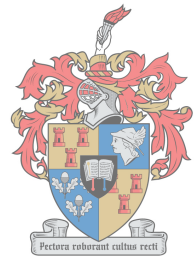
A profile of the prevention of mother-to-child transmission (pMTCT) and clinical status of HIV-infected children younger than 18 months admitted to Tygerberg Hospital over a one-year period.

by

Elri du Plooy



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DECLARATION

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ABSTRACT

Background: Combination antiretroviral therapy (cART) for all Human Immunodeficiency Virus (HIV) infected pregnant and lactating women and post-exposure prophylaxis for HIV-exposed infants prevents mother-to-child transmission of HIV and has been the standard of care in Cape Town, South Africa since May 2013. Despite high uptake and good coverage, transmission still occurs. Early identification of HIV infection in infants and access to cART are key components in reduction of morbidity and mortality in HIV- infected infants. Reasons for ongoing transmission include missed diagnosis of infection during pregnancy and the postpartum period, short maternal duration on cART and issues around retention in care. In addition, poor uptake of the early infant diagnosis opportunities and delayed access to cART for infants is well documented.

This study aimed to describe the antenatal and postnatal prevention of Mother-to-Child transmission (pMTCT) history and current medical condition of HIV-infected children younger than 18 months of age admitted to Tygerberg Hospital over a 12-month period, as well as document the availability of clinical information for these patients through an assessment of the Road-to-Health booklet (RtHB), medical records and the National Health Laboratory Service (NHLS).

Materials & Methods: This was a prospectively enrolled descriptive study from February 2015 to January 2016 that documented the pMTCT , infant diagnosis and care cascade of hospitalized HIV infected children younger than 18 months with newly diagnosed or previously confirmed HIV. Data on maternal HIV and pregnancy history, as well as child HIV-history and clinical status were collected and descriptive analysis performed.

Results: Sixty-three children were screened and 55 enrolled (6 declined; 2 unavailable for consent). The median age was 5.7 (IQR 3 - 12.5) months; 33 (60%) were male. Forty-six children (83%) were identified as HIV-exposed at birth. The majority, 31 (67%), of their mothers were aware of their HIV diagnosis prior to pregnancy. However, only 20 (65%) attended antenatal care, with 7 (23%) interrupting cART initiated prior to pregnancy. Twenty-three women (50%) began cART during pregnancy: 11/31 (35%) were known to be HIV-infected prior to pregnancy and 12/15 (80%) were diagnosed during pregnancy (p=0.4). Of these 23 women, 10 (43%) were not retained in care: 6/11 (55%) of previously diagnosed and 4/12 (33%) of women diagnosed with HIV in pregnancy (p=0.4).

Children with unknown HIV-exposure risk were older: 9.3 (IQR 5.9 – 12.8) vs 4.5 (IQR 2.2 – 12.6) months (p=0.167) for known risk. Fifteen children (27%) were diagnosed in the neonatal period, 5/15 (33%) during hospitalization at Tygerberg Hospital. Children with known exposure risk were diagnosed at a median age of 1.8 (IQR 0.1 – 3.5) months versus 9.4 (IQR 6.6 -12.1) months in unknown risk children (p=0.001). Children with unknown HIV-exposure risk had a median weight-for-age z-score of -3.4 (IQR -4.2 - -2.3) vs -2.4 (IQR -4.1 - -1.8), (p=0.228) and 8 (89%) had WHO stage 3 or 4 disease versus 36 children (78%) with known risk (p=0.195).

The median duration from HIV diagnosis to cART initiation was 8 (IQR 5 – 30) days in known-risk children; 15/46 (27%) successfully initiated cART prior to admission and remained in care. At time of hospitalization 5 children (9%) had discontinued previously initiated cART.

Seven children (13%) died in hospital, with 14/55 (25%) (13 with known risk) requiring intensive care admission. The median hospitalization duration was 17 days, similar in those with known (23 [IQR 12 – 30.5] days) vs unknown risk (15.5 [IQR 10 – 32.3] days) (p=0.67).

Forty-six (96%) of the RtHBs of our cohort were available for review during their admission. Seven of 55 children (12.7%) were still in the neonatal service and had not yet been issued a RtHB. Of the 39 (98%, N=40) children whose mothers were identified antenatally, 7 (18%) had an age-appropriately completed HIV-related page. Of the 31 children older than 6 weeks, HIV polymerase chain reaction (PCR) testing was documented in 19 (61%), but the result was only noted in 15 (79%). Initiation of co-trimoxazole at 6 weeks was documented in 15 (52%). Of the 8 children identified after delivery and outside the pMTCT service, 7 (88%) had RtBHs available, with only 1 child (14%) having any documentation of antenatal or postpartum tests noted. Age appropriate vaccinations were documented in 24 of 39 (62%) of antenatally diagnosed children and 5 of the 7 children identified postpartum.

Conclusion: We identified poor antenatal clinic attendance and cART-treatment interruption in women aware of their status prior to pregnancy as the driver of newly infected infants. Despite HIV being diagnosed relatively early, mortality and morbidity were high. Documentation of HIV in the RtHB was poorly completed by healthcare workers, with a possible impact on the care cascade. Of significant concern was the low completion of infant vaccination, a further pointer to the health seeking behaviour of mothers.

Identifying women at risk of transmitting HIV to their infants will be challenging as they often do not engage with the health care system. Further research exploring the reasons for this is needed. When these women do attend routine services, they should be identified and more effort made to retain them, not only in the pMTCT cascade of care but also into the well child follow-up system.

OPSOMMING

Agtergrond: Kombinasie antiretrovirale terapie (kART) vir alle HIV-geïnfekteerde swanger en lakterende vroue, sowel as post-blootstellingsprofilakse vir HIV-blootgestelde kinders voorkom moeder-na-kind oordrag van HIV. Dit is reeds sedert Mei 2013 die standaard van sorg in Kaapstad, Suid-Afrika. Ongeag hoë opname en goeie dekking, kom oordrag steeds voor. Vroeë identifikasie van HIV infeksie in kinders en toegang tot kART is sleutelkomponente in die vermindering van morbiditeit en mortaliteit in HIV-geïnfekteerde kinders. Redes vir volgehoue oordrag sluit infeksies wat tydens swangerskap en die postpartum periode gemis is, kort moederlike duur op kART en probleme rondom retensie in sorg, in. Daarbenewens is swak gebruikmaak van diagnoseringsgeleenthede en vertraagde toegang tot kART goed gedokumenteer.

Die doel van hierdie studie is om, deur die beskrywing van die profiel van jong geïnfekteerde gehospitaliseerde kinders, begrip vir die huidige risikofaktore vir oordrag te verbreed, mislukkings in die diagnostiese en sorg-paaie te identifiseer en die geassosieerde morbiditeit en mortaliteit te beskryf. Dokumentasie van die probleme in die sorg-paaie is ook ondersoek deur die gesondheidsorgwerkers se notas in die “Road-to-Health” boekies (RtHB) te dokumenteer en die opname van roetine sorg te assesseer deur na die vaksinasie rekords in die RtHB te kyk.

Materiale en Metodes: Hierdie was ‘n prospektief beskrywende studie vanaf Februarie 2015 tot Januarie 2016 waarin die voorkoming van Moeder-tot-Kind oordrag (pMTCT), diagnosering van kinders en sorgkontinuum van gehospitaliseerde HIV-geïnfekteerde kinders jonger as 18 maande met nuut-gediagnoseerde of voorheen bevestigde HIV, gedokumenteer is. Data van moederlike HIV en swangerskapsgeskiedenis, sowel as kind se HIV geskiedenis en kliniese status is versamel en beskrywend analiseer.

Resultate: Drie-en-sestig kinders is gesif en 55 ingesluit (6 wys deelname af; 2 nie beskikbaar vir toestemming). Die gemiddelde ouderdom was 5.7 (IQR 3 – 12.5) maande; 33 (60%) was manlik. Ses-en-veertig is identifiseer as HIV-blootgestel met geboorte. Die meerderheid, 31 (67%), van hulle moeders was bewus van hul HIV-diagnose voor swangerskap. Ten spyte daarvan het slegs 20 (65%) voorgeboortelike sorg bygewoon en 7 (23%, N=31) ook kART wat voor swangerskap iniseer is, onderbreek. Drie-en-twintig vroue (50%) het kART tydens swangerskap begin: 11/31 (35%) se positiewe HIV-status was reeds voor swangerskap bekend en 12/15 (80%) is gedurende swangerskap gediagnoseer (p=0.4). Tien (43%) van hierdie 23 vroue is nie in sorg behou nie: 6/11 (55%) van

voorheen gediagnoseerde en 4/12 (33%) van vroue tydens swangerskap met HIV gediagnoseer (p=0.4).

Kinders met 'n onbekende HIV-blootstellingsrisiko was ouer: 9,3 (IQR 5.9 – 12.8) teenoor 4.5 (IQR 2.2 – 12.6) maande vir bekende risiko (p=0.167). Vyftien kinders (27%) is tydens die neonatale periode gediagnoseer, 5/15 (33%) gedurende hospitalisasie by Tygerberg Hospitaal. Kinders met 'n bekende blootstellingsrisiko is gediagnoseer teen 'n gemiddelde ouderdom van 1.8 (IQR 0.1 – 3.5) maande teenoor 9.4 (IQR 6.6 – 12.1) maande in onbekende risiko kinders (p=0.001). Kinders met onbekende HIV-blootstellingsrisiko se gemiddelde gewig-vir-ouderdom z-telling was -3.4 (IQR -4.2 tot -2.3) teenoor -2.4 (IQR -4.1 tot -1.8), (p=0.228) en 8 (89%) het WGO (Wêreld Gesondheidsorganisasie) stadium 3 of 4 siekte teenoor 36 kinders (78%) met bekende risiko (p=0.195).

Die gemiddelde duur van HIV diagnose tot kART-inisiasie was 8 (IQR 5 – 30) dae in bekende-risiko kinders; 15/46(27%) het kART suksesvol inisieer voor toelating en het in sorg gebly. Teen die tyd van hospitalisering het 5 (9%) kinders voorheen inisieerde kART gestaak.

Sewe kinders (13%) is in die hospitaal dood, met 14/55 (25%) (13 met bekende risiko) wat opname in intensiewe sorg benodig het. Die gemiddelde hospitalisasieduur was 17 dae, ooreenstemmend in die met bekende (23 [IQR 12 – 30.5] dae) teenoor onbekende risiko (15.5 [IQR 10 – 32.3] dae) (p=0.67).

Ses-en-veertig (96%) RtHBs van die kohort was beskikbaar vir ondersoek gedurende toelating. Sewe van 55 kinders (12.7%) was nog in die neonatale diens opgeneem en dus nog nie in besit van 'n RtHB. Van die 39 (98%, N=40) kinders wie se moeders antenataal identifiseer is, het 7 (18%) 'n ouderdomstoepaslik voltooide HIV-verwante bladsy gehad. Van die 31 kinders ouer as 6 weke, was HIV PKR toetsing gedokumenteer in 19 (61%), maar resultate slegs aangedui in 15 (79%). Inisiëring van co-trimoxazole op 6 weke was gedokumenteer in 15 (52%). Van die 8 kinders wie postpartum en buite die pMTCT diens geïdentifiseer is, was 7 (88%) se RtBHs beskikbaar, met dokumentasie rakende antenatale of postpartum toetse slegs by 1 kind (14%) aangedui. Ouderdomstoepaslike vaksinasies was by 24 van die 39 (62%) antenataal gediagnoseerde kinders en 5 van die 7, postpartum geïdentifiseer, gedokumenteer.

Gevolgtrekking: Hierdie studie identifiseer swak voorgeboortelike kliniekbywoning en onderbreking van kART-behandeling by vroue bewus van hul HIV-status voor swangeskap as die dryfveer van nuut-geïnfekteerde kinders. Ten spyte daarvan dat HIV relatief vroeg gediagnoseer is, was mobiditeit en

mortaliteit hoog. Dokumentasie van HIV in die RtHB is swak voltooi deur gesondheidsorg werkers, met ‘n moontlike impak op die sorg-kontinuum. Lae voltooiing van die kindervaksinasies was ‘n ernstige bekommernis en verdere aanduiding van die gesondheidsorg-soekende gedrag van die moeders.

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ABBREVIATIONS

3TC	Lamivudine
AFB	Acid-Fast Bacilli
AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
ART	Antiretroviral treatment
ARV	Antiretroviral
AZT	Zidovudine
cART	Combination antiretroviral therapy
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CHER	Children with HIV Early Antiretroviral Therapy
Child PIP	Child Healthcare Problem Identification Programme
CMV	Cytomegalovirus
CRF	Case report form
CSF	Cerebrospinal fluid
DDI	Didanosine
DNA	Deoxyribonucleic acid
ECM	Enterprise Content Management
E. coli	Escherichia Coli
EFV	Efavirenz
EID	Early infant diagnosis
ELISA	Enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
ESBL	Extended Spectrum Beta-Lactamase
FDC	Fixed-dose combination

FTC	Emtricitabine
Global Plan	Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive
HAART	Highly active anti-retroviral therapy
HEU	HIV-exposed uninfected
HIV	Human immunodeficiency virus
HTC	HIV-testing and counselling
ICU	Intensive care unit
INH	Isoniazid
IPT	Isoniazid preventative therapy
IQR	Interquartile range
LDL	Lower than detectible limit
LPV/r	Lopinavir/ritonavir
LTFU	Loss to follow-up
MCH	Maternal & Child Health
MCS	Microscopy, Culture and Sensitivity
MRC	Medical Research Council
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
MTCT	Mother-to-child transmission
NDoH	National Department of Health
NHLS	National Health Laboratory Service
NIH	National Institutes of Health
NPA	Nasopharyngeal Aspirate
NVP	Nevirapine
PACTG Protocol 076 study	Pediatric AIDS Clinical Trials Group Protocol 076 study

PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PICU	Paediatric intensive care unit
PITC	Provider-initiated testing and counselling
PJP	Pneumocystis jiroveci pneumonia
PMTCT	Prevention of Mother-To-Child Transmission Of HIV
PROMISE study	Promoting Maternal-Infant Survival Everywhere study
RNA	Ribonucleic acid
RSV	Human Respiratory syncytial virus
RtHB	Road-to-Health Booklet
SAM	Severe acute malnutrition
sdNVP	Single-dose nevirapine
SOFA	Statistics Open for All version 1.4.6
STAT	Immediately
Stats SA	Statistics South Africa
TA	Tracheal aspirate
TB	Tuberculosis
TBH	Tygerberg Hospital
TDF/FTC	Tenofovir/Emtricitabine (Truvada)
UMCS	Urine Microscopy, Culture and Sensitivity
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VCT	Voluntary counselling and testing
WAZ	Weight-for-age Z-score
WHO	World Health Organisation

DEFINITIONS

		Source
Adherence	The extent to which a person's behaviour – taking medication, following a diet and/or changing lifestyle – corresponds with agreed recommendations from a health worker.	World Health Organization (WHO)
ARV	Antiretroviral (ARV) drugs refer to medicines used to treat HIV	WHO
ART	Antiretroviral therapy (ART) refers to the use of a combination of three or more ARV drugs for treating HIV infection. ART involves lifelong treatment. Synonyms are combination ART and highly active ART.	WHO
Birth PCR	HIV PCR done in the first 7 days of life (< 7 days)	Own
Child	A person 1 to younger than 10 years of age	WHO
Continuum of HIV care	A comprehensive package of HIV testing, prevention, treatment and care services provided for people at risk of acquiring HIV and people living with HIV and their families.	WHO
Early infant diagnosis	HIV testing of infants born to HIV-infected women within the first two months of life to determine their HIV status and eligibility for antiretroviral treatment	WHO
Exclusive breastfeeding	The infant receives only breast milk without any other liquids or solids, not even water, except for oral rehydration solution or drops or syrups of vitamins, minerals or medicines	WHO
HIV-exposed infant or child	An infant or child born to a mother living with HIV until the infant or child is reliably excluded from being HIV infected.	WHO

HIV-pages in RtHB age-appropriately completed	HIV-related pages in the RtHB fully completed as per the HIV-exposure status, child age and step in the pMTCT process	Own
In care	Previously initiated on and taking cART	Own
Infant	Child below 1 year of age (365 completed days of life)	WHO
Known HIV-Exposure Risk	Children born to mothers who were diagnosed HIV-infected prior to or during the index pregnancy.	Own
Linkage	A process of actions and activities that supports people testing for HIV and people diagnosed with HIV in engaging with prevention, treatment and care services as appropriate for their HIV status. For people with HIV, it refers to the period beginning with HIV diagnosis and ending with enrolment in care or treatment.	WHO
Maternal pMTCT CD4 count	CD4 cell count during pregnancy and up to 2 months postpartum using the test closest to delivery, preferably antenatally.	Own
Maternal pMTCT viral load	HIV viral load during pregnancy and up to 2 months postpartum, using the test result closest to time of delivery, preferably antenatally.	Own
Mixed feeding	An infant younger than six months of age is given other liquids and/or foods together with breast milk. This could be water, other types of milk or any type of solid food.	WHO
Neonatal period	From birth until 28 completed days of life	WHO
Neonate	An infant 0–28 days old.	WHO
Not in care	Initiated on and defaulted cART prior to admission	Own
Perinatal period	From birth until 7 completed days after birth	WHO

