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REVIEW

- 1 Treatment of chronic hepatitis C in patients with HIV/HCV coinfection

Coppola N, Martini S, Pisaturo M, Sagnelli C, Filippini P, Sagnelli E

MINIREVIEWS

- 13 What psychiatric screening and monitoring might be needed with the new generation of hepatitis C treatments?

Rowan PJ

- 17 Mechanistic insights on immunosenescence and chronic immune activation in HIV-tuberculosis co-infection

Shankar EM, Velu V, Kamarulzaman A, Larsson M

- 25 Current molecular methods for the detection of hepatitis C virus in high risk group population: A systematic review

Firdaus R, Saha K, Biswas A, Sadhukhan PC

LETTER TO THE EDITOR

- 33 Ledipasvir and sofosbuvir: Interferon free therapy for hepatitis C virus genotype 1 infection

Waheed Y

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Editorial Board Member of *World Journal of Virology*, David Peter Wilson, Associate Professor, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Corner West and Boundary Streets, Darlinghurst, Sydney 2010, Australia

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World Journal of Virology (*World J Virol*, *WJV*, online ISSN 2220-3249, DOI: 10.5501) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJV covers topics concerning arboviral infections, bronchiolitis, central nervous system viral diseases, DNA virus infections, encephalitis, eye infections, fatigue syndrome, hepatitis, meningitis, opportunistic infections, pneumonia, RNA virus infections, sexually transmitted diseases, skin diseases, slow virus diseases, tumor virus infections, viremia, zoonoses, and virology-related traditional medicine, and integrated Chinese and Western medicine. Priority publication will be given to articles concerning diagnosis and treatment of viral diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJV*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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World Journal of Virology

Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
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Treatment of chronic hepatitis C in patients with HIV/HCV coinfection

Nicola Coppola, Salvatore Martini, Mariantonietta Pisaturo, Caterina Sagnelli, Pietro Filippini, Evangelista Sagnelli

Nicola Coppola, Salvatore Martini, Mariantonietta Pisaturo, Pietro Filippini, Evangelista Sagnelli, Department of Mental Health and Public Medicine, Section of Infectious Diseases, Second University of Naples, 80131 Naples, Italy

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Caterina Sagnelli, Department of Clinical and Experimental Medicine and Surgery "F. Magrassi e A. Lanzara", Second University of Naples, 80131 Naples, Italy

Author contributions: Coppola N, Martini S, Pisaturo M, Sagnelli C, Filippini P and Sagnelli E authorship credit is based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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Correspondence to: Dr. Nicola Coppola, Department of Public Health and Public Medicine, Section of Infectious Diseases, Second University of Naples, Via: L. Armanni 5, 80131 Naples, Italy. nicola.coppola@unina2.it

Telephone: +39-081-5666719

Fax: +39-081-5666013

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frequent causes of comorbidity and mortality in the human immunodeficiency virus (HIV) population, and liver-related mortality is now the second highest cause of death in HIV-positive patients, so HCV infection should be countered with adequate antiviral therapy. In 2011 began the era of directly acting antivirals (DAAs) and the HCV NS3/4A protease inhibitors telaprevir and boceprevir were approved to treat HCV-genotype-1 infection, each one in combination with pegylated interferon alfa (Peg-IFN) + ribavirin (RBV). The addition of the first generation DAAs, strongly improved the efficacy of antiviral therapy in patients with HCV-genotype 1, both for the HCV-monoinfected and HIV/HCV coinfecting, and the poor response to Peg-IFN + RBV in HCV/HIV coinfection was enhanced. These treatments showed higher rates of sustained virological response than Peg-IFN + RBV but reduced tolerability and adherence due to the high pill burden and the several pharmacokinetic interactions between HCV NS3/4A protease inhibitors and antiretroviral drugs. Then in 2013 a new wave of DAAs arrived, characterized by high efficacy, good tolerability, a low pill burden and shortened treatment duration. The second and third generation DAAs also comprised IFN-free regimens, which in small recent trials on HIV-positive patients have shown comforting preliminary results in terms of efficacy, tolerability and adherence.

Key words: Hepatitis C virus infection; Human immunodeficiency virus infection; Anti-hepatitis C virus treatment; Directly acting antivirals; HIV/HCV coinfection; Chronic hepatitis C

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Core tip: The combination pegylated interferon alfa + ribavirin has been used infrequently in patients with Human immunodeficiency virus/hepatitis C virus (HIV/HCV) coinfection because of its limited efficacy in these

Abstract

Hepatitis C virus (HCV) infection is one of the most

patients, the high prevalence of medical and psychiatric comorbidities and the high incidence of serious adverse reactions. The introduction of directly acting antivirals has radically changed the scenario of the HIV/HCV coinfection treatment shown comforting preliminary results in terms of efficacy, tolerability and adherence. This paper provides a quick and comprehensive implementation guide to the management of HIV/HCV patients in a historical moment in which it is not yet clear what is the best treatment.

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INTRODUCTION

The percentage of patients with human immunodeficiency virus (HIV) infection who contemporaneously carry the hepatitis C virus (HCV) ranges from 10% to 50% worldwide, reflecting a different diffusion of HCV infection and a different impact of the environmental factors responsible for HCV transmission in each single country^[1-12].

The introduction of highly active antiretroviral therapy (ART) has increased by at least 20 years the average life expectancy of HIV-infected individuals and, consequently, the majority of HIV patients with chronic hepatitis C are at a higher risk of progressing to the more severe forms of the disease. At present HCV infection is one of the most frequent causes of comorbidity and mortality in the HIV population, and liver-related mortality is now the second highest cause of death in HIV-positive patients^[13-15]. HIV infection unfavorably influences the natural history of HCV infection by increasing the rate of acute hepatitis C that progresses to chronicity, thus favoring the development of liver cirrhosis, hepatocellular carcinoma (HCC), liver decompensation and liver failure^[13-20]. Therefore, optimized ART should be applied to reduce the unfavorable influence of HIV on HCV-related diseases. Also the HCV infection should be countered with adequate antiviral therapy.

The recent introduction of directly acting antivirals (DAAs) to treat chronic hepatitis C has enhanced the knowledge on the management and treatment of HIV/HCV coinfection.

ANTI-HCV TREATMENT FOR HIV-POSITIVE PATIENTS

The introduction of new, more effective and well-tolerated drugs for the treatment of patients with HIV infection has greatly improved the disease outcome of these patients^[21]. In this context, however, the progression of HCV-related liver damage in HIV-positive patients, less

evident in the pre-ART era because of the low average survival, has become a major life-threatening clinical condition^[22]. Fewer advances were made in this period in the treatment of HCV^[23], at that time based on the combination of pegylated interferon alfa (Peg-IFN) plus ribavirin (RBV), which was poorly tolerated and had a low rate of HCV eradication, especially in HIV-positive patients^[24-26]. However, in 2011 the era of DAAs began and the HCV NS3/4A protease inhibitors (PIs) telaprevir (TPV) and boceprevir (BOC) were approved to treat HCV-genotype-1 infection, each one in combination with Peg-IFN + RBV^[27-30]. These treatments showed higher rates of sustained virological response (SVR) than Peg-IFN + RBV^[31-38] but reduced tolerability^[39] and adherence due to the high pill burden. At the same time several pharmacokinetic interactions have been appeared between HCV NS3/4A protease inhibitors and antiretroviral drugs^[40-43]. Finally in 2013 a new wave of DAAs arrived, characterized by high efficacy, good tolerability, a low pill burden and shortened treatment duration^[44,45]. The second and third generation DAAs also comprised IFN-free regimens, which in small recent trials on HIV-positive patients have shown comforting preliminary results in terms of efficacy, tolerability and adherence^[46,47]. Table 1 shows the SVR rate in therapy-naïve patients treated with the different combinations (Table 1). However, the new DAAs are still not available for HIV-positive patients in clinical practice and their high cost may be a handicap to their use in developing countries.

INTERFERON-BASED REGIMENS

Peg-IFN + RBV

The combination Peg-IFN + RBV, although considered the treatment of choice for chronic hepatitis C until 2011, has been used infrequently in patients with HIV/HCV coinfection because of its limited efficacy in these patients, the high prevalence of medical and psychiatric comorbidities and the high incidence of serious adverse reactions. In most studies on chronic hepatitis C monoinfected patients with HCV-genotype 1 or 4, an SVR of almost 50% was achieved. In the APRICOT^[48] study, HIV/HCV coinfecting patients were treated with Peg-IFN α -2a and a fixed dose of RBV (800 mg/d) for 48 wk and an SVR was obtained in nearly 40% of the cases, in 18% of those with HCV-RNA levels greater than 800000 copies/mL and in 61% of those with a lower HCV load. The current international guidelines suggest prolonging the 48-wk treatment to 72 wk, despite reduced tolerability, for patients with HCV-genotype 1 without a rapid virological response (RVR) (EACS)^[49]. With the introduction of DAAs to treat chronic hepatitis C, Peg-IFN + RBV dual therapy should be considered obsolete at least for patients with HCV-genotype 1 or 4.

Peg-IFN + RBV + the first generation DAAs telaprevir or boceprevir

The addition of the first generation DAAs, TPV or BOC, to Peg-IFN + RBV strongly improved the efficacy of

Table 1 Sustained virological response rate in human immunodeficiency virus/hepatitis C virus coinfecting patients naïve for anti-hepatitis C virus treatment

	Ref.	SVR rate in therapy-naïve patients			
		Genotype 1	Genotype 2	Genotype 3	Genotype 4
Peg-IFN plus ribavirin	[85]	35.6% in 191 patients	72.4% in 152 patients	-	32.6% in 46 patients
Peg-IFN plus ribavirin + boceprevir	[32]	60.7% in 61 patients	-	-	-
Peg-IFN plus ribavirin + telaprevir	[51]	74% in 38 patients	-	-	-
Peg-IFN plus ribavirin + sofosbuvir	[44]	-	91% in 23 patients	-	-
Peg-IFN plus ribavirin + simeprevir	[55]	79.2% in 52 patients	-	-	-
Peg-IFN plus ribavirin + faldaprevir	[59]	73.7% in 227 patients ¹	-	-	-
Sofosbuvir plus ribavirin	[60]	76% in 114 patients ²	88% in 26 patients ³	67% in 42 patients ³	-
Sofosbuvir plus ribavirin	[62]	84% in 112 patients	90% in 19 patients	91% in 57 patients	84% in 31 patients
Sofosbuvir plus ledipasvir	[63]	100% in 13 patients	-	-	-
Paritaprevir-r/ombitasvir + dasabuvir + ribavirin	[65]	93.5% in 31 patients	-	-	-

¹Therapy-naïve or relapser patients; ²For 24 wk; ³For 12 wk. SVR: Sustained virological response; Peg-IFN: Pegylated interferon alfa.

antiviral therapy in patients with HCV-genotype 1, both for the HCV-monoinfected and HIV/HCV coinfecting, and the poor response to Peg-IFN + RBV in HCV/HIV coinfection was enhanced with the new combination therapy.

In patients with HIV/HCV coinfection, triple therapy including telaprevir 1125 mg every 12 h or 750 mg every 8 h is administered only for the first 12 wk, followed by a 36-wk Peg-IFN + RBV double therapy^[50]. TPV pills should be taken with a fat meal to improve their absorption. In a randomized trial on HIV/HCV-genotype-1 coinfecting patients naïve for anti-HCV treatment, the SVR rate was 74% for those treated with telaprevir-based triple therapy and 45% for the control group receiving Peg-IFN + RBV double therapy^[51]. Adverse events commonly observed in TPV-based triple therapy included skin rash, pruritus, anemia, and ano-rectal discomfort. In addition, TPV may reduce the glomerular filtration rate and increase RBV concentrations by 55%, inducing in these cases severe anemia^[39]. TPV cannot be administered with the ritonavir-boosted PIs used in HIV therapy due to the pharmacokinetic interactions. Thus, despite the enhanced efficacy of telaprevir-based triple therapy in eradicating HCV infection, the number of HIV/HCV patients eligible for this treatment is reduced due to its poor tolerability, interaction with ART and high pill burden.

Predictive factors of a favorable response to treatment, such as mild fibrosis, low HCV-RNA load, IL-28B CC genotype and Caucasian ethnicity should be assessed before starting telaprevir-based triple therapy.

