


Influenza A Virus Infection and Nucleotide Sequencing in HIV-Infected Children: A Case Report and Review of Literature

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Visal Moolasart, MD¹, Suthat Chottanapund, MD¹,
Jarurnsook Ausavapipit, MNS¹, Srisuda Samadchai, MNS¹,
Sirirat Likanonsakul, MSc¹, Sumonmal Uttayamakul, PhD¹,
Somkid Srisopha, MSc¹, Don Changsom, PhD²,
Hatairat Lerdsamran, PhD², and Pilaipan Puthavathana, PhD²

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Introduction

An annual seasonal influenza vaccine is the main protection against influenza infection and its complications.¹ Influenza infections have increased morbidity among HIV-infected children and adults, including pregnant women. This underscores the importance of vaccine-conferred protection. However, the effectiveness of the influenza vaccine depends on at least 2 factors, the characteristics of the vaccinated person (eg, their age and health) as well as the match between the influenza vaccine strain and the circulating strain spreading in the community at that time.²

HIV infection is a characteristic of a vaccinated person that can influence vaccine-conferred protection. Multiple studies have shown a poor antibody response to influenza vaccines in HIV-infected individuals.^{3–6} A previous study demonstrated only 38% of children had a complete seroprotective response of all strains of trivalent influenza vaccine (TIV) at both 1 month and 6 months.⁷ However, some studies demonstrated that the proportion of HIV-infected children generating a seroprotective response after influenza vaccination was as high as 79%.⁸

Case Report

A 17-year-old Thai female with human immunodeficiency virus type 1 (HIV-1) infection who had received TIV for 2012–2013 in August 2013 presented at the Bamrasnaradura Infectious Diseases Institute (BIDI) complaining of 2 days of fever, malaise, headache, cough, and sore throat in April 2014. She had been diagnosed with HIV infection confirmed by machine-based

assay (ArchiTECT, Abbott, chemiluminescent test), particle agglutination test (Serodia HIV, Fujirebio), and immunochromatography test (Allere Determine or TriLine) at BIDI. Approximately 13 years prior to presentation, she received zidovudine (AZT) plus didanosine (ddI) from 2001 to 2005; AZT, ddI, and efavirenz (EFV) from 2005 to 2007; and has been receiving EFV plus lopinavir/ritonavir in combination (LPV/r) from 2007 to present. Before TIV was given in 2013, she had a CD4 count of 922 cell/ μ L (31%), plasma HIV-1 RNA <40 copies/mL by quantitative real-time polymerase chain reaction (RT-PCR), a body weight of 85.7 kg, and a height of 165 cm. She received TIV 2011–2012 on August 1, 2012, and TIV 2012–2013 on August 28, 2013. TIV in 2012–2013 included the A/California/7/2009 (H1N1)-derived strain using NYMC X-179A, the A/Victoria/361/2011 (H3N2)-like strain using IVR-65, and the B/Wisconsin/1/2010-like strain using NYMC BX-39 derived from the B/Hubei-Wujiagang/158/2009 strains. At presentation of influenza-like illness symptoms, the physical examination was unremarkable except for a body temperature 38.5°C and body mass index of 31.48 kg/m². Because of a positive rapid influenza test (Quidel QuickVue Influenza A+B test), the patient was given oseltamivir for 5 days and the clinical symptoms

¹Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand

²Siriraj Hospital, Mahidol University, Bangkok, Thailand

Corresponding Author:

Visal Moolasart, Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Tiwanon Road, Nonthaburi 11000, Thailand.

Email: vismool@yahoo.com



Table 1. Percentage of Identity Match of Amino Acid Sequences of Full HA Gene.

Viruses	Percentage Match of Child
CA07 ^a vaccine strain	97.1
A/Nonthaburi/102/2009	97.7
A/Thailand/104/2009	97.7
H1N1 2014 isolate #1	99.4
H1N1 2014 isolate #2	99.6

^aCalifornia 2007.

resolved The positive rapid influenza test result was from the BIDI, Nonthaburi, Thailand, with a confirmatory PCR result from the Siriraj Influenza Cooperative Research Center, Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand. The specimen was identified by the amino acid sequence of full hemagglutinin (HA) gene to evaluate the match between the influenza infection and TIV strains.

To perform nucleotide sequencing, total RNA was extracted using a QIAamp viral RNA mini kit (Qiagen) from direct nasal swab specimens of a vaccinated person who had developed a PCR-confirmed influenza illness from the 2009 pandemic virus. The RNA sample was amplified for the complete influenza HA gene, and the amplified product was subjected to nucleotide sequencing. The sequence was edited, aligned, and translated into an amino acid sequence by BioEdit program (version 7.1.11; available at <http://www.mbio.ncsu.edu/bioedit/bioedit.html>). The sequence was submitted to the GenBank database with the accession number of KU144591.

