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REVIEW ARTICLE

The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report

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Abbreviations
EVR, early virological response; ETR, end of treatment response; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCV-1, hepatitis C genotype 1; HCV-2, hepatitis C genotype 2; HCV-3, hepatitis C genotype 3; HCV-4, hepatitis C genotype 4; HCV-5, hepatitis C genotype 5; HCV-6, hepatitis C genotype 6; IFN, interferon; IVDU, intravenous drug use; PEG-IFN, pegylated interferon; RVR, rapid virological response; SVR, sustained virological response.

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Abstract
Hepatitis C virus (HCV) genotypes 4, 5 and 6 represent >20% of all HCV cases worldwide. HCV-4 is mainly seen in Egypt, where it represents 90% of all HCV cases. Antischistosomal therapy was the main cause of contamination there, followed by procedures performed by informal providers and traditional healers such as dental care, wound treatment, circumcision, deliveries, excision and scarification. It is also highly prevalent in sub-Saharan Africa and in the Middle East. In Europe, its prevalence has recently increased particularly among intravenous drug users and in immigrants. HCV-5 is mainly found in South Africa, where it represents 40% of all HCV genotypes, but four pockets of HCV-5 were found in France, Spain, Syria and Belgium and sporadic cases were found elsewhere. The mode of transmission is mainly iatrogenic and transfusion. HCV-6 is found in Hong Kong, Vietnam, Thailand and Myanmar and also in American and Australian from Asian origin. The response to treatment in HCV-4 is intermediate between HCV-1 and HCV-2 and HCV-3. A sustained viral response is achieved in 43–70% with pegylated interferon and ribavirin. It is higher in Egyptians than Europeans and Africans and is negatively related to insulin resistance and to the severity of fibrosis. It increases to >80% with 24 weeks of therapy only if a rapid virological response is achieved. In HCV-5, a sustained virological response is achieved in >60% with 48 weeks of therapy. HCV-6 is also considered an easy-to-treat genotype, leading to a response in 60–85% of cases.

Six main hepatitis C virus (HCV) genotypes, called types 1–6, numerous 'subtypes' (1) as well as a recently identified seventh type (Innogenetics, unpublished data) have been identified by the phylogenetic analysis of partial or full-length sequences of HCV isolates from different regions of the world. Variants isolated principally in South East Asia were found to be divergent between types and subtypes (2–4). They were incorporated into their phylogenetically closest type (all type 6, except for one type 3 strain) (1).

The distribution of HCV genotypes reflects the epidemiology of hepatitis C and as such is also strongly associated with particular routes of transmission (5). Genotype is one of the determinants of the response to antiviral combination therapy with interferon (IFN)-α and ribavirin. HCV genotyping is currently performed

Table 1. Proportion of hepatitis C virus-4 in hepatitis C virus patients worldwide

Area	Countries	HCV-4 (%)	Countries	HCV-4 (%)
North Africa	Egypt (14)	90	Tunisia (15)	11
	Sudan (15)	5		
Sub-Saharan Africa	Congo (15)	100	Gabon (15)	97
	Cameroon (15)	36	Rwanda (15)	100
	Liberia (15)	100	Uganda (15)	100
Middle East	Syria (16)	59	KSA (17)	62
	Iraq (18)	35.4	Iran (19)	0.9
	Jordan (20)	26.6 (dialysis)	Lebanon (21)	45.7–36.5
Asia	China (11)	0–1.7		
North America	USA (22, 23)	0–2	Canada (24)	2.3–3.9
Central and South America	Argentina (25)	0.5–4.6	Brazil (26)	0.1–0.67
	Mexico (27)	1		
Europe	France (28)	4–10	Greece (29, 30)	3–15.2
	Spain (29, 31)	1.4–19	Turkey (29, 32)	0–2.2
	Portugal (29)	0	Italy (29, 33, 34)	0–2.2
	UK (unpublished)	6.7	Belgium (35)	10
	Austria (36)	5	the Netherlands (37)	10
	Germany (38)	1–2		

before initiating therapy to tailor its duration and the frequency of monitoring in the individual patient.

Genotypes 1 (HCV-1), followed by genotypes 2 (HCV-2) and 3 (HCV-3), are the most common genotypes in North and South America and Europe (6), and have been the focus of most clinical trials. Genotype 4 (HCV-4) is the most frequent cause of chronic hepatitis C in the Middle-East, North Africa and sub-Saharan Africa. It has recently spread to southern Europe, particularly among intravenous drug users (IVDUs) and in immigrants (7).

Genotype 5 (HCV-5) was initially reported in South Africa, where it represents 40% of all cases (8, 9), and recent reports have confirmed its presence in some other countries. Genotype 6 (HCV-6) is rare and confined to South East Asia (10–13), Asian Americans and Asian Australians. Although they represent >20% of all HCV cases worldwide, genotypes 4, 5 and 6 have generally been neglected in clinical trials.

The aim of this Consensus Document, drafted by a working party established by the World Gastroenterology Organization in 2007, is to review 2009 current knowledge on the prevalence, epidemiology, natural history and treatment outcome of HCV genotype 4, 5 and 6 infections, based on published and sometimes unpublished data and on expert opinions, in order to elaborate consensual recommendations because clinical trials of therapy for these genotypes are unlikely.

