THE PHYSICAL SEQUELAE OF PERINATALLY ACQUIRED HIV IN ADOLESCENTS

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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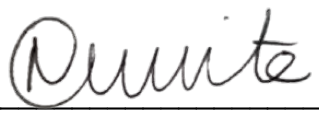
Declaration

I, Nicolette Comley-White, declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Nicolette Comley-White _____ 

Name of candidate Signature of candidate

17th day of June 2022, in Johannesburg, South Africa.

Dedication

I dedicate this thesis to all of the children who are born into a lifetime affected by HIV.

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Abstract

Human immunodeficiency virus (HIV) is a global challenge and with the continuously improving access to antiretroviral therapy (ART) the disease profile has shifted requiring chronic management. This holds true across the lifespan, and the generation of children with perinatal HIV who were born at the advent of early ART access have now aged into adolescence and young adulthood. Many perinatally HIV-infected adolescents (PHIVA) started ART at a young age and have spent their lifetime living with both the virus and on ART, two factors which have known neurotoxic effects. While the literature shows a clearly negative impact of perinatal HIV on adolescent neurocognitive development, there is limited information available on the physical sequelae that PHIVA may have. Thus, over three phases, the aim of this study was to determine the perceived physical challenges for PHIVA, to investigate the challenges clinically, and to propose a model of care for PHIVA.

A scoping review was included in the study to explore the available literature on physical sequelae in PHIVA. Of the 1291 citations that were screened, eight studies were included in the review. The majority focused on the anthropometric characteristics of PHIVA, and four studies addressed physical health and functioning. The literature showed that stunting and wasting are prevalent in PHIVA, and that physical functioning (such as reduced exercise tolerance and physical activity, and pain) are affected.

The first phase of the study was a qualitative analysis of the perceived physical challenges that PHIVA encounter. Participants were sourced from an HIV research and services clinic in Johannesburg, South Africa (for all phases of data collection) and 19 individuals were interviewed. All of the participants had early ART initiation (1 year 9 months; SD±1 year 2.3 months) and were virally suppressed, and only one adolescent reportedly did not experience any physical difficulties. The emerging codes were classified into categories of physical challenges, psychosocial challenges and other health issues. The results showed that PHIVA often experience challenges such as decreased endurance, pain and fatigue. They also struggle with decreased community participation, reduced muscle strength and motor skill, and emotional and cognitive impairments.

The second phase of the study was a quantitative, cross-sectional analysis of 147 PHIVA and 102 HIV-negative adolescents as a comparison group. The participants were assessed across a range of physical functioning outcome measures for height, weight, fatigue, motor performance (with manual dexterity, balance, and aiming and catching subscales), peripheral neuropathy, muscle strength, endurance and disability. The results found that the PHIVA group had significantly more impairments than the comparison group for height ($p<0.001$), weight ($p<0.001$), body mass index ($p=0.004$), fatigue intensity ($p=0.022$), manual dexterity ($p=0.021$), balance ($p=0.020$) and disability levels ($p=0.023$), specifically within mobility ($p=0.014$), self-care ($p=0.047$) and participation ($p<0.001$). As with the adolescents of the first phase of data collection, these participants had initiated ART at an early age (8.5 months; SD±6.6 months) and 87% of the group were virally suppressed. Despite being well managed it is clear that PHIVA experience significant physical sequelae.

The results of the study were used to develop a model of care for PHIVA. The model was validated through focus groups with PHIVA and healthcare providers who work in the field of HIV and adolescence. Input was given on the importance of different physical components as sequelae of perinatal HIV, and the roles of the healthcare providers were discussed. After the focus groups the model of care was finalised and a simplified schematic was designed.

In conclusion, this study established the physical sequelae of perinatal HIV in adolescence, showing that this population face significant challenges with height, weight, body mass index, fatigue intensity, manual dexterity, balance and disability levels. The model of care that was developed provides the basis for an understanding of the physical sequelae that PHIVA may have and who the key inter-professional healthcare team members are. It can be used within HIV clinics and the community to create awareness of the physical sequelae of perinatal HIV in adolescence, and as a guide for screening and referral to the necessary inter-professional team member. Increased awareness of the physical sequelae in PHIVA should in turn lead to early intervention and rehabilitation, bringing improved quality of life to this population.

Key words: HIV; adolescence; perinatal; physical; model of care; healthcare

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"Trust in the Lord with all your heart, and do not lean on your own understanding. In all your ways acknowledge Him, and He will make straight your paths."

Proverbs 3:5-6

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List of Abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
BBB	Blood-brain barrier
BMI	Body mass index
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CIPHER	Collaborative Initiative for Paediatric HIV Education and Research
CLHIV	Children living with HIV
CNS	Central nervous system
CRediT	Contributor Roles Taxonomy
HAND	HIV-associated neurocognitive disorder
HEI	HIV-exposed infected
HEU	HIV-exposed uninfected
HI	Human immunodeficiency
HIV	Human immunodeficiency virus
HIV-1	HIV type 1
HIV-2	HIV type 2
HIVE	Human immunodeficiency virus encephalopathy
HRQOL	Health-related quality of life
HUU	HIV-unexposed uninfected
ICF	International Classification of Functioning, Disability and Health
MDT	Multidisciplinary team
MoC	Model of care
PedsQL	Pediatric Quality of Life Inventory
PHIVA	Perinatally HIV-infected adolescents
PMTCT	Prevention of mother to child transmission
QOL	Quality of life
SSA	Sub-Saharan Africa
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0

Chapter 1 Introduction

1.1 Background

Recent data shows that deaths related to acquired immune deficiency syndrome (AIDS) have declined by 47% between 2010 and 2021 (UNAIDS, 2021). However, the human immunodeficiency virus (HIV) remains the key cause of death in adolescence globally (Slogrove and Sohn, 2018). The global scale-up of antiretroviral therapy (ART) in the management of HIV has shifted the paediatric HIV endemic to chronic disease management, with a growing body of perinatally HIV-infected adolescents (PHIVA) (Sohn and Hazra, 2013). There are approximately 2.8 million children living with HIV (CLHIV), of which 1.8 million are adolescents (UNAIDS, 2021), with 88% of adolescents with HIV living in sub-Saharan Africa (SSA) (UNICEF, 2021). Although perinatal HIV transmission forms the majority of infection route, the specific number of PHIVA is unknown (Sohn and Hazra, 2013).

Adolescence is a developmental phase characterised by puberty, formation of sexual identity and maturation of social and cognitive structures (Mark et al., 2017). It is defined as ages 10-19 years (UNICEF, 2016; World Health Organization, 2014), with early (10-15 years), middle (14 to 17 years) and late (16 to 19 years) stages (World Health Organization, 2010). For the purposes of this study, early and middle phases of 10 to 14 years and 15 to 17 years respectively will be used.

During the early phase of adolescence the body undergoes rapid growth and secondary sexual characteristics appear. These continue in the middle phase but growth begins to slow down with the adolescent reaching approximately 95% of adult growth (World Health Organization, 2010). Psychologically, early adolescence is characterised by frequent mood swings, with a lot of time and thought spent developing their body image (World Health Organization, 2010). Psychopathology, and more specifically depression, occurs more frequently once puberty begins putting adolescents in a high risk period of mental health problems (Walker, 2002).

Throughout childhood and into adolescence the brain matures and develops. The brain and cognition also undergo developmental changes in adolescence, with the early adolescent predominantly using concrete thinking and not considering the future

repercussions of a present action. In middle adolescence the prefrontal cortex grows and impacts on social and problem-solving skills, with the person being very self-absorbed (World Health Organization, 2010). Adolescent neurodevelopment goes through synaptic pruning and myelination, changes in connectivity and refinement of networks, all of which leads towards the formation of the adult brain and behaviour (Spear, 2013).

As the brain develops from birth through childhood, into adolescence and then maturity in adulthood it moves from a higher state of plasticity to less plasticity and more stability (Spear, 2013). Neural plasticity is the ability of the central nervous system (CNS) to adapt to changes in the environment (Sharma, Classen and Cohen, 2013). Neural plasticity is present across the lifespan but it plays a particularly strong role in the paediatric brain with regards to development and learning (Stiles, 2000).

Although the paediatric brain has strong neural plasticity, it also has a degree of neural-vulnerability where adverse environmental factors can impact on normal development (Anderson, Spencer-Smith and Wood, 2011). One of these adverse factors can be the human immunodeficiency (HI) virus, which is able to cross the blood-brain barrier (BBB) and infiltrate the CNS causing neurocognitive impairment (Strazza et al., 2011). A review by Hilburn et al. (2010) discusses the role of HIV and its effect on the developing nervous system, with a special focus on HIV encephalopathy (HIVE). The onset of HIVE can cause loss of brain growth, motor abnormalities and cognitive dysfunction (Mitchell, 2001). Even with the early use of ART many CLHIV still present with neurodevelopmental problems due to neuro-inflammation, vascular dysfunction and hypercoagulability (Blokhuis et al., 2016).

In addition to damage done to the developing nervous system by the HI virus, the long term use of ART needs to be considered, especially since the BBB makes it difficult to penetrate the brain with ART (Meeker, Asahchop and Power, 2014). Hepatotoxicity, mitochondrial toxicity, skin toxicity, severe hypersensitivity reactions and lipodystrophy are some well-known adverse effects of ART (Carr and Cooper, 2000; Shubber et al., 2013). Depending on the class of drug and the individual, a variety of neurotoxic adverse effects exist from ART, including mania, psychosis, insomnia, irritability and vivid dreams (Abers, Shandera and Kass, 2014).

A common neurological complication of HIV and/or ART is peripheral neuropathy (Arenas-Pinto et al., 2016; Pardo, McArthur and Griffin, 2001). Peripheral neuropathy has been found to have a prevalence of 36% in children who are HIV-positive (Benjamin et al., 2015) and 13% to 32% prevalence in adults with HIV (Evans et al., 2011; Kiwuwa-Muyingo et al., 2014). HIV peripheral neuropathy can lead to debilitating levels of pain, affecting ambulation and activities of daily living (Dorsey and Morton, 2006).

Perinatally acquired HIV results in delayed neurodevelopment, with cognitive and neurological complications in children (Abubakar et al., 2008; Crowell et al., 2014; Govender et al., 2011; Le Doare, Bland and Newell, 2012; Smith et al., 2006; Van Rie et al., 2007; Whitehead, Potterton and Coovadia, 2014). In adults, HIV also results in neurological complications, such as cognitive disorders, vacuolar myelopathy, sensory neuropathies, delirium, depression, opportunistic CNS infections, and HIV-associated neurocognitive disorder (HAND), including HIV-associated dementia (McArthur, Brew and Nath, 2005; Tan and McArthur, 2012; Watkins and Treisman, 2015). HIV-associated neurocognitive disorder has a prevalence of 21.5% to 33% in people with HIV (Sacktor et al., 2016; Yusuf et al., 2017).

Other common physical challenges that can be a result of HIV are fatigue, decreased endurance and muscle strength, motor function impairment and anthropometric changes (Chisati and Vasseljen, 2015; Jesson et al., 2019; Jong et al., 2010; Keyser et al., 2000; Khondowe et al., 2015; Macdonald et al., 2017). Prevalence of fatigue in people with HIV can be as high as 88% (Jong et al., 2010) yet its prevalence in children and adolescents with HIV is largely unknown and requires further research (Potterton, 2016). Fatigue severity can be a predictor of quality of life (QOL) in adults with HIV (Voss, 2005) and is strongly associated with depression and anxiety (Jong et al., 2010). Ter Haar et al. (2021) recently found that fatigue in PHIVA is associated with poorer health-related quality of life (HRQOL) compared to HIV-negative youth. Aerobic endurance is decreased in adults with HIV (Chisati and Vasseljen, 2015) as well as in HIV-positive children (Walker, 2015). Adolescents with HIV can present with functional aerobic impairment (Keyser et al., 2000) and decreased exercise tolerance (Ferrand et al., 2012). Muscle strength in both adults and children is negatively impacted by HIV (Grinspoon and Mulligan, 2003) with muscle power deficits still being apparent in adolescence (Macdonald et al., 2017). Motor function impairment in CLHIV has a

prevalence of up to 83% (Khondowe et al., 2015) but as yet there is no clear data on the effect of perinatal HIV infection on motor function in adolescence. Height and weight, and body mass index (BMI) are significantly lower in children and adolescents with HIV compared to HIV-negative children (Jesson et al., 2019). Stunting is a prevalent problem in adolescents with HIV and it is associated with delayed pubertal onset (Williams and Jesson, 2018).

Overall, there is a lack of data available for the challenges that PHIVA face (Laughton et al., 2013). Of the studies that have been done on neurodevelopment in PHIVA, the majority are from resource-rich countries, and not from resource-scarce countries, where there is the highest prevalence of PHIVA (Laughton et al., 2013). However, it is still worth considering the data of these studies, especially since they show that PHIVA are at risk of poorer neurocognitive outcomes, increased mental health problems; increased prevalence of neurocognitive dysfunction (specifically executive functioning and motor functioning/speed), decreased cognition and decreased processing speed (Ene et al., 2014; Laughton et al., 2013; Lowenthal et al., 2014; Smith et al., 2012; Smith and Wilkins, 2015; Willen et al., 2017).

The literature has given a clear appeal for further research to be done in the area of neurodevelopment in PHIVA (especially in resource-scarce countries), as well as for the urgent development of policies and programmes to cater for PHIVA (Laughton et al., 2013; Lowenthal et al., 2014; Smith et al., 2012). Although models of care for different areas of managing HIV are available (Bradford et al., 2007; Ford et al., 2006; Smith et al., 2012; Teasdale and Besser, 2008) to date there is no literature presented on suggested models of care for PHIVA. Furthermore, since the challenges that PHIVA face are a relatively recent development, any existing models of care may well not be sufficiently responsive to this population, as is often the case with existing models of care based on historical information (Davidson et al., 2006).

A model of care (MoC) is “an overarching design for the provision of a particular type of healthcare service that is shaped by a theoretical basis, evidence based practice and defined standards” and it should address the needs of a population through a multi-disciplinary, multifaceted approach, based on patient-centred research (Davidson et al., 2006). The needs of PHIVA are population-specific, and it is emerging that HIV-related service delivery and health programmes for adolescents need to be based on

meaningful engagement with the adolescents themselves, taking into account their views (Oliveras Rodriguez, 2017).

1.2 Problem Statement

The literature has ample information on the neurological and physical complications of HIV, both in children and in adults, however there is a paucity of data pertaining to PHIVA, a group of people who have had a lifetime exposure to the HI virus and many years of ART exposure, both of which have an effect on the neurological system. Of the data that is available, it is predominantly from resource-rich settings, not middle and low income countries who carry the majority burden of HIV. There has been a resounding call for further research in this area. Furthermore, to the author's knowledge, there is no model of service delivery which caters for this population. It is suggested that any development of health systems, or models of care, for PHIVA need to engage the adolescents themselves in order to be effective.

1.3 Research question

What are the physical sequelae of perinatally acquired HIV in adolescents and how can these be incorporated into the structure of a MoC for PHIVA?

1.4 Aims

Over three phases this study aims to determine what the perceived challenges are that PHIVA face due to physical sequelae of HIV; to then establish these challenges clinically; and lastly to propose a MoC for PHIVA.

1.5 Objectives

The following objectives will be met using a mixed methods study design:

1.5.1 Phase one: qualitative study

1. To establish the perceived challenges that PHIVA face with regards to physical sequelae in early and middle adolescence.
2. To determine the perceived impairments, activity limitations and participation restrictions experienced by PHIVA.
3. To establish if the physical challenges experienced by PHIVA are different to those identified in the literature.

1.5.2 Phase two: quantitative study

4. To establish the physical function of PHIVA.
5. To establish the physical function of adolescents who are HIV-negative.
6. To determine if there are any differences in the physical function of PHIVA and adolescents who are HIV-negative.

1.5.3 Phase three: model of care

7. To develop a MoC to address the physical sequelae of perinatally acquired HIV in adolescents.

1.6 Significance

Establishing the perceived and actual physical sequelae of perinatally transmitted HIV in adolescents will address one of the gaps of knowledge that we have as clinicians working with PHIVA. Creating a MoC will assist healthcare providers in early identification, assessment and management of potential physical problems, including the necessary referral of the PHIVA to relevant members of the inter-professional team. By addressing the challenges, one hopes to improve the QOL and community participation of PHIVA. Informing this research with the voices of the adolescents in the assessment and development of the MoC ensures that we are working for adolescents, with adolescents, and thus potentially optimising the uptake of the MoC.

1.7 Conceptual framework

The application of the International Classification of Functioning, Disability and Health (ICF) as a conceptual framework for disability has been described in the literature and is used as a common language in discussing disability (Kostajsek, 2011). Based on this, this study will utilise the ICF as its conceptual framework (as presented in Chapter 3). The impairments, activity limitations and participation restrictions identified in phase one and two will feed into the development of the MoC, as described in phase three.

1.8 Outline of the thesis

Figure 1.1 Outline of the thesis

1.9 Conclusion

This chapter introduced the background literature that lead to the development of the study aims, objectives and significance. An overview of the thesis was presented. The following chapter gives a detailed review of the literature pertaining to HIV and adolescence.

