



Horizontal HIV transmission to children of HIV-uninfected mothers: A case series and review of the global literature

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ABSTRACT

Background: Vertical transmission is the predominant route for acquisition of HIV infection in children, either in utero, intrapartum or postnatally through breast feeding. Less frequently, children may acquire HIV by horizontal transmission. Horizontal transmission may be healthcare-associated (infusion of HIV-contaminated blood products, use of contaminated needles, syringes and medical equipment, or through ingestion of HIV in expressed breastmilk). Community-acquired HIV transmission to children may occur following surrogate breastfeeding, pre-mastication of food, and sexual abuse.

Methods: Children with suspected horizontally acquired HIV infection were identified by retrospective folder review of existing patients (2004–2014) and by prospective interview and examination of new patients (from 2009 onwards), at a hospital-based paediatric antiretroviral clinic in Cape Town, South Africa. The global literature on horizontal HIV transmission to children (1 January 1986–1 November 2019) was reviewed, to contextualize the local findings.

Results: Among the 32 children with horizontal HIV transmission (15 identified retrospectively and 17 prospectively), the median age at first diagnosis was 79 months (interquartile range 28.5–91.5); most children (90.6%) had advanced HIV disease at presentation. HIV transmission was considered healthcare-associated in 15 (46.9%), community-associated in ten (31.3%), possibly healthcare or community-associated in five (15.6 %); and unknown in two children (6.3%).

Conclusion: Horizontal HIV transmission to children is an important public health issue, with prevention efforts requiring intervention at healthcare facility- and community-level. Greater effort should be made to promptly identify and comprehensively investigate each horizontally HIV-infected child to establish possible routes of transmission and inform future prevention strategies.

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Introduction

Vertical transmission of HIV, either in utero, intrapartum or post-natally through breastfeeding, is the predominant route for acquisition of HIV infection in children (Cotton et al., 2012). Since 2010, there has been an 18% decrease in the incidence of new HIV infections globally (Joint United Nations Programme on HIV/AIDS, 2018). In South Africa, expanded access to antiretroviral therapy (ART) and prevention of vertical HIV transmission programs have resulted in a substantial decline in paediatric HIV infections (le Roux et al., 2019).

Rarely, children born to HIV-uninfected women may acquire HIV by horizontal transmission (Vaz et al., 2010). This may occur

through healthcare-associated transmission by infusion of HIV-contaminated blood or blood products, re-use of contaminated needles/syringes or other medical equipment, and ingestion of HIV in expressed breastmilk in neonatal units (Cotton et al., 2012). Alternatively, community-acquired, horizontal HIV transmission may occur following surrogate breastfeeding or 'wet nursing' by a woman with HIV, pre-mastication of food, and sexual abuse (Shisana et al., 2008; Maritz et al., 2011). In most instances of horizontal HIV acquisition in children, the exact route of transmission is difficult to determine owing to the time elapsed between the HIV-exposure event/s and confirmation of HIV in the child (Vaz et al., 2010). These events require thorough investigation to establish the most likely route of transmission, although in many cases this may be undetermined.

Published data on the frequency and routes of horizontal HIV transmission to children is limited, although a few studies have reported the prevalence of horizontally acquired HIV in paediatric

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antiretroviral clinics at 1%, 5% (our clinic) and 4.8% respectively (Vaz et al., 2010; van Kooten Niekerk et al., 2006; Reid and Van Niekerk, 2009). Despite growing evidence that horizontal HIV transmission to children is not uncommon (with four published studies in South Africa), there is no national registry to document this phenomenon and no advice on its prevention (Cotton et al., 2012; Shisana et al., 2008; Reid and Van Niekerk, 2009; Eley et al., 2003). Similar reports of healthcare-associated and community-acquired HIV transmission from elsewhere in Sub-Saharan Africa, India and Pakistan have been published, highlighting the need to create awareness of this global phenomenon and investigate the likely routes of transmission and identify risky practices (Vaz et al., 2010; Okinyi et al., 2009; Maniar, 2019; ProMED-mail, 2019; Mir et al., 2020).

In this report we describe a case series of 32 children with confirmed horizontally acquired HIV at a tertiary hospital paediatric ART clinic in Cape Town, South Africa, and contextualize our findings with a review of the published literature.

