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Hepatitis A vaccination among human immunodeficiency virus (HIV)-infected adults: Current evidence and unanswered questions

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Hepatitis A virus (HAV) infection is common, can cause significant morbidity and mortality, and the prevalence may be higher in populations infected or at risk for human immunodeficiency virus (HIV). Immunization with HAV vaccine is recommended for HIV-infected individuals, particularly men who have sex with men, injection drug users, hemophiliacs, those with chronic liver disease, and international travelers without immunity to HAV. HAV vaccination is well-tolerated among HIV-infected individuals and is immunogenic, particularly among those with higher CD4⁺ cell counts. HIV-infected individuals have lower seroconversion rates and antibody concentrations in response to vaccination. However, protection against HAV as measured by HAV antibody levels is achieved for most cases. Adverse event rates are similar among those with and without HIV infection, and HAV vaccine does not have a marked impact on HIV-1 ribonucleic acid (RNA) levels, progression to acquired immune deficiency syndrome (AIDS), or CD4⁺ cell counts. Areas of controversy remain, including timing of vaccination relative to initiation of antiretroviral therapy, rate and impact of antibody decline over time, need for booster immunizations, and the benefit of follow-up antibody titer monitoring.

Key words: Hepatitis A virus, human immunodeficiency virus (HIV), vaccination, vaccine.

INTRODUCTION

Acute viral hepatitis is one of the most common infectious diseases, and hepatitis A virus (HAV) is the most frequent form of acute viral hepatitis throughout the world (Koff, 1998). There is an estimated 1.5 million clinical cases of HAV infection reported worldwide annually, a figure that greatly underestimates the true incidence of infection (Martin et al., 2006). In the United States, HAV is one of the most frequent of the reportable diseases (Wasley et al., 2008), however, since the adoption of routine HAV vaccination, the United States and other

countries have seen a dramatic decline in HAV infections and HAV-related mortality (Daniels et al., 2009; Klevens et al., 2010; Vogt et al., 2008; Wasley et al., 2005, 2006, 2008; Zhou et al., 2007). Despite this decline in incidence, HAV remains an important and preventable cause of morbidity and mortality with an estimated 25,000 cases per year in the United States (Daniels et al., 2009; Martin et al., 2006; Zhou et al., 2007), over 17,000 confirmed cases per year (based on 2009 data) in the European Union (European Centre for Disease Prevention and Control, 2011), and over 35,000 deaths per year globally (World Health Organization (WHO), 2012).

The prevalence of HAV infection in populations infected or at risk for HIV is high (Cotter et al., 2003; Fonquernie et al., 2001; O'Riordan et al., 2007; Sun et al., 2009; Villano et al., 1997), and has been estimated at 40 to 70% in resource-rich nations (Laurence, 2005) and nearly

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Abbreviations: ALT, Alanine aminotransferase; HAART, highly active antiretroviral therapy; HAV, hepatitis A virus; IDUs, injection drug users; MSM, men who have sex with men.

100% in developing countries (Jacobsen et al., 2010). A French study in the late 1990s reported an annual incidence of HAV infection of 6% among HIV-infected individuals (Fonquernie et al., 2001). Others have estimated the annual incidence of HAV among HIV-infected individuals as high as 1.5% (Wallace et al., 1998) although these estimates were generated before the vaccine-associated decline in HAV infection. Despite dramatic reductions overall, relatively high disease rates persist among adult males less than 40 years of age (Wasley et al., 2005), and the proportion of cases among men who have sex with men (MSM) is increasing (Wasley et al., 2008), making HAV infection particularly relevant to HIV-infected individuals. The US Department of Health and Human Resources guidelines for opportunistic infections recommend HAV vaccination for seronegative HIV-infected individuals, particularly MSM, injection drug users (IDUs), hemophiliacs, those with chronic liver disease including hepatitis B and C, and international travelers (Kaplan et al., 2009).

HAV vaccination rates are very low across the US (Laurence, 2005; Tedaldi et al., 2004). A study of multiple sites across the U.S. demonstrated low vaccination rates even among HIV-infected MSM (Hoover et al., 2012). Additional studies are needed to better understand the factors contributing to these low vaccination rates even among high-risk patients.

