การกระจายตัวของจีโนไทป์เชื้อไวรัสตับอักเสบซีในผู้ติดเชื้อไวรัสเอชไอวีที่เข้ารับการรักษาในสถาบันบำราศนราดูร

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บทคัดย่อ

การติดเชื้อไวรัสตับอักเสบซีพบได้บ่อยในกลุ่มผู้ติดเชื้อไวรัสเอชไอวี และผลกระทบของจีโนไทป์ไวรัสตับอักเสบซีต่อการดำเนินโรคติดเชื้อไวรัสทั้งสองชนิดและการตอบสนองต่อการรักษาโรคไวรัสตับอักเสบซี โดยเฉพาะในยุคที่ผู้ติดเชื้อส่วนใหญ่ได้รับการรักษาด้วยยาต้านไวรัสเอชไอวีนั้น ยังต้องมีการศึกษาอีกมาก การวิจัยครั้งนี้จึงมีวัตถุประสงค์เพื่อศึกษาการกระจายตัวของจีโนไทป์ไวรัสตับอักเสบซี รวมทั้งความสัมพันธ์กับลักษณะทางคลินิกที่เกี่ยวข้องกับการติดเชื้อไวรัสทั้งสองชนิด ในกลุ่มผู้ติดเชื้อร่วมกัน ที่เข้ารับการรักษาในสถาบันบำราศนราดูร ระหว่างเดือนพฤศจิกายน พ.ศ. 2560 ถึงเดือนธันวาคม พ.ศ. 2561 การศึกษาครั้งนี้เป็นแบบภาคตัดขวาง ทำในผู้ติดเชื้อไวรัสเอชไอวีร่วมกับไวรัสตับอักเสบซี จำนวน 73 ราย ซึ่งเกือบทั้งหมดได้รับการรักษาด้วยยาต้านไวรัสเอชไอวี และมีความชุกของไวรัสตับอักเสบซีจีโนไทป์ 1, 3 และ 6 เท่ากับร้อยละ 54.8, 37.0 และ 8.2 ตามลำดับ จากการทดสอบด้วย Chi-square และ Fisher's exact test พบว่า ไม่มีความสัมพันธ์ระหว่าง จีโนไทป์ของไวรัสตับอักเสบซีกับลักษณะทางคลินิกที่ทดสอบ และไม่พบความแตกต่างระหว่างค่ามัธยฐานของอายุ ระยะเวลาตั้งแต่ได้รับการวินิจฉัยว่าติดเชื้อไวรัสเอชไอวีและไวรัสตับอักเสบซี ระดับ HCV viral load ก่อนการรักษา ปริมาณ CD4 รวมทั้งระดับเอนไซม์ aspartate aminotransferase (AST) และ เอนไซม์ alanine aminotransferase (ALT) ที่พบในผู้ติดเชื้อจีโนไทป์ 3 และ 6 เปรียบเทียบกับในผู้ติดเชื้อจีโนไทป์ 1 ($p > 0.05$) การศึกษาครั้งนี้ ได้รายงานการกระจายตัวจีโนไทป์ของไวรัสตับอักเสบซี ซึ่งเป็นข้อมูลสำคัญในการกำหนดแนวทางการรักษาไวรัสตับอักเสบซี โดยเฉพาะในกลุ่มผู้ที่ติดเชื้อร่วมกับไวรัสเอชไอวี

คำสำคัญ: ไวรัสเอชไอวี ไวรัสตับอักเสบซี จีโนไทป์ไวรัสตับอักเสบซี

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Genotypic Distribution of Hepatitis C Virus in Human Immunodeficiency Virus-infected Patients in Bamrasnaradura Infectious Diseases Institute

