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MAJOR ARTICLE

Less Severe but Prolonged Course of Acute Hepatitis A in Human Immunodeficiency Virus (HIV)–Infected Patients Compared With HIV-Uninfected Patients During an Outbreak: A Multicenter Observational Study

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Background. This multicenter retrospective cohort study aimed to compare the clinical presentations and evolution of acute hepatitis A (AHA) between human immunodeficiency virus (HIV)–infected patients and HIV-uninfected counterparts during the AHA outbreak.

Methods. Clinical and laboratory data were collected from the medical records of the patients with AHA at the 14 hospitals around Taiwan between May 2015 and May 2017.

Results. A total of 297 adult patients with AHA were included during the study period. Their mean age was 31.4 years (range, 19.0–76.1 years); 93.4% were men and 58.6% were men who have sex with men. Of 265 patients with known HIV serostatus, 166 (62.6%) were HIV infected. Compared with HIV-uninfected patients, HIV-infected patients had a lower peak alanine aminotransferase (ALT) level (median, 1312 vs 2014 IU/L, $P = .003$), less coagulopathy (6.0% vs 16.2%, $P = .007$), and less hepatomegaly or splenomegaly on imaging studies, but a higher rate of delayed resolution of hepatitis (38.8% vs 21.3%, $P = .009$). HIV-infected patients with plasma RNA load <1000 copies/mL while receiving combination antiretroviral therapy (cART) had a higher peak ALT level (median, 1420 vs 978 IU/L, $P = .006$) and less delay in resolution of hepatitis (30.6% vs 48.8%, $P = .047$) than patients without cART or with plasma RNA load ≥1000 copies/mL.

Conclusions. During an AHA outbreak, HIV-infected patients had a lower severity, but delayed resolution, of AHA than HIV-uninfected patients. Better viral suppression by cART alleviated the impact of HIV infection on the disease course of AHA in HIV-infected patients.

Keywords. viral hepatitis; men who have sex with men; fecal–oral transmission; sexually transmitted disease; coagulopathy.

Hepatitis A virus (HAV) is a nonenveloped hepatotropic virus and causes acute infection through fecal–oral transmission [1]. The endemicity of HAV infection varies widely in regions across the world depending on the infrastructures of sanitation, personal hygiene, and the public health strategies of preventive vaccination [2].

Recently, several outbreaks of acute hepatitis A (AHA) were observed in specific populations such as men who have sex with men (MSM) and homeless people. In Europe, the latest outbreak of AHA among MSM was first reported in the Netherlands in July 2016 [3]. Until now, at least 16 European countries are experiencing outbreaks of AHA with >1500 reported cases involving 3 separate clusters [4]. In North America, a total of 51 cases of AHA were diagnosed among MSM in New York City from January to August 2017 [5]. The epidemic also spread to the west coast of the United States, with the largest epidemic of AHA on record in the United States being reported in San Diego, in which homeless people were the hardest hit in the ongoing AHA outbreak; as of December 2017, there were >600 confirmed cases and at least 18 patients had died [6, 7].

Between mid-2015 and late 2017, an unprecedented outbreak of AHA involving nearly 1500 patients occurred in Taiwan, where HAV vaccination has not been included in the routine vaccination schedule for toddlers [8]. According to

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the Taiwan Centers for Disease Control (CDC), at least 70% of the cases of AHA occurred in MSM and more than half occurred in patients who had received the diagnosis of HIV infection or were diagnosed with HIV infection concurrently with AHA [9, 10]. Despite the outbreaks, little is known about the impact of HIV infection on the presentations of AHA. This multicenter, retrospective cohort study aimed to compare the clinical features and outcome of AHA between HIV-infected and HIV-uninfected patients during an outbreak setting.

METHODS

Study Setting and Population

This retrospective study was conducted at 14 designated hospitals for HIV care around Taiwan between May 2015 and May 2017. Both AHA and HIV infection are reportable diseases in Taiwan. During the 2-year study period, a total of 1387 cases of acute hepatitis A had been reported to Taiwan CDC (Figure 1). All patients seeking inpatient or outpatient care for AHA at these participating hospitals were included.

A standardized case record form was used to collect information on the demographics and clinical characteristics of the patients with AHA at baseline and during follow-up, including age, sex, sexual orientation, and risk factors for HAV infection including recent travel, close contact, and potential exposures to contaminated food or water; serial laboratory testing and abdominal imaging were also recorded. The frequency and duration of laboratory testing were performed at the discretion of treating physicians at each participating hospital. The study was approved by the research ethics committees or institutional review boards of 14 participating hospitals. The informed consent was waived.

