Influenza Susceptibility, Severity, and Shedding in HIV-Infected Adults: A Review of the Literature

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Influenza is a common cause of respiratory illness in adults infected with human immunodeficiency virus (HIV), but current knowledge about seasonal and 2009 H1N1 pandemic influenza A (H1N1pdm) virus infections in HIV-infected persons is limited. In this paper, we review the existing literature regarding influenza susceptibility, severity, and shedding in HIV-infected adults. Data show HIV infection does not significantly increase susceptibility to influenza. AIDS is associated with greater seasonal influenza–related morbidity and mortality, but the risk associated with HIV infection among those with less immune suppression is largely unknown. Immunologic compromise has been shown to increase the magnitude and duration of influenza virus shedding; however, these studies are limited within HIV-infected populations. With regards to H1N1pdm, data are even more limited. Reports raise concern of increased severity among HIV-infected persons, although this may be driven by other comorbid illnesses. Prospective studies are needed among HIV-infected persons to more definitively investigate influenza susceptibility, severity, and shedding.

Susceptibility to Influenza Infection among HIV-Infected Adults

Published data on susceptibility of HIV-infected adults to influenza appear to be limited to 1 survey and 3 outbreak investigations. A study of 460 adults who presented with influenza-like illness (ILI) to an emergency department in New York City, New York, from January to April 1988 found the cumulative incidence of laboratory-confirmed influenza was 4.3%–12.5% among adults “at high risk” (not otherwise specified by the authors) for HIV infection [3]. Incidence rates among persons with and without HIV exposure risks were stated to be equivalent, but actual HIV infection status was not confirmed.

The 3 outbreak investigations compared seasonal influenza A incidence among HIV-infected and HIV-uninfected adults in residential drug rehabilitation facilities [4–6]. HIV infection was confirmed in these studies, but definitions of ILI varied (Table 1). Two of the studies conducted prior to the advent of highly...
active antiretroviral therapy (HAART) found no association between ILI and HIV infection, whereas a third conducted in 2004 did. In their 1988 investigation, Cohen et al [4] reported a nonsignificant difference in ILI attack rates in a comparison of 7 HIV-infected and 38 HIV-uninfected residents. CD4 cell counts in the HIV-infected individuals were not described. In their 1996 investigations, Fine et al [5] reported that 52% of 73 HIV-infected persons developed ILI compared with 25% of 60 HIV-uninfected persons ($P = .002$); however, after adjusting for smoking in the multivariate analysis, HIV infection was not associated with ILI. Most HIV-infected participants had CD4 cell counts of <300 cells/$\mu$L. Both studies were limited by small study populations, and neither study examined patients with high CD4 cell counts. In the third report, by Boschini et al [6] of a 2004 outbreak, the 177 HIV-infected residents of a drug rehabilitation facility were significantly more likely to have experienced ILI compared with the 1140 HIV-uninfected residents (relative risk, 1.77; 95% confidence interval [CI] 1.32–2.37). CD4 cell count (87% had >200 cells/$\mu$L and HIV RNA load (44% had <50 copies/mL) were not significantly associated with risk for developing ILI among HIV-infected persons. Although this study was larger, it did not describe or account for other potentially confounding comorbidities, most notably, tobacco smoking.

Additional data on influenza incidence in HIV-infected persons are available from influenza vaccination trials. Studies of adults in the United States military and in Japan each found that among 47 and 66 HIV-infected placebo recipients, respectively, 21% in both groups developed laboratory-confirmed influenza virus infection [7, 8]. In the Japanese study, attack rates did not differ significantly for participants with CD4 cell counts of <200 cells/$\mu$L and >200 cells/$\mu$L. In an Italian study of dual vaccination with pneumococcal and influenza vaccines, 62% of 60 HIV-infected participants receiving placebo injections developed influenza; however, the definition of influenza was not specified [9]. The findings of these studies should be interpreted with caution; they were not designed to investigate influenza illness in HIV-infected individuals and did not include HIV-uninfected comparison groups.

