PRECHTL'S OBSERVED GENERAL MOVEMENTS IN HIV AND ANTIRETROVIRAL THERAPY EXPOSED UNINFECTED INFANTS IN BLANTYRE MALAWI

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Declaration

I, James Kaunda, declare that this research report is my
own, unaided work. It is being submitted for the Master of Science in Physiotherapy (Paediatrics) at the University of the Witwatersrand, Johannesburg, South Africa.

It has not been submitted before for any degree or examination at any other University.

JAMES KAUNDA _____

Name of candidate Signature of candidate

26th Day of October 2024

Dedication

I dedicate this work to the Almighty God, whose unwavering guidance and grace have been my strength throughout this journey.

I also dedicate this to my beloved family, whose endless love, support, and encouragement have sustained me through every challenge and triumph. Your unwavering belief in me has been my greatest motivation. This achievement is a testament to our shared faith, love, and perseverance. I am forever grateful for your presence in my life.

Abstract

Background

Malawi is one of the countries with a high prevalence of human immunodeficiency virus (HIV) in the sub-Saharan region. As more HIV-reactive mothers bear children, more infants are being exposed to HIV and antiretroviral therapy (ART) leading to an increase in the number of ART- and HIV- exposed uninfected (AHEU) children. This scenario, coupled with the reports about detected neurodevelopmental challenges among the AHEU infants makes it worthwhile to study this at-risk group of infants. It is now possible to identify infants at risk of neurodisability at an early stage of development through the use of Prechtl's General Movements Assessment (GMA). This study therefore was aimed at determining the association between HIV and ART exposure on the quality of observed general movements of infants.

Objectives

- To describe the quality of general movement patterns observed among AHEU and HIV unexposed uninfected (HUU) infants.
- To investigate the association between gender and general movements.
- To compare general movement patterns of AHEU infants to those of HUU infants

Method

This was a cross-sectional study. A sample size of 65 participants was identified from Zingwangwa Health Centre. These infants were categorised into AHEU and HUU. A 3-minute video of each child was taken when they displayed spontaneous movements. Coded video clips were then analysed by two trained independent assessors.

Results

The study found a high level of agreement between scorers for general movement assessment (Kappa = 0.731, p = 0.000). All participants, aged between nine to 16 weeks with a mean of 11 weeks, were breastfed (n = 65). All infants were HIV negative, with nearly equal numbers of HUU and AHEU participants. The majority exhibited

normal general movement scores, with no significant differences observed based on gender (p = 0.276) or HIV/ART exposure (p = 0.605).

Conclusion

In this study comparing AHEU and HUU infants, normal general movements were prevalent, indicating a low risk of cerebral palsy. Gender showed no significant association with GMA scores. Larger samples and longitudinal studies are recommended to confirm these findings and understand long-term effects of HIV and ART exposure on infant neurodevelopment.

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List of Abbreviations

AHEU = antiretroviral drug and HIV-exposed uninfected infants
ART = Antiretroviral Therapy
CPG = Central Pattern Generator
CP = Cerebral Palsy
GMs = General Movements
GMA = General Movement Assessment
HEI = HIV Exposed Infected
HEU = HIV Exposed Uninfected
HIV = Human Immunodeficiency Virus
HUU = HIV Unexposed Uninfected
IQ = Intelligence Quotient
KUHeS = Kamuzu University of Health Sciences
MTCT = Mother-to-Child Transmission
SD = Standard Deviation
TB = Tuberculosis
WHO = World Health Organization
95-95-95 = UNAIDS strategy that by 2030, 95% of all people living with HIV will know their HIV status, 95% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, 95% of all people receiving antiretroviral therapy will have viral suppression.

CHAPTER 1. INTRODUCTION

1.1. Background

By the end of 2022, about 39 million people worldwide were HIV-positive, with the highest concentration in Africa. Eastern and Southern Africa alone accounted for 54% of the total (World Health Organisation, 2023). Roughly 1.3 million pregnant women globally were HIV-positive, with 81% receiving antiretroviral therapy to prevent transmitting the virus to their infants (UNAIDS, 2023a). Additionally, more than 1.2 million children are exposed to HIV annually (UNAIDS, 2023b).

The advancement in antiretroviral therapy (ART) has significantly reduced the risk of mother-to-child transmission (MTCT) of HIV. While this is a landmark achievement in as far HIV care is concerned, this has come with new challenges as the number of HIV-exposed uninfected (HEU) infants increases. As of 2018, the global estimate for number of HEU infants was at 14.8 million, with 13.2 million of them living in Sub-Saharan Africa (Slogrove et al., 2020a). There have been a number of reports on the challenges these infants face. While some studies have produced conflicting results regarding the developmental outcomes of HEU infants (Chaudhury et al., 2017), some literature has shown low neuromotor and cognitive developmental scores among HEU infants when matched with HIV-unexposed uninfected (HUU) infants (McHenry et al., 2018).

Literature has shed light on the multifaceted developmental challenges encountered by HEU children. These challenges encompass a spectrum of impairments, including but not limited to language and speech deficits, which may manifest in difficulties in articulation, comprehension, and expression (Wedderburn et al., 2019a). Additionally, a study by Kerr et al. (2014) revealed the correlation between HIV or ART exposure status and poor academic performance, potentially stemming from cognitive limitations.

HEU children have also shown reduced working memory capabilities, impacting their ability to retain and manipulate information in real-time tasks (Kerr et al., 2014). Lower Intelligence Quotient (IQ) scores have also been noted among these children (Kerr et al., 2014). These deficits may contribute to learning difficulties and hinder academic progress.

A recent study, conducted in Malawi and Uganda, looked into physical growth disparities between ART- and HIV- exposed uninfected (AHEU) and HUU children. This research explored potential implications of HIV exposure and antiretroviral therapy on growth patterns, nutritional status, and overall health outcomes among AHEU children (Fowler et al., 2022). Results indicated that AHEU children generally had lower height-for-age and weight-for-age scores (Fowler et al., 2022). Stunting rates were higher among AHEU children, particularly in Malawi (Fowler et al., 2022).

Despite indefinite results from large cohorts and retrospective studies, some studies have suggested that in-utero exposure to ARVs may negatively affect development among HEU infants (Smith et al., 2017). Delayed cognitive development has been reported among ARV-exposed infants (Alcaide et al., 2019). Atazanavir is associated with adverse effects on the neurodevelopment of perinatally HEU children. Poor language and socio-emotional development were reported among atazanavir-exposed infants in their first year of life (Caniglia et al., 2016).

Globally, about 1.5 million HIV-infected women give birth annually. Malawi stands out in this landscape, grappling with an HIV prevalence rate of 7.1% among adult women aged 15-49, as reported by UNAIDS (2023c). Despite these challenges, Malawi has shown remarkable commitment to addressing its HIV burden. Through collaborative efforts from various stakeholders, the country has set ambitious targets, notably the 95-95-95 goal, to ensure that 95% of individuals living with HIV are aware of their status, receive appropriate antiretroviral therapy, and attain viral suppression (Avert, 2023; UNAIDS, 2023c). By 2022, Malawi had made notable strides; over 94% of individuals were receiving HIV treatment and 87% had achieved viral suppression, as reported by Avert and UNAIDS (Avert, 2023; UNAIDS, 2023c).

Malawi's contribution to the global population of HEU children is approximately 3.9%, underscoring the magnitude of this challenge (Avert, 2023; Slogrove et al., 2020b). In light of this, it is imperative for Malawi to develop robust strategies for monitoring the developmental trajectory and addressing potential health challenges faced by HEU children. This involves establishing comprehensive surveillance systems, enhancing healthcare infrastructure, and implementing targeted interventions to ensure the optimal health and well-being of this vulnerable population. By prioritizing such initiatives, Malawi can continue its progress towards broader public health goals while safeguarding the future of its youngest citizens.

Cerebral palsy, is the leading cause of disability among children with a global prevalence of 1.6 to 3.6 per 1,000 live births (Goldsmith et al., 2023; McIntyre et al., 2022). In Malawi cerebral palsy is the most prevalent childhood neurodisability condition and presents significant challenges to affected children and their families (Tataryn et al., 2017).

Aside from perinatal influences like environment and nutrition, prenatal factors significantly shape a child's development. Both animal and human studies have underscored the profound impact of insults to the developing brain during pregnancy, with potential adverse consequences for the child's developmental trajectory (Knuesel et al., 2014)**.** Of particular concern is maternal immune activation resulting from HIV infection, which has been postulated to exert detrimental effects on the developing fetal brain. Research findings from Botswana suggest a potential association between maternal HIV infection during pregnancy and increased risks of cerebral palsy and neurodevelopmental delays in HEU infants. This heightened risk is attributed to various factors, including exposure to potentially teratogenic antiretroviral drugs, maternally acquired infections during pregnancy, and maternal immune activation in utero (Monokwane et al., 2017). While these findings shed light on potential mechanisms linking maternal HIV infection to adverse neurodevelopmental outcomes in HEU infants, the study authors acknowledge the limitations in their data, highlighting the need for further investigations (Monokwane et al., 2017).

Early detection and early intervention of neurological conditions are being advocated for globally. Timely assessment allows for tailored interventions aimed at optimizing developmental outcomes, minimizing long-term functional impairments, and enhancing the overall quality of life for affected individuals. This potentially mitigates long-term neurodevelopmental challenges such as permanent disability and enhances overall outcomes for affected individuals (Hadders-Algra, 2014; Ma et al., 2015; Noritz and Murphy, 2013). Early identification of neurological impairments, including those associated with conditions like cerebral palsy, poses a significant challenge in clinical practice (Tomantschger et al., 2018).

For early detection of cerebral palsy (CP) before 5 months corrected age (CA), the most reliable approach involves a combination of standardized motor assessments, neuroimaging, and a review of risk factors (Novak et al., 2017). When the General Movements Assessment (GMs) or MRI is not available, early detection of cerebral palsy (CP) should still be pursued to ensure timely access to early intervention. In such cases, the Hammersmith Infant Neurological Examination (HINE) can be used, with a score below 57 at 3 months being 96% predictive of CP. Additionally, the Test of Infant Motor Performance (TIMP) may also be applied, although the supporting evidence for its predictive value is of lower quality compared to other assessments (Novak et al., 2017).

The Prechtl GMA serves as a valuable tool in identifying early signs of cerebral palsy and developmental deficits by meticulously analysing spontaneous movement patterns in both foetal and early infancy life. Key features of Prechtl GMA are quickness, non-invasiveness and cost-effectiveness (Prechtl, 2007). It is a crucial tool in this process, as it is 95-98% predictive of CP when combined with neuroimaging. Its high predictive accuracy makes it essential for early diagnosis, allowing timely interventions (Novak et al., 2017). Additionally, MRI scans, particularly before sedation becomes necessary, are 80-90% predictive of CP when abnormalities in motor areas of the brain are detected. Using GMs alongside neuroimaging significantly improves early detection, enabling better outcomes for affected infants (Bosanquet, Copeland, Ware and Boyd, 2013; Prechtl, 2007).

In our setting, MRI scans are often prohibitively expensive and difficult to access, making the use of GMs the preferred method for early detection of CP. Given its high predictive accuracy, non-invasive nature, and cost-effectiveness, the GMs assessment will be prioritized and used in this study as the primary tool for identifying early signs of cerebral palsy.

Further exploration is required to understand the impact intrauterine exposure to HIV and/or ART on an infant's nervous system. In this study, therefore, it was hypothesised that there is an association between HIV and ART exposure and the quality of observed general movements.

1.2. Problem Statement

A report by UNAIDS (2023c) has indicated that over 980,000 adults and children are living with HIV in Malawi. The prevalence of HIV among adults aged 15–49 is at 7.1% (UNAIDS, 2023c). This is population that is in the childbearing ages. As more HIV-positive mothers bear children, an increasing number of infants are being exposed to both HIV and ART, leading to a rise in the population of AHEU infants. This, along with reports of detected developmental delays among AHEU infants, highlights the need to further investigate this group of infants. It is now possible to identify infants at risk of neurodisability early through the use of spontaneous general movements (Bosanquet, Copeland, Ware and Boyd, 2013; Prechtl, 2007). However, there is little knowledge about the quality of general movements of infants exposed to HIV and ART. Furthermore, as early detection of possible neurological impairment and early intervention among HEU infants are being advocated for worldwide, there is a need to establish the impacts of exposure to HIV and ART on the developing nervous system through the use of GMA of infants.

1.3. Research Question

Does HIV and ART exposure affect the quality of observed general movements among infants?

1.4. Research Aim and Objectives

1.4.1. Aim

To determine the association between HIV and ART exposure on the quality of observed general movements of infants.

1.4.2. Objectives

The objectives of this study were to:

- To describe the quality of general movement patterns observed among ART and HIV-exposed uninfected (AHEU) and HIV-unexposed uninfected (HUU) infants.
- To investigate the association between gender and general movements.
- To compare general movement patterns of AHEU infants to those of HUU infants.

1.5. Significance of the Study

Early identification of developmental issues is essential to mitigate complications arising from delayed rehabilitation. With scarce data on motor development in HEU infants using GMA, this study fills a critical gap by offering insights into potential misconceptions surrounding the impacts of HIV and ART exposure on HEU infants. Furthermore, the study will serve as a valuable resource for clinicians and therapists, alerting them to possible developmental challenges in this population and emphasizing the importance of early intervention. Additionally, the findings may contribute to laying the groundwork for future research endeavours focused on interventions in the neurodevelopment of HEU infants in Malawi, thereby facilitating targeted efforts to optimize the well-being and developmental outcomes of this vulnerable group.

CHAPTER 2. LITERATURE REVIEW

2.1. Introduction

In this chapter, a description of the methodology utilised for literature search is presented, followed by an in-depth discussion of the HIV pandemic. This discussion encompasses an analysis of its global epidemiology and contextualization within the landscape of Malawi. Subsequently, a comprehensive examination of cerebral palsy follows, encompassing its definition, global and local epidemiological data, diagnostic tools, and underlying pathophysiological mechanisms. A critical examination of the interrelationship between HIV and neurodevelopmental conditions such cerebral palsy comes next. Finally, the chapter discusses the Prechtl GMA tool, offering insights into its application and significance within the context of this discourse.