Laboratory Investigations

All of the laboratory testing for serological markers of viral hepatitis, syphilis, hemogram, liver and renal function, coagulation profiles, plasma HIV RNA load, and CD4 cell count in this study were performed with the use of certified commercial test kits at each participating hospital. The most commonly used test kits for determination of plasma HIV RNA load had a detection limit of 20 or 50 copies/mL.

Definitions

A case of AHA was defined as having a positive result of HAV immunoglobulin M (anti-HAV IgM) by an enzyme-linked immunosorbent assay (ELISA) or a radioisotope assay with associated clinical symptoms. Recent travel was defined as domestic or international travel within 2 months before the diagnosis of AHA. Close contact was defined as living with a person with confirmed diagnosis of AHA in the same household/dormitory; or in a working or studying relationship with a person with confirmed AHA. The status of HIV infection was determined by standard ELISA and Western blotting methods or by the medical records including the history of combination antiretroviral therapy (cART).

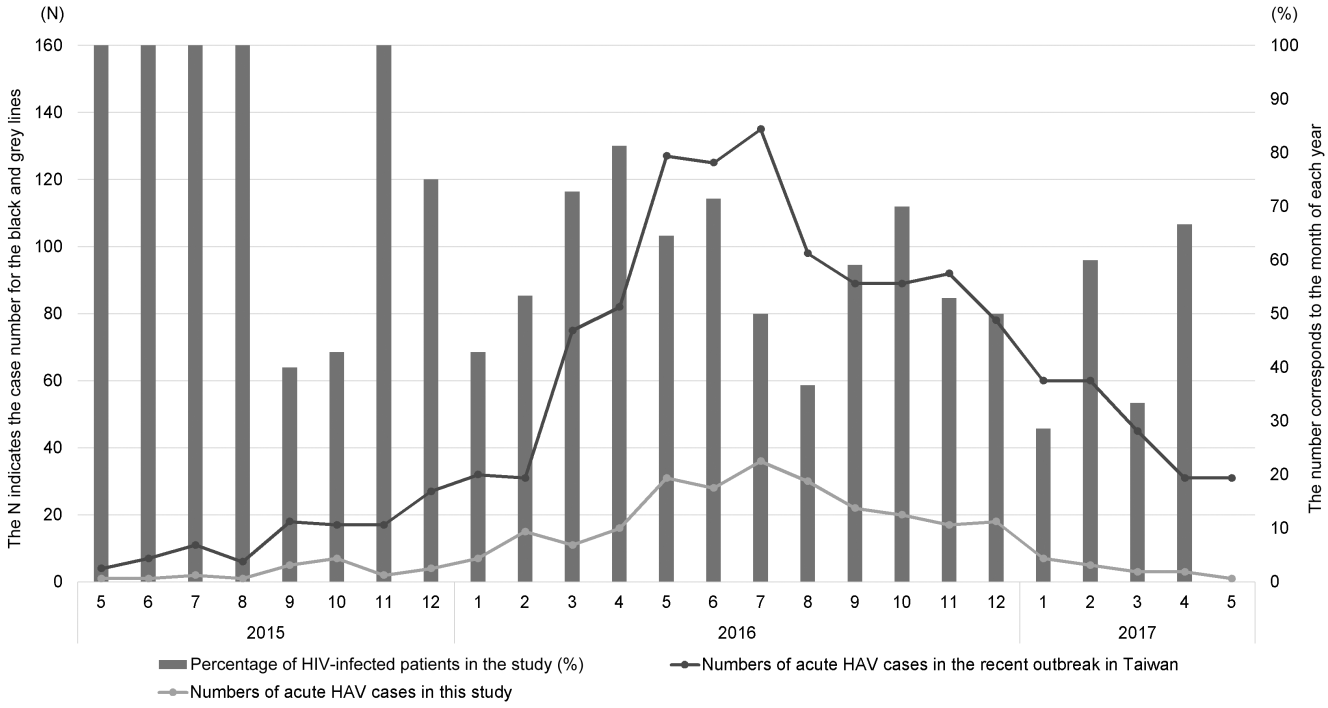

Figure 1. Total case number of acute hepatitis A reported to the Centers for Disease Control, Taiwan in each month and the case number included in this study between May 2015 and May 2017. Abbreviations: HAV, hepatitis A virus; HIV, human immunodeficiency virus.

