

Reduced frequency of wheezing respiratory illness in infants with perinatal human immunodeficiency virus-type 1 infection: A model for immunologic and inflammatory mechanisms of airway obstruction?

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A multivariate analysis using a logistic regression model evaluated odds ratio (OR) and 95% confidence limits (95% CL) of pediatrician-diagnosed wheezing respiratory illness in 75 infants with perinatal human immunodeficiency virus-type 1 (HIV-1) infection, 205 uninfected infants of HIV-1 infected mothers, and 1780 infants of HIV-1 uninfected mothers. Infants were prospectively followed-up for the first 2 years of life. Covariates were risk factors for wheezing respiratory illness (preterm delivery, low birth weight, maternal smoking, formula feeding, and neonatal respiratory disorders). Maternal use of illicit drugs in pregnancy, antiretroviral treatment in pregnancy, maternal HIV-1-related clinical condition at the time of delivery were also included in the models when infants of HIV-1 infected mothers were taken into account. Although the frequency of risk factors for wheezing respiratory illness was higher in infants of HIV-1 infected than in those of uninfected mothers, HIV-1 infection emerged as a protective factor [OR: 0.001 (95% CL: 0.0001–0.01); $p < 0.001$]. The frequency of risk factors was similarly high among infants of infected mothers, but OR was lower in HIV-1 infected than in uninfected infants of infected mothers (0.005; 95% CL: 0.0004–0.06; $p < 0.001$). Finally, OR was higher in uninfected infants of HIV-1 infected mothers (who evidenced a higher frequency of risk factors) than in infants of HIV-1 uninfected mothers (9.97; 95% CL: 4.87–20.40; $p < 0.001$). Understanding the reason why HIV-1 protects against wheezing respiratory illness could shed light on the immunologic and inflammatory mechanisms of airway obstruction.

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Intrauterine factors (1), immunologic and inflammatory mechanisms (2–6), as well as endogenous and environmental factors [including male gender, maternal age less than 21 years at delivery, premature delivery, neonatal respiratory disorders, formula feeding, and exposure to maternal tobacco smoking (1)] are influential in the pathogenesis of wheezing respiratory

illness during infancy. A complex network of immunologic and inflammatory mechanisms are part of the pathogenesis of wheezing respiratory illnesses in infancy (2–6) regardless of whether respiratory syncytial virus is the etiologic agent or not (2). Mechanisms include T lymphocytes (which regulate the proinflammatory activity of other cells), expression of CD23, CD25, CD28,

and CD69 molecules, as well as of intercellular adhesion molecules, production of IL-5, IL-8, IL-10, interferon- γ (IFN- γ) and IL-4 in response to IL-2 stimulation, neutrophil recall, production of oxygen species and neutrophil-mediated inflammation, release by macrophages of inflammatory proteins-1 α (MIP-1 α) and β (MIP-1 β), and leukotrienes, eosinophil recruitment, eosinophil cationic protein (ECP) release, and protein secretion for regulated on activation normal T-cell expressed and secreted (RANTES) in eosinophils and epithelial cells (2–6).

Infants born to human immunodeficiency virus-type 1 (HIV-1) infected mothers are exposed to maternal infectious agents, illicit drugs, and antiretroviral drugs during their intrauterine life; they are frequently delivered prematurely and almost all those born in industrialized countries are formula-fed (7–12). In those infants who acquire HIV-1 perinatal infection very early immunologic changes may develop (7, 11). Wheezing respiratory illness may be associated with prolonged viral shedding or severe manifestations in children with immune deficiency or poor protection of mucosal membranes (13). Thus the clinical impact of wheezing respiratory disease might be different in HIV-1 infected infants. Based upon all this evidence, we carried out this prospective study to verify whether the frequency of wheezing respiratory illness in infants with perinatal HIV-1 infection differs from that expected.

