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EDITORIAL

Management of hepatitis C virus infection in HIV/HCV co-infected patients: Clinical review

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Abstract

Nearly one fourth of individuals with human immunodeficiency virus (HIV) infection have hepatitis C virus (HCV) infection in the US and Western Europe. With the availability of highly active antiretroviral therapy and the consequent reduction in opportunistic infections, resulting in the prolongation of the life span of HIV-infected patients, HCV co-infection has emerged as a significant factor influencing the survival of HIV patients. Patients with HIV/HCV co-infection have a faster rate of fibrosis progression resulting in more frequent occurrences of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. However, the mechanism of interaction between the two viruses is not completely understood. The treatment for HCV in co-infected patients is similar to that of HCV mono-infection; i.e., a combination of pegylated interferon and ribavirin. The presence of any barriers to anti-HCV therapy should be identified and eliminated in order to recruit all eligible patients. The response to treatment in co-infected patients is inferior compared to the response in patients with HCV mono-infection. The sustained virologic response rate is only 38% for genotype-1 and 75% for genotype-2 and -3 infections. Liver transplantation is no longer considered a contraindication for end-stage liver disease in co-infected patients. However, the 5 year survival rate is lower in co-infected patients compared to patients with HCV mono-infection (33% *vs* 72%, P = 0.07). A better understanding of liver disease in co-infected patients is needed to derive new strategies for improving outcome and survival.

Key words: Hepatitis C virus; Human immunodeficiency virus; Coinfection; Pegylated interferon; Ribavirin

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INTRODUCTION

Co-infection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is common as both viruses share similar modes of transmission. The management of HCV infection in the HIV infected population poses a serious challenge for physicians. Approximately two thirds of co-infected patients do not receive anti-HCV treatment for reasons such as poor compliance with highly active anti-retroviral therapy (HAART), decompensated liver disease, co-morbidities, active substance use, ongoing alcohol use, and advanced HIV disease[1,2]. Thus, only a minority of such patients receive anti-HCV treatment[2-4]. In order to improve the outcome in co-infected patients, it is important to have a good understanding and knowledge of HAART and its interaction with drugs used for HCV treatment.

EPIDEMIOLOGY AND PREVALENCE OF HCV IN HIV INFECTED INDIVIDUALS

In the US, about 25% to 35% of patients with HIV are infected with HCV, with a higher prevalence (40%) in US military veterans[3,5,6]. This translates to nearly 300 000 people in the US who are co-infected with HIV and HCV. The co-infection rate is higher when transmission occurs through the parenteral route

compared to when the infection is acquired by sexual contact. The prevalence of HCV in HIV patients who acquire infection through intravenous drug abuse (IVDA) or multiple blood transfusions is 75%-90%[3,7]. Although sexual contact is a common route of HCV transmission[8,9], it is difficult to determine its true significance because other variables are frequently also involved. Bollepalli *et al*[10] reported that IVDA, snorting drugs, sharing toothbrushes/razors, being in prison, and tattooing are significant non-sexual risk factors, while sex for money or drugs, sex with IVDA users, and men who have sex with men (MSM) are significant sexual risk factors for co-infection. However, on multivariate analysis, only IVDA emerged as a risk factor for co-infection ($P = 0.001$)[10].

SIGNIFICANCE OF HCV AND HIV CO-INFECTION

With the availability of HAART, the outcome of patients infected with HIV has improved remarkably in the last decade[11,12]. Since HIV patients are now surviving longer, liver disease due to HCV co-infection has emerged as a significant problem. The presence of HIV alters the natural history of HCV infection. After acquiring HCV, the infection has a tendency to chronicity in over 90% amongst HIV patients due to the lack of critical CD4 T cell responses against HCV[13,14]. Once chronic HCV infection is established, fibrosis progression is much faster, resulting in a higher frequency of cirrhosis and its complications compared to HCV mono-infection[15,16]. A meta-analysis of 8 studies involving 1871 HCV positive patients (601 co-infected with HIV) showed a relative risk of 2.92 (95% CI 1.70-5.01) for more severe disease, 2.07 (95% CI 1.40-3.07) for histological cirrhosis and 6.14 (95% CI 2.86-13.20) for decompensated liver disease[15]. Similarly, there is a higher incidence of hepatocellular carcinoma (HCC) in co-infected patients[17,18]. Co-infected patients with HCC are younger (42 ± 10 year *vs* 69 ± 9 year, $P < 0.001$) and have a shorter duration of HCV infection (18 ± 3 year *vs* 28 ± 11 year, $P < 0.05$) compared to patients with HCC in HCV mono-infection. Tumors at presentation in co-infected patients have an infiltrative pattern, are at an advanced stage, and have more frequent extra-nodal metastasis[18].