Incidence rates for symptomatic, laboratory-confirmed H1N1pdm virus infection among HIV-infected adults have not yet been reported. Reports of the prevalence of HIV infection among persons with confirmed H1N1pdm virus infection have provided early data about influenza susceptibility among HIV-infected adults (Table 1). In Brazil (estimated adult HIV infection prevalence, .6% [10]), 1.3% of 5747 laboratory-confirmed H1N1pdm cases reported during the first 4 months of the pandemic were among HIV-infected adults [11]. In a similar report from Germany (estimated adult HIV infection prevalence, .1% [10]), the frequency of immunosuppression (not further specified) among the first 9950 laboratory-confirmed cases of H1N1pdm was .1% [12]. Laboratory testing in these studies was not random and may have been limited to persons who met specific clinical criteria or enhanced in persons with underlying medical problems (eg, HIV infection). Additionally, neither study reported the frequency of other comorbidities or immunosuppressive conditions among persons with HIV infection that could have affected influenza susceptibility, nor did they include data on CD4 cell counts. Nonetheless, neither study suggested that HIV-infected persons were substantially overrepresented among persons with H1N1pdm.

Three studies have reported rates of H1N1pdm virus infection among HIV-infected and HIV-uninfected adults. The first study found 11 (55%) of 20 HIV-infected emergency department patients with ILI in Mexico City, Mexico, had a nasopharyngeal specimen positive for H1N1pdm virus compared with 120 (15%) of 812 HIV-uninfected patients ($P < .001$) [13]. Notably, the HIV-infected patients were older, although not significantly (median age, 47 vs 36 years; $P = .12$), and more likely to smoke tobacco (63% vs 13%; $P = .001$) than the HIV-uninfected patients. Conversely, among 2106 adults with acute respiratory illness presenting for care in Barcelona, Spain, 3% of nasopharyngeal specimens collected from HIV-infected adults yielded detectable H1N1pdm virus compared with 27% of specimens collected from 567 HIV-uninfected patients [14]; like the first study, HIV-infected patients were older (mean age, 44 vs 39 years; $P = .02$) and more likely to smoke tobacco (54% vs 13%; $P < .001$). A serology-based study among women in the United States reported incidences of H1N1pdm (defined as a ≥4-fold increase in H1N1pdm hemagglutination inhibition antibody titer in serum samples collected in March–September 2009 compared with the same months in 2008 or 2007) of 20.6 (95% CI, 6.1–69.6) and 24.6 (95% CI, 7.4–81.4) per 100 person years among HIV-infected women ($n = 1270$) and similar HIV-uninfected women ($n = 531$), respectively [15].

In summary, despite limited and heterogeneous methodologies, available data suggest HIV-infected adults are not substantially more susceptible to influenza virus infection, including H1N1pdm virus infection, than adults in the general population. The role of CD4 cell count in influenza susceptibility remains unclear. Other risk factors for influenza infection, notably tobacco smoking, are more prevalent among HIV-infected individuals [16], and it may be these factors that mediate any apparent relationship between HIV infection and observed increases in influenza susceptibility.