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Abstract

Hepatitis C virus (HCV) infection is common in human immunodeficiency virus (HIV)-infected patients. The effect of HCV genotypes on HIV and HCV disease progression and responsiveness to hepatitis C therapy, particularly in the era of anti-retroviral therapy for HIV infection, still requires more clarification. The present study was aimed to investigate distribution of HCV genotypes and their association with clinical characteristics related to HIV and HCV infection in the HIV/HCV-coinfected patients attending Bamrasnaradura Infectious Diseases Institute, Thailand, between November 2016 and December 2017. A cross-sectional study was conducted in 73 HIV/HCV-coinfected patients mostly receiving combined antiretroviral therapy (ART). Prevalence of HCV genotypes 1, 3 and 6 were 54.8%, 37.0% and 8.2% respectively. The Chi-square and Fisher's exact tests indicated no statistically significant association of HCV genotypes with clinical features tested in the HIV/HCV-coinfected group, consistent with no difference in median age, duration of HIV and HCV diagnosis, pretreatment HCV RNA viral load, $CD4^+$ cell count and levels of aspartate (AST) and alanine aminotransferases (ALT), observed in the patients infected with HCV genotype 3 and 6, compared to those with genotype 1 ($p > 0.05$). This study provides HCV genotypic distribution which is essential for management of HCV treatment regimens especially in HIV/HCV coinfected patients.

Keywords: Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), HCV genotypes

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Introduction

Hepatitis C virus (HCV) coinfection is common among human immunodeficiency virus (HIV)-infected individuals due to shared common routes of transmission[1]. The Asian cohort study reported that there were up to 15.2% of HCV coinfection in HIV-infected patients[2], and studies in HIV-infected Thais also indicated the high prevalence approximately of 7-11%[3 - 5]. Accumulating studies suggested pathological roles of HIV/HCV coinfection in both HIV- and HCV-induced disease progression leading to more complicated treatment and care[6]. Moreover, advancement in management of HIV-infected patients with combined antiretroviral therapy (ART) in the last decade adds more complexity to understanding of HCV- and HIV-associated diseases. Presently, an impact of HCV infection on the disease progression and therapeutic response of HIV/HCV coinfected patients who are on combined ART requires much more investigation.

HCV is a positive single-stranded RNA virus belonging to the genus *Hapacivirus* in the family *Flaviviridae*, and presently classified into seven major genotypes or clades[1-7] and 67 subtypes[7]. Recently, a novel HCV genotype 8 has also been identified[8]. Distribution of HCV genotypes and subtypes differ substantially across the globe because of differences in modes of HCV transmission and the rapid spread of some common strains[9]. Whereas genotypes 1, 2 and 3 are prevalent widely, some other genotypes distribute in certain regions. For instance, genotypes 5 and 6 are endemic in South Africa and South East Asia respectively[10]. In Thailand, the epidemiological report in 2015 indicated that HCV genotype 1 was prevalent throughout Thailand, while genotype 3 was more common in the south and genotype 6 prevailed in the north and northeast[11]. There have also been reports in certain populations including intravenous drug users (IVDUs), HIV-infected individuals and blood donors in central and northern Thailand, suggesting genotypes 1, 3 and 6 as common strains prevalent in these groups[12 - 15]. While data on distribution patterns of HCV genotypes and subtypes are required for hepatitis C therapeutic strategies especially duration of treatment, responsive rates to therapy and the need for adjuvant interferon and ribavirin with the new direct acting antivirals (DAAs)[16], molecular epidemiology of HCV infection specifically in Thai HIV-infected patients is still limited.

Therefore, this cross-sectional study aimed to investigate distribution of HCV genotypes and their association with clinical characteristics-related to HIV and HCV infection in Thai HIV-infected patients. The study provides epidemiological data of HCV coinfection in HIV-infected individuals who are on combined ART supporting understanding of HIV/HCV coinfection in the era of ART.

Materials and Methods

Study design and population

A pilot cross-sectional study was conducted in 73 HIV patients coinfected with HCV in Bamrasnaradura Infectious Diseases Institute, Thailand, from November 2016 to December 2017. Patients aged 20 years or older with documented HIV and HCV infection, and availability of clinical and laboratory data particularly HCV genotype, were recruited. Subjects were excluded according to documented HBV infection, active opportunistic infections, alcohol consumption, herbal medicine use, steroid and paracetamol medication. All subjects provided written informed consent and the study protocol was reviewed and approved by the human Ethics Committees No. 3, Thammasat University (Project no. 070/2560) and Bamrasnaradura Infectious Diseases Institute (Project no. R005/60).