Global distribution of the 'rare' hepatitis C virus genotypes

Hepatitis C virus-4 is mainly found in Egypt, the country with the highest prevalence of HCV worldwide (>15%), where it represents 90% of all HCV cases (14). It only represents 5–11% of cases in the other North African countries. It is also highly prevalent in sub-Saharan Africa and in the Middle East, with a proportion ranging from 36 to 100% of all HCV cases. In Europe, its prevalence is low, but an increased prevalence has recently been noted in France, Italy and Belgium. HCV-4 is very rare in North, Central and South America and almost nonexistent in other parts of the world (Table 1).

Table 2. Proportion of hepatitis C virus-5 in hepatitis C virus patients worldwide

Area	Countries	HCV-5 (%)
Africa	South Africa (8, 9, 39)	40
Middle East	Syria (16)	10
Europe	France (28, 40)	3
	Belgium (41)	1–5
	UK	0.7
	Spain (42)	0–10.3
	Italy (43)	0–0.1
America	Canada (24)	0.1–4.5

Table 3. Proportion of hepatitis C virus-6 in hepatitis C virus patients worldwide

Area	Countries	HCV-6 (%)
Asia	China (10, 44)	0
	China IVDU (45, 46)	46–50
	Thailand (47)	18.7
	Hong Kong (10–12)	10–30
	Vietnam (48)	14
Asian in the US and Canada	USA (49, 50)	11
	Canada (24)	0.3–0.8

Until recently, it was thought that HCV-5 was confined to South Africa, where it represents 40% of all HCV genotypes. However, four pockets of HCV-5 have been found in France, Spain, Syria and Belgium (Table 2) and sporadic cases have been found elsewhere in the world.

Hepatitis C virus-6 is mainly found in Hong Kong, Vietnam, Thailand, Myanmar (Burma) and in Asian Americans and Asian Australians (Table 3).

Epidemiology

Hepatitis C virus-4

The risk factors for HCV-4 transmission are determined by the geographical distribution of this genotype.

The epidemiology of hepatitis C virus-4 in Egypt and in sub-Saharan Africa

Antischistosomal therapy has been the main cause of contamination in Egypt. In fact, epidemiological and molecular evolutionary studies in Egypt relate the origin of the HCV-4 epidemic to the mass antischistosomal campaign, which was administered parenterally, and only stopped in the mid-1960s (51, 52). However, the incidence of HCV remains high even after the treatment campaign was stopped and new infections continue to occur in young individuals who did not receive parenteral antischistosomal therapy. Blood transfusion was a major route for HCV-4 transmission before obligatory HCV screening in blood banks in 1994. Currently, the major route of transmission appears to be health-related procedures with inadequately sterilized instruments and supplies. Procedures performed by non-medical professionals and traditional healers such as dental care, wound treatment, circumcision, deliveries, excision and scarification have all been identified as important risk factors for HCV transmission in Egypt (53–56). Occupational transmission among healthcare workers through needle sticks and injuries from sharp objects contributes to new HCV cases because needle stick-prevention devices have not yet been adopted by most hospitals and healthcare units. Inadequate compliance to universal, standard precautions in some health facilities also remains an issue (57–59). Low prevalence rates of IVDU are reported in Egypt. However, IVDU accounts for a significant percentage of HCV-4 cases when the source is unknown (60). It has been suggested that high rates of sexual transmission are a probable mode of transmission based on seroprevalence data, although phylogenetic analysis has only been performed in one study (61). In rural Egypt, sexual transmission between monogamous spouses (62) ranged between 3 and 34% (95% CI 0–49). However, the extent of sexual transmission of HCV-4 could not be estimated because of the presence of other confounding variables such as IVDU or shared items among sexual partners.

In Sudan, Zaire, Gabon, Central African Republic, Cameroon and Kenya (63–67), scarification, circumcision practices and sexual transmission may contribute to the persistence and propagation of HCV transmission. The marked genetic diversity and many subtypes identified suggest that HCV-4 has been endemic and propagating in sub-Saharan Africa for a long time (68).

Epidemiology of hepatitis C virus-4 in Europe

Hepatitis C virus-4 has recently spread to several European countries, especially those on the Mediterranean such as Italy, France, Greece and Spain. Ten to 24% of HCV are genotype 4 in these countries (28, 30, 42, 43, 69). HCV-4 infections are frequent among IVDUs (European and non-European), HCV/HIV-coinfected patients and immigrants from North and sub-Saharan Africa (37, 38, 70–72). HCV-4 was probably introduced into Europe through immigration and the movement of IVDUs across European borders.

In Greece, a study in 277 patients with HCV-4 showed that 15% had been contaminated by organ transplantation, 19% were IVDUs, 23% had received transfusions, 4% had haemophilia while the cause was unknown in 39% (73). In Italy, a study in 339 patients with HCV-4 showed that 11.8% were IVDUs, 1.7% received blood transfusion and the cause of contamination was unknown in 86.5% (74). In Spain, a study of 855 patients with HCV-4 showed that the cause of contamination was IVDU in 37.1% and unknown in 62% (34).

