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Respiratory viruses, particularly influenza viruses, respiratory syncytial virus (RSV), parainfluenza viruses, and adenoviruses, are ubiquitous pathogens among humans, especially among young children. However, relatively little is known about the impact of these common infections on individuals with the human immunodeficiency virus (HIV). A review of the literature identifies three key areas that need further exploration. First, moderate-to-severe and even fatal lower respiratory viral illnesses in HIV-infected individuals have been reported. In general, the clinical presentation of these respiratory viral infections in persons with HIV infection is similar to their presentation in individuals without HIV infection. The major exception is the occurrence of fulminant, and often fatal, disseminated adenovirus infection in adults and children with HIV disease. Despite these reports, no information is available regarding the frequency of moderate-to-severe respiratory viral illnesses in individuals with HIV infection. Epidemiologic studies of respiratory viral illnesses in cohorts of HIV-infected adults and children are needed. Second, prolonged shedding of respiratory viruses for weeks and even months has been documented in HIV-infected adults and children. The frequency of prolonged shedding in this population has not been well defined, but data from a small newborn cohort study suggest that, at least for RSV, prolonged shedding is common. Prolonged respiratory viral shedding has implications for infection control in medical facilities where HIV-infected individuals are treated and in nursing homes, child care centers, and group foster homes that provide care for HIV-infected individuals. Therapies to help eliminate these chronic viral infections should be explored. Finally, indirect evidence suggests that respiratory viral infection may result in changes in HIV replication and, theoretically, HIV disease progression. Increased HIV-1 replication has been demonstrated in vitro in T lymphoma cells exposed to genetic material from adenovirus. Increased HIV replication in peripheral blood from adults following inactivated influenza vaccination has been reported. The impact of natural respiratory viral infection (and perhaps vaccination against these pathogens) on HIV replication and disease progression will be an important area of study. Am J Med. 1997;102(3A):19–24 © 1997 by Excerpta Medica, Inc.

Respiratory viral infections are among the most common human illnesses, particularly among young children. However, little is known regarding the impact of these ubiquitous viruses on individuals with human immunodeficiency virus (HIV) disease. HIV-infected individuals may have one of several conditions that are associated with increased morbidity and mortality from common respiratory viral infections, including humoral and cellular immunodeficiency, chronic pulmonary disease, and cardiac disease.1–4

**Epidemiology of Respiratory Viruses**

The principal viruses that cause respiratory tract infections and their common clinical presentations in children are listed in Table I. Preschool children can have 5–9 respiratory tract infections per year, the majority of which are caused by these viruses.5 Virtually all preschool children will contract infections with influenza viruses, respiratory syncytial virus (RSV), parainfluenza viruses, and adenoviruses. Rhinoviruses and coronaviruses are also frequent causes of respiratory illness. It is likely that, by adulthood, all individuals will have been infected by virtually all the viruses listed in Table I.6–9 In addition, repeated infection with RSV and influenza is very common because of either incomplete immunity resulting from primary infection (i.e., RSV) or antigenic variation of the virus itself (i.e., influenza).

**Immune Responses to Respiratory Tract Infections**

Humoral factors, and particularly serum antibody, are associated with at least partial protection from respiratory viruses in humans.10,11 Pre-existing anti-
body is associated with attenuated illness, although protection from subsequent re-infection may be incomplete. For example, children can be repeatedly infected with RSV, although subsequent illnesses are usually less severe than the primary infection. Complete recovery from and clearance of these viral infections are likely mediated by virus-specific cellular mechanisms.

HIV-infected individuals have deficiencies in both humoral and cellular defenses. Therefore, infection by common respiratory viruses may present differently in this population than in immunocompetent individuals. Since most adults with HIV disease acquired their infection as adults or adolescents, they probably have experienced infections by most of the common respiratory viruses and thus have some pre-existing immunity. For this reason, respiratory viral infections may be a greater clinical problem in HIV-infected infants and children, who may not have pre-existing immunity to these pathogens. Clearance of respiratory viruses is likely to depend on cellular immune mechanisms, and HIV-infected individuals are at theoretical risk for prolonged infections caused by these viruses.

**SEVERITY OF RESPIRATORY VIRAL ILLNESSES IN HIV-INFECTED INDIVIDUALS**

Little is known regarding the severity of viral respiratory disease in HIV-infected individuals. It may be anticipated that the immune deficiencies associated with HIV infection may result in more severe illnesses due to respiratory viruses. Immunologic mechanisms, particularly cellular immune responses, are important components of the inflammatory response to respiratory viruses, so predicting illness severity in HIV-infected individuals becomes complicated.

