HEPATOLOGY

HEPATOLOGY, VOL. 70, NO. 2, 2019

AASLD
AMERICAN ASSOCIATION FOR
THE STUDY OF LIVER DISEASES

VIRAL HEPATITIS

Early Seroreversion After 2 Doses of Hepatitis A Vaccination in Human Immunodeficiency Virus–Positive Patients: Incidence and Associated Factors

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Serological responses (Seroresponse) and durability of hepatitis A virus (HAV) vaccination are reduced among human immunodeficiency virus (HIV)-positive patients. Incidence of and associated factors with early seroreversion (loss of seroresponse) among HIV-positive patients who have achieved seroresponses after two doses of HAV vaccination remain unclear. In this multicenter study, we followed HIV-positive adults who had mounted seroresponses after completing two doses of HAV vaccination during a recent outbreak of acute hepatitis A between 2015 and 2017, a 1:4 case-control study was conducted to identify factors associated with seroreversion. Case patients were those with seroreversion, and controls were those with similar follow-up durations who were able to maintain seroresponses. During the study period, 49 of the 1,256 patients (3.9%) seroreverted after a median follow-up of 611 days. In a case-control study, seroreversion was more likely to occur in patients with a higher weight (adjusted odds ratio [aOR], 1.703; 95% confidence interval [CI], 1.292-2.323, per 10-kg increment) and HIV viremia at the time of vaccination (aOR, 2.922; 95% CI, 1.067-7.924), whereas positive seroresponse at 6 months of HAV vaccination and higher CD4 lymphocyte counts at vaccination were inversely associated with early seroreversion with an aOR of 0.059 (95% CI, 0.020-0.154) and 0.837 (95% CI, 0.704-0.979, per 100-cell/mm^3 increment), respectively, in multivariable analyses. *Conclusion:* During an outbreak setting, early seroreversion following two-dose HAV vaccination occurred in 3.9% of HIV-positive patients. Lower and delayed seroresponses to HAV vaccination, a higher weight, and HIV viremia and lower CD4 lymphocyte counts at the time of HAV vaccination were associated with early seroreversion. Regular monitoring of seroresponse and booster vaccination might be warranted, especially in HIV-positive adults with predictors of early seroreversion. (HEPATOLOGY 2019;70:465-475).

Hepatitis A virus (HAV) is an important cause of viral hepatitis worldwide.[1] Although commonly perceived as a food-borne, self-limited infection, recent outbreaks of acute hepatitis A (AHA) involving more than 4,000 patients who were mostly men who have sex with men

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(MSM) in Europe and the Americas highlighted its potential as a contagious sexually transmitted disease in high-income countries.[2-4] In the United States, a recent large outbreak of AHA centered in homeless people and injecting drug users and resulted in 1,521 cases, 1,073 admissions, and 41 deaths.[5] In addition to the public health threats to the at-risk populations, the economic losses from AHA outbreaks could also be substantial.[6]

Since 1992, HAV vaccines that are safe, immunogenic, and highly effective in the prevention of HAV infection have become available. In healthy individuals, two doses of HAV vaccination administered 6-12 months apart induce protective antibodies in 95%-100% of vaccinees,[7,8] which may last for at least 20 and 25 years in the long-term follow-up studies and mathematical models, respectively.[9] Among individuals infected with human immunodeficiency virus (HIV), however, seroprotection generated by HAV vaccination has been shown to be less robust. After two doses of HAV vaccination, rates of seroconversion ranged from 48.6% to 94% and the geometric mean concentrations of protective anti-HAV antibodies are lower in individuals with HIV infection than in those without.[10] Durability of serological response (seroresponse) to HAV vaccination in HIV-positive patients has also been a concern. In the general population, given its excellent immunogenicity and durability,

booster doses after primary HAV vaccination are not recommended in most national and international guidelines[11,12]; however, for HIV-positive patients, most guidelines provide limited or no guidance on whether booster doses are needed,[13,14] probably because there is a paucity of clinical evidence. Studies with small sample sizes have shown that 5%-20% of HIV-positive patients who had achieved seroresponses to HAV vaccination lost protective antibodies (seroreversion) within 18 months and 10%-25% within 5 years.[15-17] Based on these observations, booster HAV vaccination every 10 years for HIV-positive patients with continuous risks of exposure is recommended by the British HIV Association.[18]

Among the HIV-positive patients who lost their protective antibodies after successful primary HAV vaccination, several factors associated with seroreversion have been identified, which included higher plasma HIV-RNA load,[17,19] hepatitis C virus (HCV) coinfection,[15,16] absence of recent syphilis,[15] and a longer duration of HIV infection.[19] Understanding the predictors of HAV seroreversion after vaccination would inform the clinical guidance on serological monitoring and the need of subsequent booster HAV vaccination in the HIV-positive population. In the present study, we aimed to investigate the incidence of early seroreversion and explore its associated factors after having completed two-dose HAV vaccination

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among HIV-positive patients during an outbreak of AHA.

