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Rate of neonatal birth HIV positive tests and description of related risk factors in Johannesburg: can point of care testing be targeted effectively?

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University of the Witwatersrand

Submission of research report for MMED (Paediatrics)

Rate of neonatal birth HIV positive tests and description of related risk factors in Johannesburg - can point of care testing be targeted effectively?

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Declaration

I, Elzette Wannenburg, student number 363171 staff number A0033672, declare that this is my original work, submitted for the Master of Medicine in Paediatrics degree for the University of the Witwatersrand. It has not been submitted to any other university or for any other degree or examination. It has not yet been submitted for publication in any journal or presented at any conferences.



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Dr E Wannenburg 24/5/2023

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Abbreviation List

ART: Antiretroviral Therapy

ESRU: Empilweni Services and Research Unit

HEI: HIV Exposed Infected

HEU: HIV Exposed Uninfected

HIV: Human Immunodeficiency Virus

HIVVL: HIV Viral Load

LABT: Laboratory Based Testing

MTCT: Mother to Child Transmission

NICD: National Institute of Communicable Diseases

PCR: Polymerase Chain Reaction

POCT: Point Of Care Testing

RMMCH: Rahima Moosa Mother and Child Hospital

WLHIV: Women Living With HIV

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Key Words: PCR, HIV, diagnosis, neonate, birth, point of care

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Abstract

Background

Prompt diagnosis of Human Immunodeficiency Virus (HIV) in South Africa and early initiation of antiretroviral therapy in infected newborns remains a challenge in South Africa. Point of Care Testing could expedite this process. This study describes the rate of, and risk factors associated with birth detectable HIV infection in a South African setting.

Methods

A secondary data analysis of infant HIV polymerase chain (PCR) reaction results was done at Rahima Moosa Mother and Child Hospital in Johannesburg between June 2014 to June 2019. Annual positivity rates were calculated and association tested against characteristics (maternal, delivery and infant) using descriptive statistical methods.

Results

12466 infants had a final HIV result. The yearly positivity rate did not show significant fluctuation, ranging from 1.2-1.7%. Maternal risk factors for infant infection included adolescent age (3.6% vs 1.8% for mothers aged 20-30) ($p<0.001$); unbooked mothers (5.3% vs 1.5%) ($p<0.001$); CD4 count <200 (3.3% vs 0.75% at CD4 200-300) ($p<0.001$); antiretroviral therapy for less than a month (5.1% vs 2.3% after 1 month) ($p<0.001$); HIV diagnosis within a month of delivery (10.1% vs 1% pre-conception) ($p<0.001$) and those with viral loads >1000 (8.9% vs 1.3% if 50-1000) ($p<0.001$). Infant risk factors for infection were prematurity (2.3% vs 1.4%) ($p=0.012$); low birth weight (2.2% vs 1.4%) ($p=0.009$); ill infants warranting admission (3% vs 1.5%) ($p<0.001$) and infants born in cold seasons (1.8 vs 1.3%) ($p=0.016$).

Conclusion

Various maternal and infant factors were associated with HIV infection at birth while the birth positivity rate remained relatively constant across the study period. While universal birth point of care testing is ideal, high risk infant groups could be identified and targeted in resource constrained settings to expedite HIV diagnosis and treatment.

Introduction

In 2021, 270 000 children in South Africa were living with Human Immunodeficiency Virus (HIV).[1] Worldwide, and specifically on the African continent, combatting mother-to-child HIV transmission (MTCT) remains an obstacle to eliminating HIV related childhood morbidity and mortality. As one of the 22 countries where ninety percent of the world's HIV positive pregnant women live, South Africa has prioritised the elimination of mother-to-child transmission of HIV.[2] The vertical transmission of the virus can occur intrauterine, intrapartum or postpartum via breastfeeding.[3] Since 2015, the South African National Department of Health has recommended that all HIV Exposed infants have a polymerase chain reaction (PCR) test at birth and at later time points, instead of only at 6 weeks of age.[4] This has potentially allowed the identification and treatment of infected infants before they become symptomatic. In 2018, South African Birth HIV PCR testing coverage was as high as 93.5%, while the national percentage of intrauterine Mother to Child Transmission (MTCT) risk was 0.9%.[2] Hence, despite the widespread implementation of Prevention of Mother to Child Transmission of HIV (PMTCT) strategies in South Africa, for every 100 000 live births, 245 children are born with HIV infection.[2] These children need early diagnosis and treatment initiation to decrease their high risk of morbidity and mortality.[2, 5-13]

A significant possible intervention to expedite early treatment is the use of point of care PCR testing (POCT).[14] In a previous South African study it was shown that, compared with laboratory-based testing (LABT), POCT was associated with good performance, improved rates of result return, and reduced time to ART initiation.[15] Recent literature describes POCT as a cost effective tool for rapid diagnosis of HIV and shows POCT to improve survival and extend life expectancy.[16-20] This resource is not currently available but has recently been touted as a cost-effective and recommended strategy for sub-Saharan Africa.[15] These developments necessitate a clear understanding of risk factors associated with HIV detectable at birth. Once these risk factors are identified, recommendations can be made to expedite the diagnosis and initiation of antiretroviral therapy (ART) in high risk newborns, whilst optimising scarce resources. This would allow for the development of different models of care, for example universal vs. targeted infant testing, giving policy makers opportunity to consider a targeted approach rather than all or nothing.

This study therefore explored the maternal and infant risk factors associated with HIV exposed infants testing positive for HIV at birth, as well as the birth positivity rate over the study period.

Methods

This was a secondary data analysis of data that was, at that time, collected prospectively via the Empilweni Services and Research Unit (ESRU) at Rahima Moosa Mother and Child Hospital (RMMCH), an urban academic provincial hospital in Johannesburg, South Africa. ESRU contributed to supporting the pilot of universal birth POCT from 2014. During 2015 the HIV prevalence amongst South African women who attended antenatal care was 30.8%.[21] Infants born to women living with HIV (WLHIV) were tested at birth and these mothers were invited for further counselling. Infants who tested positive at birth were traced, confirmatory testing was done, and they were treated as per national guidelines. Point of care testing was also offered, when available, to expedite the treatment process. The median time for mothers to receive results for LABT is 10 days, while the time for POCT is within a day. [15]" Statistics were captured by the National Institute of Communicable Disease (NICD) laboratory running the PCR tests and the hospital itself.

Data pertaining to HIV was collected by counsellors and phlebotomy staff employed by ESRU in collaboration with the Department of Health staff and has been ongoing since 2014 and captured electronically. Data was de-identified and anonymised. Women were assessed and interviewed post-delivery and women living with HIV (WLHIV) were counselled and offered treatment. The process aimed to capture all live births to WLHIV. Interviewed women were invited to sign a data sharing consent. The uptake of consent, for collection of data into the Empilweni Database is >95%. An interview sheet was used for collection of routine data relevant to the HIV counselling and PMTCT. Data was collected on a secure Research Electronic Data Capture application (REDCap) hosted at the University of the Witwatersrand.[22]

A neonate was categorised to have birth detectable HIV infection when they had either a positive birth PCR; a repeat positive; repeat indeterminate; no repeat or an

initial indeterminate, with a repeat positive or indeterminate PCR. Infants with two indeterminant results or with discordant positive and negative results on two tests were classified as diagnostic dilemmas and followed up clinically for further investigation. Diagnostic dilemmas were excluded from our risk analysis. Error PCR results were repeated where possible. Infants who tested positive at birth were traced, confirmatory testing done, and treated as per national guidelines. Cepheid's point-of-care (POC) diagnostic testing (Xpert® HIV-1 Qual Test) was also offered when available to expedite the treatment process. Due to staffing and consent limitations, 56% of infants who received LABT also received POC testing. The median time for mothers to receive results for LABT is 10 days, while the time for POCT is 1 day.[15] HIV exposed infants whose mothers were interviewed during the first week of life at RMMCH from June 2014 to June 2019 were identified for collection of data. Mothers who refused permission for use of routine data for analysis were excluded. The coverage of PCR testing was described using routine hospital statistics of live births and live births to HIV positive women. Data collected from June 2014- June 2019 at RMMCH postnatal wards was analysed to describe the neonatal, maternal and birth characteristics of HIV exposed newborns and to determine the rate of HIV PCR positive infection at birth. HIV exposed infected (HEI), and HIV exposed uninfected (HEU) infants were compared to determine whether any of these characteristics are associated with testing HIV PCR positive at birth. Data was de-identified and anonymised using a numbering system and kept in password protected Microsoft Excel spreadsheet once extracted from REDCap.