	(WHO Definition: From 22 completed weeks of gestation until 7 completed days after birth)	
Postnatal transmission	Transmission of HIV to an infant or child after birth. Most postnatal transmission is through the breast milk of a woman living with HIV, but this also includes accidental infection, such as through an infected needle or through child abuse	WHO
Postpartum period	First 7 completed days after birth	Own
Prevention of mother-to-child transmission of HIV	The use of ARV drugs to prevent the transmission of HIV from the mother during pregnancy and breastfeeding	WHO
Retention in HIV care	A person living with HIV who is enrolled in HIV care routinely attends these services in accordance with the need.	WHO
Self-interruption of cART	Interruption in taking of cART initiated by women themselves, not as per order of medical professional	Own
Undetectable/ lower than detectable limit HIV viral load	HIV RNA less than 50 copies/ml ((arbitrary value of 40 copies/ml used for statistical analysis) or log 1.2 (based on cut-off values used by NHLS))	Own
Unknown HIV-Exposure Risk	Children born to mothers who were not known to be HIV-infected prior to, or during the index pregnancy.	Own
Vertical transmission	Transmission of HIV that occurs from a mother living with HIV to her infant. This may occur in utero, in the peripartum period or postnatally through breastfeeding.	WHO

1. INTRODUCTION AND LITERATURE REVIEW

Prevention of Mother-to-Child Transmission (pMTCT) has evolved markedly over the past 20 years: From Zidovudine-based recommendations studied in the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 study in 1994 in resource rich countries (1) and short course antiretroviral therapy (ART) prophylaxis, including single-dose Nevirapine (sdNVP), in resource-limited settings in 2000(2), to lifelong combination antiretroviral therapy (cART) for all pregnant and breastfeeding Human immunodeficiency virus (HIV) infected women, as well as at least 6 weeks of single or dual drug ART prophylaxis in all HIV-exposed infants irrespective of feeding choice as recommended by the World Health Organization (WHO) since 2015.(3)

The Global Health Strategy on HIV 2016 -2021 aims to eliminate the public health threat the Acquired Immunodeficiency Syndrome (AIDS) epidemic poses by 2030. Their 2020 targets include the reduction of new HIV infections to less than 500 000, with no new infections in infants; reduction of HIV-related deaths to less than 500 000; as well as the 90-90-90 targets in which 90% of people living with HIV will know their HIV status, 90% with HIV will have sustained access to antiretroviral treatment and 90% on treatment will have suppressed viral loads.(4,5) In order to achieve these goals, unprecedented scale-up of HIV programmes and policies are needed, especially in low-to-middle income countries, with sustained commitment and effort from local, national and global counterparts.

With regards mother-to-child transmission, particular attention needs to be paid to the prevention of HIV infection in women of reproductive age and, if women are infected, subsequent strategies to strengthen the existing effective, but still porous, pathway of interventions to prevent vertical transmission of HIV to their children.

In the 2017 Joint United Nations Programme on HIV/AIDS (UNAIDS) Data report, it is documented that in 2016, an estimated 2.1 million (1.7million – 2.6 million) children under 15 years of age were living with HIV. Twenty-six percent of new HIV infections in eastern and southern Africa were attributed to young women (15 – 24 years of age; 10% of the population) and globally 160 000 (110 000 – 220 000) children were newly infected.(6) Only 49% (42 – 55%) of children living with HIV were accessing antiretroviral treatment in 2015, and child AIDS-related deaths in 2016 tallied to 120 000 (79 000 – 160 000).(6,7) This highlights that, despite greater availability of and access to proven effective cART-backboned pMTCT strategies, children are still becoming HIV-infected.

Young HIV-infected children are at high risk of increased morbidity and mortality. In the absence of cART, HIV-related mortality peaks at 2-3 months of age in South Africa.(8) The Children with HIV Early Antiretroviral Therapy (CHER) study (2005-2007) showed that early HIV diagnosis and early cART at 6 to 9 weeks of age, reduced early infant mortality and HIV progression by 76% and 75% respectively, when compared to deferring cART until clinical or cluster of differentiation 4 (CD4) criteria were met. Many screened children could not be randomized due to their advanced disease at a young age.(9) A review of South African data collected between 2007 and 2010 at multiple sites in Cape town and at Chris Hani Baragwanath Academic Hospital in Soweto, found that 62% of 403 infants who initiated cART at median 8.4 weeks of age had advanced HIV disease (CD4 <25% or <1500 cells/mm^3 or WHO Stage 3 or 4 disease).(10) Early infant diagnosis (EID) and timely initiation of cART are needed to improve outcome.

1.1 PMTCT IN SOUTH AFRICA

1.2 million (1.1 million – 1.4 million) women of reproductive age were newly diagnosed with HIV infection in South Africa between 2009 and 2015. This group carries the highest number of new infections in the 21 Sub-Saharan priority countries of the UNAIDS *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive*(Global Plan).(11) Despite this, through programmatic scale-up by national and local government in line with WHO Guidelines and in keeping with the Millennium Developmental Goals and subsequent Sustainable Developmental Goals, as well as the Global Plan, the country has managed to reduce new HIV infections in South Africa by 84%, expand maternal ART coverage to more than 90%, limit the vertical transmission rate to 2% (1.9-2.2%), as well as decrease paediatric AIDS-related deaths by 90% between 2009 and 2015.(11)

1.2 THE CURRENT PMTCT GUIDELINES

The 2015/6 pMTCT guidelines of the World Health Organization, the South African National Department of Health and the Western Cape Department of Health are summarized in Table 1 below.

Table 1.1: Summarized 2015/16 WHO, South African and Western Cape pMTCT Guidelines

	WHO Consolidated Guidelines 2nd Edition 2016(3)	***National Consolidated ART Guidelines April 2015***(12)	***Western Cape Consolidated Guidelines for HIV Treatment Nov 2015***(13)
HIV Testing in Pregnant Women		First antenatal visit If Negative: - 3 monthly in pregnancy - At delivery - At 6-week EPI visit - 3 monthly while breastfeeding	First antenatal visit If Negative: - 3 monthly in pregnancy - At delivery - At 6-week EPI visit - 3 monthly while breastfeeding
Maternal ART initiation	Lifelong ART	Same day lifelong ART	Same day Lifelong ART
HIV viral load (VL) monitoring		On ART: <2 weeks since pregnancy diagnosis < 1000: 6 months >1000: 1 month Newly Diagnosed: At 3 months, then as above	On ART: <2 weeks since pregnancy diagnosis <400: 3 monthly 400 – 1000: <28weeks: 3 months >28weeks: 1 month >1000: 1 month +- 2nd line ART
Infant Prophylaxis			
		Mother ART > 4weeks NVP 6 weeks	Mother ART >12 weeks/VL <1000copies/ml NVP 6 weeks
	High Risk at birth: Breastfeeding: NVP ≥12 weeks and AZT 6 weeks Not Breastfeeding: NVP and AZT 6 weeks	Mother ART < 4 weeks NVP 12weeks	High Risk at birth: Breastfeeding: NVP ≥12 weeks and AZT 6 weeks Not Breastfeeding: NVP and AZT 6 weeks
		Maternal VL on Rx >1000copies/ml: NVP and AZT 6 weeks	High Risk during breastfeeding: Maternal VL > 1000copies/ml NVP ≥ 12 weeks No ART/Newly diagnosed: NVP ≥12 weeks and AZT 6 weeks
Infant HIV Testing Timing	Birth 4-6 weeks 9 months 18 months Clinically indicated	Birth 10 weeks or 18 weeks 6 weeks after final breastfeed 18 months Any time indicated	Birth 10 weeks or 18 weeks 9 months 6 weeks after final breastfeed 18 months Any time indicated
Breastfeeding	If authorities promote breastfeeding: 6 months exclusive breastfeeding, followed by breastfeeding with appropriate supplementary foods until 12 months of age or as long as feasible/desired	6 months exclusively At least 1 year if uninfected If HIV-infected: Until 24 months	6 months exclusively If HIV-uninfected: Until 12 months with appropriate supplementary feeds

ART – Antiretroviral therapy, AZT – Zidovudine, HIV – Human immunodeficiency virus, NVP – Nevirapine, pMTCT – prevention of Mother-to-Child transmission, VL – viral load

The April 2015 National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (pMTCT) and the Management of HIV in Children, Adolescents and Adults recommends that all pregnant and breastfeeding women who initially test HIV negative during pregnancy should be seen

as part of the pMTCT programme. They should undergo HIV testing at 3 monthly intervals during pregnancy, at delivery, at the 6-week Extended Programme on Immunization (EPI) visit, as well as 3 monthly throughout breastfeeding. These recommendations were included as 4% of women in South Africa who initially test HIV negative in pregnancy, seroconvert during or after pregnancy.(12)

The ages at which infants are tested have changed in the 2015 guidelines to assist with the early diagnosis of in-utero infected children at birth, as well as reduce the possibility of missing children whose diagnosis may be delayed by the use of postnatal antiretroviral prophylaxis during breastfeeding. In the 2015 guidelines HIV-exposed infants are tested at birth, 10 or 18 weeks and 18 months of age. Infants who receive 6 weeks of Nevirapine prophylaxis can be tested at 10 weeks, whereas infants on the extended 12-week Nevirapine schedule should only be tested at least 4 weeks after cessation of prophylaxis, at 18 weeks of age.(12)

1.3 THE PMTCT CASCADE

The pMTCT cascade/continuum is an integration of the parallel-running maternal and infant intervention and follow-up pathways indispensable for the prevention of mother-to-child transmission of HIV. This same-location integration, that encompasses family planning, antenatal and postpartum care, as well as child survival services, is expected to improve retention in care and adherence to treatment and follow-up, assist with combining maternal and infant care, and linking HIV-infected infants and children to treatment services.(14) See figure 1.1

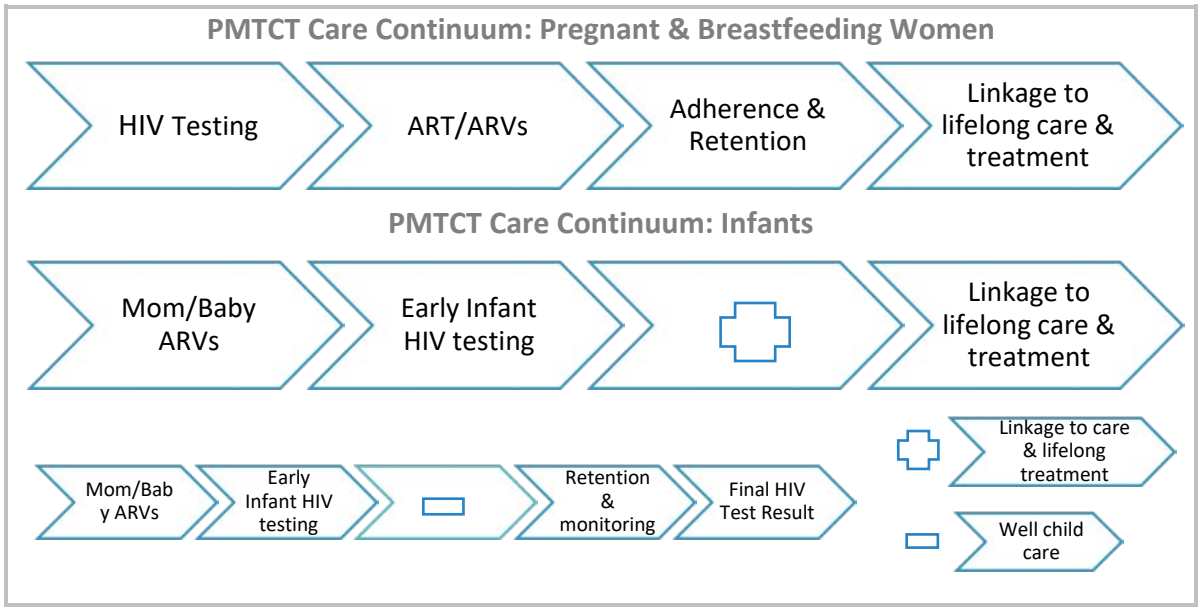

Figure 1.1: Continuum of care for pregnant and breastfeeding women and their children(14)

Adapted from Figure 1 from the IATT Option B/B+ M&E Framework

The maternal arm of the pMTCT continuum involves:(14)

- Maternal HIV testing
- ART initiation
- Retention in care and adherence with treatment (as measured by HIV viral load)
- Linkage to lifelong treatment and care
- Achieving suppression and maintaining that throughout breastfeeding

The infant arm comprises of:(14)

- Maternal and infant ART in the antenatal, peri-partum, post-partum period and for duration of breastfeeding
- Early infant testing/ diagnosis
- Linkage to lifelong treatment and care (if HIV-infected)
- If HIV negative at initial testing
    - Retention in care and monitoring
    - Repeat and final HIV-testing
    - Well-child care and follow up if remains uninfected.

Throughout the continuum of care women and children are at risk of falling off the pathway if the correct interventions and support systems are not in place. Luzuriaga and Mofenson reviewed the mother-infant pMTCT continuum to highlight areas of concern and where further research and intervention are required. Based on 2014 UNAIDS and WHO data in the 22 priority countries, they identified that only 44% of pregnant women tested for HIV, 73% of tested and infected women received antiretroviral treatment during pregnancy and 61% of HIV-infected women received and adhered to treatment during breastfeeding. Forty-four percent of HIV-exposed infants received HIV testing at 4 to 8 weeks of age and only 32% of confirmed HIV-infected infants received cART.(15)

In the following sections we will describe and discuss the gaps and barriers that lead to attrition of mothers and their children along the pMTCT cascade, as well as potential strategies to allay them.

1.3.1 MATERNAL PMTCT CASCADE

1.3.1.1 Maternal HIV testing

From 2009 to 2015 there were 4.5 million (3.8 million – 5.4 million) new HIV infections among women of reproductive age in the 21 Global Plan countries.(11) This group remains a high-risk population for acquiring HIV. WHO reported that in 2013 only 44% of pregnant women in the 21 priority countries, where 90% of the HIV-burden exists, accessed HIV testing.(15)

1.3.1.2 Bypassing Antenatal Care

Pregnancy is an ideal opportunity for identifying HIV-infection in women, but not all women utilize antenatal care (ANC). This is the first major gap in identifying HIV-infected women, as women who do not access ANC bypass the pMTCT cascade. Antenatal clinic attendance in Nigeria, for instance, is only 58%(16), whereas skilled-provider antenatal care utilization in Ethiopia between 2006 and 2010 was only 34%.(17). South Africa reported a 92.9 % first visit antenatal care attendance in 2014 (Western Cape - 85.3% coverage).(18)

A systematic review of the pMTCT cascade in China between 2003 and 2011 indicated that the 8.7% non-ANC attenders increased the 2011 national mother-to-child transmission (MTCT) rate from 2.3% (IQR 1.4% - 3.8%) when only assessing the ANC and pMTCT programme, to 11.5% (IQR 8%-15.7%) when the non-ANC attenders were factored in.(19) If lack of antenatal care and pMTCT can have such a marked effect in a low HIV prevalence country (<0.1% in pregnant women(19)), the impact on high burden countries with poorer ANC attendance is potentially devastating.

Barker et al. demonstrated how women who bypass or drop out of the antenatal care system contributed 16.5 HIV-infected children per 100 HIV-infected mothers of the 19.5 per 100 total HIV prevalence among exposed infants in their study. This was a 25% transmission rate. Mothers who attended antenatal care contributed 3 HIV-infected children per 100 infected mothers at a transmission rate of 8%. They emphasized that the desired impact of current prevention regimens would not be obtained until more than 90% of women successfully accessed and completed all steps in the pMTCT cascade.(20)

Efforts to encourage formalized antenatal care attendance are of paramount importance if the elimination of vertical HIV transmission is ever to be achieved.

1.3.1.3 HIV testing during pregnancy and breastfeeding

In women who attend antenatal care, the utilization of HIV testing as recommended in the pMTCT guidelines is paramount in detecting all HIV-infected women.