Boceprevir is an NS3/4A protease inhibitor approved for treatment of genotype-1 chronic hepatitis C^[52]. In these patients treatment with BOC + Peg-IFN + RBV begins after a 4-wk lead-in phase with Peg-IFN + RBV. BOC is stopped at week 36 and Peg-IFN + RBV continued until week 48. Cirrhotic patients or prior null responders should receive BOC + Peg-IFN + RBV until week 48. The SVR rates observed in therapy-naïve HIV + HCV co-infected patients receiving BOC + Peg-IFN + RBV or Peg-IFN + RBV in a phase II trial were 63% and 29%, respectively^[32]. Adverse reactions included anemia, dysgeusia, nausea, and neutropenia. BOC cannot be administered with ritonavir-boosted PIs or non-nucleoside retro-transcriptase

inhibitors because of the pharmacokinetic interactions^[40]. Consequently, the use of the combination BOC + Peg-IFN + RBV for HIV/HCV coinfecting patients is very limited.

Peg-IFN + RBV + a second wave DAA

In 2013, both sofosbuvir (SOF), a once-a-day oral DAA that inhibits the active site of the HCV NS5B polymerase with an anti-HCV pan-genotypic activity, and simeprevir (SMV), a once-a-day oral DAA that inhibits the HCV NS3/4A protease, were approved by the United States Food and Drug Administration (FDA) to be used in combination with Peg-IFN + RBV to treat patients coinfecting with HIV/HCV genotype 1^[44,45]. SOF was also approved to be used in combination with RBV to treat patients coinfecting with HIV and HCV genotype 2 or 3^[47]. SOF is particularly indicated for patients with HIV/HCV coinfection, since it is well tolerated and no pharmacokinetic interactions with the antiretroviral drugs have been documented^[44].

In a small study from Porto Rico a combination of SOF plus Peg-IFN and RBV given to 23 patients with HIV/HCV coinfection (19 with HCV genotype 1) for 12 wk obtained HCV eradication in 91% of cases; no severe adverse event occurred and only 2 patients discontinued treatment, one due to anemia and one to altered mood^[53].

SMV is a second generation HCV NS3/4A protease inhibitor for the treatment of patients with HCV-genotype-1 infection^[54]. The combination of SMV plus Peg-IFN and RBV has been investigated in both in HCV-monoinfected^[55-57] and HIV/HCV coinfecting patients^[58]. An overall 74% SVR rate was obtained in 106 patients coinfecting with HIV and genotype-1 HCV treated with this triple therapy and a 79% SVR was achieved in the anti-HCV treatment-naïve patients. In this study, all patients received a 12-wk SMV + Peg-IFN + RBV treatment, followed by double Peg-IFN/RBV response-guided therapy for either 12 or 36 wk. Of note, 89% of naïve or prior relapser co-infected patients without cirrhosis met the inclusion criteria to receive response-guided therapy, which required that serum HCV RNA be undetectable at week 4. Fibrosis stage, HCV sub-genotype, IL28b genotype, and baseline CD4 count above or below 500 did not influence

the SVR rates. The impact of adverse events to SMV + Peg-IFN + RBV (rash, photosensitivity, pruritus, and nausea) was limited in the Phase II/III trials. However, phase III studies, both on mono and coinfecting patients, demonstrated that the addition of SMV to the combination Peg-IFN + RBV did not improve the response rate of the dual therapy in patients with HCV-genotype 1a with a baseline NS3 Q80K polymorphism. This polymorphism is detected in nearly one third of subjects infected with HCV-genotype 1a and in only 0.5% of those with HCV-genotype 1b. Screening at baseline for the presence of the NS3 Q80K polymorphism is recommended for patients with HCV-genotype 1a to exclude positive patients from treatment including SMV. Indeed, this polymorphism has a limited effect on SMV activity, but the resistance barrier of this drug appears to be lower in patients carrying the Q80K-variant, resulting in a more frequent emergence of additional mutations and in a higher rate of treatment failure. The United States FDA approval of SMV provides specific recommendations for interactions with commonly prescribed antiretroviral agents. SMV is also a component of several interferon-free combinations currently under study.

Faldaprevir (FDV) is a second generation oral, once-daily HCV NS3/4A protease inhibitor. In the START-Verso 4^[59] multicenter study, an open-label randomized phase III trial, HIV/HCV therapy-naïve or previous relapser patients with or without cirrhosis received either FDV 120 mg + Peg-IFN+RBV for 24 wk followed by Peg-IFN + RBV dual therapy for an additional 24 wk or FDV 240 mg + Peg-IFN + RBV for 12 wk followed by a 1:1 re-randomization to either the same treatment for another 12 wk followed by a 24-wk Peg-IFN + RBV double therapy or to a 12-wk Peg-IFN+RBV double therapy. Due to drug to drug interactions, patients receiving efavirenz were placed in the 120 mg arm, and patients receiving darunavir/ritonavir or atazanavir/ritonavir were randomized to the 120 or 240 mg arms. Patients with an early treatment success stopped treatment at week 24, the others at week 48. Overall, 72% of patients achieved an SVR, the highest rates being observed in patients who had previously relapsed with Peg-IFN + RBV (83%) and in those with IL28b CC genotype (88%); HCV genotype, presence of cirrhosis and FDV dose and duration did not show any major impact on the SVR rate. Adverse events occurred in 7% of patients, neutropenia and bilirubin elevations being the most common grade 3 abnormalities; only 1% of these events were attributed to FDV. The research on this promising drug was stopped in 2014 for commercial reasons.

INTERFERON-FREE REGIMENS

Studies on HIV/HCV coinfecting patients

IFN-free clinical trials on HIV/HCV coinfecting patients are still in progress, but their preliminary data have shown that these treatments have a greater efficacy in eradicating HCV infection.

PHOTON-1 is the only study on IFN-free treatment

of HIV/HCV coinfecting patients published at present^[60]. In this study, SOF + weight-based RBV were administered to 114 patients with HCV-genotype 1 naïve for anti-HCV treatment for 24 wk and to 68 therapy-naïve patients with genotype 2 or 3 for 12 wk. The SVR rates were 76% in patients with HCV-genotype 1, 88% in those with genotype 2 and 67% in those with genotype 3.

In the phase II a COSMOS trial, the patients were randomized to SMV + SOF with or without RBV for 12 or 24 wk^[61]. The preliminary data for patients in the 12-wk arm showed a 93% SVR rate in prior null-responders to Peg-IFN + RBV and 97% overall. Serious adverse events, anemia and bilirubin increase regarded only patients who received RBV.

In a recent study a combination of SOF plus RBV given for 12 wk to genotype-2 therapy-naïve patients and for 24 wk to all other patients showed an 84% SVR in the 112 therapy-naïve genotype-1 patients, 90% in the 19 naïve genotype-2, 91% in the 57 naïve genotype-3, 84% in the 31 naïve genotype-4, 83% in the 6 therapy-experienced genotype-2 and 86% in the 49 experienced genotype-3 patients^[62].

Ledipasvir (LDV) is an oral NS5A inhibitor administered once daily. In a small trial the combination LDV + SOF ± RBV was administered to HIV/HCV genotype-1 coinfecting patients with no evidence of liver cirrhosis^[63]. This regimen was well tolerated and the preliminary data showed a 100% SVR12 rate in 12 HCV-genotype-1 patients who were naïve for anti-HIV and anti-HCV treatment.

Daclatasvir (DCV) is an HCV NS5A replication complex inhibitor administered once daily. The safety and efficacy of the combination therapy with DCV + SMV ± RBV were evaluated in the LEAGUE-1 trial, a randomized open-label phase II study enrolling therapy-naïve and null-responder HIV/HCV patients with or without cirrhosis^[64]. All patients with HCV-genotype 1b were given a 12-wk treatment with DCV + SMV ± RBV; at week 12 the patients were re-randomized to either an additional 12-wk treatment or to a 12-wk treatment-free follow up. The patients with HCV-genotype 1a received a 24-wk DCV + SMV + RBV treatment. In this study the SVR rate was 67% for patients with HCV genotype 1a and almost 82% for those with HCV genotype 1b.

Turquoise-I is a randomized, open-label study evaluating the safety and efficacy of a combination of paritaprevir/r, ombitasvir, dasabuvir and RBV in patients with HCV-genotype-1 chronic hepatitis and HIV infection^[65]. The study is still ongoing, but the preliminary data show an SVR4 in 93.5% of 31 patients treated for 12 wk and in 96.9% of 30 patients treated for 24 wk; an SVR12 was obtained in 93.5% of 31 patients treated for 12 wk. Fatigue, insomnia and headache were the most common side effects, but no patient had a serious adverse event.

Studies on HIV/HCV patients started recently whose results are awaited

The efficacy of SOF + LDV is under evaluation in 100 patients with HIV/HCV-genotype-1 coinfection either untreated for HIV infection (CD4 > 500 cells/mm³) or

with suppressed HIV-1 RNA replication with antiretroviral drugs. (ClinicalTrials.gov Identifier: NCT01878799). Still awaited are the results of the ALLY-2 study on the effect of the combination of SOF+ DCV given for 8 or 12 wk to HIV/HCV coinfecting patients with HCV genotype 1, 2, 3, 4, 5 or 6.

The C-WORTHY is a study recently started to evaluate the safety and efficacy of the combination of the second generation HCV NS3/4A protease inhibitor MK-5172 + the second generation HCV NS5A inhibitor MK-8742 ± RBV for patients with HCV-genotype 1, both HIV positive and negative^[66,67]. This study design underscores the emerging recognition that HIV-infected patients may not differ from the mono-infected in terms of the effectiveness of oral IFN-free DAA regimens.

A few trials on the efficacy of the combination DCV + SOF for HIV/HCV coinfecting patients have recently started and the results are still awaited^[68].

Recent studies on the efficacy of IFN-free DAA regimens for HCV-mono-infected patients, possibly extendible to HIV/HCV coinfection in the near future

Asunaprevir (ASV), a twice-daily NS3/4A protease inhibitor, used in combination with IFN + RBV or in IFN-free regimens, has shown promising results with fewer adverse effects. In HCV-mono-infected patients ASV was studied in a randomized, open-label, 24-wk-treatment study^[69] where all 101 patients enrolled received DCV (60 mg) once daily and ASV as follows: 38 with genotype 1b also received ASV (200 mg) twice (DUAL A1) or once daily (DUAL A2), 36 with genotype 1a and 5 with genotype 1b also received ASV twice (QUAD B1) or once daily (QUAD B2) plus Peg-IFN/RBV and 18 patients with genotype 1a and 4 with genotype 1b also received ASV twice daily plus RBV (TRIPLE B3). An SVR12 was obtained in 78% of patients in DUAL A1, 65% in DUAL A2, 95% in QUAD B1, and 95% in QUAD B2. Most patients in the TRIPLE B3 arm developed a virological breakthrough, but aminotransferase elevation grade 3 or 4 was infrequent.

The BMS-791325 (BMS), a twice-daily non-nucleoside NS5B polymerase inhibitor, was investigated in the A1443-014 trial where the efficacy of the oral combination of DCV + ASV + BMS was assessed in a large group of HCV-genotype-1 patients, including cirrhotics^[70]. The patients were randomized to DCV/ASV/BMS with BMS dosed at 75 mg or 150 mg. In this combination DCV was given twice daily. The SVR rates were above 90% in both groups. Only 2 of the 166 patients enrolled discontinued treatment due to adverse events.

The SYNERGY trial studied different combinations of DAA in order to achieve high SVR rates with shortened treatment duration in patients with HCV mono-infection^[71]. In this study, besides some well-known drugs, the Authors also used two new molecules, GS-9669, a once-daily non-nucleoside HCV NS5B inhibitor, and GS-9451, a once-daily NS3/4A protease inhibitor. The patients were randomized to one of three arms: (1) SOF + LDV for

12 wk; (2) SOF + LDV + GS-9669 for 6 wk; and (3) SOF/LDV/GS-9451 for 6 wk. Patients with cirrhosis were excluded from arms B and C. All patients, with the exception of one in arm B, achieved an SVR. No patient discontinued therapy due to an adverse event. Worthy of note is that most individuals investigated were difficult-to-treat patients because of their Afro-American ethnicity, old age, HCV-sub-genotype 1a, IL28b genotype CT/TT or advanced liver fibrosis.

