

# PAEDIATRIC HIV - LOOKING BEYOND CD4 COUNTS

**ABSTRACT:** *Paediatric HIV remains a significant health and social challenge in sub-Saharan Africa despite many countries gaining improved access to antiretroviral treatment. Paediatric HIV affects multiple body systems and has the potential to cause wide ranging impairments as well as activity and participation limitations. The aim of this paper is to highlight some of the impairments that remain, despite the children having access to better medical care, in order to establish a possible role for physiotherapists. Nine studies conducted through the department of physiotherapy at the University of the Witwatersrand, South Africa are presented. The results of these studies demonstrate the neurodevelopmental, musculoskeletal, respiratory and quality of life challenges which children infected with HIV as well as their caregivers continue to face. The need for long term, multidisciplinary follow up of children infected with HIV is emphasized.*

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## INTRODUCTION

Over 80% of the world's HIV infected children live in sub-Saharan Africa. South Africa is the country which has the highest number of HIV infected children in the world (UNAIDS, 2011). Antiretroviral therapy has been available to children in South Africa since 2004. Despite improved access to antiretroviral therapy paediatric HIV remains a significant health and social challenge in South Africa as well as other countries in sub-Saharan Africa (Hilburn et al, 2010).

Initiation of antiretroviral therapy has been found to reduce mortality and morbidity in young children significantly (Violari et al, 2008). Many developing countries still have strict criteria for

initiating antiretroviral therapy if it is available at all. This means that children are often severely immunocompromised before starting treatment and may present with irreversible impairments (Potterton et al, 2010).

Good outcome in children infected with HIV is often equated with an improved CD4 count and decreased mortality rates (Violari et al, 2008). Few studies have looked beyond this clinical marker to establish what the health concerns of children infected with HIV are, as they live longer, relatively more healthy lives.

In addition limited research has been done on the rehabilitation needs of children infected with HIV. HIV affects multiple body systems in children as in adults, and so a broad spectrum of impairments is anticipated. The aim of this paper is to highlight some of the impairments as well as the limitations in activity and participation which remain despite children achieving acceptable CD4 counts. Parenting stress of caregivers and quality of life of children infected with HIV will also be presented. This paper will provide an overview of

studies conducted by the physiotherapy department of the University of the Witwatersrand.

The results of nine separate studies conducted in Southern Africa over a period of nine years (2004-2012) will be presented. The methods of the studies have been described elsewhere and will be briefly outlined. A total of 673 children participated in these studies. All children were under the age of eight years and were attending paediatric HIV clinics. Consecutive sampling of children who met the inclusion criteria for each study was used. Caregivers gave informed consent for their children to participate in the study and children over four years of age gave assent. Ethical clearance for each of the studies was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. Outcome measures chosen for these studies were valid and reliable and were appropriately translated where necessary.

Demographic and anthropometric data were collected in all the studies and the children's CD4 counts and viral loads were recorded.

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## NEUROLOGICAL IMPAIRMENTS

### Background

HIV encephalopathy in children has been well described and the impact of HIV on the developing nervous system continues to be studied. HIV encephalopathy has been found to cause developmental delay in all facets of development with cognitive, language and motor delays being reported (Baillieu and Potterton, 2008). The prevalence of neurodevelopmental delay may be as high as 60% (Baillieu and Potterton, 2008).

Studies on neurodevelopment in HIV-infected children in Africa have revealed that a large proportion of children have moderate to severe delay in cognitive, motor, and language development, and that gross motor development is most severely affected. The severity of the encephalopathy may be dependent on a number of factors. The timing of infection, advanced stage of maternal disease at delivery, rapid disease progression with early immune suppression, and high plasma viral load in infancy have been identified as factors which predispose an infant to developing encephalopathy. The effects of timely initiation of antiretroviral therapy on alleviating the impact of encephalopathy have been described (Hilburn et al, 2010).

