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In the current era of potent antiretroviral therapy, preventive medicine has become an increasingly important aspect of primary care for those infected with HIV. Hepatitis vaccines provide an excellent opportunity to avert infections and liver toxicity, which may be more severe in immunocompromised persons. Unfortunately, HIV-infected persons respond poorly to hepatitis vaccines. Questions remain regarding the appropriate strategy to improve immunogenicity. The study of vaccine responses in HIV-infected persons has greatly advanced the understanding of the underlying immune deficits, particularly with regard to reduced CD4 cell number and function and the level of immune activation associated with chronic HIV viremia. This research has also solidified safety and utility data for vaccines in this population. Continued research of vaccine responses will further our understanding of the immune system and optimize the efficacy of routine immunizations. Ongoing medical education and vaccination campaigns can serve to improve vaccination rates among this at-risk population.

Introduction

An important preventive measure in the care of persons living with HIV is the timely administration of vaccines against pathogens for which these individuals are at risk. In clinical practice, HIV-infected persons are generally given hepatitis B and pneumococcal vaccinations shortly after their initial visit and influenza vaccinations annually. Hepatitis A vaccination is routinely recommended for all nonimmune hepatitis C virus (HCV)-coinfected patients, because of their increased risk of fulminant hepatitis A, and for persons in high-risk groups, although some clinicians routinely vaccinate all HIV-infected persons regardless of HCV status [1a,1b]. For the asymptomatic patient with a CD4 cell count greater than 350 cells/mm^3, these vaccinations are administered before antiretroviral therapy (ART) initiation, with ongoing HIV viremia. Questions remain about the appropriate timing of vaccine administration with regard to current CD4 count, nadir CD4 count, level of HIV viremia, and administration of potent ART. If clinicians wait until the plasma HIV RNA levels are undetectable or for CD4 counts to increase for persons presenting late to care, many patients may be at risk for infection with these preventable pathogens. The issue is complicated by the fact that HIV-infected persons respond poorly to vaccinations, with seroprotection rates ranging from 18% to 56% for hepatitis B and 52% to 94% for hepatitis A vaccine compared with greater than 95% in HIV-seronegative adults. This article reviews recent literature regarding hepatitis vaccine responses, the role of immune reconstitution and HIV virologic suppression on these responses, and the use of hepatitis vaccines by practitioners.

Background

The underlying cause of the poor response to hepatitis vaccination in HIV-infected individuals remains intriguing. A successful vaccination requires the induction of long-lasting immunity [1]. Host and vaccine factors both are involved in this process of creating specific memory T and B cells. Vaccine factors include the dose of antigen, the persistence of that antigen, antigen structure, and tissue distribution of the antigen [2]. Host factors include activation of antigen-presenting cells (APCs), an adequate lymphocyte population to form specific

memory cells, the presence of appropriate cytokines, persistence of memory cells, and certain underlying genetic components, such as specific HLA haplotypes [3].

The depletion of T cells in HIV-infected persons yields impaired cellular immune function and T-cell–dependent processes such as vaccination against hepatitis A and B. HIV also induces dysregulation of B lymphocytes, with the development of elevated titers of nonfunctional immunoglobulins [4]. Furthermore, HIV-infected persons have poor APC function. Other immunosuppressed individuals with impaired cellular immunity also have reduced response to hepatitis B vaccination, including hemodialysis patients (40%–67% response), patients with cirrhosis (43% response), and stem cell transplant recipients (46% response) [5]. Clearly, there are significant implications to improving vaccine responses in all these immunocompromised populations.

The large proportion of patients who are coinfected with HCV further complicates the issue of hepatitis vaccinations. HCV-infected persons also respond poorly to hepatitis vaccines. Keeffe et al. [6] found that only 73% of HCV-infected persons responded to the first dose of hepatitis A virus (HAV) vaccine and antibody titers were significantly lower than those in healthy controls. Another study reported a 51% hepatitis B virus (HBV) vaccine seroconversion rate in HCV-infected subjects, which was significantly lower in both proportion and titers than the rate in seronegative individuals [7]. This is particularly relevant to consider for HIV/HCV-coinfected patients, for whom prevention of additional hepatitis viruses is important. Although we do not fully understand the mechanism behind the responses in coinfected persons, the AIDS Clinical Trial Unit has ongoing studies to evaluate the specific impairment associated with HIV/HCV coinfection.

