Prevalence of Hepatitis C Virus in an Endemic Area of Thailand: Burden Assessment toward HCV Elimination

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Abstract. Chronic hepatitis C virus (HCV) infection can lead to liver cirrhosis and hepatocellular carcinoma. To eliminate HCV infection in an endemic area, an epidemiological baseline of the current HCV infection in the population is required. We therefore aimed to evaluate the HCV burden in the Thai Province of Phetchabun, which has the highest HCV infection rate in the country. Toward this, a province-wide district-based representative sampling of 4,769 individuals ages 35–64 years previously shown to represent high-risk age-groups were tested for anti-HCV antibodies using the automated chemiluminescent microparticle assays. Active HCV infection and subsequent genotyping were determined from serologically reactive samples by amplification of the HCV core gene. We found that 6.9% (327/4,769) were anti-HCV positive, of which 75.8% (248/327) had detectable HCV RNA and 5.8% (19/327) were in the presence of hepatitis B virus coinfection. Nucleotide sequencing and phylogenetic analysis revealed that HCV genotype 6 was the most prevalent (41%, 101/248), followed by genotype 3 (31%, 78/248), and genotype 1 (28%, 69/248). Socioeconomic and demographic factors including male gender, education, and agricultural work were associated with HCV seropositivity. From these results, we defined the regional HCV genotypes and estimated the HCV burden necessary toward the implementation of pan-genotypic direct-acting antivirals, which may be appropriate and effective toward the diversity of genotypes identified in this study. Micro-elimination of HCV in Phetchabun may serve as a model for a more comprehensive coverage of HCV treatment in Thailand.

INTRODUCTION

Approximately 71 million people worldwide are chronically infected with the hepatitis C virus (HCV).¹ It is a major contributor to morbidity and mortality that is projected to exceed the total deaths from HIV infection, tuberculosis, and malaria combined.² Effective therapy using direct-acting antivirals (DAAs) is orally administered and well tolerated. Treatment duration is short and can achieve > 90% cure rate. With the possibility of a foreseeable elimination of viral hepatitis, the WHO aims to reduce new cases of chronic HCV infection by 90%, decrease HCV-associated mortality by 65%, and treat 80% of chronic HCV infection.^{2,3} To attain these objectives, however, HCV diagnostic rate and treatment access would need to be increased.

The National Health Security Office within the Thai Ministry of Public Health adopted a pegylated-interferon (IFN) therapy for HCV infection beginning in 2012. Treatment access for patients, however, remains limited because of the stringent eligibility criteria. As such, only a small number of patients with chronic HCV have been treated. In many countries, IFN regimen is no longer the standard therapy and all HCV-infected patients are treated with DAAs; however, HCV treatment with pan-genotypic DAAs has not been implemented in Thailand. Preliminary evaluation of the existing HCV burden in Thailand shows that approximately 760,000–790,000 Thais are HCV seropositive, half of whom are living with chronic infection.^{4–6} Nevertheless, the prevalence of viral hepatitis appears to be on the decline nationally as a result of fewer new HCV

infections, improved blood donation screening, awareness of blood-borne pathogens, and decreasing number of intravenous drug users (IVDUs).^{5,7} Preventing HCV-related morbidity and mortality should therefore contribute to improved quality of life and significant savings in future healthcare costs.

Previously, we have defined a substantially high HCV seropositivity (15%) and rate of viremia (12%) among adults aged 35 years or older in some areas of Phetchabun Province in Thailand compared with the rest of the nation.^{8–10} Factors such as male gender, educational status, agriculture work, blood transfusion, IVDUs, and tattoos were found to be associated with anti-HCV positivity.^{8,10} Because of the considerable burden of HCV infection, this province was given a priority in the implementation of a sweeping HCV elimination program. To guide the national policy toward an effective treatment program, we sought to characterize the seroprevalence, active carrier rate, and the circulating HCV genotypes in the whole province. This information will be important toward implementing the HCV micro-elimination program in an endemic area and evaluating the potential feasibility of a point-of-care DAA treatment program.