Patients and methods

Study design

This was an epidemiological study carried out on HIV-1 infected or uninfected infants born to HIV-1 infected mothers and control infants born to HIV-1 uninfected mothers who were prospectively followed-up for the first 2 years of their life. The study received local Ethical Committee approval.

Data collection

Information on maternal age at the time of delivery, duration of pregnancy, birth weight, neonatal respiratory disorders, and (as far as infants born to HIV-1 infected mothers were concerned) pediatric AIDS clinical trial group (PACTG) 076 protocol to prevent HIV-1 perinatal transmission (10), maternal use of illicit drugs in pregnancy, and maternal HIV-1-related clinical condition at the time of delivery was

obtained from the mothers at their infants' first medical visit. Information was confirmed by reviewing clinical records from obstetric wards and (as far as HIV-1 infected mothers were concerned) adults' infectious disease centres and services for drug addiction. Information on maternal smoking habits, the type of infant feeding, and the infants' attendance at day care was obtained from mothers at first and each subsequent visit.

All infants were followed-up from birth. A group of infants born to HIV-1 infected mothers were followed at the tertiary level center for pediatric HIV-1 infection at the Department of Paediatrics of Florence, whereas another group was either initially followed-up from birth at other pediatric hospitals in Tuscany or the Neonatology Unit of Chieti and later cared for by the Department of Paediatrics of Florence once they had been discharged. Any information concerning these referred infants was coded in their medical records at the Department of Paediatrics of Florence. Infants born to HIV-1 infected mothers were checked on a monthly basis at the Department of Paediatrics of Florence. Infants born to HIV-1 uninfected mothers were checked once every 3 months at the Neonatology Unit of Chieti but an experienced pediatrician undertook to carefully collect information on their clinical history during monthly telephone interviews, as has been described previously (14). A detailed history was obtained at each check for all infants involved. In addition to this, parents or guardians were requested to bring their infants to us, or to their family pediatrician, whenever any signs or symptoms of disease developed. Family pediatricians received instructions to fill in a form at each medical visit, which included signs, diagnosis and treatment. All completed forms were returned to us at the next medical visit and parents or guardians were also questioned about any other information that might have been relevant. Findings at unscheduled visits or family pediatrician visits were recorded in our medical records.

Definitions

All HIV-1 infected mothers were HIV-1 diagnosed before delivery by means of an enzyme-linked immunosorbent assay (ELISA) and were confirmed positive by the Western blot technique. Their clinical condition at the time of delivery was classified according to the Centers for Disease Control and Prevention (CDC) criteria for adults' HIV-1 infection (15). The

CDC clinical category C defined severe disease (15). Perinatal HIV-1 infection was defined as we have reported previously (7, 8). According to the CDC criteria, HIV-1 infection in infants was diagnosed through detection, on at least two occasions, of proviral DNA and positive virus culture and the persistence, after 18 months of life, of HIV-1 antibodies by ELISA and the Western blot technique (16). The CDC clinical category C defined severe disease (16). We have previously described the criteria followed to define clinical conditions included in category C (10). The CDC immunologic category 3 defined severe immune suppression (16). CD3⁺CD4⁺ lymphocyte counts were obtained by the double staining fluorescent-activated cell sorting technique, as we have described previously (9, 11).

