

Hepatitis C Genotype 4: What We Know and What We Don't Yet Know

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Hepatitis C virus genotype 4 (HCV-4) is the most common variant of the hepatitis C virus (HCV) in the Middle East and Africa, particularly Egypt. This region has the highest prevalence of HCV worldwide, with more than 90% of infections due to genotype 4. HCV-4 has recently spread in several Western countries, particularly in Europe, due to variations in population structure, immigration, and routes of transmission. The features of HCV-4 infection and the appropriate therapeutic regimen have not been well characterized. This review discusses the virology, epidemiology, natural history, histology, clinical data, and treatment options for patients with HCV-4 infections. Early reports on the treatment of patients with chronic HCV-4 with conventional interferon (IFN)- α monotherapy indicated poor rates of sustained viral response (SVR), which improved slightly when combined with ribavirin. Pegylated IFN and ribavirin combination therapy has dramatically improved the response rates, with recent clinical trials showing rates that exceed 60%. These data can now be used as a platform for further research to define optimal treatment duration and predictors of SVR in patients with HCV-4 infection. *Conclusion:* HCV-4 infection is spreading beyond its strongholds in Africa and the Middle East. Recent clinical trials show that HCV-4 is not difficult to treat, as the response to treatment may be at an intermediate level compared with genotype 1 and genotypes 2 or 3. Tailored treatment options that are comparable to the treatment approaches for genotype 1, 2, and 3 patients to optimize treatment for each patient are now being developed. (HEPATOLOGY 2008;47:1371-1383.)

Hepatitis C virus (HCV), a member of the *Flaviviridae* family of RNA viruses, is characterized by genetic heterogeneity. At least 6 major HCV genotypes are identified.^{1,2} Each genotype differs from the others by 30%-35% of its nucleotide site sequence and also exists as numerous genetically distinct isolates.¹⁻³ Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy.³ Thus, each genotype can be considered a phylogenetically distinct entity requiring its own specific clinical appreciation. Knowledge of the epidemiology of HCV genotypes is essential not only for epidemiological reasons but also from a clinical standpoint. The infecting

HCV strain is known to be one of the main independent factors that influence the outcome of antiviral therapy.^{2,3} Genotypes 1, 2, and 3 are common throughout the United States and Europe^{2,4} and have thus become the focus of much interest and research. The clinical presentation and management of infections arising from these viral genotypes has advanced rapidly. In contrast, genotypes 4, 5, and 6 have not been adequately studied; therefore, the management strategies for patients infected with these genotypes are not as well developed.^{4,5}

HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections, and has recently spread to several European countries.^{4,5} Egypt has the highest prevalence of HCV worldwide (15%)⁶ and the highest prevalence of HCV-4, which is responsible for almost 90% of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver transplantation in the country.⁵⁻⁷ Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has simply not been the subject of widespread research; therefore, the features of this genotype and management strategies for patients infected with this genotype are not as well developed as for

Abbreviations: CTL, cytotoxic T lymphocyte; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCV-4, hepatitis C genotype 4; IFN, interferon; PEG-IFN, pegylated interferon; SVR, sustained virologic response.

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Table 1. Prevalence of HCV Genotype 4 and Distribution of Subtypes in Different Geographic Regions

Country	Percentage of Genotype 4	Subtypes
Egypt	90%	4a (55%), 4 (24%), 4o (7%), 4m (3%), 4l (3%), 4n (2%)
Gabon	97%	4c (36%), 4h (15%), 4e (13%), 4 (13%), 4g(13%), 4f (5%), 4a (2.6%)
Central African Republic	100%	4 (66.7%), 4k (33.3%)
Democratic Republic of Congo	100%	4 (30%), 4c (30%), 4k (24%), 4r (14%), 4a (5%)
Cameroon	36%	4f (22%), 4 (5%), 4t (5%), 4k (5%), 4e (1.4%), 4o (1%), 4p (1%)
Liberia	100%	4 (100%)
Uganda	100%	4 (66.7%), 4r (33.3%)
Tanzania	50%	4 (100%)
Rwanda	100	4k (100%)
Sudan	5%	4, 4e, 4c/4d
Tunisia	11%	4k (5%), 4a (3.6%), 4 (2.6%)
Saudi Arabia	3%–5%	4c/4d (33%); 4h (14%); 4e (7%); 4 (20%)
France	4%–10%	4d (2.3%), 4a (2.2%)
Italy	8.3%	4d (5.9%), 4 (2.4%)
Spain	3%–10%	4c/4d (76.8%), 4 (11.5%), 4a (7.2%), 4e (4.3%)
Greece	13.2%	4a (78%)

genotypes 1, 2, and 3. This review presents the available data on virology, natural history, clinical and histological aspects, as well as treatment options for HCV-4 infections.

HCV-4 Virology

Early studies attempted to define HCV-4 by analyzing sequences representing the 5'NCR, core, E1, NS4, NS5, or 3'NCR beyond the poly U regions.^{8–11} The complete nucleotide sequence of the HCV genotype 4a Egyptian variant was first described by Chamberlain et al. in 1997¹² (ED43: GenBank accession no. Y11604⁹). Reference sequences for HCV-4 and its subtypes are found in the Los Alamos HCV database¹³ (<http://hcv.lanl.gov/content/hcv-db/classification/genotable.html>). The sequence of HCV-4 contained a single open reading frame encoding a polyprotein of 3008 amino acids (aa), smaller than that reported for other HCV genotypes, which range from 3010 to 3037 aa. The differences in length of the polyprotein originated in variable regions in the E2 and NS5A genes. A slightly closer relationship was detected between genotype 4 and genotype 1 variants than to other genotypes.^{12,14} A recent study¹⁵ described the full-length sequence of HCV genotype 4d, the subtype encountered in sub-Saharan African infections, in addition to several unique 4a sequences. The degree of variation between the Egyptian genotype 4a sequence and genotype 4d sequences in this study was in the range of 10.6% to 12.4% at the nucleotide level and 7.9% to 9.8% at the amino acid level with deletion of 4 amino acids within the interferon sensitivity determining region (ISDR) of NS5A.¹⁵