The course of acute HAV infection among HIV-infected individuals is variable and may not differ from the course of those without HIV (Dabrowska et al., 2011; Wallace et al., 1998). Data are limited, however the possibility of more severe and prolonged disease in those with HIV has been raised (Costa-Mattioli et al., 2002; Fonquernie et al., 2001; Ida et al., 2002).

HAV infection in HIV-infected individuals may in some cases be associated with longer time to normalization of alanine aminotransferase (ALT) levels (Fonquernie et al., 2001) and more prolonged HAV viremia compared with healthy adults (Costa-Mattioli et al., 2002; Ida et al., 2002). Furthermore, HAV infection may impact HIV disease by increasing HIV replication, at least in part, to associated disruptions in antiretroviral therapy; however this is based on limited data and case reports (Fonquernie et al., 2001; Ridolfo et al., 2000; Wallace et al., 1998), and a more recent case series suggested that it occurred even among those who did not disrupt their antiretroviral therapy (Gallego et al., 2011). Chronic hepatitis B and C infections are common among HIV-infected individuals (Sherman et al., 2002; Shire et al., 2004) and morbidity and mortality due to chronic liver disease is increasing among those with HIV (Bica et al., 2001; Jain et al., 2003). These chronic liver conditions may predispose HIV-infected patients to fulminant hepatic injury when infected with HAV (Keeffe, 1995; Vento et al., 1998). Despite the higher rates and potentially more severe or prolonged course of HAV among HIV-infected individuals, vaccination rates remain low with estimates ranging from 6 to 54% (Hoover et al.,

2012; Overton et al., 2007; Tedaldi et al., 2004; Winnock et al., 2011).

METHODOLOGY

We searched for articles using Pubmed. Search terms included HIV, hepatitis A, and vaccination and vaccine. Approximately 500 articles were found in response to a joint search of both HIV and hepatitis A. We reviewed recent U.S. and European HIV guidelines and Advisory Committee on Immunization Practices (ACIP) guidelines. In addition, we reviewed bibliographies from relevant articles for other potential studies.

BRIEF HISTORY OF HAV VACCINATION IN THE UNITED STATES

HAV was first isolated in 1973 (Feinstone et al., 1973), followed soon after by development of the prototype vaccine and then other vaccines (Andre et al., 1992; Dagan et al., 1999; Loutan et al., 1994, 2007; Nalin et al., 1993; Provost et al., 1978). Large-scale clinical trials were then performed to demonstrate the efficacy and safety of HAV vaccines (Clemens et al., 1995; Innis et al., 1994; Werzberger et al., 1992). By 1995, a safe and effective vaccine was commercially available (Andre et al., 1992; Dienstag, 2008). Two single-antigen inactivated HAV vaccines are commonly used: HAVRIX (GlaxoSmithKline Biologicals, Rixensart, Belgium) with 2 doses at 0 and 6 to 12 months, and VAQTA (Merck & Company, Inc., Whitehouse Station, New Jersey) (Wasley et al., 2006) with 2 doses at 0 and 6 to 18 months (Wasley et al., 2006). Both are of similar efficacy and safety (Ashur et al., 1999; Orr et al., 2006). There is also a combination vaccine (TWINRIX, GlaxoSmithKline Biologicals, Rixensart, Belgium) which contains inactivated HAV and recombinant hepatitis B antigen (Wasley et al., 2006) with 3 doses at 0, 1, and 6 months (Wasley et al., 2006). However, the HAV dose in the combination vaccine is only 720 Enzyme-linked immunosorbent assay (ELISA) units, which is half the dose of the single-antigen inactivated HAV vaccines (Wasley et al., 2006).