**Severity of Influenza Illness in HIV-Infected Adults**

Early studies provided inconsistent results about the severity of influenza illness among HIV-infected adults. Several case reports
Table 1. Reported Influenza Susceptibility Among Adults With HIV Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Period</th>
<th>Influenza virus strain</th>
<th>Outcome</th>
<th>Outcome frequency</th>
<th>Additional findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seasonal influenza incidence in HIV-infected versus uninfected persons</strong></td>
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</tr>
<tr>
<td>Cohen and Macauley (1989) [4]</td>
<td>45 drug treatment facility residents with known HIV status during outbreak</td>
<td>March 1988</td>
<td>A(H1N1)</td>
<td>ILI (fever, chills, myalgia, sore throat, and nonproductive cough)</td>
<td>HIV-infected, 0/7; HIV-uninfected, 14/38 (37%)</td>
<td></td>
</tr>
<tr>
<td>Fine et al (2001) [5]</td>
<td>133 residents and staff of drug treatment facility during outbreak</td>
<td>November–December 1996</td>
<td>A(H3N2)</td>
<td>ILI (temperature of &gt;37.8°C and either cough or sore throat) or laboratory-confirmed influenza</td>
<td>HIV-infected, 38/73 (52%); HIV-uninfected, 15/60 (25%); HIV infection not associated with ILI in multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>Boschini et al (2006) [6]</td>
<td>1310 drug treatment facility residents during outbreak</td>
<td>February–March 2004</td>
<td>A(H3N2)</td>
<td>ILI (temperature of &gt;38.0°C plus constitutional symptom plus respiratory symptom)</td>
<td>HIV-infected, 44/171 (26%); HIV-uninfected, 165/1140 (14%); RR, 1.77; 95% CI, 1.32–2.37; No significant difference in ILI attack rate among HIV-infected persons by CD4 cell count or HIV RNA load</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence of immunosuppression or HIV infection among persons with 2009 H1N1 pandemic influenza A</strong></td>
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<td></td>
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<tr>
<td>Giseldorf and Poggensee (2009) [12]</td>
<td>9950 laboratory-confirmed cases in Germany</td>
<td>April–August 2009</td>
<td>2009 pandemic A(H1N1)</td>
<td>Immune suppression</td>
<td>5/5885 (.1%)</td>
<td>Population HIV infection prevalence, .1%</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; HIV, human immunodeficiency virus; ILI, influenza-like illness; RR, relative risk.
Table 2. Reported Seasonal Influenza-Associated Morbidity and Mortality Among Adults With HIV Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Period</th>
<th>Outcome(s)</th>
<th>Outcome frequency</th>
<th>Additional findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuzil et al (1999) [22]</td>
<td>Adult women enrolled in Tennessee Medicaid program</td>
<td>1974–1993</td>
<td>Influenza-attributable rates of hospitalization and death due to cardiopulmonary events during influenza seasons per 10,000 person-months of observation</td>
<td>Women with high-risk conditions (including HIV): aged 15–45 years, 10.3; aged 46–64 years, 26.4. Low-risk women: aged 15–45 years, 2.0; aged 46–64 years, 2.9.</td>
<td>HIV infection prevalence, .02%</td>
</tr>
<tr>
<td>Lin and Nichol (2001) [23]</td>
<td>Persons with AIDS and general US population &lt; 13 years old from national cause-of-death data</td>
<td>1991–1994</td>
<td>Deaths due to pneumonia or influenza during influenza seasons</td>
<td>Adults and adolescents with AIDS, 9.4–14.7/10,000; adults and adolescents in US population, 1.1–1.2/10,000</td>
<td>CD4 cell counts among HIV-infected persons with and without ILI did not differ significantly; most counts were &lt;300 cells/μL</td>
</tr>
<tr>
<td>Fine et al (2001) [5]</td>
<td>133 residents and staff of drug treatment facility during outbreak</td>
<td>November–December 1996</td>
<td>Severe influenza (ie, requiring emergency department or hospital visit or prolonged illness)</td>
<td>HIV-infected, 8/38 (21%); HIV-uninfected, 0/15; P=.06</td>
<td>With pneumonia: mean CD4 cell count, 304 cells/μL; mean HIV RNA load, 3.37 log_{10} copies/mL. Without pneumonia: mean CD4 cell count, 346 cells/μL; mean HIV RNA load, 3.25 log_{10} copies/mL</td>
</tr>
</tbody>
</table>

**NOTE.** HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; ILI, influenza-like illness; US, United States.
noted high frequencies of lower respiratory tract infection, prolonged illness, hospitalization, and death among HIV-infected patients with influenza [17–20], and one ecological study noted that the mortality among 25–44-year-old adults in cities with high cumulative AIDS incidence exhibited seasonality typical of influenza [21].

