Dissertation

Prevention, control, and therapy of hepatitis C virus infection in Austria and Egypt

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Prevention, control, and therapy of hepatitis C virus infection in Austria and Egypt

ABSTRACT

The prevalence of hepatitis C Virus (HCV) infection has been reported to be at maximum 1% among the Austrian population, in contrast to approximately 20% among the Egyptian population. In Austria, the majority of HCV-positives are infected with HCV subtype (ST) 1b, while the HCV genotype (GT) 4 predominates in Egypt. Today, the HCV GT is considered as the most important parameter for the duration of anti-HCV therapy.

In this study, the national plans for HCV prevention and control strategies in Austria and Egypt were compared. Data were obtained from health information systems and published studies and health experts were interviewed. Furthermore, the response to the combination standard therapy consisting of peginterferon alfa (PEG-IFNα) plus ribavirin (RV) in patients with HCV GT 4 infection was compared to that in patients with HCV ST 1b infection. For the clinical part of the study, a total of 18 patients with HCV GT 4 infection were randomly matched with another 18 patients with HCV ST 1b who were treated during the same time period. Both groups of patients were treated with the PEG-IFNα plus RV regimen for 48 weeks. Alaninaminotransferase (ALT) values, hemoglobin levels, and number of neutrophils were compared and side effects were recorded.

While Austria has established specific strategies to control HCV transmission and prevent sequelae of HCV infection, measures in Egypt are limited covering big cities only. Shortage of resources, lack of awareness and incapability of the administration and surveillance system were found to be the major problems to implement the infection control program in Egypt. When the response to therapy was compared, it was found that the sustained virological response rate among

patients with HCV GT 4 infection was significantly higher than that among patients with HCV ST 1b infection. For the mean ALT values, a continuous reduction was observed throughout the treatment period in both groups. The decrease of hemoglobin levels and neutrophil count was similar in both groups throughout the treatment period.

In conclusion, significant differences with regard to HCV prevention and control strategies were found when comparing Austria and Egypt. In this study, PEG-IFNα plus RV treatment revealed to be more effective in patients with HCV GT 4 infection than in those with HCV ST 1b infection.

Prävention, Kontrolle und Therapie von Hepatitis C Virus-Infektionen in Österreich und Ägypten

ABSTRACT

Die Prävalenz der Hepatitis C Virus (HCV)-Infektion beträgt in der österreichischen Bevölkerung maximal 1%, in der ägyptischen etwa 20%. Während in Österreich Infektionen mit dem HCV-Subtyp (ST) 1b dominieren, ist in Ägypten der HCV Genotyp (GT) 4 vorherrschend. Der HCV GT stellt heutzutage den entscheidenden Parameter zur Therapiedauer dar.

In dieser Studie wurden die strategischen Maßnahmen zur Kontrolle und Prävention von HCV Infektionen zwischen Österreich und Ägypten verglichen. Dafür wurden Daten von Gesundheitseinrichtungen, Interviews mit Experten und Publikationen verwendet. Darüber hinaus wurde der Erfolg der aktuellen Standard-Kombinationstherapie mit pegyliertem Interferon-alpha und Ribavirin bei 18 PatientInnen mit HCV GT 4 Infektion mit dem bei 18 zufällig ausgewählten PatientInnen mit HCV ST 1b Infektion in einer klinischen Studie verglichen.

Während in Österreich spezifische Strategien zur Prävention und Kontrolle der HCV-Infektion entwickelt wurden, sind derartige Maßnahmen in Ägypten nur auf die Großstädte beschränkt. Als Hauptursachen dafür wurden Mängel sowohl an Ressourcen und Bewusstseinsbildung als auch in der Administration und im Überwachungssystem lokalisiert. Die klinische Vergleichsstudie ergab eine signifikant höhere Anzahl an PatientInnen mit anhaltendem Therapieerfolg in der Gruppe mit HCV GT 4 Infektion. Die durchschnittlichen ALT-Werte zeigten einen kontinuierlichen Rückgang während der gesamten Therapiedauer in beiden Gruppen. Ebenso nahmen die Hämoglobinwerte und die Zahl der neutrophilen Leukozyten während der Therapie in beiden Gruppen ab.

Es bestehen signifikante Unterschiede bezüglich der Strategien zur Prävention und Kontrolle von HCV-Infektionen in Österreich und Ägypten. Die Therapie mit der aktuellen Standardtherapie scheint bei PatientInnen mit HCV GT 4 Infektion effektiver zu sein als bei PatientInnen mit einer HCV ST 1b Infektion.

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
b-DNA	Branched DNA
BL	Base line
CD81	Cluster of differentiation
cDNA	Complementary deoxyribonucleic
DNA	Deoxyribonucleic acid
E1, E2	Envelope protein
ECDC	European Centre of Disease Control
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EOTR	End of treatment response
ER	Endoplasmic reticulum
ESPA	Egyptian Service Provision Assessment
EVR	Early virological response
GT	Genotype
HB	Hemoglobin
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HLD	High level disinfection
HVR	Hypervariable region
IC	Infection control

IDUs	Injecting drug users
IRES	Internal ribosomal entry site
ISDR	Interferon sensitivity-determining region
LDLP	low density lipoprotein
MOHP	Ministry of Health and Population
NANB	Non-A, non-B
NCR	Non-coding region
NS	Non structural
NTRs	Non-translated regions
ORF	Open reading frame
PAT	Potassium antimony tartarate
PCR	Polymerase chain reaction
PEG-IFNα	Pegylated interferon alpha
RdRp	RNA dependant RNA polymerase
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
RV	Ribavirin
ST	Subtype
UTR	Untranslated region
WHO	World Health Organisation

1 INTRODUCTION

Hepatitis C virus (HCV) infection has acute and chronic forms with most of the morbidity through the development of chronic liver disease. In Austria, the prevalence rate of HCV is between 0.8% and 1% of the population with 500 – 1000 persons newly diagnosed every year (Jonas S. et al., 2004). Austria has specific strategies to prevent HCV transmission among selective target groups especially among the injecting drug users (IDUs) but the incidence of HCV infection is still difficult to reduce. Immigrants from developing countries and Eastern Europe including Russia represent a new target for disease control strategies.

In Egypt, HCV is one of the top five leading causes of death (Mohamed M.K. and El-Said Aoun, 2002). Most of infected individuals are not aware of their infective status and are not clinically ill but they are a source of infection to others. No protective vaccine against HCV is available currently (Simmods P., 2004; Brass V. et al., 2006). The treatment is costly, requires long-term medical support and follow-up and has serious side effects. Modern therapies are not affordable for the majority of HCV carriers worldwide. In Egypt, the prevalence rate of HCV infections has been reported as high as 20% (El-Ahmady O. et al., 1994). The annual infection rate is more than 70000 new cases, of which at least 35000 would have chronic hepatitis C (Available at: http://www.hepctrust.org.uk/news/2007/February). There are formal and informal health care providers in Egypt. The Egyptian Ministry of Health and Population (MOHP) has a national plan for HCV control and prevention strategies and advices the governmental and private health care providers but does not have impact on the practices of informal health care providers offering services such as wound sutures, abscess drainage, therapeutic injections, teeth extractions, birth attendance, circumcision, and bloodletting. The informal health care providers operate outside the governmental framework and lack safe and hygienic practices. There is an urgent need not only to reduce transmission of HCV infection but also to avoid chronic liver disease in HCV-infected individuals through appropriate medical management and counseling (Weekly Mortality and Morbidity Report, Center of Disease Control, 1998).

1.1 The history and discovery of hepatitis C virus

The first evidence for existence of a non-A, non-B (NANB) hepatitis agent was reported in the 1950s and confirmed in the late 1970s (Havens W. 1956; Mosley J.W. et al., 1977). Studies on patients with post-transfusion hepatitis suggested that NANB hepatitis was the major cause of this disease (Purcell R. et al., 1971; Alter H. et al., 1975). Further studies focused on the transmission of the agent from humans to chimpanzees and concluded that the NANB hepatitis agent led to chronic infection in 50% of chimpanzees producing distinctive histological abnormalities in their liver. The agent was shown to be sensitive to organic solvents and to pass through filters of 80nm pore-size, suggesting that it was a small enveloped RNA virus (Bradley D. et al., 1985). Initial studies by Choo and colleagues at the Chiron Corporation succeeded to extract the nucleic acid from infected animal plasma (Choo Q.L. et al., 1989). The authors created a cDNA expression library by cloning the random fragments into the vector and this was then screened with serum derived from patients diagnosed with chronic NANB hepatitis. After screening more than a million clones, one clone (5-1-1) was found to react with serum from several NANB hepatitis patients and also with serum from experimentally infected chimpanzees following the onset of hepatitis. Three overlapping clones were isolated by using the 5-1-1 cDNA as a hybridization probe to screen the original library and a 1089 nucleotide continuous open-reading frame (ORF) was reconstructed. The antigen (C100-3) used in the first-generation enzyme-linked immunosorbent assay (ELISA) was prepared by expressing this ORF as a fusion polypeptide with human superoxide dismutase in yeast (Kuo G. et al., 1998). Most cases of NANB hepatitis were found to be associated with C100-3 antibody and this response was used to define the infection with a new virus, hepatitis C virus (HCV).

1.2 The Hepatitis C Virus

1.2.1 Classification

The HCV belongs to the *Flaviviridae* family (from Latin *Flavus* = yellow). The *Flaviviridae* family includes three genera: the flaviviruses, the pestiviruses, and the hepaciviruses. The flaviviruses include human pathogens such as dengue virus type 1 and type 2, yellow-fever virus, the West Nile virus, and the Japanese encephalitis virus. The pestiviruses produce disease in animals and include the classical swine fever virus and the bovine viral diarrhea virus (Houghton M. et al., 1991). The hepaciviruses include HCV and the recently described hepatitis G virus that does not produce significant liver disease in humans (Linnen J. et al., 1996).

1.2.2 Morphology

To clarify the morphology of HCV, a study was carried out on two plasma samples with high HCV RNA titers using polyclonal and monoclonal antibodies specific to the putative HCV envelope protein (Kaito M. et al., 1994). Spherical virus-like particles, 50 to 65 nm in diameter, with spike-like projections, similar to those of flaviviruses, were found (Fig.1).

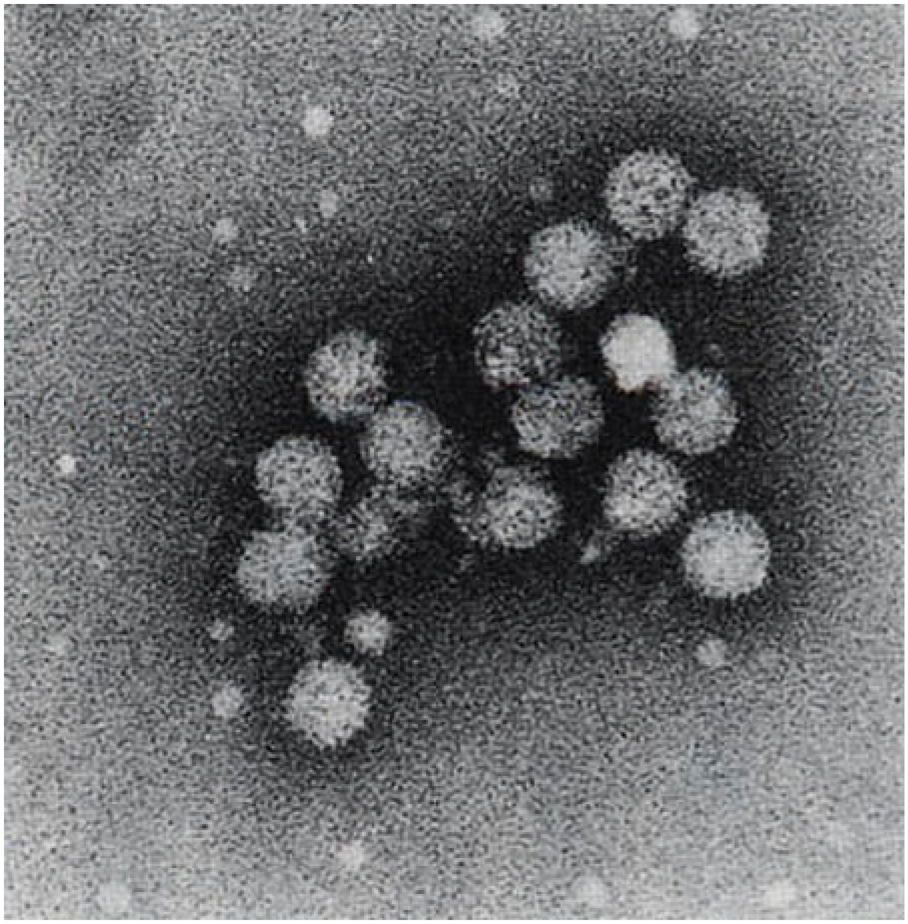


Fig. 1 HCV Morphology
(from http://www.epidemic.org/the Facts/hepatitisC/hepatitisC/)

The HCV genome consists of an RNA surrounded by an icosahedral protein capsid and a lipid envelope (Op De Beek A. et al., 2003). Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope (Fig.2).

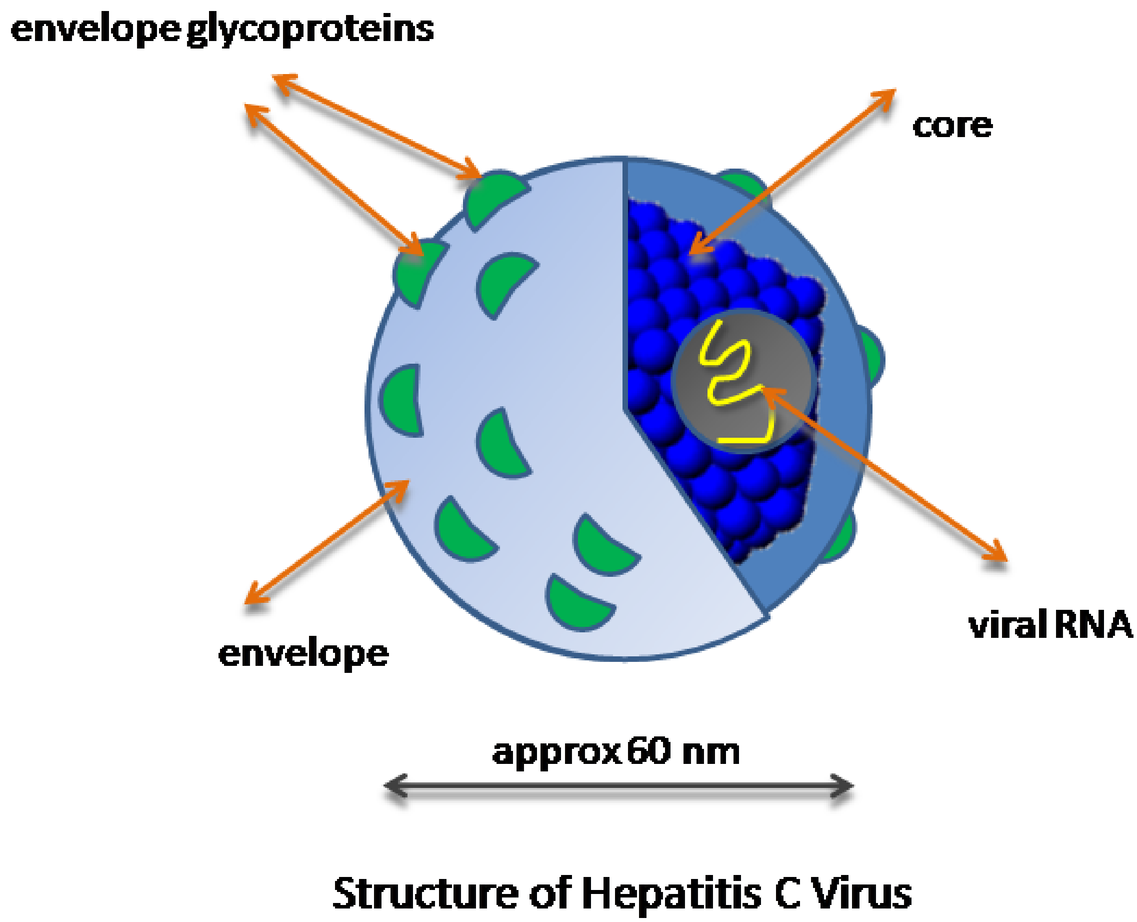


Fig. 2 Structure of the HCV
(from http://upload.wikimedia.org/wikipedia/en/9/96/ HCV_structure.png)

1.2.3 Genome structure and genetic organization

The HCV has a positive sense RNA genome that consists of a single ORF of 9600 nucleoside bases (Kato N., 2000). The ORF encodes a polyprotein precursor of about 3011 amino acids. At the 5' and 3' ends of the RNA there are regions that are not translated into proteins also called non translated regions (NTRs). The 5' NTR has an internal ribosomal entry site (IRES) which is essential for translation of the viral RNA (Jubin R., 2001). The 3' NCR is composed of a short variable region. The polyprotein precursor is processed by cellular and viral proteases into 10 mature structural and non-structural proteins (Dubuisson J., 2007).

The structural region contains sequences encoding the core protein and two envelope proteins (E1 and E2). Two regions in E2, called hypervariable region 1 and 2 (HVR 1 and HVR 2), show extreme sequence variability which is thought to be the result of selective pressure by virus-specific antibodies (Lauer G.M. et al., 2001). E2 additionally contains sequences encoding the binding site for CD81, the putative HCV receptor. The nonstructural regions encode proteases (NS2, NS3, and NS4A), the helicase (NS3), and the RNA-dependent RNA polymerase (NS5B). A part of the NS5A region has been linked to the response to interferon alpha therapy, also called the interferon sensitivity-determining region (ISDR).

