ORIGINAL PAPER

Influenza vaccination in HIV-infected patients

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Abstract

Introduction: One of the most serious threats for people infected with human immunodeficiency virus (HIV) is the risk of influenza co-infection and complications thereof. Not only is this population fundamentally more susceptible to flu but also prolonged replication and excretion of the virus, longer illness period, higher complication rate, flu-associated mortality, and risk of cardiovascular disease have all been noted.

Material and methods: The aim of our study was to assess vaccine efficacy against influenza in HIV-infected patients in various stages of the disease in comparison to a control group and estimate the influence of the vaccine on respiratory system infection rates. We prospectively studied 78 patients. Our study group included 47 patients with HIV and 31 healthy volunteers. The participants were immunised with TIV (trivalent influenza vaccine). Humoral response as an anti-AH1N1 (A/Brisbane/59/07), -AH3N2 (A/Brisbane/10/07), and -B strain (B/Florida/4/06) haemagglutinin antibody titre was measured. The assay was performed twice: before administration of the vaccine and a month after.

Results: The HIV-infected group exhibited a weaker immune response than the control group; however, the immunisation did provide partial protection against influenza. Vaccine efficacy was similar, regardless of CD4 count. Trivalent influenza vaccine successfully prevented influenza-associated bacterial pneumonia.

Conclusions: The study demonstrates that routine vaccination against influenza in HIV-infected patients, regardless of immune system deficiency, is substantiated.

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Key words: HIV, influenza, vaccination, response rate, protection rate.

Introduction

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) remains a paramount public health issue across the population, in its course leading to a progressive immune deterioration, opportunistic infections, and malignancies. Since the introduction of highly active antiretroviral drugs, patients' survival rates have markedly increased. Nevertheless, one of the serious threats to the population of HIV-infected patients remains the risk of influenza infection and complications thereof, consisting notably of bacterial pneumonia [1]. Not only are HIV-infected people more susceptible to influenza, but also prolonged replication and excretion of the virus,

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longer illness period, higher complication rate, flu-associated mortality, and risk of cardiovascular disease have all been noted in that population [2-4]. Lin *et al*. demonstrated that in a group of patients with AIDS, the flu-associated mortality rate is far higher (94-146/100 000) than in the general population (0.9-1.0/100 000 for ages 25-45 years and 64-70/100 000 for ages 65 years and over). It has also been shown that the risk of hospitalisation caused by a respiratory/cardiovascular condition in HIV-infected women is markedly higher during the flu season [5, 6]. Additional factors in a portion of the population, such as smoking, use of inhaled narcotics, and chronic respiratory diseases increase the risk of infection even more [7].

Vaccination is one of the classic methods of preventing infection. Vaccinating people with impaired immunity, regardless of the cause of impairment, presents two basic problems: the first is the possibility of adverse effects following vaccination. In HIV-infected patients, particularly with CD4 count below 200/µl, attenuated ("live") vaccines should not be used because of the immune deficiency. Live vaccines against cholera, typhoid fever, flu, tuberculosis, polio (OPV), and smallpox are contraindicated regardless of CD4 count. Killed vaccines, however, are as safe for immunodeficient patients as they are for the immunocompetent. The second problem is an insufficient or even non-existent response to vaccination, which, again, stems from the impairment to the immune system. In HIV-infected patients it is recommended to defer use of inactivated vaccines until the CD4 count exceeds 200/µl [1].

The aim of our study was to assess vaccine efficacy against influenza in HIV-infected patients in various stages of the disease in comparison to a control group and estimate the influence of the vaccine on respiratory system infection rates.

Material and methods

Patients

We prospectively studied 78 patients. Our study group consisted of 47 patients: 11 females (23.4%) and 36 males (76.6%), aged between 19 and 52 years (age average: 36.3 years) with HIV, treated at the Infectious and Tropical Diseases Department, University Hospital in Krakow, and 31 healthy volunteers: 10 females (32.3%) and 21 males (67.8%) aged 22 to 50 years (average: 26.5 years). The diagnosis of HIV infection was based on the detection of HIV-specific antibodies with an ELISA test (Hoffmann-La Roche Ltd., Basel, Switzerland), confirmed by a Western-blot (INNO-LIA, Fujirebio Inc., Pennsylvania, US). The HIV-infected group was divided into two subgroups: one with CD4 count under 350/µl and the second over 350/µl. The exclusion criteria were: contraindications to the influenza vaccine, autoimmune disorders, diseases associated with immunosuppression, diabetes, and, in the control group, HIV infection.