Methods

Research setting

The HIV prevalence rate among pregnant women in the Western Cape Province of South Africa was 15.9% in 2017 (Woldesenbet et al., 2019). Following successful implementation of the national Prevention of mother-to-child transmission (PMTCT) program, MTCT declined from about 30% in the early 2000s, to 1.5% in 2015/16 (Dramowski, 2017). In 2012, the HIV prevalence among children aged 2–14 years was 0.7% in the Western Cape Province, compared to 2.4% nationally (Dramowski, 2017). Paediatric ART access programs commenced in 2004, initially at tertiary hospitals and later expanding to form a network of community-based ART clinics (Morsheimer et al., 2014).

Study methods

Children with suspected horizontally transmitted HIV were identified by retrospective folder review of existing ART clinic attendees (2004–2014) at the Family Clinic for HIV in Tygerberg Hospital and surrounding paediatric ART clinics in Cape Town's Metro East. From 2009 onwards, children who were newly diagnosed with HIV and whose mothers were confirmed HIV-negative were prospectively recruited using a structured interview and clinical examination protocol, to standardize the assessment for possible routes of HIV transmission. Potential HIV exposure events and risk factors for HIV transmission at household, community and healthcare levels were documented to classify the most likely route of HIV infection. Horizontal HIV transmission in this cohort was defined as acquisition of HIV after birth, from a source other than the child's mother. For each child, confirmation was obtained of a negative maternal HIV ELISA, and/or confirmation of a previous negative HIV PCR or ELISA test for the child, prior to their HIV diagnosis. Children with exposure events potentially associated with HIV exposure e.g. surrogate breastfeeding, sexual abuse, pre-mastication of food, body piercings, scarification, toothbrush sharing and persons living with HIV in the household were classified as suspected household or community-associated HIV transmission. Children with exposure event/s potentially associated with HIV exposure e.g. receipt of blood products, hospitalization events with procedures including intravenous access, surgery, receipt of expressed breast milk, or outpatient receipt of immunizations or other injections were classified as suspected healthcare-associated HIV transmission. In cases where no risk factors for household, community or healthcare-associated

HIV transmission were identified, the route of HIV acquisition was classified as underdetermined. Simple descriptive data analysis was conducted using Microsoft Excel version 16.16.4. Normally distributed data was described using means and standard deviations (SD); data that was not normally distributed was described using medians and interquartile ranges (IQR).

Literature review

A literature search for English language publications was conducted in PubMed and Google Scholar from database inception until 1 November 2019, using the terms “nonvertical HIV transmission”, “horizontal HIV transmission”, “HIV” AND “children”, “HIV” AND “children” AND “Africa”, “HIV” AND “donor breastmilk”, “HIV” AND “pre-mastication”, “HIV” AND “hospital transmission”, and “HIV” AND “household transmission”. Each publication retrieved was screened for data on horizontal HIV transmission to children, possible routes of transmission, and whether the routes were healthcare-associated or household/community-associated.

Results

The derivation of the study population is shown in Figure 1 and their demographics in Table 1. The median age at HIV diagnosis was 79 (IQR 28.5–91.5) months. In most cases, HIV infection was confirmed by HIV ELISA testing (25/32; 78.1%). TB disease and failure to thrive were the most frequent indications for HIV testing. Most children had advanced HIV at diagnosis (WHO stage three or four disease) and moderate immunosuppression (mean absolute CD4-positive T-cell count 564 [SD 576] and CD4-positive T-cell percentage of 25.7% [SD 9.0%]). All children commenced ART following their HIV confirmation.

For all 32 children identified with horizontal HIV transmission, the HIV status of parents was investigated; an HIV negative status was confirmed in 29/30 mothers and 13/15 fathers who presented for testing following their children's HIV diagnosis. The one mother whose HIV test concurrent with her child's HIV diagnosis was positive, had documented evidence that the child was previously HIV-negative on two occasions (by virological assays conducted within the first six months of life) and in the absence of breastfeeding. The mother later reported non-adherence to ART in the child's father, who had allegedly fed pre-masticated food to the child before his demise.

Two fathers were known to be living with HIV, but uninvolved in the index child's care; for 15 fathers, the HIV status remained unknown as they no longer resided with the child.

