Adverse Reactions of Trivalent Influenza Vaccine in HIV-Infected Individuals

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Abstract- In this study, we assessed the adverse reactions to influenza vaccination in HIV- infected individuals. From November 2006 to January 2007, a total of 203 HIV-infected persons were recruited. Demographic data were collected. Subjects were evaluated 48 h and 15 days after vaccination for symptoms and significant health events as possible side effects. Participants were instructed to measure their temperature in the morning and evening for 2 days post-immunization and to assess injection site and systemic adverse reactions. 80.3% of the subjects were male. The mean age of the subjects was 36.9±7.9 years. Local and systemic reactions were reported by 61 (30%) and 62 (30.5%) persons, respectively. The most common adverse reactions to the influenza vaccine included skin redness (37 cases), induration (32 cases), and pain (55 cases) as local reactions, and fever (22 cases), myalgia (46 cases), headache (12 cases) and weakness (35 cases) as general reactions. 1.4 % of the subjects had fever over 38.5 ºC. There were significant associations between myalgia and flushing with CD4 counts ($P<0.05$). We found no relationship between adverse reactions and sex, history of smoking, allergy, alcohol, and drug usage, stage of HIV infection, anti-retroviral therapies, anti-TB medication and previous vaccination. We concluded that inactivated influenza vaccine administered in HIV-infected adults did not result in potential adverse events in this study population.

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Introduction

Influenza is an acute respiratory illness caused by infection with influenza virus, and outbreaks of the illness of variable severity occur nearly every year. Influenza results in considerable morbidity in the general population and increased mortality rates among certain high-risk patients such as those affected by chronic cardiovascular and/or pulmonary diseases and immunosuppressed individuals, such as the HIV-1-infected (1, 2).

Influenza vaccines are the cornerstone of medical interventions aimed at protecting individuals against epidemic influenza. The efficacy of influenza vaccines in HIV infected individuals remains poorly defined. Theoretical safety concerns stem primarily from transient increases in HIV viral loads following influenza vaccination observed in some studies (3-9), although the clinical significance of this phenomenon is unclear. Furthermore, the efficacy of influenza vaccines may be compromised by reduced antibody responses observed in some HIV infected individuals (3, 10-15). Despite these issues, the US Center for Disease Control and Prevention (CDC) recommends influenza vaccines in HIV-infected individuals (16). The general recommendations for influenza vaccination in HIV-infected population are to vaccinate annually with trivalent inactivated vaccine regardless of CD4+ cell count or HIV RNA level (17, 18). Live, attenuated, trivalent vaccine is contraindicated in HIV-infected patients.

In this study, we assessed the adverse reactions to influenza vaccination in HIV- infected individuals.

Patients and Methods

Study population

This study was a prospective study of the frequency of adverse reactions of influenza vaccination in HIV-infected individuals. From November 2006 to January

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2007, a total of 203 HIV-infected persons were recruited. Subjects with hypersensitivity to egg products, a history of Guillain-Barre syndrome, underlying chronic diseases, previous serious reaction to influenza vaccine, an influenza vaccination within the preceding six months, a febrile illness (temperature ≥38.0°C) within 24 hours before enrollment, or any other condition that in the opinion of the investigator might put a patient at risk or interfere with his or her participation in the study, were excluded from the study group. The study protocol was reviewed and approved by the Institutional Review Board of Tehran University of Medical Sciences.

Demographic data along with information on history of smoking and allergy, type of allergy, history of alcohol and drug addiction, occupation, marital status, previous influenza vaccination, anti-retroviral and anti-TB medication, and HIV risk factors were collected for all participants.

CD4 cell counts were also determined for all of the HIV patients. A written informed consent was provided to each subject.

Vaccination regimen

Influenza virus subunit vaccines inactivated with formaldehyde that were used during the study were manufactured by Solvay Pharmaceuticals (Netherlands). Vaccination was done once. The dosage per inoculation was 0.5 ml for each subject given as a deep subcutaneous or intramuscular injection into the deltoid muscle. The vaccine contained A and B strains from the component strains A/New caledonia/20/99 (H1N1)-like strain, A/Wisconsin/67/2005/(H3N2)-like strain and B /Malaysia /2506/2004-like strain propagated in embryonated hen's eggs.

Safety assessment

Participants were instructed to measure their temperature in the morning and evening for 2 days post-immunization and to assess injection site adverse reactions (redness, swelling, tenderness, limited arm movement) and systemic adverse reactions (such as headache, muscle aches, nausea, vomiting).

