HIV-exposed infants with acute respiratory failure secondary to acute lower respiratory infections managed with and without mechanical ventilation

E R Thirsk, M C Kapongo, P M Jeena, S Liebeschuetz, DF York, G Vega, S van Vuuren, H M Coovadia

Objectives. The decision to provide mechanical ventilation (intermittent positive pressure ventilation (IPPV)) to HIV-exposed infants in resource-poor settings has remained difficult owing to problems in confirming HIV infection and the lack of data on outcome. We evaluated the predictive value of the HIV antibody test in confirming infection in infants requiring mechanical ventilation for acute lower respiratory infections (ALRIs), and compared the outcome for children denied access with the outcome for similar subjects who were ventilated.

Setting and design. This investigative study was conducted over a 12-month period at the paediatric intensive care unit (PICU) at King Edward VIII Hospital (KEH) in Durban, and at Ngwelezana Hospital in northern KwaZulu-Natal.

Subjects. HIV-exposed patients with acute respiratory failure (ARF) secondary to ALRI entering the PICU at KEH were enrolled into the IPPV arm, while similar children who were refused such care at Ngwelezana Hospital were admitted into the non-IPPV arm. Standardised protocols for entry and management of enrolled subjects were utilised.

Outcome measures. HIV DNApolymerase chain reaction (PCR) testing was performed to establish HIV status. Clinical and laboratory parameters were correlated with HIV status to determine predictors of infection and outcome (survival to discharge).

Results. One hundred and sixteen HIV-exposed infants were enrolled, 49 into the IPPV arm and 67 into the non-IPPV arm. The median age of both groups was 3.0 months (0.5 - 11 months), and the male/female ratio and proportion of infants under 3 months of age were similar in both groups.

The predictive values of the HIV antibody test in determining HIV infection in the IPPV and non-IPPV arms were 87.8% and 85.0 % respectively. Splenomegaly and a serum globulin of >35 g/l increased the likelihood of being HIV PCR- positive ($p = 0.006$ and $p = 0.04$ respectively). Survival to discharge rates for HIV-infected children in the IPPV and non-IPPV arms were 41.9% and 24.6% respectively ($p = 0.08$). Age less than 3 months ($p = 0.04$) and very severe pneumonia ($p = 0.007$) were the only indicators of poor outcome.

Conclusion. Mechanical ventilation provided little benefit in HIV-infected children with ARF from ALRI. An HIV antibody test in infants with ALRI and ARF is highly suggestive of HIV infection. Splenomegaly and a serum globulin of greater than 35 g/l were the only useful markers in identifying HIV infection.

S Afr Med J 2003; **93:** 617-620.

In developing countries HIV infection in infancy is a major problem because of the uncertainties of diagnosis and the paucity of evidence on outcome following mechanical ventilation. Acute lower respiratory infection (ALRI) is a common complication among HIV-infected children, accounting for 30 - 40% of inpatient admissions and a case fatality rate of 15 - 28% in southern Africa.[1,2] The diagnosis of HIV infection in infants is problematic due to transplacental transmission of maternal HIV-1 antibodies, and the unavailability of confirmatory HIV DNApolymerase chain reaction (PCR) tests because of cost constraints. The World Health Organisation (WHO) proposed a clinical case definition for paediatric AIDS that is neither sensitive nor specific in confirming infection.[3] The decision to provide mechanical ventilation for HIV-exposed infants with severe HIV-related pneumonia is influenced by considerations of ethics, costs and likely benefits. There is no uniform opinion to assist clinicians in making such decisions.

At Ngwelezana and King Edward VIII hospitals in KwaZulu-Natal, where the public sector antenatal HIV prevalence rate is 36%, this dilemma is faced weekly.[4] We studied HIV-exposed children (less than 15 months of age) with severe or very severe pneumonia requiring mechanical

Ngwelezana Hospital, Empangeni, KwaZulu-Natal
E R Thirsk, MB BS, DA(UK), DCH (SA), DOG (SA)
M C Kapongo, MB BS, FCP(SA)
S Liebeschuetz, MB BS, MRCP
G Vega, MD
S van Vuuren, MB ChB, DCH (SA)

Department of Paediatrics and Child Health, University of Natal, Durban
P M Jeena, FCP(Paed), FCP(Pulm)
H M Coovadia, FCP(Paed), MD

Department of Virology, University of Natal, Durban
D F York, MSc, PhD

ventilation to evaluate the usefulness of HIV antibody tests in predicting infection. We also compared the outcome of children receiving intermittent positive-pressure ventilation (IPPV) with that of similar children who were denied such care.