Length of pregnancy was defined by maternal data, ultrasonography, and neonatal physical examination (17). Premature new-borns were those who born after ≤ 37 -week pregnancy (17). Low birth weight was defined as ≤ 2500 g (17). Neonatal respiratory disorders included neonatal pneumonia (≥ 24 h supplemental oxygen, chest X-ray film consistent with pneumonia, and positive blood culture), meconium aspiration syndrome (≥ 24 h supplemental oxygen consistent with pneumonia, and meconium-stained amniotic fluid), respiratory distress syndrome (tachypnea, grunting, signs of increased work, altered gas exchange, need for supplemental oxygen and ventilatory support) and bronchopulmonary dysplasia (≥ 28 day supplemental oxygen and continued chest X-ray film changes) (17). Supplemental oxygen transiently administered in the delivery room or the first few hours of life without specific changes on chest X-ray films did not define neonatal respiratory disorder (17). The type of infant feeding was defined as we have reported previously (8). Mothers were defined as smokers if they reported smoking one or more cigarettes per day during pregnancy and/or during the follow-up period. Respiratory infection was defined as a pediatrician-diagnosed febrile (rectal temperature $\geq 38.1^{\circ}\text{C}$) disease fulfilling criteria for diagnosis of acute pharyngitis and nasopharyngitis, acute laryngitis, otitis media, bronchitis, pneumonia (14). The wheezing respiratory illness was defined by means of a pediatrician-diagnosed deep cough and wheezing upon auscultation, either with or without fever (1). According to standardized criteria, all the above reported definition criteria were followed in both infants born to HIV-1 infected mothers and infants born to HIV-1 uninfected mothers.

Data set

Two hundred and eighty infants born to HIV-1 infected mothers between January 1st, 1992 and December 31st, 1998 entered the present study. These were the entire group of infants born to HIV-1 infected mothers who had been singled out before delivery and followed-up at the Department of Paediatrics of Florence during that period. Seventy-five infants had acquired the infection and 205 were uninfected. Our data set included a number of HIV-1 infected infants higher than the expected transmission rate (8, 10) because almost all infants who were proviral DNA and/or virus culture positive within few weeks after birth (but not all infants who were negative) were referred our tertiary level center for pediatric HIV-1 infection.

The control group included 1780 infants born to HIV-1 uninfected mothers who had been tested HIV-1 negative by ELISA before delivery. They were the entire group of infants followed-up from birth at the Neonatology Unit of the University of Chieti between January 1st, 1995 and December 31st 1996. The Neonatology Unit of Chieti follows children born in the Abruzzi Region. Both Tuscany and Abruzzi regions are located in central Italy. The Abruzzi population represents well the demographical and social distribution throughout the entire country (12). Because of these characteristics, Abruzzi children have already been included as controls in other studies (12).

Statistical analysis

All data were processed through the SPSSXTM (SPSS Inc., Chicago, IL, USA) statistical package. Differences in frequencies were evaluated by means of Fisher's exact test or the χ^2 -test. Differences in medians were evaluated by the non-parametric Mann-Whitney *U*-test. Differences in means and standard deviations were evaluated by the Student's *t*-test. A multivariate analysis using a logistic regression model was used to evaluate factors independently associated with the wheezing respiratory illness. Odds ratio (OR) and 95% confidence limits (95% CL) were calculated. Covariates entered into all models were maternal smoking during pregnancy and/or the follow-up period (yes vs. no), gestational age (≤ 37 vs. > 37 weeks), birth weight (≤ 2500 vs. > 2500 g), neonatal respiratory disorders (yes vs. no), infant feeding (formula-fed vs. exclusively breast-fed). In selected analyses, birth from HIV-1 infected mothers (yes vs. no), maternal use of illicit drugs in pregnancy (yes vs. no),

antiretroviral prophylaxis in pregnancy according to the PACTG 076 protocol (yes vs. no), maternal HIV-1 related clinical condition at the time of delivery (severe vs. not severe or no disease), or HIV-1 infection (yes vs. no) were also included in the models. Values of $p > 0.05$ were considered not significant.

Results

General features

When compared with infants born to HIV-1 uninfected mothers, those born to HIV-1 infected mothers had a significantly higher frequency of premature delivery and low birth weight, as well as a higher frequency of maternal smoking, formula feeding, and acute respiratory infections, whereas gender distribution, maternal age at delivery, frequency of neonatal respiratory disorders, and proportion of infants attending day care were similar (Table 1).