The mechanism of interaction between the two viruses and their impact on liver injury is not completely understood. HCV is not directly cytopathic and the pathogenesis of liver injury is believed to be immune mediated[19]. It can be argued that HIV patients should develop less severe liver injury because of immune-suppression, while the use of HAART with resultant immune restoration should lead to increased liver damage. However, such a scenario is not observed in clinical practice. Puoti *et al*[20] showed that a CD4 count of < 500 was an independent predictor ($P = 0.04$) for stage 3-4 disease in a study on 204 patients with chronic HCV infection (84 with HIV co-infection). A reduction in fibrosis progression, as well as liver disease, has been observed with successful control of the HIV infection[21,22]. In a retrospective analysis of 381 patients, Verma *et al*[21] showed that the fibrosis progression rate and cirrhosis in co-infected patients was significantly reduced in patients who received HAART as the initial therapy compared to those who received NRTIs followed by HAART (50% *vs* 68%, $P < 0.006$) It has been shown that co-infected patients are more susceptible to liver toxicity and steatosis from HAART, and more so with the use of NRTIs[23]. Despite immune suppression, HCV-specific CD8 and CD4 cell responses have been observed in the livers of patients with HIV and HCV co-infection[24]. Moreover, the HCV viral load is higher in co-infected patients compared to HCV mono-infection[25,26]. Whether high HCV load is associated with more severe liver injury is not known. The lack of an animal model prevents development of a better understanding of the pathogenesis of liver disease in co-infected patients.

MANAGEMENT OF HIV/HCV CO-INFECTION

Timing of treatment

With improved survival of HIV patients in the HAART era, liver disease has emerged as an important cause of morbidity and mortality in co-infected patients. In an analysis of the adverse events of anti-HIV drugs, 1246 patients out of a total of 23 441 died over a 5-year follow-up period; liver failure constituted 15% of the mortality and over 50% of deaths occurred despite adequate HIV suppression[27]. Therefore, effective treatment for both viruses is essential for a favorable outcome in co-infected patients.

The treatment of HCV in HIV infected patients is a challenging undertaking. Management should ideally be provided in a center with experience in treating such patients, preferably under the care of a multidisciplinary team comprised of hepatologists, infectious disease physicians, psychiatrists, pharmacists, social workers, and a substance abuse program.

All HIV patients should be tested for HCV as soon as HIV is diagnosed. An HIV patient negative for anti-HCV, but with significant risk factors for HCV, should be tested for HCV-RNA as a minority of HIV patients may have viremia despite a negative anti-HCV test[28]. Assessment of viral load of HIV and HCV along with a CD4 count should be obtained. The current recommendation is to suppress HIV before starting anti-HCV therapy[29].

Selection of patients

Patients positive for HCV RNA with ALT elevation and/or stage 2 disease (or more) on liver biopsy should be considered for treatment. Patients with mild disease (stage 1 fibrosis) may also be considered if they are good treatment candidates (low viral count, genotype-2 and -3). About 25% patients with mild disease on the initial

Table 1 Baseline assessment before starting treatment in HCV-HIV co-infected patients

Assessment of liver diseases status
CTP staging
HCV-RNA
HCV genotype
AFP and USG/CT scan for HCC
HBV markers (HBsAg and anti-HBc)
HBV-DNA for patients with isolated anti-HBc to detect low level viremia
Anti-HAV IgG
Assessment of HIV disease status
Current and past opportunistic infections
HIV-associated malignancy
CD4 count
HIV viral load
Details of HAART
Assessment for problems precluding therapy or requiring control before therapy
TSH
Screening for depression or other psychiatric diseases
Complete blood count
Blood sugar
History of significant cardiac, renal, or pulmonary disease
Fundus examination for retinopathy
Beta HCG to exclude pregnancy in females
Urine toxicology screening to exclude concurrent active substance abuse
Social support and treatment compliance

HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; CTP: Child Turcotte Pugh; AFP: α-feto protein; USG: Ultrasonogram; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular cancer; HAART: Highly active antiretroviral therapy; TSH: Thyroid stimulating hormone; HCG: Human chorionic gonadotropin.

liver biopsy develop significant fibrosis over an average period of 3 years. The occurrence of ALT elevation during the follow up period is an independent predictor of disease progression[30]. Therefore, if the treatment was deferred at the initial evaluation, regular clinical and laboratory follow-up should be pursued. A repeat liver biopsy should be performed after 3 years, especially in patients with ALT elevation on follow up.

Assessment of liver fibrosis before treatment

Assessment of fibrosis allows treatment to be deferred in patients with mild disease due to genotype-1 or -4 infections. As mentioned earlier, treatment may be considered for genotype-2 or -3 disease as the response to therapy in this population is very good. Liver biopsy is the gold standard for the assessment of fibrosis and cirrhosis. However, liver biopsy has certain disadvantages. Being an invasive procedure, serious complications such as bleeding can occur[31]. Sampling error due to tissue fragmentation and small sample size may provide inaccurate results. Moreover, the procedure adds to the overall cost of the treatment[32].

Non invasive markers of fibrosis are available and may replace liver biopsy in the future. Various surrogate serum markers such as AST to platelet ratio index (APRI), Fibrotest score (comprised of serum bilirubin, α-2 macroglobulin, Apolipoprotein A1, haptoglobin, and gamma glutamyl transpeptidase activity), SHASTA index (hyaluronic acid, AST, and albumin levels), Forn's index (platelet, GGT, age, and cholesterol), and FIB-4 (age, AST, ALT, and platelets) have been tested in HIV-HCV co-infected patients with generally favorable results[33]. The measurement of liver stiffness by elastography (Fibroscan or Elastoscan) using an ultrasonic transducer is a rapid, simple, non-invasive, and reproducible technique. It is also more accurate than serum markers in the diagnosis of cirrhosis in co-infected patients[34].

