Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: A review

Kuan-Yin Lin, Guan-Jhou Chen, Yu-Lin Lee, Yi-Chia Huang, Aristine Cheng, Hsin-Yun Sun, Sui-Yuan Chang, Chun-Eng Liu, Chien-Ching Hung

Author contributions: Lin KY, Chen GJ, LeeYL, Huang YC, Cheng A, Sun HY and Chang SY performed the literature search and review, and wrote the paper; Liu CE and Hung CC edited and revised the manuscript.

Supported by: Centers for Disease Control, Taiwan, No. JH105022.

Conflict-of-interest statement: Chien-Ching Hung has received research support from Janssen, Abbvie, Bristol-Myers Squibb, Merck, and ViIV and speaker honoraria from Gilead Sciences, and served on the advisory boards for Gilead Sciences, ViIV, Abbvie, and Janssen. Other authors report no potential conflict of interest.

Abstract

Hepatitis A virus (HAV) is one of the most common infectious etiologies of acute hepatitis worldwide. The virus is known to be transmitted fecal-orally, resulting in symptoms ranging from asymptomatic infection to fulminant hepatitis. HAV can also be transmitted through oral-anal sex. Residents from regions of low endemicity for HAV infection often remain susceptible in their adulthood. Therefore, clustered HAV infections or outbreaks of acute hepatitis A among men who have sex with men and injecting drug users have been reported in countries of low endemicity for HAV infection. The
duration of HAV viremia and stool shedding of HAV may be longer in human immunodeficiency virus (HIV)-positive individuals compared to HIV-negative individuals with acute hepatitis A. Current guidelines recommend HAV vaccination for individuals with increased risks of exposure to HAV (such as from injecting drug use, oral-anal sex, travel to or residence in endemic areas, frequent clotting factor or blood transfusions) or with increased risks of fulminating disease (such as those with chronic hepatitis). The seroconversion rates following the recommended standard adult dosing schedule (2 doses of HAVRIX 1440 U or VAQTA 50 U administered 6-12 mo apart) are lower among HIV-positive individuals compared to HIV-negative individuals. While the response rates may be augmented by adding a booster dose at week 4 sandwiched between the first dose and the 6-mo dose, the need of booster vaccination remain less clear among HIV-positive individuals who have lost anti-HAV antibodies.

Key words: Epidemiology; Viral hepatitis; Acute hepatitis; Fecal-oral transmission; Oral-anal sex; Men who have sex with men; Injecting drug use; Immunosuppression; Immunization

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We provide an updated review of hepatitis A virus (HAV) coinfection among human immunodeficiency virus (HIV)-positive individuals, focusing on the epidemiology, clinical manifestations, and prevention for HAV infection. The reported outbreaks of acute hepatitis A among men who have sex with men and injecting drug users are summarized. Updated vaccination guidelines for prevention of HIV-positive individuals against HAV infection are presented. We also review the published data of effectiveness or efficacy of HAV vaccination studies and the different approaches to improvement of the serological responses to conventional HAV vaccines among HIV-positive individuals.

HAV VIROLOGY

HAV, first identified by Feinstone et al[6] in 1973, belongs to the Hepatovirus genus of the family Picornaviridae. The genome of HAV is a positive-strand RNA (range, 7470 to 7478 nucleotides) and encodes only a single open reading frame, which is translated into a polyprotein. The polyprotein is then cleaved by the virus-encoded protease (3CPo) to yield 8 viral proteins, including VP0, VP3, VP1-2A, 2B, 2C, 3AB, 3CPo, and RNA-dependent RNA polymerase (RDRP, 3Dpo). The virus particle is composed of 3 proteins, VP0, VP1-2A, and VP3. During the assembly of the virus capsid, 2A will be removed from the VP1-2A by cellular protease or 3CPo, and at the final stage of maturation, VP0 will be cleaved into VP2 and VP4. Five copies of each protein will be assembled to form a pentamer, and 12 copies of the pentamer will form a virus capsid. Despite that there are some amino acid variations between different HAV strains, the detection of anti-HAV antibody is not as complicated as other RNA viruses due to the fact that HAV exists as a single serotype. Due to the advances of molecular technology, 7 unique genotypes (I to VII) of HAV are defined by analysis of a 168-base region, located

INTRODUCTION

Hepatitis A virus (HAV) is one of the most common infectious etiologies of acute hepatitis worldwide. According to the WHO estimates, HAV resulted in 13.7 million illnesses and 28000 deaths in 2010[1]. HAV is primarily transmitted fecal-orally via contaminated food or water, or through close contact with an infected person. With improved sanitation and provision of HAV vaccination, areas or populations with high HAV endemicity show patterns of declining endemicity, according to their socioeconomic backgrounds[3]. Based on the different age-specific HAV seroprevalence profiles, the world can be divided into countries of high, intermediate, low, and very low HAV endemicity[3]. In countries of high endemicity, most people acquire HAV in their early childhood and are immune to the virus. On the contrary, adults from low endemic areas are first exposed to HAV during travel to or residence in endemic areas, or being engaged in risky behaviors, such as contact with infected persons, being men who have sex with men (MSM), or using illicit drugs[2,4]. Several outbreaks of acute HAV infection among the MSM and injecting drug users’ (IDUs’) communities have been reported in several developed countries of low endemicity for HAV infection. The duration of HAV viremia and stool shedding of HAV may be longer in HIV-positive individuals, increasing the window of opportunity for wider transmission of HAV to those engaged in risk behaviors. HAV vaccination is the most efficient approach to prevention of acquiring HAV infection. However, the seroconversion rates following the recommended standard 2-dose HAV vaccination schedule are lower among HIV-positive individuals compared to HIV-negative individuals, and the vaccination effectiveness among HIV-positive individuals is rarely investigated in the outbreak setting[5]. In this article, we review the epidemiology and clinical manifestations of acute HAV infection and HAV vaccination among HIV-positive individuals in the era of combination antiretroviral therapy (cART).
between the C terminus of VP1 and N terminus of P2A. These 7 genotypes exhibit less than 85% of sequence identity between genotypes and no more than 15% of divergence within a genotype, a criterion used for polioviruses, another member of the family Picornaviridae. However, further detailed analyses of other viral regions reveal that the genotypes II and III should be reclassified as subtypes A and B of genotype II, and genotypes I and III could also be divided into subgenotypes A and B. Four genotypes (I, II, III, and VII) are of human origin, and 3 (IV, V, VI) are of simian origin. Genotypes I and III are the most prevalent genotypes identified in humans. Subgenotypes IA and IB are often found in North and South Americas, Europe, China, and Japan. Clusters within genotypes predominant in certain geographic regions have been reported, such as a group of subgenotype IA strains from the United States, and genotype II in the Netherlands, France, and Sierra Leone. However, in other regions, the presence of variant genotypes was reported in Europe and Japan, likely representing international spread from the endemic regions.

**Epidemiology of HAV Infection Among HIV-Positive Patients**

**HAV seroprevalence among HIV-positive patients**

Previous studies have shown higher seroprevalence and incidence of HAV infection among MSM compared to the general population, which were associated with oral-anal sex and the number of sexual contacts and partners. The HAV seroprevalence also increases with age, indicating the cohort effect. Unlike MSM, heterosexual men with risky sexual behaviors has been inconsistently associated with higher HAV seroprevalence. While a few studies reported a lower seroprevalence and incidence among heterosexual men with sexually transmitted diseases (STDs) compared to MSM, others indicated that the risks for HAV infection among heterosexual men with STDs and MSM were similar. IDUs also had a higher HAV seroprevalence than the general population. However, the high seroprevalence might not be solely attributable to needle contamination, since some reported similar elevation of the HAV seroprevalence between IDUs and non-injecting illicit drug users.

Although the direct evidence on the correlation between contracting HIV and HAV was scarce, observational data suggested that HIV-positive individuals, especially MSM and IDUs, are at increased risk of acquiring HAV. In addition, one small study including 15 HIV-positive individuals demonstrated that the duration of HAV viremia in HIV-positive individuals with acute hepatitis A was prolonged compared to that in HIV-negative individuals with acute hepatitis A, which may increase the probability of HAV transmission to others. Several studies have reported the HAV seroprevalence among HIV-positive individuals and at-risk persons in areas of different HAV endemicities and vaccine coverage. In these studies, the HAV seroprevalence among HIV-positive individuals ranged from 15.1% in Taiwan to 96.3% in Iran. While studies conducted in countries of high HAV endemicity showed no differences in the HAV seroprevalence between HIV-positive and HIV-negative individuals, the seroprevalence in countries of low endemicity was higher among HIV-positive individuals compared to HIV-negative individuals. Among HIV-positive individuals, older age and injecting drug use were identified as the independent factors associated with seropositivity for HAV; the HAV seroprevalence was lower in HIV-positive MSM despite the at-risk sexual behaviors.