Hepatitis A Vaccination

Although the clinical course of HAV infection is similar in HIV-infected and seronegative persons, acute HAV may lead to temporary discontinuation of ART, with rebound HIV viremia and possible development of antiretroviral drug resistance. Although the most recent Advisory Committee on Immunization Practices (ACIP) adult immunization schedule recommends HAV vaccination for persons with chronic liver disease, those requiring clotting factors, certain occupational risk groups, travelers to endemic areas, and persons with specific behavioral risk factors (eg, men who have sex with men [MSM] and injection drug users), it does not specifically recommend vaccination for all persons with HIV infection. Nevertheless, many providers offer HAV vaccination to their HAV-seronegative patients regardless of risk factors because of the possible complications of acute HAV and given the prevalence of HAV seropositivity in HIV-infected populations (> 20%) [8,9]. Two recent articles specifically evaluated the poor response rates in adult HIV-infected populations in the current highly active ART (HAART) era, and a third attempted to evaluate the role of immune reconstitution for HAV vaccine response.

In the first study, 334 HIV-infected patients who were seronegative for HAV antibody received HAV vaccination [9]. Of those vaccinated, 133 subjects (50%) developed protective antibody after vaccination. Two thirds of the cohort was receiving HAART at the time of vaccination. Although there was no difference among different CD4 cell count strata, responders had significantly lower HIV viral loads than nonresponders. By multivariate analysis, both low HIV viral load at time of vaccination and male gender were associated with a protective vaccine response. The second study evaluated HAV vaccine responses in 214 HIV-infected subjects with a seroconversion rate of 61% [10]. By univariate analysis, vaccine response correlated with the level of HIV viremia and current and nadir CD4 cell counts. By multivariate analysis, only higher current CD4 was associated with a response to vaccine.

Taken together, these studies confirm that response to HAV vaccine is less than optimal in HIV-infected persons and that immune status mediates the response, whether because of absolute number of CD4 cells or the level of HIV viremia. It is difficult to separate these interrelated factors. Clearly, the patient's immune status should be considered when vaccinating against HAV. The third recently published study, from the Pediatric AIDS Clinical Trials Group, attempted to address this very question [11•]. This study included 152 HAV-seronegative HIV-infected youth with a median age of 9.2 years (range, 2–21 years) who were on stable HAART with a baseline median CD4 count of 830 cells/mm^3 (median, 32%). After two vaccine doses, 97% of the subjects seroconverted, although only 53% were considered to have developed a high antibody titer (> 250 mIU/mL). A significantly higher proportion of subjects with high antibody response also had undetectable HIV viral loads. Of note, although seroconversion rates approached those of uninfected youth, the titers were lower in the HIV-infected subjects by a magnitude of approximately two. Because of this lower peak antibody production, titers waned to below the level of protection in 10% of HIV-infected children by 12 months after vaccination. Overall, this study confirms that control of viremia improves humoral responses to HAV vaccine. Whether the direct mechanism is mediated through absolute CD4 cell count, improved B-cell function, or reduction in viral loads remains to be fully elucidated. However, these studies suggest that in persons with low CD4 cell counts, HAV vaccination should be deferred until immune reconstitution has occurred with CD4 cell count increases to more than 200 cells/mm^3.

Hepatitis B

Approximately 350 million people worldwide and 1 million people in the United States are chronically infected with HBV [12]. Worldwide, this virus is the leading cause of chronic liver disease, including hepatitis, cirrhosis, and hepatocellular carcinoma. HBV accounts for 1 million to 2 million deaths annually [13]. HIV and HBV share routes of transmission, with 30% to 90% of HIV-positive patients having evidence of prior HBV infection and 10% with chronic infection [14]. Before the

introduction of HAART, the impact of HBV and liver disease was less prominent because of the natural history of HIV and the rapid progression to AIDS. However, with HAART, liver disease has become a leading cause of mortality [15].

