

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2019.08.857

Journal of GHR 2019 October 21; 8(5): 2962-2971
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

ORIGINAL ARTICLE

Baseline Characteristics and Treatment Cost of Hepatitis C at Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam in Direct-Acting Antiviral Treatment Era

Dung Nguyen Thanh¹, Thanh Tran Thi Thanh², Ngoc Nghiem My¹, Huyen Anh Nguyen², Phuong Le Thanh¹, Quang Vo Minh¹, Motiur Rahman^{2,3}, Hung Le Manh¹

1 The Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam;

2 Oxford University Clinical Research Unit, Wellcome Trust Asia Programme, The Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam;

3 Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, Oxford University, Oxford, United Kingdom.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Hung Le Manh, Vice Director, The Hospital for Tropical Diseases, 764 Vo Van Kiet Street, Ward 1, District 5, Ho Chi Minh City, Vietnam and Motiur Rahman, MBBS, Ph.D., Head of Laboratories, Centre for Tropical Medicine, Oxford University Clinical Research Unit 764 Vo Van Kiet Street, Ward 1, District 5, Ho Chi Minh City, Vietnam.

Email: mrahman@oucru.org

Telephone: +84839237954

Fax: +84839238904

Received: July 12, 2018

Revised: August 20, 2019

Accepted: August 23, 2019

Published online: October 21, 2019

ABSTRACT

BACKGROUND: Direct-Acting Antivirals (DAAs) are recommended as first-line of drugs for the treatment of chronic

hepatitis C virus (HCV) infection in Vietnam in 2016. Since then, Hospital for Tropical Diseases (HTD), Ho Chi Minh City, Vietnam introduced DAAs based treatment for all newly presented chronic HCV patients. Here, we report the sociodemographic, clinical, biochemical, and virologic characteristics of patients and the direct medical cost associated with DAAs treatment.

METHODS: We conducted a retrospective cross-sectional study among chronic HCV patients attended at HTD from March 2016 to October 2017 and treated with DAAs. We used an extract of the patient's electronic medical record containing demographics, clinical presentations, laboratory results, drug prescription, and cost of treatment at the hospital for data analysis.

RESULTS: 2817 chronic HCV patient received DAAs treatment during the study period. The mean age was 55.0 years, and 54.9% (1546/2817) of the patients were female. HCV genotype 1, 2, 3 and 6 prevalence was 32.1% (904/2817), 12.7% (359/2817), 0.4% (10/2817), and 54.7% (1542/2817) respectively. The mean HCV viral load was 3.1×10^6 copies/ml, including 46.9% (1322/2817) had $\geq 10^6$ copies/ml. 70.64% (1990/2817) and 16.15% (455/2817) of the patients received Sofosbuvir (SOF)/Ledipasvir (LDV) \pm Ribavirin (RBV) and SOF/Daclatasvir (DCV) \pm RBV therapy respectively. The average drug cost for a 12-week of SOF/LDV \pm RBV and SOF/DCV \pm RBV treatment was US\$2068 - 2230 and US\$2417 - 2472, respectively.

CONCLUSION: Genotype 6 was the most predominant genotype in southern Vietnam. The preferred treatment for chronic HCV infection was SOF/LDV \pm RBV for 12 weeks.

Key words: Hepatitis C; Vietnam; DAAs; Genotype

© 2019 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Dung NT, Thanh TTT, Ngoc NM, Nguyen HA, Phuong LT, Quang VM, Rahman M, Hung LM. Baseline Characteristics and Treatment Cost of Hepatitis C at Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam in Direct-Acting Antiviral Treatment Era. *Journal of Gastroenterology and Hepatology Research* 2019; 8(5): 2962-2971 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2633>

INTRODUCTION

Hepatitis C virus (HCV) infection is a significant public health problem. Global Health Sector Strategy (GHSS) on viral hepatitis 2016-2021 calls for the elimination of viral hepatitis, reducing new infections by 90% and mortality by 65% by 2030^[1]. WHO calls for expanding the continuum of care to ensure the treatment of 90% of the diagnosed HCV cases by 2030^[2]. Availability of Direct-Acting Antivirals (DAAs) revolutionized the HCV treatment landscape, and more and more HCV infected patients are treated globally^[3]. Global variation of DAAs based HCV treatment cost is attributed to the availability of generics, government policy on the treatment of HCV, and insurance copayment^[4]. With the availability of generic drugs, treatment of HCV is affordable in many lower middle lower countries (LMIC) including Vietnam^[5].

WHO Western Pacific region, including Vietnam, bears the highest burden of HCV, with an estimated 19.2 million infections^[5]. Vietnam is amongst the 20 countries with the highest HCV burden, with an estimated 1.5 million chronic HCV infected people (estimated HCV RNA prevalence 1.1%) (<https://www.who.int/westernpacific/health-topics/hepatitis/regional-hepatitis-data>)^[6].

Ministry of Health (MoH), Vietnam has revised HCV treatment guideline in 2016 and recommended DAAs as the first-line of treatment for chronic HCV^[7]. The revised HCV treatment guideline provides (1) list of approved DAAs for treatment of HCV (for different HCV genotypes and liver condition); (2) test recommendations before, during and after completion of treatment; and (3) the duration of treatment. The approved DAAs includes Sofosbuvir (SOF), Daclatasvir (DCV), Ledipasvir (LDV), Velpatasvir (VEL), Paritaprevir (PTV), Ombitasvir (OBV), Ritonavir (r), Dasabuvir (DSV), Simeprevir (SMV), Grazoprevir (GZR), elbasvir (EBR). The regimen recommendation includes; (1) Only DAAs combinations; (2) DAAs combination and RBV; and (3) Pegylated interferon (PegIFN), Ribavirin (RBV) and SOF. Treatment duration includes a 12-week treatment with DAAs for non-cirrhotic patients and either a 24-week treatment with only DAAs or a 12-week treatment with DAAs and RBV for cirrhotic patients. Based on HCV genotype and liver condition of the patient regimens are recommended (S1 File). The guideline outlines the laboratory tests for initiation of DAAs treatment and subsequent monitoring for different treatment regimens (S2 File). This includes routine hematology, clinical chemistry, HCV genotype, HCV RNA, and liver fibrosis assessment. Patients are referred to designated provincial hospitals or specialized hospital if district hospitals lack facilities for these tests^[8].

Real-world data on chronic HCV patients with DAAs treatment is limited in Vietnam due to insufficient HCV RNA and genotype detection facility, limited research initiatives, and a weak record keeping system. We conducted a descriptive cross-sectional study to present the sociodemographic, clinical, biochemical, virologic characteristics, and HCV treatment cost of patients attended at HTD, Vietnam.

METHODS

Study description and ethical approval

We conducted a retrospective cross-sectional study among chronic HCV patients attended at HTD hepatitis outpatient department from March 2016 to October 2017. All chronic HCV patients (treatment naïve or prior treatment failure with PegIFN + RBV) treated with DAAs at HTD during the study period were eligible for inclusion

in this study. HTD ethics review committee approved the research protocol, including data extraction and analysis (approval no CS/ND/16/02 date 23/11/2017).