2.2. Literature Search Strategy

To identify relevant literature for this study, a systematic search was conducted across multiple electronic databases including Google Scholar, PubMed, Scopus, and Web of Science. The search strategy employed a combination of keywords and controlled vocabulary terms related to the topic, including 'HIV', ‘HIV-exposed uninfected’, 'cerebral palsy', ‘neurodevelopment, 'diagnosis', and 'General Movement Assessment'. Boolean operators such as 'AND' and 'OR' were utilized to refine the search and ensure comprehensive coverage of the literature. Additionally, reference lists of relevant articles and reviews were hand-searched to identify additional studies not captured in the initial electronic search. The search was restricted to articles published in English, with no restrictions on study design. Duplicate articles were removed, and the remaining articles were screened based on title and abstract for relevance to the research question. Full-text articles meeting the inclusion criteria were then retrieved.

The subsequent sections provide comprehensive insights into the synthesized literature on the topic.

2.3. The HIV Pandemic

2.3.1. Epidemiology

About 39 million people were living with HIV globally by the end of 2022 and Africa alone accounted for two-thirds of this population (World Health Organisation, 2023). Eastern and Southern Africa was the worst affected area accounting for 54% of this global figure (UNAIDS, 2023a). It was estimated that there were about 1.3 million pregnant women living with HIV globally in 2022. About 81% of these expectant mothers were receiving ART to prevent vertical transmission to their infants (UNAIDS, 2023a), as per WHO's recommendation that all pregnant and lactating mothers living with HIV should be on lifelong ARTs.

Over 1.2 million children are exposed to HIV yearly (UNAIDS, 2023b). The use of MTCT prevention strategies has led to an increase in the number of HEU and ART-exposed infants. Despite the advancement of the MTCT prevention strategy, gaps still exist in it, leaving hundreds of thousands of children at risk of HIV leading to HIV-exposed infected (HEI) infants (UNAIDS, 2023b). Thus, all categories of children with regard to HIV exposure and status exist, namely HEI, HEU and HUU.

There are about 14·8 million HEU children globally and about 13.8 million live in sub-Saharan Africa (Slogrove et al., 2020a). On the ART front, the provision of ART to expectant mothers as well as children has shown benefits in overall child protection against HIV infection. UNAIDS (2023b) reports that over three million children have been protected against HIV since 2000. With the provision of ART, more of this population is getting exposed to ART. Exposure to ART can be in vivo as well as postnatally through breastfeeding. Exclusive breastfeeding is recommended especially for mothers in resource-limited settings for effective and safer postpartum care (WHO, 2014). As of 2022, about 82% of pregnant or breastfeeding women living with HIV were receiving treatment, up by about 34% from 2010 data (UNAIDS, 2023b), indicating that more infants are being exposed to ART.

2.3.2. HIV in Malawi

Malawi is a small Sub-Saharan nation with a total land area of 94,280 km^2 and a high population density (186 persons/ km^2). With its fast-growing population, the country also has a high burden of HIV. The last population census indicated that the country's population was at 17.6 million as of 2018 (National Statistics Office, 2019). As of 2021, the World Bank estimated that the population had grown to 19.9 million (World Bank, 2023).

UNAIDS data for 2022 indicates that the national HIV prevalence among adults (aged 15-49) in Malawi was 7.1% (UNAIDS, 2023c). Malawi's National Strategic Plan for Health Sector (Ministry of Health and Population, 2023) sets out the country's vision for ending the AIDS epidemic and outlines key priorities for action, including reducing new HIV infections, improving health outcomes for people living with and affected by HIV and addressing key populations' needs. The country's national HIV response has been guided by the WHO's 95-95-95 targets, which aims to ensure that by 2025, 95% of people living with HIV know their status, 95% of people who know their status are accessing ART, and 95% of people on ART have suppressed viral loads. By the end of 2022 the country had made significant progress in expanding access to HIV testing, treatment, and care services, with over 94% [89->98] of people living with HIV aware of their status, more than 93% [88->98] of people living with HIV were on antiretroviral therapy (ART) and 87% [82-92] of people on ART had their viral loads suppressed while global trends were 86% [73–>98], 89% [75–>98] and 93% [79–>98%], respectively (UNAIDS, 2023c; World Health Organisation, 2023).

Malawi's clinical guidelines on HIV management highlight four strategies for preventing HIV transmission from mothers to children and alleviating the HIV impact on both mothers and their offspring (Ministry of Health and Population, 2022). The following are the strategies: focusing on preventing HIV infection in the general population; preventing unintended pregnancies among HIV-positive women by promoting provider-initiated family planning in ART clinics, in line with national guidelines on sexual and reproductive health and rights; emphasizing care, treatment, and support for HIV-infected women, their children, and families; and

addressing the prevention of HIV transmission from infected women to their children, involving initiatives such as provider-initiated testing at maternal and child health (MNCH) settings, initiating lifelong ART for pregnant and breastfeeding women, ensuring safe obstetric practices, and providing infant HIV prophylaxis (Ministry of Health and Population, 2022)

Furthermore, every child born to and/or breastfeeding from HIV-infected mothers is enrolled into the HIV Care Clinic. Continuous monitoring and follow-up for these children are adhered to, the follow-up period is extended until they reach at least 24 months of age. If the breastfeeding continues beyond this timeframe, the follow-up is extended accordingly. This comprehensive approach aims to provide ongoing healthcare, support, and necessary interventions to safeguard the well-being of children exposed to HIV during birth or through breastfeeding (Ministry of Health and Population, 2022).

Drugs utilized for treating HIV-infected children in Malawi are similar to those administered to adults. Paediatric HIV treatment typically entails employing specific formulations and doses tailored for children. Antiretroviral drugs applicable to the treatment of HIV-infected children encompass nucleoside reverse transcriptase inhibitors like tenofovir (TDF), lamivudine (3TC), abacavir (ABC), zidovudine (AZT); non-nucleoside reverse transcriptase inhibitors such as efavirenz (EFV) and nevirapine (NVP); protease inhibitors including lopinavir/ritonavir (LPV/r); and integrase inhibitors exemplified by dolutegravir (DTG) (Ministry of Health and Population, 2022).

2.4. Cerebral Palsy

2.4.1. Definition

The following is the internationally accepted definition of cerebral palsy:

> Cerebral palsy is a group of permanent movement and posture disorders that result from non-progressive disturbances occurring in the developing fetal or infant brain. These neurological disorders can affect muscle coordination, balance, and motor skills. The motor disorders of cerebral palsy are often

accompanied by disturbances of sensation, perception, cognition, communication, and behaviour by epilepsy and secondary musculoskeletal problems (Rosenbaum et al., 2007).

Cerebral palsy is the most prevalent motor disability in childhood (CDC, 2024). Symptoms vary between patients and include motor delay, spasticity or hypotonia, incoordination, and difficulty with walking (Bax et al., 2005).

2.4.2. Epidemiology: Global and In Malawi

Variabilities exist in the prevalence of CP. It's been suggested that the relatively high CP prevalence in certain countries may be attributed to sustained exposure to risk factors, including low birth weight, limited access to antenatal and neonatal care, nutritional deficiencies, infections, and trauma (Dan, Mayston, Paneth and Rosenbloom, 2014). Based on the evolving but still limited dataset from diverse regions within low- and middle-income countries (LMICs), reports indicate that the birth prevalence of pre-/perinatal cerebral palsy is 3.4 per 1000 live births. Data from high-income countries (HICs) report the prevalence to be 1.6 per 1000 live births, taking into consideration post-neonatal CP cases. This sheds light on the disparity in prevalence between LMICs and HICs, stressing the importance of socioeconomic factors in the occurrence of CP (Goldsmith et al., 2023; McIntyre et al., 2022). Low- and middle-income countries face a heightened prevalence of preventable issues such as kernicterus, perinatal asphyxia, and infant infections. These challenges are more manageable in high-income countries, where preventive measures are more accessible (Eisenstat, Goldowitz, Oberlander and Yager, 2023). Since no data is available on the prevalence of CP in Malawi, estimates from LMICs are used instead.

2.4.3. Diagnostic Procedures

Early detection of neurological conditions and early intervention are key to reducing the risk of permanent and severe disability (Hadders-Algra, 2014; Ma et al., 2015; Noritz and Murphy, 2013). A clear diagnosis helps relieve uncertainty and the fear of the unknown for families (Carr and Coghill, 2016; Novak et al., 2017). It also

prevents unnecessary investigations, conserving limited resources as is the case in Malawi. Accurate diagnosis plays a key role in informing epidemiological studies and prevalence registries. Additionally, understanding the child's health status allows for better prediction of the condition's progression (Carr and Coghill, 2016). Lastly, it helps families secure necessary benefits and support when raising a child with cerebral palsy (Carr and Coghill, 2016; Novak et al., 2017). One of the tools used for the early identification of children at risk of cerebral palsy is the Prechtl GMA tool.

The Prechtl GMA tool stands as a pivotal diagnostic tool renowned for its quickness, non-invasiveness, and cost-effectiveness. A well-known tool for its remarkable sensitivity and specificity rates of 98% and 91% respectively, Prechtl GMA plays a crucial role in detecting neurological irregularities linked to conditions such as cerebral palsy and neurodevelopmental conditions (Bosanquet, Copeland, Ware and Boyd, 2013; Prechtl, 2007). This method analyses the spontaneous movement patterns exhibited by foetuses and young infants, providing invaluable insights into their neurological well-being and potential developmental challenges (Bosanquet, Copeland, Ware and Boyd, 2013; Prechtl, 2007). Although Prechtl GMA demonstrates efficacy in predicting cerebral palsy (Novak et al., 2017), it may not effectively identify the potential for subtle developmental delays in infants. Consequently, alternative diagnostic modalities such as Ultrasound (US), Magnetic Resonance Imaging (MRI), and the Hammersmith Infant Neurological Examination (HINE) are employed (Novak et al., 2017).

An interim diagnosis of high risk for cerebral palsy should be made when a definitive diagnosis cannot yet be confirmed. Since clinical signs typically appear and progress before age 2, a combination of standardized tools alongside clinical history is recommended for assessing risk (Novak et al., 2017). For infants younger than 5 months (corrected age), MRI (86%-89% sensitivity), the Prechtl GMA (98% sensitivity), and the HINE (90% sensitivity) are the most effective predictors of cerebral palsy. After 5 months, MRI and the HINE remain the most reliable tools for assessing cerebral palsy risk (Novak et al., 2017).

The development of early general movements is discussed in section 2.6 below.

2.4.4. Pathophysiology of cerebral palsy

2.4.4.1. Aetiology

Cerebral palsy has diverse risk factors. Understanding the interplay of these factors is crucial for comprehensive diagnosis and effective management strategies for individuals with cerebral palsy. These risk factors can be categorized into preconception, prenatal, perinatal, and postnatal (Novak et al., 2017). Preconception risks include a history of stillbirths, miscarriages, low socioeconomic status, assisted reproduction, and abnormal genetic copy number variations (Novak et al., 2017). Prenatal influences encompass genetic factors, where certain genetic predispositions may contribute to the development of cerebral palsy. Additionally, infections during pregnancy, including rubella, cytomegalovirus, or toxoplasmosis, have been identified as potential risk factors (Schleiss, 2014). Perinatal factors involve complications during birth such as birth asphyxia, seizures, prematurity, jaundice, hypoglycaemia and low birth weight, all of which are associated with an increased risk of cerebral palsy. Infections acquired around the time of birth also contribute to the complexity of risk factors. Postnatal influences include traumatic brain injuries sustained during early childhood, stroke and infections (Novak et al., 2017).

In most cases, cerebral palsy results from injuries to the developing brain rather than from brain anomalies (Bax, Tydeman and Flodmark, 2006). The nature of brain response to injury, the specific characteristics of lesions, and their location are intricately influenced by the stage of brain maturation during which pathogenetic events take place (Bax, Tydeman and Flodmark, 2006). Damage to cortico-striatal-thalamic-cortical and cortico-cerebellar-cortical networks significantly disrupts various aspects of motor control (Forssberg, 2014). Specifically, these disruptions adversely affect motor planning, coordination, muscle strength regulation, motor learning, and fine motor skills. In addition to network impairments, complexities of descending motor pathways projecting to the brainstem and spinal relays have also been studied (Forssberg, 2014). It's been suggested that disturbances in these pathways, combined with the persistence of circuits that would typically disappear with maturation, contribute substantially to the presence of persistent or poorly inhibited primitive reflexes. These reflexes, alongside abnormalities in movement

and posture organization, hyperactive reflexes, and altered muscle tone, notably spasticity, further characterize the motor impairments associated with cerebral palsy (Forssberg, 2014). Investigations into the interplay of neuronal, nutritional, and mechanical factors have revealed the progressive changes in muscle dynamics, contributing to hypertonia and limited motor repertoire observed in individuals with cerebral palsy (Forssberg, 2014).

2.4.4.2. Pathways

Several pathways for the development of cerebral palsy have been studied and these include brain malformations, hypoxia-ischaemia events, brain-injuring agents such as bilirubin, maternal-foetal infections and endocrine pathologies (Dan, Mayston, Paneth and Rosenbloom, 2014). This segment will cover hypoxia-ischaemia events and maternal-foetal infections for these directly or indirectly help understand how drugs (ART) and/or infections (HIV) may lead to the development of CP.

Cerebrovascular accidents (CVAs), commonly referred to as strokes, constitute a significant factor contributing to perinatal brain injury and enduring neurodevelopmental disabilities (Dan, Mayston, Paneth and Rosenbloom, 2014). The relationship between drug usage and the occurrence of CVAs during the perinatal period has been a subject of investigation, yielding inconclusive evidence and some argue that this might be a coincidental occurrence (Reynolds, Riel-Romero and Bada, 2007). Nevertheless, some case reports, such as those discussed by Finkel and Zarlengo (2004), have underscored an association between maternal drug and alternative medication use and instances of perinatal stroke.

Hypoxemia refers to reduced oxygen level in blood and ischaemia refers to a reduced amount of oxygen in the brain. Perinatal hypoxia-ischaemia may lead to the development of CP. The key factor influencing the outcome of prenatal hypoxia-ischemia is brain temperature (Dan, Mayston, Paneth and Rosenbloom, 2014). During secondary damage, hyperthermia promotes the release of glutamate and oxygen free radicals which are detrimental to brain tissue. There is release of pro-inflammatory mediators following hypoxia-ischaemia and infection. Key mediators

include cytokines (glycoproteins) such as interleukin (IL) and tumour necrosis factor-alpha (TNF-α) which can induce apoptosis of oligodendrocytes (Dan, Mayston, Paneth and Rosenbloom, 2014). Several remedies have been instituted to reverse the effects of hypoxia-ischaemia, an example of which is therapeutic hypothermia cooling of the infant to 32°C for 96 hours following a hypoxic event (Dan, Mayston, Paneth and Rosenbloom, 2014).