HIV modulates the disease caused by HBV. The incidence of acute hepatitis is lower in coinfected patients, but chronic infection occurs more often in this population [16]. The latter point has been shown with decreased clearance of hepatitis B e antigen in HIV-infected patients when compared with that of HIV-negative patients (12% vs 49% clearance at 5 years) [17]. Furthermore, in prospective studies of MSM, coinfection with HIV and HBV was associated with a 15-fold increase in mortality when compared with HBV alone [18]. Additional data suggest that HBV accelerates the course of HIV infection; however, this finding has not been proven in larger epidemiologic studies [19,20].

Three recently published international studies confirm that HIV-infected persons do not respond optimally to HBV vaccination. Ungulkraiwit et al. [21] enrolled 65 HIV-infected subjects in a series of three injections with a double dose of HBV vaccine. Mean CD4 cell count at time of vaccination was 354 cells/mm^3; 88% of the cohort was receiving HAART, with 75% having an undetectable HIV viral load at time of vaccination. Unfortunately, only 46% of the vaccinees responded. Response rates correlated with younger age and higher CD4 counts. There was also a trend toward lower viral loads in responders. The second study evaluated responses in 55 subjects observed at a single site in Brazil using the higher dose of HBV vaccine [22]. Overall, 59% of the subjects responded, and response correlated with higher CD4 cell counts and lower HIV viral loads. The third study compared standard (10 μg) versus high (40 μg) doses of HBV vaccine in 79 HIV-infected individuals observed at a single site in Mexico [23]. Overall, 61% of the subjects responded, although there was no difference between the two arms. Mean CD4 counts were 225 and 245 cells/mm^3, respectively, and only 19% had undetectable HIV viral loads at time of vaccination.

Given that these studies confirm that our current approaches yield poor responses, researchers have looked for alternative strategies. A small study from Canada evaluated the use of four intradermal injections in 12 HIV-infected subjects who failed to respond to six doses of standard intramuscular vaccine [24]. By improving antigen presentation mediated through the Langerhans cells in the dermis, this strategy has yielded protection in nonresponding health care workers and dialysis patients. Unfortunately, only 6 of the 12 HIV-infected subjects responded, with one individual maintaining protective immunity at 12 months. Therefore, the intradermal route of administration does not appear to be an effective strategy.

A second alternative strategy that has been pursued to improve antibody responses is the use of adjuvants. The formulations of hepatitis vaccines that are currently approved by the Food and Drug Administration (FDA) are precipitated with alum (potassium aluminum sulfate) to form bulk vaccine adjuvanted with amorphous aluminum hydroxyphosphate sulfate or adsorbed onto the alum. These aluminum salts are currently the only adjuvants included in vaccines licensed by the FDA [25]. It is believed that the effective adjuvanticity of alum is a function of the degree of adsorption of antigen on the adjuvant, and this in turn is the basis of the depot theory. The aluminum adjuvants allow the slow release of antigen at the site of vaccine injection, prolonging the interaction between antigen and APCs and lymphocytes. Unfortunately, as noted above, HIV-infected persons do not respond adequately to the currently available alum-adsorbed vaccines. Therefore, other adjuvants are being evaluated.

One adjuvant that has shown promise in HIV-infected patients is CpG adjuvant, an oligodeoxynucleotide-containing immunostimulatory motif that directly activates B cells and plasmacytoid dendritic cells via toll-like receptors. Cooper et al. [26] recently presented data from a randomized controlled trial of 36 HIV-infected subjects receiving 40 μg of HBV vaccine with or without this adjuvant. Response was significantly greater in those receiving the novel adjuvant (94% vs 55%) at 36 months after vaccination. These data were particularly intriguing given that the rate of response was similar to that in historical controls. Confirmatory results are expected from larger studies.

