A COMPARISON OF GROWTH BETWEEN HIV EXPOSED AND UNINFECTED AND HIV UNEXPOSED UNINFECTED INFANTS WHO RECEIVED KMC AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL.

Dr. Leshata Abigail Mapatha

Student Number: 1597059

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Supervisors:

Dr F. L Nakwa, MBBCh (Wits), FCPaed (SA), MMed Paeds (Wits), Certificate of Neonatology (SA), Certificate of Paediatric Neurology (SA).

Dr M. Mokhachane, MBBCh, FCPaed (SA), MMed (Wits), Postgraduate Diploma Health Science Education (Wits)

Declaration

I, Leshata Abigail Mapatha, hereby declare that this research is my own work, except where due acknowledgement for assistance received has been made. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted previously for any degree or examination at this or any other University.

Signed **…….** (Signature of candidate)

Date: 25 November 2022

Signed **…**  **…** Signed 

(Supervisor) (Co-Supervisor)

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Dedication

I thank the Almighty God for being with me every step of the way from day one to the last day of my research project.

Author Contribution

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL MOTHER AND CHILD UNIT

DEPARTMENT OF PAEDIATRICS, DIVISION OF NEONATOLOGY

Postgraduate Committee

PV Tobias Building

Parktown

University of the Witwatersrand

04 July 2022

Re: Dr L.A. Mapatha – submission in completion of MMed Paeds

Dr Mapatha, as the primary investigator has performed the following contributions:

1. Protocol development and study design
2. Data collection
3. Data review and statistical analysis
4. Manuscript authorship
5. Collaboration between authors
6. Manuscript submission and review process

We affirm her contribution to this project

Yours faithfully

Dr F L. Nakwa

Dr M. Mokhachane

Submission Format

This research report has been drafted in the Submissible Format as per guidelines issued by the University of the Witwatersrand.

This article is written in the manuscript style required by the journal entitled *Frontiers in Pediatrics* with the intention to publish this original manuscript.

Full, comprehensive author guidelines are available at https://www.frontiersin.org/about/author-guidelines

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- Conflicts of interest are to be declared
- Funding of the project is to be declared

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DRAFT ARTICLE

A COMPARISON OF GROWTH BETWEEN HIV EXPOSED AND UNINFECTED AND HIV UNEXPOSED UNINFECTED INFANTS WHO RECEIVED KMC AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL.

Leshata Abigail Mapatha[1], Firdose Lambey Nakwa[1] (0000-0001-8884-2517), Mantoa Mokhachane[2] (0000-0001-5596-3654).

[1]Department of Paediatrics and Child Health, Chris Hani Baragwanath Academic Hospital, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand.

2. Unit for Undergraduate Medical Education (UUME), School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand

Abstract

Introduction: Kangaroo Mother Care (KMC) has been associated with improved growth in low birthweight infants and reduction in hypothermia, hypoglycaemia, apnoeas, sepsis, hospital stay and mortality. The growth of HIV-infected children is poorer than those who are HIV-uninfected. There is paucity of data on the growth in the HIV-exposed uninfected (HEU) infants compared to HIV-unexposed uninfected (HUU) infants receiving KMC.

Aim: This study compared the growth of HEU and infants HUU from admission to the KMC ward until 12 months corrected age (CA) follow-up visit.

Methods: Retrospective record review of the neonates admitted in KMC at Chris Hani Baragwanath Hospital over a two-year period (2012-2013). The weight gain was assessed via weight velocity using the formula; weight/kg/day from admission to KMC to discharge, at term, 3, 6 and 9- and 12-months (CA). The demographics were collected and analysed using Statistica.

Results: Seventy-seven (129/166) percent of the mothers were HIV negative. HIV negative mothers were younger (25.9 vs 31.6 years; p=0.000) and had fewer pregnancies (p=0.02). There was no difference between the gestational age (30.3±2.53 vs 30.8±2.88 weeks; p=0.35) and birthweight (1345g±234 vs 1314g±209; p= 0.47) between HEU and HUU. There were no differences in the weight gain (23.83g±12.2 vs 23.22g±15.2; p=0.83) in KMC. There were no differences in weight gain at the different follow-up time points between the two groups.

Conclusion: Both HEU and HUU groups of infants showed reasonable weight gain despite maternal HIV status

Key concepts: Kangaroo Mother Care (KMC), Low birth weight (LBW), HIV, HIV Exposed Uninfected (HEU), HIV Unexposed Uninfected (HUU), growth

Background

There are 18 million low birth weight (LBW) babies born worldwide, which is 14% of all births. An estimated 2.4 million newborn babies died in their first month of life in 2020. Nearly half (47 %) of all under-five deaths in 2020 occurred during the neonatal period [(1)]. Prematurity (60-80%) and asphyxia (23%) are regarded as the commonest causes of the early neonatal deaths, whilst infections are the cause of late neonatal deaths [(2,3)]. The lack of sophisticated Neonatal Intensive Care Unit (NICU) facilities contributes to the poor survival rate of premature infants in developing countries (4). Strategies to improve neonatal survival including introduction of antenatal steroids, surfactant administration, newer modes of ventilation, strict aseptic measures and Kangaroo Mother Care (KMC) have significantly increased survival of LBW infants in low middle income countries (LMICs) such as South Africa [(5)].

Kangaroo Mother Care, also referred to as Skin-to-Skin Contact (SSC) has become an important intervention for caring for LBW infants, particularly in low middle income countries (LMIC) where there is a high mortality and morbidity rate [(6)]. The introduction of KMC in LMIC reduces the incidence of hypothermia, hypoglycemia, apnea, sepsis and hospital stay and promote overall growth of head circumference, length and weight in the premature infant which correlates with brain volume and better cognitive ability later in life [(7)].

Women living with Human Immunodeficiency Virus (WLHIV) are at a higher risk of having low birth weight infants as a result of recurrent infections related to their weak immune system (8). The adoption of the 2013 WHO recommendation of life long Anti Retro Viral Therapy for all HIV positive pregnant women (Known as PMTCT option B+) in January 2015 by the South African government has significantly reduced the number of HIV exposed and infected (HEI) infants, leading to an era of HIV exposed uninfected (HEU) infants [(9)].

Immunological alterations have been reported in HEU infants as opposed to the HIV unexposed Uninfected (HUU), leading to poor growth [(10)]. Weight, height and head circumference are generally lower in HIV exposed children than their unexposed counterparts [(11)]. Weight gain was found to be a good predictor of neurodevelopmental outcome especially in extremely low birth weight (ELBW) neonates [(12)]. High demands of health care services to improve growth in LBW infants who are also HIV exposed in

South Africa make KMC a cost-effective way to prevent neonatal mortality in the health facilities.

Growth faltering has been well described in the HEU population from studies in Sub-Saharan Africa [13–16]. Some studies reporting poorer weight gain in females and breastfed infants [15]. A few South African studies have found no differences in weight gain in HEU group [17,18]. Advanced HIV disease, being exposed to HAART in utero and exposure to certain anti-retroviral (ARV) drugs affect weight gain [14,16,17]. HIV exposure and ARV drugs have been associated with immunological dysfunction, placental insufficiencies via endothelial function impairment [14–16]. There have been varying reports on the timing and the effect of different HAART regimens on growth [13,15]. Maternal and infant nutrition, socio economic factors, maternal education and environmental factors are to be considered when describing infant weight gain in the HEU infants [16].

