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Original Article

Effectiveness of hepatitis A vaccination among people living with HIV in Taiwan: Is one dose enough?

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KEYWORDS
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Abstract *Background:* Single dose hepatitis A virus (HAV) vaccine had been proven its efficacy in immunocompetent but not immunocompromised hosts. We aim to investigate the effectiveness of one dose versus 2 doses HAV vaccine among people living with HIV (PLHIV).
Method: We conducted a 1:1 single center retrospective case–control study for PLHIV in Northern Taiwan. Case patients were those who received single dose HAV vaccine and controls were those who completed standard 2 doses HAV vaccine. Nationwide campaign of single dose HAV vaccine had been practiced for high risk population including PLHIV and those who had newly diagnosed sexually transmitted diseases.
Results: During February 2016 and December 2017, 90 cases received single dose HAV vaccine provided while the other 90 age-matched controls received 2 doses vaccine were enrolled. We found more injection drug users (22.22% vs. 1.11%, $p < 0.0001$), more co-infection with viral hepatitis C (28.89% vs. 5.56%, $p < 0.0001$), and history of syphilis infection (56.67% VS 30%, $p = 0.0003$) in single dose group than 2 doses group. Seroconversion rate at one year was significantly higher in 2 doses group (97.78% vs 56.67%, $p < 0.0001$). Among single dose group, people with hepatitis B or C virus co-infection (HBV: $p = 0.02$, aOR: 0.03, 95% CI: 0.002–0.55; HCV: $p = 0.002$, aOR: 0.22, 95% CI: 0.08–0.58) were less likely to achieve seropositivity, while those who had higher CD4 count at baseline and one year, had better response to vaccine.

Abbreviations: aOR, adjusted odds ratio; cART, combination antiretroviral therapy; CD4, cluster of differentiation 4; CI, confidence interval; ECLIA, electrochemiluminescence immunoassay; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injection drug user; MSM, men who have sex with men.

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Conclusion: Two doses HAV vaccine is necessary among PLHIV to achieve sustained seroresponse rather than single dose.

Introduction

Viral hepatitis A, the most common acute hepatitis worldwide infected mainly from food-borne, is found to be a co-infection in people with human immunodeficiency virus (HIV) infection, especially among men who have sex with men (MSM) based on their potential sexual transmitted characteristic during oral-anal sex.[1–7] Low prevalence of hepatitis A immunity among young adults is seen in many developed countries.[2,3,7–10] Viral hepatitis A within outbreak was more fatal with fulminant hepatitis and prolonged viremia in MSM, lower CD4, and higher HIV viral load HIV-infected patients.[1,3,11] Vaccine coverage helps to prevent hepatitis A and decrease its severity.[6,12]

Single dose HAV vaccine had been proven its efficacy in short-term and over 5 years effectiveness in immunocompetent hosts.[13–16] Unfortunately, HIV—infected patients have poorer responses to viral hepatitis A vaccines and carried higher long-term seroreversion rate.[17–20] Vaccine became less effective in HIV-infected individuals with obesity, high body weight, high plasma viral load, older age, and hepatitis C co-infection.[1,5,13,17,18,21–31] In addition, to use direct acting agents as effective treatment to HCV treatment in Taiwan can be reimbursed by national health insurance since January 2017 with limited indication.[32] Immunization regimens may require revision in these group.[17,27] How many doses should be provided to people living with HIV (PLHIV) remained unknown. Previous studies reported two doses may be more effective than single one,[20,24] while others showed the effectiveness of two doses similar with three doses.[3,17,19,22,33]

There were several outbreaks in people living with HIV in Europe, American, and Asia.[9,11,34] A serious outbreak also occurred among MSM in Taiwan during 2015 and 2016.[12,35] Therefore, a nationwide vaccination campaign was initiated since September 2015 for disease control. The campaign provided single dose of HAV vaccine to subjects with HIV-infection or those who had newly diagnosed sexually transmitted diseases according to the evidence provided by the study of immunocompetent subjects, while the second dose of HAV vaccine was not supplied.[13–16] However, whether single dose HAV vaccine is adequate to provide protection in the situation of outbreak of hepatitis A among HIV-infected patients still lacked evidence.

Hence, we aim to compare the evolutional change of antibody titer and the effectiveness at 48 weeks of one dose versus 2 doses HAV vaccine among PLHIV during the outbreak of acute hepatitis A in Taiwan.