Mechanisms contributing to infection-mediated injury associated with cerebral palsy involve both direct and indirect pathways, each playing a crucial role in the development of adverse outcomes. This is a general consideration for all infections without considering specific pathogens. The direct mechanisms primarily revolve around foetal infection, encompassing the transmission of infectious pathogens to the developing foetus, subsequent infection of the foetal brain, and the induction of a foetal cytokine as an inflammatory response. This response is marked by the modulation of apoptosis, a lytic viral infection of crucial neuronal and glial cells, as well as alterations in neuronal migration. Additionally, the infection can lead to complications such as calcification and hydrocephalus (Dan, Mayston, Paneth and Rosenbloom, 2014). All these events can lead to the development of CP.
On the indirect front, foetal brain injury can result from placental injury, triggering a hypoxic or anoxic state and impaired substrate delivery. Maternal infection initiates a cascade of events, including a maternal inflammatory response and the release of cytokines and mediators such as TNF and IL into the amniotic fluid. The foetal inflammatory response syndrome (FIRS) may be activated, with elevated levels of foetal IL-6 (>11pg/ml) which has been identified as a central mediator of white matter injury (Dan, Mayston, Paneth and Rosenbloom, 2014).

Foetal hypoxia-induced inflammation is a significant contributor, involving various cytokines and immune modulators such as B-lymphocyte chemoattractant, epidermal growth factor, IL-2, 5, 8, 12, 13, 15, and macrophage inflammatory protein 1-beta, as well as the involvement of CD8+ T-cells. Funisitis and umbilical cord inflammation, accompanied by elevated levels of IL-10 and 19, further exacerbate the foetal inflammatory response (Dan, Mayston, Paneth and Rosenbloom, 2014).
Given the groundwork laid by the aforementioned information, the subsequent three sub-sections delve into a detailed exploration of the existing literature that

investigates the intricate relationship between cerebral palsy and three specific categories: HEI, HEU, and infants exposed to ART.

2.5. HIV and Cerebral Palsy

2.5.1. HEI and its Impact on Child Brain

While the majority of infections that pose a threat to the developing central nervous system (CNS) are acquired early in foetal life, it's important to note that some pathogens associated with cerebral palsy, such as HIV, can also be acquired during the perinatal or postnatal period.

Pediatric HIV, primarily acquired through mother-to-child transmission during pregnancy, childbirth, or breastfeeding, remains a leading cause of childhood morbidity and mortality (Girish, Andre and Mala, 2018). Infected children often develop central nervous system (CNS) complications, with the virus directly impacting the brain, leading to conditions like progressive HIV encephalopathy (PHE). This is characterized by impaired brain growth (microcephaly), progressive motor dysfunction, and delayed neurodevelopment (Girish, Andre and Mala, 2018). While CNS infections and malignancies are less common in pediatric cases, the effects of HIV on an immature brain can be profound, leading to significant cognitive and motor deficits (Girish, Andre and Mala, 2018).

The unique nature of HIV in its ability to swiftly enter the brain shortly after initial exposure adds a layer of complexity to its potential impact on the neurodevelopment (Valcour, Sithinamsuwan, Letendre and Ances, 2011). This rapid entry is facilitated by infected monocytes and lymphocytes successfully traversing the blood-brain barrier. Intriguingly, neurons remain uninfected by the virus, prompting a deeper exploration into the mechanisms underlying neuronal injury (Valcour, Sithinamsuwan, Letendre and Ances, 2011). Contrary to direct infection of neurons by HIV, the prevailing belief is that neuronal injury occurs through indirect processes. These processes include intricate cytokine responses and the induction of apoptosis, as detailed in prior discussions (Valcour, Sithinamsuwan, Letendre and Ances, 2011). The involvement of cytokines and the initiation of apoptosis highlight the

multifaceted ways in which HIV can impact the delicate environment of the developing brain.

2.5.2. HIV Encephalopathy

HIV encephalopathy (HIVE), also known as HIV-Associated Encephalopathy, shares clinical features with cerebral palsy, although they represent distinct neuropathological entities (Mubaiwa, 2020). Encephalopathy, as defined by the World Health Organisation (2007) encompasses various clinical manifestations indicating dysfunction or damage to the brain. The primary characteristic is a significant gap between a person's chronological age and their developmental stage, resulting in an inability to achieve expected milestones or a regression of previously acquired skills. Cognitive decline, including memory issues, reduced alertness, and behavioural changes, is also common (World Health Organisation, 2007). The WHO's definition also includes the possibility of progressive impaired brain growth, seen through stagnation in head circumference, especially relevant in paediatric cases. Encephalopathy may further manifest as acquired symmetric motor deficits, such as muscle weakness, abnormal reflexes, coordination difficulties, and gait disturbances (World Health Organisation, 2007). The diagnosis typically requires symptom progression over at least two months, ruling out transient conditions, and excluding other identifiable illnesses contributing to the neurological changes. To investigate further and rule out alternative causes, brain imaging like computed tomography (CT) scans or magnetic resonance imaging (MRI) is recommended by the WHO to provide insights into brain structure and function for accurate diagnosis and management (World Health Organisation, 2007).

While HIVE pathogenesis is directly linked to HIV infection and may manifest prior to substantial immunosuppression, CP represents a neurodevelopmental disorder predominantly affecting motor coordination and movement. CP aetiology encompasses various factors, including birth-related brain injury and developmental anomalies (Bax, Tydeman and Flodmark, 2006). Notably, cerebral damage in CP is non-progressive (Bax, Tydeman and Flodmark, 2006), whereas HIVE exhibits a progressive course, leading to worsening neurological deficits over time (Mubaiwa, 2020).

Some studies have shown similarities in the manifestation of the two conditions. A study by Naik et al. (2018) compared children with spastic diplegia caused by CP and those caused by HIVE in terms of motor function, tone, and strength. Both groups showed similar motor deficits overall, but when separated by ambulant and non-ambulant categories, differences emerged. Ambulant HIV-infected children were weaker but more functional with milder tone compared to CP counterparts (Naik et al., 2018). Non-ambulant HIV-infected children were stronger with milder tone compared to CP group (Naik et al., 2018). These findings suggest distinct patterns in motor abilities between the two conditions despite similar motor deficits.

In sub-Saharan Africa, paediatric HIV remains a significant health issue causing neurological damage leading to developmental complications, particularly affecting gross motor development, cognition, and social interaction (Hilburn, Potterton and Stewart, 2010). With improved access to antiretroviral therapy, early identification and intervention by physical therapists play a crucial role in managing HIV-related encephalopathy, supporting children's optimal development and educational needs (Hilburn, Potterton and Stewart, 2010).

2.5.3. The Potential Link Between HIV Exposure-Associated Developmental Challenges and Cerebral Palsy in HEU

Neurodevelopment of HEU has been shown to differ from HUU (McHenry et al., 2018; Piske et al., 2018; Wedderburn et al., 2022). McHenry et al. (2018) conducted a meta-analysis aimed at evaluating neurodevelopmental outcomes in children born to HIV-positive mothers. Using Bayesian meta-regression, the study compared mental and motor scores among HEI, HEU, and HUU children. Apart from lower mental and motor scores among HEI children compared to HUU children, HEU children also exhibited lower scores, although not to the same extent as HEI children. Sensitivity analyses revealed variations in developmental scores based on assessment quality and antiretroviral (ARV) exposure. The findings suggest that HEU children may have worse development compared to HUU children, emphasizing the need for further research to optimize neurodevelopment in this vulnerable population. The heterogeneity of assessments and ARV regimens across

studies, as well as methodological flaws in included studies, were limitations of the study (McHenry et al., 2018)

Language development has also been found to be a challenge among HEU infants. A South African birth cohort study has revealed that HIV-exposed uninfected (HEU) children demonstrate poorer language outcomes at 24 months, but not at 6 months, compared to HIV-unexposed children (Wedderburn et al., 2019b). The study, considered the largest longitudinal one of its kind, suggests a growing trend of developmental impairment over time in the cohort. The language impairments in HEU children persisted even after accounting for potential mediators like infant feeding method, maternal depression, and prematurity. The authors discuss potential mechanisms, including maternal immune activation and neuroinflammation, and emphasize the importance of optimizing maternal health for child neurodevelopment. Despite some limitations, the study's strengths include a validated measure of neurodevelopment, a large sample size, the inclusion of an appropriate control group, and longitudinal data (Wedderburn et al., 2019b).

Hutchings and Potterton (2014) conducted a cross-sectional study aimed at comparing the development of HEI with HEU infants using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). They enrolled 60 infants (32 HEU, 28 HEI) with matched demographics. Significant differences were found in anthropometry and development; HEI infants showed malnutrition, stunted growth, smaller head circumferences, and a mean developmental delay of approximately two months across all BSID-III scales. HEI infants also had higher rates of cognitive, language, and motor delays compared to HEU infants, highlighting the risk of developmental delay in HEI infants. Overall, the study revealed that both HEI and HEU infants experienced delays in overall development and had impaired growth (Hutchings and Potterton, 2014).

The studies referenced above demonstrate the likelihood of developmental disorders among HEU. Thus, it is plausible for HEU children, due to the factors mentioned above, to develop cerebral palsy-like symptoms as a result of their compromised neurological development.

2.5.4. The Potential Link Between ART Exposure-Associated Developmental Challenges and Cerebral Palsy

Studies have shown that ART may have an impact on the neurodevelopment of the child ranging from reduced cognitive function to poor motor repertoire (Caniglia et al., 2016; Smith et al., 2017). Alcaide et al. (2019) explored the impact of maternal factors, particularly the detection of antiretroviral drugs (ARVs) and experiences of intimate partner violence (IPV), on neurodevelopmental outcomes in HEU infants in rural South Africa. Notably, HEU infants, displayed cognitive developmental delays, particularly when there was maternal ARV use for prevention of mother-to-child transmission. The study emphasizes the need for a comprehensive understanding of the effects of ARVs during pregnancy and the influence of psychosocial factors on infant neurodevelopment (Alcaide et al., 2019).

The findings of Strehlau et al. (2020) contradict Alcaide et al. (2019). In their study aimed at describing neurodevelopmental assessment results at 12 months of age from a single cohort of HEU children from similar socioeconomic backgrounds, the researcher found no significant associations between maternal or infant health indicators and Bayley-III scores in the short-term follow-up. No deleterious effects on neurodevelopment were observed due to in-utero and post-natal exposure to antiretroviral drugs (ARVs) (Strehlau et al., 2020). The study however did not have an HUU control group to control for confounders, which was acknowledged as one of the limitations of the study. The single assessment at 12 months was also noted as a limitation of the study (Strehlau et al., 2020). Likewise, Piske et al. (2018) found no adverse associations between antiretroviral drugs and neurodevelopmental disorders within AHEU children.

Although ARV exposure alone may not directly cause cerebral palsy, the cumulative effects of cognitive and motor developmental delays, combined with other factors like neuroinflammation, can contribute to the manifestation of motor dysfunctions typical of CP.

2.6. The Prechtl GMA

Foetuses and young infants display distinctive spontaneous movement patterns generated by the central pattern generators (CPGs) located in the brainstem for rhythmic functions such as breathing and chewing, and spinal cord for functional locomotion (Bucher, Haspel, Golowasch and Nadim, 2015; Peyton and Einspieler, 2018). These are specialized neural circuits that play crucial roles in orchestrating rhythmic and coordinated movements, facilitating essential functions for survival and daily activities. These are found in the spinal cord and brainstem. Within the intricate network of the spinal cord, CPGs take charge of coordinating locomotion, ensuring the seamless execution of movements such as walking or running. Additionally, they contribute to the activation of protective reflexes, which are vital for responding swiftly to potentially harmful stimuli in the environment. This spinal involvement highlights the significance of CPGs in the fundamental motor control of vertebrates. CPGs in the brainstem regulate crucial processes like breathing, ensuring the rhythmic and coordinated expansion and contraction of respiratory muscles. Furthermore, they play pivotal roles in orchestrating complex behaviours such as chewing and swallowing, contributing to the efficient processing and consumption of food (Dan, Mayston, Paneth and Rosenbloom, 2014).

The distinctive spontaneous movement patterns occur during specific stages of development and can be categorised as writhing or fidgety movements. General movements are unique in sequencing and come before isolated and functional limb movements in the human body (Prechtl, 1990). Writhing movements, occurring between nine weeks postmenstrual age and nine weeks post-term age, have slow to moderate amplitude as well as speed (Prechtl, 2007). These are then followed by circular movements of small amplitude, moderate speed and variable acceleration in all directions of the neck, trunk and limbs. These are known as fidgety movements and occur between nine and 20 weeks post-term age (Prechtl, 2007).

Abnormal GMs during the writhing period are categorised as poor repertoire, cramped-synchronised or chaotic. On the other hand, atypical GMs in the fidgety period are categorized as absent or abnormal. It has been shown that cramped-synchronized movements and the absence of fidgety movements are the best

predictors of cerebral palsy (Einspieler et al., 2012; Prechtl et al., 1997), while poor repertoire and abnormal fidgety are good predictors of minor neurological dysfunctions (Nakajima et al., 2006). Prediction of developmental outcome is best at fidgety general movement age, which concurs with the shift in cortical activity in the primary sensorimotor cortices from the subplate to the cortical plate (Hadders-Algra, 2018).

Various adverse events occurring during the prenatal, perinatal, and neonatal periods, including maternal diabetes, preterm birth, perinatal asphyxia, neonatal hyperbilirubinemia, and treatment with dexamethasone, have been associated with the development of abnormal GMs in infants (Hadders-Algra, 2001). These events can impact the central nervous system and disrupt the typical trajectory of motor development, potentially leading to delays or deviations in achieving motor milestones.

The Prechtl GMA tool depends on the gestalt perception of an observer. The evaluation focuses on whole-body movements rather than specific body parts. One challenge in this perception is that the evaluation of movement fluency can be compromised by factors like jerkiness, tremulousness and stiffness which affect movement complexity and variation (Hadders-Algra, 2001). This therefore requires training and experience to thoroughly analyse the movements. Gestalt perception is also prone to the observer's tiredness. It is therefore imperative that real-time assessment be avoided because there is a high chance of error. Video recording should instead be encouraged for one to be able to analyse movement complexity and variation (Prechtl, 1974).