Clinical data and laboratory investigation

Clinical data were obtained from patient's medical records including age, gender, diagnosed HIV, HBV and HCV infection, duration of HCV and HIV diagnosis, duration of antiretroviral therapy (ART), currently used antiretroviral (ARV) regimens, baseline HCV RNA viral load and HCV genotype, and opportunistic infection. HIV infection was previously diagnosed based on the three different HIV antibody detection test algorithm comprising ARCHITECT HIV1/2 Ag/Ab Combo chemiluminescent microparticle assay (CMIA) (Abbott, USA), Determine HIV1/HIV2 immunochromatography (Inverness Medial Japan, Japan) and One Step Anti-HIV1&2 TriLine immunochromatography (InTecProducts, China). HCV infection was determined through anti-HCV screening CMIA (Abbott, USA) and subsequent detection of HCV RNA viral load (Roche Molecular Diagnostics, Switzerland). HCV genotyping was performed by VERSANT® HCV Genotype 2.0 line probe assay (LiPA 2.0 assay) (Siemens Healthcare Diagnostics, USA) for hepatitis C virus genotypes 1-6. At enrollment, data on alcohol consumption, herbal medicine, steroid and paracetamol drug intake were collected from questionnaire administration. The enrolled patients underwent clinical examination and routine blood tests including aspartate and alanine aminotransferases (AST and ALT) (Roche Diagnostics, Switzerland), $CD4^+$ cell count (BD Biosciences, San Jose, CA, USA) and HIV viral load (Roche Molecular Diagnostics, Switzerland).

In this study, sustained virologic response (SVR) was defined as negative HCV RNA at 6-month after completing HCV therapy[16, 17]. Transaminitis was assessed by an increase level from the normal upper limit (ULNs) of AST or ALT (>40 U/L)[3].

Statistical Analysis

Prevalence of HCV genotypes in HIV/HCV coinfected participants was analyzed

by descriptive statistics and presented as percentages. Chi-square and Fisher's exact tests were used to determine the association of HCV genotypes with categorical variables, whereas a Mann-Whitney U test was used to analyze those with continuous variables. *P* values > 0.05 were considered as statistically significant. The PASW statistic 18 software (SPSS Inc.) was used for statistical analysis.

Results

A total of 73 HIV/HCV coinfected patients, 64 males (87.7%) and 9 females (12.3%), with the median age of 47 [range, 27-67] and median duration of HIV diagnosis of 10 [2-25] years, were recruited. Characteristics and clinical features of the HIV/HCV coinfected patients were summarized in Table 1. Among patients documented as HCV infected, the

Table 1 Characteristics and clinical features of HIV/HCV coinfected patients at Bamrasnaradura Infectious Diseases Institute (n = 73)

Characteristics	n (%)	Median (range)
Male	64 (87.7)	-
Age (years)	-	47 (27-67)
$CD4^+$ cell count (cells/μL)	–	529.0 (190.0–1,748.0)
HIV viral load < 20 copies/mL	69 (94.5)	-
Duration of HIV diagnosis (years)	-	10 (2-25)
Antiretroviral therapy (ART) (n = 71)		
2NRTIs and NNRTI	54 (76.0)	-
2NRTIs and PI	6 (8.5)	-
Others	11 (15.5)	-
Duration of ART (years) (n = 72)	-	9 (2-19)
HCV genotypes		
G1	40 (54.8)	-
G3	27 (37.0)	-
G6	6 (8.2)	-
Pretreatment HCV viral load (log) (n = 67)	-	6.1 (2.8-8.0)
Duration of HCV diagnosis (years) (n = 72)	-	5 (1-19)
Naïve to HCV therapy (n = 72)	29 (40.3)	-
Transaminitis (AST and/or ALT > ULN (40 U/L))	51 (69.9)	-

NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, SVR = sustained virologic response

median time since initial diagnosis was 5 [1-19] years and median pretreatment HCV RNA viral load was 6.1 [2.8-8.0] log IU/mL. There were 29 out of 72 (39.7%) patients remained naïve to HCV therapy and 51 of 73 (69.9%) patients were evaluated as having transaminitis. Prevalence of HCV genotypes 1, 3 and 6 were 54.8% (40/73), 37.0% (27/73) and 8.2% (6/73) respectively (Table 1). Of these 73 patients, there were 42 (57.5%) patients with availability of subtyping data for genotypes 1 and 3. The rates of patients infected with the subtypes 1a, 1b, 1c, 3a, 3b were 61.9% (26/42), 9.5% (4/42), 2.4% (1/42), 23.8% (10/42) and 2.4% (1/42) respectively. No mixed infection was observed in this study.