Initially, HAV vaccination was targeted at groups and individuals at increased risk of HAV or its consequences such as travelers to endemic areas, MSM, injection drug users (IDUs), and persons with clotting factor disorders or chronic liver disease (Advisory Committee on Immunization Practices (ACIP), 1996). Nevertheless, vaccination rates among these groups remained low (Arguedas et al., 2002; Bialek et al., 2011; Campbell et al., 2007; Carey et al., 2005; Diamond et al., 2003; Friedman et al., 2000; Hoover et al., 2012; Jin et al., 2004; O'Riordan et al., 2007; Shim et al., 2005; Siconolfi et al., 2009; Vong et al., 2005) despite continued outbreaks and higher rates of HAV infection among MSM (Corey and Holmes, 1980; Girardi et al., 2010; Centers for Disease Control and Prevention (CDC), 1998; Kahn,

2002; O'Riordan et al., 2007; Ochnio et al., 2001; Schomer et al., 1992; Stokes et al., 1997; Tortajada et al., 2012) and injection drug users (Ochnio et al., 2001; Quaglio et al., 2006; Villano et al., 1997), and even after reports of fulminant hepatitis due to HAV in patients with chronic liver disease (Keeffe, 1995; Vento et al., 1998).

A stepwise approach was taken to expand HAV vaccine recommendations in children. In 1996, routine vaccination was recommended for children over 2 years of age living in endemic communities (ACIP, 1996). This was expanded to include children living in 17 states with elevated HAV rates in 1999 (ACIP, 1999) and, in 2006, to all children aged 12 to 23 months nationwide (Fiore et al., 2006). Introduction of routine childhood HAV immunization has led to a reduction in HAV incidence among adults (Averhoff et al., 2001; Dagan et al., 2005; Klevens et al., 2011; Samandari et al., 2004) and contributed to the overall decline in national HAV incidence rates (Daniels et al., 2009; Samandari et al., 2004; Wasley et al., 2006; Wasley et al., 2005), as well as a decline in the overall age-adjusted HAV mortality rates (Vogt et al., 2008).

RESPONSE RATES TO HAV VACCINATION

The protective effect of HAV vaccination, typically measured as long-term persistence of vaccine-induced anti-HAV antibodies, has been established in numerous studies of vaccinated populations including infants, children, and adults (including the elderly) (Briem and Safary, 1994; Chan et al., 1999; D'Acromont et al., 2006; Dagan et al., 2000; Fan et al., 1998; Innis et al., 1994; Iwarson et al., 2002; Orr et al., 2006; Piazza et al., 1999; ACIP, 1996; Troisi et al., 1997; Van Damme et al., 2003; Van Der Wielen et al., 2007; Van Herck et al., 2001; Van Herck et al., 2004; Werzberger et al., 1992; Werzberger et al., 2002). Although studies vary, most defined a serum antibody level of 20 mIU/ml as the minimum needed to define seroconversion or protective immunity (Kourkounti et al., 2012; Tilzey et al., 1996; Weinberg et al., 2006). Early clinical trials before 1995 used a 3-dose series with HAVRIX while most recent studies have documented the efficacy of the current universally accepted two-dose schedule (Van Damme et al., 2003). Among immune competent individuals, a 2-dose vaccine series produces protective HAV antibody levels in 95 to 100% of individuals (Levy et al., 1998).

There are a number of reasons to expect a lower response rate to HAV vaccination in HIV-infected individuals compared with HIV-uninfected populations. First, the immunogenicity of most vaccines is decreased among immune compromised individuals (Pirofski et al., 1998) including those with HIV (Bekker et al., 2006; Rivas et al., 2007) and second, HIV-infected populations commonly have habits or conditions that may suppress the response to vaccination such as alcohol and tobacco use,

injection drug use, malnutrition and hepatitis C virus co-infection (Laurence, 1997).