Chapter 2 Literature Review

2.1 Introduction

Chapter 2 presents a review of the relevant literature pertaining to HIV and adolescence. Adolescence and HIV will be defined and epidemiology of HIV on a global, African and South African scale will be presented. Relevant information relating to normal development in adolescence will be discussed, providing the background to understanding the impact that HIV can have on adolescence. Information about HIV and its pathophysiology, impact on childhood development and the role of ART will be discussed. Finally, care options and models of care in HIV will be presented.

2.2 Search Strategy

This chapter reviews literature predominantly from 2011 to 2022, published in English. The following search engines were used: MEDLINE (PubMed), CINAHL (EBSCOhost), Elsevier (Scopus), Elsevier (Science Direct) and Google Scholar, with key words such as: HIV; adolescents; adolescence; youth; perinatal; vertical; physical; outcomes; sequelae; model of care; prevalence; incidence; epidemiology; pathology; pathophysiology; development; Africa; South Africa; sub-Saharan Africa; antiretroviral.

2.3 Definitions

2.3.1 HIV/AIDS

The key characteristic of HIV is cluster of differentiation (CD) 4 cell depletion which results in opportunistic infection and malignancies (Richman, 2000). As HIV infection progresses it leads to AIDS, which was first identified in 1981 with the retrovirus, HIV type 1 (HIV-1), being identified as the cause (Sharp and Hahn, 2011; van Dijk et al., 2010). There is a second virus that causes AIDS, namely HIV type 2 (HIV-2), but HIV-2 is significantly less common than HIV-1 and has a slower disease progression and lower transmission rate (Sharp and Hahn, 2011; Vidya Vijayan et al., 2017). The lineage of HIV-1 can be further divided into groups M, N, O and P, but only group M is the pandemic form of the virus (Shaw and Hunter, 2012), with the other three groups being endemic (group N and O), or only found in an individual (group P) (Alessandri-Gradt et al., 2018; Sharp and Hahn, 2011). The HIV-1 group M can be further divided into nine subtypes and over 40 circulating recombinant forms (Sharp and Hahn, 2011)

but the description of these is beyond the scope of this literature review. Due to the protracted disease course of HIV-2, as well as its lower mother to child transmission rates, HIV-2 is seldom responsible for paediatric HIV disease (Nielsen-Saines et al., 2019) and thus this literature review from hereon will be referring to HIV-1 when using the term “HIV”.

The definition of AIDS is two-fold: a CD4 count of less than 200cells/mm^3 and the development of one or more opportunistic infections as listed by the Centers for Disease Control and Prevention (CDC) (Ward et al., 1992; World Health Organization, 1986). However, in children the CD4 count in generally much higher than in adults (CDC, 1994), and as a child ages the CD4 count lowers and thus it is not a valid way of assessing HIV severity in childhood. Instead, the percentage of white blood cells that are CD4 cells (i.e. the CD4%) is used for monitoring CLHIV. The CDC describes the immunological categories by age in CLHIV as per Table 2.1, where one can see the CD4 count varies by age group but the CD4% stays constant.

Table 2.1 Immunologic categories based on age-specific CD4+ T-lymphocyte counts and percent of total lymphocytes [as per CDC, (1994)].

Immunologic category	Age of child					
	<12 mos		1–5 yrs		6–12 yrs	
	µL	(%)	µL	(%)	µL	(%)
1: No evidence of suppression	≥1,500	(≥25)	≥1,000	(≥25)	≥500	(≥25)
2: Evidence of moderate suppression	750–1,499	(15–24)	500–999	(15–24)	200–499	(15–24)
3: Severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

2.3.1.1 Exposure and transmission

Further definitions to consider when discussing HIV are: HIV-exposed infected (HEI), HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) children, all three of which pertain to perinatal HIV. While there are still many children acquiring perinatal HIV (i.e. HEI) the widespread programmes for prevention of mother to child transmission (PMTCT) have resulted in children who are born to HIV-positive mothers but are uninfected by HIV and are thus classified as HEU (Brennan et al., 2019; Chaudhury et al., 2018). The third group of children are those whose mothers do not have HIV during pregnancy and birth and thus the child is HUU.

The last definitions of HIV to address pertain to routes of transmission. Perinatal HIV is the mother to child transmission of the virus through pregnancy, birth or breastfeeding (AIDSinfo, 2020) and is also referred to vertical transmission. When HIV is transmitted from someone other than the mother it is referred to as horizontal transmission and this can occur through sexual activity, infusion of HIV-contaminated blood products or re-use of contaminated needles (Myburgh et al., 2020; Ugwu and Eneh, 2014).

2.3.2 Adolescence

Adolescence is defined as a period between childhood and adulthood, characterised by rapid physical, cognitive and psychosocial changes (World Health Organization, 2021), as well as pubertal development and sexual identity formation (Mark et al., 2017). The age of adolescence is 10-19 years (UNICEF, 2016; World Health Organization, 2014), and is divided into three stages, namely: early (10-15 years), middle (14 to 17 years) and late (16-19 years) phase (World Health Organization, 2010).

2.4 Epidemiology of HIV

2.4.1 Global

The HIV pandemic continues to be a global challenge, with 37.3 million people living with HIV in 2020, and 1.5 million new cases and 680 000 AIDS-related deaths occurring that year (UNAIDS, 2021). It is estimated that there are 1.75 million adolescents living with HIV (UNICEF, 2021).

Although many epidemiology studies do not report separate statistics for vertically- versus horizontally-acquired HIV a recent multi-regional study measured mortality incidence rates between adolescents with perinatal HIV and adolescents with non-perinatal HIV. Of the 104 846 adolescents in the study, 20% had perinatal HIV and they had a mortality incidence ratio of 0.7/100 person-years (95% confidence interval: 1.3-1.6) (Desmonde et al., 2021). Another multi-regional study that analysed data specifically for PHIVA, found a mortality rate at age 15 of 2.6% but the authors propose that this may be even higher in reality due to unavailability of data in high-burden countries and the high loss to follow up in some regions (The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration et

al., 2018). Slogrove et al.'s review of the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates reported an annual increase in mortality rates in older adolescents (aged 15-19 years) and the authors propose that this group would be made up of predominantly perinatal HIV infections because adolescents with horizontal infections would only have been recently infected (and thus not progressed far into the disease) (Slogrove et al., 2017).

2.4.2 Africa

Although ART rollout in SSA has improved over the years, there is still a need for further improvement (Taylor, 2018) which is reflected in the high prevalence of HIV in Africa. The UNAIDS 2021 estimates report that 88% of adolescents with HIV (vertically- and horizontally-acquired) live in SSA (UNICEF, 2021) while an earlier study indicates that with specifically perinatal HIV, 79% of adolescents live in SSA (CIPHER Global Cohort Collaboration et al., 2018).

2.4.3 South Africa

The rollout of ART in South Africa began in 2004 (Evans, 2013), with the initial criteria for ART initiation being the presence of an AIDS-defining condition or CD4 count of less than 200cell/mm^3 (Osler et al., 2018), and while these guidelines improved over the years, for a long period many CLHIV were not eligible for ART initiation. As early ART initiation and increased access improved, so the mortality rates of CLHIV decreased, with up to a 76% decrease in early infant mortality for infants with early HIV diagnosis and ART initiation (Violari et al., 2008). This has resulted in a shift of HIV to a chronic illness and thus the numbers of children with perinatal HIV ageing into adolescence is growing in South Africa (Anderson, Muloiwa and Davies, 2020; Fairlie et al., 2014).

Data on the prevalence of specifically *perinatally* acquired HIV in adolescents in South Africa are not readily available however Mabaso et al. (2021) analysed the trends of prevalence of HIV (vertically- and horizontally-acquired) in South African adolescents according to the 2008, 2012 and 2017 national household survey. The analysis showed a significant increase in HIV prevalence in adolescents (p=0.031), with higher odds of being HIV-positive for females than males [AOR = 2.24; 95% CI (1.73–2.91); p < 0.001] and for residing in KwaZulu-Natal province compared to the Northern Cape

[AOR = 2.01; 95% CI (1.-3.99); p = 0.027] (Mabaso et al., 2021). The KwaZulu-Natal province has the highest prevalence of HIV in South Africa, affected by factors such as low male circumcision rates and high sexual partner rates (Johnson, Dorrington and Moolla, 2017). Furthermore, female gender is shown to be a greater risk factor for HIV due to the vulnerabilities of the gender because of unequal social, cultural and economic statuses (AVERT, 2019).

2.5 Normal development in adolescence

The period of adolescence is characterised by pubertal development, sexual identity formation (Mark et al., 2017) and physical, psychosocial and cognitive changes (World Health Organization, 2021).

2.5.1 Cortical development

The adolescent brain undergoes significant changes and maturation processes during this critical phase of development (Spear, 2013) and in adolescence the brain goes through its second surge in synaptogenesis (Arain et al., 2013). The adolescent brain develops substantial changes in grey matter thickness (Blakemore, Burnett and Dahl, 2010), with dendritic pruning and myelination (Patton et al., 2016; Spear, 2013). This continues up to the age of approximately 24 years, especially in the prefrontal cortex which undergoes continuous consolidation during adolescence but is one of the last areas of the brain to mature (Arain et al., 2013). The prefrontal cortex integrates information from multiple cortical and subcortical areas and is involved in decision-making and behavioural inhibition (Caballero, Granberg and Tseng, 2016).

The adolescent brain is plastic and as the neurocircuitry improves, so the brain increases in its ability to adapt, problem-solve, multi-task and process complex information. The converse aspect of neuroplasticity is that the adolescent brain is also vulnerable to poor decision making (skill in critical and rational thinking is still developing) and the neurocircuitry has the potential to be damaged by toxins, trauma, experiences and lifestyle choices (Arain et al., 2013; Patton et al., 2016; Spear, 2013). This neuro-vulnerability also highlights the susceptibility of an immature brain to insult, with potential negative effects on development and recovery, and the young brain is in a balance of neural plasticity and neuro-vulnerability, with recovery from insult falling

on a continuum that is affected by disease/injury and environmental factors (Anderson, Spencer-Smith and Wood, 2011).

2.5.2 Physical development

Adolescence is characterised by the onset of puberty, triggered by physiological changes within the neuroendocrine system, involving the hypothalamic-pituitary-gonadal, adrenal and growth hormone axes (Chulani and Gordon, 2014). Puberty brings about changes in primary and secondary sexual characteristics, growth and body composition (Chulani and Gordon, 2014; Dorn and Biro, 2011).

Puberty involves the development of the primary sex organs and other external signs (such as breast and pubic hair development). These external signs are used to grade pubertal development with the five levels of Tanner staging (Dorn and Biro, 2011), the most popular puberty staging tool (Chulani and Gordon, 2014). The normal female age range for the start of puberty is 8-13 years, and for males it is 9-14 years (Farello et al., 2019).

A linear growth spurt occurs around the ages of 14 in males and 12 in females (Blakemore, Burnett and Dahl, 2010). The adolescent growth spurt accounts for approximately 20% of the individual's adult height (Chulani and Gordon, 2014). In addition to significant height changes in adolescence, puberty also brings about changes in body composition, with females experiencing a decrease in lean body mass percentage and an increase in adipose tissue, and males experiencing an increase in lean body mass percentage with a decrease in adipose tissue and an increase in muscle mass (Chulani and Gordon, 2014).

Brown et al. (2017) describe the other growth components affected by puberty, such as flexibility, muscle growth and strength, and bone mass. Female adolescents generally experience an increase in flexibility while males experience a decrease in flexibility. Muscle mass and strength increase in both sexes during puberty but are more marked in males. Finally, adolescence is a critical period of lifetime bone mineral density acquisition (Brown, Patel and Darmawan, 2017).

2.5.3 Psychosocial development

The developing adolescent faces psychosocial changes as they transition from childhood to adulthood, including sexual orientation, identity formation, risk-taking behaviour and mental health challenges (Alderman et al., 2019). A key feature of this phase is the need for autonomy (Daddis, 2011) and research has shown that increasing an adolescent's autonomy in a school setting results in improved engagement with learning materials (Hafen et al., 2012). This is an important finding in the context of HIV care because healthcare professionals should consider the relationship of autonomy and PHIVA engagement with their care, medication regimens, transitioning to adult care etcetera. The engagement of youth in research and policies that pertain to them is critical for those programmes to be successful (Oliveras Rodriguez, 2017).

2.6 The human immunodeficiency virus

2.6.1 Pathophysiology

The HI virus is a retrovirus (Klimas, Koneru and Fletcher, 2008) transmitted through bodily fluids [i.e. blood, semen, breast milk, cervico-vaginal and rectal secretions (Shaw and Hunter, 2012)] which cross the mucosa via dendritic cells to enter the lymphatic tissues and nodes (Klimas, Koneru and Fletcher, 2008), resulting in CD4 cell depletion (Kuroda, 2010; Richman, 2000). The CD4 lymphocyte is a white blood cell responsible for immunological responses in the body by stimulating other immune cells (such as macrophages, B cells and CD8 cells) (Chitnis, 2007; Zhang, Zhang and Zhao, 2009; Zhen et al., 2014). While the CD4 helper T cells are the main target of HIV, the virus also attacks other cells such as dendritic cells, macrophages and resting T cell subsets (Kirchhoff, 2013).

The virus attaches to the cellular surface of CD4 receptors and thereafter reverse transcriptase creates a complementary DNA strand from the viral RNA which is integrated into the cellular genome allowing viral replication (Rathbun, Lockhart and Stephens, 2006). This process is detailed in the HIV lifecycle, comprising of an early and late phase of replication, and lasts one to two days (Kirchhoff, 2013). Details of the phases of the lifecycle are depicted in Figure 2.1.

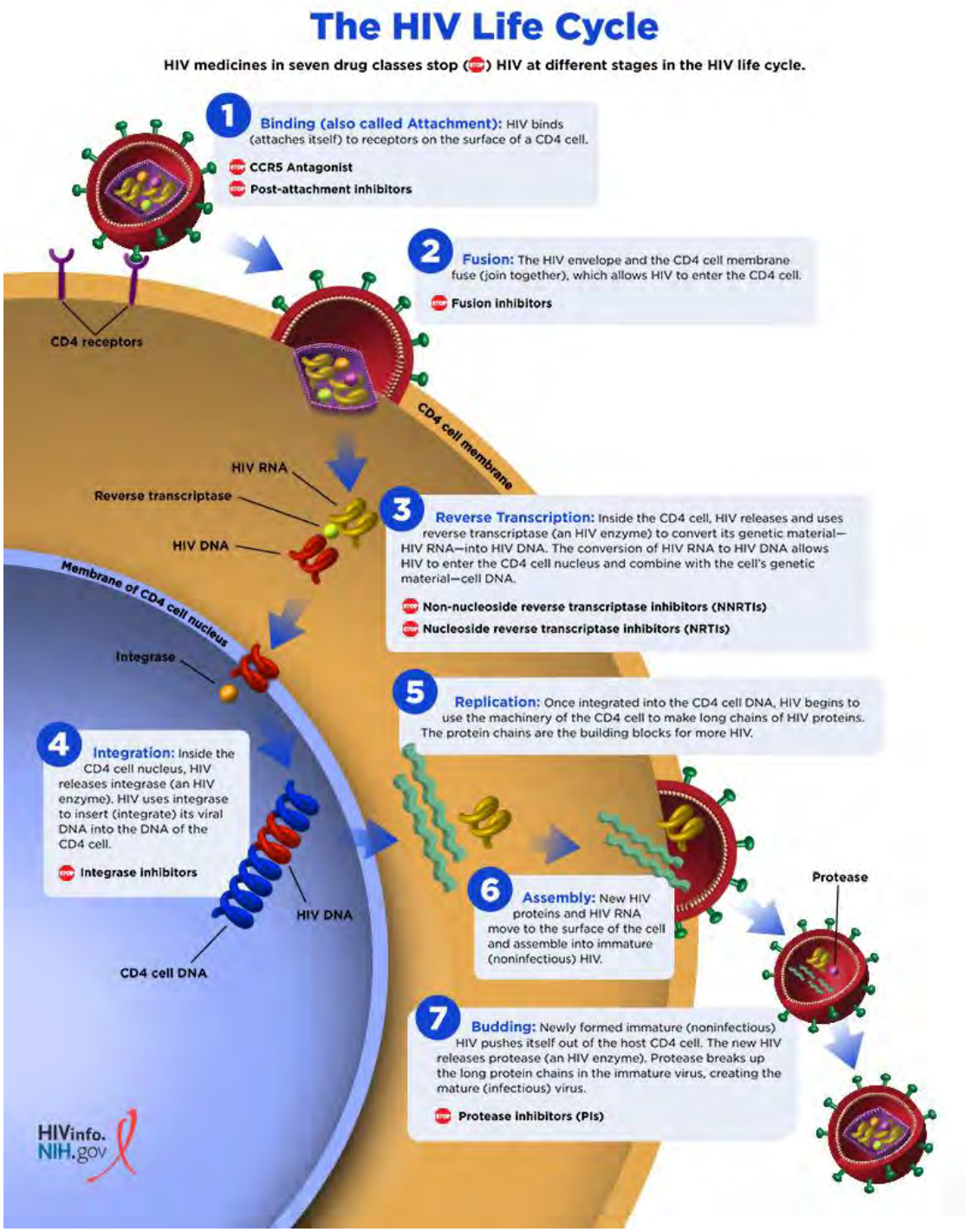

Figure 2.1 The HIV lifecycle

(Credit: The HIV Life Cycle | NIH, 2013)

Without the intervention of ART HIV infection follows a course of clinical stages. The World Health Organization (WHO) has classified these stages into four stages, namely Stage 1: asymptomatic; Stage 2: mildly symptomatic; Stage 3: moderately symptomatic, and Stage 4: severely symptomatic i.e. AIDS (Weinberg and Kovarik, 2010). These stages are based on clinical presentation and are thus useful in settings

that do not have access to laboratory data for a patient's CD4 count and viral load (Weinberg and Kovarik, 2010).