In this study, effect of HCV genotypes on clinical features of HIV/HCV coinfected patients was examined. Association between HCV genotypes and the clinical characteristics was analyzed by Chi-square and Fisher's exact tests (Table 2). All characteristics and clinical features of patients infected with HCV genotypes 1, 3 and 6 including gender, age, $CD4^+$ cell count, duration of HIV diagnosis, antiretroviral drug regimens, duration of ART, pretreatment HCV viral load, duration of HCV diagnosis, transaminitis and HCV treatment status, were similar ($p > 0.05$) as analyzed by Chi-square and Fisher's exact tests, consistent with the Mann-Whitney U analysis in Table 3 demonstrating that the medians of age, duration of HIV and HCV diagnosis, pretreatment HCV RNA viral load, $CD4^+$ cell count, levels of AST and ALT, in the patients infected with genotype 1, 3 and 6 were not significantly different ($p > 0.05$). Notably, although there was a trend, HCV genotypes were not significantly associated with levels of pretreatment HCV RNA viral load ($p = 0.057$), and no difference between the median HCV viral loads in patients infected with genotype 3 and 6, and those with genotype 1 ($p = 0.072$ and $p = 0.339$, respectively). The data analysis indicated no statistically significant association of HCV genotypes with any of the clinical characteristics tested.

Discussion

This cross-sectional study reported that major HCV genotypes 1, 3 and 6 were prevalent in Thai HIV/HCV coinfected patients mostly receiving long-term combined ART. Most patients presented undetectable levels of HIV RNA viral loads with relatively high levels of $CD4^+$ cell count status. The patients were diagnosed as HIV infected and mostly on suppressive ART for up to 9-10 years, whereas duration of HCV diagnosis was around 5 years and only 59.7 % of the patients received HCV therapy. There were up to 69.9% of this patient group assessed as having transaminitis, indicating their high potentials to develop liver disease. In this study, our statistical analysis suggested no statistically significant association of HCV genotypes with any of clinical features related to both HIV and HCV infection, potentially suggesting no influence

Table 2 General characteristics and clinical features of Thai HIV/HCV coinfected patients according to HCV genotypes (n = 73)

