

Outcomes of HIV-1-positive children with pneumonia admitted to the paediatric intensive care unit: A retrospective review

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Introduction. The outcomes of HIV-positive children with pneumonia, who require intensive care, have been poor. Advances in intensive care support for end-organ dysfunction, treatment of the primary disease and opportunistic infections could improve this outcome.

Objectives. To evaluate the incidence and outcome according to HIV status.

Methods. A retrospective chart review of the electronic dataset of children with pneumonia admitted to the paediatric intensive care unit (PICU) at Inkosi Albert Luthuli Central Hospital, Durban, South Africa was undertaken. Data on the use of ganciclovir, combination antiretroviral therapy (cART) and high frequency oscillatory ventilation (HFOV) on outcome were also evaluated.

Results. Of the 405 children with pneumonia admitted to the PICU during 2010, 77 (19%) were HIV-1-positive, and 261 (64.4%) were HIV-negative. The mortality rate among the two groups was similar (22.1% v. 15.3% ($p=0.27$), respectively). Among the HIV-positive cases, cytomegalovirus (CMV) was isolated in 39 (50.7%) cases, of which 18 (46.2%) required HFOV. Among the children who were treated with ganciclovir and cART, the survival rate was 90%. In HIV-positive children with CMV-associated pneumonia who received cART with ganciclovir therapy, the survival rate was 92.3%.

Conclusion. HIV-1-positive children with pneumonia requiring intensive care had a similar outcome to HIV-negative children with pneumonia. HIV-1-positive children with CMV-associated pneumonia on ganciclovir, cART, and HFOV have improved outcomes in comparison to previous studies.

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In South Africa (SA), the roll-out of combined antiretroviral therapy (cART) to all HIV-infected children under the age of 5, regardless of CD4 counts or HIV viral loads, has resulted in HIV-positive children being treated as chronic disease patients.^[1] This change has resulted in a new outlook for HIV-positive children with acute hypoxaemic pneumonia requiring mechanical ventilation, who have had dismal outcomes over the last three decades.^[2,3] Paediatric intensive care unit (PICU) survival of these cases could now result in long-term survival, as HIV-1-positive children receiving cART have similar long-term outcomes to HIV-negative children.^[4] The rational allocation of scarce PICU resources for HIV-1-positive children in terms of short-term outcomes remains controversial, and has created the ethical dilemma of whether or not these patients should be admitted.^[5,6]

Advanced strategies have been developed to treat both end-organ dysfunction and opportunistic infections; this warrants an updated review of the short-term outcomes of HIV-positive children in PICU.

Adequate organ support during the acute phase of the illness appears to be the primary strategy to improve PICU survival among these cases. Ventilation strategies are important in supporting lung function in HIV-positive children with very severe pneumonia and acute respiratory distress syndrome (ARDS).^[7] The early institution of high frequency oscillatory ventilation (HFOV) has been shown to improve the outcome among adults with pneumonia and ARDS.^[8] The early recognition and treatment of opportunistic infections such as *Pneumocystis jirovecii* and cytomegalovirus (CMV) has also been advocated as a means to improve outcome.^[9-11] Although intravenous

ganciclovir therapy has been advocated in many centres, its impact has not been adequately investigated.^[12] The impact of cART during the early stages of recovery from acute disease within the complex milieu of the PICU, where drug-drug interactions and adverse drug reactions frequently occur, requires further evaluation. HIV viral load reduction and CD4 improvement on cART usually takes weeks to months to occur. Neglecting or delaying cART during the immediate recovery stage has been associated with notably poorer outcomes.^[13]

In this retrospective chart review we explored the impact of mechanical ventilation practices, such as intermittent positive pressure ventilation (IPPV) and HFOV, combined with ganciclovir and early cART, on the short-term outcome of HIV-positive children with CMV-associated severe pneumonia who had been admitted to the PICU.

Methods

A review of the electronic database of all cases admitted to the PICU at Inkosi Albert Luthuli Central Hospital (IALCH), a tertiary level hospital in Durban, KwaZulu-Natal Province, SA during 2010, was undertaken. Cases were categorised according to their HIV and CMV status (exposure, infection and disease). Among HIV-positive children with pneumonia, where CMV was isolated, the use of ganciclovir, antiretroviral treatment, and the need for the use of HFOV were evaluated. The use of nevirapine for the prevention of mother-to-child transmission was also recorded.

