Early diagnosis is critical to ensure good outcomes in HIV-infected children: Outlining barriers to care

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Abstract

HIV-infected children require early initiation of antiretroviral therapy (ART) to ensure good outcomes. The aim was to investigate missed opportunities in childhood HIV diagnosis leading to delayed ART initiation.

Baseline data was reviewed of all children aged <15 years referred over a one-year period for ART initiation to the Kalafong Hospital HIV services in Gauteng, South Africa. Of the 250 children, one quarter (24.5%) were of school-going age, 34.5% in the preschool group, 18% between 6-12 months old and 23% below six months of age (median age=1.5 years [IQR 0.5-4.8]). Most children (82%) presented with advanced/severe HIV disease, particularly those aged 6-12 months (95%). Malnutrition was prominent and referrals were mostly from hospital inpatient services (61%).

A structured caregiver interview was conducted in a subgroup, with detailed review of medical records and HIV results. The majority (≥89%) of the 65 interviewed caregivers reported good access to routine healthcare, except for postnatal care (26%). Maternal HIV-testing was mostly done during the 2nd & 3rd pregnancy trimesters (69%). Maternal non-disclosure of HIV status was common (63%) and 83% of mothers reported a lack of psychosocial support. Routine infant HIV-testing was not done in 66%, and inadequate reporting on patient-held records (Road-to-Health Cards/Booklets) occurred frequently (74%). Children with symptomatic HIV disease were not investigated at primary healthcare in 53%, and in 68% of families the siblings were not tested. One-third of children (35%) had a previous HIV diagnosis, with 77% of caregivers aware of these prior results, while 50% acknowledged failing to attend ART-services despite referral.

In conclusion, a clear strategy on paediatric HIV case finding, especially at primary healthcare, is vital. Multiple barriers need to be overcome in the HIV care pathway to reach high uptake of services, of which especially maternal reasons for not attending paediatric ART services need further exploration.

Introduction

Childhood HIV infection, linked secondarily to the adult pandemic, profoundly impacts on paediatric morbidity and mortality in high-burden countries (Stephen, Bamford, Patrick, & Wittenberg, 2011). The Prevention-of-Mother-to-Child Transmission (PMTCT) programme, implemented in South Africa from 2002 and evolving since, mitigates this detrimental impact through reduction of HIV transmission to children using sequential interventions during pregnancy, at and after birth, up until childhood HIV diagnosis (Barron et al., 2013; Department of Health (DOH), 2008; DOH, 2013). Advances in antiretroviral therapy (ART) now enable good outcomes for HIV-infected children if therapy is initiated early (Violari et al., 2008). The South African ART programme commenced in 2004, cumulatively enrolling large numbers of adults on treatment, whereas paediatric ART access has lagged behind, similar to other Sub-Saharan countries (Ahmed et al., 2013; DOH, 2004; Johnson, 2012).

Diagnostic strategies should identify and test at-risk children and establish linkages to care (Ahmed et al., 2013). Extensive focus on testing HIV-exposed children from the PMTCT programme has resulted in steadily increasing HIV DNA PCR testing numbers, with majority of tests yielding negative results (Barron et al., 2013). Identification of children missed by PMTCT testing has received less attention, like those with early symptomatic disease potentially identified at primary healthcare through the Integrated Management of Childhood Illnesses (IMCI) programme (DOH, 2011). Targeted testing of children of HIV-infected adults, sibling testing of known HIV-infected children and systematic testing within malnutrition and tuberculosis (TB) programmes furthermore requires high priority (Ahmed et al., 2013; Kellerman & Essajee, 2010). Meticulous documentation on patient-held records, like the South African Road-to-Health Card/Booklet (RTHC/RTHB), can further contribute towards earlier identification and testing of at-risk children (Horwood, Voce, Vermaak, Rollins & Qazi, 2010).

Kalafong Hospital, an early South African public sector ART site, rapidly evolved into a large adult and paediatric treatment centre, initiating close to 900 children on ART prior to study commencement. It had never experienced a significant waiting list for new paediatric referrals and had close links with the inpatient services, ensuring rapid referral and ART initiation, ideally before hospital discharge. Referrals were additionally received from primary healthcare facilities, which at time of study were not initiating paediatric ART in substantial numbers (Massyn et al., 2013). The study aim was to describe the characteristics of children at time of ART referral, with detailed description of the path leading to childhood HIV diagnosis and emphasis on barriers to care.

