RESEARCH

Antiviral Regimen Complexity Index as an Independent Predictor of Sustained Virologic Response in Patients with Chronic Hepatitis C

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ABSTRACT

BACKGROUND: Hepatitis C virus (HCV) infection affects more than 170 million people worldwide, and one-third of them have human immunodeficiency virus (HIV) coinfection. Multiple studies have been conducted in order to identify the factors that may explain different responses to treatment among patients. However, the reasons why HIV-HCV coinfected patients have lower responses to treatment are not clear. In addition, no studies have evaluated the influence of the complexity of the therapeutic regimen for hepatitis C infection on clinical outcomes.

OBJECTIVES: To (a) investigate the influence of the antiviral regimen complexity in the sustained viral response (SVR) in patients with chronic hepatitis and (b) adapt a method of quantifying complexity of an antiretroviral regimen for patients infected with HCV.

METHODS: A single center, retrospective study was conducted in HCV and HIV-HCV coinfected patients. We selected patients treated with interferon alfa-2a plus ribavirin between January 2005 and December 2010. Patients with severe psychiatric disorders, those included in a clinical trial, and those known to be nonadherent to treatment were excluded. The dependent variable was the sustained virologic response and the independent variables were sex, age, race, stage fibrosis (F) ≥2, presence or absence of cirrhosis, low hepatitis C baseline viral load (defined as ≤800,000 IU), viral genotype, rapid virological response (RVR), serum gamma-glutamyltransferase (GGT) levels, ratio of alanine aminotransferase to aspartate aminotransferase (ALT/AST), serum cholesterol level, presence or absence of diabetes mellitus, and antiviral regimen complexity index. The latter variable included drugs for HCV and HIV infection, but no medication for other comorbidities. To evaluate the complexity of antiviral treatment we performed an adaptation of the system developed by Martin et al. (2007) in HIV patients. The factors determining the complexity of treatment were the number of medications, dosing schedules, administration methods, special instructions, and required preparations associated with antiviral regimens. Sample size was estimated by the Freeman equation. To determine the independent variables associated with SVR, we performed an univariate logistic regression and subsequently a multivariate analysis with those variables that demonstrated a statistically significant difference in the univariate analysis.

RESULTS: A total of 156 patients was included (76% men, mean age 44 years) of whom 45% were HIV-HCV coinfected. 75% were genotypes 1 or 4. The univariate analysis variables—genotypes 2 and 3 (OR=3.10; CI [1.38-6.95]; $P=0.006$); HIV-HCV coinfection (OR=0.36; CI [0.19-0.69]); presence of cirrhosis (OR=0.27; CI [0.10-0.73]; $P=0,01$); F≥2 (OR=0.44; CI [0.23-0.84]; $P=0.01$); low baseline viral load (OR= 2.05; CI [1.01-4.17]; $P=0.048$); RVR (OR=17,60; CI [6.84-45.30]; $P<0.001$); complexity index (OR=0.71; CI [0.58-0.87]; $P=0.001$), showed statistically significant relationships with SVR. Complexity index (OR=0.67; CI [0.52-0.87]; $P=0.002$) and RVR (OR=20.04; CI [7.33-54.85]; $P<0.001$) were independent predictors of SVR in multivariate analysis. The reliability of the multivariate analysis was checked with the Hosmer and Lemeshow test ($P=0.079$).

CONCLUSIONS: The medication regimen complexity may be a crucial factor to achieve therapeutic success when treating patients for hepatitis C. The adaptation of this index in patients with HCV provides an objective value of the antiviral regimen complexity and could help us to identify patients in clinical practice who require multidisciplinary attention. Simplification of the antiretroviral regimen might result in a greater response to treatment for hepatitis C.

J Manag Care Pharm. 2013;19(6):448-53

What is already known about this subject

- Several studies have identified clinical, virologic, histologic, biochemical, and demographic features that can predict a lower response to treatment with pegylated interferon and ribavirin.
- The role of the pharmacist has been defined for optimizing treatment response and managing adverse effects in hepatitis C virus (HCV) infection.
- Pharmacists are in an ideal position to provide care for patients with HCV due to the long duration of therapy, need for close monitoring of adverse effects and laboratory values, and potential dose adjustments required. The coordinated care between pharmacists and physicians improves patient care outcomes.