Extreme outliers and obvious errors as well as entries with incomplete parameters for each calculation were excluded. Data quality work has been ongoing during the collection of this database, as capacity allowed, to ensure that regular data cleaning was done throughout. Data was analysed using Excel (Version 16.28 19081202) and SAS software (Version 9·4, SAS Institute Inc., Cary, NC). Institutional permissions to conduct research at RMMCH were obtained from the hospital CEO and ethical clearance was granted by the University of Witwatersrand Human Research Ethics Committee (M2011161).

Results:

Between 1 June 2014 and 31 May 2019, 63610 pregnant women delivered at RMMCH, of which 13375 were living with HIV. During this time more than 99% of women were tested for HIV.[23] A total of 12554 HIV-exposed infants were tested by PCR test at birth according to our database. To assess the completeness of our dataset we compared it to both routine hospital statistics as well as NICD PCR datasets. (Figure 1)

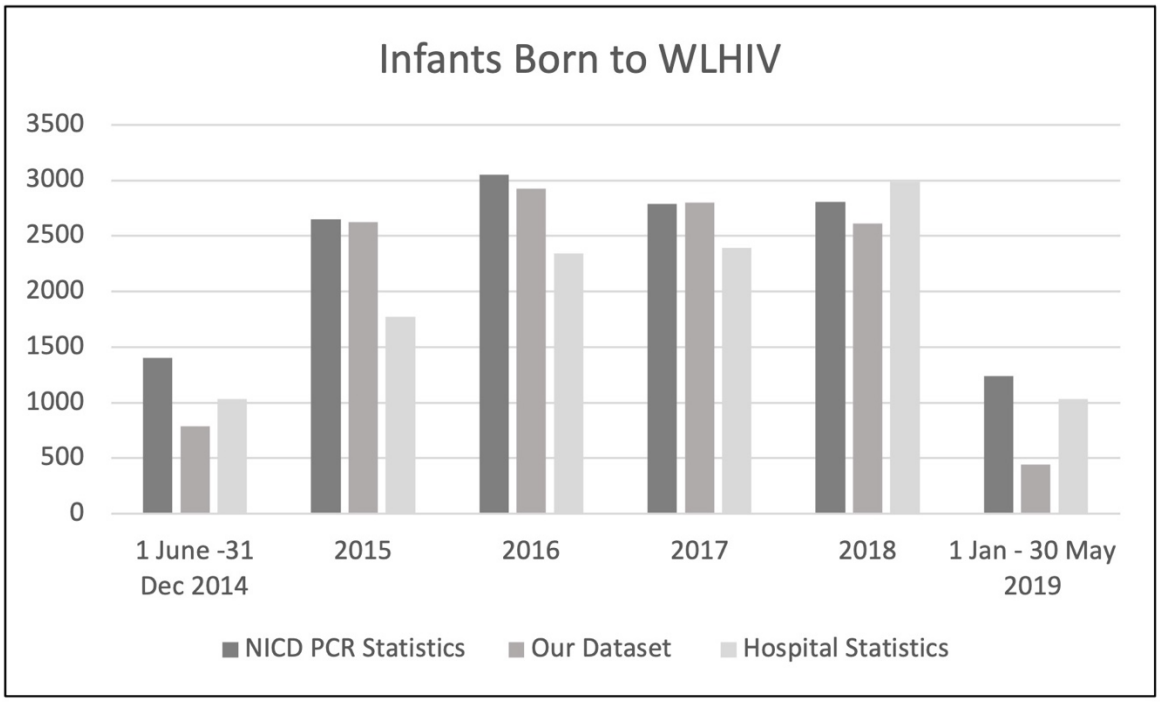


Figure 1: Dataset coverage comparison

First and last columns' Hospital Statistics and Our Dataset were calculated as 7 month and 5 month averages, respectively, as only annual hospital statistics were available

2017: No hospital data for March and August available- yearly average calculated and used

2018: Hospital data only available for Feb, May, August, September. Average calculated for year.

2019: Hospital data for 11 months available. 5 month average calculated

Our dataset looked at 13375 mother child pairs, of which 13328 mothers consented to data collection. Figure 2 illustrates the trends in neonatal HIV infection from June 2014- May 2019.

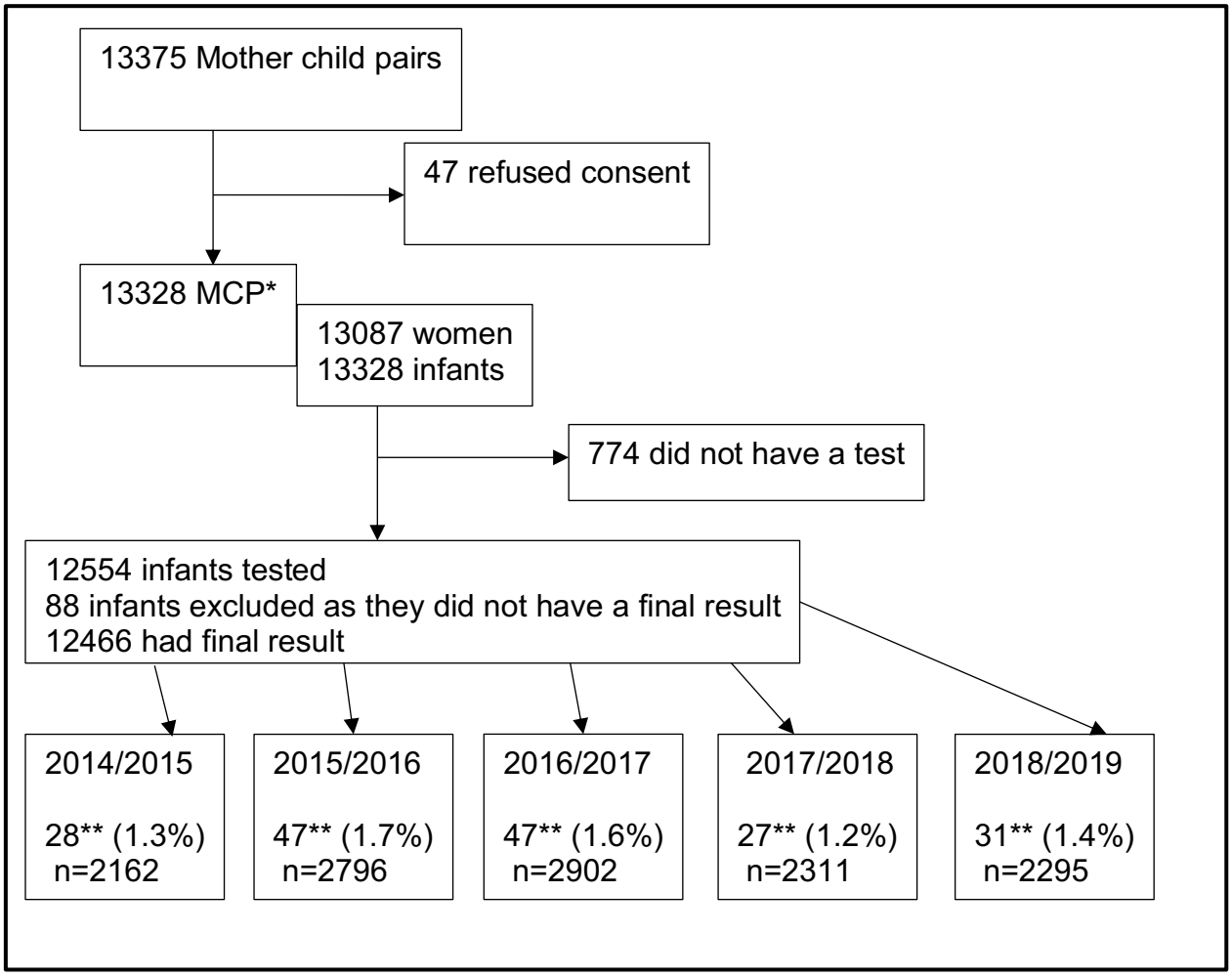


Figure 2: Trends in detectable HIV infection June 2014-May 2019

*MCP: mother child pairs

**number of infants with detectable HIV

Table 1: Characteristics of infected and non-infected infants born to WLHIV.

