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RESEARCH ARTICLE

CHARACTERISTICS AND PRE ART HOSPITALIZATION OF HIV-INFECTED CHILDREN AT ENROLMENT IN A DISTRICT HOSPITAL HIV CLINIC, GAUTENG PROVINCE, SOUTH AFRICA

Sphiwe Madiba[1], Kebogile Mokwena[2] and Mathildah Mokgatle[3]

[1]Department of Environmental and Occupational Heath, Faculty of Health Sciences, University of Limpopo, Medunsa Campus, South Africa
[2]School of Public Health, Department of Social and Behavioural Sciences, Faculty of Health Sciences, University of Limpopo, Medunsa Campus, South Africa
[3]School of Public Health, Department of Biostatistics, Faculty of Health Sciences, University of Limpopo, Medunsa Campus, South Africa

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ABSTRACT

An increasing number of older perinatally infected undiagnosed children present with advanced disease for antiretroviral treatment (ART). The study aim was to describe the demographic and the clinical characteristics, and determine pre ART hospitalization of HIV-infected children at enrolment in HIV care in Gauteng province, South Africa. A cross sectional survey and medical records analysis was conducted with 149 caregivers of HIV infected children aged between 4–17 years. High proportion (n=58, 39.6%) of children were diagnosed between 6-17 years. The majority (n=131, 88.4%) presented at WHO clinical stages 3 and 4 and were severely immune compromised. Over three quarters (n=110, 82.1 %) had CD4 cell count <500 cells/mm3, and CD4 count decreased significantly with increasing diagnosis age (OR: -18.56, CI: -30.57 -6.54, P=.003). Three quarters (n=111, 75.4%) had mixed infections and (n=62, 41.6%) had tuberculosis. Almost half (n=71, 47.7%) were hospitalized and (n=29, 40.8%) had multiple admissions. Hospitalization was significantly associated with WHO clinical staging (OR; 2.10, CI: 1.06-4.16, P=.032) and diagnosis age (OR; 1.19, CI: 0.67-0.93, P=.005). Undiagnosed perinatally infected older children and adolescents will benefit from early diagnosis and treatment by strengthening the provision of routine testing of this age group at primary care level.

INTRODUCTION

The 2008 South African household survey estimated the prevalence of HIV in children aged 2–14 years to be 2.5% [1]. Less than half of these children have access to antiretroviral treatment (ART) despite South Africa having the largest paediatric ART programme in the world [2]. Other studies report similar findings, in Tanzania, less than a third of HIV infected children estimated to be in need of ART are receiving it [3]. In many developing countries, HIV infected children receiving ART represent a small proportion of those who need it [4]. Although South Africa and other sub Saharan countries have made progress with interventions for prevention of mother to child transmission (PMTCT) of HIV, high numbers of infants were infected in the 1990s, before the introduction of these interventions [5]. Limited testing opportunities following the post natal period is a major barrier to early infant testing and access to HIV treatment for perinatally infected children [4]. According to Ramirez-Avila and colleagues [6], the 2007 World Health Organization (WHO) recommendations for provider-initiated testing for children [7] do not offer implementation guidance. Subsequently, many perinatally infected children remain undiagnosed and enter care at an advanced stage of disease progression [1, 4, 8-10]. Whereas previously untreated HIV infection in infants was characterized by rapidly progressing disease and by death occurring before the age of 5 years [8]. Now up to a third of HIV-infected infants are slow progressors with a median survival of 10 years in the absence of HIV diagnosis and care [11]. In South Africa, slow progressors also known as long term survivors, make up 2 to 3% of all undiagnosed perinatally infected 10-year-olds [12]. In a recent study conducted in KwaZulu Natal, Ramirez-Avila and colleagues [6] reported HIV prevalence of 6% among children (median age 7 years) presenting for acute medical services. The majority of long term survivors remain undiagnosed until they develop advanced disease. They then present for care at an older age with moderate to severe immunosuppression, below average for height and weight, and have had recurrent infections as well as pulmonary tuberculosis[12-14]. Although South Africa's paediatric ART programme is the largest in the world, ART provision in public health facilities was implemented in 2004. Given that the majority of children were infected in the 1990s, undiagnosed HIV infection is common among children attending primary health care facilities in South Africa [15]. Health care providers are seeing an increasing number of long-term survivors who present for care in primary health care facilities. However, few studies have focused on the morbidity related to undiagnosed HIV infection among long term