What this study adds

- The medication regimen complexity was identified as a predictor of sustained virologic response. No study has defined the role of medication regimen complexity in therapeutic success.
- We have developed a system that has allowed us to quantify an antiviral regimen's complexity. This system of quantification provides an objective and comparable measure among patients from around the world.
- The application of this tool in clinical practice will allow us to identify which patients have more complex treatments and require special attention by health care professionals as well as the development of measures to ensure therapeutic success.

Hepatitis C virus (HCV) infection affects more than 170 million people worldwide, with one-third of them presenting with human immunodeficiency virus (HIV) coinfection. HCV is a major public health problem worldwide, causing one million deaths annually.[1]

Until 2011, the standard therapy for the treatment of hepatitis C was based on the combination therapy of pegylated interferon (pegINF) alfa-2a or alfa-2b and ribavirin (RBV) administered for 24 or 48 weeks.[2] The recent emergence of direct antiviral agents has caused a radical change in the prognosis of the disease.[3]

The goal of treatment of hepatitis C infection is to eradicate the virus, thus preventing disease progression to cirrhosis and reducing the risk of hepatocellular carcinoma. The biomarker that best correlates with a cure is the achievement of sustained viral response (SVR),[4] defined as a negative HCV ribonucleic acid (RNA) 6 months after completing the antiviral treatment.

Over the past few years several studies have identified clinical, virologic, histologic, biochemical, and demographic features that can predict a lower response to treatment with pegINF and RBV.[5-7] However, we still do not know all the variables that may explain different responses among patients. The rapid virological response (RVR), defined as an undetectable hepatitis C viral load 4 weeks after the beginning of treatment, has been one of the factors most strongly associated with the achievement of SVR.[8-10] HIV-HCV coinfected patients have lower rates of HCV SVR compared with monoinfected patients (40% vs. 54-63%, respectively). Although the causes of lower response still remain unclear, coinfected patients have higher baseline viral loads and faster progression of the disease to liver fibrosis, as well as an increased risk of cirrhosis and hepatocellular carcinoma.[11] Adherence to combination therapy is known to be a crucial factor in achieving early virologic response (EVR) and subsequently SVR.[12,13] Mechanisms that may improve adherence to therapy include pharmacologic management of treatment-related adverse effects and careful selection, monitoring, and education of patients.

Pharmacists are in an ideal position to provide care for patients with HCV due to the long duration of therapy, need for close monitoring of adverse effects and laboratory values, and potential dose adjustments required.[14] Studies have suggested that coordinated care between pharmacists and physicians improves patient care outcomes.[15] Since the emergence of the concept of pharmaceutical care in Spain, hospital pharmacy departments have implemented this activity. Therefore, pharmaceutical care plays a key role in detecting drug-related problems and the development of measures to prevent them.[16] In order to do so, it is necessary to have specialized pharmacists and to create disease-specific clinics. Medication regimen complexity could be another key factor, which has not yet been considered in clinical practice. In 2011, the American Society of Health-System Pharmacists published a consensus document about optimal pharmacy practice models in hospitals and health systems.[17] One of the specific points mentioned in this consensus was that pharmacist-provided drug therapy management should be prioritized using a patient medication complexity index. However, validated methods to quantify regimen complexity need to be developed. Martin et al. (2007) developed a method for quantifying antiretroviral regimen complexity (ARC) in HIV patients.[18]

Multiple studies have been conducted in patients with HCV infection in order to identify the factors that may explain the different responses to treatment among patients. The reasons why HIV-HCV coinfected patients have lower responses to treatment are not yet clearly understood.[19] No studies have evaluated the influence of the complexity of the therapeutic regimen for hepatitis C infection on clinical outcomes. Therefore, the main objective of this study is to determine the influence of therapeutic regimen complexity on the achievement of SVR in HCV-infected patient, and to adapt a complexity index for this population based on the premise established by Martin et al. for patients with antiretroviral treatment.

Methods

We conducted a retrospective observational study that included HCV monoinfected patients and HIV-HCV coinfected patients who attended the pharmaceutical care office of a pharmacy service, which initiated treatment with pegINF and RBV between January 2005 and December 2010. We excluded patients enrolled in clinical trials, those with psychiatric disorders that may affect treatment adherence, and patients whose data were not available.

