

Brief Communication



Ten-Year Trends of Hepatitis A Seroprevalence in People Living with HIV in Korea

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OPEN ACCESS

Received: May 7, 2022

Accepted: Jun 28, 2022

Published online: Jul 22, 2022

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Funding

This work was supported by a 2-year research grant from the Pusan National University.

ABSTRACT

Epidemiological information on hepatitis A among people living with HIV (PLHIV) in Korea is scarce. This retrospective study was performed at a tertiary care hospital and included 756 PLHIV with anti-hepatitis A virus (HAV) IgG tests. Between 2012 and 2021, the age at anti-HAV IgG seroconversion is gradually delayed, and the proportion of individuals susceptible to HAV infection increased among adult PLHIV in Korea. The independent risk factors for HAV seropositivity were female sex and HBs antigen (Ag) positivity. Therefore, HAV vaccination is highly recommended for young PLHIV, especially for women or HBsAg-positive individuals.

Keywords: Hepatitis A; HAV; Seroprevalence; HIV; AIDS

Hepatitis A is caused by the hepatitis A virus (HAV), which belongs to the *Picornaviridae* family, genus *Hepatitisvirus* [1]. Although HAV transmission primarily occurs through the fecal-oral route, it can be transmitted through contaminated water or food, contaminated blood products, or between illegal intravenous drug users or homosexual males [2]. Previous epidemiological studies have demonstrated that human immunodeficiency virus (HIV)-infected people are a high-risk group for HAV infection and are more likely to develop severe liver disease if they become infected [2-4]. Therefore, hepatitis A vaccination is recommended for people living with HIV (PLHIV) who are susceptible to hepatitis A in areas with a high risk of hepatitis A outbreak.

The seroprevalence of hepatitis A has decreased over the last 30 years with improvements in socioeconomic status and general public health in Korea [5], which has led to a marked increase in the population susceptible to HAV infection in younger adults. As a result, periodic hepatitis A outbreaks have occurred recently in Korea [5]. For these reasons, hepatitis A vaccination has been recommended for Korean PLHIV. However, epidemiological information on HAV among PLHIV, which is required to make appropriate recommendations for hepatitis A vaccination, is scarce in Korea.

This retrospective descriptive study was performed from January 2012 to December 2021 at a tertiary care hospital in Busan, Korea.

Ethics Statement

The Institutional Review Board of Pusan National University Hospital approved the study protocol, and informed consent was waived (IRB No. 2203-023-113).

Conflict of Interest

SHL is editorial board of Infect Chemother; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions

Conceptualization: SL, SHL. Data curation: SL, SHL. Formal analysis: SL, SHL. Funding acquisition: SL. Investigation: SL, SHL. Resources: SL, SHL. Supervision: SL, SOL, JEL, YKS Writing - original draft: SL. Writing - review & editing: SL, SHL.

The anti-HAV-IgG test was routinely performed for initial evaluation of HIV-infected patients at our institute in 2012. All PLHIV who visited Pusan National University Hospital and underwent anti-HAV-IgG tests were identified from computerized records. Individuals under 18 years of age and those with a history of HAV vaccination when testing for anti-HAV IgG were excluded. Demographic and clinical data were collected from a retrospective review of medical records. We analyzed the trends in HAV seroprevalence at 3-year intervals during the 10-year study period.

R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. Categorical variables were compared using Pearson’s Chi-square test or Fisher’s exact test, whereas non-categorical variables were compared using the Mann–Whitney *U*-test or Kruskal–Wallis test. All tests of significance were 2-tailed; $P < 0.05$ was considered significant.

A total of 756 PLHIV who had undergone anti-HAV IgG tests were identified between January 2012 and December 2021 excluding 7 PLHIV who had a history of HAV vaccination. The number of PLHIV enrolled during study period is shown according to the year of enrollment and their age at enrollment in **Supplementary Table 1**. Of these 756 PLHIV, 686 (90.7%) were male, and the mean age of the patients was 43.01 ± 13.24 years. Seroprevalence of HAV by age was as follows: ≤ 25 years, 13.2%; 26 - 30 years, 23.9%; 31 - 35 years, 28.8%; 36 - 40 years, 45.1%; 41 - 45 years, 82.2%; 46 - 50 years, 93.6%; 51 - 55 years, 95.6%; 56 - 60 years, 98.4%; and > 60 years, 100%.

