The impact of adherence and an intervention program on patient outcomes and costs in chronic hepatitis C infection

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Abstract

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Background and aims: Both observational studies and randomized trials have shown that higher medication adherence is associated with improved outcomes in patients with chronic hepatitis C infection (CHC). Little evidence exists on the association between adherence and health care costs. We sought to evaluate the impact of adherence on long-term outcomes and costs in a population of patients with CHC genotype 1 receiving peginterferon and ribavirin (PEG-RBV). We also evaluated the impact of a potential intervention to improve adherence on long-term costs and patient outcomes.

Methods: We utilized a cohort Markov model describing the natural history of hepatitis C infection in a population of 50 year-old treatment-experienced adults to evaluate the following health states: CHC, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, liver transplant survivor, and death. Using previously published data from the HALT-C trial, we modeled four levels of medication receipt: >80% PEG-RBV, >80% PEG/<80% RBV, <80% PEG/<80% RBV, and <80% PEG-RBV. The costs and quality-adjusted life years (QALYs) associated with moving patients to higher level of adherence was compared

to the cost associated with a nursing-based intervention program. Time horizons of 5, 10, 20, 30 years and lifetime were evaluated.

Results: Over a lifetime horizon, we compared patients with the highest adherence versus lowest adherence, and found the following reductions in liver-related events: 9.9% compensated cirrhosis, 4.7% decompensated cirrhosis, 1.4% hepatocellular carcinoma, and 0.5% liver transplant. The potential cost savings over a lifetime as patients move from a cohort of lower SVR to greater SVR ranged from $12,820-$62,690, with a 1% increase in SVR associated with savings of $2137-$3284.

Conclusion: Interventions that increase patient adherence should improve outcomes in this population and have the potential to reduce costs.

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Background

Chronic hepatitis C infection (CHC) is estimated to affect over 3 million people in the United States. (1) CHC may progress to fibrosis, cirrhosis or hepatocellular carcinoma, and is the predominant cause of liver transplant in the United States.(2) Estimations of the direct economic costs of hepatitis C infection have varied from $694-$1,660 million per year. (3) In the U.S., the most common hepatitis C genotype is genotype 1; (4) patients with genotype 1 have been found to be less likely to achieve a sustained virologic response (SVR) compared to non-genotype 1 patients.(5)

The goal of hepatitis C treatment is to minimize disability and death by achieving sustained virologic response (SVR), as such a response is associated with lower mortality and morbidity.(6) Patients receiving less than 80% of prescribed medication for less than 80% of recommended treatment duration are at higher risk of viral relapse or not achieving SVR and progressing to CHC.(7-9) Until recently, standard of care treatment has been peginterferon and ribavirin.

Following the promising results of clinical trials, the NS3/4A protease inhibitors (PIs) boceprevir and telaprevir may become standard of care.(10) However, given the expense of protease inhibitors, with 12 weeks of telaprevir therapy estimated to cost approximately $49,000, and boceprevir costs ranging from approximately $26,000-$48,000 for 24-44 weeks of therapy, (11) assuring adherence to optimize ``outcomes is paramount for effective use. The potential for adherence must be assessed in patients prior to starting PI therapy, as failure to complete the recommended course of therapy may result in viral mutations precluding further PI treatment.(12)

Patients may not adhere to treatment for multiple reasons, including regimen burden (e.g. injections, number of pills, complexity of regimen), financial factors, treatment-related side effects, and comorbidities.(13) Side effects associated with treatment account for approximately 15% of treatment discontinuation in clinical studies (14) and 12-39% of e dose reductions.(15) Patient characteristics may also influence adherence. A recent study in a cohort of veterans found that preexisting substance abuse, diabetes, cirrhosis, depression, and use of hematopoietic growth factors predicted treatment dropout for genotype 1 hepatitis C virus (HCV) patients. (16)

Different intervention programs have been evaluated to increase patient eligibility for HCV treatment. A prospective, blinded, intervention trial found a difference of 24% in treatment eligibility and a 10% increase in medication initiation in subjects receiving the intervention compared to controls. (17) In a specialized Veterans Affairs (VA) hepatitis C clinic, patients receiving care from a co-located psychiatric clinic nurse specialist (PCNS) were significantly more likely to start and adhere to antiviral therapy than those not receiving such an intervention.(18) As baseline depression and social support have been found to be associated with reported symptoms during antiviral therapy such as fatigue, pain, headache, and irritability, (19) interventions focusing on well-being and mental health may help patients past side effects associated with therapy.