SVR was considered the dependent variable. We also collected the following demographic and clinical parameters described in the literature as independent predictors of SVR: age, sex, race, HIV-HCV coinfection, baseline cirrhosis, diabetes mellitus, significant fibrosis ($F \geq 2$), viral load (international units per milliliter [IU/mL]), serum gamma-glutamyltransferase (GGT; IU/L), ratio of alanine aminotransferase to aspartate aminotransferase (ALT/AST), total cholesterol (milligram per deciliter [mg/dL]), RVR, and viral genotype. In addition, an antiviral treatment complexity index was calculated for each patient.

This complexity index was calculated through the application available in Spanish at: http://www.farmaciavalmecpv.com/consulta/actividad/indice-de-complejidad/, based on an adaptation of the score created by Martin et al.[18] and whose items include the number of pills per day, the dosing schedule, dosage form, and specific instructions associated with taking drugs. The medication was obtained from a pharmacy dispensing program to outpatients.

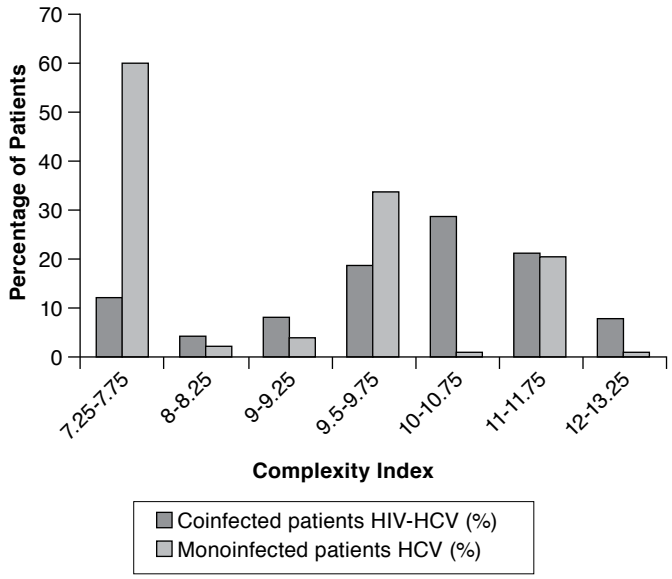
The remaining variables were obtained by consulting analytics, microbiology reports, and from review of the medical history of each patient. Continuous variables were expressed

TABLE 1 Baseline and Clinical Characteristics of the Patients Included in the Study

Variable	Frequency
Sex: male/female (% male)	119/37 (76)
Age (years)	45 ± 8.01
Caucasian race: n (%)	156 (100)
HIV-HCV coinfection: n (%)	70 (45)
Significant fibrosis (F ≥ 2): n (%)	72 (46)
Cirrhosis: n (%)	22 (14)
Diabetes mellitus: n (%)	30 (1.9)
GGT (IU/L)	100.9 ± 95.3
Total cholesterol (mg/dL)	166.6 ± 37.8
ALT/AST	0.9 ± 0.4
Genotype 1/4: n (%)	117 (75)
Viral load ≥ 800,000 (IU/mL) (%)	109 (70)
RVR: n (%)	58 (37)
SVR: n (%)	91 (54)
Complexity index	8.68 ± 1.62

ALT/AST = ratio of alanine aminotransferase to aspartate aminotransferase; GGT = gamma-glutamyltransferase; HIV-HCV = human immunodeficiency-hepatitis C virus; IU/L = international units per liter; mg/dL = milligrams per deciliter; RVR = rapid viral response; SVR = sustained viral response.

FIGURE 1 Percentage of Mono- and Coinfected Patients According to the Complexity Index Values Calculated



HCV = hepatitis C virus; HIV = human immunodeficiency virus.

as the mean value and standard deviation (SD) and categorical variables as percentages (%), calculating a 95% confidence interval (CI) when necessary.

We developed a multivariate logistic regression model that identified the role of pharmacotherapy complexity index as an independent variable predictive of SVR. The sample size was estimated according to the Freeman equation, $10 \times (k + 1)$, where k expresses the number of covariates. However, in case of dichotomous variables, there must be at least 10 cases for each of the possible values. As the population was homogeneous, we had to gather a similar percentage of patients monoinfected and coinfected. To know the relationship between each of the variables and SVR rate, we performed a logistic regression analysis. Subsequently, a multivariate analysis was performed by likelihood ratio. Variables that had shown statistical significance in the logistic regression were included as well as confounding variables such as age and sex. Validity of the model was evaluated in both cases by the Hosmer and Lemeshow test. Data analysis was performed using the statistical package SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL).

