

Hepatitis C (HCV) Viral Kinetics: Changes in HCV Viral Load During the First Two Weeks Are Associated with Virologic Response But Are not Affected by HIV Status

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UPDATED ABSTRACT

Background: HIV/HCV patients respond poorly to pegylated interferon and ribavirin therapy. We asked whether HIV-infection impacted first or second phase decline to yield the poorer virologic responses (fewer SVR) generally observed with HIV. We compared viral kinetics in a prospective, homogeneous cohort with and without HIV.

Methods: All patients received pegylated interferon alfa-2a with weight based ribavirin. HCV viral load (VL) was measured using VERSANT® 3.0 HCV RNA (bDNA) at baseline, 4, 8, 12, 18, 24, 28, and 32 hours, then day 2, 3, 4, 7, 9, 11, 14, 21, 28, 42, 56, and 12 weeks. SVR and HIV status was compared to baseline log HCV VL, HCV VL at day 2, first phase decline, second phase decline, and rebound HCV VL at day 7 by the Wilcoxon Rank Sum test. Relationship between rebound at end of first week and first phase decline, second phase and day 2 viral load, and second phase slope and first phase decline was examined with Spearman's correlations.

Results: Fifteen HCV genotype 1 Caucasians, (9 HIV+, 6 HIV-) were treated. SVR was achieved in 5 (2 HIV+, 3 HIV-; 7 were non-responder/relapser (NR) (5 HIV+, 2 HIV-). 2 are still on therapy, and 1 withdrew prior to 12 weeks. No differences were observed between HIV+ vs HIV- for viral kinetic parameters, yet those who achieved SVR had lower median baseline log HCV RNA (5.56 vs. 6.13), p=0.01. Rate of first phase decline was not associated with SVR; second phase showed greater decline in those with SVR, (0.67 vs 0.24 p=0.09). However, the magnitude of log HCV RNA decline between week 1 and 2 was larger with SVR (0.67 vs 0.15) p=0.005, while rebound at day 7 was associated with non-response (-0.27 SVR vs 0.65 NR) p=0.005. No correlation existed between rebound at end of first week and slope of first phase. Second phase decline was faster in those with a lower HCV viral load at day 2, r = -0.67, p=0.009.

Conclusions: HIV status does not affect rate of first and second phase viral decline. Lower baseline HCV VL is associated with response to HCV therapy. A faster second phase decline occurred in those with a faster first phase and lower day 2 HCV VL. Rebound of HCV VL after 1 wk may indicate a lower likelihood of SVR. SVR was associated with better decline of HCV VL within the first 2 weeks of therapy. An early indicator of poor response may be early rebound of HCV VL at day 7. Lower response in HIV patients may, in part, be due to higher baseline HCV VL but is not due to rate of first and second phase decline.

INTRODUCTION

HIV/HCV coinfecting patients response to pegylated interferon and ribavirin (SVR) in genotype 1 ranges from 17-38% which is lower than the response rates (43-52%) in those with HCV alone.

Examining viral kinetic parameters has helped us gain insight on what factors predict response. For example using kinetic models, it was found that mean efficacy of IFN in blocking HCV production was significantly lower in genotype 1 than genotype 2 at 48 hours. In addition, genotype 2 subjects had a faster infected-cell death rate than genotype 1. Thus inherent differences at the genotypic level helped predict response to IFN therapy.

Similarly, African Americans with genotype 1 have delayed first phase kinetics and second phase compared to Caucasians. In this case, perhaps host factors may play a role in impairing response to IFN therapy and clearing virus.

Does HIV-infection lead to lower first and second phase declines? Comparison between HIV/HCV coinfecting to HCV monoinfected have been limited either by having a racially mixed group and/or a mix of different genotypes which may confound the viral kinetic parameters measured.

We sought to examine viral kinetics in a prospective study using pegylated interferon and weight based ribavirin in genotype 1, Caucasian patients with and without HIV-infection.

METHODS

All patients received pegylated interferon alfa-2a 180 mcg weekly with ribavirin at 1000 mg or 1200 mg (<75kg or ≥75 kg) per day.

HCV viral load (VL) was measured by VERSANT® 3.0 HCV RNA (bDNA) at baseline, 4, 8, 12, 18, 24, 28, and 32 hours, then day 2, 3, 4, 7, 9, 11, 14, 21, 28, 42, 56, and 84 (week 12).

Sustained virologic response (SVR) and HIV status was compared to baseline log HCV VL, HCV VL at day 2, first phase decline, second phase decline and rebound HCV VL at day 7 by Wilcoxon Rank Sum test. First phase decline measured by change in HCV RNA from baseline to 48 hours. Second phase decline measured by HCV RNA decline from day 7 to day 28. Relationship between rebound at end of first week and first phase decline, second phase and day 2 viral load, and second phase slope and first phase decline was examined with Spearman correlations.