Coinfection with hepatitis C and hepatitis B virus was defined as the presence of anti-hepatitis C antibody and hepatitis B surface antigen, respectively. Recent syphilis was defined as a 4-fold rise in rapid plasma reagin or Venereal Disease Research Laboratory test titer in the presence of positive *Treponema pallidum* hemagglutination test, for which the patient received benzathine penicillin or oral doxycycline within 6 months of the onset of AHA.

In terms of outcomes, prolonged hepatitis was defined as an elevation of alanine aminotransferase (ALT) level at least 5-fold above the upper limit of normal (40 IU/L) that persisted beyond 14 days after the diagnosis of AHA. Prolonged jaundice was defined as an increase of total bilirubin to >3 mg/dL that persisted beyond 14 days after the diagnosis of AHA. A relapse of hepatitis was defined as decreasing levels of ALT to <200 IU/L in the acute phase but having a ≥1.5-fold further increase of ALT in the convalescence phase.

The imaging studies, including abdominal sonography or computed tomography, were performed at the discretion of treating physicians and interpreted by radiologists at each hospital. The abnormal imaging results were categorized into hepatomegaly, gallbladder wall thickening, splenomegaly, periportal edema, and lymphadenopathy. Other imaging findings such as liver cysts, fatty liver, or scar due to previous liver abscess were not considered related to AHA.

Statistical Analysis

All statistical analyses were performed with the use of SPSS software version 20.0 (SPSS Inc, Chicago, Illinois). Categorical variables were compared using the χ^2 or Fisher exact test, whereas noncategorical variables were compared using the Mann-Whitney *U* test. All tests were 2 tailed and a *P* value of <.05 was considered significant.

RESULTS

Baseline Characteristics and Outcomes of Patients With AHA

During the 2-year study period, a total of 297 adult patients with AHA sought medical attention at 14 participating hospitals around Taiwan, which accounted for 21.8% of the total cases reported to Taiwan CDC. The trends of the case numbers per month reported to Taiwan CDC and the case numbers of patients seeking care for AHA at these hospitals in each month were similar, in which the case number increased gradually since late 2015 and peaked between May 2016 and July 2016 (Figure 1). Information on the HIV serostatus was available in 265 patients (89.2%). More than 60% of the patients (166/265 [62.6%]) were HIV infected, which included 150 patients (56.6%) with known HIV serostatus before developing AHA and 16 patients (6.0%) with HIV infection concurrently diagnosed with AHA. The percentage of HIV-infected patients included in this study was high in the beginning of the study period, which decreased with time, suggesting an increase of HIV-uninfected patients who acquired AHA during the later period of the outbreak.

The demographic and clinical characteristics of the patients with AHA are shown in Table 1. The mean age of the patients included was 31.4 years (range, 19.0–76.1 years) and 83.4% of the patients were aged 21–40 years. The patients were predominantly male (279/297 [93.9%]) and most were MSM among the patients with known sexual orientation (177/219 [80.8%]). However, few patients had traditional risks for acquisition of HAV including international travel to endemic countries (13 [4.4%]) and close contact with patients with acute HAV infection (4 [1.3%]). During the study period, there were no identified cases of contaminated food or water supply that were related to the recent outbreak of AHA in Taiwan. Sixty-four patients (21.5%) had a history of recent treatment for syphilis within 6 months before the onset of AHA. HIV-infected patients had a significantly higher rate of recent syphilis than HIV-uninfected patients (35.5% vs 3.0%, $P < .001$).

Clinical Manifestations and Imaging Abnormalities of AHA

The symptoms of the patients with AHA are summarized in Table 2. The most common symptoms were fatigue and general malaise (67.3%), followed by loss of appetite (61.3%), jaundice (59.3%), fever (55.4%), and nausea/vomiting (53.5%). The presentations were not significantly different between HIV-infected and HIV-uninfected patients, except that a higher frequency of headache was noted among HIV-uninfected patients (1.8% for infected vs 9.1% for uninfected, $P = .006$). HIV-uninfected patients with AHA were more likely to have abdominal imaging studies including sonography or computed tomography. Gallbladder wall thickening and splenomegaly were 2 major abnormal imaging findings when AHA was diagnosed. HIV-infected patients had a higher frequency of hepatomegaly (13.6% vs 2.2%, $P = .005$) and splenomegaly (34.1% vs 14.6%, $P = .003$) than HIV-uninfected patients.