Characteristics	All patients (n = 73) n (%)	HCV genotypes			*p*
		Genotype 1 (n = 40)	Genotype 3 (n = 27)	Genotype 6 (n = 6)	
Gender					
Male	64 (87.7)	35 (87.5)	24 (88.9)	5 (83.3)	1.000[a]
Female	9 (12.3)	5 (12.5)	3 (11.1)	1 (16.7)	
Age (years)					
≤ 40	19 (26.0)	14 (35.0)	4 (14.8)	1 (16.7)	0.157[a]
41-50	29 (39.7)	14 (35.0)	12 (44.4)	3 (50.0)	
> 50	25 (34.2)	12 (30.0)	11 (40.7)	2 (33.3)	
$CD4^+$ cell count (cells/uL)					
> 500.0	43 (58.9)	25 (62.5)	14 (51.9)	4 (66.7)	0.665[a]
≤ 500.0	30 (41.1)	15 (37.5)	13 (48.1)	2 (33.3)	
Duration of HIV diagnosis (years)					
≤ 10.0	38 (52.1)	20 (50.0)	14 (51.9)	4 (66.7)	0.823[a]
>10.0	35 (47.9)	20 (50.0)	13 (48.1)	2 (33.3)	
Antiretroviral therapy (ART) (n = 71)					
2NRTIs and NNRTI	54 (76.1)	28 (71.8)	21 (80.8)	5 (83.3)	0.611[a]
2NRTIs and PI	6 (8.4)	5 (12.8)	1 (3.8)	0 (0.0)	
Others	11 (15.5)	6 (15.4)	4 (15.4)	1 (16.7)	
Duration of ART (years) (n = 72)					
≤ 10.0	45 (62.5)	25 (62.5)	16 (61.5)	4 (66.7)	1.000[a]
> 10.0	27 (37.5)	15 (37.5)	10 (38.5)	2 (33.3)	
Pretreatment HCV Viral load (log IU/mL) (n = 67)					
< 6.00	23 (34.3)	8 (22.2)	12 (46.2)	3 (60.0)	0.057[a]
≥ 6.00	44 (65.7)	28 (77.8)	14 (58.8)	2 (40.0)	
Duration of HCV diagnosis (years) (n = 72)					
≤ 5.0	37 (51.4)	21 (53.8)	15 (55.5)	1 (16.7)	0.235[a]
> 5.0	35 (48.6)	18 (46.2)	12 (44.5)	5 (83.3)	
Transaminitis					
AST and/or ALT ≤ ULN (40 U/L)	22 (30.1)	10 (25.0)	9 (33.3)	3 (50.0)	0.423[a]
AST and/or ALT > ULN (40 U/L)	51 (69.9)	30 (75.0)	18 (66.7)	3 (50.0)	
HCV therapy (n = 72)					
Naïve to HCV therapy	29 (40.3)	19 (48.7)	9 (33.3)	1 (16.7)	0.115[a]
on HCV therapy	8 (11.1)	3 (7.7)	5 (18.5)	0 (0.0)	
Non SVR	6 (8.3)	5 (12.8)	1 (3.7)	0 (0.0)	
SVR	29 (40.3)	12 (30.8)	12 (44.5)	5 (83.3)	

[a] Fisher-exact test

NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, ART = antiretroviral therapy, AST = aspartate aminotransferase, ALT = alanine aminotransferase, SVR = sustained virologic response

Table 3 Medians of age, duration of HIV and HCV infection, pretreatment HCV viral load, $CD4^+$ cell count stratified by HCV genotypes in HIV/HCV coinfected Thais (n = 73)

Characteristics	Genotype 1 N = 40	Genotype 3 N = 27	Genotype 6 N = 6	P^1	P^2	P^3
Age (years)	43.5 (27.0-67.0)	48.0 (34.0-63.0)	47.0 (37.0-61.0)	0.086	0.352	0.963
Duration of HIV diagnosis (years)	10.5 (3.0-25.0)	9.0 (2.0-25.0)	9.5 (4.0-15.0)	0.320	0.870	0.690
Duration of HCV diagnosis (years) (n = 72)	5.0 (1.0-19.0)	4.0 (2.0-11.0)	8.0 (4.0-9.0)	0.613	0.174	0.099
Pretreatment HCV viral load (log IU/mL) (n = 67)	6.3 (2.82-8.02)	6.0 (4.63-7.50)	5.95 (4.96-7.08)	0.072	0.339	0.936
$CD4^+$ cell count (cells/uL)	529.0 (249.0-1748.0)	525.0 (190.0-1288.0)	561.0 (338.0-764.0)	0.668	0.992	0.963
AST (U/L)	58.5 (19.0-188.0)	48.0 (17.0-420.0)	52.0 (18.0-109.0)	0.697	0.858	0.591
ALT (U/L)	54.5 (14.0-436.0)	41.0 (15.0-235.0)	44.0 (11.0-100.0)	0.428	0.289	0.559

P^1, P^2, and P^3 are *P* values of the Mann-Whitney U test for differences between the patients with genotype 1 and genotype 3, genotype 1 and genotype 6, and genotype 3 and genotype 6 respectively.

of HCV genotypes on HIV and HCV infection status in this study group.

Globally, HCV genotypes 1 and 3 are the first and second most common strains, respectively and others are found in smaller proportions and in certain geographic regions, particularly genotype 6 is commonly found in China and South East Asia[10, 18, 19]. In Thailand, distribution of HCV genotypes varies with geographic areas and major strains reported in several previous studies were genotype 1, 3 and 6[11-15, 20]. Similar to the previous reports, our study indicated that HCV genotype 1 was the most predominant (54%), followed by genotype 3 (37.0%) and 6 (8.2%). Notably, subtyping data suggested subtypes 1a and 3a as predominant strains. However, this finding is relatively inconsistent with data from the previous study particularly in HCV-monoinfected and HIV/HCV-coinfected patients suggesting the most prevalent genotype 3 (47%) and smaller proportions of genotype 1 (34%) and 6 (17%)[15]. The different distribution pattern of HCV genotype observed in our study is possibly due to the smaller sample size, study design and patient popula-

tion. Our study reported prevalence of HCV genotypes specifically in the HIV/HCV coinfected patient group mostly receiving combined ART.