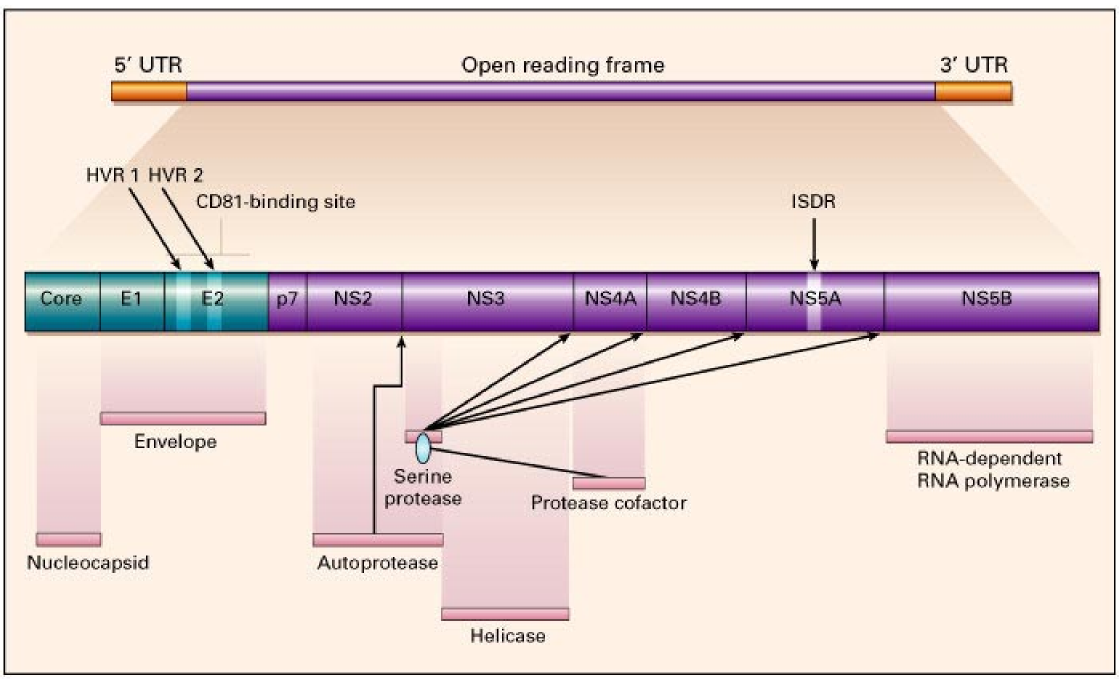


Fig. 3 The HCV genome and expressed polyprotein
(from Lauer G.M. et al., 2001)

1.2.4 Stability of the virus

The HCV can be inactivated by different measures (Table 1). The virus is relatively unstable to storage at room temperature and repeated freezing and thawing procedures (Purcell R.H., 1994).

Table 1: HCV inactivation measures

- Exposure to lipid solvents or detergents
- Heating at 60°C for 10 h or 100°C for 2 min in aqueous solution
- Formaldehyde (1:2000) at 37°C for 72 h
- ß-propriolactone
- UV irradiation

1.2.5 Replication

Replication of HCV involves several steps (Fig. 4). The virus needs a certain environment to be able to replicate and must therefore first move to such areas (Zignego A. L. et al., 1995). The HCV mainly replicates in hepatocytes but also in peripheral blood mononuclear cells (PBMCs). HCV E2 binds with high affinity to CD81 receptors which was found on the surfaces of many cell types including hepatocytes (Okuda M. et al., 1999). However, CD81 is not sufficient to mediate cell entry and several cofactors appear to be required. The low density lipoprotein receptor (LDLP) and the human scavenger receptor class B type1 (SR-B1) play an important role for cell entry. The virus/receptor complex is internalized by endocytosis. The virus leaves the endosome by membrane fusion which is pH dependent and releases in the cytoplasm. The viral capsid is disintegrated in the cytosol and the viral RNA is uncoated. The viral RNA is translated by the IRES. The newly translated polyprotein is processed by cellular and viral proteases at the endoplasmic reticulum (ER). The RNA is replicated by the viral enzyme RNA dependant RNA polymerase (RdRp). Once the viral proteins have been produced and the viral RNA has been replicated, the viral packaging and assembly is started and finally the mature virion is released from the host cell via exocytosis. In principle, each of these steps represents a target for antiviral intervention.

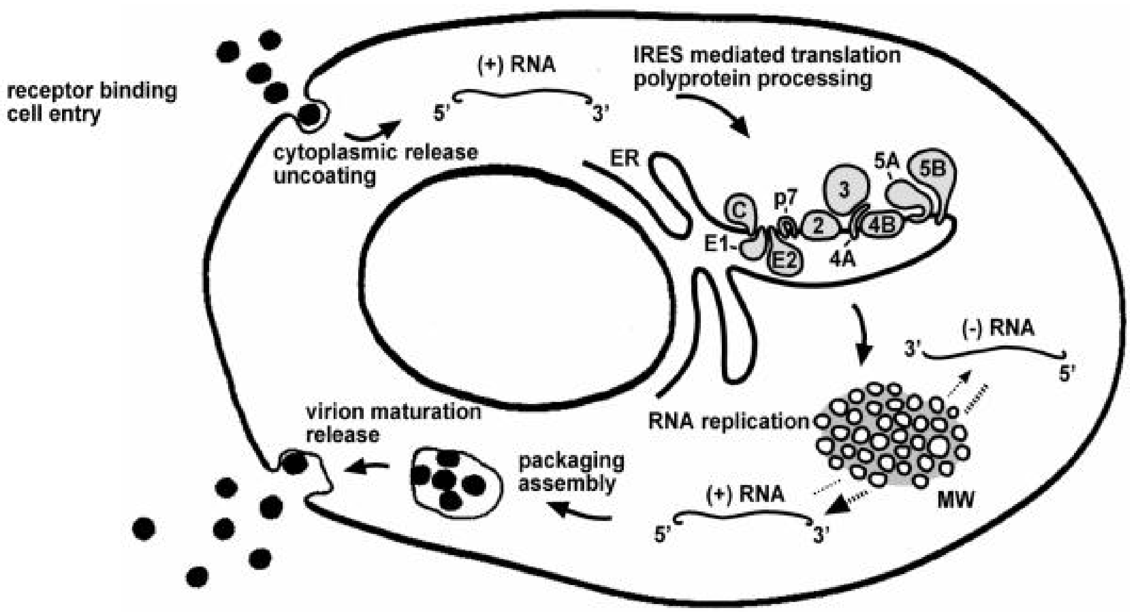


Fig. 4 Life cycle of HCV
(from Moradpour D. et al., 2004)

1.2.6 Viral dynamics and mutation

HCV infection is a highly dynamic process with a viral half-life of only a few hours and an average daily virion production of up to more than 10^{12} (Brass V. et al., 2006). The high replicative activity, together with the lack of a proof-reading function of the RdRp, provides the basis for the high genetic variability of HCV.

Once the infection has begun, hepatitis C generates different genetic variations. The mutated forms are frequently different enough from their ancestors that the immune system cannot recognize them. Thus, even if the immune system begins to succeed against one variant, the mutant strains quickly take over and become predominant strains. As a result, the development of antibodies against HCV does not mean immunity against the disease as it does with most other viruses.

There are six basic genotypes of HCV, with more than 50 recorded subtypes which vary in prevalence in different regions of the world (Fig. 5). Each of these major genotypes may differ with regard to replication, mutation rate, severity of liver damage, and treatment options (Hoofnagle J.H., 2002).

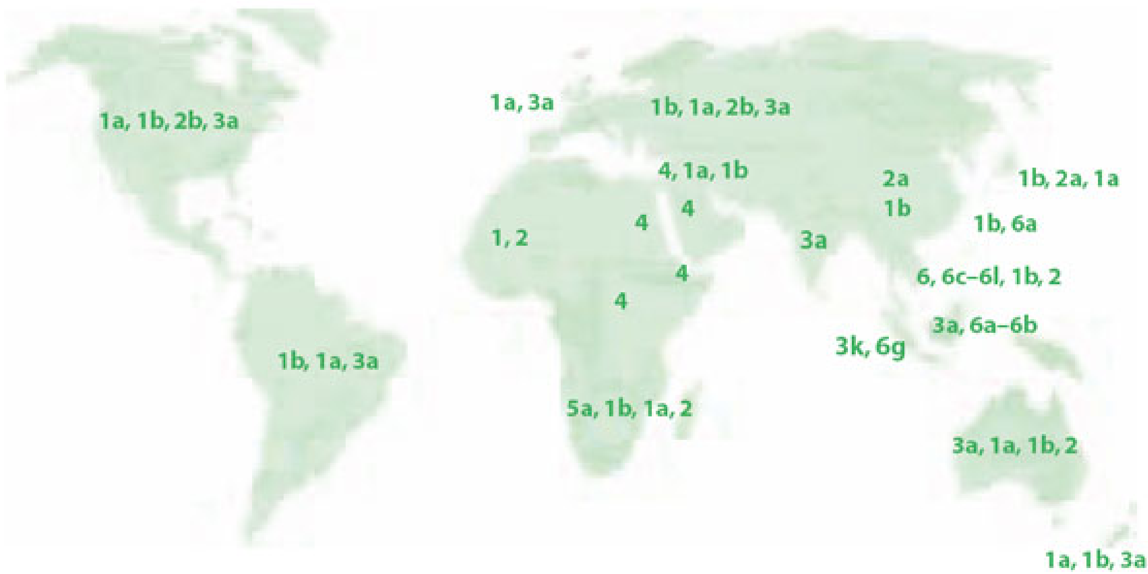


Fig. 5 The distribution of HCV genotypes in the world
(Available at: http://www.aodgp.gov.au/internet/main/publishing.nsf/Content/phd-hepc-manual-toc~phd-hepc-manual-ch1~phd-hepc-manual-ch1-5)

The different genotypes and the continuous mutation of the virus within the infected individual represent a major challenge for the development of an adequate treatment and of a future vaccine against HCV - and even for reliable detection of the virus (Fig. 6). There is no guarantee that a treatment, vaccine or test against a certain strain will be effective against another one. Moreover, individuals cured of one strain are prone to reinfection by any of the other strains (Hoofnagle J.H., 2002).

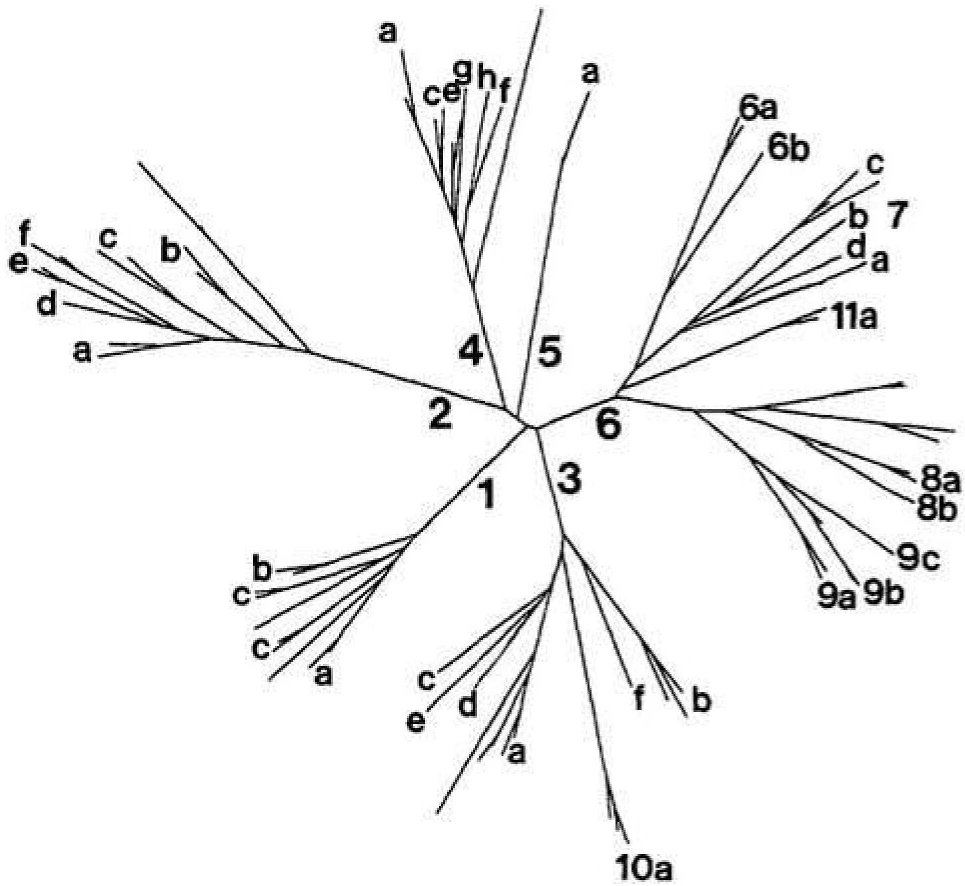


Fig. 6 Phylogenetic tree of HCV NS5B sequences.
Major branches are labelled with the type number, and minor branches with letters indicating the subtype The variant “10a” can be considered as a subtype of type 3, and the variants “7a”, “7b”, “8a,” and so forth, as subtypes of type 6 (from Simmonds P. et al., 1996)

1.2.7 Genotypes and subtypes in Europe and Austria

Genotype 1 has been found to be the predominant HCV genotype throughout Europe. In Eastern Austria, up to 75% of the patients are infected with HCV genotype 1 (Haushofer A.C. et al., 2001). Genotype 3 with 16%, 4 with 5% and 2 with 3% are less common (Fig. 7). The majority of patients with genotype 3 are drug abusers, and almost all of the patients infected with genotype 4 originate from Middle East countries. In Eastern Austria, HCV subtype 1b was found to be the most predominant among HCV infected persons (Appendix 1). In a more recent study, HCV genotype 1 was found to be responsible for the HCV infection in 60 to 65% of patients investigated (Ferenci P., 2004).

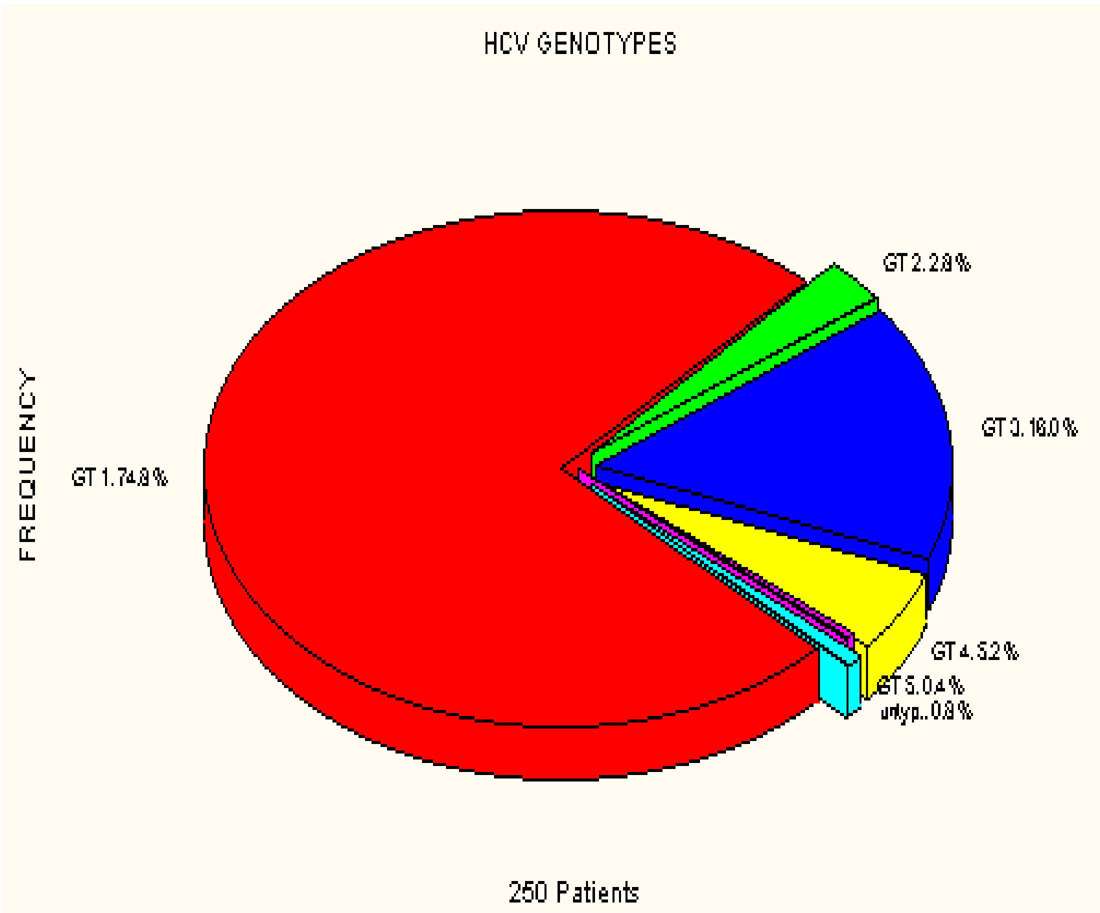


Fig. 7 Distribution of HCV genotypes in Eastern Austria
(from Haushofer A.C. et al., 2001)

1.2.8 Genotypes and subtypes in Egypt

HCV genotype 4 was found to be predominant with 91% in Egypt (Stuart C. et al., 2000). The distribution and the source of HCV isolates in each of the 15 Egyptian governorates are shown in Fig. 8 (Appendix 2).