During video recording, it is of utmost importance that the child is in an active wakefulness state (Prechtl state 4) and calm for term and post-term age assessment (Prechtl, 1974). A baby is placed in a supine position in the incubator (floor or mat). With a camera secured on a stand vertically above the baby, a video recording is taken.

The reliability of the Prechtl GMA tool depends on the quality of the video recording and analysis by trained personnel. Studies show that formal standardised training in general movement assessment is required to effectively conduct the test (Brown, Greisen, Haugsted and Jonsbo, 2016; Valentin, Uhl and Einspieler, 2005).

2.7. Literature Summary

This chapter has discussed the burden of the HIV pandemic, particularly its impact on infant neurodevelopment. The section has drawn special interest in Eastern and Southern Africa where there is the highest prevalence of HIV globally. The section has discussed cerebral palsy, its prevalence which varies globally and its diverse risk factors. The pathophysiology of CP involves various etiological factors, including prenatal, perinatal, and postnatal influences. In the context of HIV, there is a complex interplay with CP, including potential impacts on HIV-exposed infants, HIV-exposed uninfected children, and those exposed to antiretroviral drugs. Studies suggest associations between maternal HIV, ART exposure, and neurodevelopmental outcomes in HEU children, emphasizing the need for comprehensive understanding and further research.

The methodology used in this study will be presented in chapter three.

CHAPTER 3. METHODS

This chapter gives a detailed roadmap of the methods employed to address the research questions or objectives. It outlines the research design, sampling strategy, data collection methods, and analytical procedures. Additionally, it offers insights into the rationale behind methodological choices. Thus, this chapter lays the groundwork for a comprehensive understanding of the research process and its outcomes.

3.1. Study Design

This was a cross-sectional study. The design was deemed appropriate for providing a snapshot of the variables under investigation at a single point in time (Wassertheil-Smoller and Smoller, 2015). This design facilitated the efficient collection of data from a diverse sample within a relatively short timeframe, allowing for the exploration of associations between variables within the population of interest. Additionally, the cross-sectional design enabled the investigation of multiple factors (such demographic details and HIV/ART exposure) simultaneously.

3.2. Study Setting

The study was conducted at Zingwangwa Health Centre in Blantyre, Malawi. The centre is in one of the most populated areas in Blantyre. The centre was within the reach of the researcher. This helped reduce the cost of operation.

The sampling frame took into account all health centres in Blantyre. Blantyre District Health Office (DHO) oversees 28 health centres spread across the district (National Statistics Office, 2021). Zingwangwa Health Center serves a population of about 141123 people in the district. Furthermore, these centres also serve the second largest number of children (7056) under one year old (National Statistics Office, 2021). The health centre is also closer to the data collection place, Kamuzu University of Health Sciences (KUHeS), Blantyre campus. By applying the factors described above, the centre was selected. Some of the services provided at the health centre are antenatal, under-five and ART clinics.

3.3. Participants

3.3.1. Source of Participants

The study was conducted at Zingwangwa Health Centre in Blantyre, Malawi.

3.3.2. Sample Size

The ART and under-five clinics at the health centre serve an average of 40 children under five years of age a day throughout the year. Approximately 20 of these infants are below six months old, and between two and three are between nine and 20 weeks old. The clinics run for five days a week and every child is required to attend at least one visit per month. Therefore, the total population for infants between nine and 20 weeks is 100 infants in 40 days. The formula below was used to find an effective sample size of 93 infants at a 95% confidence interval and a 5% level of significance. This sample size will be spread into 46.5 (47) infants per group (AHEU and HUU). Where N = total population, n = sample size, e = significance level (0.05), the sample size was calculated as follows:

$$n = \frac{N}{1 + N(e)^2}$$

n = 93 infants

3.3.3. Sample Selection

3.3.3.1. Inclusion Criteria

- Infants with normal birth history (prenatal, perinatal and postnatal)
- Infants born at full-term (40 weeks)
- Breastfed or formula-fed infants
- Infants with a history of HIV and ART exposure (before and after birth)
- Infants not exposed to HIV and/or ART and uninfected
- Infants aged between nine and 20 weeks post-birth

3.3.3.2. Exclusion Criteria

- Infants without full birth history

- Infants with serious medical conditions other than HIV during the study period such as cerebral malaria, periventricular white matter injury, cerebral malformation and intracranial haemorrhage,
- Infants who have experienced adverse prenatal, perinatal, and neonatal events, such as maternal diabetes, preterm birth, perinatal asphyxia and neonatal hyperbilirubinemia
- Infants who are malnourished (weight for age>2 SD below WHO norms)
- Infants born of mothers with known maternal risk factors for cerebral palsy such as bleeds, preeclampsia, placental abnormalities, maternal alcohol use, multiples and intrauterine growth restriction
- Infants with known risk factors for CP
    - Hypoxic-ischemic encephalopathy.
    - Traumatic brain injury.
- Infants with congenital malformations or disorders such as arthrogryposis, microcephaly (<3rd percentile for gestational age and sex)

3.4. Variables

3.4.1. Independent variables

The independent variables comprised of demographic characteristics of participants namely age, gender and HIV and ART exposure.

3.4.2. Dependent variables

The independent variables comprised the quality of the observed general movements.

3.5. Instrumentation

This study utilized Prechtl's validated method for qualitatively assessing general movements in infants, aiming to predict their neurodevelopmental trajectories. The researchers evaluated the movement quality of both HEU and ART-exposed babies. Two independent observers, trained in the Prechtl method, conducted the assessments to ensure reliability.

3.6. Data Collection

3.6.1. Pilot Study

A pilot study was performed to identify potential sources of bias. The same procedure described for the main study was followed for the pilot study. A total of nine infants (three in each group; HUU, HEI, HEU)) were video recorded as part of the pilot study and only one change was made to the main study; the place for video recording in the main study was the health centre other than the KUHES campus. For this reason, data from the pilot study has not been used in the analysis.

3.6.2. Main Study

In this study, data collection was done in two months (40 working days) between June and July 2023. A Mark II Canon camera was used to record the videos. The infants were categorised into three groups as follows: HIV unexposed uninfected, HIV plus ART exposed uninfected, and HIV plus ART exposed infected. Exposure to HIV and ARVs was considered before and/or after birth.

The study had one researcher and two assistants. One research assistant was granted permission to look at the files of all infants scheduled to come to the clinic for their routine under-five check-ups during the period of data collection. From this exercise, infants meeting the inclusion criteria were identified. The guardian of the identified infant, having given their informed consent, was requested to bring their baby to the research room set up right at the health centre. This was on the same day or at an agreed time and day depending on circumstances. For example, infants who received their vaccination on the same day of identification were given a different time for recording general movements. This period (9 to 14 weeks after birth) is the fidgety period which also tallies with the time when children get a second dose of immunization. In Malawi, infants receive their second and third immunization shots for polio, diphtheria, tetanus, Rotavirus and hepatitis B at 10 weeks after birth. At 14 weeks after birth, they receive their third immunization against these conditions (WHO, 2005). Participants that came late for immunisation were also considered as long as they were within the nine to 20 weeks post term age.

The video recording room had a mattress on the ground and a video camera set at 1.5 meters vertically above the mattress. The infant, wearing a nappy only, was placed on the mattress in a supine position and relaxed through the presence of the mother and toys. Then a video of the child was taken by the same research assistant who identified the infant.

The research assistant then edited the videos only by cutting them into short clips of three minutes utmost for when the child was displaying movements. The research assistant then coded these video clips to mask the assessors of the infants' exposure status (HUU,HEI,HEU).

In this study, two individuals, trained under the GMA trust in 2018, were responsible for video analysis (the researcher and an assistant). The trained independent assessors (researcher and second assistant) were granted permission to analyse the videos separately. Each assessor recorded their findings on a Prechtl GMA score sheet. The two then came together to deliberate on the cases where they had different findings. From this, a consensus was reached on the result to be adopted. Where the two assessors did not reach a consensus, each result was kept and a kappa coefficient was used to determine the agreement between the two assessors. For the cases where the two assessors could not reach a consensus, both sets of results were retained. A kappa coefficient was then calculated to measure the level of agreement between the two assessors. The samples with unresolved disagreements were subsequently referred to a third independent expert, whose decision was considered final.

Each infant who showed abnormal general movements was contacted and referred to a relevant rehabilitation facility closest to the infant's home for further assessment and management. It was the researcher's responsibility to explain to the guardian the findings and the need for early intervention before making the referral.

3.7. COVID-19 Preventive Measures

All covid-19 preventive measures were strictly adhered to. This included the provision of surgical facemasks and handwashing facilities to all guardians and the research assistant. The participant spent not more than seven minutes in the video room.

3.8. Data Management

All collected demographics were entered into an Excel sheet. Data from video analysis (GMA score sheet) was then added to the Excel sheet against each participant ID. The entered data was then cleaned to eliminate data with incomplete information such as the method of feeding.

A total of 79 videos were collected. From the data-cleaning process, 14 videos were eliminated due to poor quality or incomplete information. Thus a total of 65 videos were used in the analysis stage. All categorical data, except participant ID, was coded for statistical analyses.

3.9. Interrater Reliability

The GMA outcome from the two independent observers yielded a substantial agreement (0.731 kappa coefficient). The data was then deemed ready for further analysis.

3.10. Data Analysis

Categorical data were presented as counts and percentages, while continuous data (such as age) were summarized using mean, mode, and standard deviation (SD). Visual representations of the categorical data were provided through a bar chart and a table. Statistical significance was determined using a two-sided alpha level of 0.05 with 95% confidence intervals. Data analysis was performed using IBM Statistical Package for Social Sciences (SPSS) software version 23.0 for Mac, and graphical outputs were generated using Microsoft Excel for Mac version 16.43. A biostatistician from KUHeS assisted with the research analysis. Table 3.1 below summarises the statistical tests conducted.

Table 3.1: Summary of Statistical Procedures and Tests

OBJECTIVE	EXPECTED OUTCOME	TYPE OF VARIABLE	TESTS	JUSTIFICATION FOR TEST CHOICE
To describe quality of general movement patterns observed among HEU and HUU	quality of GMs	Ordinal	GMA-frequencies tables and percentages	
To investigate the association between demographics (gender) and general movements	quality of GMs	Ordinal	Fischer Exact Test	Nominal data Some counts have <5 observations
To compare general movement patterns of AHEU against HUU children	quality of GMs	Nominal	Fischer Exact Test	Nominal data Some counts have <5 observations

3.11. Ethical Considerations

The study was cleared by the University of the Witwatersrand Human Research Ethics Committee (South Africa) with a certificate number M200859 (**Appendix *15***) and Kamuzu University of Health Sciences Research Ethics Support (Malawi) (**Appendix *14***) since the study setting is in Malawi. Furthermore, permission was granted by the Blantyre District Health Office and Zingwangwa Health Centre to get access to the under-five clinics (**Appendix *12***). Informed written assent was obtained from the guardian of the involved infant (***Appendix 6***).

The guardians of the participants were advised that they had the option to withdraw from the study at any point without suffering any repercussions. Information was only used for the purpose intended for this study and was shared with caregivers on request.

Anonymised data will be published and presented at professional conferences. All infants were assigned a study number. The key to the study numbers assigned was kept in the researcher's possession only. All video recordings were transferred into one password-protected project computer. All data collected shall be safely stored in the physiotherapy department, School of Therapeutic Sciences, University of Witwatersrand for two years if published and for six years if not published. These videos will then be deleted.

The results of this study are presented in chapter four.

CHAPTER 4. RESULTS

In this chapter, demographic details and relationships between various variables (e.g. HIV exposure status) and general movement assessment scores for participants are presented.

4.1. Data Cleaning Process

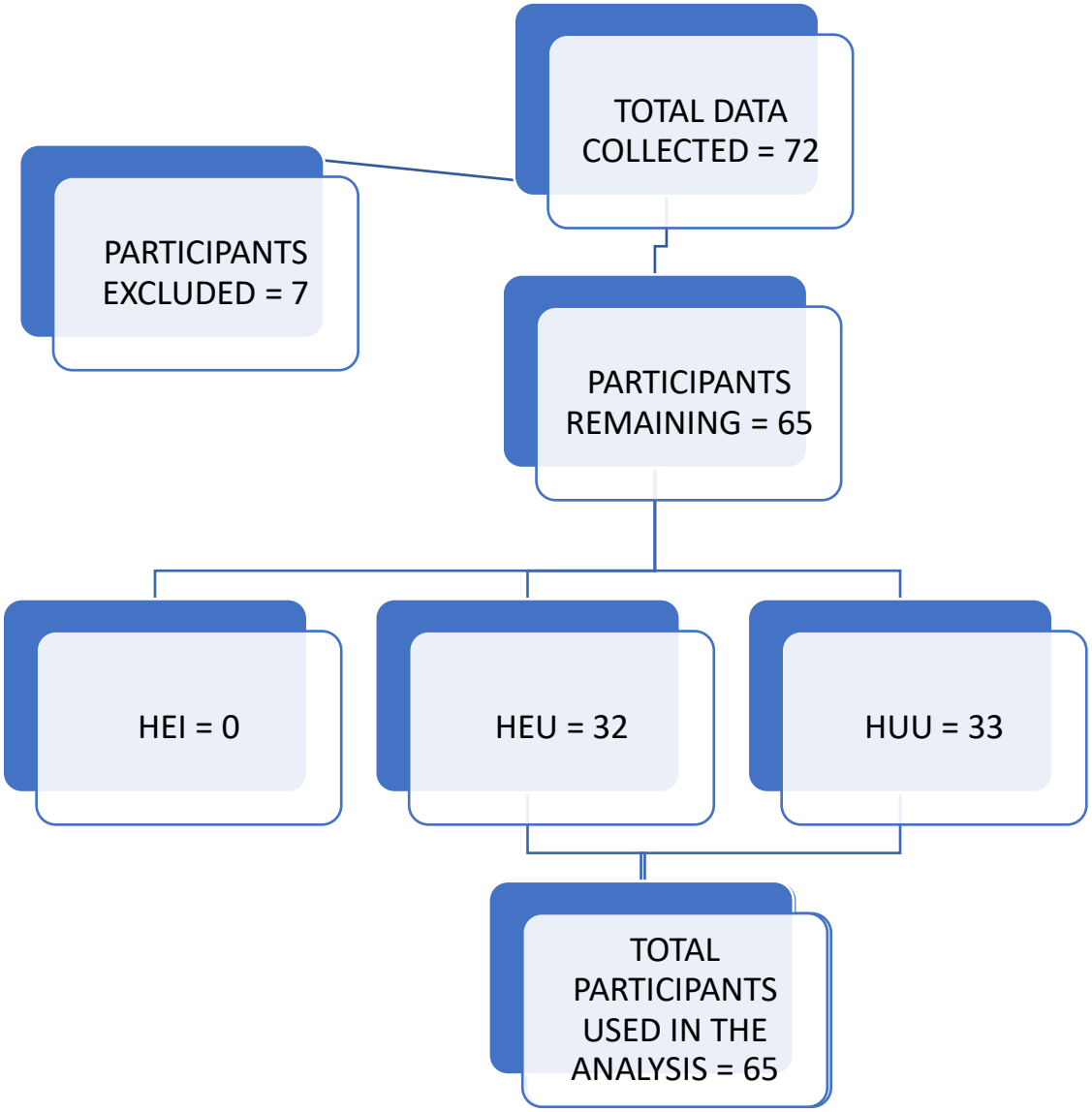

Figure 4.1 Data Cleaning Process

The flowchart in Figure 4.1 illustrates the data cleaning process. Initially, 72 videos were collected. Of these, 7 videos were excluded due to incomplete demographic information and/or poor video quality, leaving 65 videos for further analysis. No participants were categorized under the HEI group. The HEU group included 32 videos, while the HUU group comprised 33 videos. As a result, a total of 65 participants were used in the final analysis.