Adverse reactions were monitored by investigators during the fifteen days following vaccination. An adverse reaction was defined as pain, erythema, or induration at the vaccination site, fever, nausea, vomiting, weakness, myalgia, flashing, pruritus, hypotension, oral cavity edema, headache, drowsiness, face edema, face numbness, paraplegia, visual loss, palpitation, dyspnea, urine incontinency, extremity movement defect, defecation disability, and paresthesia.

Statistical analysis

The statistical analysis was performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA). We used the χ^2 test for independent proportions or Fisher's exact test if the number of expected observations was below six in one or more cells. Statistical significance was accepted at a level of $p<0.05$.

Results

We studied a total of 203 patients with HIV/AIDS. Table 1 shows the characteristics of all patients. The age ranged from 21 to 59 years with a mean of 36.9±7.9 years. Among studied patients, 80.3% (163 persons) were male. The mean ages of the male and female subjects were 37.6±7.7 and 34.2±8.6 years, respectively. Among all participants studied, the highest risk factor for HIV infection was i.v. drug abuse (58.6%) (data not shown). The mean CD4 cell count of the subjects was 425.2±271.7 cell/µl. The frequency of anti-retroviral drug usage was as follows: zidovudine (30%), biovudine (41.9%), nelfinavir (10.8%), nevirapine (15.8%), stavudine (22.2%), and efavirenz (23.6%). The frequency of TMP-SMX, fluconazole, and acyclovir administration in the last three months were 28.6%, 7.9%, and 3.5%, respectively.

Table 1. Baseline data for all patients with HIV/AIDS

Characteristic	Patients with HIV/AIDS (n=203)
Sex (%)	
male	163 (89.7%)
female	40 (10.3%)
Martial Status (%)	
single	76 (37.4%)
married	110 (54.2%)
others	17 (8.4%)
Occupation (%)	
Employed	131 (64.4%)
Unemployed	72 (35.5%)
History of drug addiction (%)	36 (17.7%)
History of alcohol addiction (%)	9 (4.4%)
History of smoking (%)	143 (70.4%)
History of allergy (%)	20 (9.9%)
Neurological diseases (%)	7 (3.4%)
Stage of HIV infection (%)	
HIV-infected	110 (54.2%)
AIDS	93 (45.8%)
Anti-retroviral drugs (%)	96 (47.3%)
Anti-TB medication (%)	43 (21.2%)
Previous vaccination (%)	52 (25.6%)

Table 2 shows the adverse reactions detected in subjects who received inactivated influenza vaccine from November 2006 to January 2007. Out of 203 subjects, 79 (38.9%) persons described adverse reactions. Local and systemic reactions were reported by 61 (30%) and 62 (30.5%) persons, respectively. The most common adverse reactions to the influenza vaccine included skin redness (37 cases), induration (32 cases), and pain (55 cases) as local reactions, and fever (22 cases), myalgia (46 cases), headache (12 cases) and weakness (35 cases) as general reactions. Pain resolved in 48 persons (82.8%) in less than 2 days. Three (9.1%) of participants had induration at injection site for more than 2 days.

Three (1.4%) of the subjects had a fever over 38.5 ºC. Paraplegia was observed in one person. Oral cavity and facial edema, facial numbness, dyspnea, extremity movement defect or defecation disability were not reported by any of the participants.

Among the adverse reactions, there were significant associations between myalgia and flushing with CD4 counts (P=0.01). Participants with CD4>200 cell/μL had a higher risk for myalgia, while flushing was observed more among subjects with CD4≤200 cell/μL (Table 2). We found no relationship between adverse reactions and sex, history of smoking, allergy, alcohol, and drug usage, stage of HIV infection, anti-retroviral therapies, anti - TB medication and previous vaccination.