A 12-wk combination of DCV+SOF ± RBV was investigated in HCV-mono-infected patients with genotype 1, 2, or 3 in the A1444040 study^[72]. The study included both therapy-naïve patients and previous non-responders to TVP- or BOC-based triple therapy; in both groups 98% of the patients achieved an SVR.

The Turquoise-II is a multicenter, randomized, open-label study evaluating the efficacy and safety of a 12-wk or 24-wk treatment with paritaprevir/r + ombitasvir + dasabuvir + RBV in patients with HCV-genotype-1 chronic hepatitis or compensated liver cirrhosis^[73]. An SVR12 was observed in 91.8% of patients treated for 12 wk and in 95.9% of those treated for 24 wk.

ART MANAGEMENT IN HIV/HCV COINFECTED PATIENTS DURING TREATMENT WITH DIRECTLY ACTING ANTIVIRALS FOR HCV INFECTION

Despite the remarkable virological response obtained with oral DAAs, the treatment of chronic hepatitis C in HIV patients remains complex and presents multiple challenges. The drug to drug interaction and the high prevalence of severe side effects influence the choice of the ART, and priority should be given to the antiretroviral drugs with fewer side effects and lesser interaction with the DAAs.

The drug to drug interaction in HIV/HCV coinfection mostly regards the use of HCV NS3 protease inhibitors, while the HCV nucleoside and non-nucleoside NS5B polymerase inhibitors and NS5A replication complex inhibitors seem to have minimal effects on the serum concentration of the HIV drugs. Both the anti-HCV and anti-HIV protease inhibitors and NNRTIs are metabolized by the cytochrome p450 pathway and, consequently, multiple complex drug to drug interactions develop that require management in highly experienced clinical centers. In addition, the knowledge on the interaction between anti-HCV protease inhibitors and anti-HIV drugs is in continuous development and even skilled clinicians should consult the www.hep-druginteractions.com web site.

TPV, BOC and SMV interact with CYP3A as inhibitors and substrates, with potential interaction and increased concentrations of drugs metabolized through this pathway and with a reduced TPV or BOC serum concentration due to drug-induced enzymatic activity^[40,74]. A recent study assessed the pharmacokinetic interactions between BOC and the ritonavir (RTV)-boosted protease inhibitors atazanavir (ATV), lopinavir (LPV) and darunavir (DRV)

Table 2 Anti-human immunodeficiency virus drugs contraindicated during anti-hepatitis C virus treatment

	Contraindicated anti-HIV drugs				
	NRTI	NNRTI	IP	INI	CCR5 antagonist
Alpha interferon	-	-	-	-	-
Ribavirin	Didanosine, stavudine, zidovudine	-	-	-	-
Boceprevir	Didanosine, stavudine, zidovudine	Efavirenz	Lopinavir/r, atazanavir/r, darunavir/r	EVG/cobi/TDF/FTC ¹	Maraviroc ³
Telaprevir	Didanosine, stavudine, zidovudine	Efavirenz ²	Lopinavir/r darunavir/r fosamprenavir/r	-	Maraviroc ³
Sofosbuvir	Didanosine, stavudine, zidovudine	-	Tipranavir/r	No data	-
Simeprevir	Didanosine, stavudine, zidovudine	Efavirenz, delavirdine etravirine, nevirapine	All protease inhibitors with or without ritonavir booster	EVG/cobi/TDF/FTC	No data
Daclatasvir	Didanosine, stavudine, zidovudine	Efavirenz ⁴ , nevirapine, etravirine	Lopinavir/r ¹ darunavir/r ¹ fosamprenavir/r ¹ tipranavir/r	-	-
Ledipasvir	Didanosine, stavudine, zidovudine	Nevirapine ¹ , etravirine ¹	Lopinavir/r ¹ fosamprenavir/r ¹ tipranavir/r	EVG/cobi/TDF/FTC ¹	No data
Dasabuvir/ ombitasvir/ paritaprevir-r	Didanosine, stavudine, zidovudine	Efavirenz, rilpivirine nevirapine ¹ etravirine ¹	lopinavir/r ¹ fosamprenavir/r tipranavir/r ¹	EVG/cobi/TDF/FTC ¹	No data

¹No data, do not co-administer; ²Increase the dose of telaprevir to 1125 mg three times a day; ³Maraviroc 150 mg twice a day; ⁴Increase the dose of daclatasvir to 90 mg a day. HIV: Hepatitis C virus.

in a randomized open-label study on 39 healthy adults. The protease inhibitor BOC decreased the exposure of all protease inhibitors; ATV/ritonavir did not significantly affect BOC exposure, whereas BOC was reduced by 45% and 32% when co-administered with LPV/ritonavir and DRV/ritonavir, respectively^[75].

In a recent study no significant drug interaction between BOC and raltegravir was found in healthy volunteers^[76].

The role of ritonavir in the drug interactions between TPV and ATV was recently investigated. In an open-label, sequential study on HCV/HIV coinfecting patients on an RTV-boosted ATV-based antiretroviral regimen (300/100 mg every 24 h) and triple therapy (telaprevir, 1125 mg every 12 h, Peg-IFN + RBV) for genotype-1 chronic hepatitis C, the pharmacokinetic profiles were acquired before and after switching from RTV-boosted to unboosted ATV (200 mg every 12 h). The Authors found RTV responsible for the adverse interactions occurring when TPV and RTV-boosted ATV were administered together since the co-administration of TPV and unboosted ATV resulted in increased exposure of both drugs^[77].

The co-administration with efavirenz led to a 20% reduction in the area under curve of TPV, thus requiring an increase in the dosage of TPV^[74,78,79]. An open-label crossover study on healthy volunteers evaluated the bioequivalence of BOC and etravirine, an HIV non-nucleoside reverse transcriptase inhibitor, and a reciprocal interaction was demonstrated^[80].

The study on the interaction between anti-HCV DAAs and antiretroviral drugs is at its real beginning and further investigation is needed to ensure the optimization of the contemporaneous administration of ART and anti-HCV therapy for HIV/HCV coinfecting patients.

Choice of the best ART during treatment with DAAs

Precise knowledge of drug interactions and of the

adverse events occurring during drug administration is indispensable in order to choose optimized ART and DAAs-based treatment for patients with HIV/HCV coinfection. Optimized ART should avoid possible interactions with protease inhibitors of HCV and improve drug tolerability and the patients' adherence. Table 2 shows a list of antiretroviral drugs incompatible with DAA administration. TPV can be safely administered in combination with RTV-boosted ATV, raltegravir, maraviroc, rilpivirine, etravirine or efavirenz (when administered with efavirenz, the TPV dosage should be 1125 mg every 8 h) and with tenofovir/emtricitabine or abacavir/lamivudine (www.hep-druginteractions.com). BOC can be safely administered in combination with raltegravir, rilpivirine or etravirine and with tenofovir/emtricitabine or abacavir/lamivudine. BOC can also be considered in combination with RTV-boosted ATV for patients with no previous HIV-treatment failure and no drug resistance^[74,78,79,81]. BOC can be safely administered in combination with raltegravir, rilpivirine and with tenofovir/emtricitabine or abacavir/lamivudine.

Some new ART regimens including the integrase inhibitor raltegravir^[82] or the entry inhibitor maraviroc^[83] have been demonstrated to be safe and their use in HIV/HCV coinfection should be evaluated in clinical studies.

Concluding on this point, the management of HCV infection for HIV-positive patients is a complex issue. The physicians in care should carefully select the patients for the most suitable treatment and monitor them closely to evaluate the efficacy and tolerability of the drugs administered, their pharmacological interaction, the virus interaction and the patients' adherence.

CONCLUSION

Treatment of chronic hepatitis C for patients with HIV infection is essential to prevent the transition to liver

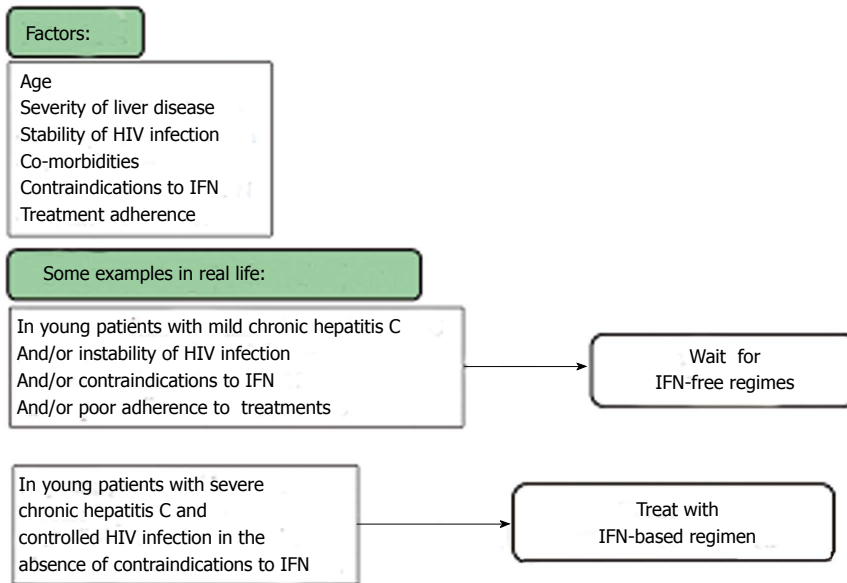


Figure 1 Factors influencing treatment decision for chronic hepatitis C in human immunodeficiency virus/hepatitis C virus-1 coinfection: treat or defer treatment. HIV: Human immunodeficiency virus; IFN: Interferon.

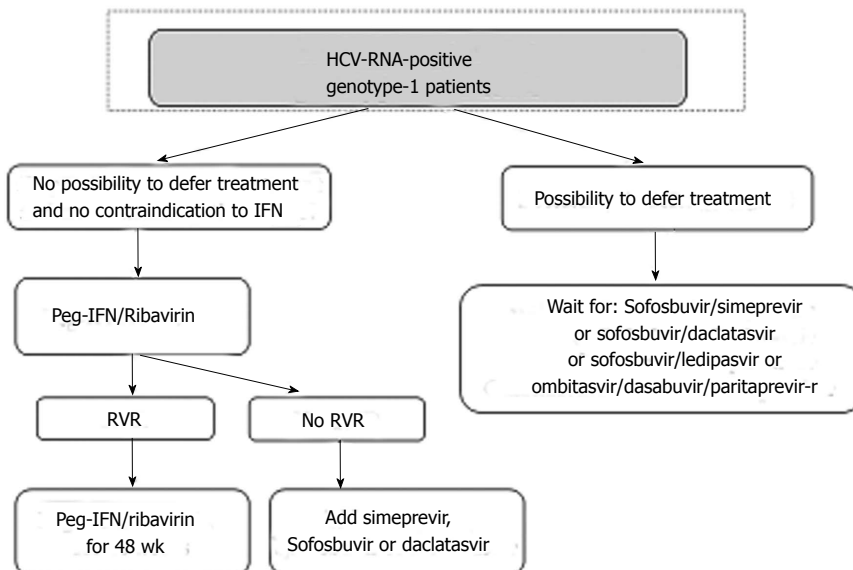


Figure 2 Treatment of chronic hepatitis C, hepatitis C virus-genotype 1 or 4, in patients with Human immunodeficiency virus/hepatitis C virus coinfection. RVR: Rapid virological response; IFN: Interferon. HCV: Hepatitis C virus.