Other possible adjuvants have been evaluated. Two recent meta-analyses have compiled data regarding the role of granulocyte-macrophage colony-stimulating factor (GM-CSF) on immune responses to HBV vaccine. The first meta-analysis identified 187 patients with end-stage renal disease from seven different prospective trials. The odds ratio of having a protective response rate was 4.63 (95% CI, 1.42–15.14) for those receiving adjuvant GM-CSF [27]. Cruciani et al. [28•] identified 734 subjects from 13 studies and also reported a benefit for GM-CSF, particularly in generating protection after the first dose of HBV vaccine.

This strategy has also been evaluated in HIV-infected subjects. Sasaki et al. [29] evaluated the efficacy of a single 20-μg dose of GM-CSF to augment response to double-dose HBV vaccine in 80 HIV-infected persons with CD4 cell counts greater than 350 cells/mm^3, 90% of whom were on HAART. A significant increase in the development of hepatitis B surface antibody (HBsAb) was noted in the GM-CSF group (62%) versus the placebo group (30%) after the second vaccine dose ($P < 0.0074$). One month after vaccination, 72% of the patients in the GM-CSF group and 60% in the placebo group developed protective titers that were significantly higher in the GM-CSF group (645 vs 375 IU/L; $P < 0.01$). These results suggest promise for the role of cytokines in augmenting immune response to vaccination in HIV-infected persons. The AIDS Clinical Trials Group has an ongoing study to evaluate the use of higher-dose GM-CSF. Data are expected by late 2008.

Issues with isolated hepatitis B core positivity

Screening for hepatitis serologies has become the standard of care for HIV care providers. As noted earlier, evidence of active or past coinfection with HBV is very common in HIV-infected patients. The pattern of hepatitis B surface antigen negative–hepatitis B core antibody (HBcAb) positive is commonly seen

in HIV-infected individuals. The question arises as to whether this reflects cleared infection in the distant past, occult HBV infection, or a false-positive HBcAb assay. For a patient who is currently receiving HAART with HBV activity, it may be difficult to discern the actual meaning of isolated HBcAb, although the presence of hepatitis B e antibody (HBeAb), detected by a serologic assay that is infrequently performed, can also confirm past infection; however, this test is not 100% reliable as the HBeAb may wane and disappear over time. Several recent studies evaluated this issue and assessed the utility of HBV vaccination for HIV-infected subjects with isolated HBcAb.

The University of Pennsylvania's Center for AIDS Research evaluated the prevalence of isolated HBcAb serology in their database and identified 699 (59%) of 1193 HIV-infected subjects with this pattern [30•]. To assess for occult HBV infection, 179 subjects were randomly selected to have stored serum sent for HBV DNA and 17 subjects (10%) were identified with occult infection. This number may actually underestimate the prevalence of occult HBV as 61% of HBV DNA–negative subjects were receiving more than one active agent against HBV. Detectable HIV viremia was associated with occult HBV, and the authors suggest that immune dysfunction may contribute to persistent low-level HBV replication. Of note, persons coinfected with HCV were less likely to have occult HBV, raising questions of either a false-positive result or the possible dominance of HCV over concomitant HBV infection.

Two additional studies also looked at the prevalence of this serologic pattern and its impact on HBV vaccination. Gandhi et al. [31•] evaluated vaccine responses in 69 subjects, 29 with isolated HBcAb and 40 with negative HBcAb. Isolated HBcAb serology was associated with HCV antibody positivity, male gender, white race, and elevated transaminases but not level of HIV viremia or CD4 cell count. An amnestic response to a single booster dose of HBV vaccine occurred in only 16% of subjects overall; this result did not differ between the groups. Interestingly, the 50% of subjects who were HBcAb positive–HBeAb positive had a significantly higher amnestic response than did isolated HBcAb–positive subjects (43% vs 7%, respectively). The authors suggested that the former pattern likely represents past infection and thereby enhanced the vaccine response. A second study from Thailand found 28 of 140 patients (20%) with isolated HBcAb [32]. Risk factors for this pattern again included HCV antibody positivity and history of intravenous drug use. Only 2 of the 28 subjects (7%) had an amnestic response to HBV vaccination.