Patients and methods

An investigative study (June 1999 - May 2000) was conducted at the paediatric intensive care unit (PICU) at King Edward VIII Hospital (KEH) and the paediatric wards at Ngwelezana Hospital in KwaZulu-Natal, South Africa. The PICU at KEH is the only public sector intensive care service available to a paediatric population of 3 - 4 million. Approximately 400 children are admitted annually, with an overall mortality rate of 25%.[5] The unit has a bed capacity of 10 and an occupancy rate of over 90%. The unit is staffed by 2 consultants and 4 registrars / medical officers. The nurse-to-patient ratio is 1:3. Criteria for entry into the unit included the need for airway support, and invasive and non-invasive monitoring.

Ngwelezana Hospital is a subregional facility serving a rural and peri-urban population of 2 million. There are 140 paediatric beds, including 9 for high care. Forty-five per cent of the 13 daily paediatric admissions are for ALRI, while 75% of those tested for HIV are positive. A consultant and 7 medical officers make up the staff complement. The nurse-to-patient ratio in the paediatric high care unit is 1:5. HIV antibody tests (enzyme-linked immunosorbent assay (ELISA) or the Rapid Stat test) are usually available but results for HIV DNAPCR confirmatory tests take 2 weeks. Transportation of babies to the PICU at KEH takes on average 6 - 12 hours after acceptance.

HIV-exposed children less than 15 months of age with ALRI were recruited if they fulfilled one or more of the following criteria: oxygen saturation < 89% on 2 l of nasopharyngeal oxygen or 8 l of headbox oxygen, type 1 or type 2 respiratory failure on 2 l of nasopharyngeal oxygen; prolonged apnoea, and persistent metabolic acidosis (p H < 7.25) after 8 hours of fluid resuscitation. Children who received sustained IPPV were included in the ventilated arm while those denied ventilation due to lack of facilities were included in the non- ventilated arm. Babies who failed to thrive, those with WHO- defined paediatric AIDS, and previous HIV-related PICU admissions were not admitted to the PICU. At Ngwelezana, patients were cared for in high care or in a general ward.

Identical admission laboratory tests, viz. a full blood count, electrolytes, liver function tests, HIV ELISA or Rapid Stat test, HIV DNAPCR, blood gases and radiology, were performed in both groups. HIV antibody-positive children were regarded as HIV-exposed, while HIV DNAPCR-positive children were regarded as HIV-infected. Antimicrobial therapy was prescribed according to WHO guidelines for severe and very severe pneumonia. High-dose intravenous cotrimoxazole and corticosteroids were used for cases of Pneumocystis carinii. Failure to respond to these medications within 72 hours resulted in an empirical change to cefotaxime and amikacin at both institutions unless microbiological culture results indicated otherwise. The need for oxygen therapy, physiotherapy, blood transfusions and fluid and feeding practices were standardised for both sites before commencement of the study. An in-house nested HIV DNA PCR that targets a conserved region of the HIV *gag* gene was used to detect the presence of HIV proviral DNA. The amplification of a visible 160 base pair product in ethidium bromide-stained agarose gels was regarded as positive for HIV infection.

A leaflet in the native language of participants explaining the need for the HIV test was given to all possible subjects before enrolment. Informed consent for HIV testing was granted in all cases. HIV testing was performed with pre- and post-test counselling and parents were offered the option of being blinded to these results. Where facilities for intensive care were not available, parents / guardians were informed accordingly. The study protocol received ethical approval from the University of Natal and the Medical Superintendent of Ngwelezana Hospital.

The principal dependent variable for analysis was outcome defined as 'survival to discharge'. Capture and analysis of data were carried out using EPI-Info version 6.04 (Centers for Disease Control, Atlanta). Analysis of anthropometric data, lymphocyte count and serum protein gap required stratification of the sample. The median value was used as the cut-off point. *p*-values are reported.

Results

One hundred and sixteen children were enrolled during the study period, 67 in the non-ventilated arm at Ngwelezana and 49 in the ventilated arm at KEH. Ten patients at Ngwelezana Hospital who presented *in extremis* and who were supported suboptimally on a transport ventilator were included into the non-ventilated arm for the analysis of outcome. The median age of both groups was 3.0 months (range 0.5 - 11 months). The male / female ratio was 1:1.63 and 1:1.04 for Ngwelezana and KEH respectively. The differences in the clinical characteristics between the two groups are shown in Table I.

