Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Chao DT. et al. (2011) Systematic review: epidemiology of hepatitis C genotype 6 and its management. *Alimentary Pharmacology & Therapeutics*, 34(3):286-296
Date of Review:	March 10, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **people HCV genotype 6 infection** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **United States** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☐	☒	☐	systematic review; review of current literature on the epidemiology, classification and treatment of HCV genotype 6
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Article mentioned further studies required for recommending 24 weeks as optimal treatment duration for patients with HCV genotype 6.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☐	☒	☐	Methodology unclear; no specific inclusion/exclusion criteria provided for the selection of relevant articles
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	HCV genotype 6 is predominantly found in countries of Southeast Asia, though

				developed countries may immigrants with HCV genotype 6
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Developing countries in Southeast Asia have high prevalence of HCV genotype 6
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Free to download from http://onlinelibrary.wiley.com
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☒	☐	☐	Dr. Mindie Nguyen received research funding from Roche Laboratories.
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Older line probe assays have been shown to mistake genotype 6 subtype variants as genotype 1 - Genotype 6 have higher SVR rate compared to HCV genotype 1 - Similar SVR rates in genotype 6 who received 24 weeks of Peg-IFN and RBV and those who received 48 weeks of therapy
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☐	☒	Unspecified
Are these data regularly collected at and/or below a national level?	☐	☐	☒	Unspecified
Are these data collected manually or electronically?	☐	☐	☐	Electronically: using PubMed
RESEARCH REPORTS				

Has this research been published in a juried journal?	☒	☐	☐	*Alimentary Pharmacology & Therapeutics*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Utilize existing data/surveillance information: 33 articles included for analysis

AP&T Alimentary Pharmacology and Therapeutics

Systematic review: epidemiology of hepatitis C genotype 6 and its management

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SUMMARY

Background
Hepatitis C virus (HCV) genotype 6 is common among patients from Southeast Asia and the surrounding regions, where HCV prevalence is also high. HCV genotype 6 has great genetic diversity and different response to antiviral therapy compared with the more commonly known genotype 1.

Aim
Our goal was to provide a systematic review of the current literature on the epidemiology, classification and treatment of HCV genotype 6.

Methods
A search using PubMed for 'hepatitis C' AND 'genotype 6' produced a total of 47 articles, of which 33 articles were found to be relevant and included in this review. Additional articles were identified using the reference lists of these 33 primary articles.

Results
The prevalence of HCV genotype 6 is estimated to be as high as 50% in some regions of Southeast Asia with demonstrated significance among intravenous drug users and thalassemia major patients. Although previous line probe assays may have misclassified HCV genotype 6 as genotype 1, newer line probe assays can more accurately and reliably determine HCV genotype. Patients infected with HCV genotype 6 respond better to interferon-based therapy compared with those infected with genotype 1, although patient baseline clinical characteristics and side effect profiles are similar between HCV genotype 6 and other HCV genotypes.

Conclusions
Future studies should seek to clarify issues regarding early predictors for treatment response in patients with HCV genotype 6, and the impact of ethnic and genotypic factors to treatment response in HCV genotype 6 patients.

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INTRODUCTION

Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease and hepatocellular carcinoma (HCC) and currently infects approximately 3% of the world's population.[1] Of the estimated 170 million people who suffer from chronic hepatitis C (CHC) worldwide, 62 million – more than one-third – are from the Western Pacific region.[2] In particular, there are approximately 32.2 million people with CHC in Southeast Asia alone.[2] In the United States, approximately 3.2 million people suffer from CHC,[3] making it the most common chronic blood-borne infection in this country with an estimated 8000–10 000 deaths annually.[4, 5] In some countries in Southeast Asia, HCV prevalence (approximately 6–7%) far exceeds the prevalence seen in the US (1.8%).

In many developing countries such as those found in Southeast Asia, nosocomial transmission of HCV through re-use of inadequately sterilized needles and other unsafe medical and dental practices may account for the majority of the infection. Southeast Asian countries are reported to have among the highest rates of needle reuse in the world.[6] A recent study by Nguyen *et al.* of risk factors for HCV in 290 Southeast Asians reported that close to half of these patients could not recall an exposure to HCV with the vast majority of the remaining patients identifying exposure risks related to medical care such as prior surgery (34%), blood transfusion (25%), acupuncture (13%) and exposure to contaminated needles (7%).[7] Studies by Dev *et al.* of Southeast Asians and Caucasians in Australia[8] and by Ho *et al.* of Caucasians and Asian-Americans in the United States[9] also suggest that unsanitary medical practices are probably the major cause of HCV infection in Asians, whereas injection drug use is responsible for the majority of HCV infection in Caucasians.