Pre-treatment assessment

A detailed clinical evaluation with history and physical examination is essential before starting anti-HCV therapy (Table 1). Patients with decompensated liver disease; i.e., with presence of ascites, variceal bleeding, jaundice, and encephalopathy (Child Turcotte Pugh or CTP stage B and C), do not tolerate interferon (IFN) based therapy well[35]. Patients should have a hemoglobin level > 11 g/dL in females and > 12 g/dL in males, a platelet count > 75 000/cm and an absolute neutrophil count (ANC) > 1500 before starting treatment. A baseline fundus examination is recommended as pegylated interferon (PEG-IFN) can cause retinopathy with visual disturbances[36]. Combination of Didanosine (DDI) and Zidovudine (AZT) should be avoided to prevent hepatic and mitochondrial toxicity[37,38].

Therapeutic regimen for treating HCV

The introduction of interferon (INF) in 1991 has revolutionized the treatment of HCV infection. In HIV/HCV co-infected patients, results obtained with PEG-IFN + ribavirin (RBV)[39-54] were superior to those with PEG-IFN alone, standard IFN alone[48], or standard IFN + RBV (Table 2). A meta-analyses of 6 randomized controlled studies showed superior sustained virologic response (SVR) with PEG-IFN + RBV compared with IFN + RBV and PEG-IFN monotherapy. The response was more favorable in males, patients with CD4 > 500, HCV load < 1000000, and in non drinkers[55]. Currently, PEG-IFN and RBV combination is the standard of care for the treatment of HCV in HIV patients.

Response rate

In an intention to treat analysis, the end of treatment response (ETR); i.e., negative HCV-RNA at the end of treatment, and SVR; i.e., negative HCV-RNA 24 wk after discontinuation of treatment with PEG-IFN + RBV, in IFN naïve HIV/HCV co-infected patients were 29%-62% and 17%-53%, respectively (Table 2). The large difference in the response rates is due to variable frequency of baseline characteristics, such as the presence of cirrhosis, frequency of genotype-1 (GT-1), baseline HIV parameters, dose of RBV, and treatment discontinuation rate. The ETR and SVR rates were superior for the GT-2/3 (44%-81% and 24%-62%, respectively) compared to GT-1/4 (19%-47% and 9%-38%, respectively)[44,46,47]. In a recent study, the treatment response rates were similar with the use of PEG-IFN 2a and 2b[56].

The highest SVR rate of 53% was reported by Hopkins *et al*[49], which may be related to the lower

Table 2 Trials of anti-HCV treatment in HIV patients

Author (yr)	Country	*n*	Schedule	Duration	Overall response (%)		GT-2/3		GT-1/4	
					ETR	SVR	ETR	SVR	ETR	SVR
Pérez-Olmeda *et al*[39] (2003)	Spain	68	PEG-IFN 150 μg/wk × 12 wk, then 100 μg/wk + RBV 400 mg bid	6 mo for GT-1/4 and 12 mo for GT-3	30.3	24.2	81[1]	52.3	30.3	24.2
Cargnel *et al*[40] (2005)	Italy Multi Center	135	PEG-IFN 1.5 μg/kg per week + RBV 400 bid	48 wk	28.9	21.7	43.7	34.4	18.7	9.4
			PEG-IFN 1.5 μg/kg per week		16.7	9.1	16.2	10.8	14.7	8.8
Bräu *et al*[41] (2004)	United States	107	IFN α-2b 3 mu tiw + RBV 800 mg /d *vs*	48 wk	18.9	11.3	50	41.7	10	2.5
			IFN α 2b 3 mu tiw + placebo × 16 wk, then RBV 800 mg/d		7.4	5.6				
Laguno *et al*[42] (2004)	Spain	95	IFN α 2b 3 mu tiw + RBV 800-1200 mg/d *vs*	48 wk for GT-¼ and 24 wk for HT-2/3	30[1]	21[1]	67	47	11	7
			PEG-IFN 100-150 μg/wk + RBV 800-1200 mg/d		52	44	68	53	41	38
Myers *et al*[43] (2004)	Canada	32	PEG-IFN α 2b (1.5 μg/kg per week) + weight based RBV (1000 mg for 75 kg or less or 1200 mg for > 75 kg) in IFN non responders	48 wk	19	16		29		9
Chung *et al*[44] (2004) ACTG	United States	133	PEG-IFN α 2a 180 μg/wk + RBV (400 mg/d × 4 wk- 600 mg/d × 4 wk - 1000 mg/d *vs*	48 wk	41[1]	27[1]	80[1]	73[1]	33[1]	29
			IFN α 2a 6 mu tiw × 12 wk, then 3 mu tiw +RBV as above		12	12	33	33	6	6
Moreno *et al*[45] (2004)	Spain	35	PEG-IFN 50 μg/wk + RBV 800 mg/d	48 wk		31		70		25
Torriani *et al*[46] (2004)	APRICOT	868	PEG-IFN α 2a 180 μg/wk + RBV 800 mg/d *vs*	48 wk	47	40[1]	64	62[1]	38	29
			PEG-IFN α 2a + Placebo *vs*		31	20	57	36	21	14
			IFN α 2a 3 mu tiw + RBV		14	12	27	20	8	7
Carrat *et al*[47] (2004) RIBAVIC	France Multi Center	412	PEG-IFN α 2b 1.5 μg/kg per week + RBV 800 mg/d *vs*	48 wk	35[1]	27[1]	50	43.7	25.6	16.8[1]
			IFN α 2b 3 mu tiw + RBV 800 mg/d		21	20	47.4	43.4	6.2	6.2
Khalili *et al*[48] (2005)	United States	154	PEG-IFN α 2a 180 μg/wk	48 wk	55	35	NA			
			PEG-IFN + Placebo		3	0				
			PEG-IFN + RBV 800 mg/d		11	5				
Hopkins *et al*[49] (2006)	United Kingdom	45	PEG-IFN α 2b 1.5 μg/kg per week + RBV (1000-1200 mg/d)	24 wk for GT- 2/3 and 48 wk for GT-1	62	53	82	75[1]	25	19
Moreno *et al*[50] (2006)	Spain	70 (HCV)	PEG-IFN α 2b 1.5 μg/kg per week + RBV 10.6 mg/kg per day	48 wk	46	37[1]	All patients had GT-1 or 4 infection and the overall ETR and SVR were 39 and 30% respectively			
		36 (HCV +HIV)			25	17[1]				
Santin *et al*[51] (2006)	Spain Multi Center	60	PEG-IFN α 2b 80-150 μg/wk + RBV 800-1200 mg/d	24 wk for GT 2/3 and 48 wk for GT ¼	33	27	53	42	24	20[1]
Voigt *et al*[52] (2006)	Germany Multi Center	122	PEG-IFN α 2b 1.5 μg/kg per week + RBV 800 mg/d	24 wk for GT 2/3 and 48 wk for GT ¼	52	25	72	44	41	18[1]
Fuster *et al*[53] (2006)	Spain Multi Center	110	PEG-IFN 180 μg/wk + RBV 800 mg/d	24 wk for GT 2/3 and 48 wk for GT ¼	53	42	68	55	47	33
Righi *et al*[54] (2008)	Italy	43	PEG-IFN 2a 180 μg/wk or 2b 1.5 μg/kg per week + RBV (10.6 mg/kg per day)	24 wk for GT 3 and 48 wk for GT-1a	51	30	Despite 51% of GT-3 infection, lower response due to high dropout rate of 63% (voluntary in 52%)	38		24