Vaccination

Participants were vaccinated with an inactivated vaccine (TIV, trivalent influenza vaccine), consistent with WHO recommendations for the 2008/2009 flu season (the study was conducted in 2008/2009). Fluarix, a GlaxoSmithKline product, was used. Subsequently, humoral response as an anti-AH1N1 (A/Brisbane/59/07), -AH3N2 (A/Brisbane/10/07), and -B strain (B/Florida/4/06) haemagglutinin antibody titre was measured. The measurement was taken twice: before administration of the vaccine and a month after.

Blood tests

Blood samples were collected in the morning (from 7.00 a.m. to 8.00 a.m.), centrifuged (3500 g/15 min), and stored at –80°C until assayed. Analysis of CD4+ and CD8+ lymphocyte subpopulations in the blood was performed with the FACSCalibur flow cytometry platform (BD Biosciences, New Jersey, US). Quantitative measurement of HIV RNA in patients' serum was performed *in vitro* with the COBAS TaqMan 48 analyser (Hoffmann-La Roche Ltd., Basel, Switzerland) as a nucleic acid amplification test. This assay, through real-time PCR technology, makes it possible to quantify HIV-1 RNA with a linear range of 47-10 000 000 copies/ml.

TIV efficacy was expressed as a defined immune response: anti-haemagglutinin titre against administered vaccine antigens. Antibody concentration was obtained through a haemagglutination inhibition assay (according to WHO guidelines), using a 0.75% turkey RBC solution and the recommended viral strains, manufactured in fertilised chicken eggs or cell cultures. Based on the obtained data, parameters of vaccine efficacy were established: protection rate (PR, the percentage of people who produced an antibody titre of at least 40), geometric mean titre (GMT), response rate (RR, the percentage of people to exhibit an at least two-fold increase in antibody titre), and mean fold increase (MFI, a geometric mean of the fold change before and after vaccination).

The study was conducted in accordance with the Declaration of Helsinki (1975) and was approved by the local Ethics Committee.

Statistical methods

Analysis of the data was conducted using parametric tests. Student's *t*-test was employed to compare the antibody titres in the analysed groups, and ANOVA to compare the HIV-infected subgroups with the control group and each other before and after the vaccination and to compare the response to each influenza antigen. Statistical analysis was performed using Statistica 10 software (StatSoft® Inc., USA). Statistical hypothesis testing yielded values of $p < 0.05$. The study was conducted in accordance with the Declaration of Helsinki (1975) and approved by the Jagiellonian University Ethics Committee. All study participants signed an informed consent form.

Table 1. Mean titres of anti-haemagglutinin antibodies for the AH1N1, AH3N2, and B strains in HIV-infected patients and the control group before immunisation and one month after

Antibody type	Control group (n = 31)		HIV-infected patients (n = 47)	
	Antibody titre (mean ± SD)	p	Antibody titre (mean ± SD)	p
Anti-H1 before immunisation	18.1 ± 56.5	0.001	8.1 ± 11.4	0.001
Anti-H1 after one month	315.5 ± 450.3		185.1 ± 361.1	
Anti-H3 before immunisation	35.6 ± 115.8	0.001	10.7 ± 16.6	0.006
Anti-H3 after one month	320.8 ± 464.6		121.70 ± 273.9	
Anti-B before immunisation	10.9 ± 14.9	0.004	9.6 ± 23.1	< 0.001
Anti-B after one month	75.9 ± 119.3		39.3 ± 68.5	

Table 2. Mean titres of anti-haemagglutinin antibodies for the AH1N1, AH3N2, and B strains in HIV-infected patients before immunisation and one month later in relation to CD4 count

Antibody type	HIV-infected patients, CD4 < 350/µl (n = 29)		HIV-infected patients, CD4 > 350/µl (n = 18)	
	Antibody titre (mean ± SD)	p	Antibody titre (mean ± SD)	p
Anti-H1 before immunisation	6.6 ± 4.0	0.03	10.6 ± 17.7	0.03
Anti-H1 after one month	149.3 ± 328.1		242.8 ± 412.1	
Anti-H3 before immunisation	11.7 ± 20.0	0.03	9.2 ± 9.1	0.01
Anti-H3 after one month	117.2 ± 261.8		128.9 ± 299.9	
Anti-B before immunisation	10.7 ± 28.7	0.02	7.8 ± 8.8	0.002
Anti-B after one month	43.6 ± 83.6		32.2 ± 32.9	