Response rates to HAV vaccination among HIV-infected individuals range between ~46 to 97% (Armstrong et al., 2010; Crisinel et al., 2012; Kemper et al., 2003; Kourkounti et al., 2012; Loutan et al., 2007; Neilsen et al., 1997; Overton et al., 2007; Santagostino et al., 1994; Siberry et al., 2008; Tilzey et al., 1996; Tseng et al., 2012; Valdez et al., 2000; Wallace et al., 2004; Weissman et al., 2006). These rates vary in part due to differences in patient characteristics including age and CD4⁺ cell count, as well as vaccination schedule and anti-body assay used to measure the response (Loutan et al., 2007; Siberry et al., 2008; Tseng et al., 2012). Despite the relatively large number of studies performed, most had small sample sizes making definitive conclusions regarding vaccine efficacy difficult. A meta-analysis including 8 studies with a combined total of 458 individuals found an overall HAV vaccine response rate among HIV-infected individuals of 64% (Shire et al., 2006). Several studies in the era before highly active antiretroviral therapy (HAART) demonstrated lower seroconversion rates among HIV-infected individuals compared with HIV-uninfected individuals (Hess et al., 1995; Neilsen et al., 1997; Santagostino et al., 1994; Tilzey et al., 1996). Direct comparison studies have found seroconversion rates of 76 to 94% versus 100% among HIV-infected and uninfected individuals, respectively (Neilsen et al., 1997; Tilzey et al., 1996; Wallace et al., 2004). One study conducted among patients with hemophilia prior to HAART reported an overall vaccine response rate of 76% at 1 year in HIV-infected individuals versus 100% in controls, with only 40% response among subjects with AIDS (Santagostino et al., 1994). In general, anti-HAV titers in HIV-infected individuals are lower by a factor of ~3 to 10 compared with HIV-uninfected vaccines (Neilsen et al., 1997; Overton et al., 2007; Tilzey et al., 1996; Wallace et al., 2004). Despite lower seroconversion rates and antibody concentrations in HIV-infected individuals, protection against HAV as measured by HAV antibody levels is achieved for most.

FACTORS ASSOCIATED WITH RESPONSE TO HAV VACCINATION AMONG HIV-INFECTED INDIVIDUALS

HIV-infected individuals with nearly normal CD4⁺ cell counts have similar vaccine response rates but lower antibody levels compared to HIV-uninfected vaccines (Wasley et al., 2006) while patients with more advanced HIV infection have lower response rates and lower antibody levels (Loutan et al., 2007; Rigaud et al., 2008; Wasley et al., 2006). In general, high CD4⁺ cell counts at the time of vaccination are associated with better seroconversion rates and higher mean anti-HAV antibody titers (Crisinel et al., 2012; Crum-Cianflone et al., 2011; Kemper et al., 2003; Lederman et al., 2003; Neilsen et

al., 1997; Siberry et al., 2008; Valdez et al., 2000; Weinberg et al., 2012; Weissman et al., 2006) (Table 1). One study of 214 vaccinated individuals reported that 80% of patients with a CD4⁺ cell count > 500 cells/mm³ at the time of vaccination responded versus < 10% of those with a CD4⁺ cell count < 50 cells/mm³ (Rimland et al., 2005). A randomized controlled trial suggested that patients with a CD4⁺ count between 350 and 500 cells/mm³ had greater vaccine response rates than those with CD4⁺ counts between 200 and 350, however this did not reach statistical significance (Launay et al., 2008).

Although the effect of CD4⁺ cell count on vaccine response rates has been examined in many studies, relatively few have investigated the impact of HIV-1 viral load on seroconversion. One study found that HAV vaccine responders had a lower HIV-1 viral load compared with non-responders (6,104 versus 26,267 copies/ml, $p = 0.03$) in unadjusted analyses, however this association did not persist after controlling for other factors (Weissman et al., 2006). In contrast, another study (N = 268) found that antibody response rates among those with an HIV-1 viral load level below 1000 copies/ml were 2.25 times higher than response rates among those with an HIV-1 viral load above 1000 copies ($p = 0.01$) (Overton et al., 2007). Most recently, a study of HIV-infected women found an association between HIV-1 viral load < 400 copies/ml and likelihood of HAV antibody response to vaccination (OR 1.7, $p = 0.04$) (Weinberg et al., 2012). Multivariate analyses among children demonstrated an association between undetectable HIV-1 viral load and higher anti-HAV antibody titers (Weinberg et al., 2006, 2009). A study of 130 HIV-infected adults demonstrated that lower HIV-1 viral load values over time were associated with maintaining higher mean anti-HAV antibody titers (Crum-Cianflone et al., 2011).

In addition to HIV disease-specific factors, other characteristics may impact response rates to HAV vaccination among HIV-infected individuals. For example, tobacco use, which is common among HIV-infected populations (Cockerham et al., 2010), is associated with poorer response rates to hepatitis B vaccine among immune competent individuals (Winter et al., 1994). Although data on the impact of smoking on HAV vaccine response rates among HIV-infected individuals is limited, one trial of 2 versus 3 dose HAV vaccination schedules among HIV-infected individuals did find that smoking was associated with a poorer response to HAV vaccine (Launay et al., 2008). Questions remain regarding other factors that may impact response as well, such as nutritional status, co-infections, genetic predisposition, and many others.