* Corresponding author: **Sphiwe Madiba**
Department of Environmental and Occupational Heath, Faculty of Health Sciences,University of Limpopo, Medunsa Campus, South Africa

survivor children presenting in public health facilities [14]. The purpose of the study was to describe the demographic and clinical characteristics, and determinepre ART hospitalization of perinatally HIV infected children at enrolment in a HIV care programme in Gauteng province, South Africa. Early identification and diagnosis is vital for survival of HIV infected children. Describing pre ART clinical characteristics of undiagnosed HIV infected children will increase awareness among health care providers for early detection and testing of these children [16].

MATERIAL AND METHODS

Study design

A survey was conducted with caregivers of HIV infected children aged between 4–17 years, using structured questionnaires and medical records analysis. Data were collected between December 2010 and January 2011 as part of a multicenter study on HIV disclosure to infected children.

Study setting and population

The data presented here were collected at Odi district hospital, situated in Tshwane Municipality, in Gauteng province, South Africa. The hospital initiated HIV treatment in 2006, and provides HIV treatment and care services to children from surrounding rural villages and informal settlements in its catchment area. Most children enrolled for ART came from the primary health care level. This includes HIV infected infants diagnosed through the PMTCT program and older children who present to primary health facilities with HIV related morbidity. At the time of the survey, only doctors could initiate ART in South Africa, hence the referral of children to this hospital for ART. However, since 2011, ART is now accessible at the primary health care level through the Nurse Initiation and Maintenance of Antiretroviral Therapy initiative of the Ministry of Health [17].

Data collection

Caregivers were eligible if their children were between 4–17 years and were receiving ART at the time of the survey. All eligible caregivers were invited to participate during the routine monthly appointments for their children's medication or follow up; the number of caregivers who did not volunteer to participate was not documented; only a few declined participation. Trained research assistants and an MPH intern collected data. A structured researcher administered questionnaire captured caregiver socio-demographic information and relation to the child. Caregivers also provided clinical information for the children under their care including the current age, age at HIV diagnosis, age at initiation of ART, time since initiation of ART, knowledge of HIV diagnosis, age at disclosure, and pre ART hospitalization. The presence of HIV related infections at ART initiation, baseline laboratory results, and WHO clinical staging at ART initiation were collected from the medical records. At the time of the survey, all children born to HIV positive mothers were initiated on ART based on the relevant or applicable national treatment guidelines. ART eligibility criteria were advanced WHO clinical stages 3 or 4, and or CD4 percentage less than 20% in children younger than 18 months, or less than 15% in children older than 18 months [18]. The 2010 national treatment guidelines recommended that all children less than 1 year of age be initiated with ART. The guidelines also recommended ART initiation for children 1-5 years with clinical stage 3 or 4 or CD4 <25 % or absolute CD4 count < 750 cells/µl, and for children > 5 years to 15 years with clinical stage 3 or 4 or CD4 < 350 cells/µl [19].

Data analysis

Data were entered and analyzed using Stata version 10 [20]. Baseline characteristics of the children at the time of ART initiation were stratified by hospitalization and compared using chi-square tests for categorical variables and t tests for continuous variables. We used bivariate and multivariable logistic regression models to identify independent factors associated with hospitalization and severe immune deficiency. The multivariate models included all significant variables in univariate models. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and P values. For all analyses, P<.05 were considered statistically significant.

RESULTS

Caregiver demographics

Almost all the caregivers (n=146, 96.6%) were female, with a mean age of 42.4 years (SD=14.9). The highest proportion of caregivers were biological mothers (n=78, 52.3%) and almost a third (n=42, 28.2%) were grandmothers. Less than a quarter (n=31, 20.8%) of the caregivers had completed 12th grade while half (n=76, 51%) completed secondary school. The majority of the caregivers (n=64, 55.7%) were unemployed. Almost half (n=71, 47.7%) were single and only about a quarter (n=36, 24.2%) were married. Data were collected on the caregiver's HIV status, and more than half (n=89, 59.7%) were HIV positive, (n=55, 36.9%) were HIV negative, and (n=5, 3.4%) did not know their HIV status (Table 1).

