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

Lin KY *et al*. HIV and HAV coinfection

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**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 fulminant 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

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**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.

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**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[2]. 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).

**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 (3Cpro) to yield 8 viral proteins, including VP0, VP3, VP1-2A, 2B, 2C, 3AB, 3Cpro, and RNA-dependent RNA polymerase (RDRP, 3Dpol). 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 3Cpro, 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 between the C terminus of VP1 and N terminus of P2A[7]. 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 VII should be reclassified as subtypes A and B of genotype II[8], and genotypes I and III could also be divided into subgenotypes A and B[9]. 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[7]. Clusters within genotypes predominant in certain geographic regions have been reported, such as a group of subgenotype IA strains from the United States[10], and genotype II in the Netherlands, France, and Sierra Leone[7,11]. 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[12-14], which were associated with oral-anal sex and the number of sexual contacts and partners[12,15-20]. The HAV seroprevalence also increases with age, indicating the cohort effect[2,12,19,21]. 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 [15, 16], others indicated that the risks for HAV infection among heterosexual men with STDs and MSM were similar[12,19,21]. IDUs also had a higher HAV seroprevalence than the general population[13,14,22,23]. 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[22,23].

 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[24]. 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[25]. Several studies have reported the HAV seroprevalence among HIV-positive individuals and at-risk persons in areas of different HAV endemicities and vaccine coverage (Table 1)[12-23,26-42]. In these studies, the HAV seroprevalence among HIV-positive individuals ranged from 15.1% in Taiwan to 96.3% in Iran[31,35]. While studies conducted in countries of high HAV endemicity showed no differences in the HAV seroprevalence between HIV-positive and HIV-negative individuals[27], the seroprevalence in countries of low endemicity was higher among HIV-positive individuals compared to HIV-negative individuals[26,30]. 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[29,30,33-36].

***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[2]. Numerous outbreaks of acute hepatitis A have been reported in the MSM population through sexual contacts, which are summarized in Table 2[43-70]. Since the early 1980s, outbreaks of acute hepatitis A among MSM have been described in Denmark[43], Sweden[44], the United Kingdom[45], and the United States[61,62]. The incidence of acute HAV infection among MSM peaked in the 1990s, and the affected countries included the UK[46,47,49,51], the Netherlands[48], Norway[50], the United States[63,65,66], Canada[64] and Australia[67-70]. 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[69]. Since 2015, Taiwan reported a large outbreak involving more than 1000 indigenous cases, with more than 70% of the affected individuals being MSM[71]. While the HAV vaccine was licensed and recommended for MSM since the mid-1990s[47], the emergence of HAV infection continued to pose a health threat to MSM in several developed European countries during the 2000s, including Italy[52,54,55,60], Denmark[53], Spain[56,58], Poland[57], and the United Kingdom[59].

 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 1998[64]. The cyclical outbreaks were noted in Australia during 1991-1996[69] and in Spain during 1989-2010[56], which might be facilitated by the continuous circulation of particular HAV strains in the MSM population[50,55,60]. The predominant circulating HAV strains among MSM belonged to genotype IA[50,55,59,60,72]. The patients contracting HAV during the outbreaks were mostly young adults with a mean or median age of 28-36 years[55,57]. HAV was recognized as being transmitted among MSM through sexual contacts[73], 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[66], having sex in gay saunas[51,53], and visiting saunas and darkrooms[48]. 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[64]. 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 infections[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 inTable 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 USA[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 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 before 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 Kigndom[79], Norway[89] and Italy[81], and harm reduction program by providing clean injecting equipment was implemented in Switzerland[90].

**CLINICAL MANIFESTATIONS OF ACUTE HAV INFECTION**

The incubation period of acute HAV infection is 2.5 to 5 wk[91]. 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[92-96]. 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[97]. Less than 25% of the patients have diarrhea though HAV is transmitted through fecal-oral route[98]. The data on the symptoms of acute hepatitis A 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[25,92,93,98-100]. 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[92]. 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*reported higher levels of ALP and γ-GT during acute hepatitis A in HIV-positive individuals than HIV-negative patients[25]. 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 cholangiopathy 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*, the median duration of HAV viremia in HIV-positive individuals with acute hepatitis A was 53 d[25], 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[25,57,91-93,95,98-100,105-109].