A final study evaluated the perception of this serologic pattern among 40 HIV practitioners at a Chicago clinic with more than 4500 HIV-infected patients [33]. Of 3810 patients with complete HBV serology, 698 (18%) were found to have isolated HBcAb. Once again this pattern was more common in HCV antibody–positive than in HIV-monoinfected patients (36% vs 13%). The majority of providers (78%) believed this pattern to reflect past infection with resulting immunity. Only six providers (15%) reported routinely vaccinating patients with this serologic pattern.

The authors of the two vaccine studies recommended additional research to evaluate the appropriate vaccine strategy for this common serologic pattern. One approach at present is to check quantitative HBsAb 2 to 4 weeks after a single dose of HBV vaccine and if an amnestic response has not occurred, complete the three-dose series. Alternatively, one could vaccinate these patients with the three-dose series and then check the HBsAb titer. The latter approach may be more practical as the amnestic response was very poor in both studies and the additional vaccine doses will serve to boost immunity and yield higher protective HBsAb titers. Furthermore, having patients return for the 2- to 4-week visit may be impractical in the clinical setting.

Perceptions About Hepatitis Vaccination

In the current era of potent ART, providers must recognize the appropriate prevention measures for HIV-infected patients, whether those are age-appropriate cancer screenings or disease-preventing vaccines. Several recent studies evaluated the perceptions of patients and providers of hepatitis vaccination and provider utilization of hepatitis vaccines and illustrated that we need appropriate medical education regarding vaccine-preventable diseases.

Ho et al. [34] interviewed 144 HIV-infected subjects at a single site in Brazil regarding receipt of several recommended vaccines, including hepatitis B, influenza, pneumococcal, and diphtheria/tetanus. Brazil's National Immunization Program offers free vaccinations to all HIV-infected persons, thus removing any financial burden related to vaccine administration. Overall, the cohort had a mean CD4 count of 443 cells/mm^3 and 87% of the subjects were receiving ART, indicating that they were engaged in care. The subjects reported vaccine coverage as follows: 77% HBV vaccine, 55% pneumococcal vaccine, 36% diphtheria/tetanus vaccine, and 24% influenza vaccine in the past 3 years. Only 17% of the entire sample had received all appropriate vaccines.

A second study from the French Aquitaine cohort specifically evaluated patient and provider perceptions regarding HBV vaccination [35•]. Almost all the physicians (93%) reported being vaccinated against HBV, whereas only 113 of 512 patients (22%) reported HBV vaccination. One of four physicians reported that they did not routinely perform HBV serologic testing, and only 23% reported that they evaluated patients with post-vaccination serologic testing. Physicians reported the following reasons for failure to vaccinate: forgetting (78%), difficulty in identifying at-risk patients (44%), and concern regarding post-vaccination complications (32%). Notably, a large majority of the HIV-infected patients (82%) reported risk factors for HBV infection. Overall, vaccination coverage was suboptimal in this at-risk population, and the authors recommended developing educational campaigns for both patients and providers.

These reports on vaccination practices by HIV providers indicate that we are missing an opportunity to prevent these diseases. These issues are important not only for the individual patient but also from the public health perspective, because more universal vaccination could improve population immunity and assist in our progress toward elimination of hepatitis infections. Two recent studies of intravenous drug user (IVDU) populations in the United States and the United Kingdom illustrate that vigilant HBV immunization programs are needed to reduce HBV in those high-risk populations as well. In a cohort of 831 IVDUs in San Francisco, only 22% of subjects had evidence of vaccine-induced immunity whereas 56% were naïve for all HBV markers and 21% had evidence of past or chronic infection [36].