The timing of accessing antenatal care is another important factor in achieving pMTCT success. The earlier cART is initiated (preferably prior to a planned pregnancy, ensuring a mother with a supressed HIV viral load antenatally) the lesser the chance of vertical HIV transmission, even in breastfeeding women postpartum. Data, however, shows poor levels of early booking, with only 53.9% of South African women having their first antenatal care visit prior to 20 weeks' gestation.(21)

A single HIV test during pregnancy is also not adequate. Serial testing at multiple points, as recommended by the local and international guidelines, assist in identifying women who sero-convert during pregnancy.(3,12,13) It is imperative to identify these women, as they contribute to a large portion of HIV-infected infants. South African national data from August 2011 to March 2012 indicated that the 3.3% of the HIV-infected mothers who sero-converted during pregnancy, were responsible for 26% of early infant HIV infections.(22)

In 2014 the United Nations Children's Fund (UNICEF) and WHO Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) identified that in the 22 Global Plan priority countries (21 in Sub-Saharan Africa and India) only half of the women who attended antenatal care received HIV counselling, testing and results. Countries of particular concern were Zambia (12%) and the Democratic Republic of the Congo (23%), Nigeria (44%), and Chad (45%). Only 9 countries achieved the set target of >80% utilization of antenatal counselling, testing and results, with South Africa achieving a 94% uptake during this time.(23) South African studies have, however, shown a decrease in HIV-testing in the pMTCT setting of 5.3 - 20.6% at a number of testing sites.(24)

Reasons for poor pMTCT-HIV-test utilization are multi-factorial. A 2013 Ethiopian study where overall HIV-test utilisation was 58.1%, indicated high perceived self-efficacy as a positive and low perceived net benefit as a negative predictor for HIV-testing.(25) Barriers to testing may be psychosocial (lack of knowledge about HIV, fear of being HIV-infected, disinterest) or health system related (lack of counsellors or tests or overburdened services).(26)

After testing for HIV, it is important that HIV-infected women receive their HIV results in order to be started on cART and linked to care. In the Western Cape we currently utilize rapid testing, a strategy that eliminates the problems associated with the non-receipt of results associated with formal laboratory testing. Further research in this care stage is necessary, as very little data is available for the 22 priority countries at present.(15)

As previously stated, 4% of women in South Africa who initially test HIV negative in pregnancy seroconvert during pregnancy and breastfeeding.(12) The importance of HIV testing in all women of childbearing age, especially breastfeeding women in high prevalence settings, can therefore not be over-emphasized, as HIV transmission is higher in newly infected cART-naive, as well as undiagnosed women, due to high viral load levels.(2)

Partner testing is also important, as sero-discordance is a major risk factor for horizontal HIV transmission. Couples should be offered routine voluntary testing and counselling and encouraged and counselled regarding mutual disclosure.(3)

1.3.1.4 Maternal cART for pMTCT

Multiple studies, including the Kesho Bora and Promoting Maternal-Infant Survival Everywhere (PROMISE) trials, have been done since the start of the use of maternal cART in pMTCT, in order to review efficacy and safety in the prevention of HIV transmission from mother to child ante-, peri- and postpartum, as well as during breastfeeding.(27–29) Combination ART has become the cornerstone in eradication of paediatric HIV, as proven by near-elimination of vertical transmission in North America and Europe (30), with rates of 1% in Europe(31) and 2% in the USA(32). The WHO defines elimination of MTCT as less than 50 new HIV cases per 100,000 live births over at least a one year period, with a transmission rate of less than 5% in breastfeeding and less than 2% in non-breastfeeding populations.(33) Elimination of MTCT has been confirmed by WHO in Cuba(34) in 2015, as well as Thailand(35), Belarus and Armenia in June 2016.(11)

The 2013 WHO Guidelines for the use of antiretroviral therapy in all pregnant and breastfeeding HIV-infected women (Option B+ and Option B in countries where programmatic difficulties made B+ unfeasible) was a paradigm shift in the prevention of mother-to-child transmission of HIV. It marked the beginning of the use of antiretroviral treatment as a preventative modality to curb transmission from mother-to-child, but also between discordant status partners irrespective of the clinical or immunological status of the HIV-infected mother.(36)

The 2015 WHO Consolidated Guidelines took this a step further with the recommendation of lifelong cART for all pregnant women, including women up until 1 year postpartum, irrespective of maternal immune status or infant feeding choice.(3)

Initiation of and access to sustained cART is the next hurdle in the pMTCT cascade. In South Africa the loss of mothers between HIV testing and cART initiation is 22 – 50%.(24) In 2014, 65% and 77% of pregnant women in the 22 high-burden pMTCT countries were receiving lifelong cART and cART to reduce MTCT respectively. Coverage for MTCT cART has improved, with 10 countries reaching the 80% target, but lifelong cART lags despite all countries but Ivory Coast, Ghana and Nigeria adopting WHO Option B+. Only 4 countries (Namibia, South Africa, Tanzania and Uganda) reached the >80% targets and in 7 countries (Burundi, Cameroon, Chad, Ivory Coast, Democratic Republic of the Congo, Ghana and Nigeria) less than 40% of HIV-infected women accessed lifelong cART.(23)

Barriers to the uptake of cART are multi-factorial and closely linked to all steps in the pMTCT continuum. A 2013 systematic review of articles published between 2000 and 2012 identifying barriers to pMTCT in sub-Saharan Africa, highlighted the key barrier levels: Individual, partner and community, and health system.(2) Stigma was an important factor, present in all 3 tiers, and the major documented reason why women shied away from taking cART in pMTCT, closely seconded by fear of partner disclosure. Individual level barriers included a lack of knowledge about HIV(37), as well as doubts about the efficacy and safety of antiretroviral treatment. Psychological factors involved in the staged grief response to their new HIV-infected status and the subsequent life-long health implications were the main barriers noted. Uptake of cART improves in circumstances where there are partner and community support. Significant health system barriers were staff and medication shortage, as well as problems, including the financial and logistical, with facility access.(2,16,37,38)

Research into adherence after same-day cART initiation shows conflicting results.(39,40) In Malawi it was found that although same-day cART initiation at the HIV-testing-and-counselling centre in the antenatal period increased the total number of women initiated on cART, the 6 month retention in cART care was worse in this group (22% v 8%, p=0.001) than in women who were diagnosed and started on cART at a later stage.(40) The main reasons noted for discontinuing cART were treatment side-effects and the lack of partner support.(38)

1.3.1.5 Duration of cART and viral load monitoring

At least 2 to 3 months on cART are required/recommended in pregnancy to have optimal chance of viral load suppression at delivery and optimal reduction in MTCT.(41) In recent years, the use of the integrase inhibitor, Raltegravir, has been studied and confirmed safe for use and effective in reducing HIV viral load in pregnancy, especially in cases where rapid decline in HIV viral load are needed or conventional drug combinations cannot be used.(42)

There are however 2 distinct groups of women that need to be catered for: Firstly, the women who were diagnosed with HIV prior to pregnancy and are treatment experienced, and secondly, those who are newly diagnosed in pregnancy or known infected, but treatment naive.(41)

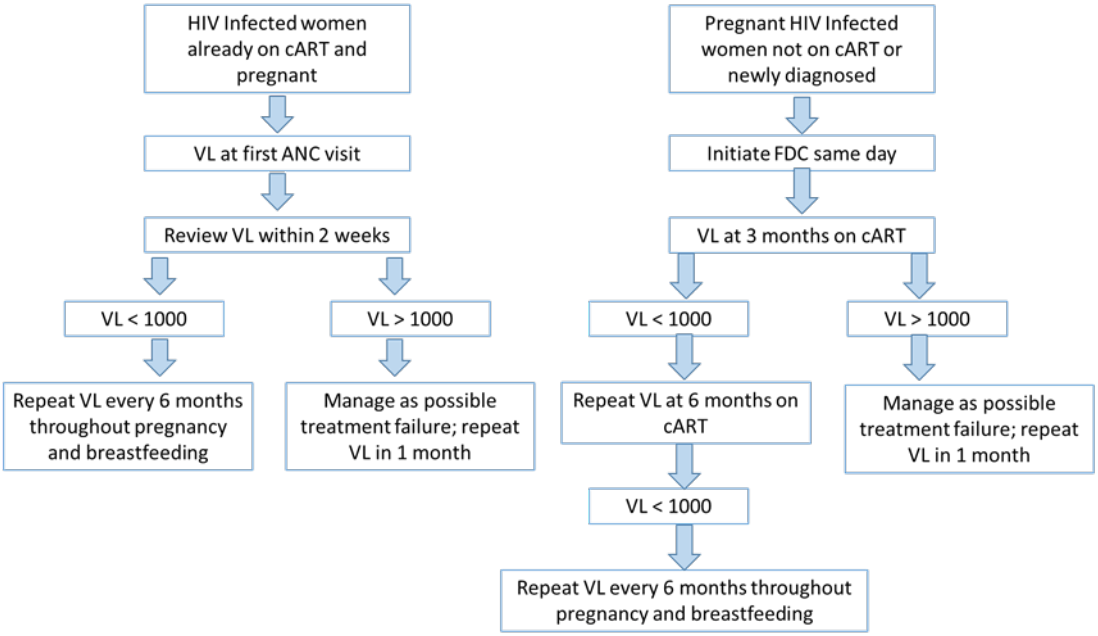

Figure 1.2: Algorithm for viral load monitoring in HIV-positive pregnant women(12)

Adapted from Figure 6 in the 2015 National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (pMTCT) and the Management of HIV in Children, Adolescents and Adults.

It is important that women who are known to be infected have a baseline HIV viral load at first contact with the antenatal service in order to assess treatment efficacy. Women who are suppressed are encouraged to continue treatment, whereas women who are not suppressed (HIV viral load > 1000 copies/ml) are reviewed, counselled regarding adherence and followed up for repeat viral load testing

in 1 month's time in order to assess for suppression and urgently switch to second-line treatment if the viral load is still not suppressed.(41) Further research into the need for earlier switching is needed.

Newly diagnosed HIV-infected women should receive same-day cART initiation (unless cART is contraindicated, in which case Zidovudine (AZT) should be initiated) and viral load testing should be done in 3 months to assess suppression. If the HIV viral load is suppressed treatment must continue, but if it is >1000 copies/ml, counselling on adherence and repeat viral load testing in a month are needed.(41)

Women who are not virally suppressed at delivery or during breastfeeding, should be switched to second line treatment if adherence is confirmed. Other options include multi-antiretroviral treatment prophylaxis for infants, as well as prolonged duration of prophylactic treatment until after breastfeeding cessation. Birth PCR testing of infants can assist in identifying in-utero infected children in this group. 2016 WHO guidelines recommend that women who are at risk of non-suppression should have a HIV viral load test performed 4 weeks prior to delivery, so that appropriate pMTCT measures can be taken.(41)

It is imperative that services for viral load testing should be upscaled in order to attain universal access to efficient viral load testing with a short turn-around time.

1.3.1.6 Delivery

Delivery outside of a healthcare institution is a further risk for vertical HIV transmission, non-institutional delivery is often accompanied by further lapses along the pMTCT cascade, including non-attendance of antenatal care. It is also the last opportunity to identify HIV-infected women in pregnancy and initiate them and their infants on the appropriate multidrug antiretroviral prophylaxis. According to Statistics South Africa (Stats SA) 85% of South African women (88% of those living in the Western Cape) delivered at a health care facility/ were assisted by skilled health care personnel.(18)

1.3.1.7 Interventions to Improve EID and Adherence

The use of cART in a preventative and prophylactic capacity lead to multiple questions regarding the long-term implications, especially with regards to adherence, retention in care and eventual resistance and side effect patterns in ART-exposed HIV-infected and -exposed infants.

Data from the 2016 UNAIDS Global Plan report shows that despite marked improvement in pMTCT strategies the HIV transmission rate increased from 4.7% (4.2% - 5.3%) at six weeks to 8.9% (8% - 10%) at the end of breastfeeding, indicating a problem with non-adherence and loss to follow up, especially during breastfeeding.(11) Available literature has showed that between 25 and 50% of women on cART at delivery may not adhere to care in the postpartum period.(43)

Improved programmes to ensure and measure adherence in the postnatal and breastfeeding period are needed, especially on a national level.(11)

Strategies incorporated to improve retention in care and ongoing adherence to treatment include, integration of pMTCT services into routine Maternal and Child Health (MCH) services whilst aiming to provide centralized holistic care. The use of technological interventions, like cell phone text messages or reminder calls has shown limited improvement in the retention of mothers in care in the first one to three months postpartum.(43) More in-depth research is required in this field.

1.3.2 INFANT CASCADE

1.3.2.1 Infant Prophylaxis

A 2014 systematic review of 7 randomized control trials evaluating the effectiveness of antiretroviral interventions in breastfed infants in low-to-middle income countries found that longer duration of NVP infant prophylaxis (6 weeks) was superior to shorter course (single dose) prophylaxis, and that the vertical transmission increased again once prophylaxis was stopped if breastfeeding was continued. Prolonged single drug prophylaxis was found preferential to prolonged dual drug (AZT and NVP) ART due to the serious side effect profile of AZT.(44) Dual drug prophylaxis is, however, more effective than single drug prophylaxis in preventing mother-to-child transmission in high risk settings (including mother not on cART for > 12 weeks or not virally suppressed; mother newly diagnosed during labour / less than 72 hours after delivery; increased transmission risk during labour, including chorioamnionitis, spontaneous preterm labour and prolonged rupture of membranes > 18 hours (13)).(5)

HIV-infected infants who received prolonged NVP prophylaxis were more likely to develop subsequent resistance to the drug.(44) Antenatal exposure to AZT is associated with more anaemia in new-borns, but at 1 to 6 months of age there is no difference between infants who received infant AZT prophylaxis,

irrespective of antenatal AZT exposure status.(45) Maternal cART initiated prior to pregnancy is associated with a statistically significant higher rate of preterm delivery.(46,47)

Mothers who do not adhere to their own antiretroviral treatment are more likely to non-adhere with infant-prophylaxis.(2) Interventions to identify these women, as well as support them (including strategies like peer-counsellors, community outreach groups and telephonic/messaging reminders) need to be put in place to minimize loss of their infants to diagnosis and future care.

1.3.2.2 Feeding Choice

The 2016 WHO recommendations for infant feeding concluded that exclusive breastfeeding in a virally suppressed mother on cART for the first 2 years of life is the ideal in low-to-middle income countries to minimize infant malnutrition, morbidity and mortality. These guidelines have not yet been adopted in South Africa.(48,49)

1.3.2.3 Timing of EID

In 2015 only 54% of HIV-exposed infants in the 21 priority countries were tested for HIV within the recommended first 2 months of life.(7) This is a disconcerting statistic as evidence shows the accelerated progression of HIV disease in untreated infants leading to 20% mortality by 3 months of age (50), 30% by one year of age, and nearly half by 2 years of age.(11)

The CHER trial showed how the early initiation of cART, at a median age of 7 weeks, induced a 76% reduction in infant mortality, as well as 75% reduction in disease progression. Programmatic schedules where infants received PCR testing at 6 weeks, results at the 10-week immunization visit and then required further time for parental preparation to initiate treatment by approximately 3 months of age, resulted in missing the all-important early initiation cut-off to prevent and reduce infant morbidity and mortality, which peaked at 8 – 12 weeks of age.(10) This necessitated the programmatic evolution to include the birth PCR, to identify and timely treat in-utero infected infants.(10,51)

Birth PCR identifies antenatal HIV infection but not HIV-infections acquired in the postnatal and breastfeeding period. Age-appropriate HIV testing needs to be done 6 – 12 weeks after cessation of

breastfeeding (See Figure 1.3) and at any other time clinically indicated, as breastfeeding can delay the diagnosis of HIV beyond 18 months.(5,12)

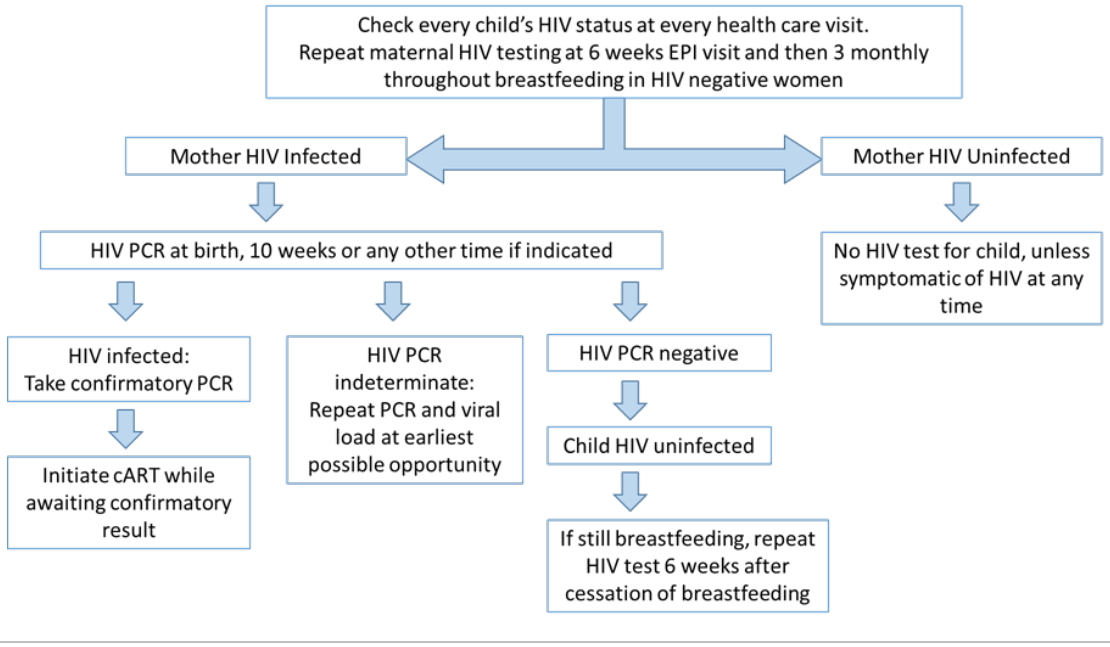

Figure 1.3: Algorithm for HIV testing in children younger than 18 months(12)
Adapted from Figure 2 in the 2015 National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (pMTCT) and the Management of HIV in Children, Adolescents and Adults.