Possible HIV exposure events for horizontally acquired HIV in these children are documented in Table 2. One third were born preterm and required neonatal unit admission. Most children had one or more paediatric ward or intensive care unit (ICU) admission prior to their HIV diagnosis (mean of 1.7 (SD 2.3) hospital admissions per child). Eight children had received blood or blood products during prior hospitalization episodes. In all cases the donor/s of the blood product/s were verified as HIV negative following recall and re-testing at the Western Province Blood Transfusion Service. The route of HIV transmission was considered healthcare-associated transmission in 15 children and community-associated in ten children. Five children had potential HIV exposure events in both the healthcare and the community setting, and in two cases, the route of acquisition was unknown. Data on the impact and outcome of horizontally acquired HIV in the prospective cohort is shown in Table 3.

Thirteen publications reporting horizontal HIV transmission to children were identified (Table 4), with the majority (8/12; 66.0%) reported from Sub-Saharan Africa. Of all reported cases (n = 1242),

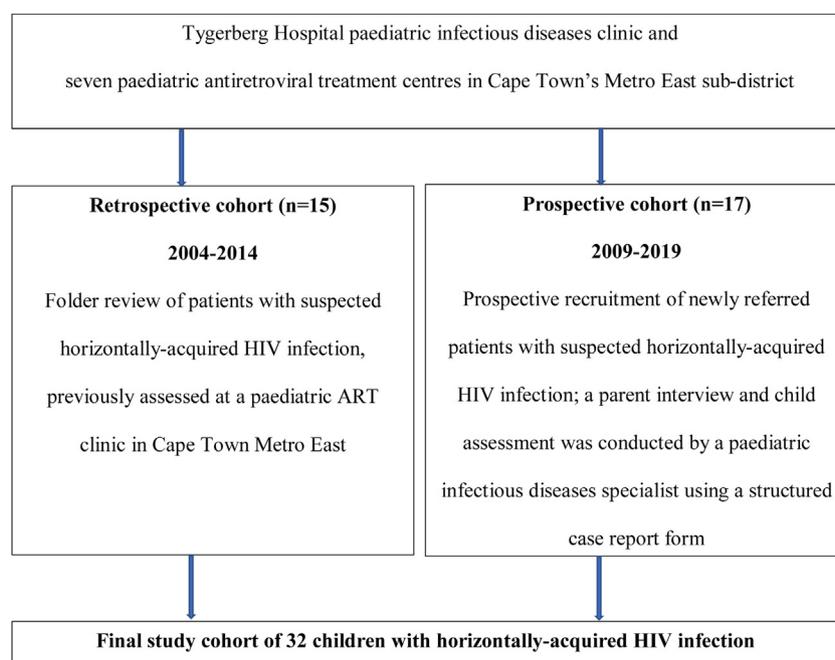


Figure 1. Participant recruitment (n = 32).

1227 (98.8%) occurred following probable healthcare-associated HIV transmission, ten (0.8%) followed suspected household or community-associated HIV transmission and in five children (0.4%), the route of HIV infection was underdetermined.

Among children with suspected healthcare-associated HIV transmission, breaches in infection prevention practices were frequently implicated. These included inadequately decontaminated surgical and dental equipment, re-use of needles and shared fluid flushes/multi-dose medication vials. Two studies (from Mozambique and Nigeria) identified HIV contaminated blood and/or blood products as the predominant cause of horizontal paediatric HIV infection (Shisana et al., 2008; Altaf et al., 2019).

Inadvertent in-hospital exposure to breastmilk from a mother living with HIV has been identified as an important route of HIV transmission in SA hospitals (Shisana et al., 2008). In 2019 an HIV outbreak linked to re-use of injection equipment was reported in Pakistan, with 371 children acquiring HIV, 332 (89.0%) of whom had HIV-negative mothers (Mir et al., 2020; Cotton and Rabie, 2020; Altaf et al., 2019). Some routes of transmission remain undetermined yet strongly point toward healthcare-associated transmission (Eley et al., 2003; Hiemstra et al., 2004).

Among the ten children with suspected household or community-associated HIV transmission, surrogate breastfeeding, pre-mastication and bites were the reported modes of transmission

Table 1
Demographics of the study population at first HIV diagnosis (n = 32).

