BRIEF REPORT

Pandemic Influenza A (H1N1) Outbreak among 15 School-Aged HIV-1–Infected Children

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Patients infected with human immunodeficiency virus type 1 (HIV-1) are considered to be at increased risk for 2009 H1N1 influenza–related complications. We performed an observational study after an outbreak of 2009 H1N1 influenza virus infection among a group of 15 HIV-1–infected school-aged children in Germany in October 2009. Clinical course, kinetics of viral shedding, and antibody response among children with CD4 cell counts >350 cells/μL and 2009 H1N1 influenza virus coinfection did not appear to differ from that among healthy children. Oseltamivir shortened the duration of viral shedding.

In spring 2009, a new pandemic swine-origin influenza A (H1N1) virus emerged in Mexico [1] and the United States [2] and spread globally thereafter. Although the infection proved to be uncomplicated in the majority of cases, severe complications and fatal outcomes have been reported. Risk factors predictive for complications include younger age (children <2 years), pregnancy, obesity, pulmonary or other comorbid conditions, and concurrent immunosuppression [3, 4]. On the basis of data from seasonal influenza, it has been postulated that patients infected with human immunodeficiency virus type 1 (HIV-1), especially those with low CD4 cell counts or advanced stage of disease, might be at increased risk for H1N1 influenza–related complications [5, 6]. Data on the clinical course of 2009 H1N1 influenza in HIV-1–infected children and adolescents have not yet been published. We describe an outbreak of 2009 H1N1 influenza among a group of 15 HIV-1–infected school-aged children in Germany, which allowed systematic monitoring of clinical features, kinetics of viral shedding, and development of H1N1-specific antibodies in these patients.

Methods. Fifteen perinatally HIV-1–infected children and adolescents, all patients at the pediatric outpatient HIV clinic, Charité, Berlin, Germany, participated in a 7-day trip to a youth camp in Germany in October 2009. All were treated with highly active antiretroviral therapy. Eleven patients (73%) had an HIV-1 load <20 copies/mL, and all had CD4 counts >350 cells/μL. Comorbid conditions (mild asthma) were present in 2 children. No patient had been vaccinated against 2009 H1N1 influenza because the vaccine was not available at this time. Baseline characteristics are summarized in Table 1.

On a second day of travel, a 16-year-old boy (patient I) had to be hospitalized for high-grade fevers and cough, which retrospectively was the first case of 2009 H1N1 influenza in the group. On the last day of the trip, 3 children developed an acute illness with high-grade fevers and influenza-like symptoms and subsequently received a diagnosis of 2009 H1N1 influenza virus infection by reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal swabs. After parental consent and approval by the institutional ethics committee, all 15 patients were closely monitored as outpatients.

Data on patients' demographic characteristics and medical history were obtained from review of medical records. Time and quality of influenza-related symptoms at onset were documented as reported by patients and their camp supervisors. During follow-up visits, scheduled every other day, disease symptoms were recorded, physical examinations were performed, and nasal swabs were collected and processed immediately for virological analysis. After documentation of 2 consecutively negative RT-PCR results from nasal swabs, monitoring and contact isolation at home were discontinued.

Virus isolation was performed on Madin-Darby canine kidney SIAT-1 cells as described elsewhere [7]. Viral RNA was extracted from nasal swabs, and the specific 2009 H1N1 influenza RNA was amplified as described elsewhere [8]. 2009 H1N1 influenza–specific antibody titers of probes obtained ~6 weeks after the onset of symptoms were compared with those from cryopreserved serum samples collected during routine clinic visits prior to the trip (baseline). Antibodies were determined

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Table 1. Characteristics and Clinical Features of the 15 Human Immunodeficiency Virus Type 1 (HIV-1)–Infected Children with 2009 H1N1 Influenza Virus Coinfection

Variable	Children (n = 15)
Sex, ratio female to male	7:8
Age, median years (range)	13.2 (8.9–16.8)
Ethnicity	
White	6 (40)
Black	8 (53)
Asian	1 (7)
CDC clinical and immunologic stages[a]	
Clinical stage N and A	4 (27)
Clinical stage B	5 (33)
Clinical stage C	6 (40)
Immunologic stage 1	1 (7)
Immunologic stage 2	7 (47)
Immunologic stage 3	7 (47)
CD4 cell count,[b] median cells/μL (range)	786 (371–1223)
HIV-1 load,[b] range copies/mL	<20–7490
BMI, median value (range)	17.9 (14.8–21.9)
Symptoms of disease	
Any symptom	14 (93)
Fever (temperature >38°C)	10 (67)
Cough	13 (87)
Fatigue	11 (73)
Headache	8 (53)
Myalgia	6 (40)
Rhinorrhea	2 (13)
Sore throat	2 (13)
Abdominal pain	2 (13)
Vomiting	1 (7)
Diarrhea	0 (0)
Dyspnea or respiratory distress	0 (0)
Duration of fever, median days (range)	1.5 (1–3)
Received antiviral treatment with oseltamivir	5 (33)
Received influenza vaccine during 2009–2010 season	7 (47)

NOTE. Data are no. (%) of children, unless otherwise indicated. BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CDC, Centers for Disease Control and Prevention.