**Hepatitis A Outbreaks in the MSM Population**

In countries of low HAV endemicity, the majority of HAV-seronegative adults remain susceptible to acute HAV infection. Outbreaks of acute hepatitis A are often caused by introduction of HAV through contaminated foods and person-to-person transmission. Numerous outbreaks of acute hepatitis A have been reported in the MSM population through sexual contacts, which are summarized in Table 2. Since the early 1980s, outbreaks of acute hepatitis A among MSM have been described in Denmark, Sweden, the United Kingdom, and the United States. The incidence of acute HAV infection among MSM peaked in the 1990s, and the affected countries included the United Kingdom, the Netherlands, Norway, and Australia. One of the largest epidemics of acute hepatitis A occurred in Sydney, Australia, where 2 outbreaks affected 323 and 186 MSM during 1991-1992 and 1995-1996, respectively. Since 2015, Taiwan reported a large outbreak involving more than 1000 indigenous cases, with more than 70% of the affected individuals being MSM. While the HAV vaccine was licensed and recommended for MSM since the mid-1990s, the emergence of HAV infection continued to pose a health threat to MSM in several developed European countries during the 2000s, including Italy, Denmark, Spain, Poland, and the United Kingdom. The duration of outbreaks of acute hepatitis A among MSM were mostly curtailed at 2 years; however, the outbreak in Canada extended from December 1994 to February 1996. The cyclical outbreaks were noted in Australia during 1991-1996 and in Spain during 1989-2010, which might be facilitated by the continuous circulation of particular HAV strains in the MSM population. The predominant circulating HAV strains among MSM belonged to genotype IA. The patients contracting HAV during the outbreaks were mostly young adults with a mean or median age of 28-36 years. HAV was recognized
Table 1  Seroprevalence of hepatitis A virus infection among human immunodeficiency virus-positive patients and at-risk populations

| Ref. | Location | Study period | Study population | Age (yr) | HIV-positive population | Other populations | Associated factors and comments |
|------|----------|--------------|------------------|----------|-------------------------|-------------------|---------------------------------|
| HIV-positive population | | | | | | | |
| Nandwani *et al*[26] | London, United Kingdom | 1993 | 255 men attending genitourinary clinics | 32 | 41.3% | MSM, 32.4% Heterosexuals, 30.0% Unknown HIV status, 26.4% | No difference between homosexual and heterosexual men |
| Fainboim *et al*[27] | Buenos Aires, Argentina | 1994-1995 | 484 HIV-positive patients | 29 | 84.0% | HIV-positive MSM, 83.3% HIV-positive heterosexuals, 86.3% HIV-positive IDUs, 85.7% Blood donors, 82.4% | High seroprevalence without difference between HIV-positive and HIV-negative individuals |
| Aloise *et al*[28] | Rio de Janeiro, Brazil | 1988-2004 | 581 HIV-positive patients | 35 | 79.8% | NA | Older age and lower educational level Seroprevalence increased with age and among heterosexuals |
| Lee *et al*[29] | Tainan, Taiwan | 2000-2005 | 484 patients with recent diagnosed HIV infection | 36 | 65.8% | HIV-positive MSM, 40.0%; HIV-positive heterosexuals, 85.2% HIV-positive IDUs, 70.1% | Older age and injecting drug use Higher seroprevalence in HIV-positive individuals |
| Sun *et al*[30] | Taiwan | 2004-2007 | 1580 HIV-positive patients | 39 | 60.9% | HIV-positive MSM, 50.5% HIV-positive heterosexuals, 79.3% HIV-positive IDUs, 62.0% HIV-negative individuals, 48.0% | Older age and being foreigners |
| Davoudi *et al*[31] | Tehran, Iran | 2005-2006 | 247 HIV-positive patients | 36 | 96.3% | NA | |
| Hoover *et al*[32] | 6 major cities2, United States | 2004-2007 | 627 HIV-positive MSM | 41 | 16.1%3 | NA | Low HAV screening and vaccination rates (28.5%) |
| Linkins *et al*[33] | Bangkok, Thailand | 2006-2008 | 1291 MSM | 27 | 32.4%3 | HIV-negative MSM, 25.5% | Older age and lower education level |
| Baek *et al*[34] | Seoul, South Korea | 2008-2010 | 188 HIV-positive patients | 39 | 62.8% | HIV-positive MSM, 57.1% HIV-positive heterosexuals, 65.8% HIV-negative MSM, 7.4% | Older age |
| Tseng *et al*[35] | Taipei, Taiwan | 2009-2010 | 1128 MSM | 18-40 | 15.1%3 | NA | No difference between HIV-positive and HIV-negative individuals |
| Kourkounti *et al*[36] | Athens, Greece | 2007-2011 | 897 HIV-positive MSM | 41 | 35.7%3 | NA | Older age and being foreigners |
| At-risk populations (MSM and IDUs) | | | | | | | |
| Corey *et al*[37] | Seattle, United States | 1977-1979 | 159 patients from STD clinics | 31 | NA | MSM, 30.4% (annual incidence, 22%) | Oral-anal sexual contact |
| McFarlane *et al*[38] | Nova Scotia, Canada | 1977-1978 | 421 patients from STD clinics | 25 | NA | MSM, 42.4% Heterosexuals, 39.2% Blood donors, 12.6% Student nurses, 13.2% | Higher seroprevalence and incidence in MSM Higher number of sex partners and older age |
| Kryger *et al*[39] | Copenhagen, Denmark | 1979 | 269 men with previous syphilis | 33 | NA | MSM, 36.0%; Heterosexual, 20.0% | More episodes of syphilis in younger MSM |
| Coutinho *et al*[40] | Amsterdam, the Netherlands | 1980-1982 | 689 MSM | 31 | NA | MSM, 42.0% (incidence, 14.0%) IDU, 43.7% Prison entrants, 60.1% Blood donors, 30.0% | Longer duration of homosexual activity History of incarceration |
| Crofts *et al*[41] | Victoria, Australia | 1990-1992 | 2175 prison entrants 293 IDUs | 30 | NA | MSM, 28.0% | Sexual and drug-using behaviors |
| Katz *et al*[42] | San Francisco and Berkeley, United States | 1992-1993 | 411 MSM | 21 | NA | | |
as being transmitted among MSM through sexual contacts[72], and case-control studies have identified several associated factors such as having anonymous sex partners, group sex, oral-anal and digital-rectal intercourse[63], contact with patients with acute hepatitis A[69], having sex in gay saunas[51,53], and visiting saunas and darkrooms[60]. In light of the risky sexual behavior, the largest HAV vaccination campaign for MSM was launched in Montréal, in which 9500-15000 first doses of HAV vaccine were administered to achieve a coverage rate between 20% and 41%. However, the decrease in the incidence of acute hepatitis A shortly after the vaccination campaign might indicate the relatively late implementation of HAV vaccination and the natural decline after herd immunity was established at the end of the outbreak[56]. The vaccination campaigns targeting MSM in Atlanta and Barcelona recruited 3,000 persons, which resulted in a 16% decrease of reported acute hepatitis A cases[56,65].

Coinfections with HAV and HIV were identified during the 2000s in Italy[52,54,55], Spain[56], and Poland[57]. Most HAV/HIV-coinfected individuals were males with known HIV status, while others were found to be HIV-positive concomitantly with acute HAV infection[52,54-57]. Among all male patients who received a diagnosis of acute hepatitis A during 2002-2008 in Italy, 15.2% (56/368) were HIV-positive[54]. After excluding those without available HIV serology, the HIV seroprevalence among was 27.6%[54]. The high proportion of HAV/HIV coinfection in the areas of low HAV endemicity highlights the importance of routine HIV testing in patients with acute hepatitis A[54].

### Hepatitis A outbreak in the IDU population

Outbreaks of acute hepatitis A in the IDU population have been reported since 1970s as the numbers of IDUs increased[74]. The studies of outbreaks of acute hepatitis A among IDUs are summarized in Table 3[74-88]. During 1970-1979, the cyclic occurrence of outbreaks of acute hepatitis A in Sweden suggested a continuously increasing pool of susceptible young IDUs in the closed communities[74]. The outbreaks were mostly described in Europe[75-78] and the United States[82,83,85] in the 1980s and 1990s, but were seldom described after the early 2000s[79-81,86]. Up to 492 IDUs were infected with HAV in Norway between 1995 and 1996[77]. In Terni, Italy; 47 cases of acute hepatitis A were reported during 2002-2003, among which included 35 IDUs and 2 HIV-positive individuals. The most recent outbreak of acute HAV infection among IDUs was described in Israel during 2012-2013, which occurred in IDUs and homeless adults with subsequent spread to the general population in Tel Aviv, despite the nation-wide implementation of universal toddler’s vaccination in 1999[88].

The outbreaks of acute hepatitis A among IDUs mainly lasted between 1 and 2 years, and young patients with a mean or median age of 20-34 years were predominantly affected[74,81]. HAV could be transmitted fecal-orally through poor personal hygiene.
Table 2  Outbreaks of acute hepatitis A in the men who have sex with men population