Viral load kinetic parameters were estimated using the equations described by Neumann et al. Nonlinear regression models using the Marquardt algorithm were run to obtain the parameters, V_0 , t_0 , c , and for each patient using data from day 0 to day 2. The kinetic parameters were compared between the mono-infected and co-infected groups with the Wilcoxon Rank Sum test.

RESULTS

Table 1: Patient demographics, HIV status, baseline laboratory and clinical outcomes in HIV/HCV or HCV genotype1.

Pt. No.	HIV status	Gender	Liver Biopsy Stage	ALT (U/L)	AST (U/L)	CD4 count Baseline (cells/mm ³)	Log HCV RNA baseline (IU/mL)	Outcome
1	Yes	M	2-3	137	78	344	6.85	Relapse
2	Yes	F	1-2	40	37	725	6.10	Relapse
3	Yes	M	4	13	22	1236	4.25	SVR
7	Yes	F	2	137	90	486	6.09	NR
10	Yes	F	N/A	61	69	594	6.25	NR
12	Yes	M	4	57	46	444	5.72	SVR
16	Yes	M	4	84	90	653	5.9	Relapse
24	Yes	M	3	65	43	352	6.85	ETR
26	Yes	M	1-2	86	59	861	4.50	EVr
5	No	F	4	96	83	---	6.16	Withdrew
6	No	F	1	19	17	---	5.58	SVR
8	No	F	1	69	48	---	5.77	SVR
9	No	F	1	72	46	---	4.91	SVR
15	No	M	2	37	32	---	5.75	Relapse
20	No	M	1	57	39	---	6.58	NR

EVr = >2 log drop at 12 weeks; ETR = undetectable viral load at week 48; SVR = undetectable viral load at 72 weeks; NR = lack of response at 12 or 24 weeks; relapse = viral rebound after 48 weeks.

Table 2: Results of fitting model to HCV RNA decline in the first phase.

Pt. No.	V_0 (log IU/mL)	t_0 (days)	c	e
1	6.76 (6.61-6.87)	0.63 (0.48-0.78)	7.62 (2.1-13.15)	0.95 (0.92-0.98)
2	6.13 (6.09-6.17)	0.53 (0.67-0.99)	1.42 (-1.11, 3.95)	0.57 (0.25-0.88)
3	4.25 (3.14-4.53)	0.05 (-0.28, 0.38)	4.25 (1.46-7.04)	0.97 (0.93-1.0)
7	6.14 (5.97-6.25)	0.33 (0.32-0.35)	Unable to estimate	0.37 (0.09-0.65)
10	6.22 (5.99-6.36)	0.33 (-0.02, 0.69)	4.58 (-1.15, 10.31)	0.87 (0.78-0.96)
12	5.74 (5.68-5.8)	0.64 (0.47-0.82)	3.37 (1.07-5.67)	0.75 (0.66-0.84)
16	5.76 (5.58-5.89)	0.48 (0.38-0.58)	7.8 (2.75-12.85)	0.92 (0.87-0.96)
24	6.83 (6.73-6.91)	0.58 (0.30-0.86)	2.1 (0.67-3.49)	0.99 (0.9-1.1)
26	5.2 (5.09-5.29)	0.67 (0.63-0.71)	14.9 (11.9-17.9)	0.99 (0.99-0.99)
5	6.18 (6.06-6.27)	0.21 (-0.19, 0.61)	1.67 (-0.34, 3.69)	0.69 (0.47-0.91)
6	5.56 (5.44-5.65)	0.32 (0.26-0.37)	Unable to estimate	0.28 (0.45-0.51)
8	5.84 (5.51-6.03)	0.73 (0.67-1.38)	1.49 (0.35-2.63)	1 (1.0-1.0)
9	4.87 (4.62-5.02)	0.69 (0.48-0.91)	5.76 (-0.08, 11.6)	0.92 (0.85-0.99)
15	5.75 (5.54-5.89)	0.11 (0.01-0.2)	12.0 (-1.14, 25.15)	0.79 (0.69-0.88)
20	6.5 (6.35-6.62)	0.62 (0.34-0.91)	4.22 (-0.14, 8.58)	0.85 (0.74-0.95)

V_0 viral load at baseline.
 t_0 delay (days) between start of treatment and onset of action
 c clearance rate of free virus (per day)
 e percent (%) efficacy of treatment in blocking viral production

Table 3: Viral kinetic parameters from model estimates and actual HCV RNA decline for first and second phase by coinfection status.