Methods

We reviewed baseline data of all HIV-infected children <15 years of age newly seen at the Kalafong Paediatric HIV services between June 2009 and May 2010. Data collection included demographic data, disease severity (nutritional status; World Health Organization staging (WHO, 2007)), laboratory data (CD4 counts/percentages; HIV viral loads) and three-year follow-up (deaths; loss-to-care).

For descriptive purposes the cohort was subdivided according to age: The first year of life, when early infant diagnosis and rapid HIV disease progression occur, was further split into the first and

second six months ('0 to <6m'; '6 to <12m'), pre-schoolers were allocated to the '1 to <3y' or '3 to <5y' groups and schoolchildren were assigned to the '5 to <15y' group.

A structured caregiver interview obtained a detailed social and clinical history regarding the mother-child pathway through PMTCT until childhood HIV diagnosis and ART referral. This subgroup included a convenience sample of 65 caregivers of children born during the South African PMTCT era: Study participants born before February 2008 were from the single-dose nevirapine (sdNVP) period (DOH, 2000), with those born thereafter from the dual-therapy era (added antenatal/postnatal zidovudine) (DOH, 2008). We furthermore studied the child's medical records (clinical notes; patient-held RTHC/RTHB), maternal medical records (if available) and National Health Laboratory Service database (HIV results).

The Ethics Review Committee, Faculty of Health Sciences, University of Pretoria, approved the study protocol.

Results

The 250 newly-diagnosed HIV-infected children had a male-to-female ratio of 1.02:1, with also no female predominance in the '10 to 15y' group (12 boys; 9 girls). The median age was 1.5 years [interquartile range 0.5-4.8], with one-quarter being schoolchildren (n=61; 24.5%) and 86 (34.5%) pre-schoolers (Table 1). Another 45 children (18%) were identified during the second six months of life and 58 children (23%) within the first six months, including 16 children younger than three months (four were asymptomatic/WHO Stage 1). The majority of children (82%) had advanced or severe disease (WHO Stages 3/4) (Figure 1) and referrals were mainly (61%) from hospital inpatient services, while 21% were sent from primary healthcare facilities and 17% from the hospital's outpatient services.

Malnutrition was prominent. The mean weight-for-age Z-score was -2.3 (standard deviation (SD) 1.8), with 53% being underweight (Z-score<-2) and 28% severely underweight (Z-score<-3) (WHO, 2006). Short stature was equally prevalent, with a mean height-for-age Z-score of -2.0 (SD 1.6) and 46% stunted (Z-score<-2) and 23% severely stunted (Z-score<-3). Wasting (Z-score<-2) occurred in 38% and severe wasting (Z-score<-3) in one-fifth (21%), with a mean body mass index (BMI)-for-age of -1.6 (SD 2.0). Infants in the '6 to <12m' group were most severely affected: 76% were underweight, 57% stunted and wasted and 95% had advanced/severe HIV disease. One-fifth of children had microcephaly (head circumference (HC)<-2SD) ('0 to <12m'=22%; '1 to <5y'=20%), while percentages for severe microcephaly (HC<-3SD) were 14% and 6% respectively in the age groups. The mean HC-for-age Z-score was -1.0 (SD 1.5) (HC measured in <5y).

The mean CD4% was 16.9% (SD 9.5) and absolute CD4 count 822 cells/μl (SD 742). Regarding CD4 categories (WHO, 2007), two-thirds (66%) had advanced/severe immunosuppression on presentation; most severe in '6 to <12m' group (80%). HIV viral loads (VL) were high throughout, with a mean $VLlog_{10}$=5.0 (SD 1.2).