Limitations in successful EID are encountered on various levels. Woldesenbet et al. documented that only 62% of known HIV-exposed infants had a documented exposure risk in the RtHB or mother who disclosed her status. In mothers who self-reported their HIV-positive status, only 49% had a corroboratively completed infant RtHB and 35% of them acknowledged having no intention to request infant HIV-testing at their child's 6-week immunization visit. With the use of provider initiated counselling and testing (PICT), 99% of these children did, however, receive early HIV testing.(52)

Despite EID services being available in more than 95% of all primary healthcare facilities, only 72% of immunization service providers were geared to offer PICT. Furthermore, dependence on poorly completed handheld records, poor continuity and linkage between antenatal and postnatal care, and lack of accountability for tracing of HIV-infected women and their exposed infants perpetuated the loss of children to EID.(52)

Improvement in EID can be attained by educating mothers about the importance and process of pMTCT and maternal treatment adherence, as well as addressing the issues around stigma and discrimination. Provider-initiated HIV testing in children with undocumented and unexposed HIV-status is imperative to discover children who fell through the pMTCT cracks.(52)

The 18-month mother-to-child transmission rate in South Africa in 2014 sat at 4.3% (IQR 3.7 – 5%), with the highest cumulative rate of HIV transmission (3.5%) and death (4% of the cumulative 6.3% mortality at 18 months) occurring in the first 6 months of life.(53) These numbers only further confirm the need for effective follow-up of HIV-exposed, but birth uninfected children.

1.4 HOSPITALIZATION AND DISEASE PROFILE

HIV-infection in children often manifests with non-specific signs and symptoms that mimic common childhood illnesses.(54)

HIV-Infected neonates and young infants present with nondescript pictures that do not follow the traditional WHO Clinical staging patterns. Jeena et al. conducted a year-long prospective study on infants younger than 60 days of age in Durban in 2003/4. HIV-infected infants required hospitalization in almost 13% of cases, and were more likely than HIV-exposed uninfected and HIV-unexposed infants to be diagnosed with pneumonia, sepsis and oral thrush. 3% of the infected infants died due to bronchopneumonia and disseminated candida infection. This study was done in a time of limited ART availability for pMTCT or treatment.(55)

Pneumonia and oral thrush, associated with unexplained malnutrition, as well as repeat hospital admissions in children aged 12 - 18 months of age are highly indicative of HIV-infection. All children presenting with these conditions who have not received HIV-testing, should receive urgent PICT. Opportunistic infections, like Mycobacterium tuberculosis (TB), Pneumocystis jiroveci (PJP) and cytomegalovirus (CMV) are common, associated with high mortality as indicated by post-mortem diagnosis, and should be aggressively diagnosed and appropriately treated.(54,56,57)

The most common conditions for which older children access healthcare or require hospitalization in Cameroon, Nigeria and India are malnutrition, persistent fever, recurrent respiratory tract infections and chronic diarrhoea (longer than 1-month duration).(58)

Pneumonia is the major cause of hospitalization and mortality for HIV-infected children younger than 5 years of age. Pathogens are commonly multiple, including bacterial, viral and opportunistic aetiologies.(59) Influenza, Respiratory syncytial virus (RSV) and Human Metapneumovirus are the most virulent pathogens associated with severe acute respiratory tract infections (SARIs) in South Africa.(60)

Opportunistic infections are common in HIV-infected children. A systematic review in children under 18 years of age evaluating 14 opportunistic infections, showed that TB (30% when disseminated, pulmonary and extra-pulmonary disease were combined), bacterial pneumonia (25%) and oropharyngeal candidiasis (8%) were the most commonly occurring opportunistic infections in HIV-infected children. Initiation of cART effected the most significant reduction in the prevalence of Cryptosporidium diarrhoea, cerebral toxoplasmosis and extra-pulmonary TB.(61)

1.4.1 Mortality

The mortality in young HIV-infected children is high, with 2011 research by Abrams et al. in Johannesburg, South Africa, showing a 19.5% mortality at 6 months follow-up review in HIV-infected children younger than 2 years, who were newly diagnosed, but not yet started on treatment at enrolment. Risk of death was quadrupled when children were diagnosed during hospitalisation, and mortality risk was increased by immunosuppression (CD4 % less than 20%) and malnutrition (Weight-for-age z-score (WAZ-score) less than -2 SD).(62)

Data also shows that antenatally infected infants progress more rapidly and are at higher risk of early death if left undiagnosed and untreated.(10)

AIDS-related deaths in South Africa for children aged 0 – 4 years have decreased by 90% between 2009 and 2015. This achievement is largely due to the reduction in new paediatric HIV-infections through increased access to quality pMTCT services, improved access to paediatric HIV treatment and, thirdly, reduction in maternal AIDS-related mortality with subsequent ability of mothers to remain healthy, care for their children and ensure adherence to child cART treatment.(11)

The 2012-2013 Saving Children Report, released by the South African Medical Research Council (MRC) Unit for Maternal and Infant Health Care Strategies on behalf of Child Healthcare Problem Identification Programme (Child PIP) in June 2016, indicates that for the mentioned period, of the hospitalized patients who died, 17.7% were known HIV-infected, 21.5% were HIV-exposed and 14% had an unknown HIV status. Only 10.5% of children were noted to be on cART and 12.7% who were supposed to be on treatment, did not receive cART. Almost 2000 deaths (17%) in that time-period were in children known to be HIV-infected, where 2405 (21.5%) were in HIV-exposed infants. Even though 35.3% of children who died were HIV-negative, an unacceptably high proportion at almost 25%, had an unknown HIV status.(63)

The main causes of death in hospitalized HIV-infected children were pneumonia (18%), septicaemia (17.2%) and acute diarrhoea or hypovolaemic shock (13.8%). Combined TB disease (including pulmonary, central nervous system and disseminated disease) contributed to approximately 9.7% of deaths. The nutritional state of HIV-infected children who died was worse than those of the other children, with 26.7% being severely malnourished, and 30% underweight for age.(63)

The largest proportion of HIV-infected children died between the ages of 28 days and 1 year (37.4%). HIV-infected children's deaths were 32.4% in 1 – 5-year olds and 25.8% in the 5 to 13-year age group. HIV-infected children who died were also more likely to require longer admissions, 21.3% with admissions of 8-14 days and 17.2% longer than 14 days.(63)

Despite marked improvement in the effectiveness of and access to pMTCT services to assist in the elimination of vertical transmission of HIV from mother to child, an unacceptably high number of children are still becoming infected, experiencing morbidity and mortality associated with delayed diagnosis and treatment initiation, and dropping out of the system through poor adherence and retention in care. It is absolutely imperative that we not only identify the holes and stumbling blocks in the HIV-diagnosis and treatment continuum, but that we actively further investigate and implement measures to ensure its optimal efficacy.

2. STUDY JUSTIFICATION

The current pMTCT cascade with lifelong cART to pregnant women, in conjunction with infant prophylaxis, despite its two-decade evolution with theoretically sound vertical HIV-transmission eliminatory power, is still fraught with obstacles in practice, especially in resource-poor settings. This study aimed to describe HIV-infected children younger than 18 months of age admitted to hospital. By describing their profile, we aimed to highlight problems in the pMTCT cascade, on a systemic and individual level, that should be addressed to assist with elimination of the mother-to-child transmission of HIV.

2.1 GAPS IN THE LITERATURE

Literature currently fails to adequately address certain aspects of the pMTCT cascade. Areas of concern where research is required in resource limited settings are:

- Rates of HIV testing in pregnant and breastfeeding women, especially in settings using rapid HIV assays
- Adherence to treatment and retention in care of HIV-infected women (and their infected children)
- The linking of mother-child pairs to postnatal, including HIV, care
- Rates of infant testing at 9 months and at 6 weeks after cessation of breastfeeding

2.2 RESEARCH QUESTION

Our research question was multifaceted. Firstly, what are the issues/obstacles resulting in the pMTCT cascade not being completed adequately at both the maternal and infant level in infants with confirmed HIV infection? Secondly, how are the HIV-related pages in RtHBs being completed?

2.3 AIMS OF THE STUDY

1. To describe the antenatal and postnatal pMTCT history and current medical condition of HIV-infected children younger than 18 months admitted to Tygerberg Hospital over a 12-month period.

2. To document the availability of clinical information for these patients through an assessment of the RtHB, medical record review and accessing the laboratory database of the National Health Laboratory Service (NHLS).

2.4 OBJECTIVES

1. To describe the antenatal and postnatal care for HIV-exposed children, including
    - Maternal factors
        - Antenatal care attendance
        - Timing of HIV diagnosis
        - CD4 count and HIV viral load
        - Timing of initiation and duration of cART prior to delivery
        - Postpartum access to care
    - Child factors
        - Infant ART prophylaxis
        - Infant feeding
        - Early infant diagnosis (EID) / HIV testing
        - CD4 count and viral load
        - cART initiation

2. To review the clinical condition of HIV-infected young children admitted to hospital, including WAZ-score, CD4 staging, HIV viral load, admission diagnosis, as well as need for intensive care unit (ICU) admission and eventual outcome (discharge/death).

3. To review the availability of relevant information in the pMTCT details section of the Road-to-Health booklet (RtHB) and the in-patient notes, as well as the NHLS database and relevant clinic, maternal obstetric unit or community health centre notes and data.

3. METHODS AND METHODOLOGY

3.1 STUDY SETTING

Tygerberg Hospital is a combined secondary-tertiary hospital in the high HIV-prevalence setting of Cape Town, South Africa. HIV prevalence in South Africa as a whole, as reported by the 2012 Human Sciences Research Council (HSRC) national survey was 12.2% (95% CI: 11.4–13.1%), with 2014 data from the UNAIDS Spectrum estimates, indicating a prevalence of 6.4% (95% CI: 5.3-7.9) for people of all ages in the Western Cape.(21) Tygerberg Hospital services a population of over 2.6 million people in the Western Cape and contains the 319 beds of the Tygerberg Children's Hospital, of which 18 are intensive care and 8 – 12 high care beds (this includes both neonatal and paediatric beds).

3.2 STUDY DESIGN

This study was a prospectively enrolled descriptive study, describing the pMTCT and clinical status of children admitted to Tygerberg Children's Hospital younger than 18 completed months of age, who were newly or previously diagnosed as HIV-infected. A non-random convenience sample of sequential patients admitted to the general and specialist paediatric service at Tygerberg Hospital from 9 February 2015 and 31 January 2016 was used.

3.3 STUDY POPULATION, INCLUSION AND EXCLUSION CRITERIA

All HIV-infected children younger than 18 completed months of age, admitted to the Tygerberg Hospital paediatric service over the one-year study period were eligible for inclusion in the study.

Inclusion criteria

- HIV-infected children: 2 x PCR (DNA/RNA) positive
- Younger than 18 completed months of age

Exclusion criteria:

- No informed consent.
- Child older than 18 months of age during current admission.
- HIV not confirmed as per case definition.
- Previous enrolment in this study during a prior Tygerberg Hospital admission.
- Discharge or death prior to enrolment

3.4 DATA COLLECTION AND MANAGEMENT

All mother-child pairs eligible for enrolment were given a sequential unique case identifier (starting from 001). Participants who consented kept their initial identifier number for the rest of the study.

Data were obtained from maternal interview, review of child clinical notes, including electronic copies on the Tygerberg Hospital Enterprise Content Management system (TBH ECM), the RtHB, as well as the NHLS, that provided access to HIV-PCR, CD4 cell count and HIV-viral load laboratory results. In cases where relevant data were not immediately available at the time of enrolment, later review of laboratory results and clinical notes were done. Missing maternal cART and pMTCT data were telephonically obtained from local clinics/ community health centres, as well as the NHLS and TBH ECM, where possible.

All data were collected onto a study-specific case report form (CRF). See Appendix 4. From the CRF the data was transcribed onto a spreadsheet (Microsoft Excel®).

3.5 DATA ANALYSIS AND STATISTICAL METHODS

Basic descriptive statistics were done with Stata® 14, Excel® 2016 and Statistics Open for All (SOFA) Version 1.4.6, with further statistical analysis in Stata® 14.

Continuous data were not normally distributed and therefore reported as medians and Interquartile ranges. Categorical data were tabulated.

Statistical testing (where permitted) was done using Chi-Square and Fisher Exact testing. A p-value of <0.05 was taken as being statistically significant.

In instances where sample number was insufficient for accurate statistical testing the p-values were noted, but only descriptive statistics were used to avoid biased reporting.

3.6 ETHICAL CONSIDERATIONS

The study was approved by the Health Research Ethics Committee (HREC) of the University of Stellenbosch (Protocol Number S14-09-183). See Appendix 2.

Informed consent for participation in the study was obtained from all mothers. See Appendix 3. In cases where consent was declined, the mother-infant pair was not included in the study.

Strict confidentiality was maintained. Only the principle investigator collected data and no personal identifiers were entered on the CRFs.

The CRFs, along with the accompanying consent form, were kept in a secure case in possession of the principle investigator. A secure copy of the unique study identifiers and patient details was kept on the principle investigator's password-protected computer. Data were stored in protected databases.

4. RESULTS:

4.1 PARTICIPANTS AND SCREENING PROCESS

Seventy eligible participants were identified and 65 were screened. (Figure 4.1)

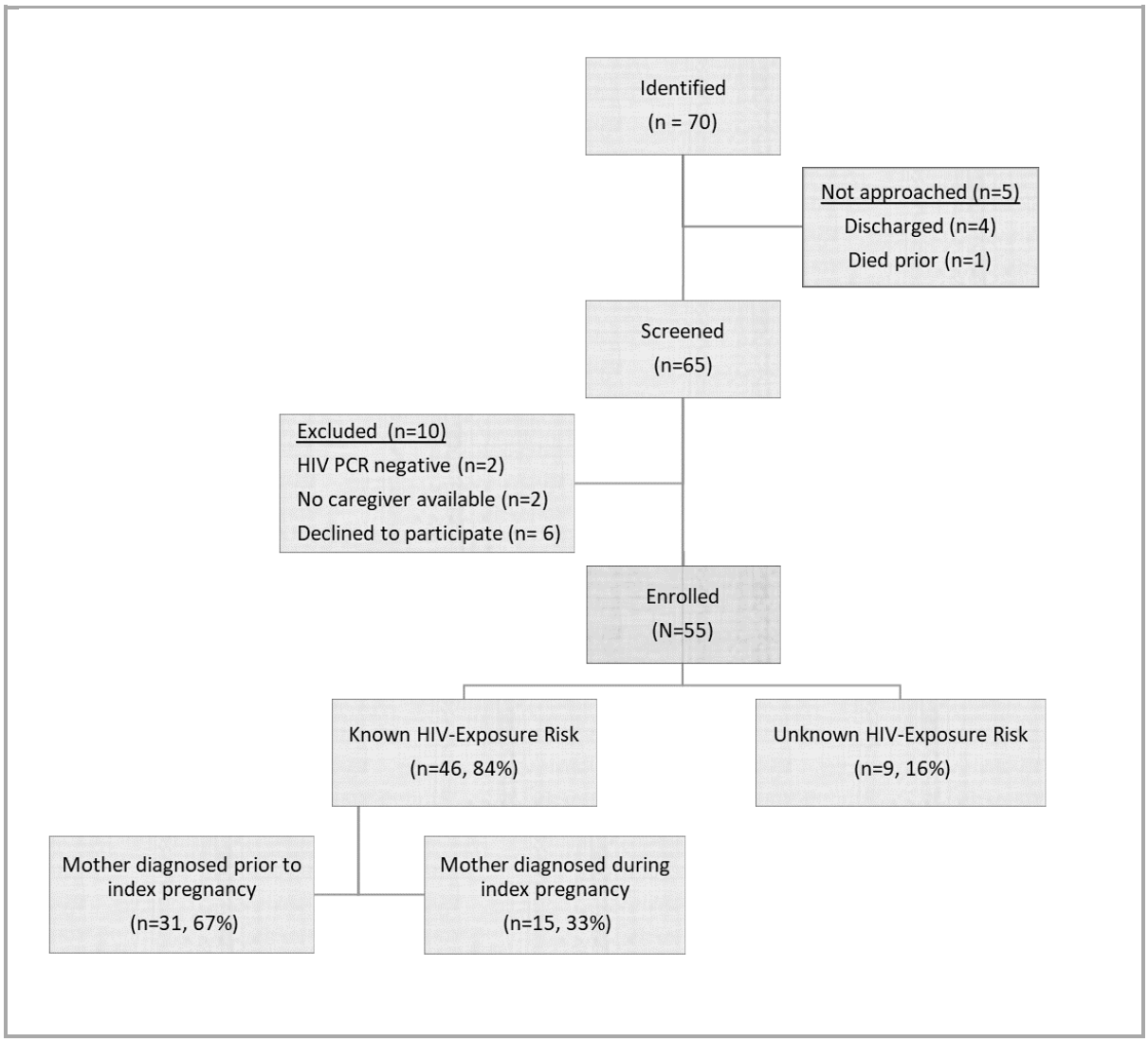

Figure 4.1: Screening and enrolment of mother-infant pairs

Fifty-five mother-infant pairs were enrolled: 46 (84%) women had known HIV transmission risk, with 31/46 (67%) known to be HIV-infected prior to the latest pregnancy and 15/46 (33%) newly diagnosed as HIV-infected during the latest pregnancy. Nine women (16%) were diagnosed with HIV in the postnatal period after provider-initiated testing identified their children as infected (Figure 4.1).