4.2. GMA Score Inter Observer Agreement

A cross tabulation was conducted to measure the agreement between two video scorers. Table 4.1 below presents the count of cases in each category. There was a substantial level of agreement between the two scorers (Kappa = 0.731, p = 0.000). This signifies that the GMA scores were fit for further analysis.

Table 4.1: Cross tabulation of GMA Scores for Two Observers

		Observer B			
		Normal Fidgety	Abnormal Fidgety	Absent Fidgety	Total
Observer A	Normal Fidgety	58	0	1	59
	Abnormal Fidgety	0	3	1	4
	Absent Fidgety	1	0	1	2
Total		59	3	3	65

Note: Kappa (n = 65) = 0.731. *p* = 0.000

4.3. Demographic Characteristics

Table 4.2 below provides summaries of the demographic characteristics of participants. In the dataset under consideration, descriptive statistics were computed for various variables. The age of participants, reported in weeks, exhibited a mean of 11 weeks, with a range of 9 to 16 weeks, and a standard deviation of 2. Gender distribution recorded more males (n = 36) than females (n = 29). All 65 participants were breastfed; no child was bottle or formula-fed. All infants in the study were HIV negative meaning no babies met the HEI category resulting in only two groups HUU

and HEU. Regarding HIV exposure status, the study had a nearly equal number of HUU (n = 33) and HEU participants (n = 32). All mothers who were HIV positive were on ART during pregnancy, thus all babies who were HIV exposed were also exposed to ART.

Table 4.2: Demographic characteristics of participants

Age in Weeks	Mean	11
	Minimum	9
	Maximum	16
	Standard Deviation	2
Gender	Female	29
	Male	36
Feeding	Breastfed	65
	Bottle/Formula-Fed	0
HIV and ART exposure	HUU	33
	HEU	32

Figure 4.1 further illustrates percentages of GMA scores in each category of fidgety movements. Of the 65 participants, the majority had normal fidgety movements (n = 58; 89%), seconded by the absent fidgety category (n=4; 6%). The abnormal fidgety category had the least number of participants (n = 3; 5%).

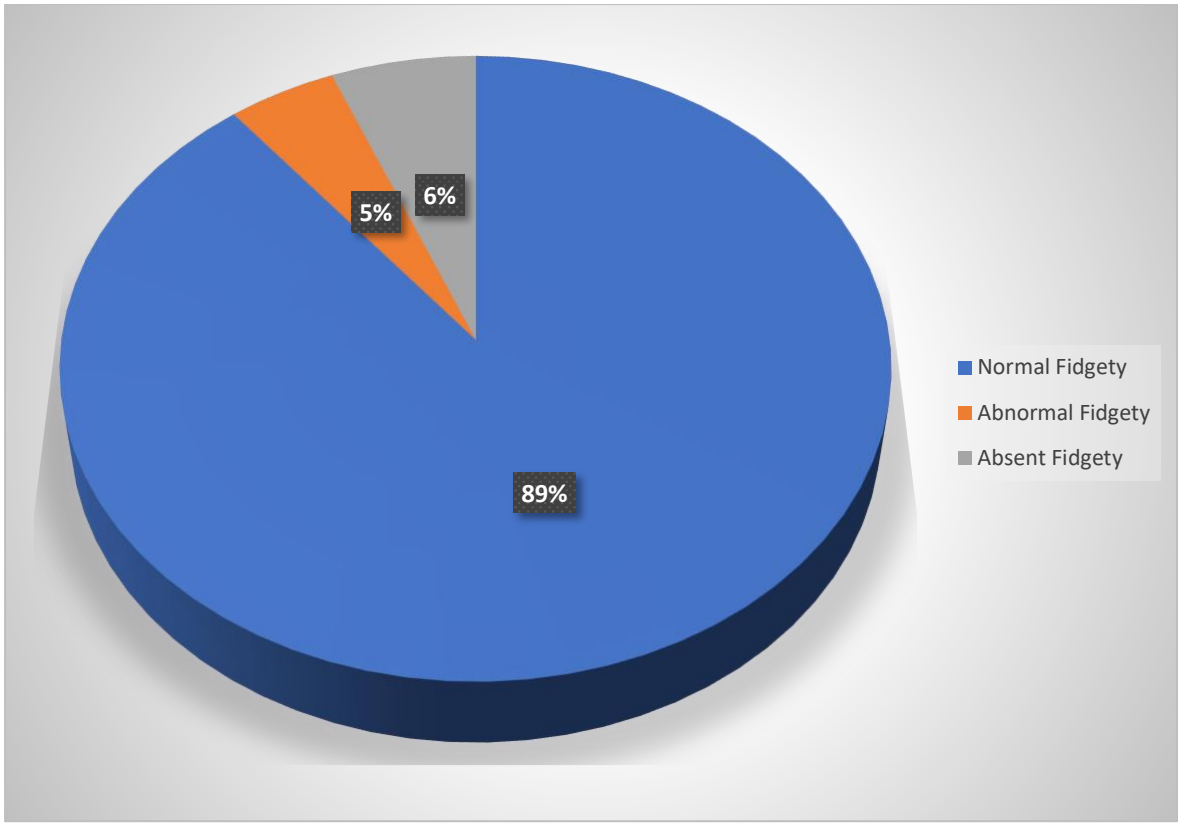

Figure 4.2 Percentage of GMA Scores (n = 65)

4.4. Objective 1: GMA scores according to HIV Exposure Status of the Infants

Table 4.3 below illustrates how GMA scores are spread among HUU and HEU participants. The majority of participants had normal GMA scores among both HUU and HEU (n = 30, 90.9%) and (n = 28, 87.5%), respectively. The least number of participants were observed among the absent fidgety category for HUU (n = 1; 3%) and abnormal fidgety for HEU (n = 1; 3.1%).

Table 4.3: GMA Scores According to HIV Exposure Status of the Participants

		HIV STATUS			
		HUU (n = 33)		HEU (n = 32)	
GMA SCORE	NORMAL	30	90.9%	28	87.5%
	ABNORMAL FIDGETY	2	6.1%	1	3.1%
	ABSENT FIDGETY	1	3.0%	3	9.4%

The figure below further illustrates the information above.

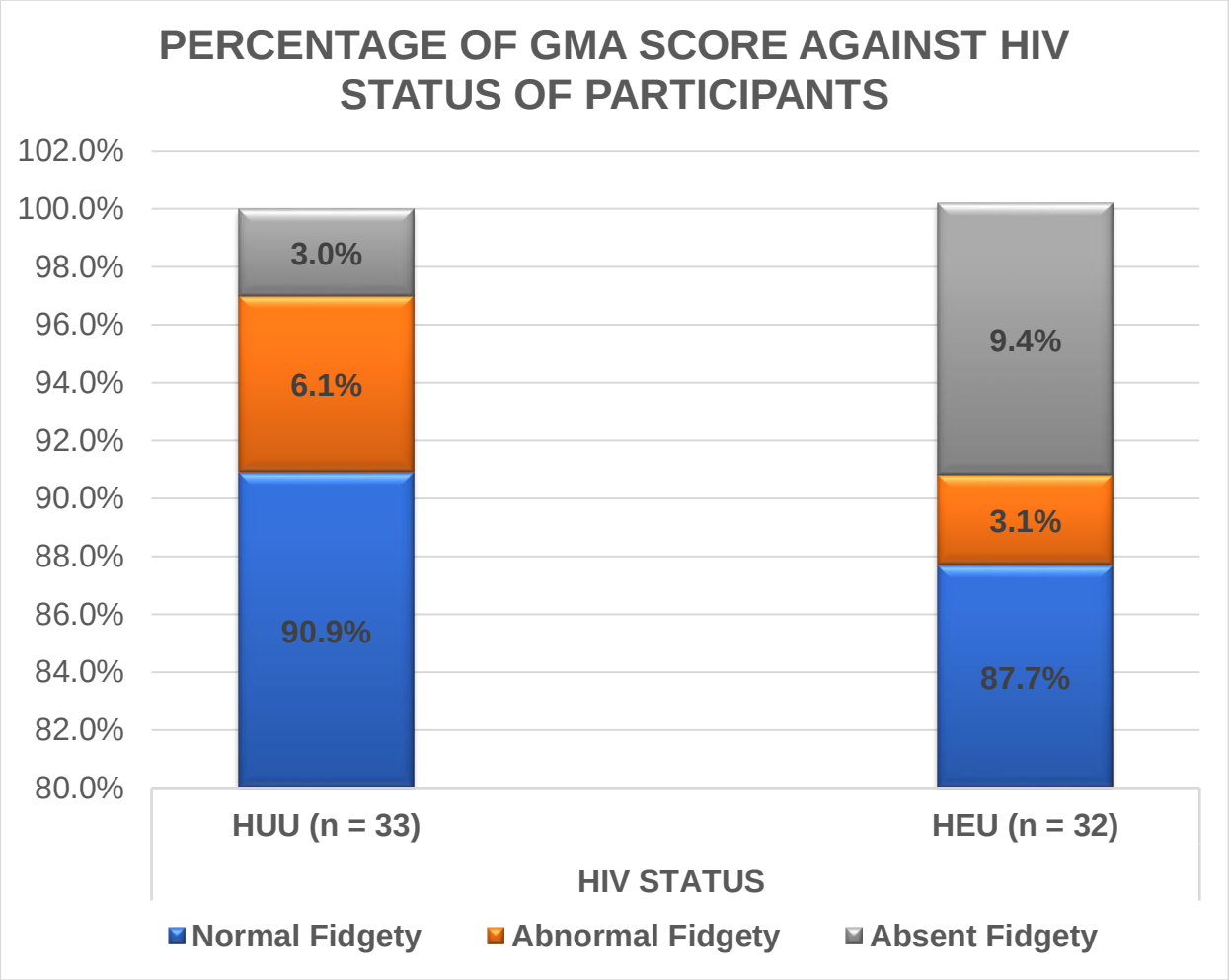

Figure 4.3: Percentage of GMA Score according to HIV (and ART) Exposure

4.5. Objective 2: Association Between Gender and GMA Score

A Fisher exact test was carried out to examine the relationship between gender and GMA score outcome. The test yielded a non-significant result (p = 0.276), suggesting that there is no statistically significant difference in general movement patterns between males and females in this sample. Notably, there were four cells in which expected count was less than five. The total number of valid cases included in the analysis was 65. Table 4.4 below illustrates this.

Table 4.4: Association Between Gender and GMA Score

		GMA SCORE			
		NORMAL	ABNORMAL FIDGETY	ABSENT FIDGETY	Total
GENDER	FEMALE	28	0	1	29
	MALE	30	3	3	36
Total		58	3	4	65

Note: Fisher's Exact Test (n = 65) = 2.892. *p* = 0.276

4.6. Objective 3: Comparison of GMA Scores between AHEU and HUU

A Fisher exact test was carried out to examine the relationship between HIV and ART exposure and GMA score. The test results suggest that there is no statistically significant difference in general movement patterns between AHEU and HUU in this sample (*p* = 0.605). It is noteworthy that four cells had expected counts less than five, with the minimum expected count being 1.48. The total number of valid cases in the analysis was 65. Table 4.5 below illustrates this.

There were also a few cases of abnormal fidgety and absent fidgety movements across both groups.

Table 4.5: Comparison of GMA between HEU and HUU

		GMA SCORE			
		NORMAL	ABNORMAL FIDGETY	ABSENT FIDGETY	TOTAL
HIV/ART-EXPOSURE STATUS	HUU	30	2	1	33
	HEU (ART-EXPOSED)	28	1	3	32
TOTAL		58	3	4	65

Note: Fisher's Exact Test (n = 65) = 1.400. p = 0.605

4.7. Summary

The majority of HEU and HUU infants displayed normal general movement patterns. Statistical tests showed no association between gender and general movements. There was no significant difference in the general movement patterns of HEU and HUU infants. Thus, there was no association between general movements, HIV and ART exposure, or gender in this population.

Chapter five below discusses these results.

CHAPTER 5. DISCUSSION

In this chapter, a comprehensive discussion is provided on the findings of this study. An emphasis is placed on how the findings align with the three study objectives and existing research.

5.1. GMA Score Inter Observer Agreement

The research revealed substantial agreement between the two assessors (Kappa = 0.731, p = 0.000). Typically, the Prechtl GMA method is known for its high interrater agreement, as evidenced by studies encompassing participants with diverse demographic characteristics or clinical profiles (Brown, Greisen, Haugsted and Jonsbo, 2016; Crowle et al., 2017; Katz and Perenyi, 2016). The high interrater agreement observed in studies utilizing the Prechtl GMA method not only gives confidence in its validity but also highlights its applicability across different settings and contexts.