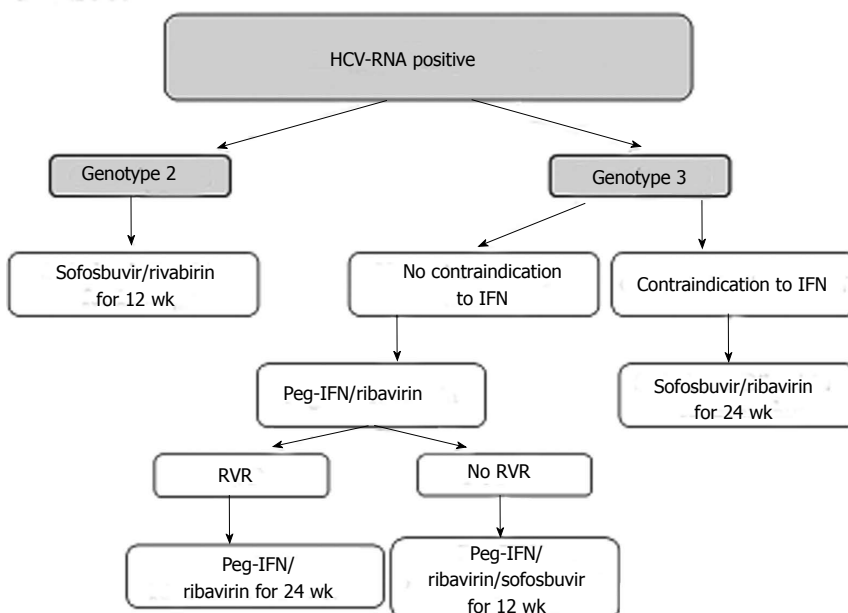


Figure 3 Treatment of chronic hepatitis C, HCV-genotype 2 or 3, in patients with human immunodeficiency virus/hepatitis C virus coinfection. RVR: Rapid virological response; IFN: Interferon.

cirrhosis, the development of HCC and liver failure. The poor tolerability of Peg-IFN + RBV double therapy and of triple therapy with Peg-IFN + RBV + boceprevir or telaprevir has been a serious obstacle to treating chronic hepatitis patients with HIV/HCV-genotype-1 coinfection. These treatment regimens compared to the new DAA-based therapies show lesser efficacy and tolerability because of the more frequent serious adverse events, a higher pill burden and longer period of treatment. Moreover, the first-generation PIs show more pharmacokinetic interactions with antiretroviral drugs than the second and third generation DAAs.

At present, treatment decisions range from waiting for all-oral second or third generation DAA regimens or treating with Peg-IFN/RBV double therapy + sofosbuvir, simeprevir or daclatasvir. A reliable guide in this difficult choice could be the entity of liver fibrosis, detected by liver biopsy or by a sensitive fibroscan assay, and other predictive factors of SVR such as the HCV viral load, the IL-28B genetic profile and the ethnic background (Figure 1). The patients' adherence, pharmacokinetic interactions between anti-HCV and antiretroviral drugs and sustainability in terms of cost-effectiveness are other important factors to be considered for a rational choice. The achievement of RVR during treatment remains the most sensitive predictor of SVR.

Currently, we deem it reasonable that HIV/HCV-genotype-1 therapy-naïve patients for whom treatment cannot be deferred should be treated with Peg-IFN + RBV dual therapy to establish whether they achieve an RVR during the first month of treatment (Figure 2). In positive cases double therapy should be administered for 12 mo, whereas for patients not achieving an RVR a second generation DAA (sofosbuvir, simeprevir, or daclatasvir) should be added, and this triple therapy administered for 3-6 mo^[84] (Figure 2).

Once combinations of second/third generation DAAs are licensed for treatment of chronic hepatitis C in HIV/HCV coinfection, the patients with HCV genotype 1 for whom the treatment has been deferred and those with contraindications to IFN + RBV should be treated with an effective IFN-free DAA-based regimen (Figure 2). The same algorithm can be hypothesized for patients with HCV-genotype 4.

For patients with HIV/HCV genotype-2 coinfection, the treatment choice should be between a 24-wk low-cost Peg-IFN/RBV double therapy and a 12-wk high-cost treatment with sofosbuvir/ribavirin (Figure 3).

For patients with HCV-genotype 3, a 24-wk high-cost schedule with sofosbuvir/ribavirin or a 24-wk low-cost Peg-IFN/ribavirin double therapy seem reasonable (Figure 3).

The several ongoing trials will better define the role of the second and third generation DAAs in treating chronic hepatitis C in HIV/HCV coinfection, but in the meantime this review article may be of some help in making reasonable therapeutic choices.

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What psychiatric screening and monitoring might be needed with the new generation of hepatitis C treatments?

Paul J Rowan

Paul J Rowan, University of Texas Health Sciences Center at Houston School of Public Health, Houston, TX 77030, United States

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Correspondence to: Paul J Rowan, PhD, MPH, University of Texas Health Sciences Center at Houston School of Public Health, 1200 Herman Pressler Drive, Houston, TX 77030, United States. paul.j.rowan@uth.tmc.edu

Telephone: +1-713-5009183

Fax: +1-713-5009171

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Abstract

Psychiatric difficulties, including depression and alcohol use disorders, pose a challenge to treatment decision-making for chronic hepatitis C. This is especially made worse because interferon-alpha, as part of the standard of care, may exacerbate depressive symptoms and cause suicidal symptoms to appear. This requires a treatment setting that has the capacity to carry out psychiatric assessment and monitoring, and the capability to deliver patient education regarding these aspects of care. Psychiatric comorbidities create a challenging decision-making situation, especially since success rates for the most common hepatitis C genotype, genotype 1, hover around 40%. In recent years, new treatments

have emerged. These significantly boost the likelihood of sustained viral response, including for genotype 1, and do not seem to have the side effects of interferon-alpha or ribavirin. Relevant data are reviewed to assess the degree that these new treatments might reduce the portion not eligible for treatment due to psychiatric comorbidities, and might reduce the emergence of psychiatric symptoms during treatment. Several organizations have recently released evidence-based treatment recommendation guidelines. It is apparent that interferon-alpha continues to be a standard of care, with the new drugs added to this recognized regimen in order to shorten treatment and to boost efficacy. Clinical settings must continue to assess appropriateness for treatment, including current or recent psychiatric comorbidities, and must continue to closely monitor patients for the emergence of psychiatric side effects. The newly developed hepatitis C treatments may affect the metabolism of several categories of psychiatric drugs, and so drug-drug interactions must also be considered and monitored. With many promising drugs under development, an all-pill regimen, with no interferon-alpha and no ribavirin, may emerge in the near future. This will greatly change the challenge of treatment decision-making, and should expand the portion of patients able to successfully complete a treatment regimen.

Key words: Depression; Therapy; Psychiatry; Review; Clinical

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Core tip: Emerging hepatitis C treatment regimens, which include newer medications such as boceprevir, telaprevir, sofosbuvir, and simeprevir, hold promise to reduce the need for psychosocial screening and monitoring. Thus far, these medications do not seem to have the same psychiatric side effect profile as interferon-alpha.

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Based upon genotype prevalence data and efficacy data, several recently emerging treatment guidelines continue to call for first-line treatment that includes interferon-alpha in combination with one or more of these newer medications. Therefore, the need for psychiatric screening, monitoring, and support continues.

As interferon-alpha became a recognized standard-of-care treatment for chronic hepatitis C, it became apparent that psychiatric side effects complicated treatment decision-making^[1]. Specifically, current or recent depression has been considered a contra-indication for interferon-based regimens because the interferon-alpha can provoke or increase depressive symptoms in those with depression or a history of depression^[2]. The effect is possibly attributable to interferon's effect on serotonin pathways, but is more likely due to interferon-alpha's function as one of the many inflammatory cytokines which are recognized to cause flu-like symptoms and also cause "sickness behavior," experienced as depression^[3,4]. It is hypothesized that acute inflammatory responses occur in response to infection and occur when tissue repair is needed, and that the cytokine-induced activation of anhedonia and low motivation serves the organism by allowing the body to devote physiological efforts to rest and healing rather than other activities^[5].

Part of the interferon-induced depression phenomenology may include suicidality, making suicidality a treatment consideration before beginning therapy, and requires close monitoring during therapy^[4]. Current or recent alcohol use has been another contra-indication: efficacy may be reduced in those drinking during treatment^[6] and because those with a drinking history are perceived as having high risk of relapse under the distress of treatment^[7].

Additionally, interferon therapies require that social circumstances needed to be assessed. This includes an appraisal of the ability of the patient to adhere to a challenging regimen across six or more months, the possible need to take leave from employment when experiencing side effects, and the need for stable residence, since interferon-alpha requires refrigeration. The revelation of the boosted efficacy of joint interferon-alpha and ribavirin treatment, circa 1994, brought more treatment success, but did not change this psychiatric aspect of the treatment decision matrix. Neither did the advent of pegylated interferon-alpha, circa 1998. Treatment guidelines have recommended a psychosocial evaluation for interferon-alpha candidates, with a period such as six months before re-assessment^[8].

Because of these difficulties of treatment, and because chronic hepatitis C is a slowly progressing disease, the clinical decision often is to delay treatment, and "watch-and-wait." In the pegylated-interferon/ribavirin era, outcomes evaluations have determined that approximately

70% of otherwise eligible patients do not begin interferon-alpha treatment due to contra-indications, with a significant portion of reasons being psychiatric^[9,10].

Further complicating the clinical picture is the fact that ribavirin, while boosting rates of sustained viral response when combined with interferon-alpha, is a teratogen. Therefore, great care and attention must be used when considering hepatitis C treatment for women of child-bearing age, and when delivering this treatment. Before beginning therapy, a pregnancy test must be conducted, and the woman must decide whether she will be able to maintain two types of birth control throughout treatment, and to conduct repeat pregnancy tests, as well as maintaining adherence to the interferon-alpha/ribavirin regimen^[11].

For quite some time, the standard of care has been to carefully consider the psychiatric profile of a potential interferon-alpha candidate. Patients with current or recent psychiatric difficulties can be referred for a course of psychiatric treatment, perhaps with re-assessment in six months, or be started on interferon-alpha therapy as long as supportive care and monitoring are in place. This requires a great deal of the hepatology or gastroenterology clinical setting: these settings must have the capacity or resources to carry out psychiatric evaluations, to provide psychiatric treatment or link a patient with psychiatric care, and to monitor psychiatric symptoms throughout therapy. Patients must also be willing to accept the treatment decision to not begin a potentially curative therapy, and follow other medical advice such as abstinence from alcohol.

Across time, clinicians have become more confident in treating patients who had current or recent psychiatric difficulties. Risks have been addressed by using a multidisciplinary team^[12-14], by conducting regular psychiatric monitoring^[15], and by prophylactic antidepressant treatment^[16]. Although clinicians have become competent at detecting and addressing these complicating factors, the inherent difficulties have driven the development of newer drugs that do not carry these challenges.

In recent years, many newer drugs have been developed. In the spring of 2011, boceprevir and telaprevir received Food and Drug Administration (FDA) approval for hepatitis C virus (HCV) treatment. In winter 2013, sofosbuvir and simeprevir received FDA approval. Daclatasvir has been approved as of July 2014 by the European Medicines Agency, and an application for approval of ledipasvir was submitted to the FDA in February 2014.

These drugs, and others under investigation, may resolve the difficulties of interferon-alpha-based therapy. Generally, since they do not behave as inflammatory cytokines, they do not share the side effect of inducing flu-like symptoms, depression, or suicidality. The new drugs do not require refrigeration, and they are not known to have the teratogenic risk of ribavirin. FDA prescribing information for the recent drugs that are thus far FDA-approved, including sofosbuvir, simeprevir, telaprevir, and boceprevir, do not note psychiatric symptoms as recognized side effects. Since they can be used in

combination with interferon-alpha and with ribavirin, or both, the prescribing information for each of these new medications does note the risks associated with the entire regimen, as approved.

Will these newer therapies make the focus upon psychiatric status a thing of the past? Will the new therapies make the psychiatric assessments and psychiatric care, and lifestyle assessments, such as the assessment of residential stability or pregnancy monitoring, a thing of the past? Ideally, the new generation of medications would eliminate these challenging treatment considerations, and far fewer treatment candidates should be delayed by psychiatric concerns.

This question can be answered by reviewing recently updated treatment guidelines. In March 2014, a guideline was developed and released jointly by the American Association for the Study of Liver Disease and the Infectious Diseases Society of America^[17]. In April 2014, guidelines were released by the World Health Organization^[18] and the European Association for the Study of the Liver^[11]. The Veterans Affairs (VA) National Hepatitis C Resource Center and Office of Public Health released a treatment consideration guide in March 2014, with an update in May 2014^[19].

These guidelines incorporate recent efficacy evidence for hepatitis C treatment. At this point in time, recommended care has not yet reached the point of being able to decrease concerns over psychiatric or social factors.

The guidelines are very consistent in recommending that the majority of patients with chronic hepatitis C, who are candidates for treatment, should still be treated with a regimen that includes interferon-alpha. The innovation provided by the recently developed medications is that one or more of these should be added in order to boost the likelihood of achieving a sustained viral response. The most common hepatitis C genotype is type 1, at possibly 46% of cases worldwide^[20]. Genotype 3 may account for approximately 30% of cases world-wide, genotype 2 may account for approximately 9% of cases, genotype 4 may account for 8%, and genotype 6 may account for 5% of cases.