Patient and data extraction

HTD is a 650-bed tertiary infectious disease hospital in the southern region of Vietnam. HTD is additionally a designated specialized hospital for hepatitis patients for Central and Southern Vietnam. The hospital has a dedicated hepatitis outpatient department (OPD). In 2015, HTD introduced electronic record keep system for OPD. The database captures sociodemographic, clinical, and treatment information for each patient under a unique ID number. The HTD clinical laboratory maintains a separate database for laboratory investigations linked to the OPD database. Hospital record management team extracted sociodemographic, clinical, laboratory, and drug prescription data of the eligible patients from the database. The patient ID was replaced with a serial number to unlink the dataset before transfer to study investigators.

Laboratory tests

A Sysmex XN-100 analyzer (Sysmex USA) and a Cobas 6000 analyzer (Roche, Basel, Switzerland) are used for full blood counts and serum biochemistry tests in HTD clinical laboratory respectively (ISO 15189; 2012 accredited). HCV viral load was measured by real-time polymerase chain reaction assay (COBAS AmpliPrep COBAS TaqMan HCV Test version 2.0; (Roche Molecular Diagnostics, Pleasanton, CA), which defines an HCV viral load < 15 IU/mL as “undetectable” as per manufacturers recommendations. HCV genotype was determined by “Real-time HCV Genotype assay II” using Abbott m2000sp/rt system (Abbott Molecular Inc, IL, USA). Liver fibrosis was measured by fibroscan (Abbott FibroScan VCTE, USA).

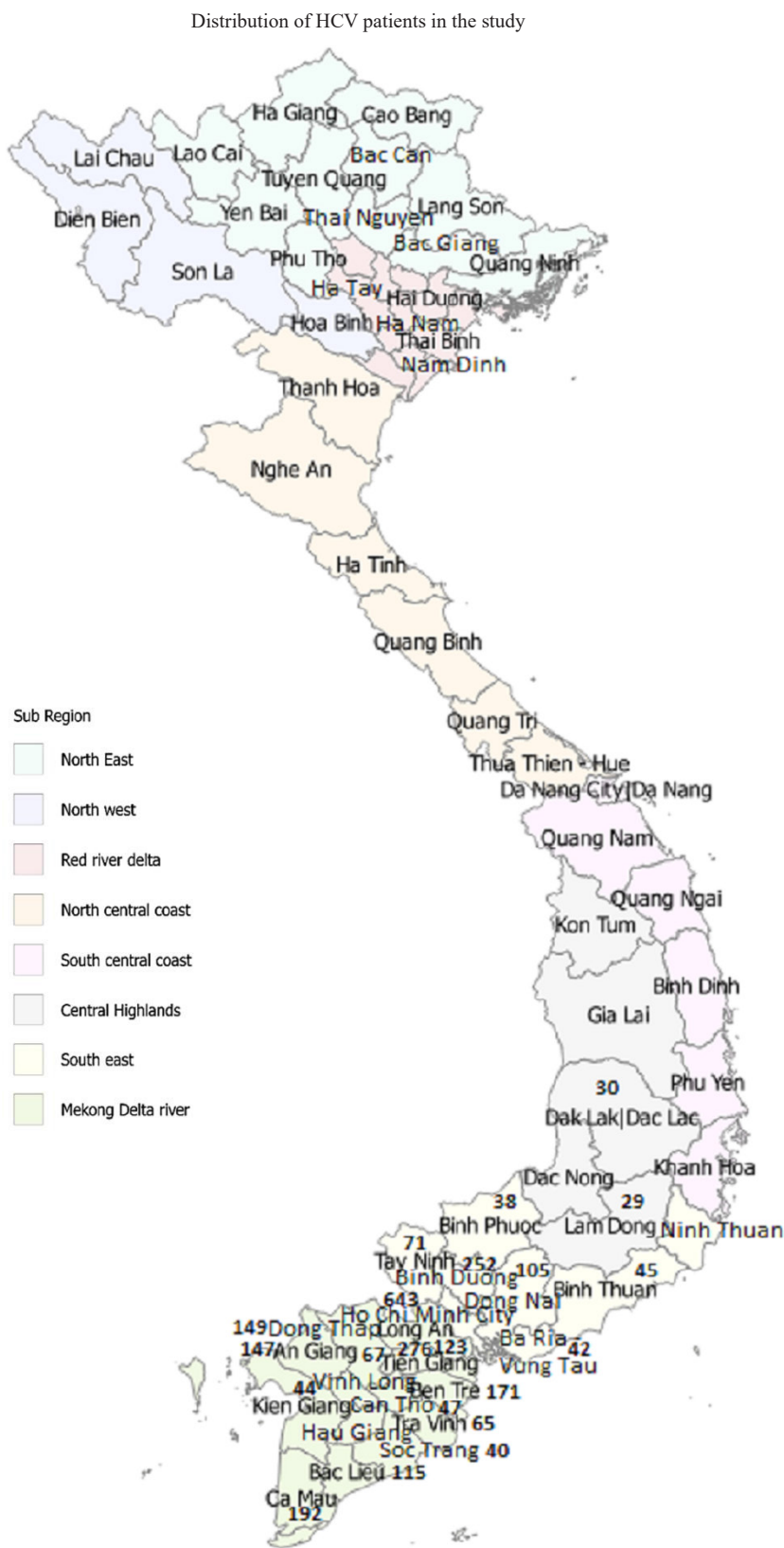
The body mass index (BMI), aspartate aminotransferase to platelet ratio index (APRI), and Fibrosis-4 (FIB-4) score were calculated as described earlier^[9]. A FIB-4 < 1.45 indicates absence of cirrhosis and > 3.25 indicates cirrhosis. An APRI score < 0.5 indicates the absence of fibrosis and > 1.5 indicates fibrosis, and > 2.0 indicates cirrhosis^[10]. Test results from selected hospitals were acceptable at HTD (e.g., provincial hospitals and ISO 15189 accredited laboratories under MoH Vietnam, mutual recognition program) for treatment initiation and monitoring; however, these data were not available in the database (maintained in the patient file) and not included in the analysis.

Treatment for chronic HCV patients

All eligible patients received DAAs based therapy. HCV genotype and liver status (non-cirrhotic, compensated cirrhosis (Child-Pugh A) and decompensated cirrhosis (Child-Pugh B or C)) were used for determination of DAAs therapy. The prescribed DAAs include (1) SOF ± RBV; (2) LDV/SOF ± RBV; (3) DAC/SOF ± RBV; and (4) Elbasvir and Grazoprevir. Non-cirrhotic patients (irrespective of HCV genotype) receive a 12-week treatment. Cirrhosis (Child-Pugh B or C) patients receive a 24-week treatment with only DAAs or a 12-week treatment with DAAs and RBV^[7]. Patients with HBV or HIV co-infections are treated as per the national treatment guideline^[11].

Health economics analysis

Cost analysis estimated the direct medical cost of HCV treatment from the health sector perspective (only includes the costs associated with the health sector, i.e., includes the costs covered by the government’s health insurance program and the patient’s



S1 Figure Geolocation of chronic HCV patients attended at HTD and treated with DAAs. Name of the province and number of patients from each province is indicated in the province boundary. Sub-regions are highlighted with different colors.