[a] CDC clinical stages of pediatric HIV-1 infection: N, no symptoms; A, mildly symptomatic; B, moderately symptomatic; C, severely symptomatic; CDC immunologic stage 1, no immunosuppression; stage 2, moderate immunosuppression; stage 3, severe immunosuppression [21].

[b] Laboratory values prior to infection with 2009 H1N1 influenza virus.

by hemagglutination inhibition analysis using the 2009 H1N1 reference strain A/California/07/2009 and erythrocytes from turkey hens. A hemagglutination inhibition titer of $\geq$1:10 was considered to be a positive result.

Categorical variables were compared using the χ^2 test and Fisher's exact test, when appropriate. Continuous variables were analyzed with the Mann-Whitney U test. All P values are 2-tailed. Statistical significance was defined as $P < .05$.

Results. 2009 H1N1 influenza infection was confirmed in all 15 patients by cell culture (n = 11), RT-PCR from nasal swabs (n = 11), or detection of 2009 H1N1–specific antibodies in serum (n = 14). This resulted in an attack rate of 100%.

Fourteen of 15 patients became symptomatic, all within a 7-day period. The most common symptoms were fever, cough, and fatigue (Table 1). Mild symptoms, mostly low-grade fevers (>38°C to 39°C) for <24 h and cough, occurred in 8 children. Five patients, who presented with high-grade fever (>39°C), cough, and fatigue received antiviral treatment with oseltamivir

Table 2. Selected Demographic Parameters, Clinical Features, and Serological Results of the 15 Study Patients Infected with 2009 H1N1 Influenza Virus

Patient	Age, years	Sex	Ethnicity	CD4 cell count, cells/μL	HIV-1 load, copies/mL	Coexisting conditions	Maximal reported body temperature, °C	Other symptoms	Received oseltamivir	Complications	Serology at baseline, HIT	Serology after influenza infection, HIT
A	13.7	F	Black	703	497	No	39.0	Cough, fatigue	No	No	<10	1:10
B	16.7	M	White	923	Negative	No	39.4	Cough, fatigue, headache, myalgia	Yes	No	<10	1:160
C	14.4	M	Asian	687	Negative	No	38.6	Cough, fatigue	No	No	<10	1:40
D	8.9	F	White	786	Negative	No	40.0	Cough, fatigue, myalgia, abdominal pain	Yes	No	<10	1:20
E	15.0	M	Black	1223	186	No	NA	No symptoms reported	No	No	<10	1:80
F	13.3	F	Black	1116	<20	No	NA	Headache, sore throat	No	No	<10	1:40
G	15.9	M	Black	672	Negative	Asthma	38.9	Cough, fatigue	No	No	<10	1:40
H	12.7	F	White	654	577	No	NA	Cough, fatigue, myalgia	No	No	<10	1:40
I	16.8	M	Black	371	7490	No	40.0	Cough, fatigue, chest pain, chill, headache, myalgia	No	Severe HSV stomatitis	<10	1:40
J	8.9	F	Black	840	Negative	No	39.6	Cough, fatigue, headache, nausea, abdominal pain, vomiting	Yes	No	<10	1:40
K	12.0	M	Black	1106	<20	No	39.1	Cough, fatigue, rhinorrhea, myalgia	Yes	No	<10	1:20
M	13.8	M	Black	917	Negative	No	NA	Cough, headache, rhinorrhea	No	No	<10	1:320
N	11.4	M	White	991	Negative	No	38.5	Cough, fatigue, headache	No	No	<10	1:160
O	10.3	F	White	676	<20	No	39.1	Cough, headache, sore throat, fatigue	Yes	No	N/A	N/A
P	12.8	F	White	588	Negative	Asthma	NA	Cough, headache, sore throat	No	No	<10	1:40

NOTE. HIT, hemagglutination inhibition antibody titer to influenza virus; HIV-1, human immunodeficiency virus type 1; HSV, herpes simplex virus; NA, not applicable; N/A, not available.

within 48 h after onset of symptoms. Because of initial concerns about severe disease in this patient population, oseltamivir was given for 7 days instead of the 5 days recommended. The medication was administered twice daily with weight-based dosing according to the manufacturer's instructions. In all treated patients, fever resolved within 24 h, and adverse effects were not observed. Patient I was hospitalized for 8 days prior to the diagnosis of 2009 H1N1 influenza and did not receive neuraminidase inhibitor treatment. No other patient was hospitalized or received antibiotics for bacterial superinfection. Further details on individual patients are summarized in Table 2.