	Prevalence of the risk factor recorded N (%)	**Birth PCR Positive N (%)**	**Birth PCR Negative N (%)**	**P-value %**
Female	6109/12407 (50)	100 (1.6)	6009 (98.4)	0.070
Male	6298/12407 (50.7)	79 (1.3)	6219 (98.8)	
Assisted Delivery	9/9690 (0.1)	0 (0)	9 (100)	0.090
Caesarean Section	3256/9690 (34)	38 (1.2)	3218 (98.8)	
Natural Vaginal Delivery	6425/9690 (67)	112 (1.7)	6313 (98.3)	
Sick infant	1069/9073 (12)	31 (3)	1038 (97)	<0.001
Well infant	8004/ 9073 (88)	118 (1.5)	7886 (98.5)	
Premature <37 weeks	816/7579 (11)	21 (2.3)	795 (97.4)	0.012
Term	6763/7579 (89)	96 (1.4)	6667 (98.6)	
ELBW <999g	81/9934 (0.8)	2 (2.5)	79 (97.5)	0.009
VLBW (1000g-1499g)	190/9934 (1.9)	7 (3.7)	183 (96.3)	
Low Birth Weight (1500-2499g)	1536/9934 (16)	33 (2.2)	1503 (97.8)	
Normal Birth Weight	8016/9934 (82)	111 (1.4)	7905 (98.6)	
Cold Months (May-August)	4411/12466 (35)	79 (1.8)	4332 (98.2)	0.016
Warm Months (September-April)	8055/12466 (65)	101 (1.3)	7954 (98.7)	
Normal apgar at 1 min (≥8)	7553/11698 (65)	116 (1.5)	7437 (98.5)	0.096
Low apgar at 1 min (<8)	4145/11698 (35)	48 (1.2)	4097(98.8)	

ELBW: extreme low birth weight; VLBW: Very Low Birth Weight

Neonatal and Birth Factors

No infants born via assisted delivery were infected and mode of delivery did not show any significance. In premature infants, 2.3% were HIV infected as opposed to only 1.4% of term infants infected (p=0.012). Higher percentages of low birth weight infants tested positive as compared to normal birth weight infants (2.2 vs 1.4%) (p=0.009). In all infants ill enough to warrant admission, 3% were HIV infected versus well infants who had a 1.5% rate of HIV infection (p<0.001). There was also a trend in seasonality, with cold seasons showing higher percentages of infected infants (1.8 vs 1.3%). (p=0.016). Apgar scores, method of delivery and gender showed no statistically significant difference.

Table 2: Maternal Factors of WLHIV at RMMCH June 2014 – May 2019

	Prevalence of mothers with risk factor recorded **N (%)**	**Birth PCR Positive Infants** **N (%)**	**Birth PCR Negative Infants** **N (%)**	**P-value %**
Parity 1	1468/9138 (16)	25 (1.7)	1443 (98.30)	0.65
2	3456/9138 (38)	59 (1.7)	3397 (98.3)	
3	2718/9138 (30)	38 (1.4)	2680 (98.6)	
≥ 4	1496/9138 (16)	28 (1.9)	1468 (98.1)	
Gravidity 1	1133/9137 (12)	21 (1.9)	1112 (98.1)	0.48
2	3052/9137 (33)	57 (1.9)	2995 (98.1)	
3	2859 (31)	40 (1.4)	2819 (98.6)	
≥4	2093 (23)	32 (1.5)	2061 (98.5)	
Maternal Age <20 (adolescent)	305/12204 (2)	11 (3.6)	294 (96.4)	<0.001
20-30	5343/12204 (44)	97 (1.8)	5246 (98.2)	
30-40	5914/12204 (48)	66 (1.1)	5848 (98.9)	
≥40	642 (5.2)	3 (0.5)	639 (99.5)	
Advanced maternal age ≥35	2896 /12204 (24)	22 (0.8)	2874 (99.2)	<0.001
Booking status Booked	8859/9239 (95.9)	129 (1.5)	8730 (98.5)	<0.001
Unbooked	380/9239 (4)	20 (5.3)	360 (94.7)	
Time of booking Booked <20 weeks gestation	5064/8899 (57)	109 (2.1)	4955 (97.9)	<0.001
Booked ≥20 weeks gestation	3835/8899 (43)	37 (0.96)	3798 (99.04)	
Maternal HIV diagnosis after delivery	139/9124 (1.5)	14(10.1)	125 (89.9)	<0.001
Pre-conception	4288/9124 (47)	42 (1)	4246 (99)	
<30 days before delivery	467/9124 (5)	32 (6.9)	435 (93.1)	
1-3 months before delivery	1166/9124 (13)	30 (2.6)	1136 (97.4)	
3-9months (+ before conception)	3064/9124 (34)	33 (1.1)	3031 (98.09)	
Duration maternal ART treatment No treatment	2912/12249 (24)	66 (2.3)	2646 (97.7)	<0.001
1 day-4 weeks	274/12249 (2.2)	14 (5.1)	260 (94.9)	
4-12 weeks	1152/12249 (9.4)	26 (2.3)	1126 (97.7)	
>12 weeks	7911/12249 (65)	71 (0.9)	7840 (64.0)	
Maternal ART Status ART by birth	9337/12249 (76)	111 (1.2)	9226 (98.8)	<0.001
No ART by birth	2912/12249 (25)	66 (2.3)	2846 (97.7)	
Most recent maternal CD4 at delivery <200	1066/6310 (17)	35 (3.3)	1031 (16.3)	<0.001
200-350	1618/6310 (26)	41 (0.7)	1577 (97.5)	
350-500	1590/6310 (25)	24 (1.5)	1566 (98.5)	

>500	2036/6310 (33)	26 (1.3)	6184 (98)	
Most recent Viral Load at delivery <50	2771/5647 (49)	2 (0.07)	2769 (99.93)	<0.001
50-1000	1687/5647 (30)	21 (1.3)	1666 (98.7)	
>1000	1189/5647 (21)	106 (8.9)	1083 (91.08)	

Maternal Factors.

In infants with birth detectable HIV results, this study found that the maternal age group with highest rate of infected infants were adolescents (3.6% vs 1.8% for mothers aged 20-30) (p<0.001). The rate of birth positive infants decreased with maternal age (p<0.001). Unbooked mothers had more than double the percentage of HIV infected infants than booked mothers (5.3% vs 1.5%) (p<0.001). In booked mothers those who booked before 20 weeks had a higher infection rate than those who booked after 20 weeks. (2.1% vs 0.96%) (p<0.001). The rate of neonatal HIV infections was high in mothers who had been on ART for less than 1 month. (5.1% vs 2.3% after 1 month) (p<0.001), had CD4 counts below 200 (3.3% vs 0.75% at CD4 200-300) (<0.001) and had a HIVVL of >1000 (8.9% vs 1.3% if VL 50-1000) (p<0.001). The rate of birth positive infants was highest when mothers were diagnosed within a month of delivery (10.1% vs 1% pre-conception) (p<0.001), followed by those whose mothers were diagnosed within three months of giving birth.