HIV-1 infected or uninfected infants born to HIV-1 infected mothers did not significantly differ in maternal age at delivery, gender distribution, frequency of premature delivery, low birth weight, neonatal respiratory disorders, maternal smoking, formula feeding, day care attendance, or acute respiratory infection (Table 1). In addition, the two groups did not differ in the frequency of infants born to mothers using illicit drugs during pregnancy (41/75 = 54.65% vs. 116/205 = 56.5%; $p = \text{NS}$). As expected, HIV-1 infected or uninfected infants did differ in the frequency of mother/child pairs receiving antiretroviral prophylaxis during pregnancy according to the PACTG 076 protocol (7/75 = 9.3%

vs. 76/205 = 37.0%; $p < 0.0001$), vaginal deliveries (63/75 = 84.0% vs. 135/205 = 65.8%; $p = 0.005$), and mothers with HIV-1-related severe disease (10/75 = 13.3% vs. 6/205 = 2.9%; $p = 0.002$).

Nineteen (25.3%) HIV-1 infected infants were given antiretroviral therapy during the follow-up period including nucleoside reverse transcriptase inhibitors [zidovudine (480 mg/m²), didanosine (180 mg/m²), lamivudine (8 mg/kg), stavudine (2 mg/kg), zalcitabine (0.03 mg/kg)] and protease inhibitors [saquinavir (900 mg/m²) or ritonavir (800 mg/m²) or nelfinavir (90 mg/kg)], starting at age 4.3 (median; range: 0.3–11.1) months. All HIV-1 infected infants were given *Pneumocystis carinii* pneumonia chemoprophylaxis (oral 150 mg/m² trimethoprim and 750 mg/m² sulfamethoxazole per day 7 days per week) starting at age 6.5 (median; range: 3.2–17.7) months. No child received intravenous immunoglobulins. At the end of follow-up, 16 (21.3%) infants were suffering from severe disease and 14 (18.6%) showed severe immune suppression.

Two (2.6%) infected infants died of HIV-1-related diseases, at the ages 11 and 18 months, but no child of HIV-1 infected mothers failed to be followed-up during the first 2 years of life. Ninety-six (5.3%) infants born to HIV-1 uninfected mothers were lost to follow-up at age 13.3 [median (range 2.1–19.7) months].

Frequency of wheezing respiratory illness

Cases of wheezing respiratory illness were recorded during the follow-up period in 159 (8.8%) infants born to HIV-1 uninfected mothers, 53

Table 1. General features of infected or uninfected infants born to HIV-1 infected mothers, and infants born to HIV-1 uninfected mothers*

	Infected infants of HIV-1 ⁺ mothers (n = 75)	Uninfected infants of HIV-1 ⁺ mothers (n = 205)	Infants of HIV-1 ⁻ mothers (n = 1780)
Maternal age at delivery	27.8 (24.5–31.1)	27.6 (24.5–30.7)	27.9 (23.8–31.0)†
Males	38 (50.6%)	103 (50.2%)	899 (50.5%)‡
Maternal smoking	39 (52.0%)	112 (54.6%)	122 (6.8%)§
Gestational age ≤ 37 weeks	19 (25.3%)	43 (20.9%)	140 (7.8%)§
Birth weight ≤ 2500 g	18 (24.0%)	40 (19.5%)	160 (8.9%)§
Neonatal respiratory disorders	4 (5.3%)	11 (5.3%)	88 (4.9%)¶
Formula fed	73 (97.3%)	202 (98.5%)	1002 (56.2%)§
Acute respiratory infections/year	3.9 ± 3.1	3.2 ± 2.7	2.2 ± 1.2**
Day care attendance	5 (6.6%)	17 (8.2%)	151 (8.4%)††

*All comparisons: infants of HIV-1 infected mothers vs. infants of HIV-1 uninfected mothers.

†Median (95% confidence limits), $p = 0.865$, Mann–Whitney U -test.

‡Number (%), $p = 0.997$, χ^2 -test.

§Number (%), $p < 0.0001$, χ^2 -test.