S2 File. Test recommendation before, during and after treatment of Chronic HCV with DAA, DAA+RBV and PegIFN+RBV+SOF (Issued together with Decision No. 5012/QĐ-BYT by MoH, Vietnam)

Time	DAA		DAA+RBV				PegIFN + RBV + SOF				
	FBC, renal, liver function	Abdominal ultrasound, AFP	Evaluation of liver fibrosis \$	HCV RNA	HIV, HBsAg, HCV genotype	FBC, renal, liver function	Thyroid function	Abdominal ultrasound, Chest X ray, ECG, AFP	Evaluation of liver fibrosis\$	HCV RNA	HBsAg, HIV, HCV genotype
Baseline	X	X	X	X	X	X	X	X	X	X	X
Week 4	X			X		X	X			X	
Week 8				X*		X				X*	
Week 12	X			X		X	X	X		X	
12 Week after EOT	X			X		X	X	X		X	
24 Week after EOT				X		X	X	X	X	X	

FBC (Full blood count); (Red blood cell count, white blood cell counts, Platelet count, HCT, MCV, MCH, MCHC, RDW hemoglobin). Renal function test; (blood urea, creatinine) Liver function test (Bilirubin, AST, ALT, GGT, AFP, albumin, glucose, prothrombin). Thyroid function test; (T3, T4 ?). * If HCV RNA at week 4 of treatment is above the detection threshold, repeat HCV RNA test at week 8. If HCV RNA increases more than 1log₁₀ IU/ml: treatment should be stopped. FBC; Full Blood Count; \$; Noninvasive method, AFP; Alpha-fetoprotein, ECG; Electrocardiogram, EOT; End of Treatment

S1File a. Treatment regimens for non-cirrhotic Chronic HCV patients.

Genotype	SOF/LDV	SOF/DCV	SOF + RBV	GZR/EBR	SOF/VEL	SMV + SOF	PTV/OBV/r + DSV	PTV/OBV/r	PegIFN + RBV+SOF
1a	12 weeks	12 weeks	NO	12 weeks	12 weeks	12 weeks	12 weeks (+RBV)	NO	12 weeks
1b	12 weeks	12 weeks	NO	12 weeks	12 weeks	12 weeks	12 weeks	NO	12 weeks
2	NO	12 weeks	12 weeks	NO	12 weeks	NO	NO	NO	12 weeks
3	NO	12 weeks	24 weeks	NO	12 weeks	NO	NO	NO	12 weeks
4	12 weeks	12 weeks	NO	12 weeks	12 weeks	12 weeks	NO	12 weeks (+RBV)	12 weeks
5,6	12 weeks	12 weeks	NO	NO	12 weeks	NO	NO	NO	12 weeks

S1File b. Treatment regimens for Chronic HCV compensated cirrhosis (Child Pugh A) patients

Genotype	SOF/LDV	SOF + DCV	SOF+RBV	GZR/EBR	SOF/VEL	SMV + SOF	PTV/OBV/r + DSV	PTV/OBV/r	PegIFN + RBV+SOF
1a	24 weeks or 12 weeks (+ RBV)	24 weeks or 12 weeks (+RBV)	NO	12 weeks	12 weeks	24 weeks or 12 weeks (+RBV)	24 weeks (+RBV)	NO	12 weeks
1b	24 weeks or 12 weeks (+ RBV)	24 weeks or 12 weeks (+RBV)	NO	12 weeks	12 weeks	24 weeks or 12 weeks (+RBV)	12 weeks (+RBV)	NO	12 weeks
2	NO	12 weeks	16 – 20 weeks	NO	12 weeks	NO	NO	NO	12 weeks
3	NO	24 weeks + RBV	NO	NO	12 weeks	NO	NO	NO	12 weeks
4	24 weeks or 12 weeks (+RBV)	24 weeks or 12 weeks (+RBV)	NO	12 weeks	12 weeks	24 weeks or 12 weeks (+RBV)	NO	24 weeks (+RBV)	12 weeks
5,6	24 weeks or 12 weeks (+RBV)	24 weeks or 12 weeks (+RBV)	NO	NO	12 weeks	NO	NO	NO	12 weeks

S1File b. Treatment regimens for Chronic HCV compensated cirrhosis (Child Pugh A) patients

Genotype	SOF/LDV	SOF + DCV	SOF+RBV	GZR/EBR	SOF/VEL	SMV + SOF	PTV/OBV/r + DSV	PTV/OBV/r	PegIFN + RBV+SOF
1a	24 weeks or 12 weeks (+ RBV)	24 weeks or 12 weeks (+RBV)	NO	12 weeks	12 weeks	24 weeks or 12 weeks (+RBV)	24 weeks (+RBV)	NO	12 weeks
1b	24 weeks or 12 weeks (+ RBV)	24 weeks or 12 weeks (+RBV)	NO	12 weeks	12 weeks	24 weeks or 12 weeks (+RBV)	12 weeks (+RBV)	NO	12 weeks
2	NO	12 weeks	16 – 20 weeks	NO	12 weeks	NO	NO	NO	12 weeks
3	NO	24 weeks + RBV	NO	NO	12 weeks	NO	NO	NO	12 weeks
4	24 weeks or 12 weeks (+RBV)	24 weeks or 12 weeks (+RBV)	NO	12 weeks	12 weeks	24 weeks or 12 weeks (+RBV)	NO	24 weeks (+RBV)	12 weeks
5,6	24 weeks or 12 weeks (+RBV)	24 weeks or 12 weeks (+RBV)	NO	NO	12 weeks	NO	NO	NO	12 weeks

S1File c. Treatment regimens for Chronic HCV decompensated cirrhosis (including moderate and severe liver failure, Child Pugh B or C) patients.

Genotype	SOF+RBV	SOF/LDV	SOF/DCV	SOF/VEL
1a	NO	24 weeks or 12 weeks (+RBV)	24 weeks or 12 weeks (+ RBV)	24 weeks or 12 weeks (+ RBV)
1b	NO			
2	16-20 weeks	NO		
3	NO	NO		
4	NO	24 weeks or 12 weeks (+RBV)		
5, 6	NO			

SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; VEL: Velpatasvir; PTV: Paritaprevir; OBV: Ombitasvir; r: Ritonavir; DSV: Dasabuvir; SMV: Simeprevir; GZR: Grazoprevir; EBR: Elbasvir; PegIFN: Pegylated interferon; RBV: Ribavirin; NO: Not recommended.

S1 File d Dosage for different Treatment regimens following Decision No. 5012/QĐ-BYT by MoH, Vietnam.

Name of Drug	Characteristic	Dosage	Available in HTD
Sofosbuvir (SOF)	Tablet 400mg	One per day	Available
Daclatasvir (DCV)	Tablet 30mg, 60mg	One per day	Available
Sofosbuvir/ Ledipasvir (LDV)	Tablet 400mg SOF /90mg LDV	One per day	Available
Sofosbuvir/ Velpatasvir (VEL)	Tablet 400mg SOF /100mg VEL	One per day	Available
Paritaprevir (PTV)/ Ombitasvir (OBV)/ Ritonavir	Tablet: 75mg PTV/ 12,5mgOBV/ 50mg ritonavir	Two per day	Not available
Dasabuvir (DSV)	Tablet 250mg	Two per day	Not available
Simeprevir (SMV)	Capsule 150 mg	One per day	Not available
Grazoprevir(GZR)/ Elbasvir (EBR)	Tablet 100mg GZR /elbasvir 50mg EBR	One per day	Available

Table 1 Socio-demographic characteristics of 2817 patient attending at HTD from March 2016 to October 2017 for treatment with DAAs.