In France, four studies have assessed the epidemiology of HCV-4 (28, 75–77). They showed an increasing prevalence of HCV-4 representing 9% of all HCV patients. HCV-4 was more common in patients <40 years old and was more frequently found among IVDUs (28). Roulot and colleagues study (76) included 1532 HCV-4 patients from 19 liver departments (69% French, 15% Egyptians and 16% Africans). It confirmed the heterogeneity of HCV-4 according to the patients' geographical origin. The patients in the African group were older than those in the French and Egyptian groups (50 ± 11, 44 ± 10 and 45 ± 10 years, respectively, $P \leq 0.001$). The route of transmission was predominantly related to IVDU in patients in the French group (56%), a history of antischistosomal therapy in the Egyptian group (62%) and a history of blood transfusion in the African group (21%). Egyptians were mainly infected with subtype 4a (93%), French with 4a (54%) or 4d (33%), while Africans were infected with diverse subtypes.

In Belgium, the prevalence of HCV-4 has also significantly increased, accounting for about 10% of the cases of chronic hepatitis C in 2002 (32). European patients harbouring HCV-4 in Belgium either had a history of IVDU and were mainly infected with the subtype 4c/4d, or were non-IVDU and showed a huge diversity of subtypes (70).

Epidemiology of hepatitis C virus-4 in the Americas, South East Asia and Australia

Hepatitis C virus-4 infections are infrequent in the US (24, 49, 78). Most HCV-4 infections are found in immigrants from endemic countries, individuals who acquired the infection overseas or IVDUs. There are no reliable data on the prevalence of HCV-4 either in Australia or in South East Asia. However, HCV-4 appears to be rare in these regions.

Hepatitis C virus-5

For many years, HCV-5 was believed to be confined to the northern part of South Africa, where it accounts for up to 40% of HCV-infected patients. But it has now also

been reported in other parts of the world including France, Belgium, Canada, Syria, Spain and Brazil (16, 42, 79–83). Recent investigations indicate that there are three pockets of HCV-5 infection outside South Africa: the West-Flanders region of Belgium, the central area of France around Clermont-Ferrand and the northern part of Syria.

An analysis of diversity based on the sequence comparison of a 470 bp fragment of the NS3-NS4B region encoding for non-structural proteins was performed comparing South African and Belgian strains. The phylogenetic study assessing viral evolutionary history showed that geographically distinct clusters have been evolving independently for a considerable period of time (>120 years) between South African and Belgian strains. It was originally thought that HCV-5 originated in South Africa. But, recently, it has been speculated that HCV-5 may have originated in Central Africa and spread through human migration associated with trade in a north–south direction (41). A case–control study and phylogenetic analysis were performed in Central France (84). This study included 131 HCV-5-infected patients. Results showed that all but two HCV-5 patients were Caucasian. HCV-5 contamination was associated with transfusion and unsafe injections performed before 1972 by the local physician. In Syria, HCV-5 represents 10% of all HCV genotypes and is almost exclusively found in the north of Syria in the province of Aleppo, with half of the cases originating from Azaz, a small city of 30 000 inhabitants close to the Turkish border. But no cases of HCV-5 have ever been reported in Turkey or any other countries neighbouring Syria and there is no immigration from Africa to Syria (16). However, a recent phylogenetic analysis of Syrian samples showed that the Syrian samples are clustered in the South African group (unpublished data).

The route of transmission is thought to be mainly blood transfusion in South Africa, iatrogenic and transfusion in France and unknown for the most part in Belgium, Syria and Spain.

Hepatitis C virus-6

Data on regional epidemiology and on risk factors of HCV-6 are lacking. Unsafe therapeutic injections, IVDU and blood transfusion are the probable modes of transmission of HCV-6.

Natural history

Hepatitis C virus-4

Few well-designed studies have investigated the natural history of HCV-4 partly because of the difficulty of conducting long-term studies over decades in well-characterized untreated cohorts. Although a possible relationship has been suggested between HCV genotype and disease progression, no such relationship has ever been validated (85). There are few data on the natural history of HCV-4 in western Europe in relation to the acute form of the disease and its progression towards chronic hepatitis. Similarly, there are few data on the progression of fibrosis to cirrhosis and hepatocellular carcinoma (HCC).

Prospective studies have shown that the overall rates of spontaneous resolution in acute HCV-4 infections range from 20 to 50% (86, 87). However, patients with acute HCV-4 and HIV or *Schistosoma mansoni* coinfection have lower rates of spontaneous viral clearance (86, 88).

The rate of progression of fibrosis in HCV-4 monoinfection (0.1 ± 0.06 fibrosis units per year) is not significantly different from the rates reported in genotype 1, 2 or 3 (88). Patients with HCV-4 and schistosomiasis coinfection have higher fibrosis scores. Coinfected patients show accelerated rates of fibrosis, reaching 0.61 ± 0.13 fibrosis unit within 8–12 years (88–91). Two French studies have evaluated the severity of the disease and the predictors of advanced fibrosis in HCV-4 patients (76, 77). The first retrospective study included a large number of HCV-4 patients from 19 French liver centres, with available liver biopsies in 1205 patients (802 French, 198 Egyptians and 205 Africans). At diagnosis, severe histological activity (Metavir score A2–A3) was present in 39% of patients and was significantly more frequent in the Egyptian group than that in the French and African groups (51.3 vs. 36.9 and 35.8%, $P < 0.0007$) (76). Similarly, the proportion of patients with cirrhosis (13.5%, on average) was higher in the Egyptian than that in the French and African groups (29.8 vs. 10.8 and 8.3%, $P < 0.001$). However, multivariate analysis was not performed in this study to determine the independent predictors of cirrhosis. In the second prospective study including 226 consecutive HCV-4 patients (Egyptians 40%, Europeans 35% and Africans 24%), the predictors (logistic regression) of severe fibrosis (Metavir score F3–F4) were assessed according to epidemiological, metabolic and virological factors. The results of this study showed that severe fibrosis was independently associated with Egyptian origin ($P < 0.001$), excessive alcohol intake ($P = 0.021$) and insulin resistance ($P < 0.001$) (77). Moreover, a subgroup analysis based on the geographical origin of patients was performed because severe fibrosis was most frequent in Egyptians (may be secondary to the longer duration of infection), and it was found that insulin resistance remained a major predictor of severe fibrosis in both groups (Egyptians and non-Egyptians). It should also be noted that HOMA-IR correlated directly with serum HCV-RNA levels in this study, confirming previous results (71) and suggesting a direct role of the virus in the development of insulin resistance.