The UK study evaluated trends regarding HBV infection among 31,913 IVDUs from 1992, when universal HBV vaccination was recommended by the World Health Organization, through 2004 [37]. Rates of HBV infection were cut in half from 1992, when 50% of IVDUs tested were HBcAb positive, to 1999, when only 25% of those tested were HBcAb positive. Unfortunately, the rates subsequently increased slightly, particularly among young IVDUs. Although these data illustrate that the current UK vaccination program focusing on intravenous drug use as a risk factor has had a tremendous impact, there is still progress to be made in terms of education and promotion of hepatitis vaccination.

Conclusions

In the current ART era, we expect the life span of HIV-infected persons to approach that of those without HIV infection. Given this fact, addressing prevention issues is critical, whether we focus on cardiovascular risk factors or vaccine-preventable diseases. In the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, liver disease was the most common cause of mortality for HIV-infected persons other than AIDS-related deaths [38]. Surprisingly, at CD4 cell counts above 200 cells/mm^3, liver-related mortality was the single most important cause of death in this large cohort. Both HBV and HCV were significantly associated with increased mortality. These findings serve as a clear reminder of the importance of hepatitis prevention.

We recommend that all HIV-infected patients undergo hepatitis serology testing (HAV antibody total, HBV core antibody total, HBV surface antibody, HBV surface antigen, and HCV antibody) at baseline and then annually to monitor for incident infection. Given the concern for liver toxicity, we recommend vaccination against both hepatitis A and B for patients who are seronegative for these viruses, even for those who do not fall into traditional risk groups for HAV. Persons with isolated HBcAb should also be offered HBV vaccination as outlined previously.

The current ACIP guidelines recommend the use of higher-dose (40 μg) HBV vaccine for dialysis patients and other immunocompromised patients [39•]. The revised US Public Health Service guidelines for opportunistic infections explicitly urge providers to vaccinate patients who have CD4 cell counts above 350 cells/mm^3 as early as possible. For patients with more advanced disease, ART should be optimized to suppress HIV replication and increase CD4 cell counts to generate a better vaccine response.

To improve the likelihood of seroconversion, we recommend the current two-dose series of HAV vaccine and a three-dose series of HBV vaccine using the higher, 40-μg dosing used in dialysis patients. We do not recommend the use of Twinrix (GlaxoSmithKline, Research Triangle Park, NC), the combination HAV/HBV vaccine, given the lower doses of HAV antigen and HBV antigen in that vaccine. We recommend checking HBsAb and HAV antibody status after vaccination and then performing yearly quantitative HBV surface antibody assays. Patients who fail to develop protective antibody after completing the vaccine series may be offered a second vaccination series, although development of protection remains low and current strategies for these patients are inadequate. For a person whose titer wanes to below 10 IU/L, one should consider administering a booster vaccine, as recommended for dialysis patients [33]. The role of adjuvants and other immunomodulating agents to improve vaccine responses is currently under study, and we hope to report these findings in the near future.

Finally, it is clear that educational campaigns targeting HIV providers and HIV-infected patients need to be initiated to raise awareness. Along with education, vaccination campaigns in settings where this at-risk population can be reached can also help us progress toward the elimination of these vaccine-preventable diseases.

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References and Recommended Reading

Papers of particular interest, published recently,
have been highlighted as:

- • Of importance
- •• Of major importance

1a. Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK; CDC; National Institutes of Health; Infectious Diseases Society of America.
Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. MMWR Recomm Rep. 2004 Dec 17;53(RR-15):1-112. Erratum in: MMWR Morb Mortal Wkly Rep. 2005 Apr 1;54(12):311

1b. Aberg JA, Gallant JE, Anderson J, Oleske JM, Libman H, Currier JS, Stone VS and Kaplan JE. Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America. Clin Infect Dis 2004;39:609-629.

