RE-INFECTION FOLLOWING A MINIMAL MONITORING APPROACH FOR TREATMENT OF HEPATITIS C VIRUS INFECTION

722

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BACKGROUND

- MINMON (ACTG A5360) trial demonstrated that a minimal monitoring approach for HCV treatment with sofosbuvir-velpatasvir (SOF/VEL) was safe and efficacious in a diverse global population.
- In a phylogenetic analysis, we estimated HCV re-infection rates and resistance associated substitutions (RASs) among participants with post-treatment HCV RNA > lower limit of quantification (LLoQ).

METHODS

- HCV RNA evaluations were scheduled at weeks 0, 24 (SVR visit), 48 and 72 for MINMON participants.
- Samples with post-baseline HCV RNA >LLoQ and paired baseline samples underwent deep sequencing of NS5A and NS5B genes. Consensus sequences determined HCV genotype. FastTree generated phylogenetic trees; FigTree provided visualization.
- Participants whose post-treatment HCV sequence was different from baseline were defined as re-infection. Intermingling of sequences represented treatment failure.
- Re-infection rates were calculated using person-time of observation starting at the final reported date of SOF/VEL and ending at the earlier of HCV RNA >LLoQ or final study visit. Re-infection rates per 100 person-years (PY) were calculated with 95% confidence intervals constructed using Poisson distribution.

RESULTS

- Sustained virologic response (SVR) in the primary analysis was 95% [95% CI 92.4-96.7] (379/399). Of 397 participants who had post-entry HCV RNA, 29 participants had HCV RNA >LLoQ and sequencing data available for re-infection analysis.
- Of these, six participants initially designated as non-SVR, and 11 participants classified as cured experienced HCV re-infections by phylogenetic analysis at a later timepoint at week 48 or week 71 (**total 17 re-infections**).
- **The SVR adjusting for re-infection was 96.5% [95%CI 94.2-97.9] (385/399)** compared to the primary estimate of SVR of 95%.

In MINMON study, sustained virologic response (SVR) at week 24 was 96.5%, including 6 participants who experienced HCV re-infections before week 24 as responders.

HCV Re-infection rate was 3.9/100 PY [95%CI 2.4-6.2] and higer among men who have sex with men, HCV genotpye 1a, people with HIV and those reporting current injection drug use at entry.

Table 1. Incidence rate of HCV Reinfection in MINMON study

		Number of Reinfection	Number of Participants	Total Person-years of follow-up	HCV Reinfection rate (per 100 person years)	95% CI
Overall		17	397	438	3.9	2.4, 6.2
Age	<30	2	32	32	6.3	1.6, 25.2
	30-50	15	206	231	6.5	3.9, 10.8
	>50	0	159	175	0	
Baseline Genotype	1	16	247	272	5.9	3.6, 9.6
	3	1	80	84	1.2	0.2, 8.4
	Other	0	69	80	0	
Country	USA	2	129	131	1.5	0.4, 6.1
	Brazil	2	131	154	1.3	0.3, 5.2
	Thailand	13	110	122	10.7	6.2, 18.3
	Uganda	0	15	18	0	
	South Africa	0	12	13	0	
HIV co-infection Status	HIV-1 infection absent	2	232	259	0.8	0.2, 3.1
	HIV-1 infection present	15	165	178	8.4	5.1, 13.9
Self-Endorsed Race	White	3	164	184	1.6	0.5, 5.1
	Black or African American	1	72	76	1.3	0.2, 9.4
	Asian	13	113	123	10.6	6.1, 18.2
	Native Hawaiian or other Pacific Islander	0	1	1	0	
	Not reported	0	47	54	0	
Self-Reported Injection Drug Use at Entry	Current	2	15	16	12.3	3.1, 49.3
	Previous	6	119	130	4.6	2.1, 10.2
	Never/Not evaluated	9	263	291	3.1	1.6, 5.9
Sex at Birth and MSM endorsement	Female	0	138	157	0	
	Male, endorse MSM	13	64	65	19.9	11.5, 34.2
	Male, unknown	4	195	215	1.9	0.7, 5.0

If incidence rate is 0, confidence interval is not applicable. Abbreviations: MSM, men who have sex with men; CI, confidence interval.