¶Number (%), $p = 0.957$, χ^2 -test.

**Mean ± standard deviation, $p < 0.0001$, Student's t -test.

††Number (%), $p = 0.957$, χ^2 -test.

(25.8%) HIV-1 uninfected infants of HIV-1 infected mothers, and 2 (2.6%) HIV-1 infected infants of HIV-1 infected mothers. Differences in frequencies among the three groups were statistically significant ($p < 0.0001$). Forty-five (2.5%) infants born to HIV-1 uninfected mothers, 11 (5.3%) HIV-1 uninfected infants born to HIV-1 infected mothers, but no HIV-1 infected child had more than one episode of wheezing respiratory illness. Both HIV-1 infected infants with wheezing respiratory illness were in the CDC clinical category B and in the CDC immunologic category 1 (16). One of them was receiving antiretroviral therapy.

Risk factors for wheezing respiratory illness

Table 2 shows that maternal smoking, premature delivery, low birth weight, neonatal respiratory disorders, and formula feeding were independent risk factors for wheezing respiratory illness in infants born to HIV-1 uninfected mothers during the first 2 years of life.

The same analysis was carried out in uninfected infants born to HIV-1 infected mothers and infants born to HIV-1 uninfected mothers. Birth from an HIV-1 infected mother was added to other covariates. This analysis aimed at evaluating the risk for wheezing respiratory illness in uninfected infants born to HIV-1 mothers. These infants had a significantly higher risk than infants born to HIV-1 uninfected mothers [OR: 9.97 (95% CL: 4.87–20.40); $p < 0.001$].

A third model included all infected or uninfected infants born to HIV-1 infected mothers. PACTG 076 protocol, maternal use of illicit drugs in pregnancy, maternal HIV-1-related clinical condition at the time of delivery, and HIV-1 infection were taken into account as independent covariates. As shown in Table 3, maternal smoking, birth weight, and neonatal respiratory disorders were independent risk factors for wheezing respiratory illness. PACTG 076 protocol, use of illicit drugs by the mother during pregnancy, maternal HIV-1-related clinical condition at the time of delivery were not found to be influential. By contrast, HIV-1 infection was found to be highly protective.

Finally, a fourth model included HIV-1 infected and uninfected infants born to HIV-1 mothers as well as those born to HIV-1 uninfected mothers. Birth from HIV-1 infected mother and HIV-1 infection were added to covariates. This analysis aimed at evaluating the risk of wheezing respiratory illness in HIV-1 infected infants and was adjusted for birth from HIV-1 infected mother. HIV-1 infection emerged as a highly

Table 2. Multivariate analysis of risk factors for wheezing respiratory illness in 1780 infants of HIV-1 uninfected mothers

	Odds ratio	95% confidence limits	p
Male sex	1.20	0.76–1.89	0.424
Maternal smoking	16.58	7.42–37.01	<0.001
Gestational age ≤ 37 weeks	22.54	12.82–39.65	<0.001
Birth weight ≤ 2500 g	11.88	6.01–23.47	<0.001
Neonatal respiratory disorders	3.93	1.91–8.12	<0.001
Formula fed	4.88	2.57–9.25	<0.001

Table 3. Multivariate analysis of risk factors for wheezing respiratory illness in 280 infants of HIV-1 infected mothers

	Odds ratio	95% confidence limits	p
Male sex	1.45	0.61–3.44	0.399
Maternal smoking	20.49	4.48–93.64	<0.001
Gestational age ≤ 37 weeks	1.82	0.49–6.76	0.368
Birth weight ≤ 2500 g	64.11	10.97–374.70	<0.001
Neonatal respiratory disorders	1.57	0.18–13.48	0.678
Formula fed	1.65	0.62–4.36	0.308
Maternal IVDU in pregnancy	1.54	0.62–3.85	0.348
PACTG 076	0.65	0.27–1.56	0.650
Maternal severe disease	3.36	0.15–67.10	0.443
Child's HIV-1 infection	0.005	0.0004–0.06	<0.001

IVDU: intravenous illicit drug use; PACTG 076: pediatric AIDS clinical trial group 076 protocol.

protective factor [OR: 0.001 (95% CL: 0.0001–0.01); $p < 0.001$].