Recent studies have also shown that the incidence of HCV-related HCC and HCV-associated HCC deaths is rising in several Asian countries.[4, 10] In the United States, Asian & Pacific Islander (API) populations continue to grow rapidly and report the highest incidence of HCC at 7.8 per 100 000 – more than double the national average of 3.2 per 100 000 – according to the most recent data published by the Center for Disease Control in 2010.[11] Besides infection with hepatitis B virus, infection with HCV is also probably a major contributing factor to this high HCC incidence rate in API. Prevalence studies of HCV among Asian-Americans are limited, but one population-based study in Los Angeles, California reported an 8% HCV prevalence.[12]

Despite implementation of successful hepatitis B screening programs, the rising worldwide incidence of HCC suggests an increasing role of HCV as a cause of underlying liver disease in addition to chronic hepatitis B.[10] In 2000, the World Health Organization estimated a 2.2% prevalence of infection with HCV across Southeast Asia.[13] Certain country-specific prevalence studies have revealed a significant variation in the distribution of HCV infection among countries in Asia, ranging from 0.5% in Singapore and Hong Kong[1] to 11.6% in Myanmar.[14] With 2–3% of its population suffering chronic infection, the Republic of China is home to approximately 30 million people with infection with HCV and is the Asian country with the largest number of people infected with HCV.[15, 16] Table 1 summarises the prevalence of HCV infection in several countries in Asia.

Table 1 | Hepatitis C prevalence in Asian countries

Country of origin	Author	Publication year	*n*	Hepatitis C prevalence (%)
Hong Kong[59]	Chan	1992	910	0.5
Indonesia[60]	Sulaiman	1995	7572	2.1
China[16]	Xia	1996	66 975	3.2
Vietnam[1]	World Health Organization	1999	NR	6.1
Singapore[1]	World Health Organization	1999	NR	0.5
Thailand[1]	World Health Organization	1999	NR	5.6
Thailand[61]	Sunanchaikarn	2007	5825	2.15
India[62]	Chowdhury	2003	3579	0.9
Myanmar[14]	Lwin	2007	1333	11.6

NR, not reported.

The aim of this review was to provide a comprehensive review of the current literature on the epidemiology, classification and treatment of HCV genotype 6. Using PubMed and the search criteria: 'hepatitis C' AND 'genotype 6', a total of 47 articles were identified, reviewed and assessed for relevance. A total of 33 articles were found to be relevant and included in this review. The reference lists of these 33 articles were also reviewed to identify additional relevant articles.

EPIDEMIOLOGY

Geographical distribution and prevalence of HCV genotype 6

Hepatitis C virus has substantial nucleotide sequence diversity. Sequence comparisons of variants from different geographic areas have led to the identification and classification of various genotypes/subtypes. So far, sequencing of HCV isolates has identified six major genotypes and more than 83 subtypes (Figure 1). Genotypes 1, 2 and 3 are widely distributed around the world, whereas genotypes 4 and 5 have been identified mainly in the Middle East and Africa. On the other hand, HCV genotype 6 is found predominantly in countries of Southeast Asia such as Singapore, Laos, Thailand, Vietnam and Myanmar as well as surrounding countries including south China, Hong Kong, Taiwan and Macao.[17] Studies of HCV genotypes in Vietnam and Myanmar have shown that genotype 6 is one of the most common genotypes in these countries with prevalence approaching 50%.[18] Reports from Thailand estimated that HCV genotype 6 accounted for 8–18% of HCV infection in Thailand, though prevalence as high as 31% has been reported by a study of blood donors in Northern Thailand.[19] Studies from countries neighbouring Southeast Asia also report a high prevalence of HCV genotype 6. In Taiwan, Korea and Japan, HCV genotype 6 is only less common than the widespread HCV genotypes 1b and 2. Underscoring the prominence of HCV genotype 6 in south China and Southeast Asia is the finding that nearly one-third of immigrants from Southeast Asia, China and Hong Kong to the United States who test positive for CHC infection have HCV genotype 6.[3, 20] This finding is corroborated in a recent study by Nguyen *et al.* which reported that HCV genotype 6 patients were as common as HCV genotype 1 (41% vs. 42%) in a large cohort of Southeast Asian immigrants in California.[7] HCV genotype 6 variants have also been reported in Cambodian and Vietnamese immigrants living in Canada.[21, 22] Studies reporting HCV genotype 6 prevalence are summarised in Table 2.