MATERIALS AND METHODS

Study population. Phetchabun Province has an overall population of 995,000, and most residents are engaged in farming and other agriculture work.^{8,11} This province is composed of 11 administrative districts collectively spanning approximately 300 km from north to south.¹² They are further subdivided into 117 subdistricts, each of which is served by at least one primary healthcare center. Enrollment took place from August through September 2018. For every 100 individuals residing in a subdistrict, one person underwent purposive sampling by the primary healthcare center for inclusion

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in this study (Supplemental Table 1). The inclusion criteria were adult aged 35–64 years (representing approximately 438,000 residents) with no apparent underlying immunodeficiency disorders, chronic diseases, HIV infection, or prior treatment for HCV. Individuals with a history of immunosuppressive therapy or clinical signs of chronic liver disease from hepatitis B virus (HBV) or HCV infection were also excluded. The Institutional Review Board of the Faculty of Medicine of Chulalongkorn University approved this cross-sectional descriptive study (Institutional Review Board no. 266/61). Participants were informed of the study objective and consented to take part in the study. The nursing staff at the primary healthcare centers obtained blood samples and basic demographic information, which were sent to their respective district hospitals for processing. In all, there were 4,769 individuals in this study (1,466 men and 3,303 women).

Serological assay. Plasma samples were tested for anti-HCV antibodies at the Center of Excellence in Clinical Virology in Bangkok by using an automated chemiluminescent microparticle immunoassay (ARCHITECT anti-HCV assay, Abbott Diagnostics, Chicago, IL) according to the manufacturer's instructions. Anti-HCV results were based on the signal-to-cutoff ratio (S/CO) in which $S/CO \geq 1.00$ was automatically assigned as reactive by the Architect i1000SR platform. Reactive samples were further tested for HBV surface antigen using the Architect HBVsAg assay (Abbott Diagnostics).

Nested reverse transcription–polymerase chain reaction (RT-PCR) and genotyping. For all anti-HCV-reactive samples, viral RNA was extracted from 200 μ L plasma using an Automatic Nucleic Acid Extraction System GENTi 32 (GeneAll Biotechnology, Seoul, Korea). Complementary DNA was synthesized from 10 μ L of extracted RNA using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. Nested RT-PCR was performed to amplify the partial HCV core gene by using the AccuStart II GelTrack PCR Super Mix (QuantaBio, Beverly, MA). For the first-round PCR, primers 954F (5'-ACTGCCTGATAGGGTGCTTGCGAG-3', nucleotide position 288–311 based on a reference strain with GenBank accession number M62321) and 410R (5'-ATG TACCCCATGAGGTGCG GC-3', position 732–751) were used. For the second-round PCR, primers 953F (5'-AGGTCTCG TAGACCGTGCATCATG-3', position 321–344) and 951R (5'-CACTGTRAGGGTATCGATGAC-3', position 705–725) were used. The PCR conditions were pre-incubation at 95°C for 3 minutes, 40 cycles of denaturation at 95°C for 1 minute, annealing at 49°C for 1 minute, extension at 72°C for 90 seconds, and final extension at 72°C for 7 minutes. Amplicons of approximately 400 base pairs were purified and subjected to Sanger sequencing. Nucleotide sequences were analyzed by using BLASTN (<http://www.ncbi.nlm.nih.gov>), and final genotypes were determined from phylogenetic analysis. Neighbor-joining trees were generated using the Kimura's two-parameter nucleotide substitution model with 1,000 bootstrap tests. Genotype was assigned according to the respective reference genotype clustering clade (genotype 1a: M62321 and M67463, 1b: D90208 and M58335, 1c: D14853 and AY051292, 2a: D00944, AB047639, and D10988, 2b: AB030907, 2c: D50409, 3a: D17763 and D28917, 3b: D49374, 4a: Y11604, 5a: Y13184, 6a: Y12083 and AY859526, 6b: D84262, 6c: EF424629, 6d: D84263, 6e: DQ314805, 6f:

DQ835760, 6g: D63822, 6h: D84265, 6i: DQ835770, 6j: DQ835769, 6k: D84264, 6l: EF424628, 6m: DQ835767, 6n: DQ278894, 6o: DQ835768 and EF424627, 6p: EF424626, 6q: EF424625, 6r: EU408328, 6s: EU408329, 6t: EF632071 and EU246939, 6u: EU246940, 6v: EU158186 and EU798760, 6w: DQ278892 and EU643834, 6xa: EU408330 and EU408332, and 7a: EF108306).¹³ The nucleotide sequences of HCV from this study were submitted to the GenBank database under the accession numbers MN451395–MN451642.

