The Identification and Treatment of Medicaid Recipients with Hepatitis C

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EXECUTIVE SUMMARY

The estimated prevalence of hepatitis C virus (HCV) in the U.S. is at least 1.8% of the population, although high HCV prevalence rates (15-50%) occur in specific subpopulations such as the homeless, incarcerated persons, and injection drug users. Consequently it is thought that HCV is highly prevalent among the uninsured and publicly funded programs. The prevalence of HCV infection and the feasibility of management and treatment in these populations was designated as an important area for research by the NIH.

According to the 2002 NIH Consensus Conference HCV is a leading cause of cirrhosis, a common cause of hepatocellular cancer, and the leading cause of liver transplantation in the United States. Because most persons with chronic HCV infection have not yet been diagnosed, the number of adults with compromised liver function may increase four-fold from 1990 to 2015.

The NIH treatment guidelines for HCV call for weekly injections of pegylated-interferon in combination with daily ribavirin by mouth. Treatment for 24 weeks appears to produce a sustained viral response in 73-78% of persons with genotypes 2 and 3, whereas 48 weeks of treatment produce a sustained viral response in 51% of those with genotype 1. Significant side effects often result in premature discontinuation of treatment.

The aim of this study was to estimate the prevalence of HCV in the Florida Medicaid program, examine patterns of treatment according to NIH guidelines and expenditures incurred by Medicaid.

FINDINGS AND POLICY IMPLICATIONS

- The prevalence of HCV documented among Florida Medicaid adult recipients by this analysis was less than one percent. This is well below national estimates of 1.8% for the population in general, and far below the estimated prevalence in sub-populations known to be at higher risk. This estimate suggests that there are a significant number of persons in the Florida Medicaid program with HCV that is not diagnosed or documented.

- Among the 15,612 persons whose records included a diagnosis of HCV, one-third had fibrosis or cirrhosis of the liver, 103 had cancer of the liver and 275 had received a liver transplant. Conversely, among the 718 persons identified with a liver transplant, 40% had a diagnosis of HCV.

- From FY2000 through FY2003, there was a record of HCV treatment for approximately 15% of persons whose records carried a diagnosis of HCV.

- Out of 1,657 persons receiving a single course of treatment, about one-third reached the recommended duration of 24 weeks therapy for genotype 2 or 3.

Less than 10% received the full course of 48 weeks of treatment that is recommended for genotype 1.

- An additional 438 persons received multiple episodes of treatment ranging from 2-7 episodes over the 4-year observation period. This group represents persons on long term maintenance therapy or persons who terminated treatment prematurely and subsequently were re-treated.

- Considering all patients treated for HCV with either single or multiple episodes of therapy, 13% received at least one episode of treatment over a period of 48 weeks or longer.

- There was a group of 1,273 individuals without a diagnosis of HCV who were treated with drug therapy indicated only for HCV. A utilization review is recommended.

- The average annual cost to Florida Medicaid for each person with a diagnosis of hepatitis C was $15,144 between FY 2000 and FY 2003. Additional studies using a comparison population are warranted to estimate the marginal cost of HCV over the frequently occurring co-morbid conditions.

BACKGROUND

The estimated prevalence of hepatitis C virus (HCV) in the U.S. is at least 1.8% of the population, making HCV the most common chronic blood-borne infection nationally. High HCV prevalence rates (15-50%) occur in specific subpopulations, such as the homeless, incarcerated persons, injection drug users, and persons with hemophilia who were treated with clotting factors before 1992. The 2002 NIH Consensus Conference on Hepatitis C noted that HCV is highly prevalent in patient populations without health insurance or with publicly funded healthcare payers, although there are no data to support this assumption. The prevalence of HCV infection and the feasibility of management and treatment in these populations was designated as an important area for research by the conferees.

According to the NIH Consensus Conference Hepatitis C is a leading cause of cirrhosis, a common cause of hepatocellular cancer, and the leading cause of liver transplantation in the United States. Prospective studies show that 60-85% of HCV-infected persons develop chronic infections. An estimated 10-15% of those chronically infected will develop cirrhosis 20 years after initial infection. Deaths associated with chronic hepatitis C are most likely to be the result of decompensated cirrhosis, and the only treatment option for persons with decompensated cirrhosis is liver transplantation. Also, it is estimated that HCV accounts for one-third of hepatocellular cancer in the U.S.

The NIH treatment guidelines for hepatitis C call for weekly injections of pegylated-interferon in combination with daily ribavirin by mouth. Treatment for 24 weeks appears to produce a sustained viral response in 73-78% of persons with genotypes 2 and 3 whereas patients with genotype 1 need 48 weeks of treatment with higher doses of ribavirin to achieve a sustained viral response in 51% of those treated. However, significant side effects often result in premature discontinuation of treatment.

Risk factors for hepatitis C are well known and there has been a dramatic decrease in the incidence of new HCV infections in recent years (Davis et al. 2003). Because most persons with chronic HCV infection have not yet been diagnosed, the number of adults diagnosed with compromised liver function is projected to increase four-fold from 1990-2015.

The goals of this study are to estimate (1) the prevalence of a diagnosis for hepatitis C within the Florida Medicaid program, (2) the number of persons who have undergone treatment for this condition in accordance with NIH guidelines, and (3) total Medicaid expenditures for those who received treatment and those who did not receive treatment.

METHODS

Data for the study were obtained from Florida Medicaid for paid claims covering services rendered in fiscal years (FY) 2000 through 2003, that is, for four years beginning July 1, 1999 and ending June 30, 2003 inclusive. Personnel at the Agency for Health Care Administration created a list of study subjects who had a claim with diagnostic code for HCV and/or drug treatment unique to HCV based upon our specifications. All

persons with a history of liver transplant were added to the list. Medicaid eligibility files provided demographic data for each subject. Specifications for the data extraction and the analyses are given in the appendices.