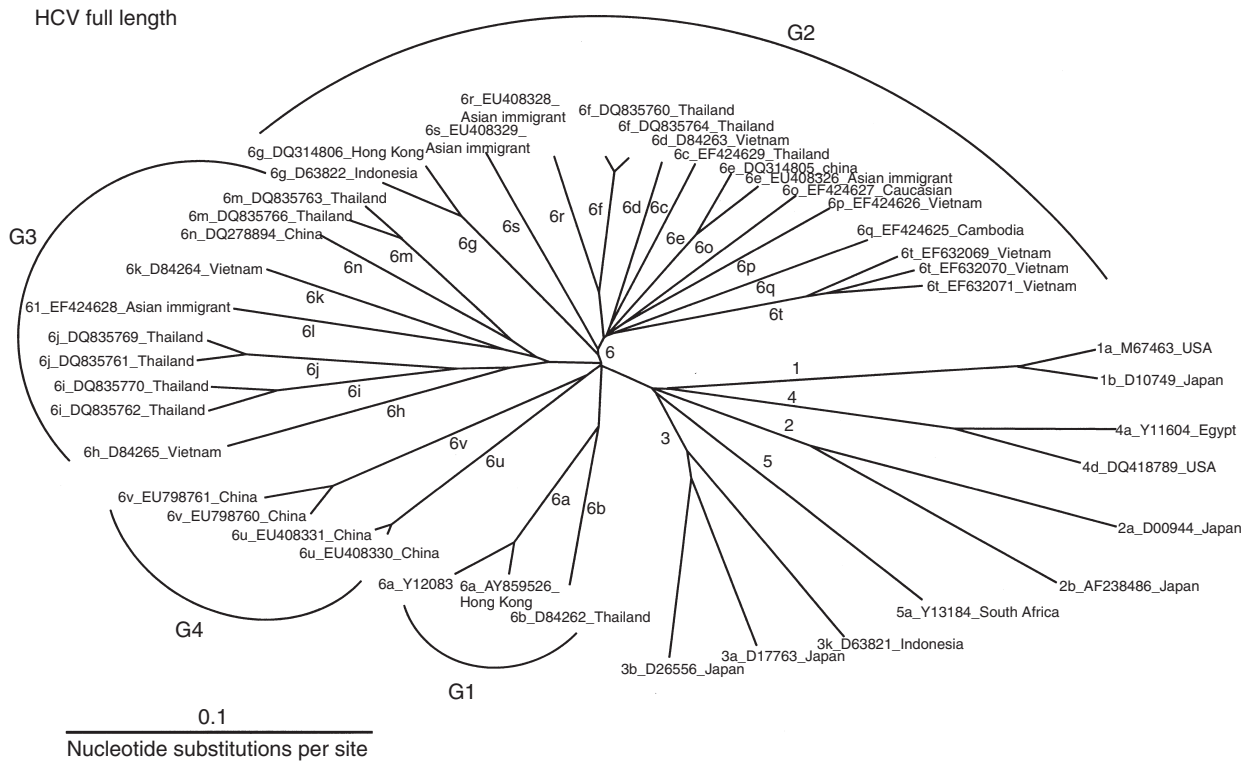

Figure 1 | Phylogenetic relationships among hepatitis C genotypes and genotype 6 subtypes.