A possible association between HCV-4 and the high rates of HCC in Egypt has been suggested based on the similarity of distribution of HCC and HCV-4. More than 65% of HCC cases in Egypt are anti-HCV positive. Currently, liver cancer constitutes 13% of all cancers in Egypt and is now considered the second most frequent

cancer in men, and more frequent among rural residents and farmers (92), when it was fourth in 1999 (93). One study showed a significant association not only with subtype 4a but also with subtype 4o (94). However, care should be taken not to overinterpret any potential relationship between HCV-4 and HCC based on epidemiological data, while other factors related to HCC such as extensive use of pesticides and prevalence of aflatoxins have not been taken into account (95).

Hepatitis C virus-5

Limited data are available on the natural history of genotype 5.

A large multicentre multinational South African database of 285 patients has been compiled (S. W. van der Merwe, unpublished data). The mean age of these patients was 59 years, and 54% were females. Eighty-three per cent of infections were thought to have been contracted through blood transfusions. Baseline alanine aminotransferase was normal in 52% and cirrhosis was already present in 26% at first presentation. The baseline viral load was recently assessed in a viral kinetic study; the mean HCV-RNA was 6.33 ± 0.28 ($\log_{10}$ IU/ml) in the HCV-5 cohort, 6.23 ± 0.66 in the HCV-1 cohort and 6.15 ± 0.85 in the HCV-2/3 cohort. These values were comparable to those of large historical cohorts of genotypes 1, 2 and 3 (96).

In a French study, viral characteristics were studied in 26 patients infected with genotype 5. The mean age was 57 years, 58% of the patients were women, the mean pretreatment viral load was 5.97 log U/ml, 50% of the patients were infected by blood transfusion and cirrhosis was present in 35% of the individuals (79).

Finally, in a Syrian study, data from 64 HCV-5 patients also showed that most patients were women (61%), with a mean age of 52 years, significantly older than non-genotype 5 patients ($P < 0.0001$). The cause of transmission was only known in 30%, blood transfusion being reported in 14% of the patients. Cirrhosis was present in 23% of the patients (16).

In conclusion, all available data showed that more women are infected with HCV-5, with a mean age that is older than non-genotype 5 patients. Viral load is usually high and cirrhosis is frequently found at diagnosis.

Hepatitis C virus-6

In the only study of the natural history of HCV-6 in 80 Hong Kong Chinese patients (97), no differences were found between HCV-1 and HCV-6 patients in baseline liver biochemistry, HCV-RNA titres, cumulative risk of development of cirrhotic complications and HCC, even when patients were stratified according to age and gender.

Treatment

Hepatitis C virus-4

A few clinical trials have been performed in acute HCV-4 and have demonstrated high sustained virological response (SVR) rates with IFN-based therapies compared

Table 4. Therapy of human immunodeficiency virus/hepatitis C virus-4 coinfected patients and therapy of acute hepatitis C virus-4

References	Study design	Number of patients	Treatment	Duration of treatment (weeks)	SVR (%)*
Legrand-Abravanel *et al*. (100)	A case–control study of patients with HCV-4 in France; 13 of 28 were HIV coinfected	28	PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day†	48	15
Soriano *et al*. (101)	A retrospective analysis of open-label clinical trials in HCV-4 patients with HCV and HIV coinfection‡	42	IFN-α-3 MU three times a week ($n = 9$)	48	11.1
			IFN-α-3 MU three times a week plus RBV 800 mg/day ($n = 11$)		9.1
			PEG-IFN-α-2b 1.5 mcg/week plus RBV 800 mg/day ($n = 22$)		22.7
Martín-Carbonero *et al*. (102)	A retrospective analysis of clinical trials in HCV-4 patients with HCV and HIV coinfection in Italian and Spanish studies.	75	PEG-IFN-α-2b and α-2a	48	28
Kamal *et al*. (98)	Randomized controlled trial of Egyptian patients with acute HCV-4	53	PEG-IFN-α-2b monotherapy	12	84
Kamal *et al*. (99)	Randomized controlled trial of Egyptian patients with acute HCV-4	40	PEG-IFN-α-2b monotherapy	8	77
				12	93
				24	100

Adapted with permission from Kamal and Nasser (15) and Kamal (120).

*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.