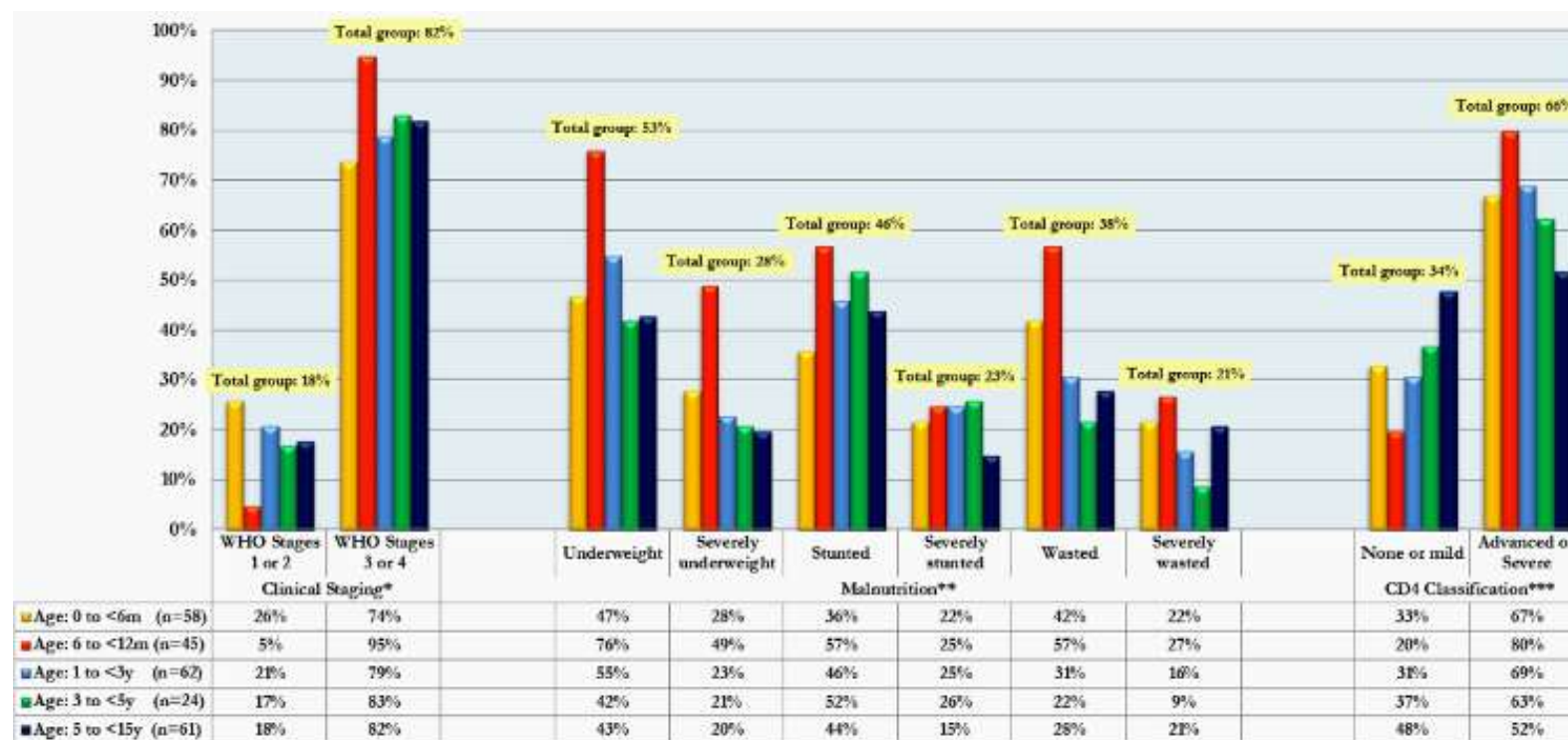**Table 1: Clinical and laboratory characteristics of the cohort according to age groups**

			<12m (n=103)		1 to <5y (n=86)		5 to <15y (n=61)	Total (n=250)
			0 to <6m (n=58)	6 to <12m (n=45)	1 to <3y (n=62)	3 to <5y (n=24)		
Nutritional Parameters*	**Weight-for-age Z-score**		-2.4 (2.0) (0)	-3.1 (1.5) (0)	-2.2 (1.7) (0)	-1.9 (1.5) (0)	-1.8 (1.8) (21)	**-2.3 (1.8) (21)**
	Height-for-age Z-score		-1.9 (2.1) (3)	-2.3 (1.7) (1)	-2.1 (1.5) (1)	-2.3 (1.2) (1)	-1.8 (1.4) (1)	**-2.0 (1.6) (7)**
	BMI-for-age Z-score	Mean (SD) (Missing)	-1.8 (1.9) (3)	-2.4 (1.9) (1)	-1.3 (1.8) (1)	-0.6 (2.0) (1)	-1.4 (2.2) (1)	**-1.6 (2.0) (7)**
	HC-for-age Z-score		-0.9 (1.8) (2)	-1.2 (1.4) (2)	-0.9 (1.4) (4)	-0.8 (1.3) (11)	N/A	**-1.0 (1.5) (80)**
CD4	**CD4 absolute count**		1345 (994) (4)	899 (825) (1)	780 (500) (1)	755 (484) (0)	373 (266) (0)	**822 (742) (6)**
	CD4%		19.8% (10.3) (4)	15.9% (8.9) (1)	16.7% (9.5) (1)	18.8% (8.2) (0)	14.3% (9.0) (0)	**16.9% (9.5) (6)**
HIV viral load	**Viral load log$_{10}$**		5.6 (1.2) (9)	5.5 (1.1) (6)	5.1 (1.1) (7)	4.5 (1.2) (0)	4.4 (0.9) (4)	**5.0 (1.2) (26)**
Referral site	**Primary healthcare facility**		27.5%	13%	21%	21%	20%	**21%**
	Hospital outpatients		8.5%	9%	21%	25%	23%	**17%**
	Hospital inpatients		62%	76%	58%	54%	54%	**61%**
	Other**	Percentage	2%	2%	0%	0%	3%	**2%**
Death	**Within 6m of referral**		16%	18%	8%	0%	0%	**9%**
	From 6 to 36m of referral		2%	4%	4%	0%	3%	**3%**
Loss-to-care	**Within 6m of referral**		22%	13%	19%	8%	11%	**16%**
	From 6 to 36m of referral		5%	16%	9%	17%	2%	**9%**