HCV genotype 4 is a very heterogeneous genotype showing significant genetic divergence and more subtypes compared with other genotypes. To date, 18 subtypes (subtypes 4a, 4c, 4d, 4e, 4f, 4g, 4h, 4k, 4l, 4m, 4n, 4o, 4p,

4q, 4r, 4s, 4t, 4u) have been identified in different geographic regions^{8,14} (Table 1). The clear difference in subtype prevalence in different geographic regions is of molecular epidemiologic importance, because it helps in tracing the origin of HCV infection in a given region.^{16,17} However, the full clinical significance of HCV subtypes is not known, because only very few studies correlated HCV-4 subtypes to the natural history, pathogenicity, disease severity, or outcomes of therapy.^{18,19} A recent study¹⁹ reported a significant association between subtype 4o and hepatocellular carcinoma in Egypt. A French study¹⁸ suggested a possible relation between HCV-4 subtypes and the degree of liver fibrosis and outcome of therapy. Viral genetic diversity can influence the recognition of epitopes by cytotoxic T lymphocytes (CTLs) since each step of CTL epitope generation and recognition is potentially constrained by sequence specificity. Mutations within and proximal to epitopes can influence their immunogenic potential.^{20,21} Conformational epitopes are crucial for the induction of a successful HCV-specific CTL response necessary for viral clearance, long-term control of HCV, and the development of an effective vaccine.^{20–22} Therefore, for development of an effective vaccine, several factors such as the proper folding of the HCV structural proteins used, the recognition of epitopes by CTLs, and the eliciting of a neutralizing immune response should be taken into account when designing a potential vaccine that provides cross-protection against HCV-4 in areas where this genotype is endemic and a vaccine is needed most.

The Origin and Epidemiology of HCV-4 in Different Geographic Regions

The origin, evolution, and dynamics of HCV-4 are difficult to determine given the limited population-based

epidemiological studies and phylogenetic analysis of this genotype in the geographic regions in which it is endemic, such as Egypt and Central and West Africa. The information available from small-scale field surveys from Central African countries (Zaire, Gabon, Central African Republic, and Tanzania) and Cameroon in addition to sequence analysis studies applying the Bayesian coalescent approach indicate that HCV-4 strains circulating in Central Africa and Cameroon are extremely heterogeneous (Table 1) and that the estimated date of the most recent common ancestors for HCV-4 was 1500 (95% CI: 1350-1700), suggesting that it probably has been endemic for a long time.^{16,17,22-29} An exponential spread of genotype between 1920 and 1960 was detected in Cameroon, which coincided with the mass campaign against trypanosomiasis and mass vaccinations.^{25,26} This great genetic diversity in sub-Saharan Africa might lead to the hypothesis that HCV-4 originated and propagated in Central and West Africa before spreading to other regions.^{16,17} However, it is not clear how HCV infection was maintained for long periods among these populations prior to the known parenteral routes of transmission such as blood transfusion and injection. It is likely that other routes of transmission such as scarification, circumcision practices, or sexual transmission might have contributed to persistence and propagation of HCV transmission in tropical and subtropical settings.

Egypt has the highest prevalence of HCV worldwide, where it infects about 15% of the general population.⁶ Several combined population genetic and epidemiological analyses were conducted to determine the origin and the historical changes in Egyptian HCV prevalence.^{10,27-31} Despite the high prevalence of HCV in Egypt, studies have suggested that the epidemic pattern of type 4a infection in Egypt was more recent and quite different from the endemic pattern in sub-Saharan Africa.^{28,29} HCV's lack of genetic diversity in Egypt compared with the sub-Saharan African strains and the predominance of HCV-4a suggest a relatively common source for the epidemic rather than long endemicity and propagation. Molecular evolutionary analysis on Egyptian genotype 4a isolates indicates that the Egyptian HCV epidemic was initiated and propagated by extensive anti-schistosomiasis mass treatment campaigns, during which tartar emetic (potassium antimony tartarate) was administered as a series of intravenous injections and the syringes and needles were reused without being properly sterilized.^{10,27-32} The spread of HCV-4a increased exponentially in rural areas during the 1930s through the early 1980s, coinciding with the mass campaigns, with the most rapid exponential growth between 1930 and 1955.^{27,28}

Although the anti-schistosomal campaigns were terminated in the early 1980s, the prevalence and incidence of HCV remains high in Egypt. Thus, it seems that the current status of HCV in Egypt is not only a consequence of the mass anti-schistosomal therapy but also due to new infections acquired beyond that era, given that HCV currently represents more than 30% of the annually reported acute hepatitis cases.³³ Blood transfusion was a common route for HCV-4 transmission in Egypt until 1993, after which blood and blood products were screened for HCV. Illicit drug use is not common in Egypt and does not represent a major risk of HCV transmission.^{30,33} A set of risk factors, mostly related to prevailing social and cultural conditions, are responsible for maintaining the high rates of HCV-4 transmission in Egypt. In several large community-based studies, medical procedures such as circumcision, dentistry, excision, and wound treatment performed by informal health care providers in rural health units were identified as important risk factors for HCV transmission in Egypt.³⁵⁻³⁸ In rural Egypt, about 50% of deliveries are attended by traditional birth assistants who do not perform appropriate cleaning or disinfection of the equipment used.^{35,36} Traditional scarification and tattooing practices may play some role in transmission of HCV-4 in rural Egypt.³⁶ Occupational transmission among health care workers through needlesticks and sharp injuries is common in Egypt and contributes to the high rates of HCV infection among health care providers in Egypt, given that needleless systems are not adopted in Egyptian hospitals and health care units.^{36,37} Although not considered efficient routes for HCV transmission in the West, intrafamilial and sexual transmission play a role in the high prevalence of HCV-4 in Egypt.³⁸⁻⁴⁰

The prevalence of HCV in Saudi Arabia is 3%-5% among Saudis,⁴¹ with predominance of genotype 4 (62%) followed by genotypes 1b (21.4%), 1a (14.3%), and 2a (3.6%). Unlike the predominance of subtype 4a in Egypt, subtypes 4c/4d are the most prevalent subtypes among Saudis, followed by subtypes 4h, 4e, and 4a,⁴¹ suggesting that the origin and transmission of HCV-4 is different from that in Egypt.