Accumulating studies have revealed an impact of HCV infection on the natural history of HIV and HCV diseases[6, 21, 22]. Before the era of ART, HCV genotypes were demonstrated to affect HIV disease progression. Hemophilic patients with HCV genotype 1 infection experienced acceleration of progression to acquired immunodeficiency syndrome (AIDs) and death[23]. In the hemophilic group with a low proportion of patients initiating ART, patients infected with HCV genotype 1 presented lower mean $CD4^+$ cell count and percentage of $CD4^+$ T cells than those infected with non-genotype 1, and were at risk for progression to AIDs-associated mortality[24]. However, in the patient group with higher proportion of patients receiving ART, HCV genotypes appeared to have no impact on the levels of HIV RNA viral load and $CD4^+$ cell numbers[25]. Consistent with the later report, our data analysis in the patients who are on standard combined ART indicated no significant correlation between HCV genotypes and levels of $CD4^+$ cell count, and no difference in median $CD4^+$ cell numbers observed in patients infected with HCV genotype 1, 3 and 6. Several previous studies also suggested an influence of HCV genotypes in HCV disease status. Patients infected with different genotypes of HCV had significantly different levels of HCV RNA[15, 24], probably correlated with our data indicating that there was non-significant trend of association between HCV genotypes and pretreatment HCV RNA (p = 0.057). However, there was no significant difference in median HCV RNA viral loads among patients infected with HCV genotypes. The previous study in untreated HCV-infected patients indicated difference in levels of ALT and degree of hepatic fibrosis among patients infected with genotype 1, 3 and 6, and infection of genotype 6 was less likely to develop advanced liver fibrosis[15]. In contrast, our data analyzed in the group with relatively high percentages of the treated patients achieving SVR (41.7%) indicated that there was no statistically significant association between HCV genotypes and transaminitis, and no difference in the medians of AST and ALT detected in patients infected with genotype 3 and 6, compared to those with genotype 1. Moreover, our analysis did not show a significant association of HCV genotypes with HCV treatment status in this studied group, while many previous studies have clearly demonstrated an impact of HCV genotypes and subtypes on responsiveness to HCV treatment[6, 16]. With conventional interferon (IFN)-based therapy, genotypes 2 and 3 are more responsive than genotypes 1 and 4, however genotype 3 appears to be the most challenging to eradicate with the new DAA regimens. HCV genotyping and subtyping continues to be a critical aspect of HCV

treatments in the era of IFN-free DAAs[6, 16].

Limitations of the study should be mentioned. Firstly, our sample size is small and may not be representative of Thai HIV/HCV-coinfected individuals. This may also limit statistical significance for the variables tested. For example, very low number of patients achieving non-SVR and SVR may affect statistical analysis for association of HCV genotypes with HCV treatment status. Secondly, clinical data were obtained from retrospective review with unavailability of liver fibrosis assessment and drug regimens for hepatitis C therapy that may be required for further prospective cohort studies in this HIV/HCV coinfected group. However, this preliminary data report distribution of HCV genotypes and subtypes and their association with clinical status involving HIV and HCV infection in HIV/HCV-infected Thais attending Bamrasnaradura Infectious Diseases Institute that are critical for management of hepatitis C treatment in the HIV/HCV coinfected Thai patients.

Conclusion

This pilot cross-sectional analysis provides frequencies of HCV genotypes and subtypes in Thai HIV population and demonstrated a lack of association of the HCV genotypes with HIV- and HCV- associated clinical status. A further analysis in a larger sample size may be required to verify this finding. The study provides preliminary data which are essential for development of hepatitis C treatment strategies in the HIV/HCV-coinfected group.

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