Abbreviations: m= months; y= years; BMI= body mass index; HC= head circumference, SD= standard deviation; N/A= not applicable

*Age- and sex-adjusted nutritional parameters in Z-scores, using WHO reference standards (WHO, 2006)

**Other referral sites include private sector and other hospitals

Figure 1: Severity of childhood HIV disease, malnutrition and immunological suppression at presentation for care, according to age groups (n=250)

	WHO Stages 1 or 2	WHO Stages 3 or 4		Underweight	Severely underweight	Stunted	Severely stunted	Wasted	Severely wasted		None or mild	Advanced or Severe
	Clinical Staging*			**Malnutrition****							**CD4 Classification****	
Age: 0 to <6m (n=58)	26%	74%		47%	28%	36%	22%	42%	22%		33%	67%
Age: 6 to <12m (n=45)	5%	95%		76%	49%	57%	25%	57%	27%		20%	80%
Age: 1 to <3y (n=62)	21%	79%		55%	23%	46%	25%	31%	16%		31%	69%
Age: 3 to <5y (n=24)	17%	83%		42%	21%	52%	26%	22%	9%		37%	63%
Age: 5 to <15y (n=61)	18%	82%		43%	20%	44%	15%	28%	21%		48%	52%

Legend for figure 1:

Abbreviations: WHO= World Health Organization; m= months; y= years

***Clinical staging for HIV in Children and Adolescents (WHO, 2007**) (One case each not documented in age groups '0 to <6m' and '6 to <12m')

****Nutritional classification indicating percentage of cohort with malnutrition (WHO, 2006)**:

- **Underweight:** Weight-for-age (W/A) Z-score <-2SD; **Severely underweight:** W/A Z-score <-3SD
- **Stunted:** Height-for-age (H/A) Z-score <-2SD; **Severely stunted:** H/A Z-score <-3SD
- **Wasted:** Body mass index (BMI) Z-score <-2SD; **Severely wasted:** BMI Z-score <-3SD

*****CD4 classification (WHO, 2007):**

- **None:** >35% (age <12m); >25% (age 13-59m); >500/mm³ (age >5y)
- **Mild:** 25-34% (age <12m); 20-24% (age 13-59m); 350-499 mm³ (age >5y)
- **Advanced:** 20-24% (age <12m); 15-19% (age 13-59m); 200-349 mm³ (age >5y)
- **Severe:** <20% (age <12m); <15% (age 13-59m); <200 mm³ (age >5y)

The late presentation resulted in 22 deaths (9%) within six months of ART (21 from inpatient referrals), with the highest mortality (18%) in the '6 to <12m' group. Another 40 children (16%) were lost-to-care within six months (33 were inpatient referrals), with additional 9% loss-to-care later. Therefore over one-third of children (37%) were lost, either to death or follow-up, within three years of ART referral.

The pathway to childhood ART access:

The 65 in-depth interviews revealed that majority of families lived under poor socio-economic circumstances (Table 2): Only 45% had regular employment, 58% lived in brick houses, less than half (42%) had running water inside the home and 97% used public transportation. At time of interview nine children (14%) were not in maternal care, including four maternal orphans (6%). Mothers were slightly younger at time of birth than fathers (maternal mean age=28.5y (SD 6.2), paternal mean age=34y (SD 11.3)). At time of interview six fathers had died, while eight were unwell and the whereabouts of four fathers was unknown. Twenty fathers (32%) were known HIV-infected, the remaining had not tested or caregivers were unaware of the results. Forty study participants had siblings, but in 27 of these families (68%) sibling testing had not been done.