Discussion

This study illustrates that the rate of HIV infection among infants at birth remained relatively consistent from June 2014- May 2019, ranging from 1.3-1.7%. This was slightly lower to a similar hospital in Cape Town studied from July 2013 and August 2015 which showed a 2% positivity rate.[24] It is evident that there are risk factors that increase the likelihood that an HIV exposed newborn will be infected. This has been studied in various populations and multiple centres around the world. One of the crucial factors identified as contributing to higher mother-to-child HIV transmission in South Africa is poor control of maternal HIV viral load (VL). Absence and shorter duration of maternal antiretroviral treatment has been linked to higher rates of infected infants.[25] Our study correlates with previous studies showing lower

maternal CD4 and higher maternal viral loads corresponding with higher rates of infected infants.[26, 27]
In our study, adolescent maternal age and unbooked mothers were significant risk factors. Infant risk factors identified include prematurity, low birth weight, ill infants and those born in cold seasons.

Our results were in keeping with a KwaZulu-Natal based hospital study from 2002-2005, which found that the median HIVVL in mothers of HIV-infected infants was higher than in mothers of HIV-uninfected infants.[27] In Rwanda, lack of maternal disclosure of HIV status was also found to be a significant contributary factor. This risk factor was not explored in this study and could be included in future South African studies.[28] Absence of ART during pregnancy, and prolonged rupture of membranes have all been described to increase the risk of MTCT. In 1992, a European Collaborative Study showed that MTCT was higher in vaginal deliveries in which episiotomy, scalp electrodes, forceps, or vacuum extractors were used, but only in centres where these procedures were not routine.[25, 26, 29] In contrast, method of delivery was not found to be significant in our study. They also showed higher rates in mothers with lower CD4 counts and infants born at less than 34 weeks' gestation. The findings of our study illustrates maternal and infant risk factors for HIV infection. Infants born to mothers who are newly diagnosed as HIV positive, adolescent mothers, unbooked mothers, mothers with viral loads > 1000, CD4 <500. Mothers on ART for less than three months had a higher risk for being diagnosed with HIV, in keeping with current data.

Our dataset trends showed significant infant risk factors including premature birth, infants with low birth weight, infants ill enough to warrant admission, and infants born in colder seasons. Further research is needed to explore the effects of climate on the transmission of HIV from mother to child. Surprisingly, in booked mothers, those who booked before 20 weeks' gestation had a higher infection rate than those who booked after 20 weeks (2.1% vs 0.96%) ($p<0.001$). This finding requires further studies.

Children in sub-Saharan Africa infected with HIV perinatally have a much higher risk of dying than those infected through breastfeeding. Early diagnosis and treatment of HIV in newborns is crucial so as to alleviate the burden of morbidity and mortality.[2, 5-13] In a previous study done at RMMCH, it was shown that, compared with laboratory-based testing (LABT), POCT was associated with good performance, improved rates of result return, and reduced time to ART initiation.[15] It therefore stands to reason that POCT is a worthwhile endeavour for healthcare administrations in countries with a high burden of HIV.[16-19] POCT has been shown to decrease time to diagnosis and treatment of HIV, as well as increase the amount of infants initiated on ART within the first two months post delivery.[16-19] The identification of high-risk infants at birth could allow more targeted testing and follow-up measures, decreasing the morbidity and mortality of untreated neonatal HIV and thereby ultimately saving costs in a resource constrained environment.

Diagnostic challenges within the realm of neonatal HIV testing are also commonly seen and are a significant obstacle toward infant HIV diagnosis.[12] Indeterminate results, discordant results and lab errors, among others, all contribute to the delay in identification and initiation of ART in HIV exposed infected (HEI) infants.[12] The use of POCT for initial, as well as repeat testing in children with diagnostically ambiguous results would help to lessen the already significant delay in therapeutic management as median time of result return for POCT has been shown to be one day, compared to ten days for LABT results.[15]

In our setting one also cannot ignore the socio-economic factors that play a role in the diagnosis and treatment of HIV. Faster identification of HIV infection may result in less missed opportunities in treatment initiation as patients face social obstacles such as transport costs and inability to miss workdays to obtain their results at follow-up appointments. There is a significant need to further stratify and identify both the physical and socio-economic risks and trends of HIV infection within an exposed population of infants in the South African setting, in order to optimise available resources and provide just and relevant care to patients. Targeting interventions such as POCT to high risk infants could expedite treatment and save overall costs by decreasing the toll of morbidity within a limited national health budget.

Our study had limitations and strengths. Hospital and NICD datasets were used for comparison to assess completeness of our dataset. Limitations of these datasets are that the NICD tests include repeats and errors. We did not have access to the individual identified data to remove duplications as that was beyond the scope of the study. While routine hospital statistics are kept, they were inconsistent, as staffing for these purposes fluctuates. There was also a high patient turnover in obstetric units leading to inaccurate data collection. Some positive tests were not repeated, and hospital data is not always complete as it is dependent on staffing. Patient factors such as patients moving out of testing areas due to high turnover also have to be considered as a limitation to our data collection. For hospital data, months from 2017-2019 had missing data due to staff shortages and averages had to be calculated, making it difficult to compare trends such as seasonality with hospital data. NICD data shows total number of PCR tests but does not account for errors or repeat tests.

In our study population 774 infants were not tested at birth. Possible reasons for this include lack of consent, high patient turnover, insufficient staffing, infants not identified at birth and similar obstacles. Due to the long processing time of PCR tests patients are often discharged before PCR results are obtained and this leads to poor rates of repeat tests. Of 148 PCR error results only 63 were repeated. PCR tests repeated at local clinics and other centres were not captured in our dataset. This additionally illustrates the barrier that high conventional PCR turnover time adds to continuity of patient care. The major strength of our study included a large dataset, collected over a number of years by dedicated staff. This yielded a large study population.

Conclusion

While it is ideal for all HIV exposed infants to have point of care HIV testing, it may, at least initially, not be financially feasible in a resource constrained environment. High risk infant groups could be targeted to implement POCT to expedite HIV diagnosis to reduce morbidity and mortality, which would also decrease the overall financial burden of this disease on healthcare systems. Maternal risk factors that could be targeted include those who are newly diagnosed as HIV positive,

adolescent mothers, unbooked mothers, mothers with viral loads > 1000, CD4 <500, or mothers on ART for less than three months. HIV exposed infants who are born premature (<37 weeks), those born with a birth weight below 2499g and those ill enough to warrant admission could also be classified as high risk and targeted for POCT to expedite diagnosis and treatment of HIV.

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Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr E Wannenburg

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M2011161

NAME: (Principal Investigator)	Dr E Wannenburg
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*Rate of neonatal birth HIV positive tests and description of related risk factors in Johannesburg - can point of care testing be targeted effectively?*
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M170778
SUPERVISOR:	Professor KG Technau and Dr J Fredericks
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/01/27

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

Plagiarism Certificate



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Elzette Wannenburg (Student number: 363171) am a student registered for the degree of MMED in the academic year 2023.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 09/03/2023

Submissible format Guideline: The Pediatric Infectious Disease Journal (PIDJ)

HIV Reports: The section comprises of high-quality, high-impact original articles and brief reports of epidemiologic, clinical, translational and implementation science studies pertaining to the prevention, treatment and outcomes of HIV infection in infants, children, and adolescents. HIV reports should contain a maximum of 3,000 words. Word count does not include title page, abstract, tables, figures, references, or reference citations in the text.

Text: Organize the manuscript into four main headings, Introduction, Materials and Methods, Results, and Discussion. If a brand name is cited, supply the manufacturer's name and address (city and state/country).

Structured abstract for Original Studies and Supplement Articles: Abstracts must be submitted as a separate file. Limit the abstract to 250 words. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. Use the following subheads: Background, Methods, Results, and Conclusions

Abbreviations: Write out the full term for each abbreviation at its first use unless it is a standard unit of measure. Abbreviations are allowed only if used three times or more in text. For a list of standard abbreviations, consult the American Medical Association Manual of Style, 9th edition, or other standard sources. An abbreviation list is not necessary.

Remember:
Cite figures consecutively in your manuscript.
Number figures in the figure legend in the order in which they are discussed.
Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.
If format or guidelines, specifically exceeding number of tables or figures, is not adhered to, the Editorial Board reserves the right to move data to Supplemental Content as they best see fit.