Given the limited data available in long-term outcomes of CHC patients and the evidence that targeted interventions may increase adherence, we sought to utilize data from previously published clinical trials to evaluate long-term patient outcomes and costs in a cohort of patients previously treated for HCV. Additionally, we quantified the difference in outcomes and costs resulting from a hypothetical intervention program to improve adherence.

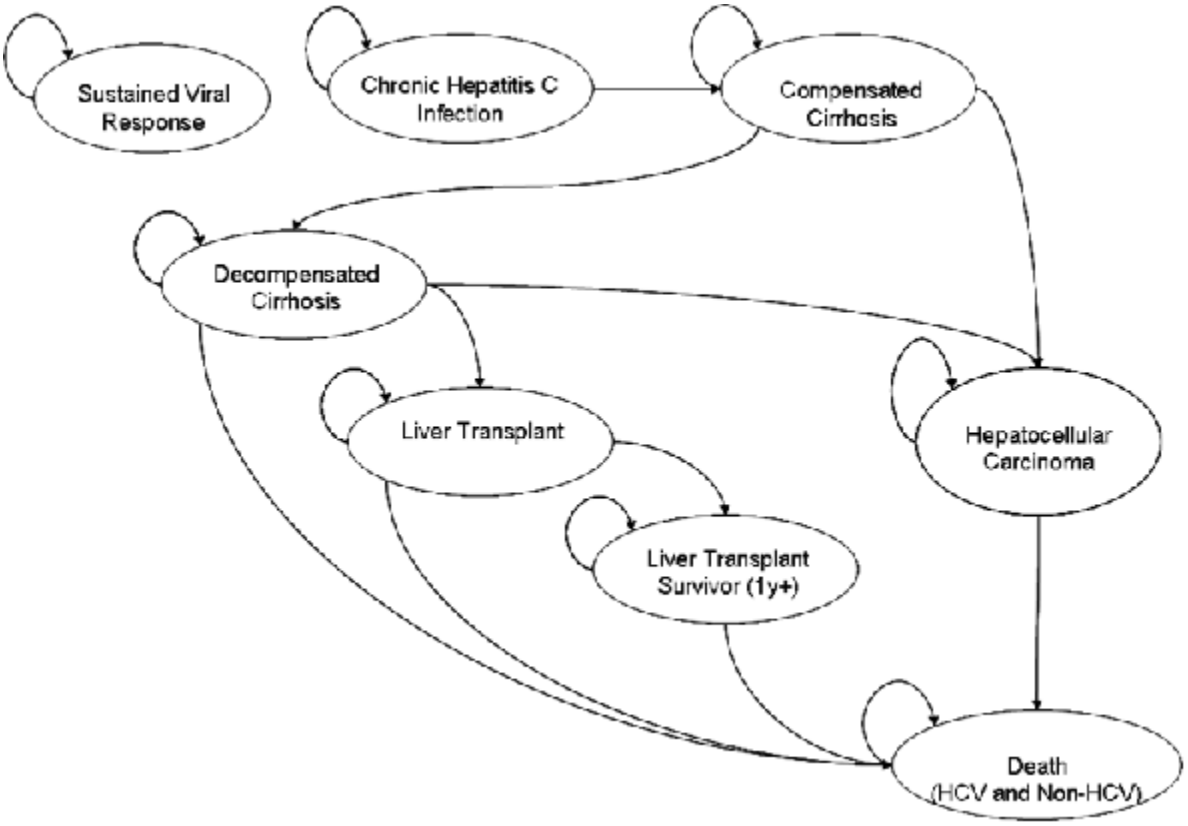
Methods

Analytical model

A Markov cohort simulation model, developed in Microsoft® Excel®, modeled the natural history of HCV infection and estimated the costs and outcomes for a population of treatment-experienced adults with genotype 1 HCV. The model included the following health states: CHC, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, liver transplant survivor, and death (Figure 1). The cycle length was 1 year and the model allowed for various time horizons (5 years, 10 years, 20 years, 30 years, and lifetime) to be evaluated.