The aim of this study was to compare the growth of HEU and HUU infants from admission to the KMC ward until 12 months corrected age at follow-up visit.

Methods

This study was conducted at Chris Hani Baragwanath Hospital, a tertiary hospital located in Soweto, South of Johannesburg, affiliated to the University of the Witwatersrand, South Africa. The unit has a 175 neonatal beds and 25 KMC beds during the study period. This is a retrospective study based on a review of medical records of LBW infants admitted in KMC over a 2-year period between 1st January 2012 and 31st December 2013. The study population included all HIV exposed and unexposed neonates weighing < 1.650kg admitted to the KMC ward during the study period. All HIV positive neonates were excluded from the study. Data was retrieved from medical records of the neonates that were admitted to the KMC and entered onto a datasheet. The data was entered onto an Excel Spreadsheet. Identifiers were kept separate from the neonatal and maternal demographics. A study number was assigned to the neonate, which was used to link the identifiers with the neonate's details. Neonatal records were divided into the HEU group and HUU group based on a documented maternal HIV status. All HIV exposed neonates

(all neonates with positive maternal HIV test) had to have at least one documented polymerase chain reaction (PCR) result before being assigned to either the HEU or HUU group.

At the time of the study, HIV in children was only tested at 6 weeks of age, 6 weeks post cessation of breast-feeding and 18 months of age [(9)].

Neonates were followed up at term [Corrected age (CA)- 40 weeks], 3 months, 6 months, 9 months and 12 months corrected age. To account for neonates not seen at the months mentioned above, a 1-month grace period on either side of the month was used for the infant's data to be included in the age group. For example, if the infant is seen at 4 months, the information was included in the 3-month age group. Information to be extracted from files included gestational age (GA), chronological age, corrected age (CA), birth weight, gender, HIV exposure, HIV status, mother's choice of feeds (breast fed or formula fed) supplements given (including FM85, a breastmilk fortifier) and the neonates primary diagnosis (admitting diagnosis).

Neonates weekly weight was documented from date of admission into KMC ward until discharge. The discharge weight was 1650g at the time of the study in the KMC ward. Since participants were weighed daily during admission in KMC ward, only weights documented on Mondays and Thursdays were considered for the purpose of the study to avoid confusion. The median weight was calculated between the two weights. The patients were then weighed only on the day of follow up after discharge. To calculate the weight gained per week in g/week, the researcher used this formula: neonate's current weight in grams minus previous weight, divided by the number of weeks between the 2 weights. Adequate weight gain in KMC will be 15g/kg/day, from 0-6 months will be 140 -200g/week and 85-140g/week at 6-12 months. [(19)].

Data Analysis

The data were analyzed utilizing Statistica (Statsoft USA, version 13). The data on categorical variables was reported as numbers and percentages and those for continuous variables as means and standard deviations, if the data were normally distributed; if not normally distributed the data were represented as medians and interquartile ranges. To

compare the HEU and the HUU groups, the Student-t tests were used for continuous variables and Chi-square tests were used for categorical variables. To assess for risk factors for the outcomes such as choice of feed, type of feeds other than formula and breast milk, supplements given during admission (e.g., FM 85 which is a breastmilk fortifier for the dietary supplementation of the premature and low birth weight neonate, medium chain triglyceride (MCT) oil), severity of primary diagnosis (e.g., previous ICU admissions, chronic illness that might affect weight gain), logistic regression analyses were performed. A p-value <0.05 was considered as significant.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of Witwatersrand (M180430). Permission to conduct the study was also obtained from the CHBAH hospital chief executive officer (CEO), the Pediatric and Neonatal Departmental Heads and National Department Health (NDoH).

Results

A total of 201 neonates with accessible medical records were included in the study. Of the 201 mother infant pairs, 178 mothers had a documented HIV status. Of the 178 infants, 2 were PCR positive and 10 had no PCR results, therefore HIV PCR negative results were available on 166 infants. A total of 166 mother- infant pairs were included in the study.

The baseline maternal characteristics were similar between the two groups (Table.1). Of the 166 mothers who were involved in the study, 129 (77%) were HIV negative and 37 (22%) were HIV positive. Of the 37 HIV positive mothers, 31 (83.7%) received highly active anti-retroviral treatment (HAART) and 1 did not receive HAART and the Prevention of Mother to Child Transmission (PMTCT) records were unknown in 6 (16.2%). Thirty-two (84.2%) infants born to HIV positive mothers received NVP, three (8.1%) received AZT and twenty-five (67.6%) received Bactrim.

Eighty –two (49%) infants were born via Caesarian section, fifty-five (33%) born via normal vaginal delivery (NVD). The booking, employment and marital status of both maternal groups were not significant. (Table 1)

There were no significant differences between the gestational ages (30.3±2.53 vs. 30.8± 2.88 weeks; p=0.35) and birthweight (1345.3g±234 vs. 1314.8g±209.52; p= 0.47) in both groups. The majority of the infants involved in the study were female (N=89, 54%). The incidence of RDS (p=0.44) congenital pneumonia (p=0.766), and necrotizing enterocolitis (p=0.89) were not significant between the two groups. Eighty (63%) of the 129 HUU and 13 (35%) of the 37 HEU neonates had neonatal jaundice (NNJ) during their stay in the neonatal unit (p=0.03). Length of stay in KMC was the same in both groups (13.2±8.4 days in HUU vs. 14.0±9.7 days in the HEU; p=0.83). (Table 2) .

There was no differences in mean weigh gain in g/day in KMC and g/week at the different follow up visits between HUU and HEU (Table 3. Weight velocity in HUU infants was greater (205.4±74.7 vs 192.8±49.9, p=0.44) than HEU infants at term. However, this was not significant. (Table 3)

All infants in the HEU and HUU had adequate weight gain of greater than 15g/kg/day in KMC, 140-200g at Term, 3months and 6 months CA. Both groups had adequate weight gain of between 85-140g/week at 9months and 12months CA However, there was a high attrition rate at each visit in both the groups and this could have affected the comparison in each group..

Discussion

KMC has many benefits to the low-birth-weight infant including improvement in weight gain and haemodynamic stability. Infants in KMC feed more frequently and this further promotes overall maternal-infant bonding. In the growing group of HIV exposed infants, this form of intervention becomes even more necessary to implement as this group of infants is already vulnerable to infections and poor growth. In our study, both HUU and HEU had adequate weight gain from term to 12 months CA. The transition to complimentary feeding could lead to feeding difficulties and thus weight loss until adequate and sustained feeding is established [20]. In Kenya, growth decline was documented in an HEU group after 6 months [21]. This finding is not consistent with most of the literature. In a cohort study of HEU children from the pre-ART era in Zimbabwe, it was shown that HEU children had a 23% higher chance of stunting than the HUU children at 12 months of age [22]. This is similar to studies done in Uganda and Zambia which both showed lower weight- for- age and lower height -for- age in the HEU vs HUU infants [23,24]. In a more recent study done in Zimbabwe, a larger number of HEU were born preterm and had low birth weight when compared to the HUU infants. In the same study, the mean weight- for- age and length- for- age were significantly lower in HEU compared to HUU infants from birth to 16 weeks [25]. HIV replicates in the placenta during pregnancy and may affect the T-cytokine profile in the placenta and thus restrict foetal growth and development which might contribute to LBW in HIV exposed infants [11]. We had not commented on the birthweights of the cohort however, there were no differences in admission weight to the KMC ward. A study in Cape Town has reported on lower birth weights in HEU neonates [14]. The duration of HAART antenatally may be a factor as this may affect the placenta, despite no differences found dependent on the timing of exposure. More studies are to be conducted investigating the HAART regimens and the timing of exposure [14]. To the contrary, another South African study found no differences in birthweight in HEU compared to HUU neonates, and longitudinal growth was greater in formula fed infants [15]. The lack of a significant difference in weight gain between the HEU and HUU was an important finding. This supports the positive impact KMC has on weight gain in very low birth weight infants regardless of maternal HIV