[1]Responses are on intent to treat analysis. ETR: End of treatment response (HCVRNA < 50 copies/mL); SVR: Sustained virologic response (HCVRNA < 50 copies/mL 6 mo after discontinuing treatment); PEG-IFN: Pegylated interferon; RBV-ribavirin; GT: Genotype; tiw: Three times a week; ACTG: AIDS clinical trial group; APRICOT: AIDS pegasys ribavirin international coinfection trial.

proportion of GT-1 patients (33%) compared with other studies (48%-77%) (Table 2). The pooled SVR rate with the use of PEG-IFN + RBV obtained from 7 randomized controlled trials or prospective cohort studies involving 784 HIV + HCV co-infected patients was 33.3% (27.3%-44.2%)[57]. The SVR rate in HCV mono-infection with PEG-IFN + RBV was much better (52% for GT-1 and 80% for GT-3)[58]. A head-to-head comparison of the two groups also showed superior ETR and SVR rates for GT-1 infection (46% *vs* 25%, $P < 0.05$ and 37% *vs* 17%, $P < 0.05$, respectively)[50]. These inferior response rates in co-infected patients can be explained to some extent by the greater number of patients with cirrhosis (43% *vs* 11%, $P = 0.0001$), and lower doses of RBV used (12.75 ± 1.46 *vs* 14.10 ± 1.88, $P = 0.0001$) in these patients.

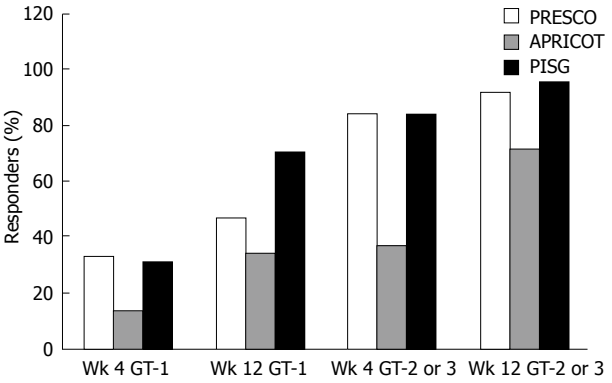

Figure 1 Patients who consumed > 80% of their anti-HCV medications showed a trend towards better sustained virologic response (SVR) compared to those with < 80% drug compliance (72% *vs* 57%, *P* = 0.06). The SVR was much better in GT-1 infections (63% *vs* 34%, *P* = 0.008) but not in GT-2 or -3 infections (94% *vs* 95%, *P* = 0.88). Wk: Week.