The final important pathophysiological consideration of the HI virus is its ability to cross the BBB. The BBB is a selectively permeable barrier protecting the brain and is essential for normal CNS function (Atluri et al., 2015; Strazza et al., 2011). It consists of highly specialised endothelial cells on top of a basal lamina (Eugenin et al., 2011) and limits molecules and foreign substances from entering the CNS (Atluri et al., 2015; Louboutin and Strayer, 2012), however, the HI virus is able to penetrate the BBB and enter the CNS as passengers in cells that usually cross the BBB, such as T cells and monocytes (Atluri et al., 2015; Strazza et al., 2011). This then disrupts the normal functioning of the BBB allowing the virus to enter the CNS directly, as well as in the form of infected cells (Strazza et al., 2011). Once the virus is in the CNS it continues to replicate and causes further damage by infecting resident CNS cells, for example astrocytes, which advances the breakdown of the BBB (Strazza et al., 2011). In infants the BBB is more permeable than in adults (Cornford, Braun and Oldendorf, 1982) and the tightness of the BBB improves through gestation and early development (Malaeb et al., 2012). The younger the CLHIV, the more likely they are to have viral penetration of the CNS, resulting in neurological signs and symptoms earlier on in the disease process than in adults (Donald et al., 2015).

The HI virus is a neurotropic virus, causing inflammation and neurotoxicity, largely due to the surface protein, Gp120 (Atluri et al., 2015; Louboutin and Strayer, 2012). The presence of HIV in the CNS causes a spectrum of neurological disorders, collectively known in adult literature as HAND: a prevalent sequelae of HIV (Louboutin and Strayer, 2012). The virus crosses the BBB from early on in HIV infection (Rahimy et al., 2017) and thus CNS damage may occur before a person is aware of being HIV-positive or starting ART (Williams et al., 2012). While HAND is a prevalent sequelae of HIV infection in adults, it has also been shown that HAND can occur in up to 45% of PHIVA (Hoare et al., 2016). However, the most common CNS HIV-complication in children is HIVE, resulting in delayed milestones and frequent school failure (Donald et al., 2015).

2.6.2 Antiretroviral therapy

2.6.2.1 Overview of antiretroviral therapy

In 1987 the first ART drug, azidothymidine, was approved for the treatment of HIV/AIDS and ART has developed greatly since then, with increased efficacy and decreased side-effects (Forsythe et al., 2019). Southern Africa has five classes of ART available: nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and entry inhibitors (Meintjes et al., 2017). Patients are prescribed a combination of different drug classes in an attempt to target multiple steps in the HI virus lifecycle (Shah et al., 2016).

The goals of ART are to suppress the viral load, improve immune functioning, reduce morbidity, prolong life expectancy, improve QOL, prevent further HIV transmission and to minimise adverse effects of ART (Meintjes et al., 2017). Antiretroviral drugs are divided into different classes, each of which are able to interrupt the virus replication at different stages of its lifecycle (Klimas, Koneru and Fletcher, 2008). With this decrease in viral replication there is an increase in CD4 and CD8 cells (Richman, 2000) and thus an increase in the person's immune system and health (Meintjes et al., 2017). Research has shown that the earlier that a person initiates ART, the better the outcomes (Boyd et al., 2019; Mateo-Urdiales et al., 2019; The INSIGHT START Study Group, 2015) and their HRQOL (Dutra et al., 2019). Likewise with children, studies with early initiation of ART in children have shown that the participants have more positive outcomes, with lower mortality and morbidity rates (Laughton et al., 2012; Shiau et al., 2013; Violari et al., 2008), and that these positive outcomes carry through into adolescence (Persaud et al., 2014). However, it is important to remember that in PHIVA many of the adolescents would have started ART over a decade ago, before treatment regimens were at their optimum, and they may also be on their second or third line of treatment by the time they reach adolescence (Fairlie et al., 2014; Sohn and Hazra, 2013).

A challenge with HIV and the CNS is that the BBB remains relatively impermeable to ART and thus ART can influence viral load in the peripheral system more so than in the CNS (Atluri et al., 2015), making treatment difficult. However, it is important to note that certain drug classes are more efficacious in penetrating the BBB than others (Nwogu et al., 2016; Osborne et al., 2020) and thus the optimal regimen administration is very important in CLHIV.

2.6.2.2 Adverse reactions to antiretroviral therapy

Although ART is generally well tolerated, there may be adverse drug reactions. These often occur in the first few weeks of initiating ART and are often mild (Meintjes et al., 2017). Some of the more significant adverse events that may be experienced are: peripheral neuropathy, hepatotoxicity, hyperlactataemia and lactic acidosis, dyslipidaemia and lipodystrophy, hypersensitivity and nephrotoxicity, neuropsychiatric toxicity, dysglycaemia and gynaecomastia (Meintjes et al., 2017; Peters et al., 2014). Adverse reactions can cause non-adherence to ART which in turn can lead to drug resistance (Klimas, Koneru and Fletcher, 2008). Drug resistance comes about due to the ability of the HI virus to adapt and change, i.e. mutate, and leads to decreased efficacy of the drug (Klimas, Koneru and Fletcher, 2008). In addition to adverse reactions, ART adherence can be influenced by the functional impairments of disability, morbidity, mental health challenges, stigma, poor healthcare access and a lack of support structures (Carpenter, Hanass-Hancock and Myezwa, 2020; Chirambo et al., 2019; Lai et al., 2021; Neupane, Dhungana and Ghimire, 2019; Pokhrel et al., 2019)

As discussed in section 2.6.2.1, the impenetrability of the BBB to ART creates a reservoir of the HI virus in the CNS (Bertrand, Velichkovska and Toborek, 2021), often leading the presentation of HAND/HIVE. However, it is not only the virus that is neurotoxic but also ART that has been shown to potentially cause CNS side-effects (Bertrand, Velichkovska and Toborek, 2021; Meeker, Asahchop and Power, 2014; Shah et al., 2016), with presentations such as dizziness, suicidal ideation, impaired neuropsychological performance, sleep disturbances and headache (Meeker, Asahchop and Power, 2014).

2.6.2.3 Antiretroviral therapy in adolescents

South Africa started its ART rollout in 2004 (Evans, 2013) and is now the country with the largest ART programme worldwide (Hodes et al., 2020). Over the years, ART initiation guidelines have shifted from eligibility criteria of CD4 count <200 cell/mm^3 to all people living with HIV qualifying for ART as of 2016 (Osler et al., 2018). Despite this, the adolescent population carries a disproportionate burden of HIV and rollout is not having maximum effect, where many adolescents still have high rates of virologic failure on ART, drug resistance and a high mortality rate (Anderson, Muloiwa and

Davies, 2020; Fairlie et al., 2014; Hodes et al., 2020). This is due to the substantial challenges with drug adherence in the adolescent population (Cluver et al., 2016; Fairlie et al., 2014; Hodes et al., 2020), which is a challenge regardless of a country being resource-rich or resource-limited (Agwu and Fairlie, 2013).

Non-adherence is the greatest barrier in achieving successful HIV management (Agwu and Fairlie, 2013) and is a multifactorial issue in adolescence. In addition to the reasons for non-adherence previously discussed, adolescents specifically face issues such as parents not disclosing the child's status to them, substance abuse, managing ART schedules in school and extra-mural times, fear of stigma from peers (Fairlie et al., 2014), and the general risk-taking, feeling-of-invincibility characteristics of adolescence (Agwu and Fairlie, 2013).

Adolescents with perinatal HIV also face unique challenges in terms of their diagnosis and ART management. Despite the progressive upscale of PMTCT programmes, there are still a considerable number of children that go undiagnosed for many years and only enter care later on in life, presenting with significant morbidity (Agwu and Fairlie, 2013). Conversely, the CLHIV who start ART early in life may be on their second or third line ART by the time they reach adolescence (Fairlie et al., 2014) which brings its own problems in terms of potential drug resistance and virologic failure.

Adolescents require specific ART dosage as they intersect between the paediatric and adult guidelines. The physiological changes associated with puberty can affect pharmacokinetics, thus post-puberty adolescents can be dosed according to adult guidelines but early-puberty adolescent management should follow the paediatric guidelines (Agwu and Fairlie, 2013). Side-effects of ART should be carefully monitored, with special attention on gynaecomastia, bone and renal toxicity, and lipodystrophy (Agwu and Fairlie, 2013; Fairlie et al., 2014), as these present unique challenges in puberty and adolescence.

2.6.3 Impact of perinatal HIV on child development

In the absence of PMTCT, approximately 15% to 30% of babies of HIV-positive mothers will contract HIV during pregnancy or birth, and an additional 5% to 20% will contract HIV from breastfeeding (Le Doare, Bland and Newell, 2012; Nielsen-Saines et al., 2019). Perinatal HIV has a faster disease progression than in adults (even more

so for infants infected *in utero*) due to the immature immune system in children at the time of high viral load (Nielsen-Saines et al., 2019). Infection with HIV has long-standing, serious consequences for neurodevelopment (Nielsen-Saines et al., 2019). In terms of development, perinatal HIV results in HIVE and microcephaly, causing growth failure, developmental delay and a loss of developmental milestones (Le Doare, Bland and Newell, 2012; Nielsen-Saines et al., 2019). However, ART has been shown to be highly beneficial in reducing the incidence of encephalopathy (Patel et al., 2009). A cohort study of 2398 perinatally infected HIV-positive children from 1993 to 2006 found that the introduction of ART was associated with a 50% decrease in the incidence of HIVE versus non-use of ART, thus showing its efficacy (Patel et al., 2009).

Despite the efficacy of ART in decreasing HIVE there are still substantial neurocognitive and developmental sequelae in perinatal HIV to consider. Even with ART, mild to moderate cognitive delay is still a significant problem in CLHIV, even with viral suppression (Boivin, Ruisenor-Escudero and Familiar-Lopez, 2016). A South African study of CLHIV aged 3 to 5 years found that, despite majority viral suppression and normal growth, there was severe overall developmental delay in 56% of the study participants, with the most affected components being speech, cognition and perception (Potterton, Hilburn and Strehlau, 2016). Similarly, a study looking at the prevalence of disability in CLHIV (aged 2 to 9 years) in a clinic in South Africa found that 50.5% of the participants had a disability, of which 58.4% had more than one disability (Brassell and Potterton, 2019). These findings are comparable to a study done in a similar geographical area in which 51.9% of adults living with HIV had functional limitations (Myezwa et al., 2018). Other studies have echoed the findings of Brassell and Potterton (2019), showing that perinatal HIV causes considerable neurocognitive and development delay in CLHIV (Hutchings and Potterton, 2014; Le Doare, Bland and Newell, 2012; McHenry et al., 2019; Struyf et al., 2020).

Although early ART initiation and virologic suppression has better neurocognitive outcomes (Crowell and Malee, 2017), there are still implications from using a neurotoxic drug (i.e. ART) during a vital time of neural plasticity. One of the associations of ART usage is severe prematurity which in itself gives rise to developmental delay and neurocognitive sequelae (Le Doare, Bland and Newell, 2012). Not only can ART have potential neurotoxic effects on a foetus, but other HIV-related mechanisms in an HIV-positive mother need to be considered, such as the

exposure to the HI virus itself; effects of maternal inflammation on the uterine environment; and immune activation/inflammation within the foetus (Wedderburn et al., 2019).

The impact of ART is also seen in HIV-negative children who have been exposed to HIV *in utero* (Wedderburn et al., 2019). Although there is some conflicting literature, the majority of studies point towards HEU children still facing unfavourable growth and development sequelae despite their negative status (Wedderburn et al., 2019). A recent meta-analysis of 11 studies found that HEU children had worse developmental outcomes, with lower cognitive and motor scores compared to their HUU peers (McHenry et al., 2018). The study does, however, acknowledge that all of the high quality studies were based in the United States of America. Other African studies have established similar results, with le Roux et al. (2018) and Ntozini et al. (2020) finding significantly poorer outcomes in HEU compared to HUU children in South Africa and Zimbabwe, respectively. Furthermore, Moraleda et al. (2014) found that HEU children in Mozambique had significantly higher levels of anaemia, poor nutritional status and immunological dysfunction compared to HUU peers. Mortality levels (Wedderburn et al., 2019), infectious-cause hospitalisations (Anderson et al., 2021) and risk of acute diarrhoea and pneumonia (Brennan et al., 2019) are also higher in HEU children compared to HUU children.

2.7 HIV and adolescence

South Africa's population of adolescents with HIV is a combination of individuals with either vertical and horizontal transmission, with horizontal transmission occurring through sexual activity and intravenous drug use (Sohn and Hazra, 2013). With increased access to ART, the vertically-acquired HIV population of children have aged into a population living with a chronic disease and thus the prevalence of adolescents living with HIV has increased over the years (Anderson, Muloiwa and Davies, 2020; Fairlie et al., 2014; Mofenson and Cotton, 2013). The unique challenges and emerging needs for this distinctive population have been highlighted for over a decade (Koenig, Nesheim and Abramowitz, 2011) yet there are still many unknown aspects (Anderson, Muloiwa and Davies, 2020). One of the shortcomings within the available literature for this population is that most studies and data bases do not differentiate between participants with vertical or horizontal transmission (Anderson, Muloiwa and Davies, 2020; Laughton et al., 2013), nor do they disaggregate data by sex (Sohn and Hazra,

2013). This makes it difficult for one to discuss which sequelae are specific to PHIVA and which are more pertinent to adolescents who acquired HIV horizontally (i.e. behaviourally).

Another challenge within the literature on adolescents with HIV is that there is heterogeneity between studies on the age definition of adolescence (Laughton et al., 2013), with some studies presenting adolescent data from as young as eight years old and up to 24 years old. Research also differs between populations in terms of the duration of ART usage (Cruz and Cardoso, 2015; Laughton et al., 2013) and the varying cultural expectations for adolescence (for example, in some countries the focus of adolescence may be on school performance, while in other countries it may be on starting and/or caring for a family) (Laughton et al., 2013).

2.7.1 Perinatal HIV and adolescence

Section 2.6.2.3 addressed ART within the context of adolescence, with a specific concern around non-adherence and virologic failure in PHIVA (Anderson, Muloiwa and Davies, 2020; Fairlie et al., 2014; Hodes et al., 2020). Virologic failure is a problematic trend within this population, based on various factors: many of the adolescents initiated ART early in life and thus by adolescence they may be on their third line of treatment already, and depending on the era of their ART initiation they may have received sub-optimal regimens and/or a limited range of ART (Fairlie et al., 2014; Sohn and Hazra, 2013). Virologic failure can cause virus mutations, with a risk of the mutated virus being transmitted horizontally (Cruz and Cardoso, 2015) as many PHIVA enter the phase of sexual activity (Koenig, Nesheim and Abramowitz, 2011).

Lowenthal et al. (2014) reviewed the emerging challenges for PHIVA in SSA and highlighted that the difference one is likely to see in infectious diseases in adolescents with HIV (compared to young children and infants) is that they are more likely to present as young adults with HIV do i.e. with higher incidences of Cryptococcus and tuberculosis infections. They are also more prone to other vaccine-preventable diseases due to a lowered vaccine efficacy in combination with a now weakened immune system (Lowenthal et al., 2014). A recent South African study assessed the hospitalisation rates of PHIVA versus an HIV-negative group and found that the PHIVA group had significantly more hospitalisations over the study period (149

hospitalisations occurred in 17.7% of the PHIVA group compared to 10 hospitalisations in 6.4% of the HIV-negative group; p<0.01) (Frigati et al., 2020).

Another area of emerging concern for PHIVA health is chronic disease such as chronic lung disease, cardiac disease, growth failure and delayed puberty, neurocognitive impairment, renal disease, bone disease, mental health challenges and physical dysfunction (Cruz and Cardoso, 2015; Koenig, Nesheim and Abramowitz, 2011; Lowenthal et al., 2014). These impairments will be discussed further in sections 2.7.1.1 to 2.7.1.8, and additionally Chapter 4 will detail the physical sequelae of perinatal HIV.

2.7.1.1 Chronic lung disease

Chronic lung disease symptoms (such as cough, reduced exercise tolerance, hypoxia and dyspnoea) are prevalent in children and adolescents with perinatal HIV (Ferrand et al., 2012; Flynn and Abrams, 2019; Frigati et al., 2020; Githinji et al., 2018; Rylance et al., 2016), and even with good ART management and viral load suppression chronic lung disease continues to be a challenge (Rylance et al., 2016). Githinji et al. (2017) assessed 515 PHIVA in South Africa and compared their cardiopulmonary function to 110 age- and ethnicity-matched HIV-negative adolescents. Despite being well-controlled on ART, the PHIVA group had significantly lower lung functioning than their HIV-negative peers, and previous lower respiratory tract or pulmonary tuberculosis infection were associated with reduced lung function (Githinji et al., 2017). An additional study as a longitudinal follow-up over two years of PHIVA found that while their lung function did not catch up to the HIV-negative comparison group, it did not deteriorate i.e. their lung growth was preserved (Githinji et al., 2020). The authors note that this cohort was well controlled and had close follow-up over the two years which can explain the positive findings of minimal lung function deterioration. The authors also propose that damage to the PHIVA's lungs may have occurred early in life as the mean ART initiation age was four years thus uncontrolled HIV infection prior to this may have resulted in lung dysfunction (Githinji et al., 2020). This highlights the long-term impact that perinatal HIV has and the importance of early ART initiation to optimise lung function (Githinji and Zar, 2021).