Table 1 Characteristics of the primary caregivers of HIV infected children in Odi Hospital at the time of the survey (n=149)

	Frequency	Percent
Primary caregiver age		
Mean age	42.4 yeas	SD 14.9
Primary caregiver		
Mother	78	52.4
Father	3	2.0
Grandmother	42	28.2
Other relatives	26	17.4
Employment status		
Employed	41	27.5
Unemployed	83	55.7
Pensioner	21	14.1
Attending school	4	2.7
Level of education		
Primary	37	24.8
Secondary	76	51.0
High school	31	20.8
Tertiary	5	3.4
Marital status		
Single	85	57.0
Married	36	24.2
Divorced	7	4.7
widowed	21	14.1
HIV status, primary caregiver		
Positive	89	59.7
Negative	55	36.9
Unknown	5	3.4

Child demographics

The mean age of the children was 8.2 years, (SD=3.1). Over half (n=79, 53%) were between 6-10 years while almost a quarter (n=34, 23.5%) were between 11-17 years. Based on caregiver reports, (n=59, 39.6%) of the children knew about their HIV diagnosis. Half of the children (n=30, 50.9%) were between 11-17

Table 2 Characteristics and history of hospital admission of HIV infected children at ART initiation at Odi Hospital

	All (n=149)	History of admission (n=71)	No history of admission (n=78)	unadjusted OR (95% CI)	P value
Age group, years					
4-5 years	35 (23.5)	17 (21.8)	18 (25.4)	1	0.892
6-10 years	79 (53.0)	41 (52.6)	38 (53.5)	1.38 (0.17-11.1)	
11-15 years	31 (20.8)	18 (23.1)	13 (18.3)	1.46 (0.55-3.88)	
16-17 years	4 (2.7)	2 (2.6)	2 (2.8)	1.28 (0.55-2.96)	
Mean age (SD)	8.3 (3.19)				
Gender					
Female	86 (57.7)	47 (60.3)	39 (54.9)	1	0.511
Male	63 (42.3)	31 (39.7)	32 (45.1)	1.24 (0.64-2.38)	
Attending school					
Not schooling	128 (85.9)	11 (14.1)	10 (14.1)	1	0.997
Attending school	21(14.1)	67 (85.9)	61 (85.9)	1.00 (0.39-2.52)	
HIV disclosure status					
Know HIV status	59 (39.6)	31 (39.7)	28 (39.4)	1	0.969
HIV status not known	90 (60.4)	47 (60.3)	43 (60.6)	0.98 (0.51-1.90)	
Orphan hood					
Paternal	24 (16.1)	16 (20.5)	8 (11.3)	1	0.291
Maternal	37 (24.8)	21 (26.9)	16 (22.5)	1.52 (0.52- 4.43)	
Double orphan	20 (13.4)	10 (12.8)	10 (14.1)	2 (0.59- 6.77)	
Unknown	5 (3.36	1 (1.3)	4 (5.6)	8 (0.76 -83.8)	
Both parents alive	63 (42.3)	30 (38.5)	33 (46.5)	2.2 (0.82- 5.87)	

Table 3 Baseline Clinical information of HIV infected children by hospital admission (n=149)