### Study Findings

A single blinded randomized controlled trial conducted in Soweto, South Africa in 2004 found that 122 young children infected with HIV were severely delayed in both cognitive and motor development. The children were assessed with the Bayley Scales of Infant Development II. The Bayley Scales has been normed on South African children (Richter et al, 1992). Healthy South African children from rural and urban communities score well within the normal ranges of this test.

Seventy two percent of the children presented with severe motor delay and 52% presented with severe cognitive delay (Potterton et al, 2010). The mean CD4 count for the children in this study was only 14.35%. The majority of the children (85%) were antiretroviral naïve. In a subsequent cohort study conducted

in Soweto, South Africa (Hilburn et al, 2011) the majority of children (68%) were already receiving HAART when they were assessed. Their CD4 counts were significantly higher (23.16%) than the children assessed in 2004 yet despite this the children still presented with delayed development across all facets of development (Hilburn et al, 2011).

The results of the above studies are supported by a non randomized cohort study which was conducted in Kenya in 2007. This study followed up 36 infants under 30 months of age for at least six months after starting HAART. In this study 83.3% of the children had motor delay and 61.2% had cognitive delay (Kigira M, 2007). Almost 80% of the children in this sample had CD4 count below 20%.

In a single blinded, randomised controlled trial conducted in South Africa it was found that the implementation of a basic home stimulation programme which was taught to the caregivers resulted in significant improvements in the cognitive (MDI 62.6% to 69.3%;  $p=0.01$ ) and motor (49.8% to 70.5%;  $p=0.02$ ) development of young children infected with HIV (Potterton et al, 2010). The children's CD4 counts improved significantly (14.2% to 21.9%;  $p=0.00$ ) over the course of the study as more children gained access to antiretrovirals. The mean CD4 percentage at the end of the study was not optimal and many of the children were still immunocompromised (Potterton et al, 2010). Despite the improvements in motor and cognitive scores the children still presented with developmental delays in all facets of development at the end of the study period.

Many of the children in the above study started HAART after enrolling in the study. For this group of children it was found that although their motor development improved significantly (PDI 49.69 to 63.64;  $p=0.04$ ), their cognitive development did not (MDI 66.44 to 65.64;  $p=0.77$ ). This is postulated to be due to the fact that irreversible brain damage had already occurred. Despite some improvement being found in motor development the children still presented with developmental scores well below normal despite having received HAART (Potterton et al, 2010).

In 2011 two studies were conducted to compare the development of infants diagnosed with HIV to that of age matched HIV exposed but uninfected infants. The longitudinal study conducted in South Africa ( $n=56$ ) found that the HIV infected infants were significantly delayed in all aspects of development when compared to the HIV exposed but uninfected group. The development of these infants was followed up for six months after initiating HAART, the infected group remained delayed despite starting HAART at a very early age (4.87 months  $\pm 2.8$ ) (Whitehead et al, 2013). The group of infants assessed in a cohort study in Zimbabwe ( $n=60$ ) showed similar results with the HIV infected infants faring significantly worse in all facets of development than the exposed uninfected infants (Hutchings and Potterton, 2013).

## MUSCULOSKELETAL IMPAIRMENT

### Background

Myopathy and muscle weakness in HIV infected adults has been described (O'Brien et al, 2008), however very little research has been done on the muscle strength of children infected with HIV. It has been hypothesized that HIV may cause reduced muscle strength which then has the effect of delaying gross motor function (Baillieu & Potterton, 2008). HIV is associated with protein malabsorption, loss of body protein and abnormal protein metabolism (Hsu et al, 2005). These protein metabolism problems can also lead to decreased muscle bulk which may affect muscle strength (O'Brien et al, 2008).

Another factor that could cause muscle weakness in children infected with HIV is undiagnosed, asymptomatic myopathy. Myopathy may be present in children infected with HIV as it has been shown to exist in adults infected with HIV (O'Brian et al, 2008).

