SVR12 OUTCOMES FOR NOVEL HCV GENOTYPE/SUBTYPES WITH SOF/VEL IN A5360 (MINMON) STUDY

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BACKGROUND

- The characterization of response to direct antiviral agents for rare or novel HCV subtypes is important for global elimination strategies.
- Genotypes (GT) 1, 2, 3, 4 and 6 are comprised of multiple subtypes with a high degree of genetic variability.
- Certain rare subtypes (e.g., 3b or 4r) frequently possess resistance associated substitutions (RASs) and may have lower response rates to DAA therapy.[1-3]
- Here, we describe the identification of novel GT-4 subtypes and a GT-7 HCV isolate distinct from 7a and 7b and their sustained virologic response (SVR) outcomes.

METHODS

- A5360 [MINMON] was a phase 4 open-label study of minimal monitoring with 12 weeks sofosbuvir/velpatasvir (SOF/VEL) for treatment-naive HCV infection.
- **399 participants** were enrolled across 38 sites in Brazil (n=131), South Africa (n=12), Thailand (n=110), Uganda (n=15) and the USA (n=132).
- Amplicon-based deep sequencing analyses of NS3, NS5A and/or NS5B were conducted for all baseline samples. HCV full genome using random primer Nugen amplification followed by Illumina MiSeq sequencing was performed on plasma samples which failed standard amplification.
- Nucleotide Blast analysis followed by phylogenetic analyses was used to confirm HCV subtype.

RESULTS

- In MINMON study, **SVR12 was achieved in 95%** (379/399) of participants.[4]
- For 389 participants, HCV subtype was assigned based on close genetic relationship to described subtypes.
- However, for 7 participants from Brazil, South Africa and Uganda, sequences obtained from plasma HCV RNA showed <85% sequence homology to all known HCV subtype reference strains.

In MINMON study, 95% of participants achieved SVR12.
A new strain of **HCV subtype 7c** and
novel subtypes of **GT-4** were identified.
Despite the presence of NS5A and NS5B RASs,
all participants with novel subtypes of GT-4 and GT-7 HCV
treated with SOF/VEL achieved SVR12 (100% SVR12).

Table 1. Genotype/Subtypes# with Geographic Locations of Participants

HCV GT/Subtype, n	Brazil	South Africa	Thailand	Uganda	USA	Total
1	**94**	**2**	**63**		**89**	**248**
1a	45	1	59		73	178
1b	49	1	4		16	70
2	**4**	**2**			**20**	**26**
2a		1			1	2
2b	3				19	22
2c	1	1				2
3	**28**	**2**	**33**		**17**	**80**
3a	28	2	24		17	71
3b			9			9
4	**4**	**1**	**1**	**10**	**3**	**19**
4a					2	2
4d	4		1		1	6
4q				1		1
4r		1		1		2
4v				8		8
5		**3**				**3**
5a		3				3
6			**10**			**10**
6f			3			3
6i			1			1
6m			1			1
6n			5			5
Unresolved subtypes*	**1**	**2**	**1**	**5**	**1**	**10**
No Data			**2**		**1**	**3**
Total	**131**	**12**	**110**	**15**	**131**	**399**

Genotype/subtype determination by standard amplification of NS3, NS5A and NS5B.
*HCV full-genome sequencing was applied to samples with unresolved subtypes

Figure 1. Participants With Unresolved HCV Genotype/Subtype

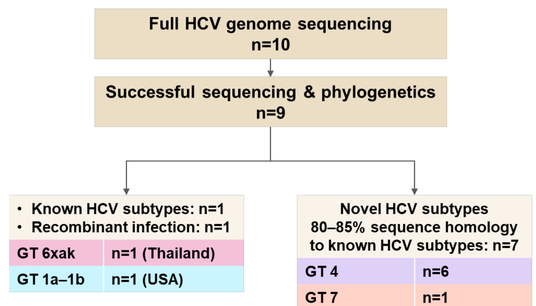
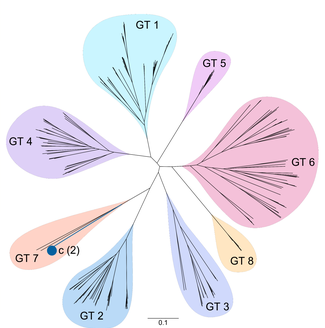


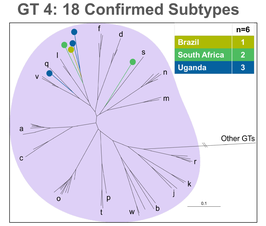
Figure 2: Maximal Likelihood Phylogenetic Tree*



*8841 nucleotides, including 68 of 86 confirmed subtypes and provisional GT 7c.