Recently, HCV-4 has become increasingly prevalent in some southern European countries on the Mediterranean Sea—particularly Italy, France, Greece, and Spain, where prevalence rates of 10% to 24% have been reported in some areas.⁴²⁻⁴⁷ The epidemiological patterns of HCV-4 and the risk factors for transmission of this genotype in Europe are not well defined. However, it has been shown in some reports that HCV-4 infections are more frequent among intravenous drug users (European and non-European), patients coinfecting with HCV and human immunodeficiency virus (HIV), and immigrants from North

and sub-Saharan Africa.⁴²⁻⁴⁷ The major subtypes reported from southern Europe are genotypes 4d and 4a.⁴²⁻⁴⁵ These data suggest that 2 factors were likely responsible for the introduction and spread of HCV-4 in Europe, namely the movement of injecting drug users (IDUs) across European borders and the active immigration of individuals from regions where HCV-4 is endemic toward Europe. Given that individuals infected with HCV-4 are relatively younger, this fact may suggest that the genotype has been introduced recently and will likely show further progression.

HCV-4 infections are uncommon in the United States, Canada, and South America. The prevalence of HCV-4 in the United States is about 1%.⁴⁸ Most HCV-4 cases reported from the United States were clustered among intravenous drug users or immigrants from countries where subtype HCV-4 is known to be most prevalent or among individuals who acquired the infection in these countries.^{48,49} However, given the active immigration and population movement within the Americas, the prevalence of HCV genotypes may vary due to introduction and spread of new or rare genotypes.

Outcome and Progression of HCV-4 Infection

The natural history of hepatitis C is highly variable. The major clinical consequence of acute hepatitis C infection is evolution into chronic hepatitis while the consequences of chronic hepatitis C include liver cirrhosis and its potential complications as end-stage liver disease or primary liver cancer.⁵⁰ Several viral-related, patient-related, and external or environmental factors may affect the outcome of HCV infection and the rate of disease progression.^{50,51} Studies investigating the impact of the genotype on the progression of chronic hepatitis C yielded conflicting results. Most investigators have failed to identify genotype as an indicator of likely progression,^{52,53} although a few reports suggest a possible association between genotype 1b and rapid disease progression.⁵⁴ These conflicting results could be explained either by nonexistence of any relation between genotype and disease progression or by the difficulty in conducting long-term prospective or prospective/retrospective studies to assess the natural history of HCV infection across different genotypes in well-characterized cohorts given the protracted course of infection.

Examination of the natural history of acute hepatitis C has been limited by the small study populations in most studies. Very few published studies addressed the outcome of acute HCV-4 infection. In a few prospective studies including patients with acute hepatitis due to different HCV genotypes, it was observed that the rate of

spontaneous resolution of acute HCV-4 infection was relatively higher than that caused by genotype 1 but lower than spontaneous resolution rates in genotypes 2 and 3.⁵⁵ The studies published so far estimate the overall rates of spontaneous resolution in acute HCV-4 infections to range between 20% and 50%,⁵⁵⁻⁵⁸ which is not historically different than other genotypes. This broad range suggests that there is no accurate estimation of the rate of spontaneous resolution in patients with spontaneous clearance of acute HCV-4 infection given the small sample size in most studies and the difficulty in attributing the spontaneous resolution solely to the HCV genotype. Several factors, such as presence of symptoms, female sex, and age, have been identified as potential predictors of spontaneous resolution of acute HCV infection.^{56,57} Coinfections also play a role, because patients with acute HCV-4 and HIV or *Schistosoma mansoni* coinfection show very low rates of spontaneous viral clearance.^{58,59}

The fibrosis progression in chronic HCV-4 has been assessed in few longitudinal studies.^{58,60,61} The fibrosis progression rate in patients with chronic HCV-4 was 0.1 ± 0.06 fibrosis units per year,^{60,61} which is not significantly different from rates reported in genotype 1, 2, or 3.⁵¹ Cross-sectional studies^{18,29,62} showed slightly higher grading and/or staging scores in patients with chronic HCV-4. In a French study of a large cohort of French, Egyptian, and African patients with chronic HCV infection, significantly higher grading and staging scores were found in Egyptian patients infected with HCV-4a compared with other individuals.¹⁸ It is not clear from the study if the differences in the severity of liver fibrosis in Egyptians with HCV-4 and non-Egyptians in the French study persisted when adjusted for confounding variables such as duration of infection and mode of transmission in multivariable analyses. The higher fibrosis scores in this study might be attributed to concomitant schistosomiasis in the Egyptian patients rather than ethnicity or HCV subtype, given that previous studies showed that patients with chronic HCV-4 and schistosomiasis coinfection have more accelerated fibrosis with progression rates of 0.61 ± 0.13 .^{60,61} Similarly, HIV/HCV-4–coinfected patients tended to have more advanced liver fibrosis with higher staging scores (F3-F4) compared with those infected with HCV-1 (33.3% versus 9.1%; $P = 0.2$) as shown in a cross-sectional study evaluating liver fibrosis stage using transient elastography (FibroScan).⁶³ Taken together, there is no sufficient evidence from the studies published so far that genotype 4 is by itself more pathogenic, and it seems that the fibrosis progression rates in chronic HCV-4 mono-infection are comparable to those reported with other genotypes. Higher grading or staging scores observed in some studies^{60,61,63} are probably due to

HIV/HCV-4 coinfections or HCV-4/*Schistosoma mansoni* coinfection.