Other atypical presentations of acute hepatitis A include renal insufficiency and relapsing hepatitis[93], which are usually present in children. Some individuals experienced a prolonged hepatitis (5.8%)[93] or cholestasis (6.8%), especially in the presence of hepatitis B virus[94]. Severe hepatic failure is rare and occurs more commonly in patients with underlying diseases or advanced age. Reported case fatality rates were 0.1% in infants and children, 0.45% in those aged 15 to 39 years, and 1.1% in those aged > 40 years. Patients with chronic hepatitis C virus (HCV) infection have a substantial risk of fulminant hepatitis and death associated with HAV superinfection[110]. HIV-positive individuals acquire HAV infection mostly in their adulthood and often have other underlying liver disease[25,57], which may increase the risk of hepatic failure and fatality caused by HAV. Therefore, prevention by HAV vaccination is important, especially for the HIV/HCV-coinfected individuals.

**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)[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[115-129].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[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%[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 compared to HIV-negative healthy adults, ranging from 48.6%-94.0%[122-125]. 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[132]. 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[132].

Other attempts were by increasing the number of doses of vaccine administered[115,120,121]. 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/mm3 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 (PEP) 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[133].

***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[135,136], 85-85.4% after 4 years[136,137], 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[136]. 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[135,137], 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[111]. 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 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.

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**Table 1 Seroprevalence of hepatitis A virus infection among HIV-positive patients and at-risk populations**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Location** | **Study period** | **Study population** | **Age, yr** | **HIV-positive****Population, %** | **Other populations** | **Associated factors1 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 |
| 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% | Seroprevalence increased with age and among heterosexuals  |
| 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 injecting drug use Higher seroprevalence in HIV-positive individuals |
| 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 | 16.13 | NA | Low HAV screening and vaccination rates (28.5%) |
| Linkins *et al*[33] | Bangkok, Thailand | 2006-2008 | 1291 MSM  | 27 | 32.43 | 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% | Older age |
| Tseng *et al*[35] | Taipei, Taiwan | 2009-2010 | 1128 MSM  | 18-40 | 15.13 | HIV-negative MSM, 7.4% | Older age No difference between HIV-positive and HIV-negative individuals |
| Kourkounti *et al*[36] | Athens, Greece | 2007-2011 | 897 HIV-positive MSM  | 41 | 35.73 | NA | Older age and being foreigners  |
| **At-risk populations (MSM and IDUs)** |  |  |  |  |  |  |  |
| Corey *et al*[15] | Seattle, United States | 1977-1979 | 159 patients from STD clinics | 31 | NA | MSM, 30.4% (annual incidence, 22%)Heterosexuals, 12.3% (annual incidence, 0%) | Oral-anal sexual contactHigher seroprevalence and incidence in MSM  |
| McFarlane *et al*[12] | 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 number of sex partners and older age  |
| Kryger *et al*[16] | 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*[17] | Amsterdam, the Netherlands | 1980-1982 | 689 MSM  | 31 | NA | MSM, 42.0% (incidence, 14.0%) | Longer duration of homosexual activity |
| Crofts *et al*[22] | Victoria, Australia | 1990-1992 | 2175 prison entrants 293 IDUs | 30 | NA | IDU, 43.7%Prison entrants, 60.1%Blood donors, 30.0% | History of incarceration |
| Katz *et al*[18] | San Francisco and Berkeley, United States | 1992-1993 | 411 MSM | 21 | NA | MSM, 28.0% | Sexual and drug-using behaviors |
| Villano *et al*[13] | Baltimore, United States | 1993-1994 | 294 MSM 292 IDUs  | NA | NA | MSM, 32.3%IDU, 66.4%Blood donors, 13.7% | Increased risk for HAV infection in MSM and IDUs  |
| Corona *et al*[19] | Rome, Italy | 1997 | 432 male patients from STD clinics  | NA | NA | MSM, 60.3%Heterosexual, 62.2% | Older age and more sexual partner |
| Ochnio *et al*[14] | Vancouver, Canada | 1998 | 494 individuals from street outreach clinics | 32 | NA | MSM, 25.5%IDU, 42.6%Street youth, 6.3% | Increased risk for HAV infection in MSM and IDUs |
| Ross *et al*[21] | Birmingham, United Kingdom | 2000 | 210 men attending genitourinary clinics  | NA | NA | MSM, 23.0%;Heterosexual men, 32.0% | Ethnicity, older age, and history of sex in a sauna |
| Diamond *et al*[37] | Washington, United States | 1997-2000 | 833 MSM  | 15-29 | NA | MSM, 21.0% | Ethnicity, IDU, HBV and HIV infectionVaccination rate, 21% |
| Bialek *et al*[20] | 7 major cities4, United States | 1994-2000 | 2708 MSM  | 15-29 | NA | MSM, 18.4% | More male sex partners and unprotected anal sex  |
| O’Riordan *et al*[38] | London, United Kingdom | 2004 | 395 MSM attending genitourinary clinics | NA | NA | MSM, 49.9% |  |
| van Rijckevorsel *et al*[39] | Amsterdam, the Netherlands | 1992-2006 | 1697 hepatitis A patients | NA | NA | Incidence, 0.97/1000 MSM | Clustered transmission in social MSM networks  |
| Removille *et al*[23] | Luxembourg | 2005 | 368 problem drug users  | NA | NA | IDUs, 57.1%nIDUs, 65.9% |   |
| Bozicevic *et al*[40] | Zagreb, Croatia | 2006 | 360 MSM | 27 | NA | MSM, 14.2% |  |
| Weerakoon *et al*[41] | Melbourne, Australia | 2002-2011 | 3055 MSM | 33 | NA | MSM, 39.0% | Vaccination levels over 40%-50% to prevent outbreaks |
| Ali *et al*[42] | Sydney, Australia | 1996-2012 | 14799 MSM | 30 | NA | MSM, 31.9% in 1996 to 63.8% in 2012 | Vaccination rate, 9.8% in 1996 to 45.2% in 2012 |
| 1Factors associated with HAV seropositivity were identified by bivariate or multivariable logistic regression analysis; 2The 6 major cities included Atlanta, Chicago, Los Angeles, Miami, New York City, and San Francisco; 3Only HIV-positive MSM were included; 4The 7 major cities included Baltimore, Dallas, Los Angeles, Miami, New York City, San Francisco, and Seattle. HAV: Hepatitis A virus; IDUs: Injecting drug users; MSM: Men who have sex with men; NA: Not available; nIDUs: Non-injecting drug users; STD: Sexually transmitted disease. |