Figure legends: Include legends for all figures. They should be brief and specific, and they should appear on a separate manuscript page after the references. Legends should be part of the manuscript file on the disk. Use scale markers in the image for electron micrographs and indicate the type of stain used.

Color figures: The journal accepts for publication color figures that enhance an article. Authors who submit color figures will be given the option to pay the cost to publish the figures in color in print. If the authors decline to pay the color cost, color figures will be published in black-and-white in print and in color in the electronic version at no charge. There is no charge for publication of color figures as Supplemental Digital Content or in online only articles.

Tables: Create tables using the table creating and editing feature of your word processing software (e.g., Word, WordPerfect). Do not use Excel or comparable spreadsheet programs. Provide a separate document for each table. Cite tables consecutively in the text, and number them in that order. Key each on a separate sheet, and include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviation not already defined in the text). Do not embed tables within the body of the manuscript. They should be self-explanatory and should supplement, rather than duplicate, the material in the text. In each table, the genus of each genus-species must be written out at its first appearance.
Style: Stedman's Medical Dictionary (27th edition) and Merriam Webster's Collegiate Dictionary (10th edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. Capitalize the trade names of drugs and place them in parentheses after the generic names. To comply with trademark law, include the name and location (city and state/country) of the manufacturer of any drug, supply, or equipment mentioned in the manuscript. Use the metric system to express units of measure and degrees Celsius or degrees Fahrenheit consistently throughout the manuscript to express temperatures and use SI units rather than conventional units. Abbreviate "litre" in such forms as "3 units/L" and "5 mL"; write out when used alone (10 litres; 0.5-liter gavage). See also Day RA, ed. How to Write and Publish a Scientific Paper. 5th ed. Phoenix, AZ: The Oryx Press, 1998.

References: The authors are responsible for the accuracy of the references. Cite the references in text in the order of appearance with superscript numbers, outside of punctuation, including those references cited in tables and figure legends at the chronologic citation of the tables and figures in text. Key the references (double-spaced) at the end of the manuscript. Cite unpublished data, such as papers submitted but not yet accepted for publication or personal communications, in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names or access the list at https://www.nlm.nih.gov/bsd/serfile_addedinfo.html. Sample references are given below.

https://edmgr.ovid.com/pidj/accounts/ifauth.htm

Appendix E: Research Protocol

Title

Rate of neonatal birth HIV positive tests and description of related risk factors in Johannesburg - can point of care testing be targeted effectively?

Student

Dr Elzette Wannenburg 363171

Supervisors

Assoc. Prof Karl Technau
Dr Joy Fredericks

Abstract

HIV exposed neonates may test HIV PCR negative or positive at birth, the first time-point of testing. Recent data describing the rate of birth HIV infection as well as risk factors within the population of neonates in the South African setting requires updating. The question also remains whether there are any changes in the rate of testing HIV positive at birth over time and what the current important associations are within this population. Once these risk factors are stratified, recommendations can be made to expedite the diagnosis and initiation of antiretroviral therapy in high risk newborns, whilst optimising scarce resources, for example point of care polymerase chain reaction (PCR) testing (POCT). It is currently being debated whether the Department of Health should invest in POCT for HIV diagnosis and management. This descriptive study is a secondary data analysis of a prospectively collected dataset (June 2014 onwards) and aims to examine the existing HIV database at Rahima Moosa Mother and Child Hospital to evaluate the rate of HIV infection amongst HIV exposed newborns at birth and to identify risk factors associated with HIV transmission from mother-to-child (detectable at birth) in order to provide a potential strategy for use of POCT in the neonatal population, and thereby expedite diagnosis and treatment to decrease the mortality and morbidity of infected neonates.

Introduction

Since the discovery of human immunodeficiency virus (HIV), substantial effort has been made to prevent the transmission of the virus to children. In 2018, 260 000 children in South Africa were living with HIV.[30] Worldwide, and specifically on the African continent, combatting mother-to-child HIV transmission (MTCT) remains one of the largest obstacles to eliminating HIV related childhood morbidity and mortality.

MTCT of HIV poses challenges at multiple biological, social and psychological levels.[31] The vertical transmission of the virus can occur intrauterine, intrapartum or postpartum via breastfeeding.[3] Since 2015, the South African National Department of Health has recommended that all HIV Exposed neonates have a polymerase chain reaction (PCR) test at birth and at later time points, instead of only at 6 weeks of age. This has potentially allowed the identification and treatment of infected neonates before they become symptomatic.[32] In 2018, South African Birth HIV PCR testing coverage was as high as 93.5%, while the national percentage of intrauterine percent Mother to Child Transmission (MTCT) risk was 0.9%.[31] Hence, despite the widespread implementation of Prevention of Mother to Child Transmission of HIV (PMTCT) strategies in South Africa, for every 100 000 live births in South Africa, 245 children are born with HIV infection.[31] These children need early diagnosis and treatment initiation to decrease their high risk of morbidity and mortality. [12, 31, 33-40]

If initial HIV infection is not prevented the most effective secondary intervention is to initiate antiretroviral therapy (ART) as soon as possible. For this reason every effort must be made to diagnose newborns at birth, as a high mortality has been associated with these children once they are admitted for HIV related symptoms.[40] Children in sub-Saharan Africa infected with HIV perinatally have a much higher risk of dying than those infected through breastfeeding. Marston et al described that only 33% of perinatally infected patients survived five years post HIV diagnosis and only 1 in 4 survived past the age of ten.[34] Early diagnosis and treatment of HIV in newborns is crucial so as to alleviate the burden of morbidity and mortality[12, 31, 33-40]

Since 2014, the policy at Rahima Moosa Mother and Child Hospital has been to test all HIV exposed neonates at birth for HIV via PCR testing. A significant possible intervention to expedite early treatment is the use of point of care PCR testing (POCT)[14]. In a previous study done at this centre it was shown that compared with laboratory-based testing (LABT), POCT was associated with good performance, improved rates of result return, and reduced time to ART initiation.[41] It is currently being debated whether the POCT technology currently already available in the tuberculosis diagnostic field (TB GeneXpert) should be broadened to include HIV diagnostic and monitoring tests. This could make a significant difference with regards to early diagnosis and initiation of antiretroviral therapy. The identification of high-risk neonates at birth would allow more targeted testing and follow up measures, decreasing the morbidity and mortality of untreated neonatal HIV and thereby ultimately saving costs in a resource constrained environment. Diagnostic challenges within the realm of neonatal HIV testing are commonly seen and are a significant obstacle toward infant HIV diagnosis. [12] Indeterminate results, discordant results and lab errors, among others, all contribute to the delay in identification and initiation of ART in HIV exposed infected (HEI) neonates. [12] The use of POCT for initial, as well as repeat testing in children with diagnostically ambiguous results would help to lessen the already significant delay in therapeutic management as median time of result return for POCT has been shown to be one day, compared to ten days for LABT results. [41] There is also room for more research regarding the value of point of care maternal viral load testing to stratify perinatal transmission risk and to prioritize testing of high-risk neonates as well as to optimise immediate antiretroviral prophylaxis in uninfected exposed high-risk neonates.

It is evident that there are risk factors that increase the likelihood that an HIV exposed newborn will be infected. This has been studied in various populations and multiple centres around the world. One of the crucial factors identified as contributing to higher mother-to-child HIV transmission in South Africa is poor control of maternal HIV viral load (HIVVL). From 2002-2005 a KwaZulu-Natal based Hospital study found that the median HIVVL in mothers of HIV-infected infants was higher than in mothers of HIV-uninfected infants[42] In Rwanda, lack of maternal disclosure of HIV status was also found to be a significant contributary factor. [43] Absence of antiviral therapy during pregnancy [44], and prolonged rupture of membranes [45] have all been

described to increase the risk of MTCT. In 1992 a European Collaborative Study[46] showed that MTCT was higher in vaginal deliveries in which episiotomy, scalp electrodes, forceps, or vacuum extractors were used, but only in centers where these procedures were not routine. They also showed higher rates in mothers with lower CD4 counts and neonates less than 34 weeks gestation. More studies are needed in the South African neonatal population to describe relevant risk factors for HIV infection in HIV exposed neonates to identify high risk groups and target them specifically and follow them up closely to ensure urgent testing and treatment.