Histological Patterns of Chronic HCV-4

The pathological findings in chronic HCV-4 are in general similar to other types of viral hepatitis C. However, certain features stand out in this genotype, one of which is the presence of moderate to severe steatosis⁶⁴⁻⁶⁶ with no associated sinusoidal fibrosis.⁶⁶ HCV directly induces steatosis through multiple mechanisms that are not understood. Host and viral factors contribute to the development of steatosis in hepatitis C, but their relative importance varies with genotype.⁶⁷⁻⁶⁹ The prevalence of steatosis is significantly higher in patients infected with HCV-3, which seems to directly induce steatosis.^{67,69} In contrast, host factors, especially those associated with metabolic dysfunction, are strongly associated with the metabolic steatosis in patients with genotypes 1 and 2.⁶⁷⁻⁶⁹ The mechanism of steatosis in chronic HCV-4 is not clear, and a causal relationship between HCV-4 infection and hepatic steatosis has not been established. Several studies have shown that steatosis in chronic HCV-4 is macrovesicular⁶⁴⁻⁶⁶ and is seen without any prominent zonal preference.⁶⁶ Tsochatzis et al.⁶⁴ showed that moderate/severe steatosis was more frequent in genotype 3 than in genotype 4 (44% versus 26%; $P = 0.025$) and similar between genotype 4 and genotype 1 patients. In 150 nondiabetic patients with a body mass index ≤ 25 kg/m², moderate/severe steatosis was present in 15%, 40%, and 11% of genotype 1, 3, and 4 patients, respectively ($P = 0.005$), and was independently associated only with genotype 3, suggesting that steatosis in HCV-4 is mostly associated with metabolic factors, similar to those in genotype 1.⁶⁴ Recently, in a series of 185 patients with chronic HCV-4, various grades of steatosis were identified in 70% of nondiabetic, nonoverweight patients. No lobular neutrophils or intracytoplasmic hyaline were detected, which is contrary to nonalcoholic steatohepatitis or alcoholic etiology.⁶⁶ Another observed feature that needs additional evaluation and quantitation is that the nodules in cirrhosis from patients infected with HCV-4 appear to be on the smaller size compared with other types of postnecrotic cirrhosis.⁶⁶ More detailed studies are needed to determine if there is a characteristic histological pattern that might distinguish chronic HCV-4.

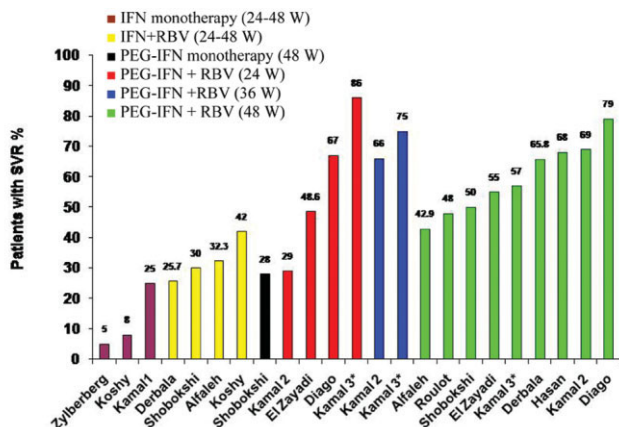
HCV-4 and Hepatocellular Carcinoma

Attempts to identify any clinical and virological factors that may influence the development of cirrhosis and hepatocellular carcinoma (HCC) in individuals infected with HCV have been largely inconclusive, but several studies

have suggested that HCV-1b might be associated with a significantly higher risk of developing HCC.⁷⁰⁻⁷² An association between HCV-4 and the high rates of HCC in Egypt has been speculated. Data from the National Cancer Registry of Egypt, the National Cancer Institute,⁷³ and the Middle East Cancer Consortium (MECC),⁷⁴ as well as several published studies,^{11,29,31} show a close association between HCC and HCV-4 in addition to a significant annual increase of newly diagnosed patients with HCC. Currently, liver cancer constitutes 13% of all cancers in Egypt and is considered the second most frequent cancer in males after being the fourth in 1999.⁷³ More than 65% of Egyptian patients with HCC are positive for HCV-4, and 11% had HCV/HBV coinfection.^{73,74} Moreover, the distribution of HCC in Egypt closely parallels that of HCV-4, being more frequent among rural residents and farmers.⁷³ A recent study¹¹ reported a significant association not only with subtype 4a but also with subtype 4o. Although an association between genotype 4 and HCC seems likely based on epidemiological data, one should consider other risk factors that might contribute to the high incidence of HCC in Egypt, such as coinfection with schistosomiasis, which was shown to increase frequency of HCC,^{29,3} or contamination of food by aflatoxin.