Table 1. Baseline characteristics of children admitted to the PICU according to their HIV status (N=405)

Characteristics	HIV-positive (n=77)	HIV-exposed negative (n=48)	HIV-negative (n=261)	HIV status unknown (n=19)	Total (N=405)
Males, n (%)	39 (50.6)	24 (50)	134 (51.3)	11 (57.9)	208 (51.4)
Age (months), median (IQR)	3.8 (1 - 14)	4.4 (2 - 10)	8.9 (1 - 24)	6.7 (1 - 32)	4.9 (1 - 32)
Age <12 months, n (%)	60 (77.9)	37 (77.1)	160 (61.3)	12 (63.2)	269 (66.4)
Malnourished, >3 SD from the mean, n (%)	19 (24.7)	9 (18.8)	61 (23.4)	7 (36.8)	96 (23.7)
Diagnosis, n (%)					
LRTI	57 (74)	28 (58)	167 (64)	7 (37)	259 (64)
Sepsis	16 (21)	12 (25)	53 (20)	12 (63)	93 (23)
Pathogens, n (%)					
Gram-negative	34 (44)	21 (44)	132 (51)	5 (26)	192 (47)
Gram-positive	11 (14)	6 (14)	36 (14)	0	13 (3)
All viruses	41 (53)	3 (6)	40 (15)	1 (5)	85 (21)
CMV	39 (50.6)	0	20 (7.7)	1 (5)	60 (15)
All fungi	30 (39)	5 (10)	34 (13)	0	69 (17)
PCP	9 (11.7)	0	0	0	9 (2)
<i>M. tuberculosis</i>	5 (6)	1 (2)	2 (1)	0	8 (2)

PICU = paediatric intensive care unit; LRTI = lower respiratory tract infection; CMV = cytomegalovirus; PCP = *Pneumocystis jirovecii* pneumonia; *M. tuberculosis* = *Mycobacterium tuberculosis*.

Standard management protocol

The standard management of cases admitted to the PICU included a full blood count, urea and electrolyte measurements, liver function tests and C-reactive protein assays. The HIV status was determined with informed consent by an HIV DNA PCR (COBAS AmpliPrep/COBAS TaqMan HIV-1 Qualitative Test (Roche Molecular Systems, Inc., USA). Endotracheal aspirates were sent for bacteriological and respiratory viral screens. Blood CMV DNA PCR (Roche Diagnostics GmbH, Germany) was performed in children who were HIV-exposed, or suspected of being HIV-positive. The standard antimicrobial policy for all cases included the use of co-amoxiclav and gentamicin as first-line therapy for community-acquired infections, and empirical changes to piperacillin/tazobactam/amikacin in non-responsive cases, or those with hospital-acquired infections. Culture- and sensitivity-driven antibiotic changes were made once microbiological isolates was established. All infants who were clinically suspected of being HIV-positive or HIV-exposed, were treated empirically with trimethoprim-sulphamethoxazole (120 mg/kg/day). Fluconazole was added for clinical cases of candidiasis secondary to prolonged antibiotic treatment (>7 days), with fungal growth, or a positive blood (1,3)- β -D-glucan test. For the first 21 days, ganciclovir was administered intravenously at a 12-hourly dose of 5 mg/kg. For the next 21 days, it was administered daily at 5 mg/kg/day to patients who were CMV DNA-positive by PCR and had interstitial pneumonia confirmed by chest radiography. Caregivers and/or parents of HIV-positive children were counselled and cART was commenced as soon as patients were stable, usually during the second week of illness. Patients with a partial pressure arterial oxygen (PaO₂)/FiO₂ ratio of <200, or an oxygen index of >25, on a peak inspiratory pressure of

>30 cmH₂O and a fraction of inspired oxygen (FiO₂) of >0.6, were placed on HFOV. Outcomes were documented upon discharge from the PICU or failure of treatment. Consent for this review was obtained from the Biomedical Ethics Research Committee at the University of KwaZulu-Natal (ref. no. BE151/11).

Results

Of the 405 patients admitted to the PICU at IALCH in 2010, 82 (20.2%) died. The baseline characteristics of admissions to the PICU in 2010 are shown in Table 1: 77 (19.0%) were HIV-positive; 48 (11.9%) were HIV-exposed; 261 (64.4%) were HIV-negative, and in 19 (4.7%) the HIV status was unknown. Among the HIV-positive children, 34 (44.2%) had a detectable HIV viral load of 2 335 963 copies (760 464 - >10 million). Two patients had an undetectable viral load owing to early commencement of cART. CD4% was performed in 24 (31.2%) patients with a median (interquartile range) value of 34.9% (21.3 - 44.5) recorded.

The outcome of children with pneumonia, who were HIV-positive and required mechanical ventilation, was similar to children who were HIV-exposed, but uninfected, and slightly higher than HIV-negative children; however, this finding was not statistically significant ($p=0.27$) (Table 2).