Evolution of Liver Function Testing and Coagulation Profiles of AHA

Two-thirds of the patients were hospitalized, with 1 death. HIV-uninfected patients were more likely to be hospitalized than HIV-infected patients (82.8% vs 69.9%, $P = .028$). The most obvious laboratory abnormalities observed during the course of AHA were elevations of ALT, aspartate aminotransferase (AST), and total bilirubin (Table 2). The median peak ALT, AST, and total bilirubin level was 1512 IU/L, 866 IU/L, and 8.0 mg/dL, respectively. While the difference of the peak levels of total bilirubin was not observed, higher peak ALT and AST levels were noted among HIV-uninfected patients than HIV-infected patients with AHA at presentation. Moreover, HIV-uninfected patients with AHA were also more likely than HIV-infected patients to have prolonged international normalized ratio of prothrombin time (16/99 [16.2%] vs 10/166 [6.0%], $P = .007$). In contrast, HIV-infected patients were more likely to have a prolonged

Table 1. Comparisons of Demographic and Comorbidities of Acute Hepatitis A Between Human Immunodeficiency Virus (HIV)–Infected Patients and HIV-Uninfected Patients

Characteristic	Total	HIV-Infected	HIV-Uninfected	*P* Value[a]
Cases, No.[b]	297	166	99	
Male sex	279 (93.9)	166 (100)	87 (87.9)	<.001
Age, y, median (IQR)	30.0 (26.0–36.0)	30.0 (27.0–35.3)	30.0 (24.0–36.0)	.968
Sexual orientation				<.001
Men who have sex with men	177 (59.6)	156 (94.0)	18 (18.2)	
Heterosexuals	42 (14.1)	3 (1.8)	24 (24.2)	
Unknown	78 (26.3)	7 (4.2)	57 (57.6)	
Risk factor for hepatitis A infection				
Travel to endemic countries	13 (4.4)	0 (0.0)	10 (10.1)	<.001
Close contact	4 (1.3)	1 (0.6)	3 (3.0)	.148
HIV infection diagnosed concurrently with AHA	16 (5.3)	16 (9.6)	…	
HBsAg-positive	26 (8.8)	14 (8.4)	6 (6.1)	.248
Anti-HCV positive	25 (8.3)	23 (13.9)	2 (2.0)	.005
Recent syphilis	64 (21.5)	59 (35.5)	3 (3.0)	<.001
Prodromal period, d, mean ± SD	5.4 ± 4.4	5.1 ± 4.4	6.0 ± 4.3	.118
HIV status[c]				
CD4 count, cells/μL, median (IQR)	…	483 (323–657)	NA	
CD8 count, cells/μL, median (IQR)	…	889 (626–1318)	NA	
Viral suppression <1000 copies/mL when AHA occurred	…	96/140 (68.6)	NA	
Receiving cART when AHA occurred[d]	…	113 (68.1)	NA	
Backbone				
Tenofovir/emtricitabine	…	59/113 (52.2)	NA	
Zidovudine/lamivudine	…	38/113 (33.6)	NA	
Abacavir/lamivudine	…	14/113 (12.4)	NA	
Lamivudine alone	…	2/113 (1.8)	NA	
Third agents				
NNRTI	…	57/113 (50.4)	NA	
Protease inhibitor	…	41/113 (36.3)	…	
Integrase inhibitor	…	15/113 (13.3)	…	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AHA, acute hepatitis A; cART, combination antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; SD, standard deviation.

[a] *P* value for comparison between HIV-infected and HIV uninfected patients.

[b] Two hundred sixty-five patients had known HIV serostatus for comparisons.

[c] One hundred forty patients had available data on CD4 and plasma HIV RNA load within 3 months before acute hepatitis A was diagnosed.

[d] One hundred thirteen patients were receiving cART when acute hepatitis A was diagnosed.

course of hepatitis (52/134 [38.8%] vs 16/75 [21.3%], $P = .009$) (Table 2). The ALT levels at 3 different periods of AHA course revealed a lower ALT level at the initial period but a prolonged hepatitis course among HIV-infected patients compared with HIV-uninfected patients (Figure 2 and Supplementary Figure). In addition, a relapse of hepatitis was noted in 9 (6.0%) patients. More HIV-infected patients than HIV-uninfected patients had relapse of hepatitis, although the difference did not reach statistical significance (7/75 [9.3%] vs 1/59 [1.7%], $P = .078$; Table 2).

Because more HIV-infected patients were coinfected with hepatitis C virus (HCV) than HIV-uninfected patients, we repeated the comparisons by excluding all HCV-infected patients. The results of lower ALT level (median, 1241 vs 2174 IU/L, $P = .008$) and higher risk of prolonged hepatitis (45/113 [39.8%] vs 16/73 [21.9%], $P = .017$) were still noted in HIV-infected patients than HIV-uninfected patients.