The model input consisted of a hypothetical cohort of 1000 patients receiving peginterferon and ribavirin therapy with varying levels of adherence. Based on prior research, we defined adherence as greater than 80% of medication receipt.(9) The evaluation used a health systems perspective; we report costs, outcomes, survival, quality-adjusted survival, and quality-adjusted life years (QALY) gained with costs and outcomes discounted at 3% per annum.

Figure 1, Markov model



Inputs

Clinical data inputs

SVR and adherence

SVR and adherence data for this study are from the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial. The HALT-C trial was conducted between 2000 and 2003, and recruited 1145 patients who previously received interferon-based therapy with or without ribavirin who had persistent viremia. Patients received either pegylated interferon-alfa2a-based treatment or were monitored for disease progression; the methods of the HALT-C trial have been described previously.(20) Patients in the trial may have received sub-optimal doses of medication as the result of physician-directed changes or patient factors. Based on the

demographics of the HALT-C trial, the entry case for this model is a 50 year old Caucasian patient who previously received interferon-based therapy.

In this model, we utilized data from 269 patients observed over 48 weeks who received combination-based peginterferon-based therapy and at 20 weeks had undetectable HCV RNA (Table 1).(7) Medication receipt over 48 weeks' time (Table 2) was assumed to decrease with increasing time in therapy, (8, 16) with a greater reduction in medication receipt in patients who are less adherent to therapy overall.

Table 1, input parameters for Markov model

Description	Value	Reference
SVR for >80% PEG-IFN, >80% RBV	0.50	(7)
SVR for >80% PEG-IFN, <80% RBV	0.44	(7)
SVR for <80% PEG-IFN, >80% RBV	0.60	(7)
SVR for <80% PEG-IFN, <80% RBV	0.38	(7)
CHC->Comp. Cirrhosis	0.0730	(21)
Comp. Cirrhosis->Decomp Cirrhosis	0.0400	(21)
Comp. Cirrhosis->HCC	0.0100	(21)
Decomp Cirrhosis->HCC	0.0140	(22)
Decomp Cirrhosis->Liver Tx	0.0220	(23)
Decomp Cirrhosis->Death (HCV)	0.1380	(22)
HCC->Death (HCV)	0.4270	(22)
Liver Tx->LTx Survivor	0.7900	(22)
Liver Tx->Death (HCV)	0.2100	(22)
LTx Survivor->Death (HCV)	0.0570	(22)

Table 2, modeled medication receipt by scenario

Medication adherence scenario	Time in treatment and percent medications received							
	Week 4		Week 12		Week 24		Week 48	
	PEG	RBV	PEG	RBV	PEG	RBV	PEG	RBV
>80% PEG and RBV	100	100	90	90	85	85	80	80
>80% PEG, <80% RBV	100	100	90	80	85	70	80	60
<80% PEG, >80% RBV	100	100	80	90	70	85	60	80
<80% PEG and RBV	90	90	80	80	70	70	60	60

Health state transitions

Following a literature search to populate the Markov model, we utilized multiple studies for input parameters for health state transitions (Table 1). Studies included were a retrospective cohort study of 329 patients followed for 5 years (22) and a model which utilized a cross-sectional survey of German hepatitis patients.(23) Non-HCV related mortality rates were applied to all health states from the U.S. life tables. (24)

Hypothetical intervention program

The structure of a hypothetical program is based on an integrated care model used in a Minneapolis Veterans Affairs HCV specialty clinic. Among patients receiving integrated care from a PCNS, SVR was 7% higher than those not receiving the intervention. (18) We assumed that patients achieving SVR via the intervention did not experience viral relapse and did not contribute additional hepatitis-related costs over their lifetime.

Utility data

Markov state utilities are listed in Table 3. Multiple utilities are drawn from a systematic review of health-related quality of life utilities among chronic hepatitis C patients. (25) If multiple methods were reported for utility computation (e.g. Nichol, Fryback, and Schmuel), then we used mid-range utility values in the model. We also incorporated utilities constructed

using the time trade off method in interviews with 751 HCV patients. (26). An analysis of quality of life from 252 liver transplant patients followed over time informed the liver transplant-associated utility. (27) We assumed a disutility associated with peginterferon injections similar to the disutility associated with injection site reactions in other disease states.(28)

Table 3, utilities with health states

Description	Utility	Reference
Chronic hepatitis C infection	0.80	(26)
Compensated cirrhosis	0.780	(26)
Decompensated cirrhosis	0.690	(25)
Hepatocellular carcinoma	0.670	(25)
Liver transplantation	0.800	(26)
Liver transplantation survivor (+1 year)	0.895	(27)