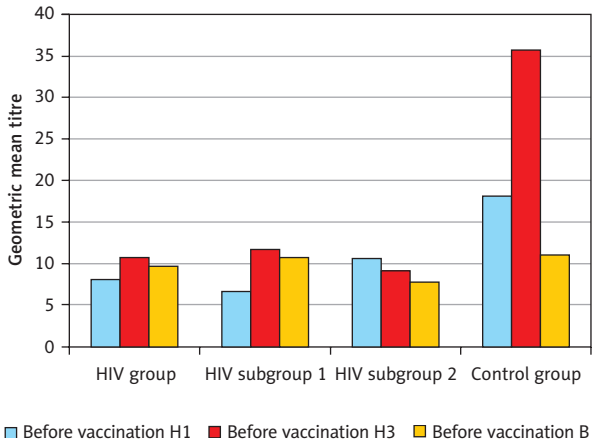

Figure 1. Antibody titre in each group before immunisation

Results

Vaccine efficacy in the studied groups

Both groups were demonstrated to show significantly higher anti-haemagglutinin antibody titre values one month after vaccination in comparison to the titre before immunisation. TIV was efficacious for the whole analysed population.

It was shown that anti-haemagglutinin specific antibody titre values were significantly higher one month after vaccination in both groups. TIV in the HIV-infected patient group with CD4 count below 350/µl was efficacious as well.

Disparity in protective antibody titres between the HIV-group and the control group before and after immunisation

Differences in antibody titre between the analysed groups were compared before administering the vaccine. Although titres of all the tested antibodies were noticeably higher in the control group in comparison to the HIV-infected group, the differences were not statistically significant (Fig. 1). A similar comparison was made of the titre in the analysed groups one month after immunisation. The mean antibody titre against AH3N2 after immunisation in the HIV-infected group was significantly lower than in the control group. The rest of the range did not show statistical significance (Fig. 2).

Response to vaccine antigens in the HIV-infected group

In the HIV-infected patient group average values of anti-H1, -H3, and -B anti-haemagglutinin titre values were varied. The strongest response observed was to the AH1N1 strain and the weakest for B/Florida/4/06. A statistically significant difference, however, was only observed between antigen AH1N1 and B antibody titre (p = 0.008) (Fig. 3).