Impact of Antiretroviral Therapy on the Outcome of AHA Among HIV-Infected Patients

Among the 166 HIV-infected patients, 140 had known plasma HIV RNA load within 3 months before the diagnosis of AHA. To further investigate the influence of HIV infection on the outcomes of AHA, we divided the 140 HIV-infected patients with available data of plasma HIV RNA load into 2 groups: 96 patients who had better HIV viral suppression with plasma HIV RNA load <1000 copies/mL (81 [84.4%] with plasma HIV RNA load <50 copies/mL) and 44 patients with a median plasma HIV RNA load of 4.8 $\log_{10}$ copies/mL (range, 3.1–6.9 $\log_{10}$ copies/mL). Among the 96 patients with better HIV viral suppression, 94 (97.9%) received regular cART. In the subgroup analysis, HIV-infected patients with better viral suppression had a higher median peak ALT level (1420 vs 978 IU/L, $P = .006$) and were less likely to have prolonged hepatitis

Table 2. Comparison of Symptoms and Signs and the Results of Imaging Studies and Laboratory Data of Acute Hepatitis A Between Human Immunodeficiency Virus (HIV)–Infected and HIV-Uninfected Patients

Symptom/Sign	Total[a] (N = 297)	HIV-Infected (n = 166)	HIV-Uninfected (n = 99)	*P* Value[b]
Symptoms, No. (%)				
Fever	164 (55.4)	85 (51.2)	61 (61.6)	.125
Chills	49 (16.5)	26 (15.7)	13 (13.1)	.574
Fatigue/malaise	200 (67.3)	112 (67.5)	66 (66.7)	.893
Headache	16 (5.4)	3 (1.8)	9 (9.1)	.006
Sore throat	15 (5.1)	10 (6.0)	4 (4.0)	.485
Nausea/vomiting	159 (53.5)	89 (53.6)	56 (56.6)	.641
Jaundice	176 (59.3)	101 (60.8)	57 (57.6)	.600
Dark urine	154 (51.9)	93 (56.0)	50 (50.5)	.383
Diarrhea	61 (20.5)	35 (21.1)	23 (23.2)	.682
Loss of appetite	182 (61.3)	103 (62.0)	62 (62.6)	.925
Abdominal discomfort	146 (49.2)	81 (48.8)	51 (51.5)	.668
Clay-colored stool	34 (11.4)	19 (11.4)	11 (11.0)	.934
Arthralgia/myalgia	22 (7.4)	9 (5.4)	11 (11.1)	.090
Pruritus	5 (1.7)	2 (1.2)	2 (2.0)	.598
Skin rash	7 (2.4)	5 (3.0)	0 (0)	.161
Hepatic encephalopathy	3 (1.0)	0 (0)	2 (2.0)	.139
Lymphadenopathy	5 (1.7)	2 (1.2)	2 (2.0)	.631
Splenomegaly	62 (20.9)	32 (19.3)	20 (20.2)	.854
Imaging study, No. (%)	198 (66.7)	88 (53.0)	89 (89.0)	<.001
Sonography	160 (53.9)	76 (45.8)	64 (64.6)	.003
Computed tomography	53 (17.8)	19 (11.4)	32 (32.3)	<.001
Imaging finding, No. (%)				
Hepatomegaly	16 (8.0)	12 (13.6)	2 (2.2)	.005
Gallbladder wall thickening	59 (29.8)	27 (30.7)	27 (30.3)	.960
Splenomegaly	51 (25.8)	30 (34.1)	13 (14.6)	.003
Periportal edema	6 (3.0)	1 (1.1)	5 (5.6)	.211
Lymphadenopathy	8 (4.0)	5 (5.7)	2 (2.2)	.278
Laboratory abnormalities				
WBC count, ×1000/μL, mean ± SD	5.9 ± 2.1	5.8 ± 1.7	6.2 ± 2.5	.276
Hemoglobin, g/dL, mean ± SD	14.6 ± 1.8	14.6 ± 1.5	14.8 ± 2.3	.443
Platelet, ×1000/μL, mean ± SD	198.3 ± 78.8	211.9 ± 74.1	178.9 ± 79.6	.001
PT INR, mean ± SD	1.2 ± 0.6	1.2 ± 0.8	1.3 ± 0.5	.516
Creatinine, mg/dL, mean ± SD	0.8 ± 0.6	0.7 ± 0.4	1.0 ± 0.9	<.001
Peak ALT, IU/L, median (range)	1512 (800–2624)	1312 (645–2178)	2014 (1039–3124)	.002
Peak AST, IU/L, median (range)	866 (235–1803)	702 (203–1467)	1037 (273–2146)	.056
Peak total bilirubin, mg/dL, mean ± SD	8.0 ± 5.4	7.8 ± 4.5	8.5 ± 6.4	.276
Prolonged PT INR, No. (%)	29 (9.8)	10 (6.0)	16 (16.2)	.007
Peak ALT >2000 IU/L, No. (%)	122 (41.1)	51 (30.7)	57 (57.6)	<.001
Outcome, No. (%)				
Hospitalization	218 (73.4)	116 (69.9)	82 (82.8)	.028
Mortality	1 (0.3)	0 (0)	1 (1.0)	.130
Relapse of hepatitis	9/150 (6.0)	7/75 (9.3)	1/59 (1.7)	.078
Prolonged hepatitis	72/222 (32.4)	52/134 (38.8)	16/75 (21.3)	.009
Prolonged jaundice	33/215 (15.3)	18/127 (14.2)	12/75 (16.0)	.724