| Ref.                  | Location                     | Study period | Case number | Male | MSM | HIV-positive patients | Age (yr) | Risk factors and comments                                                                 |
|-----------------------|------------------------------|--------------|-------------|------|-----|------------------------|----------|----------------------------------------------------------------------------------------------|
| Høybye et al[43]      | Copenhagen, Denmark          | 1977-1978    | 45          | 45   | 21  | NA                     | 29       | Multiple partners and oral-anal sexual contact                                                |
| Christensen et al[44] | Stockholm, Sweden            | 1979-1980    | 145         | 145  | 145 | NA                     | NA       | HAV infection was associated with homosexual activity                                        |
| Mindel et al[45]      | London, United Kingdom       | 1980         | 24          | NA   | 23  | NA                     | NA       | Oral-anal sexual contact and sexual promiscuity                                              |
| Kani et al[46]        | London, United Kingdom       | 1989-1990    | 7000        | NA   | 41  | NA                     | NA       | Visiting saunas and darkrooms                                                                |
| Atkins et al[47]      | London, United Kingdom       | 1989-1992    | 206         | 121  | 65  | NA                     | NA       | Eating shellfish and sex in gay saunas                                                       |
| Leentvaa-Kuijpers et al[48] | Amsterdam, the Netherlands | 1992-1993    | 293         | NA   | 39  | NA                     | NA       | Unprotected sexual contact                                                                  |
| Walsh et al[49]       | Thames region, United Kingdom | 1995         | 481         | NA   | 58  | NA                     | NA       | Oral-anal and digital-rectal intercourse                                                      |
| Stene-Johansen et al[50] | Oslo, Norway               | 1995-1998    | 26          | 26   | 26  | NA                     | NA       | Routine HIV test in HAV-infected patients should be considered                               |
| Bell et al[51]        | London and East Sussex, United Kingdom | 1999-2004 | 122         | 104  | 81  | 11                     | 28       | Monophyletic HAV strain sustained the outbreak                                              |
| Manfredi et al[52]    | Bologna, Italy              | 2001         | 18          | 18   | 18  | NA                     | NA       | The outbreak strain was indistinguishable from that in Estonia                               |
| Mazick et al[53]      | Copenhagen, Denmark         | 2004         | 18          | 18   | 18  | NA                     | NA       | A unique circulating HAV strain                                                              |
| Gizaraldi et al[54]   | Rome, Italy                 | 2002-2008    | 473         | 368  | 115 | 37                     | 25-64    | Vaccination campaign achieving 20–41% coverage in MSM                                       |
| Bordi et al[55]       | Rome, Italy                 | 2008-2010    | 162         | 143  | 34  | 14                     | 36       | Vaccination campaign in MSM decreased incidence rapidly                                        |
| Tortajada et al[56]   | Barcelona, Spain            | 2002-2003    | 48          | 47   | NA  | 28%                    | 31       | Contact with jaundiced persons to be factors associated with acute hepatitis A in IDUs[80,81,85] |
| Dabrowska et al[57]   | Warsaw, Poland              | 2007-2008    | 860         | NA   | 50  | 6                      | 28       | Anonymous sex partner, group sex, oral-anal and digital-rectal intercourse                  |
| Tortajada et al[58]   | Barcelona, Spain            | 2008-2009    | 150         | 126  | 87  | NA                     | 33       | No difference in disease severity between HIV-positive and HIV-negative individuals           |
| Sfetcu et al[59]      | Northern Ireland, United Kingdom | 2008-2009 | 38          | 36   | 26  | NA                     | 29       | The outbreak strain was indistinguishable from that in England                               |
| Taffon et al[60]      | Tuscany, Italy              | 2008         | 240         | NA   | 32% | NA                     | NA       | A unique circulating HAV strain                                                              |
| Kosatsky et al[61]    | Anchorage, Alaska           | 1982-1983    | 17          | 17   | 17  | NA                     | 19-31    | Anonymous sex partner, group sex, oral-anal and digital-rectal intercourse                  |
| Desenclos et al[62]   | Florida, United States      | 1988-1989    | 311         | 69   | 26  | NA                     | NA       | Contact with jaundiced persons to be factors associated with acute hepatitis A in IDUs[80,81,85] |
| Henning et al[63]     | New York, United States     | 1991         | 180         | 180  | 62  | NA                     | 20-49    | Household or sexual contact                                                                  |
| Allard et al[64]      | Montréal, Canada            | 1996-1997    | 376         | 376  | 376 | NA                     | 33       | Vaccination campaign achieving 20–41% coverage in MSM                                       |
| Finton et al[65]      | Atlanta, United States      | 1996         | 222         | NA   | 75% | NA                     | NA       | Vaccination campaign in MSM decreased incidence rapidly                                        |
| Cotter et al[66]      | Ohio, United States         | 1996         | 136         | 118  | 47  | NA                     | 33       | Anonymous sex partner, group sex, oral-anal and digital-rectal intercourse                  |
| Stewart et al[67]     | Melbourne, Australia        | 1991-1992    | 495         | 407  | 210 | NA                     | NA       | Vaccination campaign in MSM decreased reported cases                                          |
| Stokes et al[68]      | Sydney, Australia           | 1991-1992    | 570         | 515  | 330 | NA                     | NA       | Contact with jaundiced persons to be factors associated with acute hepatitis A in IDUs[80,81,85] |
| Ferson et al[69]      | Sydney, Australia           | 1991-1996    | 1138        | 991  | 587 | NA                     | 30       | Sexual contact was the most reported contact type                                            |
| Delpech et al[70]     | Sydney, Australia           | 1997-1999    | 354         | 265  | 139 | NA                     | 32       | Household or sexual contact                                                                  |
| Chen et al[71]        | Taiwan                      | 2015-2016    | > 1000      | NA   | 70% | > 60%                  | NA       | A total of 1296 cases reported as of February, 2017                                         |

1Risk factors of acquiring HAV infection were identified by case-control studies. HAV: Hepatitis A virus; MSM: Men who have sex with men; NA: Not available.

and living conditions, or percutaneously through contamination of illicit drugs or injecting equipment by fecal materials or blood[81]. Three case-control studies identified not washing hands after using the toilet or preparing food, not washing hands prior to preparing drugs, sharing of needles or syringes, use of contaminated illicit drugs, and contact with jaundiced persons to be factors associated with acute hepatitis A in IDUs[80,81,85]. To curb the epidemic of acute hepatitis A, HAV vaccination programs were implemented in
the United Kingdom, Norway, and Italy, and harm reduction program by providing clean injecting equipment was implemented in Switzerland.

CLINICAL MANIFESTATIONS OF ACUTE HAV INFECTION

The incubation period of acute HAV infection is 2.5 to 5 wk. The typical symptoms of acute hepatitis A include fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain. The frequencies of symptoms or signs of acute hepatitis A are listed in Table 4. While most of acute HAV infections are self-limited, the severity of the symptoms may vary with age and concurrent comorbidities, particularly chronic viral hepatitis. Acute HAV infection is usually silent or subclinical in children, but approximately 30% of the infected patients older than 6 years have symptoms including hepatitis, jaundice, and abdominal pain. Less than 25% of the patients have diarrhea though HAV is transmitted through fecal-oral route. The data on the symptoms of acute hepatitis A

### Table 3 Outbreaks of acute hepatitis A in the injecting drug user population

| Ref. | Location | Study period | Total patients | IDU | HIV-positive individuals | Age (yr) | Risk factors and comments |
|------|----------|--------------|----------------|-----|--------------------------|----------|--------------------------|
| Widell et al. | Malmo, Sweden | 1970-1979 | 323 | 188 | NA | NA | The outbreak associated with intrarectal transportation of illicit drugs |
| Sundkvist et al. | Helsingborg, Sweden | 1983-1984 | 36 | 32 | NA | 18-35 | The outbreak associated with intrarectal transportation of illicit drugs |
| Letino et al. | Helsinki, Finland | 1994-1995 | 238 | 131 | NA | 31 | The outbreak associated with needle sharing |
| Stene-Johansen et al. | Oslo, Norway | 1995-1996 | 621 | 492 | NA | NA | The outbreak associated with needle sharing |
| O’Donovan et al. | United Kingdom | 1998-1999 | 27 | 14 | NA | 25 | The outbreak associated with parenteral transmission from contaminated illicit drugs; HAV vaccination of IDUs decreased the reported cases |
| Syed et al. | Bristol, United Kingdom | 2000 | 123 | 69 | NA | 25 | The outbreak associated with parenteral transmission from contaminated illicit drugs; HAV vaccination of IDUs decreased the reported cases |
| Roy et al. | Aberdeen, Scotland | 2000-2002 | 106 | 74 | NA | NA | Not washing hands after using the toilet, or before preparing food or drugs, sharing needles/syringes, and injecting contact with jaundiced persons |
| Spada et al. | Terni, Italy | 2002-2003 | 47 | 35 | 2 | 34 | Contact with jaundiced persons, but not related to injecting practices; HAV vaccination of IDUs decreased the reported cases |
| Harkess et al. | Oklahoma, United States | 1984-1987 | 79 | 42 | NA | 23-27 | Methamphetamine injection, sharing methamphetamine use, using brown methamphetamine, and needle sharing |
| Jenkerson et al. | New York, United States | 1986-1987 | 256 | 70 | NA | NA | HAV vaccination in jail decreased the reported cases |
| Jin et al. | Canada | 1987-1989 | 65 | 59 | NA | NA | HAV vaccination in jail decreased the reported cases |
| Huttin et al. | Iowa, United States | 1996-1997 | 158 | 9.7% | NA | NA | Methamphetamine injection, sharing methamphetamine use, using brown methamphetamine, and needle sharing |
| Vong et al. | Florida, United States | 2001-2002 | 403 | 11% | NA | 32 | HAV vaccination in jail decreased the reported cases |
| Shaw et al. | Queensland, Australia | 1997 | 875 | 118 | NA | NA | Sharing of instruments for smoking marijuana |
| Manor et al. | Tel-Aviv, Israel | 2012-2013 | 75 | 9 | NA | 33 | NA | |

1Risk factors of acquiring HAV infection were identified by case-control studies. HAV: Hepatitis A virus; HIV: Human immunodeficiency virus; IDU: Injecting drug user; NA: Not available.

### Table 4 Clinical symptoms and signs of patients with acute hepatitis A infection

| Symptoms | Frequency |
|----------|-----------|
| Asymptomatic | 14% |
| Fever | 48%-87% |
| Nausea/vomiting | 56%-88% |
| Anorexia | 66%-96% |
| Fatigue/malaise | 49%-80% |
| Upper abdominal pain | 42.5%-82% |
| Diarrhea | 8%-23% |
| Signs | |
| Jaundice | 24%-99% |
| Hepatomegaly | 7%-78% |
| Splenomegaly | 18%-30% |
among HIV-positive individuals are limited, and the study by Ida et al\(^{25}\) of 15 HIV-positive and 15 HIV-negative individuals with acute hepatitis A suggested no differences in the frequency and severity of clinical symptoms of acute hepatitis A between the two groups.