A review of the literature on lung function in CLHIV and PHIVA found that the predominant impairments were irreversible lower airway obstruction, reduced exercise tolerance and reduced diffusion capacity (Githinji, Gray and Zar, 2018). Potential

causes for lung dysfunction in PHIVA include damage to the airway epithelium from the virus and/or from opportunistic infections; chronic inflammation that is commonly associated with HIV; airway diseases such as bronchiectasis or obliterative bronchiolitis; lymphoid interstitial pneumonitis; tuberculosis and chronic aspiration pneumonia (Desai et al., 2018; Flynn and Abrams, 2019; Githinji, Gray and Zar, 2018; Weber, Gie and Cotton, 2013). Low-income countries often lack the diagnostic equipment (for example, high resolution computerised tomography or spirometry) needed for chronic lung disease diagnosis and management, and thus PHIVA with chronic lung disease may often be misdiagnosed and mismanaged with repeated antibiotics or tuberculosis medication (Frigati et al., 2020). Additionally, chronic lung disease in PHIVA lacks specific management guidelines (Frigati et al., 2020) and thus PHIVA can potentially be further mismanaged. Recommendations for the prevention of respiratory complications are to ensure early ART initiation; optimal nutrition; full childhood immunisation; prevent tobacco smoke and pollution exposure; chemoprophylaxis (i.e. prophylactic medication for pneumonia and tuberculosis, to name a few); and optimal maternal health (Githinji and Zar, 2021).

2.7.1.2 Cardiac disease

Acquired heart disease (particularly atherosclerosis, heart failure and pulmonary arterial hypertension) is primarily caused by HIV, especially over a long-term period (Lipshultz et al., 2013) thus cardiac disease is an area of concern with PHIVA (Flynn and Abrams, 2019; Lowenthal et al., 2014). However, with CLHIV who are well-managed with ART, the risk of symptomatic cardiac disease decreases substantially as there is suggestive evidence about the cardioprotective effects of ART (Lipshultz et al., 2017; Sainz et al., 2015), however PHIVA may still be susceptible to subclinical cardiac complications (Dirajlal-Fargo et al., 2017). An example of markers of subclinical complications are carotid intima-medial thickening (Dirajlal-Fargo et al., 2017) which has been shown to be significantly increased in PHIVA specifically on protease-inhibitor ART regimens compared to HIV-negative peers (Chanthong et al., 2014). Sainz et al. (2015) also found significantly increased intima-medial thickening in their group of PHIVA compared to the HIV-negative group.

A study with Zimbabwean children and adolescents established on ART found echocardiac abnormalities in 42% of the sample, with left ventricular hypertrophy and left ventricular diastolic dysfunction being the most common impairment (11% and

23%, respectively). The study population were all perinatally infected (with the exception of one participant) and 78% had a viral load less than 400cells/mm^3 (Majonga et al., 2018). Similarly, a recent cross-sectional study of perinatally infected children and young adults (up to the age of 25 years) in Kenya found that 27.7% of the participants demonstrated echocardiographic evidence of early cardiac dysfunction and this was associated with increased levels of systemic inflammation (McCrary et al., 2020). Githinji et al. (2019) assessed cardiopulmonary dysfunction in South African PHIVA and found that more PHIVA (13%) presented with cardiopulmonary dysfunction compared to the HIV-negative group (8%), however the differences did not reach statistical significance (p=0.136). It should be noted that it could not be established if the HIV-negative comparison group were HEU and there are no known validated local African reference values for a true comparison. Additionally, the PHIVA cohort were all on ART and overall had good virologic suppression. An important finding from the study was that there were significantly higher levels of small airway disease markers in the PHIVA group, which is consistent with other study findings (Githinji et al., 2019).

Cardiac dysfunction should not be viewed as an isolated sequelae of perinatal HIV. A recent study in South Africa found that PHIVA face multisystem impairments: over 86.7% of the participants who had cardiac impairments had additional system impairments (for example, neurocognitive or respiratory impairments) (Frigati et al., 2019). This highlights the necessity of thorough cardiac evaluation and monitoring in PHIVA management (Lipshultz et al., 2013; Sainz et al., 2015).

2.7.1.3 Growth failure and delayed puberty

Chapter 4 expands on the physical sequelae in PHIVA via a scoping review, however, this section will still give a brief overview of the growth and puberty effects of perinatal HIV.

A recent systematic review and meta-analysis assessed the aerobic capacity, muscle strength and body composition of adolescents with HIV compared to HIV-negative adolescents. They found that the adolescents with HIV had a significantly lower BMI, as well as impaired aerobic capacity and muscle strength but they acknowledge that the findings are not strong since there are limited studies available and only small sample sizes (da Silva Cunha de Medeiros et al., 2021). Nonetheless, this study still highlights the importance of evaluating the physical sequelae of perinatal HIV.

It is well established that perinatal HIV impacts negatively on birth weight and development (Strehlau, van Aswegen and Potterton, 2019; Whitehead, Potterton and Coovadia, 2014), resulting in slow gains which carries over into adolescence (Cruz and Cardoso, 2015). The later that ART is initiated in CLHIV, the poorer the growth outcomes (Jesson et al., 2019). Jesson et al. (2019) analysed stunting and growth data from 8737 PHIVA. Their findings showed that at age 10 39% of female PHIVA and 34% of males were stunted. Despite the higher prevalence of stunting in females, their growth over time was better than the males, with more males than females being stunted at 15 and 18 years old (Jesson et al., 2019). A review of the long-term growth outcomes in PHIVA presented global data stratified by income status as well as findings specific to South Africa (Anderson, Muloiwa and Davies, 2020). All of the lower to middle income country studies found that despite improvement over time in the PHIVA height-for-age scores, the participants consistently remained at least one standard deviation below the normal height. Even with the high prevalence of stunting, BMI fell in the normal ranges and is thus it is proposed that BMI is less severely affected (Anderson, Muloiwa and Davies, 2020). Since BMI is a ratio calculation of height and weight, it is important to consider weight even when BMI appears to be unaffected. Wasting is still problematic in PHIVA, with many studies showing that PHIVA are at risk of wasting (Ferrand et al., 2012; Miller et al., 2013) or have significantly lower weight than HIV-negative comparison groups (Arbeitman et al., 2014; Martins et al., 2017).

Stunting in childhood can lead to late pubertal development (Williams and Jesson, 2018) and PHIVA are at risk of pubertal delay (Cruz and Cardoso, 2015; Ferrand et al., 2012; Iloh et al., 2017; Vreeman et al., 2015). Bellavia et al. (2018) assessed the onset of puberty in 2539 PHIVA and HEU adolescents and found that the PHIVA reached puberty on average six months later than the HEU peers, with height *z*-scores mediating the effect of HIV infection on sexual maturity (Bellavia et al., 2017).

2.7.1.4 Neurocognitive impairment

Neurocognitive impairment is a prevalent and significant sequelae of perinatal HIV in adolescence (Flynn and Abrams, 2019; Frigati et al., 2020; Laughton et al., 2013). The HI virus causes accelerated epigenetic aging in PHIVA (Horvath et al., 2018), which results in altered brain structures such as brain volume, cortical thickness, cortical

surface area, decreased gyrification and neuronal microstructures (Hoare et al., 2021; Hoare et al., 2018). Furthermore epigenetic ageing in PHIVA is negatively correlated with measures of cognitive function such as working memory, executive function and processing speed (Horvath et al., 2018). A meta-analysis determined that executive functioning and working memory are the most commonly affected domains by perinatal HIV (Phillips et al., 2016). The meta-analysis included children from six to 18 years and thus the findings were not specific to only PHIVA. Other studies have established that PHIVA experience significantly greater impairments in cognitive and achievement scores, intelligence, visual recognition memory and executive functioning compared to their HIV-negative peers (Garvie et al., 2014; Hoare et al., 2018; Laughton et al., 2013; Nichols et al., 2016; Van den Hof et al., 2019), and that a CD4%<25 is associated with poorer verbal learning (Nichols et al., 2016).

The degree of cognitive impairment is strongly correlated with functional impairment (e.g. school work; interpersonal relationships; repeating a grade) (Phillips et al., 2021) and PHIVA have been shown to struggle with academic performance. A recent systematic review and meta-analysis of data from perinatally infected children aged four to 18 years showed that CLHIV and PHIVA have greater challenges with school performance then their HIV-negative and HEU peers, with the most noteworthy variances being with regards to reading and mathematical performance scores, usage of special education services, and general learning challenges (van Opstal et al., 2021). It is important to note that this systematic review only included studies specifically from high income countries, and even with good access to resources PHIVA struggled with school performance thus making school performance for PHIVA in low- to middle-income countries with fewer resources an even greater concern. In addition to the impact of neurocognitive impairment on school performance, PHIVA are also five times more likely than their HIV-negative peers to face a period of school disruption (i.e. a delay of one or more year of school for the expected age per grade; or dropout from school; or non-formal schooling), with neurocognitive difficulties and growth delay significantly associated with school disruption (Merville et al., 2021). Frigati et al. (2019) assessed the prevalence of multisystem impairments in South African PHIVA and reported that PHIVA who had repeated a year of school were significantly more likely to a dual or multisystem impairment (such as renal, cardiac, respiratory etc. impairments) and of those who had a neurocognitive impairment, nearly 60% had additional system impairments (Frigati et al., 2019).

The neurocognitive impairments experienced by PHIVA do not appear to resolve over time. Studies involving older PHIVA and young adults with perinatal HIV have found significant neurocognitive impairment compared to HIV-negative counterparts (Abrams et al., 2018; Ene et al., 2014; García-Navarro et al., 2020; Willen et al., 2017). Willen et al. (2017) assessed perinatally infected 18 to 24 year olds with a neuropsychological assessment battery. The study compared the outcomes to HIV-negative young adults and found that the HIV-positive participants scored significantly lower in attention/working memory, letter-number sequencing, set-shifting (i.e. task switching) and motor speed (Willen et al., 2017). With the high risk of poor academic performance in PHIVA, it is imperative to have regular school monitoring for the population (van Opstal et al., 2021), and a simple question such as if a child has repeated a grade serves as a red flag for further investigation of neurocognitive impairment (Phillips et al., 2021).

The use of ART has positive outcomes for PHIVA and neurocognitive dysfunction. The earlier it is initiated, and the longer an individual is using ART, the better their performance in memory and executive function scores (García-Navarro et al., 2020; Van den Hof et al., 2019). Hoare et al. (2015) investigated the white matter micro-structural changes and the role of ART in CLHIV in South Africa. Their findings show that those on ART had significantly less myelin loss compared to those who were ART-naïve, however, they still had significant axonal damage in the corpus callosum, highlighting that ART can reduce CNS inflammation and myelin loss but it is unable to reverse any axonal damage that may have already occurred, reiterating the importance of early ART initiation (Hoare et al., 2015).

2.7.1.5 Renal disease

Kidney disease in CLHIV is a prevalent condition, with manifestations such as HIV-associated nephropathy, HIV immune complex kidney disease, thrombotic microangiopathy, vasculitis, interstitial nephritis and nephrotoxicity of ART (Jindal, Tiewsoh and Pilania, 2018). The virus itself can be damaging to the renal structures, but other causes of renal disease in HIV can be due to opportunistic infections, immune dysregulation, host genetics or from ART toxicity (Flynn and Abrams, 2019; Jindal, Tiewsoh and Pilania, 2018).

The increasing availability of ART has led to a decrease in HIV associated nephropathy (Frigati et al., 2019) however it is still an area of concern for PHIVA. A study of 255 PHIVA found that 14.1% of the participants had persistent renal dysfunction (Bunupuradah et al., 2018) while Drak et al. (2021) found that baseline renal function predicted mortality rates in ART-naïve adolescents with HIV (Drak et al., 2021), highlighting the importance of regular renal function assessments.

2.7.1.6 Bone disease

Decreased bone mineral density and bone quality in CLHIV is a prevalent HIV complication (Arpadi et al., 2019; Gregson et al., 2019; Jacobson et al., 2020; Mahtab et al., 2020; Puthanakit and Siberry, 2013). A two year follow up of CLHIV in South Africa showed that they persistently have significantly lower bone mass, bone turnover and macrophage activation compared to HIV-negative peers (Shen et al., 2021). Furthermore, a study found that CLHIV under 6 years old had significantly more fractures than HEU children (but by adolescence the number of fractures were not significantly different) (Jacobson et al., 2020).

Rukuni et al. (2021) assessed bone mineral content and density in adolescents with HIV (98% of the sample had perinatal HIV) and without HIV in Zimbabwe. The authors found significantly lower *z*-scores for the outcomes in the HIV-positive group, despite ART usage, with negative associations between HIV and bone density becoming more pronounced with pubertal maturation (Rukuni et al., 2021). These skeletal deficit findings are similar to other studies on bone health in PHIVA (Mahtab et al., 2020; Schtscherbyna et al., 2012). Puberty is an important phase of bone mass development and forms a critical period in which sufficient bone mineral is acquired to form adult bone mass, without which an individual has greater risk of bone fragility and osteoporosis in later life (Cruz and Cardoso, 2015; Flynn and Abrams, 2019; Sudjaritruk and Puthanakit, 2015). Stunting and delayed puberty in PHIVA (which has already been discussed as a prevalent problem for this population) affects bone mineral accrual and maturation, and thus adult bone health (Rukuni et al., 2021; Williams and Jesson, 2018). Other factors that affect bone mineral density in PHIVA are decreased physical activity, lower socio-economic status and malnutrition, decreased calcium and vitamin D intake, the action of the HI virus itself on osteoclasts, chronic systemic inflammation and exposure to the common ART medication, tenofovir disoproxil fumarate (Frigati et al., 2020; Mahtab et al., 2020; Rukuni et al., 2021;

Sudjaritruk and Puthanakit, 2015). Additionally, the age of ART initiation predicts bone mineral density, with an older age of initiation resulting in lower bone mineral density (Gregson et al., 2019).

The prevalence of bone health complications in PHIVA, and the serious consequence for adulthood thereafter, highlights the importance of routine measurement of bone mineral density in PHIVA (Mahtab et al., 2020). To ensure PHIVA have optimum health as they enter adulthood healthcare systems need to develop strategies to address the long-term complications (Rukuni et al., 2021) and regular basic health messages (frequent exercise, calcium intake etc.) should form part of standard patient management (Sudjaritruk and Puthanakit, 2015). A study of 219 CLHIV in South Africa found that switching ART regimens from ritonavir-boosted lopinavir to efavirenz was associated with increased accrued bone mass (Arpadi et al., 2016), thus careful consideration needs to be paid to CLHIV ART regimens to optimise bone health in adolescence and adulthood.

2.7.1.7 Mental health challenges

An extensively researched area of perinatal HIV is mental health (Flynn and Abrams, 2019) and PHIVA have been shown to be at particular risk for depression, suicidal ideation, anxiety, anger and disruptive behaviour, and attention deficit hyperactivity disorder (Dessauvagie et al., 2020; Hoare et al., 2019; West et al., 2019). A recent systematic review of adolescents with HIV in SSA reported that a prevalence of 24% to 27% of adolescents experience psychiatric problems and 30% to 50% experience behavioural or emotional difficulties or significant psychological distress (Dessauvagie et al., 2020). Although this systematic review did not specify data for perinatally-acquired HIV it still provides valuable information about the high prevalence of mental health challenges in this vulnerable population.

Poor mental health impacts negatively on ART adherence and QOL but is frequently given little attention (Frigati et al., 2020). Being on ART is associated with four times more likely to have better mental health, while other associations with better mental health in PHIVA are having a secondary or tertiary education, and having future child-bearing intentions (Mbalinda et al., 2015). Stunting in PHIVA can also negatively affect depression, self-esteem and stigma (Williams and Jesson, 2018). Risk factors of depression and suicidal ideation in PHIVA are the diagnosis itself, and repeating a

grade at school or school exclusion (Buckley et al., 2020; Dessauvagie et al., 2020; Le Prevost et al., 2018), the latter of which is particularly pertinent since PHIVA are five times more likely to have a period of school disruption compared to HIV-negative adolescents (Merville et al., 2021). Conversely, a study in South Africa of adolescents with HIV (92% of the sample were PHIVA) showed that there was less likelihood of having mental health problems for those adolescents who had high measures of social support (West et al., 2019), which was supported by the findings of the previously discussed literature review by Dessauvagie et al. (2020).

Not only is it important to pay attention to social support structures when managing the mental health of PHIVA (West et al., 2019), but other recommendations for care and services include services incorporating family interventions, regular screening for mental health problems, addressing stigma, and integrating mental health and ART services for adolescents (Bhana et al., 2016; Dessauvagie et al., 2020; Hoare et al., 2019; Vreeman et al., 2015).

2.7.1.8 Physical functioning

The final cluster of impairments to address in adolescence and perinatal HIV pertains to physical functioning. The details of this warranted a thorough analysis of the literature and thus Chapter 4 presents a scoping review of the physical sequelae in PHIVA. However, in summary, PHIVA experience impairments in physical activity, physical functioning and exercise tolerance.