All claims for services rendered to the subjects during the observation period were retrieved. Patient identifiers were scrambled and encrypted files transferred to researchers at the University of Florida in Gainesville for analysis.

There is a lag time between date of service and claims adjudication (primarily physician and hospital claims). Approximately 90-95% of Florida Medicaid claims are recorded within 6 months of the date of service. There may be some claims that were not recorded at the time the data were extracted in November 2003. However, the observation period through July 1, 2003 was selected to capture the use of peginterferon alfa-2a, which was newly approved by the FDA in October 2002 for treatment of hepatitis C. The availability of the newer product reduces the number of injections from three per week for interferon to one injection per week for the pegylated form, and purportedly increases the likelihood of patients experiencing a sustained viral response.

The total expenditures for each subject were computed for all services rendered rather than limiting the analysis to claims where HCV was listed as the primary diagnosis. This decision was made because complications of HCV and services needed to monitor the disease may be submitted with general codes associated with diseases of the liver or for symptoms. In addition, it is known that the presence of HCV increases the cost of care for other health care services due to the presence and potential for liver damage.

The data include every patient with a diagnostic code associated with HCV. This population may include some individuals just undergoing testing for the condition. A closer examination of the services and pattern of treatment associated with a HCV-related diagnostic code, and possibly a medical record review, would be needed to define the affected population more precisely.

FINDINGS

Research question 1. What percentage of Florida Medicaid patients have a diagnosis HCV recorded and/or are taking drug therapy specific to HCV?

Table 1. HCV Diagnosis and Treatment in Florida Medicaid Population, FY 00-03	
Recipients with ICD-9 Diagnosis of HCV	
HCV Diagnosis without drug therapy	13,049 (83.6%)
HCV Diagnosis with drug therapy	2,288 (14.6%)
HCV Diagnosis and liver transplant	275 (1.8%)
Total	15,612 (100.0%)

Enrollment history data for Florida Medicaid is shown in Appendix III. The number of unique recipients served through fee-for service and Medipass in FY2003 provides a conservative estimate of the number of individuals with claims for service during the 4-year observation period covered by this study. HMO members were not included in the estimate because no claims for individual services are in the database. Thus, the 15,612 cases of HCV among 2,732,056 recipients represents about 0.5% of the FY2003 Medicaid population. The CDC estimates that 2 percent of the U.S. population is infected with HCV and the NIH Consensus Conference concluded that it is likely that the percentage is higher among persons covered by publicly funded insurance. This estimate suggests that there are a significant number of persons in the Florida Medicaid program with HCV that is not diagnosed or documented.

The age distribution is consistent with the prevalence of hepatitic C from national estimates (Alter et al. 1999).

As seen in Table 1, a large majority (83.6%) of patients with a diagnosis of HCV did not receive treatment with medication or liver transplant during the observation period. Factors to be considered in recommending treatment include favorable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of co-morbid illness, and patient age (Muir and Provenzale 2002, Zeuzem 2004).

Table 2. Demographic Composition of Persons with HCV Diagnosis by History of Liver Transplant and Drug Treatment

	Percentage of all Persons with HCV Diagnosis	No HCV Rx No Transplant	HCV Rx No Transplant	Transplant No HCV Rx	Transplant HCV Rx
Total	15,612 (100%)	13,049 (83.6%)	2,288 (14.6%)	183 (1.2%)	92 (0.6%)
Age					
≤ 21	490 (3.1%)	459 (93.7%)	13 (2.7%)	16 (0.1%)	2 (0.0%)
22-44	5,483 (35.1%)	4,636 (84.5%)	804 (14.7%)	29 (0.2%)	14 (0.1%)
45-54	6,593 (42.2%)	5,375 (81.5%)	1,078 (16.4%)	84 (0.5%)	56 (0.4%)
55-64	2,303 (14.8%)	1,921 (83.4%)	320 (13.9%)	45 (0.3%)	17 (0.1%)
≥ 65	743 (4.8%)	658 (88.6%)	73 (9.8%)	9 (0.1%)	3 (0.0%)
Gender					
Male	7,735 (49.5%)	6,544 (84.6%)	1,090 (14.1%)	70 (0.5%)	31 (0.2%)
Female	7,877 (50.5%)	6,505 (82.6%)	1,198 (15.2%)	113 (0.7%)	61(0.4%)
Race					
White	9,068 (58.1%)	7,556 (83.3%)	1,365 (15.1%)	106 (0.7%)	42 (0.3%)
Black	3,089 (19.8%)	2,643 (85.5%)	422 (13.7%)	20 (0.1%)	4 (0.0%)
Native American	7 (0.0%)	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)
Oriental	53 (0.3%)	44 (83.0%)	7 (13.2%)	2 (0.0%)	0 (0.0%)
Hispanic	1,019 (6.5%)	826 (81.0%)	168 (16.5%)	13 (0.1%)	12 (0.1%)
Other	2,376 (15.2%)	1,977 (83.2%)	323 (13.6%)	42 (0.3%)	34 (0.2%)

Table 2 shows that there is a relatively small number of children under 21 with HCV who received any form of treatment, likely because serious liver damage did not have time to emerge. Those who are age 65 and older, who are more likely to have advanced liver disease, are less likely to receive drug treatment for their HCV. The age group between 45 and 54 years old receives the greatest proportion of treatment overall.

Women are more likely than men to receive drug treatment and more likely to receive a liver transplant. Conclusions regarding race are drawn with caution because there is a large number of recipients where race is not known and the number of liver transplant cases is relatively few. It appears that there is a disproportionately higher frequency of drug treatment and liver transplant among Hispanics and a disproportionately lower frequency of both treatment modalities among Blacks. Whereas the percentage of white persons treated with drug therapy is proportionally higher, there are proportionately fewer recipients of a liver transplant in this group. The number of those identified as Native American or Oriental is quite small and it is difficult to draw conclusions about treatment patterns in these groups, although the proportion of Oriental persons who receive treatment appears to be higher than any other racial group.