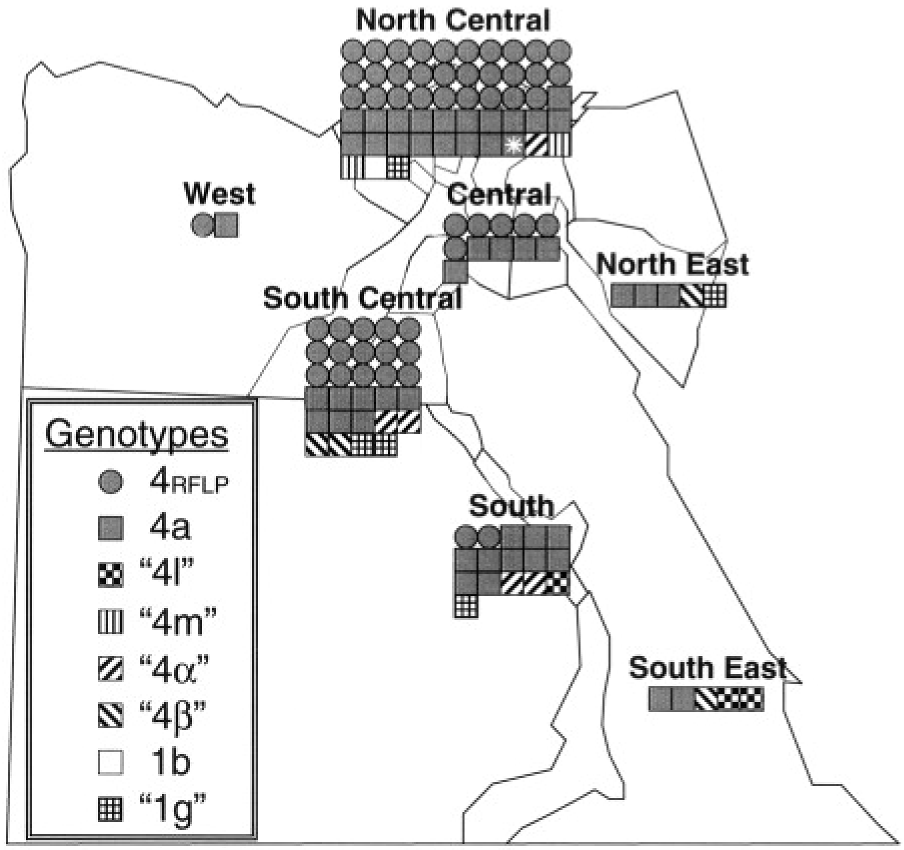


Fig. 8 Map of Egypt indicating regions from which specimens were obtained. Governorates composing each region are listed in Appendix 2. Each symbol represents a serum specimen from that region and HCV virus subtype assigned by both restriction fragment length polymorphism (RFLP) and phylogenetic analysis (squares) or RFLP only (circles). The asterisk (*) overlying square in North Central region indicates only the specimen for which RFLP and phylogenetic analysis were discordant (subtype 1a by RFLP, subtype 4a by phylogenetic analysis).

1.3 The HCV infection

1.3.1 Symptoms

The natural history of HCV infection is very difficult to assess, because of both the usually silent onset of disease and the lack of symptoms during the early stages of chronic infection. Symptoms develop usually within 7 to 8 weeks (range, 2 to 26) after exposure to HCV (Booth J.C.L., 1998). The majority of infected persons do not show symptoms or develop mild ones such as Flu-like symptoms, weakness, nausea, loss of appetite, and tiredness (Lauer G.M. and Walker B.D., 2001). Less than 20% develop symptoms such as jaundice, dark urine, and light (acholic) stool. Patients with chronic HCV often do not show any symptoms or they have non-specific symptoms such as tiredness, fatigue, nausea, vomiting, loss of appetite, and fever.

1.3.2 Natural history

Infected individuals may clear the virus spontaneously at the acute infection stage. However, 50-90% of acute HCV infections proceed to the chronic stage (Fig. 9). Risk of progression may be decreased in females and younger age at infection. Alcohol, drug addiction, and co-infection with HIV contribute to the progression of chronic liver disease among individuals with hepatitis C (Lauer G.M. and Walker B.D., 2001). Liver cirrhosis develops in 10 to 20 percent of patients with chronic hepatitis C over a period of 20-30 years, while hepatocellular carcinoma (HCC) develops in 1-5%.

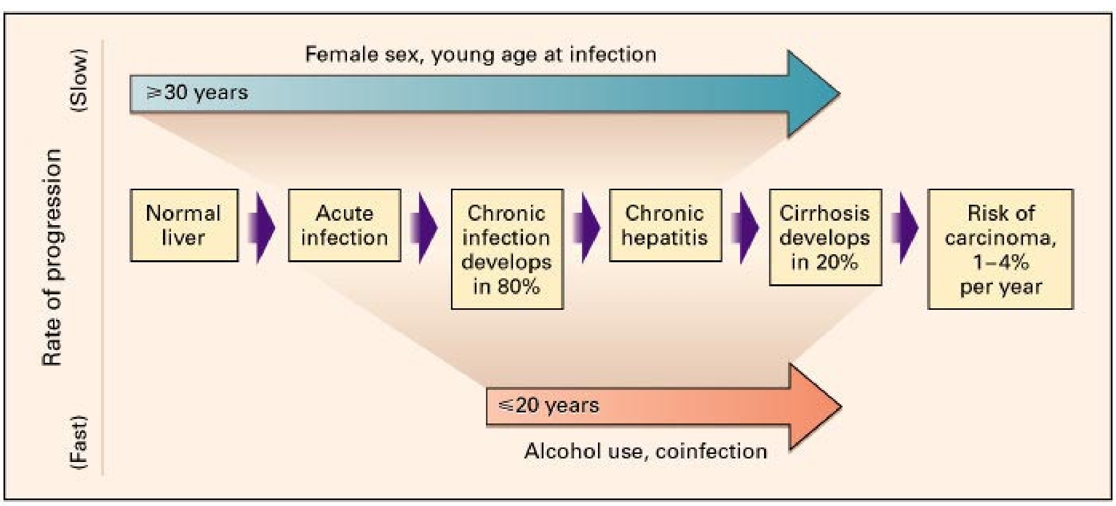


Fig. 9 Natural history of HCV infection
(from Lauer G.M. et al., 2001)

1.3.3 Transmission

HCV is a blood-borne pathogen. The main risk factors of HCV infection are transfusion with unscreened blood or blood products and needle-sharing among injecting drug users. Individuals at increased risk of acquiring HCV infection include hemodialysis patients, hemophiliacs, and health care workers. Vertical transmission, multiple sex partners, and percutaneous infection (through a needle stick injury, ear and body piercing, circumcision or tattooing) are considered as minor risk factor.

In the European Union, the most frequent source of HCV transmission was nosocomial such as transfusion with blood and blood products before 1990, hemodialysis, endoscopy, and surgical procedures. Today, intravenous drug abuse is considered as the main route of transmission. The most frequent sources of HCV transmission in Germany are shown in Fig. 10, those recognized in Austria in Fig. 11 (Zeuzem S. et al., 1996; Ferenci P. et al., 2004). It is remarkable that the source of transmission remains unknown in a relative high number of patients (Haushofer A.C. et al., 2001) (Appendix 3).

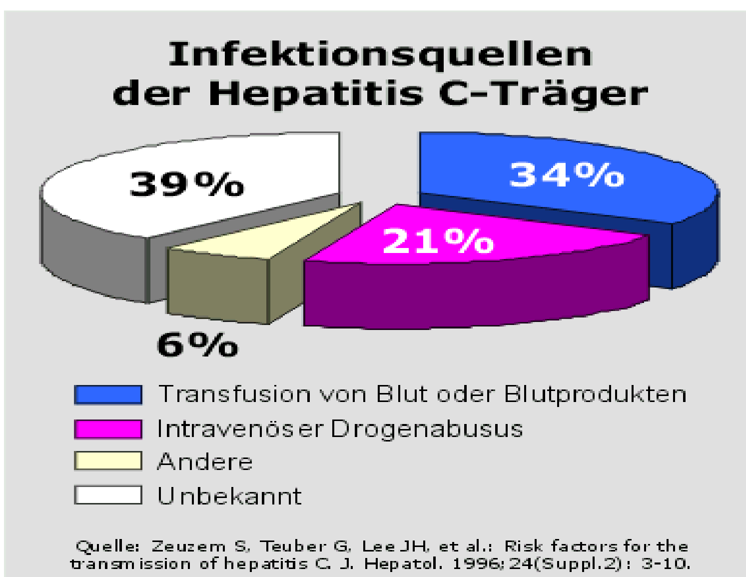


Fig. 10 Sources of HCV transmission in Germany
(from Zeuzem S. et al., 1996)

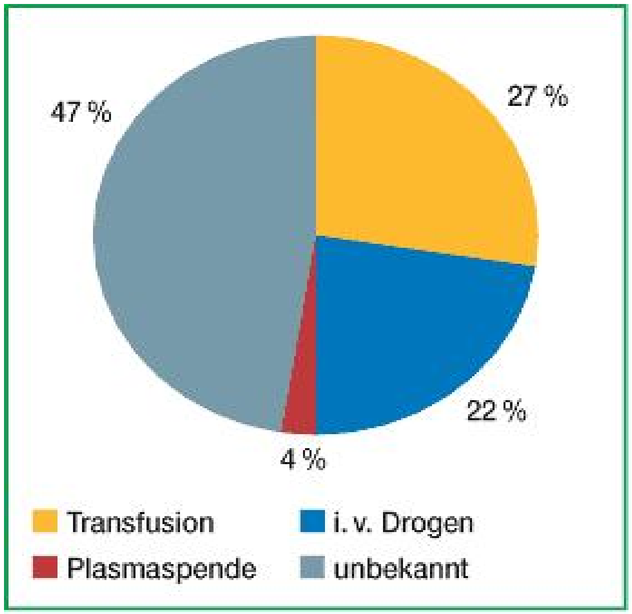


Fig. 11 Sources of HCV transmission in Austria
(from Ferenci P. et al., 2004)

The risk of both sexual and vertical HCV transmission seems to be low (Neumayer A. et al., 1999). The vertical HCV transmission seems to depend on the virus load of the mother (Ruiz-Moreno M. et al., 1999; Danda M. et al., 2002).

1.3.4 Routes of HCV transmission in Egypt

In Egypt, it has been suggested that the HCV epidemic results from the use of unsterile injection equipment during mass treatment of the general population with parenteral antischistosomal therapy (PAT) (Quinti I. et al., 1995; Frank C. et al., 2000).

PAT was extensively practiced in Egypt from the 1930s to the 1980s. The most common PAT drug was tartar emetic (potassium antimony tartarate) which was administered over a few weeks as a series of intravenous injections and was given to more than seven million individuals above the age of 6 years (Maegraith B.G., 1964).

This mode of transmission ended in 1982, when oral praziquantel was introduced for the treatment of schistosomiasis. However, this did not stop the transmission of HCV completely, as shown by the presence of infection in children born after 1982 and by the continued diagnosis of acute hepatitis C among hospital patients in Egypt. Risk factors, such as endoscopy, dental care, and intravenous drug use were reported to be responsible for acquiring HCV infection (El Gaafary M.M. et al., 2005).

In rural areas with both formal and informal health care providers, high risk factors of HCV infection were found to be wound suturing, surgery, abscess drainage, intravenous and urinary catheterization, obstetrical procedures such as cesarean section, uterine curettage, circumcision, and receiving multiple injections. Both the community barber and smoking tobacco with a water pipe (goza) were considered as low risk exposure factors. Less-common community exposures were tattoos, ear piercing, and cautery (Habib M. et al., 2001).

1.4 Epidemiology of HCV infection

Data on HCV epidemiology rely strongly upon HCV seroprevalence studies. Those studies are typically cross-sectional in design and are done in selected populations; e.g. blood donors, injecting drug users, hemophiliacs, hemodialysis patients, patients with chronic liver disease or individuals who received blood transfusions before 1990. Prevalence data may thus be not representative of the community or region in which the populations reside. Population-based studies representative of an entire community are far more useful but those data are not available for most parts of the world.

The incidence of HCV infection is difficult to determine because the majority of infections are asymptomatic initially and serological studies do not distinguish acute from chronic or resolved infection. For some countries, such as US, France, Australia, and Italy, modeled trends in HCV incidence have been reported using age-specific cases of acute disease, death rates from HCC, new HCV infections, and data from cross-sectional survey done within a specific period of time (Shepard C.W. et al., 2005).

1.4.1 Global epidemiology of hepatitis C virus infection

A total of 170 million people representing 3% of the world population are infected with HCV according to data published by the World Health Organization (WHO) (http://ecdpc.europa.eu/health_topics.html). Large variability regarding geographic distribution has been found. Countries with the highest prevalence rates are located in Africa and Asia; areas with lower prevalence include North America, Northern and Western Europe, and Australia (Table 2) (Theodore Sy., 2006).

Table 2: Hepatitis C estimated prevalence and number infected by WHO Region (from Weekly Epidemiological Records, 1999)

WHO region	**Total population**	**Hepatitis C prevalence**	**Infected population**	**No. of countries with no data available**
	(mio.)	**(%)**	**(mio.)**	
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	14.6	21.3	7
Europe	858	1.03	8.9	19
South-East Asia	1.500	2.15	32.3	3
Western Pacific	1.600	3.9	62.2	11
Total	**5.811**	**3.1**	**169.7**	**57**

The prevalence rates of HCV infection vary considerably in different countries and even in different regions of a single country. Prevalence ranges from as low as 0.3% in Sweden to more than 22% in Egypt. Prevalence of HCV infection also varies depending on the subpopulation observed, e.g. injecting drug users (60-90%), hemophiliacs (50-70%), hemodialysis patients (15-60%), and individuals who received a blood transfusion before 1990 (5-10%) (Kew M. et al., 2004).

1.4.2 HCV in Europe

In Europe, the prevalence of HCV infection is estimated to be approximately 1% with a North-South gradient. The majority of infections are found in the Mediterranean region.

From 2005 onwards, the top priority of the European Center of Disease Control (ECDC) has been strengthening and improving the EU-wide disease surveillance system. In collaboration with the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) and the WHO Regional Office for Europe, the ECDC has held meetings with stakeholders to discuss past, current and future activities in this field (ECDC, 2007). At the world hepatitis awareness day 2007, the following data were presented:

- In the EU, 29167 cases were reported with an overall estimated incidence of 8.7 per 100000.
- Males were more affected (62% of reported cases) and the highest incidence was in the age group of 25-44 years (9.74 per 100000).
- Data over the last decade suggest that HCV infection is the EU's most common form of viral hepatitis.

The European plan for HCV control and prevention among IDUs has been implemented in most of the members of the European Union (http://www.emcdda.europa.eu/stats07/inftab02) (Appendix 4).

1.4.3 HCV epidemiology in Austria

The prevalence of HCV in Austria was estimated as 0.5%-1% of the population with an estimation of 80000 infected individuals (Jonas S. et al., 2004). The prevalence of HCV infection in Austria according to the hospital discharge register 1993 to 2000 was 0.7% in the general population. However, Austrian hepatologists have estimated a total of 60000 individuals to be infected (Strauss R. et al., 2003). The highest prevalence was found in Vienna (30.6 per 100000) followed by Upper Austria (24 per 100 000) (Fig.12) (Appendix 5).

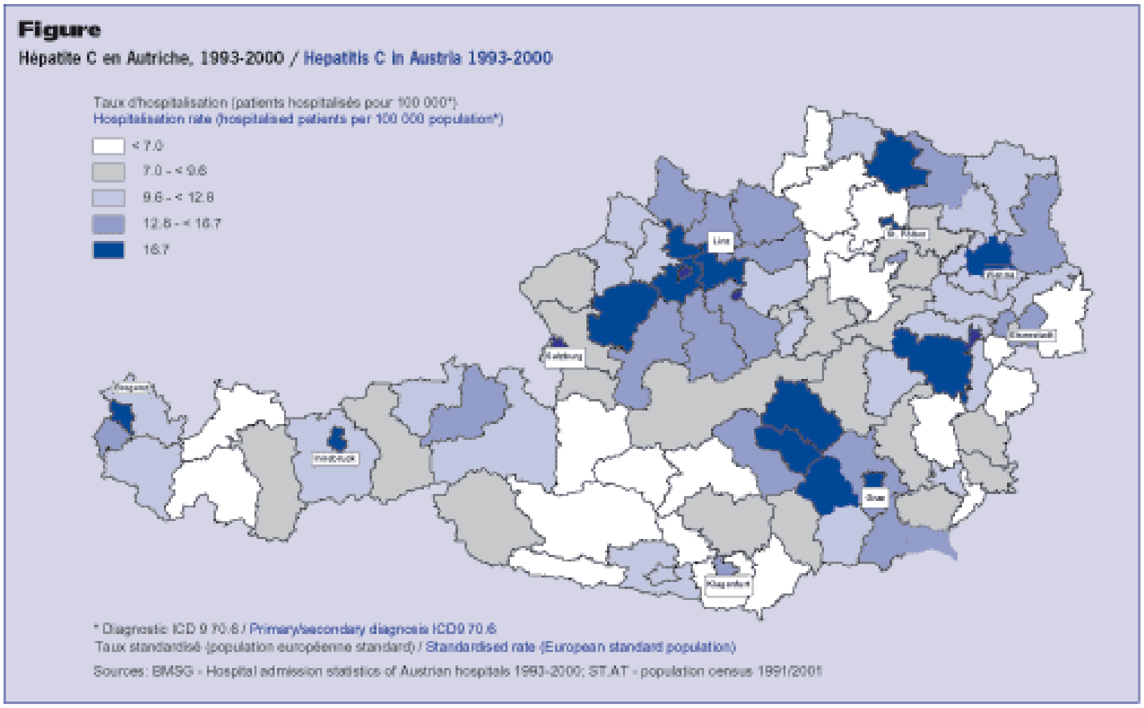


Fig. 12. Hepatitis C in Austria
(from Strauss R. et al., 2003)

About 0.06% of the blood donors in Austria were found to be anti-HCV positive. In 2003, of 208794 blood donors 116 were recorded to be anti-HCV positive (Blood Transfusion Department in Vienna, 2004). The prevalence of HCV infection among IDUs in Austria has been reported to be 48% according to EMCDDA data (Appendix 4).