Of the 116 children recruited, 100 (86.2%) were PCR-positive, being similarly represented in the Ngwelezana and KEH cohorts (85.0% and 87.8% respectively) (Table II). The presence of splenomegaly ($p = 0.006$) and a serum globulin level of > 35 g / l ($p = 0.04$) were associated with an increased likelihood of being HIV DNAPCR-positive. No association could be found between the HIV-exposed and infected children for age less than or greater than 3 months ($p = 0.75$), sex ($p = 0.34$), nutritional status (mean *z*-score less than or greater than 3, $p = 0.21$), hepatomegaly ($p = 0.24$), lymphadenopathy ($p = 0.2$),

Table I. Differences in the clinical characteristics of cases receiving and not receiving mechanical ventilation

Variables	HIV-exposed, no IPPV (*N* = 67)	HIV-exposed, IPPV (*N* = 49)	*p*-value
Z-score (3 SD)	-1.86 (1.23)	-0.78 (1.41)	0.003
Lymphadenopathy (*N* (%))			
Yes	17 (25.4)	23 (46.9)	0.05
No	50 (74.6)	26 (53.1)	NS
Paediatric AIDS(WHO) (*N* (%))			
Yes	27 (40.3)	3 (6.1)	< 0.01
No	40 (59.7)	46 (93.9)	< 0.001
Severity of pneumonia (*N* (%))			
Severe	43 (64.2)	17 (34.7)	0.001
Very severe	24 (35.8)	32 (65.3)	0.001

IPPV = intermittent positive pressure ventilation; SD = standard deviations.

Table II. HIV infectivity and survival among HIV antibody-positive children receiving and not receiving mechanical ventilation (*N* (%))

Variables	HIV antibody-positive, no IPPV	HIV antibody positive, IPPV
HIV DNAPCR-positive	57/67 (85.0)	43/49 (87.8)
HIV DNAPCR-negative	10/67 (14.9)	6/49 (12.2)
Survival		
HIV DNAPCR-positive	14/57 (24.6)	18/43 (41.9)
HIV DNAPCR-negative	6/10 (60)	4/6 (66.7)

IPPV = intermittent positive pressure ventilation.

previous hospitalisations (p = 0.28), lymphocyte counts (p = 0.93) or WHO-defined paediatric AIDS (p = 0.27).

There was no statistically significant difference between the survival to discharge of HIV DNAPCR-positive children who received IPPV and that of children who did not receive IPPV (41.9% v. 24.6%, p = 0.08) (Table II). The survival to discharge for cases with negative HIV DNAPCR results were similar for those receiving IPPV and those not ventilated (66.7% v. 60%, p = 0.20). Overall, the survival to discharge of HIV DNAPCR-negative children was higher than that for HIV DNAPCR-positive children (63% v. 32%, p = 0.02).

At both sites, age less than 3 months compared with age above 3 months (OR 2.3, p = 0.04) and WHO-defined very severe pneumonia (OR 3.37, p = 0.007) were predictive of poor outcome. Failure to thrive (p = 1.00), previous hospital admissions (p = 0.84), hepatomegaly (p = 0.86), splenomegaly (p = 0.74), lymphadenopathy (p = 0.04), WHO-defined clinical AIDS (p = 0.86), a high serum globulin level (p = 0.23) and a low total lymphocyte count (p = 0.2) were of no prognostic value in determining outcome.

The median lengths of stay for all patients and survivors at KEH were 10 (range 1 - 50) and 9 (range 1 - 50) days respectively. At Ngwelezana the median lengths of stay for all patients and survivors were 4 (range 0 - 34) and 9 (range 3 - 20) days respectively. The median duration of IPPV and ICU stays were 9 and 16 days respectively.

P. carinii pneumonia (PCP) (N = 16), mixed infections (PCP, *Candida*, cytomegalovirus and bacteria N = 9), nosocomial Gram-negative bacteria (*Acinetobacter anitratus* and *Klebsiella pneumoniae* N = 8), and community-acquired bacterial pneumonia (*Staphylococcus aureus* and *Streptococcus pneumoniae* N = 7) were the common pathogens identified in the HIV DNAPCR-positive cohort receiving intensive care. *Bordetella pertussis* (N = 2), *S. aureus* (N = 2), *Moraxella catarrhalis* (N = 1) and tuberculosis (N = 1) were the pathogens identified in the HIV DNAPCR-negative children who were ventilated. PCP (44%), mixed infections (36%) and nosocomial pneumonias (16%) were responsible for the majority of deaths in this cohort. The aetiology of the pneumonia for children managed at Ngwelezana was not determined.

Discussion

Rational allocation of limited intensive care facilities can only be accomplished with adequate knowledge of outcome of conditions requiring such care. Ethical concerns do not allow medical emergencies to be evaluated using double-blind randomised control studies, but where such cases are continually being denied optimal care due to the lack of facilities, investigational studies are deemed clinically justified. The most important finding of this study, the first in the world, is the lack of benefit of mechanical ventilation in HIV-infected children under 15 months of age with ALRI and ARF compared with similar children who were refused ventilatory support. This was especially so in infants under 3 months of

age and those with WHO-defined very severe pneumonia. HIV-exposed but uninfected children with similar severity of illness have better outcomes than HIV-infected children.