Mothers had excellent access to antenatal care (97%), and 63% had attended at least four antenatal visits. Maternal HIV-testing was mostly done during the second (32%) or third (37%) trimesters, while 13 mothers (20%) had no antenatal HIV test and two women (4%) had not received their results (Table 3). Post-test counselling had not been provided to 13% of those tested and 83% of women reported lack of psychosocial support. Of the 49 mothers who tested for HIV before/during pregnancy, 63% had not disclosed their HIV status to anyone during pregnancy. Antenatal infant feeding counselling was not done in one-third (34%), while 72% were not screened for TB during pregnancy.

Majority of births (97%) occurred within healthcare facilities, but in one-third of cases (33%) health workers attending to the delivery were unaware of the maternal HIV infection. In two-thirds of mother-infant-pairs appropriate ART interventions were not administered and inadequate infant feeding counselling occurred in one-quarter (23%). Early postnatal care occurred in only 26%, but most infants (89%) attended healthcare at age six weeks, with 29% of mothers utilizing a different health facility compared to antenatal care. The PMTCT coding, previously used to implicitly indicate HIV exposure, was charted incorrectly on 61% of RTHCs (n=46), while on 74% there was lack of documentation of HIV PCR results, infant feeding choice and cotrimoxazole prophylaxis.

One infant had a positive HIV DNA PCR at birth and 20 infants (31%) were tested at six weeks (as per PMTCT guidelines). Three mothers reported an initial negative HIV result, but one case was found to have been positive on laboratory review. Maternal barriers to childhood ART access included not returning for the child's HIV or CD4 results (n=1 each) because of maternal anxiety and shame. Not attending ART care after referral was due to maternal fear (n=2), traditional health practitioner visit (n=1) and undisclosed reason (n=1). Health system barriers included repeat PCR due to specimen loss (n=1), inability to retrieve the child's HIV or CD4 results (n=1 each) and delay in appointment (n=1). In some infants no CD4 count, clinical staging or ART-initiation/referral was done (n=4 respectively) despite a positive PCR test, including two cases in whom incorrect information was provided regarding ART eligibility.

Table 2: Socio-demographic characteristics and information on HIV-testing (interview subgroup; n=65)

Socio-demographic characteristics	**Parental age at child's birth**	Maternal age (Mean (SD) (range))	28.5y (6.2) (17-42)
		Paternal age (Mean (SD) (range))	34y (11.3) (26-42)
	Household members	Number (Mean (SD) (range))	4.7 (2.3) (2-14)
	Caregiver	Mother is primary caregiver	86%
		Different caregivers over time	14%
	Child's rank in household	1st child	38%
		2nd child	42%
		3rd child or more	20%
	Housing	Permanent brick structure	58%
		Running water indoors	42%
	Main source of income	Regular income employment	45%
		Temporary employment	15%
		Grants	23%
		Grandparent's state pension	17%
	Transport to health facility	Communal taxi	94%
		Public transport (bus or train)	3%
		Private transport	3%
Parental HIV-testing	**Maternal HIV-testing**	Pre-conceptual	2%
		1st trimester of pregnancy	9%
		2nd trimester of pregnancy	32%
		3rd trimester of pregnancy	37%
		After delivery	20%
	Paternal HIV status	Positive	32%
		Negative	0%
		Never tested/ refused/ unknown	68%
Child's HIV-testing and referral	**Reason for HIV test, which led to referral**	Birth/ 6w PCR*	14%
		HIV exposure identified**	8%
		Symptomatic***	78%
	ART access interval	From HIV test to ART attendance (Median [IQR])	18d [41]
	Age at 1st ART clinic visit	Age in years (Mean (SD) (range))	1.4y (1.7) (0.1-8.2)

Abbreviations: SD= standard deviation; y= years; w= weeks; PCR= polymerase chain reaction; ART= antiretroviral therapy; IQR= interquartile range; d= days; m= months; WHO= World Health Organization

*PCR done at birth in one case

** Timing of test: Post-weaning=2; At 18m=1; Retest after loss-to-care=1; Presenting with minor illness=1

***Symptomatic HIV disease: WHO Stage 2 in 2 cases, WHO Stage 3 in 12 cases; WHO Stage 4 in 37 cases

Table 3: Barriers to access to paediatric HIV care (interview subgroup, n= 65)