### Study Findings

Thirty two children between the ages of four and eight years of age had their muscle strength tested. Eight muscle groups were tested bilaterally using a MicroFET 2 hand-held dynamometer. The muscles tested included flexors and abductors of the shoulders, and flexors

and extensors of the elbows, hips and knees. This pilot study was a descriptive cohort study.

The children presented with muscle strength of 50% of the expected norm for their ages. A decrease in CD4 count correlated to a decrease in muscle strength ( $r>0.5$ ), but muscle strength did not automatically improve when children started HAART and the other clinical parameters improved. Participants in this study were from families of low socio-economic status and their heights and weights were significantly below the norm for their age ( $p<0.001$ ) (Humphries, 2011).

## RESPIRATORY IMPAIRMENT

### Background

Respiratory disease is a major cause of morbidity and mortality in children infected with HIV (Zar, 2008). Ninety percent of children infected with HIV will develop a respiratory illness sometime during the course of their HIV infection (Zar and Mulholland, 2003). Pneumocystis jirovecii pneumonia is by far the most common opportunistic infection seen in children infected with HIV. Cytomegalovirus, mycobacterium avium complex and pulmonary tuberculosis are also opportunistic infections that are frequently seen.

Pulmonary infection may become chronic as evident in the large number of children who present with secondary bronchiectasis. This is more marked in those with lymphoid interstitial pneumonitis, recurrent bacterial pneumonia and unresolved pneumonia (Sheikh et al, 1997).

### Study Findings

One hundred and twenty five children infected with HIV who were hospitalised were assessed to determine the burden of respiratory disease in this observational study. The burden of disease was based on the clinical diagnosis recorded in the child's file. The mean age of the children was 20.5 months ( $\pm 23.6$ ). Indications for chest physiotherapy were also determined.

The burden of respiratory disease in this sample of hospitalized children under the age of eight years was high, with 68.8% presenting with two or

more respiratory diagnoses. The most common clinical diagnoses were bacterial pneumonia (66.4%), tuberculosis (48%) and pneumocystis jirovecii pneumonia (23.3%). A large proportion (90%) of the children had indications for chest physiotherapy, namely excessive retained secretions and/or decreased air entry, however very few of the children had been referred for chest physiotherapy. Just over 40% of the children were receiving antiretroviral therapy with the average length of use 9.81 months ( $\pm 11.61$ ). The mean length of hospital stay was 18.76 days ( $\pm 19.19$ ). The mean CD4 count was low at 17.33% ( $\pm 10.96$ ) (Da Cunha, 2011).

## QUALITY OF LIFE

### Background

Paediatric HIV is a multigenerational disease. The diagnosis of the child as being HIV positive almost invariably means the mother is positive too and possibly the father as well. This sets HIV apart from other chronic diseases of childhood. Families affected by HIV are often poor and have limited access to quality healthcare (Potterton, 2007). These families may experience multiple losses that add to the psychosocial distress experienced by the family. Paediatric HIV therefore has the potential to negatively affect the quality of life of the children themselves as well as their caregivers.

### Study Findings

The Parenting Stress Index (Short Form) was used to assess parenting stress levels of the caregivers of young children, under two and a half years of age infected with HIV who were enrolled in a randomized controlled trial. Parenting stress of the caregivers of children infected with HIV increased significantly as their children started antiretroviral therapy ( $p=0.01$ ) despite the fact that the children's CD4 counts improved indicating improved health status (Potterton et al, 2007). Overall the parenting stress levels of the caregivers was extremely high with PSI (SF) levels of over 100 where a score of 90 or above is considered to indicate the need for clinical intervention (Abidin, 1995).

In a separate cohort study 45 children

infected with HIV and 45 healthy, age-matched controls completed the PedsQL. All the children were between six and seven years old and were in grade one. The children infected with HIV were all on antiretroviral therapy and had CD4 counts of over 25%. They were clinically well (Goldberg, 2010).