Control analyses were carried out which excluded infants who had died as a result of HIV-1-related disease and those born to HIV-1 uninfected mothers who were lost to follow-up, with the aim of evaluating potential biases due to the shorter follow-up period in such infants. These analyses gave rise to results which were similar to those observed in the entire study groups.

Discussion

A higher frequency of risk factors for wheezing respiratory illness (maternal smoking, premature delivery, low birth weight, and formula feeding) may predispose infants born to HIV-1 infected mothers to the illness during the first 2 years of life, but this effect may be overwhelmed by some mechanism(s) in infants who acquire the infection. In fact, uninfected infants of HIV-1 infected mothers, compared with infants born to uninfected mothers, showed a higher frequency of wheezing respiratory illness, probably because of the higher frequency of risk factors for the illness. Notwithstanding a similar frequency of risk factors, HIV-1 infected infants, compared with

uninfected infants born to HIV-1 infected mothers, showed a reduced frequency in the occurrence of the illness. Finally, infected infants, when compared with infants born to HIV-1 uninfected mothers, showed an even lower frequency of the wheezing respiratory illness, in spite of a higher frequency of risk factors. To the best of our knowledge, there are no Italian prospective data about the incidence of wheezing respiratory illness in infancy to compare our control group. However, a retrospective study carried out on 16 333 children living in eight areas of northern and central Italy showed that 7.5% of them had had at least one wheezing respiratory illness during the first 2 years of life (18). This proportion is comparable to the 8.8% frequency observed in our control group.

Maternal smoking, premature delivery, low birth weight, neonatal respiratory disorders, and formula feeding were included in the multivariate analysis as these factors are recognized risk factors for wheezing respiratory illness (1). Maternal age of less than 21 years at the time of delivery was not included in the model because very few infants in our data set were born to mothers so young and maternal ages at delivery were similar in infected and uninfected infants born to infected mothers and infants born to uninfected mothers. A high frequency of acute respiratory infections is likely to be a risk factor for wheezing respiratory disease, but no sound evidence has yet been reported in the literature so far. For this reason this particular variable was not included in the model, but it might be reasonable to suppose that the higher frequency of acute respiratory infections in infected infants could further support our findings. An increased frequency of premature deliveries and low birth weight, as well as a normal frequency of neonatal respiratory disorders, have already been described in infants born to HIV-1 infected mothers (17). The frequency of neonatal respiratory disorders in infants born to infected mothers was what we expected in Italian new-borns (19). The high frequency of formula feeding in these infants is due to the counseling carried out in industrialized countries with the aim of preventing HIV-1 transmission through maternal milk (8). Furthermore, in infants born to HIV-1 infected mothers the possible effects of PACTG 076 protocol and maternal use of illicit drugs in pregnancy were taken into account as both antiretroviral drugs and illicit drugs may exert immune modulatory effects (10, 20).

Some possible biases need to be discussed. This was an epidemiological study which could not take into account pulmonary function, allergies,