The VA guideline is organized by genotype, then by other parameters such as whether the patient is treatment-naïve, and whether or not cirrhosis is present. This guideline suggests that treatment-naïve patients with genotype 1 and no notable contra-indications be treated with a regimen of pegylated interferon-alpha combined with ribavirin, and also combined with either sofosbuvir or simeprevir.

Thus, the greatest numbers of patients coming under consideration, those with genotype 1 who are treatment naïve, are still advised to receive a regimen that includes interferon-alpha and ribavirin, and so includes the treatment challenges inherent with those regimens. Treatment-naïve patients with genotype 3 may be started on a regimen of ribavirin combined with sofosbuvir for 24 wk, with an alternative, 12-wk regimen including pegylated interferon along with the ribavirin and the sofosbuvir. Therefore, for genotype 3, the second-most prevalent

genotype, the concern about pregnancy remains when following recommended care. It thus remains the case that, for a majority of treatment-naïve patients, a hepatitis C treatment setting must have the capacity to carry out psychosocial assessment, education, intervention, and monitoring, even though a new generation of much more benign drugs have been developed and are receiving FDA approval.

One problem affecting some of these new drugs is that they may affect the metabolism of psychiatric drugs^[21]. Because of this possibility, the clinical care team will need to monitor for any drug-drug interactions for drugs that the patient may have already been prescribed, or may consider taking while being treated for hepatitis C. For example, FDA prescribing information notes that sofosbuvir may interact with anti-epileptic medications, such as carbamazepine and phenytoin, which are both used for the treatment of bipolar disorder and other psychiatric conditions. Telaprevir has a longer list of potential interactions with psychiatric drugs, including anti-epileptics, some antidepressants, and some benzodiazepenes. Kiser *et al*^[21] note possible interactions with some of the atypical anti-psychotics, as well. Treatment may call for close monitoring, or the patient may want to discontinue a drug for the length of hepatitis C treatment, or the patient might switch to another drug, with no interaction risk, for the noted indication.

Drawing upon the same set of available efficacy data, the Veterans Affairs guidelines are very concordant with those from the other noted organizations. Overall, when considering the epidemiology of hepatitis C genotype and the first line of treatment suggested by recently developed guideline statements, interferon-alpha with ribavirin continues to be a mainstay of treatment, with the innovation being the boosted rates of sustained viral response when adding the newly approved drugs.

Since interferon-alpha and ribavirin will continue to be mainstays of care, treatment settings will continue to be required to accommodate the problem of psychiatric comorbidities in their clinical populations, and to be able to address treatment-based psychiatric side effects including depressive symptoms and suicidality. A strong emphasis on patient education continues to be required to convey information regarding regimen adherence, dosing, timing, drug-drug interactions, and the problem of the teratogenicity of ribavirin.

The AASLD/IDSA 2014 recommendations^[17] note that “evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.” They proceed further on this issue to note that such comprehensive care is not common for settings diagnosing and treating liver disease, but strategies, such as co-localization of care and collaborative care arrangements, can be developed to meet this recommended style of comprehensive care.

At the same time, evaluation of new drugs, including combinations of new drugs, is actively being pursued, largely with the goal of an all-pill regimen that avoids

interferon-alpha, and also avoids, where possible, ribavirin. With FDA approval for four new drugs thus far, and several more under evaluation, the pragmatics of providing effective, evidence-based treatment for chronic hepatitis C, with a much more benign patient experience, may be much easier in the near future. In many cases, a “watch-and-wait” approach remains appropriate, as the treatment options may soon increase dramatically. “Watch-and-wait” may be acceptable for much of the patient population as long as the decision-making process has been patient-centered^[22].

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Mechanistic insights on immunosenescence and chronic immune activation in HIV-tuberculosis co-infection

Esaki M Shankar, Vijayakumar Velu, Adeeba Kamarulzaman, Marie Larsson

Esaki M Shankar, Tropical Infectious Disease Research and Education Center, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur 50603, Malaysia

Vijayakumar Velu, Department of Microbiology and Immunology, Emory Vaccine Center, Yerkes National Primate Research Center, Atlanta, GA 30329, United States

Adeeba Kamarulzaman, Center of Excellence for Research in AIDS, University of Malaya, Lembah Pantai, Kuala Lumpur 50603, Malaysia

Marie Larsson, Division of Molecular Virology, Department of Clinical and Experimental Medicine, Linköping University, 58185 Linköping, Sweden

Author contributions: Shankar EM designed research; Shankar EM and Velu V performed research; Kamarulzaman A and Larsson M contributed new reagents or analytic tools; Shankar EM and Velu V analyzed data; Shankar EM and Velu V wrote the paper.

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Correspondence to: Esaki M Shankar, Associate professor, Tropical Infectious Disease Research and Education Center, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur 50603, Malaysia. shankarem@um.edu.my

Telephone: +60-3-79492755

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Abstract

Immunosenescence is marked by accelerated degradation of host immune responses leading to the onset of opportunistic infections, where senescent T cells show remarkably higher ontogenic defects as compared to healthy T cells. The mechanistic association between T-cell immunosenescence and human immunodeficiency virus (HIV) disease progression, and functional T-cell responses in HIV-tuberculosis (HIV-TB) co-infection remains to be elaborately discussed. Here, we discussed the association of immunosenescence and chronic immune activation in HIV-TB co-infection and reviewed the role played by mediators of immune deterioration in HIV-TB co-infection necessitating the importance of designing therapeutic strategies against HIV disease progression and pathogenesis.

Key words: Cluster of differentiation 38; Human immunodeficiency virus-tuberculosis co-infection; Immunosenescence

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Core tip: The mechanistic aspects associated with increased expression of senescence and immune activation markers cluster of differentiation (CD) 38, CD69, CD57, human leukocyte antigen-DR, and the down-regulation of functional molecules, viz., CD28, CD27, CD40L and CD127 on human immunodeficiency virus-specific T cells appear to be crucial in the immunopathogenesis of HIV-tuberculosis (HIV-TB) co-infection. *Mycobacterium tuberculosis* appears to play a major role in accelerating HIV disease progression, by directly or indirectly facilitating factors associated

with immune senescence. Measures to ameliorate immunosenescence and immune activation appear to stem from identification of novel targets of downstream senescence signaling. Restoration of molecules associated with T-cell homeostasis, differentiation, cell survival and proliferation abilities of HIV-specific CD8⁺ T cells is key to foster functional immune responses.

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INTRODUCTION

The hallmark of human immunodeficiency virus type 1 (HIV-1) disease is the destruction of cluster of differentiation (CD) 4⁺ T cells eventually leading to the failure of functional attributes of the host immune system in containing viral establishment. The key target cells of HIV infection are CD4⁺ T cells, dendritic cells (DCs), monocytes/macrophages, thymocytes and microglial cells^[1,2]. HIV enters these cells *via* binding primarily but not limited to target receptors/coreceptors CD4, chemokine coreceptor 5 (CCR5) and CC-chemokine receptor 4 (CXCR4)^[3-5]. The CCR5-tropic HIV (macrophage-tropic R5 strain) appears to predominate primarily during the onset of infection, and eventually the CXCR4 HIV (T cell-tropic X4 virus) takes over to establish a chronic phase leading to eventual destruction of CD4⁺ T cells harnessed by the onset of opportunistic infections and neoplasms^[6].

HIV reportedly evades the immune system through several ways to effect direct or indirect killing of infected and uninfected cells^[7]. HIV facilitates CD4⁺ T cell depletion primarily *via* accelerated destruction, chronic immune activation (CIA) and also by impairing the regeneration of new T cells from existing T-cell precursors^[8]. Evidence suggests that monocytes and macrophages although may not be significantly affected in HIV-infected individuals, their role as reservoirs for HIV-1 provides homes for long-term survival following infection and can therefore be transmitted to bystander T cells^[9,10]. DCs contribute even more to HIV-1 pathogenesis and studies have reported reduced levels of peripheral blood DCs in HIV-1 patients and changes in their phenotypic and functional properties^[11]. Evidence also suggests that HIV could alter the expression of costimulatory molecules as well as chemokine receptors^[11]. HIV-1 infected DC in contact with T cells fail to provide optimal feedback to T cells partly due to impaired release of IL-12, which in turn fail to provide optimal survival signals for DCs owing to impairment in the expression of CD40L on T cells. Furthermore, sustenance of T-cell proliferation is also impaired due partly to decreased secretion of IL-2 by activated T cells^[12,13].

IMMUNOSENESCENCE AND CHRONIC IMMUNE ACTIVATION - KEY CULPRITS OF HIV DISEASE PROGRESSION

Immunosenescence is a common biological phenomenon occurring in elderly individuals, and represents gradual deterioration of the immune system leading to attenuated responses to infections and vaccinations^[14]. Roy Walford was the first to use the term “immunosenescence” in 1969. He believed that normal ageing in humans and animals is related to deficient immune functions^[15]. Like any other cells in the body, immune cells undergo senescence. Immune senescence is characterized by changes in T-cell subsets, molecular alterations and often involves atrophy of lymphoid organs, eventually culminating in the decline of T- and B-cell functions^[16]. Recent studies have shown that immunosenescence can occur involving both the adaptive and innate arms of the immune systems^[17]. However, the major immune cells severely affected by immunosenescence are the T cells, which ultimately result in compromised responses to antigens and increased rates of differentiation of naïve T cells to terminally-differentiated T cells^[18,19].

Immunosenescence is marked by accelerated degradation of immune system with increased turn-over of senescent T cell phenotypes showing remarkable ontogenic defects^[20]. The cells possess reduced life-span with shorter telomere lengths, reduced proliferation abilities, dysfunctional cytokine-secreting abilities, deficient anti-viral responses (exhausted effector T cells), and suppression of T-cell responses due to expansion of suppressor T cells and up-regulation of multiple negative immune receptors^[21-25]. Currently, there is increasing evidence of the expansion of senescent T cells expressing surface markers such as CD28, CD27, CD57 and CD127, especially in HIV and cytomegalovirus (CMV) infections^[26-30]. This suggests that persistent viral infections (PVI) can induce the expansion of senescent T cells *via* a mechanism called “replication senescence” or “Hayflick phenomenon”, also defined as the decrease in the ability of a cell to proliferate, with significant mark of terminal differentiation^[31,32].

Interestingly, immunosenescence also appears to occur in younger individuals with underlying malignancies and autoimmune conditions. An overwhelming body of evidence shows that persistent microbial infections with highly sustained levels of chronic antigenic stimulation, especially with HIV and CMV, could lead to functional impairment of Ag-specific T cells including proliferative abilities^[33]. Furthermore, premature senescence of CD4⁺ and CD8⁺ T cells is well-characterized in chronic HIV infection with evidence of up-regulated surface markers and functions similar to that seen in elderly HIV-uninfected individuals^[34,35]. Chronic HIV-infected patients have also shared some similarities in T-cell dysfunction with that of ‘healthy’ aging elderly^[36,37]. Interestingly, the persistence of immune activation is exceptionally notable in chronic HIV disease both in mono-infected and co-infected with

other infectious agents such as HCV, HBV and MTB, despite that highly-active antiretroviral therapy suppressed viral replication in these subjects^[38-40]. This phenomenon appears to be attributed to the up-regulation of immune activation markers namely ki-67, CD38, human leukocyte antigen - DR (HLA-DR), and CD69 on HIV-specific CD4⁺ and CD8⁺ T cells^[41,42]. Of these, CD38 expression has been reported to serve as a reliable marker of disease progression and acquired immunodeficiency syndrome (AIDS)-associated mortality^[43].

Markers of CIA apart from T cells, are also expressed in a plethora of other immune cells such as monocytes, DCs, and natural killer (NK) cells^[44]. Elevated immune activation of T cell appears to be one of the potent predictors of HIV disease progression^[45,46] as highly sustained immune activation may contribute to rapid disease progression by impairing the ability of the immune system to respond to antigens^[47], suggesting that CIA could be a key player in HIV pathogenesis and indirectly predicts progression to non-AIDS related morbidity and mortality^[34]. Accumulating line of evidence also suggests that increased expression of CD57 and reduced levels of CD127 in patients with CIA highly correlated with T-cell dysfunction and senescence^[26,27,48,49] supporting the notion of potential association between CIA and immunosenescence, especially in T cells.