Methods

In Taiwan, an outbreak of acute viral hepatitis A among MSM was detected between June 2015 and December 2017. National Vaccination Campaign was launched immediately for disease control since September 2015. Far Eastern Memorial Hospital is a medical center in Northern Taiwan, contains 1000 beds, and it offers care to more than 1100 HIV-infected individuals with annually increased around 130 new-diagnosed HIV-infected patients. Based on launched vaccination policy in Taiwan, both HAVRIX 1440 enzyme-linked immunosorbent assay units (GlaxoSmithKline, Biologicals, Rixensart, Belgium) and VAQTA 50 units (Merck and Co., Inc., West Point, PA) were provided in Taiwan. With previous documentation, both vaccines had similar efficacy and safety even switching to each other as booster dose.[5,30,31,36] In our hospital, almost all patients received VAQTA with this new policy and those who received HARVRIX were excluded.

During 2016 to 2018, according to the vaccination campaign, we checked every encountering HIV patient's serum HAV IgG as baseline, and followed their antibody titers 1, 4, and 12 weeks after the first injection of HAV vaccine and then every 24 weeks. The second dose HAV vaccine was not provided by the campaign and the patients will receive the second dose HAV vaccine if they can afford the expense at 24 weeks apart from the first dose. Their baseline biochemistry, CD4 count, HIV viral load, and markers for HBV and HCV were also collected retrospectively. HIV viral suppression was defined as less than 50 copies/ml. This retrospective study was approved by the Institutional Review Boards of Far Eastern Memorial Hospital with approval number 105040-F.

Laboratory investigations

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 Cobas Anti-HAV (Roche, Mannheim Germany), a quantitative electrochemiluminescence immunoassay (ECLIA) with a cut-off value of 20 IU/L and a detection range of 3—60 IU/L. Detection limits of the test kits for plasma HIV-RNA load were 20 copies/mL.

Statistical analysis

Statistical analyses were performed using Medcalc software (MedCalc - version 19.3.1). Non-categorical variables were compared using the ANOVA, and categorical variables were compared using Chi square. In the case—control study, variables with $P < 0.05$ were entered into Logistic regression model with mean to identify factors associated with HAV seroconversion and determine the adjusted odds ratio (aOR) of each variable. Variables with a P value < 0.05 were deemed statistically significant throughout the analyses.

Results

From February 2016 to December 2017, total 688 HIV-positive individuals were encountered while 508 patients received two doses and 180 patients received single dose HAV vaccine. Individuals with missing data, female sex, heterosexual, lost to follow up, received different brand of vaccine, or unexpected booster dose were excluded from this study (Fig. 1). There were 90 HIV-infected patients who received single dose HAV vaccine while the other 333 subjects received 2 doses HAV vaccine were finally enrolled. The control group was chosen by age-adjusted among the 333 subjects who received 2 doses. The baseline characteristics were demonstrated in Table 1.

The enrolled HIV-infected subjects were transmitted mainly by MSM (88.33%) while the other 11.67% were injection drug users (IDU). The mean age of overall population was 32.63 years old, and 92.78% of them received combination antiretroviral therapy (cART). Moreover, the average baseline CD4 cell count was 629.48 cells/uL. In the single dose group, the percentage of history of syphilis infection (56.67% vs. 30%, $p = 0.0003$), IDU (22.22% vs. 1.11%, $p = 0.0001$), and HCV co-infection (28.89% vs. 5.56%, $p < 0.0001$) were higher than 2 doses group. Other factors such as mean CD4 cell count, antiretroviral status, or viral suppression when initiating vaccination showed no significant difference.

Fig. 2a demonstrates the effectiveness of one dose and 2 doses HAV vaccine for up to 2 years follow up. After the first dose of vaccination, the seroconversion rate was numerically higher in 2 doses group than one dose group at 4 weeks