Moderate to severe illnesses caused by these viruses in HIV-infected adults and children have been reported. Few prospective cohort or population-based studies are available with which to address their frequency. Also, it must be recognized that severe and even fatal respiratory illnesses can occur in the general population, albeit infrequently.

**Influenza Viruses**

There have been several reports of influenza infections in HIV-infected adults and children (Table II). In HIV-infected adults, influenza has been associated with lower respiratory tract illness (LRTI), but the clinical presentation was not dramatically different from that seen in the general population. The only evidence to support increased severity of influenza in adults with HIV disease is a report of an increase in pneumonia deaths among persons aged 25–44 (primary adult acquired immunodeficiency syndrome [AIDS] group) during the peak influenza months in cities with a high incidence of HIV infection. However, in this report, no direct association between AIDS and deaths from influenza could be made.

There has been one case report involving a 7-year-old HIV-infected child who had a common clinical presentation, albeit prolonged illness, associated with influenza A infection. A second report involved an HIV-infected child who had a febrile seizure associated with influenza B infection that was otherwise typical. A fatal LRTI was associated with influenza A (H3N2) in an HIV-infected child with pre-existing cardiomyopathy. Another HIV-infected infant had a fatal LRTI associated with H3N2 infection; however, cytomegalovirus (CMV) and *Pneumocystis carinii* were also isolated from the lung of this patient.

**Respiratory Syncytial Virus**

RSV infections in HIV-infected individuals have not been dramatically more severe than those observed in the general population (Table II). A somewhat prolonged LRTI infection caused by RSV has been reported in an HIV-infected adult.
### Summary of Reports Regarding Respiratory Viral Illnesses in HIV-Infected Individuals

| Virus       | Ref | Population                | Severity of Disease                                                                 | Evidence of Prolonged Infection |
|-------------|-----|---------------------------|-------------------------------------------------------------------------------------|---------------------------------|
| Influenza   | 17  | Population of adults      | Increased pneumonia deaths among HIV age risk group during influenza season          | NA                              |
|             | 15  | Six HIV + adults          | Relatively common clinical presentation (4 cases type B, 2 cases H1N1)               | Prolonged fever                 |
|             | 16  | Case: HIV + adult         | Typical clinical presentation (H3N2)                                                | NA                              |
|             | 18  | Case: HIV + child         | Typical but prolonged illness (type A, not subtyped)                                 | Prolonged shedding (at least 2 months) |
|             | 19  | Case: HIV + child         | Fatal LRTI (H3N2, pre-existing cardiomyopathy)                                      | Shed H3N2 “at least 3.5 weeks”  |
|             | 20  | Case: HIV + child         | Typical presentation with influenza B                                               | NA                              |
| RSV         | 21  | Case: HIV + adult         | Hypoxic LRTI, recovered                                                             | Shed RSV 17 days                |
|             | 22  | Series: 10 HIV + children | 20% mortality (both had bacterial superinfection), paucity of wheezing              | 3 children shed RSV from 30 to 90 days |
|             | 19  | 16 cases in HIV + children| 2 deaths: 1 infected with CMV & P. aeruginosa; 2nd no infection reported          | Shedding up to 56 days          |
|             | 23  | Case report: HIV + child  | Severe respiratory distress, coinfected with parainfluenza type 3 & P. carinii     | Shed RSV at least 3 weeks       |
|             | 24  | Series: 10 HIV + children | Typical clinical presentation with exception of paucity of wheezing                  | Median RSV shedding 30 days (range, 1-199) in children with advanced HIV disease |
| Parainfluenza| 23  | Cases: 2 HIV + children   | Both had “respiratory distress,” one “severe.” Both had coinfection with parainfluenza type 3 & P. carinii; 1 also had adenovirus | Shed parainfluenza for 1 to 3 months |
|             | 25  | Case: HIV + child         | Pneumonia (not fatal); also Legionella and P. carinii with parainfluenza type 3    | NA                              |
|             | 26  | Case: HIV + child         | Fatal measles giant cell pneumonia with parainfluenza type 3 & CMV present          | NA                              |
|             | 19  | Cases: 5 HIV + children   | Status asthmaticus with parainfluenza type 2                                      | Shed parainfluenza type 2 “about 1 year” |
|             |     |                           | Four children had parainfluenza type 3: 1 asymptomatic, 1 wheezing, 2 pneumonia (one fatal associated with P. carinii) | Two children shed parainfluenza type 3 for 2 and 9 months, respectively. |
| Adenovirus  | 27  | Case: HIV + adult         | Fatal respiratory failure with adenovirus type 29                                   | NA                              |
|             | 28  | Cases: HIV + adult and 2 children | All fatal disseminated disease with hepatic necrosis. Two children had adenovirus types 1 and 2; one adult had type 3 | NA                              |
|             | 29  | Case: HIV + child         | Fatal disseminated disease with type 5                                              | NA                              |
|             | 19  | Case: HIV + child         | Fatal pneumonia with type 5                                                         | NA                              |