Table 1 shows the percentage of identity match of amino acid sequences of the full HA gene. The specimen of the present case matches TIV strains CA 07 vaccine strain, H1N1 A/Nonthaburi/102/2009, and H1N1 A/Thailand/104/2009 by 97%, 98%, and 98%, respectively. The matches of the specimen for H1N1 2014 isolates are 99% to 100%.

To perform phylogenetic analysis, the HA amino acid sequence of virus from the case was analyzed for its correlation with the sequences from A/California/07/2009 (H1N1) vaccine strain, 2 Thai virus isolates obtained from the first epidemic wave (A/Nonthaburi/102/2009 and A/Thailand/104/2009), and 2 more virus isolates from 2014 (A/Thailand/NMA_1/2014 and A/Thailand/BKK_1/2014) See Figure 1. The results demonstrate a closer relationship between the causative virus and the circulating strains rather than the vaccine strain closely related to the Thai viruses from the first epidemic wave.

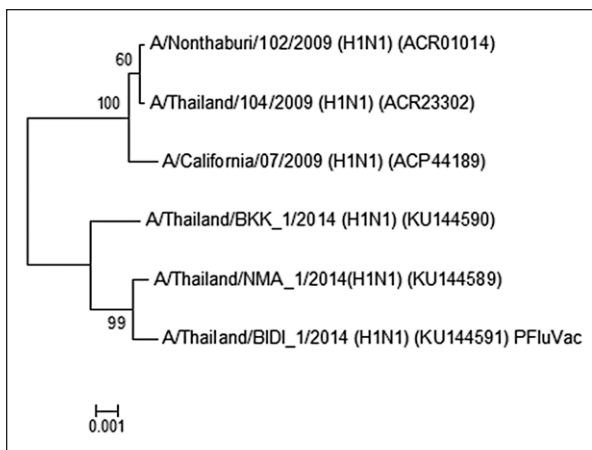


Figure 1. Phylogenetic analysis of HA amino acid sequences derived from 2009 pandemic influenza viruses by maximum likelihood technique using MEGA 5 software (PFuVac = patient).

Discussion

In this case, we were unable to determine the degree of vaccine-conferred protection of TIV For 2012-2013 given in August 2013 against the illness caused by the PCR-confirmed strain of influenza A virus in April 2014. The case illustrates the issues causing this uncertainty, including an issue of matching the vaccine virus strain and causative virus strain as well as other issues about the peculiar characteristics of the vaccinated person, some of which are relevant to HIV infection.

The results demonstrate a closer relationship between the causative virus and the circulating strains rather than the vaccine strain. Because the viral components of the TIV for 2012-2013 vaccine are not well matched with circulating influenza viruses of 2014 in Thailand, the benefits of influenza vaccination may have been reduced. However, the degree of antigenic drift of the circulating viruses of 2014 from vaccine viruses and the proportion of circulating drifted viruses could have varied. If the circulating virus of 2014 that caused the illness of the patient was mildly or moderately drifted compared to one of the strains in the TIV 2012-2013 used, some degree of protection may have occurred.⁹

There are several interesting characteristics of the vaccinated person in the present case. First, she was 17 years old. The seroprotection of TIV among HIV-infected children is reported to be low. A previous double-blinded, placebo randomized controlled trial of 410 young HIV-infected children demonstrated that the proportions of TIV-vaccinated children seroconverting after a second dose against the vaccine strains of H1N1, H3N2, and influenza B were as low as 47.5%, 50%, and

40%, respectively.¹⁰ However, a previous systematic review reported that TIV prevented laboratory-confirmed influenza with a pooled efficacy as low as 11% in young children and as high as 85% in adults.¹¹ Second, the influenza A virus symptom of the present case occurred 216 days after TIV vaccination was given. The durability of the seroprotection for influenza vaccine often spans only an estimated 180 days.¹² Third, she had a confirmed HIV infection. Thus, the response to the vaccine may have depended on the B-cell subset distribution rather than CD4 counts or viral load.¹³ The present case had a high CD4 count and viral suppression. Fourth, she had a high body mass index. The previous study demonstrated that a high body mass index was associated with a greater decline in influenza antibody titers at 12 months post TIV.¹⁴ Obesity may impair the ability to mount a protective immune response to influenza virus.

Conclusion

The closer relationship between the causative virus and the circulating strains, the low seroprotection of TIV among HIV-infected children, the durability of seroprotection against influenza vaccine that often spans only an estimated 180 days, and obesity may have reduced the effectiveness of the influenza vaccine in the present case.

Author Contributions

VM: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SC: Contributed to design; contributed to acquisition and interpretation; drafted manuscript; critically revised manuscript.

JA: Contributed to conception; contributed to acquisition.

SSa: Contributed to conception; contributed to acquisition.

SL: Contributed to conception; contributed to acquisition.

SU: Contributed to conception; contributed to acquisition.

SSr: Contributed to conception; contributed to acquisition.

DC: Contributed to conception; contributed to acquisition.

HL: Contributed to conception; contributed to acquisition.

PP: Contributed to conception; contributed to acquisition, analysis, and interpretation.

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.

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