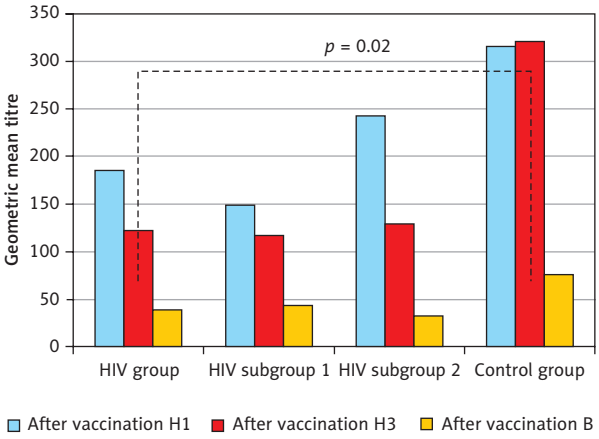

Figure 2. Antibody titre in each group after immunisation

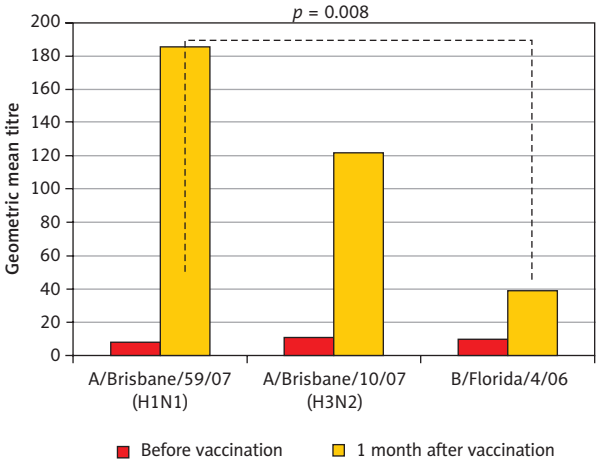

Figure 3. Response to vaccine antigens in HIV-infected patients

Table 3. Parameters of influenza vaccine efficacy in studied groups

Antigen	Group	GMT		MFI	PR [%]		RR [%]
		Before immunisation	One month after immunisation	One month after immunisation	Before immunisation	One month after immunisation	One month after immunisation
A/Brisbane/59/07 (H1N1)	HIV	6.2	35.0	5.6	2.1	51.1	57.5
	Control	7.3	111.9	15.3	6.5	83.9	74.2
A/Brisbane/10/07 (H3N2)	HIV	6.9	27.3	3.9	10.6	44.7	48.9
	Control	9.8	83.7	8.6	16.1	74.19	67.7
B/Florida/4/06	HIV	5.9	15.1	2.6	4.3	36.2	38.3
	Control	7.5	32.7	4.4	6.5	54.8	54.8

GMT – geometric mean titre, MFI – mean fold increase, PR – protection rate, RR – response rate

Calculation of the parameters conductive to the assessment of vaccine efficacy

The values of the first two parameters (PR and GMT) may be overestimated, since a fraction of the patients had already been immunised (seropositive before vaccination). The last two parameters, namely RR and MFI, account for the change dynamic, but may in turn underestimate the results [8]. The parameters used to evaluate the influenza vaccination efficacy are presented in Table 3.

Incidence of sequelae bacterial respiratory infections

Based on patients' medical records, no complications in the form of bacterial respiratory tract infections (pneumoniae) were found.

Discussion

Yearly vaccination is the most effective method of preventing influenza and its complications. The most commonly used vaccines are inactivated and consist of three viruses: two different influenza type A strains and one influenza type B strain. Due to high mutation rate of the virus, the WHO issues annual recommendations for influenza vaccine formulations before every flu season. The markers of post-immunisation protection are anti-haemagglutinin and virus-neutralising antibody titres in the serum. An increase in antibody titre post-vaccination lowers the risk of disease caused by strains similar to those included in the vaccine. Parameters such as PR (usually defined as haemagglutination titre of 1 : 32 or 1 : 40) correlate well with immunity at a population level [9, 10].

According to the requirements of the Commission of the European Communities and the Committee for Proprietary Medicinal Products for influenza vaccination for people aged 18-60 years, average antibody level MFI should be ≥ 2.5, PR ≥ 70%, and RR ≥ 40%. In our study the immunisation induced a significant titre of anti-haemagglutinin antibodies in all the participants. In the control group, the increase in antibody level averaged from 4.3 (B strain) through 8.6 (AH1N2) to 15.3 (AH1N1). PR > 70% was achieved for the AH1N1 and AH3N2 strains; only for the B strain was

it 54.8%. Response rates fluctuated between 54.8% and 74.1%. In a healthy population the vaccine is usually highly immunogenic and effective, which proved to be true in our study as well. The HIV-infected patients exhibited a weaker response to the immunisation. Antibody GMT after vaccination was 2-3 times lower than in the control group; statistical significance, however, was shown only in the response to AH3N2 antigen. Despite that, MFI exceeded the recommended level of 2.5 for all the strains. PR fluctuated between 36.1% (B strain) and 51% (AH1N1 strain) and did not reach the desirable level of 70%. RR exceeded 40% for the first two strains, and for the B strain it was 38.2%, essentially meeting the requirements [11-14].

Analysis of studies comparing incidence rates of influenza among vaccinated and unvaccinated HIV-infected patients has indicated a moderate advantage of vaccinating [3, 15-17]. Mahdi *et al.* conducted an extensive, randomised, double-blind trial among HIV-infected citizens of Johannesburg, South Africa. It yielded a percentage of seroconversion of 52.6-60.8%. The average increase in antibody concentration ranged from 4.1-10.2, which was higher than in our study. Efficacy in preventing laboratory-confirmed influenza was high and reached 75.5% [18]. Atashili *et al.* conducted a meta-analysis of four studies, encompassing 646 HIV-infected patients in total, and found TIV to be moderately efficacious in limiting the influenza incidence rate [19]. The only study on an adult HIV-infected population in Poland involved 34 patients. PR after a month ranged from 18% (AH1N1 strain) through 41% (B strain) to 79% (AH3N2 strain). However, the value for the latter has been overestimated due to a high percentage (50%) of patients with a pre-existing high protective antibody titre. It stemmed from prior contact with said subtype, which dominated at that time in Poland. Antibody GMT increased by a factor of 1.5-5.5, which is comparable to our results, yielding an increase by a factor of 2.6-5.6. Like here, no statistically significant difference in humoral response between patients with different CD4 values nor between patients in different clinical stages of the disease was shown [20].