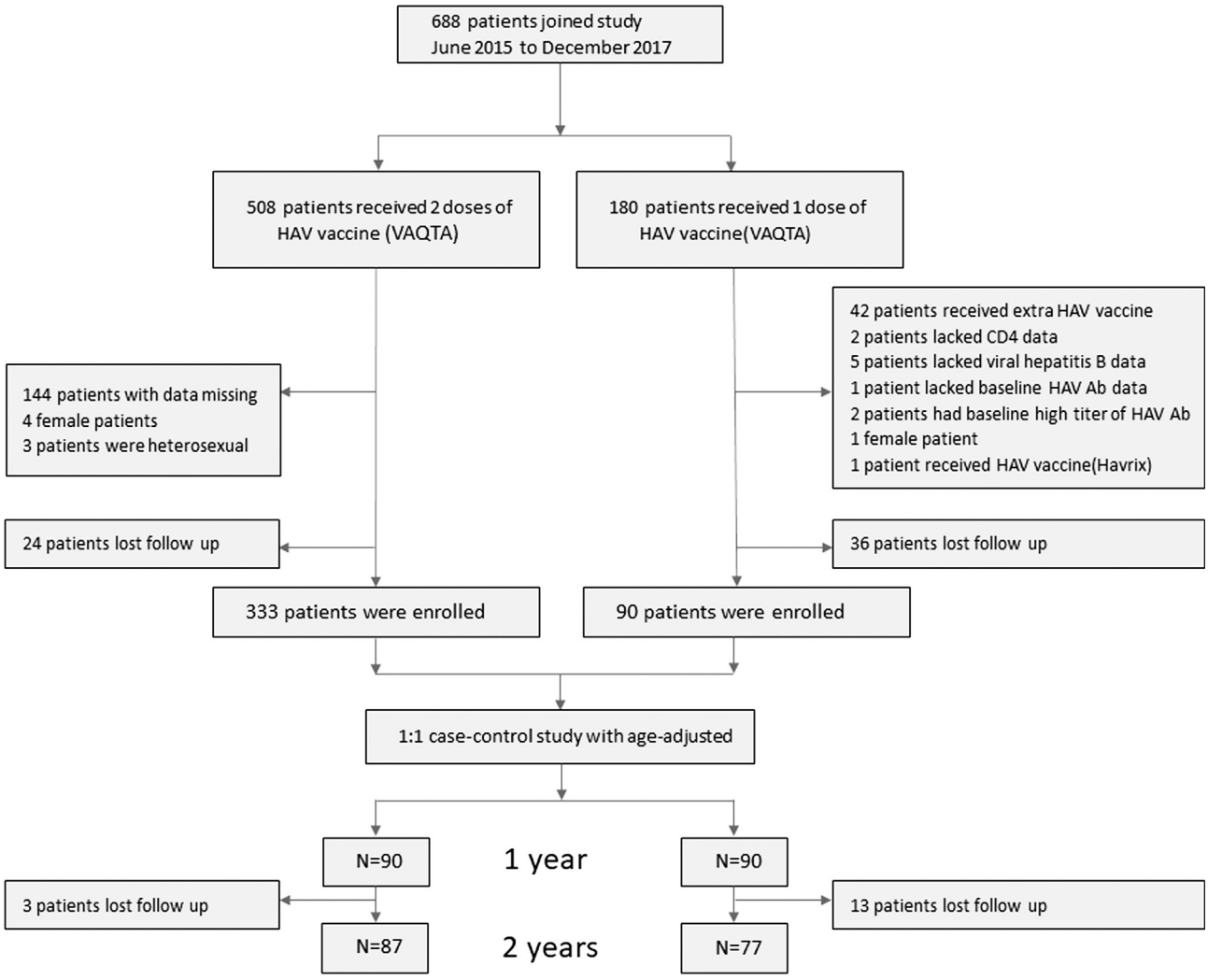

Figure 1. Diagram of patients who received one dose vs. 2 doses group.

Table 1 Baseline characteristics of people living with HIV received one dose vs. 2 doses groups.