Patients with acute hepatitis A usually have significantly elevated levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. In previous studies, the average peak levels of total bilirubin were 7-8 mg/dL and the levels of AST and ALT were higher than 1000 IU/L\(^{25,92,93,96-100}\). Alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GT) are also elevated in patients with acute hepatitis A. Resolution of the abnormal biochemical tests generally occurs within 1 to 6 wk after the onset of the illness\(^{99}\). Approximately 85% of the patients who are infected with HAV have full clinical and biochemical recovery within 3 mo and nearly all have a complete recovery by 6 mo\(^{102}\). The study by Ida et al\(^{25}\) reported lower elevations in total bilirubin, AST, and ALT in HIV-positive individuals during acute hepatitis A than HIV-negative individuals, which were considered to be related to the weaker immune responses in HIV-positive patients or clonal spreading of a specific HAV strain that was able to escape from immunity in the study. Regulatory T cells (Tregs) normally suppress the T-cell responses directed against hepatitis viruses and down-regulate the immune reaction that is responsible for liver damage in viral hepatitis\(^{101}\). The study by Choi et al\(^{102}\) suggested a decrease in Tregs leading to a severe liver injury during acute hepatitis A. HIV-positive individuals however are known to have high Tregs, compared to their HIV-negative counterparts, hence they may experience less severe injury during acute hepatitis A\(^{103}\). On the other hand, Ida et al\(^{25}\) reported higher levels of ALP and γ-GT during acute hepatitis A in HIV-positive individuals than HIV-negative patients. Biliary tract is not the primary target of HAV infection. Lymphocytic cholangitis is rarely seen with acute HAV infection\(^{104}\). However, HIV-related cholangitis or cholangiography is a well-recognized late complication of acquired immunodeficiency syndrome (AIDS). Opportunistic infections such as cytomegalovirus infection or cryptosporidiosis may also cause cholangitis. HIV is also able to cause direct cytopathic effects on the biliary tract mucosa. Hence, the higher levels of ALP and γ-GT observed in HIV-positive patients with acute hepatitis A may be explained by multiple factors other than the liver injury caused by HAV itself.

In the general population, stool shedding of HAV antigen can be detected 19 d before the peak elevation of ALT levels and continue for at least 25 d\(^{105}\) and even up to 80 d\(^{106}\). The duration of viremia is estimated to last around 20 to 40 d\(^{25,106,107}\) and even longer than 3 mo\(^{108}\). In the study by Ida et al\(^{25}\), the median duration of HAV viremia in HIV-positive individuals with acute hepatitis A was 53 d, which was longer than that of HIV-negative individuals. A longer duration of HAV viremia may be related to impaired host immunity\(^{100}\). Besides, the relationship between duration of viremia and specific HAV genotypes is still inconclusive\(^{106,107}\). The comparisons of clinical manifestations of acute hepatitis A between HIV-positive and HIV-negative individuals are summarized in Table 5.

### Table 5  Comparison of clinical manifestations of hepatitis A virus between human immunodeficiency virus-positive patients or human immunodeficiency virus-negative patients with acute hepatitis A

| HIV-positive patients | HIV-negative patients |
|----------------------|----------------------|
| Natural course of acute HAV infection | NA | 2-5 yr\(^{97}\) |
| Incubation period (wk) | NA | 25 (HAV antigen)\(^{107}\) |
| Duration of stool shedding (d) | NA | 81 (HAV RNA)\(^{104}\) |
| Duration of viremia (d) | 53 (10-89)\(^{10\} | 22-95\(^{105,106}\) |
| Laboratory findings | | |
| Peak T-bilirubin (mg/dL) | 5.1-5.9\(^{102}\) | 5.7-8.7\(^{25,92,93,95,98}\) |
| Peak AST (IU/L) | 929-1339\(^{10\} | 1231-2271\(^{25,92,93,95,98}\) |
| Peak ALT (IU/L) | 1995-2608\(^ {10\} | 1079-3442\(^{25,92,93,95,98}\) |
| Duration of elevated AST/ALT (d) | 63 ± 38\(^{102}\) | 51\(^{100}\) |
| Peak ALP (IU/L) | 80±128\(^{10\} | 228-396\(^{102}\) |

HIV: Human immunodeficiency virus; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HAV: Hepatitis A virus; NA: Not available.

**HAV VACCINATION AND FACTORS ASSOCIATED WITH IMMUNOGENICITY AND PERSISTENT PROTECTION**

**Vaccine immunogenicity and factors associated with immunogenicity**

HAV vaccination is not universally recommended for HIV-positive individuals but specifically for those with
increased risks of exposure (such as from injecting drug use, oral-anal sex, travel to or residence in endemic areas, frequent clotting factor or blood transfusions) or with increased risks of fulminant disease (such as those with chronic hepatitis) (Table 6)\textsuperscript{111-114}. Of the two types of HAV vaccines that are currently available internationally, the live attenuated vaccine (based on H2 or LA-1 HAV strains and manufactured as well as mainly used in China or India) and the inactivated HAV vaccine (based on clinical trials since 1991 and licensed in the United States since 1995), only the latter is recommended for HIV-positive individuals. There are 3 formulations of inactivated HAV vaccines that have been assessed in HIV-positive individuals with varying degrees of immunodeficiency as shown in Table 7\textsuperscript{115-120}. Although different specific anti-HAV IgG titers have been used to define seroconversion (10, 18, 20, or 33 mIU/mL), the majority of these studies have adopted 20 mIU/mL as the surrogate titer for seroprotection.

The earliest studies of HAV vaccination in moderately to severely immunodeficient HIV-positive individuals preceded the licensure of the adult formulation of HAVRIX 1440 U wherein a triple-mini dosing scheme (3 pediatric doses of HAVRIX 720 U administered at 0, 1, and 6 mo) was applied to hemophiliac patients and MSM with or without HIV\textsuperscript{127-129}. The seroconversion rates among such HIV-positive hemophiliacs and MSM at month 7 were consistently between 76.0%-76.9% and lower than their HIV-negative counterparts at 100\%\textsuperscript{127-129}. Later studies of HIV-positive individuals without hemophilia but with other risk factors such as MSM confirmed that the seroconversion rates following the recommended standard adult dosing schedule (2 doses of HAVRIX 1440 U or VAQTA 50 U administered 6-12 mo apart) were lower among HIV-positive adults
## Table 7: Primary response rates and predictors of seroconversion after hepatitis A virus vaccination in human immunodeficiency virus-positive patients

| Ref. | Dates        | Design/ Country | No. of patient | HAV / dosing schedules (mo) | CD4, cells/ mm$^3$ | PVL, log$_{10}$ copies/ mL | ART | Timing of response$^2$, mo/cut-off$^3$, mIU/mL/assay | Response rate (%) : ITT/PP | Predictors and comments$^4$ |
|------|--------------|-----------------|----------------|-----------------------------|-------------------|-----------------------------|-----|-----------------------------------------------|----------------------------|--------------------------------|
| Tseng et al$^{[52]}$ | 2009-2010 Prospective, Taiwan | Standard 2-dose schedule | 126; All | HAVRIX 1440 U / 2 doses (0, 6) | Mean, 538 | Mean, 2.5 | 67.1% | 12, 18/20; | 12 m (CIA): 75.7/81.7; 12 m (ELISA): NA/88.6 | MSM only study; Higher baseline CD4 count and suppressed PVL; 3 doses over 2 doses |
| | | | | | | | | | | | |
| Mena et al$^{[60]}$ | 1997-2009 Retrospective, Spain | Standard 2-dose schedule | 241 | HAVRIX 1440 / (0, 6-12) | Median, 531 | Median, 3.1 | 70.0% | Variable $< 0.8$ signal relative to cut-off, CIA (Vitros Eci) | NA/54 | Higher baseline CD4 count and suppressed PVL |
| | | | | TWINRIX 720 / (0.7, 21 d, 6-12) | Median, 543 | Median, 3.1 | 70.0% | | NA/53 | |
| | | | | | | | | | Higher baseline CD4 count |
| Jimenez et al$^{[67]}$ | 2002-2008 Retrospective, United States | Standard 2-dose schedule | 125 | HAVRIX 1440 / (0, 6-12) | Median, 410 | Median, 3.1 | 70.0% | Variable $< 0.8$ signal relative to cut-off, CIA (Vitros Eci) | NA/54 | Higher baseline CD4 count and suppressed PVL |
| | | | | TWINRIX 720 / (0.1, 6-12) | Median, 419 | Median, 3.1 | 70.0% | | NA/53 | |
| | | | | | | | | | Higher baseline CD4 count |
| Kourkounti et al$^{[49]}$ | 1994-2010 Prospective observational trial, Greece | cART-experienced, 63 | 149 | HAVRIX 1440 or Vaqta 50 / (0, 6-12) | Median, 472 | Median, 3.9 | 100.0% | 7-13/20, ELISA (VIDAS) | NA/78 | Higher baseline CD4 count |
| | | | | | | | | | | |
| | | | | | | | | | Women only study; Higher baseline CD4 count and suppressed PVL |
| Weinberg et al$^{[69]}$ | 2003-2005 Randomized controlled trial, France | Hormone oral contraceptive, 13 | 149 | HAVRIX 1440 / (0, 6-12) | Median, 478 | Median, 3.9 | 100.0% | 7-13/20, ELISA (VIDAS) | NA/76 | Higher baseline CD4 count |
| | | | | | | | | | | |
| | | | | | | | | | Absence of tobacco smoking |
| Launay et al$^{[20]}$ | 2003-2005 Randomized controlled trial, France | Standard 2-dose schedule | 49 | HAVRIX 1440 / (0, 6-12) | Mean, 447 | Mean, 2.9 | 67.5% | NA/NA ELISA (Not specified) | NA/49.6 | Male; PVL < 1000 copies/mL |
| | | | | | | | | | | |
| | | | | | | | | | Female; CD4 count at vaccination > 200 cells/mm$^3$ |
| Overton et al$^{[35]}$ | 1997-2004 Retrospective, United States | 1 or 2-dose schedule | 268 | HAVRIX 1440 / NA (1 or 2 doses) | Mean, 447 | Mean, 2.9 | 67.5% | NA/NA ELISA (Not specified) | 48.6 (67/138) | 100% of subjects with CD4 counts $>$ 300 cells/mm$^3$ seroconverted |
| | | | | | | | | | | |
| Weissman et al$^{[22]}$ | 2001-2003 Retrospective, United States | Standard 2-dose schedule | 138 | HAVRIX 1440 / (0, 6-12) | Mean, 424 | Mean, 4.52 | 76.0% | 1 m: NA/61, CD4 < 300/300+ 48/74 | 12 m: NA/90, CD4 < 300/300+ 80/100 | Female; CD4 count at vaccination > 200 cells/mm$^3$ |
| | | | | Vaqta 50 / (0, 6) | Mean, 457.5 | Mean, 4.52 | 76.0% | | | 100% of subjects with CD4 counts $>$ 300 cells/mm$^3$ seroconverted |
| Wallace et al$^{[23]}$ | 1997-1998 Randomized controlled trial, United States | Standard 2-dose schedule | 55 | HAVRIX 1440 / (0, 6-12) | Mean, 457.5 | Mean, 4.52 | 76.0% | 1 m: NA/61, CD4 < 300/300+ 48/74 | 12 m: NA/90, CD4 < 300/300+ 80/100 | Female; CD4 count at vaccination > 200 cells/mm$^3$ |
| | | | | | | | | | | |
| | | | | | | | | | 100% of subjects with CD4 counts $>$ 300 cells/mm$^3$ seroconverted |