Results

We included 156 patients in the study, whose baseline and clinical characteristics are detailed in Table 1. As noted, all patients were Caucasian, most were men, and the mean age was 44 years. Regarding clinical characteristics, the number of HIV-HCV coinfected patients and the number of patients with significant fibrosis were similar and approached 50% of the population. In contrast, the percentage of patients with cirrhosis and diabetes was low. Average cholesterol levels were within the normal range. However, the mean values of GGT were above normal limits. The majority (75%) of patients were infected with viral genotype 1 or 4. High viral load occurred in a high percentage (70%) of patients. On the other hand, 37% of patients achieved RVR, and SVR was achieved in 54% of patients. The mean complexity index was 9.13 ± 1.72.

The percentages of mono- and coinfected patients according to the complexity index values calculated are shown in Figure 1. The complexity index values were lower in monoinfected patients, ranging from 7.25 to 9.75, compared with coinfected patients, whose values reached 13.25. The complexity index variability in patients was due mainly to the number of pills per day, number of pills per dose, and specific instructions associated with taking drugs (with food or on an empty stomach). Patients with more complex regimens were those treated with HIV protease inhibitors, followed by those treated with zidovudine, didanosine, raltegravir, and maraviroc. However, etravirine did not have a high complexity index because it can be taken in a single dose, which facilitates administration. However, patients treated with atripla (coformulation efavirenz/emtricitabine/tenofovir) had a similar complexity index to that of monoinfected patients.

TABLE 2 Descriptive Analysis of Independent Predictors of SVR

Variable	SVR
Sex (% male)	51
Sex (% female)	62
HIV-HCV coinfection (%)	40
HIV infection (%)	65
RVR (%)	90
No RVR (%)	33
Significant fibrosis (F≥2) (%)	43
Fibrosis (F < 2) (%)	64
Cirrhosis (%)	27
No cirrhosis (%)	58
Genotype 1/4 (%)	48
Genotype 2/3 (%)	74
Viral load ≤800,000 (IU/mL) (%)	49
Viral load 800,000 (IU/mL) (%)	66

HIV-HCV = human immunodeficiency-hepatitis C virus; IU/mL = international units per milliliter; RVR = rapid viral response; SVR = sustained viral response.

Table 2 includes the rates of SVR according to demographic, virologic, and histologic characteristics. Regarding the qualitative variables, there are major differences in SVR rates according to clinical characteristics. Regarding the qualitative variables, there are major differences in SVR rates according to clinical characteristics. Thus, 90% of patients with RVR achieved SVR. Other important variables were the presence of cirrhosis (58% without cirrhosis achieved SVR vs. 27% with cirrhosis) and viral genotype (74% with genotype 2 or 3 achieved SVR vs. 48% for genotype 1 or 4). On the other hand, values of GGT and AST/ALT ratio were higher in patients who did not achieve SVR, reflecting increased hepatic progression among patients who had not responded to treatment. Similarly, the average value of the complexity index was higher in patients who did not achieve SVR.

The limited presence of diabetes mellitus in the study population (3 patients) led to the exclusion of this variable in the logistic regression analysis. Variables that reached statistical significance with the SVR rate in the univariate regression analysis were genotype 2 or 3, HCV monoinfection, low viral load (≤800.000 IU), no cirrhosis, no significant fibrosis, achievement of RVR, and lower complexity index. Table 3 shows the relationship between these variables and the SVR expressed by the odds ratio for a confidence interval of 95%. The value of the Hosmer and Lemeshow test confirmed the validity of this model ($P = 0.606$).

Subsequently, multivariate analysis showed that RVR and the complexity index were the only independent predictors of SVR (Table 4). Similarly, the Hosmer and Lemeshow test showed the validity of the analysis ($P = 0.079$) despite not having achieved the sample size estimate.

TABLE 3 Univariate Analysis[a]

Variable	Odds Ratio (95% CI)	
Genotype 2/3	3.10	(1.38-6.95)
HIV-HCV coinfection	0.36	(0.19-0.69)
Cirrhosis	0.27	(0.10-0.73)
Significant fibrosis (F ≥ 2)	0.44	(0.23-0.84)
Viral load ≤800,000 (IU/mL)	2.05	(1.01-4.17)
RVR	17.60	(6.84-45.3)
Complexity index	0.71	(0.58-0.87)

[a]*Only variables with a significant association with SVR are included.*
CI = confidence interval; HIV-HCV = human immunodeficiency-hepatitis C virus; IU/mL = international units per milliliter; RVR = rapid viral response; SVR = sustained viral response.