5.2. Objective 1: GMA scores according to HIV Exposure Status of the Infants

The predominant observation, among both categories of participants according to HIV status, was normal general movements, accounting for 90.9% (n = 33) of HUU infants and 87.5% (n = 32) of HEU infants. The presence of absent fidgety movements was minimal among HUU participants, with only one infant (n = 33, 3%). Within the HEU group, there was only one infant (n = 32, 3.1%), who exhibited absent fidgety movements, indicating a low observation of this characteristic within the cohort.

The results of this study concur with what Krynauw, Du Preez, Van Zyl and Burger (2022) found. Their study aimed to investigate the correlation between adverse perinatal factors and the trajectories of General Movements (GMs) in very low-birthweight (VLBW) and extremely low-birthweight (ELBW) infants admitted to Tygerberg Children's Hospital in Cape Town, South Africa, from preterm age until 12-14 weeks corrected age (Krynauw, Du Preez, Van Zyl and Burger, 2022). In a univariable analysis, no statistically significant relationship was observed between

HIV exposure during pregnancy and the development of an abnormal GM trajectory (Krynauw, Du Preez, Van Zyl and Burger, 2022).

The Prechtl GMA tool serves as a predictive indicator of neurodevelopmental outcomes in infants. Hence, based on the predominant occurrence of normal GMA scores among the participants, it can be inferred that a majority of these infants are less likely to develop cerebral palsy. However, it's important to note that this finding might not provide conclusive evidence despite the assessment being conducted during the highly predictive period of the GMA assessment, known as the fidgety period.

The limitation arises from the cross-sectional nature of the study, which offers a singular snapshot of neurodevelopmental status. In contrast, the Prechtl method, upon which GMA is based, recommends a longitudinal approach involving a series of assessments, particularly during the fidgety period, to establish a comprehensive potential developmental trajectory for the infant (Prechtl, 2001). By conducting multiple assessments during this period, a clearer understanding of the infant's developmental progression and potential risk for the development of conditions like cerebral palsy can be obtained, enhancing the accuracy and reliability of the predictive model (Prechtl, 2001). It is important to note that follow-up assessments are only necessary if infants display absent or abnormal fidgety movements (FMs). Since the majority of infants in the current study exhibited normal FMs, conducting follow-up assessments would not be necessary.

5.3. Objective 2: Association Between Gender and GMA Score

A number of demographic factors have been found to influence the neurodevelopment of an infant and concerns about gender are increasing (Breach and Lenz, 2023). There is data indicating that sex differences may relate to brain development (Breach and Lenz, 2023). Conditions like Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) have shown male-biases in prevalence rates and sex differences in symptomology (Breach and Lenz, 2023).

Mohamed and Aly (2010) also reported on differences in clinical outcomes between male and female premature infants. In their study they investigated the association between gender and intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) in very low birth weight (VLBW) infants, controlling for various factors (Mohamed and Aly, 2010). It found that male gender was linked to higher rates of IVH, particularly severe IVH, across different birth weight categories, but no gender difference was observed in PVL incidence (Mohamed and Aly, 2010). Mechanisms such as differences in apoptotic mechanisms and cytokine levels were suggested to contribute to these gender disparities in response to brain insults. Additionally, hormonal influences, particularly oestrogen and progesterone, were implicated in potentially protecting against brain injury, with male infants showing increased vulnerability (Mohamed and Aly, 2010). The study also noted that male vulnerability extended to other complications such as respiratory distress syndrome (RDS) and pulmonary haemorrhage (Mohamed and Aly, 2010), which are risk factors for brain injury through the hypoxia-ischemia pathway as reported by Dan, Mayston, Paneth and Rosenbloom (2014). While the study had limitations regarding maternal data and postnatal events, it analysed a large national cohort to draw these conclusions (Mohamed and Aly, 2010).

Findings from Strehlau et al. (2020) partly support this. In their study on early neurodevelopment in a cohort of HEU infants, they found that females had higher scores on the language subscale, indicating potentially better language development compared to males among these infants. Furthermore, in terms of receptive communication, which involves understanding and receiving language input, females also scored significantly higher than males, indicating better receptive language abilities among females. However, there was no sex difference in expressive communication, which involves the ability to express oneself verbally (Strehlau et al., 2020).

This study, however, demonstrates no statistically significant association between gender and Prechtl GMA score outcomes in this particular sample. Nevertheless, given the constraints imposed by small expected cell counts, additional research with larger sample sizes may be imperative to corroborate these findings.

The study utilized a limited sample size, whereas studies reporting differences have employed larger sample sizes, as exemplified in the study by Mohamed and Aly (2010), which was conducted on a national scale. It is noteworthy that despite examining different variables and employing distinct methodologies, both studies aim to investigate potential neurodevelopmental outcomes in at-risk infants, thus warranting a comparison of their respective findings.

5.4. Objective 3: Comparison of GMA Scores between HEU (ART-exposed) and HUU

The results of the Fisher exact test comparing GMA scores between HEU (ART-exposed) infants and HUU infants indicate that there is no statistically significant difference in general movement patterns between these two groups within the sample. This suggests that, at least within the parameters of this study, ART exposure among HEU infants does not have a discernible impact on their general movement patterns as assessed by GMA scores when compared to HUU infants. The results of this study support the findings of Boivin et al. (2019). Their study compared neurodevelopmental outcomes between HEU and HUU children exposed to ARV during pregnancy and breastfeeding. It found that children whose mothers consistently received triple-ARV throughout both ante- and postpartum phases showed similar neurodevelopmental outcomes to HUU children up to 60 months of age (Boivin et al., 2019). In their conclusion, they suggested that maternal ARV treatment during pregnancy and breastfeeding did not increase developmental risks for HEU children and may have offered neuroprotective protective effects (Boivin et al., 2019). Their study was conducted in Malawi and Uganda, thus sharing some similarity in terms of the study population with the current study. In the current study it would have been interesting to note what ART regimen the mothers were on as certain drugs are known to have better neuroprotective properties than others (Cross et al., 2011; Kolson, 2022).

Jankiewicz et al. (2017) conducted a study aimed to investigate the long-term effects of perinatal HIV infection and early ART on brain development in children using diffusion tensor imaging (DTI) to examine white matter (WM) integrity. They assessed 65 HEI children and 46 controls (HEU) and HUU at seven years

(Jankiewicz et al., 2017). One of their finding was that HEU children showed differences in WM integrity compared to HUU children, suggesting a long-term impact of perinatal HIV/ART exposure on WM development (Jankiewicz et al., 2017).

The findings of Jankiewicz et al. (2017) are echoed by van de Wijer et al. (2019). In their pre-clinical study, they aimed at investigating behavioural and neurodevelopmental impact of perinatal exposure to efavirenz, a drug commonly used in pregnant women with HIV (van de Wijer et al., 2019). Pregnant rats were treated with efavirenz from the first day of their gestation period to the seventh day of postnatal period, and their male offspring were assessed for behavioural outcomes during various developmental stages. Results showed decreased body weight and impaired reflex and motor development in the offspring (van de Wijer et al., 2019). During adulthood, alterations were noted in the motor cortex, encompassing a reduction in both total cell count and mature neurons, alongside an elevation in Caspase-3-positive cells and serotonergic fibres (van de Wijer et al., 2019). These results imply that exposure to efavirenz during the perinatal period leads to developmental delays and lasting changes in the motor cortex of the brain (van de Wijer et al., 2019). Comparing their study comprehensively is challenging because it focused solely on exposure to efavirenz without considering HIV exposure. Nonetheless, their findings provide valuable insights into the effects of one of the drugs used in HIV management and their potential impact on development. It is, unfortunately, not known what ART regimen the infants in this study were exposed to and whether or not it included efavirenz. However the first line of treatment in Malawi is DTG or EFV in women of reproductive age and so one can assume that most of the children were exposed to this drug combination in utero and through breastfeeding (Ministry of Health and Population, 2022).

Overall, while this study suggest no immediate cause for concern regarding ART and HIV exposure among HEU infants and their general movement patterns, the limitations stemming from the small sample size and low expected cell counts underscore the need for further research with larger sample sizes to validate these findings and provide more robust insights into the potential impacts of HIV/ART exposure on neurodevelopmental outcomes among HEU infants.

5.5. Summary

Among HEU and HUU infants, normal general movements predominated, suggesting a lower likelihood of developing cerebral palsy. Gender did not show a statistically significant association with GMA scores in this study, contrasting with previous research indicating sex differences in neurodevelopmental outcomes. Additionally, ART exposure among HEU infants did not significantly impact general movement patterns compared to HUU infants, aligning with similar findings from other studies. Nonetheless, the study emphasizes the importance of larger sample sizes and longitudinal research to confirm these findings and understand the potential long-term effects of HIV and ART exposure on neurodevelopment in infants.

CHAPTER 6. CONCLUSION

6.1. Main Findings

The study aimed to assess and compare the quality of general movement patterns among HEU and HUU infants, investigate any potential association between gender and general movements, and compare general movement patterns of HEU infants exposed to ART against HUU infants. The findings revealed that both HEU and HUU infants predominantly exhibited normal general movement patterns, indicating a low likelihood of developing cerebral palsy. There was no statistically significant association found between gender and general movement patterns, suggesting similar neurodevelopmental outcomes between male and female infants in this sample. Furthermore, the study found no significant difference in general movement patterns between HEU infants exposed to ART and HUU infants, indicating that ART exposure did not impact general movement quality in these infants compared to their unexposed counterparts.

6.2. Implications of the Study

These findings highlight the importance of understanding the potential effects of HIV and ART exposure on neurodevelopmental outcomes in infants, emphasizing the need for continued research in this area.

6.3. Strengths of the Study

The use of the Prechtl GMA tool ensures a standardized and widely accepted method for assessing infant neurodevelopment, enhancing the reliability and comparability of the results.

Reliable Interobserver Agreement: The substantial agreement between assessors in the GMA scoring indicates a high level of reliability in the assessment process, minimizing potential bias and enhancing the validity of the findings.

Clinical Relevance: The study's findings have significant clinical implications, particularly in informing healthcare providers about the neurodevelopmental

outcomes of infants exposed to HIV and ART, thereby potentially guiding clinical management and interventions.

Contribution to Literature: The study contributes to the existing literature by addressing a gap in knowledge regarding the neurodevelopmental outcomes of HEU infants and the potential effects of ART exposure, thereby advancing our understanding of HIV-related neurodevelopmental risks in infants.

6.4. Limitations of the Study

Limitations	Solutions
Guardian's unwillingness to have their child participate in the study.	The researcher clearly described the study to participants and assured them that their information would be kept confidential
Fear of contracting COVID 19 during video recording (Guardians)	The researcher ensured safe distance was maintained during the interviews Face shields and masks were used to protect both participant and researcher.

6.5. Recommendations for Future Research

Future studies should consider the following:

a) Motor Optimality Score – revised (MOS-R): Future studies should incorporate this tool for assessing neuromotor outcomes during the fidgety movement stage (3-5 months post-term). This semi-quantitative approach captures subtle changes in motor behavior and has been linked to motor and language dysfunction, minor neurological issues, and learning difficulties later in life (Einspieler et al., 2019).

b) Longitudinal Studies: Conduct longitudinal studies to follow infants over time, particularly during critical developmental periods such as the fidgety period, to better understand the long-term effects of HIV and ART exposure on neurodevelopmental outcomes.

c) Large-Scale Studies: Conduct studies with larger sample sizes to improve statistical power and generalizability of findings, allowing for more robust conclusions regarding the association between HIV exposure, ART, gender, and general movement patterns.

d) Exploration of Specific ART Regimens: Investigate the potential differential effects of specific ART regimens on neurodevelopmental outcomes in infants, considering variations in drug exposure and timing during pregnancy and infancy.

e) Evaluation of Other Neurodevelopmental Measures: Explore additional neurodevelopmental measures beyond general movement patterns, such as cognitive and motor function assessments, to provide a comprehensive understanding of the impact of HIV exposure and ART on infant neurodevelopment beyond the period evaluated by GMAs.

f) Examination of Potential Mediating Factors: Investigate potential mediating factors that may influence neurodevelopmental outcomes in HIV-exposed infants, such as maternal health status, socioeconomic factors, and prenatal care, to identify potential targets for intervention and support.

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Appendix 1: Information About Infant Feeding And Mother's HIV Status

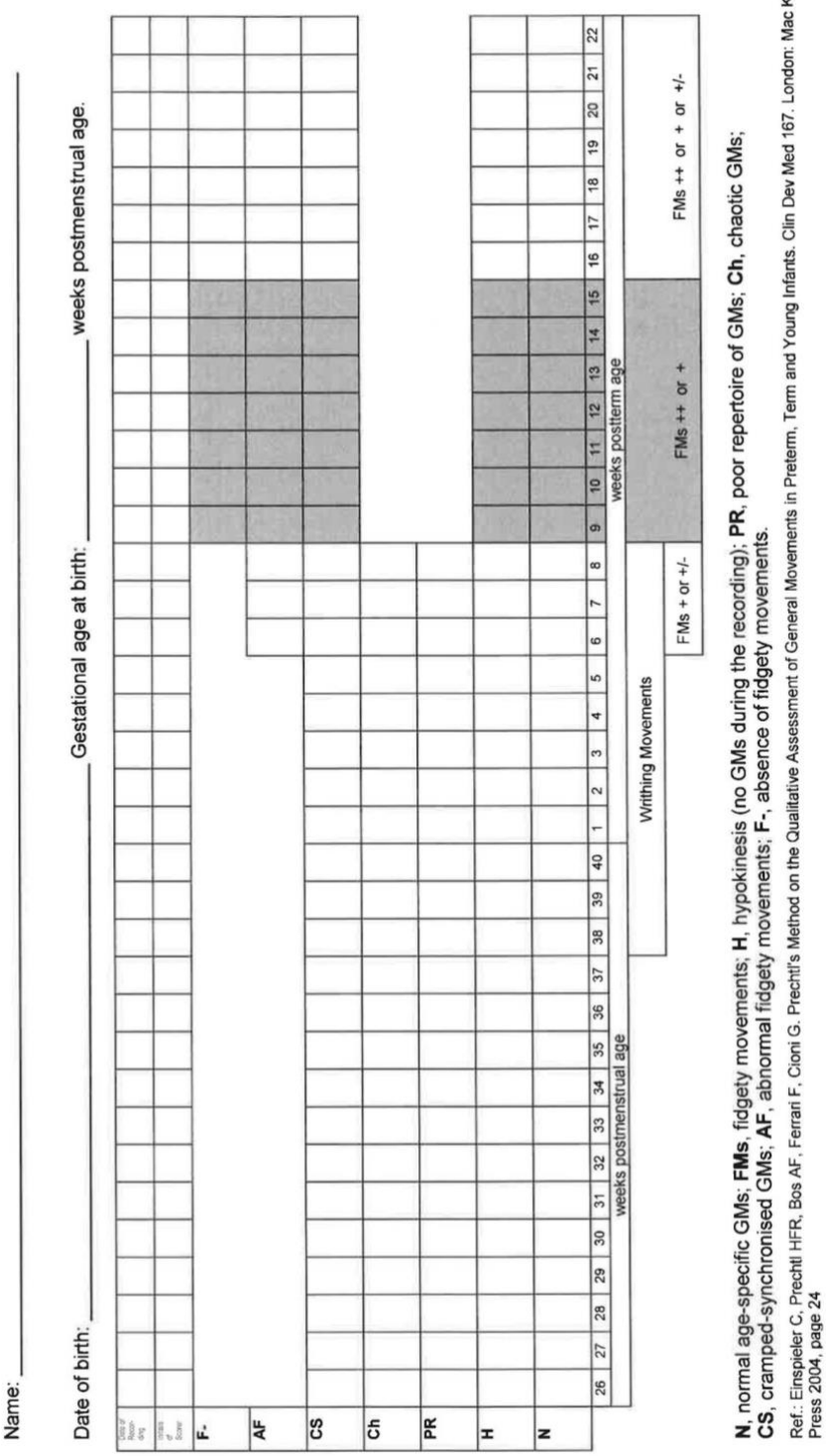
INFANT'S ID_____ INFANTS AGE_____

INFANT'S GENDER_____

1. Is the child breastfed or formula-fed? _____
2. HIV status of the mother at the time of delivery:_____ (indicate reactive or non-reactive). If non-reactive, end here
3. If reactive, has the mother been on ART from the time she was pregnant for this baby to date? _____ (Yes or No)