Participants and Methods

STUDY SETTING

In Taiwan, an unprecedented outbreak of AHA occurred among MSM between June 2015 and December 2017.[20,21] To control the outbreak, an HAV vaccination campaign was launched in September 2015 and a subsidized HAV vaccination program was implemented in October 2016 among HIV-positive patients and those with sexually transmitted diseases.[22,23] Following this large-scale HAV vaccination program among at-risk populations, high serological response rates to HAV vaccination were observed and HAV vaccination was effective in preventing AHA.[22,23] Because of the supply shortage of HAVRIX 1440 enzyme-linked immunosorbent assay units (GlaxoSmithKline, Biologicals, Rixensart, Belgium) during the outbreak, it was gradually substituted by VAQTA 50 units (Merck and Co., Inc., West Point, PA) in the participating hospitals between May and October 2016.[24]

This study was conducted at 11 designated hospitals for HIV care around Taiwan. In response to the outbreak of HAV in Taiwan since June 2015, HIV-positive patients who sought care in these hospitals were screened for anti-HAV antibodies and those who were seronegative were advised to receive two doses of HAV vaccine administered at 6 months apart.[21] After vaccination, anti-HAV antibodies were determined at 4-24 weeks after the first dose and the second dose.[22] For patients who successfully seroconverted following vaccination, anti-HAV antibodies were monitored every 6 months to evaluate durability of seroprotection following two doses of HAV vaccination.

HIV-related medical services, including combination antiretroviral therapy (cART) and monitoring of plasma HIV-RNA load and CD4 count, have been provided free of charge in the designated hospitals around Taiwan. Routine care for HIV-positive patients in the study hospitals included clinical assessment and determinations of immunological and virological status every 3-6 months and regular serological evaluations for hepatitis B, hepatitis C, and syphilis according to Taiwanese HIV treatment guidelines.[25]

STUDY POPULATION AND PROCEDURE

This study population included patients aged at least 18 years who had received their first dose of HAV vaccine between June 2015 and June 2017, had positive anti-HAV antibodies after completion of two doses of HAV vaccination, and had follow-up measurements of anti-HAV antibodies more than 12 months after the first dose of HAV vaccination. Those who had received more than two doses of HAV vaccines or had AHA during the follow-up period were excluded.

We recorded demographics and clinical characteristics of patients, including age, sex, route for HIV transmission, use of tobacco, weight, height, use of cART, and serostatus of hepatitis B virus (HBV) and HCV. Overweight was defined by a body mass index (BMI) between 24 and 27 kg/m^2 and obesity by a BMI of greater than 27 kg/m^2 according to Taiwanese consensus.[26] Plasma HIV-RNA loads and CD4 lymphocyte counts at nadir stage, time of HAV vaccination, and 1 year after the first dose of vaccination were recorded. Recent syphilis was defined as presence of symptoms or signs consistent with primary syphilis or secondary syphilis or a 4-fold increase from baseline in rapid plasma reagin (RPR) titers within 1 year after the first dose of HAV vaccination with a reactive *Treponema pallidum* particle agglutination (TPPA) test.

All patients were followed until occurrence of HAV seroreversion, loss to follow-up, or the end of this study on August 31, 2018, whichever occurred first. This retrospective study was approved by the research ethics committee or institutional review boards of the 11 participating hospitals, and informed consent was waived. The study was carried out in accord with the approved ethical guidelines and regulations.

CASE-CONTROL STUDY

A case patient with seroreversion, a seroreverter, was defined as an individual who lost his or her anti-HAV antibodies during the follow-up period, whereas a control, a nonseroreverter, was the one with persistently positive anti-HAV antibodies. After identification of seroreverters, we conducted a 1:4 matched case-control study to examine the associated factors with seroreversion. Controls were matched to case

patients by the month of first dose of HAV vaccination (±3 months), duration of follow-up (±3 months), and hospitals where the case patients were followed. If less than 4 controls could be identified within the same hospital, patients from a nearest hospital from the same region were matched instead. If more than 4 controls were available for matching, 4 controls were selected randomly by EXCEL software (version 15.27; Microsoft Corporation, Albuquerque, NM).

