Annals of Pharmacotherapy
47(12) 1712–1716

DOI: 10.1177/1060028013507901
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Booster and Higher Antigen Doses of Inactivated Influenza Vaccine in HIV-Infected Patients

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Abstract

Objective: To review the literature regarding booster or higher doses of influenza antigen for increasing immunogenicity of inactivated influenza vaccine (IIV) in HIV-infected patients. **Data Sources:** MEDLINE (1966 to September 2013) was searched using the terms *immunize, influenza, vaccine*, and *HIV* or *AIDS* in combination with *two-dose, booster-dose, increased antigen*, or *high-dose*. One trial of booster dosing with standard doses (SDs) of IIV, trivalent (IIV3); 2 trials of booster dosing with intermediate doses (ID) of H1N1 IIV or IIV3; and 1 trial of high-dose (HD) IIV3 were identified. **Study Selection and Data Extraction:** Trials administering 2-dose, booster-dose, or increased antigen of influenza vaccine to patients with HIV were reviewed. Because adjuvanted IIV is not available and IIV, quadrivalent was recently approved in the United States, studies evaluating these vaccines were excluded. **Data Synthesis:** HIV-infected individuals are at high risk for influenza-related complications; however, vaccination with SD IIV may not confer optimal protection. It has been postulated that booster or higher doses of influenza antigen may lead to increased immunogenicity. When ID and SD or ID with boosters were evaluated in HIV-infected patients, significant increases in surrogate markers for influenza protection were not achieved. However, HD IIV3 did result in significant increases in seroprotective antibody levels, though 'clinical' influenza was not evaluated. **Conclusions:** Currently, evidence is insufficient to reach conclusions about the efficacy of booster dosing, ID, or HD influenza vaccine in HIV-infected patients..Trials evaluating booster or higher-antigen doses of IIV for 'clinical' influenza are necessary before routinely recommending for HIV-infected patients.

Keywords

immunize, influenza, vaccine, booster, increased antigen, high dose, HIV

Request

Should individuals infected with HIV receive higher doses of the influenza vaccine antigen to improve immunogenicity from the vaccine?

Response

Background

The Centers for Disease Control (CDC) classifies individuals infected with HIV/AIDS as a high-risk group for developing influenza complications (eg, pneumonia, bronchitis, and sinus and ear infections).[1] Before the use of antiretroviral therapy (ART) with at least three antiretroviral (ARV) drugs, clinical trials reported that individuals infected with HIV may also experience prolonged influenza-related symptoms and increased hospitalizations and mortality when compared with the general population.[2-4] In the more recent ART era, a 53% reduction in cardiopulmonary hospitalization rates was shown during the influenza season in HIV-infected patients; however, hospitalization rates were similar to those of other high-risk influenza populations (eg, elderly or pregnant women).[3] Because of the seriousness of these complications, the CDC's Advisory Committee on Immunization Practices recommend that all persons 6

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months of age or older receive routine annual vaccination with the influenza vaccine to prevent the occurrence of influenza illness.[5]

Immunogenicity against influenza is defined using geometric mean titer (GMT) and seroconversion rates of either a prevaccination hemagglutination inhibition (HAI) antibody titer <1:10 and a postvaccination HAI antibody titer >1:40 or a prevaccination HAI antibody titer >1:10 and a minimum 4-fold rise in postvaccination HAI antibody titer. Moreover, titers ≥1:40 are considered seroprotective from influenza illness.[6,7] It has been reported that when healthy individuals are vaccinated with the inactivated influenza vaccine, trivalent (IIV3), a 70% to 90% protective efficacy is achieved.[8] Although data are mixed, a number of trials have reported "blunted" antibody responses to IIV3 in patients with HIV as compared with uninfected patients.[9-12] Moreover, when HIV-infected patients were vaccinated with the H1N1 influenza vaccine, nearly 40% of patients did not achieve a protective titer.[13] Reasons for decreased antibody responses to the IIV3 in HIV-infected patients are not fully understood; however, it has been reported that the 2 main predictors for achieving an optimal influenza vaccine response may be higher CD4 cell counts (≥200 cells/μL) and undetectable viral loads (<50 copies/mL).[12,14,15] It is known that the humoral immune response to IIV3 is primarily T-cell mediated. Because HIV attacks CD4 helper T-cells and causes a reduction in the number of functional T-cells, an adequate response to the IIV3 may not be mounted, particularly in those with very low CD4 counts or high viral loads.[14] To overcome this blunted response, researchers have hypothesized that administering higher antigen doses of influenza vaccine may improve immunogenicity and, ultimately, prevent clinical influenza and complications in this patient population. This review focuses on evaluating evidence for using higher influenza antigen doses in patients with HIV. Adjuvant IIV3 is not available and IIV quadrivalent is newly approved in the United States; therefore, they are not discussed in this article.