IMMUNOSENESCENCE AND HIV-TB CO-INFECTION

Current investigations in human HIV/TB co-infection have provided several fundamental principles to understand how these distinct pathogens additively interact to accelerate the rates of disease progression. Although the precise mechanism of co-pathogenesis still remains elusive, it has widely been shown that both TB and HIV exert substantial influence on the host immune system. Hence, investigations underpinning the influence of TB in HIV/TB co-infection, and the importance of T-cell responses to elucidate the mechanisms underlying the failure of the immune system resulting from the dreadful interaction between HIV and TB are urgently required.

While it is increasingly becoming clear that persistent HIV disease facilitates the onset of CIA and consequently to premature senescence^[20,24,28,45,47,50], existing hypotheses suggest that MTB exacerbates HIV disease by enhancing viral transmission and entry into immune cell by causing alternations in signal transduction, cytokine modulation; overcoming anti-viral responses with overwhelming HIV promoting responses; and facilitating HIV amplification by rendering the formation of granuloma^[51-54]. The up-regulation of immunosenescence markers on T cells appears to accelerate the depletion of functional T cells, hastening a shift to terminally-differentiated T cells with altered immune functions^[55], and hence we speculate that this potentially might facilitate the onset of AIDS, and disseminated and extra-pulmonary TB infections. Based on this mechanistic viewpoint it is also possible to

correlate immunosenescence with CIA in HIV-TB co-infection.

CD38 AND HLA-DR - IMMUNE ACTIVATION MARKERS IN HIV-TB CO-INFECTION

CD38 and HLA-DR have been widely used to deduce the activation status of various immune cells, apart from other markers such as CD27, CD28, Ki-67 and CD69^[41,42]. CD38 is a glycoprotein receptor found on the surface of T cells, B cells and NK cells with key roles in signal transduction and calcium mobilization associated with their activation^[56]. On the other hand, HLA-DR is an major histocompatibility complex class II molecule that presents antigens to APCs and acts as a marker of T-cell stimulation and activation^[56-58]. Numerous literatures have established that immune activation is a direct measure of HIV disease progression^[45,59-61], which has previously been shown with CD38 expression on CD8⁺ T cells^[43,46,62]. Multiple studies have also shown that concomitant with HCV, HBV, and MTB can directly impact HIV disease progression with excessive T-cell activation in the peripheral blood^[40,63-65]. Increased expression of CD38 on both CD4⁺ and CD8⁺ T-cells of HIV-TB co-infected subjects has been described relative to HIV mono-infection^[63,66,67]. This was also consistent with existing evidences that explain the association of HIV/TB co-infection with sustained levels of peripheral activation in immune compartment following pathogenic persistence^[67-69]. Indeed, TB infection fosters immune activation as evident from up-regulated CD38 expression on T-cell subsets as compared to uninfected subjects^[66,70]. Besides this, CD38 expressions in both the CD4⁺ and CD8⁺ T-cell subsets have been inversely correlated with CD8⁺ T-cell counts and HIV plasma viral load, and that enhanced CD38 expression could lead to rapid HIV disease progression^[66,70]. The mechanism whereby MTB appears to attenuate the expression of HLA-DR, particularly on innate cells such as macrophages and DCs, is *via* the synthesis of bacterial proteins (such as 19kD lipoprotein and lipoprotein rG), which subsequently cause impaired antigen presentation and processing, potentially affecting the downstream signaling for HLA-DR expression on T cells^[71-74]. In addition, MTB can evade phagocytosis by macrophages and eventually delay the onset of adaptive immune responses^[75,76]. Active MTB infection can suppress the expression of HLA-DR *via* innate receptors (*i.e.*, TLR2), gene repression (*i.e.*, histone deacetylation), and cytokine-mediated inhibition (*i.e.*, IFN- γ) in infected individuals.

HOW DOES HIV-TB CO-INFECTION ENGINEER THE DIFFERENTIATION OF SENESCENT PHENOTYPES?

Cellular differentiation is the process by which a less specialized cell becomes a more specific phenotype with

unique functions. Upon antigenic stimulation, naïve T cells are activated and undergo differentiation into various subsets that possess distinct functionalities. CCR7 and CD45RA are two markers of T-cell differentiation but many others do exist, with two intriguing co-stimulatory molecules, CD27 and CD28^[16]. Others have proposed a model of differentiation using co-expression of CD27 and CD28 to subdivide CD8⁺ T cells into three distinct subsets based on their proliferation history, *viz.*, early (CD28⁺CD27⁺), intermediate (CD28-CD27⁺), and late (CD28⁺CD27⁻) T-cell subsets^[77]. Subsequent research also showed that intermediate-differentiated CD4⁺ T-cell subsets lose CD27 prior to CD28 (CD28⁺CD27⁻)^[36,78]. CD27 and CD28 has also been reported to indicate the stage of T-cell activation and proliferation^[79,80]. Lowered expression of CD28 indicates immunosenescence, marked by shortened telomeres and diminished replicative abilities^[81], whereas CD27 has been recently characterized as a modulator of T-cell functions, and has been suggested as a better correlate of proliferative potentials^[55]. Late-differentiated subsets have been associated with strong cytotoxic potentials, and gradual up-regulation of CD57 expression suggesting a closer relationship between senescence and differentiation^[77]. It has also been established that persistent infections might lead to loss of CD27 and CD28, which reflects that more proliferation cycles have taken place in response to pathogens, eventually leading to increased T-cell activation and advanced stages of differentiation^[82,83]. Hence, HIV-TB co-infection appears to have a synergistic effect in down-regulating CD27 and CD28 in accelerated rate as in HIV mono-infection.

Research also shows that persistent HIV infection impacts the differentiation of CD8⁺ T-cell subsets resulting in the over-presentation of intermediate-differentiation stage^[84,85]. This could largely be due to a block in maturation of CD8⁺ T cells engineered by HIV to maintain chronicity leading to ineffective cytokine and cytotoxic responses following antigenic stimulation^[85-87]. Hence it is speculated that MTB may be involved in accelerating T-cell differentiation despite the blockade of maturation exerted by HIV, leading to biased distribution of advanced stage of differentiation.

ROLE OF CD57 AND CD127 IN IMMUNE CELLULAR SENESCENCE

CD57 is a marker of senescence that has been associated with *in vitro* replicative senescence, or proliferation incompetence in both CD4⁺ and CD8⁺ T cells of healthy elders as well as PVIs^[48,88,89]. Extensive investigations have also been carried to decipher the functional role of CD57 in apoptosis, activation-induced cell death, senescence and overwhelming cytokine and cytotoxic responses. Outside HIV infection, CD57 has also been associated with various diseases and cancers^[88]. Both HIV and MTB alone have been shown to facilitate the expansion of CD57⁺CD8⁺ T cells with wide range of functionality changes and contributing to the immunopathogenesis of each disease

progression^[48,90]. Furthermore, expansion of CD57⁺CD8⁺ T cells upon stimulation by MTB have more extensive cytokine and cytolytic potential with secretion of TNF- α and IL-6^[53], and this abnormality of modulation may eventually promote HIV manifestation in co-infected individuals.

Based on our understanding, immunosenescence is best characterized by T cells showing increased CD57 and decreased CD28 expressions, also known as “late-differentiated” or senescent cells, despite several studies have proposed that co-expression of CD57 and CD27 may be a better correlate compared to CD28 as an indicator of replicative senescence^[55,87]. It is also evident that loss of CD27 and CD28 with concurrent up-regulation of CD57 descriptively represents increase of replicative inability when T cells differentiate further^[24,91]. Co-infection appears to foster the expansion of late “senescent” CD8⁺ T cells (CD57⁺CD28/CD27⁻) compared to early “senescent” CD8⁺ T cells (CD57⁺CD28/CD27⁺), whereas HIV mono-infection has over-presentation of intermediate “senescent” CD8⁺ T cells (CD57⁺CD28⁺/CD27⁻). Hence, given that late “senescent” CD8⁺ T cell is associated with decreased telomerase activity with the shortest telomere length, and a reduction in activation-induced activation^[92], there appears to be more turnover of late-differentiated CD8⁺ T cells in co-infected individuals with expanded expression of CD57, which suggests that more T cells have reached the stage of true senescence^[93].

CD127 has been indicated in activation, homeostasis, differentiation, and cell survival of different T cell populations^[94,95]. Decrease of CD127 expression has been associated with HIV disease progression^[49,96]. The importance of maintenance CD127 for T-cell survival, especially during chronic HIV infection has also been suggested^[27]. The down-regulation of CD127 may ensue due to several mechanisms, one involving HIV infection where there is a dysfunctional cytokine response when excessive IL-7 may cause an inhibitory effect on CD127 expression; while the other may be due to imbalance of IL-7 levels in the peripheral circulation^[97,98].

CONCLUSION

Despite the disparity in pathogenesis and natural history HIV-TB disease, current literature suggest that both the pathogens harness a higher quantum of symbiotic impact on each other leading to accelerated rates of deterioration of host's immune responses. Existing understanding of pathogen interaction based on immunology research has contributed to genesis of several novel hypotheses to precisely address how contemporaneous manifestations of HIV aggravate TB disease progression and vice versa^[51]. However, these evidences have not been conclusively successful in deciphering the mechanism underlying the role of MTB and HIV in accelerating immune deterioration. A better understanding of immunosenescence, and the development of strategies aimed to rejuvenate T cells, especially in PVIs will direct to improved quality of life of infected individuals. In addition, extension of knowledge

on immunosenescence to precisely identify therapeutic targets and surrogate biomarkers to validate senescence phenomena as clinical endpoints may be key to better healthcare requirements.

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Current molecular methods for the detection of hepatitis C virus in high risk group population: A systematic review

Rushna Firdaus, Kallol Saha, Aritra Biswas, Provash Chandra Sadhukhan

Rushna Firdaus, Kallol Saha, Aritra Biswas, Provash Chandra Sadhukhan, ICMR Virus Unit, I.D and B.G Hospital Campus, GB-4 (East Wing), Beliaghata, Kolkata 700010, India

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Correspondence to: Dr. Provash Chandra Sadhukhan, I.C.M.R. Virus Unit Kolkata, I.D and B.G Hospital Campus, GB-4 (East Wing), 1st Floor, 57, Dr. Suresh Chandra Banerjee Road, Beliaghata, Kolkata 700010,

India. provash2000@gmail.com

Telephone: +91-33-23537425

Fax: +91-33-23537424

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group population as these individuals are severely immunocompromised. Enzyme Immunoassays are the most common detection techniques but they provide no evidence of active viremia or identification of infected individuals in the antibody-negative phase and their efficacy is limited in individuals within high risk group population. Molecular virological techniques have an important role in detecting active infection with utmost specificity and sensitivity. Technologies for assessment of HCV antibody and RNA levels have improved remarkably, as well as our understanding of how to best use these tests in patient management. This review aims to give an overview of the different serological and molecular methods employed in detecting HCV infection used nowadays. Additionally, the review gives an insight in the new molecular techniques that are being developed to improve the detection techniques particularly in High Risk Group population who are severely immunocompromised.

Key words: Molecular detection; Enzyme immunoassay; High risk group population; Nucleic acid amplification assays; Polymerase chain reaction

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Core tip: The review focuses on the current molecular diagnostic techniques that are being used to detect hepatitis C virus worldwide. Special emphasis is given on the detection techniques that can be used to screen the individuals with repeated blood transfusion history; particularly thalassaemic individuals, intravenous drug users and persons on hemodialysis.

Abstract

Hepatitis C virus (HCV) is an emerging infection worldwide and the numbers of persons infected are increasing every year. Poor blood transfusion methods along with unsafe injection practices are potential sources for the rapid spread of infection. Early detection of HCV is the need of the hour especially in high risk

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INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem which has affected around 170 million people worldwide and is one of the major causes of deaths related to liver cirrhosis and hepatocellular carcinoma^[1]. HCV can be classified to seven major genotypes and 80 subtypes^[2-4]. HCV genotypes vary in patterns of geographical distribution and therapeutic response. However, the geographical and genetic diversity of this RNA virus is constantly evolving because of rapid globalization. In India, HCV infection has been reported in 0%-21% population and responsible for 14%-26% cases of chronic liver disease^[5]. HCV infection is mostly transmitted through transfusion of blood or blood products. A high prevalence of HCV is found in many high-risk groups (HRG) exposed to blood or blood products like intra venous drug users (IDUs), patients with pediatric hematologic malignancies and those with thalassemia and hemophilia. India reported a higher percentage of blood donors (1%-1.5%) than in any developed country^[6,7].