Costs

HCV-related cost data (Table 4) is from an analysis of a managed care organization database for U.S. patients with chronic hepatitis C infection, using costs inflation-normalized to 2009 U.S. dollars. (29) In the model, patients who attain SVR do not contribute to future HCV-related costs.(30) Drug costs were calculated using wholesale acquisition costs. (11, 31) Based on previous studies, (8, 16) medication use was modeled to decline over time in each cohort of patients, utilizing published data on HCV medication persistence and adherence.(32)

We were unable to locate published information regarding the costs of an intervention program to increase adherence among patients receiving HCV therapy. Given this, we estimated the total cost of a hypothetical intervention program provided by skilled nurse managers at $800 per patient, based on an intervention among patients with bipolar disorder. (33)

Table 4, inputs for cost data

Markov annual costs	Value (USD)	Reference
Chronic hepatitis C infection	14,915	(29)
Compensated cirrhosis	16,911	(29)
Decompensated cirrhosis	41,943	(29)
Hepatocellular carcinoma	58,208	(29)
Liver transplantation	190,995	(29)
Liver transplantation survivor (+1 year)	54,885	(29)

Results

Natural history

Over a lifetime horizon in a cohort of 1000 patients, the model predicts 139-215 cases of decompensated cirrhosis, 43-67 cases of hepatocellular carcinoma, and 13-20 liver transplants (Table 5). As expected, patients with less adherence and thus lower SVR had a higher incidence of deleterious events across all time points. A 10% decrease in SVR resulted in 20 more cases of compensated cirrhosis and 5 more decompensated cirrhosis events (Table 6).

Table 5, patient outcomes in cohort of 1000 patients at various time points

Five years							
	CHC	CC	DCC	HCC	LT	LTS	Death
>80% both meds	359	117	7	2	0	0	29
>80% PEG-IFN, <80% RBV	402	131	8	2	0	0	29
<80% PEG-IFN, >80% RBV	287	94	6	1	0	0	29
<80% both meds	445	145	9	2	0	0	30
Ten years							
	CHC	CC	DCC	HCC	LT	LTS	Death
>80% both meds	236	185	24	4	0	1	84
>80% PEG-IFN, <80% RBV	264	207	27	5	0	1	86
<80% PEG-IFN, >80% RBV	189	148	19	3	0	1	80
<80% both meds	292	229	30	5	0	1	88
Twenty years							
	CHC	CC	DCC	HCC	LT	LTS	Death
>80% both meds	95	179	39	5	1	4	276

>80% PEG-IFN, <80% RBV	106	201	43	6	1	4	286
<80% PEG-IFN, >80% RBV	76	143	31	4	1	3	260
<80% both meds	118	222	48	7	1	4	295
Thirty years							
	CHC	CC	DCC	HCC	LT	LTS	Death
>80% both meds	31	100	26	3	1	4	560
>80% PEG-IFN, <80% RBV	34	112	29	3	1	5	574
<80% PEG-IFN, >80% RBV	25	80	21	3	0	3	538
<80% both meds	38	124	32	4	1	5	587

**CHC=chronic hepatitis C, CC=compensated cirrhosis; DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma; LT=liver transplant (0-12 month); LTS=liver transplant survivor (13+ months)

Table 6, cumulative outcomes over lifetime horizon in cohort of 1000 patients

	Medication regimens			
	>80% both meds	>80% PEG, <80% RBV	<80% PEG, >80% RBV	<80% both meds
Compensated cirrhosis	412	462	330	511
Decompensated cirrhosis	196	220	157	243
Hepatocellular carcinoma	62	69	49	76
Liver transplants	20	23	16	25

Health Care Costs

The cohort who received greater than 80% of both medications had average total discounted costs of $186,160 per patient, compared to $216,010 in the cohort receiving less than 80% PEG-RBV, a difference of $29,850 (Table 7). Patients with the highest SVR (>80% RBV/<80% PEG) had the lowest total costs at $153,320, whereas those receiving <80% RBV/>80% PEG had costs less than the least adherence cohort, but higher than the most adherent, at $203,190.