Data analysis. Differences between groups of categorical variables (gender, geography, and age-group) were analyzed by the chi-square test. The logistic regression model evaluated the association between anti-HCV-positive status and demographic parameters (gender and age). Odds ratios (ORs) with 95% CIs were derived from univariate and multivariate analyses. A P -value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics version 22 (IBM Corporation, Armonk, NY). From the anti-HCV and HCV RNA prevalence found in this study, we estimated the HCV seropositivity and viremic carriers in Phetchabun by extrapolation from the age-stratified population census registry retrieved from the Health Data Center database of Thailand.¹⁴

RESULTS

Characteristics of the survey population. The mean age of individuals in this study was 49.8 ± 7.3 years (median age 50 years), of whom 69.3% were women (Table 1). Most of the participants possessed at least primary education (2,882/4,753; 60.6%) and were involved in agriculture-related occupations (3,221/4,752; 67.8%).

Prevalence of HCV infection. The overall anti-HCV prevalence was 6.9% (327/4,769), which was higher among men (71%, 233/327) than women (29%, 94/327) (Table 1). Men were more likely to possess anti-HCV (15.9%, 233/1,466) than women (2.8%, 94/3,303) (Table 1, $P < 0.001$). Seropositivity rates were significantly different among the 11 districts of Phetchabun and were generally higher in the northern districts than in the south ($P < 0.001$) (Table 2, Figure 1). The prevalence was highest in district 3 (15.5%) and lowest in district 8 (0.9%). Seropositivity also significantly differed among age-groups ($P = 0.034$) and was highest in adults aged 50–54 years (8.7%) (Table 1, Supplemental Table 2).

The majority of the 327 HCV-seropositive individuals had detectable HCV RNA (75.8%, 248/327), and approximately three of four (76.6%, 190/248) were men (Table 2). In addition, 81.5% (190/233) of seropositive men had detectable HCV RNA compared with 61.7% (58/94) of women, which indicated active infection. Hepatitis B virus coinfection was found in 5.8% (19/327) and 4% (10/248) of individuals with HCV seropositive and active infection, respectively.

Genetic distribution of HCV genotypes. From 248 HCV sequences identified from HCV RNA-positive samples, phylogenetic analysis with reference strains showed that 27.8% (69/248) were genotype 1 (1a: 22.4% or 56/248, 1b: 5.2% or 13/248), 31.5% (78/248) were genotype 3 (3a: 30% or 75/248, 3b: 1.2% or 3/248), and 40.7% (101/248) were genotype 6 (6f: 34.4% or 86/248, 6i: 2.0% or 5/248, 6n: 4.0% or 10/248) (Figure 2).

Estimates of HCV seropositivity and viremia. Using the results from this study, we estimated the gender-adjusted

TABLE 1
Demographic factors associated with anti-HCV seropositivity in this study