LABORATORY INVESTIGATIONS

During the study period, the determinations of plasma HIV-RNA load, CD4 lymphocyte count, and serological tests for syphilis, and hepatitis A, B, and C were performed using certified commercial test kits. Anti-HAV antibodies were determined by ARCHITECT HAV antibody (Ab) immunoglobulin G (IgG; Abbott, Weisbaden Germany), a semiquantitative chemiluminescence immunoassay (CLIA) with a cut-off signal-to-cut-off (S/CO) value of 1,[22,24] in six hospitals; by Cobas Anti-HAV (Roche, Mannhein Germany), a quantitative electrochemiluminescence immunoassay (ECLIA) with a cut-off value of 20 IU/L and a detection range of 3-60 IU/L,[27,28] in four hospitals; and by ADVIA Centaur HAV Total (Siemens Healthcare Diagnostics Inc., Tarrytown, NY), a competitive chemiluminometric immunoassay with a cut-off value of 20 IU/L and detection range of 0-100 IU/L in one hospital.[29,30] Detection limits of the test kits for plasma HIV-RNA load were 20, 40, or 50 copies/mL at the participating hospitals.

STATISTICAL ANAYLSIS

Statistical analyses were performed using R statistics software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). Noncategorical variables were compared using the Mann-Whitney U test, and categorical variables were compared using Fisher's exact test. In the case-control study, variables with $P < 0.2$ were entered into a multivariable general linear regression model with backward selection and missing values treated by imputation with mean to identify factors associated with early HAV seroreversion and determine the adjusted odds ratio (aOR) of each variable. Before being entered into multivariable analysis, variables with apparent correlation, such as weight, BMI, and obesity, were compared and only

the variable with the smallest P value was selected into the model. A sensitivity analysis was carried out using another multivariable model that included only those matched patients from the hospitals using the CLIA method for determination of anti-HAV IgG titers. Variables with a P value <0.05 were deemed statistically significant throughout the analyses.

Results

From June 2015 to June 2017, 2,183 HIV-positive adult patients who completed two doses of HAV vaccination had been seeking HIV care at the 11 hospitals and 1,923 (88.1%) had confirmed vaccine-induced seroconversion within 12 months. Among patients with seroresponses, 1,256 (65.3%) were included in this case-control study, which included 1,253 who had follow-up measurements of anti-HAV antibodies more than 1 year after the first dose of HAV vaccination and 3 who seroreverted within 12 months (Fig. 1). The majority of the included patients were MSM (98.6%) with a median age of 32 years (interquartile range [IQR], 28-38; Table 1). At the time of HAV vaccination, more than 95% of the study population were taking cART, 85.7% had achieved plasma HIV-RNA load to <50 copies/mL, and median CD4-lymphocyte count was 575 cells/mm^3 (IQR, 433-748). Following vaccination, 64.5% of vaccinees achieved seroresponses at month 6, before administration of the second dose of HAV vaccine, whereas the rest did so after receiving the second dose. Overall, baseline characteristics of patients not included in this study were generally similar to those who were included, except that the former group of patients were more likely to be seropositive for HCV, to have received HAV vaccine later in the study period with a shorter follow-up duration, and to have had positive anti-HAV antibodies before the second dose of HAV vaccine (Supporting Table S1).

After a median follow-up of 611 days (IQR, 526-721) since the first dose of HAV vaccination, seroreversion of anti-HAV antibodies occurred in 49 (3.9%) of the included patients and in 6.8% of those with CD4 counts <350 cells/mm^3 (Supporting Table S2). The earliest seroreversion was observed at day 310 of the first dose of HAV vaccination, and half of the seroreverters lost their anti-HAV antibodies by day 549. Evolution of median anti-HAV antibody titers
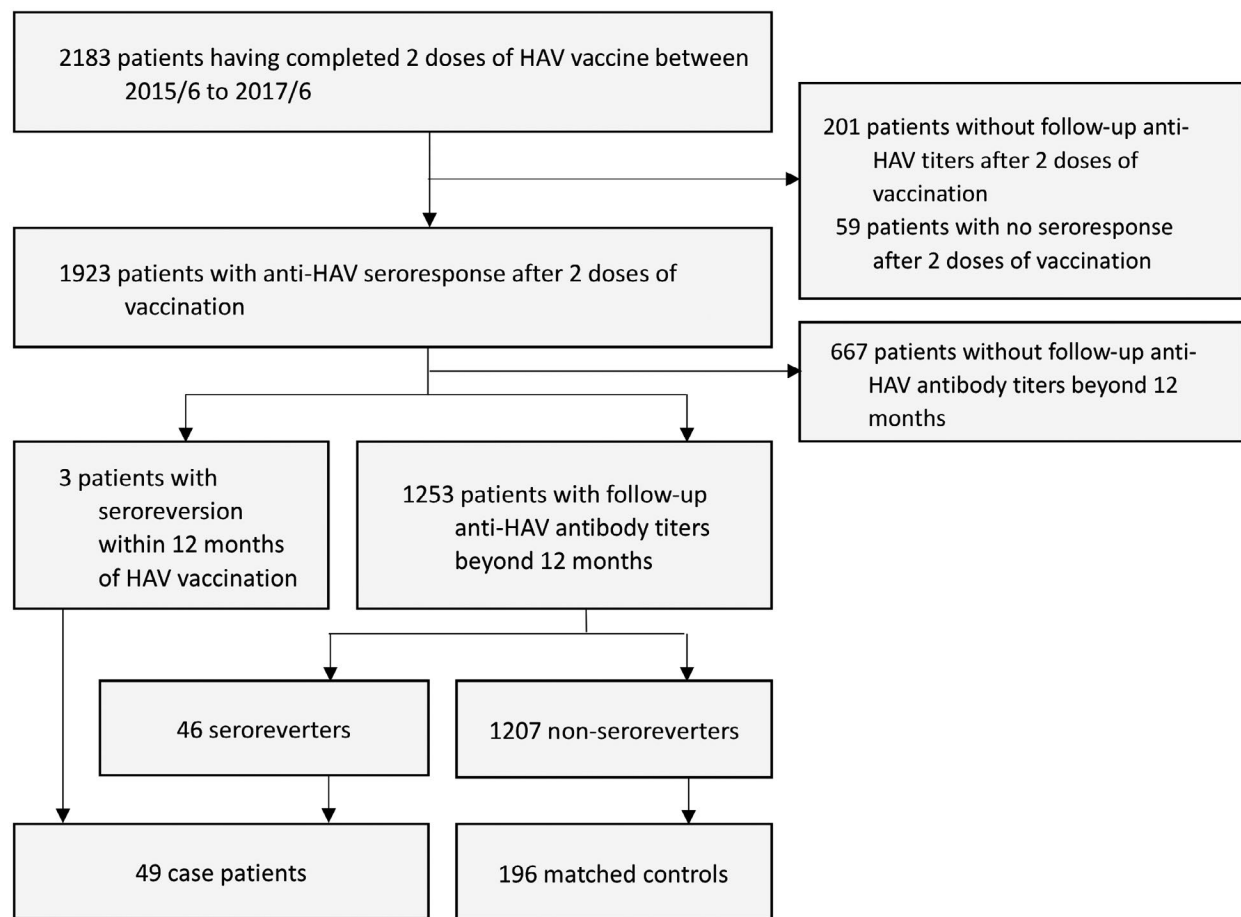
FIG. 1. Study flow.