Dose	1 dose (n = 90)	2 doses (n = 90)	p-value
Age (mean ± SD)	33.26 (±7.06)	31.99 (±6.6)	0.22
Men, n (%)	90 (100%)	90 (100%)	–
HIV transmission Risk, n (%)			<0.0001
MSM	70 (77.78%)	89 (98.89%)	
IDU	20 (22.22%)	1 (1.11%)	
HBsAg (+), n (%)	9 (10%)	8 (8.89%)	0.8
Anti-HCV (+), n (%)	26 (28.89%)	5 (5.56%)	<0.0001
History of Syphilis, n (%)	51 (56.67%)	27 (30%)	0.0003
CD4 (cells/μL) at vaccination, mean (range)	610.09 (21–1607)	648.86 (231–1473)	0.34
CD4 (cells/μL) >200 at vaccination, n (%)	86 (95.56%)	90 (100%)	0.044
CD4 (cells/μL) at 48 weeks, mean (range)	655.81 (3–1554)	725.52 (286–1229)	0.09
CD4 (cells/μL) >200 at 48 weeks, n (%)	84 (93.33%)	90 (100%)	0.013
PVL (copies/ml) at vaccination, mean (range)	4076.48 (20–96400)	3118.55 (20–63500)	0.628
Suppressed PVL (<50 copies/ml) at vaccination, n (%)	65 (72.22%)	71 (78.89%)	0.2994
PVL (copies/ml) at 48 weeks, mean (range)	3791.87 (20–129000)	133.63 (20–9920)	0.074
Suppressed PVL (<50 copies/ml) at 48 weeks, n (%)	78 (86.67%)	88 (97.78%)	0.0055
Use cART at vaccination, n (%)	86 (96.56%)	81 (90.0%)	0.15
Use cART at 24 weeks, n (%)	77 (85.56%)	89 (98.89%)	0.0009

HIV: Human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; MSM: men who have sex with men; IDU: injection drug users; CD4: cluster of differentiation 4; PVL: plasma viral load; cART: combination antiretroviral therapy.

without statistically significance (77.78% vs. 67.14%, p = 0.14) and 24 weeks (84.88% vs. 64.2%, p = 0.0027) with significant difference. However, in contrast to decreased seroconversion rate of one dose group at 48 weeks and 96 weeks, the effectiveness of 2 doses group was kept increasing after the second dose of vaccine (Table 2. 48 weeks: 97.78% vs 56.67%, p < 0.0001, aOR: 33.65, 95% CI: 7.80–145.21; 96 weeks: 95.4% vs 42.86%, p < 0.0001, aOR: 27.67, 95% CI: 9.21–83.13).

The evolutional change of anti-HAV IgG was demonstrated in Fig. 2b. Along with the different rates of seroconversion mentioned in Fig. 2a, the mean anti-HAV-IgG titer decreased after 24 weeks without booster dose (p < 0.001). Booster dose of HAV vaccine significantly help to maintain long-term seroconversion rate according to logistic regression (p = 0.0027).

In addition, compared to IDU group, MSM had better seroresponse in single dose group (aOR: 5.75, 95% CI: 1.86–17.73, p = 0.002) and all patients (aOR: 12.79, 95% CI: 4.54–36.03, p < 0.0001). Meanwhile, HBV and HCV coinfection were both associated with less seroresponse among single dose group (HBV: aOR: 0.03, 95% CI: 0.002–0.55, p = 0.02; HCV: aOR: 0.22, 95% CI: 0.08–0.58, p = 0.002) and all patients (HBV: aOR: 0.22, 95% CI: 0.08–0.61, p = 0.004; HCV: aOR: 0.13, 95% CI: 0.06–0.31, p < 0.0001) at one year. However, in 2 doses group, none of the above findings presented (Table 2). Regardless of one dose or 2 doses vaccination, higher CD4 level at vaccination and at one year, with sustained cART use at 24 weeks and with HIV viral suppression at one year were associated with higher seroconversion rate. (CD4 at vaccination: p = 0.0369; CD4 at one year: p = 0.0005; cART use at 6 months: aOR: 3.88, 95% CI: 1.28–11.82, p = 0.017; Undetected Plasma viral load at one year: aOR: 3.88, 95% CI: 1.28–11.82, p = 0.017) However, in the model of multivariate logistic regression demonstrated in Table 3, we found that standard 2 doses vaccination (aOR: 17.64, 95% CI: 2.7–115.11, p = 0.0027), MSM (aOR: 7.28, 95% CI: 1.28–41.31, p = 0.025) and without HBV coinfection (positive HBsAg, aOR: 0.065, 95% CI: 0.009–0.48, p = 0.007) were independent factors to be associated with seroresponse at 1 year.

Discussion

Two doses of HAV vaccination provided more protective and sustained benefit according to the trend of antibody titer evolution. We also found that PLHIV without HBV and HCV coinfection had better seroconversion rate, while those who had higher CD4 level and adhered to cART also showed better response to vaccine.