The HAV seroprevalence by year and age is shown in **Figure 1A** and **1B**. The HAV IgG seropositivity among PLHIV gradually increased from 31 years of age in 2012 and 2013 - 2015, while HAV IgG seropositivity among PLHIV rapidly increased from 41 years of age in 2016 - 2018 and 2019 - 2021 (**Fig. 1A**). These findings suggest that the age at HAV seroconversion increased over time.

In patients aged ≤ 40 years, HAV seropositivity has significantly decreased from 2016 - 2021 (31.6% from 2012 - 2015 *vs.* 21.4% from 2016 - 2021; $P = 0.049$), while there was no trend in HAV seropositivity during the study period in patients aged ≥ 41 years (**Fig. 1B**).

Further analyses were performed on patients aged ≤ 40 years because they had lower probability of HAV seropositivity and greater susceptibility to HAV infection than patients

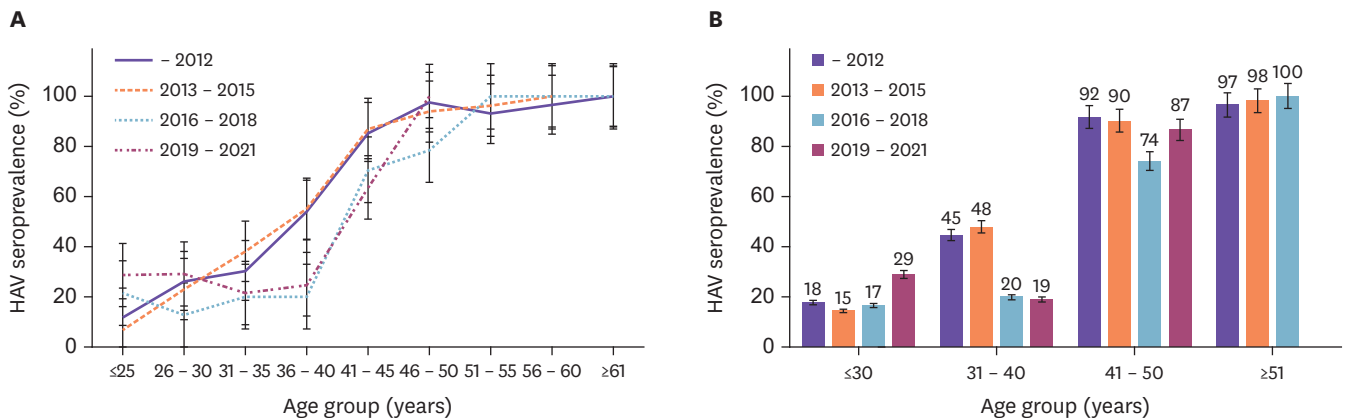
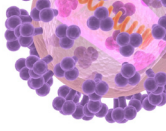


Figure 1. HAV seroprevalence by years and age among people living with HIV at a tertiary care hospital in Busan, Korea from 2012 to 2021. (A) The trend of HAV seropositivity according to age for each period. (B) The difference in HAV seropositivity according to period of time for each age group. HAV, hepatitis A virus; HIV, human immunodeficiency virus.



aged >40 years. Comparison of demographic and clinical characteristics between the anti-HAV IgG-positive and anti-HAV IgG-negative groups is shown in **Supplementary Table 2**. Multivariable logistic regression analysis of PLHIV in patients aged ≤40 years indicated that HAV seropositivity was more likely in patients older than 30 years (adjusted odds ratio [aOR]: 2.364, 95% confidence interval [CI]: 1.325 - 4.219, $P = 0.004$), female sex (aOR: 3.413, 95% CI: 1.339 - 8.696, $P = 0.010$), and positive HBs antigen (Ag) test (aOR: 4.300; 95% CI: 1.104 - 16.756, $P = 0.036$). However, men who have sex with men (MSM) was not significantly associated with HAV seropositivity (aOR: 1.296, 95% CI: 0.710 - 2.366, $P = 0.399$) (**Table 1**).