Variable	Total cohort N = 32 (%)	Prospective cohort N = 17 (%)	Retrospective cohort N = 15 (%)
Male gender	22 (68.8)	14 (82.4)	8 (53.3)
Age in months at HIV diagnosis, median (IQR)	79 (28.5–91.5)	89 (32.0–76.0)	72 (24.0–96.0)
Indication for HIV testing			
Failure to thrive	4 (12.5)	2 (11.8)	2 (13.3)
New tuberculosis diagnosis	11 (34.4)	4 (23.5)	7 (46.7)
Other indications ^a	17 (53.1)	11 (64.7)	6 (40.0)
WHO stage at HIV diagnosis			
Stage 2	3 (9.4)	3 (17.6)	0
Stage 3	24 (75.0)	11 (64.7)	13 (86.7)
Stage 4	5 (15.6)	3 (17.6)	2 (13.3)
Staging condition:			
Pulmonary tuberculosis	14 (43.8)	5 (29.4)	9 (60.0)
Failure to thrive	6 (18.8)	4 (23.5)	2 (13.3)
Disseminated tuberculosis	4 (12.5)	2 (11.8)	2 (13.3)
Varicella zoster	2 (6.3)	2 (11.8)	0
Oral thrush	2 (6.3)	2 (11.8)	0
Chronic lung disease	2 (6.3)	1 (5.9)	1 (6.7)
Bronchopneumonia	1 (3.1)	1 (5.9)	0
Recurrent otitis media	1 (3.1)	1 (5.9)	0
Hematological disease	1 (3.1)	1 (5.9)	0
Absolute CD4-positive T-cell count at time of HIV diagnosis, mean (SD)	563.9 (SD 575.5)	563.9 (SD 575.5)	No CD4 counts available
CD4-positive T-cell percentage at time of HIV diagnosis, mean (SD)	25.7 (SD 9.0)	25.7 (SD 9.0)	No CD4% available

SD = standard deviation; IQR = interquartile range.

^a Other indications included oral thrush (2), current/recurrent respiratory tract infections (2), herpes zoster (2), low CD4 (2), bronchiectasis (2), arthritis (2), conjunctivitis (2), lymphadenopathy (2), testing following needlestick injury by healthcare worker (2), unknown (2), and other (14).

Table 2
Possible HIV exposure/s events and presumed route of HIV infection.

Variable	Total cohort N = 32 (%)	Prospective cohort N = 17 (%)	Retrospective cohort N = 15 (%)
History of preterm birth	10 (31.2)	5 (29.4)	5 (33.3)
Mode of delivery			
Delivery by caesarian section	8 (25.0)	6 (35.3)	2 (13.3)
Normal vaginal delivery	13 (40.6)	11 (64.7)	2 (13.3)
Neonatal resuscitation required	2 (6.3)	2 (11.8)	0
Neonatal ward and/or NICU admission	11 (34.4)	6 (35.3)	5 (33.3)
Number of other hospital admission episode/s prior to HIV diagnosis, mean (SD)	1.7 (SD 2.3)	2.3 (SD 2.9)	1 (SD 0.6)
Main reasons for admissions			
Lower respiratory tract infection	10 (31.2)	8 (47.1)	2 (13.3)
Gastroenteritis	6 (18.8)	6 (35.3)	0
Tuberculosis	7 (21.9)	4 (23.5)	3 (20.0)
History of any potential HIV-exposure event/s	31 (96.9)	17 (100.0)	14 (93.3)
Type of exposure event (number)			
Any blood products received	8	4	4
Central line ^a	2	2	0
Intravenous antibiotics ^b	20	12	8
Intravenous cannula ^c	19	12	7
Surgery ^d	5	3	2
Expressed breast milk ^e	8	3	5
Immunizations ^f	19	17	2
Other injections ^g	0	0	0
Blood tests ^h	4	4	0
Tuberculin skin test ⁱ	6	6	0
Urinary catheter ^j	0	0	0
Surrogate breast feeding ^k	6	3	3
Premastication ^l	1	0	1
Piercings ^m	6	5	1
Scarification ⁿ	2	2	0
HIV-infected person in the household ^o	6	5	1
Bed sharing ^p	8	8	0
Toothbrush sharing ^q	0	0	0
Cuts present ^r	2	2	0
Sharps injury ^s	0	0	0
Sexual abuse ^t	0	0	0
Physical abuse ^u	0	0	0
Presumed route of HIV transmission			
Healthcare-associated	15 (46.9)	7 (41.2)	8 (53.3)
Household/community-associated	10 (31.2)	7 (41.2)	3 (20.0)
Both healthcare and community HIV exposures present	5 (15.6)	3 (17.6)	2 (13.3)
Unknown	2 (6.3)	0	2 (13.3)

SD = standard deviation.