Blood cell counts during influenza infection were available in 6 patients. Even though 5 patients had a transient neutropenia (<1500 neutrophils/μL), severe lymphopenia ($\leqslant$800 lymphocytes/μL) was not observed.

Nasal swabs were available from all 15 patients; the first specimen was collected at a median of 3 days (range, 1–9 days) after onset of symptoms. Initial samples from 11 patients (73%) had positive results by RT-PCR; all of them also had positive culture results. The median time from onset of symptoms to first negative RT-PCR result was 9 days (range, 5–14 days), whereas culture results became negative after 6 days (range, 3–11 days). Four patients who had negative results by RT-PCR also had negative results by culture.

Because of more severe initial symptoms, 5 patients received antiviral therapy with oseltamivir. There was a significant difference in the duration of viral shedding in oseltamivir-treated versus untreated patients; among oseltamivir-treated children, 2009 H1N1–specific RNA was detected for a median of 4 days (range, 4–5 days), compared with 8 days (range, 8–13 days) among untreated patients ($P = .005$). Virus was detectable by culture for a median of 3 days (range, 2–3 days) among oseltamivir-treated patients, compared with 6 days (range, 5–10 days) among untreated patients ($P = .005$).

Comparative serum samples were available for 14 patients. Although all baseline probes were antibody negative, all follow-up samples had positive results (median titer, 1:40; range, 1:10 to 1:320), including samples from patients who had negative results by RT-PCR or culture. Eleven (79%) of 14 patients had an antibody titer of $\geqslant$1:40 (Table 2).

Discussion. All 15 participants in a travel group of HIV-1–infected school-aged patients were found to be infected with 2009 H1N1 influenza virus, which emphasizes the high level of contagiosity of the virus in this setting. This observation is in contrast to the relatively low transmissibility of the 2009 H1N1 influenza virus reported among immunocompetent household contacts [9] and may be explained by the very close contact of the children during the trip. According to current Centers for Disease Control and Prevention guidelines, patients with HIV-1 infection or other forms of immunodeficiency are considered to be at risk for complications of 2009 H1N1 influenza [10]. However, our observations revealed a mostly self-limited and mild clinical course with clinical features similar to those reported in the general pediatric population [4, 11, 12]. Relatively few patients in our cohort had fever (10 [67%] of 15 children), compared with the incidence reported among mostly immunocompetent children with 2009 H1N1 influenza (88% [12] to 95% [11]). This may be explained by the fact that these studies included mostly hospitalized patients. Severe lymphopenia ($\leqslant$800 lymphocytes/μL), which may be a predictor for respiratory failure [13], was not observed among our patients.

The benign clinical course in this HIV-1–infected population may be explained by the lack of severe immunodeficiency attributable to successful antiretroviral treatment, the absence of relevant comorbidities, and in light of an underlying chronic disease, increased awareness by patients and care providers, leading to earlier diagnosis and intervention.

Studies of seasonal influenza [14] and 2009 H1N1 influenza [15] have indicated that viral shedding might be prolonged in immunocompromised patients. Aside from an anecdotal report [16], very little is known about the duration of viral shedding after influenza infection in HIV-1–infected patients. In our cohort, viral shedding lasted a median of 8 and 5 days, measured by RT-PCR and culture, respectively, which was similar to published reports in general populations [17, 18]. Because early antiviral treatment with oseltamivir resulted in a significantly shorter duration of viral shedding, this treatment may not only mitigate symptoms but may also reduce transmissions to susceptible household members who may be at increased risk of complications (eg, because of HIV-1 infection with advanced immunodeficiency) [19].

It has been hypothesized that immunocompromised patients may not develop protective immunity after 2009 H1N1 influenza infection. In our study group, all patients tested developed 2009 H1N1–specific antibodies. Whether this confers long lasting protection remains to be determined. However, 11 of 14 patients had a hemagglutination inhibition antibody titer of $\geqslant$1:40, which is considered to be protective in vaccine studies [20].

In conclusion, the clinical course of 2009 H1N1 influenza among HIV-1–infected school-aged children with CD4 counts >350 cells/μL receiving highly active antiretroviral therapy did not differ from that described for healthy children. Viral shedding was not prolonged and could be further shortened by early neuraminidase inhibitor treatment, and the humoral immune response seems to be preserved. However, the same may not apply for HIV-1–infected patients with advanced immunodeficiency and/or comorbid conditions and for those living in areas with restricted access to medical care. Therefore, in accordance with current recommendations, HIV-1–infected patients should be vaccinated, and in cases of suspected influenza

infection, an empirical early antiviral treatment is strongly advised.

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