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HIV, human immunodeficiency virus; INR, international normalized ratio; PT, prothrombin time; SD, standard deviation; WBC, white blood cell.

[a]Including HIV-infected, HIV-uninfected and cases with unknown HIV status.

[b]*P* value for comparison between HIV-infected and HIV-uninfected patients.

(26/85 [30.6%] vs 20/41 [48.8%], $P = .047$) than patients with poorer viral control (Figure 3A) On the other hand, there were no statistically significant differences observed in ALT elevation and prolonged hepatitis when the patients were categorized into 3 groups according to the CD4 count cutoff values of <350, 350–499, and ≥500 cells/μL at the onset of AHA (Figure 3B) or nadir CD4 count cutoff values before AHA (Supplementary Table).

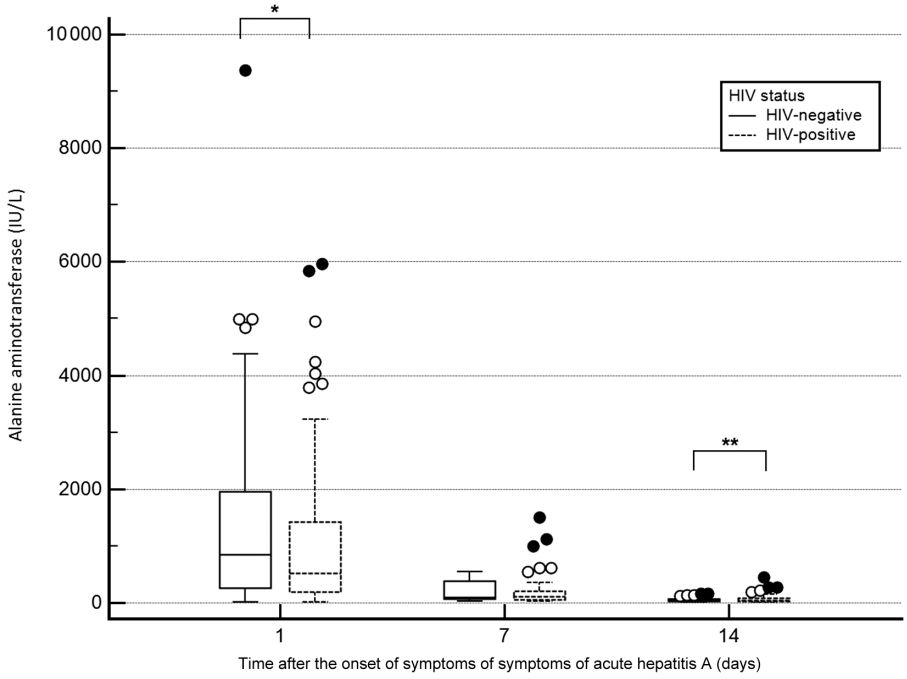

Figure 2. Differences of alanine aminotransferase (ALT) levels observed in three periods of acute hepatitis A between human immunodeficiency virus (HIV)-positive and HIV-negative patients. Boxplot: In the box, first quartile, median and third quartile of ALT level; upper and lower limit, 1.5 interquartile range (IQR) of ALT level; white circle: suspected outliers, 1.5-fold to 3-fold IQR more above the third quartile; black dot: outliers, 3-fold IQR more above the third quartile. *The median ALT level of HIV-uninfected patients was higher than that of HIV-positive patients on the first day of seeking medical attention for acute hepatitis A ($P < .05$). **The median ALT level of HIV-infected patients was higher than that of HIV-negative patients on the 14th day of seeking medical attention for acute hepatitis A ($P < .05$). Abbreviation: HIV, human immunodeficiency virus.