Table 2 | Prevalence of HCV genotype 6 in Asians

Author	Country of origin (population)	Publication year	Genotyping method	*n*	Proportion with HCV genotype 6 (%)
Kanistanon[63]	Thailand (Blood donors throughout country)	1997	Reverse hybridization	236	18
Zhou[27]	Hong Kong (The Prince of Wales Hospital, Chinese University of Hong Kong)	2006	Core sequencing	1055 949 (non-IVDU) 106 (IVDU)	27.1 23.6 (non-IVDU) 58.5 (IVDU)
Leung[64]	Hong Kong (Blood donors)	2006	Unknown (data review of hospital records)	212	27
Lwin[14]	Myanmar (Four border cities around Myanmar)	2007	Core sequencing	145	49
Jutavigittum[19]	Thailand (Blood donors in northern Thailand provinces: Chiang Mai, Chiamg Rai, Lampang, Lamphu, and Mae Hong Son)	2009	Core sequencing	126	31
Pham[32]	Vietnam (Blood donors at the National Institute of Haematology and Blood transfusion, Hanoi, Vietnam)	2009	Core sequencing NS5B sequencing	70 65	47.1 (6a: 26/70, 6e: 6/70, 6l: 1/70) 44.6 (6a: 24/65, 6e: 4/65, 6l: 1/65)
Akkarathamrongsin[23]	Thailand (Blood donors from central Thailand)	2010	Core & NS5B sequencing	375	18.9
Nguyen[7]	USA (Southeast Asian immigrants from community-based clinics in Northern California)	2010	Core sequencing	181	41

RT, reverse transcriptase; PCR, polymerase chain reaction; IVDU, intravenous drug user.

Risk factors for HCV acquisition in patients with HCV genotype 6 are similar to Asian patients with other HCV genotypes with the majority of patients without recollection of specific exposure risks.[7] Presumably, unsanitary medical and/or dental practices frequently encountered in developing countries are the primary transmission routes for infection with HCV in these cases. Other common causes of HCV acquisition are blood transfusion, prior surgeries and known exposures to contaminated needles. Injection drug use is only a minor cause of HCV infection in this population.

Special populations

Higher prevalence of HCV genotype 6 has also been reported in certain populations such as thalassemia major patients and intravenous drug users.[23–26] In a study by Wong *et al.*, 20 of 32 intravenous drug users and 10 of 20 study subjects with thalassemia major were infected with HCV genotype 6.[26] A latter study in 2006 by Zhou *et al.* found an HCV genotype 6 prevalence of 58.5% in a group of 106 intravenous drug users with HCV infection.[27] Most recently, Seto *et al.* reported in 2010 that intravenous drug use was responsible for HCV transmission in 28.2% of patients with HCV genotype 6 when compared with only 8.7% for those with HCV genotype 1.[28]

DIAGNOSIS AND CLASSIFICATION

At the molecular level, HCV is recognised as a member of the *Flaviviridae* family with its linear, positive-sense, single-stranded RNA genome translated through a single open reading frame. Flanked by highly conserved untranslated regions (UTR) at both the 5′ and the 3′ ends, the 9.6 kilobase genome encodes for a large polyprotein precursor that is further processed into three structural proteins (core, E1, E2) and seven nonstructural

Figure 2 | Representation of hepatitis C genome. UTR, untranslated region; C, core; E, envelope; P, protein crucial for viral particle production; NS, nonstructural protein.

proteins (P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) (Figure 2). Replication by RNA-dependent RNA-polymerase is an imperfect process with high mutation rates and thus leads to the vast HCV genomic diversity. It is this sequence diversity that forms the basis for classification of HCV into genotypes and subtypes.

Proper classification of HCV genotypes and subtypes is dependent on nucleotide sequence disparity. In 2005, HCV experts met for the purpose of reaching a consensus for the standardised classification of HCV genotype and subtypes for research and database purposes. The proposal was to maintain the classification system with primarily 6 HCV genotypes with each being differentiated from another by at least a 30% nucleotide disparity, whereas the various subtypes would be distinguished by a 20–25% sequence difference.[29, 30] Experts also agreed to require a minimum of three examples demonstrating at least 15% nucleotide variation in the core/E1 and NS5B regions to propose a provisional recognition for new HCV subtypes.[29] On the basis of such classification criteria, there are currently over 80 HCV subtypes recognised within the six established HCV genotypes 1 through 6. Speculation of the existence of a seventh and even eighth genotype from samples collected from emigrants of the Democratic Republic of Congo has also been proposed recently.[31]

The 5′-UTR is used for HCV viral detection, whereas both the core and NS5B are used for genotyping of HCV.[32] The importance and necessity of involving core sequencing in HCV genotype determination is underscored by the recognition that genotype 6 variants appear to share identical 5′-UTR sequences as genotype 1b. Consequently, earlier genotyping methods based solely on 5′-UTR sequences such as INNO-LiPA HCV I (Innogenetics, Zwijnaarde, Belgium) have since proven to be unreliable for the accurate classification of patients with HCV infection. Providing additional core sequencing information, the updated INNO-LiPA HCV II genotyping assay (Innogenetics, Zwijnaarde, Belgium) has demonstrated remarkable improvement in genotyping accuracy and differentiation between HCV genotype 1 and genotype 6 variants.[33–35]