In patients aged 31 - 40 years, the HAV seroprevalence significantly decreased from 46.2% in 2012 - 2015, to 18.4% in 2016 - 2021 ($P = 0.001$) (**Fig. 1B**). In PLHIV under 30 years of age, the HAV seroprevalence was 16.2% in 2012 - 2018 and increased to 28.9% in 2019 - 2021, although the difference was not statistically significant ($P = 0.077$) (**Fig. 1B**).

We performed a subgroup analysis of HAV seroprevalence in MSM and men who have sex with women (MSW) among PLHIV to investigate whether the recent increase in HAV seroprevalence in young PLHIV was due to an increase in HAV seroprevalence among MSM. The HAV seroprevalence in both MSM and MSW PLHIV gradually decreased in those aged 31 - 40 years (**Fig. 2A**). However, the HAV seroprevalence in MSM under 30 years of age has recently increased in 2019 - 2021 (**Fig. 2B**). In the younger (≤30 years) MSM group, HAV seropositivity was significantly higher in 2019 - 2021 than before 2019 (40.0% in 2019 - 2021 vs. 11.0% in 2012 - 2018, $P = 0.002$).

Table 1. The result of multivariable logistic regression analysis of risk factors for HAV seropositivity among people living with HIV in age ≤40 years

Characteristics	Adjusted OR (95% CI)	P-value
Age ≥30 years	2.364 (1.325 - 4.219)	0.004
Female Sex	3.413 (1.339 - 8.696)	0.010
MSM gender orientation	1.296 (0.710 - 2.366)	0.399
Marital status (married)	1.715 (0.772 - 3.809)	0.186
CD4 + T cell count <200/mm ³	1.322 (0.737 - 2.374)	0.349
Psychological disorder	1.752 (0.607 - 5.054)	0.300
HBs Antigen positive	4.300 (1.104 - 16.756)	0.036
RPR (VDRL) Positive	0.675 (0.329 - 1.385)	0.283

HAV, hepatitis A virus; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; MSM, men who have sex with men; RPR, rapid plasma resin; VDRL, venereal disease research laboratory.

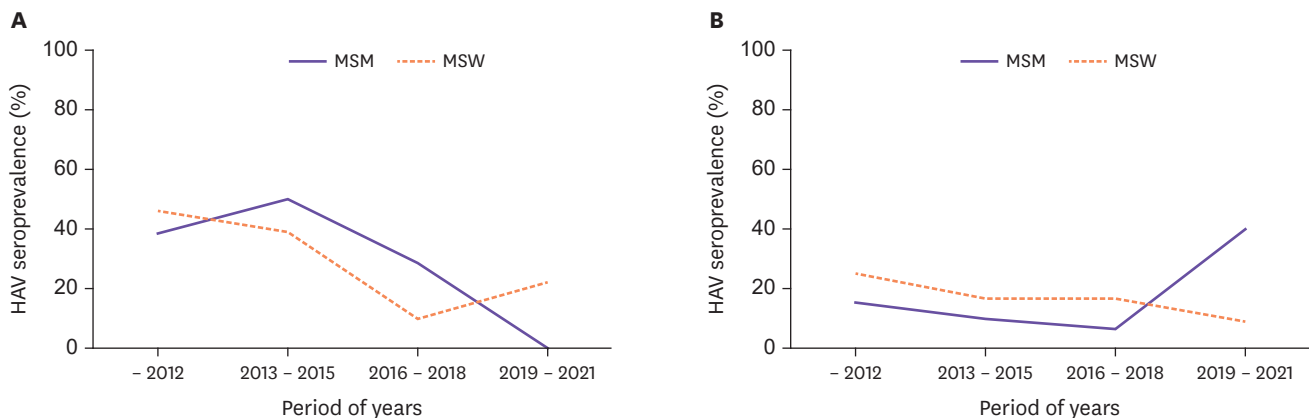


Figure 2. Comparison of the HAV seropositivity trends between men who have sex with men (MSM) and men who have sex with women (MSW) among patients with HIV infection attending a tertiary care hospital in Busan, Korea from 2012 to 2021. (A) Trends in patients aged 31 - 40 years and (B) aged ≤30 years. HAV, hepatitis A virus; HIV, human immunodeficiency virus.