Category	Item	n	%	Notes
Antenatal care	No antenatal care	n=65	3%	
	No maternal HIV test in pregnancy		20%	
	Mother did not receive HIV result		4%	No HIV test=13
	No post-test counselling	n=52	13%	
	No HIV disclosure during pregnancy		63%	Unknown=1
	No infant feeding counselling		34%	
	No psychosocial support offered	n=65	83%	
	No TB screening in pregnancy		72%	
Labour and delivery	Delivery did not take place at health facility	n=65	3%	
	Maternal HIV infection not known at delivery	n=63	33%	Home birth=1; unknown=1
	Maternal ART not given as per guideline		65%	
	Infant ART not given as per guideline	n=65	66%	
	No infant feeding counselling		23%	
Postnatal access to care	Different postnatal than antenatal clinic		29%	
	No early postnatal care		74%	
	No healthcare visit at 6w	n=65	11%	
	No HIV PCR at 6w		66%	
	No cotrimoxazole prophylaxis given at 6w		69%	
	No follow-up scheduled for PCR result	n=21	0%	No 6w PCR=43
	Mother did not return for PCR result		5%	Initial PCR negative=2
	No clinical staging after PCR result		24%	Unknown=1
	No CD4 count after PCR result	n=18	24%	No CD4 result=1; unknown=1
	No ART-referral for child		24%	Unknown=1
	Weaning advised after positive PCR	n=11	45%	Formula feeding=7
Use of patient-held Road-to-Health Card	Incorrect charting of implicit PMTCT code		61%	RTHC unavailable=19
	No documentation that HIV PCR was done	n=46	70%	
	No documentation of HIV PCR result		74%	
	Infant feeding choice not charted		74%	
	Cotrimoxazole prophylaxis not charted		74%	
IMCI clinical criteria for HIV-testing*	Symptomatic children with documented IMCI criteria on RTHC with no HIV-testing done	n=17	53%	1 or 2 criteria=6; ≥3 criteria=11
HIV disease / comorbidities at ART presentation	Advanced/ severe HIV disease		82%	
	Moderate/ severe malnutrition	n=65	63%	
	TB diagnosis prior to/ at ART referral		35%	
	HIV-testing not done at TB diagnosis	n=23	9%	
	No cotrimoxazole prophylaxis at ART referral	n=65	68%	
Prior HIV-testing of child	Positive HIV test prior to current diagnosis	n=65	35%	
	Caregiver aware of previous HIV result		77%	Unknown=1
	Previous HIV result on laboratory database	n=23	43%	
	Previous ART referral but non-attendance		50%	Unknown=1
	Previous ART attendance, but loss-to-care		13%	

Abbreviations: TB= tuberculosis; ART= antiretroviral therapy; w= weeks; PCR= polymerase chain reaction; IMCI= Integrated Management of Childhood Illnesses; RTHC= Road-to-Health Card

*IMCI: Clinical criteria for HIV-testing (DOH, 2011):
- Criteria: Pneumonia, persistent diarrhoea, ear discharge, low weight–for-age, unsatisfactory weight gain, oral thrush, parotid enlargement and enlarged lymph glands in the neck, axilla or groin
- No criteria= HIV infection unlikely; 1 or 2 criteria= possible HIV infection; ≥3 criteria= suspected symptomatic HIV infection

Early infant diagnosis, if done, therefore did not guarantee access to appropriate HIV care. Only nine infants (14%) presented for ART due to routine early infant PCR testing, of whom four were already symptomatic (WHO Stages 3/4). Another five asymptomatic children (ages 3-18 months) were identified as HIV-exposed and tested, including post-weaning testing (n=2), 18 month-testing (n=1), retesting after loss-to-care (n=1) and testing at minor illness (n=1). In the remaining 51 children (78%), HIV-testing was done because of symptomatic disease.

The IMCI criteria, aimed at alerting health workers at primary healthcare facilities to consider early symptomatic HIV disease (DOH, 2011), were documented on RTHCs but with no HIV-testing done in 53% of the symptomatic children. Majority (82%) of children had advanced/severe disease at presentation. Besides the prevalent malnutrition, 23 children (35%) had previous/current TB, with HIV-testing at TB diagnosis not done in two cases (9%). Other WHO Stage 3 conditions were oral candidiasis (25%) and chronic diarrhoea (15%), while WHO Stage 4 events included *Pneumocystis jiroveci* pneumonia (11%), HIV encephalopathy (6%) and recurrent severe bacterial infections (6%).

Past medical history revealed that 23 children (35%) had prior HIV-testing done, with 18 caregivers (77%) aware of these HIV-positive results. Ten results (43%) were found after review of laboratory databases (caregivers unaware in four cases). Three children were lost-to-care after previous ART and referred again.