Variable (n)		All patient (n = 2817)	Genotype 1 (n = 904)	Genotype 2 (n = 359)	Genotype 3 (n = 10)	Genotype 6 (n = 1542)	p value*	p value**
Age (2817)	Mean ± SD	55.0 ± 12.8	52.3 ± 13.0	58.4 ± 11.4	44.0 ± 14.3	55.8 ± 12.6	< 0.001	< 0.001
							< 0.001	< 0.001
	<40	16.3 (459)	23.7 (214)	7.8 (28)	60.0 (6)	13.7 (211)		
	41-55	30.3 (853)	30.0 (271)	29.0 (104)	30.0 (3)	30.7 (474)		
	>55	53.4 (1505)	46.3 (419)	63.2 (227)	10.0 (1)	55.6 (857)		
Gender (2817)							0.0001	< 0.001
	Female	54.9 (1546)	49.8 (450)	56.3 (202)	30.0 (3)	57.8 (891)		
	Male	45.1 (1271)	50.2 (454)	43.7 (157)	70.0 (7)	42.2 (651)		
Sub-Region (2817)							< 0.001	< 0.001
North		0.0 (1)						
	North East	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)		
	Red river delta	0.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)		
	North west	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)		
Central		5.7 (161)						
	North central coast	0.1 (3)	0.1 (1)	0.0 (0)	0.0 (0)	0.1 (2)		
	South central coast	2.5 (70)	2.9 (26)	0.8 (3)	10.0 (1)	2.5 (39)		
	Central Highlands	3.1 (88)	4.3 (39)	1.9 (7)	30.0 (3)	2.5 (39)		
South		94.2 (2654)						
	Mekong Delta river	51.7 (1455)	38.6 (349)	71.6 (257)	0.0 (0)	55.0 (848)	< 0.001	< 0.001
	South east	42.6 (1199)	54.1 (489)	25.6 (92)	60.0 (6)	39.7 (612)		
BMI (kg/m ²) (2243)								
	Mean ± SD	22.7 ± 3.4	22.8 ± 3.3	22.6 ± 3.4	26.0 ± 8.1	22.7 ± 3.3	0.054	0.655
							0.476	0.311
	<18	5.3 (120)	4.3 (31)	6.2 (17)	0.0 (0)	5.8 (72)		
	18-25	74.0 (1659)	74.1 (537)	76.2 (208)	66.7 (6)	73.5 (908)		
	>25	20.7 (464)	21.7 (157)	17.6 (48)	33.3 (3)	20.6 (255)		

*Compared between Genotype 1 vs Genotype 2 vs Genotype 3 vs Genotype 6. **Genotype 1 vs Genotype 6.

copayment for the medical services). We estimated the costs for a range of different regimens of DAAs (namely SOF/LDV ± RBV, SOF + DCV ± RBV, SOF + RBV, SOF/VEL, and GZR/EBR). Cost analysis does not include DAAs not available (for example, DSV, OBV, PTV, SMV) at HTD. The main output was the total cost of different treatments. This included three main cost components: the cost of the drugs, the cost of the medical tests, and the costs related to the clinical consultation fees. These costs are calculated following the national HCV treatment guideline and the service/test price list of HTD in 2017^[7]. All the costs were converted to US dollar (US\$) using the average 2017 exchange rate: 22,370 Vietnamese dong (VND) equal to 1 US\$^[12].

Data analysis

We used Statistical Package for Social Science (SPSS) software (IBM SPSS Statistics 23, NY USA) for data analysis. Geo-location data (at ward level) collected from the hospital database was recorded in QGIS v2.18 software, and QGIS v2.18 generates the geolocation map. We used Chi-Square or Fisher's exact test for categorical variables and Mann-Whitney U-test or Student's t-test continuous variables as appropriate. A *p*-value < 0.05 was considered statistically significant.

RESULTS

From March 2016 to October 2017, 2817, chronic HCV patients attending at hepatitis OPD received DAAs treatment. This include 2264 (80.4%: 2265/2817) patients in 2016 and 553 (19.6%: 553/2817)

in 2017. The prevalence of HCV genotype 1, 2, 3 and 6 was 32.1% (904/2817), 12.7% (359/2817), 0.4% (10/2817), and 54.7% (1542/2817) respectively. Among the patients, 45.1% (1271/2817) were male, and 83.7% (2358/2817) of the patients was ≥40 years old (Table 1). Patients with genotype 2 were significantly older than other genotypes (58.8 years versus 55.0 years; *p* < 0.001 chi-square test). Among genotype 1 and 6, genotype 6 patients were significantly older than genotype 1 (55.8 years versus 55.3 years; *p* < 0.001 chi-square test). Significantly more female patients were infected with HCV genotype 6 (57.8% versus 54.9%; *p* = 0.001 chi-square test).

94.3% (2654/2817) and 5.6% (161/2817) of the patients were from the southern and central region, respectively. Among the patients from the southern region, 42.6% (1199/2817) were from Southeast sub-region and 51.7% (1455/2817) from Mekong delta sub-region. 24.2% (643/2654) of the patients were from Ho Chi Minh City, and the rest were from the 19 provinces of the southern region (Table 1, S1 Fig). Within the southern region, the prevalence of genotype 1 was significantly higher in the Southwest sub-region (54.1% Southwest sub-region versus 39.7% Mekong delta sub-region), and genotype 6 was significantly higher in the Mekong delta sub-region (55.0% Mekong delta sub-region versus 38.6% Southwest sub-region, *p* ≤ 0.001, Chi-square test). Genotype 2 and 3 was significantly higher in Mekong Delta and southeast sub-region, respectively (Table 1). The BMI (mean ± standard deviation (SD)) was 22.7 ± 3.4 including 22.6 ± 3.3 for male patients and 22.7 ± 3.3 female patients (normal range for Vietnamese population is 18kg/m² to 25kg/m²). BMI > 25kg/m² was higher in genotype 3 patients (Table 1).

95.0% (2675/2817) patients were treatment naïve, and the

Table 2 Clinical characteristics of 2817 patient attending at HTD from March 2016 to October 2017 for treatment with DAAs.