	All (n=149)	History of admission (n=71)	No history of admission (n=78)	Unadjusted OR (95% CI)	P value
Age at HIV diagnosis					
1-5 years	90 (60.4)	42 (53.6)	48 (67.6)	1	0.201
6-10 years	41 (27.5)	26 (33.3)	15 (21.1)	0.53 (0.11-2.52)	
11-17 years	17 (12.1)	9 (12.8)	8 (11.3)	0.70 (0.25-1.95)	
Mean age (SD)	5.3 (3.6)				
Age at initiation of ART					
1-5 years	76 (51.0)	37 (47.4)	39 (54.9)	1	0.497
6-10 years	53 (35.6)	31 (39.7)	22 (31.0)	1.05 (0.38-2.88)	
11-17 years	20 (13.4)	9 (11.5)	11 (14.1)	0.67 (0.33-1.36)	
Mean age (SD)	5.9 (3.5)				
WHO clinical staging at initiation of ART					
Stage 2	18 (12.1)	14 (18.0)	4 (5.6)	1	0.043
Stage 3	109 (73.6)	55 (70.5)	54 (76.1)	3.43 (1.06 -11.1)	
Stage 4	22 (14.8)	9 (11.5)	13 (18.3)	5.05 (1.24 -20.4)	
CD4 cell count at initiation of ART					
<100 cells/mm^3	34 (25.4)	20 (27.0)	18 (28.1)	1	0.826
<200 cells/mm^3	20 (14.4)	11 (14.9)	9 (14.1)	1.2 (0.52 =2.74)	
200–499 cells/mm^3	56 (41.8)	32 (43.2)	24 (37.5)	1.09 (0.39 -3.04)	
≥500 cells/mm^3	24 (17.9)	11 (14.9)	13 (20.3)	1.57 (0.60 -4.12)	
Missing data	18				
Mean (SD)	300 (249.5)				
TB infection at initiation of ART					
No	87 (58.4)	35 (49.3)	52 (66.7)	1	0.031
Yes	62 (41.6)	36 (50.7)	26 (33.3)	2.05 (1.06 -3.98)	

years when they learned about their HIV status, more than a third (n=26, 44.1%) were between 6-10 years, and a fifth (n=3, 5.1%) were younger than 6 years. The mean age at disclosure was 9.3 years, (SD=2.9). A quarter (n=37, 24.8%) of the children were maternal orphans, (n=24, 16.9%) were paternal orphans, whilst (n=20, 13.4%) were double orphans. The majority of the children (n=128, 85.9%) were attending school (Table 2).

Clinical characteristics

The majority (n=90, 60.4%) of children were diagnosed between 1-5 years, over a quarter (n=41, 27.5%) was diagnosed between 6-10 years, and a tenth (n=18, 12.1%) between 11-17 years.

The mean age at diagnosis was 5.3 years, (SD=3.6). Half of the children (n=76, 51%) were between 1-5 years at ART initiation, (n=53, 35.5%) were between 6-10 years, (n=20, 13.5%) were between 11-17 years, and the mean age at ART initiation was 5.9 years, (SD=3.5) (Table 3).

Table 4 Presenting opportunist infections at initiation of ART in HIV infected children in Odi Hospital (n=149)

	Number and % of total complaints
Skin infections	78 (52.3)
Chronic diarrhoea	67 (45.0)
Tuberculosis	62 (41.6)
Oral candidiasis	51(34.2)
Chronic and recurrent respiratory tract infections	48 (32.2)
Pneumonia	10 (6.7)
Enlarged lymph nodes	13 (8.7)
Chronic vomiting	10 (6.7)
Otitis media	9 (6.0)
Eye infections	9 (6.0)

* Children presented with multiple infections, the total percentage is more than 100%

Table 5 Hospitalization information of HIV infected children at initiation of ART at Odi Hospital

	History of admission (n=71)	No history of admission (n=78)	adjusted OR (95% CI)	P value
Age at HIV diagnosis				
1-5 years	42 (53.6)	48 (67.6)	0.19 (0.67-0.94)	0.005
6-10 years	26 (33.3)	15 (21.1)		
11-17 years	9 (12.8)	8 (11.3)		
Child age				
4-5 years	17 (21.8)	18 (25.4)	1.17 (0.97-1.42)	0.093
6-10 years	41 (52.6)	38 (53.5)		
11-15 years	18 (23.1)	13 (18.3)		
16-17 years	2 (2.6)	2 (2.8)		
WHO clinical staging at initiation of ART				
Stage 2	14 (18.0)	4 (5.6)	2.10 (1.06-4.16)	0.038
Stage 3	55 (70.5)	54 (76.1)		
Stage 4	9 (11.5)	13 (18.3)		
TB infection at initiation of ART				
No	35 (49.3)	52 (66.7)	1.70 (0.84-3.41)	0.135
Yes	36 (50.7)	26 (33.3)		