In a resource limited country such as South Africa, policy makers and health care professionals must constantly re-evaluate the ethical use and distribution of available resources. Updated HIV infection rates and trends allow us to tailor our clinical approach to diagnosis and management of our patients. Newer diagnostic methods such as POCT do come with a significant cost difference as opposed to the previously used LABT. It therefore stands to reason that these tests would be best used in the population group that would have the highest benefit, while ensuring that those who need instant testing are not missed. In our setting one also cannot ignore the socio-economic factors that play a role in the initiation and treatment of HIV. Faster identification of HIV infection may result in less missed opportunities in treatment initiation as patients face obstacles such as transport costs and inability to miss workdays to obtain their results at follow up appointments. Looking at the bigger picture, this could likely result in a net decrease in the overall cost burden of HIV related morbidity and mortality on a strained healthcare system. There is a significant need to stratify and identify the risks and trends of HIV infection within an exposed population of neonates in the South African setting, in order to optimise our available resources and provide just and relevant care to patients. Targeting interventions such as POCT to high risk neonates can possibly expedite treatment and save overall costs within our limited national health budget.

Aims & Objectives

Problem Statement

HIV exposed neonates may test HIV PCR negative or positive at birth. Recent data describing the rate of birth HIV infection within the population of neonates at RMMCH requires updating. The question also remains whether there are any associations with an increased risk of testing HIV positive at birth within this population. Once these risk factors are stratified, recommendations can be made to expedite the diagnosis and initiation of antiretroviral therapy in high risk newborns, whilst optimising scarce resources.

Aim

To evaluate the rate of HIV infection detectable at birth amongst HIV exposed newborns at Rahima Moosa Mother and Child Hospital and to identify risk factors associated with HIV transmission from mother-to-child in order to offer a potential strategy of optimal POCT use should it become available.

Objectives

- To determine the rate of HIV infection detected during universal birth HIV PCR testing of (HIV) exposed neonates tested during the first week of life at Rahima Moosa Mother and Child Hospital (RMMCH) from June 2014 to June 2019
    - By describing the diagnostic outcomes
        - Infected
            - Confirmed Infected
            - Unconfirmed Infected
        - Non-infected
        - Missed opportunities
        - Diagnostic dilemmas
- To describe the population of HIV exposed neonates at birth in terms of maternal, neonatal and birth characteristics at the time of birth HIV PCR testing and assess associations with birth detectable HIV infection.

- Based on the above characteristics, to develop a simple screening algorithm to distinguish high risk groups for more targeted instant birth testing such as POCT to optimize use of the resource towards the highest possible yield

Study Design & Methods

Study Design – retrospective descriptive cohort study.

- This is a secondary data analysis of data that was at that time collected prospectively.
- The coverage of PCR testing will be described using routine hospital statistics of live births and live births to HIV positive women.
- Data collected from June 2014- June 2019 at RMMCH postnatal wards will be analysed to describe the neonatal, maternal and birth characteristics of HIV exposed newborns and to determine the rate of HIV PCR positive infection at birth. HEI and HEU neonates will be compared to determine whether any of these characteristics are associated with testing HIV PCR positive at birth.

- ***Setting.***
  - Rahima Moosa Mother and Child Hospital.
    - This is an urban academic provincial hospital in Johannesburg, South Africa. RMMCH specializes in Maternity, Neonatal and Paediatric services.
    - Within the South African setting, the Empilweni Services and Research Unit (ESRU) at Rahima Moosa Mother and Child Hospital has been actively involved in HIV research and trials since 2003. The clinic manages HIV Exposed Uninfected (HEU) as well as HIV Exposed Infected (HEI) infants and children. It is one of the largest Paediatric HIV clinics in the country and currently has over 1600 children in its care. In 2014, a pilot project was initiated via Empilweni to introduce universal birth HIV testing. In the preceding 9 months there had been intensive testing of high-risk neonates at birth and prior to this there had been ad hoc testing from 2013. In 2015 the South African National Consolidated guidelines for the prevention of mother to child transmission of HIV (PMTCT) and the

management of HIV in children, adolescents and adults were published and followed.

- Data pertaining to HIV is collected by counsellors and phlebotomy staff employed by the Empilweni Services and Research Unit (ESRU) in collaboration with the Department of Health staff and has been ongoing since 2014 and captured electronically. Women are assessed and interviewed post-delivery and any women who are found to be living with HIV are counselled and offered treatment. The process aimed to capture all live births to women living with HIV (WLHIV). Interviewed women were invited to sign a data sharing consent (current version attached as Appendix A). An interview sheet was used for collection of routine data relevant to the HIV counselling and PMTCT process (current version attached as Appendix B). Data was collected on a REDCap database hosted at the University of the Witwatersrand. [22] Data was collected under the Human Research Ethics Committee Protocols "Cohort Study of HIV-infected and exposed Children receiving care at Rahima Moosa Mother and Child Hospital supported by the Empilweni Services and Research Unit and participation in the International epidemiological Databases to Evaluate AIDS (IeDEA) Collaboration" (M170778 [Appendix C] – previously M140760, M090501) as well as "Operational evaluation of standard and point-of-care birth testing of HIV-exposed infants (Protocols M140555 M140639 [Appendix D]).

- Within RMMCH maternal HIV testing is offered to all women and documented in their patient care records. Roughly 1000 babies are born in the obstetric unit each month. During 2015 the HIV prevalence amongst South African women who attended antenatal care was 30.8% [21]
- Neonates born to WLHIV are tested at birth and these mothers were invited for further counselling. Neonates who test positive at birth are traced confirmatory testing is done and they are treated as

per national guidelines. Point of care testing is also offered when available to expedite the treatment process [14]

- ***Participants***
    - Inclusion criteria
        - HIV exposed neonates whose mothers were interviewed during the first week of life at Rahima Moosa Mother and Child Hospital (RMMCH) from June 2014 to June 2019 collection of data
        - The existing database consists of an estimated 220 non negative results for the time period and ~13,000 live birth deliveries to WLHIV recorded

    - Exclusion criteria
        - HIV exposed neonates during the first week of life at Rahima Moosa Mother and Child Hospital (RMMCH) from June 2014 to June 2019 whose mothers refused permission for use of routine data for analysis.

Data Elements and Variables

The following data variables will be *extracted from the existing mother child database* and coded for each neonate:

Neonatal Factors	Maternal Factors	Birth Factors

Month and year of birth
Admission status
• Stayed with mom
• Required observation or admission
  ○ ICU
  ○ High care
• Lodger
  ○ Mother ill
Gestational age in weeks (by Ballard score, early ultrasound or sure dates)
  ▪ Prematurity defined as gestation <37 weeks
Sex of the infant (Male or female)
Birth Weight in grams
• Low birth weight <2500g
• Very low birth weight <1500g
• Extremely low birth weight <1kg
APGAR scores at 1 and 5minutes
	HIV exposure defined as maternal HIV positive via previous diagnosis on history or positive rapid or Elisa test.
	Parity
	Gravidity
	Timing of maternal diagnosis
	• Before pregnancy
	• During pregnancy
	• After delivery
	• unknown
	Maternal age at time of delivery in years
	• <20 years of age
	• 20-30 years of age
	• 30-40 years of age
	• Adolescent defined as age <20 years at time of birth
	• Advanced maternal age defined as >35 years at time of birth
	Most recent maternal HIV VL (RNA copies per ml) and CD4 (cells per microlitre)
	Booking status
	• Booked
	• Unbooked
	Timing of booking (if booked)
	• <20 weeks' gestation
	• >20 weeks' gestation
		Mode of delivery
		• Caesarean section
		(Elective/Emergency/Unknown indication)
		• Normal Vaginal Delivery (NVD)
		• Assisted
		• Unknown

HIV PCR result within first week of life and any follow up testing triggered by a non-negative result • Repeats for errors, positives, indeterminates)	Maternal treatment • Started or not started at time of neonatal testing Duration of maternal HIV treatment in months • Pre-conception • <1 month • 1-4 months • >4 months but after conception	

Outcome measures.