Literature Review

A literature search of MEDLINE (1966 to September 2013) was conducted using the search terms *immunize, influenza, vaccine*, and *HIV* or *AIDS* in combination with *two-dose, booster dose, increased antigen*, or *high dose* (HD). Limits were set for clinical trials, English-language, and humans. This search resulted in 1 trial of booster dosing with standard doses (SDs) of IIV3, 2 trials of booster dosing with intermediate doses (IDs) of H1N1 IIV or IIV3, and 1 trial of HD IIV3.

Boosting With SD

Miotti et al[16] first evaluated the effect of a 2-dose regimen of SD IIV3 on antibody response in HIV-seropositive patients as compared with HIV-seronegative patients in a prospective, nonrandomized, single-arm design. Of the 109 patients enrolled, 31 were HIV-seronegative men, 32 were asymptomatic HIV-seropositive men, and 46 were HIV-seropositive men with AIDS or AIDS-related complex. All participants received 2 doses of SD IIV3 (15 μg of hemagglutinin [HA] per strain) at 1-month intervals during peak influenza season (November-February). The primary end point was seroconversion. Among HIV-seronegative patients, the frequency of seroconversion for each of the 2 influenza A vaccine antigens varied from 55% to 75% after the first immunization and increased only marginally (from 73% to 80%) following the booster dose. Similarly, the rate of seroconversion for influenza B vaccine antigen ranged from 60% to 64% after the first immunization and from 65% to 73% after the booster dose. Among HIV-seropositive patients, 78% to 84% of asymptomatic patients achieved seroconversion for each influenza A vaccine antigen following the first immunization, compared with 67% to 78% of those with AIDS-related complex and 32% to 38% of those with AIDS. After booster vaccination, seroconversion was obtained by only 1 additional participant with asymptomatic HIV, no participant with AIDS-related complex, and by 4 additional participants with AIDS. Although the study failed to show an improvement in seroconversion to IIV3 booster vaccination, it did confirm that patients with HIV have a suboptimal serologic response following immunization with IIV3 as compared with HIV-negative patients. Additionally, it was observed that the CD4 count prior to immunization was independently related to antibody titers achieved following booster immunization ($P < .03$).[16] Limitations of this study include enrollment of only men and the inability to perform hypothesis testing among groups before and after booster immunization. Furthermore, this study was conducted prior to optimal combination ARV use, which limits its generalizability and application to most patients today.

Boosting With IDs

The efficacy of ID IIV3 (30 μg of HA per strain) and the administration of a vaccine booster dose were evaluated in a multicenter, double-blind, randomized controlled trial of 298 HIV-positive volunteers.[17] Participants were otherwise healthy, mostly male (90%), and on ART (89%), with 76% having HIV RNA levels below detection (<50 copies/mL) and a median CD4 count of 470 cells/μL (9% with CD4 <200 cells/μL). Participants were stratified by CD4 count (<200 cells/μL vs ≥200 cells/μL) and randomized to 1 of 3 treatment groups: SD IIV3 (15 μg of HA per strain) followed by SD IIV3 booster dose 28 days later, ID IIV3 (30 μg of HA per strain) followed by a ID IIV3 booster 28 days later, or SD IIV3 with no booster dose. The primary outcome was defined as the proportion of participants achieving doubling of serum HAI antibody titers from baseline at