Table 4.1: Maternal diagnosis and cART during pregnancy and the postpartum period

	All Mothers (N = 55)		Known HIV-Exposure Risk (N=46)							Unknown HIV-Exposure Risk (N=9)		P
			Total Known HIV-Exposure Risk (N=46)		Mother Diagnosed Prior to Pregnancy (N=31)		Mother Diagnosed during pregnancy (N=15)		P			
	N/n		N/n		N/n		N/n			N/n		
Age at delivery median(IQR)		28 (24-31)		28 (24.8 - 31)		28 (25 - 31)		27 (24 - 32)	0.716		25 (23 - 31)	0.724
Gravida median(IQR)		2 (2-4)		2 (2-4)		3 (2-4)		2 (1-4)	0.445		2 (2-3)	0.945
Antenatal care attended n(%)		42 (76)		35 (76)		20 (65)		15 (100)	0.008		7 (78)	0.913
First antenatal visit ≥ 28 weeks n(%)		5 (12)		5 (14)		3 (15)		2 (13)			0	
First antenatal visit <14 weeks n(%)		6 (14)		3 (9)		2 (10)		1 (7)			3 (33)	
cART initiated prior to pregnancy and in care				7 (15)		7 (23)		0 (0)				
cART initiated prior to pregnancy and not in Care n(%)				7 (15)		7 (23)		0 (0)				
cART started in Pregnancy (new & previous defaulted) n(%)				23 (50)		11 (35)		12 (80)				
No cART in pregnancy n(%)				9 (20)		6 (19)		3 (20)				
CD4 count during pregnancy in cells/mm3 median(IQR)			41*	280 (176 – 363)	26*	270 (176 – 365)	15	281 (182 – 361)	0.685			
CD4 <200 cells/mm3 n(%)				14 (34)		9 (35)		5 (33)				
CD4 <500 cells/mm3 n(%)				36 (88)		23 (88)		13 (87)				
HIV Viral load log during pregnancy median(IQR)			19*	3.7 (2.8 – 4.8)	14*	4.1 (2.9 - 4.8)	5*	2.7 (2.4 – 4.3)	0.392			
Prior cART, in Care			4	3.6 (2.7 – 5)	4	3.6 (2.7 - 5)						
cART started in Pregnancy			10	3.3 (2.8 – 4.8)	7	3.6 (2.8 – 5.1)	3	2.7 (2.2 – 4.8)				
No cART			5	4.1 (3.2 – 4.7)	3	4.6 (4.1 – 4.8)	2	3.2 (2.7 – 3.7)				
Mode of delivery n(%)	55		46		31		15			9		
Vaginal deliveries in health facility n(%)		33 (60)		25 (54)		19 (61)		6 (40)			8 (89)	
Caesarean section n(%)		16 (29)		15 (33)		8 (26)		7 (44)			1 (11)	
Birth before arrival n(%)		6 (11)		6 (13)		4 (13)		2 (13)			0	
Mothers on cART at delivery n(%)				25 (54)		13 (42)		12 (80)	0.015			
Time on cART at delivery in months median(IQR)			25*	2 (1 - 7.5)	13*	2 (0.5 – 48)	12*	0.5 (1 – 3)	0.176			
Maternal cART status enrolment n(%)	55		46		31		15		0.583	9		
Prior cART, in Care		22 (40)		22 (48)		13 (42)		9 (60)				
Prior cART, not in Care		15 (27)		15 (33)		11 (35)		4 (27)				
No cART		14 (26)		7 (15)		5 (16)		2 (13)			7 (78)	
cART initiated during child admission		4 (7)		2 (4)		2 (6)		0			2 (22)	
Latest CD4 count in cells/mm3 median(IQR	52*	291 (178 – 413)	46	281 (167–394)	31	280 (166 - 384)	15	281 (182 - 443)	0.631	6*	340 (307-816)	0.165
Latest HIV Viral Load log median (IQR)	31*	4.2 (2 - 4.9)	28*	3.9 (1.9 – 4.9)	21*	4.1 (1.9 – 5)	7*	3.7 (LDL – 4.8)	0.770	3*	4.8 (4.3 – 4.9)	0.349
Latest HIV Viral load LDL n(%)			28*	6 (21)	21*	4 (19)	7*	2 (29)	0.306			

cART – combination antiretroviral therapy, CD4 – Cluster of differentiation 4, HIV – Human immunodeficiency virus, IQR – interquartile range, LDL – lower than detectable limit

* Discrepancy in denominator value in concordance with availability of data for the specific parameter

4.2 MATERNAL DIAGNOSIS AND CARE

4.2.1 Timing of maternal HIV diagnosis, attending antenatal care and antiretroviral therapy use

4.2.1.1 Mothers identified prior to and during pregnancy

Forty-six women were known to be HIV-infected during the pregnancy of the enrolled child: 31 (67%) were diagnosed prior to the pregnancy and 15 (33%) during pregnancy. The median maternal age at delivery was 28 years (Interquartile range (IQR) 25 – 31). The median gravidity for women diagnosed with HIV prior to pregnancy was 3 (IQR 2-4) and during pregnancy 2 (IQR 1-4), p = 0.445. Seventy-six percent (35/46) of women with HIV-infection diagnosed prior to or during pregnancy attended antenatal care. The majority 27/35 (77%) presented for antenatal between 14 and 28 weeks gestation, but 5/35 (14%) booked after 28 weeks' gestation (Table 4.1).

Women who initiated or reinitiated cART during pregnancy (23/46, 50%) had a median duration on cART of 1 month (IQR 0 – 3, n=19), while those previously initiated on cART were on treatment for a median of 48 months (IQR 8 – 72, n=6), (table 4.1). One woman received only intrapartum prophylaxis (stat and 3 hourly AZT, sdNVP + Tenofovir/Emtricitabine (TDF/FTC)).

Due to the fact that we used verbal report of any antenatal antiretroviral use, we did not ascertain whether monotherapy with AZT were provided to women who did not initiate cART. We also did not explore the reasons for the non-initiation of therapy. We documented one clear case of health systems failure: In this case, a woman who tested negative early in pregnancy had a CD4 count done when she presented with preterm labour to a local facility, we assume this was in response to a reactive point of care test, however this was not clearly documented. No further tests were performed and no maternal or infant ART was provided. At 3 months of age the infant presented with severe pneumonia requiring Paediatric intensive care unit (PICU) admission and was diagnosed with HIV infection.

Mothers who previously defaulted cART were less likely to restart cART in the current pregnancy (p=0.01). Knowledge of partner status, disclosure and family support as reported by women at enrolment, were not predictive of cART not being initiated. (Table 4.2)

Infants of mothers not on cART at conception were delivered at late preterm gestation of 36 weeks (IQR 33-40): Where mothers initiated cART during pregnancy, the median birth gestation was 35 weeks (IQR 33-38) versus 40 weeks (IQR 34 – 40) where mothers did not initiate cART, p=0.068 (Table

4.2). Just over half (54%) of women known with HIV delivered vaginally at a healthcare facility and 13% delivered at home. Approximately a third (30%) had caesarean sections. (Table 4.1)

4.2.1.2 Mothers identified after pregnancy

The 9 women diagnosed postpartum had a median age of 25 years (IQR 23 - 31) and gravidity of 2 (IQR 1-4). Seven (78%) attended antenatal care, all initiating antenatal care prior to 28 weeks of gestation (Table 4.1). Infants were delivered at a median gestation of 39 weeks (IQR 34 - 40) (Table 4.4), and all except one were born via vaginal delivery at a healthcare facility. (Table 4.1)

4.2.2 Maternal Disease Severity (Table 4.1)

Women were severely immune suppressed in pregnancy: The median CD4 cell count was 280 cells/mm^3 (IQR 176 – 363, N = 41), with 34% (14/41) having CD4 cell counts less than 200 cells/mm^3; 43% (10/23) of those started on cART during pregnancy. (Table 4.4)

An antenatal HIV viral load was known for 13 (28%) women; an additional 4 (9%) women had viral load tests within the 7 days after delivery. The median absolute HIV viral load log during pMTCT was 3.7 (2.8 – 4.8). None of the women with HIV viral loads available during pregnancy were virally suppressed (HIV viral load <50 copies/ml). (Table 4.1)

Three women were treated for tuberculosis during pregnancy and 3 women were diagnosed with syphilis. All 3 infants exposed to tuberculosis received Isoniazide (INH) prophylaxis as indicated. None of the women with syphilis (all diagnosed HIV-infected prior to pregnancy) completed treatment: 1 (33%) was partially treated and 2 (67%) received no treatment. Two (67%) of their children received treatment postnatally.

At enrolment the median CD4 count remained low, 280 cells/mm^3 (IQR 167 – 394). Six of the 28 (21%) women with known HIV-transmission risk with an available HIV viral load at child admission, were virally suppressed (HIV VL LDL): 4/21 (19%) of women diagnosed prior to pregnancy and 2/7 (29%) diagnosed during pregnancy. All these women were on cART at some point, but 2 women diagnosed prior to pregnancy defaulted treatment subsequent to the suppressed viral load. (Table 4.1)

4.2.3 Maternal Retention in care (Table 4.1, 4.2 and 4.3)

Of the 31 women known with HIV prior to pregnancy, 14 (46%) were on cART prior to pregnancy but only 7 were in care at the time of pregnancy. Although 76% (35/46) of women known with HIV attended antenatal care, only two (29%, N=7) women who defaulted previously initiated cART attended antenatal clinic. At delivery, 42% (13/31) of women previously known to be HIV-infected and 80% (12/15) of women diagnosed during pregnancy were on lifelong cART. (Table 4.1)

However, at the time of enrolment only 22/46 (48%) were on cART and in care. Fifteen (33%) were previously on cART, but had defaulted treatment: 11/31 (35%) diagnosed prior to pregnancy, and 4/15 (27%) diagnosed during pregnancy. Four women interrupted cART during pregnancy, all known with HIV prior to pregnancy, and 12 women interrupted cART in the postpartum period, 5 (38%) diagnosed during pregnancy.

Table 4.2: Comparing mothers who initiated antiretroviral therapy in pregnancy and those who did not

	Not on cART at conception (N=39)		**Started or restarted cART in pregnancy** (N=23)		**cART not started** (N=16)		**P**
	N/n		N/n		N/n		
Age median(IQR)		28 (24 – 32)		28 (23 – 33)		27 (25 – 32)	0.987
Antenatal care attended n(%)		29 (74)		20 (87)		9 (56)	0.031
Booked after 28 weeks gestation n(%)	29*	5 (17)	20*	4 (20)	9*	1 (11)	0.558
Previously defaulted cART n(%)		9 (23)		2 (9)		7 (44)	0.011
Gestation at delivery median(IQR)	38*	36 (33 – 40)		35 (33 – 38)		40 (34 – 40)	0.068
Gravidity median(IQR)		3 (2 – 4)		2 (2 – 4)		3 (2 – 4)	0.361
CD4 count in cells/mm3 median(IQR)	35*	280 (176 – 361)		240 (176 – 350)	12*	308 (221 – 453)	0.175
WHO immunosuppression classification: n(%) **Mild: 350 – 499 cells/mm3**		6 (17)		4 (17)		2 (17)	
Advanced: 200 – 349 cells/mm3		11 (31)		7 (30)		4 (33)	
Severe < 200 cells/mm3		13 (37)		10 (44)		3 (25)	
Viral load log in pMTCT median(IQR)	15*	3.7 (2.8 – 4.8)	10*	3.3 (2.8 – 4.8)	5*	4.1 (3.2 – 4.7)	0.807
Tuberculosis in pregnancy n(%)		2 (5)		2 (9)		0	0.226
Syphilis in pregnancy n(%)		3 (8)		2 (9)		1 (6)	0.778
Same site cART and antenatal care n(%)	25*	18 (72)	20*	16 (80)	5*	2 (40)	0.075
Single n(%)	38*	18 (47)		13 (57)	15*	5 (33)	0.162
Grant n(%)	33*	15 (46)	18*	8 (44)	15*	7 (47)	0.898
Contraception n(%)	35*	16 (46)	20*	11 (55)	15*	5 (33)	0.245
Partner HIV status known n(%)	38*	19 (50)	23*	12 (52)	15*	7 (47)	0.640
Child status disclosed to partner/family n(%)	38*	25 (66)	23*	15 (65)	15*	10 (67)	0.927
Partner involved in child HIV care n(%)	26*	16 (62)	14*	9 (64)	12*	7 (58)	0.756
Family involved in child treatment n(%)	25*	16 (64)	14*	10 (71)	11*	6 (55)	0.383

cART – combination antiretroviral therapy, CD4 – Clusters of differentiation 4, HIV – Human immunodeficiency virus, IQR – Interquartile range, pMTCT – prevention of Mother-to-Child transmission, WHO – World Health Organisation

* Discrepancy in denominator value in concordance with availability of data for the specific parameter

Table 4.3: Comparing mothers who interrupted cART prior to enrolment with those who did not

	All started on cART (N=37)		cART prior, in Care (N=22, 59%)		Defaulted prior cART (N=15, 41%)		p
	N/n		N/n		N/n		
Time on cART between booking and delivery in months median(IQR)	25*	2 (1 – 7.5)	17*	3 (1 – 18)	8*	0.5 (0 – 2.5)	0.030
Gestation at initial visit	30*		21*		9*		0.082
< 14 weeks		2 (7)		2 (10)		0	
14 to <28 weeks		24 (80)		18 (86)		6 (67)	
≥ 28 weeks		4 (13)		1 (5)		3 (33)	
Gestation at delivery in weeks median(IQR)	36*	37 (34.5 – 40)	21*	37 (35 – 38.5)		37 (34 – 40)	0.710
Gravidity median(IQR)		2 (2 – 4)		2 (2 – 3)		3 (1 – 4)	0.285
Defaulted prior to pregnancy n(%)		5 (14)		2 (9)		3 (20)	0.341
Started cART in pregnancy for first time n(%)		20 (54)		11 (50)		9 (60)	0.549
Started cART prior to pregnancy, incl. defaulters n(%)		15 (41)		9 (41)		6 (40)	0.956
Started postpartum n(%)		2 (5)		2 (9)		0	0.230
Tuberculosis in pregnancy n(%)		3 (8)		2 (9)		1 (7)	0.791
Syphilis in pregnancy n(%)		2 (5)		0		2 (13)	0.078
Home delivery n(%)		5 (14)		4 (18)		1 (7)	0.314
Partner HIV status known n(%)		18 (49)		10 (46)		8 (53)	0.374
Child status disclosed to partner/family n(%)		26 (70)		14 (64)		12 (80)	0.285
Partner involved in child treatment n(%)	26*	15 (58)	15*	7 (47)	11*	8 (72)	0.184
Family involved in child treatment n(%)	25*	17 (68)	15*	10 (67)	10*	7 (70)	0.861
Latest maternal CD4 count in cells/mm3 median(IQR)		261 (162 – 375)		262 (149 – 443)		261 (166 – 356)	0.901
Latest maternal HIV viral load log median(IQR)	23*	2.9 (LDL – 5)	14*	2.8 (LDL – 4.4)	9*	5 (1.5 – 5.1)	0.282
HIV viral load LDL	23*	6 (26)	14*	4 (29)	9*	2 (33)	

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, IQR – Interquartile range, LDL – Lower than detectable limit

* Discrepancy in denominator value in concordance with availability of data for the specific parameter

4.2.4 Maternal Sociodemographic context

Fifty-two percent of women (28/54) were single. Only 13% (7/54) were employed and 50% (24/48) accessed money through the social grant system.