Variable	Numbers	Anti-HCV-positive (%)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age*	49.8 (7.3)		1.2 (1.0, 1.4)	0.010	1.1 (0.9, 1.3)	0.517
Age-groups (years)†			NA	NA	NA	NA
35–39	446	23 (5.2)				
40–44	757	42 (5.5)				
45–49	1,087	64 (5.9)				
50–54	1,108	96 (8.7)				
55–59	868	64 (7.4)				
60–64	503	38 (7.6)				
Total	4,769	327 (6.9)				
Gender			6.5 (5.0, 8.3)	< 0.001	6.3 (4.9, 8.1)	< 0.001
Male	1,466	233 (15.9)				
Female	3,303	94 (2.8)				
Geographic residence			4.1 (3.1, 5.4)	< 0.001	4.0 (3.0, 5.3)	< 0.001
North‡	2,396	259 (10.8)				
South§	2,373	68 (2.9)				
Education attained						
≤ Grade 6	2,882	230 (8.0)	2.0 (1.4, 2.7)	< 0.001	1.7 (1.2, 2.4)	0.003
Grade 7–9	643	45 (7.0)	1.7 (1.1, 2.6)	0.011	1.5 (1.0, 2.4)	0.050
≥ Grade 10	1,228	52 (4.2)	1 (0)		1 (0)	
Total	4,753	327 (6.9)				
Occupation						
Agriculture	3,221	241 (7.5)	2.5 (1.6, 4.0)	< 0.001	1.9 (1.2, 3.0)	0.009
Temporary employee	816	64 (7.8)	2.7 (1.6, 4.4)	< 0.001	2.1 (1.2, 3.5)	0.006
Non-agriculture	715	22 (3.1)	1 (0)		1 (0)	
Total	4,752	327 (6.9)				

HCV = hepatitis C virus; NA = not analyzed.

* Age, data presented as mean (SD); age with 10-year interval was used in statistical analysis.

† P-value < 0.034 (categorical analysis).

‡ Districts 1, 3, 4, 9, and 11.

§ Districts 2, 5, 6, 7, 8, and 10.

prevalence of anti-HCV and active HCV infection to capture the burden of HCV in Phetchabun (Table 3). Among the population ages 35–65 years in which there were 451,631 residents (according to the 2019 population census registry), we determined that approximately 38,502 (8.5%) of Phetchabun residents in this age-group possess anti-HCV, of whom 82.8% (31,881/38,502) are men. In addition, we calculated that 30,239 or 6.7% of the residents are currently infected with HCV, the overwhelming majority of whom are men (86.5%, 26,143/30,239). Thus, men are roughly five times (31,881: 6,621) more likely to be HCV seropositive and 6.4 times

(26,143:4,096) more likely to have active HCV infection than women in this region.

Factors associated with HCV infection. We examined factors associated with HCV infection using logistic regression to elucidate the relationships between anti-HCV-reactive samples with age, gender, geography, education attained, and occupation. By univariate analysis, the anti-HCV-positive individuals were more likely to be older ($P = 0.010$), men ($P < 0.001$), residing in northern Phetchabun ($P < 0.001$), possessed less than grade-10 education ($P < 0.012$), and engaged in either agriculture ($P < 0.001$), or were temporarily

TABLE 2
HCV prevalence and HBV coinfection in Phetchabun Province

District	Number of samples			Anti-HCV-positive (%)			HCV RNA positive (%)			HBVsAg positive (%)	
	Men	Women	Total	Men	Women	Total*	Men	Women	Total	Anti-HCV†	HCV RNA
1	270	789	1,059	61 (22.6)	31 (3.9)	92 (8.7%)	53 (69.7)	23 (30.3)	76 (82.6)	5 (5.4)	4 (5.3)
2	136	220	356	10 (7.4)	6 (2.7)	16 (4.5)	8 (72.7)	3 (27.3)	11 (68.8)	2 (12.5)	1 (9.1)
3	361	430	791	105 (29.1)	18 (4.2)	123 (15.5)	85 (87.6)	12 (12.4)	97 (77.2)	8 (6.5)	4 (4.1)
4	75	228	303	17 (22.7)	10 (4.4)	27 (8.9)	16 (69.6)	7 (30.4)	23 (85.2)	1 (3.7)	0 (0.0)
5	172	428	600	8 (4.7)	6 (1.4)	14 (2.3)	6 (66.7)	3 (33.3)	9 (64.3)	2 (14.2)	1 (11.1)
6	83	256	339	1 (1.2)	4 (1.6)	5 (1.5)	0 (0.0)	2 (100)	2 (40.0)	0 (0.0)	0 (0.0)
7	146	400	546	17 (11.6)	8 (2.0)	25 (4.6)	12 (75.0)	4 (25.0)	16 (64.0)	0 (0.0)	0 (0.0)
8	106	243	349	1 (0.9)	2 (0.8)	3 (0.9)	0 (0.0)	1 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)
9	28	61	89	3 (10.7)	3 (4.9)	6 (6.7)	2 (66.7)	1 (33.3)	3 (50.0)	0 (0.0)	0 (0.0)
10	36	147	183	1 (2.8)	4 (2.7)	5 (2.7)	1 (100.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
11	53	101	154	9 (17.0)	2 (2.0)	11 (7.1)	7 (77.8)	2 (22.2)	9 (81.8)	1 (9.1)	0 (0.0)
Total	1,466	3,303	4,769	233 (15.9)	94 (2.8)	327 (6.9)	190 (76.6)	58 (23.4)	248 (75.8)	19 (5.8)‡	10 (4.0)§