Two studies conducted before the widespread use of HAART estimated excess influenza-associated morbidity and mortality in HIV-infected compared with HIV-uninfected persons while accounting for severity of illness. Both studies suggested that HIV-infected persons with influenza experienced higher rates of hospitalization and death [22, 23]. The first study compared the incidence rates of acute cardiopulmonary events resulting in hospitalization or death among adult women enrolled in a state Medicaid program between 1973 and 1993 during influenza and peri-influenza seasons [22]. HIV-infected women experienced the highest influenza-attributable risk of acute cardiopulmonary events; however, this risk did not differ statistically significantly from corresponding rates for women with other high-risk conditions (eg, chronic heart disease, malignancy, or diabetes). In addition, HIV infection prevalence was low (.02%), so confidence intervals for the estimated risk of influenza attributable to HIV infection overlapped with the estimates for many other high-risk conditions. The second study estimated excess deaths due to pneumonia or influenza for adolescents and adults with AIDS from the multiple cause-of-death data of the Centers for Disease Control and Prevention. The authors calculated the differences in annual rates of death during each of 3 influenza seasons (1991–1992, 1992–1993, and 1993–1994) and corresponding non–influenza periods for HIV-infected persons compared with the remaining population of presumed uninfected persons in each group [23]. Excess death rates attributable to pneumonia or influenza were 8.5–10.3 times higher in patients with AIDS compared with the persons in the general population and 106–161 times higher compared with the subset of adults aged 25–54 years. Notable limitations of both studies were the inability to account for other respiratory infections, such as pneumococcal pneumonia, that demonstrate seasonality and could have contributed to excess mortality or events in this population, and the lack of data regarding the immune status (eg, CD4 cell count) of the HIV-infected populations.

Four additional studies conducted during the HAART era provide insight into the relationship between CD4 cell count and seasonal influenza severity, although these studies reached differing conclusions. In the above-mentioned influenza outbreak investigation at a drug treatment facility [5], 8 (21.1%) of 38 HIV-infected patients with ILI had “more severe disease” (ie, they required an emergency department visit, required hospitalization, or experienced >14 days of illness) compared with 0 of 15 HIV-uninfected individuals with ILI (P = .06). However, the 8 HIV-infected persons with more severe disease were all tobacco smokers, and 3 had additional comorbid illnesses, making it difficult to draw conclusions about the independent contribution of HIV infection to influenza severity in this study. Median CD4 cell counts did not differ significantly among HIV-infected patients when stratified by ILI severity, but nearly all patients in this study had CD4 cell counts of <300 cells/μL. In another above-described outbreak investigation [6], HIV-infected persons had a higher risk of complications (odds ratio, 5.12; 95% CI, 2.52–10.20); however, low CD4 cell counts and older age were not associated with increased risk of complications (eg, bronchitis, pneumonia, meningitis, and sinusitis). Additional comorbidities were not described. A review of 43 cases of laboratory-confirmed influenza occurring over a 3-year period at a large, hospital-affiliated HIV clinic with a primarily rural patient population found that 16% of HIV-infected patients were diagnosed with pneumonia—a rate the authors state was comparable to that previously reported for the general population [24]. In this study, most patients had CD4 cell counts of >200 cells/μL and were receiving HAART. Finally, a second study by Neuzil et al [25] compared hospitalizations for cardiopulmonary illness during influenza seasons from 1995 through 1999 using a state Medicaid database. The authors observed that HIV-infected enrollees experienced fewer influenza-attributable hospitalizations in the years during which HAART use increased (5 hospitalizations per 1000 persons; 95% CI, −0.5 to 11) compared with prior years (48 hospitalizations per 1000 persons; 95% CI, 16–91). CD4 cell counts were not reported, and it is thus difficult to directly associate reductions in hospitalizations with improved immune function, although this seems a reasonable hypothesis.

Early reports of patients hospitalized with probable or confirmed H1N1pdm virus infection have found that the fraction of persons with HIV infection exceeded the prevalence of HIV infection in the general population (Table 3). In 1 French and 3 North American studies, 1%–6% of patients hospitalized with H1N1pdm were HIV-infected [26–29], although HIV infection prevalence in the corresponding regions was <1% [10]. Studies from Reunion Island, Ireland, Mexico, Andalusia, and the Netherlands reported that the prevalences of any immunosuppressive condition not otherwise specified among patients hospitalized with H1N1pdm were 2%–12% [30–34]. However, in those studies that also reported outcome data, the durations of hospitalization, rates of intensive care unit (ICU) admission, and death rates among patients with H1N1pdm did not differ meaningfully between patients with or without either HIV infection or an otherwise unspecified immunosuppressive condition.