HCV-4 and Liver Transplantation

Studies have also suggested that genotype can affect both the rate and degree of hepatitis C recurrence following orthotopic liver transplantation surgery. In particular, genotype 1b is associated with a higher recurrence rate following orthotopic liver transplantation and more aggressive disease.^{76,77} The natural history of HCV-4 reinfection after liver transplantation is inadequately described in the literature. Zekry et al.⁷⁸ reported that HCV-4 patients undergoing liver transplantation had a worse outcome, higher incidence of HCV-related complications, and higher mortality rates compared with patients infected with other genotypes. Wali et al.⁷⁹ found that significantly more genotype 4 patients had severe recurrent fibrosis following orthotopic liver transplantation than non-genotype 4 patients (26.3% versus 6.7%; $P = 0.04$). The median total histological score for patients infected by genotype 4 was 8 versus 7 for those infected by type non-4. Median stage was 1, and the median grade was 5 for both genotype-4 and non-4 patients ($P > .05$). Genotype 4 patients showed signs of greater confluent necrosis than genotype 1 or genotype 2/3 patients (mean scores 2 versus 0, $p = 0.03$). Multivariate analysis indicated that rapid fibrosis after liver transplantation was associated with older recipient and donor age (> 50 years), prolonged graft warm ischemic time, and the



Studies are as follows: Zylienberg[80], Koshy[82], Kamal (1)[81], Derbala[92], Alfaleh[83], Shobokshi[85], Kamal(2)[90], El-Zayadi[90], Diago[88], Hasan[87], Roulot [18], Kamal 3 [66]

Fig. 1. Evolution of treatment for chronic HCV-4. Kamal 3*⁶⁶ patients were allocated to study arm according to virologic response at week 4 (rapid virologic response), complete early virologic response (undetectable HCV RNA at week 12), or partial early virologic response (>2 log decline of HCV RNA at week 12).

presence of genotype 4 infection.⁷⁹ Overall, the cumulative risk for the development of severe fibrosis was 30% for genotype 1 patients, 20% for genotype 2/3 patients, and 85% for genotype 4 patients ($P = 0.02$ for genotype 4 versus non-genotype 4).⁷⁸ These 2 studies suggest that genotype 4 might be a predictor of a worse outcome after liver transplantation. Further studies are warranted to confirm these observations for the HCV-4 population and to establish effective strategies for limiting the progression of liver disease in post-orthotopic liver transplantation HCV-4 patients.

Evolution of Chronic HCV-4 Treatment

HCV-4 has been considered difficult to treat because initial clinical trials using conventional interferon (IFN)- α monotherapy produced limited success (Fig. 1). These studies found that conventional IFN- α monotherapy resulted in a sustained virologic response (SVR) in only 5%-25% of treated patients.^{80,81} The subsequent inclusion of ribavirin in treatment regimens improved SVR, with rates of 8% and 42% reported for patients receiving IFN- α alone and in combination with ribavirin (1000-1200 mg/day), respectively.⁸²

Pegylated interferon markedly improved the rates of SVR in chronic HCV-4 (Fig. 2). Although 2 early studies^{83,84} failed to demonstrate a significant difference in SVR rates between pegylated interferon (PEG-IFN)- α 2b plus ribavirin and conventional IFN- α 2b plus ribavirin (e.g., 42.9% versus 32.3%; $P = 0.43$),⁸³ subsequent investigations reported SVR rates of 50%-79% in patients receiving PEG-IFN- α 2b plus ribavirin (800-1200 mg/

day) for 48 weeks and suggested that HCV-4 is easier to treat than previously believed.⁸⁵⁻⁹³ Meta-analysis of clinical trial data shows that SVR rates are significantly higher among genotype 4 patients receiving PEG-IFN- α plus ribavirin than in those receiving IFN- α plus ribavirin (55% versus 30%; $P = 0.0088$).^{8,9}

Challenges in Treating Chronic HCV-4

Duration of Treatment. The optimization of treatment duration is critical in ensuring that SVR rates are maximized without exposing the patient to an unnecessarily long treatment regimen that may have unfavorable implications in terms of cost and tolerability. The question of optimal treatment duration for chronic HCV-4 was addressed in 3 prospective randomized studies.^{66,90,91} In the first study,⁹⁰ patients received PEG-IFN- α 2b (1.5 μ g/kg/week) plus ribavirin (1000-1200 mg/day) for 24, 36, or 48 weeks. Overall, SVR rates were significantly higher in patients receiving treatment for 36 or 48 weeks than in those treated for 24 weeks (66% and 69% versus 29%; $P = 0.001$ for each comparison) (Table 2, Fig. 2). Relapse appeared to be a major factor in determining treatment outcomes: virologic relapse during follow-up was highest among patients treated for 24 weeks [20/45 (44%)] but relatively rare among the longer treatment arms. There was no significant difference between the 36-week and 48-week treatment regimens for the overall cohort. However, among patients with a baseline viral load of more than 2 million copies/mL who attained SVR, 65% were treated for 48 weeks and 35% were treated for 36 weeks. All patients with high baseline viral load treated for 24 weeks failed to attain SVR, suggesting

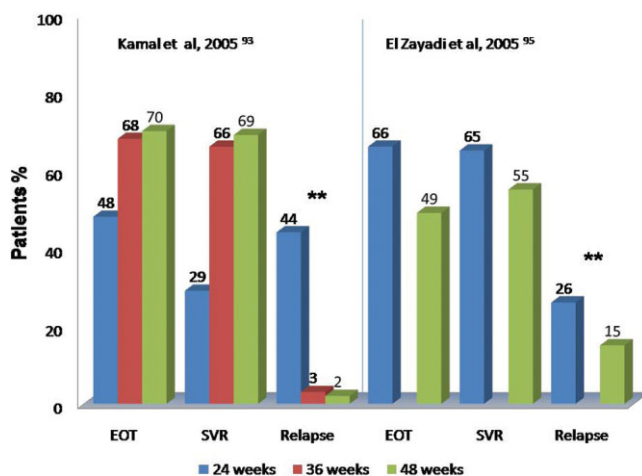


Fig. 2. Impact of treatment duration on virologic outcomes in patients with chronic HCV-4 receiving PEG-IFN- α (1.5 μ g/kg/week⁶⁶ or 100 μ g/week⁹¹) plus ribavirin (1000-1200 mg/day) for 24, 36, or 48 weeks. * $P < 0.05$, ** $P = 0.001$ versus 24-week treatment arm.