Martins et al. (2017) assessed the physical activity levels of PHIVA compared to HIV-negative peers and found that the PHIVA presented with overall lower physical activity ($p<0.001$). These findings are similar to that of a study done with South African CLHIV which found that the HIV-positive participants attended less physical education ($p=0.0003$) and after school sport ($p<0.0001$) than their HIV-negative peers. These low levels of physical activity are most likely to be an indication of the high prevalence of cardiac dysfunction found in PHIVA (Miller et al., 2013) and the decreased exercise tolerance that they experience (Ferrand et al., 2012). When PHIVA are on ART they are twice as likely to have better physical function compared to those who are not on ART (Mbalinda et al., 2015), re-emphasising the need for early diagnosis and ART initiation.

Lastly, fatigue is an important impairment to be considered in PHIVA. Fatigue is not well explored in CLHIV but it is a common complaint in adults living with HIV (Potterton, 2016) and has been shown to affect adolescents with HIV, impacting on schooling, social interactions and participation (Loades et al., 2018). A recent study from the Netherlands showed that fatigue in PHIVA negatively impacts on their HRQOL, however the study had a small sample size (14 participants) and is an indication of the need for further research in fatigue levels of PHIVA.

2.7.1.9 A summary of perinatal HIV and adolescence

Section 2.7.1 reviewed the impact of perinatal HIV on adolescence. The ICF is frequently used as a tool for discussing disability (Kostajsek, 2011) and, based on this, Table 2.2 lists a summary of the impairments, activity limitations and participation restrictions experienced by PHIVA, as detailed in section 2.7.1.

Table 2.2 Impairments, activity limitations and participation restrictions in PHIVA

Impairments	**Activity limitations**	**Participation restrictions**
Chronic lung disease	Decreased exercise tolerance	Poor drug adherence
Cardiac disease	Poor academic performance	School under-achievement
Growth failure	Decreased physical activity and functioning	Poor interpersonal relationships
Delayed puberty	Poor decision-making	Decreased quality of life
Neurocognitive dysfunction	Risk of fractures	Poor sport participation
Renal disease	Reduced activities of daily living	Reduced school and social engagement
Bone disease		
Mental health challenges		
Fatigue		

2.8 HIV care in adolescence

2.8.1 Challenges with HIV care in adolescence

There are two important concepts to consider when addressing adolescent HIV care: disclosure of the adolescent's HIV status to them and transitioning from paediatric HIV care to adult HIV care. Despite the growing rate of the PHIVA population, many clinics and healthcare systems are not well equipped, nor staff trained, to deal with this unique population (Anderson, Muloiwa and Davies, 2020). Mark et al. (2017) did a situational analysis of 218 healthcare facilities across 23 SSA countries to determine the HIV treatment and care services for adolescents. Key findings of the study were: 26% of the facilities did not have a working definition of adolescence; 39% did not have adequate policies to define and manage non-adherence; 66% of the facilities managed adolescents within paediatric or adult services, not an individual service; and 49% did not have protocols for transition to adult care (Mark et al., 2017). This highlights the service gaps and necessity for improved HIV care for adolescents.

Issues around disclosure is one of the factors that affect ART adherence in an already poorly-adherent population (Anderson, Muloiwa and Davies, 2020; Fairlie et al., 2014). Frequently PHIVA are not aware of their HIV status (both in high- and low-resource settings) (Mofenson and Cotton, 2013) and in this critical life phase where autonomy is valued it is important to equip the adolescent with knowledge about their status and health (Fairlie et al., 2014). The WHO recommend that a child has had full status disclosure by the time they are 12 years old, but this process is a phased process instead of an isolated event (World Health Organization, 2011). Disclosure prior to the age of 12 is associated with higher ART adherence in PHIVA (Cluver et al., 2015) but despite its value, early disclosure is not always done. A recent review highlighted that disclosure to PHIVA in SSA occurs at a late age (median of 13 years) and is impacted by challenges such as caregiver fear, stigma and guilt, as well as healthcare worker barriers such as a lack of training, poor team communication or excess workload (Dahourou et al., 2017).

Early disclosure has been shown to be a factor in facilitating engagement in care in PHIVA and thus impacting on their successful transition to adult care (Zanoni et al., 2021a). The age of transition varies globally: the United States transition their PHIVA around 18 to 25 years, meanwhile in South Africa it occurs more commonly between 10 and 14 years (Flynn and Abrams, 2019). Transition to adult care is a time in

healthcare where many PHIVA have decreased adherence and/or loss to follow up, with 10 to 25% of youth dropping out of care (Flynn and Abrams, 2019) and an increased risk of mortality (Berzosa Sánchez et al., 2021; Buchholz and Niehues, 2020). Many individuals feel a sense of abandonment as they leave the familiar support structures behind and move to a phase of independent health management in an adult setting (Mofenson and Cotton, 2013), while other barriers to successful transition in South African PHIVA are a loss of clinic relationships with staff and peers, as well as rigid clinic schedules that do not allow for flexibility around school commitments (Zanoni et al., 2021b). Mental health is a critical component to consider when PHIVA transition to adult healthcare (Vreeman et al., 2015), and this phase may cause a substantial increase in anxiety (Fairlie et al., 2014). Due to the complexities of all of the sequelae of perinatal HIV (as discussed in this literature review) it is imperative that clinicians working in adult HIV clinics are aware of the impairments that PHIVA face as they reach adulthood (Fairlie et al., 2014).

2.8.2 Models of care in HIV

A MoC is a framework upon which healthcare provision for a condition can be provided to a population, ensuring that the healthcare workers involved are working collectively and viewing the patient through the same lens (Davidson et al., 2006). A MoC in HIV is not “one size fits all” and differentiated care needs to be considered (Reif et al., 2018; Roy et al., 2019). While the necessity of specific healthcare systems for PHIVA has been addressed in the literature (Lowenthal et al., 2014), many systems are still not prepared for the individual needs of this population (Anderson, Muloiwa and Davies, 2020; Mark et al., 2017). A review of the MoCs for adolescents with HIV in Africa addressed adherence and transition to adult care (Dahourou et al., 2017), and a MoC has been proposed for the rehabilitation of adults living with HIV (Chetty, 2014), but MoCs specific to perinatal HIV and the physical sequelae thereof are lacking. Even without focusing on PHIVA specifically, there is a lack of models that address integrated rehabilitation for CLHIV (Chetty et al., 2018) .

For CLHIV, schooling, social interactions and home life is affected by HIV and thus MoCs need to address interventions at both a school and family level (Chetty et al., 2018). A recent study by Maddocks, Perumal and Chetty (2020) explored healthcare workers’ and educators’ perceptions on schooling for CLHIV in a semi-rural South African setting. One of the dominant themes from their study was the influence of HIV

on school readiness and progression, with a particular challenge around delayed screening of disabilities in CLHIV (Maddocks, Perumal and Chetty, 2020), highlighting the necessity of a MoC that addresses disability screening in CLHIV. This is also emphasised in a study by Maddocks, Mthethwa and Chetty (2020) who recommend that disability screening would assist with early identification and referral for CLHIV experiencing disability. Poor access to rehabilitation services for CLHIV creates a challenge for the caregivers of the children resulting in increased caregiver burden (Maddocks et al., 2020).

In Lowenthal et al.'s (2014) review of the emerging challenges for PHIVA suggestions are given for healthcare programmes for this population: to integrate the clinical care with other services (such as reproductive health, psychosocial and mental health, educational services, social services, screening for chronic complications). The role of the multidisciplinary team (MDT), rather than only the medical doctor, for MoCs in PHIVA is ideal (Cruz and Cardoso, 2015; Fairlie et al., 2014) and the role of the family in supporting the PHIVA is emphasized (Cruz and Cardoso, 2015). A recent study in South African CLHIV attending an urban clinic found that only 46% of the participants with disability were referred to the necessary MDT member (Brassell and Potterton, 2019), highlighting the need for a MoC that involves the MDT.

2.9 Conclusion

This chapter reviewed the available literature on HIV and adolescence, starting with pertinent definitions and epidemiological information. The review discussed the pathophysiology of HIV and the relevant information on ART, followed by the impact of perinatal HIV on child development. An overview of adolescence was given, with a discussion on the effects of perinatal HIV on this phase of development. Finally, literature on the healthcare of PHIVA was presented. This chapter has highlighted the prevalence and importance of addressing the unique healthcare needs of PHIVA. The following chapter will present the study protocol that was proposed to address some of these needs.

Chapter 3 Study Protocol

3.1 Publication details

This chapter is presented as a publication of the study protocol, which proposes the three phases of a mixed-methods study. The article gives a brief overview of the physical sequelae that PHIVA face, followed by a description of the phases involved in developing a MoC for this population. The protocol was published with *BMC Research Notes*, an open-access journal that publishes scientific research protocols. Information about the publication is presented in Table 3.1.

Table 3.1 Publication specifics of the study protocol

Title of publication	The physical sequelae of perinatally acquired HIV in adolescents: a research proposal
Authors	Nicolette Comley-White; Joanne Potterton; Veronica Ntsiea
Journal name	*BMC Research Notes*
ISSN	1756-0500
Impact factor	1.66
Year	2019
Volume	12
DOI number	10.1186/s13104-019-4079-5

3.2 Author contributions

The authors' contributions are described in Table 3.2 using the terminology laid out by Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019) and the definitions of the terms are in Appendix 1.

Table 3.2 Author contributions for the study protocol

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Funding acquisition	√	√	√

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3.4 Associated documentation

The documentation associated with this study was not able to be attached as appendices to the publication but are included in this thesis as appendices per the following:

- Appendix 2: Ethical clearance certificate
- Appendix 3: Letter of permission from hospital
- Appendix 4: Letter of permission from research site

3.5 Published article: The physical sequelae of perinatally acquired HIV in adolescents: a research proposal

BMC Research Notes

RESEARCH NOTE

Open Access

The physical sequelae of perinatally acquired HIV in adolescents: a research proposal

Nicolette Comley-White*, Joanne Potterton and Veronica Ntsiea

Abstract

Objectives: As the global access of antiretrovirals for HIV-infected infants improves, so the body of perinatally HIV-infected adolescents (PHIVA) grows. The neurological and physical complications of HIV, both in children and in adults, are well established, however there is a paucity of data pertaining to PHIVA, a group of people who have had a lifetime exposure to the virus and to antiretrovirals. There has been a resounding call for further research in this area, as well as for the development of policies and programmes for this population. The aim of this study is to determine the physical sequelae in PHIVA and to propose a model of care for this population.

Methods: Through interviews with PHIVA, the perceived physical challenges will be established. Thereafter a cohort study with age-matched participants will determine if PHIVA have any limitations in fatigue, endurance, motor function and muscle strength, body mass index, peripheral neuropathy, level of disability and quality of life. Using these results, a model of care will be proposed through the nominal group technique with both PHIVA and clinicians working in HIV and adolescence.

Keywords: HIV, Perinatally infected, Adolescents, Physical

Introduction

Current data shows that AIDS-related deaths have declined by 48% from 2005 to 2016 [1], however the human immunodeficiency virus (HIV) remains the second leading cause of death in adolescence globally [2] and the leading cause in Africa [3]. The global scale-up of antiretroviral therapy (ART) in the management of HIV has shifted the paediatric HIV pandemic to chronic disease management, with a growing body of perinatally HIV-infected adolescents (PHIVA) [4]. In 2016 there were an estimated 2.1 million adolescents aged 10–19 years living with HIV, with 84% living in sub-Saharan Africa [3] and although perinatal HIV transmission forms the majority of infection route, the specific number of PHIVA is unknown [4].

While the paediatric brain has strong neural plasticity, it also has a degree of neural vulnerability where adverse environmental factors can impact on normal development [5, 6]. One of these adverse factors can be the HI virus, which is able to cross the blood brain barrier and infiltrate the central nervous system causing neurocognitive impairment [7]. Even with the early use of ART many children with HIV still present with neurodevelopmental problems due to neuroinflammation, vascular dysfunction and hypercoagulability [8]. In addition to damage done to the developing nervous system by the HI virus, the long term use of ART needs to be considered. Hepatotoxicity, mitochondrial toxicity, skin toxicity, hypersensitivity and lipodystrophy are some well-known adverse effects of ART [9, 10]. Depending on the class of drug and the individual, a variety of neurotoxic adverse effects exist from ART, including mania, psychosis, insomnia, irritability, vivid dreams [11].

Some of the established challenges that children and adults with HIV face are peripheral neuropathy, fatigue, decreased endurance and muscle strength, motor function impairments and body mass index changes [12–21]. Concerning these challenges, there is little data available on what PHIVA face.

With the advent of ART and its increased availability to perinatally infected HIV positive children, there is

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a growing number of adolescents living with HIV and ART use since birth, facing a lifetime of chronic illness management [22–25], the consequences of which are still being established [4]. Overall, there is a lack of data available for the challenges that PHIVA face [26]. Of the studies that have been done on neurodevelopment in PHIVA, the majority are from resource-rich countries, and not from resource-scarce countries (where PHIVA are more likely to face running a child-headed household; have poorer access to health care; face poverty, deprivation and opportunistic infections [26]), where there is the highest prevalence of PHIVA [26].

The literature has identified a clear need for further research to be done in the area of neurodevelopment in PHIVA (especially in resource-scarce countries), as well as for the urgent development of policies and programmes to cater for PHIVA [26–28]. Although models of care for different areas of managing HIV are available [29–32] to date there is no literature presented on suggested models of care for PHIVA. Furthermore, since the challenges that PHIVA face is a relatively new area of concern, any existing models of care may well not be sufficiently responsive to this population, as is often the case with existing models of care based on historical information [33].

The aim of this study is, over three phases, to determine what the perceived challenges are that PHIVA face due to physical sequelae of HIV; to then establish these challenges clinically; and lastly to propose a model of care for PHIVA. This manuscript will provide the outline of the research proposal used to meet the study's intentions.

Main text

The study is designed as a mixed methods study over three phases. In the first phase qualitative information will be gathered through semi-structured individual interviews. The second phase is designed as a cohort study with a comparison group of age-matched participants. In the third phase, a model of care for PHIVA will be proposed and consensus will be obtained through the nominal group technique.

Subject selection

Adolescence is defined as ages 10–19 years [2, 34], with early (10–15 years), middle (14–17 years) and late (16–19 years) stages [35]. For the purposes of this study, early and middle phases of 10–14 years and 15–17 years respectively will be used (late phase adolescents will not be included due to the age limitations of the outcome measures). Participants will be recruited from an existing cohort of PHIVA involved in a clinical trial looking at the chronic effects of growing up with HIV: the childhood HAART alterations in normal growth, genes and aGing evaluation study (CHANGES) (M120871). To date CHANGES has approximately 255 PHIVA (aged 10 and above) attending a clinic every 6 months, as well as a data base of HIV negative adolescents, providing the ideal source of participants for this study. The CHANGES trial is based at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg, South Africa. Data routinely collected for CHANGES includes (but is not limited to) the participant's body mass index, quality of life scores, clinical data (such as viral load, CD4 count etcetera).

This study has been approved by the Human Research Ethics Committee of the University of the Witwatersrand (certificate number M180226), and registered with the South African National Health Research Database (reference GP_201806_010). Written, informed consent, assent and permission will be obtained from the necessary parties.

Sample size and inclusion/exclusion criteria

For the first phase, data will be collected for participants in two groups, namely early adolescence and middle adolescence. This will continue until data saturation is reached in each age group. Initially eight participants per age group (i.e. 16 participants) will be invited to participate and booked for interviews. Adolescents aged 10–17 years will be invited to take part in the study, but will be excluded if they have physical and/or cognitive impairments rendering them unable to participate in the interview process or if they have impairments not related to HIV (e.g. traumatic brain injury).

For phase two, the inclusion and exclusion criteria remain the same, but in addition, age-matched HIV negative participants will be invited to participate as the age-matched, comparison cohort. To date, CHANGES has an age appropriate population of 255 HIV positive participants. These adolescents are representative of the community of PHIVA. A sample of 154 HIV positive participants would give a confidence level of 95% (5% margin of error). A further 154 HIV negative participants would comprise the age-matched, comparison cohort, thus a total of 308 adolescents would be required for phase two of this study. (Sample size was calculated using Raosoft, Inc© [36]).

Based on the findings of phase one and two, phase three will involve the development of a model of care for PHIVA. This will be put forward for consensus using the nominal group technique (NGT) to two populations, namely a group of PHIVA (sourced from CHANGES), and a group of clinical experts in the field of HIV and adolescents. During phase one and two the principal investigator (PI) will take note of the clinical experts encountered at RMMCH. Snow-ball sampling will also be used to source participants as the clinical experts, who

would need to have worked with adolescents with HIV as a nurse, medical doctor, physiotherapist or occupational therapist. It is recommended that five to nine people are used per group for NGT [37].

Study procedures

Phase one

Adolescents and their parent/guardian will be approached and invited to participate in phase one on the day that they are attending the clinic. Through semi-structured interviews participants will meet with the PI individually to explore what the participant perceives as challenges due to the physical sequelae of HIV and how this impacts on their activity and participation levels. The interviewer will use open-ended questions to explore what the participant enjoys doing socially; what they find physically difficult; what they feel that they are not able to do that their friends can do; what their attitude is towards their health etcetera.

The interviews will be audio-recorded and transcribed verbatim at a later stage. The PI will take field notes during the interview and at the end of each interview the PI will capture the essence of the interview session [38].