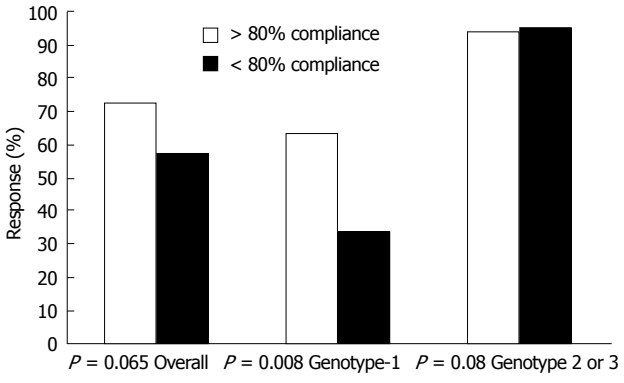

Figure 2 Results of virologic response in different studies. PRESCO study 33% and 84%, respectively, at weeks 4 and 12 for GT-1 infections; APRICOT study 13% and 34%; PISG study 31% and 71% respectively. Similar figures for GT-2 and -3 infections were 47% and 92%, 37% and 72%, 84% and 96%, respectively.

Table 3 Barriers against anti-HCV therapy in co-infected patients

Patient-related factors
Active substance abuse
Concern regarding adverse effects
Cost of treatment
Lack of social support
Lack of transport
Number of pills and dosing frequency (including HAART)
Physician-related factors
Lack of experience
Lack of awareness
Lack of motivation for referral
Fear of adverse effects

HAART: Highly active anti-retroviral therapy.

Another important reason for the lower SVR in the co-infected population is the high treatment dropout rate (12%-51%) (Table 3). The importance of medication compliance was shown in a recent retrospective analysis on HCV mono-infected patients[59]. Patients who consumed > 80% of the medications (PEG-IFN + RBV), had a superior SVR compared to those with < 80% compliance (Figure 1). The difference in SVR was noted for GT-1 but not for GT-2/3 infection. The treatment discontinuation rates were 39% in both the APRICOT and RIBAVIC trials, and 12% in the ACTG study[44,46,47]. Discontinuation of treatment due to adverse effects was observed in 13%, 17%, and 12% of patients, respectively. These figures are similar to discontinuation rates in the HIV negative population[60]. Other reasons for treatment discontinuation were patient refusal (4%), lack of follow up (4%), and violation of the study protocol (1%) in the APRICOT study. Another reason was relapse of substance abuse in 1%-4% patients[41,48].

The barriers to anti-HCV treatment may be patient as well as physician related (Table 3). Education and motivation of patients with intensive training and provision of better infrastructure for the treating physicians may improve the outcome. Most studies to date have excluded patients with active substance abuse (Table 3). A recent NIH consensus conference has recommended that active substance abuse should not be considered a contraindication to anti-HCV treatment[61]. Instead, greater integration of HCV treatment in HIV clinics and detoxification programs and provision of additional social support should be encouraged[62]. In a retrospective analysis of 73 patients with HCV infection (32% with HIV) treated at a methadone maintenance treatment program, encouraging ETR and SVR rates of 55% and 45%, respectively, were obtained[63].

Drug doses

The recommended dose of PEG-IFN 2a is 180 μg/wk and for PEG-IFN 2b is 1.5 μg/kg per week (Table 2). Because of the wider systemic distribution of PEG-IFN 2b, it is essential to adjust the dose for body weight, as compared to PEG-IFN 2a, which is restricted to blood and interstitial fluids only. In most studies, RBV has been used at a dose of 800 mg/d or 10.6 mg/kg per day in co-infected patients (Table 2). Virologic response at weeks 4 and 12 were superior with the use of 1000-1200 mg of RBV compared to 800 mg/d of RBV (Figure 2). Improved SVR rates, similar to that seen in HCV mono-infection, were observed when RBV was used at a dose of 1000-1200 mg[49,64,65]. Based on the current data, it is recommended that weight-based RBV (1000 mg/d for < 75/kg and 1200 mg/d for 75 kg and above) should be used in co-infected patients.

Duration of therapy

The use of PEG-IFN + RBV for 48 wk in GT-1/4 and 24 wk in GT-2/3 infections yielded ETR in 53%-82% and SVR in 42%-75% patients (Table 2). On the other hand, treatment for 48 wk for all GTs achieved an ETR in 50%-80% and SVR in 44%-73% co-infected patients[44,46,47]. In the recently completed PRESCO trial, PEG-IFN and weight-based RBV were used for 48 wk or 72 wk for GT-1/4 and 24 wk or 48 wk for GT-2/3[65]. The overall SVR was 49.6% (72.4% in GT-2/3 and 35% in GT-1/4, $P < 0.001$). In patients with GT-2/3, a higher relapse rate was seen in patients treated for 24 wk compared to those receiving 48 wk of treatment (40% *vs*

Table 4 Morbidity and mortality with PEG-IFN + RBV: results of three large trials