status. South Africa is a poorly resourced LMIC country and thus most LBW infants do not have access to sophisticated neonatal care and equipment. This further highlights the important need for more KMC units in health care centers especially in the rural and semi-rural communities [7].

Maternal drugs such as HAART and HIV prophylactic drugs received by the HEU infants such as NVP, AZT and Bactrim does not affect growth in the HEU group [26]. However, some studies showed poor growth in the HEU infants due to in utero exposure to HIV and maternal HAART [27]. Severe advanced maternal disease had poorer growth patterns whilst exposure to HAART was associated with better weight gain. [15]. Pre-pregnancy maternal HAART was associated with stunting and poor weight gain in another study [16]. These differences in studies may be related to the different regimens that are available in the various countries. Ejigu et al reported on slower growth in HEU neonates, with growth faltering related to earlier exposure to HAART, maternal disease and the type of HAART [13]. Our study did not have information on the maternal CD4 count nor viral load or the duration of maternal HAART. More prospective studies regarding the timing of HAART, the combination of HAART, maternal disease severity is warranted to document the effects on growth patterns in our setting.

The incidence of developing RDS, Congenital pneumonia and NEC was similar in both groups. This is similar to a study done in British Columbia, Canada which showed similar incidences of infectious respiratory and non-respiratory illnesses in HUU and HEU neonates. In this particular study the HEU were prone to acquiring infections requiring NICU admission compared to their HUU counterparts [28]. The results in our study only focused on co-morbidities at admission to the neonatal unit, prior to admission to the KMC ward and no differences were noted between the two groups.

A higher proportion of HUU neonates had neonatal jaundice. This finding is in keeping with a study done in a hospital in Malawi, which showed a higher incidence of jaundice in HIV unexposed neonates as compared to the HIV exposed neonates. One of the possible hypotheses for this finding as postulated by the authors is the use of drugs such

as efavirenz, tenofovir and lamivudine in pregnant and breast-feeding women as part of the prevention of mother-to-child transmission (PMTCT) programmer in Malawi. Efavirenz may act as a foetal liver enzyme inducer which helps in the conjugation of bilirubin and thus reducing the risk of jaundice in the HIV exposed infants [29].

Our study did not show any significant neonatal characteristics that affected length of stay as compared to the study done at Chris Hani Baragwanath which attributed prolonged length of stay in hospital to the severity of low birth weight [30]. The differences in the two studies could be due to the fact that our study focused more on admission weight and discharge weight to the KMC unit length of stay in KMC as opposed to factors associated with total length of stay in hospital.

Maternal well-being is central to all aspects of infant's growth as documented by the above results. Other factors which include nutritional, socioeconomic, health and environmental factors have an impact on childhood growth patterns. In addition maternal height, body mass index (BMI) and education contribute to growth faltering [16]. Mothers with a higher parity and age are more likely to have poor attitudes towards KMC [31]. This could be due to stress relating to their family, e.g., other children left at home in poor socioeconomic backgrounds and lack of support from hospital staff and family members [32]. Lack of mentorship, support, enthusiasm and training amongst health care workers with added stress from lack of family support (most especially lack of paternal support) were most likely to affect maternal attitude towards KMC [33]. These will further affect bonding between mother and infant [33]. This is especially significant in mothers who are HIV positive due to their general poor health and the stigma associated with being HIV positive.

The strength of our study is that it included a comparator group from the same community with similar socioeconomic status. Limitations of the study include that it was a single center study, and the fact that we mainly assessed growth in terms of weight gain at different ages and did not include the lengths and head circumferences for age of our study participants. In addition, birthweights and age at admission were not included. This would have given us information as to whether the HEU infants were of lower birthweight and were older at admission to the KMC

ward. A further delineation of the maternal HIV status in terms of advanced disease, viral loads, CD 4 counts and HAART regimens and when it was commenced were not investigated. The number of neonates and weights that were included at the different follow-up visits decreased over time. The number of HUU and HEU infants decreased during the follow periods. The loss of participants over time could lead to attrition bias when comparing the weight velocity between the two groups.

Conclusion

Patients in this study gained weight at a normal rate with no difference in weight gain between HEU and HUU infants from admission to KMC until 12 months CA. Interventions promoting KMC should be implemented as KMC is simple, effective and can be implemented with minimal resources. Future studies should assess changes in length and head circumference as well as weight gain, and a control group of LBW infants who were not admitted to the KMC should be added as a comparator group. .

Studies looking at other factors contributing to the increased incidence of jaundice in the HEU infants as compared to the HUU infants as found in this study should be conducted in the future. This could further encourage more studies on other issues affecting the growing population HEU infants in South Africa. There is a continuous need to minimize infant HIV exposure, additional measures are still essential to decrease the number of women being HIV-infected.

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Competing interests

None

Authors contribution

All authors contributed equally to the article.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

References

1. UNICEF, WHO WB & UN. Levels and Trends in Child Mortality - Report 2021 Estimates developed by the UN inter-agency Group for Child Mortality Estimation, United Nations Children's Fund (UNICEF), 2021 ISBN: 978-92-806-5321-2.

2. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? The lancet. 2005 Mar 5;365(9462):891-900. https://doi.org/10.1016/s0140-6736(05)71048-5.

3. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. BMC pregnancy and childbirth. 2015 Dec;15(1):1-7. https://doi.org/10.1186/s12884-015-0472-9.

4. Desalew A, Sintayehu Y, Teferi N, Amare F, Geda B, Worku T, et. al. . Cause and predictors of neonatal mortality among neonates admitted to neonatal intensive care units of public hospitals in eastern Ethiopia: a facility-based prospective follow-up study. BMC pediatrics. 2020 Dec;20(1):1-1. https://doi.org/10.1186/s12887-020-02051-7.

5. Rhoda NR, Velaphi S, Gebhardt GS, Kauchali S, Barron P. Reducing neonatal deaths in South Africa: Progress and challenges. South African Medical Journal. 2018 May 7;108(3):9-16. https://doi.org/10.7196/samj.2017.v108i3b.12804.

6. Thakur N, Saili A, Kumar A, Kumar V. Predictors of mortality of extremely low birthweight babies in a tertiary care centre of a developing country. Postgraduate medical journal. 2013 Dec 1;89(1058):679-84. https://doi.org/10.1136/postgradmedj-2012-131736.