1. Hilleman MR: **Overview of the pathogenesis, prophylaxis, and therapeutics of viral hepatitis B, with focus on reduction to practical applications.** *Vaccine* 2001, **19:**1837–1848.
2. Campos M, Godson DL: **The effectiveness and limitations of immune memory: understanding protective immune responses.** *Int J Parasitol* 2003, **33:**655–661.
3. Egea E, Iglesia A, Salazar M, et al.: **The cellular basis for lack of antibody response to hepatitis B vaccine in humans.** *J Exp Med* 1991, **173:**531–538.
4. Lane HC, Masur H, Edgar LC, et al.: **Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome.** *N Engl J Med* 1983, **309:**453–458.
5. Idilman R, Colantoni A, De Maria N, et al.: **Impaired antibody response rates after high dose short interval hepatitis B virus vaccination of immunosuppressed individuals.** *Hepatogastroenterology* 2003, **50:**217–221.
6. Keeffe EB, Iwarson S, McMahon BJ, et al.: **Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease.** *Hepatology* 1998, **27:**881–886.
7. Wiedmann M, Liebert UG, Oesen U, et al.: **Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C.** *Hepatology* 2000, **31:**230–234.
8. Overton ET, Nurutdinova D, Sungkanuparph S, et al.: **Predictors of immunity after hepatitis A vaccination in HIV-infected persons.** *J Viral Hepat* 2007, **14:**189–193.
9. Tedaldi EM, Baker RK, Moorman AC, et al.: **Hepatitis A and B vaccination practices for ambulatory patients infected with HIV.** *Clin Infect Dis* 2004, **38:**1478–1484.
10. Rimland D, Guest JL: **Response to hepatitis A vaccine in HIV patients in the HAART era.** *AIDS* 2005, **19:**1702–1704.
11.• Weinberg A, Gona P, Nachman SA, et al.: **Antibody responses to hepatitis A virus vaccine in HIV-infected children with evidence of immunologic reconstitution while receiving highly active antiretroviral therapy.** *J Infect Dis* 2006, **193:**302–311.

This research article outlines the role of immune reconstitution, particularly control of HIV viremia, in the development of protective responses to HAV vaccine.

12. Lee W: **Hepatitis B virus infection.** *N Engl J Med* 1997, **337:**1733–1745.
13. Mahoney FJ: **Update on diagnosis, management, and prevention of hepatitis B virus infection.** *Clin Microbial Rev* 1999, **12:**351–366.
14. Homann C, Krogsgaard K, Pedersen C, et al.: **High incidence of hepatitis B infection and evolution of chronic hepatitis B infection in patients with advanced HIV infection.** *J Acquir Immune Defic Syndr* 1991, **4:**441–420.
15. Bica I, McGovern B, Dhar R, et al.: **Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection.** *Clin Infect Dis* 2001, **32:**492–497.
16. Bodsworth N, Cooper D, Donovan B: **The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state.** *J Infect Dis* 1991, **163:**1138–1140.
17. Gilson RJ, Hawkins AE, Beecham MR, et al.: **Interactions between HIV and hepatitis B in homosexual men: effects on the natural history of infection.** *AIDS* 1997, **11:**597–606.
18. Thio CL, Seaberg EC, Skolasdy R Jr, et al.: **HIV-1, hepatitis B, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS).** *Lancet* 2002, **360:**1921–1926.
19. Eskild A, Magnus P, Petersen G, et al.: **Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS.** *AIDS* 1992, **6:**571–574.
20. Solomon RE, Van Raden M, Kaslow RA, et al.: **Association of hepatitis B surface antigen and core antibody with acquisition and manifestations of HIV-1 infection.** *Am J Public Health* 1990, **80:**1475–1478.
21. Ungulkraiwit P, Jongjirawisan Y, Atamasirikul K, Sungkanuparph S: **Factors for predicting successful immune response to hepatitis B vaccination in HIV-1 infected patients.** *Southeast Asian J Trop Med Public Health.* 2007, **38:**680–685.
22. Veiga AP, Casseb J, Duarte AJ: **Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naïve) and CD45RO+ (memory) subsets in HIV-1-infected subjects.** *Vaccine* 2006, **24:**7124–7128.
23. Cornejo-Juarez P, Volkow-Fernandez P, Escobedo-Lopez K: **Randomized controlled trial of hepatitis B virus vaccine in HIV-1-infected patients comparing two different doses.** *AIDS Res Ther* 2006, **6:**3–9.
24. Shafran SD, Mashinter LD, Lindemulder A, et al.: **Poor efficacy of intradermal administration of recombinant hepatitis B virus immunization in HIV-infected individuals who fail to respond to intramuscular administration of hepatitis B virus vaccine.** *HIV Med* 2007, **8:**295–299.
25. Baylor NW, Egan W, Richman P: **Aluminum salts in vaccines—US perspective.** *Vaccine* 2002, **20:**S18–S23.
26. Cooper C, Angel J, Seguin I, et al.: **CpG adjuvant + HBV vaccination in HIV infection achieves long-term seroprotection for as long as 5 years [abstract 134].** *Proceedings of the 14th Conference on Retroviruses and Opportunistic Infections.* Los Angeles; February 25–28, 2007.
27. Fabrizi F, Ganeshan SV, Dixit V, Martin P: **Meta-analysis: the adjuvant role of granulocyte macrophage-colony stimulating factor on immunological response to hepatitis B virus vaccine in end-stage renal disease.** *Aliment Pharmacol Ther* 2006, **24:**789–796.
28.• Cruciani M, Mengoli C, Serpelloni G, et al.: **Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis.** *Vaccine* 2007, **25:**709–718.