Phase two

Participants and their guardians will be invited to take part in phase two of the study on the day that they attend the clinic. After they complete their doctor's appointment, they will meet with the researcher and data will be collected from the participants as per Table 1.

Phase three

Data gathered in phase one and two will inform phase three: the development of a model of care for PHIVA. The model of care will be put forward for consensus via the NGT. Two groups of five to nine participants [37] will be used: one of PHIVA and one of clinical experts (as described in the inclusion criteria). The participants and PI will meet on an allocated date and the NGT structure will follow the method as described in the literature, namely, to give an explanation of the purpose and procedure; allow for the silent generation of ideas; participants then share ideas; a group discussion; followed by voting and ranking to prioritise the ideas [37].

The application of the international classification of functioning, disability and health (ICF) as a conceptual framework for disability has been described in the literature and is used as a common language in discussing disability [39]. Based on this, this study will utilise the ICF as its conceptual framework (as shown in Fig. 1). The impairments, activity limitations and participation restrictions identified in phase one and two will feed into the development of the model of care for phase three.

Table 1 Data collection parameters for phase two

Data collected during clinical assessments	Outcome measure tool	Explanation of outcome measure
Fatigue	HIV related fatigue scale	A 56-item questionnaire used to establish levels of fatigue in people with HIV
Endurance	Six minute walk test	A measure of distance walked in 6 min to establish a person's endurance
Motor function impairment	Movement assessment battery for children—second edition (movement ABC-2)	A tool used to assess fine and gross motor impairment in children and adolescents
Peripheral neuropathy	Brief peripheral neuropathy screen	A tool used to assess peripheral neuropathy in people with HIV
Muscle strength	Standing broad jump	An index of muscular fitness in children and adolescents established through three attempts at a standing broad jump
Disability	World Health Organisation disability assessment schedule for children (WHODAS-Child)	A 36-item questionnaire for assessing disability in children and adolescents through rating levels of difficulty in daily activities
Data collected from patient files	**Outcome measure tool**	**Explanation of outcome measure**
Quality of life (QOL)	Pediatric quality of life inventory version 4.0 (PedsQL™ 4.0)	A 23-item tool establishing the quality of life in children and adolescents with chronic illness
Body mass index	Weight/height squared	A measurement of weight in relation to height
Clinical data	CD4; nadir CD4; viral load; age at initiation; drug regime; key co-morbidities	Clinical data pertaining to the participant's HIV management

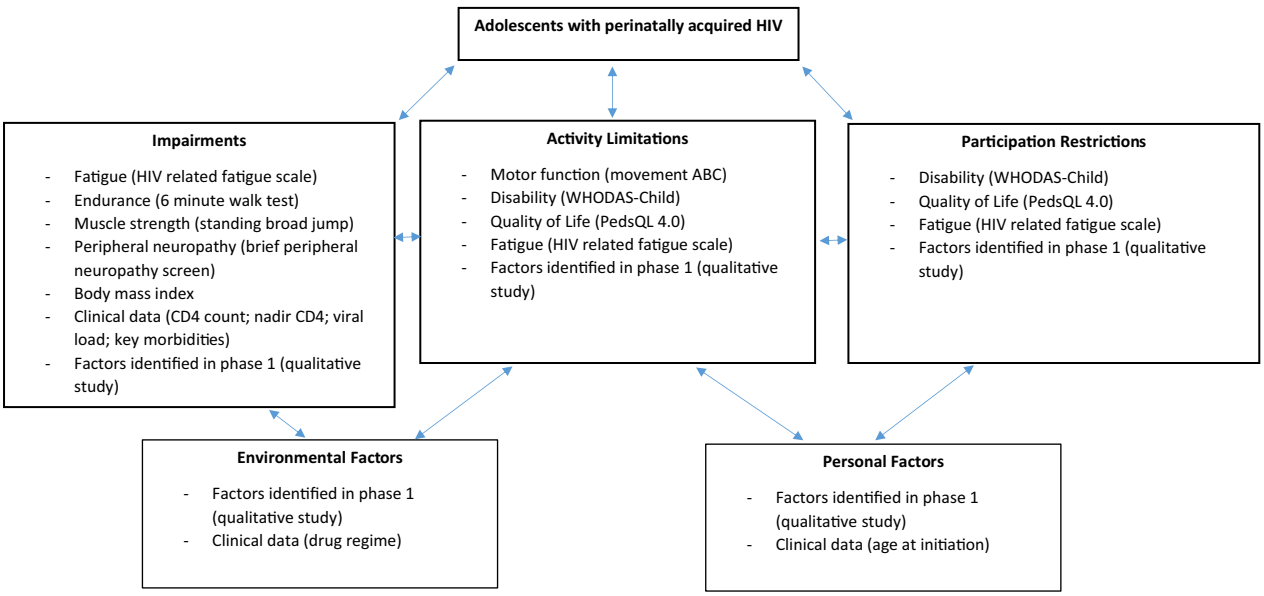

Fig. 1 Conceptual framework for the physical sequelae of perinatally acquired HIV in adolescents [39]

Data analysis

The data from the interviews will be organised, coded and analysed by the PI and another coder. Substantive statements will be identified in the transcribed interviews and thematic analysis will be undertaken using the general inductive approach to analyse the data [40], with manifest analysis being used to quantify the content [41]. Thereafter the coders will discuss the material and identify the themes, categories and sub-categories [41]. This improves the validity through triangulation [41]. The field notes taken during the data collection will be an added aspect of triangulation.

Data collected in phase two will be transferred to Microsoft Excel™ 2016 where frequencies, means and standard deviations will be calculated for descriptive statistical analysis. Statistica™ will be used to analyse the data further. The authors hypothesise that the age-matched, comparison cohort will acquire better scores. P values of < 0.05 will be considered statistically significant. T tests will compare clinical data, demographic data and data from the outcome measures. Mean composite scores will be compared between the PHIVA and age-matched, comparison cohort. To measure the variable difference between the two groups the Chi squared test and Kruskal–Wallis one-way ANOVA will be used. A logistic regression will be used to analyse factors associated with disability.

For phase three, due to the nature of the ranking, NGT yields both quantitative and qualitative data [42]. The qualitative data will be analysed inductively (as per phase one) and the ranking of items will be analysed as quantitative data using descriptive statistics with frequencies and means.

Table 2 gives a summary of the methodology for the study across the three phases.

Conclusion

Establishing the perceived and actual physical sequelae of perinatally transmitted HIV in adolescents will address one of the gaps in knowledge that we have as clinicians working with PHIVA. Creating a model of care will assist health care providers in early identification, assessment and management of potential physical problems, including the necessary referral of the PHIVA to relevant members of the interdisciplinary team. By addressing the challenges, one hopes to improve the quality of life and community participation of PHIVA. Informing this research with the voice of the affected population in the assessment and development of the model of care ensures that we are working for adolescents, with adolescents, and thus potentially optimising the uptake of the model of care.

Limitations

Although the study site has a large feeder area, taking participants from only one site results in a somewhat homogeneous population and thus may not produce results generalizable to the global population. However, this study will provide the starting point for determining the physical sequelae in PHIVA and the basis of a model of care for this population, which could be tested in further research.

Table 2 Summary of the methodology for the study across three phases

	Phase one	Phase two	Phase three
Study design	Semi-structured interviews	A cohort study with a comparison group of age-matched participants	Consensus for a model of care using NGT
Source of participants	CHANGES at RMMCH (for phase three medical professionals will be sourced from the site)		
Sample size	Eight participants per group; 2 groups (early and middle phase adolescence: ages 10–14 and 15–17 years, respectively)	308 (154 HIV+ and 154 HIV− [matched]) participants	Five to nine participants per group; 2 groups (representatives of PHIVA and of clinical experts)
Inclusion criteria	PHIVA in CHANGES, aged 10–17 years	Adolescents aged 10–17 years (HIV+ and −)	PHIVA in CHANGES, aged 10–17 years Interdisciplinary team member in field of HIV and adolescence
Exclusion criteria	Physical/cognitive impairments preventing their participation Physical/cognitive impairment not due to HIV		
Procedure and instrumentation	Individual, semi-structured interviews	HIV related fatigue scale Six minute walk test MABC-2 Brief peripheral neuropathy screen WHODAS-child Standing broad jump PedsQL 4.0 Body mass index	Nominal group technique for consensus on a model of care [37]
Data analysis	Identify substantive statements Inductive approach Manifest analysis Separate coding done to identify themes, subthemes and categories	Descriptive statistics Appropriate tests of association Logistic regression analysis	Qualitative data: inductive analysis as per phase one Quantitative data: descriptive statistics of averages and means

Furthermore, the HIV related fatigue scale has not yet been used in adolescents, nor tested across all cultures, however, it remains one of the few tools that are available for the use of establishing fatigue in HIV [43].

Abbreviations

ART: antiretroviral therapy; CHANGES: childhood HAART alterations in normal growth, genes and aGing evaluation study; HIV: human immunodeficiency virus; ICF: international classification of functioning, disability and health; Movement ABC-2: movement assessment battery for children—second edition; NGT: nominal group technique; PedsQL™ 4.0: pediatric quality of life inventory version 4.0; PHIVA: perinatally HIV-infected adolescents; PI: principal investigator; QOL: quality of life; RMMCH: Rahima Moosa Mother and Child Hospital; WHODAS-Child: World Health Organisation disability assessment schedule for children.

Authors' contributions

NCW, JP and VN were involved in the conception and design of the study. NCW drafted the manuscript. JP and VN reviewed the manuscript. All authors read and approved the final manuscript.

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We wish to acknowledge the CHANGES team for allowing access to the study site and providing the authors with the patient numbers required for the sample size calculations.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Not applicable. This article is a research proposal and no datasets were generated or analysed.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study has been approved by the Human Research Ethics Committee of the University of the Witwatersrand (Certificate Number M180226), and registered with the South African National Health Research Database (reference GP_201806_010). Written, informed consent, assent and permission will be obtained from the necessary parties.

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3.6 Conclusion

This chapter presented the study protocol as published in *BMC Research Notes*. The following chapter is a scoping review of the physical sequelae in PHIVA, presented as publications for the protocol and the scoping review.

Chapter 4 Scoping Review

This chapter is presented as two published articles: a scoping review protocol and a scoping review. The aim of the scoping review was to identify and describe the physical sequelae of PHIVA.

4.1 Scoping review protocol

4.1.1 Publication details

The scoping review protocol was published in *JBI Evidence Synthesis*, the official journal of the Johanna Briggs Institute, which publishes scoping reviews and systematic reviews (and the protocols thereof) relating to multidisciplinary healthcare-related topics. The protocol lays out the precise methodology, including a search strategy example, used for the scoping review itself. Details on the publication are presented in Table 4.1.

Table 4.1 Publication specifics of the scoping review protocol

Title of publication	Physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review protocol
Authors	Nicolette Comley-White; Joanne Potterton; Veronica Ntsiea
Journal name	*JBI Evidence Synthesis*
ISSN	2689-8381
Impact factor	Not available
Year	2021
Volume (issue)	19(11)
Pages	3149-3154
DOI number	10.11124/JBIES-20-00338

4.1.2 Author contributions

Table 4.2 presents the authors' contributions, as described by the Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019). Appendix 1 gives the full definitions of terms.

Table 4.2 Author contributions for the scoping review protocol

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Funding acquisition	√	√	√

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4.1.4 Published article: Physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review protocol

Physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review protocol

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ABSTRACT

Objective: This scoping review aims to identify and describe the physical sequelae experienced by adolescents with perinatally acquired HIV.

Introduction: Perinatally acquired HIV is a prevalent condition affecting adolescents. It results in neurocognitive dysfunction and mental health challenges. Data show that some of the physical challenges facing this population include stunted growth and delayed puberty; however, other physical challenges remain largely unknown.

Inclusion criteria: This review will consider studies that include adolescents aged 10 to 19 years, with perinatally (vertically) acquired HIV. Adolescents from any geographic area, of any ethnicity or socioeconomic background will be considered. The concepts included will be all physical sequelae of perinatally acquired HIV. Studies of any research design, including quantitative, qualitative, and mixed methods, as well as systematic reviews, will be considered.

Methods: This review will utilize a three-step search strategy. There will be an initial search of MEDLINE (PubMed), followed by a full search of MEDLINE (PubMed), PEDro, CINAHL (EBSCO), Scopus (Elsevier), ScienceDirect (Elsevier), and Google Scholar. Gray literature will be searched using CDC Stacks and OpenGrey. Lastly, the reference lists of all articles will be checked for additional studies. Titles and abstracts will be screened by two independent reviewers against the inclusion criteria, and a third reviewer will resolve any discrepancies. Results will be charted on a data extraction tool and presented with a table, diagrammatic representation, and a descriptive narrative.

Keywords: adolescence; HIV; human immunodeficiency virus; perinatal

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Introduction

HIV is one of the leading causes of death in adolescents globally,[1] and especially of concern in Africa.[2] There were approximately 1.7 million adolescents living with HIV worldwide in 2019.[3] The infection in these adolescents is transmitted either vertically (from mother to child) or horizontally (from someone other than the mother), and although data show that the most common route of transmission is vertical, there are no exact numbers on the prevalence of adolescents with perinatal HIV across the globe.[4]

Due to the increasing availability of antiretroviral therapy (ART), there is a growing number of adolescents with perinatally acquired HIV, at which point the disease is considered a chronic condition. This creates the challenge of living with a chronic disease and using lifelong medication.[5,6] Although the pediatric brain has high levels of neural plasticity, it is vulnerable to environmental changes, and adverse environmental factors can affect normal development.[7] HIV is a neurotropic virus that is able to cross the blood-brain barrier, thus changing the environment of the developing pediatric brain.[8] In addition, the blood-brain barrier makes it challenging for ART to penetrate the central nervous system,[9] and ART medications themselves have a variety of neurotoxic effects.[10]

Research has shown the adverse effects of perinatally acquired HIV on neurodevelopment, including cognitive and neurological complications in children.[11-13] Adults also face a range of neurological complications from HIV.[14,15] However, literature is emerging showing the sequelae of perinatally acquired HIV in adolescents, with most of the data

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pertaining to neurocognitive challenges (as opposed to physical and developmental impairments), and the majority of the studies are from resource-rich countries,[16] despite 84% of adolescents with HIV living in sub-Saharan Africa.[2] These studies show that adolescents with perinatally acquired HIV are at a higher risk of mental health challenges, neurocognitive dysfunction, decreased cognition, and decreased processing speed.[5,16-18]

In addition to neurocognitive sequelae, studies have shown that this population also faces certain physical challenges, such as stunting[19,20] and delayed puberty.[21] Stunted growth in children with perinatal HIV is well-established[22] and appears to continue into adolescence, with up to 34.4% of males and 39.5% of females stunted in adolescence.[19] Poor growth has been shown to mediate a delayed onset of sexual maturation in adolescents with perinatally acquired HIV,[21] resulting in late onset of puberty.[18] Stunted growth and pubertal delay are multifactorial consequences of perinatal HIV, with some of the key factors to consider including chronic inflammation, endocrine dysfunction, other infectious or immunological diseases (eg, tuberculosis, pneumonia), and nutritional disorders.[19,23,24]

There is a call in the literature for further research and development of policies in the field of neurodevelopment in adolescents with perinatally acquired HIV.[16,18] Although there are emerging data on the neurocognitive (and some physical) effects of perinatal HIV in adolescence, there are still gaps in the knowledge base. Establishing the existing evidence will aid researchers in identifying these gaps in knowledge, thus informing future studies and research. Additionally, a scoping review will collate and present the known physical sequelae in this population, which may be useful to clinicians for developing a model of care. The aim of this scoping review is therefore to identify and describe the physical sequelae experienced by adolescents with perinatally acquired HIV.

A preliminary search of the Cochrane Database of Systematic Reviews and *JBI Evidence Synthesis* was conducted, which showed no current scoping reviews or systematic reviews on the topic.

Review question

What does the literature report about the physical sequelae of perinatally acquired HIV in adolescents?

Inclusion criteria

The inclusion criteria for this scoping review were guided using the population, concept, and context model (PCC) following JBI methodology.[25]

Participants

This review will consider studies that include participants who are adolescents (ranging from 10 to 19 years of age[26,27]) living with perinatally acquired HIV infection.

Concept

This review will consider studies that identify the physical sequelae for perinatally acquired HIV in adolescence. This incorporates (but is not limited to) body mass index, endurance, muscle strength, fatigue, pain, height, weight, head circumference, and pubertal changes.

Perinatally acquired HIV is defined as the mother-to-child transmission of HIV through pregnancy, birth, or breastfeeding.[28] This is also known as vertical transmission.

Context

This review will consider studies that are from countries of any income classifications, rural or urban location, and any ethnic or socioeconomic background.

Types of sources

This scoping review will include all study designs: quantitative, qualitative, and mixed methods. In addition, systematic reviews and meta-analyses will be considered. Gray (unpublished) literature will also be considered.

Methods

The proposed review will be conducted in accordance with the JBI methodology for scoping reviews,[25] following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.[29]

Search strategy

A three-step search strategy will be used. The first step was an initial limited search of MEDLINE (PubMed) and CINAHL (EBSCO) to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, as well as the index

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terms used to describe the articles, were used to develop a full search strategy for MEDLINE (PubMed; see Appendix I). Subsequently, a full second search across all of the included databases will be implemented. Thirdly, the reference lists of all included articles will be searched for additional studies. The reviewers will contact the authors of key studies for further information if needed. All studies published in English will be considered, with no date limit. It is expected that the majority of the studies will be published from 2005 onwards because ART initiation occurred globally between 1996 and 2003,[30] allowing babies with perinatally acquired HIV infection to live into adolescence and beyond. However, the search will not be limited to this time period to allow for maximum citation yield.