measured by ARCHITECT HAV Ab IgG with time is illustrated in Fig. 2, which shows that antibody response started to decay early after completion of two doses of HAV vaccination in both seroreverters and nonseroreverters. Seroreverters mounted positive anti-HAV seroresponses later in the course, compared to nonseroreverters, and their peak anti-HAV titers were lower (Fig. 2).

In the case-control analysis, 196 controls who were able to maintain seroresponses following HAV vaccination were matched to 49 case patients with seroreversion. Clinical and laboratory characteristics of case patients and controls are shown in Table 2. The two groups were well matched in their timing of vaccination and follow-up durations. Compared to controls in the univariable analysis, case patients (seroreverters) had a higher weight (median, 72 vs. 66 kg; P = 0.001) and BMI (median, 23.7 vs. 22.3 kg/m^2;

P = 0.003), were more likely to be overweight or obese (47.7% vs. 29.8%; P = 0.032), were less likely to have achieved HIV viral suppression at vaccination (71.4% vs. 85.2%; P = 0.034), had a lower median CD4 lymphocyte count at vaccination (486 vs. 576 cells/mm^3; P = 0.024), were less likely to have achieved seroresponses before the second dose of HAV vaccination (5.5% vs. 67.1%; P < 0.001), and mounted lower peak anti-HAV titers (P < 0.001) whether determined by CLIA or other quantitative methods (Table 2).

Weight, use of cART, HIV-RNA load >200 copies/mL, and CD4 lymphocyte counts at the time of HAV vaccination and positive anti-HAV seroresponse at 6 months were entered into the multivariable analysis. Peak anti-HAV titers were not included because values from different test methods were not directly comparable. In the model, early seroreversion was more likely to occur in patients with a higher weight (aOR, 1.703; 95%