7. Charpak N, Gabriel Ruiz J, Zupan J, Cattaneo A, Figueroa Z, Tessier R, et. al. Kangaroo mother care: 25 years after. Acta Paediatrica. 2005 May;94(5):514-22. https://doi.org/10.1111/j.1651-2227.2005.tb01930.x.

8. Chaula T, Seni J, Ng'walida N, Kajura A, Mirambo MM, DeVinney R, et. al. . Urinary tract infections among HIV-positive pregnant women in Mwanza city, Tanzania, are

high and predicted by low CD4+ count. International journal of microbiology. 2017 Oct;2017. https://doi.org/10.1155/2017/4042686.

9. National Department of Health. The South African antiretroviral treatment guidelines. Pretoria. 2013,16-21. Result score too low.

10. Xiao PL, Zhou YB, Chen Y, Yang MX, Song XX, Shi Y, Jiang QW. Association between maternal HIV infection and low birth weight and prematurity: a meta-analysis of cohort studies. BMC pregnancy and childbirth. 2015 Dec;15(1):1-1. https://doi.org/10.1186/s12884-015-0684-z.

11. de Deus N, Moraleda C, Serna-Bolea C, Renom M, Menendez C, Naniche D. Impact of elevated maternal HIV viral load at delivery on T-cell populations in HIV exposed uninfected infants in Mozambique. BMC infectious diseases. 2015 Dec;15(1):1-8. https://doi.org/10.1186/s12879-015-0766-6.

12. Sofeu CL, Warszawski J, Ateba Ndongo F, Penda IC, Tetang Ndiang S, Guemkam G, Makwet N, Owona F, Kfutwah A, Tchendjou P, Texier G. Low birth weight in perinatally HIV-exposed uninfected infants: observations in urban settings in Cameroon. PLoS One. 2014 Apr 3;9(4):e93554. https://doi.org/10.1371/journal.pone.0093554.

13. Ejigu Y, Magnus JH, Sundby J, Magnus MC. Differences in Growth of HIV-exposed Uninfected Infants in Ethiopia According to Timing of In-utero Antiretroviral Therapy Exposure. *Pediatr Infect Dis J* (2020) 39:730–736. doi: 10.1097/INF.0000000000002678

14. Nyemba DC, Kalk E, Madlala HP, Malaba TR, Slogrove AL, Davies M-A, Boulle A, Myer L, Powis KM. Lower birth weight-for-age and length-for-age z-scores in infants with in-utero HIV and ART exposure: a prospective study in Cape Town, South Africa. *BMC Pregnancy Childbirth* (2021) 21:354. doi: 10.1186/s12884-021-03836-z

15. Morden E, Technau K-G, Giddy J, Maxwell N, Keiser O, Davies M-A. Growth of HIV-Exposed Uninfected Infants in the First 6 Months of Life in South Africa: The IeDEA-SA Collaboration. *PLOS ONE* (2016) 11:e0151762. doi: 10.1371/journal.pone.0151762

16. Neary J, Langat A, Singa B, et al. Higher prevalence of stunting and poor growth outcomes in HIV-exposed uninfected than HIV-unexposed infants in Kenya. AIDS. 2022;36(4):605-610. doi:10.1097/QAD.0000000000003124.

17. Patel D, Bland R, Coovadia H, Rollins N, Coutsoudis A, Newell ML. Breastfeeding, HIV status and weights in South African children: a comparison of HIV-exposed and unexposed children. AIDS. 2010;24(3):437-445. doi:10.1097/QAD.0b013e3283345f91.

18. Ramokolo V, Lombard C, Fadnes LT, et al. HIV infection, viral load, low birth weight, and nevirapine are independent influences on growth velocity in HIV-exposed South African infants. J Nutr. 2014;144(1):42-48. doi:10.3945/jn.113.178616.

19. https://www.mayoclinic.org/healthy-lifestyle/infant-and-toddler-health/expert-answers/infant-growth/faq-20058037.

20. Fernández Gallardo MA, Rojas Contreras DP, Vargas Keith JF. Development of feeding skills in preterm infants: a critical literature review. Revista CEFAC. 2017 Jul; 19:539-50. Revista CEFAC. 2017 Jul; 19:539-50. https://doi.org/10.1590/1982-021620171946417.

21. McGrath CJ, Nduati R, Richardson BA, Kristal AR, Mbori-Ngacha D, Farquhar C, John-Stewart GC. The prevalence of stunting is high in HIV-1-exposed uninfected infants in Kenya. *J Nutr* (2012) 142:757–763. doi: 10.3945/jn.111.148874

22. Omoni AO, Ntozini R, Evans C, Prendergast AJ, Moulton LH, Christian PS, Humphrey JH. Child growth according to maternal and child HIV status in Zimbabwe. The Pediatric infectious disease journal. 2017 Sep;36(9):869. https://doi.org/10.1097/inf.0000000000001574.

23. Rosala-Hallas A, Bartlett JW, Filteau S. Growth of HIV-exposed uninfected, compared with HIV-unexposed, Zambian children: a longitudinal analysis from infancy to school age. BMC pediatrics. 2017 Dec;17(1):1-9. https://doi.org/10.1186/s12887-017-0828-6.

24. Owor M, Mwatha A, Donnell D, Musoke P, Mmiro F, Allen M, Jackson JB, Fowler MG, Guay LA. Long Term Follow-up of Children in the HIVNET 012 Perinatal HIV Prevention Trial: Five-Year Growth and Survival. Journal of acquired immune deficiency syndromes (1999). 2013 Dec 15;64(5):464. https://doi.org/10.1097/qai.0000000000000015.

25. Mabaya L, Matarira HT, Tanyanyiwa DM, Musarurwa C, Mukwembi J. Growth Trajectories of HIV Exposed and HIV Unexposed Infants. A Prospective Study in Gweru, Zimbabwe. Global pediatric health. 2021 Feb;8:2333794X21990338. https://doi.org/10.1177/2333794x21990338.

26. Piske M, Budd MA, Qiu AQ, Maan EJ, Sauvé LJ, Forbes JC, Alimenti A, Janssen P, Côté HC. Neurodevelopmental outcomes and in-utero antiretroviral exposure in HIV-exposed uninfected children. Aids. 2018 Nov 13;32(17):2583-92. https://doi.org/10.1097/qad.0000000000001985.

27. Ramokolo V, Goga AE, Lombard C, Doherty T, Jackson DJ, Engebretsen I. In utero ART exposure and birth and early growth outcomes among HIV-exposed uninfected infants attending immunization services: results from national PMTCT surveillance, South Africa. InOpen forum infectious diseases 2017 Oct 1 (Vol. 4, No. 4). Oxford University Press. https://doi.org/10.1093/ofid/ofx187.

28. Li SN, Albert A, Piske M, Janssen PA, Alimenti A, Jesson J, Côté HC, Sauvé L. Higher Hospitalization Rates in Children Born HIV-exposed Uninfected in British Columbia, Canada, Between 1990 and 2012. The Pediatric infectious disease journal. 2021 Dec 28;41(2):124-30. https://doi.org/10.1097/inf.0000000000003365.

29. Nakanga W, Patel P, Panjwani S, Kennedy N, Kawaza K. Supra-treatment threshold neonatal jaundice: Incidence in HIV-exposed compared to non-exposed neonates at Queen Elizabeth Central Hospital in Blantyre, Malawi. Malawi Medical Journal. 2015;27(3):104-8. https://doi.org/10.4314/mmj.v27i3.7.