Parameter	Sub-parameter	ACTG (*n* = 66)	APRICOT (*n* = 286)	RIBAVIC (*n* = 194)
Treatment related adverse events	Influenza like symptoms	31 (47)		172 (89)
	Fatigue		128 (44)	
	Pyrexia		128 (44)	
	Headache		111 (39)	
	Myalgia		103 (36)	
	Nausea		85 (30)	
	Diarrhea		81 (28)	
	Depression	7 (11)	76 (26)	46 (24)
	Weight loss		82 (28)	46 (24)
	Injection site reaction			44 (21)
	Anorexia			38 (20)
	Irritability			32 (16)
	Bronchitis/cough			26 (13)
	Insomnia		76 (26)	19 (10)
	Elevated lipase/amylase	9 (14)		
	Glucose: high or low	19 (28)		
HIV-related adverse events	Lipodystrophy			37 (19)
	Oral candidiasis		2 (< 1)	30 (15)
	AIDS defining event		2 (< 1)	
Specific serious adverse events	Psychiatric disorders			8 (4)
	Liver failure		1 (< 1)	4 (2)
	Liver decompensation		5 (2)	
	Pneumonia/sepsis		2 (1)	6 (3)
	Symptomatic increased lactate		4 (1)	9 (5)
	Pancreatitis		2 (1)	
	Lactic acidosis	0 (0)	2 (1)	
	ELAT > 10 ULN	20 (30)		16 (8)
	Neutropenia < 500/μL	5 (8)		10 (5)
	Anemia	2 (3)	6 (2)	
	Thrombocytopenia	1 (2)	1 (< 1)	
	Drug abuse		4 (1)	
	Deep vein thrombosis		3 (1)	
	Bacterial infection		3 (1)	
	Gastroenteritis		2 (1)	
Any serious event	Total		50 (17)	68 (35)
	Treatment-related		24 (8)	30 (15)
Deaths	Total	1 (2)	4 (1)	5 (3)

Table 5 Hepatotoxicity of highly active anti-retroviral therapy drugs and guidelines for their use in patients with liver disease

Group	Drug	Dose adjustment
NRTI	Didanosine	Use cautiously
NNRTI	Delavirdine, Efavirenz, Nevirapine	Caution with hepatic impairment
PIs	Lopinavir, Nelfinavir, Ritonavir, Saquinavir	Caution with hepatic impairment
	Atazanavir	Reduce 25% of dose in patients with CTP stage B and C
	Indinavir	Reduce dose by 25% in CTP stage B and C
	Tipranavir	Avoid in patients with CTP stage B or C
	Fosamprenavir	Avoid in patients with CTP stage C
	Darunavir	Avoid in patients with CTP stage C

10%, $P = 0.02$). Patients treated for 48 wk were 5.4 times more likely to achieve SVR. If these data are confirmed in other studies, the standard of care in co-infected patients will be 48 wk of treatment with PEG-IFN and weight based RBV, irrespective of the GT.

Safety and tolerability of medications

Adverse effects are seen in the majority of patients (Tables 4 and 5). The most common adverse effects are influenza-like symptoms (Table 4). About one third of patients experience a drop in hematologic parameters. In most cases, the adverse effects are mild, but, treatment discontinuation was needed in 12%-17% of patients and dose modification of PEG-IFN and RBV, due to either adverse events or a change in laboratory values (neutropenia or thrombocytopenia with PEG-IFN and anemia with RBV), was required in 25%-33% patients[35,47]. RBV-induced anemia is exacerbated with the concomitant use of AZT[38]. This was confirmed in the PRESCO study where RBV-induced anemia was observed in only 2.6% patients, despite using weight-based higher doses of RBV[65]. Every effort should be made to maintain patients on the medications, while simultaneously managing the hematologic abnormalities

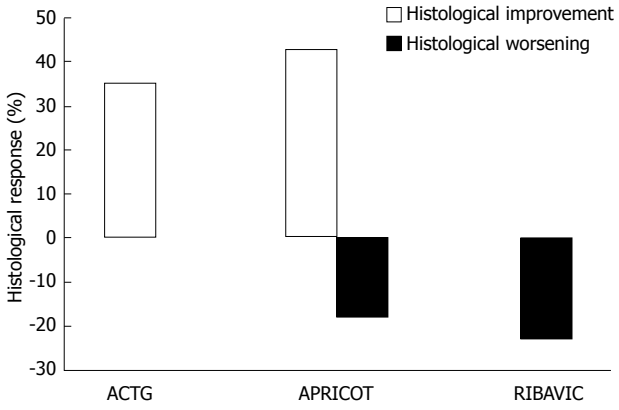

Figure 3 A beneficial histological response was seen in 35% and 43%, respectively, in patients with no sustained virologic response (SVR) in the ACTG and APRICOT trials. Worsening histology was seen in 18% patients with no SVR in the APRICOT study; similar data were not available in the ACTG study. In the RIBAVIC study, histological worsening was seen in 23% without SVR while histology remained stable in the remaining patients.

using blood products and growth factors. In a recent study, the use of Eicosapentaenoic acid prevented RBV dose reduction during first 12 wk of treatment[66].

Patient monitoring during therapy

To ensure the safety of treatment, patients should have regular assessment with complete blood count and liver tests. Efficacy of treatment is assessed by quantitative HCV-RNA at weeks 4, 12, 24, 48, and 72. The goal of therapy is to achieve a SVR as this is associated with < 1% recurrence of infection at 5 years[67]. Assessment of a 2 log reduction in the HCV viral load at week 12 is crucial; lack of such a reduction has a 98%-100% probability of not achieving a SVR. Recently, data have emerged that patients who become HCV-RNA negative at wk 4 (rapid virologic response or RVR) have a SVR rate of 82%, while 99% of those who fail to achieve a 1-log reduction at week 4 are unlikely to have a SVR[68]. However, the current recommendation is to stop further treatment in patients who fail to achieve a 2-log reduction at week 12 of treatment.