$^1$ See Table 1 for numerical values reported.

$^2$ 12 months for HAVRIX; 18 months for TWINRIX.

$^3$ 720 or 1440 U/mIU/mL/assay.

$^4$ CD4 < 300 cells/mm$^3$.
| Study | Type | Duration | Comparator | Comparator Dose | Comparator Anti-HAV Titers | Comparator CD4 Counts | MSN Only Study | HAV Coinfection |
|-------|------|----------|-------------|-----------------|---------------------------|------------------------|----------------|----------------|
| Kemper et al.\(^{[23]}\) | Pre-1995 | Prospective, United Kingdom | Three mini-dose, HAV-positive hemophiliacs, 25 | HAVRIX 720/0 (0.1, 6) | Median 450 (IgG positive after 2 doses) | Median 335 (IgG positive after 3 doses) | 12 m: NA/100 | Subjects with higher baseline CD4 counts were more likely to seroconvert and to have higher antibody titers |
| Neilsen et al.\(^{[22]}\) | Pre-1996 | Randomized controlled trial, Australia | Standard 2-dose, HAV-positive, 48 | HAVRIX 1440/0 (0, 6) | Mean 569 | NA | 1 m: NA/80.0 | MSM only study; subjects with higher baseline CD4 counts were more likely to seroconvert and to have higher antibody titers |
| Wilde et al.\(^{[24]}\) | Pre-1995 | Prospective, United Kingdom | Three mini-dose, HAV-positive hemophiliacs, 31 | HAVRIX 720/0 (0, 1, 6) | Median 450 (IgG positive after 2 doses) | Median 335 (IgG positive after 3 doses) | 2 m: NA/29 | Hemophiliacs only (all anti-HCV positive); no patients with CD4 counts < 170 cells/mm\(^3\) seroconverted |
| Tilzey et al.\(^{[25]}\) | Pre-1995 | Prospective, United Kingdom | Three mini-dose, HAV-positive hemophiliacs, 25 | HAVRIX 720/0 (0, 1, 6) | NA | NA | 1 m: NA/26 | Men only study; After 3 doses, all HIV-positive hemophiliacs with anti-HAV titers of < 50 mIU/mL had CD4 counts < 100 cells/mm\(^3\); HAVRIX 1440 was given as a 4th booster dose to the 4 HIV vaccinees with anti-HAV < 50 mIU/mL after 3 doses; only 1 subsequently developed anti-HAV > 50 mIU/mL |
| Hess et al.\(^{[26]}\) | Pre-1994 | Prospective, controlled, Germany | Three mini-dose, HAV-positive MSM, 26 | HAVRIX 720/0 (0, 1, 6) | NA | NA | 2 m: NA/100 | MSM only study; Seroconversion rates were independent of CD4 counts |
| Santagostino et al.\(^{[27]}\) | Pre-1994 | NA, Italy | Three mini-dose, HAV-positive hemophiliacs, 47 | HAVRIX 720/0 (0, 1, 6) | NA | NA | 12 m: NA/76.6 | Hemophiliacs; Seroconversion rates were dependent on stage of HIV disease |

1Number of HIV-positive individuals with baseline negative anti-HAV and data available; 2Duration specified after the first dose when primary serological response was assayed; 3Cut-off value of specific anti-HAV IgG used to define serological response; 4Factors identified by multivariate analysis in HIV-positive individuals unless specified; 5Percentage of patients with undetectable plasma HIV RNA load; cART: Combination of antiretroviral therapy; CIA: Chemiluminescence immunoassay; EIA: Enzyme immunoassay; ELISA: Enzyme linked immunosorbent assay; HAV: Hepatitis A virus; HCV: Hepatitis C virus; ITT: Intention-to-treat; NA: Not available; PVL: Plasma HIV RNA load; PP: Per-protocol.
compared to HIV-negative healthy adults, ranging from 48.6%–94.0% [122-129]. In a meta-analysis including 8 studies, combining a total of 458 HIV-positive patients, the overall rate of serological response to HAV vaccination was 64% [130]. In addition, the geometric mean titers (GMTs) of specific antibodies were also lower among HIV-positive individuals compared to the healthy population [115,123,127].

Overall, factors that correlated best with the poor response to HAV vaccination among HIV-positive individuals were surrogates of immune status such as low CD4 cell counts and high plasma HIV RNA loads at the time of vaccination as shown in Table 7 [115-129]. Other factors identified with low rates of seroconversion were HCV coinfection and tobacco smoking [116,120]. Both male and female genders have been associated with seroconversion [121,122].

While the vaccination effectiveness among HIV-positive individuals was mostly evaluated by seroconversion rates in the countries of low endemicities, the serological and clinical responses to HAV vaccination were rarely investigated in the outbreak setting. In a recent prospective observational study during the outbreak of acute hepatitis A among MSM in Taiwan, the overall seroconversion rate among HIV-positive MSM was 39.7% and 93.4% after receiving 1 dose and completing 2-dose series of HAV vaccination, respectively. Despite the delayed serological response, HAV vaccination had led to a 93% reduction in the risk of acute HAV infection among HIV-positive MSM during the outbreak setting. Higher CD4 cell counts were consistently correlated with higher seroconversion rates [131].

Studies published after the meta-analysis in 2006 made various attempts to augment the immune response to the inactivated HAV vaccine despite the aforementioned non-modifiable adverse factors. One attempt was by using a virosome-formulated HAV vaccine (Epaxal1, Berna Biotech Ltd.) to enhance the immune responses of 14 HIV-positive individuals compared to 64 healthy adults [122]. After a primary dose at day 1 and a booster dose 12 mo later, the seroconversion rates (anti-HAV IgG > 20 mIU/mL) at month 13 were 91.7% and 100% in HIV-positive adults and in healthy adults, respectively. The GMTs of anti-HAV increased from 25.5 mIU/mL after the primary immunization to 659.2 mIU/mL after the booster dose in HIV-positive adults [122].

Other attempts were by increasing the number of doses of vaccine administered [118,120,121]. Two doses over 1 dose of HIV vaccine increased seroconversion rates in HIV-positive individuals [121,123,124]. There is less convincing evidence to show that 3 doses over 2 doses further increased seroconversion rates, possibly due to the smaller margin of benefit and the relatively larger sample size of adequate power needed to demonstrate the benefit. However, 2 studies showed trends of augmented responses in terms of seroconversion rates and GMTs by adding a booster dose at week 4 sandwiched between the first dose and the second dose at week 24 [115,120]. In the intention-to-treat (ITT) analysis, seroconversion at week 28 was observed in 82.6% vs 69.4% (P = 0.13) and at week 48 in 84.2% vs 78.1% (P = 0.23) in the 3-dose vs the 2-dose group for the French and Taiwanese studies, respectively.

When multiple doses have been used, the timing of the second and third dose did not affect immunogenicity in persons with limited immunodeficiency [125]. Hence, in the outbreak settings, an accelerated schedule, i.e., delivering the second or third booster dose at an interval of less than 3 mo from the first dose may be preferable although more studies are needed [131]. However, in HIV-positive individuals with more advanced immunodeficiency (CD4 < 300 cells/mm² or AIDS status), it may be preferable to wait for the CD4 count to recover before delivering the booster doses [123,127]. In the most primitive example, of the 2 HIV-positive hemophiliacs with CD4 counts below 100 cells/mm³ who, after the third dose of HAVRIX 720 U, went on to receive a fourth booster dose of HAVRIX 1440 U, neither seroconverted [127].

To our knowledge, there is limited experience with using HAV vaccination as post-exposure prophylaxis in HIV-positive individuals. Although in healthy individuals, HAV vaccine has been demonstrated to be capable of protecting susceptible contacts with benefits of long-term protection when compared to passive immunization by immunoglobulins [132].