Treatment costs were $24,270 for patients receiving >80% of both medications, compared to $20,930 for those receiving <80% of both medications. The most compliant patients had follow-up costs of $16,140 versus follow-up costs of $15,020 for the least compliant patients.

Table 7, Average lifetime costs per patient

	Medication regimens			
	>80% both meds	>80% PEG, <80% RBV	<80% PEG, >80% RBV	<80% both meds
Treatment costs	24,270	24,070	21,130	20,930
Discounted treatment costs	23,570	23,370	20,520	20,320
Follow-up costs	16,140	15,720	15,720	15,020
Discounted follow-up costs	15,670	15,260	15,260	14,590
CHC costs	85,600	95,880	68,485	106,150
Discounted CHC costs	65,170	72,990	52,140	80,810
CC costs	85,958	96,270	68,770	106,590
Discounted CC costs	51,315	57,470	41,050	63,630
DC costs	39,620	44,380	31,700	49,130
Discounted DC costs	21,570	24,160	17,260	26,750
HCC costs	7,540	8,450	6,030	9,350
Discounted HCC costs	4,260	4,770	3,400	5,280
Liver transplant costs	3,870	4,330	3,100	4,800
Discounted LT costs	2,050	2,300	1,650	2,550
LTS costs	5,500	6,160	4,400	6,820
Discounted LT costs	2,550	2,890	2,040	3,160
Total costs of hepatitis and complications	228,090	255,460	182,472	282,830
Total discounted costs of hepatitis and complications	146,930	164,560	117,543	182,190
Sum of treatment and hepatitis costs	268,500	295,250	219,320	317,670
Sum of discounted treatment and hepatitis costs	186,160	203,190	153,320	216,010

**CHC=chronic hepatitis C, CC=compensated cirrhosis; DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma; LT=liver transplant (0-12 months); LTS=liver transplant survivor (13+ months)

Life years gained and QALYs

Life years gained and QALYs are listed in Table 8. Discounted treatment QALYs were lower among patient cohorts receiving more medication (0.54 QALY for >80% PEG/RBV vs. 0.58 across all other cohorts). Overall, discounted QALYs ranged from 14.23-15.26, a difference of 1.03 QALYs between the patients with lowest SVR and highest SVR. Comparing the lowest SVR to highest SVR, discounted life years gained ranged from 17.01 to 17.54, a difference of 0.53 life years gained.

Table 8, life years gained and quality adjusted life years (QALY)

	Medication regimens			
	>80% both meds	>80% PEG, <80% RBV	<80% PEG, >80% RBV	<80% both meds
Life years	26.72	26.40	27.26	26.08
Life years (discounted)	17.30	17.16	17.54	17.01
QALYs	22.19	21.79	22.87	21.38
QALYs (discounted)	14.37	14.16	14.71	13.95
Treatment QALYs	0.5563	0.5972	0.5991	0.5955
Treatment QALYs (discounted)	0.5401	0.5798	0.5816	0.5781
Overall QALYs	22.75	22.35	23.44	21.97
Overall QALYs(discounted)	14.91	14.70	15.26	14.53

Hypothetical intervention program

Assuming that a hypothetical intervention program resulted in increased adherence and increased SVR, we calculated the differences in events and costs between different levels of adherence. Lifetime differences and costs related to hepatitis-related events are noted in Table 9. The total cost savings associated with a 1% increase in SVR ranged from $2137-$3284. The incremental savings per avoided cases of compensated and decompensated cirrhosis $125 and $110, respectively. Savings related to hepatocellular carcinoma ranged from $510-$1880, with an average savings of $71 for each case avoided. Each liver transplant prevented saved $222 per event.

Table 9, differences in costs and events between different levels of adherence

	Medication regimens				
Beginning scenario	<80% both meds	<80% both meds	<80% both meds	>80% PEG, <80% RBV	<80% PEG, >80% RBV
Ending scenario	>80% both	>80% PEG, <80% RBV	<80% PEG, >80% RBV	>80% both	>80% both
SVR difference	12%	6%	22%	6%	(10%)
Total cost difference	$29850	$12820	$62690	$17030	($32840)
Savings per percent increase in SVR	$2488	$2137	$2850	$2838	($3284)
*Event difference**					
Compensated cirrhosis	99	49	181	50	(82)
Cost difference	$12315	$6160	$22580	$6155	($10265)
Savings per event avoided	$124	$126	$125	$123	($125)