Management of non-responders and relapsers

The role of induction therapy using a higher IFN dose was tested in the CORAL-1 study[69]. The use of PEG-IFN α-2a at a dose of 270 μg for 4 wk followed by 180 μg for 8 wk was compared with the standard dose of 180 μg for 12 wk. Both groups received 1000-1200 mg/d of weight-based RBV. Although the induction dose was safe and well tolerated, it failed to provide any efficacy benefit. Treatment for an extended duration was assessed in another study in which patients who failed to achieve a 2-log reduction at 12 wk were randomized to receive either 48 wk or 72 wk of PEG-IFN + RBV. This approach also lacked efficacy as only one (2.5%) patient achieved an SVR.

The lack of an animal model has hampered the development of a vaccine against HCV. Several new drugs for treating HCV are under various stages of development[70]. These include improved IFN molecules (albumin fused with IFN-α, Ω IFN, sequential treatment with IFN-α and IFN-γ), improved RBV molecules (Viramidine with a lower potential for hemolysis, and Levovirin), immunomodulators (histamine dihydrochloride, thymosin α, and isatoribine), and directly acting anti-HCV agents (HCV protease inhibitors, HCV entry inhibitors, ribozymes, and antisense nucleotides)[70].

The anti-fibrotic effect of IFN, with the potential of reducing fibrosis and HCC, is the basis for its use as a maintenance therapy. A beneficial histological response (HR) was observed in all 3 trials with co-infected patients who did not achieve a SVR (Figure 3). In the ACTG and APRICOT studies, HR was defined as an improvement of $\geqslant$ 2 points in the HAI[35,44], and an improvement of $\geqslant$ 1 point in the Metavir score in the RIBAVIC study[47]. Currently, other studies (SLAM-C and ENDURE) are in progress to confirm the role of maintenance therapy in HIV patients who fail anti-HCV treatment[71].

General advice

Patients should be counseled on treatment compliance, and should be encouraged to consume a healthy diet. Patients should abstain from alcohol as HCV and alcohol have a synergistic effect on liver injury[72]. Patients with active substance abuse use should be enrolled in drug detoxification programs. Safe sex practices should be encouraged amongst high risk populations, such as multiple sexual partners, active sexually transmitted disease, and MSM. Patients should be instructed to report to their physician if they experience any unusual symptoms, and should avoid herbal or over the counter medications. Patients who are negative for anti-HBs and antibodies to hepatitis A virus (HAV) should be vaccinated against HAV and HBV[73].

MANAGEMENT OF SPECIAL GROUPS

Patients with normal aminotransferase (PNAL)

PNAL is defined as the presence of at least 3 normal ALT values, each at least 2 mo apart, over a period of 12 mo. The prevalence of PNAL in co-infected patients is 8%-30%[74-76]. Although, the prevalence of stage 3-4 disease in patients with HCV mono-infection and PNAL was lower compared to patients with elevated ALT (5% *vs* 20%, $P = 0.01$), the prevalence was similar in co-infected patients (37% *vs* 32%, $P = 0.6$)[77]. Five year follow-up of 27 co-infected patients with PNAL showed intermittent or persistent elevation of ALT in more than one third of the patients, with the development of decompensated cirrhosis in 2 patients and death in one patient[75].

Treatment of every co-infected patient with PNAL is a daunting task, with considerable expenditure of time and cost. Therefore, it is important to identify factors that may induce rapid FPR in these patients. Currently, it is recommended that treatment should be considered in highly motivated patients and/or those with GT-2/3 infection[29].

Management of acute HCV infection

In the US, about 30 000 cases of acute HCV infection occur annually with increasing incidence in MSM[78-80]. The diagnosis is important since unrecognized infection tends to become chronic in 90%-95% co-infected patients[79]. The criteria for diagnosis are: elevation of ALT > 10 times the upper limit of normal (ULN), a positive HCV-RNA test and exposure to HCV during the preceding 2-12 mo[78]. A high index of suspicion is required, and acute HCV should be excluded before attributing the elevated of ALT to HAART.

The current data on the treatment of acute hepatitis C in HIV patients is limited to a few case studies with SVR of 59% to 91%[81-83]. The large difference in the response rates may be due to factors such as clinical presentation (anicteric *vs* symptomatic) and compliance with therapy. The timing of treatment in co-infected patients is not clear. In HCV mono-infection, a 12 wk waiting period is recommended to allow spontaneous clearance of the virus. Consideration should be given to early treatment of acute HCV in HIV patients because of a higher frequency of chronic disease. However, issues such as the timing of treatment, treatment with PEG-IFN alone, and the role of extended treatment can only be determined by properly conducted controlled trials. Until then, it is recommended that acute HCV infection in HIV positive subjects should be treated with PEG-IFN and RBV for a total of 24 wk, irrespective of the GT[14].