Should HIV antibody-positive children be offered intensive care? In the USA, children with HIV-related acute respiratory failure requiring IPPV have ICU survival rates of 50 - 81%.[6,7] PCP was the commonest cause of ICU admission and had the worst outcomes.[8] The introduction of corticosteroids to the management of these children improved the short-term outcome, but long-term survival at 30 months remains the same at 0 - 60%.[9,10]

Poor prognostic factors have been identified in these studies. CD4 counts < 50 cells/µl, lactate dehydrogenase (LDH) levels > 1 000 IU, serum albumin < 20 g/dl, serum creatinine > 24 µg/dl, a diagnosis of AIDS of less than 1 year's duration, persistent hypoxaemia and pneumothoraces have been associated with worse outcome,[11] but have not been tested in developing countries.

A second important finding of this study was the high predictive value of the HIV antibody test for this population. The overall figure of 86.2% PCR positivity should be viewed in the context of the disease studied and the high HIV prevalence for the region. An estimated 12% of the general population served by these hospitals are HIV-infected.[4] It is useful for doctors working in these and similar regions to assume that a positive HIV antibody result in babies under 15 months requiring ventilation for pneumonia is suggestive of true HIV infection. Only splenomegaly and serum globulin > 35 g/l were useful in predicting HIV infection, although these features need verification.

The use of the PCR to detect HIV-proviral DNAand the reverse transcriptase PCR to detect free virus have been widely used to identify HIV-infected infants reliably at all ages after birth. The commercial assays, while sensitive and specific, are costly and not readily available. The HIV DNAPCR assay utilised in this study has undergone prior evaluation and achieved sensitivities and specificities equal to the commercial kits, but is more affordable (D F York — personal communication).

There are several limitations to the utilisation of these findings. Although great effort was taken to ensure that the two groups would be comparable, the difference in the nurse/patient ratios between the two groups, the lack of microbiological evaluations in the Ngwelezana cohort, the delay in transportation of cases to the PICU after acceptance, and the different locations where patients were nursed may have influenced the outcome significantly. No case received antiretroviral therapy and therefore these findings would only be applicable in HIV treatment-naïve populations.

In this limited study, conventional mechanical ventilation does not offer substantial gains over non-ventilatory care for HIV-infected children under 15 months of age with ALRI and ARF. HIV-exposed but uninfected children with similar illness fare better than HIV-infected children. Children with very severe pneumonia or those less than 3 months of age have the worst outcome. A positive HIV antibody test in children with ALRI and ARF has an 86.2% predictive value of true HIV infection. Only splenomegaly and a serum globulin of greater than 35 g/l are predictive of true HIV infection.

References

1. Madhi SA, Schoub B, Simmank K, Blackburn N, Klugman KP. Increased burden of respiratory associated severe lower respiratory tract infections in children infected with human immuno-deficiency virus type 1. J Pediatr 2000; **137:** 78-84.
2. Zwi KJ, Pettifor JM, Soderland N, Meyers T. HIV infection and in hospital mortality at an academic hospital in South Africa. *Arch Dis Child* 2000; **83:** 227-230.
3. Jeena PM, Coovadia HM, Bhagwanjee S. Prospective controlled study of the outcome of human immuno-deficiency virus-antibody positive children admitted to an intensive care unit. *Crit Care Med* 1996; **24:** 963 - 967.
4. United Nations AIDS Organisation. *UNAIDS Report HIV/AIDS 2001*. Geneva: UNAIDS, 2002.
5. Jeena PM, Wesley AG, Coovadia HM. The pattern of ICU admission at a PICU over a 25 year period from Durban, South Africa. *Intensive Care Med* 1998; **1:** 80-85.
6. Abadco D, Rao M, Kravath R. The role of assisted ventilation in survival after respiratory failure in children with Aids. *Am J Dis Child* 1992; **146:** 1052.
7. Notterman D, Greenwald B, Di Maio-Hunter A, *et al*. Outcome after assisted ventilation in children with acquired immunodeficiency syndrome. *Crit Care Med* 1990; **18:** 18-24.
8. Wong H, Chundu K. Improved outcome for young children with AIDS. *Pneumocystiscarinii* pneumonia and acute respiratory failure. *Pediatr Pulmonol* 1994; **18:** 114.
9. Bye M, Cairns-Bazarian A, Ewig J. Markedly reduced mortality associated with corticosteroids therapy of *Pneumocystis carinii* pneumonia in children with acquired immunodeficiency syndrome. *Arch Pediatr Adolesc Med* 1994; **148:** 638.
10. Leifild L, Rockstroh J, Skaide S. Indications, outcomes and follow up of intensive care patients with HIV infection. *Eur J Med Res* 2000; **5:** 199 -202.
11. el-Solh A, Stateusz D, Grant H, *et al*. Outcome of AIDS patients requiring mechanical ventilation predicted by recursive partitioning. *Chest* 1996; **109:** 1584.

Accepted 14 April 2003.