30. Mahovo R, Velaphi S. Duration of hospital stay and factors associated with prolonged hospital stay in very low birth weight infants surviving to hospital discharge. Journal of Pediatrics, Perinatology and Child Health. 2019;3(4):208-20. https://doi.org/10.26502/jppch.74050032.

31. Bilal SM, Tadele H, Abebo TA, Tadesse BT, Muleta M, Alemayehu A, Haji Y, Kassa DH, Astatkie A, Asefa A, Teshome M. Barriers for kangaroo mother care (KMC) acceptance, and practices in southern Ethiopia: a model for scaling up uptake and adherence using qualitative study. BMC pregnancy and childbirth. 2021 Dec;21(1):1-2. https://doi.org/10.1186/s12884-020-03409-6.

32. Kinshella ML, Hiwa T, Pickerill K, Vidler M, Dube Q, Goldfarb D, Nyondo-Mipando AL, Kawaza K. Barriers and facilitators of facility-based kangaroo mother care in sub-Saharan Africa: a systematic review. BMC pregnancy and childbirth. 2021 Dec;21(1):1-0. https://doi.org/10.1186/s12884-021-03646-3.

33. Mathias CT, Mianda S, Ginindza TG. Facilitating factors and barriers to accessibility and utilization of kangaroo mother care service among parents of low birth weight infants in Mangochi District, Malawi: a qualitative study. BMC pediatrics. 2020 Dec;20(1):1-2 https://doi.org/10.1186/s12887-020-02251-1.

Table 1: MATERNAL DEMOGRAPHICS of NEONATES ADMITTED TO THE KMC WARD.

Characteristics	**Total** **N (%)** N= 166	**HIV Negative** **N (%)** N= 129	**HIV Positive** **N (%)** N= 37	**p-value**
Mean Age *	27.23 (±6.26)	25.9 (±2.5)	31.6 (±2.7)	0.00
Mean Gravidity*	2.36 (±1.26)	2.17 (±1.17)	2.9 (±1.35)	0.02
Mean Parity*	1.66 (±0.98)	2 (±1)	3 (±1)	0.00
Mode of delivery				
Caesarean section	82 (60)	65 (50)	17 (46)	0.83
NVD	55 (33)	40 (31)	15 (41)	
Missing	29 (18)	24 (19)	5 (13)	
Booked				
Yes	164 (99)	127 (98.5)	37 (100)	1.00
No	2 (1)	2 (1.5)	0	
Employed				
Yes	39 (24)	33 (26)	6 (16)	0.17
No	67 (40)	49 (38)	18 (49)	
Unknown	60 (36)	47 (36)	13 (35)	
Marital Status				
Married	11 (7)	7 (5)	4 (11)	0.12
Single	114 (67)	89 (69)	25 (68)	0.28
Unknown	41 (26)	33 (26)	8 (21)	

* Mean (SD)

Table 2: CHARACTERISTICS OF NEONATES ADMITTED TO THE KMC WARD

Characteristics	**Total**	**HUU** Mean (SD)	**HEU** Mean (SD)	**p-value**
Birth weight in grams	1338.49 ±228)	1345.3 (±234)	1314.8 (±209)	0.47
Gestational age in weeks	30.4 (±2.61)	30.3 (±2.53)	30.8 (±2.88)	0.35
Apgar score				
1 minute	7 (±1.9)	7 (±2)	7 (±2)	0.44
5 minutes	9 (±1.13)	9 (±1)	9 (±1)	0.15
Female	89 (54)	70 (55)	19 (51)	0.625
RDS*	128 (78)	101 (79)	27 (73)	0.44
Congenital Pneumonia*	17 (10)	14 (11)	3 (8)	0.76
NEC*	29 (17)	23 (18)	6 (16)	0.89
NNJ*	93 (56)	80 (63)	13 (35)	0.03
Weight at admission to KMC (grams)	1408.9 (±1.46)	1402.0 (±145.12)	1434.8 (±151.11)	0.3
Weight at discharge from KMC (grams)	1674.5 (±100.89)	1673.6 (105.19)	1677.6 (85.60)	0.83
Length of stay in KMC in days	13.3 (±8.7)	13.2 (±8.4)	14.0 (±9.7)	0.64

* N (%)

Table 3: GROWTH VELOCITY IN KMC AND AT TERM, 3 MONTHS, 6 MONTHS, 9 MONTHS AND 12 MONTHS

Characteristic	HUU Means (SD)	HEU Means (SD)	P-value
Weight gain in KMC g/day	n=91 23.83 (±12.2)	n=24 23.22 (±15.2)	0.83
Term g/week	n=86 205.4 (±74.7)	n=24 192.8 (±49.9)	0.44
3 months g/week	n=71 194.4 (±56.2)	n=22 189.6 (±49.7)	0.72
6 months g/week	n=48 173.5 (±46.6)	n=14 163.1 (±33.9)	0. 91
9 months g/week	n=26 136.6 (±31.7)	n=15 135.5 (±21.3)	0.90
12 months g/week	n=20 117.9 (±22.6)	n=7 115.7 (±15.8)	0.81

RESEARCH PROTOCOL

TITLE: A COMPARISON OF GROWTH BETWEEN HIV EXPOSED AND UNINFECTED AND HIV UNEXPOSED INFANTS WHO RECEIVED KMC AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

RESEARCHER: DR L.A MAPATHA

STUDENT NO: 1597059

MMED (PAEDIATRICS)

SUPERVISORS:

Dr F. L Nakwa MBBCH (Wits), FCPaed (SA), MMed Paeds (Wits), Certificate of Neonatology (SA), Certificate of Paediatric Neurology (SA).

Dr M. Mokhachane, MBBCh, FCPaed (SA), MMed (Wits), Postgraduate Diploma Health Science Education (Wits)

OUTLINE

List of abbreviations

1. **ART** Antiretroviral Therapy
2. **CA** Corrected Age
3. **CHBAH** Chris Hani Baragwanath Academic Hospital
4. **ELBW** Extreme Low Birth Weight
5. **ELISA** Enzyme Linked Immunosorbent Assay
6. **GA** Gestational Age
7. **GBS** Group B Streptococcus
8. **HEU** HIV-Exposed Uninfected
9. **HIV** Human Immune Deficiency Virus
10. **HUU** HIV -Unexposed Uninfected
11. **KMC** Kangaroo Mother Care
12. **LBW** Low Birth Weight
13. **NCPAP** Nasal Continuous Positive Airway Pressure
14. **NDoH** National Department of Health
15. **NICU** Neonatal Intensive Care Unit
16. **PCR** Polymerase Chain Reaction
17. **PMTCT** Prevention of Mother to Child Transmission
18. **SBAH** Steve Biko Academic Hospital
19. **SCC** Skin to Skin Care
20. **UTI** Urinary tract infection
21. **VLBW** Very Low Birth Weight
22. **WHO** World Health Organization

Background

There are 18 million low birth weight babies born worldwide. These account for 14% of all births. Three quarters of the neonatal deaths are classified as early neonatal deaths. Prematurity (60-80%) and asphyxia (23%) are regarded as the commonest causes of the early neonatal deaths, whilst infections are the cause of late neonatal deaths (1).