In clinical trials with pegylated interferon and ribavirin, researchers found significant side effects that resulted in discontinuation of treatment in approximately 10-14% of patients. Major side effects of combination therapy include influenza-like symptoms, hematologic abnormalities and neuropsychiatric symptoms. Psychological conditions, particularly depression, are common among persons with HCV and are frequent side effects of interferon (Jensen et al. 2004). However, there are very little data outside the clinical trials about side effects and important co-morbidities among patients who present for treatment.

Due to the likelihood that treatment would not be tolerated or successful in certain individuals, the Durham Veterans Affairs Medical Center set eligibility criteria for HCV treatment (Muir and Provenzale 2002). Patients considered ineligible for treatment were those with severe mental illness, hazardous alcohol consumption, current drug abuse, decompensated cirrhosis, dementia, terminal illness, diabetic ketoacidoses, severe cardiac or pulmonary disease, or were homeless. HIV infection was also considered a factor complicating treatment but these patients remained eligible for treatment.

Subsequent to the adoption of these eligibility criteria, clinicians at the Durham VA Medical Center found that only 32 out of 100 consecutively diagnosed veterans met the criteria for treatment. Excessive alcohol consumption eliminated 44 percent and major depressive symptoms accounted for an additional 12 percent being removed from the treatment pool. Ineligible patients were referred for psychiatric and substance abuse treatment. Thirteen percent remained eligible but were infected with the HIV virus.

We examined the data for the presence of similar factors that could influence the decision to treat individual patients with HCV or that could affect their adherence to therapy. The pool of subjects was divided by the presence or absence of drug treatment, irrespective of the receipt of a liver transplant. The number receiving any

form of drug therapy was 2,380. There were 13,232 persons having no claim for interferon, ribavirin or a combination of the two. An analysis of co-morbidities and a comparison between the two groups is displayed in Table 3.

Table 3. Co-Morbidities Among Persons with a Diagnosis of HCV, Treated and Not Treated

	Persons with HCV and Co-Morbidity as Percentage of Total (N=15,612)	No HCV Rx Treatment (N = 13,232; 84.8%)	HCV Rx Treatment (N = 2,380; 15.2%)
Alcohol Abuse	3,734 (23.9%)	3,401 (91.1%)	333 (8.9%)
Drug Dependence	2,080 (13.3%)	1,785 (85.8%)	295 (14.2%)
Alcohol Abuse and Drug Dependence	887 (5.4%)	790 (89.1%)	97 (10.9%)
Psychosis	1,681 (10.5%)	1,466 (87.2%)	215 (12.8%)
Depression	920 (5.9%)	767 (83.4%)	153 (16.6%)
Psychosis and Depression	171 (1.1%)	151 (88.3%)	20 (11.7%)
All of the Above	58 (0.4%)	54 (93.1%)	4 (6.9%)
One of the Above	6,158 (39.4%)	5,418 (88.0%)	740 (12.0%)
None of the above	9,454 (60.5%)	7,814 (82.7%)	1,640 (17.3%)
Advanced Liver Disease	3,446 (22.1%)	2,952 (22.3%)	494 (20.8%)
HIV/AIDS	2,783 (17.8%)	2,332 (83.8%)	451 (16.2%)

Note: Appendix gives ICD-9 codes used to identify co-morbidities.

If treatment had been restricted to persons with no evidence of alcohol abuse, drug abuse or serious mental illness, then 6,158 (39.4%) of the individuals in the pool would be considered ineligible for treatment. It appears that alcohol abuse reduced the likelihood of drug therapy for HCV more than evidence of drug abuse and serious mental illness. In the case of a diagnosis of depression, it is difficult to know if treatment was more likely – a counter-intuitive finding – or if there is a greater likelihood of depression as the result of the disease or treatment itself. Up to 20% of patients with HCV infection are thought to have psychological disorders including depression (NIH Consensus Statement 2002).

Collectively, however, those with at least one of the risk factors were somewhat less likely to receive treatment (12.0%) than those with none of the risk factors (17.3%). Drug therapy was given to a greater proportion of those whose liver deterioration had advanced. The presence of HIV/AIDS was not a factor in deferring drug therapy.

Research question 2. What percentage of persons with a diagnosis for HCV also have a diagnosis of fibrosis, cirrhosis, cancer of the liver, or a liver transplant?

Cirrhosis, cancer of the liver, and liver transplant are markers for persons with HCV in the terminal stages.

Table 4. Florida Medicaid Recipients with HCV Diagnosis (N=15612) with Advanced Liver Disease,* FY 00-03	
Advanced Liver Disease	3446 (22.1%)
Cancer of the liver	103 (0.7%)
Liver Transplant	275 (1.8%)

** categories are not mutually exclusive*

Research question 3. Of those who have had a liver transplant, what percentage had a diagnosis of hepatitis C and/or a record of drug treatment for HCV?

It is expected that HCV infection will recur after liver transplantation in nearly all persons who are HCV-positive prior to the transplant procedure. Immunosupppresive therapy used to prevent organ rejection contributes to the risk of HCV recurrence. Up to 30% of HCV patients will develop severe graft hepatitis and cirrhosis within 10 years after the transplant procedure, most within the first year (Neumann et al., 2004).

The 5 and 10 year survival rate among HCV patients with liver transplants has been estimated at 76% and 69%, respectively (Neumann et al., 2004). A recent study following 209 HCV patients who received a liver transplant found that 18 died because of HCV recurrence within ten years after the transplant procedure. That is, the cause of death was attributed to HCV recurrence for approximately one in three of those who died over the 10-year observation period.