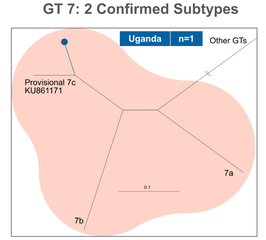
Novel HCV GT 4 Subtypes

GT 4: 18 Confirmed Subtypes



Novel HCV GT 7c Subtype

GT 7: 2 Confirmed Subtypes



Provisional GT 7c
- Isolate KU861171 was collected from Uganda[5]
- Likely a new GT 7 subtype, but only 1 isolate was found, which didn't meet the current classification guidelines (≥2 strains needed)

Table 2. NS3, NS5A, and NS5B Resistance-Associated Substitutions in HCV GT 4 With Novel Subtypes and GT 7 HCV Isolates

Sequence ID (Study)	GT	Rx	SVR12 (yes/no)	Country of Origin	RAVs		
					NS3	NS5A	NS5B
EF108306	7a	NA	NA	Canada (via DRC)	V36L, T54G, V55P, Q80D, D168Q	M28L, Q30S, H58P, A92S, Y93H	E237S, C289M
L89915 (Astral)	7b	SOF/VEL 12 wk	Yes	Belgium (via DRC)	V36L, V55A, Q80D, D168Q	M28L, Q30L, H58P, Y93H	E237C, C289F
KU861171	7c	NA	NA	Uganda	V36L, Q80E, D168Q	Q30S, H58G, Y93H	E237N, C289M
1241918 (A5360)	7c	SOF/VEL 12 wk	**Yes**	Uganda	No coverage	No coverage	No coverage
1241903 (A5360)	4	SOF/VEL 12 wk	**Yes**	Uganda	V36L	M28L, Q30R, H58L	C289F
1241909 (A5360)	4	SOF/VEL 12 wk	**Yes**	Uganda	No coverage	M28L, Q30R, L31M, H58P	C289F
1241910 (A5360)	4	SOF/VEL 12 wk	**Yes**	Uganda	V36L	Q30R, L31M, H58P	None
892840 (A5360)	4	SOF/VEL 12 wk	**Yes**	South Africa	V36L	M28L, Q30L, L31M, H58P	C289F
1112511 (A5360)	4	SOF/VEL 12 wk	**Yes**	South Africa	No coverage	Q30C, L31M, H58P	No coverage
1241901 (A5360)	4	SOF/VEL 12 wk	**Yes**	Uganda	No coverage	Q30R, L31M, H58P	No coverage

RESULTS

- Blast analyses of publicly available datasets revealed close homology to **a provisional GT-7c HCV isolate originating from Uganda** (KU861171).
- In addition, there were N=5 patients from Uganda and South Africa with GT-4 HCV that showed <85% amplicon homology to all known GT-4 subtypes.
- Presence of NS3, NS5A and NS5B resistance associated substitutions in GT-4 with novel subtypes and GT-7 HCV isolates are summarized in **Table 2**. The S282T RAS, that is associated with reduced susceptibility to SOF, was not found.
- All participants with novel subtypes of **GT-4** and **GT-7** HCV treated with SOF/VEL achieved SVR12 despite the presence of NS5A RASs and NS5B nucleos(t)ide RASs (**100% SVR12**).

CONCLUSIONS

- A new strain of HCV subtype 7c and novel subtypes of GT-4 were identified. SOF/VEL treatment for 12 weeks was efficacious against these novel strains of HCV.
- These findings highlight even greater genetic diversity of HCV subtypes than previously recognized. Global HCV elimination strategies need to monitor for HCV diversity and subsequent treatment responses.

References
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