that the 48-week treatment regimen may be better suited to patients with high baseline viremia.⁹⁰

A nonrandomized study⁹¹ compared PEG-IFN- α 2b (100 μ g/week) plus ribavirin (1000-1200 mg/day) for 24 or 48 weeks with a triple therapy induction regimen consisting of conventional IFN- α 2b (3 MU/day for 4 weeks, then 3 times a week for 20 weeks) plus ribavirin (1000-1200 mg/day) and amantadine (100 mg twice daily for 24 weeks). In this study, patients were assigned to the different study arms according to financial affordability to any of the study regimens. Virologic outcomes were similar in patients receiving PEG-IFN- α plus ribavirin for 24 or 48 weeks (end of treatment responses, 65.7% versus 65.0%; SVR, 48.6% versus 55.0%; $P = 0.517$) (Fig. 2).⁹¹

A recent study⁶⁶ assessed the predictability of response in patients with chronic HCV-4 and determined the efficacy of an adaptive shorter-duration PEG-IFN- α 2b plus ribavirin treatment regimen based on viral load at weeks 4 and 12. Patients with chronic HCV-4 and undetectable HCV RNA at weeks 4 and 12 treated with PEG-IFN- α 2b and ribavirin for 24 weeks and 36 weeks achieved high SVR rates with significantly less adverse events and better compliance (Fig. 3).⁶⁶ The positive predictive value for rapid virologic response and early virologic response was 88% and 83%, respectively. After controlling for predictors, low baseline histological grade and stage, low baseline HCV RNA ($P < 0.001$), and low baseline body mass index ($P = 0.013$) were associated with SVR. Overall, these data suggest that patients with undetectable HCV RNA during the early stages of treatment attain SVR de-

spite shorter treatment regimens compared with those with slower viral kinetics, and are thus suitable for reduced treatment durations without compromising SVR rates.

Impact of Ethnicity on SVR Rates. Currently, very little is known about the influence ethnic origin has on treatment outcomes in patients with chronic HCV-4; however, because of the prevalence of this disease across Africa and the Middle East and its recent spread to European countries, it is vitally important that an understanding of the role of ethnic origin be developed. Clinical trials conducted in Egypt, Saudi Arabia, Qatar, and Kuwait indicate that the use of PEG-IFN- α 2a (180 μ g/week) or PEG-IFN- α 2b (1.5 μ g/kg/week) plus ribavirin (1000-1200 mg/day) results in SVR rates of 65%-69%.^{66,85-87,90-92} However, studies conducted in Europe^{18,88,93-95} have shown that the SVR rates in Africans or Europeans with chronic HCV-4 treated with PEG-IFN- α plus ribavirin are lower than those achieved in studies conducted in the Middle East. A retrospective analysis of SVR rates in French and Egyptian patients with chronic HCV-4 showed an overall better response in Egyptians infected with the 4a subtype, and European patients infected with HCV-4a had higher SVR rates than those infected with HCV-4d.¹⁸ It is not clear from the study if the difference in SVR is related to ethnicity or other factors such as HCV-4 subtype or HIV coinfection or intravenous drug use. Nevertheless, these data can be taken as a preliminary indicator that ethnic origin or HCV-4 subtype may influence treatment outcomes in patients with chronic

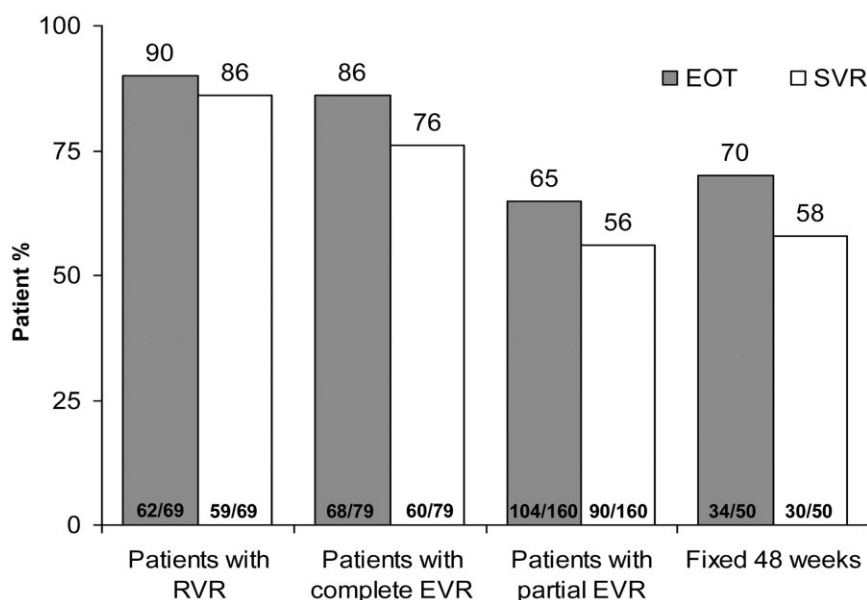


Fig. 3. Rapid and early virologic response as predictors of SVR in patients with chronic HCV-4 receiving PEG-IFN- α (1.5 μ g/kg/week) plus ribavirin for 24, 36, or 48 weeks. Percent values indicate the proportion of the intent-to-treat population in each treatment arm that attained early virologic response.⁶⁶