**Table 2 Outbreaks of acute hepatitis A in the MSM population**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Location** | **Study period** | **Case number** | **Male** | **MSM,** ***n* or %** | **HIV-positive patients, *n* or %** | **Age, y** | **Risk factors1 and comments** |
|  | **Europe** |  |  |  |  |  |  |  |
| Hoybye *et al*[43] | Copenhagen, Denmark | 1977-1978 | 45 | 45 | 21 | NA | 29 |  |
| Christenson *et al*[44] | Stockholm, Sweden | 1979-1980 | 145 | 145 | 145 | NA | NA | Multiple partners and oral-anal sexual contact |
| Mindel *et al*[45] | London, United Kingdom | 1980 | 24 | NA | 23 | NA | NA | HAV infection was associated with homosexual activity |
| Kani *et al*[46] | London, United Kingdom | 1989-1990 | 7000  | NA | 41 | NA | NA | Oral-anal sexual contact |
| Atkins *et al*[47] | London, United Kingdom | 1989-1992 | 206 | 121 | 65 | NA | NA | Oral-anal sexual contact and sexual promiscuity  |
| Leentvaar-Kuijper *et al*[48] | Amsterdam, the Netherlands | 1992-1993 | 293  | NA | 39 | NA | NA | Visiting saunas and darkrooms |
| 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 |  |
| Bell *et al*[51] | London and East Sussex, United Kingdom | 1997 | 48  | NA | 41 | NA | NA | Eating shellfish and sex in gay saunas |
| Manfredi *et al*[52] | Bologna, Italy | 1999-2004 | 122  | 104 | 81 | 11 | 28 | Unprotected sexual contact |
| Mazick *et al*[53] | Copenhagen, Denmark | 2004 | 18 | 18 | 18 | NA | NA | Casual sex and sex in gay saunas |
| Girardi *et al*[54] | Rome, Italy | 2002-2008 | 473  | 368 | 115 | 57 | 25-64 | Same gender sex Routine HIV test in HAV-infected patients should be considered  |
| Bordi *et al*[55] | Rome, Italy | 2008-2010 | 162  | 143 | 34 | 14 | 36 | Monophyletic HAV strain sustained the outbreak |
| Tortajada *et al*[56] | Barcelona, Spain | 2002 | 48  | 47 | NA | 28% | 31 |  |
|  |  | 2003-2004 | 60  | 60 | NA | 24% | 32 |  |
|  |  | 2008-2009 | 189  | 185 | NA | 21% | 33 |  |
| Dabrowska *et al*[57] | Warsaw, Poland | 2007-2008 | 860  | NA | 50 | 6 | 28 | No difference in disease severity between HIV-positive and HIV-negative individuals  |
| Tortajada *et al*[58] | Barcelona, Spain | 2008-2009 | 150  | 126 | 87 | NA | 33 |  |
| Sfetcu *et al*[59] | Northern Ireland, United Kingdom | 2008-2009 | 38  | 36 | 26 | NA | 29 | The outbreak strain was indistinguishable from that in Czech Republic |
| Taffon *et al*[60] | Tuscany, Italy | 2008 | 240  | NA | 32% | NA | NA | A unique circulating HAV strain |
|  | **North America** |  |  |  |  |  |  |  |
| Kosatsky *et al*[61] | Anchorage, Alaska | 1982-1983 | 17  | 17 | 17 | NA | 19-31 |  |
| Desenclos *et al*[62] | Florida, United States | 1988-1989 | 311  | 69 | 26 | NA | NA |  |
| Henning *et al*[63] | New York, United States | 1991 | 180  | 180 | 62 | NA | 20-49 | Anonymous sex partner, group sex, oral-anal and digital-rectal intercourse |
| Allard *et al*[64] | Montréal, Canada | 1996-1997 | 376  | 376 | 376 | NA | 33 | Vaccination campaign achieving 20%-41% coverage in MSM decreased incidence rapidly |
| Finton *et al*[65] | Atlanta, United States | 1996 | 222  | NA | 75% | NA | NA | Vaccination campaign in MSM decreased reported cases  |
| Cotter *et al*[66] | Ohio, United States | 1998-1999 | 136  | 118 | 47 | NA | 33 | Contact with hepatitis A cases |
|  | **Asia-Pacific region** |  |  |  |  |  |  |  |
| Stewart *et al*[67] | Melbourne, Australia | 1991 | 495  | 407 | 210 | NA | NA | Sexual and social contact |
| Stokes *et al*[68] | Sydney, Australia | 1991-1992 | 570  | 515 | 330 | NA | 31 | Sexual contact was the most reported contact type |
| Ferson *et al*[69] | Sydney, Australia | 1991-1996 | 1138  | 991 | 587 | NA | 30 | Household or sexual contact |
| Delpech *et al*[70] | Sydney, Australia | 1997-1999 | 354  | 265 | 139 | NA | 32 |  |
| 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. |