An increasing burden of HCV related liver complications has been estimated particularly taking into account those who were infected before safety precautions of blood transfusions happened. A major concern is careful screening of blood and blood related products, but in developing countries like in India, the regulations for strict checking of blood and blood related products came to place only in 2001^[8,9]. Recent surveys have reported that testing of blood and blood related products are poorly regulated in India^[10]. In United States, data showed that death related to HCV exceeded than those by HIV. Though novel antiviral therapies are recently in the horizon with enhanced efficacy and fewer side effects but the challenge remains in detecting HCV at an early stage.

During HCV infection, though attempts are made to diagnose and differentiate acute from chronic hepatitis C infection, it is often not possible to distinguish between the two phases. The infection may be recognized only when it becomes chronic^[11,12]. The serologic diagnostic tests used as first step for detecting the infection cannot distinguish between acute and chronic infection^[13]. Investigations for patients with HCV infection include serological assays for antibodies to hepatitis C (anti-HCV) and molecular assays for detection of viral RNA.

The importance of low cost molecular diagnostic assays are especially important for the developing nations as they are already burdened with increasing number of hepatitis C patients who are generally economically backward. The advent of molecular diagnostic approaches has allowed for the development of nucleic acid assays that are more sensitive and specific than antibody based technologies. The linking of these assays with appropriate detection systems, therefore, makes them highly desirable for detecting HCV RNA in patient samples. Molecular techniques not only help to detect HCV RNA but confirm active state of infection, *i.e.*, the virus is in replicating state in the patient's body. In individuals falling in high risk diagnosis of HCV can give false negative results as these

patients are already immuno-suppressed, in this scenario, molecular testing remains the best choice for detection.

This review aims to give an overview of the different serological and viral genome based laboratory tests which has become instrumental in the management of HCV infection to diagnose viral infection, and more importantly guide treatment decisions which could be of enormous help to clinicians.

LABORATORY INVESTIGATION

The investigation of HCV diagnosis starts with serological assays for detecting antibodies to HCV followed by molecular assays for detecting HCV RNA (Figure 1). Initial diagnosis of HCV infection is classically done by serologic methods either by determining anti HCV antibody by EIAs or by immunoblot assays and by determining the presence of HCV RNA. The advent of simple rapid immunoassays has significantly reduced the risk of HCV transmission, but concern remains for patients in high risk groups^[13-16]. Studies have shown that false negative results in rapid tests might arise in patients who are severely immunocompromised such as those co-infected with HIV^[17], in patients on hemodialysis, IDUs, thalassaemic. In these patient groups molecular detection by reverse transcription polymerase chain reaction (RT-PCR) remains the best method for detection.

RAPID IMMUNOASSAYS FOR DETECTION OF HCV IN SERUM OR PLASMA

Rapid immunoassay tests are based on the principle to detect HCV antigens from core, NS3, NS4 and NS5 regions of the virus. In western countries, these tests are used besides nucleic acid testing, and used only as point of care tests, but in developing countries these tests are solely relied in commercial places for detection of HCV^[18]. Commercial kits like OraQuick rapid HCV antibody test use device that delivers HCV antibody test results in 20 min using a single drop of whole blood. The kit was approved for laboratory use in United States from June 2010. The OraQuick is very accurate, with sensitivity and specificity performance that meets the standards for FDA approval^[19]. Though rapid kits have been extensively used for surveillance purposes, they are not well suited for high risk groups and immunocompromised patients^[20,21]. In developing countries like India, WHO has recommended certain kits for rapid testing for surveillance purposes.

ENZYME IMMUNOASSAY FOR HCV DETECTION IN SERUM OR PLASMA

Enzyme immunoassays are the most common screening test for HCV [enzyme immunoassay (EIA), microparticle EIA, chemiluminescence immunoassay (CIA)] that detects anti-HCV antibodies in plasma or serum. These assays are

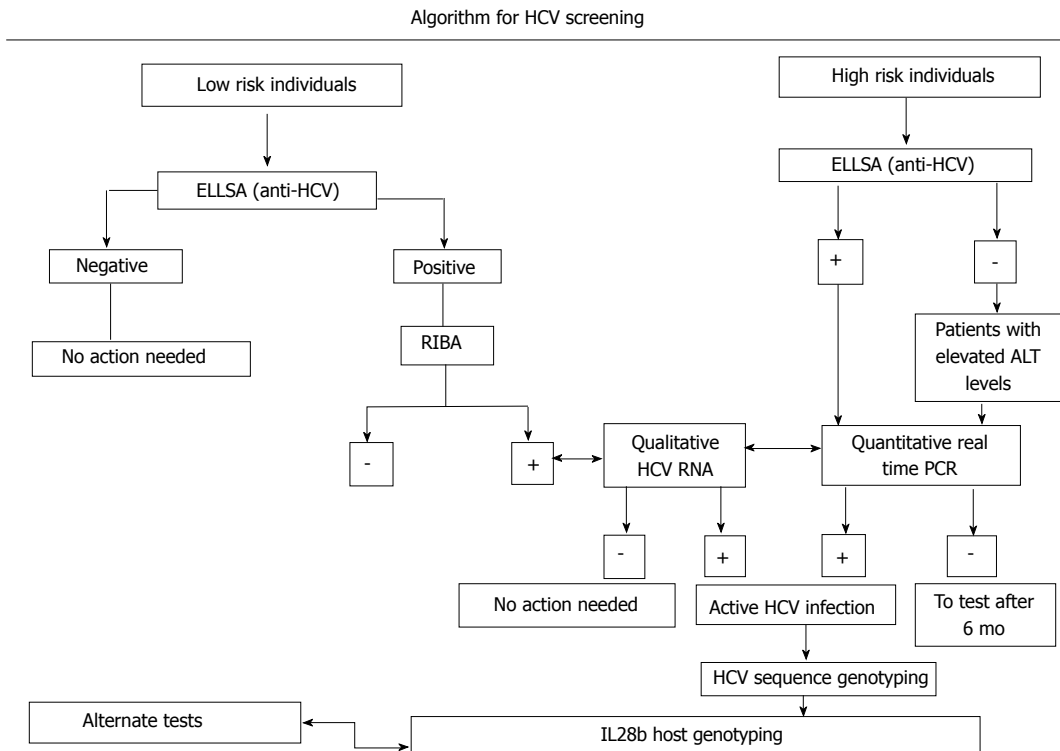


Figure 1 Algorithm for hepatitis C virus screening and detection. HCV: Hepatitis C virus; PCR: Polymerase chain reaction.

relatively easy to use, does not require expert technicians, automation is simple, have a low variability and are inexpensive.

Three generations of EIA antibody testing have been developed since 1989. In the first generation of EIA developed in 1992, c100-3 epitope from the non-structural NS4 regions was incorporated. A newer and better second generation EIA-2 was developed next which contained HCV antigens from core, NS3, NS4 regions^[22-24]. The third generation of EIA developed contained modified antigens from core, NS3, and a slightly modified antigen from NS5 region. The incorporation of these antigens increased the overall sensitivity to 97%, which was better than the second generation assays. The mean time to seroconversion in the improved third generation kits has gone down to 2-3 wk as compared to 4-6 wk in the second generation kits. EIA methods have several advantages as the kits are relatively inexpensive and highly sensitive too, but one of the disadvantages is that it may give false positive results in routine blood donors and asymptomatic adults. For this reason, Centres for Disease control and prevention has recommended the supplementary tests like RIBA or PCR based methods to confirm positive ELISA tests unless the signal-to-cut-off ratio is above a predetermined threshold^[25].

False-negative EIA especially occur in patients with major immunosuppression (advanced HIV infection or organ transplantation recipients), patients with chronic renal failure on long-term hemodialysis, and patients with acute or early HCV infection have been reported in HCV EIA^[26].

In developing countries like India, WHO recommends

the use of 3rd generation HCV EIA kits. Several commercial kits which employ the structural and non-structural antigens *i.e.*, core, E1, E2, NS3, NS4 and NS5 are in use. The 3rd generation kits are better than the previous versions with improved specificity and sensitivity. The use of EIA kits in India is limited as it requires expertise in handling and in developing countries like India where the health care resources are already burdened; it becomes very difficult to reach the people^[27].

RECOMBINANT IMMUNOBLOT ASSAY FOR HCV ANTIGEN DETECTION

In the recombinant immunoblot assay (RIBA) assays, multiple HCV antigens are individually displayed on a nitrocellulose strips as bands. In positive HCV infection, RIBA results show two reactive bands, in intermediate infection show one positive band. Since positive cases in RIBA, show two bands they are considered more sensitive than EIA. However, they are not considered as independent gold standard as two tests contain similar antigens to detect HCV antibody^[28-30].

DETECTION OF HCV CORE ANTIGEN IN PLASMA OR SERUM

HCV core antigen testing was developed as an alternative to nucleic acid testing (NAT assays). The HCV core antigen detects viral antibodies within the sero-conversion period and can be used to utilize to monitor antiviral therapy. But till now is not commercially used as detection

system^[31]. The Architect HCV Ag assay (Abbott) which is a quantitative core antigen based assay, is commercially available in Europe. The assay is chemiluminescence based immunoassay in an automated platform^[32]. In these assay, micro particles are coated with a monoclonal antibody against HCV core antigen. Studies have shown that HCV core antigen could be detected within first two weeks of acute infection. The core antigen based testing has a sensitivity ranging from 80% to 99% and a specificity ranging from 96% to 100%. The core antigen based assay could be an important detection technique in individuals who are in High Risk Group, because the core protein is the most conserved viral antigen amongst HCV types and, was therefore, a likely antigenic probe. Also the core protein is one the first protein which is synthesized and therefore could be an attractive target for molecular detection in high risk group patients who are immunocompromised. Studies have demonstrated two major B-cell epitopes at the N-terminus of core: amino acids (aa) 5-23 and 39-74 using peptide reactivity to sera from patients with chronic HCV can be used as antigenic determinants^[33,34].

NAT FOR DETECTION OF HCV RNA

Molecular diagnostic assays are an integral part in the management of HCV patients. Both qualitative and quantitative HCV molecular assays are used in the diagnosis of acute and chronic infection. The principle of qualitative HCV assays includes viral RNA isolation, complementary DNA (cDNA) synthesis, PCR amplification and detection of PCR amplicons. Qualitative HCV RNA test detects the presence of HCV circulating in the blood and is among the most sensitive tests available. Since HCV is a RNA virus, reverse transcription PCR is used to detect viral RNA^[35-37]. The viral genome is 9.6kb long, contains a single open reading frame that is translated to produce a single protein product, which is then further processed to produce functional proteins for viral replication and propagation^[36]. At the 5' and 3' ends of the viral RNA are the untranslated region (UTR) that are not translated into proteins but are important to translation and replication of the viral RNA. Most of the commercial and in-house PCR amplification strategies are targeted against the 5' UTR region as there is more than 90% sequence identity among different HCV genotypes, with some segments nearly identical among different strains^[37-39]. The secondary and tertiary structures of this region are also largely conserved and this is one of the first regions which is transcribed of the first regions which is transcribed.

Other than the 5' UTR region, the core and the 3' UTR region are also targeted for PCR based detection of HCV^[40-44]. A recent study showed that detection based on the sequence of the core region could reliably identify subtypes as well as major genotypes since the sequence divergence was greater than the divergence of the 5'UTR sequence. Though there are other regions like the E1, E2, NS2, which can be used as detection targets for PCR amplification but they are not in much use as there is a lack of conservation in the primer binding sites^[45-50].