CMV = cytomegalovirus; HIV = human immunodeficiency virus; LRTI = lower respiratory tract infection; NA = not applicable; RSV = respiratory syncytial virus.

RSV infection has been reported more often in HIV-infected children than in HIV-infected adults. In one series of 10 hospitalized HIV-infected children with RSV infection, the mortality rate was 20%.22 However, the two children who died had bacterial superinfection at the time of death. Of note, few of the HIV-infected children with RSV illness had wheezing, which was frequently present in non-HIV-infected controls hospitalized with RSV. In another report of 16 cases of RSV in HIV-infected children, two deaths were reported: One child was co-infected with CMV and P. carinii, and the other had no other pathogen identified at the time of death.19 The remaining 14 cases were described as unremarkable. Asymptomatic RSV infection was documented for at least 3 weeks in an HIV-infected child recovering from severe LRTI associated with parainfluenza type 3 and other pathogens.23 Finally, in a prospective birth cohort study that specifically addressed respiratory viruses, the severity of RSV illness was similar.
in HIV- and non-HIV-infected children. In this study, no deaths were associated with 10 RSV infections in eight HIV-infected children. However, HIV-infected children with LRTI were more likely to have pneumonia than non-HIV-infected children, who were more likely to have bronchiolitis (wheezing).

Parainfluenza Viruses

There have been case reports of parainfluenza virus infections in HIV-infected children (Table II). In one report, parainfluenza type 3 was isolated from two children, one with “severe respiratory distress” and the other with pneumonia. Both of these children had coinfections with *P. carinii* as well as other possible pathogens. In another report, a child had interstitial pneumonia associated with *P. carinii* and Legionella, as well as parainfluenza type 3. One fatal case of measles giant cell pneumonia was reported in which the child also had CMV and parainfluenza type 3 at the time of illness. Another fatality was associated with *P. carinii* and coinfection with parainfluenza type 3. In all these reports, it was difficult to attribute severe or fatal illnesses solely to infection by parainfluenza virus.

In cases involving solely parainfluenza viruses, the illnesses were generally less severe. One case involved parainfluenza type 2 isolated from a 6-year-old HIV-infected child hospitalized with status asthmaticus. In this same review, the author relates three cases of isolated parainfluenza type 3 infections in HIV-infected children: One child was asymptomatic, another presented with wheezing and a lower lobe infiltrate, and a third child had an exacerbation of lymphoid interstitial pneumonitis.

Adenoviruses

The most consistently severe cases of respiratory viral infections involved adenovirus infection in HIV-infected individuals (Table II). One case report described an adult with pneumonia associated with adenovirus type 29 infection that progressed to respiratory failure and death. In a review of 16 patients with fatal disseminated adenovirus infection involving hepatic necrosis, three had HIV infection (two were children), and adenovirus types 1, 2, and 3 were involved in these fatal cases. In another report, an HIV-infected child initially had respiratory distress associated with an adenovirus type 5 infection that progressed to disseminated disease and death. Finally, an untyped adenovirus was isolated from a 6-month-old baby with presumed HIV infection in whom a fatal hemorrhagic illness developed.

Rhinoviruses and Coronaviruses

No severe illnesses associated with these viruses have been reported.

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**PROLONGED INFECTION DUE TO RESPIRATORY VIRUSES IN HIV-INFECTED INDIVIDUALS**

In immunocompetent individuals, RSV, influenza viruses, and the parainfluenza viruses result in self-limited infections, with virus shedding often detected for the first 1–2 weeks after infection. Despite relatively few published reports, respiratory viral infections in HIV-infected individuals appear to be prolonged compared with such infection in immunocompetent individuals. Impaired cell-mediated clearance of respiratory viruses from HIV-infected individuals may be responsible for these prolonged infections. Long-term shedding of respiratory viruses has important infection control implications, because HIV-infected individuals frequently visit medical facilities or are admitted to the hospital. In addition, prolonged respiratory viral shedding by HIV-infected individuals may have an impact on nursing homes, day care centers, or group foster homes, where other high-risk individuals may be exposed to these respiratory viruses.