**Table 3 Outbreaks of acute hepatitis A in the IDU population**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Location** | **Study period** | **Total patients** | **IDU, *n* or %** | **HIV-positive individuals** | **Age, yr** | **Risk factors1 and comments** |
|  | **Europe** |  |  |  |  |  |  |
| Widell *et al*[74] | Malmo, Sweden | 1970-1979 | 323  | 188 | NA | NA |  |
| Sundkvist *et al*[75] | Helsingborg, Sweden | 1983-1984 | 36  | 32 | NA | 18-35 | The outbreak was associated with intrarectal transportation of illicit drugs |
| Leino *et al*[76] | Helsinki, Finland | 1994-1995 | 238  | 131 | NA | 31 | The outbreak was associated with intrarectal transportation of illicit drugs |
| Stene-Johansen *et al*[77] | Oslo, Norway | 1995-1996 | 621  | 492 | NA | NA | The outbreak was associated with needle sharing |
| O’Donovan *et al*[78] | United Kingdom | 1998-1999 | 27  | 14 | NA | 25 |  |
| Syed *et al*[79] | Bristol, United Kingdom | 2000 | 123 | 69 | NA | 25 | The outbreak was associated with parenteral transmission from contaminated illicit drugs; HAV vaccination of IDUs decreased the reported cases |
| Roy *et al*[80] | 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*[81] | 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  |
|  | **North America** |  |  |  |  |  |  |
| Harkess *et al*[82] | Oklahoma, United States | 1984-1987 | 79 | 42 | NA | 23-27 |  |
| Jenkerson *et al*[83] | New York, United States | 1986-1987 | 256  | 70 | NA | NA |   |
| Jin *et al*[84] | Canada | 1987-1989 | 65  | 59 | NA | NA |  |
| Hutin *et al*[85] | Iowa, United States | 1996-1997 | 158 | 9.7% | NA | NA | Methamphetamine injection, sharing methamphetamine use, using brown methamphetamine, and needle sharing |
| Vong *et al*[86] | Florida, United States | 2001-2002 | 403  | 11% | NA | 32 | HAV vaccination in jail decreased the reported cases |
|  | **Asia-Pacific region** |  |  |  |  |  |  |
| Shaw *et al*[87] | Queensland, Australia | 1997 | 875  | 118 | NA | NA | Sharing of instruments for smoking marijuana |
| Manor *et al*[88] | Tel-Aviv, Israel | 2012-2013 | 75 | 9 | NA | 33 |  |
| 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**[92-96]