TABLE 1. Characteristics of the 1,256 Included Patients

Age, medium (IQR), years	32 (28, 38)
Male, n (%)	1,238 (98.6)
MSM, n (%) (N = 1,222)	1,177 (96.3)
Weight, median (IQR), kg (N = 1,154)	66 (60,74)
BMI, median (IQR) (N = 993)	22.4 (20.4, 24.7)
Overweight or obesity*, n (%)	312 (31.4)
Obesity*, n (%)	112 (11.3)
Use of cART, n (%)	
At the first dose of HAV vaccination	1,194 (95.1)
At month 6 of vaccination	1,236 (98.4)
Viral hepatitis coinfection, n (%)	
HBsAg positive	123 (9.8)
Anti-HCV positive (N = 1,255)	65 (5.2)
Recent syphilis[†], n (%)	288 (22.9)
Current smoker, n (%) (N=1128)	305 (27.0)
Plasma HIV-RNA load at vaccination	
HIV-RNA load >50 copies/mL, n (%)	180 (14.3)
HIV-RNA load >200 copies/mL, n (%)	119 (9.5)
Plasma HIV-RNA load at month 12 (N = 1,249)	
HIV-RNA load >50 copies/mL, n (%)	47 (3.8)
HIV-RNA load >200 copies/mL, n (%)	23 (1.8)
Nadir CD4 count, median (IQR), cells/mm^3 (N = 1,194)	292 (154, 413)
Nadir CD4 <200 cells/mm^3, n (%)	395 (33.1)
CD4 count at vaccination, median (IQR), cells/mm^3 (N = 1,255)	575 (433, 748)
CD4 at vaccination <200 cells/mm^3, n (%)	29 (2.3)
CD4 count at month 12 (M12), median (IQR), cells/ mm^3 (N = 1,248)	636 (496, 815)
CD4 at M12 <200 cells/mm^3, n (%)	14 (1.1)
Date of vaccination, n (%)	
Before June 30, 2016	541 (43.1)
After July 1, 2016	715 (56.9)
Brand of the first dose of HAV vaccine, n (%)	
Havrix	306 (24.4)
Vaqta	950 (75.6)
Brand of the second dose of HAV vaccine, n (%)	
Havrix	15 (1.2)
Vaqta	1,241 (98.8)
Positive anti-HAV IgG at month 6, n (%) (N = 910)	587 (64.5)
Peak anti-HAV IgG titer, median (IQR)	
By ARCHITECT HAV Ab IgG, S/CO (N = 799)	10.35 (8.35, 12.03)
By Cobas Anti-HAV and ADVIA Centaur HAV Total, IU/L (N = 395)	>60 (>60, >60)
Follow-up duration, median (IQR), days after the first dose of HAV vaccination	611 (526, 721)

*Overweight was defined by a BMI between 24 and 27 kg/m^2 and obesity by BMI of 27 kg/m^2 or greater.
†Recent syphilis was defined by presence of symptoms or signs consistent with primary syphilis or secondary syphilis, or a 4-fold increase from baseline in RPR titer with a reactive TPPA test within 1 year after the first dose of HAV vaccination.
Abbreviation: HBsAg, hepatitis B surface antigen.

CI, 1.292-2.323, per 10-kg increment) and those with plasma HIV-RNA load >200 copies/mL at the time of vaccination (aOR, 2.922; 95% CI, 1.067-7.924), whereas positive anti-HAV seroresponse at 6 months and higher CD4 lymphocyte counts at vaccination were inversely associated with early seroreversion with an aOR of 0.059 (95% CI, 0.020-0.154) and 0.837 (95% CI, 0.704-0.979, per 100-cell/mm^3 increment), respectively (Table 3).

A sensitivity analysis including only the patients whose anti-HAV titers were determined by ARCHITECT HAV Ab IgG showed that the most significant factor associated with early seroreversion was peak anti-HAV titers. The rest of the findings were similar to the primary analysis, except that in this model the association between seroreversion and CD4 lymphocyte counts at time of vaccination was no longer statistically significant (Supporting Table S3).

Discussion

In this study, we identified a cohort of HIV-positive adult patients who successfully seroconverted after completing the standard two doses of HAV vaccination and found a seroreversion rate of 3.9% after a median duration of 1.7 years. To our knowledge, this is the largest longitudinal follow-up study to date that focuses on HAV seroreversion after vaccination among HIV-positive patients. A higher weight, plasma HIV-RNA load >200 copies/mL and lower CD4 lymphocyte counts at the time of vaccination, and lower peak anti-HAV titers and lack of anti-HAV seroresponse before the second dose of HAV vaccination were independently associated with higher odds for HAV seroreversion.