HAV VACCINE SAFETY

Safety among HIV-uninfected individuals

Cumulative global experiences from several hundred

million doses have demonstrated that the overall safety profile of hepatitis A vaccine has been excellent (Demicheli and Tiberti, 2003; WHO, 2012). Data from worldwide pre-licensure clinical studies of over 60,000 individuals did not definitively attribute any serious adverse events to HAV vaccine (Fiore et al., 2006; ACIP, 1996). Among adults, the most frequent side effects were tenderness at the injection site (56%), headache (14%), and malaise (7%), with an incidence similar to HBV vaccine (ACIP, 1996). Another study found the most frequent side effects after vaccination were tenderness (53%), pain (51%), warmth (17%) at the injection site, and headache (16%) (Fiore et al., 2006).

Reports of rare serious adverse events included anaphylaxis, Guillain-Barre syndrome, transverse myelitis, encephalitis, and multiple sclerosis (ACIP, 1999). However, regarding these serious adverse events for which background incidence data were known, the rates among vaccine recipients were not higher than expected for an unvaccinated population (ACIP, 1999). The initial 2-year safety review by the Vaccine Adverse Event Reporting System reported few unexpected HAV vaccine associated serious events despite the use of at least a million vaccine doses in the US, and stated that it reaffirmed the safety of the HAV vaccine in the general population (Niu et al., 1998). The safety of the vaccine is continually assessed through ongoing data monitoring from the Vaccine Adverse Event Reporting System and it is excellent (Fiore et al., 2006).

HAV vaccine side-effects among HIV-infected individuals

HAV vaccines have typically been well-tolerated among HIV-infected individuals with common mild local reactions but rare systemic reactions. A study of MSM reported local tenderness as the most common side-effect, occurring in 10% of HIV-infected versus 9% of HIV-uninfected men (Nielsen et al., 1997). Mild systemic symptoms such as headache, rash, nausea, lightheadedness, and myalgias were reported by 33% of HIV-infected and 15% of HIV-uninfected individuals (Nielsen et al., 1997). A study of 90 HIV-infected and 90 HIV-uninfected individuals found rates of systemic adverse events; predominantly self-limited headache and fever were more common among HIV-infected vaccine recipients (37%) compared with HIV-infected placebo recipients (23%) or HIV-uninfected individuals who received the vaccine (21%) (Wallace et al., 2004). Similarly, a trial among HIV-infected individuals found no significant differences in the frequency of reported signs and symptoms within 4 days of receiving either vaccine or placebo (Kemper et al., 2003).

Severe vaccine-related adverse events were uncommon (1.6% in both placebo and vaccine group with severe headache, and 1.6% of vaccine group with severe fatigue). Among patients with hemophilia, high rates of

Table 1. Selected studies on response to HAV vaccination among HIV-infected individuals.