|  |  |
| --- | --- |
| **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% |

**Table 5 Comparison of clinial manifestations of HAV between HIV-positive patients or HIV-negative patients with acute hepatitis A**

|  |  |  |
| --- | --- | --- |
|  | **HIV-positive patients** | **HIV-negative patients** |
| Natural course of acute HAV infection |
| Incubation period, weeks | NA | 2.5-5[91] |
| Duration of stool shedding, days | NA | 25 (HAV antigen)[105] |
| 81 (HAV RNA)[106] |
| Duration of viremia, d | 53 (10-89)[25]  | 22–95[25,106-108] |
| Laboratory findings |
| Peak T-bilirubin, mg/dl | 5.1-5.9[25]  | 5.7-8.7[25,92,93,95,98,99] |
| Peak AST, IU/L | 929-1339[25,57] | 1231-2271[25,92,93,99] |
| Peak ALT, IU/L | 1995-2368[25,57] | 1079-3442[25,92,93,99,100] |
| Duration of elevated AST/ALT, d | 63 ± 38[109] | 51[92] |
| Peak ALP, IU/L  | 807[25,57] | 228-396[25,92] |

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

**Table 6 HAV vaccination recommendations by the British HIV Association, the European AIDS Clinical Society, the US Advisory Committee for Immunization Practices and the World Health Organization**

|  |  |  |  |
| --- | --- | --- | --- |
| **Health Authority** | **Target candidates**  | **Dosing Schedule** | **Comments** |
| BHIVA[111] | • Household and sexual contacts of infected persons • Travellers • MSM • Injecting and non-injecting drug users • Individuals at risk of infection during outbreaks • Those with occupational exposure to HAV (*e.g.,* laboratory workers, sewage workers) • Hemophiliacs• Residents of care institutions, and their care givers | • Monovalent HAV vaccine recommended.• Patients with CD4 counts > 350 cells/mm3 should be offered 2 vaccine doses at 0 and 6 mo. • Patients with CD4 counts < 350 cells/mm3 should receive 3 vaccine doses at 0, 1, and 6 mo. • Patients at continued risk of exposure receive a boosting vaccine dose every 10 yr.• Following a significant exposure, HIV-positive contacts who are HAV-seronegative receive post-exposure prophylaxis with the HAV vaccine, with the first dose given as soon as possible and within 14 d of exposure; if the CD4 count is < 200 cells/mm3, they should also receive human normal immunoglobulin. | We support the BHIVA’s recommendations of targeted vaccination during outbreaks and of stratifying dosing schedule by CD4 counts, particularly administering a 3-dose schedule for those with lower CD4 counts. Despite waning antibody levels, we could not find evidence to justify routine boosters every 10 yr for those at risk. It may be preferable to follow antibody titers and revaccinate seroreverters.  |
| EACS[112] | • Travellers• MSM • IVDU• Active hepatitis B or C infection | • Vaccinate if seronegative. Did not specify how. | Shorter list of at risk candidates for vaccination. Our review supports their recommendation to check antibody titers in individuals with risk profile to guide the need for primary or booster vaccinations. |
| ACIP[113] | • MSM • Injection or non-injection illicit drugs users• Persons working with HAV-infected primates or with HAV in a research laboratory setting• Persons with chronic liver disease• Persons who receive clotting factor concentrates • Travellers• Close personal contact (*e.g.*, household or regular babysitting) with an international adoptee during the first 60 d after arrival in the United States from a country with high or intermediate endemicity | • Monovalent vaccine formulations should be administered in a 2-dose schedule at either 0 and 6–12 mo (Havrix), or 0 and 6–18 mo (Vaqta). • If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 mo; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21–30 followed by a booster dose at 12 mo. | Unlike BHIVA, in addition to the monovalent vaccine formulations, ACIP also recommends the combined hepatitis A and B vaccine.No mention of the need to follow antibody titers or booster vaccines or the application of immunization during outbreaks. |
| WHO[114] | • Travellers • Immunosuppressed patients • Patients with chronic liver disease | Inactivated vaccine: 2 doses, the second dose normally 6 mo after the first. If needed, this interval may be extended to 18–36 mo | Does not specify whether all HIV-positive persons should be considered as immunosuppressed patients although evidence from Table 5 suggests that except for the duration of viremia acute HAV is not more severe in HIV-positive compared to HIV-negative patients. |