Recent studies have taken interest in the distribution of HCV genotype 6 subtypes and its potential use as a tool for tracking human migration. Models suggest that HCV genotype 6 subtypes evolved from a common ancestor existing over 1000 years ago, including an estimate between 1100 and 1350 years ago by Pybus *et al.*[18] Phylogenetic maps constructed by comparing nucleotide sequences of the subtypes reflect that the molecular similarities among the various HCV genotype 6 subtypes can be classified into at least four different groups: group 1 (G1: 6a and 6b), group 2 (G2: 6c, 6d, 6e, 6f, 6g, 6o, 6p, 6q, 6r, 6s, 6t), group 3 (G3: 6h, 6i, 6j, 6k, 6l, 6m, 6n) and group 4 (G4: 6u and 6v) respectively (Figure 1). Considering the endemic presence of certain subtypes (such as subtype 6d in Vietnam, 6f in Thailand, 6g in Indonesia and 6q in Cambodia)[18] together with the discovery of these subtypes in neighbouring countries, the geographic distribution of HCV genotype 6 subtypes reflect patterns of human migration and viral transmission.

Hepatitis C virus genotype 6 is unique for its extreme subtype diversity with 22 currently recognised subtypes designated alphabetically from 6a to 6v.[23, 36] Improved sequencing techniques and an expanding database have contributed to the recent growth in discovering new genotype 6 subtypes. Of the 22 subtypes, 6a has been reported in China, Vietnam, Thailand and Myanmar.[32] In Vietnam, HCV subtype 6a is found throughout the country, and is the predominant form in North Vietnam with one study reporting 37.1% prevalence among blood donors with HCV infection from this region.[32] Subtype 6a is also a common subtype present in major cities across China as well as blood donors and intravenous drug users from Hong Kong.[24] Its presence in Thailand, Myanmar and Vietnam, but absence in Singapore, Indonesia and the Philippines suggests 6a is found mainly in northern Southeast Asian countries.[32] Subtypes 6b and 6c are found primarily in Thailand, which currently also serves as the exclusive home for subtypes 6f, 6i and 6j.[23]

Subtypes 6d, 6e, 6h, 6l and 6t have been discovered mainly in Vietnam, where the identification of ten genotype 6 subtypes makes it the most diverse of any country.[21, 23] One study reports a high nucleotide sequence similarity between 6e and 6u,[37] which so far has only been reported in China,[38] and therefore suggests a more recent common ancestor between these two subtypes. China and Vietnam are also the reported homes of subtypes 6k, 6o and 6p. Subtypes 6m and 6n are more prominent in Thailand and Myanmar with 6m common in Burmese male patients younger than 20 years old and 6n common in Burmese women aged 20–39 years old.[14] Subtype 6n is also reported as the most common HCV genotype 6 subtype in Myanmar, where genotype 6 accounts for nearly 50% of HCV infections and even upwards of 60% in certain cities.[14] Subtypes 6r, 6s and 6t have been discovered in Cambodian immigrants,[21, 22] whereas the most recently discovered subtype, 6v, has been reported in both Thailand and China in 2008.[36]

Methods used for HCV genotyping

Several methods have been developed to determine HCV genotype. Although the most reliable method is by directly sequencing the entire genome,[39, 40] attempts to accurately and reliably identify HCV genotypes using partial genome sequences and other more resourceful methods have been sought. At present, commercially available methods generally use distinct motifs found within the HCV genome to either indirectly or directly genotype HCV. As the sole indirect method of HCV genotype determination, serotyping uses type-specific antibodies and competitive enzyme immunoassays (Murex HCV Serotyping 1–3 and 1–6 Assays, Murex Diagnostics, Dartfort, UK). Direct methods of genotype determination include direct sequence analysis of 5′-UTR only (TruGene HCV 5′NC, Visible Genetics, Toronto, Ontario, Canada), restriction fragment length polymorphism analysis and line probe assays, which involve reverse hybridisation to genotype-specific probes of the 5′-UTR only (INNO-LiPA HCV I, Innogenetics, Zwijnaarde, Belgium) or both 5′-UTR and core regions (INNO-LiPA HCV II, Innogenetics, Ghent, Belgium).[17, 41–43]