Discussion

Mothers are the gateway to childhood HIV-prevention. We identified multiple missed opportunities along the PMTCT continuum, despite our data showing excellent access to routine maternal- and child healthcare ($\geq$89%), except for postnatal care (26%), which is in line with published reports (Chopra, Daviaud, Pattinson, Fonn, & Lawn, 2009). Maternal HIV infection was mostly identified in the second or third trimesters (69%), limiting timely ART interventions, while one-fifth of HIV diagnoses were only made post-delivery. We documented missed opportunities in post-test counselling (13%) and psychosocial support (83%), with frequent maternal HIV non-disclosure (61%). Lack of support for pregnant newly-diagnosed HIV-infected mothers is of concern, since these initial steps were followed by multiple gaps along the ensuing care pathway, with maternal diagnosis not translating into universal care retention for mother-infant pairs, also described in other reports (Gourlay, Birdthistle, Mburu, Iorpenda, & Wringe, 2013; Watson-Jones, Balira, Ross, Weiss, & Mabey, 2012).

If PMTCT fails, early disease identification and ART initiation are essential to reduce mortality in infants with rapid disease progression, known since publication of the CHER-study in 2008 (Violari et al., 2008). This remains challenging though, with only few of our study participants (n=16; 6%) diagnosed before age three months and only four asymptomatic. Published South African data show greatly increased six-week PCR numbers in recent past, indicating a health system focus area (Barron et al., 2013), but only 31% of study participants had a six-weeks HIV-test done, although our cohort also included older children who may not have benefitted from the more recent infant diagnosis scale-up. According to national PMTCT guidelines, HIV-testing should additionally occur after weaning and at 18 months (DOH, 2008), but a

countrywide situational analysis (2010) showed that only 40% of sampled facilities offered all tests (Woldesenbet, Goga & Jackson, 2012).

Paediatric HIV-testing needs are unlikely to be met if healthcare services continue to predominantly target HIV-exposed infants from the PMTCT programme who, because of maternal ART interventions, are at lower risk of HIV acquisition than those born to mothers with undocumented HIV infection (Rollins, Mzolo, Moodley, Esterhuizen & Van Rooyen, 2009; Woldesenbet et al., 2012). Majority of study participants (82%) presented with advanced/severe disease, particularly those aged 6-12 months (95%), indicating health system failure in early identification of HIV-infected infants. Malnutrition was prominent, and microcephaly, associated with impaired brain growth, occurred in one-fifth of children, with early ART necessary for survival and good neurological outcomes (Crowell, Malee, Yogev, & Muller, 2014). Childhood tuberculosis was additionally very common (35%), reflecting the devastating effect of the adult HIV/TB co-epidemics on children (Hesseling et al, 2009). TB screening during pregnancy, potentially leading to reduced infant TB-exposure through maternal disease identification, was not done in majority of mothers (72%), which requires intervention (Gounder et al., 2011).

Multiple entry points for paediatric HIV-testing are needed, guided by a clear strategy on paediatric case finding outside of PMTCT testing (Ahmed et al., 2013). This includes provider-initiated HIV-testing in paediatric wards and TB programmes in high-prevalence areas, with its well-described efficiency to identify previously undiagnosed children, although mortality in these children remains high due to late diagnosis (Ahmed et al., 2013; Kankasa et al., 2009; Mutanga et al., 2012). In our study majority of children were referred with advanced disease from hospital inpatient services (61%), with resultant high death rate (9% within six months). PMTCT is a very successful HIV-prevention strategy, but children who nonetheless acquire HIV still have a high mortality risk if untreated (Davies et al., 2009).

Early HIV identification at primary healthcare level is vital to prevent disease progression and link children to care. The IMCI strategy for improved child survival was adopted by South Africa in 1997 and later adapted to include a validated HIV component (DOH, 2011; Horwood, Liebeschuetz, Blaauw, Cassol & Qazi, 2003; Horwood et al., 2010; Qazi & Muhe, 2006). Effective implementation depends on health workers' knowledge, skills and willingness to identify HIV-infected children during routine care. In our study 53% of symptomatic children with documented features suggestive of HIV infection were not appropriately investigated, consistent with previously described suboptimal implementation, with skills weaknesses contributing towards non-testing of at-risk/symptomatic children (Ahmed et al., 2013; Horwood et al., 2010). Adequate recordkeeping is vital, as childhood HIV care otherwise depends on maternal HIV disclosure to healthcare workers, previously identified as problematic, and places children at risk who are not in maternal care (Ginsburg, Hoblitzelle, Sripipatana & Wilfert, 2007; Horwood et al., 2010). We found gaps in documentation on patient-held records, like HIV-testing and infant feeding choice, while almost one-third of mothers visited a postnatal clinic different to their antenatal clinic, emphasising the crucial role of tools like patient-held records in promoting continuity of care (Woldesenbet et al, 2012).