Four reports have described the prevalences of HIV infection or otherwise unspecified immunosuppressive conditions among fatal cases of confirmed H1N1pdm. In a summary report of 684 influenza-associated deaths in 28 countries, comorbid
Table 3. Reported Prevalences of Comorbid Conditions, Rates of Intensive Care Unit Admission, Duration of Hospitalization, and Death Rates Among Persons Hospitalized With 2009 H1N1 Pandemic Influenza A

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Regional HIV infection prevalence [%]</th>
<th>Study population</th>
<th>Total cases</th>
<th>HIV/IS (%)</th>
<th>Total admitted to ICU</th>
<th>Median hospital stay, days (range)</th>
<th>Died</th>
<th>Total cases</th>
<th>HIV/IS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain et al (2009), Peters et al (2010) [26, 51]</td>
<td>United States</td>
<td>.6%</td>
<td>Hospitalized adults with laboratory-confirmed infection</td>
<td>150</td>
<td>9 (6)</td>
<td>43</td>
<td>1 (2)</td>
<td>3 (1–49)</td>
<td>5 (1–10)</td>
<td>14</td>
</tr>
<tr>
<td>Louie et al (2009) [28]</td>
<td>California</td>
<td>&lt;.5% [52]</td>
<td>Adults and children who were hospitalized or died with confirmed or probable infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>744</td>
<td>22 (3)</td>
<td>250</td>
<td>NR</td>
<td>4 (1–74)</td>
<td>NR</td>
<td>110</td>
</tr>
<tr>
<td>Kumar et al (2009) [27]</td>
<td>Canada</td>
<td>.4%</td>
<td>Critically ill hospitalized persons with confirmed or probable infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>168</td>
<td>2 (1)</td>
<td>168</td>
<td>2 (1)</td>
<td>NR</td>
<td>NR</td>
<td>29</td>
</tr>
<tr>
<td>Fuhrman et al (2010) [29]</td>
<td>France</td>
<td>.4%</td>
<td>Hospitalized persons with probable or laboratory-confirmed infection</td>
<td>758</td>
<td>NR</td>
<td>244</td>
<td>2 (&lt;1)</td>
<td>NR</td>
<td>NR</td>
<td>37</td>
</tr>
<tr>
<td>Martinez et al (2010) [14]</td>
<td>Spain</td>
<td>.5%</td>
<td>Adults with confirmed infection</td>
<td>623</td>
<td>56 (9)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Immunosuppressive condition not otherwise specified**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Regional HIV infection prevalence [%]</th>
<th>Study population</th>
<th>Total cases</th>
<th>HIV/IS (%)</th>
<th>Total admitted to ICU</th>
<th>Median hospital stay, days (range)</th>
<th>Died</th>
<th>Total cases</th>
<th>HIV/IS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullen et al (2009) [31]</td>
<td>Ireland</td>
<td>.2%</td>
<td>Hospitalized persons with laboratory-confirmed infection</td>
<td>205</td>
<td>17 (9)</td>
<td>19</td>
<td>0 (0)</td>
<td>6 (0–79)</td>
<td>4 (1–22)</td>
<td>4</td>
</tr>
<tr>
<td>Dominguez-Cherit et al (2009) [32]</td>
<td>Mexico</td>
<td>.3%</td>
<td>Critically ill persons with confirmed, probable, or suspected infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58</td>
<td>2 (3)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>Mayoral-Cortés et al (2009) [33]</td>
<td>Andalusia, Spain</td>
<td>NR</td>
<td>Hospitalized persons with laboratory-confirmed infection (data on comorbid conditions reported for 137 persons)</td>
<td>311</td>
<td>17 (12) &lt;sup&gt;d&lt;/sup&gt;</td>
<td>28</td>
<td>2 (7)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>van ’t Klooster et al (2010) [34]</td>
<td>Netherlands</td>
<td>.2%</td>
<td>Hospitalized persons with laboratory-confirmed infection (data on comorbid conditions reported for 1152 persons)</td>
<td>2181</td>
<td>24 (1) &lt;sup&gt;d&lt;/sup&gt;</td>
<td>219</td>
<td>3 (1)</td>
<td>NR</td>
<td>NR</td>
<td>53</td>
</tr>
</tbody>
</table>

**Note.** ICU, intensive care unit; IS, immunosuppressive condition not otherwise specified; HIV, human immunodeficiency virus; HIV/IS, persons with HIV infection or immunosuppressive condition not otherwise specified; NR, not reported.