Knowledge of partner status was poor, with less than half of women (47%, 21/47) knowing their partner's HIV status and the child's HIV status only being disclosed in 67% of cases (30/45). Family was involved in the HIV treatment of the child in 68% (21/31) and partners in 56% (18/32) of cases.

Fifty-nine percent (17/29) of previously HIV-infected women and 46% (6/13) of index pregnancy diagnosed women used contraception postnatally.

4.3 PMTCT, DIAGNOSIS, CLINICAL FEATURES AND ACCESS TO CART OF THE CHILDREN

4.3.1 PMTCT continuation (Table 4.4)

Sixty percent of the children (33/55) were male with a median birthweight of 2525g (IQR 2025-2890) and a median gestation at birth of 37 weeks (IQR 34-40). The median birthweight of known exposure-risk children was 2440g (IQR 2025-2920) versus 2595g (IQR 2180 - 2830) in those with unknown HIV-exposure risk, p=0.972. Birth gestation was 37 weeks (IQR 34-40) in known exposure-risk versus 39 weeks (34-40) in unknown exposure-risk children, p=0.364. Thirteen infants (87%, N=15), whose mothers were diagnosed HIV-infected during the index pregnancy, breastfed exclusively during the first six months, while 16/31 infants (52%) whose mothers were HIV-infected prior to pregnancy opted to exclusively formula feed in the first 6 months. Children with unknown HIV-exposure risk breastfed exclusively during the first 6 months of life in 87% (8/9) of cases.

4.3.2 HIV diagnosis (Table 4.4, 4.5)

The majority of infants had in utero or early postpartum transmission, with 59% (24/41) having their first positive PCR prior to completing postpartum ART prophylaxis. A third of children with known HIV-exposure (15/46) had the first positive PCR in the first 28 days of life. Ten (22%) were diagnosed at their community health centre/clinic at a median age of 50 days (IQR 42 – 93), while the rest were diagnosed in hospital during acute illness or in the neonatal period, at 54 days (IQR 3-108). Infants of mothers identified prior to pregnancy were diagnosed at a median age of 56 days (IQR 19-134), while infants of mothers diagnosed during pregnancy were 46 days (IQR 0-94) old at diagnosis, p=0.27.

Seven children (15%) were only diagnosed after 6 months of age (180 days) of age, 4 of these children (57%) with a previously documented non-reactive HIV-PCR. One child had 3 negative HIV-PCRs prior to the reactive test.

Children with unknown HIV-exposure risk were diagnosed HIV-infected at a median age of 286 days (200-369).

Table 4.4: Infant HIV prevention, feeding choice, HIV diagnosis and time to initiation of therapy

	All Children (N=55)		Known HIV-Exposure Risk (N=46)		Unknown HIV-Exposure Risk (N=9)		p
	N/n		N/n		N/n		
Male n(%)		33 (60)		31 (67)		2 (22)	0.011
Birthweight in gram median(IQR)	54*	2525 (2025-2890)	45*	2440 (2025 – 2920)		2595 (2180 - 2830)	0.972
Gestational age at birth in weeks median(IQR)	53*	37 (34-40)	44*	37 (34 – 40)		39 (34 - 40)	0.364
Feeding choice during initial 6 months n(%)							0.060
Exclusive breastfeeding		29 (53)		22 (48)		7 (78)	0.721
Exclusive formula feeding		18 (33)		18 (39)		1 (11)	
ARV prophylaxis n(%)			45*	42 (93)			
Age at HIV diagnosis in days median(IQR)		59 (6-184)		54 (3 – 106)		285 (200-369)	0.001
Age at cART initiation in days median (IQR)		107 (24 – 205)		76 (20 – 178)		286 (190 – 392)	<0.001
Time from HIV diagnosis to cART initiation in days median(IQR)		8 (5-27)		9 (5 – 30)		5 (2-8)	0.039
Time from HIV Diagnosis to admission in days median(IQR)	45*	47 (1.5-187.5)	40*	56.5 (3 – 285.5)	5*	1 (0 – 14)	0.039
Children on ART prior to admission n(%)				20 (43)			
Time from cART initiation to admission in days median(IQR) those still on cART			15*	105 (29 – 360)			
Age at start (all previously initiated) median(IQR)			20*	70 (14 – 110)			
First CD4 % median(IQR)	49*	23.7 (17.9 – 36.3)	42*	23.4 (17.7 – 36.5)	7*	24.7 (20.5 – 33.3)	0.842
WHO CD4% Immunodeficiency Staging n(%)	49*		42*		7*		
Mild immunodeficiency (≤11 months: 30-35%; 12-35 months: 25-30%)		6 (12)		4 (10)		2 (29)	
Advanced Immunodeficiency (≤11 months: 25-29%; 12-35months: 20-24%)		5 (11)		3 (7)		2 (29)	
Severe immunodeficiency (≤11 months: <25%; 12-35 months: <20%)		23 (47)		20 (48)		3 (43)	
First HIV Viral load log median(IQR)	50*	5.7 (4.2 – 6.4)	42*	5.5 (4.2 – 6.3)	8*	6.3 (5 – 6.7)	0.161
cART status during admission n(%)							0.034
Newly Diagnosed		25 (45)		17 (37)		8 (89)	
Prior cART, In Care		15 (27)		15 (33)		0 (0)	
Prior cART, Not in Care		5 (9)		5 (11)		0 (0)	
Prior Diagnosis, No cART		10 (18)		9 (20)		1 (11)	

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, IQR – Interquartile range, WHO – World Health Organization
* Discrepancy in denominator value in concordance with availability of data for the specific parameter

4.3.3 Clinical disease severity and causes of hospitalization at enrolment (Table 4.7, 4.8)

The median age at hospital admission during enrolment was 174 days (IQR 90 – 381): Children with known exposure were younger (median age 138 days) than children without antenatal identification (median 282 days), p=<0.001.

Children had advanced HIV: 80% (44/55) had WHO Stage 3 and 4 clinical disease. Malnutrition was prevalent, the median weight-for-age z-scores was -2.4 (IQR -4.1 to -1.8) in the known exposure-risk group and -3.4 (IQR -4.2 to -2.3) in the unknown risk group, p = 0.228. Weight-for-height could not be assessed due to poor recording of height.

Almost half (47%, 23/49) of children had severe immunosuppression according to WHO immunodeficiency classification, with 69% (34/49) having some degree of immunosuppression.

The 3 most common admission diagnoses were pneumonia (45%, 25/55), gastroenteritis (36%, 20/55) and severe acute malnutrition (40%, 22/55). Ten of the 55 children (18%) were diagnosed with tuberculosis (6 cases were pulmonary and 4 disseminated TB).

Eighty-seven blood cultures were done in 37 children of which 10 were positive (we did not differentiate hospital and community acquired organisms). No cases of pneumococcal disease were confirmed. Forty-three respiratory viral panels were performed on 22 patients resulting in 31 positive results in 17 different patients. Cytomegalovirus (CMV) was common (24 isolates in 12 patients), and 25 CMV viral loads were done. Five patients had an initial CMV viral load log > 5, indicating significant viraemia that could be indicative of disease requiring therapy. A variety of other viruses were found, but only 1 case of influenza A and 1 case of influenza B. Two children tested positive for pneumocystis pneumonia and one had a positive gene Xpert and positive microscopy for acid fast bacilli (AFB) on gastric washing. Only one of the 26 urine cultures performed grew a bacterial pathogen, and only one of the 21 cerebrospinal fluid cultures were positive yielding an Acinetobacter baumanii (hospital acquired). (Table 4.8)

Thirteen children (24%) were admitted to the PICU; 92% (12/13) known to be HIV-exposed. Their median age on admission was 96 days (IQR 58 – 229), with a median age at HIV diagnosis of 67 days (IQR 44-214). Just over half (54%, 7/13) were newly diagnosed HIV-infected, while a third (31%, 4/13) were previously diagnosed but had not initiated cART. Two children were previously started on cART

(at age 15 and 105 days respectively). The majority of children admitted to PICU were markedly immune suppressed, with 54% (7) having severe immunodeficiency according to WHO CD4 Immunodeficiency Staging. The children had high HIV viral loads (median HIV viral load Log 5.6 (IQR 5.4 – 6.7)) and were underweight for age (median WAZ-score -2.57 (IQR -3.39 - -2.37)). Pneumonia was the principal reason for admission (77%). Three children in this group died (23%) but PICU admission was not predictive of death in the cohort. (Table 4.9)

4.3.4 Access to therapy (Table 4.4, 4.5, 4.6 & Figure 4.2)

The median time from HIV diagnosis to cART initiation was 9 days (IQR 5-30) in children with known HIV-exposure risk versus 5 days (IQR 2-8) in those with unknown exposure risk, p=0.039. There was a statistically significant difference in the duration from diagnosis to cART initiation between the groups: children initiating therapy as outpatients started therapy at a median of 33 days (IQR 28-63) after the first positive PCR, while hospitals initiated cART within 8 days (IQR 5-15) of the first positive PCR, p=0.005. Twenty children initiated therapy prior to enrolment of whom 5 were lost to follow up. There were no risk factors identified that predicted child default of treatment. (Table 4.6)

4.3.5 Outcomes (Table 4.7, 4.10)

Seven children (13%) died in hospital. These children were older [median age 350 days (IQR 68-511)], and diagnosed later [median 200 days (IQR 43-335)]. They died after a median of 30 days in hospital, 53 days after their HIV diagnosis and 33 days on cART. Three children were previously diagnosed and not on cART at hospitalization: 2 never started cART and one defaulted. All but one child (who died prior to re-initiation of previously defaulted cART) were started on treatment during admission.

Children who died tended to be severely underweight-for-age [median WAZ-score -3.3 (IQR -5.45 to -2.93), and although they had a low median CD4% of 22.9% (IQR 20.5 – 29.3) and high viral loads [median log 6.2 (5.6 - 6.5)], these were not significantly different from children who survived.

Pneumonia was the most commonly noted cause of death (n=4, 31%) with concomitant severe acute malnutrition as a secondary contributor (n=6, 46%). Three (43%) of the children who died were admitted to PICU for a median duration of 27 days (IQR 4 – 39). Median duration of hospitalization was 30 days (IQR 13 – 54). There were no factors that predicted deaths in this study.

HIV infection was associated with long hospitalization, the median duration was 17 days (IQR 10-31days), similar in those with known (23 [IQR 12 – 30.5] days) versus unknown exposure-risk (15.5 [IQR 10 – 32.3] days), p=0.67. (Table 4.7)

Table 4.5: HIV diagnosis and treatment initiation for children with known HIV-exposure risk

	All children with known HIV-exposure risk (N=46)		**Diagnosed in Primary Health Care Clinic** (N=10, 22%)		**Hospital Diagnosed** (N= 36, 78%)		
	n(%)	Days Median(IQR)	n(%)	Days Median(IQR)	n(%)	Days Median(IQR)	**p**
Age at HIV diagnosis		54 (3-106)		49.5 (42-93)		54 (2.5-107.5)	0.989
Diagnosed by 28 days	14 (30)	0.5 (0-3)	1 (10)	1	13 (36)	1 (0-3)	
Diagnosed by 42 days	18 (39)	2 (0-19)	4 (40)	41 (20-42)	14 (39)	1.5 (0-3)	
Diagnosed by 98 days	33 (72)	42 (1.5-56.5)	8 (80)	42.5 (41-56.5)	25 (69)	19 (0.5-57.5)	
Diagnosed by 180 days	39 (84)	46 (2-91)	9 (90)	43 (41-75)	30 (83)	46.5 (2-91)	
Time from diagnosis to cART initiation		9 (5-30)		32.5 (28-63)		8 (5-14.5)	0.005
Time to cART initiation by diagnosis age 28 days	14 (30)	5 (4-8)	1 (10)	2	13 (36)	5 (4.5-8.5)	
42 days/6 weeks	18 (39)	6.5 (5-17)	4 (40)	31.5 (16-69)	14 (39)	5.5 (5-8)	
98 days/ 14 weeks	33 (72)	8 (5-30)	8 (80)	32.5 (29-81)	25 (69)	7 (5-14)	
180 days/ 6 months	39 (84)	9 (5-30)	9 (90)	33 (29-84)	30 (83)	7.5 (5-14)	

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, IQR – Interquartile range

Table 4.6: Children initiated on cART prior to admission

	All on previous cART (N = 20)	**On cART, in care** (N=15)	**Defaulted cART** (N=5)	**P**
HIV diagnosis age in days median(IQR)	48 (3 – 83)	56 (2-91)	42 (2 – 68)	0.432
Diagnosed in Hospital n(%)	13 (65)	11 (73)	2 (40)	0.176
Time to cART initiation in days median(IQR)	14 (5 – 30)	8 (5-30)	28 (12 – 122)	0.115
Maternal cART and care default at any time prior to child admission n(%)	9 (45)	6 (40) Additional 3 moms never on cART	3 (60)	0.436
Immunization UTD n(%)	12 (60)	9 (60)	3 (60)	1

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, IQR – Interquartile range, UTD – Up to date

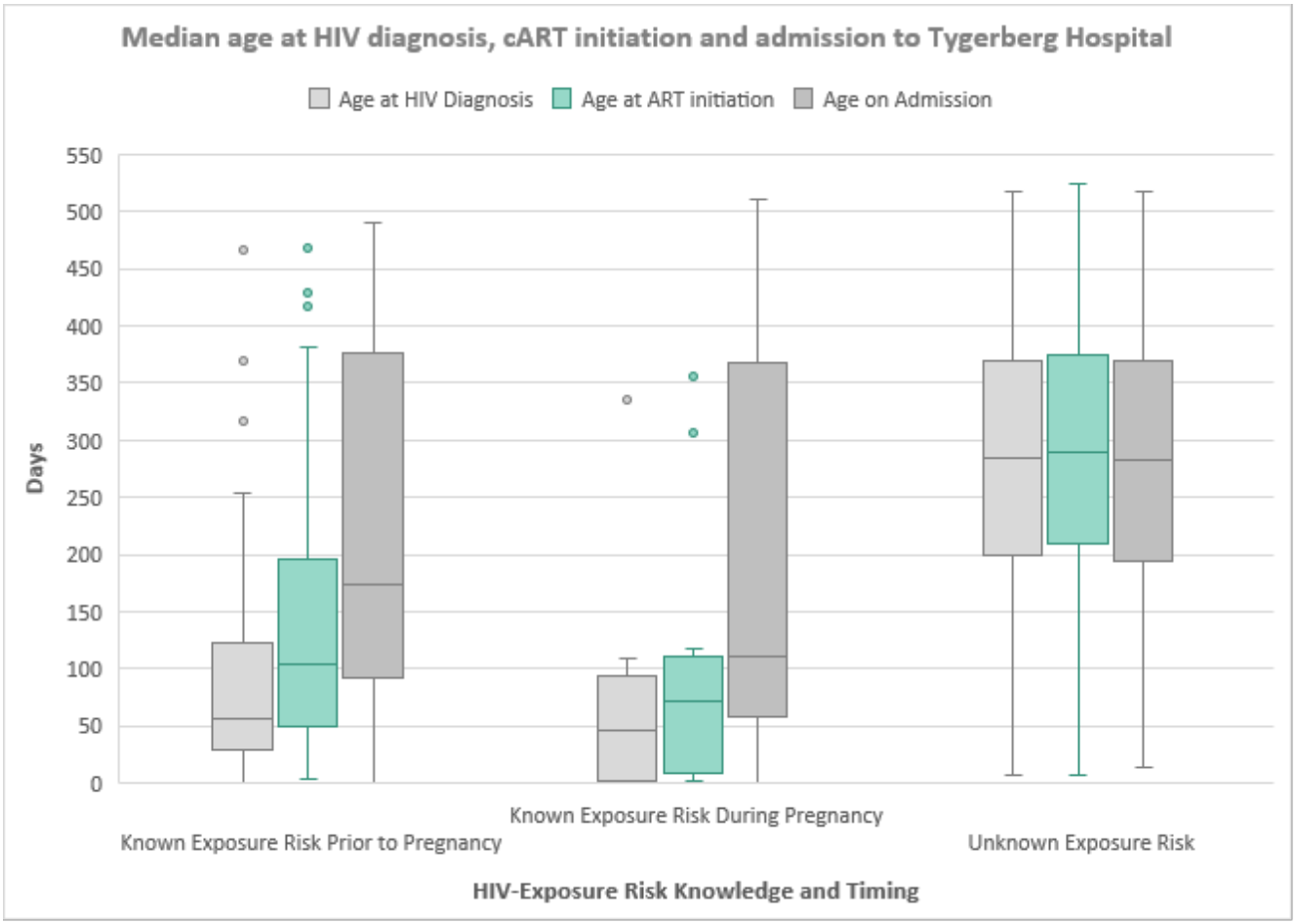

Figure 4.2: Median age at HIV diagnosis, cART initiation and admission to Tygerberg Hospital by HIV-exposure risk knowledge and timing