Table 2. Overview of Studies of PEG-IFN- α in Patients with Chronic HCV-4

Reference	Study Design	No. of Patients	Treatment	Duration of Treatment	EVR* (%)	EOTR† (%)	SVR‡ (%)
Kamal et al. ⁹⁰	Prospective, double-blind, randomized study of Egyptian patients with HCV-4	260	PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§] for 24 weeks (n = 95)	24 weeks	69	48	29
			PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§] for 36 weeks (n = 96)	36 weeks	68	68	66 [#]
			PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§] for 48 weeks (n = 69)	48 weeks	69	70 ^{**}	69 [#]
Alfaleh et al. ⁸³	Randomized, parallel-group study of Saudi patients with HCV	59	PEG-IFN- α 2b 100 μ g/week plus RBV 800 mg/day (n = 28) ^{††}	48 weeks	NR	67.9	42.9
			IFN- α 2b 3 MU 3 times a week plus RBV 800 mg/day (n = 31) ^{††}			54.8	32.3
El-Zayadi et al. ⁹¹	Nonrandomized study ^{††} of patients in Egypt with HCV-4	180	PEG-IFN- α 2b 100 μ g/week + RBV 1000-1200 mg/day [§] (n = 40)	48 weeks	72.5	65.0	55.0 ^{§§}
			PEG-IFN- α 2b 100 μ g/week + RBV 1000-1200 mg/day (n = 70)	24 weeks	72.9	65.7	48.6
			IFN- α 2b 3 MU ^{##} + RBV 1000-1200 mg/day + AMD 200 mg/day (n = 70)	24 weeks	54.3	47.1	28.6
Hasan et al. ⁸⁷	Open-label, prospective study of treatment-naïve HCV-4 patients in Kuwait	66	PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§]	48 weeks	78	77	68
Derbala et al. ⁹²	Randomized, controlled study of patients in Qatar with HCV-4 and a history of bilharziasis	73	PEG-IFN- α 2a 180 μ g/week + RBV 1200 mg/day for (n = 38)	48 weeks	NR	76.3 ^{***}	65.8 ^{†††}
			IFN- α 2b 3 MU 3 times a week plus RBV 1200 mg/day (n = 35)			40.0	25.7
Roulot et al. ¹⁸	Retrospective, nonrandomized study of French, Egyptian, and African patients with chronic HCV-4	242	PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§]	48 weeks	NA	NA	Egyptian: 48 French: 37 African: 25
Kamal et al. ⁶⁶	Prospective treatment duration study based on virologic response at week 4 or 12 of Egyptian patients with chronic HCV-4	308	PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§] according to virologic response at weeks 4 or 12	24 weeks 36 weeks 48 weeks	RVR: 69 Complete EVR: 79 Partial EVR: 160	90 86 70	RVR: 86 Complete EVR: 76 Partial EVR: 58
Diago et al. ⁸⁸	<i>Post hoc</i> analysis of patients with HCV-4 from 2 large, double-blind clinical trials ²²	98	Study 1: PEG-IFN- α 2a 180 μ g/week + RBV 1000-1200 mg/day [§] (n = 13)	48 weeks	NR	NR	79
				48 weeks			63
			Study 2: PEG-IFN- α 2a 180 μ g/week + RBV 800-1200 mg/day [§] for 24 or 48 weeks	24 weeks			67
			High-dose RBV (n = 24)	24 weeks			0
			Low-dose RBV (n = 8)				
	High-dose RBV (n = 12)						
	Low-dose RBV (n = 5)						

Table 2. Continued

Reference	Study Design	No. of Patients	Treatment	Duration of Treatment	EVR* (%)	EOTr† (%)	SVR‡ (%)
Shobokshi et al. ⁸⁵	Open-label study of Saudi and Egyptian patients with chronic HCV-4	–	PEG-IFN- α 2a 180 μ g/week + RBV 800 mg/day PEG-IFN- α 2a 180 μ g/week IFN- α 2a 4.5 MU 3 times a week + RBV 800 mg/day	48 weeks	NR	NR	50 28 30
Esmat et al. ⁸⁴	Prospective, open-label, randomized study of Egyptian patients with chronic HCV-4	–	PEG-IFN- α 2b 100 μ g/week plus RBV 800-1000 mg/day IFN- α 2b 2 MU 3 times a week + RBV 800-1000 mg/day	48 weeks	NR	NR	55 40
Thakeb et al. ⁸⁶	Open-label study of Egyptian patients with chronic HCV-4	100	PEG-IFN- α 2a 180 μ g/week + RBV 1000-1200 mg/day (n = 51) IFN- α 2a 3 MU 3 times/week + RBV 800-1000 mg/day (n = 49)	48 weeks	NR	NR	69
Trapero-Marugan et al. ⁹³	Open-label study of Spanish patients with chronic HCV-4	29	IFN- α 2b 3 MU 3 times/week + RBV 800-1000 mg/day (n = 19) PEG-IFN- α 2b (1.5 μ g/kg/week) + RBV (1-1.2 g/day) (n = 10)	48 weeks	NR	NR	55
Legrand-Abravanel et al. ⁹⁴	Case-control study of patients with HCV-4 in France; 13 of 28 were coinfecting with HIV	28	PEG-IFN- α 2b 1.5 μ g/kg/week + RBV 1000-1200 mg/day [§]	48 weeks	50		32 ^{###}
Soriano et al. ⁹⁵	Retrospective analysis of open-label clinical trials in HCV-G4 patients with HCV/HIV coinfection ^{††}	42	IFN- α 3 MU 3 times a week (n = 9) IFN- α 3 MU 3 times a week + RBV 800 mg/day (n = 11) PEG-IFN- α 2b 1.5 μ g/week + RBV 800 mg/day (n = 22)	48 weeks	NR	NR	11.1 9.1 22.7

Abbreviations: AMD, amantadine; EVR, early virologic response; G, genotype; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.

*EVR was defined as undetectable HCV RNA or a ≥ 2 log₁₀ decrease at week 12.

†End-of-treatment response was defined as undetectable HCV RNA at the end of the scheduled treatment period.

‡SVR was defined as undetectable HCV RNA at the end of a 24-week follow-up period.

§RBV was administered according to a weight-based administration schedule.

¶P = 0.04.

#P = 0.001 versus 24-week treatment regimen.

**P = 0.02.

††Data presented for HCV-4 patients only.