4. If not in 'e' above, is she on treatment now? _____ (indicate Yes or No)
5. If yes in 'f' above, when did she start the HIV treatment? _____
6. How old was the child when the mother commenced HIV treatment? _____

Appendix 2: GMA Individual Score Sheet



Appendix 3: GMA Records

Prechtl's Method of Qualitative Assessment of General Movements
3 to 5 Months: Fidgety Movements

The GM Trust

N, normal. A, abnormal. AF, abnormal fidgety movements. F-, absence of fidgety movements.

Case Age	N	A AF F-	COMMENTS
Case Age	N	A AF F-	COMMENTS
Case Age	N	A AF F-	COMMENTS
Case Age	N	A AF F-	COMMENTS
Case Age	N	A AF F-	COMMENTS
Case Age	N	A AF F-	COMMENTS
Case Age	N	A AF F-	COMMENTS

Appendix 4: Information Sheet – Guardian/Parents (English)

Physiotherapy

Faculty of Health Sciences · Private Bag 3, Wits, 2050, South Africa
Tel: +265 882 634 969 E-mail: 1916302@students.wits.ac.za

INFORMATION DOCUMENT: Parent/guardian

Study title: Observed general movements in the HIV and ARV-exposed uninfected infants in Blantyre, Malawi

Dear Parent,

I, James Kaunda, am researching general movements among HIV and ARV-exposed uninfected infants. In this study, we want to learn if exposure to HIV and/or ARVs affects the spontaneous movements of an infant. We also want to see if there are differences in general movement patterns between those exposed to HIV and/or ARV and those unexposed. Various adverse factors in the womb (such as infections and poor nutrition) before birth are known to be associated with neurodevelopmental challenges in the infant. All infants display characteristic movement patterns from the period they are in the womb to around 20 weeks after birth. These are known as normal general movements. Abnormal general movements have been shown to predict possible neurodevelopmental challenges like cerebral palsy among infants. Early detection of abnormal movements can allow health workers (doctors/rehabilitation workers) and parents to have the child commence early intervention to prevent or reduce disability in the child.

I would be most grateful if you would allow your child to participate in this research project. The project is scheduled to commence in October 2020 and finish in January 2021.

Who is eligible to take part in this study?

Male and female infants aged between nine and 20 weeks with normal birth history and no history of serious medical conditions. These can be children who have been exposed to HIV and/or ARV or without any exposure to these.

What is involved in the study?

Having been identified at your under-five clinic at Zingwangwa Health Centre, you will be invited to the Department of Rehabilitation Sciences, Kamuzu University of Health Sciences, Blantyre campus. At the department, there will be a video recording room with a mattress on the ground and a video camera set at 1.5 meters vertically above the mattress. The infant will be placed on the mattress facing the ceiling and relaxed through the presence of the mother and toys. Then a video of the child will be taken. The study shall cover transport costs.

Are there any risks of taking part in this study?

Your child will not be exposed to any risks during this study.

What are the benefits of taking part in this study?

The general movements of the infant will be analysed. If any concerns are identified you will be referred to your doctor or therapist to assess the infant for possible neurodevelopmental challenges. No monetary award will be given for taking part in this study.

Will information be handled as confidential?

Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. To ensure the confidentiality of participants, each infant will be assigned a study number. The key to the study numbers assigned will be kept by the researcher only. Names of participants are only to be written on the consent form and not on the questionnaire.

Additionally, consent forms are to be kept separate from the questionnaires. All information will be used only for the purpose intended in this study only. After publishing this study, all videos will be edited to mask the child's face for identification. These videos will then be backed up on a secure online (cloud) storage for future referencing. Access to this data shall be done only for purposes related to general movement assessment.

For further information, you are welcome to contact me at +265882634969 or send an email to 1916302@students.wits.ac.za

For more information on or the reporting of ethical concerns, you may contact the chair of the Human Research Ethics Committee of the Kamuzu University of Health Sciences: Telephone +265 888118993; Email comrec@medcol.mw

Kind regards

James Kaunda
Physiotherapy Department
University of the Witwatersrand

Appendix 5: Information Sheet – Guardian/Parents (Chichewa)

Physiotherapy

Faculty of Health Sciences · Private Bag 3, Wits, 2050, South Africa
Tel: +265 882 634 969 E-mail: 1916302@students.wits.ac.za

ZOKHUDZA KAFUKUFUKU: Makolo/ Osamalira mwana

Okondedwa Makolo,

Ine, James Kaunda, ndikupanga kafukufuku okhudza kasunthidwe ka ziwalo za ana omwe anabadwa kucchoka kwa makolo omwe ali ndi kachilombo koyambitsa matenda a Edzi ndipo omwe makolo awo akumwa mankhwala otalikitsa moyo (ARVs). Kafukufukuyu akupangidwa ndi cholinga chofuna kudziwa ngati kubadwa kuchoka kwa kholo lomwe lili ndi kachilombo komanso mankhwala otalikitsa moyo (ARVs) amakhudza kasunthidwe ka ziwalo za mwana. Tikufunanso kudziwa ngati pali kusiyana pa pa kasunthidwe ka ziwalo pakati pa ana omwe ana omwe anabadwa kwa makolo omwe ali ndi kahilombo ka HIV komanso akulandira mankhwala a ARVs ndi ana omwe anabadwa kwa makolo omwe alibe kachilomboka. Panthawi yomwe mayi ali oyembekezera, pali zinthu zingapo (matenda komanso zakudya) zomwe zikhodza kusokoneza kakulidwe ka ubongo ndi misempha ya mwana. Mwana aliyense amayembekezeredwa kuonetsa kasunthidwe ka ziwalo pamene adakali mu mimba ya mayi wake kufikira atabadwa ndi kukwanitsa masabata makumi awiri (20). Kasunthidwe ka ziwalo aka ndi komwe kali koyembekezeredwa kwa mwana aliyense. Pamene mwana akuonetsa kasunthidwe ka ziwalo komwe kakusiyana ndi kasunthidwe koyembekezeredwaka, chimatha kukhala chizindikiro cha matenda okudza chifukwa cha kusakula bwino kwa ubongo komanso misempha. Kuzindikira vutoli mwachangu kumatha kuthandiza a chipatala komanso makolo kumuthandiza mwana kuti vutoli lithetsedwe komanso kupewa kupuwala kwa ziwalo za mwanayo.

Ndingathokoze ngati mungamulore mwana wanu kuti atengepo gawo mu kafukufukuyu, yemwe akuyembekezeredwa kuyamba mu December 2021 ndi kudzatha mu January 2022.

Oyenera kutengapo gawo mu kafukufuku

Ana aamuna ndi aakazi omwe akwanitsa ma sabata khumi (10) koma osaposera masabata khumi ndi anayi (14). Anawa akuyembekezeredwa kukhala oti anabadwa opanda vuto lililonse komanso sanadwalepo matenda odetsa nkhwawa. Anawa okhoza kukhala kuti anabadwa kuchoka kwa makolo omwe ali ndi kachilombo ka HIV komanso akumwa mankhwala a ARVs kapena ana oti anabadwa kuchoka kwa makolo omwe alibe kachilomboka.

Zochitika mu kafukufukuyu

Kulemba anthu otengapo gawo mu kafukufukuyu kudzachitikira ku sikelo yak u Zingwangwa Health Center ndipo omwe atadzatenge nawo gawo mu kafukufukuyu adzaitanidwa kupita ku department ya rehabilitation sciences, Kamuzu University of Health Sciences (KUHeS), ku Blantyre. Kumeneku, kudzakhala chipinda chomwe kanema adzajambulidwe ndipo kudzakhala matilesi ndi makina ojambulira kanema (camera) yomwe idzaikidwe pa mtunda wa mita imodzi ndi theka (1.5 meters). Mwanayu adzagonekedwa pa matilesi moyang'ana kumwamba ndipo adzapatsidwa zoseweretsa komanso adzakhala ndi mayi wake kapena omusamala. Kanema adzajambulidwa.

Zoopsa kapena mavuto okudza chifukwa chotengapo gawo mu kafukufukuyu

Palibe choopsa kapena vuto lililonse lomwe lingadze chifukwa chotengapo gawo mu kafukufukuyu.

Phindu lobwera chifukwa chotengapo gawo mu kafukufukuyu

Mwana aliyense azayezedwa ndi achipatala kasunthidwe ka ziwalo zake. Ngati mwana atadzaonetse zizindikiro za matenda a ubongo kapena misempha, adzatumizidwa kwa madotolo kuti akayezedwe ndi kulandira thandizo ngati kuli koyenera kutelo. Sipadzakhala chiongola dzanja cha ndalama chomwe chitadzaperekedwe kwa otengapo gawo mu kafukufukuyu koma, amayi ndi ana adzabwezeredwa ndalama yomwe atadzagwiritse ntchito kupita komanso kubwelera kuchoka ku malo a kafukufuku.

Kusunga Chinsisi

Zokambirana za mkafukufukuyu komanso uthenga okhudza otengapo gawo udzasungidwa mwa Chinsisi. Okhawo omwe ali oloredwa mogwirizana ndi malamulo

ndi omwe atadzakhale ndi mpata odziwa za uthengawu. Pofuna kusunga chinsisi, ana onse otengapo gawo mu kafukufuku adzapatsidwa ma nambala omwe adzagwiritsidwe ntchito mmalo mwa mayina awo. Mwini kafukufuku yekha ndi yekhayo yemwe atazasunge mndandanda wa mayina ndi manambala a otengapo gawo. Mayina a otenga gawo mu kafukufuku adzalembedwa pa kalata yopempha chilolezo cha kafukufukuyu pokha. Kuonjezera apo, ma kalata a chilolezo adzasungidwa mwapadera. Uthenga onse omwe utadzatengedwe mu nthawi ya kafukufukuyu udzagwiritsidwa ntchito pa kafukufuku yekhayu basi. Zotsatira za kafukufukuyu zikadzasindikizidwa, ma kanema onse adzakonzedwa kuti nkhope za ana onse omwe atadzajambulidwe zidzaphimbidwe. Ma kanema amenewa adzasungidwa pa malo osamalidwa bwino.

Ngati muli ndi mafunso okhudza kafukufukuyu, mutha kulumikizana nane pa +265 (0) 882 634 969 kapena kulemba email ku 1916302@students.wts.ac.za

Ngati muli ndi mafunso okhudza ufulu wanu potengapo gawo mu kafukufukuyu, mutha kulumikizana ndi wapampando wa Human Research Ethics Committee ku sukulu ya ukachenjede ya Kamuzu University of Health Sciences pa Telephone +265 888118993 kapena kulemba email ku comrec@medcol.mw

.

Zikomo

James Kaunda

Physiotherapy Department

University of Witwatersrand

Appendix 6: Informed Consent Form – Guardian/Parents (English)

PARTICIPATION CONSENT FORM: Parent/Guardian Consent Form

Study Title: Observed General Movements In The HIV And ARV Exposed Uninfected Infants In Blantyre, Malawi

I, _____, hereby agree for my child, _____ (name of child), to participate in the study as described to me in the information sheet. I am aware that he/she will not be exposed to any additional risks. I understand that there are no monetary rewards for his/her participation and that participation is voluntary.

Signature of parent _____ Date _____

Or thumbprint:

Signature of researcher _____

For office use only:
Study number:_____

Appendix 7: Informed Consent Form – Guardian/Parents (Chichewa)

CHILOLEZO CHOTENGAPO GAWO MU KAFUKUFUKU: Makolo/osamalira mwana

Study Title: Observed General Movements in The HIV And ARV Exposed Uninfected Infants in Blantyre, Malawi

Ine,_____(dzina la kholo/osamala mwana), ndikuvomereza mmalo mwa mwana wanga, _____ (dzina la mwana), kutengapo mbali mu kafukufukuyu, mogwirizana ndi ndondomeko za kafukufuku zomwe andilongosolera. Ndikutsimikiza kumvesetsa kuti palibe phindu la ndalama lomwe litapezeke kudzera mu kutengapo mbali mu kafukufukuyu ndipo kuti kutengapo gawo mu kafukufukuyu ndi kosakakamizidwa.

Sayini ya kholo (Signature) _____ Date ____/_____/_____

Kapena dindani chala:

Sayini ya opanga kafukufuku (Signature) _____

For office use only:
Study number:_____

Appendix 8: Informed Consent Form – Guardian/Parents (English)

VIDEO RECORDING CONSENT FORM: Parent/Guardian Consent Form

Study Title: Observed General Movements In The HIV And ARV Exposed Uninfected Infants In Blantyre, Malawi

I, _____, hereby agree for my child, _____ (name of child), to have a video of his/her general movements recorded as described to me in the information sheet. I am aware that he/she will not be exposed to any additional risks. I understand that there are no monetary rewards for his/her participation and that participation is voluntary.