Maternal complications such as hypertension, antepartum haemorrhage and spontaneous preterm labour are amongst the commonest risk factors of perinatal mortalities (2). Poor survival rate of premature infants in developing countries is mainly attributed to lack of sophisticated Neonatal Intensive Care Unit (NICU) facilities(3).

In the last decade, advances in perinatal and neonatal care have led to an increased survival of extremely premature infants. New treatment strategies such as antenatal steroid therapy, surfactant administration, and newer modes of ventilation, strict aseptic measures and improved control of nosocomial sepsis have contributed to improved survival of premature babies, especially extreme low birth weight infants (ELBW) (3).

Survival rates of neonates with ELBW improved from 20.4 % to 52.4 % percent in 2006/2007 to 2013 in a study done in central Johannesburg (4).The improvement in survival in this cohort was due to the use of nasal continuous positive airway pressure (nCPAP) and surfactant administration. Cost effective ways such as antibiotics for preterm premature rupture of membranes, breast feeding , prevention of hypothermia and KMC can reduce neonatal deaths by 41-72% (5). Antenatal steroids showed a significant improvement in neonatal morbidity and death in studies done at Steve Biko Academic Hospital (SBAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) respectively. According to Lloyd et al steroids were given to only 61,2 % of their patients who were less than 33 weeks gestation and this showed decreased morbidity and mortality(6) . A study done at CHBAH by Bopape-Chinyanga et. al shows that very low birthweight (VLBW) babies born to mothers who had not received antenatal steroids had more severe disease despite being on nCPAP. Most of these neonates would later require mechanical ventilation if they survive. Only 20 % of the survivors did not require mechanical ventilation(7).

Human Immunodeficiency Virus (HIV) has contributed largely to some of the maternal complications leading to premature labour. HIV infected women are at higher risk of having

low birth weight infants or preterm deliveries compared to uninfected women(8).They are prone to developing infections such as Urinary Tract Infections (UTIs) due to their weak immune system which renders them at risk of preterm labour if left untreated(9). During the year 2000 alone, an estimated 24, 5% (quarter of a million) of pregnant women attending public health facilities in South Africa were HIV positive. This had increased to 29% by 2008. According to a study done at CHBAH in Soweto, early diagnosis of HIV in infants born to HIV positive mothers was 62% in 2008, and with increased number of new cases being seen in the institution by 2009(10).

The adoption of the 2013 WHO recommendation of life long Anti Retro Viral Therapy (ART) for all HIV positive pregnant women (known as PMTCT option B+) in January 2015 by the South African government has significantly reduced the number of HIV exposed and infected infants, leading to an era of HIV exposed but uninfected infants. New HIV infections in children was reduced by 47% in 2010, from 300 000 to 160 000 in 2016 (11, 12) . Many studies comparing outcomes of HIV positive and HIV negative infants have been carried out with most studies showing poor outcomes in HIV positive infants as opposed to their HIV negative counterparts(13).

It is always assumed that the infant will thrive but in reality, that does not seem to be the case. Some studies suggest an increase in morbidity and mortality in HIV Exposed Uninfected (HEU) infants (14). Immunological alterations have been reported in HEU infants as compared with HIV Unexposed Uninfected infants (HUU) (14). An increase in the level of CD8 T cells and decreased naïve CD4 T cells, altered cytokine production and lower thymus output have been implicated in the depression of immunity and increased susceptibility to infections in these infants. Increased frequency of anaemia and poor nutritional outcome also plays a role in the morbidity and mortality of HEU infants.

Mortality in the HEU peaks at 3-6months (15). These mortalities are attributed mainly to lower respiratory tract infections. Streptococcal pneumonia and Group B Streptococcal (GBS) infections were four and thirteen times higher respectively in HIV Exposed Uninfected (HEU) in the first year of life (16). Recurrent admissions to hospital and mortality from respiratory illnesses was seen in the HEU patients. Studies in Botswana and Durban, South Africa, demonstrated higher rates of treatment failure in HEU infants with pneumonia.

Other factors being implicated are mitochondrial dysfunction by maternal ARTs and poor feeding practices.

HIV exposed children are more prone to stunting, underweight and wasting. Their birth weight, height and head circumference are generally lower than their unexposed counterparts (17). Weight gain was found to be a good predictor of neurodevelopmental outcome especially in ELBW in a study done in Japan for the Neonatal Research Network of Japan (18).

The causes of poor growth are often multifactorial. Infections, including HIV have been shown to replicate in the placenta during pregnancy and may affect the cytokine profile in the placenta and thus restrict foetal growth (8) . This will restrict foetal development and might contribute to LBW in HIV exposed infants. In a study done in Rwanda HEU infants had lower lengths and weights at 6 months of age (19). Maternal deaths and orphanhood are some of the contributing factors to poor growth in HEU infants.

Growth in babies born prematurely continues to be a challenge. Very low birth weight babies continue to remain smaller in weight at 1 year corrected age when seen at follow up visits, even if gaining weight adequately (20) . Adequate weight gain is generally accepted as 140 - 200g/week or 15g/kg/day (21).There is however initial weight loss after birth in these infants secondary to loss in body water and inadequate intake of required nutrition, which is later followed by catch up growth (22). Infants born to mothers with advanced HIV (CD4 count less than 200 cells/microliter and mothers who did not receive ART have lower birth weights compared with infants born to mothers with CD4 counts > 500 cell/microliter and those who received ART. There is still conflicting evidence on which feeding choice, breast vs formula can best promote growth in all HIV exposed infants (23) . Feeding choice in all HIV exposed infants remains a huge challenge in most health care facilities due to paucity of evidence. Feeding choice is still a confusion to most pregnant women and mothers. Most health institutions have implemented "AFASS" (Acceptable, Feasible, Affordable, Sustainable and Safe) criteria to facilitate appropriate feeding choices. The correct feeding choice will promote adequate weight and the opposite is true.

The implementation of facilities such Kangaroo Mother Care (KMC) wards at hospitals in developing countries has helped facilitate growth in this vulnerable group of infants. Dr Edgar Rey proposed and developed KMC in 1978 at the Institute Materno Infantil in Santa Fe

de Bogota, Colombia. It was initiated as an alternative to the conventional contemporary method of care for LBW infants due to lack of incubators. The mothers are used as ‘‘incubators’’ to maintain the infant body temperature (24). During KMC, the mother uses her own body temperature to keep her infant warm. KMC has been shown to reduce incidence of hypothermia, hypoglycaemia, apnoea, sepsis and hospital stay. It promotes overall growth of head circumference, length and weight. Adequate growth in head circumference in the premature infant correlates with brain volume and better cognitive ability later in life (25). Kangaroo mother care (KMC) or skin-to-skin care (SSC) is a simple, easy and cheap method of caring for new-born infants.

KMC is comprised of four components: Kangaroo position, which is skin-to-skin contact, nutrition (mainly breastfeeding), support, early discharge and follow-up. Babies are followed up to a minimum of 1-year corrected age thereafter. This has been shown to improve these infants' quality of life and survival (26).