Variable (n)		All patient (n = 2817)	Genotype 1 (n = 904)	Genotype 2 (n = 359)	Genotype 3 (n = 10)	Genotype 6 (n = 1542)	p value*	p value**
Prior treatment (2817)	No	95.0 (2675)	93.0 (841)	97.5 (350)	100.0 (10)	95.5 (1472)	0.004	0.011
	Yes	5.0 (142)	7.0 (63)	2.5 (9)	0.0 (0)	4.5 (70)		
Liver status (2811)							< 0.001	0.1
Non cirrhosis		64.5 (1818)	61.9 (560)	71.0 (255)	90.0 (9)	64.5 (994)		
Cirrhosis (Compensated)		34.6 (974)	36.8 (333)	27.6 (99)	10.0 (1)	35.1 (541)		
Cirrhosis (Decompensated)		0.7 (19)	1.1 (10)	0.6 (2)	0.0 (0)	0.5 (7)		
Diabetes (2817)							< 0.001	0.039
	No	96.1 (2708)	95.6 (864)	93.6 (336)	80.0 (8)	97.1 (1498)		
	Yes	3.9 (109)	4.4 (40)	6.4 (23)	20.0 (2)	2.9 (44)		
HBV coinfection (2817)							0.519	0.277
	No	97.4 (2743)	96.8 (875)	98.1 (352)	100.0 (10)	97.5 (1504)		
	Yes	2.6 (74)	3.2 (29)	1.9 (7)	0.0 (0)	2.5 (38)		
HIV coinfection (2817)	No	98.8 (2784)	97.6 (882)	100.0 (359)	100.0 (10)	99.3 (1531)	< 0.001	< 0.001
	Yes	1.2 (33)	2.4 (22)	0.0 (0)	0.0 (0)	0.7 (11)		
HCV VL (2460)								
	Mean \pm SD(IU/mL)	3.1x10 ⁶ \pm 5.2 x10 ⁶	2.1x10 ⁶ \pm 3.0 x10 ⁶	3.0x10 ⁶ \pm 4.9 x10 ⁶	5.5x10 ⁶ \pm 1.2 x10 ⁷	3.7x10 ⁶ \pm 6.2 x10 ⁶	0.002	< 0.001
							0.001	< 0.001
	\leq 6000000 IU/mL	40.4 (1138)	41.4 (374)	44.0 (158)	30.0 (3)	39.1 (603)		
	> 6000000 IU/mL	46.9 (1322)	43.3 (391)	42.1 (151)	50.0 (5)	50.3 (775)		
Fibroscan (1154)	Mean \pm SD (Kpa)	12.9 \pm 11.5	13.3 \pm 12.2	13.1 \pm 12.1	10.5 \pm 5.8	12.7 \pm 11.0	0.936	0.601
APRI (2564)	Mean \pm SD	0.71 \pm 0.84	0.69 \pm 0.72	0.81 \pm 1.12	0.47 \pm 0.24	0.70 \pm 0.84	0.725	0.322
	\geq 2	5.5 (137)	6.1 (48)	8.6 (28)	0.0 (0)	4.4 (61)	0.014	0.074
	< 2	94.5 (2372)	93.9 (736)	91.4 (296)	100.0 (9)	95.6 (1331)		
FIB-4 (2464)	Mean \pm SD	3.02 \pm 3.53	2.90 \pm 3.10	3.44 \pm 4.49	2.15 \pm 1.24	3.00 \pm 3.52	0.465	0.268
	\geq 3.5	26.1 (655)	25.1 (197)	28.7 (93)	11.1 (1)	26.1 (364)	0.462	0.601
	< 3.5	73.9 (1854)	74.9 (587)	71.3 (231)	88.9 (8)	73.9 (1028)		

*; Compared between Genotype 1 vs Genotype 2 vs Genotype 3 vs Genotype 6; **, Genotype 1 vs Genotype 6. n; Number of patients for whom the variable data is available, VL: viral load.

Table 3 The biochemistry parameters of 2817 patient attending at HTD from March 2016 to October 2017 for treatment with DAAs.

Variable	All patient (n = 2817) (mean \pm SD)	Genotype 1 (N = 904) (mean \pm SD)	Genotype 2 (N = 359) (mean \pm SD)	Genotype 3 (N = 10) (mean \pm SD)	Genotype 6 (N = 1542) (mean \pm SD)	p value*	p value**
ALT (U/L)	72.6 \pm 64.8	77.9 \pm 69.8	70.9 \pm 70.3	128.6 \pm 62.5	69.6 \pm 60.2	0	0
AST (U/L)	63.7 \pm 46.8	66.2 \pm 44.6	64.9 \pm 57.2	85.0 \pm 31.0	61.9 \pm 45.3	0.001	0.002
BILIRUBIN (μ mol/L)	7.4 \pm 15.6	8.8 \pm 22.5	6.6 \pm 6.9	4.4 \pm 4.6	6.7 \pm 11.0	0.879	0.575
Creatinine (μ mol/L)	74.4 \pm 30.5	77.3 \pm 49.1	74.1 \pm 15.3	94.1 \pm 19.7	72.7 \pm 15.6	0.001	0.059
Albumin (g/L)	40.5 \pm 4.3	40.6 \pm 4.4	40.3 \pm 4.3	40.7 \pm 3.5	40.5 \pm 4.3	0.409	0.195
AFP (ng/ml)	15.3 \pm 43.4	22.8 \pm 67.2	13.1 \pm 21.9	5.9 \pm 4.1	11.8 \pm 28.2	0.053	0.005
GGT (U/L)	74.4 \pm 86.9	88.0 \pm 106.2	68.0 \pm 86.4	133.4 \pm 112.6	67.9 \pm 72.7	0	0
Glucose (mmol/L)	5.9 \pm 1.9	6.0 \pm 2.1	6.2 \pm 2.3	5.6 \pm 0.7	5.9 \pm 1.8	0.749	0.423

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: Alpha-fetoprotein; GGT: Gamma-glutamyltransferase; *: Compared between Genotype 1 vs Genotype 2 vs Genotype 3 vs Genotype 6; **: Genotype 1 vs Genotype 6.

remaining 5% (142/2817) had a history of prior treatment failure PegIFN \pm RBV (Table 2). One-third of the patients had cirrhosis, including 34.5% (974/2817) compensated cirrhosis. 2.6% (74/2817) and 1.2% (33/2817) of the patients had HCV-HBV and HCV-HIV co-infection, respectively. HCV-HIV coinfection was significantly higher in genotype 1 patients (2.4% (22/904) in genotype 1 versus 0.7% (11/1542) in genotype 6; $p \leq 0.001$). The HCV viral load (mean \pm SD) was $3.1 \times 10^6 \pm 5.2 \times 10^6$; and 40.4% (1138/2817) of patients had $< 10^6$ copies/ml viral load. There was no difference in HCV viral load among male and female patients. HCV viral load was significantly higher in Genotype 3 patients compared to other genotypes ($p = 0.002$). Among genotype 1 and 6 patients, HCV viral load was significantly higher in genotype 6 patients ($p \leq 0.001$). The fibroscan results (mean \pm SD kpa) was 12.9 ± 11.5 (females 13.3

± 12.3 ($n = 643$) and males 12.3 ± 10.2 ($n = 511$). Majority of the patients (94.5%; 2372/2718) had an APRI < 2 and 26.1% (655/2817) had a FIB-4 score of ≥ 3.5 (Table 2).

Table 3 presents the liver enzyme profile (mean \pm SD) of the patients. Serum alanine aminotransferase (ALT) (local reference range is < 37 IU/L and < 40 IU/L, for females and males, respectively) was < 2 times and < 3 times the upper normal limit (UNL) in 38% and 13% of the patients. Serum AST, ALT, Creatinine, and GGT level was significantly higher in genotype 3 patients compared to other genotypes. Among genotype 1 and 6 patients, AST, ALT, AFP, and GGT were significantly higher in genotype 1 patients.

Table 4 presents the treatment prescribed to the patients. 70.6% (1990/2817) and 16.2% (455/2817) of the patients received SOF/

Table 4 Treatment regimen and duration of treatment prescribed to 2817 patients.