Management of HIV- HCV co-infected patients with end-stage liver disease

With the reduction in occurrence of opportunistic infections with the use of HAART, HCV-induced end-stage liver disease (ESLD) is now one of the leading causes of death (denominator effect) in these patients[84]. Indeed, HCV is considered as an OI in HIV patients[85]. The development of HCC is an important reason for high mortality in co-infected patients, and its incidence has increased from 4.7% in 1995 to 25% in 2000[86]. Whether co-infected patients with cirrhosis and end-stage liver disease (ESLD) should be screened for HCC every 6 mo or earlier is not clear. In one study, 5 of 8 patients diagnosed with advanced HCC were tumor negative 6 mo earlier[18]. Until more data on the screening interval and the factors that influence progression to HCC becomes available, we recommend that co-infected patients should be screened for HCC every 6 mo[87].

Previously, HIV infection was considered a contraindication for liver transplantation (LT). However, in the HAART era, the outcome after LT has improved considerably, with survival at 1 year and 3 years of 87%-91% and 64%-73% ,respectively[88]. A recent retrospective analysis of the United Network for Organ Sharing (UNOS) database showed that although the 2 year survival of HIV patients (n = 138) was inferior to HIV -ve patients (70% *vs* 81%), the survival was similar in HIV -ve patients and HIV +ve patients without HCV or HBV co-infection[89]. Similar poor outcome in HIV patients with concomitant HCV infection has been observed in other studies[88,90-95]. Survival of co-infected patients was inferior to HCV mono-infected patients at 1 year, 3 years, and 5 years (68%-80% *vs* 76%-87%, 56%-57% *vs* 72%-81%, and 33%-51% *vs* 72%-81%, respectively)[88,93,94]. Poor survival with co-infection has been attributed to the recurrence of HCV, which runs an aggressive course, with frequent development of fibrosing cholestatic hepatitis[93]. Moreover, the treatment of recurrent HCV is associated with inferior results (SVR of 27%-28%) compared with treatment of post-LT HCV recurrence in mono-infected patients[93,96]. Other factors affecting post-LT survival were intolerance to HAART, CD4 < 200, HIV viral load > 400 cpm, African American race, and model of end-stage liver disease (MELD) score of > 20[88,93]. Whether such patients should be treated with pre-emptive anti-HCV therapy or maintenance treatment is unclear. Moreover, the ethical consideration of performing LT in HIV/HCV patients is questionable given the short supply of organ donors in the US[97]. An NIH sponsored prospective study on OLT in co-infected patients reported 1 year and 3 year patient survival of 91% and 64%, with graft survival of 82% and 64%, respectively[98]. Based on these data, it can be concluded that OLT should be performed only on selected HIV patients in centers with adequate expertise.

The criteria for LT are the same as for HIV -ve patients, including abstinence from drugs for ⩾ 2 years and abstinence from alcohol for ⩾ 6 mo. HIV should be adequately controlled with VL < 400 cpm and CD4 > 100. OIs precluding LT are multifocal leucoencephalopathy and multi-drug resistant fungal infections[99]. The major issues after LT in co-infected patients are the interaction of HAART with immunosuppressive drugs and recurrence of HCV disease. Most of the immunosuppressive medications are metabolized by the cytochrome P450 system. Protease inhibitors, such as ritonavir, can reduce metabolism of calcineurin inhibitors (CIs), such as cyclosporine and tacrolimus. Therefore, the doses of CIs need to be reduced by about 50%-75% with concomitant administration of PIs. On the other hand, drugs like mycophenolate mofetil interact with nucleoside analogues with decreases in efficacy of zidovudine and stavudine and increases in activity of abacavir and didanosine[100].

FUTURE DIRECTIONS

Based on the literature, recommendations on management of HCV in HIV patients can be made (Table 6). However, there are still many gaps in knowledge and new areas for future research. To better understand the pathogenesis of co-infection, there is an urgent need for *in vitro* and *in vivo* models of dual HIV/HCV infection. The issue of non-invasive means of assessing hepatic fibrosis requires further study. Strategies for the treatment of acute hepatitis C in HIV patients are unclear and involve issues such as the timing of treatment and treatment regimens. The response rate with PEG-IFN and RBV combination for chronic

Table 6 Recommendations for management of HCV in HIV patients

All HIV patients should be screened for concomitant HCV infection
Effective management of HCV is crucial to improve the survival of HIV patients
Patients with stage 2 or more disease are candidates for therapy provided their HIV disease is controlled
Pegylated interferon and weight based ribavirin combination is recommended
Liver transplantation is no longer a contra-indication in the presence of HIV and should be considered in appropriate patients
Patients with cirrhosis should be screened for esophageal varices and for hepatocellular carcinoma

HCV in HIV patients is low. The safety and efficacy of newer anti-HCV drugs needs to be determined. It should be noted that patients with PNAL have significant disease and therefore should be considered for treatment. However, whether prolonged PEG-IFN therapy or maintenance IFN therapy has any role in non-responders remains to be determined. Currently, co-infected patients with ESLD are screened for HCC every 6 mo, however, advanced HCC has been known to occur within the 6 mo interval. The cost-efficacy of more frequent screening is unknown. In order to improve the post-OLT survival of co-infected patients, strategies to prevent and treat HCV recurrence in this setting are crucial.

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