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Table 4.7: Clinical profile of HIV-infected children at enrolment

	All Children (N=55)		Known HIV-Exposure Risk (N=46)		Unknown HIV-Exposure Risk (N=9)		P
	N/n		N/n		N/n		
Age on admission in days median(IQR)		174 (90-381)		138 (68 – 382)		282 (180 – 389)	<0.001
Diagnosed during current admission n(%)		25 (46%)		17 (37)		8 (89)	
Admission weight in gram median(IQR)		5282 (2900 - 6215)		5236 (2800 - 6129)		6000 (3815 - 6543)	0.562
Weight-for-Age Z-score median(IQR)		-2.6 (-4.0 to -1.9)		-2.4 (-4.1 to -1.8)		-3.4 (-4.2 to -2.3)	0.228
WHO Stage III + IV n(%)		44 (80)		36 (78)		8 (89)	0.195
Latest CD4 % median(IQR)	49*		42*	27.7	7*	24.7	0.731
WHO CD4% Immunodeficiency Staging **n**(%)	49*		42*		7*		
Mild immunodeficiency (≤11 months: 30-35%; 12-35 months: 25-30%)		6 (12)		4 (10)		2 (29)	
Advanced Immunodeficiency (≤11 months: 25-29%; 12-35months: 20-24%)		9 (18)		7 (17)		2 (29)	
Severe immunodeficiency (≤11 months: <25%; 12-35 months: <20%)		17 (35)		15 (36)		2 (29)	
Latest HIV viral load log median(IQR)	50*	5.5 (4.1 – 6.3)	42*	5.4 (3.9 – 6.2)	8*	6.3 (5 – 6.7)	0.095
cART prior, in Care	14	3.9 (2.2 – 5.4)	14	3.9 (2.2 – 5.4)			
cART prior, not in Care	5	5.9 (5.4 – 6.7)	5	5.9 (5.4 – 6.7)			
Previously Diagnosed, no cART	9	6.2 (5.2 – 6.6)	8	6 (5.2 – 6.5)	1	6.7	
Newly Diagnosed	22	5.5 (4.2 – 6.4)	15	5.4 (4.2 – 6)	7	6.2 (4.1 – 6.7)	
Latest Viral load LDL n(%)	50*	3 (6)	42*	3 (7)	8*		
Most common diagnoses n(%)							
Pneumonia		25 (45)		22 (48)		3 (33)	0.425
Gastroenteritis		20 (36)		17 (37)		3 (33)	0.836
Severe acute malnutrition		22 (40)		17 (37)		5 (56)	0.191
Tuberculosis		10 (18)		8 (17)		2 (22)	0.731
Admitted to ICU n(%)		14 (25)		13 (28)		1 (11)	0.280
ICU admission duration in days median(IQR)	14*	8 (4.8-22.5)	13*	8 (.5 – 18.5)	1*	21	0.122
Duration of hospital admission in days median(IQR)		17 (10-31)		15.5 (10 – 32.3)		23 (12 – 30.5)	0.674
Died n(%)		7 (13)		5 (11)		2 (22)	0.321

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, ICU – Intensive Care Unit, IQR – Interquartile range, LDL – Lower than detectable limit, WHO – World Health Organization

* Discrepancy in denominator value in concordance with availability of data for the specific parameter

Table 4.8: Investigations done and organisms found

Blood cultures		
	Total Number	**Number of patients tested**
Blood culture done	83	37
Blood culture positive	10	6
MSSA	2	2
MRSA	2	1
ESBL Klebsiella pneumoniae	1	1
E coli	1	1
Serratia Marcescens	1	1
Enterobacter cloacae	2	1
Candida Albicans	1	1
Respiratory viral panel on NPA or Tracheal aspirate		
	Total Number	**Number of patients tested**
NPA/TA done	43	22
Respiratory viral panel positive	31	17
CMV	24	12
Serum CMV VL done	25	18
1st VL positive Log <3	1	
Log 3-5	9	
Log >5	5	
Adenovirus	2	
RSV	3	
Parainfluenza	2	
Influenza A	1	
Influenza B	1	
Rhinovirus	4	
Coronavirus OC43	3	
Bacterial and opportunistic infection on sputum/TA		
	Total Number	**Number of Patients tested**
Tracheal aspirates done	23	13
Organisms found		
ESBL Klebsiella pneumonia	4	
Pseudomonas aeruginosa	1	
PJP (15 tests, 11 patients)	2	
TB testing		
	Total Number	**Number of patients tested**
Gastric washings/sputum	62	31
Gene Xpert and TB MCS +	1	
Urine Microscopy, Culture and Sensitivity (MCS)		
	Total Number	**Number of patients tested**
Urine MCS done	26	18
Positive culture	1	
ESBL Klebsiella pneumoniae	1	
Cerebrospinal fluid (CSF) MCS		
	Total Number	**Number of patients tested**
CSF done	21	17
Positive culture	1	
Acinetobacter baumanii	1	

CMV – Cytomegalovirus, CSF – cerebrospinal fluid, E coli – Escherichia coli, ESBL – Extended spectrum beta-lactamases, MCS – Microscopy, culture and sensitivity, MRSA - Methicillin-resistant Staphylococcus aureus, MSSA - Methicillin-sensitive Staphylococcus aureus, NPA – nasopharyngeal aspirate, PJP – pneumocystis jirovecii pneumonia, RSV – Respiratory syncytial virus, TA – Tracheal aspirate, TB – Tuberculosis

Table 4.9: Profile of children by PICU admission status

	All Children (N=55)		PICU admission (N=13,24%)		No PICU admission (N=42,76%)		P
	N/n		N/n		N/n		
Male n(%)		33 (60)		5 (39)		28 (67)	0.070
Known risk n(%)		46 (84)		12 (92)		34 (81)	0.334
Age on admission (days) Median (IQR)		174 (90-381)		96 (58 - 228.5)		194.5 (108 – 389)	0.076
Age at HIV diagnosis (days) Median (IQR)		59 (6-184)		67 (44 - 213.5)		57.5 (3 - 184)	0.476
Time from HIV diagnosis to cART initiation (days) Median (IQR)		8 (5-27)		9 (4.5 - 30)		8 (5 – 17)	0.751
Child cART Status n(%)							0.243
Newly diagnosed		25 (45)		7 (54)		18 (43)	
Prior cART, In Care		15 (27)		2 (15)		13 (31)	
Prior cART, not in care		5 (9)				5 (12)	
Previously Diagnosed, No cART		10 (18)		4 (31)		6 (14)	
CD4 Latest (%) median(IQR)	49*	23.7 (17.9 – 36.3)		23.7 (16.4 – 43.4)	36*	27.7 (20.6 – 36.3)	0.803
WHO CD4% Immunodeficiency Staging **n**(%)	49*				36*		
Mild immunodeficiency (≤11 months: 30-35%; 12-35 months: 25-30%)		6 (12)		1 (8)		5 (14)	
Advanced Immunodeficiency (≤11 months: 25-29%; 12-35months: 20-24%)		9 (20)		1 (8)		8 (22)	
Severe immunodeficiency (≤11 months: <25%; 12-35 months: <20%)		17 (35)		7 (54)		10 (28)	
Viral load (log) latest Median (IQR)	50*	5.5 (4.1 – 6.3)	12*	5.6 (5.4 - 6.7)	38*	5.3 (3.8 – 6.2)	0.053
Viral load LDL n(%)	50*	3 (6)	12*	0	38*	3 (8)	
Viral load <1000 copies/ml n(%)	50*	5 (10)	12*	0	38*	5 (13)	
Weight-for-Age Z score Median (IQR)		-2.6 (-4.0 to -1.9)		-2.57 (-3.39 to -2.37)		-2.58 (-4.34 to -1.55)	1
Diagnosis n(%)							
Pneumonia		25 (45)		10 (77)		15 (36)	
Gastroenteritis		20 (36)		2 (15)		18 (43)	
Severe acute malnutrition		22 (40)		5 (38)		17 (40)	
Tuberculosis		10 (18)		3 (23)		7 (17)	
ICU duration Median (IQR)				8 (5.5 - 24)			
Hospitalization duration in days median(IQR)		17 (10 – 31)		32 (16 – 55)		14 (9 – 26)	<0.005
Deaths n(%)		7 (13)		3 (23)		4 (10)	0.200

All LDL on cART, 1 <1000 newly diagnosed

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, PICU – Paediatric Intensive Care Unit, IQR – Interquartile range, LDL – Lower than detectable limit, WHO – World Health Organization

* Discrepancy in denominator value in concordance with availability of data for the specific parameter

Table 4.10: Comparing children that died with those who survived

	All Children (N=55)		Deaths (N=7,13%)		Survived (N=48,87%)		P
	N/n		N/n		N/n		
Male n(%)		33 (60)		2 (29)		31 (65)	0.070
Known risk n(%)		46 (84)		5 (71)		41 (85)	0.350
Age on admission (days) Median(IQR)		174 (90-381)		350 (68 - 511)		154 (93 – 370)	0.235
Age at HIV diagnosis (days) Median(IQR)		59 (6-184)		200 (43 - 335)		57 (6 – 136)	0.165
Time from HIV diagnosis to cART initiation (days) Median(IQR)		8 (5-27)		10 (7 - 28)		8 (5 – 22)	0.419
Child cART Status n(%)							0.370
Newly diagnosed		25 (45)		4 (57)		21 (44)	
Prior cART, In Care		15 (27)		0		15 (31)	
Prior cART, not in care		5 (9)		1 (14)		4 (8)	
Previously Diagnosed, No cART		10 (18)		2 (29)		8 (17)	
CD4 % Latest median(IQR)	49*	23.7 (17.9 – 36.3)	6*	22.9 (20.5 – 29.3)	43*	28.2 (17.7 – 37.2)	0.784
WHO CD4% Immunodeficiency Staging n(%)	49*		6*		43*		
Mild immunodeficiency (≤11 months: 30-35%; 12-35 months: 25-30%)		6 (12)		1 (17)		5 (12)	
Advanced Immunodeficiency (≤11 months: 25-29%; 12-35months: 20-24%)		9 (20)		1 (17)		8 (19)	
Severe immunodeficiency (≤11 months: <25%; 12-35 months: <20%)		17 (35)		3 (50)		14 (33)	
Viral load (log) latest Median(IQR)	50*	5.5 (4.1 – 6.3)		6.2 (5.6 - 6.5)	43*	5.4 (3.9 – 6.3)	0.096
Weight-for-Age Z -core Median (IQR)		-2.6 (-4.0 to -1.9)		-3.3 (-5.26 to -2.93)		-2.43 (-3.88 to -1.88)	0.123
Diagnosis n(%)							
Pneumonia		25 (45)		4 (31)		21 (44)	
Gastroenteritis		20 (36)		0		20 (42)	
Severe Acute Malnutrition		22 (40)		6 (46)		16 (33)	
Tuberculosis		10 (18)		1 (8)		9 (19)	
ICU admission n(%)		14 (25)		3 (43)		11 (23)	0.258
ICU duration Median(IQR)	14*	8 (4.8-22.5)	3*	27 (4 – 39)	11*	8 (5 – 10)	0.390
Hospitalization duration (days) Median(IQR)		17 (10-31)		30 (13 – 54)		14 (10 – 27)	0.136
Time from HIV Diagnosis to death (days) Median(IQR)				53 (34 – 104)			
Time from cART initiation until death (days) Median(IQR)				33.5 (17 – 47)			

cART – combination antiretroviral therapy, HIV – Human immunodeficiency virus, ICU – Intensive Care Unit, IQR – Interquartile range, LDL – Lower than detectable limit, WHO – World Health Organization

* Discrepancy in denominator value in concordance with availability of data for the specific parameter

4.4 ROAD-TO-HEALTH BOOKLET AND VACCINATION STATUS

Table 4.11: Road-to-Health Booklet HIV-related data completion and vaccination status review

	All Cases		Known Risk						Unknown Risk	
			All Known Risk		Mother Diagnosed Prior to Pregnancy		Mother Diagnosed during Pregnancy			
	Assessed (N)	Complete n (%)	Assessed (N)	Complete n (%)	Assessed (N)	Complete n (%)	Assessed (N)	Complete n (%)	Assessed (N)	Complete n (%)
RtHB present	48 ∞	46 (96)	40	39 (98)	28	27 (96)	12	12 (100)	8	7 (88)
HIV-Related pages completed	46	8 (17)	39	7 (18)	27	4 (15)	12	3 (25)	7	1 (14)
6-week PCR done*	31	19 (61)	31	19 (61)	22	14 (64)	9	5 (56)		
6-week PCR result documented*	19	15 (79)	19	15 (79)	14	10 (71)	5	5 (100)		
Bactrim Prophylaxis at 6 weeks*	29	15 (52)	29	15 (52)	21	11 (52)	8	4 (50)		
Appropriately vaccinated for age	46	29 (63)	39	24 (62)	27	16 (59)	12	8 (67)	7	5 (71)

HIV – Human immunodeficiency virus, PCR – polymerase chain reaction, RtHB – Road-to-Health Booklet
∞ 7 of the 55 enrolled children still in neonatal period and with no RtHB issued excluded
* Only RtHBs of children older than 6 weeks of age were assessed
Denominator value reported dependent on availability of data for the specific parameter

Seven of the 55 children (12.7%) were in the neonatal service and had not yet been issued RtHBs. Of the remaining 48 children, 46 (96%) had RtHBs available for review. The median age of these 46 children was 6.4 (IQR 3.6 – 12.7) months: Known risk 5.7 (IQR 3.2 – 12.8) and unknown exposure 9.3 (IQR 6.4 – 12.1) months, p=0.343.

Of the 39 children, whose mothers had known antenatal HIV-infection, the HIV-pages were fully age-appropriately completed in 7 (18%). Performance of diagnostic PCRs in children older than 6 weeks was noted in 19/31 children (61%) and results documented in 15/19 (79%). Initiation of co-trimoxazole at 6-week age was documented in 15/29 (52%). Of the 8 HIV-infected children without known antenatal HIV-exposure, 7 (88%) had RtHBs available; 1 (14%) had appropriate documentation of maternal HIV status during pregnancy.

The age-appropriate vaccination uptake was 62% (24/39) in antenatally known-risk and 71% (5/7) in children identified postpartum, p=0.801.

5. DISCUSSION

5.1 GENERAL FINDINGS WITH REGARDS CARE OF HIV-INFECTED WOMEN

South Africa has a 94% uptake of HIV-testing in pregnant women(23) and pMTCT programmes in approximately 98% of healthcare facilities.(12) Reviews of the HIV infection outcomes of perinatally exposed infants report a transmission rate of 1.5%.(21)

In previous local and international studies, failure to recognise the exposure-risk, and therefore absence of preventative ART, was identified as the major driver of HIV-infection in the era of effective HIV prevention. This was noted even prior to all mothers accessing cART during pregnancy and before data on the importance of treating all infected adults regardless of clinical state and CD4 count had emerged. In contrast however, in our review, the minority (16%) of patients were not identified during the antenatal period. We identified poor antenatal clinic attendance and cART interruption in women aware of their HIV-status prior to pregnancy and failure of women on cART prior to pregnancy to achieve viral suppression as the driver of newly infected infants. For women identified during pregnancy, the short duration on cART was an important factor to consider as the median time on cART at delivery was 0.5 months (IQR 1 – 3), an insufficient time to achieve viral suppression.

Furthermore, although we were unable to verify this, 9 mothers reported that they were aware of their HIV-status during pregnancy and attended antenatal clinic, but did not receive any prevention. These women all attended antenatal care for the first time after 28 weeks, but we did not collect data on the exact gestation at which they presented. We could also not verify access to AZT antenatally and intrapartum NVP, TDF/FTC and AZT, nor were there any indication of prevention in the RtHB of their infants. However, we noted that women who did not access cART were delivering babies at term in the majority of cases.