- HIV infection status
  - Confirmed HIV infection
    - defined as birth PCR positive result with confirmatory PCR positive result or detectable viral load result
  - Unconfirmed HIV Infection
    - Defined as only one positive PCR result with no confirmatory PCR or viral load
  - HIV non-infection defined as birth PCR negative result
  - Missed opportunities defined as
    - Patients not identified in time for testing
    - Patients identified but not tested
    - Laboratory errors
      - Clinic factors e.g. incomplete forms, illegible handwriting, wrong specimen tube submitted, insufficient sample
      - Laboratory service factors e.g. Lost in transit, spilled sample, invalid results
  - Diagnostic dilemmas
    - defined as an indeterminate PCR result or discordant first and second PCR results. Results with unclear outcome despite retesting
- PCR testing coverage at birth

    - As a percentage
        - Numerator – number of HIV exposed neonates tested
        - Denominator – live births to HIV positive women at RMMCH from June 2014 to June 2019
- Rate of HIV infection at birth
    - As a percentage
    - Numerator – number of birth HIV PCR positive neonates
    - Denominator – total number of HIV exposed neonates tested with available result

Data Collection, Management & Analysis Methods

Data Collection

- Data will be extracted, with permission, from the existing Empilweni database. At Rahima Moosa Mother and Child Hospital, mothers give consent after birth for testing and data collection. The uptake of consent, for collection of data into the Empilweni Database, is >95%.

Data Management

- Data will be kept in password protected Microsoft Excel spreadsheet once extracted from REDCap. [22] Only the researchers mentioned in this protocol will have access to the dataset. Dataset will be reviewed, and a quality check will be done to identify and describe outliers, incorrect values and missing values. Data will be cleaned by assessing all variables for outliers and implausible values. File review will not be done, nor will additional data be sought from other sources. Data quality work has been ongoing during the collection of this database as capacity allowed to ensure that regular data cleaning was done throughout.

Data Analysis – for each objective

- Data will be analysed using Excel (Version 16.28 19081202), Epi-Info (Version 5.3 CDC, Atlanta, GA, USA, 2011), SAS software (Version 9·4, SAS Institute Inc., Cary, NC).
- Describe rates as frequencies and proportions

- Comparison of the trends in rate of HEI newborns over the 5 years studied, expressed graphically
- Identification of associations / possible risk factors for birth PCR positive results in HIV exposed neonates
    - Comparison of all neonatal, maternal and birth characteristics looking at the frequencies and percentages of neonates testing HIV PCR positive for each variable and using $\chi 2$ test analysis to ascertain whether there is a statistically significant relationship between the two categorical variables and t-test for continuous variables.
    - Multivariate logistic regression to assess effects of associations.
- Risk factor analysis
    - Ascertain the most common risk factors in PCR positive babies by assessing 1) completeness of data for each risk factor, 2) the rate of occurrence of each risk factor in the infected and uninfected infants 3) comparing whether there is a statistically significant difference between the groups
    - Risk factors which tend to occur together. This will be done by assessing which risk factors that have been found can be practically grouped together taking into account clinical context and feasibility.

- Tabulated results of tally numbers, frequencies, percentages and p values for the dataset and variables
- Missing data will be described as such, possible reasons for missing data will be discussed

Ethical Issues

- Data will be de-identified and anonymised using a numbering system.
- There are no sponsors for this research.
- Consent requiring data that has already been collected by Empilweni clinic for research
    - There is prior ethics approval of the Empilweni database with regards to research and specifically birth testing. Advice will be sought from the paediatric research protocol review committee with proposal that a

waiver from HREC be requested to use this data for the purposes of this study.

- Permission to receive a de-identified data extract of the above data fields in the Empilweni database has been sought from the gatekeeper, Leslie Rose.
- Institutional permissions to conduct research at Rahima Moosa Mother and Child Hospital will be obtained from the hospital CEO.
- Current birth and data collection forms attached – see appendix attached.

Resource Requirements

- Own laptop
- Own paper, printing equipment and stationery
- No hospital or additional resources used

Study Plan

	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**
Protocol Development							
Protocol Submission							
Protocol Amendments (if needed)							
Data Collection							
Data Analysis							
Submission of final research report							

Dissemination & Outcome

- Submission to University of Witwatersrand for Masters of Medicine
- Presentation at department, faculty research days as well as local conference will be attempted.
- Aim for publication of research
    - Possible journals that will be targeted:
        - International
            - Paediatric Infectious Diseases Journal
        - Local
            - Southern African HIV Clinicians Society Journal

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Protocol Abbreviation List

ESRU : Empilweni Services and Research Unit

HEI : HIV Exposed Infected

HEU : HIV Exposed Uninfected

HIVVL : HIV Viral Load

LABT : Laboratory Based Testing

MTCT : Mother to Child Transmission

PCR : Polymerase Chain Reaction

POCT : Point Of Care Testing

RMMCH : Rahima Moosa Mother and Child Hospital

WLHIV : Women Living With HIV

Protocol Appendices

Appendix A : data sharing consent

Appendix B : current data form

Appendix C : ethics and approvals

CONSENT FORM: USE OF CLINICAL INFORMATION

Dear Guardian, Parent and Patient,

You/your child are currently attending Rahima Moosa Mother and Child Hospital for treatment of problems you/your child are/is currently experiencing. The Hospital not only renders treatment but is also actively involved in conducting research aimed at improving the quality of care we deliver. From time to time such research involves the use of patient records from which information is extracted. The use of such information is subject to:

1) Approval from the Committee for Research on Human Subjects (University of the Witwatersrand)
2) Anonymity i.e. the identity of the patient from whose file information is extracted is never revealed to anyone but the researcher unless specific consent is obtained to do so.

We are part of an international collaboration called IeDEA that aims to improve our knowledge about HIV/AIDS by sharing information with other sites and doing scientific analysis. We share our routine

clinic information (e.g. weight and height measurements, blood test results and treatment details which are all routinely collected) with IeDEA regularly but do not include your name or any identifying details.

Part of the IeDEA work involves specific “LINKAGE” projects where we use identifying details (e.g. names or ID numbers) to match with other databases (e.g. the home affairs data or the cancer register) with the purpose of understanding patient movement between institutions and services. In the process data is transferred with high level security and only by professionals approved by the Ethics committee so that no information is accidentally released. If data is matched with other databases, only the match is reported, not the person who is matched. We will then only use the information to help services improve. Only in rare cases where we see that the match may help us to help you/your child (e.g. we see that a parent of one of the children in our clinic has died) will we act or try help.

As other projects using routinely collected data arise we would like to obtain your consent to use information from your file for the purpose of research, subject to the aforementioned conditions. If research arises that needs more detailed information we will approach you for further specific consent first. If you choose not to give consent, this will not compromise your treatment in any way. If at any time you choose to withdraw consent you are free to do so and will not be prejudiced in any way. For any concerns about the approval processes followed at the University of the Witwatersrand please contact the Human Research Ethics Committee: Ms Zanele Ndlovu (Administrative Officer) 011 717 2700, zanele.ndlovu@wits.ac.za or Mr Rhulani Mkansi (Administrative Officer) 011 717 2656, Rhulani.mkansi@wits.ac.za .

PATIENT NAME:…….

A.

I.....hereby give consent for my/my child’s records to be used as per the abovementioned conditions for the purposes of research:

GUARDIAN NAME and RELATION:.....

SIGNATURE:…….. DATE:.....

CHILD/ADOLESCENT:..... WITNESS:.....