HAV vaccine belongs to travel medicine in Taiwan, and it was not regular introduced to general population. It was also defined as alternative beyond routine vaccine schedule in Western countries, and health insurance or the public health budget is main reason for the coverage rate in many countries, such as Greek.[21,37,38]

Both single dose inactivated or live attenuated hepatitis A vaccine had been previously documented five-year antibody persistence in children without HIV infection.[14–16] The data showed seropositivity at one year for about 91.8%–95.3% and maintained the efficacy up to 5 years for about 85.9–90.7%. However, the result of sustained response cannot be applied generally to immunocompromised host such as PLHIV. In our study population, although most of them received cART at vaccination and achieved viral suppression at 48 weeks, the antibody titer decayed earlier after 24 weeks without second dose. Therefore, to complete 2 doses HAV vaccination is required to maintain long-term efficacy. In addition, the response to hepatitis A vaccine is weakened earlier in HIV positive patients and

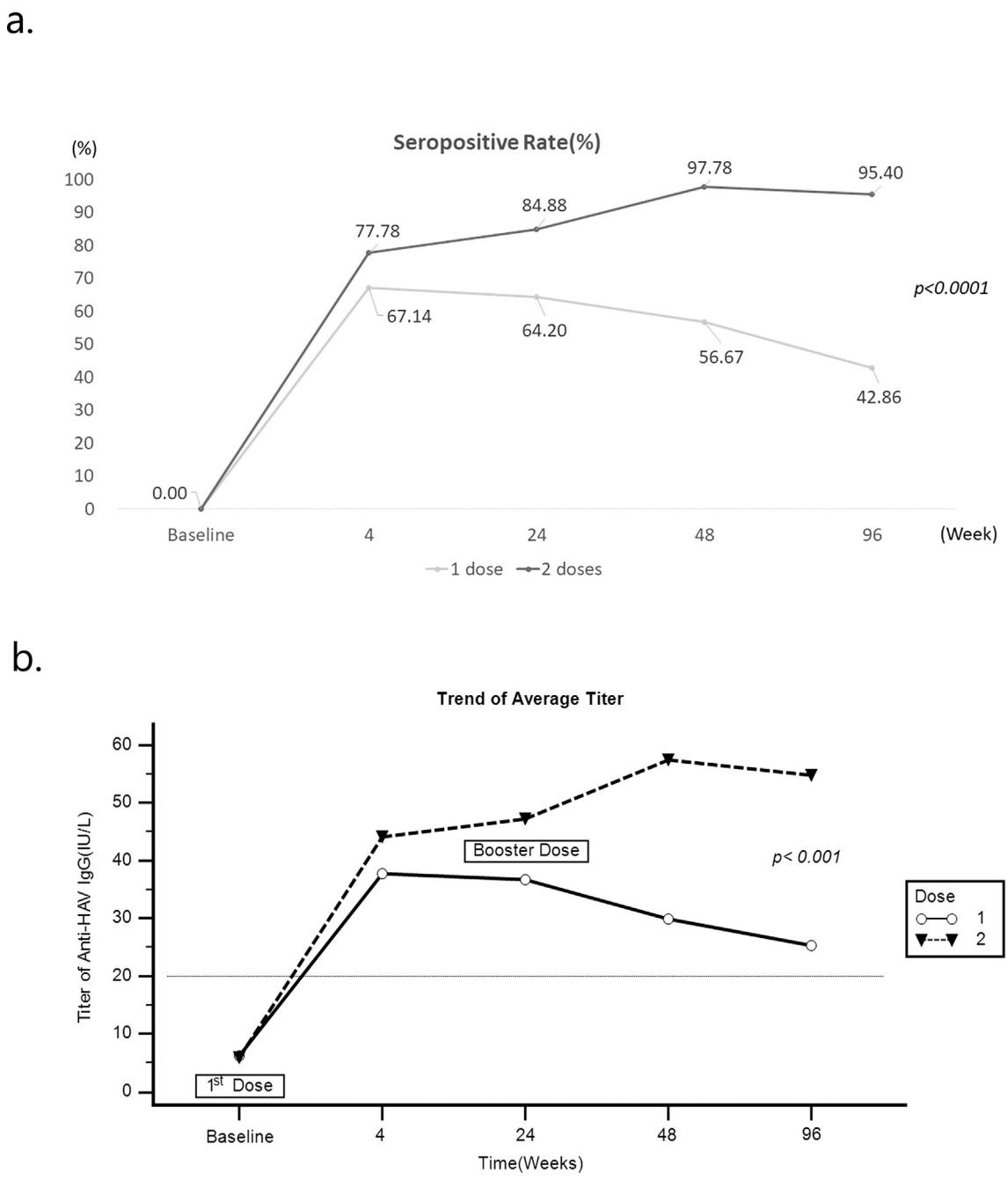

Figure 2. a. Evolution of seroconversion rates among one dose vs. 2 doses vaccination b. Evolution of ani-HAV IgG titers of one dose vs. 2 doses vaccination.