<sup>a</sup> Data in table includes adults only except for hospital days.

<sup>b</sup> Critically ill persons were defined as having been admitted to an ICU, required mechanical ventilation, had a fraction of inspired oxygen of >60%, or received inotropic or vasopressor infusions.

<sup>c</sup> Admitted to ICU or died.

<sup>d</sup> Among the patients for whom data on the presence or absence of comorbid conditions were available.
conditions were reported present in 193 (28%) deaths, but HIV infection was not specifically among the listed conditions [35]. Sixteen patients had underlying “immunodepression” and 19 had “infectious diseases other than flu.” Most of the countries that contributed data to this report had low HIV infection prevalences (<1%). A study in Peru, where HIV infection prevalence is ~.5%, reported that 3.5% of 143 deaths due to confirmed H1N1pdm had an “infectious” comorbidity, presumably an immunosuppressive condition [36]. A report from South Africa, where HIV infection prevalence is ~18% [10], observed that among 91 patients who died of confirmed H1N1pdm, 17 (53%) of 32 patients whose HIV status was known were HIV-infected. Data on CD4 cell counts, use of antiretroviral therapy or anti-influenza antiviral therapy, and comorbid conditions (most notably tuberculosis) were not provided. Tuberculosis was reported in 10% of patients who died of influenza, and nearly two-thirds of HIV-infected patients who died were also pregnant. It is thus difficult to discern to what degree immunosuppression from HIV infection might have contributed to these deaths; however, this single study raises concern that HIV infection increased influenza severity and risk of death, and that during influenza pandemics, countries with high HIV infection prevalences could experience substantial excess influenza-related mortality. Finally, in a study from New York City, New York, where HIV prevalence is ~1.4% [37], 7 (15%) of 47 confirmed fatal H1N1pdm cases occurred among HIV-infected persons [38]. Among a separate convenience sample of patients hospitalized with confirmed or probable H1N1pdm, the fraction diagnosed with immunosuppression (not otherwise specified) was greater among the 28 decedents than among the 95 survivors (29% vs 3%; P < .05); however, other underlying risk conditions were quite prevalent, including obesity (58%) and chronic pulmonary disease (32%), and the independent contribution of HIV infection to risk of death was not reported.

Four additional studies compared H1N1pdm severity in HIV-infected individuals with that in HIV-uninfected individuals. The first, from Mexico City, Mexico, reported similar rates of hospitalization (27% vs 25%; P = .81), severe disease (9% vs 7%; P = .68), and death (9% vs 5%; P = .86) in HIV-infected persons compared with HIV-uninfected persons diagnosed with laboratory-confirmed H1N1pdm virus infection [13]. Another study, also from Mexico City, reported high rates of hospitalization (52%), mechanical ventilation (26%), and death (22%) among 27 HIV-infected patients with confirmed H1N1pdm virus infection [39]. Thirteen (48%) of these patients were diagnosed with HIV-associated pulmonary opportunistic infections (OIs) at presentation, and it was these severely immunosuppressed patients (median CD4 cell count, 83 cells/μL; interquartile range [IQR], 43–169 cells/μL) who comprised all persons who required mechanical ventilation (n = 7) or who died (n = 6). Among the 14 patients without OIs (median CD4 cell count, 326 cells/μL; IQR, 162–402 cells/μL), only 2 required hospitalization, none required mechanical ventilation, and none died, suggesting that severity of illness may have been related to the pulmonary OI and not necessarily influenza. A third report from a case-control study conducted in Barcelona, Spain, found that among a subset of patients with confirmed H1N1pdm virus infection and no additional comorbidities, HIV-infected persons compared with HIV-uninfected were not more likely to have longer hospitalizations (mean duration, 1.1 vs 2.0 days; P = .08), develop complications (13% vs 11%; P = .71), or die (0% vs 2%; P = .74) [14]. Finally, a fourth report from Singapore compared 11 HIV-infected persons (cases; median CD4 cell count, 223 cells/μL; range, 113–158 cells/μL) with confirmed H1N1pdm virus infection to 33 persons without known HIV infection (controls) and without any known comorbid conditions and to 33 persons (controls) with at least 1 comorbid condition; no significant differences were observed comparing cases to either control group in terms of durations of illness, fractions of the populations hospitalized, fractions of the populations administered ICU care, or lengths of hospitalization [40].

