology Reviewers

Damon Deming, PhD
Eric Donaldson, PhD
Takashi Komatsu, PhD
Lalji Mishra, PhD
Lisa Naeger, PhD
Jules O'Rear, PhD, Team Leader

Clinical Reviewers

Sarita Boyd, PharmD
Wendy Carter, DO
Sarah Connelly, MD
Russ Fleischer, PA-C,MPH, Acting TL
Poonam Mishra, MD, Dep. Dir. Safety
Adam Sherwat, MD, Team Leader
Kim Struble, PharmD, Team Leader

Debbie Birnkrant, MD, Division Director
Jeffrey Murray, MD, MPH, Deputy Division Director

New HCV Resistance Template !?

HCV VERTICAL RESITANCE ANALYSIS TEMPLATE (DRAFT)

VERSION: AUGUST 2015

Introduction

This document describes data standards for the creation of analysis datasets to support the review conducted by FDA virologists in the Division of Antiviral Products (DAVP) for submissions which contain a drug resistance analysis component. The data standards presented below include the following three categories of variables: 1) subject level characteristics, 2) pharmacogenomics results, and 3) phenotypic results. Most of the subject level characteristics would be traceable to the ADaM ADSL analysis dataset. In SDTM, the PF and MS domains contain the pharmacogenomic data and phenotypic data, respectively.

- Simplified, vertical analysis dataset structure, fewer columns
- Eliminates many unnecessary or redundant variables
- Data are traceable to ADaM and SDTM datasets
- Variables for reporting NGS analysis data
- Will be used to update/finalize HCV resistance guidance
- May be used in the future for other viruses