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

PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response.

with no treatment. SVR was achieved in 60 and 88% of genotype 1 patients and in 93 and 100% of HCV-4 patients after 12 and 24 weeks of pegylated interferon (PEG-IFN) monotherapy respectively (98, 99) (Table 4).

Early reports on the treatment of chronic HCV-4 with IFN monotherapy showed disappointing SVR rates ranging between 5 and 25% (103, 104). Addition of ribavirin improved SVR rates to 25–42%, which were similar to SVR in HCV genotype 1 patients but much lower than HCV-2 and HCV-3 patients (105–108). It was then concluded that HCV-4, like HCV-1, was a 'difficult-to-treat' genotype even with PEG-IFN and thus early studies from the western countries reported response to treatment of HCV-1 and HCV-4 together. However, studies from Egypt, France and other countries in the Middle East have shown that treatment of chronic HCV-4 with PEG-IFN and ribavirin was associated with better rates of SVR ranging from 43 to 70% (76, 108–118). But studies from Egypt showed a higher SVR than SVR from European studies. This was intriguing until the publication of two French studies, which evaluated SVR in monoinfected HCV-4 patients treated with PEG-IFN and ribavirin in different groups (76, 77). In the first retrospective study, which include 242 HCV-4-treated patients (55% French, 30% Egyptians and 15% Africans), the overall rate of SVR was 43.4%. The SVR rates were significantly higher in the Egyptian group than in the French and African groups: 54.9 vs. 40.3 and 32.4% respectively. By univariate analyses, SVR was also associated with age < 45 years, HCV-4 subtype 4a, low serum HCV-RNA levels and mild fibrosis. In multivariate analysis, two factors were independently associated with SVR: an Egyptian origin and the absence of severe fibrosis. The second study was prospective and included 108 consecutive HCV-4-treated patients (48% Egyptians, 30% Europeans and 21% Africans), the overall SVR rate was 54%, but the SVR rates were significantly different according to the geographical origin of the patients: Egyptians (63%) vs. Europeans (51%) vs. Africans (39%). Besides geographical origin ($P < 0.001$), SVR was independently associated with HOMA-IR < 2 ($P = 0.001$) and non-severe fibrosis ($P < 0.001$). Moreover, HOMA-IR remained a major predictor of SVR when Egyptians and non-Egyptians were analysed separately. It is interesting to note that 80 patients (74%) achieved an early virological response (EVR) in this study, defined as a $\geq 2 \log_{10}$ decline in serum HCV-RNA levels from baseline (partial EVR) or undetectable HCV-RNA in serum (complete EVR) at treatment week 12. An EVR had a good positive predictive value (PPV = 72%) and an excellent negative predictive value (NPV = 96%) of SVR (Tables 5 and 6).

Defining the optimal treatment duration ensures successful long-term treatment outcomes with the shortest possible treatment duration to reduce cost and maximize tolerance (120). In a double-blind, randomized study conducted to determine the optimum treatment duration for patients with HCV-4 (112), patients received PEG-IFN-α-2b and ribavirin according to a weight-based administration schedule for 24, 36 or 48 weeks. In this study, SVRs were significantly higher in patients receiving treatment for 36 or 48 weeks (66 and 69% respectively) than in those in the 24-week regimen (29%) ($P = 0.001$). In addition, for the group of patients who have achieved a complete EVR, the SVR rate was 86% with 36 weeks of therapy and 92% with 48 weeks of therapy ($P = 0.8$) Although the frequency and type of general adverse events were similar in each group, PEG-IFN dose reductions were significantly more common in patients receiving 48 weeks of therapy than in those receiving 24 or 36 weeks of therapy ($P < 0.05$).

Rapid virological response (RVR), defined as undetectable serum HCV-RNA levels at week 4 of therapy, has been a useful tool for determining the duration of PEG-IFN and ribavirin therapy for HCV-1 (121). Two studies (72, 115) have shown that 24 weeks of therapy induce an SVR in chronic HCV-4 patients achieving RVR. The first study (115) demonstrated that patients with RVR and EVR assigned to PEG-IFN-α-2b and ribavirin therapy for 24 and 36 weeks, respectively, had high SVR rates (86 and 76% respectively), with significantly fewer adverse events and better compliance than those treated for 48 weeks. After controlling for predictors, low baseline histological activity grade and fibrosis stage were associated with SVR ($P < 0.029$) in all groups.

The second study was a prospective study conducted in 13 centres and including 516 chronic HCV patients (genotype 1, $n = 450$; genotype 4, $n = 66$) treated with PEG-IFN plus ribavirin (72). Patients with HCV-4 more frequently had an RVR than those with genotype 1 (45 vs. 26%) in that study. Moreover, 86% of HCV-4 patients with RVR achieved an SVR after 24 weeks of treatment compared with 78% of HCV-1 patients with RVR and the same duration of treatment. Interestingly, the SVR rate was not influenced in HCV-4 patients with RVR (unlike HCV-1 patients) by the level of serum HCV-RNA or the stage of liver fibrosis.

Recently, the combination of nitazoxanide, PEG-IFN-α-2a and ribavirin increased the percentages of patients achieving an RVR and SVR, compared with patients receiving only PEG-IFN plus ribavirin (SVR 79 and 50% respectively) with no increase in adverse events (119).