The prevalence of HCV infection in blood donors in Styria was 12.27 per 100000 in 2001 (Available at: www.meduni-graz.at/UBT/organisation/ infektionsserologie.htm).

However, the registered cases with HCV infection in hospital admission decreased to 11.8 per 100.000 in 2004 and 10.9 per 100.000 in 2005 (Statistik Austria, 2006) (Appendix 6).

In 2000, the number of deaths because of chronic liver disease and liver cirrhosis was 1644 (1157 males and 487 females), the number of deaths because of liver cancer 704 (459 males and 245 females) (Hackl M. and Bayer P., 2004).

In 2007, the death rate because of hepatitis, liver cirrhosis, and HCC was 10.9 per 100000 of the Austrian population (Appendix 7). HCV infection contributes to 40% of liver cirrhosis and 60% of HCC as well as 30% of liver transplantation in Austria (Stauber R., 2003).

1.4.4 HCV epidemiology in Egypt

The prevalence of HCV infection in Egypt differs from region to region and also between the subpopulation groups. In the Egyptian governorates survey, HCV antibodies were detected in 24.8% of surveyed individuals. The maximum rate of HCV infection (28%) was found in the Nile Delta and the lowest (6%) in Alexandria (Fig. 13).

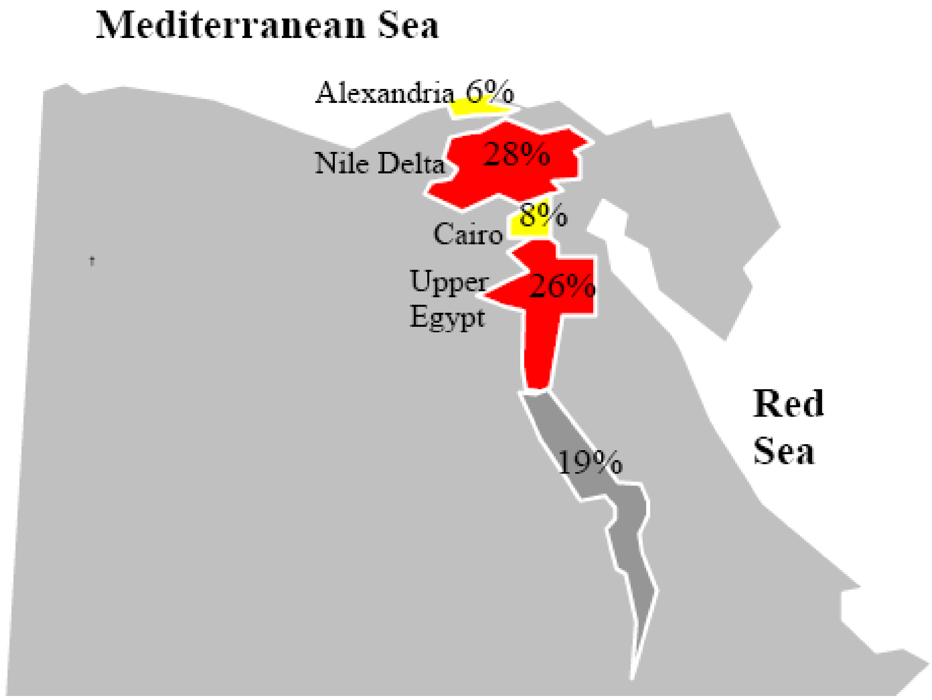


Fig. 13. Prevalence of HCV antibodies among individuals of 10-50 years of age according to the geographical area
(Ministry of Health and Population, 1996)

The HCV seroprevalence in blood donors from the 24 governorates ranged from zero in North Sinai governorate to 38.2% in Beni Suef (Arthur R.R., 1997) (Appendix 8).

In 1992, screening tests for HCV antibodies were carried out in seven different populations of children and adults living in a rural village in Egypt. Anti-HCV was found in 12.1% of primary schoolchildren, 18.1% of residents of the village, 22.1% of army recruits, 16.4% of children with hepatosplenomegaly, 54.9% of hospitalized, multitransfused children, 46.2% of adults on hemodialysis, and 47.2% of adults with chronic liver disease or hepatoma. These data demonstrate the magnitude of HCV infection and its importance in chronic liver disease in Egypt (Abdel-Wahab M.F., 1994). In another study, HCV infection was reported to be 31% among Egyptians applying to work abroad (Mohamed M.K. et al., 1996).

The prevalence of anti-HCV antibodies increases with the age of the individuals. The HCV prevalence in Cairo and in the Nile Delta is lower in children than in adults (Fig.14) (Frank C. et al., 2000).

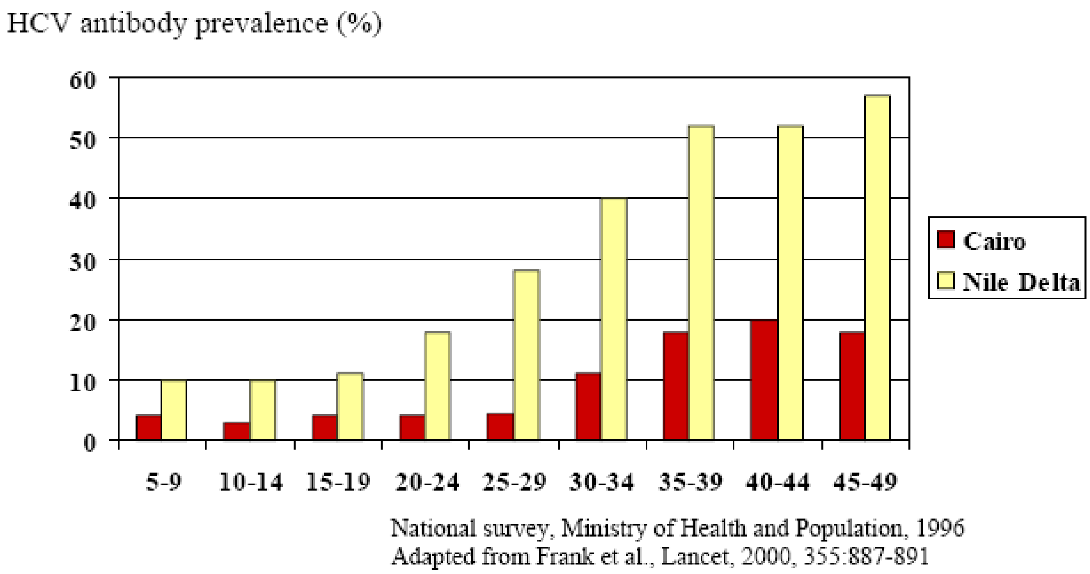


Fig. 14. Distribution of HCV antibody prevalence in Cairo and the Nile Delta according to the age of individuals

1.5 Diagnosis of HCV infection

For detection of HCV infection, there are unspecific and specific tests available. The liver enzymes, especially the alanine aminotransferase (ALT), are unspecific parameters for detection of an infectious hepatitis. The ALT additionally contributes to the monitoring of HCV infection and the evaluation of the efficacy of anti-HCV therapy.

Histological investigation of the liver-biopsy specimen remains the standard for determining the activity of liver disease.

1.5.1 Indirect tests

The enzyme immunoassay (EIA) is the primary serologic assay for detection of HCV infection. The currently used third generation enzyme immunoassays contain core protein as well as nonstructural proteins 3, 4, and 5. EIAs can detect HCV antibodies within 6 to 10 weeks after infection. The advantages of the EIA assay are easy to use and relatively inexpensive. The disadvantages are the extended serodiagnostic window period and weak or missing antibody production in immunosuppressed patients. The EIA is usually employed to determine the prevalence rate in a specific target population.

Because of limited specificity each positive result obtained by the EIA must be confirmed by molecular detection of HCV RNA (Fig. 15). If HCV RNA is not detectable, an immunoblot assay (recombinant immunoblot assay or Western blot assay) may be performed in order to reveal unspecific reactivity of the EIA.

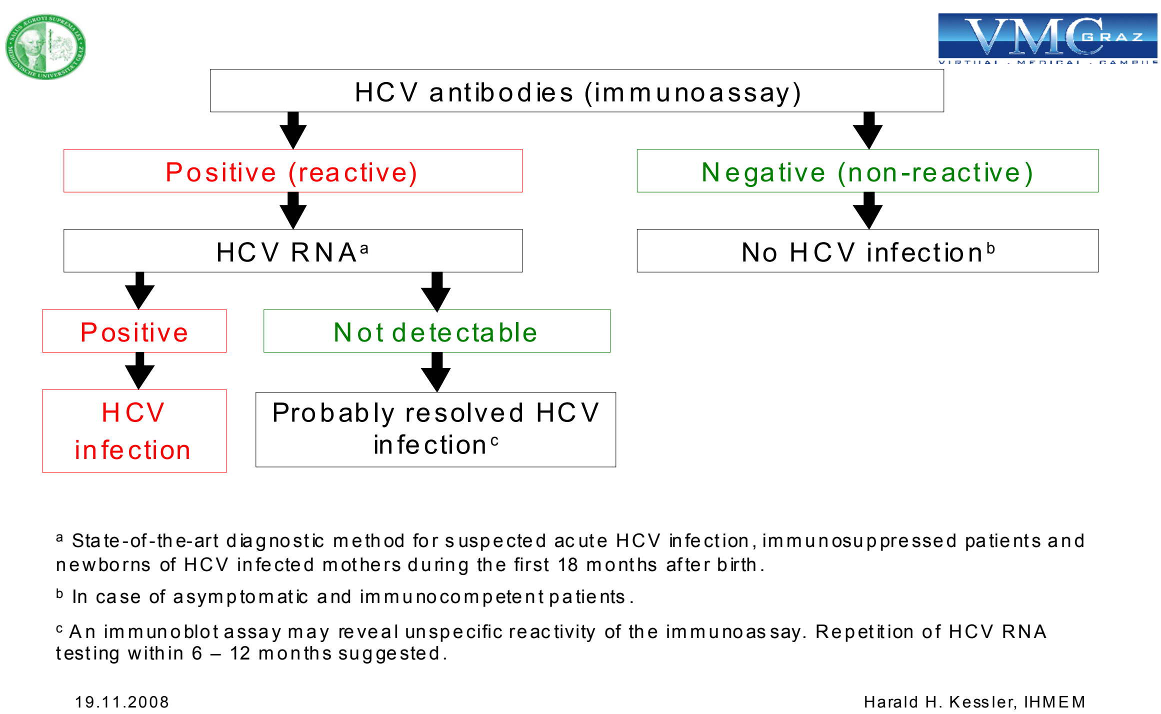


Fig. **15**. Flowchart showing the primary diagnostic steps for detection of HCV infection (Kessler H.H., modified from Upgrade der Leitlinie, AWMF-Register-Nr.: 021/012, Kompetenznetz Hepatitis, 2008)

1.5.2 Direct tests

Molecular assays are designed to determine the presence of HCV RNA. The majority of molecular assays are based on target amplification by reverse transcriptase polymerase chain reaction (RT-PCR) or transcription-mediated amplification (TMA) and on signal amplification by the branched DNA (b-DNA) assay. Qualitative assays provide only a positive (presence of HCV) or negative (absence of HCV) result; quantitative RT-PCR measures the amount of virus.

Viral genotyping is of maximum importance for the duration of anti-HCV therapy (see Heading 1.6). Different methods are available for the genotyping of HCV, most of which are based on amplification with the PCR assay.

Table 3: Diagnostic tests for hepatitis C

Test	Purpose	Comments
Anti-HCV antibodies	Indicates past or present infection but does not differentiate between acute, chronic or past.	High false-positive rate. Positive EIA must be confirmed by HCV RNA detection. Detects anti-HCV antibodies in 80% of patients within 5-6 weeks of onset of disease. Late seroconversion may occur.
HCV RNA	Detects presence or absence of viral RNA. Determines the HCV load. Used to monitor patients on antiviral therapy.	Detects virus 10-14 days after infection. False positive and false negative results may occur from improper handling, storage, and contamination of test sample.
HCV core antigen	Detects presence or absence of virus.	May detect virus 1-3 weeks after exposure. Under evaluation.
HCV genotype/subtype	Determines the duration of therapy. May clarify way of transmission.	Genotype 1 and possibly 4 are associated with a lower response to antiviral therapy.

1.6 HCV treatment

The duration of anti-HCV therapy depends on the HCV genotype. Phylogenetic analysis of the complete genomic sequence of genotype 4 revealed a closer relationship between genotype 4 and genotype 1 than with other genotypes, as evidenced by the short branch and slightly greater degree of nucleotide sequence similarity between genotype 1 and 4 than that found between other genotypes (Bhattacherjee V. et al., 1995; Chamberlain R.W. et al., 1997). Consequently, it has been recommended that patients infected with chronic HCV genotype 4 should be treated similarly to patients infected with genotype 1 (Mohammad S.K. et al., 2004).

The response to therapy can be evaluated by the HCV RNA level (virological response) and the ALT level (biochemical response) (Fig. 16). Today, the combination of pegylated interferon alfa (PEG-IFNα) and ribavirin (RV) is the standard therapy.

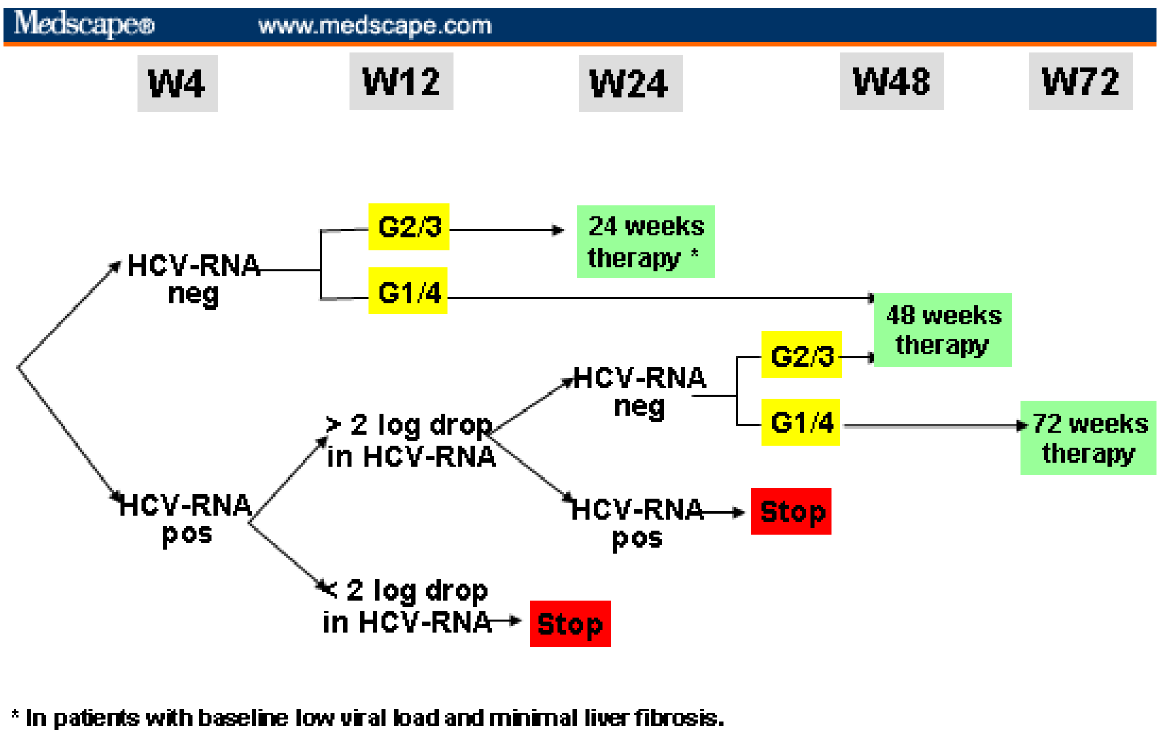


Fig. 16. The algorithm of HCV infection treatment

Patients infected with HCV genotype 2 and 3 respond better to the combination therapy than those infected with genotype 1. Data regarding HCV genotype 4 response rates are limited and controversial. Nevertheless, in Egypt and the

Middle East, high sustained virological response rates have been reported in patients infected with HCV genotype 4 and treated with the combination therapy consisting of PEG-IFNα plus RV for 48 weeks (Hasan F. et al., 2004; Roulot D. et al., 2007; Ferenci et al., 2008).

Alternative medicine for HCV infection is heavily used in Egypt. Silymarin, vitamin B complex, Hepamax, Levanox, Levarosa, biphenyl dimethyl dicarboxylate (DDB), and other antioxidant herbal supplements are prescribed to the patients and they take it life long. Other patients do not apply any therapy with the argument “let the virus sleep and do not awake it”.

1.7 Prevention strategy of HCV infection

Immunization against HCV infection is not available. In general, there are two levels of prevention. Primary prevention activities can reduce or eliminate potential risk for HCV transmission from: (a) blood and blood products, (b) high-risk activities as injecting drug use, and (c) percutaneous exposures to blood in health care and other (e.g. tattooing, body piercing) settings. Furthermore, identifying individuals at risk but not yet infected with HCV provides opportunity for counseling on how to reduce their risk for becoming infected. Secondary prevention activities can reduce risks by identifying HCV-infected individuals through adequate diagnostic testing and by providing appropriate medical management and antiviral therapy.

In Austria prevention strategies have been implemented in the national consensus (Kessler H.H., 2005) and there is also a national strategy plan for HCV control among IDUs (National strategies EMCDDA country Profile Last update December 2002 available at: http://www.emcdda.europa.eu/stats07/inftab02).