HBV = hepatitis B virus; HCV = hepatitis C virus.

* P-value < 0.001 (categorical analysis).

† P-value = 0.778 (categorical analysis).

‡ Percentage calculated based on anti-HCV-positive sample ($N = 327$).

§ Percentage calculated based on HCV RNA-positive sample ($N = 248$).

FIGURE 1. Hepatitis C virus (HCV) seroprevalence in 11 districts of Phetchabun Province. Approximately 1% of randomly represented adults aged 35–64 years were tested for anti-HCV. The district numbers and their corresponding seroprevalence rates are shown. This figure appears in color at www.ajtmh.org.

employed ($P < 0.001$) (Table 1). After adjusting for age, the multivariate analysis confirmed that being men ($P < 0.001$, adjusted OR 6.3, 95% CI: 4.9–8.1), residents of northern Phetchabun ($P < 0.001$, adjusted OR 4.0, 95% CI: 3.0–5.3), primary education ($P = 0.003$, adjusted OR 1.7, 95% CI: 1.2–2.4) and occupation in agriculture ($P = 0.009$, adjusted OR 1.9, 95% CI: 1.2–3.0) or temporary worker ($P = 0.006$, adjusted OR 2.1, 95% CI: 1.2–3.5) were independently associated with HCV seropositivity.

DISCUSSION

In this study, we conducted a comprehensive assessment of the HCV burden in an endemic region of Thailand. Although the overall HCV seroprevalence in Phetchabun was 6.9%, which was already considerably higher than the national average of 0.9%, evidence of past HCV infection was as high as 15.5% in some places.^{5,8,15} We estimated that as many

as 6.7% of residents in this region may be actively infected with HCV, far higher than the 0.4% nationally.⁵ Most are men engaged in agricultural work who may not be aware of their hepatitis C status because of limited educational background.

Hepatitis C virus infection is not vaccine preventable and remains substantial in many developing countries with emerging economies and in the population of working-age.^{16,17} In Southeast Asia alone, it is estimated that at least 4.7 million people may harbor HCV.¹ Almost half a million Thais may have chronic HCV infection and will require treatment in the near future to prevent the potential development of liver cirrhosis and hepatocellular carcinoma.^{1,5} This endeavor poses logistical, budgetary, and healthcare constraints because latent HCV infection is asymptomatic and patients are unlikely to be aware of their infection status. Focusing on the population-wide screening of individuals most likely to be at risk of infection by geographical region or demographic

FIGURE 2. Phylogenetic analysis of the partial core gene sequences identified from hepatitis C virus-positive individuals. (A) The neighbor-joining tree was constructed using Kimura's two-parameter nucleotide substitution model with 1,000 bootstraps. Reference sequences are dotted (●). Condensed clusters of genotype 1a (B), genotype 3a (C), and genotype 6f (D) are shown.

group, termed micro-elimination, may be more feasible before nationwide implementation.^{18–20} Targeted diagnosis and delivery of HCV treatment regionally, as opposed to referrals to distantly located physician specialists, are anticipated to be more expeditious and cost-effective to initiate. As such, establishing the epidemiological baseline is crucial to assess

the regional burden of HCV infection, especially in some communities with limited healthcare infrastructure.