Table 5. Florida Medicaid Recipients with Liver Transplant, FY 00-03	
Liver transplant without diagnosis of HCV	
No drug therapy for HCV	430 (60%)
With drug therapy for HCV	13 (2%)
Liver transplant and diagnosis of HCV	
No drug therapy for HCV	183 (25%)
With drug therapy for HCV	92 (13%)
Total	718 (100%)

Among 275 Florida Medicaid recipients who had a liver transplant and a diagnosis of HCV, about one-third have received drug therapy for HCV. However, additional analyses are needed to determine whether the diagnosis and drug therapy occurred before or after the liver transplant procedure.

Research question 4. Of those receiving treatment with pegylated interferon and ribavirin, what is the therapeutic possession ratio for each drug?

Effective treatment for HCV requires the use of both ribavirin administered orally and interferon administered by injection. Among 2,380 persons receiving drug therapy, there were 255 who received the injection but had no claim for the oral agent. One reason that may account for this observation is that oral ribavirin is contraindicated in persons with end stage renal failure (ESRD). Alternative explanations are that there are some individuals who obtain the medication from another source or are not compliant with the oral component of the treatment.

There were an additional 30 persons who had claims for the oral component, but no claims recorded for the injection. This could be attributed to the injection being covered by other insurance or administered in a clinic or physician office and not being billed on a Medicaid pharmacy claim. A preliminary examination of the data found at least one non-pharmacy claim for 11 patients where injection treatment was billed using the CMS billing code J9212.

This leaves 2,095 persons who received both oral and injectable therapy. We examined the data for continuity of treatment as indicated by monthly billing. When ever there was a lapse in claims for 90 days or more, we assumed the individual had stopped drug therapy for some reason and were re-started on therapy at the later date. There were 438 persons who had multiple episodes of drug therapy for HCV by this definition. This group was analyzed separately under Research question 6 (page 11).

For the remaining 1,658 patients we estimated the number who received both oral and injectable components in adequate quantities for effective treatment. We did this by estimating a therapeutic possession ratio that divides the days supply of oral ribavirin therapy by the days supply of injectable interferon therapy. If the patient received both components in appropriate quantities, the ratio will be 1.0. A ratio less than one than one would suggest under-treatment with the oral component and a ratio greater than one implies under-treatment with the injectable.

The median and modal possession ratio was 1.0. In fact, the possession ratio was equal to 1.0 for 903 (54.5%) of the group and there were a substantial number of persons with a possession ratio close to 1.0 that would be considered clinically sufficient.

Table 6. Therapeutic Possession Ratio for Persons Undergoing Oral Treatment with Ribavirin and Injection Treatment with Interferon alfa (N=1657)

Possession Ratio		Possession Ratio		Possession Ratio	
1.00	903 (54.5%)	0.99-1.01	972 (58.6%)	0.90-1.10	1237 (74.6%)
<1.00	435 (26.3%)	<0.99	422 (25.5%)	<0.90	322 (19.5%)
>1.00	319 (19.2%)	>1.01	263 (15.9%)	>1.10	98 (5.9%)

There were more patients with a possession ratio below 1.0 than over 1.0. The interpretation is that patients are less likely to obtain a sufficient quantity of the oral ribavirin relative to the injection. Overall, however, three out of four patients received both drugs in the appropriate ratio. The next question was to determine if the treatment was sustained over an adequate period consistent with current practice guidelines.

Research question 5. Of those with continuous Medicaid eligibility who received treatment with pegylated interferon and ribavirin, what proportion receive quantities sufficient for continuous treatment for less than 12 weeks; for 12 weeks; more than 12 weeks but less than 24 weeks; more than 24 weeks but less than 48 weeks; more than 48 weeks?

The NIH Consensus Conference concluded that patients who fail to achieve an early viral response by week 12 have only a small chance of achieving a sustained viral response, even if therapy is continued for a full year. Treatment need not be extended beyond 12 weeks in these patients. Individuals with HCV genotype 2 or 3 who show a positive response to treatment should continue treatment for a total of 24 weeks; individuals with genotype 1, the form that is most prevalent in the U.S., should maintain therapy for 48 weeks.

An examination of the length of therapy among those who were treated for HCV found that about one-third (N=537) did not have claims sufficient for 12 weeks of treatment. These patients may be those who did not tolerate the side effects of treatment or otherwise did not adhere to the treatment regimen that requires weekly injections. In clinical trials 10% to 14% of subjects withdrew due to adverse effects of treatment (NIH Consensus Conference 2002). Presumably, those who stopped therapy after 12 weeks (N=156) and at least some who stopped before 24 weeks (N=274), were individuals who did not experience a significant response to the therapy.

Table 7. Length of HCV Treatment for Persons with a Single Episode of Treatment

Length of HCV Therapy	Number of Patients
Less than 12 weeks	537 (32.4%)
12 weeks	156 (9.4%)
More than 12 weeks but less than 24 weeks	274 (16.5%)
24 weeks	155 (9.3%)
More than 24 weeks but less than 48 weeks	380 (22.9%)
48 weeks	81 (4.9%)
More than 48 weeks	74 (4.5%)
Total Number of Persons Treated	1657 (100%)

Note: treatment duration was estimated from days supply of medication ± 10%.

About one-third of those undergoing treatment had claims for a duration of at least 24 weeks but less than 48 weeks. Less than 10% of those who started therapy had treatment claims for the full 48 weeks recommended by the NIH Guidelines for genotype 1. Given that approximately two-thirds of HCV cases in the U.S. are genotype

1, it would be expected that two-thirds of those treated would require 48 weeks of treatment.