CD4 count is a key factor in immune system function of HIV-infected patients. As the disease progresses, the B memory cell function declines, which is particularly evident in patients with high viral load. Hence, they exhibit a weaker humoral response to immunisation. It has been established that the independent factors correlated with post-vaccination response strength are CD4 count and viral load [21, 22]. Low CD4 count, especially < 200/µl, reduces vaccine efficacy in general and similarly for the influenza vaccine [23-25]. It has been shown that in patients with high CD4 count the immunisation induced a high specific protective antibody titre [23, 24, 26]. Patients in the AIDS phase, in turn, often did not achieve a protective antibody titre [23, 24]. Moreover, administration of a second dose of the vaccine did not improve the response [23, 27]. In a randomised trial in children with average CD4 count above 400/µl, immunisation was efficacious in preventing laboratory-confirmed influenza at a similar rate as in the general population [28]. Fine *et al.* showed efficacy only in patients whose CD4 count exceeded 100/µl or whose viral load was under 30 000/ml [3]. Furthermore, patients undergoing antiretroviral therapy (ART) longer than three months, with a CD4 count increase of at least 15% and viral load decrease to under 1000 copies/ml, respond better to treatment. An additional benefit of ART is an increase in concentration of specific antibodies left over from prior immunisations when no booster dose has been given. It has been shown that immunogenicity of the influenza vaccine is higher in patients successfully treated with ART and without progression of the disease [29]. Our study did not find such a relation. TIV was efficacious for patients with CD4 counts both over and under 350/µl. Presumably application of a different patient distribution (with a significantly lower CD4 count) would show an impact of a nominal CD4 cell level on vaccine efficacy in said groups.

Influenza, in contrast to many diseases entirely preventable with immunisation, is very common with a high incidence rate worldwide. That poses a challenge for studies on vaccine immunogenicity because a sizeable portion of the studied population may already have a protective antibody titre from prior contact with a given virus upon entrance into the study. In our study, the geometric mean of antibody titres was low and in HIV-infected patients was in the range of 5.97 to 6.24, and in the control group 7.31 to 9.77. No statistically significant difference between the groups was shown. This proves that most patients had not had prior contact with viral antigens corresponding to vaccine antigens.

Inactivated influenza vaccines available in Poland contain three flu strain antigens. One element of the study was an assessment of the response to individual antigens in HIV-infected patients, where a weaker response was observed to the B strain. This tendency has not been backed by any of the quoted publications by other authors and possibly stems from a weaker immunogenicity of the antigen used in said flu season.

In a typical flu season in Poland (autumn to early spring months) we observe raised mortality and hospitalisation rates during the circulation of the virus. Based on the correlation between influenza activity and seasonality of pneumococcal pneumonia, one could infer that in some patients admitted for invasive pneumococcal pneumonia we might expect a comorbid influenza infection [30]. The unnecessary deaths and admissions in flu season, which are, at least partly, caused by influenza infection, fit into a broad category of respiratory and circulatory hospitalisations [31, 32]. In our study we analysed medical records of HIV-infected patients, finding no instances of bacterial respiratory infections throughout nine months post-vaccination. We can therefore speculate that TIV in HIV-infected patients successfully prevents complications in the form of pneumonia. A meta-analysis of 15 cohort studies and clinically controlled trials evaluating the factual effectiveness of TIV in preventing flu/pneumonia-associated hospitalisations in patients above 65 years old showed that TIV use helped avert 6-26% of doc-

tor visits and reduced the relative risk of death due to flu or pneumonia [33].

In conclusion, immune response to influenza vaccination was weaker in HIV-infected patients than in the healthy population; nevertheless, the immunisation did provide partial protection against the flu. Vaccine efficacy was comparable regardless of CD4 count. Immunisation successfully prevented flu-associated bacterial pneumonia. The study demonstrates that routine vaccination against influenza in HIV-infected patients, regardless of immune system deficiency, is substantiated.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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