‡‡Patients were allocated to treatment groups according to personal financial ability to afford treatment.

§§P = 0.006.

¶¶P = 0.015 versus induction dose regimen.

###Interferon was administered daily for the first 4 weeks of the study and then 3 times a week for the remaining 20 weeks.

***P < 0.002 versus native IFN.

†††P < 0.05 versus native IFN.

####SVR occurred in 15% of HIV/HCV-coinfecting patients and in 50% of HCV-monoinfecting patients.

HCV-4. Furthermore, this area is deserving of further clinical study.

Impact of Liver Disease on Treatment Outcome.

Fibrosis, cirrhosis, and steatosis have been identified as significant factors in determining treatment outcomes for patients with chronic hepatitis C. In general, advanced liver disease is associated with poorer outcomes; however, PEG-IFN- α treatment is recognized to slow or even reverse the extent of liver disease in many patients.⁹⁶

Early studies using conventional IFN- α plus ribavirin showed that SVR rates were lower among genotype 4 patients with cirrhosis than in patients with normal liver function. In patients without cirrhosis, SVR rates were 8% in patients receiving IFN- α monotherapy and 42% in those receiving IFN- α combined with ribavirin. Conversely, among genotype 4 patients with cirrhosis, no patients receiving IFN- α monotherapy attained SVR, and only 14% of combination therapy recipients attained

SVR.^{80,82} Two studies^{87,90} reported that treatment outcomes were improved in genotype 4 patients with mild liver disease compared with those patients who had more advanced liver disease.

Hepatic steatosis is an important variable for fibrosis progression and therapeutic response to IFN-based therapies. Steatosis is present in 40%-73% of patients with chronic HCV-4.⁶⁴⁻⁶⁶ In a recent study,⁶⁶ among a subgroup of patients analyzed for pretreatment steatosis, a greater proportion of patients without steatosis attained SVR than those without. A similar trend of SVR rates was observed among patients with or without steatosis after treatment. This strong association of steatosis with reduced SVR rates persisted even after adjustment for factors that influence treatment response, such as viral load, fibrosis, age, sex, pretreatment and posttreatment body mass index, glucose, and triglyceride values.

In patients receiving PEG-IFN- α 2b plus ribavirin (1000-1200 mg/day) for 48 weeks, SVR rates were significantly higher among those with no or mild fibrosis [F0 (no fibrosis) to F2 (portal fibrosis with rare septa)⁴⁹] than in those with severe fibrosis or cirrhosis [F3 (numerous septa without cirrhosis) to F4 (cirrhosis)] (84% versus 29%, $P < 0.0002$).⁹⁶

Treatment of Human Immunodeficiency Virus and HCV Coinfection. The treatment of chronic hepatitis C among patients with HIV coinfection is generally less successful than treatment of chronic hepatitis C in HCV-monoinfected individuals. Overall, SVR was attained by 11.1% of patients receiving IFN- α monotherapy, 9.1% of patients receiving IFN- α plus ribavirin combination therapy, and 22.7% of patients receiving PEG-IFN- α 2b (1.5 μ g/week) plus ribavirin (800 mg/day).⁹⁴ In another study,⁹⁵ SVR rates were lower in HIV/HCV-coinfected patients (30% versus 66%; $P = 0.06$) than in HCV-monoinfected patients (15% versus 50%; $P = 0.06$) receiving PEG-IFN- α plus ribavirin (1000-1200 mg/day) for 48 weeks, although in neither case did the difference between cohorts achieve statistical significance.⁹⁵

Cost Effectiveness of Chronic HCV-4 Treatment. Cost-effectiveness analyses based on clinical trial data in primarily genotype 1 patients have endorsed the tailored use of the combination therapy of PEG-IFN- α plus ribavirin. These studies have shown that this combination therapy is a more cost-effective option than conventional IFN- α plus ribavirin and that administration of ribavirin according to patient body weight increases the efficiency of this approach.⁹⁷⁻⁹⁹ Furthermore, tailoring treatment according to week 4 and week 12 viral responses^{66,100} also promotes a more efficient use of this combination therapy by stopping treatment in patients with a high likelihood of treatment failure and shortening regimens in patients

who show early viral responses that are predictive of favorable treatment outcomes.

No cost effectiveness studies have been conducted in genotype 4 patients, particularly in countries with high prevalence such as Egypt. These types of analyses are now urgently required for genotype 4 patients. In particular, economic analyses that are relevant to the health care delivery systems currently used in the regions of the world where genotype 4 predominates would enhance the value of such studies. In countries in which genotype 4 HCV is most commonly found, cost represents a considerable hurdle to patients seeking health care. Many patients are required to fund their own treatment, and failure to complete treatment regimens because of financial constraints is common. Zayadi et al.⁹¹ attempted to treat patients for 24 or 48 weeks according to financial affordability rather than pretreatment or treatment predictors. These investigators aimed to make therapy available to a larger number of patients, but nonresponse and relapse rates were high. This dilemma has no easy solution, but financial constraints do not mean less effective treatments to patients in developing countries. Every effort should be made to make the most effective treatments affordable and available to infected persons to maximize the individual's opportunity for treatment success. Funding of therapeutic options should be considered alongside other measures aimed at limiting the spread of the infection, such as education programs, needle share programs for intravenous drug users, and use of safer needle devices and needleless systems in health care units.

In conclusion, epidemiological trials have shown that HCV-4 has started to spread beyond its strongholds in Africa and the Middle East to Western countries. Recent clinical data have provided new insight into HCV-4 infection and have resulted in a refinement of the treatment strategies. Baseline viremia, early viral kinetics, treatment duration, and stage of liver disease each represent important considerations that can be used to individualize therapy. These data can now be used as a platform for further research to determine optimal treatment regimens for patients infected with HCV-4.

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