Davis et al (2003) used a previously published natural history model of HCV to project the number of cases of HCV infection, cirrhosis, and liver failure that will occur over the next four decades. By assuming a positive treatment response rate of 50%, they examined the impact of treating various proportions of patients. As shown in Figure 2 from Davis et al., with 10% successfully treated, one could expect a 4.9% reduction in cases of liver decompensation over a 20 year period.

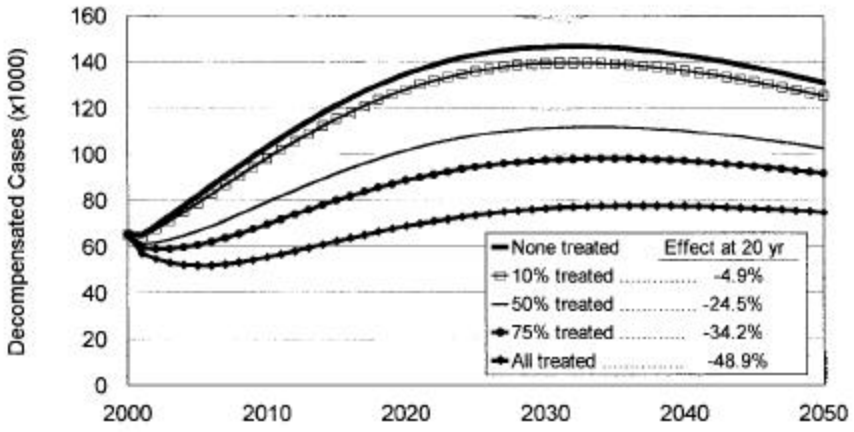

Figure 2. Projected impact on cases of hepatic decompensation by treating different proportions of HCV-infected patients with interferon-ribavirin combination therapy.

Source: Liver Transplantation 2003; 9: 335.

Furthermore, as shown in the following table from Davis et al., any reduction in morbidity and mortality will occur over several decades depending upon the stage of hepatic decompensation at the time that therapy is initiated. For persons with cirrhosis, a response to treatment is expected to reduce disease complications by an average of 88% during the first five years following treatment. On the other hand, treating patients with mild chronic hepatitis would account for an 11% reduction in complication after 10 years, nearly 32% reduction after 20 years and a 58.5% decrease after 40 years. Treatment of patients with liver function in normal range would have relatively little impact on disease complications in this population.

Table 2. Proportion of Treatment-Related Reduction in Hepatic Decompensation Accounted for by Different Subgroups of Patients

Treated Group	2010	2020	2030	2040
Cirrhosis (excluding cases with complications)	54.5%	26.8%	14.9%	9.1%
Moderate chronic hepatitis	33.5%	37.7%	32.1%	25.7%
Minimal-to-mild chronic hepatitis	11.0%	31.9%	48.0%	58.5%
Persistently normal serum ALT levels	2.0%	3.5%	5.0%	6.7%

NOTE. Data shown at decade intervals.

Source: Liver Transplantation 2003; 9: 335.

Research question 6. Of those with continuous Medicaid eligibility who initiated treatment with either interferon and ribavirin, or pegylated interferon and ribavirin, what proportion received a second course of therapy? (Re-treatment is defined as lapse in any prescription claim for interferon, pegylated interferon, or ribavirin of 90 days or more.)

Selected patients who fail to achieve a sustained viral response may benefit from re-treatment according to the NIH Consensus Conference. Individuals who were initially treated with interferon alfa, may have attempted a second course of treatment with the pegylated interferon when it was introduced as a new alternative. Preliminary research data suggest that 15-20% of those who did not respond to treatment with a standard interferon-ribavirin combination will achieve a sustained viral response on re-treatment with pegylated interferon-ribavirin (Zeuzem 2004).

The expected outcome of a complete second course of treatment for persons who stopped therapy prematurely in earlier treatment attempts is unknown. Likewise, it is not possible to predict the expected outcome for those who undertake multiple, short courses of treatment.

In addition to the 1,657 persons with a single course of treatment with ribavirin and interferon described previously, there were 438 (20.9%) who underwent multiple episodes of treatment ranging from 2 to 7 episodes as shown in Table 8. Assuming that at least one course of therapy must meet NIH guidelines for length of treatment, we examined the records to determine the number of persons having one or more sustained periods of treatment. There were similar proportions of persons with a

sustained course of therapy irrespective of the number of attempts. Table 9 summarizes the findings and compares the groups with single and multiple courses.

Table 8. Episodes of HCV therapy	Number of patients
1	1657 (79.0%)
2	63 (3.0%)
3	251 (12.0%)
4	87 (4.2%)
5	30 (1.4%)
6	4 (0.2%)
7	3 (0.1%)

It appears that the proportion of patients who undergo a sustained course of therapy over 48 weeks to meet the NIH guidelines for the most common genotype increased by allowing them to undertake multiple treatment episodes. Nonetheless, only 12.9% of the entire group met this goal.

It must be acknowledged that some persons with multiple episodes of therapy might undergo retreatment because they were re-infected. More likely, retreatment occurs among those who relapse or are treated to slow liver deterioration. Among the 438 patients with multiple episodes there were 31 persons who completed 2 year-long episodes of treatment and 3 people who had 3 year-long episodes over the four-year observation period.

Table 9. Length of Sustained HCV Treatment Period for Persons with Single and Multiple Treatment Episodes			
Length of HCV Therapy	Single Episode	Multiple Episodes	Total
Less than 12 wks	537 (32.4%)	48 (11.0%)	585 (27.9%)
12 wks or more but less than 24 wks	430 (25.9%)	107 (24.4%)	537 (25.6%)
24 wks or more but less than 48 wks	535 (32.3%)	168 (38.3%)	703 (33.6%)
48 wks or more	155 (9.4%)	115 (25.2%)	270 (12.9%)
Total Number of Persons Treated	1657 (100%)	438 (100%)	2095 (100%)

Note: treatment duration was estimated from days supply of medication ± 10%.