Treatment regimen	Duration	All patient (N = 2817) % (n)	Genotype 1 (N = 904) % (n)	Genotype 2 (N = 359) % (n)	Genotype 3 (N = 10) % (n)	Genotype 6 (N = 1542) % (n)
		N=2817	N = 904	N = 359	N = 10	N = 1542
		% (n)	% (n)	% (n)	% (n)	% (n)
Sofosbuvir only	NA			4		
Sofosbuvir + Ribavirin	12 weeks	6.8% (193)		53.8 (193)		
	16 weeks	2.3 (67)		18.7 (67)		
	20 weeks	0.1 (4)		1.1 (4)		
	24 weeks	0.1 (5)			50.0 (5)	
Ledipasvir + Sofosbuvir - without Ribavirin	12 weeks	42.4 (1197)	44.2 (400)			51.1 (797)
	24 weeks	2.4% (69)	2.8 (25)			2.9 (44)
Ledipasvir + Sofosbuvir + Ribavirin	12 weeks	25.1 (709)	25.2 (228)			31.2 (481)
	24 weeks	0.53 (15)	1.7 (15)			
Daclatasvir + Sofosbuvir - without Ribavirin	12 weeks	14.2 (402)	13.4 (121)	24.2 (87)	40.0 (4)	10.0 (154)
	24 weeks	1.2 (36)	1.0 (9)	0.8 (3)	10.0 (1)	1.5 (23)
Daclatasvir + Sofosbuvir + Ribavirin	12 weeks	3.0 (87)	4.6 (42)	0.6 (2)		2.8 (43)
	24 weeks	0.07 (2)	0.2 (2)			
Elbasvir + Grazoprevir	12 weeks	2.1 (61)	6.7 (61)			

NA; Data not available.

Table 5 The estimated direct medical cost (US\$) of a standard 12 and 24 week treatment with DAAs following different regimens and disease stages.

Genotype	Regime					
	SOF/LDV	SOF + DCV	SOF + RBV	SOF/VEL	GZR/EBR	PegIFN + RBV+SOF
Non-cirrhotic chronic HCV patients						
1	12 weeks (2068 - 2201)	12 weeks (2417 - 2443)	NA	12 weeks (2372 - 2398)	12 weeks (3806)	12 weeks (2437 - 2943)
2	NA		12 weeks (1392 - 1619)		NA	
3	NA		NA		NA	
4	12 weeks (2068 - 2201)		NA		12 weeks (3806)	
5,6	12 weeks (2068 - 2201)		NA		NA	
Compensated cirrhosis chronic HCV patients						
1	12 weeks (+ RBV) (2096 - 2230) 24 weeks (3626 - 3891)	12 weeks (+ RBV) (2444 - 2472) 24 weeks (4323 - 4375)	NA	12 weeks (2372 - 2398)	12 weeks (3806)	12 weeks (2437 - 2943)
2	NA		16 weeks (1646 - 1951) 20 weeks (1930 - 2312)		NA	
3	NA		NA		NA	
4	12 weeks (+ RBV) (2096 - 2230) 24 weeks (3626 - 3891)		NA		12 weeks 3806	
5,6	12 weeks (+ RBV) (2096 - 2230) 24 weeks (3626 - 3891)		NA		NA	
Decompensated cirrhosis chronic HCV patients						
1	12 weeks (+ RBV) (2096 - 2230) 24 weeks (3626 - 3891)	12 weeks (+ RBV) (2444 - 2472) 24 weeks (4323 - 4375)	NA	12 weeks (+ RBV) (2399 - 2427) 24 weeks (4233 - 4284)	NA	12 weeks (2437 - 2943)
2	NA		16 weeks (1646 - 1951) 20 weeks (1930 - 2312)		NA	
3	NA		NA		NA	
4,5,6	12 weeks (+ RBV) (096 - 2230) 24 weeks (3626 - 3891)		NA		NA	

Costs are in 2017 prices. The range in the costs for a given regimen is due to the variation in the costs of the different brands of the drugs (minimum and maximum values are shown). NA: Not applicable; regime not recommend for this genotype; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; VEL: Velpatasvir; GZR: Grazoprevir; EBR: Elbasvir; PegIFN: Pegylated interferon; RBV: Ribavirin.

LED ± RBV and SOF/DAC ± RBV treatment, respectively. Among genotype 1 patients, 93.7% (843/904) received either LED/SOF ± RBV or DAC/SOF ± RBV. The remaining 6.7% (61/904) patients received with ELB/GRA. Similarly, 85.2% (1322/1542) and 14.3% (220/1542) of the genotype 6 patients were treated with LED/SOF ± RBV and DAC/SOF ± RBV, respectively. 73.6% (264/359) and 25.6% (92/359) of the Genotype 2 patients were treated with SOF ± RBV and DAC/SOF ± RBV, respectively. A 12-week treatment was prescribed to 98.2% (2513/2817) of the patients. Overall, 38.4% (1082/2817) patients received RBV and it is more commonly prescribed in 12-week SOF/LDV based treatment. 84.3% (837/993)

of patients with cirrhosis received RBV compared to 13.5% (245/1818) non-cirrhotic patients ($p \leq 0.001$).

Cost analysis

The estimated direct medical costs of DAA based treatments for the different regimens and stages of chronic disease are presented in Table 5. These were estimated from three main parts: the cost of drugs, cost of tests, and cost of consultations. The cost related to the tests and consultations were the same across all DAA regimens - US\$511 per treatment except for the DAA with PegIFN (which was slightly higher - US\$547). In contrast, the cost related to the

drugs varied due to differences in the duration of treatment, the costs of different regimens and even different brands of the same drug. The average drug cost for a 12-week SOF/LDV±RBV and SOF/DCV±RBV treatment was US\$ 2068 - 2230 and US\$ 2417 - 2472 respectively. The regime using Sofosbuvir (SOF+RBV) had the cheapest direct medical cost (US\$1,392 - US\$1,619 per treatment 12 weeks) and was the only regimen below US\$2,000. The costs of treating patients with cirrhosis were only slightly higher if patients take treatment combined with ribavirin at 12 weeks but were notably higher (US\$ 4323 - 4375) if patients take treatment without ribavirin at 24 weeks (S2 File a,b and c).

DISCUSSION

In this retrospective study, we present the patient profile, clinical and biochemical characteristics, HCV viral load, and genotypes of patients presenting at a tertiary hospital in southern Vietnam. HTD is designated HCV referral center for central and southern provinces of Vietnam; however, the majority of the HCV patients attended at HTD are from Southern Vietnam. Patients from the central region may prefer to visit their nearest provincial hospital (Dak Lak hospital, Khanh Hoa hospital, and Hue hospital) due to more accessible transportation.

Research studies often enroll patients who fulfill study inclusion and exclusion criteria and may not represent the patient population^[13]. The majority of the patients seeking HCV treatment were ≤40 years. Chronic HCV infections are often asymptomatic; it is possible that routine health care or screening for other illness identified these infections. Earlier studies reported a higher prevalence of HCV infection in men, which is contrary to our real-world data^[6]. It is possible that female patients are less interested in joining research studies due to fear, stigma, or time limitations to fulfill the study requirement, including follow up visits.

In our study, 20% of the patients had a BMI of ≥25. Patients with BMI ≥25 responds poorly to HCV therapy, and BMI is used as predictors of SVR12 after DAA therapy^[14]. One-third of the patients treated with DAAs had liver cirrhosis and treated with RBV in our study. Patients with cirrhosis are usually had a long history of HCV infection and require a longer duration of treatment with DAA and RBV. One-quarter of the patients had FIB-4 score was > 3.5. Patients with higher FIB-4 score respond poorly to DAAs therapy and have a lower SVR rate^[15].