The initial keywords searched will be HIV, adolescence, adolescents, perinatal, perinatally acquired HIV, vertically transmitted, and sequelae.

The databases to be searched include MEDLINE (PubMed), PEDro, CINAHL (EBSCO), Scopus (Elsevier), ScienceDirect (Elsevier), and Google Scholar. A search for gray literature will be conducted in CDC Stacks and OpenGrey.

Study selection

Following the search, all identified records will be collated and uploaded into Zotero v5.0.89 (Corporation for Digital Scholarship and Roy Rosenzweig Center for History and New Media, VA, USA), and duplicates removed. Titles and abstracts will then be screened by two independent reviewers (JP and NCW, both of whom are physiotherapists with a clinical research and publication-related background in HIV) for assessment against the inclusion criteria for the review. Studies that meet the inclusion criteria will be retrieved in full and reassessed by the reviewers. Reasons for exclusion of papers at the full-text screening stage will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion and consensus, and if consensus cannot be reached, then a third reviewer (VN) will be consulted. A PRISMA-ScR checklist[29] and the PRISMA flow diagram[31] will be used to present the results of the search.

Data extraction

Results from articles meeting the inclusion criteria will be charted using a data extraction tool under the following headings: author(s), year of publication, title, study design, aim/purpose, population/participants, sample size, concept, context, key findings (specific to physical sequelae), reviewer's summary, and other points of note (see Appendix II). The data will be extracted from the papers by the primary reviewer (NCW) and captured on the data extraction tool. Because charting is an iterative process, the tool will be updated with additional data if it is deemed necessary in the process, and any modifications will be described in the full scoping review. A second, independent reviewer (JP) will verify the data extraction by checking the results against the full-text articles.

Data analysis and presentation

The extracted data will be presented in a table to map the existing literature specific to the key findings of physical sequelae in adolescents with perinatally acquired HIV. A diagrammatic representation will be used to summarize these sequelae, and a descriptive narrative of the available literature will be provided linking the results to the review's objective and question.

Acknowledgments

This scoping review will contribute toward the completion of a doctoral degree for author NCW.

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Appendix I: Search strategy

MEDLINE (PubMed)
Search performed in August 5, 2020

No.	Search	Records retrieved
#10 (#4 OR #9)	Search (((((((perinatal HIV[Text Word]) OR perinatally acquired HIV[Text Word]) OR vertical HIV[Text Word]) OR vertically transmitted[Text Word])) AND adolescen*[Text Word]) AND (((sequel*[Text Word]) OR outcome*[Text Word]) OR complication*[Text Word])))) OR ((((complications[MeSH Subheading]) AND HIV[MeSH Terms]) AND ((adolescent[MeSH Terms]) OR pediatric[MeSH Terms])) AND "infectious disease transmission, vertical"[MeSH Terms])	655
#9 (#5 AND #6 AND #7 AND #8)	Search (((complications[MeSH Subheading]) AND HIV[MeSH Terms]) AND ((adolescent[MeSH Terms]) OR pediatric[MeSH Terms])) AND "infectious disease transmission, vertical"[MeSH Terms]	13
#8	Search "infectious disease transmission, vertical"[MeSH Terms]	3639
#7	Search (adolescent[MeSH Terms]) OR pediatric[MeSH Terms]	273,740
#6	Search HIV[MeSH Terms]	30,854
#5	Search complications[MeSH Subheading]	234,688
#4 (#1 AND #2 AND #3)	Search ((((((perinatal HIV[Text Word]) OR perinatally acquired HIV[Text Word]) OR vertical HIV[Text Word]) OR vertically transmitted[Text Word])) AND adolescen*[Text Word]) AND (((sequel*[Text Word]) OR outcome*[Text Word]) OR complication*[Text Word])	645
#3	Search ((sequel*[Text Word]) OR outcome*[Text Word]) OR complication*[Text Word]	1,958,956
#2	Search adolescen*[Text Word]	157,008
#1	Search (((perinatal HIV[Text Word]) OR perinatally acquired HIV[Text Word]) OR vertical HIV[Text Word]) OR vertically transmitted[Text Word]	8293

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Appendix II: Data extraction form

Author(s)	Year of publication	Title	Study design	Aim/ purpose	Population/ participant details (eg, age, sex, number)	Sample size	Concept	Context	Key findings (specific to physical sequelae)	Reviewer's summary	Other points of note

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4.2 Scoping review

4.2.1 Publication details

The scoping review was published in *Physical Therapy Reviews*, a journal that publishes reviews whose basis is physical therapy and that is aimed at people involved in research, teaching and practice. The article presents a review of the established physical sequelae that PHIVA potentially develop, highlighting the importance of further research in this area. Details on the publication are presented in Table 4.3.

Table 4.3 Publication specifics of the scoping review

Title of publication	The physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review
Authors	Nicolette Comley-White; Joanne Potterton; Veronica Ntsiea
Journal name	*Physical Therapy Reviews*
ISSN	1743-288X
Impact factor	0.554
Year	2022
DOI number	10.1080/10833196.2022.2026009

4.2.2 Author contributions

The contributions from each author are presented in Table 4.4, based on the terminology established by Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019), with a full explanation of terms presented in Appendix 1.

Table 4.4 Author contributions for the scoping review

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Formal analysis	√		
Investigation	√	√	
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Project administration	√		
Funding acquisition	√	√	√

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4.2.4 Published article: Physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review

PHYSICAL THERAPY REVIEWS
https://doi.org/10.1080/10833196.2022.2026009

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The physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review

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ABSTRACT

Background: Adolescents living with perinatal HIV (PHIVA) are a growing population with unique needs. While the impact of HIV on pediatric physical wellbeing is expansively documented, there is only emerging data on the long-term impact of perinatal HIV infection on adolescence and the resultant physical sequelae.

Objective: This scoping review aimed to identify and describe what is currently known about the physical sequelae that PHIVA face.

Method: A scoping review was conducted, following the methodology described by the Johanna Briggs Institute manual for Evidence Synthesis. Electronic databases of MEDLINE (PubMed), PEDro, CINAHL (EBSCOhost), Elsevier (Scopus), Elsevier (Science Direct), Google Scholar, CDC Stacks and Open Grey, and reference lists were searched. Two investigators screened the article titles, abstracts and full texts against the inclusion criteria. Data was charted on a data extraction tool, with a descriptive narrative presenting the results.

Results: Of the 1291 citations screened, eight studies were included. All of the studies were cross-sectional analyses, with only two studies using an HIV-negative comparison group. The studies addressed the physical outcomes of height, weight, body mass index, delayed puberty, physical functioning and activity levels, exercise tolerance and lung function, and pain. These sequelae were categorized into two subgroups: 1) anthropometric characteristics and 2) physical health and functioning.

Conclusion: The results of this scoping review show that PHIVA face significant physical challenges despite access to antiretroviral therapy. Thus this distinctive population requires unique and specialized healthcare.

KEYWORDS
HIV; adolescence; perinatal; physical sequelae; vertically transmitted

Introduction

The human immunodeficiency virus (HIV) continues to be a global challenge across the lifespan. Recent data estimates that 1.7 million adolescents are living with HIV, of which 1.5 million live in sub-Saharan Africa [1]. As access to antiretroviral therapy (ART) continues to improve so the population of adolescents with perinatal HIV (PHIVA) expands [2]. This population is unique in that they have spent their entire growth and development phase living with a neurotoxic virus [3], as well as taking ART which presents its own set of challenges and side-effects [4–6].

The negative impact of perinatal HIV on development and growth in childhood is well-established [7,8] but there are still many questions around what the resultant effects of perinatal HIV are on adolescence. Research has shown that there are multiple challenges related to neurocognitive dysfunction and mental health in PHIVA [9–12] however there are still many gaps in the knowledge around the physical sequelae that these adolescents face.

Studies have shown that PHIVA are often stunted [13,14] and have delayed pubertal onset [15] however there are still numerous areas of physical development and functioning that need to be explored. It has been shown that children living with HIV (CLHIV) have decreased physical functioning and motor deficits [16–18] which raises potential challenges in adolescence [10]. Stunted growth can continue through childhood into adolescents with HIV, with as many as 34.4% of male, and 39.5% of female, PHIVA presenting with stunting [14]. Poor growth in PHIVA mediates a delay in onset of sexual maturation [15] and thus delayed puberty [10]. The multifactorial nature of HIV impacts on these physical complications, with some of the key issues being nutritional disorders, chronic inflammation, endocrine dysfunction, other infectious/immunological diseases, and the dyslipidemia and cardiovascular atherosclerotic changes associated with HIV and ART [14, 19–21].

Although it is evident that stunting and delayed puberty can be problematic in PHIVA [13–15] there

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is still a large gap in research on other potential physical problems in PHIVA, such as endurance, muscle strength, fatigue and pain. Although many of these impairments have been shown to present in children and in adults living with HIV there is a lack of information about it in PHIVA [22]. In order to inform clinical practice and future research it is important to map the existing literature of these physical challenges and thus the aim of this scoping review was to identify and describe the physical sequelae that PHIVA face.

Methods

A scoping review was conducted. The decision to do a scoping review over a systematic review was based on the aim of the study. Systematic reviews are performed in order to synthesize the evidence to inform practice, policy and treatment, using rigorous and clearly-defined criteria. Whereas a scoping review is used to explore the scope of available literature to answer broader, exploratory research questions, determining knowledge gaps and identifying all available evidence [23]. Thus a scoping review was appropriate for this emerging area of research.

The scoping review followed the methodology described by the Johanna Briggs Institute manual for Evidence Synthesis using the Population, Concept, Context (PPC) model [24] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews checklist [25]. The study protocol was registered with the Open Science Framework and is available as a full publication [26]. The research question used to guide this review was: What does the literature report about the physical sequelae of perinatally acquired HIV?

Study identification

Using the PPC model [24] the following inclusion criteria were used to search the literature:

- Population: studies with participants who were adolescents, defined as ages 10 to 19 years [27,28], living with a confirmed diagnosis of perinatal HIV.
- Concept: studies were included if they explored any of the physical sequelae of perinatal HIV. Perinatal HIV is defined as the mother to child transmission of HIV through pregnancy, birth or breastfeeding [29]. This can also be referred to as vertical transmission, or vertically acquired HIV. Physical sequelae were defined as, but not limited to, body mass index, endurance, muscle strength, fatigue, pain, height, weight, head circumference and pubertal changes. Studies with data from CLHIV below the age of 10 were excluded.
- Context: the review considered studies from countries of all income classifications, all study sites and included all ethnicities and sociodemographic backgrounds.

Search strategy

The scoping review was conducted according to the three step search strategy presented by the Johanna Briggs Institute [24]. First, articles addressing the research question were identified through initial limited search of MEDLINE (Pubmed) and CINAHL (EBSCOHost). The key text words in these articles' titles, abstracts and index terms were used to formulate the key search terms for a full search strategy for MEDLINE (Pubmed). Table 1 shows the search strategy for MEDLINE (Pubmed) as an example.

The next step involved a full search across all of the following databases: MEDLINE (PubMed), PEDro, CINAHL (EBSCOhost), Elsevier (Scopus), Elsevier (Science Direct) and Google Scholar. A search for grey literature was done through CDC Stacks and Open Grey. The keywords included 'HIV', 'human immunodeficiency virus', 'adolescence', 'adolescents', 'youth' 'perinatal', 'perinatally acquired HIV', 'vertically transmitted', 'sequelae' and 'outcomes'.

In the third step, a hand search of the reference lists was done to identify any further studies.

Study selection

For the study selection, all citations were compiled in the bibliographic manager, Zotero v5.0.89. Duplicate citations were removed and the remaining titles and abstracts were screened against the inclusion criteria by two reviewers (NCW and JP). When the reviewers had differing results a discussion was held and consensus reached. In the event that consensus might not have been reached then a third reviewer (VN) would have been consulted. Once the screening process was complete full text articles were retrieved and assessed for eligibility by the two reviewers.

Any qualitative, quantitative or mixed method study design was considered eligible, as well as systematic reviews and meta-analyses. However, narrative reviews were not considered as they did not provide the depth of data analysis required for this scoping review.

Table 1. Search strategy for MEDLINE (PubMed).

No.	Search	Records retrieved
#10 (#4 OR #9)	Search ((((((perinatal HIV[Text Word]) OR perinatally acquired HIV[Text Word]) OR vertical HIV[Text Word]) OR vertically transmitted[Text Word])) AND adolescen*[Text Word]) AND (((sequel*[Text Word]) OR outcome*[Text Word]) OR complication*[Text Word]))) OR ((((complications[MeSH Subheading]) AND HIV[MeSH Terms]) AND ((adolescent[MeSH Terms]) OR pediatric[MeSH Terms])) AND "infectious disease transmission, vertical"[MeSH Terms])	655
#9 (#5 AND #6 AND #7 AND #8)	Search (((complications[MeSH Subheading]) AND HIV[MeSH Terms]) AND ((adolescent[MeSH Terms]) OR pediatric[MeSH Terms])) AND "infectious disease transmission, vertical"[MeSH Terms]	13
#8	Search "infectious disease transmission, vertical"[MeSH Terms]	3639
#7	Search (adolescent[MeSH Terms]) OR pediatric[MeSH Terms]	273740
#6	Search HIV[MeSH Terms]	30854
#5	Search complications[MeSH Subheading]	234688
#4 (#1 AND #2 AND #3)	Search ((((((perinatal HIV[Text Word]) OR perinatally acquired HIV[Text Word]) OR vertical HIV[Text Word]) OR vertically transmitted[Text Word])) AND adolescen*[Text Word]) AND (((sequel*[Text Word]) OR outcome*[Text Word]) OR complication*[Text Word])	645
#3	Search ((sequel*[Text Word]) OR outcome*[Text Word]) OR complication*[Text Word]	1958956
#2	Search adolescen*[Text Word]	157008
#1	Search (((perinatal HIV[Text Word]) OR perinatally acquired HIV[Text Word]) OR vertical HIV[Text Word]) OR vertically transmitted[Text Word]	8293

Data extraction

In order to map the literature, the data was charted on a data extraction form summarizing information such as the title, author, year of publication, study design, aim, population, concept, context and key findings (specific to physical sequelae). Data was captured by one reviewer (NCW) and checked by the second reviewer (JP) to confirm accuracy. Finally, a narrative review was developed to describe the literature.

Results

A database search performed in August 2020, and subsequently updated in February 2021, resulted in 1619 relevant citations. A further 8 citations were identified from the authors' literature repository. Once duplicates were removed there were 1291 citations that were screened, resulting in 1222 records being excluded. From the remaining 69 full-text articles that were assessed for eligibility, 62 were excluded. One further study was identified from the reference list search and screened, resulting in eight studies that met the inclusion criteria for this scoping review. Figure 1 depicts a summary of the selection process.

Study characteristics

All of the studies were cross-sectional analyses, four of which were of cohorts from larger studies. One study's age range was 10 to 17 years, and another had an age range of 10 to 15 years. The remaining studies' age range was 10 to 19 years. The population sizes ranged from 49 to 8737 PHIVA and only two studies had a comparison group of adolescents who were HIV negative. The studies covered a wide geographical area and addressed the physical outcomes of height, weight, body mass index, delayed puberty, physical functioning and activity levels, exercise tolerance and lung function, and pain. Table 2 summarizes the extracted data. The physical sequelae identified in the studies were categorized into two subgroups: 1) anthropometric characteristics and 2) physical health and functioning. Figure 2 presents a diagrammatic representation of the results.

Anthropometric characteristics

Four of the studies addressed anthropometric changes in PHIVA as their primary study objective [14, 30–32], while two studies focused on other physical sequelae but still reported the anthropometric variables of their participants [33,34].