TABLE 4 Multivariate Analysis[a]

Variable	Odds Ratio (95% CI)	
RVR	19.60	(6.30-60.7)
Complexity index	0.675	(0.52-0.88)

[a]*Only variables with a significant association with SVR are included.*
CI = confidence interval; RVR = rapid viral response; SVR = sustained viral response.

Discussion

In our study, the complexity index was identified as a predictor of SVR. The variables that showed statistically significant relationships with the SVR were consistent with the results obtained in previous studies.[20] However, in the multivariate analysis, only RVR and the complexity index were identified as independent predictors of response. The influence of the complexity of medication regimen on response to treatment for hepatitis C has not previously been evaluated.

Also, in this study we have adapted a system that has allowed us to quantify antiviral regimen complexity. This system was initially developed for other patient populations, such as HIV-infected and elderly patients.[18,21] However, no studies have been conducted in patients with hepatitis C.

As in many other chronic illnesses with detrimental sequelae, pharmacists may be a resource to manage the disease and mitigate negative outcomes.[22] In fact, the role of pharmacists in optimizing treatment response and managing adverse effects in HCV infection is recognized.[23,24] Mariño et al. (2009) described the results of pharmacist interventions for optimizing response in treatment-naïve patients with chronic HCV-1.[25] They noted that the SVR may be higher due to the low rate of early treatment discontinuation in the study. Additionally, the overall mean adherence rate was 85.7%; the adherence rate in the patients achieving SVR reached an impressive 95.5%. Therefore, this study shows that pharmacists can strongly influence patients with respect to education, adherence, and management of adverse effects. However, there are no tools for pharmaceutical care to optimize therapeutic results in patients

with chronic hepatitis C. In our study, we propose a simple tool to be applied in the clinical practice of pharmacy departments.

To date, pharmaceutical activity has been based on adherence, but we include in our study the concept of medication regimen complexity. Adherence and complexity are closely linked, since adherence can be compromised by a high complexity of the treatment. Several studies have found that adherence is a key factor in achieving EVR and SVR.[12,13,26]

The application of this tool in clinical practice will allow us to identify which patients have more complex treatments and require special attention by health care professionals and to help develop measures to ensure therapeutic success. Currently, the complexity index could play a key role due to the emergence of direct-acting antiviral agents that selectively target HCV, since the addition of these agents to the combination therapy of peg-IFN and RBV implies a significant increase in the complexity of treatment.[27]

The main objective of the multidisciplinary team responsible for the care of HCV patients is to achieve therapeutic success. This requires the development of new pharmacotherapeutic tools for patient follow-up. Further studies are needed to explore the benefits of the pharmacist's application of this tool in hepatitis C-infected patient management.

Limitations

The limitations of this study relate to the retrospective nature of the data and the difficulty in collecting all variables. This is the reason why the sample size was lower than estimated. However, the Hosmer and Lemeshow test confirmed the stability of the model, as well as the reliability and veracity of the results.

Adherence was not included as a variable in our study due to its retrospective design, but it was assessed through the electronic dispensing records from our pharmacy program, from which we excluded patients who did not regularly fill their prescriptions.

Inclusion of coinfected HIV-HCV patients could have been considered a complicating factor, since the response in these patients is lower, although the specific causes of this response are currently not known. To address this complication, we included the main predictors of SVR described in the literature and conducted a multivariate analysis. Nevertheless, the increased regimen complexity in coinfected patients may be one of the causes that would justify the lower response seen in this patient population. However, some coinfected patients included in our study had complexity indices similar to those of monoinfected patients. This may be due to the advancement of antiretroviral therapy in recent years.

Conclusions

Medication regimen complexity may be a crucial factor in achieving therapeutic success in the treatment of HCV. Pharmacists may apply this system of quantification to identify patients with more complex regimens and conduct measures to ensure that therapeutic goals are achieved. On the other hand, the simplification of highly active antiretroviral therapy in HIV-HCV coinfected patients could increase the response rates to the treatment of hepatitis C.

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DISCLOSURES

The authors report no financial conflicts of interest related to the subjects discussed in this article.