Genotype 6 is the predominant genotype in our study; more than half of the patients were genotype 6 (58.2% and 51.0% from Mekong Delta and Southeast sub-region respectively). The high prevalence of genotype 6 patients in our study is significant for several reasons. Genotype 6 is the most diverse among all HCV genotypes^[16,17]. Genotype 6 contains the highest prevalence of preexisting drug resistance mutations^[18] Genotype 6 patients are generally under-represented in previous clinical trials evaluating the efficacy of DAA regimens^[19,20]. Earlier studies from southern Vietnam have shown that the prevalence of genotype 6 is higher in chronic HCV patients compared to acute patients^[6]. The high prevalence of genotype 6 among chronic HCV patients in our study may be for several reasons including low spontaneous clearance of acute HCV infection with genotype 6 compared to other genotype or poor response to non-DAA therapy (e.g., PegINF±RBV). The prevalence of genotype 6 was higher in patients from Mekong delta sub-region compared to Southeast sub-region. It has been reported that genotype 6 might have originated in Laos and transmitted through population movement to southern Vietnam via Cambodia^[21].

Genotype 1 was the second most common genotype in our study. Genotype 1 has two subtypes; 1a and 1b. Subtype 1a is the most common genotype among injection drug users (IDUs), and HIV-HCV coinfecting patients and subtype 1b is common among the general population in Vietnam^[6,22]. Subtype 1b is the predominant subtype in Vietnam's neighboring countries, accounting for 66% of HCV infection in China, 64.4% in Japan, and 66% in South Korea^[23-25] and is also a major subtype in Europe^[23]. Subtype data would be useful to describe the epidemiology of genotype among different population group. High prevalence of genotype 1 in southwest sub-region including Ho Chi Minh City may result from population migration from neighboring countries.

12.7% (359/2817) patients had HCV genotype 2 and patients with HCV genotype 2 were significantly older than other genotypes. HCV genotype 2 was originated in Africa and was brought outside Africa by European explorers. As genotype 2 patients were significantly older, it is possible that HCV genotype 2 was introduced to Vietnam during the French colonization during the 18th century^[21]. Genotype 3 was the least common genotype in Vietnam; however, genotype 3 is the most predominant genotype in neighboring countries, including Thailand and Myanmar. The low genotype 3 might be explained by lower population migration from these countries to Vietnam. Genotype 3 patients had significantly higher liver enzymes, a potential marker for liver damage and high BMI, a predictor for poor treatment response. The prevalence of genotype 3 is relatively high in central region and our data is in agreement with earlier studies demonstrating a higher prevalence of genotype 3 in central highland sub-region^[6].

Several studies have evaluated 8-week versus 12-week treatment in patients with genotype 1 and 3, and there was no significant difference in SVR^[26-29]. Studies comparing the SVR rates in a 8-week versus a 12-week SOF/LDV therapy showed that the results are comparable^[28]. However, SVR data of genotype 6 patients on a 8-week therapy is lacking. Shorter treatment duration will reduce treatment cost and might increase patient compliance with treatment. While ASSLD recommends shorter treatment duration, clinical trials on the shorter treatment duration in genotypes 6 is necessary to inform policymakers. AASLD supports an 8-week and 12-week treatment with daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for genotype 6 patients without cirrhosis and with cirrhosis respectively^[11].

In Vietnam, the per capita average income in 2016 is US\$ 136 per month^[30]. The cost analysis highlights that the cost of DAA based treatment in 2017 was still substantial. If patients receiving the maximum level of support from the government health insurance program, a substantial out-of-pocket cost burden will be associated with the DAAs treatment. It is possible that many patients will not be able to afford the treatment or it may lead to "catastrophic health expenditures"^[31]. The costs of DAAs are continually falling, and this highlight the importance of further in-depth costing studies on DAA treatment.

Our study has several limitations; this is a retrospective study, and we could only analyze the patient's data that were available in the HTD database. Laboratory test data from other healthcare facility was not available for analysis although those data were available for the selection of treatment. Patients who can afford DAAs treatment were included in the study and might not represent all HCV patients. Our genotype epidemiology data might be biased as patients might visit other provincial hospitals for treatment. As the cost of DAAs are continuously falling, the cost data might not be accurate representation of present treatment cost.

ACKNOWLEDGMENT

We thanks Dr. Hugo Turner for review of the manuscript. We thank Oxford University Clinical Research Unit, Vietnam and Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam for resources for Data analysis.