Signature of parent _____ Date _____

Or thumbprint:

Signature of researcher _____

For office use only:
Study number:_____

Appendix 9: Informed Consent – Guardian/Parent (Chichewa)

CHILOREZO CHOJAMBULA KANEMA: Makolo/ osamalira mwana

Study Title: Observed General Movements in The HIV And ARV Exposed Uninfected Infants in Blantyre, Malawi

Ine, _____ (dzina la kholo/ osamala mwana), ndikuvomereza mmalo mwa mwana wanga _____ (dzina la mwana), kuti kanema wowonetsa kasunthidwe ka ziwalo zake ajambulidwe mogwirizana ndi mmene malamulo a kafukufukuyu akunenera. Ndatsimikiziridwa kuti mwana wanga sakhala pa chiopsezo chilichonse chifukwa chotengapo gawo mu kafukufukuyu. Ndikutsimikiza kumvesetsa kuti palibe phindu la ndalama lomwe litapezeke kudzera mu kutengapo mbali mu kafukufukuyu ndipo kuti kutengapo gawo mu kafukufukuyu ndi kosakakamizidwa.

Sayini ya kholo (Signature) _____ Date ____/_____/_____

Kapena dindani chala:

Sayini ya opanga kafukufuku (Signature) _____

For office use only:
Study number:_____

Appendix 10: Informed Consent Form – Guardian/Parents (English)

PERMISSION TO KEEP VIDEO RECORDING: Parent/Guardian Consent Form

Study Title: Observed General Movements In The HIV And ARV Exposed Uninfected Infants In Blantyre, Malawi

I, _____, hereby agree for my child, _____ (name of child), to have the video recording of his/her general movements safely kept for future referencing as described to me in the information sheet. I am aware that he/she will not be exposed to any additional risks. I understand that there are no monetary rewards for his/her participation and that participation is voluntary.

Signature of parent _____ Date _____

Or thumbprint:

Signature of researcher _____

For office use only:
Study number:_____

Appendix 11: Informed Consent – Guardian/Parent (Chichewa)

CHILOREZO CHOSUNGA KANEMA: Makolo/ osamalira mwana

Study Title: Observed General Movements in The HIV And ARV Exposed Uninfected Infants In Blantyre, Malawi

Ine, _____ (dzina la kholo/ osamala mwana), ndikuvomereza mmalo mwa mwana wanga _____ (dzina la mwana), kuti kanema wowonetsa kasunthidwe ka ziwalo zake, asungidwe motetezedwa kuti adzagwiritsidwe ntchito mtsogolo mogwirizana ndi mmene malamulo a kafukufukuyu akunenera. Ndatsimikiziridwa kuti mwana wanga sakhala pa chiopsezo chilichonse chifukwa chotengapo gawo mu kafukufukuyu. Ndikutsimikiza kumvesetsa kuti palibe phindu la ndalama lomwe litapezeke kudzera mu kutengapo mbali mu kafukufukuyu ndipo kuti kutengapo gawo mu kafukufukuyu ndi kosakakamizidwa.

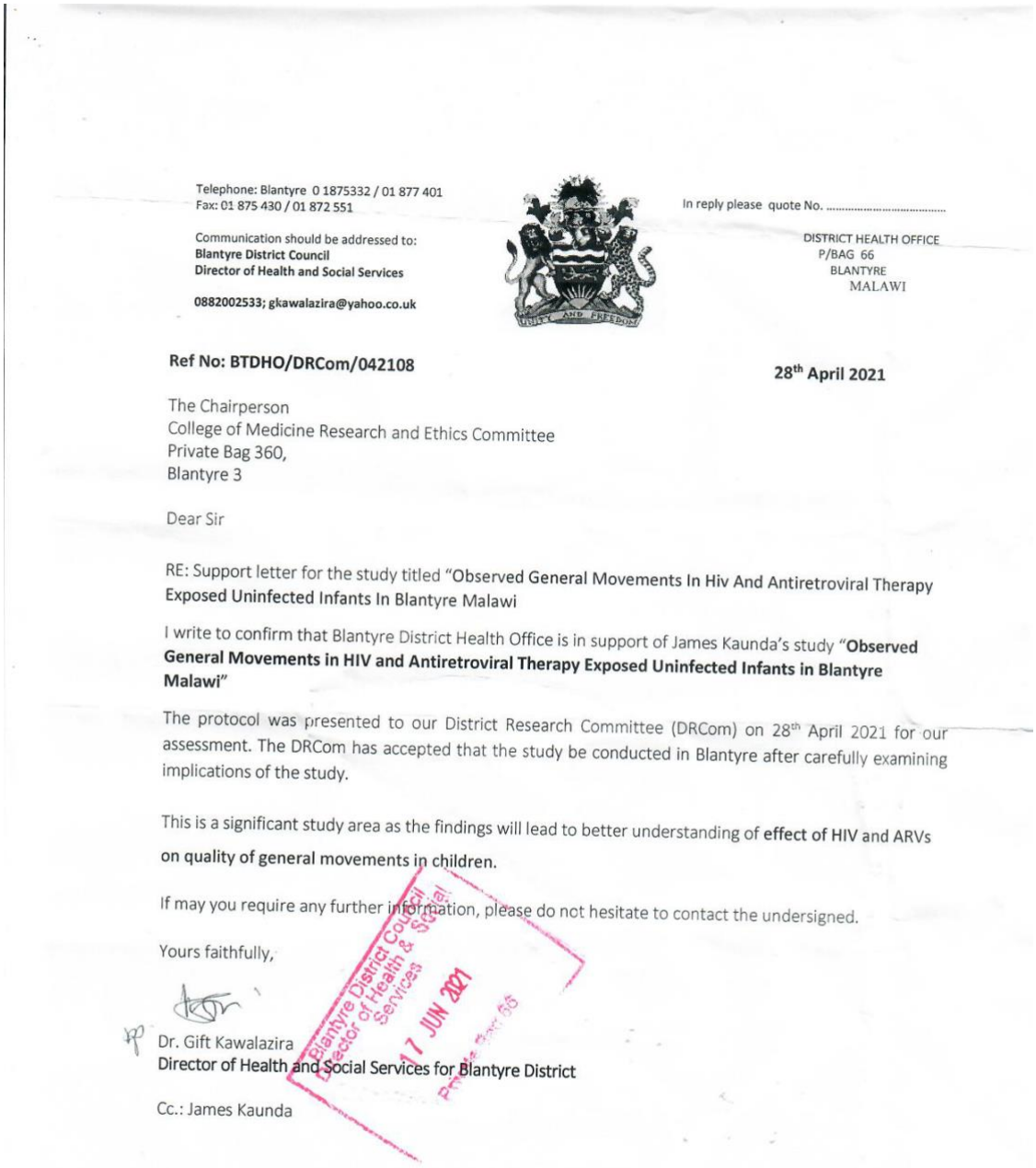
Sayini ya kholo (Signature) _____ Date ____/_____/_____

Kapena dindani chala:

Sayini ya opanga kafukufuku (Signature) _____

For office use only: Study number:_____

Appendix 12: Blantyre District Hospital Office Support Letter



Telephone: Blantyre 0 1875332 / 01 877 401
Fax: 01 875 430 / 01 872 551

Communication should be addressed to:
Blantyre District Council
Director of Health and Social Services

0882002533; gkawalazira@yahoo.co.uk

In reply please quote No. .....

DISTRICT HEALTH OFFICE
P/BAG 66
BLANTYRE
MALAWI

Ref No: BTDHO/DRCom/042108

28th April 2021

The Chairperson
College of Medicine Research and Ethics Committee
Private Bag 360,
Blantyre 3

Dear Sir

RE: Support letter for the study titled "**Observed General Movements In Hiv And Antiretroviral Therapy Exposed Uninfected Infants In Blantyre Malawi**

I write to confirm that Blantyre District Health Office is in support of James Kaunda's study "**Observed General Movements in HIV and Antiretroviral Therapy Exposed Uninfected Infants in Blantyre Malawi**"

The protocol was presented to our District Research Committee (DRCom) on 28th April 2021 for our assessment. The DRCom has accepted that the study be conducted in Blantyre after carefully examining implications of the study.

This is a significant study area as the findings will lead to better understanding of **effect of HIV and ARVs on quality of general movements in children.**

If may you require any further information, please do not hesitate to contact the undersigned.

Yours faithfully,

Blantyre District Council Director of Health & Social Services 17 JUN 2021 Private Bag 66

pp Dr. Gift Kawalazira
Director of Health and Social Services for Blantyre District

Cc.: James Kaunda

Appendix 13: Kamuzu University of Health Sciences - Support Letter

KAMUZU UNIVERSITY
OF HEALTH SCIENCES

MEMO

OFFICE OF THE HEAD OF DEPARTMENT

Rehabilitation Sciences

To: Chairperson-COMREC
From: HOD: Rehabilitation Sciences
Date: 10/01/2022

Dear Sir

Support Letter for the Study Titled "Observed General Movements In HIV And Antiretroviral Therapy Exposed Uninfected Infants in Blantyre Malawi"

This is to confirm that the department of rehabilitation sciences, Kamuzu University of Health Sciences (KUHeS) is in support of this study following a thorough examination of the significance and implications of the study. The department has reserved a room in its physiotherapy clinic at KUHeS, Blantyre campus where video recording for this study will be done.

For more information, please contact the head of department.

Yours faithfully,

Anderson Mughogho

UNIVERSITY OF MALAWI
COLLEGE OF MEDICINE
10 JAN 2022
PHYSIOTHERAPY DEPARTMENT
PRIVATE BAG 360
CHICHIRI BLANTYRE 3

EXCELLENCE FOR LIFE

www.kuhes.ac.mw @KuHeS_mw

Appendix 14: COMREC Ethical Clearance Certificate

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.12/21/3534 - Observed general movements in HIV and antiretroviral therapy exposed uninfected infants in Blantyre Malawi by James Kaunda

On 09-Feb-22

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

09-Feb-22

Prof. E. Ihnar -Chairperson (COMREC) — Date

Approved by College of Medicine 09-Feb-2022 (COMREC) Research and Ethics Committee

Appendix 15: University of Witwatersrand Ethical Clearance Certificate

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

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Mr J Kaunda School of Therapeutic Sciences Department of Physiotherapy Medical School University E-mail: 1916302@students.wits.ac.za
CC:	Supervisor: Professor J Potterton <Joanne.Potterton@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/05/20
REF:	R14/49
PROTOCOL NO:	**M200859** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Observed general movements in Human Immunodeficiency Virus and antiretroviral therapy exposed uninfected infants in Blantyre, Malawi*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Mr J Kaunda

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200859

NAME: (Principal Investigator)	Mr J Kaunda
DEPARTMENT:	School of Therapeutic Sciences Department of Physiotherapy Medical School University
PROJECT TITLE:	*Observed general movements in Human Immunodeficiency Virus and antiretroviral therapy exposed uninfected infants in Blantyre, Malawi*
DATE CONSIDERED:	2020/08/28
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor J Potterton
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/05/20

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and therefore reports and re-certification will be due in the month of August each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Appendix 16: Turnitin Summary Report

ORIGINALITY REPORT

4%	3%	2%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.frontiersin.org Internet Source	<1%
2	hdl.handle.net Internet Source	<1%
3	Submitted to University of Witwatersrand Student Paper	<1%
4	www.science.gov Internet Source	<1%
5	www.omicsdi.org Internet Source	<1%
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10	d.docksci.com Internet Source	<1 %
11	Lucy Mabaya, Hilda Tendisa Matarira, Donald Moshen Tanyanyiwa, Cuthbert Musarurwa, Johannes Mukwembi. "Growth Trajectories of HIV Exposed and HIV Unexposed Infants. A Prospective Study in Gweru, Zimbabwe", Global Pediatric Health, 2021 Publication	<1 %
12	Submitted to London School of Hygiene and Tropical Medicine Student Paper	<1 %
13	researchonline.lshtm.ac.uk Internet Source	<1 %
14	Baphaleng Monokwane, Allison Johnson, Claudia Gambrah-Sampaney, Esha Khurana et al. "Risk Factors for Cerebral Palsy in Children in Botswana", Pediatric Neurology, 2017 Publication	<1 %
15	Submitted to Napier University Student Paper	<1 %
16	cdn.bcm.edu Internet Source	<1 %
17	www.psi.org Internet Source	<1 %
	Submitted to University of Malawi	

18	Student Paper	<1 %
19	pubmed.ncbi.nlm.nih.gov Internet Source	<1 %
20	"The 9th International Child Neurology Congress The 7th Asian and Oceanian Congress of Child Neurology", Brain and Development, 2002 Publication	<1 %
21	Catherine J Wedderburn, Shunmay Yeung, Andrea M Rehman, Jacob A M Stadler et al. "Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study", The Lancet Child & Adolescent Health, 2019 Publication	<1 %
22	Mary Glenn Fowler, Michael J. Boivin, Itziar Familiar, Betty Nyangoma. "Central Nervous System and Neurodevelopmental Outcomes of HIV+ and HIV exposed children: A Mini Review of Recent Findings and Lessons Learned from the Field", Neuroscience Letters, 2022 Publication	<1 %
23	N. Stahlmann, C. Härtel, A. Knopp, B. Gehring, H. Kiecksee, U. Thyen. "Predictive Value of Neurodevelopmental Assessment versus	<1 %

	Evaluation of General Movements for Motor Outcome in Preterm Infants with Birth Weights <1500 g", Neuropediatrics, 2007 Publication	
24	clinicalinfo.hiv.gov Internet Source	<1 %
25	discovery.researcher.life Internet Source	<1 %
26	"Encyclopedia of AIDS", Springer Science and Business Media LLC, 2018 Publication	<1 %
27	Submitted to Mancosa Student Paper	<1 %
28	f1000research.com Internet Source	<1 %
29	www.texilajournal.com Internet Source	<1 %
30	Cathryn Crowle, Karen Walker, Claire Galea, Iona Novak, Nadia Badawi. "General movement trajectories and neurodevelopment at 3 months of age following neonatal surgery", Early Human Development, 2017 Publication	<1 %

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Exclude bibliography	On		