In Egypt, the MOHP is trying to establish consensus regarding the current hepatitis situation and research techniques. The MOHP has a national plan to minimize the risk factors of HCV transmission and started a treatment program in Alexandria, Cairo, and Assiut (El Katsha S., 2006; Talaat M. et al., 2006).

1.8 Future intervention for HCV antiviral strategies

Each step of the HCV live cycle may represent a target for antiviral intervention: (1) binding to cell surface receptor and internalization of the host cell, (2) cytoplasmic release and uncoating of the viral RNA genome, (3) IRES-mediated translation and polyprotein processing by cellular and viral protease, (4) RNA replication, (5) packaging and assembly, and (6) virion maturation and release from the host cell (Moradpour D. et al., 2004).

Specific inhibitors of the biochemically and structurally well-characterized NS3 serine protease as well as both the RNA helicase and the NS5B RdRp are currently being developed as antiviral agents and the first candidates are already in clinical trials.

Gene therapy strategies aimed at inhibiting HCV replication and gene expression are currently being explores in various experimental systems.

Immunotherapeutic strategies aimed at enhancing the cellular immune response against HCV are currently being investigated (Stauber R. and Kessler H.H., 2008).

1.9 Aims of the study

In this study, the national plans for HCV control and prevention strategies in Austria and Egypt were compared. Data were obtained from health system information and published studies. Furthermore, the response to the combination standard therapy with PEG-IFNα and RV in patients with HCV genotype 4 infection was evaluated and compared to that in patients with HCV subtype 1b infection.

2 MATERIALS AND METHODS

2.1 Sources of information

Information was collected from published articles in scientific journals, from brochures available in health care settings, and from local regulations in Austria and Egypt. The Egyptian Central Laboratory, the National Liver Institute in Cairo, and the Preventive Medicine and Health Promotion Department of the Egyptian Ministry of Health and Population were visited. Details about local activities including prevention of HCV transmission which were not yet published were obtained through interviewing health experts and HCV project managers in Cairo.

2.2 Patients

A total of 36 patients with chronic HCV infection and anti-HCV therapy at the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, were studied. Patients received treatment with PEG-IFNα (Pegasys; Roche, Basel, Switzerland), 180 µg/kg/week, subcutaneously in combination with oral RV (Copegus; Roche) 1000 or 1200 mg/day, according to body weight (cutoff 75 kg). Patients were treated for 48 weeks. Eighteen patients with HCV GT 4 and another 18 patients with HCV ST 1b were randomly matched.

2.3 Laboratory tests

2.3.1 Clinical chemistry parameters

The serum ALT level was tested with the ALT assay for the Hitachi System 912 (Roche Diagnostics, Mannheim, Germany). If the ALT level exceeded 35 IU/L in a female patient and 50 IU/L in a male patient, respectively, it was considered abnormal. The blood count including the differential blood count was determined on the Cell-Dyne 3500 R (Abbott, Abbott Park, Ill.).

2.3.2 Molecular parameters

The HCV RNA was quantified with the COBAS AmpliPrep/COBAS TaqMan HCV test (Roche Molecular Systems, Inc., Branchburg, NJ), which includes an automated sample preparation on the COBAS AmpliPrep instrument followed by real-time PCR and detection on the COBAS TaqMan instrument, according to the manufacturer's package insert instructions. This assay has a lower limit of detection of 15 IU/ml. Positive results below this HCV RNA concentration are referred to as “low-positive”. HCV genotypes and subtypes were determined by using the TruGene HCV 5´NC Genotyping Kit (Bayer Health care LLC, Tarrytown, NY) according to the manufacturer's package insert instructions. Amplification products generated by the COBAS Amplicor HCV Monitor Test (Roche) were used.

2.4 Response to anti-HCV treatment

The early virological response (EVR) was defined as undetectable HCV RNA at week 12 after the start of treatment. The sustained virological response (SVR) was defined as undetectable HCV RNA at the end of treatment and up to 24 weeks after the end of treatment. The relapse was defined as reappearance of HCV RNA after the end of treatment. If the HCV RNA reappeared during treatment, it was considered as breakthrough.

2.5 Comparison studies

Patients with HCV GT 4 were compared to those with HCV ST 1b. The ALT level, the hemoglobin concentration (HB), and the neutrophil count were compared at the baseline (BL) and at weeks 12, 24, 36, and 48 of the treatment and week 24 of follow up.

The serum HCV RNA load was tested at weeks 12, 24, 36, and 48 of the treatment and week 24 of follow up. The EVR, the end of treatment response (EOTR), and the SVR were compared.

Adverse effects of the therapy were recorded for each patient.

2.6 Statistical analysis

For descriptive statistics, absolute numbers and percentages were recorded and the mean, median and standard deviation were calculated. The comparison between the two groups of patients (patients with HCV GT 4 vs. those with HCV ST 1b) was done using chi-square test and the *p*-value of ≤ 0.05 was considered as statistically significant.

3 RESULTS

3.1 National strategies of HCV prevention

In Austria, the national strategy aims at improvement of patient safety through prevention and control of health care associated infections.

In Egypt, the MOHP established a five years' national strategy aiming at prevention of nosocomial transmission through focusing on medical behavior to ensure safe medical procedures and minimize the risk factors of HCV transmission through informal health care providers by media and awareness campaign (available at: http://www.ems.org.eg/esic/index.htm).

3.1.1 Strategies to prevent HCV transmission

Austria has established specific strategies to prevent HCV transmission among selective target groups including health care providers and infected individuals and their families. In addition, at provincial level, the drug policy targets include awareness of blood borne diseases and prevention of transmission among IDUs. Information about HCV infection is integrated in the HIV, HBV and STD awareness program and discussed during the IDU counseling sessions. The needle exchange-program ensures the hygienic use of drug injecting utensils and safe disposal of contaminated needles. All IDUs access vending machines with automatic dispense of the injecting equipment pack. Brochures are distributed at liver disease centers, at national insurance centers, and at blood donor centers. Some of the national insurance centers offer counseling and information about HCV infection to the patients and their families. Seminars and training sessions are offered to the medical staff in order to increase their knowledge about HCV risk factors, diagnosis, and therapy. In addition, self-help groups support those infected and their families with the necessary medical and social information.

In Egypt, training programs for the health care workers are carried out in three governorates including Cairo, Alexandria, and Assiut. These programs contain awareness issues for blood born diseases including HCV infection such as screening of blood and blood products, central management, reporting system, supervision of laboratory equipment, supplies, training, and monitoring procedures, and establishment of protocols for infection control. Furthermore, health care personnel is trained on safe injection practices, destruction of disposable needles, adequate disposal of contaminated invasive materials, adequate sterilization of reusable materials, universal precautions and barrier techniques, and adequate counseling of patients and their families.

Public education issues include awareness regarding contaminated materials, the administration of injections by nonprofessionals, and practices such as shaving, circumcision, and body arts. Brochures about the mode of HCV transmission are published in a simplified way to be understood especially from those people who are living in rural and suburban areas (Appendix 9). Self-help groups do not exist in Egypt.

3.1.2 Control of HCV infection

3.1.2.1 Health care quality and safe medical procedures

The Austrian Society for Quality Assurance and Quality Management in Medical Care (Österreichische Gesellschaft für Qualitätssicherung und Qualitätsmanagement in der Medizin; available at: http://www.oeqmed.at/fileadmin/Downloads/Muster_Evaluierungsfragen.pdf) supervises all health care providers. It has the authority to close health care centers if they do not meet the Austrian norm of hygiene and health care quality.

The Egyptian MOHP has established an Infection Control (IC) program to improve the quality of care and to reduce transmission of hospital-acquired infections. The implementation of the IC program started in 72 hospitals of 13 governorates in late 2001. During this program, 235 IC professionals were trained (Talaat M. et al., 2006). In 2004, the Egypt Service Provision Assessment (ESPA) collected detailed information on health care infrastructure, resources, and management systems including supervision and support systems for quality assurance and infection control (available at http://www.mohp.gov.eg/Sec/Statistics/English-Key-Findings-ESPA.pdf). Facilities checked included a total of 304 rural health units, 100 non governmental organization (NGO) facilities, 71 mobile units, 69 mother and child health centers and urban health units, 68 general, district and integrated hospitals, 34 health offices, and 13 fever hospitals. The survey represented all facilities at the regional level. The ESPA found that 54% of the facilities had the necessary equipment or chemicals for sterilization or high level disinfection (HLD) and 35% had a timer and at least one adequately trained staff member. In about one-tenth of the facilities, standard operation protocols for sterilization or HLD were available (Fig. 17). Facilities with all components for sterilization or HLD varied from 60% of mobile units to 8% of health offices.

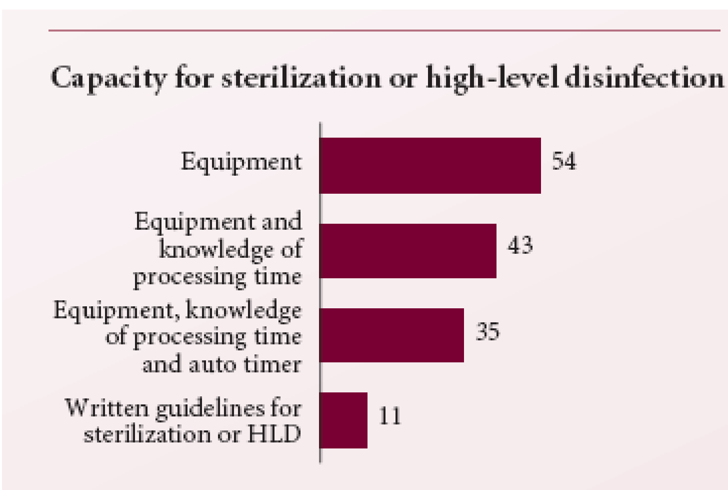


Fig. 17. Capacity for sterilization or high-level disinfection in Egypt (%)

The ESPA assessed conditions and practices for infection control in each facility. Only 4 percent of all facilities had all items needed for infection control in all of the service delivery areas assessed. Hand-washing soap and clean latex gloves were those items most commonly lacking. Half of the facilities had sharps boxes available in all relevant areas. Disinfectant solution was available in about two-third of all relevant service areas (Fig. 18). About 8 of 10 facilities used appropriate systems for disposal of contaminated waste, such as collection and disposal by an outsourced service and incineration. However, only 23% of the facilities ensured that contaminated waste was kept in a protected environment prior to disposal. Practices for immunizations followed standards for good quality. Almost all facilities used new syringes and needles for injections. Sharps boxes were more widely used by providers of immunizations (in more than 85% of injections) than by providers of therapeutic injections (in more than 60% of injections).

Fig. 18. Items available for infection control in Egypt (%)

3.1.2.2 Screening Test

In Austria, all blood donors are screened on HCV infection. Furthermore, all IDUs attending a drug withdrawal or socio-medical center are offered to be screened voluntarily.

In Egypt, blood donors, military recruits, and individuals who intend to work in Saudi Arabia, Gulf countries, and in private Egyptian companies are screened on HCV infection.

3.1.2.3 Treatment of HCV

In Austria, HCV ST 1b and HCV GT 4 infections are treated by combination therapy with PEG IFN alpha and RV for 48 weeks according to the Austrian Consensus statement (Austrian Consensus Statement, 2005). In Egypt, the MOHP supports the international guideline of HCV treatment with PEG IFN alpha and RV for those who are treated in the governmental sector (MOHP, teaching and university hospitals and the Ministries of interior and Defense). However, the Egyptian hepatitis committee applies this kind of therapy only in selected centers (Hepatitis C Trust, 2004). There is no general consensus for treatment of HCV infection.

3.2 Financial coverage of HCV diagnosis and treatment

In Austria, expenses for anti-HCV therapy are covered by the social health insurance. The chief medical officer of the social health insurance approves the treatment if HCV diagnosis was managed and HCV treatment will be performed by a specialist in the field. Expenses for liver transplantation are also covered if necessary. In 2001, the Austrian Ministry of Social Security and Generations established funds for supporting persons who were infected with HCV through contaminated blood and blood products (Ministry of Health and Women, 2001).

In Egypt, the MOHP covers the expenses for diagnosis and treatment of individuals infected with HCV who are employed by the government. For infected individuals working in private business, on the ground of collective contract or seasonal work, the health insurance decides which drugs will be administered ((MOHP et al., 2002; Abdel-Hamid M., 2007; Reem L., 2007).

The majority of infected individuals pay fees for health services. In 2007, more than 45000 patients visited treatment centers and received consultations. The government has allocated EGP 240 million which equals to EUR 3.5 million towards HCV treatment and 90% of the 14000 individuals needing treatment are supported by the government and the health insurance. There are different organizations and foundations which help in supporting individuals with HCV infection additionally. Organizations include the Egyptian Liver Care Association, charity organizations, private foundations, and international organizations such as the Orascom Group, the Sawiris Foundation, the EFG-Hermes Foundation, the USAID, the John Hopkins Communication for Healthy Living, Roche, Schering, GlaxoSmithKline, and the Health Forum volunteers.

3.3 Management of HCV patients

3.3.1 Austria

The indication of anti-HCV therapy is given according to the clinical laboratory report. The determination of the HCV genotype is obligatory for the therapy duration. In patients with HCV genotype 1 or 4, the level of serum or plasma HCV RNA is determined at the start of therapy, at week 12 after the start of therapy (optional detection after 4 weeks), at week 24, at week 48, and at 6 months after the end of therapy (Austrian consensus 2005). Patients are usually treated in the outpatient department. Liver biopsy is not obligatory but it is performed selectively.

Liver transplantation, if necessary, is performed at specialized departments at the University hospitals in Graz, Innsbruck, and Vienna. The decision is made by a committee consisting of a surgeon, a gastroenterologist, an anesthetist, and a psychologist. The outpatient department provides the postoperative care.

3.3.2 Egypt

Patients who are involved in a research project conducted by the MOHP and an international agency are well-managed according to international guidelines of HCV treatment. The Physicians Syndicate authorities organize meetings with the National Insurance authorities to develop guidelines for patient management.

In all other patients, the medical doctor decides the kind and the duration of therapy regarding to the economic status of the patient. Wealthy patients can afford standard treatment but people with low income receive alternative treatment. Some patients do not receive therapy at all.

Information obtained from interviewing Egyptian health professionals

Dr. Nabil Riyad, a surgeon who uses herbals for treatment of HCV infection, stated that he achieved success in more than 90 percent of the patients. The anti-viral herbal medicines include glycyrrhizin (licorice root powder) which may induce the production of natural interferon, may protect and heal liver cells from damage, and may act as an anti-allergic, anti-inflammatory and detoxifying substance. Other virostatics include olivessence capsules (olive leaf extract) which may interfere with the specific amino acid production processes essential for the life cycle of the virus. They also may interfere with viral invasion by inactivating the virus and prohibiting its shedding, budding or assembly at the cell membrane. Herbs used to cure liver cell inflammation include Schizandra fructus (its synthetic analogue is biphenyl dimethyl dicarboxylate DDB, the famous yellow pill) which may lower liver enzymes rapidly and may improve liver cell function. Other herbs include ligustrin and dandelion root. Immune stimulators include Cordyceps sinensis (caterpillar mushroom), Reishi mushroom (used by

Tibetan monks to keep their bodies and brains in top condition), and Astralagus membranaceus root powder. Dr. Riyad prescribes these herbs as powder, capsule or syrup. Unfortunately, most of these herbs are not available in Egypt, so he tells the patients to try getting them from abroad. Most of the patients can afford their medicine and receive it. Additionally, Dr. Riyad said that herbal therapy would be relatively inexpensive. The expenses of a one year-treatment are just 50% of a single interferon injection. Furthermore, the overall quality of life of the patient improves. Patients who receive interferon therapy suffer from several in contrast to patients receiving herbal medicine. Dr. Riyad advised that therapy with herbals should be supervised by a certified physician. He admits that visiting the Attar (herbalist) without a physicians's prescription may be very dangerous.

Dr. El-Tabbakh, medical doctor at the National Liver Institute in El Menoufyia, said, “Most of our patients are infected with HCV. Usually they show up when it is too late to try to eradicate the virus with interferon. They are end-stage patients who have been suffering from HCV for 20 or 30 years. They have liver cirrhosis and are vomiting blood. We have to work on the symptoms, try to stop the vomiting.”

Dr. Omran El-Bishlawi, senior researcher at the National Hepatology and Tropical Medicine Reasearch Institute in Qasr El-Aini, Cairo, believes that interferon may often be futile. He said, “There is nothing to treat as long as HCV infection does not show symptoms.” He added that interferon is a naturally existing cytokine that boosts the immune system. He does not check whether the patient has a low or a high interferon level. Interferon has severe side effects ranging from retinal fibrosis to bone marrow deterioration and psychological depression that may lead to suicide. He concluded, “Above all, the course of treatment takes LE 80.000 per year (€11,500); who can afford that?”

Dr. Hatem Qunswa, director of El Menoufyia Health Centre, brushed HCV off as a ridiculously weak virus. It would be easily destroyed at temperatures exceeding 60°C. Only 50 percent of the patients would develop chronic liver disease which will proceed to cirrhosis within 20 years or more. People should not worry. He said, "It is not as dangerous as another virus; it can be overcome if the immune system is strong." He added, "We are religious people. We know that the virus can do something to us 20 or 30 years later and we know that God will take us whenever he deems it suitable. So why worry?" Dr. Qunswa does not believe in interferon as HCV therapy. He said, "A medication which has a success rate of 50% and half of those who respond to the treatment will relapse within six months should not be considered as a medication. Medicine should cure at least 80 – 90% of the patients. He stated, "Interferon causes serious side effects such as decrease of leucocytes and immune-inflammation in the liver and blood cells and may also lead to the formation of a tumor. There is no cure for any virus because viruses mutate and are resistant to the immune response." To the question of what kind of treatment he would recommend, he stated, "It is not your business what I prescribe."