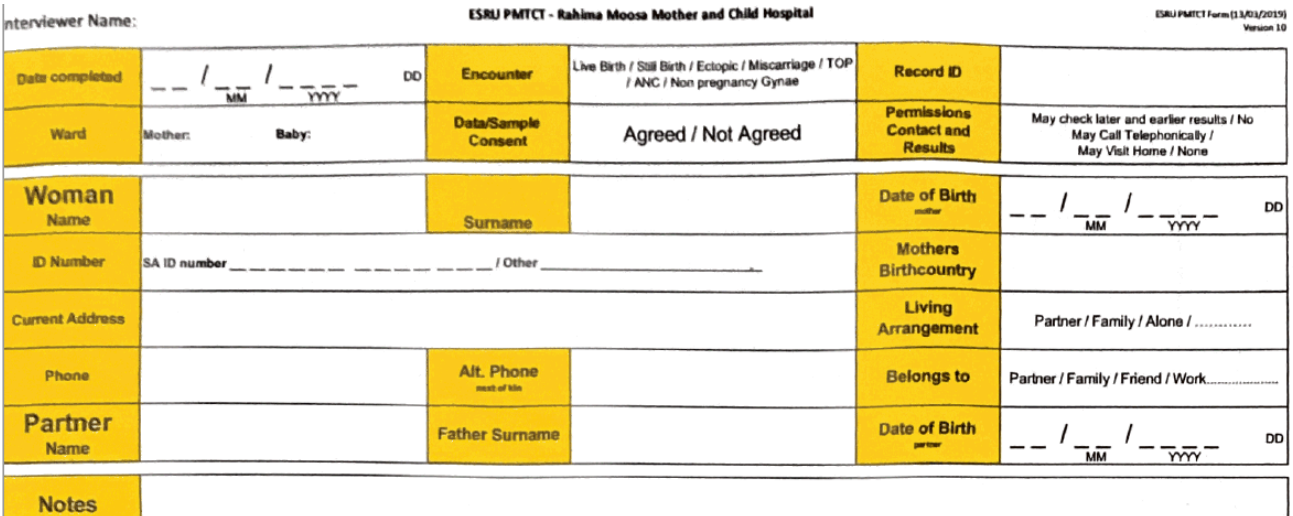
B.

I.....do not give consent for my/my child’s records to be used:

GUARDIAN NAME and RELATION:……..

SIGNATURE:..... DATE:.....

CHILD/ADOLESCENT:..... WITNESS:.....



Interviewer Name:

ESRU PMTCT - Rahima Moosa Mother and Child Hospital

ESRU PMTCT Form (13/03/2019) Version 10

Date completed	__ / __ / __ __ __ __ DD MM YYYY	Encounter	Live Birth / Still Birth / Ectopic / Miscarriage / TOP / ANC / Non pregnancy Gynae	Record ID	
Ward	Mother: Baby:	Data/Sample Consent	Agreed / Not Agreed	Permissions Contact and Results	May check later and earlier results / No May Call Telephonically / May Visit Home / None
Woman Name		Surname		Date of Birth mother	__ / __ / __ __ __ __ DD MM YYYY
ID Number	SA ID number __ __ __ __ __ __ __ __ __ __ __ __ __ / Other _____			Mothers Birthcountry	
Current Address				Living Arrangement	Partner / Family / Alone / .....
Phone		Alt. Phone next of kin		Belongs to	Partner / Family / Friend / Work.....
Partner Name		Father Surname		Date of Birth partner	__ / __ / __ __ __ __ DD MM YYYY
Notes					

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2019/07/26

Professor KG Technau
School of Clinical Medicine
Department of Paediatrics and Child Health
Empilweni Services and Research Unit
Rahima Moosa Mother and Child Hospital

Sent by e-mail to: Karl-Gunter.Technau@wits.ac.za

Dear Professor Technau

Re: **Protocol Ref No: M170778**
Protocol Title: *Cohort study of HIV-infected and exposed children receiving care at Rahima Moosa Mother and Child Hospital Supported by Empilweni Services and Research Unit*
Principal Investigator: Professor KG Technau

Thank you for your letter of 2019/06/18 and for hosting an interesting site visit by Dr Penny and myself on 2019/07/24.

I confirm that the annual progress report provided in your letter is satisfactory and therefore that the Clearance Certificate No. M170778 remains valid until 4 September 2022, subject to continued satisfactory progress. I trust that this assurance will be adequate for the NIH's purposes.

Thank you for keeping us informed.

Yours Sincerely

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

Works2000/Iain0007/Acknowledge.docx

R14/49 Dr Karl-Gunter Technau et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140639

NAME: (Principal Investigator) Dr Karl-Gunter Technau et al

DEPARTMENT: Paediatrics and Child Health
Rahima Moosa Hospital

PROJECT TITLE: Operational Evaluation of Standard and Point-of-Care Birth Testing of HIV-Exposed Infants

DATE CONSIDERED: 27/06/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR:

APPROVED BY: _____
Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)

DATE OF APPROVAL: 25/07/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

_____ _____
Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Rahima Moosa Mother and Child Hospital
Empilweni Clinic

South Africa (Private Bag X20 Newclare 2112) Tel:+27(0)114709421
Fax: +27(0)11 4774117 Email:Lesley.Rose@wits.ac.za

25 October 2019

Dear Dr Elzette Wannenburg

Re: Access to Empilweni Services and Research Unit Birth Testing Database

As gatekeeper access is granted to use Empilweni Services and Research Unit database for the study titled" *Rate of neonatal birth HIV positive tests and description of related risk factors in Johannesburg - can point of care testing be targeting effectively?"*

This permission excludes data from patients that have not signed our data sharing consent forms.

Yours sincerely,

Lesley Rose

Date: 251/10/2019
RN, ADM, BA (CUR)UNISA
Gatekeeper
Empilweni Services and Research Unit
Assistant Manager, Nursing
Empilweni Clinic, Rahima Moosa Mother and Child Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries : Karen Marshall
Tel : (011) 470 9284
Fax : 086 553 4623
Email : Karen.Marshall@wits.ac.za

TITLE OF RESEARCH PROJECT:
"RATE OF NEONATAL BIRTH HIV POSITIVE TESTS AND DESCRIPTION OF RELATED RISK FACTORS IN JOHANNESBURG – CAN POINT OF CARE TESTING BE TARGETED EFFECTIVELY?"

NAME OF RESEARCHER:
Dr Elzette Wannenburg
Department of Paediatrics and Child Health
University of the Witwatersrand

NAME OF SUPERVISOR:
Professor Karl Technau

NHRD REF NO: GP_202008_057

Dear Dr Wannenburg,

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form so as to ensure that the terms of this agreement are complied with at all times.

Yours sincerely,

ACTING CHIEF EXECUTIVE OFFICER
2020:09:21

ADDRESS: Cnr FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB

Empilweni Services and Research Unit
Rahima Moosa Mother and Child Hospital, JHB

South Africa (Private Bag X20 Newclare 2112) • Tel: +27(0)11 470 9421 Cel: +27 (0)82 687 3633 Fax: +27(0)86 553 5046 •
E-mail:karltechnau@gmail.com

23rd February 2020

Dear Dr Wannenburg

Re: Proposed MMed Project titled:
Rate of neonatal birth HIV positive tests and description of related risk factors in Johannesburg - can point of care testing be targeted effectively?

As PI of the study: "Cohort Study of HIV-infected and exposed Children receiving care at Rahima Moosa Mother and Child Hospital supported by the Empilweni Services and Research Unit and participation in the International epidemiological Databases to Evaluate AIDS (IeDEA) Collaboration" (M170778) I have no objection for you to use de-identified data gathered during the project to answer your protocol objectives and am happy to support you in that venture and make the required data available.

Yours sincerely

Karl Technau, MBBCh, Dip HIV Man, DCH, MSc (Med), PhD
Associate Professor, Deputy Director Empilweni Services and Research Unit (ESRU)
Department of Paediatrics and Child Health, University of The Witwatersrand (Wits)
Rahima Moosa Mother and Child Hospital

Tel : +27 11 470 9421
Mobile : +27 82 687 3633
Email : Karl-gunter.technau@wits.ac.za

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