Late Disease Stage at Presentation

The medical records analysis showed that at first presentation, the majority of children (n=109, 73.6%) were in WHO clinical stage 3, (n=22, 14.8%) were in clinical stage 4, whilst over a tenth (n=18, 12.1%) were in clinical stage 2. The most common presenting symptoms and diagnoses at initiation of ART included, chronic skin infections, chronic diarrhoea, tuberculosis, oral candidiasis, chronic or recurrent upper respiratory tract infections, pneumonia, enlarged lymph nodes, chronic vomiting, otitis media, and eye infections. A high proportion of the children (n=62, 41.6%) were diagnosed with pulmonary tuberculosis at ART initiation. The majority of children (n=111, 75.4%) presented with mixed infections (Table 4). Severe immunodeficiency according to a decreased CD4 cell count-for-age was present at initiation of ART. The majority (n=54, 39.8%) had CD4 cell count of <200 cells/mm3, (n=56, 41.8%) had CD4 cell count of between 200–499 cells/mm3, and (n=24, 17.9%) had CD4 cell count of ≥500 cells/mm3. The mean CD4 cell count was 300 cell/mm3 (SD=249.5). Simple linear regression showed that CD4 count decreased significantly with increasing diagnosis age (OR: -18.56, CI: -30.57 -6.54, P=.003). Children presenting with severe immunodeficiency at ART initiation were more likely to have been diagnosed late when compared to children who were not severely immune compromised. Data were incomplete for viral load readings and were not included in the analysis.

Hospitalization at initiation of ART

Caregivers provided information on the history of hospitalization of the children prior to ART initiation, and almost half of the children (n=71, 47.7%) were ever admitted in hospital. Of the children who were ever admitted (n=71), a high proportion (n=29, 40.8%) had multiple admissions. At bivariate analysis, we determined associations between the child's clinical characteristics and hospitalization. We found that hospitalization was associated with age at diagnosis (OR; 0.89, CI: 0.81-0.98, P=.01), TB infection (OR; 2.057, CI: 1.06-3.98, P=.03), and WHO clinical staging (OR; 2.10, CI: 1.08-4.09, P=.02). When we compared children at different WHO clinical stages, children on stage 4 (OR; 5.05, CI: 1.24-20.47, P=.02) were five times more likely to be admitted as compared to children on WHO clinical stage 2, children on stage 3 (OR; 3.43, CI: 1.06-11.10, P=.03) were three times more likely to be admitted as compared to children on stage 2.

Children who were hospitalized were 11% most likely to be diagnosed early as compared to children who were never hospitalized. At multivariable analysis using stepwise regression and adjusting for age at ART initiation, TB infection, and child age, hospitalization was significantly associated with WHO clinical staging (OR; 2.10, CI: 1.06-4.16, P=.03) and diagnosis age (OR; 1.19, CI: 0.67-0.93, P=.005) (Table 5).

DISCUSSION

The results show that children presented for ART initiation at a relatively older age, almost half of the children were between 6-17 years when they were tested and enrolled for treatment. The mean age at ART initiation was 5.9 years. Although early infant diagnosis is now available in many PMTCT programs in South Africa, the majority of HIV-infected older children and adolescents were born to mothers who were never enrolled in the PMTCT program. The majority of these children enter care at a late stage of disease progression due to poor access to early infant diagnosis and ART provision [1, 9]. In many communities, in sub Saharan Africa, older children are diagnosed late despite most caregivers suspecting their children of being HIV infected before diagnosis. Data from a study conducted in Zimbabwe show that only 25% of caregivers had not suspected HIV infection before their children were diagnosed [21]. Other studies show that many perinatally infected children remain undiagnosed despite the fact that their HIV-infected mothers were already in HIV care and receiving ART [6, 22]. In this study, about 40% (n=24) of the children who presented late for HIV diagnosis and treatment, were living with their biological parents who were already receiving ART. Caregivers, particularly biological mothers, find it difficult to deal with the HIV diagnosis of a child [22], resulting in delaying HIV testing until the child is critically ill and had suffered from numerous opportunistic infections. The majority of the children presented at advanced WHO clinical stages 3 and 4. The findings concur with previous data from Uganda [23], Zimbabwe [12, 14], and South Africa [24]. Consistent with other studies, the advance WHO clinical stage was attributed to the late presentation of children for treatment [24]. High proportion of perinatally HIV infected children are undiagnosed slow progressors, and according to Ferrand and colleagues[14], these children present for treatment with severe immunodeficiency or chronic complications of untreated HIV as seen in this study. While WHO recommends HIV diagnostic testing for all infants born to HIV-infected mothers at 4-6 weeks of age [25], children born to mothers who were never tested will remain undiagnosed if