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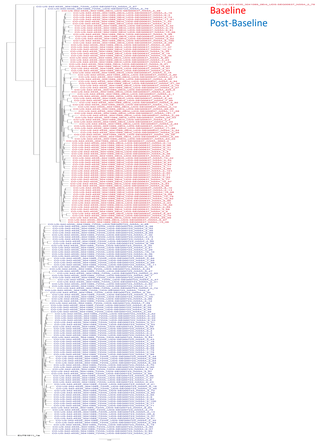


Figure 1. Phylogenetic tree* demonstrating probable reinfection.
*Genotype 1a NS5A position 350-500 (nucleotide coordinates)

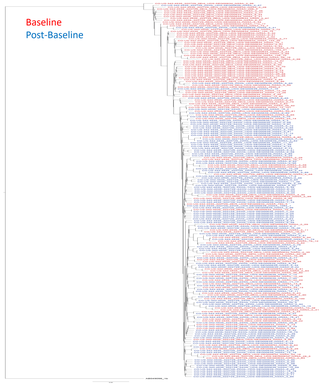


Figure 2. Phylogenetic tree* demonstrating probable relapse.
*Genotype 3a NS5A position 350-500 (nucleotide coordinates)

Table 2. Baseline and post-treatment NS5A VEL-specific RASs for participants with HCV failure

PID	Study Week of Relapse	Study Visit of Relapse	Baseline HCV Genotype	Baseline VEL Resistance	Baseline VEL-Specific RASs	Post-Treatment VEL Resistance	Post-Treatment VEL-Specific RASs
1	22	UNPLANNED	1b	RESISTANT	Y93Y/H	NOT RESISTANT	
2	23	WEEK 24 VISIT	1a	NOT RESISTANT		NOT RESISTANT	
3	24	WEEK 24 VISIT	1a	NOT RESISTANT		NOT RESISTANT	
4	24	WEEK 24 VISIT	3a	NOT RESISTANT		RESISTANT	Y93H
5	24	WEEK 24 VISIT	3b	RESISTANT	A30K, L31M	RESISTANT	A30K, L31M
6	24	WEEK 24 VISIT	3b	RESISTANT	A30K, L31M	RESISTANT	A30K, L31M
7	24	WEEK 24 VISIT	3a	NOT RESISTANT		RESISTANT	Y93H
8	24	WEEK 24 VISIT	3a	NOT RESISTANT		RESISTANT	Y93H
9	25	WEEK 24 VISIT	1a	NOT RESISTANT		RESISTANT	Y93Y/H
10	25	WEEK 24 VISIT	1a	NOT RESISTANT		NOT RESISTANT	
11	25	WEEK 24 VISIT	3a	NOT RESISTANT		NOT RESISTANT	
12	29	SVR EVALUATION VISIT	1a	NOT RESISTANT		NOT RESISTANT	

No participants with HCV failure or re-infection had resistance to SOF at baseline or post-treatment.

RESULTS

- Of all participants, 17 had re-infection during 438 person-years of follow-up (**re-infection rate 3.9 per 100 PY [95% CI 2.4-6.2**]). Of 17 re-infections, 12 were from HCV RNA collected at week 48 or 72. All 17 participants with HCV re-infection were assigned male sex at birth (13 endorsing MSM), 15 living with HIV, 14 had baseline genotype 1a, and 13 were from Thailand (of whom 11 were MSM with HIV and genotype 1a) (**Table 1**).
- At baseline, VEL-specific RASs were detected in three of the 12 participants (25%) who experienced HCV treatment failure and in 43 of 385 participants (11%) who either achieved SVR or were re-infected.
- Four participants without SVR or who later experienced HCV RNA relapse had developed VEL-specific RASs post-treatment (all with Y93H or Y93Y/H) (**Table 2**). Two participants with confirmed HCV re-infection and without baseline resistance also had VEL-specific RAS post-treatment (1 with Y93H and another with F28V, T93S).
- The SVR among those with and without baseline RASs was 94% (43/46) and 97% (324/351), respectively.

CONCLUSIONS

- Considering re-infections, **SVR observed in MINMON was 96.5%**.
- The high HCV reinfection rate even prior to SVR, especially among MSM living with HIV underscores the need to scale-up evidence-based interventions to reduce re-infection while simultaneously increasing screening and treatment to minimize HCV viremic burden in the population.

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