The children infected with HIV had significantly lower PedsQL scores than their healthy peers ( $p=0.00$ ), despite having CD4 counts of over 25%. There were differences in all the domains measured by the PedsQL, namely Physical, Emotional, Social and School Functioning. The most significant difference was in the Physical Functioning domain ( $p<0.01$ ).

## DISCUSSION

The studies presented above show that despite children gaining access to antiretroviral therapy a number still present with significant impairments that potentially result in limitations in activity and participation. These children will potentially benefit from rehabilitation.

The impact of HIV on the developing central nervous system has been well documented. However there is an assumption that as children get better access to antiretroviral therapy the neurological complications will cease to be a significant clinical concern (Kigira M, 2007). This has not been the case in Southern Africa. HIV is neurotrophic and crosses the immature blood brain barrier easily, neurologic involvement is therefore possible early on in the disease progression. At the end of 2010 antiretroviral therapy became available to all HIV infected children in South Africa below one year of age, regardless of what their CD4 counts are. Despite the fact that infants are gaining access to HAART so much earlier they are still presenting with moderate developmental delay as early as four months of age (Whitehead et al, 2013; Hutchings and Potterton, 2013).

The decreased muscle strength measured in young children could be related directly to the effects of the HI virus on the muscular system. Although very few studies have been done on children (Ramos et al, 2012), data from adult studies show that HIV can lead to a clinical myopathy (O'Brian et al,

2008). Prolonged illness and frequent hospitalization may lead to disuse atrophy (Humphries C, 2009). The children in this study were underweight. Decreased muscle strength may also be due to the fact that the children had decreased muscle mass as a result of protein malnutrition (O'Brian et al, 2008). Further research is required in this field. There is a need to establish age specific norms for muscle strength of South African children.

Quality of life in children infected with HIV may be affected by a number of factors, both clinical and social. The control group used in the study presented came from a similar socio-economic background to the group of children infected with HIV. The differences in quality of life between the two groups can therefore be attributed to the HIV infection (Goldberg, 2010).

Parenting stress has been shown to be high for caregivers of children with chronic diseases and HIV has proven to be no exception. The multigenerational aspect of HIV sets it apart from most other chronic childhood disabilities. The mothers in this study had to deal with their own diagnosis, ill health and stigma as well as care for their children. Extreme poverty and lack of social support exacerbated their stress levels (Potterton et al, 2007).

The high burden of respiratory disease observed in the hospitalised children infected with HIV is of concern. The conditions with which the children presented are not very different from those seen in HIV uninfected children (Graham, 2003) with the exception of PJP and the high incidence of TB. The fact that children present involvement of multiple body systems means that their disease course is complicated. Further studies are required to determine whether or not physiotherapy can have an impact on the clinical outcome of these children. Of particular concern are the children who have chronic respiratory conditions which may impact on endurance and muscle strength as well as directly on the respiratory system. Children with bronchiectasis and lymphoid interstitial pneumonitis will potentially benefit from long term physiotherapy management on an out-patient basis. Further research into the effect of physiotherapy in the

management of HIV infected children with different respiratory pathologies is required.

## CONCLUSION

This review provides a brief overview of the diverse and complex effects of HIV infection on young children. It is beyond the scope of this paper to give detailed or specific results and analysis in this limited format. The relevance of paediatric HIV for South African physiotherapists is of essence.

Placing children on antiretroviral therapy does improve many of their health parameters. An improved CD4 count and a decreased viral load do not always lead to an improvement in all facets of a child's health and well-being. The children in the abovementioned studies presented with developmental delay, muscle weakness, decreased quality of life and a high burden of respiratory disease despite having access to antiretroviral therapy.

Physiotherapists need to continue to be involved in the long term management of children infected with HIV, despite more children gaining access to antiretroviral therapy. Detailed multi-system assessments of all children infected with HIV are required. Holistic, appropriate intervention programmes, that meet the needs of the children and their caregivers, need to be developed and tested.

Paediatric HIV is a global problem that will affect children around the world for many years to come. Small pockets of success should not lead to professional apathy.

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