This article outlines the mechanisms by which GM-CSF improves vaccine response and reviews 13 studies evaluating this adjuvant for HBV vaccination in diverse populations.

29. Sasaki M, Foccacia R, deMessias-Reason IJ: **Efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) as a vaccine adjuvant for hepatitis B virus in patients with HIV infection.** *Vaccine* 2003, **21:**4545–4549.
30.• Re VL 3rd, Frank I, Gross R, et al.: **Prevalence, risk factors, and outcomes for occult hepatitis B virus infection among HIV-infected patients.** *J Acquir Immune Defic Syndr* 2007, **44:**315–320.

This article outlines the prevalence of occult HBV infection among HIV-infected populations and illustrates the importance of evaluating for hepatitis coinfection.

31.• Gandhi RT, Wurcel A, Lee H, et al.: **Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies.** *J Infect Dis* 2005, **191:**1435–1441.

This article reemphasizes the need for ongoing surveillance for coinfection for hepatitis viruses and the importance of offering HBV vaccination to patients with isolated HBcAb.

32. Jongjirawisan Y, Ungulkraiwit P, Sungkanuparph S: **Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response.** *J Med Assoc Thai* 2006, **89:**2028–2034.
33. Thomas-Gosain N, Adeyemi OM: **Perceived significance of isolated HBcAb in patients with HIV: a survey of practitioners.** *AIDS Patient Care STDS* 2007, **21:**385–389.
34. Ho YL, Enohata T, Lopes MH, et al.: **Vaccination in Brazilian HIV-infected adults: a cross-sectional study.** *AIDS Patient Care STDS* 2007 Dec 20 (Epub ahead of print).
35.• Winnock M, Neau D, Castera L, et al.: **Hepatitis B vaccination in HIV-infected patients: a survey of physicians and patients participating in the Aquitaine cohort.** *Gastroenterol Clin Biol* 2006, **30:**189–195.

This article delineates provider biases and concerns related to vaccine administration among HIV care providers.

36. Lum PJ, Hahn JA, Shafer KP, et al.: **Hepatitis B virus infection and immunization status in a new generation of injection drug users in San Francisco.** *J Viral Hepat* 2008, **15:**229–236.
37. Judd A, Hickman M, Hope VD, et al.: **Twenty years of selective hepatitis B vaccination: is hepatitis B declining among injecting drug users in England and Wales?** *J Viral Hepat* 2007, **14:**584–591.
38. Weber R, Sabin CA, Friis-Møller N, et al.: **Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study.** *Arch Intern Med* 2006, **166:**1632–1641.
39.• Centers for Disease Control and Prevention: **Recommended adult immunization schedule—United States, October 2007–September 2008.** *MMWR Morb Mortal Wkly Rep* 2007, **56:**Q1–Q4.

A concise reference to appropriate vaccines for adults, with specific recommendations for HIV-infected persons.

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