Although PLHIV are known to be a high-risk group for HAV infection, epidemiological information on HAV seroprevalence in PLHIV in Korea is lacking. Therefore, we performed an epidemiologic study of HAV among Korean PLHIV to provide useful clinical information about HAV infection in Korean PLHIV.

First, we demonstrated the trends in HAV seroprevalence in PLHIV over the last decade. In a nationwide study of the seroprevalence of HAV among the Korean general population, the HAV seroprevalence among participants aged 20 – 29 years increased from 10.1% in 2010 to 32.8% in 2019, while that among participants aged 30 – 39 years (39.5% in 2010 to 32.4% in 2019) and 40 – 49 years (88.5% in 2010 to 63.2% in 2019) decreased [6]. That study also revealed that individuals aged 20 – 39 years had the lowest HAV seroprevalence. This is probably because they had fewer opportunities to attain natural immunity due to improvements in personal hygiene and limited opportunities to receive a vaccination [6]. In our study, the seroprevalence of HAV decreased in young adult PLHIV over time, similar to the findings in non-PLHIV [6]. These findings imply that the population susceptible to HAV infection is gradually increasing among young adult Korean PLHIV. HAV infection usually presents with a serious course in adulthood and an even higher chance of progressing to fulminant courses in PLHIV [2]. In addition to the periodic occurrence of HAV epidemics in Korea, our findings suggest that HAV vaccination should be recommended for young adult PLHIV.

Second, our study demonstrated that female sex and HBsAg positivity were factors associated with HAV seropositivity. HAV transmission may occur through household, sexual contact, and illegal drug use, and some risk factors are shared with HBV [7]. HAV infection in patients with chronic liver disease is associated with an increased frequency of fulminant hepatitis A infection and is more likely to cause severe complications [7]. Therefore, our findings underline the necessity of HAV vaccination in PLHIV with HBsAg. In addition, female PLHIV might also be recommended for HAV vaccination, although the reason for the high seroprevalence in this group has not been elucidated.

Third, we observed an unusual recent increase in HAV seropositivity in the younger MSM group. Throughout the study period, there was no significant difference in HAV seropositivity between the MSM and MSW groups among Korean PLHIV. However, we observed a significant increase in HAV seroprevalence in the younger MSM group. The reason for this finding is unclear, and we could not clarify whether this was a temporary event or a continuous trend. Previous studies have reported that some acute hepatitis A epidemics were associated with PLHIV, especially in the MSM group [8-10]. Therefore, we should monitor this group cautiously and recommend HAV vaccination to them.

This study had several limitations. First, our study was a retrospective observational study; therefore, we cannot rule out the presence of unmeasured confounding factors. In addition, the vaccination status might not have been accurately assessed because vaccination status of the patients was determined by a retrospective review of their medical records. Second, our study was conducted at a single center in the south-eastern region of Korea. Therefore, our findings should be generalized to other regions of the country with caution.

In conclusion, the timing of seroconversion of anti-HAV IgG is gradually delayed, and the proportion of susceptible HAV infections is increasing among PLHIV in Korea. Therefore, HAV vaccination is highly recommended for young PLHIV, especially for women and HBsAg-positive individuals.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Number of participants enrolled in the study by year of enrolment and age at enrolment

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Supplementary Table 2

Demographic and clinical characteristics of people living with HIV (PLHIV) aged ≤40 years in the anti-HAV IgG-positive and anti-HAV IgG-negative groups

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