In summary, AIDS is associated with greater influenza-related morbidity and mortality, but the risk associated with HIV infection at higher CD4 cell counts is largely unknown. Limited available data indicate that a greater proportion of persons hospitalized with confirmed H1N1pdm virus infections are HIV-infected compared with the general population; however, a potential bias to hospitalize and test HIV-infected persons with suspected ILI could have increased their representation among hospitalized patients. There does not appear to be a substantially increased risk for H1N1pdm-associated ICU admission or death among HIV-infected adults in areas with low HIV infection prevalence. Data from a single resource-limited region raise concerns about the possibility of more widespread severe influenza illness in regions with high HIV infection prevalence. Prospective studies of laboratory-confirmed influenza infection that include information on CD4 cell counts, HAART use, comorbid conditions, and clinical outcomes are necessary to define the contribution of HIV infection to the severity of influenza.

Influenza Shedding in HIV-Infected Adults

Knowing whether HIV-infected persons shed influenza virus differently from HIV-uninfected persons would help inform infection control measures and influenza prevention and treatment guidelines for this population. Comprehensive data on shedding of influenza viruses among adults living with HIV infection do not yet exist. In otherwise healthy adults, the median time to cessation of viral shedding has been reported to be <1 week [41]; early antiviral therapy may decrease the duration of shedding [42]. Case reports in persons immunosuppressed for reasons other than HIV infection have described shedding of seasonal influenza virus [43–
and of H1N1pdm virus [48, 49] for weeks to months and not uncommonly in association with the development of resistance to antivirals used to treat the infection, including resistance of H1N1pdm virus to oseltamivir [48]. Among the cases described in one of the Mexico City, Mexico, series of H1N1pdm virus infections, shedding (ie, nasopharyngeal swabs that tested positive by reverse-transcription polymerase chain reaction) was detected among 6 (60%) of 10 HIV-infected adults tested 2–10 days after beginning oseltamivir treatment [39]. One study has examined shedding following intranasal administration of a live attenuated vaccine containing 3 influenza strains; this study included 54 HIV-uninfected and 57 HIV-infected adults (all CD4 cell counts, >200 cells/μL; all HIV RNA loads, <10,000 copies/mL) [50]. Culturable virus (an influenza B strain) was recovered from 1 adult, an HIV-infected participant, 5 days after vaccination; clinical illness was not described.

Conclusions

Although HIV infection does not appear to significantly increase susceptibility to seasonal influenza virus infections, case series and retrospective cohort studies from the pre-HAART era have demonstrated increased illness severity among HIV-infected adults, particularly those with AIDS. Data on illness severity for seasonal influenza are lacking for contemporary patients, but observed reductions in influenza-associated hospitalizations among HIV-infected persons with the advent of HAART suggest that seasonal influenza severity may be lower among patients with higher CD4 cell counts. Some reports raise concern that hospitalizations and deaths due to H1N1pdm could be more common among HIV-infected persons, although these outcomes might have been related to other comorbid illnesses. Reports from regions with low HIV infection prevalence are reassuring; however, data from a single high-prevalence, resource-constrained setting raises concern that HIV-infected persons might experience a substantially increased risk for death, due to greater immunocompromise and a higher prevalence of other comorbid conditions, such as tuberculosis. Prospective studies are needed to better define influenza susceptibility, severity, and shedding among HIV-infected persons. Prevention and treatment of other underlying conditions (including tobacco cessation counseling), in addition to annual influenza vaccination, should continue to be part of routine HIV clinical care.

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References