no efforts are made for their early identification and testing. Although provider initiated routine testing of children is recommended; it is not usually possible [26]. Routine testing for children should become an element of care in primary health care facilities until PMTCT coverage reaches all HIV-infected pregnant women [4]. Implementing testing and counseling at the primary care level will reduce diagnostic delays and increase entry into HIV care for perinatally infected undiagnosed children [14].

Undiagnosed perinatally HIV infected children experience a high burden of opportunistic infections [27]. The majority (75%) of children in this study presented with mixed opportunistic infections and a high prevalence (41.6%) of tuberculosis infection. Common opportunistic infections included chronic skin infections, chronic diarrhoea, oral candidiasis, chronic or recurrent upper respiratory tract infections, pneumonia, chronic vomiting, otitis media, and eye infections. The common opportunistic infections observed in the current study were similar to what was reported in other studies [14-16, 21, 28]. The prevalence of tuberculosis infection was higher than that reported in other studies [16, 24], but in line with the high prevalence reported in Zimbabwe [21] and the high prevalence of TB-HIV co-infection in adults, in South Africa. Consistent with other studies [21], the immunologic status of the children was severely compromised. The mean CD4 cell count at ART initiation was 300 cell/mm3. Children with severe immunodeficiency were more likely to have been diagnosed late when compared to children who were not severely immune compromised. Based on caregiver reports, almost half of the children were ever admitted to hospital and 40.2% had multiple hospital admissions. Children in this study experienced a high burden of opportunistic infections and high prevalence of tuberculosis which might account for the multiple hospital admissions. However, the current study could not establish causes for hospital admissions because the children were hospitalized prior to enrolment for ART, and the admission records were not kept in the study site. Data from other studies show that the most common reasons for admission of perinatally infected children were pneumonia, gastroenteritis, pulmonary tuberculosis, and meningitis [16, 21]. These opportunistic infections are similar to the presenting infections the children in this study suffered from. Factors associated with hospital admission were WHO clinical staging and diagnosis age. Children presenting at WHO clinical staging 3 and 4 were more likely to be hospitalized compared to children at WHO clinical stage 2. While hospitalization was associated with early diagnosis, children who were hospitalized were most likely to be diagnosed early as compared to children who were never hospitalized. Over half of the children were brought to the clinic by their biological mothers on the day of the survey, the rest (47%) were accompanied by grandparents, aunts, and older siblings. We found a high prevalence of orphan hood in this setting where 40.9% of the children were single orphans while 20% were double orphans. There was a predominance of maternal orphans among the single orphans. This finding is consistent with the high prevalence of orphan-hood in South Africa and is similar to previous reports in sub Saharan Africa [16, 21].

CONCLUSION

High proportion of perinatally infected children presented late for HIV testing and treatment in this setting. At ART initiation the majority of children showed signs of long-term illnesses and severe immunodeficiency. These data support the need to strengthen early detection of infections related to undiagnosed perinatally HIV infection in older children through awareness and training of primary health care professionals. Undiagnosed perinatally infected older children and adolescents will benefit from earlier diagnosis and entry into care. This could be achieved by strengthening the provision of routine testing of this age group at the primary care level. Hospitalization prior to treatment initiation was also prevalent in these children. Although hospitalization was associated with younger age at diagnosis, the high proportion of children with multiple hospital admissions prior to HIV diagnosis suggests a low index of suspicion of HIV infection among older children and adolescents in hospital settings. The provider initiated counselling and testing at all points of contact adopted in South Africa should also focus on the testing of older children and adolescents. It is also important to recognize the role played by the caregivers in the testing and diagnosis of undiagnosed perinatally infected children. Interventions should target both the health care providers and the communities at the primary health care level.

Ethical Considerations

The Medunsa Research Ethics Committee of the University of Limpopo granted ethical approval for the study. The hospital management gave permission to conduct the study. All caregivers gave informed written consent.

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