Few trials have addressed treatment outcome in HCV/HIV-coinfected patients. In one report, the overall SVR was 11.1% in patients receiving IFN-α monotherapy, 9.1% in patients receiving IFN-α plus ribavirin combination therapy and 22.7% in patients receiving PEG-IFN-α-2b (1.5 μg/week) plus ribavirin (800 mg/day) (101). In another study, end of treatment response and SVR rates were lower in HIV/HCV-coinfected patients than that in HCV-monoinfected patients (30 vs. 66%, $P = 0.06$; 15 vs. 50%, $P = 0.06$ respectively) receiving PEG-IFN-α plus ribavirin (1000–1200 mg/day) for 48 weeks (100). A recent Italian Spanish study assessed the efficacy of PEG-IFN and ribavirin therapy in 75 HCV-4 patients coinfected with HIV. The overall SVR was 28% in an intention-to-treat analysis (102).

Table 5. Summary of randomized control trials and studies with control groups of pegylated interferon-α in patients with hepatitis C virus-4

References	Study design	Number of patients	Treatment	Duration of treatment (weeks)	SVR (%)*
Kamal *et al.* (112)	Prospective, double-blind, randomized study of Egyptian patients with HCV-4	260	PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day† for 24 weeks ($n = 95$)	24	29
			PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day† for 36 weeks ($n = 96$)	36	66‡
			PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day† for 48 weeks ($n = 69$)	48	69‡
Alfaleh *et al*. (109)	Randomized, parallel-group study of Saudi patients with HCV	59	PEG-IFN-α-2b 100 mcg/week plus RBV 800 mg/day ($n = 28$)§	48	42.9
			IFN-α-2b 3 MU three times a week plus RBV 800 mg/day ($n = 31$)§	48	32.3
Derbala *et al*. (114)	Randomized controlled study of patients in Qatar with HCV-4 and a history of bilharziasis	73	PEG-IFN-α-2a 180 mcg/week + RBV 1200 mg/day for ($n = 38$)	48	65.8¶
			IFN-α-2b 3 MU three times a week plus RBV 1200 mg/day ($n = 35$)	48	25.7
Kamal *et al*. (115)	Prospective, treatment duration based on virological response at week 4 or 12 in Egyptian patients with chronic HCV-4	308	PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day† for according to virological response at weeks 4 or 12 respectively	24 36 48	86 (RVR) 76 (complete EVR) 58 (partial EVR)
Esmat *et al*. (105)	Prospective, open-label randomized study of Egyptian patients with chronic HCV-4		PEG-IFN-α-2b 100 mcg/week plus RBV 800–1000 mg/day	48	55
			IFN-α-2b 2 MU three times a week plus RBV 800–1000 mg/day		40
Ferenci *et al*. (72)	Prospective trial investigating response-guided therapy.	66	PEG-α-2a (180 μg/week plus ribavirin 1000 or 1200 mg/day according to virological response at weeks 4	24 (if RVR) 48 72	87
Rossignol *et al*. (119)	Prospective trial Triple therapy: PEG-IFN plus ribavirin plus nitazoxanide	96	PEG-IFN-2a and ribavirin for 48 weeks, $n = 40$), nitazoxanide monotherapy for 12 weeks followed by nitazoxanide plus PEG-IFN-2a for 36 weeks ($n = 28$), or nitazoxanide monotherapy for 12 weeks followed by nitazoxanide plus peginterferon-α-2a and ribavirin for 36 weeks ($n = 28$). Therapeutics included nitazoxanide (500 mg) twice daily, peginterferon-α-2a (180 μg) once weekly, and weight-based ribavirin (1000–1200 mg/day).	48 36 36	50 61 79
Moucari *et al*. (77)	Prospective study on Egyptian, European African patients	108	PEG-IFN-α-2a 62% PEG-IFN-α-2b 38%	48	Egyptians: 63% Europeans: 51% Africans: 39%

Adapted with permission from Kamal and Nasser (15) and Kamal (120).

*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.

‡$P = 0.001$ vs. 24-week treatment regimen.

§Data presented for HCV-4 patients only.

¶$P < 0.05$ vs. conventional IFN.

PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response.

Table 6. Summary of non-randomized control trials, retrospective and *post hoc* studies of pegylated interferon-α in patients with hepatitis C virus-4

References	Study design	Number of patients	Treatment	Duration of treatment (weeks)	SVR (%)*
El-Zayadi *et al*. (113)	Non-randomized study of patients in Egypt with HCV-4†	180	PEG-IFN-α-2b 100 mcg/week + RBV 1000–1200 mg/day (*n* = 40)‡	48	55.0§
			PEG-IFN-α-2b 100 mcg/week + RBV 1000–1200 mg/day (*n* = 70)	24	48.6¶
			IFN-α-2b 3 MU‖ + RBV 1000–1200 mg/day + AMD 200 mg/day (*n* = 70)	24	28.6
Hasan *et al*. (107)	Open-label, prospective study of treatment-naive HCV-4 patients in Kuwait	66	PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day‡	48	68
Roulot *et al*. (76)	A retrospective non-randomized study French, Egyptian and African patients with chronic HCV-4	242	PEG-IFN-α-2b 1.5 mcg/kg/week + RBV 1000–1200 mg/day‡	48	Egyptians: 54.9 French: 40.3 Africans: 32.4
Diago *et al*. (108)	*Post hoc* analysis of patients with HCV-4 from two large, double-blind clinical trials	98	Study 1: PEG-IFN-α-2a 180 mcg/week + RBV 1000–1200 mg/day‡ (*n* = 13)	48	79
			Study 2: PEG-IFN-α-2a 180 mcg/week + RBV 800–1200 mg/day‡ for 24 or 48 weeks	48	63
			High-dose RBV (*n* = 24)	48	67
			Low-dose RBV (*n* = 8)	24	0
			High-dose RBV (*n* = 12)	24	
			Low-dose RBV (*n* = 5)		
Trapero-Marugan *et al*. (118)	Open-label study of Spanish patients with chronic HCV-4	29	IFN-α-2b 3 MU three times/week plus RBV 800–1000 mg/day (*n* = 19) Peg-IFN-α-2b (1.5 μg/kg/week) plus ribavirin (1–1.2 g/day) (*n* = 10)	48	55