KMC has become an important form of intervention for caring for low-birth-weight infants, particularly in third world countries where there is a high mortality and morbidity rate in hospitals, which lack sophisticated care, such as neonatal intensive care facility

Chris Hani Baragwanath Academic Hospital (CHBAH) has on average 20000 deliveries a year with a 20 percent low birth weight rate. The HIV positive rate is 28% annually. High demands for health care services in the hospital make KMC a cheap and effective way to prevent neonatal mortality in the facility.

2. AIM OF THE STUDY:

The aim of this study is to compare growth of HEU vs HUU from admission in KMC until 12 months corrected age (CA) follow up visits.

3. OBJECTIVE

3.1 To describe the difference in mean weight gain (in g/ week) in low-birth-weight infant who are HEU vs those who are HUU during KMC admission

3.2 To look at factors associated with length of stay in KMC between the two groups

3.3 To assess the association of comorbidities on admission to KMC unit and growth in low-birth-weight HEU and HUU infants

3.4 To compare the mean weight gain in g/week at follow up clinic between HEU and HUU infants who were admitted in Kangaroo Mother Care (KMC) at Chris Hani Baragwanath Academic hospital (CHBAH).

4. STUDY DESIGN

This is a retrospective data review of patients admitted over a 2-year period between 1st January 2012 and 31st December 2013. Data collected from approximately 150 patients' records at Chris Hani Baragwanath Academic Hospital admitted in the KMC unit and followed up after discharge, will be retrieved and analysed.

5. METHODS

Patients will be identified by using admission and follow up records from KMC unit collected during the study period. Patients should have met the KMC ward admission eligibility criteria, which includes being on full feeds, no intravenous cannulas, not on any antibiotics, 2 consecutive weight gains whilst in the general wards, weight below 1650g. Patients will be followed up from admission in KMC until 12months C.A. Demographic data will be retrieved from the records and entered onto a datasheet (Appendix A). The data will be entered onto an Excel Spreadsheet. Identifiers will be kept separate from the patient demographics. A study number will be assigned to the patient and will be used to link the identifiers with the patient's details. Patients whose information fits the exclusion criteria will be excluded from participating in the study. Patient's records will be divided into the HEU group and HUU group based on a documented maternal HIV status. Mothers must be documented as either HIV negative or positive at least once in their hospital records or patient's records. All HIV exposed patients (all patients with positive maternal HIV test) must have at least one documented PCR result before being assigned to either the HEU or HUU group. At the time of the study HIV in children was only tested at 6 weeks of age, 6 weeks post cessation of breast feeding and 18 months of age.

Patients were followed up at term, 3 months, 6 months, 9 months and 12 months corrected age. To account for patients not seen at the months mentioned above a 1-month grace period on either side of the month will be used for the infant's data to be included in the age group for example, if the infant is seen at 4 months, the information will be included in the 3-month age group.

Information to be extracted from files includes gestational age (GA), chronological age, corrected age (CA), birth weight, gender, HIV exposure, HIV status, moms choice of feeds (breast fed or formulary fed) supplements given (including FM85) and the patient's primary diagnosis.

Patient's weekly weight will then be documented from date of admission into KMC ward until discharge. Since participants were weighed daily during admission in KMC ward, only weights done on Mondays and Thursdays will be considered for the purpose of the study to avoid confusion. We will calculate the median weight between the two weights. The patients were then weighed only on the day of follow up after discharge. To calculate the weight gained per week in g/week we will use this formula; patient's current weight in grams minus previous weight, divided by the number of weeks between the 2 weights. Adequate weight gain per week will be 140 -200g/week or 15g/kg/day.

5.1 INCLUSION CRITERIA

5.1.1 All patients admitted to the KMC ward during the study period

5.1.1 LBW infants <1.650 kg on admission to KMC

5.1.2 Infants whose maternal HIV status is documented

5.1.3 Infants who are HIV exposed and negative

5.1.4 Infants who are HIV unexposed

5.1.5 Infants discharged and continued to follow up at the facility during the research period and meet the above inclusion criteria

5.2 EXCLUSION CRITERIA

5.2.1 Infants who test HIV positive at any point during the study period

6. DATA ANALYSIS

Data will be entered into an Excel spreadsheet. Thereafter, the data will be analysed utilizing Statistica (Statsoft USA, version 13). Categorical variables will be reported as numbers and percentages. Continuous variables will be reported as means and standard deviations, if the data is normally distributed; if not normally distributed the data will be represented as medians and interquartile ranges. To compare the HEU and the HUU groups the Student-t tests or Mann-Whitney U tests will be used for continuous variables and Chi-square or Fischer-exact tests will be used for categorical variables. To assess for risk factors for the outcomes such as choice of feed, type of feeds other than formula and breast milk, supplements given during admission (e.g. FM 85, medium chain triglyceride (MCT) oil), severity of primary diagnosis e.g. previous ICU, admissions, chronic illness that might affect weight gain, logistic regression analyses will be performed. A p-value <0.05 will be considered as significant.

7. ETHICS

Approval will be requested from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Permission to conduct the study will also be obtained from the CHBAH hospital chief executive officer (CEO) and National Department of Health (NDoH).

8. LIMITATIONS OF THE STUDY

Due the retrospective nature of the study, it is expected that some patients' records might be missing, especially the inpatients records as these were stored separate from the outpatient/follow up records. Although feeding choice is often established before birth or during admission to the neonatal unit, it will be difficult to be certain if the infants involved in the study were exclusively breast fed or formula fed as expected or if solids were introduced earlier given at home upon discharge. Poor documentation of supplements such as FM 85 given to infants during admission, as this is not routinely documented on discharge summaries or at follow up. Initial HIV PCR testing of HIV exposed infants was only done at 6 weeks of life during the study period and repeated at 6 weeks post cessation of breastfeeding or HIV Elisa (Enzyme-Linked Immunosorbent assay) done at 18 months if the 6-week PCR was negative. This may lead to some patients who tested HIV positive later in infancy being missed or added to the study due to prolonged HIV testing intervals at the time.

9. FUNDING

Stationery used, from papers to writing utensils and photocopying and printing costs will all be funded by KMC funds.

10 GANTT CHART

	FEB 2018	MAR 2018	APR 2018	MAY 2018	JUN 2018	JUL 2018	AUG 2018	SEP 2018	OCT 2018	NOV 2018	DEC 2018	JAN 2019
Literature review												
Protocol preparation												
Protocol submission and assessment												
Ethical clearance												
Postgraduate committee clearance												
Data collection												
Data analysis and report write up												

Appendix A
10. Data collection sheet

Demographic Information

Study Number: _____
Gender: Male/Female
Gestational age: _____
Date of admission to KMC __/__/__
Date of discharge from KMC _____
Birth weight (in grams) _____
Birth length _____
Birth Head circumference _____
Discharge weight (in grams) _____
Discharge length _____
Discharge Head circumference _____

Growth parameters at different Corrected ages at follow up (table.10.1)

	Term	3/12	6/12	9/12	12/12
Weight (g)					
Length					
Head Circumference					
Weight Velocity /week					