Durability of responses to vaccination has been a concern among HIV-positive patients because of their impaired immunity compared to HIV-negative individuals.[31] Although seroreversion cannot be translated directly into loss of protection, as shown in the anamnestic response after hepatitis B vaccination,[32,33] AHA in HIV-positive individuals who had had positive anti-HAV antibodies has been reported,[34] indicating that loss of seroprotective antibodies may lead to susceptibility to hepatitis A infection in the HIV-positive population. Several studies reported a substantial rate of loss of HAV antibodies after vaccine-induced seroconversion.[15,16,19] Launay et al. and
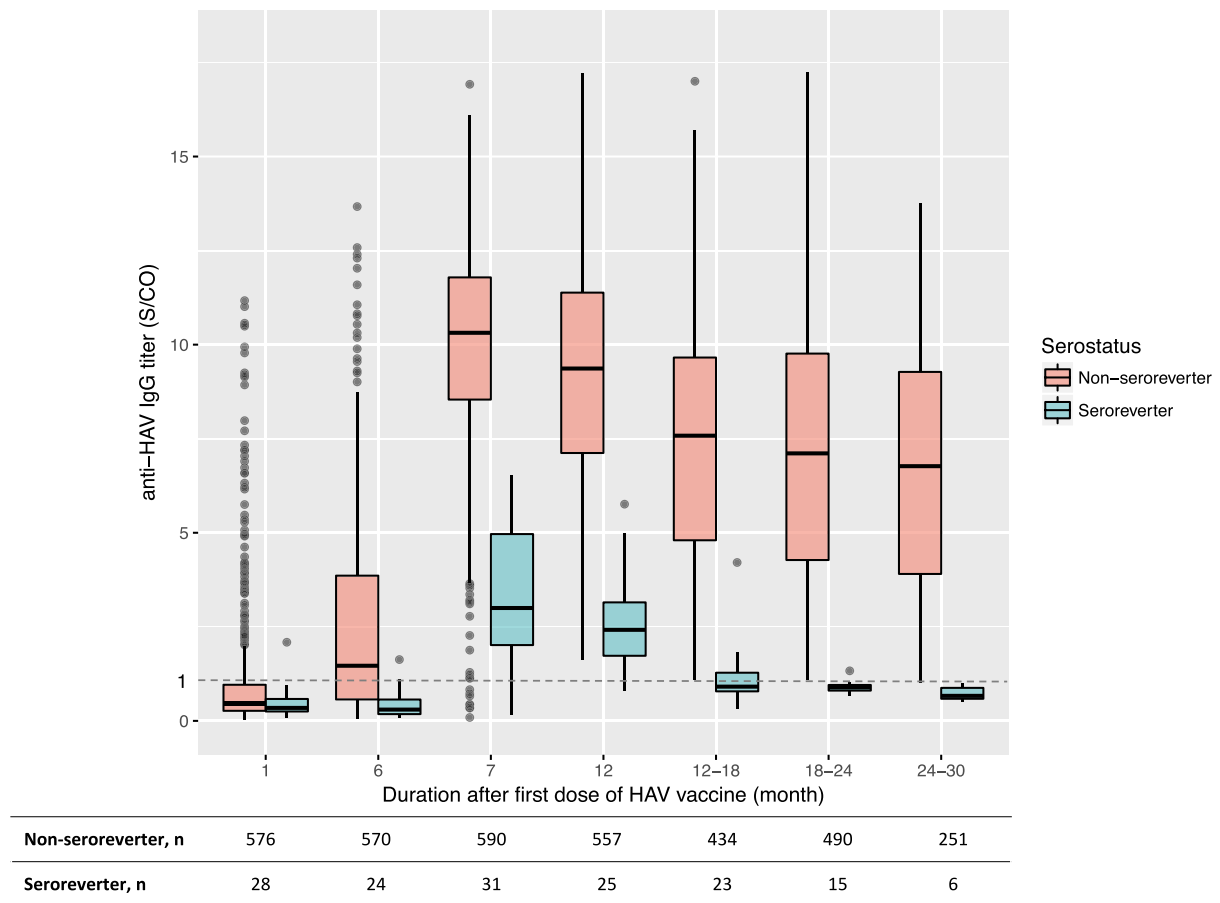
	1	6	7	12	12–18	18–24	24–30
Non-seroreverter, n	576	570	590	557	434	490	251
Seroreverter, n	28	24	31	25	23	15	6

FIG. 2. Evolution of serological responses after HAV vaccination in HIV-positive patients according to their status of seroreversion. Serereverters were less likely to mount anti-HAV IgG responses before the second dose of HAV vaccination (month 6) had lower peak anti-HAV IgG titers after completion of two doses of vaccination.

Cheng et al., in their previous investigations, found that, at 18 months after vaccination, seroreversion rates were 6% and 13%, respectively.[15,35] By comparison, the seroreversion rate in our study was a little bit lower, which may be reassuring in an outbreak setting. The retrospective design of our study of a shorter observation duration and the natural booster effect that might occur during an ongoing HAV outbreak may have contributed to the discrepancies observed. Another potential explanation could be that the population in our study was mostly virally suppressed and had higher baseline CD4 lymphocyte counts compared to those included in the previous studies.[15-17] Of note, the sample size of the current study was 5 times as large as the two previously mentioned studies combined.