REFERENCE

- World Health Organization WH. Global report on access to hepatitis C treatment. Focus on overcoming barriers. 2016; October(WHO/HIV/2016.20).
- World Health Organization. Global Health Sector Strategies; Viral Hepatitis 2016-2021. Towards elimination of viral hepatitis. 2016; June(WHO/HIV/2016.06).
- Hurley R. Slashed cost of hepatitis C drugs spurs drive to eliminate the disease. *BMJ* 2018; **361**: k1679. [DOI: 10.1136/bmj.k1679]. [PMID: 29661805]
- Rosenthal ES, Graham CS. Price and affordability of direct-acting antiviral regimens for hepatitis C virus in the United States. *Infect Agent Cancer* 2016; **11**: 24. [DOI: 10.1186/s13027-016-0071-z]; [PMCID: PMC4867525]; [PMID: 27186235]
- World Health Organization. Global Hepatitis Report 2017. In: World Health Organization; 2017.
- Le Ngoc C, Tran Thi Thanh T, Tran Thi Lan P, Nguyen Mai T, Nguyen Hoa T, Nghiem My N, Le Van T, Le Manh H, Le Thanh P, Nguyen Van Vinh C, Thwaites G, Cooke G, Heilek GM, Shikuma C, Le T, Baker S1,3, Rahman M; VIZIONS consortium. Differential prevalence and geographic distribution of hepatitis C virus genotypes in acute and chronic hepatitis C patients in Vietnam. *PLoS One*. 2019 Mar 13; **14**(3): e0212734. [DOI: 10.1371/journal.pone.0212734]. eCollection 2019. [PMCID: PMC6415813]; [PMID: 30865664]
- Vietnam MoH. DECISION ON THE ISSUANCE OF GUIDELINES FOR DIAGNOSIS AND TREATMENT FOR HEPATITIS C In: *5012/QĐ-BYT*. Edited by Ministry of Health V. Hanoi, Vietnam: Ministry of Health, Vietnam; 2016.
- Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, Amarapurkar D, Chen CH, Dou X, El Khayat H, Elshazly M, Esmat G, Guan R, Han KH, Koike K, Largen A, McCaughan G, Mogafer S, Monis A, Nawaz A, Piratvisuth T, Sanai FM, Sharara AI, Sibbel S, Sood A, Suh DJ, Wallace C, Young K, Negro F. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int* 2011; **31** Suppl 2: 61-80. [DOI: 10.1111/j.1478-3231.2011.02540.x]; [PMID: 21651703]
- Yen YH, Kuo FY, Kee KM, Chang KC, Tsai MC, Hu TH, Lu SN, Wang JH, Hung CH, Chen CH. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. *PLoS One* 2018; **13**(6): e0199760. [DOI: 10.1371/journal.pone.0199760]; [PMCID: PMC6023204]; [PMID: 29953518]
- Teshale E, Lu M, Rupp LB, Holmberg SD, Moorman AC, Spradling P, Vijayadeva V, Boscarino JA, Schmidt MA, Gordon SC; CHeCS Investigators. APRI and FIB-4 are good predictors of the stage of liver fibrosis in chronic hepatitis B: the Chronic Hepatitis Cohort Study (CHeCS). *J Viral Hepat* 2014; **21**(12): 917-920. [DOI: 10.1111/jvh.12279]; [PMID: 25131445]
- Panel A-IHG. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clin Infect Dis* 2018; **67**(10): 1477-1492. [DOI: 10.1093/cid/ciy585]; [PMID: 30215672]
- The World Bank. Gross national income (current US\$). In; 2017.
- Shin HP, Burman B, Kozarek RA, Zeigler A, Wang C, Lee H, Zehr T, Edwards AM, Siddique A. Real-World Single-Center Experience with Sofosbuvir-Based Regimens for the Treatment of Chronic Hepatitis C Genotype 1 Patients. *Gut Liver* 2017; **11**(5): 711-720. [DOI: 10.5009/gnl16447]; [PMCID: PMC5593334]; [PMID: 28651301]
- Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology* 2003; **38**(3): 639-644. [DOI: 10.1053/jhep.2003.50350]; [PMID: 12939590]
- Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. *Hepatology* 2016; **64**(2): 405-414. [DOI: 10.1002/hep.28625]; [PMID: 27115523]
- Fu Y, Qin W, Cao H, Xu R, Tan Y, Lu T, Wang H, Tong W, Rong X, Li G, Yuan M, Li C, Abe K, Lu L, Chen G. HCV 6a prevalence in Guangdong province had the origin from Vietnam and recent dissemination to other regions of China: phylogeographic analyses. *PLoS One* 2012; **7**(1): e28006. [DOI: 10.1371/journal.pone.0028006]; [PMCID: PMC3253785]; [PMID: 22253686]
- Garten RJ, Zhang J, Lai S, Liu W, Chen J, Yu XF. Coinfection with HIV and hepatitis C virus among injection drug users in southern China. *Clin Infect Dis* 2005; **41** Suppl 1: S18-24. [DOI: 10.1086/429491]; [PMID: 16265609]
- Chen ZW, Li H, Ren H, Hu P. Global prevalence of pre-existing HCV variants resistant to direct-acting antiviral agents (DAAs): mining the GenBank HCV genome data. *Sci Rep* 2016; **6**: 20310. [PMCID: PMC4740856]; [PMID: 26842909]
- Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai CL, Chan HL, Mazzotta F, Moreno C, Yoshida E, Shafran SD, Townner WJ, Tran TT, McNally J, Osinus A, Svarovskaia E, Zhu Y, Brainard DM, McHutchison JG, Agarwal K, Zeuzem S; ASTRAL-1 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *N Engl J Med* 2015; **373**(27): 2599-2607. [DOI: 10.1056/NEJMoa1512610]; [PMID: 26571066]
- Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, Morelli G, Darling JM, Feld JJ, Brown RS, Frazier LM, Stewart TG, Fried MW, Nelson DR, Jacobson IM; HCV-TARGET Study Group. Effectiveness of Simeprevir Plus Sofosbuvir, With or Without Ribavirin, in Real-World Patients With HCV Genotype 1 Infection. *Gastroenterology* 2016; **150**(2): 419-429. [DOI: 10.1053/j.gastro.2015.10.013]; [PMCID: PMC4727992]; [PMID: 26497081]
- Li C, Yuan M, Lu L, Lu T, Xia W, Pham VH, Vo AXD, Nguyen MH, Abe K. The genetic diversity and evolutionary history of hepatitis C virus in Vietnam. *Virology* 2014; **468-470**: 197-206. [DOI: 10.1016/j.virol.2014.07.026]; [PMCID: PMC4252705]; [PMID: 25193655]
- Dunford L, Carr MJ, Dean J, Nguyen LT, Ta Thi TH, Nguyen BT, Connell J, Coughlan S, Nguyen HT, Hall WW, Nguyen ATL. A multicentre molecular analysis of hepatitis B and blood-borne virus coinfections in Viet Nam. *PLoS One* 2012; **7**(6): e39027. [DOI: 10.1371/journal.pone.0039027]; [PMCID: PMC3374772]; [PMID: 22720022]
- Esteban JI, Saulede S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol* 2008; **48**(1): 148-162. [DOI: 10.1016/j.jhep.2007.07.033]; [PMID: 18022726]
- Ohno O, Mizokami M, Wu RR, Saleh MG, Ohba K, Orito E, Mukaide M, Williams R, and Lau JY. New hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a. *J Clin Microbiol* 1997; **35**(1): 201-207. [DOI: 10.1188.957]; [PMCID: PMC229539]; [PMID: 8968908]
- Lu L, Nakano T, He Y, Fu Y, Hagedorn CH, Robertson BH. Hepatitis C virus genotype distribution in China: predominance of closely related subtype 1b isolates and existence of new genotype 6 variants. *J Med Virol* 2005; **75**(4): 538-549. [DOI: 10.1002/jmv.20307]; [PMID: 15714489]
- Yanny B, Saab S, Durazo F, Latt N, Mitry A, Mikhail MM, Hanna RM, Aziz A, Sahota A. Eight-Week Hepatitis C Treatment with New Direct Acting Antivirals Has a Better Safety Profile While

- Being Effective in the Treatment-Naïve Geriatric Population Without Liver Cirrhosis and Hepatitis C Virus-RNA < 6 Million IU/mL. *Dig Dis Sci* 2018; **63(12)**: 3480-3486. [DOI: 10.1007/s10620-018-5283-1]; [PMID: 30259281]
27. Latt NL, Yanny BT, Gharibian D, Gevorkyan R, Sahota AK. Eight-week ledipasvir/sofosbuvir in non-cirrhotic, treatment-naïve hepatitis C genotype-1 patients with hepatitis C virus-RNA < 6 million: Single center, real world effectiveness and safety. *World J Gastroenterol* 2017; **23(26)**: 4759-4766. [DOI: 10.3748/wjg.v23.i26.4759]; [PMCID: PMC5514641]; [PMID: 28765697]
 28. Lai JB, Witt MA, Pauly MP, Ready J, Allerton M, Seo S, Witt DJ. Eight- or 12-Week Treatment of Hepatitis C with Ledipasvir/Sofosbuvir: Real-World Experience in a Large Integrated Health System. *Drugs* 2017; **77(3)**: 313-318. [DOI: 10.1007/s40265-016-0684-y]; [PMID: 28078644]
 29. Andres J, Lott S, Qureshi K. Eight-Week Outcomes of Ledipasvir/Sofosbuvir in Noncirrhotic Treatment-Naïve Patients with Hepatitis C: Analysis of Pharmacy-Based Data. *J Manag Care Spec Pharm* 2018; **24(1)**: 23-28. [DOI: 10.18553/jmcp.2018.24.1.23]; [PMID: 29290174]
 30. General Statistics Office of Viet Nam. Monthly average income per capita at current prices by residence and by region. In; 2016.
 31. Xu K, Evans DB, Kawabata K, Zeramini R, Klavus J, Murray CJ. Household catastrophic health expenditure: a multicountry analysis. *The lancet* 2003; **362(9378)**: 111-117. [DOI: 10.1016/S0140-6736(03)13861-5]; [PMID: 12867110]