Additional strategies are sibling testing and targeted testing of children of HIV-infected adults (Ahmed et al., 2013). In our study sibling testing had not been done in 68% of families, similar to a Malawian report showing >80% of children of adult ART patients not tested for HIV, clearly indicating need for a more family-centred approach (Cohen, Lungu & van Oosterhout, 2010; Koo, Makin & Forsyth, 2013). As many as one-third of HIV-infected children have slow disease progression and survive to adolescence without treatment (Ferrand et al., 2007; Ferrand et al., 2009). One-quarter of our cohort were schoolchildren, therefore necessitating alternative strategies, like family testing, to prevent disease progression.

Substantial patient losses can occur at every stage of the HIV care pathway, and a positive HIV test does not equate to receiving appropriate care, as previously reported from India (Gupta et al., 2013) and Africa, where a pooled estimate from five studies showed 45% loss-to-care (range 30%-68%) after early infant diagnosis programmes (Sibanda, Weller, Hakim, & Cowan, 2013). In our study one-third of children had a previous HIV diagnosis, with three-quarters of caregivers aware of prior results and half acknowledged failing to attend the free ART services despite referral. These realities underline the pivotal role that caregivers play in children's healthcare pathway. Additionally we documented substantial loss-to-care after ART access (25% in 36 months), even in severely symptomatic children referred from hospital wards, despite the onsite dedicated paediatric ART team (including social worker). In very ill children time for extensive caregiver counselling before ART-initiation may have been too short and the concomitant disease affliction with resultant high pill burden possibly problematic. Lost-to-care children could also have died. The care pathway is a dynamic process of linkage, retention, loss and re-engagement, making it hard to assess and challenging to deal with for clinicians when encountering children in need of life-saving care (Govindasamya, Ford, & Kranzer, 2012; Kranzer, Govindasamy, Ford, Johnston, & Lawn, 2012).

Multiple care barriers need to be overcome in a culturally sensitive manner if healthcare interventions are to reach high uptake (Sibanda et al., 2013). Previously documented care obstacles include maternal disbelief of own HIV diagnosis, fear of involuntary HIV disclosure, anxiety regarding possible child HIV infection, unfriendly healthcare workers, poor parental education, poverty, inadequate family support and stigma (Donahue, Dube, Dow, Umar, & Van Rie, 2012; Horwood et al., 2010; Wachira, Middlestadt, Vreeman, & Braitstein, 2012). Integration of child health services, PMTCT and ART programmes is vital, and clear guidance to health workers is necessary in dealing with the confidentiality dilemma of maternal HIV infection in relation to documentation of relevant child information, including HIV exposure (Horwood et al., 2010; WHO, 2010). Active follow-up to reduce loss-to-care is beneficial, as shown in Tanzania, but defaulter tracing needs to be part of health systems planning, implementation and monitoring if to be successful at scale (Nuwagaba-Biribonwoha et al., 2010). The new ward-based outreach teams, which are part of the current South African primary healthcare reengineering process, are ideally positioned to improve the follow-up of children at household level. Additionally family support groups, which were not active during the time of our study, can further potentially facilitate retention in care, while community mobilization and stigma reduction are vital to strengthen treatment and support of HIV-infected children within their family context (Sibanda et al., 2013).

Study limitations include that this hospital-based ART site may not represent the broader population of HIV-infected children, although at time of study minimal paediatric ART initiation occurred at local primary healthcare facilities. In the interview subgroup information was self-reported by primary caregivers, with possible recall bias. Verbal information was validated using medical records as far as possible and translators were used to mitigate language barriers. It was not possible to ascertain the mode or timing of participants' HIV acquisition, and the PMTCT pathway was applied to all. Older children were not included in the interviews, as the questionnaire was designed to track the maternal-child PMTCT path until childhood diagnosis, requiring additional research in this group.

In conclusion, our data demonstrates substantial bottlenecks in paediatric HIV diagnosis and access to ART care, resulting in significant childhood morbidity and mortality. A clear strategy on case finding is essential to ensure multiple HIV-testing entry points for children missed by PMTCT testing, especially at primary healthcare level. Diligent use of patient-held records will potentially assist with identification and testing of at-risk children and retention in care. Multiple missed HIV care opportunities need attention to ensure high uptake of services, of which maternal non-attendance of paediatric ART services is especially worrisome and requires further exploration and urgent social interventions.

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