Study author, year	Patient population	Percentage (%) who responded to vaccination*	Association of CD4+ cell counts with response	Association of plasma HIV-1 viral load with response	Geometric mean titers IU/L
Crum-Cianflone et al. (2011)	130 HIV-infected individuals (military)	89	78% and 94% responded at 1 year among those with a baseline CD4<350 and ≥350 cells/mm ₃ respectively, ($p=0.006$)	82% and 94% responded at 1 year among those with <1000 and ≥1000 copies/ml, respectively	87 and 199 at 1 year among those with <350, and ≥ 350 CD4+ cells/mm ₃ , respectively ($p=0.02$). 104 and 196 among those with a baseline HIV viral load < 1000 and ≥ 1000 copies/ml, respectively
Overton et al. (2007)	268 HIV-infected individuals	50	Current CD4+ cell count and CD4+ nadir not associated with response rate	Those with <1000 copies/ml were 2.25 times more likely to respond than those with >1000 copies/ml	-
Kourkounti et al. (2012)	351 HIV-infected individuals with CD4 count ≥200 cells/mm ₃	74 at 1 month, 68 at 6 months, 61 at 12 months, and 56 at 18 months	Responders had a higher median current CD4+ cell count (580 cells/mm ₃) than non-responders (528 cells/mm ₃ ; $p=0.007$).	-	315 at 1 month, 203 at 6 months, 153 at 12 months, and 126 at 18 months
Tilzey et al. (1996)	Group 1: 25 HIV-infected patients with hemophilia; Group 2: 8 HIV-uninfected with hemophilia ; Group 3: 25 HIV-uninfected controls	Group 1: 76; Group 2: 100; Group 3: 100	Among Group 1, with one exception, all poor responders had CD4+ counts of < 100 cells/mm ₃	-	Group 1: 204; Group 2: 720; Group 3: 1354
Neilsen et al. (1997)	Group 1: 83 HIV-infected MSM; Group 2: 39 HIV-uninfected MSM	Group 1: 88; Group 2: 100	Group 1 responders had a higher mean CD4+ cell count (540 cells/mm ₃) than poor responders (280 cells/mm ₃ ; $p=0.03$). Only 9 (64%) of Group 1 with CD4+ cell counts <200 cells/mm ₃ responded	-	Group 1: 107; Group 2: 1086 ($p<0.001$) Group 1 with CD4+ cell count ≥200 cells/mm ₃ 130 versus 20 if CD4+ cell count <200 cells/mm ₃ ($p=0.001$)
Weissman et al. (2006)	138 HIV-infected	49	Responders had higher CD4+ counts than poor responders (509 cells/mm ₃ vs. 344 cells/mm ₃ $p = 0.001$). Responders were less likely to have a CD4+ count <200 cells/mm ₃ (11% vs. 34% $p = 0.002$)	There was a trend towards having a lower log viral load among responders than non-responders (2.6 vs. 2.9, $p=0.07$)	-
Kemper et al. (2003)	68 HIV-infected individuals as part of a RCT	52	9%, 68%, and 67% responded among those with a CD4<200, 200-499, and >500 cells/mm ₃ respectively, ($p=0.004$)	-	23, 82, and 145 in those with <200, 200-499, and >500 CD4+ cells/mm ₃ , respectively ($p=0.02$)
Wallace et al. (2004)	Group 1: 60 HIV-infected patients; Group 2: 90 HIV-uninfected as part of a RCT	Group 1: 61, 94; Group 2: 90, 100 after 1st and 2nd injections, respectively	Group 1 with a CD4+ count <300 cells/mm ₃ , 87% responded vs. 100% with a CD4+ count ≥300 cells/mm ₃ at week 28	-	Group 1 with CD4+<300 cells/mm ₃ 517; Group 1 with CD4+≥ 300 1959; Group 2: 3471
Launay et al. (2008)	RCT of 99 individuals with HIV and CD4 counts between 200 to 500 cells/mm ₃ . Group 1: 3-dose vaccine schedule; Group 2: 2-dose vaccine schedule	Group 1: 83; Group 2: 69	Group 1 with a CD4+ count between 200 and 349 cells/mm ₃ , 78% responded vs. 87% with a CD4+ count between 350 and 500 cells/mm ₃ ; Group 2 with a CD4+ count between 200 and 349 cells/mm ₃ , 57% responded vs. 81% with a CD4+ count between 350 and 500 cells/mm ₃	-	Group 1: 324; Group 2: 138 at 28 weeks, ($p=0.03$)

Table 1. Contd.

Tseng et al. (2012)	Group 1: 140 HIV-infected MSM, 2-dose vaccine schedule; Group 2: 225 HIV-infected MSM, 3-dose vaccine schedule; Group 3: 217 HIV-uninfected MSM, 2-dose vaccine schedule	Group 1: 76; Group 2: 78; Group 3: 89	Among patients with HIV (Groups 1 and 2), higher CD4+ counts were associated with seroconversion (adjusted odds ratio 1.13 per 50 cells/mm ³)	Undetectable viral loads (<40 copies/ml) were associated with seroconversion (adjusted odds ratio 1.90)	Group 1: 1.74; Group 2: 2.29 at 48 weeks ($p<0.01$); Group 1: 1.78; Group 2: 2.08 log ₁₀ mLU/ml at 72 weeks ($p<0.01$)
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MSM; men who have sex with men, RCT; randomized controlled trial. *These studies varied in the timing of assessment of response to vaccination and this table includes selected studies rather than all studies. It includes some of the larger studies and those that represent particular periods or include specific distinct subgroups.

adverse events after vaccination were noted, predominantly local site reactions (80%, 20 of 25 HIV-infected patients with hemophilia); however reaction rates were higher among HIV-uninfected individuals with hemophilia (96%, 24 of 25 HIV-uninfected individuals) (Tilzey et al., 1996). Another study of patients with hemophilia found no difference in the frequency of side-effects between those with and without HIV infection (Santagostino et al., 1994).