Impact of ganciclovir therapy in CMV-positive patients admitted to the PICU

Of the 77 HIV-positive children, 50.6% were CMV DNA-positive by PCR. Ganciclovir treatment was commenced in 79.5% of CMV-positive patients, of whom 83.9% survived to PICU discharge ($p=0.56$) (Fig. 1). Ganciclovir was commenced at a mean (IQR) of 4 (3 - 7) days after PICU admission.

Table 2. Outcomes of patients admitted to the PICU at IALCH in 2010 according to HIV status (N=405)

		Survivors, n (%)	Deaths, n (%)
Total admissions	405	323	82 (20.2)
HIV status			
HIV PCR +	77 (19.0)	60 (77.9)	17 (22.1)*
HIV-exposed, PCR –	48 (11.9)	34 (70.8)	10 (20.8)
HIV-negative, PCR –	261 (64.4)	216 (82.8)	40 (15.3)*
Unknown	19 (4.7)	10 (52.6)	9 (47.3)

PICU = paediatric intensive care unit; IALCH = Inkosi Albert Luthuli Central Hospital;
PCR = polymerase chain reaction.
*p=0.27.

Table 3. Survival of HIV-positive infants with pneumonia who received cART (n=33) according to CMV status

CMV status	Received cART, n (%)	Survival, n (%)
CMV + PCR +	15 (45.)	13 (86.7)
CMV – PCR –	12 (36.4)	8 (66.7)
Not tested	6 (18.2)	5 (83.3)

The impact of the use of cART alone, and in combination with ganciclovir, among HIV-positive children with CMV-associated pneumonia

Of the 77 HIV-positive children, 42.9% were on cART. Patients receiving cART had a 79% survival rate upon discharge. Fifteen cART patients were CMV PCR-positive, with a survival rate of 86.7% (Table 3). The 13 HIV-positive children with CMV disease who were on cART and ganciclovir therapy had a survival rate of 92.3% on discharge from the PICU. The 14 HIV-positive children with CMV-associated pneumonia treated with ganciclovir alone had a survival rate of 78.6% (Table 4).

Usefulness of HFOV in the management of HIV-positive children with CMV-associated pneumonia and ARDS

Among the 77 HIV-positive children with pneumonia and ARDS, 24 children received HFOV following an inadequate response to conventional IPPV, while 53 patients received IPPV alone. The isolation of CMV was significantly higher among children requiring HFOV than those that did not (75% v. 39.6%; p=0.04), but the outcomes for the two groups were similar (Table 5). Eighteen HIV-1-positive children with CMV-associated pneumonia required HFOV; 94.4% of these were on ganciclovir and 55.5% were on cART and ganciclovir. Patients receiving a combination of HFOV, ganciclovir and cART had a survival rate of 90% (Table 5).

Discussion

The main finding of this retrospective review was the 90% survival among critically ill HIV-positive children with CMV-associated severe pneumonia, who developed ARDS and who were placed on cART, ganciclovir and HFOV. This intervention improved the short-

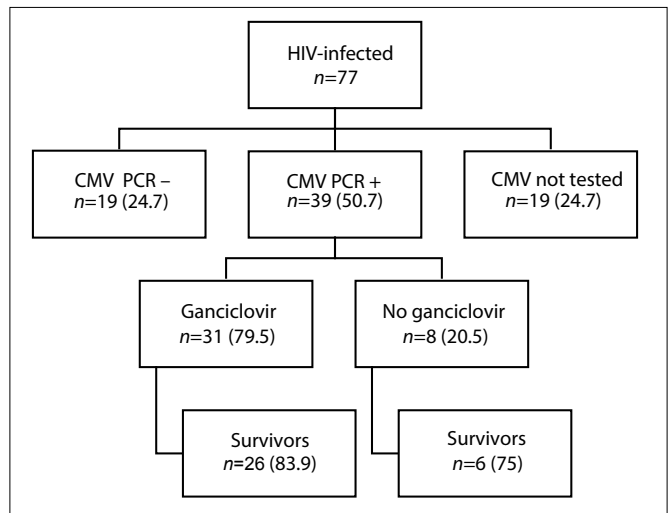


Fig. 1. Impact of ganciclovir in HIV- and CMV-infected children, n (%).

Table 4. Impact of ganciclovir and cART in HIV-positive children with CMV-associated pneumonia (N=39)

Characteristics	cART+ (n=15)	PMTCT+* (n=4)	cART- (n=20)
Ganciclovir	13	3	14
Survival, n (%)	12 (92.3) [†]	2 (66.7)	11 (78.6) [†]
No ganciclovir	2	1	6
Survival, n (%)	1 (50)	1 (100)	5 (83.3)

CMV = cytomegalovirus; cART = combined antiretroviral therapy; PMTCT = prevention of mother-to-child transmission.