Measurements of antibody titers are the most common method to evaluate the host responses to vaccination and have been used as surrogate markers of clinical endpoints in many vaccine trials.[36,37] It is not unexpected that a lower peak anti-HAV antibody titer after vaccination was associated with early seroreversion in this study. Unfortunately, anti-HAV antibody measurements used in this study were not standardized. Most of the participating hospitals utilized a semiquantitative CLIA method to measure anti-HAV IgG, whereas the other hospitals used quantitative CLIA and ECLIA kits to measure total anti-HAV antibody titers with detection limits only up to 60 and 100 IU/L. This could potentially limit the clinical implication of our study, because meaningful cut-off values of anti-HAV titers to predict

TABLE 2. Case-Control Analysis of Factors Associated With Early Seroreversion After HAV Vaccination

	Seroreverters	Nonseroreverters	
	N = 49	N = 196	P Value
Age, median (IQR), years	34 (29, 39)	33 (28, 39)	0.331
Male, n (%)	49 (100)	194 (99.0)	>0.999
MSM, n (%) (N = 241)	48/49 (98.0)	185/192 (96.4)	>0.999
Weight, median (IQR), kg (N = 225)	72 (62, 85)	66 (58, 73)	0.001
BMI, median (IQR), (N = 215)	23.7 (21.2, 27.0)	22.3 (20.1, 24.5)	0.003
Overweight or obesity*, n (%)	21/44 (47.7)	51/171 (29.8)	0.032
Obesity*, n (%)	11/44 (25.0)	14/171 (8.2)	0.006
Use of cART, n (%)			
At the first dose of HAV vaccination	43 (87.8)	185 (94.4)	0.117
At month 6 of vaccination	49 (100)	195 (99.5)	>0.999
Viral hepatitis coinfection, n (%)			
HBsAg positive	4 (8.2)	18 (9.2)	>0.999
Anti-HCV positive	3 (6.1)	11 (5.6)	>0.999
Recent syphilis†, n (%)	14 (28.6)	47 (24.0)	0.580
Current smoker, n (%) (N = 230)	16/47 (34.0)	54/183 (29.5)	0.595
Plasma HIV-RNA load at vaccination			
HIV-RNA load >50 copies/mL, n (%)	14 (28.6)	29 (14.8)	0.034
HIV-RNA load >200 copies/mL, n (%)	11 (22.4)	18 (9.2)	0.023
Plasma HIV-RNA load at month 12			
HIV-RNA load >50 copies/mL, n (%)	4 (8.2)	7 (3.6)	0.238
HIV-RNA load >200 copies/mL, n (%)	1 (2.0)	3 (1.5)	>0.999
Nadir CD4 count, median (IQR), cells/mm^3 (N = 234)	264 (153, 431)	304 (145, 453)	0.615
Nadir CD4 <200 cells/mm^3, n (%)	16/49 (32.7)	67/185 (36.2)	0.738
CD4 count at vaccination, median (IQR), cells/mm^3	486 (394, 662)	576 (452, 760)	0.024
CD4 at vaccination <200 cells/mm^3, n (%)	2 (4.1)	4 (2.0)	0.345
CD4 count at month 12 (M12), median (IQR), cells/mm^3	606 (444, 842)	639 (489, 834)	0.498
CD4 at M12 <200 cells/mm^3, n (%)	1 (2.0)	3 (1.5)	>0.999
Date of vaccination, n (%)			>0.999
Before June 30, 2016	26 (53.1)	104 (53.1)	
After July 1, 2016	23 (46.9)	92 (46.9)	
Brand of the first dose of HAV vaccine, n (%)			0.325
Havrix	21 (42.9)	69 (35.2)	
Vaqta	28 (57.1)	127 (64.8)	
Positive anti-HAV IgG at month 6, n (%) (N = 185)	2/36 (5.5)	100/149 (67.1)	<0.001
Peak anti-HAV IgG titer, median (IQR)			
By ARCHITECT HAV Ab IgG, S/CO (N = 166)	3.15 (2.50, 5.06)	10.89 (8.60, 11.99)	<0.001
By Cobas Anti-HAV, IU/L (N = 79)	38.44 (32.94, 57.28)	>60 (>60, >60)	<0.001
Duration of follow-up, median (IQR), days after first dose of HAV vaccination	549 (450, 648)	566 (489, 665)	0.291

*Overweight was defined by a BMI between 24 and 27 kg/m^2 and obesity by BMI of 27 kg/m^2 or greater.
†Recent syphilis was defined by presence of symptoms or signs compatible with primary syphilis or secondary syphilis, or a 4-fold increase from baseline in RPR titer with a reactive TPPA test within 1 year after the first dose of HAV vaccination.
Abbreviation: HBsAg, hepatitis B surface antigen.

early seroreversion cannot be analyzed from the data collected. Nevertheless, a positive anti-HAV seroresponse before the second dose of HAV vaccination can be a useful tool for clinical follow-ups. As expected, patients with no seroresponse before administration of the second dose of HAV vaccine were more likely to lose seroprotective antibodies early in the course.