Maternal HIV Status

Positive Yes/No
HIV on ART: Yes/No/Unknown

Negative Yes/No
Unknown _____

HIV Status of infant

Positive Yes/No
Negative Yes/No
Unknown _____

Feeding choice

Exclusive breastfeeding Yes/No Exclusive Formula feeding Yes/No

Mixed feeding _____ Unknown _____

Type of feed	Supplements	FM 85 given	Mct oil given	Frequency of feeds

Primary diagnosis

Respiratory

1. Respiratory distress syndrome Yes/No
2. Transient tachypnea of the newborn Yes/No
3. Congenital pneumonia Yes/No

4 other _____

Cardiac Yes/No

Central nervous system

1. Intraventricular haemorrhage Yes/No
2. Other _____

Surgical disorders

1. Intestinal atresia Yes/No
2. Tracheoesophageal fistula Yes/No
3. NEC Yes/No
4. Chromosomal abnormality Yes/No
5. Congenital anomaly Yes/No
6. Other _____

Previous neonatal ICU admissions

1. Nasal CPAP Yes/No
2. Ventilation Yes/No
3. High frequency oscillation Yes/No
4. Other _____

Outcome

1. Transfer to other hospital Yes/No
2. Refused hospital treatment Yes/No
3. Follow-up Yes/No

4. Defaulted follow up Yes/No
5. Admission since discharge Yes/No

6. Demised Yes/No
7. Other _____

12. References

1. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365(9462):891-900.
2. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. BMC Pregnancy Childbirth. 2015;15:1-7.
3. Thakur N, Saili A, Kumar A, Kumar V. Predictors of mortality of extremely low birthweight babies in a tertiary care centre of a developing country. Postgrad Med J. 2013;89(1058):679-684.
4. Ballot DE, Chirwa T, Ramdin T, Chirwa L, Mare I, Davies VA, et al. Comparison of morbidity and mortality of very low birth weight infants in a Central Hospital in Johannesburg between 2006/2007 and 2013. BMC Pediatr. 2015;15:1-11.
5. Martines J, Paul VK, Bhutta ZA, Koblinsky M, Soucat A, Walker N, et al. Neonatal survival: a call for action. Lancet. 2005;365(9465):1189-1197.
6. Lloyd LG, de Witt TW. Neonatal mortality in South Africa: how are we doing and can we do better? S Afr Med J. 2013;103(8):518-519.
7. Bopape-Chinyanga TC, Thomas R, Velaphi S. Outcome of very-low-birth-weight babies managed with nasal continuous positive airway pressure, with or without surfactant, in a high-care nursery. South African Journal of Child Health. 2016;10(4):199-206.
8. Xiao PL, Zhou YB, Chen Y, Yang MX, Song XX, Shi Y, et al. Association between maternal HIV infection and low birth weight and prematurity: a meta-analysis of cohort studies. BMC Pregnancy Childbirth. 2015;15:1-11.
9. Chaula T, Seni J, Ng'walida N, Kajura A, Mirambo MM, DeVinney R, et al. Urinary Tract Infections among HIV-Positive Pregnant Women in Mwanza City, Tanzania, Are High and Predicted by Low CD4+ Count. Int J Microbiol. 2017;2017:1-7.
10. Laher F, Cescon A, Lazarus E, Kaida A, Makongoza M, Hogg RS, et al. Conversations with mothers: exploring reasons for prevention of mother-to-child transmission (PMTCT) failures in the era of programmatic scale-up in Soweto, South Africa. AIDS Behav. 2012;16(1):91-98.
11. UNAIDS. Fact sheet - Latest global and regional statistics on the status of the AIDS epidemic 2017 [cited 2018 June 15,2018]. Available from: : http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf<UNAIDS_FactSheet_.
12. Ramokolo V, Goga AE, Lombard C, Doherty T, Jackson DJ, Engebretsen IM. In Utero ART Exposure and Birth and Early Growth Outcomes Among HIV-Exposed Uninfected Infants Attending Immunization Services: Results From National PMTCT Surveillance, South Africa. Open Forum Infect Dis. 2017;4(4):1-10.
13. Martinsen V, Grewal SK. Comparison of Growth in Infants according to Maternal HIV-status in Harare, Zimbabwe [cited 2018 June 13,2018]. Available from: file:///C:/Users/leshata%20mapatha/Desktop/martinsen-grewal%20COMPARISON%20OF%20GROWTH.pdf.
14. de Deus N, Moraleda C, Serna-Bolea C, Renom M, Menendez C, Naniche D. Impact of elevated maternal HIV viral load at delivery on T-cell populations in HIV exposed uninfected infants in Mozambique. BMC Infect Dis. 2015;15:1-8.

15. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: a growing population with a vulnerable immune system? Clin Exp Immunol. 2014;176(1):11-22.
16. Adler C, Haelterman E, Barlow P, Marchant A, Levy J, Goetghebuer T. Severe Infections in HIV-Exposed Uninfected Infants Born in a European Country. PLoS One. 2015;10(8):1-14.
17. Sofeu CL, Warszawski J, Ateba Ndongo F, Penda IC, Tetang Ndiang S, Guemkam G, et al. Low birth weight in perinatally HIV-exposed uninfected infants: observations in urban settings in Cameroon. PLoS One. 2014;9(4):1-10.
18. Maruyama H, Yonemoto N, Kono Y, Kusuda S, Fujimura M. Weight Growth Velocity and Neurodevelopmental Outcomes in Extremely Low Birth Weight Infants. PLoS One. 2015;10(9):1-12.
19. Spira R, Lepage P, Msellati P, Van De Perre P, Leroy V, Simonon A, et al. Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. Pediatrics. 1999;104(5):1-9.
20. Modi M, Saluja S, Kler N, Batra A, Kaur A, Garg P, et al. Growth and neurodevelopmental outcome of VLBW infants at 1 year corrected age. Indian Pediatr. 2013;50(6):573-577.
21. Slusher T, Vaucher Y, Zamora T, Curtis B. Feeding and Fluids in the Premature and Sick Newborn in the Low-Middle Income Countries: Research Gate; 2012 [cited 2018 April 12,2018]. Available from: https://www.researchgate.net/publication/221929309.
22. Mackay CA, Ballot DE, Cooper PA. Growth of a cohort of very low birth weight infants in Johannesburg, South Africa. BMC Pediatr. 2011;11:1-6.
23. Morden E, Technau KG, Giddy J, Maxwell N, Keiser O, Davies MA. Growth of HIV-Exposed Uninfected Infants in the First 6 Months of Life in South Africa: The IeDEA-SA Collaboration. PLoS One. 2016;11(4):1-15.
24. Conde-Agudelo A, Diaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev. 2016(8):196-144.
25. Swarnkar K, Vagha J. Effect of Kangaroo Mother Care on Growth and Morbidity Pattern in Low Birth Weight Infants. The Journal of Krishna Institute of Medical Sciences University. 2016;5:91-99.
26. Charpak N, Ruiz JG, Zupan J, Cattaneo A, Figueroa Z, Tessier R, et al. Kangaroo Mother Care: 25 years after. Acta Paediatr. 2005;94(5):514-522.

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R14/49 Dr Leshata Abigail Mapatha

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160430

NAME: (Principal Investigator)	Dr Leshata Abigail Mapatha
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Effect of kangaroo mother care on weight gain in low birth weight infants who are HIV exposed and uninfected vs HIV unexposed at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	04/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Firdose Nakwa and Dr Mantoa Mokhachane
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/07/2018

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 Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

12/07/18
Date

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