Dr. Amr Qandil, director of the Infection Control Program at the Ministry of Health, believes that HCV is not dangerous. He said, "HBV is much more dangerous than HCV. HCV can only be controlled through educating the people." He is proud of implementing the IC program in 70 hospitals and there are IC staff members in each department.

Dr. Mohammed Saurwat, vice director of the IC program at the MOHP, said that there is no cure for this disease, so why should we spend money for treatment without guarantee for an effective outcome. Most of HCV infected individuals do not exhibit symptoms; why should they be treated? He stated, "No pain no gain."

Dr. Alaa Eddin Ismail, Dean of the National Hepatology and Tropical Medicine Reasearch Institute in Qasr El-Aini, Cairo, said that cautions generating panic would not be good to anyone. "HCV is not the end of the world. It does not affect the quality of life of a patient except at its end stages.” He mentioned that not all patients need treatment. “One third of the patients have normal liver enzymes and only need to take anti-oxidants and a lot of rest. Another third of the patients have already reached the stage of cirrhosis and vomit blood. It is too late to cure them; only the symptoms are treated. Only one third of the patients need interferon and ribavirin, only if they are fit to take them.” Although the response to treatment would not be guaranteed, Ismail believes combination therapy with PEG-IFNα and RV to be the only available therapy to patients. In Egypt, the ministry pays the full amount of money to patients eligible for the treatment. However, the physician prescribes only interferon in order to save money. Dr. Ismail concluded, “The seven percent difference in efficiency is negligible.”

Dr. Hosni Salama, professor of hepatology at Cairo University, has gone back to the ancient Egyptians for inspiration. The ancient Egyptians used to bury patients in hot sand. He said that a temperature of 40°C would be a signal for all the body’s natural immune cells to wake up and work efficiently. This is where thermotherapy comes from. He explained that interferon would boost immunity and only 20 percent of patients would need it. Because of the high expenses, only 3 or 4 percent of patients would afford it. And it won’t be efficient despite it would be the only treatment available. Three years ago, he carried out an experiment in collaboration with an Italian team of doctors. They obtained the consent of 22 patients and raised their blood temperature to 41°C to 42°C for an hour. Dr. Salama concluded, “After a few weeks of treatment, 16 of the 22 patients were found to be completely free of HCV.”

In Egypt, people easily believe that there are magic cures for HCV. For instance, a veterinarian announced that she would be able to cure HCV successfully using the urine of a suckling camel mixed with milk from the mother camel.

3.4 Health information system and documentation

In Austria, it is obligatory to report HCV infection to the Austrian Health Information System. However, this system does not work well because several physicians do not report. The reason is that they consider treating medical records confidentially; therefore, several patients' data are missing. Currently, an electronic documentation system is developed including anonymous documentation and a recall system.

In Egypt, the health information system is based on the statistical data obtained from the governmental health services. In the private sector and in marginalized areas, documentation and administration techniques are lacking.

3.5 Burden of the HCV infection

It may be a long and difficult way for the patient from the detection of abnormal liver enzymes or the incidental detection of HCV infection to the specialized center. Under treatment, side effects may be the reason for absence from work, unemployment, social conflict, social stigma and/or decreased quality of life. Furthermore, it may be difficult for the patient who is not able to work getting financial support from the social authorities.

In Egypt, expenses for the treatment are not affordable by the majority of the patients. Sometimes, they invest all what they have to cover these expenses. Chronic HCV infection is not a stigma for those infected but the fear that their families may have insecure income in future may cause a psychological stress. For the majority of the patients, HCV infection does not affect the quality of life as much as in Western countries. However, especially among farmers, the disease may be a heavy burden for their families.

3.6 Informal health care providers in Egypt

The informal health care providers include the traditional midwives, male health barbers who provide first aid and wound care, trained injectionists, pharmacy assistants, and nurses who provide services such as injections to neighbors on an informal ground. Informal health care providers are widely known throughout Egypt.

To the question why they use informal providers**,** the villagers reported that the main reason for visiting informal health care providers would be that they are accessible during day and night. The most respected providers had been practicing in the villages for 30 years or more and were recognized for their experience. Informal health care providers, some of whom have facilities for treating patients in their own homes, would charge far less than private doctors and would often accept whatever a patient could afford.

The following comments indicate peoples' trust in informal health care providers:

"The doctor cannot compete with him because he does not have such a lot of experience."

"Even if I would live next door to a doctor and he would be a professor, I would never go to him for treatment."

"Mohammed is a very experienced with circumcising boys; all of those who work in the health care unit have their children circumcised through him."

Furthermore, they stated that physicians at rural health units would be young and inexperienced. Villagers still have a great respect for age and experience (El-Katsha S. et al., 2006).

3.7 Comparing the response to treatment in patients with HCV ST 1b infection to those with HCV GT 4 infection

3.7.1 Characteristics of HCV patients

Characteristics of patients are summarized in Table 4. Patients infected with either HCV ST 1b or HCV GT 4 had a comparable age range. There were more males than females included in the study. The mean body weight of patients infected with HCV GT 4 was higher than those infected with HCV ST 1b.

Table 4: Characteristics of HCV patients

	HCV ST 1b	HCV GT 4
Age range (years)	22-70	31-57
Sex (M/F)	11/7	15/3
Weight (kg) and mean standard deviation	74 ±11	83 ±15

3.7.2 Clinical chemistry parameters

ALT and HB levels and neutrophils were measured at the baseline (BL) and at weeks 12, 24, 36, and 48 of the treatment and week 24 of follow up (Tables 5 and 6).

Table 5: Results for clinical chemistry parameters for patients infected with HCV GT 4

	BL	W 12	W 24	W 36	W 48	W 72
ALT (U/L)	107.5	47.1	38.8	38.9	49.9	40.5
HB (mg/L)	14.6	12.2	12.0	12.0	12.6	14.4
Neutro (cells/μL)	2.2	1.3	1.4	1.5	1.9	2.6

BL, baseline; W, week; ALT, alanine aminotransferase; HB, hemoglobin; Neutro, neutrophils

Table 6: Results for clinical chemistry parameters for patients infected with HCV ST 1b

	BL	W 12	W 24	W 36	W 48	W 72
ALT (U/L)	91.0	54.5	61.4	66.7	49.6	65.8
HB (g/dL)	14.9	11.2	11.9	11.8	12.7	14.7
Neutro (cells/μL)	3.8	1.7	1.8	1.7	2.3	3.6

BL, baseline; W, week; ALT, alanine aminotransferase; HB, hemoglobin; Neutro, neutrophils

At BL, the mean ALT level was slightly higher in patients infected with HCV GT 4 (107.5 U/L) than those infected with HCV ST 1b (91.0 U/L). There was a decrease of mean ALT levels during the course of treatment in both groups (Fig. 19).

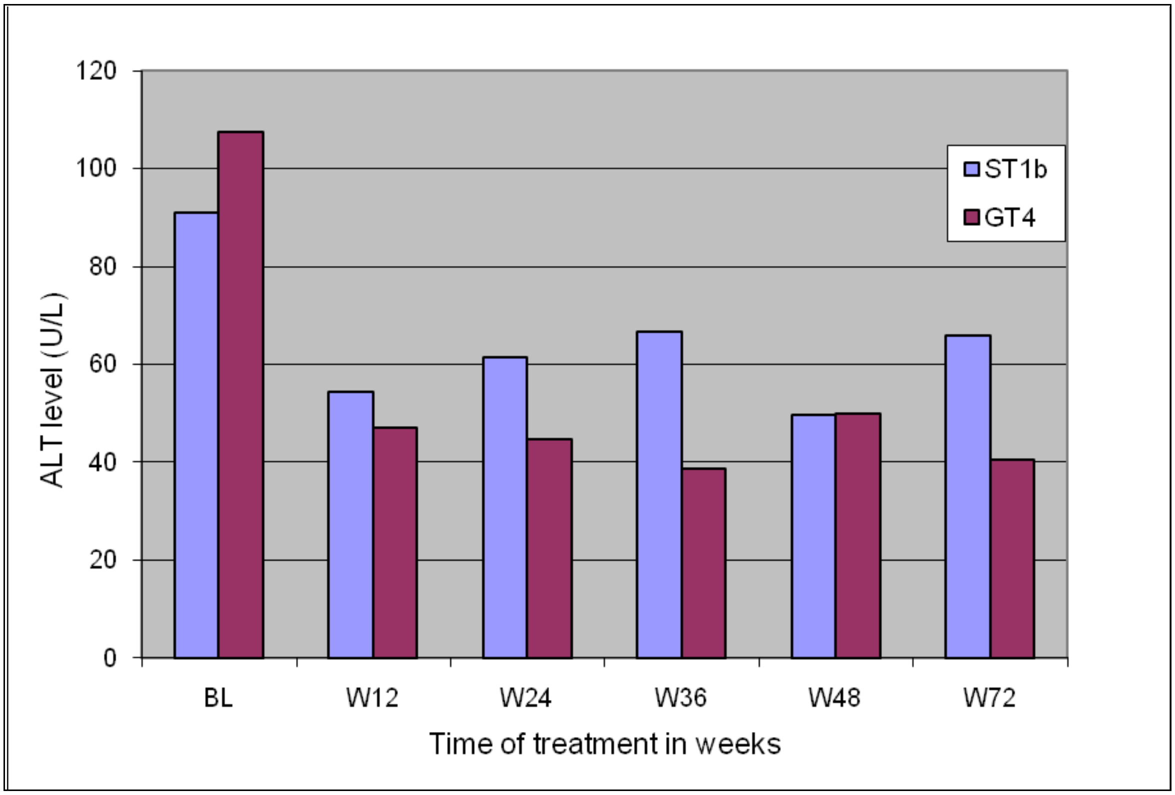


Fig. 19. Mean ALT levels in patients with HCV GT 4 infection and those with HCV ST 1b infection during combination therapy with PEG-IFN and RV.
ALT, alanin aminotransferase; BL, baseline; W, week

There was almost no difference in hemoglobin levels between the two groups. Hemoglobin levels decreased slightly during treatment but increased again during the follow-up period (Fig. 20).

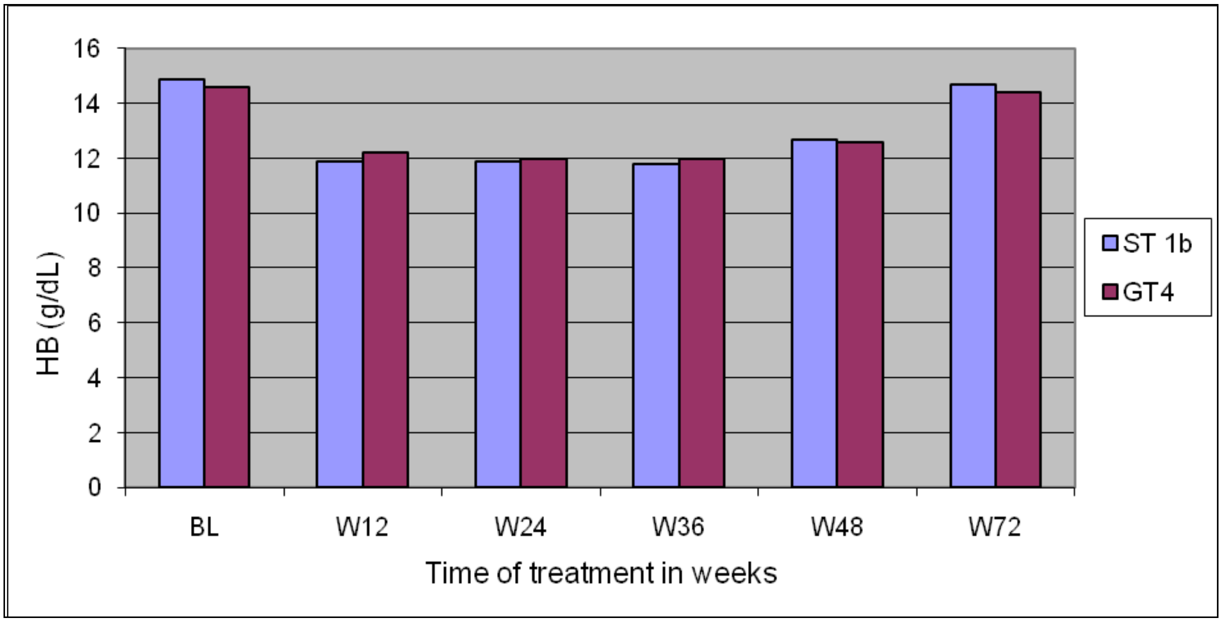


Fig. 20. Mean hemoglobin levels in patients with HCV GT 4 infection and those with HCV ST 1b infection during combination therapy with PEG-IFN and RV.
HB, hemoglobin; BL, baseline; W, week

Neutrophil counts are shown in Fig. 21. The counts were higher in patients infected with HCV ST 1b than those infected with HCV GT 4 throughout the study period.

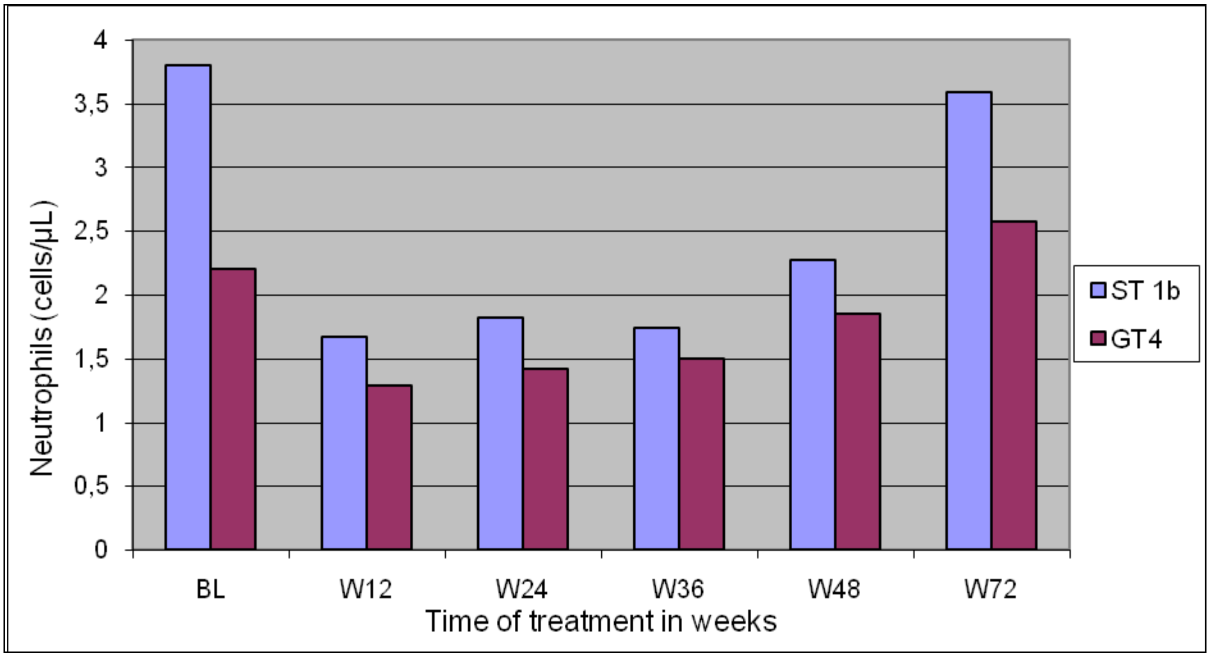


Fig. 21. Mean neutrophil counts in patients with HCV GT 4 infection and those with HCV ST 1b infection during combination therapy with PEG-IFN and RV.
BL, baseline; W, week

3.7.3 Molecular parameters

The median baseline serum HCV RNA load was 9.7×10^5 IU/ml in patients with HCV ST 1b infection and 2.0×10^5 IU/ml in patients with HCV GT 4 infection. All patients infected with HCV ST 1b were Austrians while the majority of HCV GT 4 infected patients were immigrants from Egypt. Subtypes of HCV GT 4 included 4a (6 patients), 4e (2 patients), 4c (1 patient), and 4o (1 patient). In 8 patients, the subtype could not be determined.

3.7.4 Response to anti-HCV treatment

The early virological response rate (EVR), the end of treatment response rate (EOTR), and the sustained virological response rate (SVR) were found to be significantly higher in patients with HCV GT 4 than those with HCV ST 1b (Fig.

22). In the HCV GT 4 group, 17 of 18 patients achieved EVR compared to 11 of 18 patients with HCV ST 1b ($p<0.02$). In the HCV GT 4 group, 17 of 18 patients achieved EOTR compared to 9 of 18 patients with HCV ST 1b ($p<0.001$). Corresponding data for SVR were 16 of 18 patients in the HCV GT 4 group and 8 of 18 patients in the HCV ST 1b group ($p<0.01$).