HAV, hepatitis A virus; HIV: human immunodeficiency virus.

**Table 7 Primary response rates and predictors of seroconversion after HAV vaccination in HIV-positive patients**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **References** | **Dates** | **Design/ Country** | **1Patient no.** | **HAV/Dosing schedules (mo)** | **CD4, cells/mm3** | **PVL, log10, copies/ml** | **ART,%** | **2Timing of response, mo/3Cut-off, mIU/ml/Assay** | **Response rate (%):****ITT/PP** | **4Predictors and comments** |
| Tseng *et al*[115] | 2009-2010 | Prospective, Taiwan | Standard 2-doseAll 126; CD4 matched, 114 | HAVRIX 1440 U/2 doses (0, 6)  | Mean, 538 | Mean, 2.5 | 67.1 | 12, 18/20,a. CIA (ARCHITECT HAVAb-IgG)b. ELISA (ETIAB-HAVK PLUS) | 12 m (CIA): 75.7/81.712 m (ELISA): NA/88.618 m (ELISA): NA/86.6 | MSM only study;Higher baseline CD4 and suppressed PVL; 3 doses over 2 doses |
| 3-doseAll, 213; CD4 matched, 114 | HAVRIX 1440/3 doses (0, 1, 6) | Mean, 452 | Mean, 3 | 58.2 | 12 m (CIA): 77.8/81.812 m (ELISA): NA/89.218 m (ELISA): NA/86.9 |
| Standard 2-dose HIV-negative, 193  | HAVRIX 1440/2 doses (0, 6) | NA | NA | NA | 12 m (CIA): 88.5/97.912 m (ELISA): NA/10018 m (ELISA): NA/100 |
| Mena *et al*[116] | 1997-2009 | Retrospective,Spain | Standard 2-dose, 241 | HAVRIX 1440/(0, 6-12) | Median, 531 | 555.3% | 61.4 | 10-16/20,CIA (Advia Centaur) | NA/80.7 | Higher CD4/CD8 ratio; 2 or more doses compared to 1 dose only; female; no HCV infection |
| Accelerated, 41 | TWINRIX 720/(0, 7, 21 day, 6-12) | Median, 543 | 573.2% | 80.5 | 5/20,CIA (Advia Centaur) | NA/70.7 |
| Jimenez *et al*[117] | 2002-2008 | Retrospective,United States | Standard 2-dose, 125 | HAVRIX 1440/ (0, 6-12) | Median, 410 | Median, 3.1 | 70 | Variable/<0.8 signal relative to cut-off,CIA (Vitros ECi) | NA/54  | Higher baseline CD4 count and suppressed PVL |
| 101 | TWINRIX 720/(0, 1, 6-12) | NA/53 |
| Kourkounti *et al*[118] |  | Retrospective,Greece | cART-experienced, 63 | HAVRIX 1440 or Vaqta 50/(0, 6-12) | 628 | <1.7 | 100 | 7-13/20,ELFA (VIDAS) | NA/78 | Higher baseline CD4 count  |
| cART-naïve, 50 | 472 | 3.9 | 0 | NA/76 |
| Weinberg *et al*[119] | 1994-2010 | Prospective observational, United States | Hormone oral contraceptive, 13 | 2 doses (0, 6) or 3 doses (0, 2, 6) | 478 | 547% | 78 | NA/20,ELISA (Mediagnost) | NA/62 | Women only study; Higher baseline CD4 count and suppressed PVL |
| No contraceptive, 149 | NA/51 |
| Launay *et al*[120] | 2003-2005 | Randomized controlled trial,France | Standard 2-dose, 49 | HAVRIX 1440/(0, 6) | Median, 355 | Median, < 1.7 | 78 | 6-18/20,ELISA (ETIAB-HAVK PLUS) | 6 m: 44.9/46.87 m: 69.4/72.318 m: 61.2/69.8 | Absence of tobacco smoking  |
| 3-dose, 46 | HAVRIX 1440/(0, 1, 6) | Median, 351 | Median,< 1.7 | 83 | 6 m: 69.6/74.47 m: 82.6/88.418 m: 78.3/85.7 |
| Overton *et al*[121] | 1997-2004 | Retrospective,United States | 1 or 2-dose, 268 | HAVRIX 1440/NA (1 or 2 doses) | Mean, 447 | Mean, 2.9 | 67.5 | NA/NAELISA (Not specified) | NA/49.6 | Male; PVL <1000 copies/mL |
| Weissman *et al*[122] | 2001-2003 | Retrospective, United States | Standard 2-dose, 138 | HAVRIX 1440/(0, 6-12) | Mean, 424 | NA | 81.9 | 6-13/18EIA (Abbot IMx HAV Ab) | 48.6 (67/138) | Female; CD4 count at vaccination >200 cells/mm3 |