Adapted with permission from Kamal and Nasser (15) and Kamal (120).

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

§$P = 0.006$.

¶$P = 0.015$ vs. induction dose regimen.

‖Interferon was administered daily for the first four weeks of the study and then thrice weekly for the remaining 20 weeks.

AMD, amantadine; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response.

Hepatitis C virus-5

There are no prospective studies on the treatment of HCV-5. Only five non-randomized retrospective studies have been performed reporting treatment response rates for HCV-5 including a limited number of patients. D'Heygere (122) reported a 48% SVR in 21 patients. In a study on 26 Syrian patients, Antaki *et al*. (123) reported an overall SVR of 54% in patients treated either with IFN (17 patients, SVR 47%) or PEG-IFN (nine patients, SVR 66.6%). A similar SVR rate was found in patients treated for 24 weeks (13 patients, SVR 54%) or 48 weeks (13 patients, SVR 54%) in this study. Finally, Bonny *et al*. (80) showed an overall SVR rate of 60% (52/87), which was not different according to the type of treatment (IFN vs. PEG-IFN). In patients who received PEG-IFN, an EVR was achieved in 98% of patients. In the same study, 107 patients with HCV-1 and 51 patients with HCV-2 and HCV-3 treated with PEG-IFN plus ribavirin were compared with the 27 HCV-5 patients treated with the same regimen in one of the participating centres. Even though HCV-5 patients were older, had more severe liver fibrosis and more frequently had higher levels of viraemia than HCV-2/3 patients, the SVR rates were similar in both groups (60 vs. 63%, $P = 0.8098$) and significantly higher than that in HCV-1 patients (37%, $P = 0.0499$).

The low success rate in the D'Heygere study is probably related to the inclusion of prior relapsers. Because of the limited number of patients included, the retrospective nature of the studies reported and the lack of evidence from controlled-randomized clinical trials, the ideal treatment duration cannot be determined. However, overall, the different studies have shown that the response to treatment in genotype 5, like genotype 4, is intermediate between genotype 1 and genotypes 2 and 3 and the SVR varies between 55 and 87%. In

addition, the SVR was almost similar with the use of IFN or PEG-IFN (with ribavirin). Antaki's study also showed a similar SVR for a treatment course of 24 or 48 weeks (Table 7).

Recently, the first viral kinetic study has been conducted assessing viral kinetic parameters in non-cirrhotic HCV-5 patients and comparing this with historical cohorts of HCV-1, HCV-2 and HCV-3 patients (96). The first phase viral decline in HCV-5 patients was significantly more pronounced than that of HCV-1, and similar to that observed for HCV-2 and HCV-3. The viral decline pattern in all genotype 5 patients was bi-phasic, similar to genotype 2–3 patients, and did not show a transient rebound in HCV-RNA that occurs in some genotype 1 patients treated with PEG-IFN-α2a. The second phase decline slope was significantly faster for HCV-5 (mean 1.6 $\log_{10}$ IU/ml/week) than HCV-1 (0.7 $\log_{10}$ IU/ml/week) and similar to that of HCV-2 and HCV-3 patients (1.5 $\log_{10}$ IU/ml/week). These findings in South African HCV-5 patients showed that the decrease of viraemia was more marked in HCV-5 than in HCV-1 and similar to those in HCV-2 and -3, suggesting that a shorter duration of therapy may be warranted in HCV-5; however, the geographic variations in the treatment outcome must be further evaluated.