With regards to overall antenatal clinic attendance, 2014 data suggests that in South Africa 7.1 % and in the Western Cape 14.7% of pregnant women did not seek antenatal care.(18) Although this is a bias sample, in this study antenatal clinic attendance was unacceptably poor, especially in women aware of their HIV-status and with prior cART exposure. We found a combined ANC attendance of 76% (42/55): Known HIV-exposure risk cases 35/46 (76%) and unknown HIV-exposure risk cases 7/9 (78%). Only 20 of the 31 women (65%) with known HIV-infection prior to the index pregnancy attended antenatal clinic. This is in contrast to a case-control study by Mnyani et al. conducted in Johannesburg from Nov 2010 to May 2012 where 85.7% of women with infected infants attended

antenatal care.(64) Also, in Johannesburg, in a five facility operational follow-up study of HIV-infected children under 2 years, Technau et al. documented that 96% of mothers attended antenatal clinic at least once.(65) In keeping with data documented in Gauteng (that found a median gestation at ANC presentation of 24 weeks (IQR 16 - 28)(65)), and Kwazulu-Natal (where a 25% booking rate after 28 weeks gestation and 63% between 13 – 27 weeks was documented(66)), women in our study who attended antenatal clinic tended to present late for antenatal care, with only 6.5% (3/46) presenting prior to 14 weeks' gestation. The reasons for this lack of early presentation are complex and may include maternal perceptions of the role of the antenatal service, as well as the healthcare system not actively encouraging early pregnancy attendance. Interestingly, all women who attended antenatal care but did not start therapy presented after 28 weeks' gestation.

Longer treatment duration prior to delivery with effective control of HIV-viraemia, is essential to prevent in-utero and intrapartum transmission, but also makes breastfeeding safer.(64) Where women in our study initiated cART during pregnancy, the duration on therapy was not long enough to achieve viral suppression, even though few infants were very premature. Mothers diagnosed during pregnancy tended to deliver late preterm infants [median of 35 weeks' gestation (IQR 33-38)]. Late premature delivery and low birthweight is common in South Africa and other developing countries, even in infants without HIV-exposure, as corroborated by the 2010 global estimated low birthweight rate of 15.5% (96% of which occurred in developing countries) and preterm delivery rate of 11.1%.(67)

In infants of HIV-infected mothers, high rates of late prematurity are also reported in mothers on cART prior to pregnancy and those who initiate cART during pregnancy. The causes are complex and multifactorial. Cohort studies from other African countries also report late prematurity and low birthweight in HIV-infected infants, both of mothers on cART prior to pregnancy, mothers initiating cART during pregnancy and mothers not on cART.(68,69)

The women in this study had a median age of 28 years (IQR 24 – 31) at delivery of the index pregnancy. Of note is the absence of teenage pregnancy in this cohort, as failure of adolescent girls to attend antenatal care and adhere to therapy, in this sub-group of pregnant women, is a well-known phenomenon, but cannot be implicated in the poor health-seeking behaviour in the majority of women in this cohort.(70,71) Our higher maternal age is in keeping with the median ages of women enrolled in other pMTCT and EID trials and studies in South Africa. In these studies women ranged from 27 - 28 years of age, and in the majority of cases were not primigravida.(64–66)

Mothers were markedly immune-suppressed during pregnancy, a further risk factor for transmission, as well as when their children were enrolled. Forty-one of the 46 (89%) women known to be HIV-infected antenatally, had a CD4 count done during pregnancy or in the immediate postpartum period, 88% (36/41) having CD4 counts less than 500 cells/mm^3 of which 14 (34%) had a CD4 count less than 200 cells/mm^3. This is comparable to data from Kwazulu-Natal that showed 27% of HIV-infected pregnant women having a CD4 count of less than 200 cells/mm^3 and 86% less than 500 cells/mm^3.(66) Although CD4 counts are no longer needed to initiate cART in pregnancy, they are still part of care and the test is used as the basis for screening for cryptococcal infection.(12) Low CD4 counts are a known risk factor for transmission, even with access to pMTCT.(69)

We noted high rates of infectious co-morbidity, including tuberculosis and syphilis. This trifecta of late presentation, advanced disease with low CD4 cell count and high HIV viral load with additional co-morbidities may indicate that these women were at higher risk of pMTCT failure. However, we do not have denominator data that will allow us to further describe these specific risk factors.

At the time the child was enrolled, 22 (48%) of the mothers were in care, and 15 (33%) indicated that they were not currently taking a previously initiated cART regimen and were not attending clinical care for their own health. The high postpartum loss to follow-up in our cohort is not unique and is well documented in local and international settings. An earlier study from Cape Town showed a loss to follow-up (LTFU) of 32% (72), while in Malawi, the first country to start all pregnant women on cART and keep them on cART postpartum, up to 30% loss to follow-up is reported.(71) In a USA cohort, only 31% of women initiating cART during pregnancy were virally suppressed (HIV VL ≤200 copies/ml) and in care by one year postpartum, while data from the UK and Ireland indicated that 27% of women who initiated cART during pregnancy were not virally suppressed (HIV VL >200 copies/ml) by a year postpartum.(73)

In order to promote not just cART-initiation, but also retention in care for both mothers and their infants, maternal-child-health units with integrated antenatal and postnatal care, pMTCT, cART care, as well as routine healthy child visits may improve retention outcome. Eighteen women in this cohort, not on cART at conception, received antenatal care and cART care at the same facility, 6 of them defaulted care. Not receiving care at the same facility did not predict defaulting in this group. Operational research in Cape Town showed that, in women randomized to receive either postpartum standard of care or otherwise being managed in the well-baby service, those getting care in the well-baby service had improved duration of breastfeeding (3 months to 9 months) and 77% of the mothers

remained in care and were suppressed (as a combined end-point) vs 56% of mothers in the standard of care arm, <p=0.001.(74) Though this is a substantial improvement, there still remains significant loss to care, in routine services.

Postpartum contraception uptake was very low in this cohort, only 55%, leading to the risk of further pregnancies and ongoing future risk of HIV transmission for women presenting late to ANC or not in care. Mothers also had low levels of knowledge about partner status and disclosure-status is still unacceptably low.

5.2 GENERAL FINDINGS WITH REGARDS CARE OF HIV-INFECTED CHILDREN

The median birthweight of infants born to mothers known with HIV-infection was less than 2500g. This included those born to mothers with HIV diagnosed prior to pregnancy, despite their median gestation being slightly higher. High rates of low birthweight are reported in this context.(46) Notably infants born to mothers not identified in pregnancy were also small (median BW 2595g (IQR 2180 - 2830).

The uptake of infant prophylaxis was good, with 93% of infants accessing antiretroviral drug prevention.

Mothers diagnosed during pregnancy chose to exclusively breastfeed in 87% of cases, in contrast to 52% of previously diagnosed mothers choosing exclusive formula feeding from birth. We were not able to explore the reasons for the low uptake of breastfeeding in these mothers or whether the feeding choice was adhered too. Mothers with prior engagement with the healthcare system may have been exposed to prior guidance on formula feeding, and/or understand their inability to adhere to medication with subsequent fear of HIV-transmission to the infant. These feeding trends are similar to those of pMTCT programmatic failure research in Johannesburg by Technau et al., where children were more likely to be exclusively breastfed during the first 6 months in mothers diagnosed during pregnancy (45%) or postpartum (56%), than if they were diagnosed prior to the index pregnancy (27%).(65)

The median age at diagnosis of HIV in infants with known exposure risk was similar to that of studies from Johannesburg: 49 days for babies born to mothers diagnosed prior to pregnancy and 77 days if diagnosed during pregnancy in data by Technau et al. (65), and a mean of 63 days in data by Mnyani

et al. (64). Fourteen (30%) of these infants were diagnosed in the neonatal period, with 72% (33/46) diagnosed prior to 3 months of age. Of note is the high number of children diagnosed during hospitalization, similar to routine data from both the CHER sites that highlighted the very rapid progression to severe disease in infants identified as infected at a young age.(10) This rapid progression emphasizes the need to ensure early testing and access to cART.

Despite being clinically symptomatic, children with unknown HIV-risk were older. We did not explore possible reasons for a delay in their testing. At enrolment children were symptomatic and 27% of children with an available CD4 count (13/49) were severely immune suppressed. The province has since implemented birth PCR and this may again facilitate access to care. Though the majority of infants identified were young, the importance of ongoing follow-up is clear from the number of children diagnosed after 6 months of age with an initially negative PCR.

Despite 30 children (55%, N=55, one child with unknown exposure risk diagnosed prior to current admission, but not started on cART, all other unknown risk children were newly diagnosed) being diagnosed prior to admission to Tygerberg Hospital, only 20 initiated cART, of which 5 defaulted care prior to admission. Of the 15 still in care, 5 were virally suppressed (with HIV VL < 400 copies/ml).

The median age at cART initiation in our cohort was 76 days (IQR 20-178) in children with known exposure risk, with time from diagnosis to cART initiation being 9 days (IQR 5-30). This is similar to Johannesburg data where cART was initiated at 76 days of age and within 12.6 days of diagnosis in the Mnyani et al. cohort(64) and at 112 days, but only within 71 days of diagnosis in the Lillian et al. cohort.(75) Children diagnosed in the clinic setting, despite statistically insignificant difference in diagnosis age [50 days (IQR 42 – 93) in clinic versus 54 days (IQR 3 – 108) in hospital, p = 0.989], took 33 days (IQR 28 – 63) to be initiated on cART versus 8 days (IQR 5-15) in hospitalized children, p = 0.005. Follow-up and rapid initiation systems in primary care will need to be strengthened in order to facilitate rapid access to cART once infants are infected so that mortality and morbidity can be prevented.

Even though marked progress has been made in the early identification of HIV-infected children from within the pMTCT programme, including the introduction of the birth PCR, we are still too late in identifying these children prior to them presenting with severe disease. Furthermore, once identified and initial linkage to care, initiation on treatment and retention in care is a problem. Interventions need to be put in place along all these steps in the treatment continuum to ensure maximal effectiveness. They may include, the linking of babies to care by means of ward-based outreach teams

and early social support intervention where needed; the linking of infants to a national/provincial data system so that information can be easily accessed electronically, as well as the use of specialized RtHB identifier coding for all NHLS blood tests to ensure easy access to results. Retention in care can be addressed by maternal counselling and education, as well as addressing issues such as stigma and fear, lack of partner disclosure and support, as well as poor or difficult access to health care services.(49)

5.2.1 Clinical condition during admission:

Children from this cohort most commonly suffered from Pneumonia (45%, 25/55), gastroenteritis (36%, 20/55) and malnutrition (40%, 22/55). Tuberculosis, mostly pulmonary, was diagnosed in 10 children (18%). High rates of pulmonary tuberculosis are well documented in this setting. Walters et al, in a cohort review at the same facility reported that the number of TB cases per 100 patient years were 53.3 during the 9 months prior to HAART initiation, and 6.4 during post HAART follow-up [odds ratio (OR) 16.6; 95% confidence interval (CI) 12.5–22.4].(76)

There were few confirmed cases of PJP (2), no pneumococcal infections and only 2 cases of influenza. However, other viral infections, particularly CMV, were found in a number of children. Confirming CMV disease is complex, but high viraemia supports that CMV is an important pathogen in these children.(56) Access to Ganciclovir is limited and if we want to make further gains in the early mortality of HIV-infected children, this needs attention.

Of particular concern is the high mortality (13%), need for intensive care (25% of children) and long duration of hospitalization. The main causes of death, poor nutritional state and prolonged hospitalization of deceased children in our cohort were similar to those identified by Child PIP in the 2012-2013 Saving Children Report.(63)

5.2.2 Road-to-Health Booklet and vaccination status

Review of this important tool showed 2 major concerns:

Firstly, health care workers are not completing the document fully. This is congruent with findings from Kalafong hospital, Tswane, South Africa where inadequate reporting of infant testing on the RtHB occurred in 74% of cases.(77) National cross-sectional survey data from 2011 by Woldensebet et al. also reiterates these findings, with only 34% of surveyed RtHBs indicating maternal or child HIV-status and only 49% of booklets of infants of self-reported HIV-infected mothers being corroboratively

completed.(24) We know that healthcare workers and mothers may be concerned that the documentation of HIV status may lead to inadvertent status disclosure, for instance at day care and preschool, however failure to complete this document properly may cause significant delay in care. It is imperative that healthcare workers be trained and guided to comply with the correct completion of this very important document, as it has far-reaching medical benefits and implications. The practice of non-completion of the HIV-related pages on maternal request to protect her own status, is something that needs to be addressed through advocacy and communicating with mothers.

Secondly, there is poor vaccine uptake in this group of infants, contributing to their already significant risk for illness. We did not explore the reasons for this further, but it may potentially indicate a deeper issue in the care of these children, and in conjunction with the data on maternal adherence and defaulting of infant cART, may indicate poor maternal health-seeking behaviour. This trend does not only influence vaccination-status, but has far-reaching complications in the health of the woman herself, if she does not adhere to her own treatment, as well as her child's future morbidity and possible mortality.

5.2.3 Disclosure of HIV status and support

HIV, despite marked advances in treatment and management, is a complex chronic disease marred by its current incurability and the internal and external stigma that surrounds it. It is imperative that a sound support system is available. Partners especially have a vital role to play, and it is important that they too are aware of their HIV status, in order to protect them in cases of discordance, or for them to receive treatment when indicated.

Results from this study shows poor levels of knowledge of partner HIV status at only 56%. The child's status was only disclosed in 79% of cases (26/33), and family and the partner were only involved with the child's care in 65% (17/26) and 59% (16/27) of previously diagnosed cases respectively. These low levels of knowledge of partner-status and the involvement of partners and other family members are very concerning. Partner-involvement and testing is a subject that needs more attention. Programmes focusing on testing women together with partners, as well as encourage antenatal attendance of men with their partners need to be developed and implemented.

6. STRENGTHS AND LIMITATIONS

The fact that HIV-infected children were prospectively enrolled, with a maternal interview and questionnaire at the time of enrolment strengthened the data collection, as there was less reliance on folder review.

This study is limited by the lack of controls in the form of HIV-exposed HIV non-reactive children less than 18 months in order to qualify and quantify the risk factors most influential in causing pMTCT failure.

As this study was done in Tygerberg Hospital, a secondary/tertiary centre, with a prominent neonatal setting, there may be bias as the study participant profile may not accurately reflect that of the drainage population or South Africa as a whole.

Our reliance on patient reports that were not always verifiable through additional sources, was a further limitation.

7. CONCLUSIONS

This study highlighted that the majority of HIV transmission from mother to child occurs in women known to be HIV-infected, but who we are struggling to engage consistently in care. Prior disengagement from cART, no or late antenatal attendance and poor viral suppression rates in women on cART are driving transmission in this group. Patients who have a history of disengagement of care and who present late to antenatal clinic may need to receive particularly targeted interventions during the pregnancy and postpartum period.

Mothers and their children were poorly retained in care once initiated, which again emphasizes the need for a perhaps more personalized approach in pMTCT and subsequent cART treatment continuation, incorporating multiple spheres. This may include interventions like integration of all services into Maternal & Child Health (MCH) centres, utilizing social support networks; addressing stigma, whether internal or external(21); use of technology and messaging as reminders; partner testing and support; reducing unwanted pregnancies through contraception.

Despite children with known HIV-exposure risk being diagnosed at a young age (median 54 days) and being timeously initiated on treatment (9 days), the level of morbidity and mortality (13%) is still very high. Most children are being diagnosed in hospital during acute illness episodes, prior to the designated outpatient EID point. Children with unknown HIV exposure risk were diagnosed late (median age of 285 days) during hospitalization with marked immunosuppression and concomitant malnutrition. Viral pneumonia and gastroenteritis were the main reasons for admission, with tuberculosis also prominent. These findings highlight the need for early provider initiated testing in all symptomatic children irrespective of their HIV-exposure status.

Road-to-Health Booklets, although present in most cases, were poorly completed. This may be indicative of not only a maternal disclosure and stigma issue, but also a further reaching healthcare worker and system issue, where the importance and consequences of missed infant HIV infection is not fully comprehended. The poor vaccination uptake in these children indicates the possibility of poor health-seeking behaviour in this cohort. This once again emphasizes the potential need for improved and more individualized ways to identify, support and manage these mother-infant pairs in order to improve adherence and retention in care.

8. FURTHER RESEARCH

Further research is needed along multiple points in the pMTCT continuum.

Topics may include:

- An exploration of reasons why HIV-infected women do not engage in care.
- Methods of successfully linking women and children to care and retaining them.
- Methods to identify and re-admit women who have been lost from the HIV care continuum.
- Improved identification of HIV-infected but unknown exposure children.
- Interventions to improve utilization of the RtHB as an important tool in the child HIV management.
- Methods to improve partner testing, disclosure and involvement.

9. RECOMMENDATIONS

Despite the high quality, effective pMTCT regimen in place, health system and human factors continue to play a major part in failure of prevention of mother-to-child transmission of HIV.

Improvements in voluntary counselling and testing (VCT) and PICT are not enough. Women who are tested need to be started on cART in a timely fashion in conjunction with a dependable, non-judgemental, trustworthy support system (of health care, community and family origin). Adherence and retention in care are major pressure points that need attention.

We have identified major gaps in the pMTCT continuum that need to be explored further. Possible suggestions for alleviating these problems may include: One-stop mother-and-child health and HIV-care, use of cellular reminders/messages, support groups and peer-counsellors, the improved involvement of partners/spouses/family members, as well as efforts towards the de-stigmatization of HIV in the community.

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