Several studies have assessed the reliability of different tests to successfully characterise HCV genotype 6 and its subtypes. One study in 2006 by Chinchai *et al.* concluded that sequencing a 222-base pair fragment in the NS5B region as suggested by Simmonds *et al.* to be representative of the entire genome was inaccurate and unreliable for discriminating HCV genotype 6 from other genotypes.[44] Chinchai *et al.* also concluded in an earlier 2003 study comparing differences in methods for genotyping HCV genotype 6 that two restriction fragment length polymorphism methods as suggested by Buoro *et al.* and Mellor *et al.* can produce too many untypable and/or indeterminate results to be useful for identifying HCV genotypes and genotype 6 variants.[45] In this same study, Chinchai *et al.* also assessed the validity of a line probe assay (INNO-LiPA HCV I; Innogenetics, Zwijnaarde, Belgium) that characterised genotypes by the hybridisation of denatured 5′-UTR products and concluded that this method consistently misidentified samples of HCV genotype 6a as 1b.[45] Further studies have likewise reported that this line probe assay may incorrectly identify HCV genotype 6c to 6l variants as genotype 1b due to a shared identical 5′-UTR that is probably responsible for the cross reactivity between 1b probes with 6c to 6l sequences.[33]

Although INNO-LiPA HCV I had limited accuracy and failed to reliably discriminate HCV genotype 6 subtypes from genotype 1, INNO-LiPA HCV II, which builds upon INNO-LiPA HCV I using additional sequencing information from the core region of the HCV genome, has demonstrated improved ability to distinguish between genotype 6c-l and genotype 1.[35] A study by Noppornpanth *et al.* in 2006 supports improved characterisation of HCV genotype 6 by INNO-LiPA HCV II, revealing a 96% (70 out of 73) accuracy rate in classifying HCV genotypes and 100% success rate in distinguishing HCV genotype 6 variants from genotype 1.[35] A 2007 study by Bouchardeau *et al.* also supported the findings of improved accuracy of INNO-LiPA HCV II compared with INNO-LiPA HCV I, although their sample pool consisted of just two HCV genotype 6 variants.[34] Most recently, Verbeeck *et al.* contributed further evidence that INNO-LiPA HCV II is more effective than INNO-LiPA HCV I in distinguishing HCV genotype 6c to 6l from genotype 1b in a study involving 326 specimens.[33]

CLINICAL CHARACTERISTICS

To date, there is only one published study that specifically addresses the clinical characteristics of patients with HCV genotype 6. In this retrospective study, Nguyen *et al.* assessed 181 patients with HCV infections determined by core sequencing to be either genotype 1, 2, 3 or 6 and noted that genotype 1 patients were more likely to be male ($P = 0.08$) at baseline compared with patients of other genotypes.[7] HCV genotype 1 and genotype 6 patients also had higher baseline median hepatitis C RNA levels compared with patients with genotypes 2 and 3; however, these differences were not statistically significant. HCV genotype 6 patients did not otherwise

demonstrate any significant differences with regard to host factors (e.g. age, history of smoking/alcohol use, family history of CHC/hepatitis B/hepatocellular carcinoma/liver-related death), baseline laboratory values (e.g. ALT, total bilirubin, albumin, white blood cell count, platelet count) or liver histology compared with patients with other HCV genotypes.[7]

TREATMENT

Hepatitis C virus genotype is recognised as a major independent predictor of response to anti-HCV therapy.[25] Two primary measures of treatment response include end-of-treatment response (ETR), defined as undetectable hepatitis C RNA at the end-of-treatment, and sustained virological response (SVR), defined as undetectable hepatitis C RNA 24 weeks after the end-of-treatment.[3, 20, 24]

Prior studies have established that HCV genotypes 1 and 4 appear to be more resistant to therapy compared with genotypes 2 and 3.[2] The few published treatment studies involving HCV genotype 6 generally suggest that genotype 6 behaves more similar to genotypes 2 and 3[2, 3, 46] and responds better to therapy than genotype 1.

