Sometimes, More Is Better

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(See the article by El Sahly et al, on pages 703–12.)

Influenza causes significant morbidity and mortality with an estimated 36 000 attributable deaths in the United States annually [1]. Human immunodeficiency virus (HIV) infection, specifically, advanced disease (CD4 count <200 cells/μL), has been associated with excess morbidity and mortality [2]. With the use of combination antiretroviral therapy (cART), hospitalization rates due to influenza among HIV-infected persons declined 10-fold [3]. Although these data highlight the striking beneficial effects of cART, this rate of hospitalization remains similar to that in elderly adults and other high-risk groups. In the current era, respiratory viral pathogens, particularly influenza, cause significant morbidity for HIV-infected individuals [4, 5]. This finding is particularly striking given that one of these studies reported that 76% of the subjects had received annual influenza vaccination [6]. These observations highlight 2 key issues for current HIV care: (1) HIV-infected persons engaged in care are often on cART and more likely to experience usual pathogens rather than classic opportunistic infections, and (2) despite effective cART, preventative vaccines are not as effective as we would like. Important questions arise: How can we improve the efficacy of preventative vaccines for this immunocompromised population? Will higher antigen dose vaccines yield better protection?

For influenza, these questions are particularly relevant given that timely vaccine administration is an important preventive measure in the general population [7]. Unfortunately, current formulations of influenza vaccines are not uniformly protective. Although healthy children and young adults develop sufficient neutralizing antibodies 90% of the time, certain populations at greatest risk for severe influenza (the immunocompromised, elderly adults, and infants) have significantly lower seroprotection rates after influenza vaccination [8–10]. This variability suggests an underlying inconsistency in the process of generation of immunity across populations and has been previously demonstrated among HIV-infected persons [11]. Nevertheless, a recent meta-analysis demonstrated that influenza vaccine provided a 66% relative risk reduction for the development of influenza illness among HIV-infected individuals [12]. Hence, current guidelines recommend routine vaccination of all HIV-infected persons [13].

Despite clear benefit, how can we improve the immune response in this population? Influenza vaccines induce a T cell–dependent process that leads to the propagation of effective humoral immunity [14]. The depletion of T-helper cells in HIV infection serves as an extreme example of how vaccination can fail because of inadequate T-cell signaling. Different strategies can be used to improve the immune response: increasing the amount of antigen in the vaccine, increasing the number of doses of the vaccine (ie, booster vaccination), giving an adjuvant with the vaccine, alternative routes of vaccination, and stimulating the immune system with a different vaccine strategy such as a DNA prime-protein boost approach. Increasing antigen quantity can lead to a more robust response by improving dendritic cell uptake and subsequent signaling of B and T cells [15].

In this issue of the *Journal of Infectious Diseases*, El Sahly et al [16] present data on 2 strategies to overcome the poor response to influenza vaccine in HIV-infected persons: increased antigen and booster vaccination. By capitalizing on the emergence of the pandemic H1N1 strain in 2009, the authors evaluated the immunogenicity of the vaccine with limited impact of preexisting immunity. Furthermore, the authors stratified participants on the basis of CD4 cell counts at baseline to assess the immunogenicity of these strategies in individuals at greatest risk for complications of influenza infection, persons with CD4 cell

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count <200 cells/μL. Finally, the data on extended follow-up provide an opportunity to better characterize waning antibody responses in HIV-infected individuals.

Approximately 1 in 5 persons included in the study had baseline immunity against pH1N1 as evidenced by hemagglutination inhibition (HAI) titer >40 at baseline. This likely reflects the fact that pH1N1 circulated for months before the vaccine was available. Regardless, there was clear benefit from the higher antigen dose (30 μg) at the day 21 time point for geometrical mean titers (GMTs) for both HAI and microneutralization (MN) assays, seroconversion for both HAI and MN assays, and seroprotection rates for HAI but not MN assays. There did not appear to be an advantage to administration of the second dose of vaccine for either dose administered, given that there was little increase in the GMTs or rates of seroconversion or seroprotection beyond the level achieved at day 21. However, in light of the fact that all persons received 2 doses of vaccine, it is plausible that the second dose improved the durability of seroprotection with maintenance of higher GMTs. The most striking effect was demonstrated in the improved GMT with higher antigen dose in the group with CD4 cell counts <200 cells/μL, representative of patients for whom influenza morbidity and mortality are of most concern. Given that this stratum was underpowered because of difficulty with enrollment, the data are very convincing and indicate clear benefit to increasing the antigen dose for improved immunogenicity.