Targeting a subpopulation with the highest HCV prevalence for treatment with DAAs has been proposed to be a feasible strategy toward an overall elimination of viral hepatitis, especially in countries with emerging economies.^{18,21,22} As such,

TABLE 3
Estimated HCV antibody and RNA positivity among Phetchabun residents

District	% Anti-HCV	% HCV RNA	Target population*			Estimated HCV-seropositive population			Estimated HCV viremic population		
	Male/female	Male/female	Male	Female	Total	Male	Female	Total	Male	Female	Total
1	22.6/3.9	86.9/74.2	46,105	49,999	96,104	10,420	1,950	12,370	9,053	1,447	10,500
2	7.4/2.7	80.0/50.0	17,796	18,241	36,037	1,317	493	1,809	1,054	246	1,300
3	29.1/4.2	81.0/66.7	35,014	37,266	72,280	10,189	1,565	11,754	8,248	1,043	9,291
4	22.7/4.4	94.1/70.0	14,887	15,307	30,194	3,379	674	4,053	3,181	471	3,652
5	4.7/1.4	75.0/50.0	29,389	30,967	60,356	1,381	434	1,815	1,036	217	1,253
6	1.2/1.6	0.0/50.0	15,658	16,373	32,031	188	262	450	0	131	131
7	11.6/2	70.6/50.0	25,372	26,175	51,547	2,943	524	3,467	2,078	262	2,340
8	0.9/0.8	0.0/50.0	15,977	16,736	32,713	144	134	278	0	67	67
9	10.7/4.9	66.7/33.3	4,449	4,130	8,579	476	202	678	317	67	384
10	2.8/2.7	100.0/0.0	8,580	8,876	17,456	240	240	480	240	0	240
11	17.0/2.0	77.8/100.0	7,080	7,254	14,334	1,204	145	1,349	936	145	1,081
Total	15.9/2.8	81.5/61.7	220,307	231,324	451,631	31,881	6,621	38,502	26,143	4,096	30,239

HCV = hepatitis C virus.

* Target population data were extrapolated from the 2019 population census registry (for age 35–65 years) (cited: September 20, 2019).¹¹

Phetchabun is an ideal candidate for HCV micro-elimination owing to the availability of essential epidemiological baseline, defined demographics and healthcare infrastructure, and ongoing disease surveillance.^{9,10} From this study, most active HCV infection occurs in men of working age who are the primary wage earners and identify residences in northern domicile, agriculture or temporary work, and primary education as risk factors. Micro-elimination programs have successfully been implemented and have led to significant reductions in chronic hepatitis C infection in several countries, including Australia, Spain, Portugal, Iceland, Georgia, and Egypt.^{18,22} The inclusion of targeted populations at high risk of HCV has involved region-based or demographic vulnerability. This strategy has been helped by several factors. First, there is a tendency for a natural decline in new HCV infection as a result of mortality associated with hepatitis due to an aging population. Second, some illicit drugs have supplanted intravenous drug use, which is a major risk factor for this blood-borne pathogen. Third, better and improved screening of blood donations have now become the standard even for many resource-limited settings. These factors have been seen in Thailand where surveillance among Thai blood donors and the general population showed a decrease in HCV carrier rate from ~2% to < 1% in recent years.⁵ Furthermore, it is projected that a further reduction is expected in the next 20 years in which untreated HCV infection could account for less than 0.2%. Finally, major advances in the development and extensive use of DAAs would be expected to further reduce the prevalence of infection to < 0.001% if prices become affordable.²³

The current rate of high HCV infection in Phetchabun emphasizes the urgent need to initiate a test-to-treat program with pan-genotypic DAAs in Thailand. Unlike the rest of Thailand in which genotype 3a is predominant, the high prevalence of genotype 6 (41%) in Phetchabun affords an opportunity to further evaluate the efficacy of DAAs on this genotype because data from previous efficacy studies have been limited. Interestingly, genotype 6a is common in southern China and Vietnam, whereas genotypes 6p and 6r are common in Cambodia.²⁴ Elsewhere in the region, Laos also reported diverse subtypes for genotype 6, which includes genotype 6m and 6n reported in Myanmar.^{25,26} By contrast, Malaysia reported few genotype 6 infection.²⁷ Although the HCV treatment response rate has historically depended on the