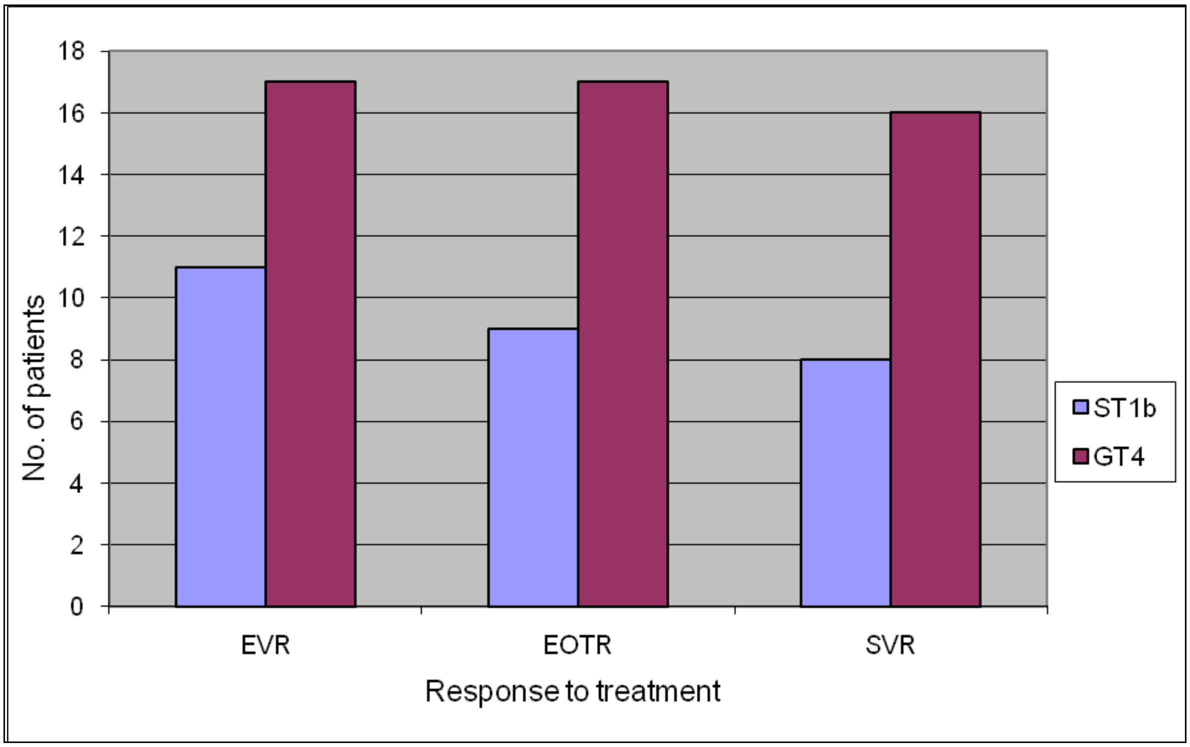


Fig. 22. Response to combination therapy with PEG-IFN and RV in patients with HCV ST 1b infection and those with HCV GT 4 infection.

Of the patients with HCV GT 4 infection, the only non responder patient had shown a serum HCV RNA load of 1.7 x 10^7 IU/L at the start of treatment. The serum HCV RNA load dropped to 2.1 x 10^3 IU/L at week 12 and increased to 5.1 x 10^5 IU/L at the end of the treatment.

Two patients with HCV ST 1b infection showed a breakthrough, another two were relapsers, and seven were non responders.

The most common side effects were Flu-like symptoms, weight loss, hair loss, itching, loss of appetite, and depression.

4 DISCUSSION

4.1 Information regarding to HCV prevention and control strategies

Efforts to prevent transmission of HCV infection seek to reduce the incidence of new infections. From the introduction of blood donor screening onwards, the risk of acquiring HCV infection through transfusion of blood or blood products has dramatically decreased in industrialized countries. Nevertheless, nosocomial transmission of HCV continues to occur. Recent studies provided evidence of patient-to-patient transmission in the majority of nosocomial transmission; however, several studies also reported transmission from health care workers to patients and vice versa (Allander T. et al., 1995; Bronowicki J.P. et al., 1997; Ross R.S. et al., 2000; Thompson N.D. et al., 2009).

Most countries in the developing world do not screen blood donations for the presence of HCV. WHO Global Database on Blood Safety estimates that 43% of donated blood in the developing world is not screened adequately for transfusion-transmitted infections, including HCV. The obstacles to generate a nationwide system of all-volunteer blood donors in the developing world are complex and vary widely (WHO, 1999). In Egypt, blood transfusion remains a major risk of HCV transmission among Egyptian children. A recent study reported detection of serum HCV RNA in more than 58% of children with a history of blood transfusion (El-Raziky M.S. et al., 2004). In contrast, risk factors could not be identified in 70% of HCV infected children in another study (El-Raziky M.S. et al., 2007). In the EU, blood donors are screened on HCV RNA from 1999 onwards, contributing to a significant increase of safety of blood and blood products (World hepatitis awareness day, Sept. 2006, Copenhagen, Denmark).

One of the cornerstones of an HCV prevention strategy is the identification of individuals at risk. In Austria, the highest prevalence of HCV infection has been among the IDUs with usually more than 50%. Identification of individuals with HCV infection has the potential limiting further transmission through counseling (EMCDDA, 2002).

In many countries including Austria, needle exchange programs together with special services have been implemented to prevent HCV transmission among IDU (available at: http://en.wikipedia.org/wiki/Needle-exchange_programme, http://streetwork.caritas-steiermark.at). These services have a key role to play in reducing new hepatitis C infections through provision of sterile equipment and safe disposal of contaminated needles and syringes (Drug in Focus, 2003). In UK, about 60% of injecting drug users was not infected in 2002. This means that there is the chance to prevent additional infections and existing practices of delivering health promotion need to be enhanced and invigorated (Hepatitis C strategy for England 2002). However, in many developing countries, supply of sterile syringes may be inadequate or non-existent and non-professionals often give injections outside the medical setting.

In Egypt, the intravenous injecting campaign of anti-schistosomiasis therapy was the main source HCV transmission which affected up to 30% of the general adult population. Similarly, the mass campaign focusing on the diagnosis and treatment for trypanosomiasis carried out in Central Africa between 1920 and 1960 was the reason for the high prevalence of HCV in Sub-Saharan Africa reaching 12% in the general population of Cameroon (Madhava V. et al., 2002). In different regions of India, an association between HCV infection and frequent visits to “freelance” or unlicensed practitioners of medicine, as well as a history of therapeutic injections using reusable syringes was found (Chowdhury A. et al., 2003). In Pakistan, medical injections were identified as the most important cause for HCV transmission (Lupy S. P. et al., 1997). In Taiwan, HCV infected individuals reported that they received frequent medical injections from “freelance” practitioners (Lin C.C. et al., 2003).

In Egypt, the informal health providers, mainly barbers and midwives, are not aware that blood could be a source of transmission of disease. They do not wear gloves and do not use any sterilization procedure. All of them used disposable syringes but they did not have any regular way of disposing of used needles and syringes. Presently, only a few nongovernmental organizations are training and educating some traditional midwives including family planning and eradication of female genital mutilation but they are not training them on the prevention of blood borne infection (El Katsha S. et al., 2006).

HCV transmission still occurs because of lack of infection-control practices including sterilization of medical, surgical and dental equipment. Furthermore, disposals are reused, reusable injection equipment is sterilized improperly, multidose vials are contaminated, injections are overused, and medications are delivered that could otherwise be delivered by the oral route (WHO Report, 1999).

Awareness of risk associated with cultural practices that involve penetration of the skin is essential to prevent transmission of HCV. In Austria, tattoos and piercing is prohibited for individuals who suffer from HIV infection and hepatitis (http://www.transgender.at/presse/shownews.cgi?id=1126758663). In Germany, studios for tattoos and piercing have been informed about hygiene and are checked annually using a special check list including cleanness and disinfection and sterilization procedures. For tattoo and piercing practices, special hygienic rules are mandatory (Heudorf U. et al., 2000).

In Egypt, infection control has been a national program established by the MOHP in the public and private sectors. However, several challenges are facing the implementation including administrative, financial, and motivational difficulties (Talaat M. et al., 2006). Lack of health articles such as disposable latex gloves, syringes, needles, disinfectants and hygienic precautions regarding hospital waste represent a great obstacle for effective control of infections (ESPA, 2004). Additionally, health care services are not provided equally for the people. The financial support and health resources allocations differ among the rural and urban facilities. Individuals from rural areas are treated in a different way in comparison to those who are living in urban areas. The poorest income quintile receives 16.4% of public health expenditures compared to 23.6% for the richest quintile. This distribution indicates that access to health care is not equal for all Egyptians (Rannan-Eliya R.P. et al., 2000).

In UK, some of the hospitals have a Hospital Infection Control Committee as the main forum for regular routine consultation between the Infection Control Team and the rest of the hospital. The Infection Control Team collaborates with the Occupational Health Service providing advice to staff on measures how to avoid the transmission of infection between staff and patients. The new guidance, which is consistent with existing policy, intends restriction of healthcare workers infected with bloodborne viruses from working in the National Health System in clinical areas where their infection may pose a risk to patients in their care. Testing is a one-off and relies on the current obligation for healthcare workers to seek confidential professional advice if they believe that they may have been exposed to a serious communicable disease (New guidance in UK 2007).

In recent years, the use of molecular techniques has proven to be a powerful tool in the epidemiological investigation of HCV infection in health care facilities and other settings. In particular, HCV genotyping and phylogenetic tree analysis has often been used to identify the original source of infection (Hosokawa N. et al., 2000; Bruguera M. et al., 2002).

The Austrian Society of Gastroenterology and Hepatology is responsible for updating the national consensus for HCV. Recent guidelines and consensus declarations developed in Austria, France, and the United States recommend that the decision about treatment should be made on a case by case basis and that injecting drug users should not be excluded automatically (Drug in Focus 2003). In Austria, the specialists in addiction medicine published guidelines for treatment of chronic hepatitis C in drug users from the point of view of addiction medicine. They indicated that patients are eligible for treatment after at least 6 months of abstinence, in case of substitution treatment without additional drug use and in case of drug use but no injection drug use or intoxication (Haltmayer H. el al., 2001; Reimer J. 2005).

There are large variations in reimbursement and access to treatment. While many countries reported 100% coverage of hepatitis C treatment expenses in the European Liver Patients Association survey, Bosnia and Egypt offer no reimbursement. Belgium covers 85% and Switzerland 90% of expenses. According to a recent WHO Europe survey, Latvia reimburses 75% of hepatitis C treatment expenses, while people with hepatitis in the remaining former Soviet Union countries have to cover expenses for medication themselves (World hepatitis awareness day, Sept. 2006, Copenhagen, Denmark).

In Austria, the social insurance system covers the whole population. In contrast, the public health insurance system covered only 52% of the Egyptian population in 2005 (Abdel-Hamid M., 2007). The majority of beneficiaries (73.8%) are infants, preschool children and students. Employees in the public and private sectors accounted for another 20.6% and the remaining 5.5% are retired people and widows. The state is keen on extending health insurance coverage to include non-insured individuals.

The Egyptians carry a heavier burden on the health bill than citizens of high-income countries (61.8% vs. 59.4% on average). Therefore, Egyptians have become more exposed to poor health and disease (Abdel-Hamid M., 2007). Out-of-pocket payments are the most unprogressive type of contribution to health care. Because of the high percentage of out-of-pocket payments, ability to pay is a major barrier to accessing health services. University hospitals are available to all Egyptians but in practice their urban location and their practice of charging modest user fees would discourage poor people and rural residents from benefiting from their services (Gericke C.A., 2004).

The burden of chronic HCV infection varies according to the cultural and regional differences. Patients who are aware of being infected may show a greater reduction in quality of life compared to those who are unaware of being infected. Alteration in the quality of life of patients undergoing treatment is mainly related to the side effects of PEG-IFNα and RV and is most severe during the first weeks of therapy (Teixeira S.E., 2006).

4.2 Comparison between the treatment response of HCV subtype (ST) 1b and genotype (GT) 4 infection

Individuals infected with HCV GT 4 constitute around 20% of the world's HCV-infected population (WHO, 1997). Nonetheless, these patients have been underrepresented in clinical trials conducted mostly in the Western countries where infection with HCV GT 4 is rare. Patients with HCV GT 4 infection have been described as ‘difficult-to-treat’, with SVR rates between 0 and 8% among patients with IFN monotherapy and between 14 and 42% among patients with IFN plus RV combination therapy (Mohammad S.K. et al., 2004). In contrast, SVR rates found in patients infected with chronic HCV GT 1 infection has been between 33 and 36% and in those infected with HCV GT 2 or HCV GT 3 has been between 61 and 79%. The Egyptian national hepatitis committee reported that monotherapy with IFN was not efficient because 40% of patients had developed resistance against this drug (The Hepatitis Trust 2007. Available at: www.hepctrust.org.uk/news/2007).

A great improvement in response has been attributed to the introduction of PEG-IFN, whether as monotherapy or in combination with RV. PEG-IFN in combination with RV shows the highest SVR rates in patients infected with HCV GT 2 and HCV GT 3, whereas patients infected with HCV GT 1 show a less successful outcome (Manns M.P. et al., 2001). More recent clinical trials in Western and Middle East countries showed that HCV GT 4 infection is not difficult to treat, as the response to treatment may be at an intermediate level compared with HCV GT 1 on the one hand and HCV GT 2 or HCV GT 3 on the other (Diago M. et al., 2004; Mohammad S.K. et al., 2004; Kamal S.M. et al., 2007; Ferenci P. et al., 2008).

This study showed a significantly higher SVR in patients infected with HCV GT 4 than in those infected with HCV ST 1b. Although the PEG-IFNα plus RV combination therapy has lead to a significant progress in the management of chronic hepatitis C, the response to therapy is still variable and depends on host characteristics and virological factors. Host characteristics include factors such as geographical origin, sex, body weight, histological score, and fibrosis grade, whereas virological factors include mode of transmission, HCV genotype, and baseline serum ALT and HCV RNA levels.

A French study reported that the SVR rate may differ in HCV GT 4 patients according to the geographical origin of the infection (Roulot D. et al., 2007). SVR rates were found to be higher in Egyptian (54.9%) than in French (40.3%) and African (32.4%) patients. The SVR rate in Egyptian patients without severe fibrosis was 65% and a better response was observed among patients with HCV ST 4a infection when compared to those infected with other subtypes of HCV GT 4. In this study, body weight was higher in patients with HCV GT 4 infection than in those with HCV ST 1b infection corresponding to similar studies (Kamal S.M. et al., 2005; Kamal S.M. et al., 2007; Roulot D. et al., 2007). In contrast, correlation between SVR rates and factors such as sex, mode of transmission, baseline ALT level, and histological score were never found among patients treated with PEG-IFNα plus RV combination therapy.

However, the serum HCV load may play a role in prediction of SVR. For HCV GT 1, a low baseline serum HCV load has been found to be significantly associated with a better response to treatment (Fried M.W. et al., 2002). The results of this study showed that this may be also true for HCV GT 4. In a recently published Austrian study, SVR rate has been shown to be affected by the baseline HCV

RNA level (Ferenci P. et al., 2008). However, this effect was different among HCV genotypes. Among patients infected with HCV GT 1, the rate of those with SVR was slightly higher in patients with a baseline HCV RNA level ≤400,000 IU/mL (89.9%) than in those with >800,000 IU/mL (86.7%). This trend was not observed among patients with HCV GT 4 infection.

Hassan et al. reported an SVR rate among patients with HCV GT 4 infection of 68% in comparison to 45% among patients with HCV GT 1 infection (Hassan F. et al., 2004). In another study, patients with low viremia were more likely to respond than patients with a high viral load; patients with a baseline serum HCV RNA level of $<2 \times 10^6$ copies/mL had a significantly higher rate of SVR compared to patients with a baseline serum HCV RNA level of $\geq 2 \times 10^6$ copies/mL (Kamal S.M. et al., 2007). Baseline serum HCV RNA levels were associated not only with non-response but also with an increased risk of virological relapse. In this study, the SVR rate among patients with HCV GT 4 infection and PEG-IFN plus RV combination therapy was significantly higher than among those with HCV ST 1b infection. Recent Austrian and Egyptian studies revealed that advanced fibrosis at the baseline did not affect either the rate of relapse or that of SVR in patients with either HCV GT 1 or HCV GT 4 infection (Kamal S.M., 2007; Ferenci P. et al., 2008).

A recent Egyptian study revealed that patients with HCV GT 4 infection and RVR showed a significantly higher SVR rate than those without RVR (Kamal S.M. et al., 2004). Among patients with HCV GT 1 who were enrolled in a 24-week treatment, SVR rates were significantly higher in patients with RVR than in those without RVR (Jensen D.M. et al., 2006). Hadziyannis et al. showed that among HCV GT 1 patients with low baseline HCV RNA load and RVR, the rate of SVR was 89% in patients treated for 24 weeks and 90% in patients treated for 48 weeks (Hadziyannis S. et al., 2004). These results may lead to future recommendations towards a shorter treatment in patients with rapid viral clearance.

In a recent study, the duration of combination treatment with PEG-IFNα and RV for 24, 36 and 48 weeks was compared between patients with HCV GT 1 and those with HCV GT 4 (Diago M, et al 2004). The SVR in patients with HCV GT 4 and treatment for 24 weeks was 67%, while in those treated for 48 weeks was 79%. In another study, the SVR among HCV GT 4 patients and treatment for 24 weeks was significantly lower than among those treated for 36 weeks and those treated for 48 weeks (Kamal SM et al., 2005). Another Egyptian study performed according to financial affordability rather than the standard procedure revealed SVR rates after 24, 36 and 48 weeks of the therapy of 28.6%, 48.6%, and 55%, respectively (El-Zayadi et al., 2005).

There are novel antiviral agents in development (Stauber R.E. and Kessler H.H., 2008). The investigational protease inhibitor telaprevir (Vertex Pharmaceutical, Inc, Cambridge, MA, formerly VX-950) rapidly inhibits HCV RNA replication within 12 weeks of the initiation of therapy (McHutchison J.G. et al., 2007). A recently completed phase II study on triple combination treatment with telaprevir, PEG-IFN, and RV given for 12 or 24 weeks reported sustained virological response in up to 68% of patients with treatment-naïve HCV GT 1 infection (Dusheiko G.M. et al., 2008).

In conclusion, this study reveals significant differences with regard to management of HCV infection in Egypt and Austria. When the response to combination therapy with PEG-IFNα plus RV was compared among patients with HCV GT 4 and those with HCV ST 1b infection, a significantly higher number of patients with HCV GT 4 infection achieved SVR. Although a limited number of patients were investigated in this study, results correspond well to those obtained by recently published studies with similar design. The optimization of treatment appears to be crucial in ensuring that SVR rates are maximized without exposing the patient to an unnecessarily extended treatment regime that may have unfavorable implications regarding tolerability and expenses.