DISCUSSION

In this study, we describe and compare the clinical manifestations of AHA and the evolution of aminotransferases over time between HIV-infected and HIV-uninfected patients in a large outbreak of AHA, in which a significant proportion of the affected individuals were MSM and HIV infected in Taiwan between 2015 and 2017. It is a unique opportunity for us to examine the impact of HIV infection on the course of AHA. In this study, we found that elevations of AST and ALT related to AHA were less marked in the acute phase, but the resolution of acute hepatitis was delayed in the convalescence phase among HIV-infected patients compared with HIV-uninfected patients. The influence of HIV

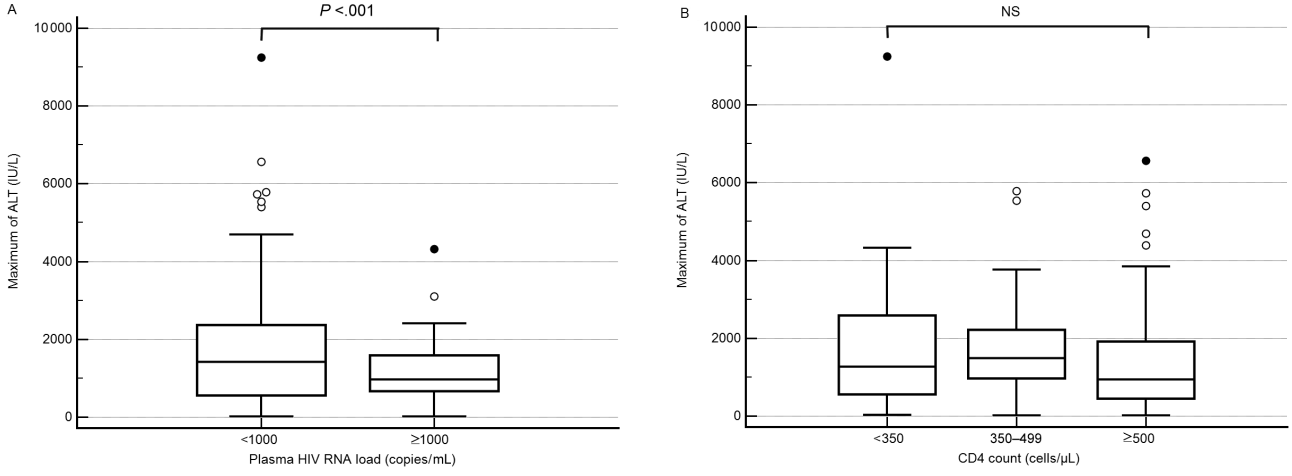

Figure 3. Different peak alanine aminotransferase (ALT) levels of acute hepatitis A in human immunodeficiency virus (HIV)-infected patients with different plasma HIV RNA loads (*A*) and CD4 counts (*B*). Boxplot: In the box, first quartile, median and third quartile of ALT level; upper and lower limit, 1.5 interquartile range (IQR) of ALT level; white circle: suspected outliers, 1.5-fold to 3-fold IQR more above the third quartile, black dot: outliers, 3-fold IQR more above the third quartile. NS: No significant difference observed among the 3 groups according to CD4 counts <350, 350–499 and ≥500 cells/μL. Abbreviations: ALT, alanine aminotransferase; HIV, human immunodeficiency virus.

infection on the course of AHA could be alleviated by cART in that the evolution of AHA among HIV-infected patients who had better viral suppression with cART was similar to the patterns observed among HIV-uninfected patients.

The interactions between HIV infection and HAV infection have been an issue of research interest during these outbreaks of AHA. However, few studies of a large case number have been conducted to investigate the interactions. The most recent study of the interactions between acute HAV infection and HIV infection was performed by Ida et al in 2002 [11]. In this case-matched study, 30 patients with acute HAV infection, 15 HIV-infected and 15 HIV-uninfected patients, were compared for clinical characteristics, laboratory test results, titers of plasma HAV load, and the duration of HAV viremia after onset of symptoms of acute HAV infection. The HIV-infected patients were found to have a higher plasma HAV load ($P < .001$) and a significantly longer duration of HAV viremia (53 vs 22 days, $P < .05$) than HIV-uninfected patients. However, even with higher HAV load, the levels of AST and ALT were significantly lower in the HIV-infected patients than HIV-uninfected patients [11]. Our study involving 166 HIV-infected patients and 99 HIV-uninfected patients reproduced similar results to those of the published studies [11, 12], and furthermore, we demonstrated that HIV-infected patients, regardless of CD4 counts, who had better control of HIV replication had clinical features of AHA similar to their HIV-uninfected counterparts, suggesting that HIV replication is associated with a prolonged course of elevated aminotransferases.