Hepatitis C virus-6

Only six studies have been published so far comparing the SVR rate of patients infected with HCV-1 with that of patients infected with HCV-6. After 12 months of combination treatment with IFN and ribavirin, Hui reported a 62.5% SVR rate in 16 Hong Kong patients with HCV-6 and a 29.2% SVR rate in 24 patients with HCV-1 (124). Following combination therapy for 52 weeks with IFN and ribavirin, Dev reported an 82.5% SVR rate in 40 Asian Australian patients with HCV-6 compared with a 61.9% SVR rate in 21 patients with HCV-1 (13). Notably, patients in the latter study received a daily dose of 5 million units of IFN for 8 weeks as induction therapy, which may explain the differences in SVR rates observed between the two studies. Fung and colleagues analysed treatment response data after a 48-week PEG-IFN and ribavirin regimen in 21 Hong Kong patients with HCV-6 and in 21 patients with HCV-1. SVR rate was 86% for patients infected with HCV-6 and 52% for those infected with HCV-1 (125). In their retrospective study of a group of Asian American patients infected with HCV-6, Nguyen *et al.* (126) analysed the response to treatment of 66 patients. These patients were divided into three groups: group 1 consisted of 31 patients treated by combination therapy with IFN and ribavirin for 24 weeks, group 2 included 23 patients who completed a 24-week combination treatment course with PEG-IFN and ribavirin and group 3 consisted of 12 patients who completed a 48-week treatment course with PEG-IFN and ribavirin. The SVR rate was 51.6% for group 1, 39% for group 2 and 75% for group 3. The difference in the SVR rate was not statistically significant between groups 1 and 2 ($P = 0.363$) but was significant between groups 2 and 3 ($P = 0.044$). These results indicate that a higher SVR rate is obtained when treating patients with HCV-6 with a 48-week course of PEG-IFN and ribavirin than with a 24-week regimen. Li reported an SVR in eight out of nine HCV-6 patients from Hong Kong treated with PEG-IFN and ribavirin. Two of the patients were treated for 24 weeks (127). Finally, PThi reported the response to treatment in 75 HCV-6 Vietnamese patients. SVR was achieved in 69% of 42 naïve patients and in 60% of 33 non-responder patients to previous treatment with standard IFN and ribavirin. All patients were treated with a 48-week course of PEG-IFN-α-2a and ribavirin. All patients who had achieved an RVR achieved an SVR (128) (Table 8).

In conclusion, the SVR rate in HCV-6 patients treated with a 48-week regimen of PEG-IFN and ribavirin varies

Table 7. Sustained virological response in hepatitis C virus-5

References	Number of patients treated	SVR (%)
Delwaide *et al.* (81)	6	83
Legrand-Abravanel *et al.* (79)	12	67
D'Heygere *et al.* (122)	21 (including relapsers)	48
Antaki *et al.* (123)	26	54
Bonny *et al.* (80)	87	60

Table 8. Sustained virological response in hepatitis C virus-6

References	Number of HCV-6 patients/number of HCV-1 patients	SVR in HCV-6 (%)	SVR in HCV-1 as a control group (%)
Hui *et al.* (124)	16 (Hong Kong)/24	62.5	29.2
Dev *et al.* (13)	40 (Asian Australian)/21	82	61.9
Fung *et al.* (125)	21 (Hong Kong)/21	86	52
Nguyen *et al.* (126)	31 (24 weeks IFN plus ribavirin)	51	
	23 (24 weeks PEG-IFN plus ribavirin)	39	
	12 (48 weeks PEG-IFN plus ribavirin)	75	
Li *et al.* (127)	9	89	
PThi (128)	42 naïve	69	
	33 non-responders	60	

HCV, hepatitis C virus; PEG-IFN, pegylated interferon; SVR, sustained virological response.

between 66 and 86%, which makes HCV-6 one of the so-called 'easy-to-treat' genotypes (129).

Conclusion and recommendations

Hepatitis C virus genotypes 4, 5 and 6 represent 20% of all HCV infection cases worldwide. They are spreading outside their main foci and reaching western countries, and so they should not be neglected by the medical community. Although useful data and prospective studies are available for HCV-4, there are still many issues that need to be clarified, mainly the optimal duration of treatment. For the patients achieving an RVR, it seems reasonable to recommend a 24-week therapy regimen. Two studies have confirmed that patients achieving an RVR have an 86% SVR rate (72, 115). For the patients achieving a complete EVR and who have a low baseline viral load and mild fibrosis, an SVR is obtained in 86% with 36 weeks of therapy regimen compared with an SVR of 92% for the patients with EVR treated for 48 weeks. The difference is not statistically significant (115). Two other issues are still debatable in HCV-4: the benefit of adding nitazoxanide to combination therapy and the cause of the discrepancy in response to antiviral therapy in terms of SVR between Egyptian patients and others infected with HCV-4: ethnicity, the different subtypes or the insulin resistance? Prospective studies are needed in HCV-5 and HCV-6 to determine the optimal duration of treatment. However, HCV-5 and HCV-6 may be considered 'easy-to-treat' genotypes as they may have similar SVR as HCV-2 and HCV-3 but with a longer duration of treatment (48 vs. 24 weeks).

In conclusion, the experts' panel would like to recommend the following:

(1) *HCV-4*

1. If RVR is achieved, treat for 24 weeks regardless of viral load at baseline.
2. It has been suggested in two studies that if a patient achieves a complete EVR and if the viral load at baseline is low and the fibrosis is mild, treatment for 36 weeks is an acceptable option. But these data need further confirmation in genotype 4 and other genotypes.
3. If partial EVR, treat for 48 weeks.

(2) *HCV-5*

1. Treat for 48 weeks. If there is no EVR, consider discontinuation (data are lacking for RVR and EVR).
2. Prospective study should address the role of RVR and will determine whether and when a shorter duration is possible.

(3) *HCV-6*

1. Evidence of higher SVR with 48 weeks than 24 weeks.
2. If there is no EVR, consider discontinuation (data are lacking for RVR and EVR).

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Appendix 1

The authors are members of a working party established by the World Gastroenterology Organization in 2007. The objective of the party was to produce a document on 'HCV genotypes 4, 5 and 6: the neglected genotypes' which was presented at the London World Congress 'Gastro 2009'.