or infectious causes of wheezing respiratory illness. Familial history of asthma was not taken into account because paternal data were not available in many infants of HIV-1 infected mothers. The data set of infants born to HIV-1 infected mothers included more infected subjects than expected (8), essentially because not all infants who were proviral DNA and/or virus culture negative within a few weeks after birth were referred to our tertiary level center. This selection among uninfected infants (which was based exclusively on HIV-1 diagnosis potential in peripheral hospitals) could bias our results. The data set of infants born to HIV-1 infected mothers was collected between 1992 and 1998, whereas the data set of children of uninfected mothers was collected in 1995 and 1996. However, there is no evidence that epidemiology of wheezing respiratory illness in Italy has changed over this period of time. The two groups of infants lived in the same central area of Italy and there is no evidence that epidemiology of wheezing respiratory illness differs within this area of the country. Possible marginal differences should not be considered influential, taking full account of the strength of statistical differences observed. No information was available concerning illicit drug use in uninfected mothers. However, we found no evidence that maternal illicit drug use changed the risk of wheezing respiratory illness, at least in infants born to HIV-1 infected mothers. Infants born to HIV-1 infected mothers were checked monthly (either because infected or because they were at risk of infection), whereas infants born to uninfected mothers were checked every 3 months (these were healthy infants). However, if the lower frequency of medical visits in the latter group led us to underestimate the frequency of wheezing respiratory illness in these infants, then this would obviously strengthen our findings. Finally, it could be hypothesized that the criteria to diagnose the wheezing respiratory illness differed in infants born to HIV-1 infected mothers and infants born to uninfected mothers. However, the same definition criteria for wheezing respiratory illness were followed at both the Department of Paediatrics of Florence and the Department of Paediatrics of Chieti. In addition, the strongest difference in the frequency of respiratory illness was observed between infected and uninfected infants of infected mothers. Both groups were followed at the Department of Paediatrics of Florence.

Some of the mechanisms involved in wheezing respiratory illness (2–6) do not seem to be affected by perinatal HIV-1 infection. During

the early stage of infection, MIP-1 α , MIP-1 β , and RANTES mRNA transcripts are normally found in infants' lymph node or peripheral blood mononuclear cells and eosinophil numbers as well as ECP production are similar to those of healthy children (21, 22). By contrast, there is evidence that HIV-1 infection may heavily affect other mechanisms. Both the number and function of CD4-positive lymphocytes are decreased and the expression of CD23, IL-2 CD25 receptor, and T-lymphocyte activation signaling molecules CD28 and CD69 is down regulated (23, 24). IL-2 secretion is impaired in HIV-1 infection and IL-2 mRNA transcripts (as well as those of IL-4 and IL-5) can not be detected in lymph node or peripheral blood mononuclear cells of infants with the infection in its early stage (21). IL-10 production is decreased and IFN- γ production is reduced and its mRNA transcripts can be found only in CD8⁺ lymphocytes (21). Neutrophil recall and neutrophil-mediated inflammation is impaired, as chemotaxis, adhesion molecule expression, oxygen species production, and IL-8 secretion are reduced (25).

An increased production of neutrophil chemo-attractant IL-8 has been found in children with bronchiolitis (26). Thus, a defective neutrophil degranulation induced by IL-8 has been reported in HIV-1 infected children (27) and this finding may contribute to a less frequent finding of wheezing respiratory disease. In vitro exposure of monocytes to HIV-1 reduces their ability to produce eicosanoids, and ex vivo alveolar macrophages of HIV-1 infected patients highlight impaired expression of 5-lipoxygenase protein as well as a reduced production of proinflammatory leukotrienes and other 5-lipoxygenase metabolites of arachidonic acid (28). These changes can not be attributed to in vivo activation (28). In conclusion, several inflammatory and immunological factors involved in wheezing respiratory illness, such as chemokine production by CD4-positive lymphocytes, monocytes and neutrophil may be modified during HIV-1 infection.

HIV-1 does not seem to increase the risk of bronchial hyperresponsiveness or asthma in adults and children (9, 29). A study carried out in the United States did not show a modified frequency of bronchiolitis/reactive airway disease in 93 HIV-1 perinatally infected infants during the first year of life (30). By contrast, our study suggests that perinatal HIV-1 infection may exert a sort of protective role against wheezing respiratory illness in infancy. This finding is of speculative significance, because understanding the mechanisms by which HIV-1 interferes with

wheezing respiratory illness may shed light on the pathogenesis of this illness itself.

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