Research question 7. What were the total Medicaid expenditures per member per month (PMPM) for the population with hepatitis C and its sub-groups?

Hepatitis C is a chronic condition that may be present for decades before the disease progression requires extensive medical intervention. We examined medical expenditures for all persons identified in the study, although the observation period may be too short to capture trends in the care and treatment of HCV in the program.

Likewise it was not possible to track expenditures for individuals because the disease progresses so slowly.

Table 10. Total Florida Medicaid Expenditures for Persons with HCV, FY 00-03				
	HCV Diagnosis	HCV with Liver Transplant	TOTAL	Cost PMPM
Pharmacy services	$256,260,518	$4,220,049	$260,480,566 (43.4%)	$548
Inpatient services	175,155,561	7,557,490	182,713,051 (30.4%)	$384
Physician services	121,728,667	2,158,311	123,886,978 (20.6%)	$260
Outpatient services	32,316,556	646,727	32,963,283 (5.6%)	$69
Total Medicaid	$585,461,301	$14,582,576	$ 600,043,878 (100%)	$1262

The total Florida Medicaid expenditures for 15,612 patients with a diagnosis of HCV over the four-year observation period was $600,043,878. A breakdown of expenditures by category shows the greatest proportion of charges were for pharmacy services .

POLICY IMPLICATIONS

- Experts believe that hepatitis C is under-diagnosed, even among patients at high risk of infection. Knowing the prevalence of diagnosed and treated cases allows planners to estimate the additional demand for services among current cases and those yet to be identified. The prevalence of hepatitis C documented among Florida Medicaid recipients by this analysis was less than 0.5 percent. This is far below national estimates of 1.8% for the population in general, and far below the estimated prevalence in sub-populations known to be at higher risk for contracting the infection.

- Treatment response estimates are based upon controlled trials with patients who are informed and consent to participation in the trials, and are closely monitored by researchers, often in academic medical centers. There are few data from clinical practice outside these trials (Jensen et al. 2004). There is considerable variability in patients' willingness to undergo treatment, their tolerance for side effects and the therapeutic response. Baseline data from this study illustrate the variance in treatment patterns and adherence to treatment guidelines for HCV among those patients who receive services from Florida Medicaid.

- Two-thirds of the patients who initiated a single episode of drug therapy for HCV maintained the treatment for 12 weeks or longer. It is not necessary to continue treatment beyond this point for persons who fail to demonstrate an adequate response to therapy. About one-third of those who initiated therapy remained

on treatment for 24 weeks but less than 48 weeks, the recommended duration of therapy for those with genotypes 2 or 3.

- The recommended duration of treatment for genotype 1, the most common form, is 48 weeks. Slightly less than 10% of those who had a single course of drug therapy maintained the treatment for the full 48 weeks. If patients who received multiple courses of therapy are considered, the percentage of patients achieving the full duration of treatment increased to about 13 percent. This suggests that treated patients are poor candidates for therapy or there is inadequate monitoring. Patients receiving drug therapy for HCV should receive close monitoring and support to enhance the likelihood that the treatment can be tolerated and sustained.

- This study identified a group of 1,273 individuals without a diagnosis of HCV who were treated with drug therapy that is only indicated for the treatment of that disease.

Recipients without ICD-9 Diagnosis of Hepatitis C Receiving Drug Therapy for Hepatitis C	
Drug therapy specific for HCV	1,260
Liver transplant with drug therapy	13
Total	1,273

  A preliminary examination of possible reasons for use of drug therapy in cases where HCV is not documented failed to produce a discernable pattern to support the use of these agents. The need for drug therapy of HCV after a liver transplant is not supported in the literature, although it may be appropriate for individuals who contract the HCV after the liver transplant has occurred. There was no diagnostic pattern apparent to account for use of these agents or a pattern of off-label use. We recommend that this group be referred for utilization review.

- The average annual cost to Florida Medicaid for each person with a diagnosis of hepatitis C was $15,144 between FY 2000 and FY 2003. However, this study suffers from the lack of a comparison population that would provide an estimate of the marginal cost of health care services incurred due to HCV status relative to a similar population without HCV. Additional studies, conducted over time, are warranted in order to capture the added burden due to HCV.

REFERENCES

Adinolfi LE, Utili R, Tonziello, Ruggiero. Effects of alspha interferon induction plus ribavirin with or without amantadine in the treatment of interferon nonresponsive chronic hepatitis C: a randomized trial. Gut 2003; 52: 701.

Allen SA, Spaulding AC, Osei AM, Taylor LE, Cabral AM, and Rich JD. Treatment of chronic hepatitis C in a state correctional facility. *Ann Intern Med* 2003;138:187-191.

Alter M. Prevention of spread of hepatitis C. *Hepatology* 2002; 36:S93-S98.

Alter MY, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United State, 1988 through 1994. N Engl J Med 1999; 341: 556-562.

Alter HJ, Seeff LB. Recovery, persistence and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Seminars in Liver Disease 2000; 20:17-35.

American Liver Foundation. Hepatitis C: an information resource. 2003. www.liverfoundation.org. Accessed Nov. 24, 2003.

Bernstein D. Hepatitis C: advances in treatment. 54th Annual Meeting of the American Association for the Study of Liver Diseases. http://www.medscape.com/viewarticle/464166. Accessed Nov. 18, 2003.

Cassidy W. Hepatitis C infection in prisons. http://www.hcvadvocate.org/Medical_Writers_Circle/cassidy-1.htm. Accessed Aug. 18, 2003.

CDC. National Hepatitis C Prevention Strategy. Summer 2001. http://www.cdc.gov/ncidod/diseases/hepatitis/c/plan/index.htm Accessed Nov. 24, 2003.

CDC. Transmission of hepaptitis B and C viruses in outpatient settings---New York, Oklahoma, and Nebraska, 2000-2002. MMWR 2003; 52:901-906.