5 APPENDICES

Appendix 1. Distribution of HCV genotypes/subtypes in Vienna, Austria

Distribution of HCV genotypes/subtypes in Vienna and surrounding areas Surroundings (n=250) (Haushofer AC, et al. 2001)

Genotype	Subtype	Number of patients (%)	
1		187 (74.8)	
	1a		39 (15.6)
	1b		135 (54.0)
	1a/1b		12 (4.8)
	Unidentified		1 (0.4)
2		7 (2.8)	
	2b		5 (2.0)
	2a/2c		2 (0.8)
3		40 (16.0)	
	3a		39 (15.6)
	3c		1 (0.4)
4		13 (5.2)	
	4a		1 (0.4)
	4f		1 (0.4)
	4h		4 (1.6)
	4c/4d		4 (1.6)
	Unidentified		3 (1.2)
5	5a	1 (0.4)	
Unidentified		2 (0.8)	

Genotype	Subtype	Number of patients (%)			
		Transfusion-associated (*n*=54)		Intravenous drug abuse (*n*=75)	
1		45 (83.4)		40 (53.3)	
	1a		7 (13.0)		16 (21.3)
	1b		36 (66.7)*		20 (26.7)
2		2 (3.7)		1 (1.3)	
3		3 (5.6)		30 (40.0)**	
4		2 (3.7)		4 (5.3)	
Other		2 (3.7)		0	

Appendix 2. Distribution of HCV genotypes/subtypes in Egypt

Results of restriction fragment length polymorphism (RFLP) genotyping of HCV isolates in the Egyptian governorates. (Stuart CR, et al. 2000)

Governorate	Region[a]	*n*	RFLP result				
			NA	1a	1b	4	NT
Alexandria	North Central	6	1	0	0	4	1
Assiut	South	21	15	0	0	6	0
Beheira	North Central	21	12	1	0	8	0
Beni Suef	South Central	14	4	0	0	8	2
Cairo	Central	13	2	0	0	11	0
Daqahliya	North Central	15	6	0	1	7	1
Damietta	North Central	10	3	0	0	7	0
Qalyubiya	North Central	16	4	0	0	10	2
Qena	South	15	5	0	0	9	1
Matrouh	West	5	3	0	0	2	0
Menoufiya	North Central	16	5	0	0	11	0
Minya	South Central	21	7	0	0	14	0

Governorate	Region[a]	*n*	RFLP result				
			NA	**1a**	**1b**	**4**	**NT**
Red Sea	South East	5	0	0	0	5	0
South Sinai	North East	5	0	0	0	4	1
Suez	South Central	7	1	0	0	5	1
Total		190	68	1	1	111	9

NOTE. NA, not amplified; NT, not typed by this method

Appendix 3. Sources of HCV transmission in Austria

Sources of HCV transmission in the studied patients (*n*=250) (Haushofer AC, et al. 2001)

Sources	Number of patients (%)
Transfusion of blood or blood products	54 (21.6)
Intravenous drug abuse	75 (30.0)
Sexual transmission	4 (1.6)
Hemodialysis	1 (0.4)
Plasmapheresis	2 (0.8)
Piercing	1 (0.4)
Professional contact with HCV-contaminated material (medical staff)	1 (0.4)
Unknown	112 (44.8)

Appendix 4. Prevalence of HCV antibody among drug users in Euroup

IFNα- Prevalence of HCV antibody among injecting drug users in the EU, 2005 or most recent year available - Summary table by country (http://www.emcdda.europa.eu/stats07/inftab02)

Country	**Year**	**Number tested**	**% infected (1)**	**Study design (2)**	**Setting/comments (2) (3) (4) (5)**	**References**
Belgium	2005	375	[50.0-80.7]	DT	LTS, DTC; serum	8 ; 14
Bulgaria	2005	815	[53.6]	DT	DTC, NSP, LTS, HTC; serum	2 ; 3
Czech Republic	2002-03	1853	52.0 [29.7]	DT ; SP	LTS, PRI; IDUnkT; serum	3 ; 4
Denmark	2005	220	58.0	SP (UAT)	ODD; All drug related deaths who have a blood sample taken at autopsy; IDUnk	7
Germany	2004	1134	[75.0]	n.a.	Vacination study; serum, IDUnk	24
Estonia	2002	100	[89.2-90.5]	SP	LTS	3
Ireland	2003	65	[72.3]	SP	DTC; serum	14
Greece	2005	1881	43.3-61.7 [21.4-88.2]	DT	DTC, LTS, OHC, PHL; serum	1 ; 2 ; 9
Spain	2003	669	[59.1-73.3]	SP	STR, Heroin users age 30 or less recruited in community. Injectors+non injectors. Dried blood spots.	29 ; 34
France	2004	817	[44.0-66.0]	SP (UAT)	n.a.	19
Italy	2005	75213	61.4 [18.1-92.3]	DT	DTC, PRI; saliva, serum; IDUnk	31
Cyprus	2004	98	9.1	DT	DTC, PRI; serum	1
Latvia	2001	261	[83.0]	n.a.	NSP	2

Country	Year	Number tested	% infected (1)	Study design (2)	Setting/comments (2) (3) (4) (5)	References
Lithuania	2005	923	[81.8-93.7]	DT	NSP, LTS, DTC; serum, dried blood spots	5 ; 8
Luxembourg	2005	536	71.8-90.7	SP	DTC, NSP, LTS, STI, ANT, OHC, PRI; serum	6
Hungary	2005	82	11.0	DT	PHL; serum; IDUnk	1
Malta	2005	138	30.4	DT	DTC; serum	3
Netherlands	2005	89	[64.6]	SP	DTC, LTS; serum	27
Austria	2005	501	48.0 [17.2-58.6]	DT	LTS, PHL, GPS, HTC, ODD, DTC, NSP; serum	6 ; 7 ; 8 ; 10 ; 11
Poland	2005	347	[43.7-64.0]	SP	DTC, LTS, PRI; serum	5 ; 6
Portugal	2005	5897	38.4-84.3	DT	DTC, Detoxification units, Outpatient units, Therapeutic communities, Public detoxification units; serum, dried blood spots; IDUnk	23 ; 24
Romania	2005	177	[45.8]	DT ; SP	DTC; serum	2
Slovenia	2004	467	22.5	DT	DTC; serum	1
Slovakia	2004	72	[45.8]	DT	DTC	7
Finland	2004-05	695	[23.0-56.6]	DT ; SP (UAT)	NSP; serum, saliva	6
Sweden	2006	21	[83.8]	SP	DTC, OHC, PRI; serum	9
United Kingdom	2005	4233	[28.0-57.0]	SP (UAT)	DTC, NSP, LTS, primary care and outreach; saliva	36 ; 39
Turkey	2004	38	[47.4]	DT	DTC; serum	1
Norway	2005	258	[69.0]	SP	NSP, STR; serum	8

Notes:

This summary table gives a global overview of the prevalence of HCV antibody in IDUs in the EU, 2004-2005 or most recent year available. Data for more than one year are combined if they clearly improve generalisability (e.g. national data, out-of-treatment data). Prevalence in this table should not be compared with previous versions to follow changes over time, as inclusion of sources may vary according to data availability. For time trends see Tables 11-13 in the annex of this statistical bulletin.

(1) The figures given in brackets show local estimates (or range of estimates) within the country.

(2) Saliva tests for hepatitis C antibodies underestimate prevalence. If test sensitivity is known then figures can be adjusted upwards by dividing prevalence by test sensitivity. Test sensitivity is around 70-90% in older studies and may be up to 90-95% in some recent studies. Figures have not been adjusted.

DT: Diagnostic testing; SP: Seroprevalence study; SP-UAT: Seroprevalence study with unlinked anonymous testing; SR: Data (partly) based on self reported test results.

(3) Having health problems is one selection criterion for admission to drug treatment in some countries or cities (Greece, Portugal, Rome), due to long waiting lists or special programmes for infected IDUs, and this may result in upward bias of prevalence. Prevalence from treatment data should therefore be interpreted in combination with non-treatment data. On the other hand, data from Italy and Portugal include non-IDUs and may thus underestimate prevalence in IDUs.

(4) IDUnk = IDU status not known, prevalence may be too low.

(5) ODD = overdose deaths; DEM = drug emergencies; DTC = drug treatment centres; NSP = needle exchanges; LTS = low-threshold services; PHL = public health laboratories; STI = STI clinics; ANT = antenatal clinics; OHC = other hospital or clinics; PRI = prisons; ARR = arrests; GPS = general practitioners; HTC = HIV testing centres; STR = street; OTH = other.

Czech Republic: The national study available is IDUnk (n =1319; 52.0% infected). Bulgaria: One sub-national study available is IDUnk (N=115; 16.5% infected).

Appendix 5. HCV prevalence distribution of hospital discharge data in Austria (2000)

HCV prevalence distribution of hospital discharge data in Austria (Strauss R, et al. 2003)

	1993		1994		1995		1996		1997		1998		1999		2000		Σ	
	n	inc	n	inc	n	inc	n	inc	n	inc	n	inc	n	inc	n	inc	n	inc
Burgenland	11	3,7	10	3,5	13	4,3	25	8,6	28	9,8	37	12,3	43	13,6	30	9,6	197	7,0
Kärnten	19	3,1	27	4,5	38	6,6	63	11,3	96	15,7	118	19,9	68	11,3	76	12,0	505	9,1
NÖ	50	3,1	88	5,2	125	7,6	205	12,2	251	15,3	350	21,6	367	21,8	392	22,8	1828	11,9
OÖ	170	12,5	198	14,3	312	22,3	375	26,9	492	34,2	577	39,2	623	42,4	673	45,1	3420	24,5
Salzburg	14	2,8	18	3,5	21	4,0	51	9,4	130	24,1	145	27,4	97	18,4	105	20,2	581	11,8
Steiermark	54	4,6	94	7,4	103	7,9	176	12,8	278	21,2	311	23,0	385	28,6	421	30,4	1822	14,5
Tirol	24	3,4	49	6,8	41	6,1	68	10,0	152	21,3	137	19,0	143	19,6	160	21,9	774	12,2
Vorarlberg	7	1,9	11	3,1	24	7,4	57	16,1	86	23,6	87	24,7	100	28,4	84	23,0	456	13,7
Wien	116	6,6	237	13,6	283	15,9	483	28,5	702	41,4	863	50,5	996	57,2	1115	63,8	4795	30,6
Österreich	**465**	**5,6**	**732**	**8,6**	**960**	**11,2**	**1503**	**17,6**	**2215**	**25,8**	**2625**	**30,2**	**2822**	**32,1**	**3056**	**31,2**	**14378**	**19,4**

N= no. of infected individuals, inc= incidence in 100 000 of the population

Appendix 6. Prevalence of HCV in the Austrian regions (2005)

Prevalence of HCV in the Austrian regions according to the hospital admission (Statistik Austria 2006)

Region	**2004**	**2005**
Burgenland	17	14
Corenthia	8	23
Lower Austria	221	207
Upper Austria	179	216
Salzburg	18	18
Styria	30	18
Tyrol	185	134
Vorarlberg	33	30
Vienna	273	234
Total in Austria	964	894
Distribution in100.000	11,8	10,9

Appendix 7. Death rate because of liver diseases in Austria

Death rate because of hepatitis, Liver Cirrhosis and HCC in Austria (Statistik Austria 2007)

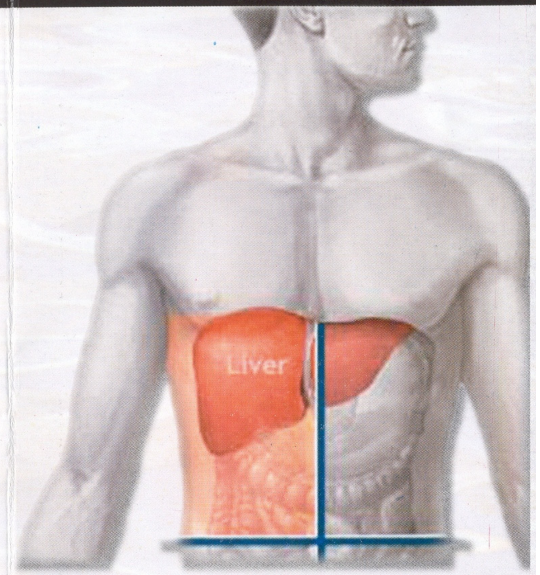
Region	**Hepatitis (no.)**	**Chronic Hepatitis & HCC (no.)**	**Chronic Hepatitis & HCC (deaths per 100.000)**
Burgenland	7	61	21,7
Carinthia	12	117	20,9
Lower Austria	25	346	21,7
Upper Austria	39	247	17,6
Salzburg	11	80	15,1
Styria	38	231	19,2
Tyrol	16	80	11,4
Vorarlberg	4	52	14,2
Vienna	80	345	20,7
Total in Austria	223	1559	18,8

Appendix 8. The prevalence of HCV antibodies in blood donors in Egypt

The prevalence of HCV antibodies in blood donor in the Egyptian governorates (Arthur Ray R., 1997)

Governorate	No. of Samples	Anti-HCV	Anti-HCV %
Alexandria	135	15	11,1%
Assiut	139	34	24,5%
Aswan	58	2	3,4%
Beheira	193	43	22,3%
Beni Suef	89	34	38,2%
Cairo	349	68	19,5%
Damietta	45	17	37,8%
Daqahliya	181	51	28,2%
Fayoum	0	-	-
Gharbiya	169	56	33,1%
Giza	99	24	24,2%
Ismailia	56	9	16,1%
Kafr El-Sheikh	134	36	26,9%
Matrouh	28	5	17,9%
Menoufiya	136	32	23,5%
Menya	154	57	37,0%
North Sinai	30	0	-
Port Said	29	6	20,7%
Qalyubiya	136	43	31,6%
Qena	135	44	32,6%
Red Sea	30	5	16,7%
Sharqiya	130	38	29,2%
Sohag	129	25	19,4%
South Sinai	29	5	17,2%
Suez	30	7	23,3%
Wadi El-Gedid	0	-	-
Total	2644	656	24,8%

Appendix 9. HCV Brochure in Egypt



ما هو الكبد وما هى وظائفة؟

١. الكبد أكبر أعضاء الجسم البشري حجماً ويقع في الجزء الأيمن العلوي من تجويف البطن تحت الحجاب الحاجز خلف الأضلع.

٢. يقوم الكبد بعمليات التمثيل الغذائي بالجسم حيث يقوم بدور رئيسي في التعامل مع السكريات والبروتينات والدهون في جسم الإنسان.

٣. يصنع مئات الأنواع من الأنزيمات والهرمونات والبروتينات التي يحتاج إليها الجسم في بناء خلايا الجسم .

٤. يفرز العصارة المرارية التى تقوم بدور رئيسي في هضم وامتصاص الدهون.

٥. الكبد له دور فى رفع كفاءة الجهاز المناعي بالجسم.

٦. تحويل أغلب المركبات الكيميائية والعقاقير المختلفة من مواد سامة إلى مواد غير سامة أو مواد نافعة بواسطة الأنزيمات المتنوعة التى يفرزها.

٧. الكبد له مهام أخرى كثيرة مثل:
- تكوين خلايا الدم الحمراء في الجنين داخل الرحم.
- تخزين الحديد وبعض المعادن الأخرى بالإضافة إلى الفيتامينات المهمة في الجسم.
- حفظ التوازن الهرموني في جسم الإنسان.

ما هو مرض الالتهاب الكبدي الفيروسي (سى)؟

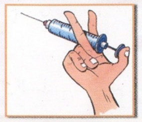
مرض معدي يصيب الكبد ويسببه فيروس الالتهاب الكبدي (سى).

كيف يصاب الإنسان بالمرض؟

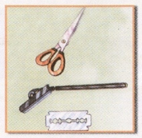
يصاب الشخص السليم بالمرض عن طريق دخول فيروس الالتهاب الكبدي (سى) إلى دمه من دم شخص مصاب أو حامل للفيروس.

كيف ينتقل مرض الالتهاب الكبدي الفيروسي (سى)؟

نقل الدم أو مشتقاته من الشخص المريض أو حامل فيروس إلى الشخص السليم.



استخدام سرنجة أو أدوات جراحية ملوثة بفيروس الإلتهاب الكبدى الفيروسى (سى).



المشاركة في استعمال أي أدوات تخترق الجلد وتكون ملوثة بدم شخص مريض أو حامل لفيروس الالتهاب الكبدي (سى) مثل (فرش الأسنان– أمواس الحلاقة– أدوات الوشم– أدوات ثقب الأذن ...).

ما هي أعراض المرض ؟ وما هي مضاعفاته؟

معظم المصابين بمرض الإلتهاب الكبدى الفيروسى (سى) لا تظهر عليهم أعراض ملحوظة ولكن بعض المصابين قد تظهر عليهم الأعراض في بداية الإصابة ومن هذه الأعراض (الصفراء "اصفرار الجلد وبياض العينين"–فقدان الشهية – ارتباك في البطن – غثيان وقيء – آلام في المفاصل – ارتفاع درجة حرارة المريض).

فى بعض الحالات يتغلب جسم المريض على الفيروس وفى حالات أخرى تظهر مضاعفات المرض بعد فترة مثل تليف الكبد الذى يؤدى إلى تورم بالقدمين واستسقاء بالبطن والقيء الدموي وسرطان الكبد.

كيف نحمى أنفسنا من مرض الالتهاب الكبدي الفيروسي (سى)؟

طرق الوقاية:

استخدام سرنجة جديدة في الحقن كل مرة حتى لنفس الشخص.

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