**Durability of seroprotection and factors associated with persistent seroprotection**

In healthy adults following a primary 2-dose schedule, mathematical models indicate that anti-HAV antibodies may persist in > 90% of vaccinees for 40 years or more [134]. In HIV-positive individuals, a slight decrease was observed over time; 88.6%–100% of responders were still seroprotected after 1 year [115,120], 86.8%–90% after 3 years [115,116,135,136], 85%–85.4% after 4 years [126,137], and 75.5%–88.4% after 5 years [135,136,138]. Percentages of seroprotection at the end of 5 years of follow-up were 78.9% vs 76.4% by ITT analysis (P = 0.61) (Table 8) [135-138]. GMTs were significantly higher throughout each consecutive year with the 3-dose schedule as compared to the standard 2-dose schedule [138]. Factors associated with persistent seroprotection include virologic suppression at vaccination and maintained lower levels of HIV viremia as denoted by time-updated plasma HIV RNA load [137,138], 3-dose compared to 2-dose schedule (adjusted odds ratio 3.36; 95%CI: 1.14–9.93), acute syphilis and absence of acute hepatitis C [136,138].

Given the lower initial antibody levels, the apparent waning of antibody levels and the increasing life expectancy of HIV-positive individuals, post-vaccination booster doses may be necessary to maintain anti-
HAV levels after 10 years in HIV-positive individuals in the absence of virologic suppression\(^1\). Currently, only the British HIV Association (BHIVA) recommends delivering booster vaccination every 10 years whilst other health authorities recommend regular monitoring of anti-HAV IgG and booster vaccinations only if at continued risk after seroconversion (Table 6)\(^{111-114}\). However, among immunocompetent hosts, memory responses to HAV may exist even in the absence of detectable antibodies\(^{139}\), and in the era of cART, the same may apply to HIV-positive patients with immune reconstitution\(^{131}\). Nevertheless, the strategies of booster HAV vaccination to those with waning immunity or non-responders need more studies to confirm the effectiveness.

**Vaccine safety**

Serious adverse events following HAV vaccination in HIV-positive individuals are rare and not more common among HIV-positive individuals compared to HIV-negative vaccinees. HAV vaccination does not have a significant impact on plasma HIV RNA load, progression to AIDS, or CD4 cell count\(^{123,124,130}\).

### CONCLUSION

In this review, we have found that, in developed countries of low HAV endemicity, HIV-positive individuals remain susceptible to HAV infection because of low adherence to recommended HAV vaccination, at-risk sexual behaviors, and injecting drug use, as demonstrated by the recent outbreaks of acute HAV infections among MSM and IDUs in Taiwan and Israel, respectively\(^{71,88}\), despite the implementation of HAV vaccination programs in children. Serological response rates to the recommended 2-dose HAV vaccination are lower in HIV-positive individuals than HIV-negative individuals; an additional dose of HAV vaccine may improve serological responses and durability of seroprotection in HIV-positive individuals with initial low CD4 cell counts. While clinical trials are warranted to confirm the HAV vaccine efficacy in the outbreak

---

**Table 8** Long-term response rates and predictors of sustained seroprotection after hepatitis A virus vaccination in human immunodeficiency virus-positive patients

| Ref. | Dates      | Design/Country | No. of patient\(^1\) | HAV/ dosing schedules (mo) | CD4, cells/ mm\(^3\) | PVL, log\(_10\) copies/mL | ART (%) | Timing of assay\(^2\), yr/cut-off, mL/mL Assay | Response rate (%)\(^3\): ITT/PP | Predictors of persistent response and comments\(^4\) |
|------|------------|----------------|----------------------|-----------------------------|---------------------|---------------------------|---------|-----------------------------------------------|---------------------------------|----------------------------------|
| Cheng et al\(^{[137]}\) | 2010-2015  | Prospective, Taiwan | Primary responders: 2 doses, 110, 3 doses, 185 | HAVRIX 1440 U/ 2 doses (0, 6) 3 doses (0, 1, 6) | 560/415 2.5/2.8 70/56 | 5/20 ELISA (ETIAB-HAVK PLUS) | 2, 3, 4 yr: 90.0/93.4 3 doses: 87.0/94.7 | At 1.5 yr: 2 doses: 75.8/81.9 | NA | MSM only study; 3-doses over 2-dose, syphilis, lack of acute HCV |
| Kernéis et al\(^{[136]}\) | 2006-2009  | Prospective, France | Primary responders: 71 (52) | HAVRIX 1440/ 2 doses (0, 6) 3 doses (0, 1, 6) | 362 62\(^5\) NA | 7, 43/20 ELISA (ETIAB-HAVK PLUS) | At 3.7 yr: Overall: 89.0/84.6 | PVL < 50 copies/mL at time of last vaccine dose and a short duration of HIV infection |
| Jablomowska et al\(^{[135]}\) | 2004      | Prospective, Poland | Primary responders: 66 | HAVRIX 1440 (0, 6) | 450 NA | 1.5, 5/20 CIA (Cobas, Roche) | At 1.5 yr: 75.8/81.9 | Lack of co-infection with HCV |
| Crum-Cianflone et al\(^{[124]}\) | 1996-2003  | Retrospective, United States | 116 | Vaqta 50 or HAVRIX 1440 (0, 6-18) | Median, 467 50\(^5\) 62 | 3, 6-10/10 | At 3 yr: 90 | Lower PVL; PVVL < 400 copies/mL |

\(^1\)Number of vaccinees with primary seroconversion after the last dose of vaccine (figure in parentheses is the number of vaccinees with primary conversion and subsequent sera for follow-up of antibody persistence); \(^2\)Duration specified after the first dose when primary serological response was assayed; \(^3\)Cut-off value of specific anti-HAV IgG used to define serological response; \(^4\)Factors identified by multivariate analysis in HIV-positive individuals unless specified; \(^5\)Percentage of patients with undetectable plasma HIV RNA load. ART: Antiretroviral therapy; CIA: Chemiluminescence immunoassay; ELISA: Enzyme linked immunosorbent assay; HAV: Hepatitis A virus; HCV: Hepatitis C virus; ITT: Intention-to-treat; MSM: Men who have sex with men; NA: Not available; PVL: Plasma HIV RNA load; PP: Per-protocol.
setting of acute HAV infection, the recent observational study suggested that implementation of the 2-dose HAV vaccination was effective in preventing acute HAV infection among MSM. With ongoing improvements in survival and quality of life with modern cART, the importance of awareness of and adherence to HAV vaccination recommendations cannot be overemphasized among health care providers as well as at-risk populations.

REFERENCES

1. Havelaar AH, Kirk MD, Torgerson PR, Gibb-HJ, Hald T, Lake RJ, Praet N, Bellinger DC, de Silva NR, Gargouri N, Speybroeck N, Cawthorne A, Mathers C, Stein C, Angulo FJ, DeVleesschaever B. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. PLoS Med 2015; 12: e1001923 [PMID: 2663896 DOI: 10.1371/journal.pmed.1001923]

2. Aggarwal R, Goel A. Hepatitis A: epidemiology in resource-poor countries. Curr Opin Infect Dis 2015; 28: 488-496 [PMID: 26203853 DOI: 10.1097/QCO.0000000000000188]

3. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010; 28: 6653-6657 [PMID: 20723630 DOI: 10.1016/j.vaccine.2010.08.037]

4. Nelson NP, Murphy TV. Hepatitis A: The changing epidemiology of hepatitis A. Clin Liver Dis ( Hoboken) 2013; 2: 227-230 [PMID: 25666433 DOI: 10.1002/clld.230]

5. Mena G, García-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: A review. Hum Vacc Immunother 2015; 11: 2582-2598 [PMID: 26208679 DOI: 10.1080/21645515.2015.1055424]

6. Feinstein SM, Kapikian AZ, Purcell RH. Hepatitis A: Detection by immune electron microscopy of a viruslike antigen associated with acute illness. Science 1973; 182: 1026-1028 [PMID: 4536028]

7. Robertson BH, Janssen RW, Khanha B, Totsuka A, Nainan OV, Siegl G, Wedill A, Margolis HS, Isomura S, Ito K. Genetic relatedness of hepatitis A virus strains recovered from different geographical regions. J Gen Virol 1992; 73 (Pt 6): 1365-1377 [PMID: 13189490 DOI: 10.1099/0022-1317-73-6-1365]

8. Costa-Mattiliol M, Cristina J, Romero H, Perez-Bercof R, Casane D, Colina R, Garcia L, Vega I, Glikman G, Romanovsky V, Castello A, Nicand E, Gassin M, Billaudel S, Ferré V. Molecular relatedness of hepatitis A virus strains recovered from different geographical regions. J Gen Virol 2005; 86: 333-338 [PMID: 15448357 DOI: 10.1099/vir.0.80304-0]

9. Nainan OV, Armstrong GL, Han XH, Williams L, Bell BP, Margolis HS. Hepatitis A molecular epidemiology in the United States, 1996-1997: sources of infection and implications of vaccination policy. J Infect Dis 2005; 191: 957-963 [PMID: 15717272 DOI: 10.1086/427992]

10. Tjon GM, Wijkmans CJ, Coutinho RA, Koek AG, van den Hoek JA, Leenders AC, Schneeberger PM, Bruisten SM. Molecular epidemiology of hepatitis A in Noord-Brabant, The Netherlands. J Clin Virol 2005; 32: 128-136 [PMID: 15653415 DOI: 10.1016/j.jcv.2004.03.008]