week 8. The proportion of patients achieving seroconversion at weeks 4, 8, and 20 was also assessed. Secondary outcomes included self-reported influenza-like illness and PCR-confirmed influenza. Although the overall vaccine immunogenicity observed in this study was poorer than expected, the administration of a SD IIV3 plus booster dose as compared with a single SD IIV3 increased the proportion of those achieving a doubling of HIA titers for strain B/Florida at week 8 (50% vs 35%, $P = .04$) and week 20 (38% vs 23%, $P = .03$). However, a SD IIV3 plus booster dose did not increase the proportion of participants achieving seroconversion at weeks 8 or 20 as compared with a single SD IIV3. Administration of ID IIV3 plus booster as compared with a single SD IIV3 increased the proportion of those achieving a doubling of HIA titers at week 8 for strain A/Brisbane (61% vs 44%, $P = .02$) and B/Florida (50% vs 35%, $P = .03$) and at week 20 for A/Brisbane (47% vs 31%, $P = .02$). Those who received ID IIV3 plus booster also had significantly higher rates of seroconversion than those receiving a single SD IIV3 for strain A/Brisbane at week 8 (37% vs 20%, $P = .01$). Rates of self-reported influenza-like illness and PCR-confirmed influenza were similar between all 3 groups. Thus, the use of SD IIV3 booster or ID IIV3 booster only marginally and inconsistently improved immunogenicity to the 3 strains within the IIV3, with little clinical improvement observed. It is interesting to note that when looking at subgroup analyses, increased immunogenicity with increased antigen dose and booster dosing was most evident when participants had an unsuppressed HIV RNA at baseline. When controlled for by baseline HIV RNA and other possible confounders, CD4 count was not a predictor of immunogenicity.[15] Limitations to this study exist. It primarily enrolled men, only had 9% of patients with a CD4 count <200 cells/μL, had fewer cases of influenza illness than expected in the general population for the influenza season, and used self-reporting, which makes it difficult to generalize and fully evaluate the effects of alternative vaccination strategies in this population.

The immunogenicity of 1 or 2 doses of either SD or ID H1N1 IIV was evaluated in a multicenter, open-label, randomized trial of 192 HIV-infected individuals who received the 2009-2010 IIV3 at least 2 weeks before enrollment.[18] Participants were medically stable and mostly men (79%) on ART (89%), with 61% having HIV RNA below detection levels. Participants were stratified by CD4 count (<200 cells/μL vs ≥200 cells/μL) and randomized to receive 2 doses of single-strain vaccine, 15 μg HA or 30 μg HA, 21 days apart. The primary end point was HAI GMTs on days 10, 21, 31, 42, and 201. The proportion achieving HAI seroconversion and seroprotection was also assessed. Recipients of the 30-μg HA vaccine had significantly higher HAI GMTs compared with those receiving 15-μg HA on days 10 (139.0 vs 51.9, $P = .01$), 21 (106.7 vs 51.9, $P = .001$), and 31 (130.0 vs 73.7, $P = .03$), but not on days 42 (91.8 vs 61.6, $P = .11$) or 201 (43.0 vs 27.0, $P = .08$). Rates of HAI seroconversion were significantly higher in the 30-μg HA group on days 10 (70.7% vs 48.9%, $P = .03$), 21 (68.5% vs 47.8%, $P = .007$), 31 (71.1% vs 52.8%, $P = .01$), and 201 (46.0% vs 28.7%, $P = .03$). Furthermore, HAI seroprotection was higher at all time periods for individuals vaccinated with the 30-μg HA vaccine as compared with the 15-μg HA vaccine, but statistical significance was only achieved on days 10 (75% vs 59.6%, $P = .03$), 21 (72.8% vs 57.6%, $P = .04$), and 201 (58.6% vs 42.5%, $P = .048$). When evaluating only those with CD4 count <200 cells/μL, more participants in the 30-μg HA group achieved seroconversion than those in the 15-μg HA group on day 31 (69.7% vs 44.1%, $P < .05$) but not at the other time points. As evidenced by the statistical significance between groups at the early time points but not at later evaluations, a second dose of vaccine did not result in a significant increase in GMTs, seroconversion, or seroprotection. However, an increased antigen dose did result in an improved immune response, even among those with CD4 count <200 cells/μL.[18] Although this study failed to collect clinical outcomes data, it did include a larger proportion (37%) of patients with CD4 count <200 cells/μL and indicates that an increased dose of antigen may have some benefit in patients with more advanced disease.