| Weissman *et al*[123] | 1997-1998 | Randomized controlled trial, United States | Standard 2-dose, HIV-positive, 55 | Vaqta 50/(0, 6) | Mean, 457.5 | 4.52 | 76 | 1, 6, 7, 12/10,Quantitative modified HAVAb assay (NA) | 1 m: NA/61,  CD4 <300/300+, 48/747 m: NA/94,  CD4<300/300+, 87/10012 m: NA/90, CD4<300/300+, 80/100 | 100% of subjects with CD4 counts ≥300 cells/mm3 seroconverted |
| Standard 2-dose, HIV-negative,72 | Vaqta 50/(0, 6) | NA | NA | NA | 1 m: NA/907 m: NA/10013 m: NA/90 |
| Kemper *et al*[124] | 1995-1997 | Double-blind, placebo-controlled trial,United States | Standard 2-dose, HIV-positive,48 | HAVRIX 1440/(0, 6) | 376 | 3.29 | 91 | 1, 6, 7, 9/33,ELISA (Enzymun; Boehringer Mannheim) | 1 m: NA/11 CD4 <200/200+, 0/166 m: NA/9 CD4 <200/200+, 0/137 m: NA/49,  CD4 <200/200+, 11/629 m: NA/52, CD4 <200/200+, 9/67 | Subjects with higher baseline CD4 counts were more likely to seroconvert and to have higher antibody titers |
| Neilsen *et al*[125] | Pre-1996 | Randomized controlled trial, Australia | Accelerated 2-dose, HIV-positive, 48 | HAVRIX 1440/(0, 1) | Mean 569 | NA | NA | 1, 3/20, ELISA (Enzymun; Boehringer Mannheim) | 1 m: NA/80.07 m: NA/93.2 CD4 ≤200, 64 | MSM only study; subjects with higher baseline CD4 counts were more likely to seroconvert and to have higher antibody titers; Vaccine schedule did not affect response; HIV-negative subjects had higher seroconversion rates and GMTs |
| Standard 2-dose, HIV-positive, 42 | HAVRIX 1440/(0, 6) | Mean454 | NA | NA | 1, 7/20ELISA (Enzymun; Boehringer Mannheim) | 1 m: NA/75.67 m: NA/81.3 CD4 ≤200, 64 |
| Standard 2-dose, HIV-negative, 46 | HAVRIX 1440/(0, 6) | NA | NA | NA | 1, 7/20 ELISA (Enzymun; Boehringer Mannheim) | 1 m: NA/90.27 m: NA/100 |
| Wilde *et al*[126] | Pre-1995 | Prospective,United Kingdom | Three mini-dose,HIV-positive hemophiliacs,31 | HAVRIX 720/(0, 1, 6)  | Median 450 (IgG positive after 2 doses)Median 335 (IgG positive after 3 doses). | NA | 0 | 1, 2, 7/20EIA (SORIN Biomedica INCstar, Italy) | 2 m: NA/297 m: NA/55 | Hemophiliacs only (all anti-HCV positive); no patients with CD4 counts<170 cells/mm3 seroconverted  |
| Tilzey *et al*[127] | Pre-1995 | Prospective, United Kingdom | Three mini-dose, HIV-positive hemophiliacs,25 | HAVRIX 720/(0, 1, 6) | NA | NA | NA | 1, 2, 6, 7/20ELISA (Boehringer-Mannheim) | 1 m: NA/262 m: NA/506 m: NA/477 m: NA/76 | Men only study;After 3 doses, all HIV-positive hemophiliacs with anti-HAV titers of <50 mIU/ml had CD4 counts <100 cells/mm3. 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  |
| Three mini-dose, HIV-negative hemophiliacs,8 | HAVRIX 720/(0, 1, 6) | NA | NA | NA | 1 m: NA/572 m: NA/866 m: NA/1007 m: NA/100 |
| Three mini-dose,HIV-negative healthy controls,25 | HAVRIX 720/(0, 1, 6) | NA | NA | NA | 1 m: NA/1002 m: NA/1006 m: NA/1007 m: NA/100 |
| Hess *et al*[128] | Pre-1994 | Prospective, controlled, Germany | Three mini-dose, HIV-positive MSM,26 | HAVRIX 720/(0, 1, 6) | 495 | NA | NA | 1, 2, 6, 7/20ELISA (SB Biologicals) | 2 m: NA/78.67 m: NA/76.9 | MSM only study; Seroconversion rates were independent of CD4 counts |
| Three mini-dose,HIV-negative MSM,20 | HAVRIX 720/(0, 1, 6) | NA | NA | NA | 2 m: NA/1007 m: NA/100 |
| Santagostino *et al*[129] | Pre-1994 | NA, Italy | Three mini-dose, HIV-positive hemophiliacs,47 | HAVRIX 720(0, 1, 6) | NA | NA | NA | 1, 2, 7, 12/20NA | 12 m: NA/76.6 | Hemophiliacs; Seroconversion rates were dependent on stage of HIV disease |
| Three mini-dose, HIV-negative hemophiliacs,66 | HAVRIX 720(0, 1, 6) | NA | NA | NA | 12 m: NA/100 |