11. McFarlane ES, Embil JA, Manuel FR, Thébault HJ. Antibodies to hepatitis A antigen in relation to the number of lifetime sexual partners in patients attending an STD clinic. Br J Ven Dis 1981; 57: 58-61 [PMID: 6258702]

12. Villano SA, Nelson KE, Vlahov D, Purcell RH, Saah AJ, Thomas DL. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. Clin Infect Dis 1997; 25: 726-728 [PMID: 9314468]

13. Ochnio JJ, Patrick D, Ho M, Talling DN, Dobson SR. Past infection with hepatitis A virus among Vancouver street youth, injection drug users and men who have sex with men: implications for vaccination programs. CMAJ 2001; 165: 293-297 [PMID: 11517645]

14. Corey L, Holmes KK. Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. N Engl J Med 1980; 302: 435-438 [PMID: 6243391 DOI: 10.1056/nejm19800213020804]

15. Kryger P, Pedersen NS, Mathiesen L, Nielsen JO. Increased risk of infection with hepatitis A and B viruses in men with a history of syphilis: relation to sexual contacts. J Infect Dis 1982; 145: 23-26 [PMID: 6274966]

16. Coutinho RA, Albrecht-van Lent P, Lelie N, Nagelkerke N, Kuipers H, Rijssijk T. Prevalence and incidence of hepatitis A among male homosexuals. Br Med J (Clin Res Ed) 1983; 287: 1743-1745 [PMID: 6416573]

17. Katz MH, Hsu L, Wong E, Liska S, Anderson L, Janssen RS. Seroprevalence and of risk factors for hepatitis A infection among young homosexual and bisexual men. J Infect Dis 1997; 175: 1225-1229 [PMID: 9120901]

18. Corona RA, Stroffolini T, Giglio A, Cotichini R, Toosti ME, Prignano G, Di Carlo A, Maini A, Mele A. Lack of evidence for increased risk of hepatitis A infection in homosexual men. Epidemiol Infect 1999; 123: 89-93 [PMID: 10487644]

19. Blaek SR, Barry V, Bell BP, Valleroy LA, Behel S, Mackellar DA, Secura G, Thiede H, McFarland W, Ford WL, Bingham TA, Shehan DA, Celentano DD. Seroprevalence and correlates of hepatitis a among HIV-negative American men who have sex with men. Sex Health 2011; 8: 343-348 [PMID: 21851774 DOI: 10.1016/j.shid.2010.10.001]

20. Ross JD, Ghanem M, Tariq A, Gilleran G, Winder AT. Seroprevalence of hepatitis A immunity in male genitourinary medicine clinic attenders: a case control study of heterosexual and homosexual men. Sex Transm Infect 2002; 78: 174-179 [PMID: 12238647]

21. Crofts N, Cooper G, Stewart T, Kiely P, Coghlan P, Hearne P, Hocking J. Exposure to hepatitis A virus among blood donors, injecting drug users and prison entrants in Victoria. J Viral Hepat 1997; 4: 333-338 [PMID: 9310932]

22. Remoille V, Origer A, Couffignal S, Vaillant M, Schmit JC, Lair ML. A hepatitis A, B, C and HIV prevalence and risk factor study in ever injecting and non-injecting drug users in Luxembourg associated with HAV and HBV immunisations. BMC Public Health 2011; 11: 351 [PMID: 21595969 DOI: 10.1186/1471-2458-11-351]

23. Franco E, Giambi C, Ialacci R, Coppola RC, Zanetti AR. Risk groups for hepatitis A virus infection. Vaccine 2003; 21: 2224-2233 [PMID: 12744847]

24. Iida S, Tachikawa N, Nakajima A, Daikoku M, Yano M, Kikuchi Y, Yatsuoka A, Kimura S, Oka S. Influence of human immunodeficiency virus type 1 infection on acute hepatitis A virus infection. Clin Infect Dis 2002; 34: 379-385 [PMID: 11774086 DOI: 10.1086/338152]

25. Nandwani R, Caswell S, Boag F, Lawrence AG, Coleman JC. Hepatitis A seroprevalence in homosexual and heterosexual men. Genitourin Med 1994; 70: 325-328 [PMID: 8001944]

26. Fainboim H, Gonzalez J, Fassio E, Martinez A, Otegui L, Eposo M, Cahn P, Marino R, Landeira G, Suaya G, Gancedo E, Castro R, Bajetarian L, Lapumé H. Prevalence of hepatitis viruses in an anti-human immunodeficiency virus-positive population from Argentina. A multicentre study. J Viral Hepat 1999; 6: 53-57 [PMID: 10847130]

27. Aloise R, de Almeida AJ, Sion FS, Morais-de-Sá CA, Gaspar AM, de Paula VS. Changes in hepatitis A virus seroepidemiology in HIV-infected Brazilian patients. Int J STD AIDS 2008; 19: 321-326 [PMID: 18482962 DOI: 10.1258/ija.2007.007100]

28. Lee HC, Ko NY, Lee NY, Chang CM, Ko WC. Seroprevalence of viral hepatitis and sexually transmitted disease among adults with recently diagnosed HIV infection in Southern Taiwan, 2000-2005: upsurge in hepatitis C virus infections among injection drug users.
Centers for Disease Control and Prevention (CDC). Hepatitis A vaccination during an outbreak among gay men in Montreal, Canada, 1995-1997. *J Epidemiol Community Health* 2001; 55: 251-256 [PMID: 11238580]

Centers for Disease Control (CDC). Hepatitis A outbreak of hepatitis A amongst injecting drug users. *MMWR Morb Mortal Wkly Rep* 1998; 47: 708-711 [PMID: 9746398]

Centers for Disease Control (CDC). Hepatitis A among drug abusers. *MMWR Morb Mortal Wkly Rep* 1998; 37: 297-300, 305 [PMID: 3130560]

Jin A. Bardsley J. Intravenous drug use and hepatitis A: an investigation of an outbreak. *Can J Public Health* 1990; 81: 79-81 [PMID: 2311058]

Huntj J, Sabin KM, Huttwagner LC, Schaben L, Shipp GM, Lin KY, Burns JS, Kindig DA, Smith SD, Messer L. Outbreak of hepatitis A in the 1990s in Sydney, Australia. *Clin Infect Dis* 2006; 43: 203-206 [PMID: 16766002 DOI: 10.1086/499833]

Ferson MJ, Young LC: Outbreaks of hepatitis A and B among injecting drug users. *Commun Dis Intell* 2000; 24: 203-206 [PMID: 10981351]

Chen GJ, Lin KY, Hung CC, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. *J Hepatol* 2017; 67: 1339-1340 [PMID: 28323951 DOI: 10.1016/j.jhep.2017.04.006]

Stene-Johansen K, Delpech V, van der Laar TJ, Coutinho RA. Viral transmission in young adult men in Florida 1988-9. *Scand J Infect Dis* 1997-1999: continuing concerns for gay men and an outbreak amongst intravenous drug users. *Clin Infect Dis* 2000; 30: 35-38 [PMID: 9670536]

O’Donovan D, Cooke RP, Joce R, Eastbury A, Waite J, Stene-Johansen K. An outbreak of hepatitis A amongst injecting drug users. *Epidemiol Infect* 2001; 127: 469-473 [PMID: 11811880]

Syed NA, Hearing SD, Shaw JS, Probert CS, Brooklyn TN, Caul EO, Barry RE, Sarangi J. Hepatitis A and injecting drug abuse and homeless populations in Bristol: control by a targeted vaccination programme and possible parental transmission. *Eur J Gastroenterol Hepatol* 2003; 15: 901-906 [PMID: 12867801]

Roy K, Howie H, Sweeney C, Parry J, Molyneaux P, Goldberg D, Taylor A. Hepatitis A virus and injecting drug misuse in Aberdeen, Scotland: a case-control study. *J Viral Hepat* 2004; 11: 277-282 [PMID: 15117332 DOI: 10.1111/j.1365-2893.2004.00503.x]

Spada E, Genovese D, Tosti ME, Mariano A, Cuccuini M, Proietti L, Giuli CD, Lavagna A, Crapa GE, Morace G, Taffoni S, Mele A, Rezza G, Rapicetta M. An outbreak of hepatitis A virus infection with a high case-fatality rate among injecting drug users. *J Hepatol* 2005; 43: 958-964 [PMID: 16143420 DOI: 10.1016/j.jhep.2005.06.012]

Harkess J, Gildon B, Istre GR. Outbreaks of hepatitis A among illicit drug users, Oklahoma, 1984-87. *Am J Public Health* 1989; 79: 463-466 [PMID: 2929004]

Delpech V, Thackray SV, Young L, Pontivito G, Smedley E, Morgan K, Ferson MJ. Hepatitis A in south-eastern Sydney 1997-1999: continuing concerns for gay men and an outbreak among illicit drug users. *Med J Aust* 1999; 115: 519-521 [PMID: 8387627]

Ferson MJ, Young LC, Stokes ML. Changing epidemiology of hepatitis A in the 1990s in Sydney, Australia. *Epidemiol Infect* 1998; 121: 631-636 [PMID: 10030713]

von Houdt R, van de Laar TJ, Coutinho RA. Viral transmission in young adult men in Florida 1988-9. *Scand J Infect Dis* 1997-1999: continuing concerns for gay men and an outbreak amongst intravenous drug users. *Clin Infect Dis* 2000; 30: 203-206 [PMID: 9431300]

Chen GJ, Lin KY, Hung CC, Chang SC. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. *J Infect Dis* 2017; 215: 1339-1340 [PMID: 28323951 DOI: 10.1093/infdis/jix123]