Table 2. Frequency of adverse reactions and association with CD4 Counts in the study population who received influenza vaccine

Characteristic	No. (%) of participants	CD4≤200/μL (N)	CD4>200/μL (N)	*P- Value
Local Reaction				
Pain	55 (27.1)	8	47	0.76
Erythema	37 (18.2)	5	32	0.67
Induration	32 (15.5)	5	27	0.97
Pruritus	1 (0.5)	0	1	0.66
Systemic Reaction				
Fever	22 (10.8)	3	19	0.76
Nausea	10 (4.9)	2	8	0.71
Vomiting	4 (2)	0	4	0.38
Weakness	35 (17.2)	4	31	0.43
Myalgia	46 (22.7)	2	44	**0.01**
Flushing	3 (1.5)	2	1	**0.01**
Hypotension	2 (1)	0	2	0.54
Oral cavity edema	0 (0)	0	0	*
Headache	12 (5.9)	2	10	0.94
Drowsiness	5 (2.5)	0	5	0.33
Face edema	0 (0)	0	0	*
Face numbness	0 (0)	0	0	*
Paraplegia	1 (0.5)	0	1	0.66
Visual loss	1 (0.5)	0	1	0.66
Palpitation	1 (0.5)	0	1	0.66
Dyspnea	0 (0)	0	0	*
Urine incontinency	2 (1)	0	2	0.54
Extremity movement defect	0 (0)	0	0	*
Defecation disability	0 (0)	0	0	*
Paresthesia	1 (0.5)	0	1	0.83

* No statistics are computed because the characteristic is a constant.

Discussion

Individuals infected with HIV, particularly children who have a high incidence of cardiac and respiratory dysfunction, are at risk for the complications of viral respiratory infections. Influenza vaccination has been recommended in HIV-infected patients, but there has been concern about immune system activation of HIV-infected CD4+ cells by influenza vaccine (19).

A placebo-controlled study of 102 HIV-infected patients with CD4+ cell counts of approximately 400/μL reported in 1999 showed that influenza vaccination reduced the incidence of respiratory illness from 49% to 29% (P=0.04) and that of laboratory-confirmed influenza from 21% to 0% (P<0.001; 20), with no observed adverse effect of vaccination on CD4+ cell count or HIV viral load. Several groups have reported increases in plasma viremia that follow the kinetics of the antibody response in influenza vaccinated HIV-infected individuals (4, 8). Following influenza vaccination with a trivalent split-virus preparation, threefold or greater increases in plasma viremia were documented in 90% of HIV-infected individuals with more than 500 CD4+ cells.

Taking into consideration the impaired antibody responses of HIV-infected individuals to influenza vaccination and the possibility that vaccine-elicited immune activation will activate HIV-infected CD4+ cells and increase viral production, caution should be exercised regarding influenza vaccination in this population. Some have suggested that amantadine prophylaxis rather than vaccination should be considered (8).

Influenza vaccines are well tolerated in high-risk patients (elderly people, patients with pulmonary disease, renal disease, diabetes mellitus, cancer and hemophilia, and those with HIV infection) and all adverse reactions are generally mild and similar to those observed in healthy people (21).

Most studies have found a low incidence of local (up to 20%) and systemic (up to 5%) adverse reactions to influenza vaccination (22-26). However, a Canadian survey showed local side effects in 87% of patients and systemic effects in 49% (27). We found local side effects in 30% of study population and systemic effects in 30.5%. Gabutti et al. found that vaccination with a conventional subunit or one adjuvanted with MF59 was not associated with serious adverse events; local and systemic effects were mild and of short duration (28). Zuccoti et al. also evaluated the immunogenicity and tolerability of a trivalent virosomal influenza vaccine in a cohort of HIV-infected children. Vaccination was well tolerated with only a few mild transient symptoms (29).

The most frequent side effect was tenderness around the injection site. Fever, malaise and myalgia infrequently affect persons who have had no exposure to the influenza virus antigens. Symptoms usually occur six to 12 hours after the vaccination and can persist for one to two days. Immediate, presumably allergic reactions are extremely rare post influenza vaccination (30). In our study, 27.1% of the participants had pain as a local reaction and 22.7% had myalgia as a general reaction.

Patients with CD4>200 cell/μL and ≤200 had a higher risk for myalgia and flushing, respectively (P<0.05). We did not find any correlation between sex and adverse events, however, other studies have suggested that the side effects are more common in women than in men (31-33). Also, we found no relationship between adverse reactions and history of smoking, allergy, alcohol, and drug usage, stage of HIV infection, anti-retroviral therapies, anti-TB medication and previous vaccination. We did not detect any potentially delayed reactions to the vaccine 15 days post vaccination.

We conclude that inactivated influenza vaccine administered to HIV-infected adults did not result in potential adverse events in this study population. However, it is necessary to assess the clinical efficacy of influenza vaccine early in the influenza season. It is also important to consider influenza antiviral prophylaxis regardless of immunization status.

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