The mechanism for the different disease course of AHA between HIV-infected and HIV-uninfected patients remains speculative. The liver injury caused by acute HAV infection may not be completely associated with HAV itself but, instead, with the host immune response. The activation of HAV-specific $CD8^+$ T lymphocytes and release of interferon-γ may play important roles in hepatocellular damage and destruction of infected hepatocytes [13, 14]. In addition, the levels of tumor necrosis factor produced by stimulated T-regulatory (Treg) cells were recently found to correlate with the severity of liver injury in patients with AHA [15]. In HIV-infected patients, $CD8^+$ T-cell function, viability, and maturation were interfered with through decreasing co-stimulatory signals from $CD4^+$ T cells and dendritic cells [16, 17]. In addition, HIV infection may also mediate Treg cell depletion [17]. The $CD8^+$ T-cell dysfunction and depletion of Treg cells might both contribute to the less severe hepatitis among HIV-infected patients with AHA than HIV-uninfected patients. Similarly, HIV-infected patients also have fewer increases of mean maximum ALT level than HIV-uninfected patients when acute HCV infection occurs. Previous studies have shown that HIV-infected patients who had higher CD4 counts were more often associated with typical symptoms or signs of hepatitis than patients with advanced immunodeficiency [18, 19].

The high male-to-female ratio in recent outbreaks of AHA worldwide, including Taiwan, indicates that non-HAV-immune MSM are a particular at-risk group. In a previous study conducted in Australia, the transmission was more efficient among MSM than other heterosexual populations [20]. Factors contributing to the higher efficiency of HAV transmission among MSM may include a rapid increase of susceptibility in the young population, especially in developed countries without HAV vaccination; risk behaviors including oral–anal sex, digital–anal sex, or use of recreational drugs; and the prolonged infectiousness due to HIV coinfection [5, 11, 21]. Both the study by Ida et al [11] and our study suggest that a prolonged course of viremia and symptomatic hepatitis might be associated with prolonged infectiousness. Furthermore, our study also implies the benefit from cART in that HIV-infected patients with better viral suppression by cART had a less prolonged course of AHA. In addition to implementation of vaccination programs and safe-sex counseling, our study highlights the importance of engaging HIV-infected patients to initiate cART early because adequate viral suppression alleviates the influence of HIV on acute HAV courses.

There are several limitations to our study. First, although this observational study included the largest number of patients with AHA to investigate the clinical features, only 21.6% of cases were included from the affected patients in the recent outbreak of AHA in Taiwan. The results may not be necessarily representative of all cases diagnosed nationwide. Second, we did not characterize the genotype of HAV identified from each patient, though genotype Ia was identified early in this outbreak in Taiwan [3]. We were not able to examine if different genotypes of HAV might cause different clinical manifestations. Third, the timing of ALT and AST follow-up was not uniform for all patients because of the retrospective study design. In clinical practice, patients who had lower levels of initial ALT/AST or rapid resolution of hepatitis may be less likely to undergo frequent blood testing during the convalescence phase. The irregular follow-up of the patients might have led to overestimation of hepatitis in later stages of AHA. Finally, gallbladder wall thickening is a common imaging finding in patients with AHA. Due to the retrospective study design, we were unable to provide data on the extent of gallbladder wall thickness and link it to patient prognosis, as has been done in previous studies [22, 23].

In conclusion, HIV-infected patients with AHA presented with lower levels of aminotransferases but a prolonged course of hepatitis compared with HIV-uninfected patients. Use of cART in patients with better HIV viral suppression, compared to those with poorer viral suppression, was beneficial in shortening the disease course of AHA.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Y.-L. L., N.-Y. C., P.-L. L., C.-E. L., and C.-C. H. designed the study. Y.-L. L., G.-J. C., N.-Y. C., P.-H. L., N.-C. W., C.-E. L., Y.-T. L., C.-J. Y., Y.-S. H., H.-J. T., H.-S. H., P.-L. L., C.-Y. C., C.-H. L., T.-C. C., and C.-C. H. contributed to clinical management and follow-up and data collection. Y.-L. L., N.-Y. C., P.-L. L., C.-E. L., and C.-C. H. contributed to data analysis. The first draft was written by Y.-L. L. and C.-C. H. with substantial revisions and input from all authors. All authors have read and approved the final manuscript.

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