**Influenza**

One series of six HIV-infected adults hospitalized with influenza has been reported. Although viral shedding was not assessed, clinical illness appeared to be prolonged (median duration of fever, 7.5 days) compared with such illness in normal adults. Prolonged shedding of influenza virus has been reported in HIV-infected children. Influenza A (H3N2) was detected for “at least 3.5 weeks” in one child, and another report documented influenza A (not subtyped) nasopharyngeal shedding for at least 2 months. The child in the latter report was treated with rimantadine, with temporary disappearance of influenza A. Nasopharyngeal shedding of influenza A virus later recurred in this patient and was detected up to 150 days after the initial infection.

**Respiratory Syncytial Virus**

Several reports of prolonged RSV shedding in HIV-infected individuals have been published. One HIV-infected adult shed RSV for at least 17 days. In a series of 10 HIV-infected children hospitalized with RSV, three children shed virus for 30, 45, and 90 days, respectively. Two of these long-term RSV shedders were treated with ribavirin (presumably initially), without apparent cessation of shedding. In another report of 16 cases of RSV in HIV-infected children, RSV shedding was detected “up to 56 days.” A third report demonstrated RSV shedding for at least 3 weeks. In a prospective cohort study, RSV shedding was prolonged in children with more advanced HIV disease (median, 30 days; range, 1–199 days).
In the child who shed RSV for 199 days, neither nebulized ribavirin for 5 days nor 1 g/day of commercial intravenous immunoglobulin (unknown RSV titer) for 5 days was able to eradicate RSV shedding.

Parainfluenza

Prolonged shedding of parainfluenza viruses in HIV-infected children has been reported. In the first report, two children shed parainfluenza type 3 virus for 1 and 3 months, respectively. A second report also documented parainfluenza type 3 virus shedding for 2 and 9 months, respectively. Perhaps the most impressive case of shedding involved an HIV-infected child who shed parainfluenza type 2 virus for “about a year.”

Adenoviruses

Discussing prolonged infection of these viruses is difficult, in that adenoviruses may remain latent in their hosts. No cases of prolonged shedding of adenovirus from the respiratory tract of HIV-infected individuals have been reported.

Rhinoviruses and Coronaviruses

No reports of prolonged shedding of these viruses have been found.

RELATIONSHIP OF COMMON RESPIRATORY VIRUSES AND HIV REPLICATION/DISEASE

It has been speculated that any antigenic stimulus to the immune system of HIV-infected individuals could activate HIV-1 replication in quiescent T cells. No investigations that assessed HIV replication in individuals with respiratory viral infection have been reported. These infections occur frequently enough to warrant this type of investigation.

Some studies have indirectly addressed the issue of HIV activation by respiratory viruses. Specific genes from adenovirus (and herpes simplex virus) have been identified that activate HIV replication in vitro in T lymphoma cells. Also, there have been reports that vaccination with inactivated influenza vaccine can increase replication of HIV-1 in adults. However, one report did not find any difference in circulating HIV-1 RNA levels in vaccinees compared with controls. Specifically for influenza, it will be important to compare HIV activation in individuals who receive influenza vaccine with HIV activation in those who contract natural influenza infection, so that the risk/benefit ratio of influenza vaccination in individuals with HIV disease can be addressed.

CONCLUSION

To date, the severity of respiratory viral illnesses in HIV-infected individuals has not been demonstrated to be dramatically different from that in the population as a whole. The possible exception to this would be adenovirus infection, for which fatal cases predominate in HIV-infected adults and children. Further epidemiologic studies are needed to help define the true frequency of severe respiratory viral disease in HIV-infected individuals.

It is clear from the literature that prolonged infection and shedding of common respiratory viruses can occur in HIV-infected individuals. Data from one cohort study reveal that, at least for RSV, prolonged shedding occurs quite often. Epidemiologic studies are needed to address these issues. Long-term respiratory viral shedding has important infection control implications, and therapies to interrupt this shedding need to be developed.

Finally, the impact of respiratory viral infections on HIV replication and disease progression, particularly in HIV-infected children, would seem to be an important area of study. As vaccines against respiratory viruses are developed, it will be important to compare their impact on HIV replication with that resulting from natural respiratory viral infection to properly assess their risk/benefit ratio. This is particularly important in light of reports of prolonged respiratory viral infection in HIV-infected individuals.

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