Davis GL, Albright JE, Cook SF, Rosenber DM. Projecting future complication of chronic hepatitis C in the United States. *Liver Tranpsl* 2003; 9:331-338.

Florida Department of Health. Florida Hepatitis Support Groups. http://www.doh.state.fl.us/Disease_ctrl/aids/hep/support.htm. Accessed Aug 18, 2003.

Florida Department of Health. Hepatitis Vaccine and Laboratory Testing. http://www.doh.state.fl.us/Disease_ctrl/aids/hep/index.html Accessed Aug 18, 2003.

Florida Department of Health. Hepatitis C Treatment. http://www.doh.state.fl.us/Disease_ctrl/aids/hep/hepCtreat.htm Accessed Aug 18, 2003.

Florida Department of Health. Hepatitis C Symptoms. http://www.doh.state.fl.us/Disease_ctrl/aids/hep/hepCsymp.htm

Franciscus A. Freedom to be cured: who is driving the decisions on which groups of patients should be eligible for hepatitis C treatments? http://www.hcvadvocate.org/freedom.htm Accessed Aug. 18, 2003.

Gonzalez SA, Jacobson IM. The role of hematopoietic growth factos in special populations with chronic hepatitis C. *Cleve Clin J Med* 2004: 71(supplement 3):S22-S26.

Heathcote EJ, Shiffman ML, Cooksley WG, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000: 343:1673-1680.

Heathcote J. Patients with hepatitis C: who should be treated? http://www.hcvadvocate.org/Medical_Writers_Circle/heathcote-1.htm Accessed Aug. 18, 2003.

Huang K. Checkup: hepatitis C. *The Wall Street Journal Online*, October 9, 2003.

Jensen DM, Cotler SJ, Lam H, Harb G, Shillington A. A comparison of hepatitis C treatement and outcomes at academic, private and Veterans' Affairs treatment centers. *Aliment Pharmacol Ther* 2004; 19:69-77.

Katz D. Hepatitis C virus. http://www.doh.state.fl.us/Disease_ctrl/aids/hep/hepCbrief.html Accessed Aug. 18, 2003.

Keuhne FC, Bethe U, Freedberg K, and Goldie SJ. Treatment for hepatitis C virus in human immunodeficiency virus infected patients. *Arch Intern Med* 2002;162:2545-2566.

Leigh JP, Bowlus CL, Leistikow BN, and Schenker M. Cost of hepatitis C. *Arch Intern Med* 2001;161:2231-2237.

Malone DC. Cost-effectiveness analysis of interferon a-2b with ribavirin for chronic hepatitis C infection. *Formulary* 2000;35:681-689.

Muir A. Hepatitis C in African Americans. Hepatitis C Support Project. http://www.hcvadvocate.org/Medical_Writers_Circle/muir-1.htm Accessed Aug. 18, 2003.

Muir AJ, Provenzale D. A descriptive evaluation of eligibility for therapy among veterans with chronic hepatitis C virus infection. *J Clin Gastroenterol* 2002; 34: 268-271.

Neumann UP, Berg T, Bahra N, Puhl G, Guckelberger O, Langrehr JM, Neuhaus P. Long-term outcome of liver transplants for chronic hepatitis C: a 10-year follow-up. *Transplantation* 2004; 77:226-231.

NIH Consensus Statement. Management of hepatitis C: 2002. Sep.12, 2002. http://www.consensus.nih.gov/cons/116/116cdc_intro.htm

Osbon C. Appropriate drug utilization in the treatment of hepatitis C. Presentation to Florida Medicaid DUR Board. Tampa: February 8, 2003.

Pockros PJ. The management of adverse effects with PEG-interferon/ribavirin combination therapy is a significant challenge. http://www.hcvadvocate.org/Medical_Writers_Circle/pockros-2.htm Accessed Aug. 18, 2003.

Rosenberg DM, Cook SF, Lanza LL. Health care, treatment patterns and cost of services for patients infected with chronic hepatitis C virus in a large insured New England population. *J Viral Hepat* 2000; 7: 361-367.

Salomon JA, Weinstein MC, Hammit JK, and Goldie SJ. Cost-Effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population. *JAMA* 2003; 290:228-237.

Schaefer M, Schmidt F, Folwaczny C, Lorenz R, et al. Adherence and mental side effects during hepatitis C treatment interferon alfa and ribavirin in psychiatric risk groups. *Hepatology* 2003; 37:443-451.

Shatin D, Schech SD, Patel K, McHutchison JG. Population-based hepatitis C surveillance and treatment in a national managed care organization. *Am J Manag Care* 2004; 10:250-256.

Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med* 2003: 138:197-207.

Tan SL, Pause A, Shi Y, Sonenberg N. Hepatitis C therapeutics: current status and emerging strategies., *Nature Reviews Drug Discovery* 2002;1: 867-881.

Veteran's health care: standards and accountability could improve hepatitis C screening and testing performance. GAO-01-807T, Jun. 14, 2001.

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. Pegylated interferon criteria for use. March 2003. http://www.vapbm.org or http://vaww.pbm.med.va.gov Accessed Mar. 3, 2003.

Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis* 2000; 20:1-16.

Weisbord JS, Trepka MJ, Zhang G, Smith IP, and Brewer T. Prevalence of and risk factors for hepatitis C virus infection among STD clinic clientele in Miami, Florida. *Sex Transm Infect* 2003; 79:E1.

Williams T, Honeywell M, Branch E, Thompson M. Peginterferon alfa-2a: a new agent for hepatitis C virus infection. *P&T* 2003; 28(5): 302-304.

Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000; 90:1562-1569.

Zeuzem S. Heterogeneous virologic response rates to interferon-based therapy in patients with chronic hepatitis C: who responds less well? *Ann Intern Med* 2004; 140: 370-381.