Detectable or higher plasma HIV-RNA load at time of vaccination or time of follow-up of antibody response has been reported in several studies,

TABLE 3. Multivariable Analysis of Factors Associated With Early Seroreversion After HAV Vaccination

	aOR	P Value
Weight, per 10-kg increment	1.703 (1.292-2.323)	<0.001
HIV-RNA load >200 copies/mL at vaccination	2.922 (1.067-7.924)	0.035
CD4 count at vaccination, per 100-cell/mm^3 increment	0.837 (0.704-0.979)	0.034
Positive anti-HAV at month 6	0.059 (0.020-0.154)	<0.001

including ours, to be associated with poorer HAV vaccine durability.[17,19] Similar findings were also reported in HBV vaccination studies.[38] Higher baseline CD4 lymphocyte counts have been shown to be associated with primary HAV vaccine seroresponse in many studies.[39] The present study suggests that the correlation also existed between levels of CD4 cell counts and durability of seroresponse to HAV vaccination. Although the exact mechanism behind these phenomena warrants further investigations, these findings have been suggested to be related to a quantitative and functional decline in activated T cells among HIV-positive patients despite cART.[38]

Correlation between obesity and poorer vaccine response had been reported in studies of hepatitis B, tetanus, and rabies vaccines.[40,41] In this study, patients with higher weights had higher odds for early seroreversion after HAV vaccination, and seroreversion rates increased from 6.3% in patients with a weight of 70 kg or higher to 23.8% in those with a weight of 100 kg or higher (Supporting Table S4). Two studies of HAV vaccination in nonimmunocompromised subjects also demonstrated a slower and lower seroresponse after vaccination among those with higher BMI.[42,43] This poorer seroresponse resulted in delayed seroconversion and lower antibody titers, which could explain the association between the higher weight and early HAV seroreversion observed in the present study. It has been postulated that the adipose tissue and inflammatory cytokines and hormones produced could induce a chronic state of inflammation and interfere with proper vaccine-induce immune response.[41] Exact mechanisms by which obesity affects our adaptive immune responses are yet to be elucidated.

Specific sexually transmitted diseases, including syphilis and HCV infection, have been proposed as surrogate markers of higher-risk sexual behavior[22] and shown to be associated with better durability of

seroresponse to HAV vaccination[15,16] because of higher chance to confer natural booster through new risky exposures. This was not found in the present study, however. Because this is a vaccine durability study taking place in a setting of AHA outbreak, we suspected the background circulating HAV natural boosters might occur irrespective of higher-risk sexual behaviors, though the rate of recent syphilis observed were similar between seroreverters and nonseroreverters. The link between high-risk sexual behaviors and persistence of anti-HAV seroresponse will need further clarification in a nonoutbreak setting.

The HAV vaccines administered in this study included two different brands (HAVRIX and VAQTA), and this could potentially affect vaccine response. Most of the included vaccinees received HAVRIX-VAQTA or VAQTA-VAQTA, and our previous analysis showed comparable serological response between the two combinations at 48 weeks.[24] The current analysis did not detect any association between vaccine brands received and early seroreversion, which further supports their comparability in the short term. However, whether different combinations of vaccines would result in different durability of vaccine responses in the long-term follow-up remains to be investigated.

Despite well-documented effectiveness of hepatitis A vaccination, coverage among people living with HIV remains poor in many parts of the world.[44] Also, the lack of monitoring of serological response after vaccination to evaluate the need for repeated or booster vaccination among HIV-positive individuals could result in a substantial number of susceptible hosts and the subsequent persistence of HAV transmission in communities. The impact would be even more significant in countries where obesity and suboptimal control of HIV infection are prevalent, according to the findings of the present study. More studies to investigate the optimal timing for follow-up of seroresponse after HAV vaccination and booster vaccination are urgently needed to inform the current guidelines. In the recent study conducted during the outbreak of AHA, we found that HIV-positive patients who had lost their anti-HAV antibodies after primary vaccination could mount rapid and robust seroresponses to one single-dose HAV vaccination.[45]

Other than previously mentioned limitations, necessary cautions are needed in the interpretation

of our study results. First, selection bias is expected from the retrospective design of this study, because only those patients with follow-up of seroresponses were included in this study. Indeed, approximately one third of patients who had completed two doses of HAV vaccination with seroresponse were not included because they did not have anti-HAV antibodies measured after 12 months. These patients received HAV vaccines later in the study period, close to the end of the AHA outbreak, and thus they were probably less likely to experience natural booster. Second, the majority of the included patients were males, who had been receiving successful cART with HIV viral suppression. Cautions should be exercised to generalize our results to female HIV-positive patients, those who have not initiated cART, or those who experienced virological failure.

In conclusion, we found a low, but substantial, rate of early seroreversion among HIV-positive patients after two doses of HAV vaccination. These patients were more likely to serorevert if they had higher weights, had detectable plasma HIV RNA loads or lower CD4 lymphocyte counts at the time of vaccination, or had lower peak anti-HAV antibody titers and negative anti-HAV antibodies before the second dose of HAV vaccination. Regular monitoring of seroresponse and booster vaccination after primary HAV vaccination is warranted, especially in these subsets of HIV-positive patients.

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