^a 21 patients were screened, 16 did not have the risk factor, 3 had an unknown result.

^b 23 were screened, 2 did not have the risk factor, 1 had an unknown result.

^c 22 were screened, 2 did not have the risk factor, 1 had an unknown result.

^d 25 were screened, 20 did not have the risk factor.

^e 21 were screened, 13 did not have the risk factor.

^f 19 were screened.

^g 20 were screened, all negative.

^h 20 were screened, 16 did not have the risk factor.

ⁱ 20 were screened, 14 did not have the risk factor.

^j 20 were screened, all negative.

^k 24 were screened, 18 did not have the risk factor.

^l 22 were screened, 6 had possible exposure, 3 had an unknown result.

^m 22 were screened, 14 were negative and 2 had an unknown result.

ⁿ 23 were screened, 19 were negative and 2 had an unknown result.

^o 24 were screened, 16 did not have the risk factor, 2 had an unknown result.

^p 19 were screened, 9 did not have the risk factor and 2 had an unknown result.

^q 21 were screened, 1 had a possible risk and 2 had unknown results.

^r 20 were screened, 16 did not have the risk factor, 2 had an unknown result.

^s 20 were screened, 18 negative and 2 unknown results.

^t 22 were screened, 20 did not have the risk factor, 2 had an unknown result.

^u 21 were screened, 1 had a possible risk and 2 had unknown results.

(Maniar, 2019; Morsheimer et al., 2014; Cotton and Rabie, 2020; Altaf et al., 2019). Premastication (chewing of food by an adult for ingestion by an infant) is a common practice in South Africa and an important risk for transmission of HIV (Maritz et al., 2011).

Discussion

Over 15 years, we identified 32 incidents of horizontal HIV infection (on average two cases/year) among children attending

ART clinics in Cape Town's Metro East. In both the prospective and retrospective cohorts, HIV diagnosis was delayed beyond six years of age with most children exhibiting late stage HIV disease, with immunosuppression, HIV-associated morbidities and multiple hospitalization episodes. In the last decade, South Africa has made rapid progress in the roll-out of PMTCT programs, with subsequent decline in paediatric HIV prevalence. Therefore, clinicians caring for children should be aware of horizontally transmitted paediatric HIV disease, and consider possible HIV

Table 3
Impact and outcome of horizontal HIV infection (prospective cohort only, n = 17).

Variable	Prospective cohort N = 17 (%)
Time from HIV diagnosis to ART initiation in months, mean (SD)	2.4 (11.1)
HIV-associated co-morbidities present at initial assessment	14 (82.4)
One or more complications ^a of chronic HIV infection	10 (58.8)
Current place of HIV care	
Community ART clinic	10 (58.8)
Tertiary hospital ART clinic	7 (41.2)
Patient years of follow-up since HIV diagnosis, mean (SD)	6.9 (3.9)
Absolute CD4-positive T-cell count from most recent HIV clinic visit, mean (SD)	786.9 (428.0)
CD4-positive T-cell percentage from most recent HIV clinic visit, mean (SD)	29.8 (12.2)
Proportion of children with virological suppression (VL < 25 copies/ml) at their most recent HIV clinic visit	9/15 (60)

SD = standard deviation.

^a Complications included: chronic sinusitis, chronic lung disease, recurrent lower respiratory tract infections, chronic suppurative otitis media and several opportunistic infections e.g. herpes zoster, varicella zoster, and pulmonary, extra-pulmonary and disseminated TB.**Table 4**
Summary of the literature describing horizontal transmission of HIV to children.