HD Influenza Vaccine

The efficacy of HD IIV3 in HIV-positive patients was first evaluated in a single-center, double-blind, randomized controlled trial enrolling 195 participants.[19] Participants were mostly men (70%) on ART (91%), with 79% having HIV RNA levels below detection (<50 copies/mL), and only 11% with CD4 <200 cells/μL. Participants were vaccinated with either SD IIV3 (15 μg HA per strain) or HD IIV3 (60 μg HA per strain). The primary end point was the proportion of patients with seroprotective antibody levels at 21 to 28 days after vaccination. Secondary end points included rate of seroconversion and HAI GMTs before and after receiving the vaccine. At days 21 to 28 following vaccination, significantly more recipients of HD IIV3 had seroprotective titers as compared with those who received the SD IIV3 for strain A/California/7 (96% vs 87%, $P = .029$) and strain B (91% vs 80%, $P = .03$). Rates of seroconversion for strain A/California/7 (75% vs 59%, $P = .018$) and strain B (56% vs 34%, $P = .003$) were also significantly higher in participants who received HD IIV3. Although improved immunogenicity was also seen for strain A/Victoria/210, the differences were not statistically significant. Postvaccination HAI GMTs, however, were significantly higher in patients who received HD IIV3 as compared with those who received SD IIV3 for all 3 strains. This study demonstrated that a quadruple dose (60 μg HA per strain) significantly improved immunogenicity of the IIV3 among patients with HIV.[19] However, this study is limited by the

use of surrogate outcomes because rates of clinical influenza between groups were not assessed. Furthermore, half of the participants had seroprotective titers at baseline, perhaps a result of the 2009-2010 H1N1 influenza pandemic or possibly because of an increase in vaccination rates among the participants. The rates of baseline seroprotectivity were similar between groups, but it is unknown how these high baseline titers may have influenced the results. Finally, this study included very few patients with advanced HIV (low CD4 count or ongoing HIV viremia); thus, it is unknown if the improved immunogenicity would occur in patients at the greatest risk for significant morbidity and mortality from influenza.

Discussion

Evidence evaluating different strategies to improve immunogenicity to the IIV in HIV-infected patients is conflicting. In clinical trials, when ID, and ID or SD with booster strategies were evaluated, significant increases in surrogate markers for influenza protection were not consistently achieved.[16-18] However, vaccination of HIV-infected patients with HD IIV3 did result in significant increases in seroprotective antibody levels.[19] Yet it is important to remember that seroprotective antibody levels are only measures of immunogenicity and do not necessarily translate into protection from 'clinical' influenza disease. Recently, initial results for the first completed efficacy study for HD IIV3 in elderly individuals were released and reported that HD IIV3 was 24.2% more effective in preventing clinical influenza in those 65 years of age and older than SD IIV3.[20] At this time, it remains to be seen if these results can be replicated in other high-risk groups—specifically, HIV-infected patients.

The initial trial was conducted prior to the optimal use ART; thus, its results are no longer generalizable.[16] All patients enrolled in the other trials were HIV positive, nonetheless, the severity of disease sometimes differed, and the number of patients with CD4 counts <200 cells/μL or ongoing HIV viremia was often low.[17-19] In these trials, a number of surrogate end points were evaluated (ie, HAI GMTs, seroconversion, and seroprotection), which makes it difficult to compare vaccine strategies across trials. Furthermore, different influenza strains were administered in each of the trials because the seasonal influenza vaccine generally changes annually. Finally, in 1 study because of the H1N1 influenza epidemic, only a single A strain of vaccine was evaluated.[16-18]

Summary

Individuals with HIV are considered to be at high risk for developing influenza complications. It has been suggested that HIV-infected persons are not able to achieve adequate antibody responses to achieve protection when vaccinated with IIV. Four published studies evaluated different dose strategies for influenza vaccination. Unfortunately, results of trials evaluating ID and SD or ID with booster strategies have not consistently shown significant increases in surrogate markers for influenza protection. However, in the most recently published study, vaccination of HIV-infected patients with HD IIV3 did result in significant increases in immunogenicity, though rates of clinical influenza were not evaluated. At this time, evidence is insufficient to reach conclusions about the efficacy of booster dosing, ID, or HD influenza vaccine in patients with HIV/AIDS. Larger efficacy trials that are designed to compare different dose strategies of IIV on 'clinical' influenza in populations by CD4 count and viral load are necessary before booster or higher antigen doses of IIV can be routinely recommended for vaccinating HIV-infected patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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