Treatment outcomes in HCV genotype 1 vs. genotype 6

Sustained virological response to inteferon-based therapy is generally higher in patients with HCV genotype 6 compared with those with HCV genotype 1 (Table 3a). Dev *et al.* arrived at this conclusion in a 2002 study reporting an 82.5% SVR rate in those with HCV genotype 6 compared with a 61.9% in those with genotype 1.[47] In 2003, Hui *et al.* demonstrated significantly lower SVR and ETR rates in HCV genotype 1 patients compared with those infected with genotype 6.[48] These findings were again replicated in 2008 by Fung *et al.*[25] Recently, Nguyen *et al.* also reported significantly higher SVR achieved by patients with genotype 6 compared with those with genotype 1 (74% vs. 49%).[3]

Duration of treatment

With improved SVR achieved by patients infected with HCV genotype 6, consideration was given to whether 48 weeks of treatment was necessary or whether 24 weeks of treatment would be sufficient. A small retrospective study of Asian-American patients comparing 12 patients receiving a 48-week course of peginterferon and ribavirin with 23 patients receiving a shortened 24-week course reported that significantly higher SVR was achieved by the 48-week cohort compared with those in the 24-week cohort (75% vs. 39%).[49] However, the analysis performed in this study was not by intention-to-treat analysis.[50] More recently, results of a prospective randomized controlled study of 60 HCV genotype 6 patients treated for 24 weeks vs. 48 weeks suggest that these two patient groups have fairly similar SVR rates (70% vs. 79%; $P = 0.45$) (Table 3b).[51] Larger studies, however, are needed to definitively determine the optimal treatment duration for these patients.

Safety and side effect profile of treatment

Hepatitis C virus genotypes clearly play a role in achieving SVR, but there is no significant difference in the frequency or types of side effects experienced among patients of genotypes 1, 2, 3 or 6.[3, 25, 47] However, although the incidence and types of side effects caused by therapy with PEG IFN and RBV are similar among patients of different HCV genotypes, side effect profiles appear to differ among patients of different ethnicities. As almost all patients with HCV genotype 6 are from Asia, their side effect profile would probably mirror those of patients of similar heritage. In a study by Vutien *et al.*, Asian patients were more likely than Caucasians to require ribavirin dose reduction and were more likely to discontinue treatment because of anaemia. In addition, they were also more likely to report fatigue, muscle aches, anorexia and insomnia.[20] On the other hand, Caucasian patients were more likely to report side effects of fever, dyspnoea and depression, although it has been previously suggested that Asian patients are comparatively less likely to report depression because of the associated social stigma.[3, 20, 52]

The impact of race on treatment response

The effect of race and ethnicity in treatment of hepatitis C genotype 6 patients is not clearly defined. Multiple studies have demonstrated that African-American and Hispanic patients appear to respond more poorly to antiviral treatment for chronic hepatitis C compared with Caucasian patients.[53–56] On the other hand, higher SVR rate in Asian patients with chronic hepatitis C compared with Caucasian patients has been reported by some authors.[47, 57] Dev *et al.* reported higher SVR rate in Asian patients compared with Caucasian patients with genotype 1b. With recent studies reporting that INNO-LiPA HCV I may confuse HCV genotype 6 as genotype 1 because of a shared 5′-UTR sequence, the question was raised whether Asian patients with HCV genotype 1 were truly exhibiting better treatment response than their Caucasian counterparts or whether 'easier-to-treat' HCV genotype 6 patients who were mistyped by early INNO-LiPA assays were included in the genotype 1 cohort. In a more recent study of Caucasians and Asian-Americans with chronic hepati-

Table 3a | Treatment outcomes of HCV genotype 6 (and genotype 1)

Author	Year	Country	Study design	Treatment	Treatment duration (weeks)	Diagnosis	Genotype	*n*	SVR (%)	*P*-value
Dev[47]	2002	Australia	Retrospective	IFN2b + RBV	52	INNO-LiPA HCV I* and core sequencing	6	33†	82.5	NR
							1	17	61.9	
Hui[48]	2003	Hong Kong	Prospective	IFN2b + RBV	52	VERSANT HCV Genotype Assay LiPA‡	6	16	62.5	0.04
							1	24	29.2	
Cheng[65]	2006	USA	Retrospective	PEG/IFN + RBV	NR	NR	6	13	69.2	0.026
							1	61	32.8	
Fung[25]	2008	Hong Kong	Prospective	PEG2a (20)/PEG2b (22) + RBV	52	Linear Array Detection Kit	6	21	85.7	0.019
							1	21	52.4	
Nguyen[3]	2009	USA	Retrospective	PEG2a/PEG2b + RBV	48	Core sequencing§	6	34	74	0.016
							1	70	49	
Seto[28]	2010	Hong Kong	Retrospective	IFN/PEG + RBV	52	Linear Array Detection Kit	6	26	92.3	NR
							1	21	42.9	
Tsang[66]	2010	Hong Kong	Retrospective	PEG2a/PEG2b + RBV	48	VERSANT HCV Genotype Assay LiPA	6	70	75.7	NR
							1	70	57.1	