Author	Year published	Country	Number of children included ^c	Mode of HIV transmission (presumed or confirmed)	Route of HIV transmission (presumed or confirmed)
Maniar, J.K. (Maniar, 2019)	2019	India	1	Community-associated	In household, route undetermined
Mir, F et al. (Mir et al., 2020)	2019	Pakistan	371	Healthcare-associated	Injection equipment
Ugwu, R et al. (Ugwu and Eneh, 2014)	2014	Nigeria	71 (71/620)	Healthcare-associated and Community-associated	47 blood transfusions, 13 contaminated sharps, 6 sexual abuse, 5 undetermined
Cotton, M et al. (Cotton et al., 2012)	2012	South Africa	10	Healthcare-associated and Community-associated	Unsterile hospital practices, possibly also surrogate breastfeeding and pre-mastication
Vaz, P et al. (Vaz et al., 2010)	2010	Mozambique	22 (22/450)	Healthcare-associated	Blood transfusions, injections, scarifications, surgery and dental extractions
^b Reid, S et al. (Reid and Van Niekerk, 2009)	2009	South Africa	±768	Healthcare-associated	Injections
Okinyi, M et al. (Okinyi et al., 2009)	2009	Swaziland	11 (11/50)	Healthcare-associated	Injections, phlebotomy, dental surgery
Shisana, O et al. (Shisana et al., 2008)	2008	South Africa	7 (7/3471)	Healthcare-associated and Community-associated	Breastmilk from nonbiological mother, donor milk, dental procedures
Hiemstra, R et al. (Hiemstra et al., 2004)	2004	South Africa	14	Healthcare-associated	Unsterile hospital practices
^a Eley, B et al. (Eley et al., 2003)	2003	South Africa	2	Healthcare-associated	Unknown
^a Orth, H et al. (Orth et al., 2000)	2000	South Africa	2	Community-associated	Community/household-associated
Nielsen, H et al. (Nielsen et al., 1998)	1998	Unknown	1	Healthcare-associated	Healthcare-associated
Wahn, V et al. (Wahn et al., 1986)	1986	Germany	1	Community-associated	Bite from sibling

^a Both these papers' data are used in the Hiemstra, R et al. study.^b This paper is a systematic data search and an estimate of cases through interpretation of findings.^c Denominators have been added where applicable and/or available from the source cited.

infection when appropriate among children of HIV-uninfected parents.

In all but one child, we identified at least one potential HIV exposure event in the household, community or a healthcare facility. Most potential healthcare-associated HIV-exposure events involved intravenous access, injections or immunizations, whereas surrogate breastfeeding and body piercings were the most frequent community/household-associated HIV-exposure events.

Despite the delay in HIV diagnosis and commencement of ART at advanced clinical and immunological stages of HIV, most children responded very well to therapy. Among children in the prospective cohort, ART was started promptly (2.4 months following HIV diagnosis) with sustained virological suppression in 60.0%.

This South African cohort of children with horizontal acquisition of HIV (in keeping with international literature) documented a predominance of suspected healthcare-associated routes of HIV transmission. However, in contrast to the literature, HIV-contaminated blood and blood products were not implicated in our cohort. Exposures to potential HIV in breastmilk (whether in hospital or through surrogate breastfeeding) occurred frequently and should always be considered when screening for HIV exposures. Rarely, transmission within the household has occurred due to exposure

to secretions and sharing of tooth brushes. The risk of HIV transmission from pre-mastication of food is high, particularly from individuals with concomitant poor oral hygiene and gingivitis (Maritz et al., 2011).

Limitations of this study include the inability to definitively determine the route of HIV exposure in each child, the low number of fathers available for HIV testing, and the lack of phylogenetic analysis to compare HIV strains, in the few cases where an HIV-infected family member lived with the index case. We did confirm phylogenetic linkage in one of our earliest cases (Orth et al., 2000). However, this cohort of horizontally HIV-infected children is one of the largest published to date, and includes a detailed assessment of potential HIV exposures, as well as long term follow-up of virological suppression among children in the prospective cohort.

Conclusion

Despite major global progress in prevention of vertical HIV transmission, children still acquire HIV, albeit in low numbers, through lapses in infection control practices in healthcare facilities or lack of public awareness of the risks associated with surrogate breast feeding and pre-mastication. The true incidence of and major contributors to horizontal HIV transmission in children is

unknown. Infection prevention breaches, re-use of medical devices, premastication and surrogate breastfeeding are likely to be major risk factors for horizontal HIV transmission in resource-limited settings. We recommend a careful public campaign, e.g. posters in healthcare facilities. Greater effort should be made to thoroughly investigate each horizontally infected child at the time of HIV diagnosis, to establish possible routes of transmission and inform future HIV prevention strategies.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Ethical approval was obtained from the Stellenbosch University Health Research Ethics Committee and the Tygerberg Hospital management (protocol number N11_03_066).

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