HAV vaccination impact on HIV disease severity

Safety of HAV vaccines among HIV-infected individuals is a key area of consideration given that several (Brichacek et al., 1996; Gunthard et al., 2000; O'Brien et al., 1995; Ostrowski et al., 1997; Stanley et al., 1996; Staprans et al., 1995) [but not all (Farber et al., 1996; Kroon et al., 1996)] early reports suggested HIV-1 viral load may be transiently increased by influenza and other vaccinations. An early safety study of HAV vaccine compared 90 vaccinated HIV-infected patients with 90 HIV-infected controls with similar CD4⁺ cell counts at baseline. At 12 months, there were no significant differences in immunologic status, progression to AIDS, or death rate. Between cases and controls (Bodsworth et al.,

1997). A more recent study of 90 HIV-infected individuals found no significant differences between vaccine and placebo groups in CD4⁺ counts or HIV-1 viral load levels at a number of time points after vaccination (Wallace et al., 2004). Similarly, a trial of vaccinated HIV-infected patients found no significant differences between vaccine and placebo recipients in HIV-related events including change in CDC HIV disease stage or transient increases in viral load due to vaccination (Kemper et al., 2003). These studies suggest that HAV vaccine is safe for HIV-infected individuals with no demonstrable effect on HIV-1 viral load levels, progression to AIDS, or CD4⁺ cell counts.

CLINICAL IMPLICATIONS AND UNANSWERED QUESTIONS

Vaccination timing

Ideally, patients with HIV should be vaccinated before significant immunologic deterioration occurs. While this is not feasible for patients who present to care late in their disease course, the increased emphasis on HIV testing may lead to fewer patients with undiagnosed HIV infection. Guidelines do not make specific recommendations regarding the timing of vaccination relative to

initiation of antiretroviral therapy or CD4⁺ count, but note that response rates are poorer among those with lower CD4⁺ cell counts (Fiore et al., 2006). Although data are lacking, a number of approaches to this problem have been described for HAV-susceptible patients including:

1. Vaccinate patients regardless of antiretroviral therapy status, check antibody levels a month or more after vaccination, and repeat vaccination for those without a vaccine response after antiretroviral therapy has been initiated, and the CD4⁺ cell count is above 200 cells/mm³ (Rimland et al., 2005);
2. Initiate antiretroviral therapy but delay HAV vaccination until CD4⁺ cell counts are above > 200 cells/mm³ (Rimland et al., 2005);
3. Initiate antiretroviral therapy and delay vaccination until HIV viral replication is controlled regardless of CD4⁺ cell count (Overton et al., 2007).

Data regarding which strategy to pick are limited and may be further complicated in some settings by lack of availability of quantitative HAV IgG antibody testing. According to recent guidelines, data on delaying vaccination until a CD4⁺ count is over 200 are graded as category C (“evidence for efficacy is insufficient to support a recommendation for or against”) (Kaplan et al., 2009). Furthermore, delaying vaccination until immune

vaccination until immune restoration may place patients at risk of never receiving the vaccine (Tedaldi et al., 2004). In addition, the benefit of revaccination among non-responders remains unclear, graded as category B ("moderate evidence for efficacy") (Kaplan et al., 2009).

Each of these strategies focus on HAV-susceptible patients. Determining HAV-susceptibility before vaccination has implications including costs, potential vaccination delays and missed opportunities. However, given the varying prevalence rates of HAV-susceptibility in different patient groups, and the now universal childhood vaccination recommendations, screening likely remains preferable in many, if not most settings.