SEA, Southeast Asian; PEG, pegylated interferon; IFN, interferon; RBV, ribavirin; SVR, sustained virological response; NR, not reported; HCV, hepatitis C virus.

* SEA patients with HCV genotype 1, 1a, 1b, and 6a and Caucasian patients with genotype 1b determined using INNO-LiPA were further analysed by sequencing the HCV core region.

† HCV genotype 6 reported as genotypes 7, 8, 9, which were later determined in future studies to be more accurately classified as subtypes of genotype 6.

‡ Patients with HCV genotype 1 had samples retested by amplification of part of HCV HS5B region and subsequent phylogenetic analysis to confirm samples were not genotypes 7,8 or 9.

§ For patients sequenced using INNO-LiPA, 85% of HCV genotype 6 patients reported achieving SVR compared with 63% of HCV genotype 1 patients.

Table 3b | Treatment outcomes of HCV genotype 6, by treatment duration

Author	Year	Country	Study design	Treatment	Treatment duration (weeks)	*n*	SVR (%)
Nguyen[49]	2008	USA	Retrospective cohort	PEG IFN + RBV	24	23	39
					48	12	75
Lam[51]	2010	USA	Randomized control trial	PEG IFN + RBV	24	27	70
					48	33	79

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

tis C by Vutien *et al.*, Asian patients with HCV genotype 1 as diagnosed using INNO-LiPA assays demonstrated higher SVR to 48-week therapy of PEG IFN and RBV compared with Caucasian counterparts, but similar SVR rates when the Asian HCV genotype 1 group only included those who were diagnosed with HCV genotype 1 using core sequencing methods.[20] Taken together, these observations suggest the earlier claims of improved treatment response in Asian patients with genotype 1 could be due to HCV genotyping error rather than ethnic differences, though in some cases improved responses can also be due to higher prevalence of treatment-responsive haplotype IL-28B in this population.[20, 58]

Predictors of SVR

As in studies of patients with chronic hepatitis C with other genotypes, treatment adherence was also found to be an independent favourable predictor for SVR in studies of patients with HCV genotype 6.[3] Independent predictors of poor SVR in the patients with HCV genotype 6 include BMI > 25 and increased age.[3]

Rapid virological response (undetectable HCV RNA after 4 weeks of treatment) was found to be a statistically significant predictor of SVR in HCV genotype 6 patients on 48 weeks of antiviral treatment in a recent randomised controlled trial of patients with HCV genotype 6.[51] However, this study as well as another study by Fung *et al.* did not find early virological response (undetectable HCV RNA at 12 weeks) to be associated with SVR in genotype 6 patients.[25] The small sample sizes in both of these studies, however, limit their conclusions and further studies are needed.

SUMMARY

Chronic hepatitis C is a significant worldwide health burden that is underappreciated among Asians and Southeast Asians, the latter carrying the greatest burden of HCV genotype 6 in Asia. Current literature suggests that Southeast and East Asian patients face different risk factors for HCV acquisition compared with Caucasian patients and are often exposed to HCV through nosocomial spread and other unsanitary medical practices rather than more traditional risk factors recognised in the United States such as intravenous drug use. HCV genotype 6 patients do not demonstrate any significantly different clinical characteristics compared with patients infected with HCV of other genotypes. Accurate diagnosis of HCV genotype 6 requires core sequencing assays or newer INNO-LiPA assays, as older line probe assays have been shown to mistake genotype 6 subtype variants as genotype 1. Patients infected with HCV genotype 6 can expect higher SVR compared with patients with HCV genotype 1 and their SVR to PEG IFN and RBV is probably similar to that of patients with HCV genotypes 2 and 3. SVR rates also appear to be similar in patients with HCV genotype 6 who receive 24 weeks of PEG IFN and RBV and those who receive 48 weeks of therapy, though additional studies are needed to recommend 24 weeks as the optimal treatment duration for these patients.

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