Concept and design were performed by Galán and Verdugo. Data were collected by Galán and Cidoncha and interpreted by Galán, Cidoncha, and González. The manuscript was written by Galán, Cindoncha, Martin, and Rodriguez and revised by Martin, Rodriguez and Verdugo.

REFERENCES

1. Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet*. 2003; 362(9401):2095-100.

2. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001; 358(9286):958-65.

3. Thomas DL. Advances in the treatment of hepatitis C virus infection. *Top Antivir Med*. 2012;20(1):5-10.

4. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology*. 2010;139(5):1593-601.

5. Ferenci P. Predictors of response to therapy for chronic hepatitis C. *Semin Liver Dis*. 2004;24(Suppl)2:25-31.

6. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol*. 2008;49(4):634-51.

7. McHutchison JG, Lawitx EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Eng J Med*. 2009;361(6):580-93.

8. Vergara M, Gallach M, Dalmau B, et al. Results of pegylated interferon and ribavirin for the treatment of chronic hepatitis C in clinical practice: a 5-year experience. *Gastroenterol Hepatol*. 2008;31(5):274-79.

9. Aziz H, Raza A, Waheed Y, Gill U, Gill ML. Analysis of variables and interactions among variables associated with a sustained virological response to pegylated interferon alfa-2a plus ribavirin in hepatitis C virus genotype 3-infected patients. *Int J Infect Dis.* 2012;16(8):597-602.

10. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49(4):1335-74.

11. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis.* 2001;33(4):562-69.

12. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology.* 2002;123(4):1061-69.

13. Lo Re V 3rd, Amorosa VK, Localio AR, et al. Adherence to hepatitis C virus therapy and early virologic outcomes. *Clin Infect Dis.* 2009;48(2):186-93.

14. Kolor B. Patient education and treatment strategies implemented at a pharmacist-managed hepatitis C virus clinic. *Pharmacotherapy.* 2005;25(9):1230-41.

15. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med.* 2006;166(9):955-64.

16. Viktil KK, Blix HS. The impact of clinical pharmacists on drug-related problems and clinical outcomes. *Basic Clin Pharmacol Toxicol.* 2008;102(3):275-80.

17. The consensus of the Pharmacy Practice Model Summit. *Am J Health-Syst Pharm.* 2011;68(12):1148-52.

18. Martin S, Wolters PL, Calabrese SK, et al. The Antiretroviral Regimen Complexity Index: a novel method of quantifying regimen complexity. *J Acquir Immune Defic Syndr.* 2007;45(5):535-44.

19. Barreiro P, Vispo E, Labarga P, Soriano V. Management and treatment of chronic hepatitis C in HIV patients. *Semin Liver Dis.* 2012;32(2):138-46.

20. Moraes Coelho HS, Villela-Nogueira CA. Predictors of response to chronic hepatitis C treatment. *Ann Hepatol.* 2010;9(Suppl):54-60.

21. Mansur N, Weiss A, Beloosesky Y. Looking beyond polypharmacy: quantification of medication regimen complexity in the elderly. *Am J Geriatr Pharmacother.* 2012;10(4):223-29.

22. Pellegrino AN, Martin MT, Tilton JJ, Touchette DR. Medication therapy management services: definitions and outcomes. *Drugs.* 2009;69(4):393-406.

23. Hammond RW, Schwartz AH, Campbell MJ, et al. Collaborative drug therapy management by pharmacists. *Pharmacotherapy.* 2003;23(9):1210-25.

24. Spooner, L. The critical need for pharmacist involvement in the management of patients with hepatitis C. *J Manag Care Pharm.* 2009;15(2):151-53. Available at: http://www.amcp.org/data/jmcp/151-153.pdf.

25. Mariño EL, Alvarez-Rubio L, Miró S, et al. Pharmacist intervention in treatment of patients with genotype 1 chronic hepatitis C. *J Manag Care Pharm.* 2009;15(2):147-50. Available at: http://www.amcp.org/data/jmcp/147-150.pdf.

26. Cacoub P, Ouzan D, Melin P, et al. Patient education improves adherence to peg-interferon and ribavirin in chronic genotype 2 or 3 hepatitis C virus infection: a prospective, real-life, observational study. *World J Gastroenterol.* 2008;14(40):6195-203.

27. Gaglio PJ, Moss N, McGaw C, Reinus J. Direct-acting antiviral therapy for hepatitis C: attitudes regarding future use. *Dig Dis Sci.* 2011;56(5):1509-15.