they should be tested for seroconversion after vaccination.[19]

The known average seropositivity rate at 24 weeks after first dose was 64%, which was similar to our result in single dose group.[3] Our patients in 2 doses group showed higher seropositivity rate at 24 weeks, which may be resulted from less IDU, HCV co-infection status, higher sustained cART coverage at 24 weeks and better viral suppression rate at 48 weeks. Impaired seroconversion rate in HIV/HCV co-infected people was found to be related to systemic inflammation response. Serum IL-6, sCD14, sCD163, and IP10 levels are elevated in people with chronic HCV and HIV infection, while pre-vaccine elevation of plasma levels of sCD14 was negatively associated with HAV antibody levels at week 8 after vaccination.[39]

In contrast to single dose HAV vaccine, 2 doses had higher seroconversion rates in HIV-positive individuals in previous literature review.[3,26] Our study also reported evolutional change of antibody level, which was less discussed before. In contrast to seropositivity defined as anti-HAV-IgG titer higher than 20 IU/ml, we described the change of average anti-HAV-IgG titer which showed the same trend as seropositivity. The decay of antibody titer developed early after 24 weeks. It could be caused by lower

Table 2 Analysis of factors associated with anti-HAV IgG Seroconversion at one year.

	1 Dose group (n = 90)	OR (CI)	p-value	2 Doses group (n = 90)	OR (CI)	p-value	All (n = 180)	OR (CI)	p-value
Seroconversion at 48wks, n (%)	51 (56.67%)			88 (97.78%)			139 (77.22%)	33.65 (7.8—145.21)	<0.0001
HIV transmission Risk, n (%)		5.75 (1.86—17.73)	0.002		11.67 (0.37—363.38)	0.16		12.79 (4.54—36.03)	<0.0001
MSM	46 (65.71%)			87 (97.75%)			133 (83.65%)		
IDU	5 (25%)			1 (100%)			6 (28.57%)		
HBsAg (+), n (%)	0 (0%)	0.03 (0.002—0.55)	0.02	8 (100%)	0.53 (0.023—11.93)	0.69	8 (47.1%)	0.22 (0.08—0.61)	0.004
Anti-HCV (+), n (%)	8 (30.77%)	0.22 (0.08—0.58)	0.002	5 (100%)	0.33 (0.01—7.74)	0.49	13 (41.94%)	0.13 (0.06—0.31)	<0.0001
History of Syphilis, n (%)	31 (60.78%)	1.47 (0.63—3.42)	0.37	25 (92.59%)	0.08 (0.004—1.73)	0.11	56 (71.79%)	0.58 (0.29—1.17)	0.13
CD4 (cells/μL) at vaccination, mean	648.90		0.15	654.84		0.13	652.66		0.0369
CD4 (cells/μL) at vaccination>200, n (%)	50 (58.14%)	4.17 (0.42—41.7)	0.22	88 (97.78%)			138 (78.41%)	10.89 (1.1—107.75)	0.04
CD4 (cells/μL) at 48 weeks, mean	732.61		0.012	729.16		0.29	730.42		0.0005
CD4 (cells/μL) at 48 weeks > 200, n (%)	49 (58.33%)	2.8 (0.49—16.14)	0.25	88 (97.78%)			137 (78.74%)	7.41 (1.31—42.02)	0.024
PVL (copies/ml) at vaccination, mean	4333.89		0.86	3188.97		0.666	3609.5		0.983
Suppressed PVL (<50 copies/ml) at vaccination, n (%)	37 (56.92%)	1.04 (0.41—2.63)	0.94	69 (97.18%)	0.71 (0.03—15.47)	0.83	106 (77.94%)	1.18 (0.53—2.6)	0.69
PVL (copies/ml) at 48 weeks, mean	2788.33		0.575	136.21		0.877	1109.29		0.125
Suppressed PVL (<50 copies/ml) at 48 weeks, n (%)	46 (58.97%)	2.01 (0.59—6.91)	0.27	86 (97.73%)	6.92 (0.26—185.1)	0.25	132 (79.52%)	3.88 (1.28—11.82)	0.017
Use cART at vaccination, n (%)	48 (55.81%)	0.42 (0.04—4.21)	0.46	79 (97.53%)	1.67 (0.07—37.53)	0.75	127 (76.05%)	0.27 (0.03—2.098)	0.21
Use cART at 24 weeks, n (%)	45 (58.44%)	1.64 (0.50—5.34)	0.41	87 (97.75%)	11.67 (0.37—363.38)	0.16	132 (79.52%)	3.88 (1.28—11.82)	0.017