Viral Kinetic Parameters	HIV/HCV (n=9)	HCV (n=6)	P value
V_0	6.13 (4.25-6.85)	5.8 (4.87-6.50)	0.69
Epsilon (e)	0.92 (0.37-1.0)	0.82 (0.28-1.0)	0.58
Clearance (c)*	4.04 (1.42-14.95)	4.22 (1.49-12.0)	0.83
t_0	0.53 (0.05-0.67)	0.47 (0.11-0.72)	1.0
First phase decline	-0.95 (-1.46, -0.16)	-0.88 (-1.1, -0.09)	0.49
Second phase decline	0.30 (0.10-0.74)	0.38 (0.23-0.67)	0.55

*missing data

No differences were seen between HIV/HCV coinfecting and HCV monoinfected patients.

Table 4: Variables and relationship to SVR.

	SVR (n=5)	NR/Relapse (n=7)	P value
V_0	5.56 (4.25-5.84)	6.14 (5.75-6.76)	0.01
Epsilon (e)	0.92 (0.28-1.0)	0.84 (0.37-0.95)	0.53
Clearance (c)*	3.8 (1.49-5.76)	5.92 (1.42-12.0)	0.48
t_0	0.64 (0.05-0.73)	0.48 (0.11-0.63)	0.53
First phase decline	-0.82 (-1.46, -0.57)	-0.93 (-1.28, -0.16)	0.76
Second phase decline	0.67 (0.32-0.67)	0.25 (0.11-0.74)	0.09
Changes in HCV RNA at day 4	-1.07 (-1.046, -0.57)	-0.62 (-0.95, 0.00)	0.03
Rebound at day 7	-0.27 (-0.58, 0.0)	0.65 (-0.1, 0.91)	0.005
HCV RNA (<615 IU/mL) at 4 wk	4 (80%)	1 (12.5%)	0.01

*missing data

A greater magnitude of change in HCV RNA from baseline to day 7 and from day 7 to 14 was seen in those with SVR compared to those with NR/Relapse.
 SVR was not associated with first phase estimated parameters from the model.
 >1 log decline in HCV RNA by day 4 was associated with SVR.
 Rebound at day 7 was associated with non-response.
 Undetectable HCV RNA at 4 weeks was associated with SVR.

Figure 1: Log HCV RNA decline over time in those with HIV/HCV.

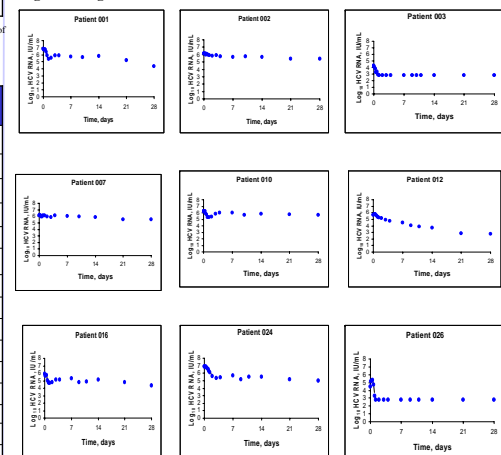


Figure 2: Log HCV RNA decline over time in HCV monoinfected patients.

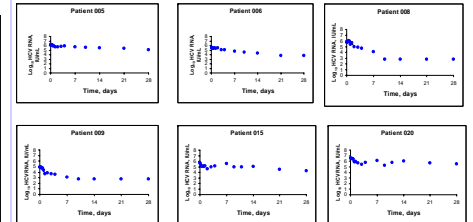
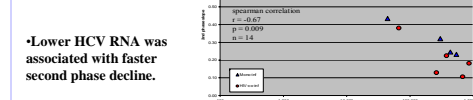


Figure 3: Relationship of log HCV RNA at day 2 and second phase slope.



Lower HCV RNA was associated with faster second phase decline.

SUMMARY & CONCLUSIONS

Early viral kinetics appears to be similar in those with HIV/HCV coinfection compared to those with HCV alone. Coinfected patients compared to those with HCV alone had similar first and second phase declines based on observed viral loads, and also had similar viral kinetic parameters based on the fitted model.

SVR was associated with lower baseline HCV RNA, and lower baseline HCV RNA was associated with faster second phase decline.

Non-response or relapse was associated with rebound of HCV RNA at day 7.

A trend towards those with a higher magnitude of second phase decline and SVR was seen, which may be due in part to a lower baseline HCV RNA.

Greater than 1 log decline at day 4 was associated with SVR regardless of HIV status.

Undetectable HCV RNA (<615 IU/mL) at 4 weeks was associated with SVR.

Higher baseline HCV RNA in coinfecting patients may be a reason for lower response rates but it is not due to the rate of first or second phase decline.

Our results may differ from others because of the prospective nature of our study, limitation of analysis to those with genotype 1 and Caucasians, and use of weight based ribavirin.

Larger number of patients are needed to confirm our findings.

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