Decompensated cirrhosis	47	23	86	24	(39)
Cost difference	$5180	$2590	$9490	$2590	($4310)
Savings per event avoided	$110	$113	$110	$108	($111)
Hepatocellular carcinoma	14	7	27	7	(13)
Cost difference	$1020	$510	$1880	$510	($860)
Savings per event avoided	$73	$73	$70	$73	($66)
Liver transplant	5	2	9	3	(4)
Cost difference	$1110	$520	$2020	$590	($910)
Savings per event avoided	$222	$260	$224	$197	($228)

*Numbers in () indicate a negative difference, e.g. loss in savings, decrease in SVR, and increase rather than decrease in events.

Discussion

In this analysis, we projected the effects of adherence on long-term patient outcomes and quantified the associated costs. While other studies have reported outcomes for patients in the first decade following therapy completion, (34-39) this study projects morbidity and mortality over a lifetime horizon for patients with CHC receiving retreatment. Additionally, we report the incremental differences in outcomes and costs associated with increases or decreases in SVR attainment. Such information may be used to inform the planning of intervention programs to increase adherence.

Over a lifetime horizon, the cohort with greater adherence had the following reductions in the liver-related events: 9.9% fewer compensated cirrhosis, 4.7% decompensated cirrhosis, 1.4% less hepatocellular carcinoma, and a 0.5% reduction in liver transplants when compared to those with the least adherence. We found that short-term costs were higher among patients with higher adherence, reflecting higher monitoring and medication costs. Treatment-related QALYs were lower, which is reasonable given the disutility associated with medication side effects and

injections. Overall discounted QALYs differed by 1.03 for the cohorts with lowest SVR compared to highest SVR.

Our cost calculations echo previous findings (29, 40, 41) that patients who are adherent to PEG-RBV are more likely to have higher short-term medication costs however those who achieve SVR will have lower hepatitis-related costs over time. The total discounted cost difference between various levels of adherence differed by $62,690 across cohorts with the lowest SVR and highest SVR; a 1% increase in SVR corresponded to an average cost savings of $2720.

There are several limitations to this study. As there are limited data regarding adherence and SVR for protease inhibitor therapy, this analysis is limited to costs and patient outcomes in those receiving PEG-RBV. This analysis should be repeated when data become available on medication receipt and SVR in patients receiving PIs. Limited data are available with respect to state transitions in non-white populations; additional data is needed to facilitate an analysis of a more diverse racial cohort.

In the HALT-C trial, 38% of retreated patients had already progressed to cirrhosis. It is possible that cirrhosis may play a role in patient adherence, and may have affected the observed adherence either as the result of physician-directed dose reductions to account for the condition of patient's livers, or as the result of patient factors such as illness from cirrhosis. However, we do not believe this factor changes the findings of this model because the projected patient outcomes for hepatocellular carcinoma, decompensated cirrhosis, liver transplantation, and death in our model are similar to published outcomes among HALT-C patients at 7.5 years who achieved SVR or had viral breakthrough/relapse following SVR.(42) We acknowledge that the HALT-C trial data is older than other published clinical trials however the availability of data

appropriate to populate this model with respect to adherence to combination therapy and SVR is limited.

As limited data exist to evaluate adherence and SVR, we utilized a subset of patients enrolled in the HALT-C trial with undetectable viral RNA at week 20 of treatment. For patients with data available at weeks 20-48, those with higher adherence to ribavirin (>80%) but lower adherence to peginterferon (<80%) had 10% higher SVR compared to patients who had greater than 80% adherence to both medications. However, we do not advocate changes in peginterferon adherence to increase SVR. First, we utilized data from a subset of study patients that may have had underlying characteristics which differed from other participants. Overall, the HALT-C investigators found that decreasing both peginterferon and ribavirin in the first 20 weeks of therapy decreased SVR. (7) Additionally as adherence to peginterferon is associated with adherence to ribavirin, (8) it is unknown if patients who discontinue one drug would then be adherent to the other drug.

This analysis describes the long-term outcomes and associated costs of non-adherence to peginterferon-ribavirin therapy among CHC patients. We have evaluated such costs compared to a hypothetical intervention program, and found that such an intervention program may be cost saving and improve patient outcomes. Further research should explore adherence and patient outcomes among patients receiving PI therapy and patients in more diverse cohorts.

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