The study also addressed several key safety concerns. Although common local and systemic mild reactions were identified, there were no severe or serious adverse events associated with the administration of vaccine at either antigen dose during the study (even among persons with detectable HIV viremia at baseline). Importantly, there were no adverse effects on CD4 counts or plasma HIV loads during the study. These latter points are important, as there has been a bias among providers to avoid vaccination among HIV-infected persons with low CD4 counts and detectable HIV viremia because of concern for progression of disease or perception of futility with severe immunosuppression. Although persons with lower CD4 cell counts and detectable viremia have more modest responses, vaccination itself does not pose increased risk.

Several other groups have evaluated the monovalent 15-μg H1N1 vaccine in HIV-infected individuals [17–19]. Taken together, the data corroborate the findings presented by El Sahly et al [16] in that GMTs and seroconversion rates are more robust in individuals with CD4 counts >200 cells/μL compared with those with lower CD4 cell counts. Two of these studies illustrate that HIV-infected persons fail to achieve antibody levels comparable to healthy controls with the standard 15-μg dose. The data demonstrate that lower antigen content in the vaccine is inadequate, particularly for persons with low CD4 cell counts. The current study shows that higher antigen content improved responses regardless of baseline CD4 cell count. A recent study from the Canadian HIV Trials Network reported a similar trend toward improved responses with higher antigen content, although the effect failed to approximate that reported in healthy individuals [20].

The current study also adds to our understanding regarding durability of vaccine responses among this population. Six months after administration of the second vaccine dose, immune responses were improved with higher antigen dose. The data demonstrating that nearly 60% of patients in both the low and high CD4 strata maintain seroprotection by HAI titers and >60% maintain seroprotection by MN titers at this time are reassuring. Unfortunately, one cannot discern which component of the vaccine regimen was more important: higher antigen dose or booster vaccination. Although the pH1N1 virus provided a unique opportunity to explore these issues, we can continue to evaluate alternative strategies for influenza vaccination. For example, Tebas et al have performed a study evaluating the 2010 trivalent influenza vaccine, using standard dose (15 μg) vs high dose (60 μg) and found that GMTs and seroprotection rates are significantly improved with the high dose [21].

It is particularly relevant to determine whether a single high dose is as effective as multiple doses, given that there are challenges to timely administration of the influenza vaccine. For example, the HIV Outpatient Study investigators have explored rates of influenza vaccination from 1999 to 2008 [22]. Despite clear recommendations that all HIV-infected persons receive annual influenza vaccination [13], only 35% of the cohort received influenza vaccination in any given year, despite 4–6 annual clinic visits. The authors reported that receipt of vaccine was independently associated with being on cART and having an undetectable plasma HIV load. These findings suggest that significant biases continue to inform HIV providers regarding influenza vaccination. Two of the most relevant of these biases are addressed in the current study: (1) the vaccine is poorly immunogenic, and (2) there are potential negative consequences of vaccination with respect to HIV disease course. The limited impact of vaccination on CD4 counts and plasma HIV loads in the present study confirms safety data from numerous other vaccine studies among HIV-infected persons. More importantly, higher antigen dosing of influenza vaccine improved immune responses to the vaccine. These findings affirm that higher antigen content is warranted for influenza vaccine in HIV-infected individuals, as approved by the Food and Drug Administration for elderly persons in 2009 [23, 24].

In conclusion, more influenza vaccine antigen is better but likely not optimal

for HIV-infected persons. Additional research is needed to determine which alternative vaccination strategies will provide similar immune responses to those reported in healthy uninfected adults. Future studies will inform preventative vaccination efforts so that we are appropriately prepared for the next severe pandemic.

Notes

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