Zeuzem S, Feinman SV, Raseneck J, et al. Peginterferon alfa2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666-72.

APPENDIX I. Specifications for Medicaid Claims Extraction and Data Definitions.

GENERAL INSTRUCTIONS

1. Data request is made with all IRB and HIPPA review and approvals in place. Data are transferred as the encrypted files.
2. This request for a data extract begins with date of service from July 1, 1999 and extends through June 30, 2003.
3. Do not include any personal identifiers but create a unique identifier for each subject in the study so that we may link all claim records for an individual subject. In addition,

   Please give us the subject's age in years on the date the claims review is initiated, i.e., July 1, 1999. Anyone 90 years or older should be coded as 90+

   Exclude all geographic identifiers. If we note patterns, trends or outliers based upon the study criteria, we will recommend that findings be forwarded to the Prescribing Pattern Review Panel for an examination of regional trends.

DATA EXTRACTION REQUEST

1. Select recipients.

   Examine paid claims with dates of service from July 1, 1999 through June 30, 2003 inclusive.

   Build a list of study subjects using presence of diagnostic codes and/or drug treatment for hepatitis C. Add all persons with liver transplant to the list of persons eligible for study.

   A list of the ICD-9, CPT/HCPCS, and NDC codes that identify the subjects is attached to this request.

2. Retrieve claims for relevant health services use under Medicaid, i.e.,

   - Pharmacy claims: date of service, NDC, generic code, therapeutic class, quantity, days supply, amt billed, amt paid, pharmacy ID
   - Hospital inpatient claims: date admit, provider ID, LOS, primary, secondary and tertiary ICD-9 codes, CPT codes, amt. billed, amt paid
   - Hospital outpatient claims: date admit, provider ID, primary, secondary and tertiary ICD-9 code, procedure (CPT) code, amt billed, amt paid
   - Physician claims: date, primary, secondary and tertiary ICD-9 code, procedure (CPT) code, provider ID, provider type, provider specialty, amt billed, amt paid

3. Use recipient eligibility file to generate a file for each subject including the following

   Age; Sex; Race; NH status; Medicaid eligibility dates; Medicare eligibility (0 or 1);

   Death if recorded; AIDS waiver flag; CMS flag; Organ transplant indicator (0 or 1)

DATA DEFINITIONS

Positive HCV identification

ICD-9-CM	
070.41	Acute Hepatitis C with coma
070.44	Chronic Hepatitis C with coma
070.51	Acute Hepatitis C without coma
070.54	Chronic Hepatitis C without coma

CPT/HCPCS	
J9212	Infergen

Identification of Liver Transplant Recipient

ICD-DM-9	Disease Name
V42.7	Liver transplant status

ICD-9 Codes Used to Identify Selected Co-morbidities

ICD-DM-9	Disease Name
042	HIV/AIDS
303, 305, 571	Alcohol abuse
304	Drug Dependence
295, 296, 297	Psychosis including schizophrenia
300.4	Depression
456.2, 572, 573.1, 573.8, 573.9	Fibrosis or cirrhosis of the liver, esophageal varices

Diagnoses Used to Identify Advanced Liver Disease

ICD-DM-9	Disease Name
155.0	Hepatocelluar Cancer
286.9	Coagulopathy
289.4	Hypersplenism
456.0/572.2	Esophageal varices
571.5	Cirrhosis
572.2	Hepatic encephalopathy
572.3	Portal hypertension
573.8	Liver failure
782.4	Jaundice
789.5	Ascites

Drug Treatment for Hepatitis C

Therapeutic Code	Generic Code	NDC	Drug
W5G (Z2G in before 2001)	22222	00085-1236-01	Rebetron (pegylated interferon and ribavirin)
	22221	00085-1236-02	
	22220	00085-1236-03	
	22222	00085-1241-01	
	22221	00085-1241-02	
	22220	00085-1241-03	
	22225	00085-1258-01	
	22224	00085-1258-02	
	22223	00085-1258-03	
	14179	00085-1194-03	Rebetol (ribavirin)
	14179	00085-1327-04	
	14179	00085-1351-05	
	14179	00085-1385-07	
Z2G &W5G	89389	00085-1368-01	Peg-Intron (pegylated interferon)
	89391	00085-1291-01	
	14752	00085-1304-01	
	14753	00085-1270-01	
	18926	00004-0350-39	Pegasys (ribavirin)
	18287	00004-3500-09	
Z2G	51624	55513-0554-06	Infergen (interferon alfacon-1)
	51623	55513-0562-06	
	51623	64116-0031-01	
	51623	64116-0031-06	
Z2G	46472	00085-1168-04	Intron A (interferon alfa-2b)
	47525	00085-1133-01	
	47528	00085-1179-02	
	47602	00085-0571-02	
	47604	00085-0539-01	
	47605	00085-1110-01	
	47661	00085-1234-01	
	47663	00085-1242-01	
	47512	00004-2016-09	Roferon-A (interferon alfa-2a)
	47513	00004-2017-07	

APPENDIX II.

Count of Eligible Recipients in FFS and MediPass

Member Plan	CNTof Unique Members
	FY9900
FFS	1,535,688
MediPass	842,779
	FY0001
FFS	1,587,457
MediPass	903,052
	FY0102
FFS	1,765,708
MediPass	895,140
	FY0203
FFS	1,787,439
MediPass	944,617

Member Plan	CNTof Unique Members
	December '99
FFS	696,708
MediPass	519,849
	December '00
FFS	745,550
MediPass	592,203
	December '01
FFS	789,010
MediPass	599,509
	December '02
FFS	813,149
MediPass	642,631

Not Shown: HMO Recips, PSN Recips and Children's Medical Services

Data provided by ACHA (Chris Mallison): May, 20, 2004.