viral genotype and the types of the antiviral regimen, DAAs have now made that prerequisite increasingly obsolete. DAAs such as sofosbuvir–ledipasvir (SOF-LDV) yielded a 64% sustained virological response (SVR) at week 12 after treatment (SVR12) for genotype 3 and 100% if combined with ribavirin (RBV).²⁸ Another study found that the SVR for SOF-LDV was 100% with and 92% without RBV.²⁹ The virological response rate of SOF-LDV treatment can sometimes be lower in patients with HCV genotypes 3 (75.0% SVR12) and 6 (64.1% SVR12) than genotype 1 (96.8% SVR), whereas pan-genotypic treatment such as sofosbuvir–velpatasvir (SOF-VEL) yielded a high cure rate in patients infected with genotypes 3 (97.4%) and 6 (90.4%).³⁰ In some studies, the SVR12 rate was up to 99% in patients treated with SOF-VEL (with or without RBV), regardless of HCV genotype.³¹ Similarly, sofosbuvir–daclatasvir pan-genotypic regimen resulted in 96.9% and 93.3% SVR for genotypes 3 and 6, respectively.³² Thus, the high prevalence of HCV genotype 6 and to a lesser extent genotypes 3 and 1 from this study suggest that treatment with a pan-genotypic DAAs regimen is most appropriate and is expected to be highly safe and effective.

Increasing HCV diagnostic rates and treatment coverage in Thailand will be challenging for several reasons. Insufficient healthcare infrastructure where trained healthcare workers can accurately and quickly diagnose HCV infection especially in remote communities remains a major obstacle. Patients are sometimes expected to bear the cost of disease screening as the government neither provides reimbursements nor incentives toward medical fees associated with hepatitis treatment. The recent availability of generic DAAs in Thailand beginning in 2018 has enabled its inclusion into the national treatment guideline and its accessibility to a greater number of HCV-infected patients. Thus far, the fact that pan-genotypic DAAs are not currently the standard therapy in Thailand has been hindered by the lack of defined HCV epidemiological baseline, cost, and complexity in program implementation. To partially overcome these obstacles, HCV treatment at the local primary healthcare centers rather than referrals to specialists at larger hospitals should reduce the test-to-treat time and provide greater treatment access for HCV-infected Thai patients.

Decentralized HCV treatment and care have proven effective in several resource-limited countries. This approach, which allows primary care providers such as trained nurses, primary care physicians, and even pharmacists the ability to

administer DAAs to patients, would greatly increase treatment access and unburden both the physician specialists and patients from treatment restrictions. Without a simplified diagnostic strategy, there is also a risk of reduced medication compliance and dose continuity leading to failed treatment plans. Any antiviral resistance would necessitate newer and possibly more expensive antivirals. The effectiveness of decentralized care was previously demonstrated by a study in Columbia, where they found no significant differences in the treatment outcome using SOF-LDV whether administered by nurse practitioners, point-of-care physicians, or specialists (84–89%).³³ Similarly, a study from Pakistan showed that with a simplified HCV testing, SOF-RBV therapy, and monitoring by local healthcare workers resulted in an SVR of 83% with a relatively low 10% loss to follow-up.³⁴

Admittedly, this study has several limitations. Although attempts were made in choosing participants at random, selection bias cannot be ruled out because local healthcare workers were given the discretion in randomizing participant selection. There were more women who visited healthcare centers than men during the enrollment period. Our estimates of HCV focused on working-age adults and did not include those older than 64 years. Such inclusion might increase the overall prevalence and increase the number of adults requiring treatment. For these reasons, findings in Phetchabun may not be generalizable for the entire country. We used an automated HCV assay, which is not available or financially feasible for screening the population at large. It is known that some chronic HBV infections are coinfecting with hepatitis D virus. Epidemiological screening for the latter was not performed in this study, but continued decline in HBV infection in Thailand may obviate such need. Despite these limitations, this epidemiological study in Phetchabun can help guide policies toward managing HCV elimination and developing a cost-effective population-based screening strategy. In the near future, the combined implementation of HCV screening using rapid diagnostic tests and initiating treatment at the point of care by local healthcare providers is foreseeable to achieve HCV elimination in many emerging economies.

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