HIV: Human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; MSM: men who have sex with men; IDU: injection drug users; OR: odds ratio; CI: confidence interval; CD4: cluster of differentiation 4; PVL: plasma viral load; cART: combination antiretroviral therapy.

Table 3 Multivariate logistic regression analysis for factors associated with seroconversion at one year.

	aOR (CI)	p-value
2 doses vs. one dose	17.64 (2.7—115.11)	0.0027
HIV transmission Risk, MSM	7.28 (1.28—41.31)	0.025
HBsAg (+)	0.065 (0.009—0.48)	0.007
Anti-HCV (+)	0.43 (0.099—1.84)	0.2531
History of Syphilis	0.35 (0.09—1.33)	0.1241
CD4 (cells/μL) at vaccination	0.9997 (0.997—1.003)	0.8544
CD4 (cells/μL) at vaccination >200	4.4 (0.27—71.92)	0.2989
CD4 (cells/μL) at 48 weeks	1.002 (0.999—1.005)	0.1956
CD4 (cells/μL) at 48 weeks > 200	1.39 (0.09—22.09)	0.8154
PVL (copies/ml) at vaccination	1 (1.0000—1.0001)	0.4483
Suppressed PVL (<50 copies/ml) at vaccination	1.05 (0.25—4.39)	0.9419
PVL (copies/ml) at 48 weeks	1 (1.0000—1.0000)	0.7594
Suppressed PVL (<50 copies/ml) at 48 weeks	1.83 (0.31—10.67)	0.5028
Use cART at vaccination	0.35 (0.02—6.2)	0.4703
Use cART at 24 weeks	2.38 (0.52—10.84)	0.263

Hosmer & Lemeshow test: Chi-squared: 5.6; DF: 8; Significance level: P = 0.69.
aOR: adjusted odds ratio; CI: confidence interval; CD4: cluster of differentiation 4; HIV: Human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; MSM: men who have sex with men; IDU: injection drug users; PVL: plasma viral load; cART: combination antiretroviral therapy.

viral suppression rate of single dose group as mentioned by the other study.[21] However, in a short-term outbreak of acute hepatitis A, a strategy targeting high risk group provided at least a period of protection for the outbreak control of acute hepatitis A.[12]

Our study had several limitations. First of all, MSM and IDU cases are not equally distributed among 2 groups, and thus may result in unbalanced HCV carriers between two groups.[40] The difference could be attributed to poor socioeconomic status among IDUs and thus the IDUs preferred only to receive single dose HAV vaccine provided by the nationwide campaign. Second, the control cases were matched by age instead of immune status, thus single dose group had less cART coverage rate at 24 weeks and lower viral suppression rate at 48 weeks. It may indicate relative impaired immunity among single dose group which may potentially hinder the antibody response to vaccine. However, we found no significant association between seroresponse and mean CD4 cell count or CD4 cell count >200 cells/μL at vaccination according to multivariate analysis from our case—control population or all population (Table 3 and supplementary table 2). In addition, cases with baseline suppressed viral load showed no significant difference could also indicate balanced immune function among our case—control population (Table 1). We also matched another control group by "CD4>200 cells/μL and CD4 <200 cells/μL" which demonstrated similar result of seropositivity and average antibody titer trend as our study (supplementary figure 2). The finding could be due to too few cases with CD4 cell counts <200 cells/μL to demonstrate relevant difference. Third, the record of body weight was not complete that it was considered a factor to influence vaccine response and a clue for health status monitor. Finally, our sample size is relatively small which could be a bias.

In conclusion, we found 2 doses HAV vaccine are necessary among PLHIV to achieve sustained seroresponse at one year in the setting of HAV outbreak and the second dose HAV vaccine can certainly boost the elevation of anti-HAV IgG.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2020.06.014.