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REVIEW

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

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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

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 ($3C^{pro}$) to yield 8 viral proteins, including VP0, VP3, VP1-2A, 2B, 2C, 3AB, $3C^{pro}$, and RNA-dependent RNA polymerase (RDRP, $3D^{pol}$). 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 $3C^{pro}$, 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 United Kingdom[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

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[1] 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 cities[2], 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%	Older age
Tseng *et al*[35]	Taipei, Taiwan	2009-2010	1128 MSM	18-40	15.1%[3]	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	35.7%[3]	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 contact Higher 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 infection Vaccination rate, 21%
Bialek *et al*[20]	7 major cities[4], 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

[1]Factors associated with HAV seropositivity were identified by bivariate or multivariable logistic regression analysis; [2]The 6 major cities included Atlanta, Chicago, Los Angeles, Miami, New York City, and San Francisco; [3]Only HIV-positive MSM were included; [4]The 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.

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 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[1] and comments
	Europe							
Høybye *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-Kuijpers *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

[1]Risk 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 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

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[1] 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	

[1]Risk 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%

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

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		
Incubation period (wk)	NA	2.5-5[91]
Duration of stool shedding (d)	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.

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*[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[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

Table 6 Hepatitis A virus vaccination recommendations by the British human immunodeficiency virus 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/mm^3 should be offered 2 vaccine doses at 0 and 6 mo Patients with CD4 counts < 350 cells/mm^3 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/mm^3, 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 IDUs 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; IDUs: Injecting drug users.

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

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[1]	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*[115]	2009-2010	Prospective, Taiwan	Standard 2-dose All 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): 75.7/81.7 12 m (ELISA): NA/88.6 18 m (ELISA): NA/86.6	MSM only study; Higher baseline CD4 and suppressed PVL; 3 doses over 2 doses
			3-dose All, 213; CD4 matched, 114	HAVRIX 1440/ 3 doses (0, 1, 6)	Mean, 452	Mean, 3	58.2%		12 m (CIA): 77.8/81.8 12 m (ELISA): NA/89.2 18 m (ELISA): NA/86.9	
			Standard 2-dose HIV-negative, 193	HAVRIX 1440/ 2 doses (0, 6)	NA	NA	NA		12 m (CIA): 88.5/97.9 12 m (ELISA): NA/100 18 m (ELISA): NA/100	
Mena *et al*[116]	1997-2009	Retrospective, Spain	Standard 2-dose, 241	HAVRIX 1440/ (0, 6-12)	Median, 531	55.3%[5]	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 d, 6-12)	Median, 543	73.2%	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	70.0%	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	100.0%	7-13/20, ELFA (VIDAS)	NA/78	Higher baseline CD4 count
			cART-naïve, 50		472	3.9	0.0%		NA/76	
Weinberg *et al*[119]	1994-2010	Prospective observational, United States	Hormone oral contraceptive, 13 No contraceptive, 149	2 doses (0, 6) or 3 doses (0, 2, 6)	478	47%[5]	78.0%	NA/20, ELISA (Mediagnost)	NA/62 NA/51	Women only study; Higher baseline CD4 count and suppressed PVL
Launay *et al*[120]	2003-2005	Randomized controlled trial, France	Standard 2-dose, 49	HAVRIX 1440/ (0, 6)	Median, 355	Median, < 1.7	78.0%	6-18/20, ELISA (ETIAB-HAVK PLUS)	6 m: 44.9/46.8 7 m: 69.4/72.3 18 m: 61.2/69.8	Absence of tobacco smoking
			3-dose, 46	HAVRIX 1440/ (0, 1, 6)	Median, 351	Median, < 1.7	83.0%		6 m: 69.6/74.4 7 m: 82.6/88.4 18 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/NA ELISA (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%	6-13/18, EIA (Abbot IMx HAV Ab)	48.6 (67/138)	Female; CD4 count at vaccination > 200 cells/mm^3
Wallace *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	76.0%	1, 6, 7, 12/10, Quantitative modified HAVAb assay (NA)	1 m: NA/61, CD4 < 300/ 300+, 48/74 7 m: NA/94, CD4 < 300/ 300+, 87/100 12 m: NA/90, CD4 < 300/ 300+, 80/100	100% of subjects with CD4 counts ⩾ 300 cells/mm^3 seroconverted
			Standard 2-dose, HIV-negative, 72	Vaqta 50/ (0, 6)	NA	NA	NA		1 m: NA/90 7 m: NA/100 13 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	91.0%	1, 6, 7, 9/33, ELISA (Enzymun; Boehringer Mannheim)	1 m: NA/11 CD4 < 200/ 200+, 0/16 6 m: NA/9 CD4 < 200/ 200+, 0/13 7 m: NA/49, CD4 < 200/ 200+, 11/62 9 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/80.0 7 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)	Mean 454	NA	NA	1, 7/20, ELISA (Enzymun; Boehringer Mannheim)	1 m: NA/75.6 7 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/90.2 7 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, 7/20, EIA (SORIN Biomedica INCstar, Italy)	2 m: NA/29 7 m: NA/55	Hemophiliacs only (all anti-HCV positive); no patients with CD4 counts < 170 cells/mm^3 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, 7/20, ELISA (Boehringer-Mannheim)	1 m: NA/26 2 m: NA/50 6 m: NA/47 7 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/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
			Three mini-dose, HIV-negative hemophiliacs, 8	HAVRIX 720/ (0, 1, 6)	NA	NA	NA		1 m: NA/57 2 m: NA/86 6 m: NA/100 7 m: NA/100	
			Three mini-dose, HIV-negative healthy controls, 25	HAVRIX 720/ (0, 1, 6)	NA	NA	NA		1 m: NA/100 2 m: NA/100 6 m: NA/100 7 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, 7/20, ELISA (SB Biologicals)	2 m: NA/78.6 7 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/100 7 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, 12/20	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	NA	12 m: NA/100	

[1]Number of HIV-positive individuals with baseline negative anti-HAV and data available; [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. 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%[122-125]. 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/mm^3 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/mm^3 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[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-

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[3], mIU/ mL/Assay	Response rate (%): ITT/PP	Predictors of persistent response and comments[4]
Cheng *et al*[136]	2010-2015	Prospective, Taiwan	Primary responders: 2 doses, 110 3 doses, 185 Non-responders: 2 doses, 16 3 doses, 23	HAVRIX 1440 U/ 2 doses (0, 6) 3 doses (0, 1, 6)	560/415 470/315	2.5/2.8 2.9/3.3	70/56 59/63	2, 3, 4, 5/20 ELISA (ETIAB-HAVK PLUS)	At 1.5 yr: 2 doses: 90.0/93.4 3 doses: 87.0/94.7 At 5 yr: 2 doses: 76.4/88.4 3 doses: 78.9/94.2	MSM only study; 3-doses over 2-dose, syphilis, lack of acute HCV
Kernéis *et al*[137]	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: 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, 5/20 CIA (Cobas, Roche)	At 1.5 yr: 75.8/81.9 At 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	50%[5]	62	3, 6-10/10	At 3 yr: 90 At 6-10 yr: 85	Lower PVL; PVL < 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.

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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