*PMTCT of HIV, which included the administration of nevirapine to all HIV-exposed infants for 6 weeks. Nevirapine was also administered for the duration of breastfeeding and 1 week beyond cessation of breastfeeding.

[†]p=0.28.

Table 5. Impact of combination of the mode of ventilation, use of ganciclovir and cART on survival among HIV-positive children with CMV-associated pneumonia (N=77)

Treatment	n (%)	CMV+, n (%)	Survival, n (%)
IPPV only	53 (68.8)	21 (39.6)	43 (81.1)
IPPV, HFOV	24 (31.2)	18 (75)	14 (77.8)
HFOV, ganciclovir	17 (22.1)	17 (100)	14 (82.3)
HFOV, ganciclovir, cART	10 (13.0)	10 (100)	9 (90)

cART = combined antiretroviral therapy; CMV = cytomegalovirus; IPPV = intermittent positive pressure ventilation; HFOV = high frequency oscillatory ventilation.

term outcomes in the patients, in comparison with similar historical controls with survival rates of 0 - 12%. The better outcomes may be attributed to better organ support, rapid responses to the diagnoses and management of primary and opportunistic infections.^[14,15] In HIV-positive children with CMV-associated pneumonia who developed ARDS and required HFOV, ganciclovir treatment and cART resulted in excellent outcomes. The overall outcome of all

HIV-positive children with CMV-associated pneumonia was also favourable on ganciclovir treatment alone, or with cART (83.9% and 92.3%, respectively). This improvement contributed to the overall reduced all-cause mortality rates among HIV-positive children with pneumonia admitted to the PICU, and provides support for the continued access of these patients to scarce and expensive resources in developing countries. These findings were dissimilar to studies in the pre-cART and pre-ganciclovir era in 2004/5 by Goussard *et al.*,^[16] from the PICU at Tygerberg Academic Hospital (TBH), Cape Town, SA, and by Zampoli *et al.*,^[17] from paediatric wards at the Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, SA. At TBH, the mortality rate of CMV-associated pneumonia in HIV-positive children was 72%, while at RCWMCH, it was 55%.^[16,17]

A second major finding of this retrospective review was the significant burden of disease that CMV has among HIV-positive children admitted to the PICU with pneumonia. CMV was isolated from just over half of the HIV-positive children with pneumonia, similar to the prevalence rate of 22 - 78% from necropsy studies and 36 - 75% among antemortem studies.^[12,16-20] The debate on the true pathogenic role of CMV in blood in molecular testing (CMV DNA PCR) of children is ongoing; however, both the related organ involvement (interstitial lung infiltrates, occasional hepatitis) and the clinical improvement in outcome on ganciclovir compared with historical controls suggest its pathogenic role.^[21] Histological diagnoses of CMV pneumonitis by lung biopsy could not be performed on these children given their level of critical illness. While the impact of utilising other treatments like HFOV and cART could also have contributed to the improved outcomes, the management of the CMV appears particularly important. HFOV is merely supportive and the benefits of cART are likely to occur over several weeks to months post commencement and may therefore have little impact on short-term recovery.

Thirdly, 19% of children admitted to the PICU were HIV-positive, reduced from ~30% in earlier studies from the same PICU during the 1990s.^[22,23] The implementation of the PMTCT programme has reduced the transmission rate to <5% in this population.^[24,25] However, given the nature of patients admitted to PICUs, the finding of a 19% HIV prevalence rate among PICU admissions is likely to stabilise for as long as PICUs attract cases where the PMTCT programme has failed or has not been implemented effectively. Failure of PMTCT is indicative of poor access to health services, which often results in delayed presentation and a subsequent increase in the severity of the disease.

Limitations

The few limitations of this review were the retrospective nature, the admission criteria, the small numbers and not determining the severity of disease on admission were concerns that could limit interpretation of the findings. Furthermore, the CMV viral load assessment and tissue diagnoses were not performed as part of the routine standard of care and so the diagnosis of CMV disease and the response to treatment could not be evaluated. The impact of other comorbidities on outcome was not analysed and medium-term outcomes of these cases were not evaluated, therefore the true value of improved short-term PICU outcomes could not be translated into overall survival benefits.

Conclusion

The findings of this retrospective review are important to support continued access of HIV-1-positive patients with pneumonia to scarce resources; the outcomes of these cases are now similar to those of other children with the same severity of illness requiring such services. In addition, the early introduction of cART should occur once a patient is stable, as delays in treatment have been associated with adverse outcomes.^[13,26-29] While this retrospective review clearly shows an improved survival rate among HIV-positive children with CMV-associated pneumonia which was managed with ganciclovir, cART and HFOV, further prospective studies are required to clearly define CMV disease and the benefits of these interventions.

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