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.

**Table 8 Long-term response rates and predictors of sustained seroprotection after HAV vaccination in HIV-positive patients**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Dates** | **Design/ Country** | **1Patient no.** | **HAV/Dosing schedules (mo)** | **CD4, cells/mm3** | **PVL, log10, copies/ml** | **ART,%** | **2Timing of assay, yr/3Cut-off, mIU/ml/Assay** | **Response rate (%):****ITT/PP** | **4Predictors of persistent response and comments** |
| Cheng *et al*[136] | 2010-2015 | Prospective, Taiwan | Primary responders:2 doses, 1103 doses, 185 | HAVRIX 1440 U/2 doses (0, 6) 3 doses (0, 1, 6) | 560/415 | 2.5/2.8 | 70/56 | 2, 3, 4, 5/20ELISA (ETIAB-HAVK PLUS) | At 1.5 yr:2 doses: 90.0/93.43 doses: 87.0/94.7At 5 yr:2 doses: 76.4/88.43 doses: 78.9/94.2 | MSM only study;3-doses over 2-dose, syphilis, lack of acute HCV |
| Non-responders:2 doses, 163 doses, 23 | 470/315 | 2.9/3.3 | 59/63 |
| Kerneis *et al*[137] | 2006-2009 | Prospective,France | Primary responders:71 (52) | HAVRIX 1440/2 doses (0, 6) 3 doses (0, 1, 6) | 362 | 562% | NA | 7, 43/20ELISA (ETIAB-HAVK PLUS) | At 3.7 yr:Overall: 61.9/84.6 | PVL <50 copies/ml at time of last vaccine dose and a short duration of HIV infection  |
| Jablonowska *et al*[138]  | 2004 | Prospective,Poland | Primary responders:66 | HAVRIX 1440(0, 6) | 450 | NA | 37 | 1.5, 5/20CIA (Cobas, Roche) | At 1.5 yr:75.8/81.9At 5 yr:56.1/75.5 | Lack of co-infection with HCV |
| Crum-Cianflone *et al*[135] | 1996-2003 | Retrospective,United States | 116 | Vaqta 50 or HAVRIX 1440 (0, 6-18) | Median, 467 | 550% | 62 | 3, 6-10/10 | At 3 yr:90 At 6-10 yr:85 | Lower PVL; PVL <400 copies/ml |

1number 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); 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. 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.