Detection of viral RNA is useful in diagnosing HCV infection prior to sero-conversion, distinguishing active from resolved infection, and diagnosing chronic hepatitis carriers who are HCV antibody negative, especially among HRGs. Nucleic acid testing is recommended: (1) for confirmation of HCV RNA in cases where patients are HCV seropositive; (2) to confirm the presence of HCV viremia in patients who are seronegative but immunocompromised such as HIV infected individuals; (3) in babies who are born to HCV positive mothers- as antibody testing in babies can give false positive results upto 18 mo of age; and (4) for determining the baseline value before starting the anti-viral therapy. Molecular detection of HCV includes both qualitative and quantitative assays. The qualitative HCV RNA testing is very popular due to its higher sensitivity, but a major disadvantage of the qualitative assays is that it only determines the presence or absence of HCV RNA. On the other hand, quantitative HCV RNA determines the HCV RNA level and thus provides prognostic information for treatment. Nowadays, there are several widely used commercial tests which are used to detect the presence of HCV RNA in patient's serum. One of the commercial assays used is the Cobas AmpliCor HCV version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA, United States) based on a standard RT-PCR is available for the qualitative measurement of HCV RNA. The lowest detection limit is 50 IU/mL whatever the HCV genotype^[51,52]. Another assay commercially used is versant HCV qualitative assay (Siemens Healthcare Diagnostics, Deerfield, IL, United States) which is based on transcription mediated amplification technique. In this assay, first viral RNA is isolated from the patient's serum and then amplified by utilizing two enzymes (reverse transcriptase and T7 RNA polymerase). These amplicons are further detected *via* hybridization protection assay (HPA) in which only hybridized probes remain chemiluminescent and are detected in a luminometer. Analytical sensitivity is 10 IU/mL for most genotypes and 5.3 IU/mL for genotype 1^[53].

QUANTITATIVE ASSAY

HCV quantitative assay is used to determine the number of international units of HCV RNA per millimeter of serum or plasma (IU/mL) in known HCV positive patients.

Recently, real time PCR based detection systems have become widely available and are considered as the detection method of choice by many clinicians. The advantages of this technique are that they have a very low limit of detection, have a broad dynamic range. Several companies now market the real time PCR assays: the COBASs Ampliprep/Cobas TaqMan assay (CAP/CTM, Roche Molecular Diagnostics) and the real-time HCV assay (also named AccuGenes HCV, Abbott Molecular Inc., Des Plaines, IL, United States). These assays have the advantage of having a broad dynamic range of amplification, thus improving the limits of detection (LOD) to 10 IU/mL, and linear quantification up to 10^7 - 10^8 IU/mL^[54,55].

The quantitation of HCV viral RNA in Cobas AmpliCor is performed using the HCV Quantitation

Standard. The HCV quantitation standard is a non-infectious armoured RNA construct of HCV sequences with identical primer binding sites as the HCV RNA target and a unique probe binding region that allows HCV Quantitation Standard amplicon to be distinguished from HCV target amplicon. The HCV Quantitation Standard is pipetted into each individual sample and control at a known copy number and is then amplified by PCR. The COBAS TaqMan HCV Test, v2.0 uses reverse transcription and PCR amplification primers against the highly conserved 5' untranslated region of the HCV genome^[56].

The Versant HCV quantitative test (Siemens Healthcare Diagnostics) which is HCV RNA assay based on signal amplification by branched DNA (bDNA). In this assay, single stranded DNA molecules are present; which acts as probe DNA molecules. Next an extender DNA molecule is added. Once the capture and extender molecules are in their proper place they are hybridized and the sample is added. The bDNA assay version 3.0 has been reported to have a lower detection limit of 615 IU/mL to 8 million IU/mL whatever the HCV genotype^[57].

The advantage of RT-PCR is that it allows continuous monitoring of amplicon kinetics during the exponential phase before the amplification reaches its plateau. This allows for a good correlation between the initial numbers of template copies whereas in qualitative assays based on PCR, amplicon detection was at the end^[56,58]. Thus the use of quantitation techniques have greatly enhanced the sensitivity and reliability in detection techniques.

VIRAL GENOTYPING ASSAYS

There are at least seven genotypes and over 80 subtypes of HCV. Different assays are used to determine genotype such as sequencing and hybridization^[2]. Most genotype assays use amplification of specific region of viral genome by PCR followed by direct DNA sequencing. While a variety of techniques are used, the gold standard for HCV genotyping is nucleotide sequencing, which can be done by using core (C), envelope (E1), or the non-structural (NS5B) regions which can be amplified by reverse transcription followed by polymerase chain reaction^[59-63]. Most diagnostic assays commonly target the 5' UTR but in research settings core and or NS5B region is usually sequenced as this region is more conserved amongst all genotypes. Genotypes are very useful for determining the duration of treatment regimens and predicting treatment response^[64-68].

EMERGING MOLECULES TECHNIQUES

One of the emerging diagnostic assays is nanoparticle based diagnostic assay. Quantum dot and gold based nanoparticle based diagnostic assay^[69-71]. Quantum dots are nanoparticles made of semiconductors that emit light at different spectra; the emission is dependent on the size which greatly increases the ability to multiplex^[72-74]. Another novel technique being developed recently is the use of aptamers as capture molecules. Aptamers are short,

single stranded oligonucleotide that can fold into specific 3-dimensional structures and recognize target molecules such as small chemicals, proteins, and even cells^[75]. These techniques have been used for various diagnostic applications because of their ability to bind their targets with high affinity and specificity.

CONCLUSION

Molecular diagnostic testing for HCV has provided a crucial tool for addressing significant controversies in HCV management. NATs for detecting HCV RNA remain the mainstay for detecting HCV infection in individuals in high risk group population. Nucleic acid test not only helps to detect HCV RNA but confirms active state of viral infection, *i.e.*, the virus is in replicating state in the patient's body. However, in developing countries due to financial constraints and lack of technical expertise in clinical settings, these tests are difficult to perform and time consuming. In these settings, the most widely employed screening tests are the HCV rapid immunoassays. However, it is the need of the hour to effectively design strategies to detect HCV infection even in sero-conversion period.

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Ledipasvir and sofosbuvir: Interferon free therapy for hepatitis C virus genotype 1 infection

Yasir Waheed

Yasir Waheed, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad 44000, Pakistan

Yasir Waheed, Foundation University Medical College, Foundation University Islamabad, DHA Phase I, Islamabad 44000, Pakistan

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Correspondence to: Yasir Waheed, PhD, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, H-12, Islamabad 44000, Pakistan. yasir_waheed_199@hotmail.com

Telephone: +92-300-5338171

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naïve patients, 12 wk of therapy with ledipasvir and sofosbuvir showed a sustained virological response (SVR) rate of 99%. In treatment experienced patients, 12-24 wk of therapy with ledipasvir and sofosbuvir in the absence or presence of ribavirin showed an SVR rate of 94%-99%. In cirrhotic patients the rate of SVR was 86% and 99% for 12 and 24 wk of therapy, respectively. The ledipasvir and sofosbuvir therapy showed very good results in different subgroups of patients regardless of patient's race, alanine aminotransferase levels, sex and host genetic factors. The combination therapy was well tolerated with no emergence of resistant mutants. The most common adverse effects were nausea, headache and fatigue. With the availability of interferon free therapy with minimal adverse effects, it will be easy to decrease the future morbidity and mortality caused by HCV infection.

Key words: Hepatitis C; Interferon; Ledipasvir; Sofosbuvir; Genotype

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Core tip: The interferon based therapy for hepatitis C patients has a limited response with a number of adverse effects. The ledipasvir and sofosbuvir combination therapy showed a sustained virological response (SVR) rate of 99% in treatment naïve patients. The rate of SVR was 94%-99% in treatment experienced patients, while in cirrhotic patients the rate of SVR was 86%-99%. The treatment response was not affected by ethnicity or host genetic factors.

Abstract

Hepatitis C virus (HCV) has infected more than 200 million people around the globe. From 2001-2011, interferon plus ribavirin remained the standard of care for patients with HCV infection. The therapy had a limited response with a number of side effects. Recently, results for phase III trials of ledipasvir and sofosbuvir combination therapy have been announced. In treatment

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TO THE EDITOR

Hepatitis C virus (HCV) infection is a major health problem around the globe, with more than 200 million people infected worldwide. Although the rate of HCV infection is continuously declining, the rates of HCV associated morbidity and mortality are continuously increasing.

From 2001-2011, interferon and ribavirin therapy remained the standard of care for patients living with HCV. The therapy had a limited response with a number of side effects. The major adverse effects associated with interferon administration were flu like symptoms, cytopenia and depression, whereas ribavirin therapy causes fatigue, anemia, rash and pruritus. The major objective of recent treatment regimens is to eliminate the interferon and ribavirin from the treatment regimen so that the adverse effects of therapy can be reduced and the therapy become available for patients who are ineligible for the interferon and ribavirin therapy.

Sofosbuvir is a nucleoside analogue that can inhibit the HCV polymerase, approved by the Food and Drug Administration for the treatment of patients living with HCV. Ledipasvir is an inhibitor of HCV NS5A protein, showing antiviral activity against HCV genotype 1 infection.

In a phase II clinical trial, 120 patients with HCV genotype 1 infection who were treatment naïve or previously treated with protease inhibitors were enrolled at a centre in the United States. The patients were given a fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg). In cohort A, 60 treatment naïve, non-cirrhotic patients who were given sofosbuvir plus ledipasvir (8 wk), sofosbuvir plus ledipasvir along with ribavirin (8 wk), or sofosbuvir plus ledipasvir (12 wk) showed an SVR rate of 95%, 100%, and 95% respectively. In cohort B, 40 previous non-responders to protease therapy were included. They were given sofosbuvir plus ledipasvir (12 wk) or sofosbuvir plus ledipasvir along with ribavirin (12 wk), and the sustained virological response (SVR) rate was 95% and 100%, respectively^[1]. The sofosbuvir-ledipasvir combination therapy cured most of patients with HCV genotype 1 infection, irrespective of their treatment history. Further investigations were required to optimize the treatment duration and the role of ribavirin in treatment response.

In a phase III clinical trial, 865 previously untreated patients were enrolled and they were randomly divided into four groups. Group 1 received ledipasvir and sofosbuvir for 12 wk and showed an SVR rate of 99%. Group 2 received ledipasvir and sofosbuvir along with ribavirin for 12 wk and showed an SVR rate of 97%. Group 3 received ledipasvir and sofosbuvir for 24 wk and showed an SVR rate of 98%. Group 4 received ledipasvir and sofosbuvir along with ribavirin for 24 wk and showed an SVR rate of 99%. The study concluded that the 12 wk therapy with ledipasvir and sofosbuvir was highly effective for patients living with HCV genotype 1 infection. No additional benefit was observed by the addition of ribavirin or by the extension of therapy to 24 wk^[2].

In another phase III trial, 440 previously treated pa-

tients were enrolled, 20% of whom had cirrhosis. The patients were given ledipasvir and sofosbuvir in the presence or absence of ribavirin from 12 or 24 wk. The rate of SVR achieved was 94%-99%. In patients with cirrhosis the rate of SVR was 86% (ledipasvir-sofosbuvir) and 82% (ledipasvir-sofosbuvir plus ribavirin) with 12 wk of treatment, while the rate of SVR was 99% (with both regimens) in patients having 24 wk of treatment. The study concluded that the single tablet of ledipasvir-sofosbuvir showed a better rate of SVR even in the patients who were not responders to the interferon based therapy^[3].

The ledipasvir and sofosbuvir therapy produced very good results in different subgroups of patients regardless of patient's race, alanine aminotransferase levels, sex and host genetic factors. The combination therapy was well tolerated. No S282T variant was observed. The most common adverse effects were nausea, headache and fatigue^[2-4].

A total of 1952 patients were enrolled in three different phase III trials of ledipasvir and sofosbuvir, out of which 97% showed SVR^[2-4]. Out of the remaining 3%, half of them withdrew consent or were lost to follow-up. Undetectable viral RNA was not achieved in only two patients. The rate of relapse was observed in only 2% after stopping therapy. The rate of relapse was also linked with the treatment duration. The rate of relapse was observed in 5%, 2% and 0.2% of patients who received 8 wk, 12 wk and 24 wk of treatment, respectively^[5].

With the availability of oral, short duration, interferon free therapy with minimal adverse effects, the future morbidity and mortality associated with HCV infection will decrease. The major problem with the therapy is its cost. The cost of 12 wk therapy with sofosbuvir alone is \$84000 and the addition of ledipasvir will further increase the cost^[5]. The high cost of the therapy will affect the goal of providing safe and effective treatment for millions of patients living with HCV around the globe.

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