HAV booster vaccination or 3-dose vaccine schedules

The need for HAV booster vaccination in those without HIV remains controversial (Van Damme et al., 2003). Among HIV-uninfected individuals, initial response rates are very high, HAV antibody persistence appears to be greater than 10 years, and underlying immune memory may provide protection after the disappearance of anti-HAV antibodies (Hammit et al., 2008; Rendi-Wagner et al., 2007; Van Damme et al., 2003; Van Herck et al., 2001). Therefore, post-vaccination testing in HIV-uninfected adults or children is not recommended (ACIP, 1996). Studies have suggested that antibodies may wane faster among HIV-infected individuals than controls (Santagostino et al., 1994; Wallace et al., 2004). One study found that 89% of HIV-infected patients responded to vaccine, among the responders, 90% still had protective HAV IgG levels ≥ 10 mIU/ml 3 years later, and 85% were still protected 6 to 10 years after vaccination (Crum-Cianflone et al., 2011).

Another small study found that among HIV-infected individuals who had initially responded to vaccination, 85% still had protective anti-HAV antibodies at ~4 years after vaccination, although antibody levels had decreased by ~90%, with longer duration of HIV infection and a detectable HIV viral load considered as the key predictors of loss of protection (Kerneis et al., 2011). A small trial among HIV-infected individuals with a $CD4^+$ cell count < 500 cells/mm³ found that a 3-dose schedule seemed to induce higher seroconversion rates and higher antibody titers than the standard 2-dose schedule (Launay et al., 2008). This expanded dosing schedule added an additional dose at 1 month which may also have advantages of accelerating immunization for individuals for whom quick protection is needed, such as for travelers with unexpected trips to developing countries. More recently, a study of 2 versus 3 dose schedules found only slightly higher seroconversion rates with a 3-dose schedule but higher geometric mean titre (GMT) at 48 and 72 weeks (Tseng et al., 2012).

Further research on the rate and impact of antibody

decline among HIV-infected populations is needed to inform recommendations regarding post-vaccination antibody testing, expanded dosing schedules, or booster vaccinations (Van Damme et al., 2003). However, recent European guidelines are now recommending checking anti-HAV antibody titers in high-risk patient populations such as MSM (European AIDS Clinical Society, 2011).

Clinical implications summary

Based on these studies, HAV vaccination is recommended for all HAV seronegative HIV-infected individuals (Tasker et al., 2000), or at least those with risk factors for HAV such as MSM, IDUs, as well as those with chronic liver disease (European AIDS Clinical Society, 2011; Fiore et al., 2006; Geretti et al., 2008; Kaplan et al., 2009; ACIP, 1999). Although complete data are lacking, several studies demonstrate a lower response rate to HAV vaccine among HIV-infected adults, raising the question of whether there is benefit in measuring anti-HAV antibodies after vaccination. European guidelines have recommended checking anti-HAV antibody titers in high-risk patient populations (European AIDS Clinical Society, 2011). Non-responders could then be re-vaccinated once $CD4^+$ cell counts have risen, ideally above 300 to 500 cells/mm³ in response to HAART (Rivas et al., 2007). In addition, there may be benefit in monitoring post-vaccination HAV antibodies and providing booster vaccines to those individuals with waning antibody titers, although definitive recommendations regarding this strategy must await the results of additional studies.

Conclusions

HIV-infected individuals are often at increased risk for HAV infection, and HAV infection can cause significant morbidity and mortality among HIV-infected patients. HAV vaccination is well-tolerated and immunogenic among most HIV-infected individuals, particularly those with higher $CD4^+$ cell counts. Adverse event rates are similar among HIV-infected individuals and HIV-uninfected individuals, and HAV vaccine does not have a marked impact on HIV-1 RNA levels, progression to AIDS, or $CD4^+$ cell counts. Despite decreased immunogenicity of HAV vaccine in HIV-infected compared with uninfected individuals, seroconversion rates are still high, suggesting HAV vaccine will be effective for most HIV-infected individuals. Additional studies are needed to develop effective health promotion programs such as for hepatitis A vaccination among patients with HIV, and to determine the most effective vaccination strategies for HIV-infected patients in relation to $CD4^+$ count, HIV-1 viral load, and HAART as well as the need for re-vaccination in those with poor vaccine responses or waning antibody titers.

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