Stene-Johansen K, Delpech V, van der Laar TJ, Coutinho RA. Viral transmission in young adult men in Florida 1988-9. *Scand J Infect Dis* 1997-1999: continuing concerns for gay men and an outbreak amongst intravenous drug users. *Clin Infect Dis* 2000; 30: 203-206 [PMID: 9431300]

Stene-Johansen K, Tjon G, Schreier E, Bremer V, Brusten S, Ngu SL, King M, Pinto RM, Arangés L, Mazick A, Corbet S, Sundqvist L, Blystad H, Norder H, Skaug K. Molecular epidemiologic studies show that hepatitis A virus is endemic among active homosexual men in Europe. *Am J Epidemiol* 1995; 142-147 [PMID: 21094265 DOI: 10.1093/epidemiology/8.2.142]

Stene-Johansen K. An outbreak of hepatitis A amongst injecting drug users. *Epidemiol Infect* 2001; 127: 469-473 [PMID: 11811880]
British HIV Association. BHIVA guidelines on the use of vaccines in HIV-positive adults. 2015. Available from: URL: http://www.bhiva.org/documents/Guidelines/Vaccination/2015-Vaccination-Guidelines.pdf

European AIDS Clinical Society. EACS Treatment Guidelines updated. 2016. Available from: URL: http://www.eacsociety.org/files/guidelines_8.2-english.pdf

Advisory Committee for Immunization Practices. Hepatitis A ACIP Vaccine Recommendations. 2017. Available from: URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5507a1.htm

World Health Organization. Hepatitis A. 2017. Available from: URL: http://www.who.int/ith/vaccines/hepatitisA/en/

Mena G, Garcia-Bastiero AL, Llipua A, Diez C, Costa J, Gatell JM, Garcia F, Bayas JM. Factors associated with the immune response to hepatitis A vaccination in HIV-infected patients in the era of highly active antiretroviral therapy. Vaccine 2013; 31: 3668-3674 [PMID: 23777950 DOI: 10.1016/j.vaccine.2013.06.012]

Jimenez HR, Hallit RR, Debari VA, Slim J. Hepatitis A virus response in HIV-infected patients: are TWINRIX and HAVRIX interchangeable? Vaccine 2013; 31: 1328-1333 [PMID: 23277097 DOI: 10.1016/j.vaccine.2012.12.045]

Kourkounti S, Mavrianno N, Paparizos VA, Kyriakis K, Hatzivassiliou M, Kordosis T, Katsambas A. Immune response to hepatitis A vaccination in HIV-infected men in Greece. Int J STD AIDS 2012; 23: 464-467 [PMID: 22843998 DOI: 10.1258/ijsa.2011.011297]

Weinberg A, Allshouse AA, Mawhinney S, Canniff J, Benning L, Wentz EL, Minkoff H, Young M, Nowicki M, Greenblatt R, Cohen MH, Golub ET. Responses to hepatitis A virus vaccine in HIV-infected women: effect of hormonal contraceptives and HIV drug interactions. J Acquir Immune Defic Syndr 2012; 60: e15-e18 [PMID: 22517417 DOI: 10.1097/QAI.0b013e31824340bd]

Launay O, Grabar S, Gordien E, Desaint C, Jegou D, Abad S, Ford JC. Infective Hepatitis. 300 Cases in an Outer London Borough. Lancet 1943; 241: 657-678

Huyun J, Seo YS, An H, Yim SY, Seo MH, Kim HS, Kim CH, Kim JH, Keum B, Kim YS, Yim JH, Lee HS, Um SH, Kim CD, Ryu HS. Optimal time for repeating the IgM anti-hepatitis A virus antibody test in acute hepatitis A patients with a negative initial test. Korean J Hepatol 2012; 18: 56-62 [PMID: 22511904 DOI: 10.3335/kjhep.2012.18.1.56]

Su CW, Wu JC, Huang YS, Hsiao TL, Huang YH, Lin CC, Chang FY, Lee SD. Comparison of clinical manifestations and epidemiology between acute hepatitis A and acute hepatitis E in Taiwan. J Gastroenterol Hepatol 2002; 17: 1187-1191 [PMID: 12453278]

Atalatrachi N, Koziel M. Regulatory T cells and viral liver disease. J Viral Hepat 2009; 16: 223-229 [PMID: 19222773 DOI: 10.1111/j.1365-2893.2009.01081.x]

Choi YS, Lee J, Lee HW, Chang DY, Sung PS, Jung MK, Park JY, Kim JK, Lee JI, Park H, Cheong JY, Suh KS, Kim JH, Lee JS, Kim KA, Shin EC. Liver injury in acute hepatitis A is associated with decreased frequency of regulatory T cells caused by Fas-mediated apoptosis. Gut 2015; 64: 1303-1313 [PMID: 25007815 DOI: 10.1136/gutjnl-2013-306213]

Chevalier MF, Weiss L. The split personality of regulatory T cells in hepatitis. Blood 2013; 121: 29-37 [PMID: 23040372 DOI: 10.1182/blood-2012-07-409755]

Gupta E, Chakravarti A. Viral infections of the biliary tract. Saudi J Gastroenterol 2008; 14: 158-160 [PMID: 19568530 DOI: 10.4103/1319-3767.41740]

Mao JS, Yu PH, Ding ZS, Chen NL, Huang BZ, Xie RY, Chai Medhi S, Verghese A, Raish M, Theamboonlers A, Poovorawan Y, Kar P. Viral route of hepatitis A virus as determined by real time RT-PCR: Correlation with biochemical, immunological and genotypic profiles. J World J Gastroenterol 2006; 12: 4683-4688 [PMID: 16937439 DOI: 10.3748/wjg.v12.i29.4683]

Wu JC, Huang YS, Huo TI, Huang YH, Lin CC, Chang FY, Lee SD. Comparison of clinical manifestations and epidemiology between acute hepatitis A and acute hepatitis E in Taiwan. J Gastroenterol Hepatol 2002; 17: 1187-1191 [PMID: 12453278]
Lin KY et al. HIV and HAV coinfection

A vaccine responses in HIV-positive persons with haemophilia. Vaccine 1996; 14: 1039-1041 [PMID: 8879099]

128 Hess G, Clemens R, Bienzle U, Schönfeld C, Schunck B, Bock HL. Immunogenicity and safety of an inactivated hepatitis A vaccine in anti-HIV positive and negative homosexual men. J Med Viral 1995; 46: 40-42 [PMID: 7623005]

129 Santagostino E, Gringeri A, Rocino A, Zanetti A, de Biasi R, Mannucci PM. Patterns of immunogenicity of an inactivated hepatitis A vaccine in anti-HIV positive and negative hemophilic patients. Thromb Haemost 1994; 72: 508-510 [PMID: 7878624]

130 Shire NJ, Welge JA, Sherman KE. Efficacy of inactivated hepatitis A vaccine in HIV-infected patients: a hierarchical bayesian meta-analysis. Vaccine 2006; 24: 272-279 [PMID: 16139398 DOI: 10.1016/j.vaccine.2005.07.102]

131 Lin KY, Hsieh SM, Sun HY, Lo YC, Sheng WH, Chuang YC, Pan SC, Hung CC, Chang SC. Effectiveness of HAV vaccination among HIV-positive patients during an acute hepatitis A outbreak. the 22th Conference of Retroviruses and Opportunistic Infections Abstract no 582. Seattle, WA, 2017

132 Loutan L, Bovier P, Herzog C. Immunogenicity and safety of a virosomal hepatitis A vaccine in HIV-positive patients. Vaccine 2007; 25: 6310-6312 [PMID: 17640777 DOI: 10.1016/j.vaccine.2007.06.013]

133 Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, Margolis HS, Bell BP. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med 2007; 357: 1685-1694 [PMID: 17947390 DOI: 10.1056/NEJMoa070546]

134 Theeten H, Van Herck K, Van Der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. Vaccine 2015; 33: 5723-5727 [PMID: 26190091 DOI: 10.1016/j.vaccine.2015.07.008]

135 Crum-Cianflone NF, Wilkins K, Lee AW, Grosso A, Landrum ML, Weintrob A, Ganasan A, Maguire J, Klopfer S, Brandt C, Bradley WP, Wallace MR, Agan BK, Infectious Disease Clinical Research Program HIVWG. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. J Infect Dis 2011; 203: 1815-1823 [PMID: 21606540 DOI: 10.1093/infdis/jir180]

136 Cheng A, Chang SY, Sun HY, Tsai MS, Liu WC, Su YC, Wu PY, Hung CC, Chang SC. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in human immunodeficiency virus-positive adults on antiretroviral therapy. J Infect Dis 2017; 215: 606-613 [PMID: 28011921 DOI: 10.1093/infdis/jiw605]

137 Kernéis S, Desaint C, Brichler S, Rey D, Belarbi L, Gordien E, Pacanowski J, Lortholary O, Abgrall S, Boëlle PY, Grabar S, Launay O. Long-term persistence of humoral immunity after hepatitis A vaccination in HIV-infected adults. J Acquir Immune Defic Syndr 2011; 57: e63-e66 [PMID: 21860353 DOI: 10.1097/QAI.0b013e31821fdec3]

138 Jablonowska E, Kuydowicz J. Durability of response to vaccination against viral hepatitis A in HIV-infected patients: a 5-year observation. Int J STD AIDS 2014; 25: 745-750 [PMID: 24452731 DOI: 10.1177/0956462413518902]

139 Iwarson S. Are we giving too many doses of hepatitis A and B vaccines? Vaccine 2002; 20: 2017-2018 [PMID: 11972968]

P- Reviewer: Castiella A, Otsuka M  S- Editor: Ma YJ  L- Editor: A  E- Editor: Wang CH