Height

The earliest publication found that median height z scores in 210 HIVA did not differ significantly from national French norms [30]. The remaining three studies found contrasting results to the Dollfus *et al.* study. Arbeitman *et al.* presented data for 134 PHIVA and compared it to 75 HIV-uninfected youth and 3216 adolescents from a national database, with a sub-analysis of African-American adolescents [32]. The HIV-infected group had significantly lower height z scores compared to the

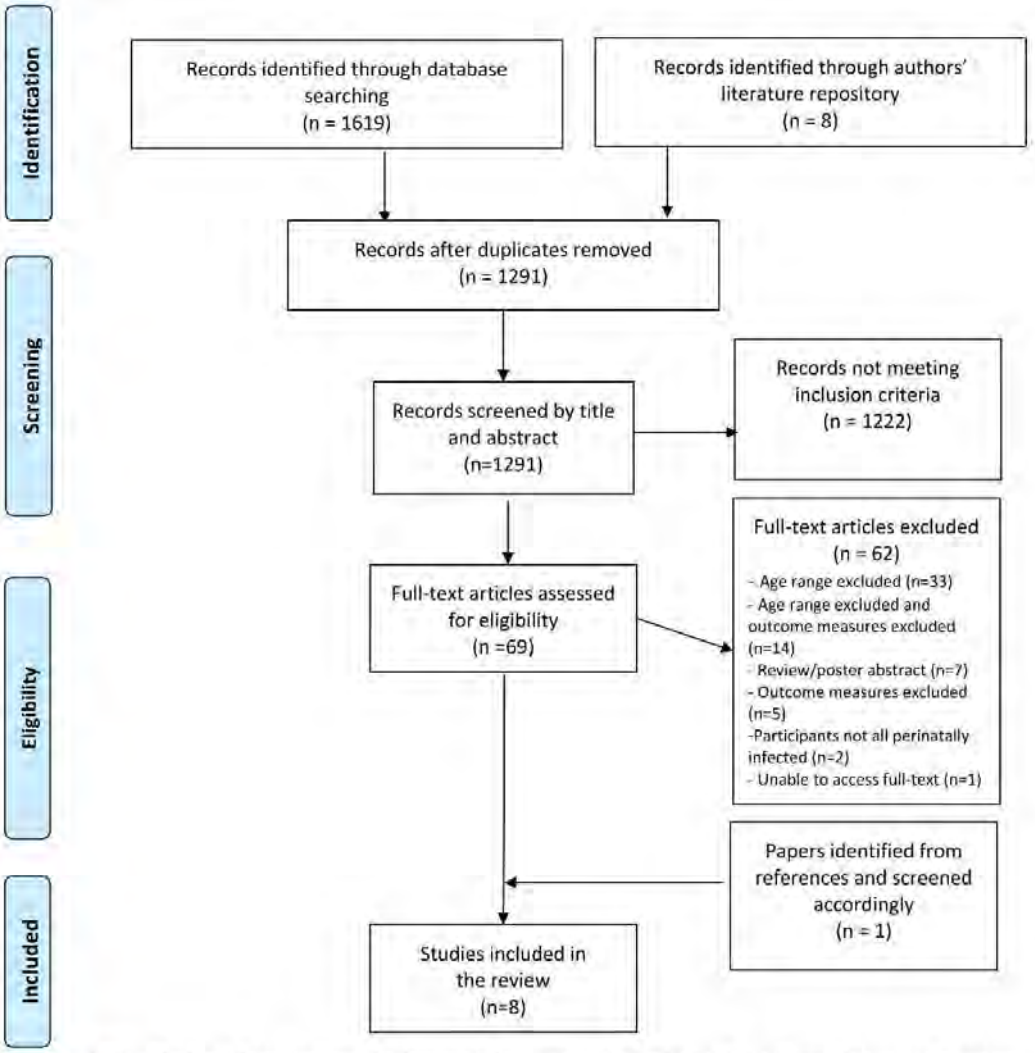

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrating the process of article selection (adapted from Tricco *et al.*).

HIV-uninfected group ($p = 0.03$) and the national database ($p < 0.001$), and the racial subset were also significantly shorter ($p < 0.001$).

Jesson *et al.* analyzed data from a global consortium of 8737 PHIVA, looking at stunting and growth velocity [14]. At 10 years old, 34% of the males and 39% of the females were stunted ($p < 0.001$). Over time the females had had better growth, resulting in more males being stunted than females at ages 15 and 18 years. When correlates of growth for males and females were analyzed, it was found that older age of ART initiation and low CD4 count were associated with poor growth ($p < 0.001$).

Lastly, a comparison of 57 PHIVA and HIV-negative adolescents in Brazil found the PHIVA group to be significantly shorter ($p < 0.001$) and to have significantly lower height-for-age z scores ($p < 0.001$) [31].

Neither of the two studies who reported anthropometry secondarily had a comparison group, however the data were analyzed as height-for-age z scores, with participants in Miller *et al.*'s study presenting as stunted (median height-for-age z score of −2.22) [34] and Ferrand *et al.*'s PHIVA being at risk of stunting (median height-for-age z score of −1.96) [33].

Weight

While Dollfus *et al.* reported similar median weight z scores for their population of PHIVA compared to national norms [30], the remaining studies found that the PHIVA cohorts had significantly lower

Table 2. Summary of studies mapping the physical sequelae of perinatal HIV in adolescents.

Title, Authors, year of publication	Study aim	Study design	Population Number of PHIVA (n); age (years)	Concept	Context	Summary of main findings
Body Mass Index and Waist Circumference of HIV-Infected Youth in a Miami Cohort: Comparison to Local and National Cohorts. *Arbeitman et al.*	To compare BMI, the prevalence of overweight and obesity, and waist circumference between PHIVA, adolescents without HIV and the national population	Cross-sectional analysis of a cohort of PHIVA followed in a larger study	134; 10–19	Height; weight; BMI	1 clinic in United States of America; subset analysis of African American youth	PHIVA group significantly shorter than HIV-uninfected group ($p = 0.003$) and national cohort ($p < 0.001$). PHIVA group significantly lower BMI than national cohort ($p = 0.01$)
Long-Term Outcomes in Adolescents Perinatally Infected with HIV-1 and Followed Up since Birth in the French Perinatal Cohort. *Dollfus et al.*	To report the long-term clinical outcomes in PHIVA	Cross-sectional analysis of a cohort of PHIVA followed in a larger study	210; 10–17	Height, weight; BMI	90 healthcare centres in France	Well-managed PHIVA did not differ to population norms for weight, height and BMI
Chronic Lung Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection. *Ferrand et al.*	To investigate the clinical features and morphologic characteristics of chronic lung disease in PHIVA	Cross-sectional analysis	116; 10–19	Exercise tolerance; weight; height; BMI; pubertal delay	2 clinics in Zimbabwe	21% of PHIVA had reduced exercise tolerance; 13% had hypoxaemia at rest and 29% on exercise; and lung function tests in PHIVA
Stunting and growth velocity of adolescents with perinatally acquired HIV: differential evolution for males and females. A multiregional analysis from the IeDEA global paediatric collaboration. *Jesson et al.*	To describe growth evolution and its associated factors in PHIVA	Cross-sectional analysis of larger HIV care cohorts	8737; 10–19	Height, weight; growth velocity	Sub-Saharan Africa; Asia-Pacific; Caribbean; Central and South Americas	At 10 years old, 34% of males and 39% of females were stunted ($p < 0.001$). Females had better subsequent growth, resulting in 48% of males and 25% of females being stunted at age 15. Older age of ART initiation and low CD4 count associated with poorer growth.
Physical activity and body fat in adolescents living with HIV: a comparative study. *Martins et al.*	To compare regular physical activity among PHIVA with their healthy peers, and to evaluate the relationship with anthropometric indicators of body fat.	Cross-sectional analysis with a comparison group	57; 10–15	Physical activity	1 hospital in Brazil	PHIVA had significantly lower overall physical activity scores (1.73) compared to HIV-negative counterparts (2.14) ($p < 0.001$)
Reproductive health and lifestyle factors associated with health-related quality of life among perinatally HIV-infected adolescents in Uganda. *Mbalinda et al.*	To describe health-related quality of life in PHIVA and to assess the association with sexual reproductive health or lifestyle experiences.	Cross-sectional analysis	614; 10–19	Health related quality of life; physical health	12 clinics in Uganda	Adolescents on ART were twice as likely to have better physical health
Cardiac Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection. *Miller et al.*	To describe the clinical characteristics and echocardiographic features of cardiac disease among PHIVA	Cross-sectional analysis	110; 10–19	Exertional dyspnoea; chest pain; ankle swelling	Two clinics in Zimbabwe	Burden of cardiac disease in PHIVA: exertional dyspnoea in 43% of PHIVA, chest pain on exertion in 39%, ankle swelling in 6%
Long-term Follow-up Outcomes of Perinatally HIV-	To describe socio-demographic, clinical, and	Cross-sectional analysis of a cohort of PHIVA	49; 10–19	Physical functioning on	One clinic in Brazil	High score in self-reported physical functioning (9.1 on

(*continued*)

Table 2. Continued.

Title, Authors, year of publication	Study aim	Study design	Population Number of PHIVA (n); age (years)	Concept	Context	Summary of main findings
infected Adolescents: infection Control but School Failure. *Souza et al.*	laboratory characteristics and quality of life in PHIVA	followed in a larger study		a quality of life scale		the Quality of Life Assessment-Revised)

PHIVA: perinatally HIV-infected adolescents; BMI: body mass index.

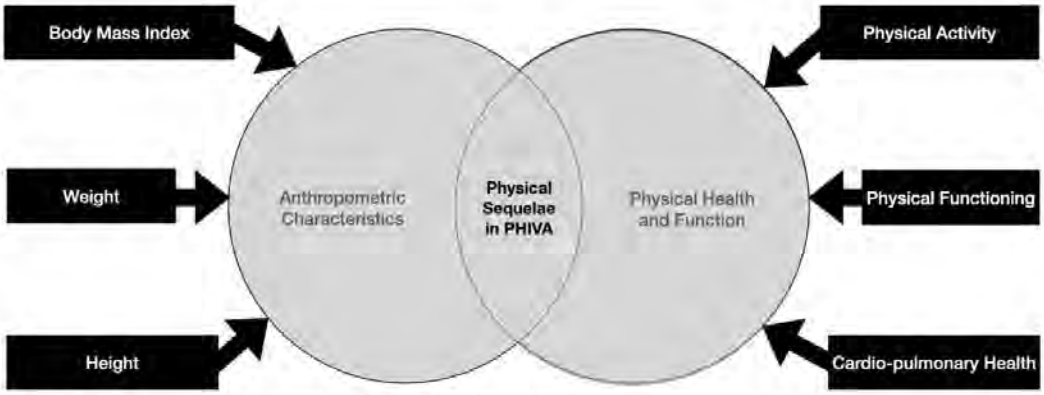

Figure 2. A diagrammatic representation of the results of the scoping review.

weight than the comparison groups [31,32] or presented as at risk of being wasted with median weight-for-age z scores of −1.74 [33] and −1.84 [34]. Additionally, Ferrand *et al.* reported 18% of their PHIVA population had pubertal delay [33].

Body mass index

Findings for BMI varied between the studies. Dollfus *et al.* [30], Martins *et al.* [31] and Arbeitman *et al.* [32] found no significant difference between PHIVA and the comparison group, however in the latter study upon analysis of the racial differences the African-American PHIVA had significantly lower BMI z scores than the HIV-negative counterparts ($p = 0.04$) [32]. Neither Ferrand *et al.* nor Miller *et al.* had a comparison group in their studies but the median BMI z scores for both groups was −0.69 [33,34].

Physical health and functioning

Five studies addressed the physical health and functioning of PHIVA. Martins *et al.* [31] assessed physical activity in 57 PHIVA, aged 10 to 15 years, and compared the results to that of 54 HIV negative comparison participants. The findings showed that PHIVA had a lower total activity score than their healthy peers ($p < 0.001$).

A study in Uganda assessed the health-related quality of life in 614 PHIVA [35]. One of the sections of the quality of life outcome measure pertained to physical functioning and the results showed that adolescents on ART were twice as likely to have better physical health compared to adolescents not on ART. Additionally, PHIVA who did not smoke, or whose friends did not smoke, were more likely to present with better physical health. Similarly, physical function was reported for a Brazilian cohort of PHIVA on ART, using a quality of life outcome measure [36]. Physical function was one component of the study results and although not presented in detail, the authors found that the adolescents in this cohort reported high scores for quality of life, showing good physical function.

Another component of physical health and functioning to consider is cardio-pulmonary health and its impact on physical activity. Two studies were included in the review that addressed this. The first study assessed cardiac disease in PHIVA in Zimbabwe [34]. Of the 110 youth included in the analysis, 43% had exertional dyspnea, 39% had chest pain on exertion and 6% had ankle swelling. The second study assessed chronic lung disease in PHIVA [33]. Components of the study data collection included a 200 m brisk walk and interview data. Of the 116 participants, 21% reported reduced exercise tolerance, 13% had hypoxemia at rest and 29% on exercise, and 42% reported exertional chest tightness.

Discussion

The aim of this scoping review was to identify and describe the physical sequelae of perinatal HIV in adolescence. Eight articles met the inclusion criteria for this review. Of the eight studies, four focused on anthropometric characteristics and the other studies primarily addressed physical health and functioning (and additionally presented anthropometric data).

Anthropometric characteristics

The anthropometric data of PHIVA shows that stunting and wasting is a concern in this population, with stunting being a greater risk. It is well established that perinatal HIV negatively affects growth in children [37,38] and it appears that this continues through to adolescence, with a delayed initiation of ART resulting in poorer growth [14]. Perinatal HIV is an established risk factor for undernutrition in children [39,40]. Even with access to ART undernutrition in CLHIV remains a problem due to factors such as poor access to quality health care, limited resources and food security, and the increased susceptibility to other infectious diseases as a result of a compromised immune system [41]. Undernutrition can lead to stunting due to reduced insulin and essential amino acids and increased cortisol levels, impacting on growth hormone resistance [42]. Other factors influencing growth and development in children born to HIV positive mothers are low-birth weight, a lack of micronutrients, chronic inflammation, endocrine abnormalities and HIV-associated illnesses such as diarrhea and anemia [38,39, 43–45]. These multiple factors all play an important role in understanding the anthropometric sequelae of perinatal HIV, however, the studies included in this review had limited information pertaining to the background characteristics of the study populations. Of the four studies that focused on anthropometry [14, 30–32], one excluded participants if they had not initiated ART [14] and the remainder had the majority of PHIVA ART exposed (98%[30], 90%[32] and 86% [31]) and with high levels of undetectable viral load (43%[30], 42%[32] and 54.4%[31] and respectively).

Stunting in CLHIV increases the risk of mortality, disease progression, cognitive developmental delay, poor educational performance and psychosocial health challenges [38, 44, 46]. The effects of stunted growth in childhood continue into adolescence and adulthood [47] and impact on pubertal onset, with PHIVA presenting with delayed sexual maturation and puberty [15, 37,38, 48]. This is in agreement with the findings of the only study in the review to report on pubertal delay, which presented a prevalence of 18% [33].

Jesson *et al.* [14] compared the growth velocities of male and female PHIVA. While more females than males (39% vs. 34%) were stunted at 10 years old, the female adolescents had better subsequent growth, leading to more males than females being stunted at age 15 (48% vs. 25%) and 18 (31% vs. 15%). The authors acknowledge that there is no clear explanation as to why they found a difference in the growth velocity between the two sexes, and that other literary evidence on this is scarce. Another finding in this study was that PHIVA with late age ART initiation had a strong association with stunting. The proposed reasons for this are that with uncontrolled HIV children are exposed to the long-term effects of chronic inflammation and to repeated opportunistic infections, which adversely affects growth [14]. Lastly, in this cohort of PHIVA those with low CD4 counts over time showed greater stunting. Children with low CD4 counts are also at greater risk of drug resistance, opportunistic infections and mortality [49]. These risks strengthen the argument for the necessity of early ART initiation.

This review found only one study that presented data contrary to the other results pertaining to stunting and wasting in PHIVA [30]. It is noteworthy that the participants for this study were born between 1985 and 1993, prior to the availability of perinatal prophylaxis and at the time of evolving monotherapy and varying treatment combinations that lead to current ART regimes available today. The authors propose that their survival through a childhood during this time with limited treatment options may be suggestive of genetic or other characteristics that may have predisposed them to better health status. They also highlight the important role of diagnosis in the first weeks of life, regular health care and treatment availability in managing the long-term impact of HIV.

Physical health and functioning

The data presented by Souza *et al.* [36] was emergent research in PHIVA and their findings showed relatively good physical functioning in the population. Some limitations to note in this study are the sample size of only 49 participants and that there was minimal information about what the physical function domains entailed and how these compared to healthy individuals. There was therefore a lack of depth in the data on physical functioning and few conclusions could be drawn. The authors did however discuss the role of ART and its potential of improving quality of life (of which physical function is one of domains) in PHIVA.

As ART became more accessible over time and the PHIVA population expanded, so further research developed and physical functioning has been explored in more detail since Souza *et al.*'s [36] study. The physical health limitations found in this review (reduced exercise tolerance, dyspnea, chest pain,

hypoxemia and exertional chest tightness) can all impact on a person's ability to participate in activities of daily living and in society. A recent qualitative analysis of the perceived challenges of perinatal HIV in adolescents found that many PHIVA complain of reduced endurance, pain and fatigue, all of which impacts on their participation levels [50].

Decreased cardiopulmonary endurance and health was reported consistently in the studies of this review [33,34]. Although the understanding of the pathogenesis of chronic lung disease (CLD) in HIV is not well understood [51], it is a widely-established complication of HIV in children and adolescents, especially in those with delayed diagnosis and ART initiation [52,53]. Other risk factors for CLD in adolescents with HIV include pulmonary infection, household air pollution, malnutrition and stunting [52]. Poor lung function and chronic respiratory impairment are frequently reported in adolescents and CLHIV, with symptoms such as chronic cough, increased sputum production, increased respiratory rate, hypoxia post submaximal exercise, abnormal spirometry, airflow obstruction and restriction, and functional aerobic impairment on exercise [52,53]. A systematic review and meta-analysis reported a 14% prevalence of pulmonary hypertension in adolescents with HIV, compared to the 1% prevalence in the general global population [54].

Considering the prevalence of CLD and the physical limitations experienced by PHIVA, the findings of Martins *et al.* [31] are not unexpected, with PHIVA having decreased levels of physical activity. Similar results were found in a sample of adolescents with HIV, showing that the majority of the participants (71.4%) were sedentary [55]. Decreased physical activity is not limited to PHIVA but is also found in CLHIV. A study in South African CLHIV, age 5–9 years, found that 41% and 38% of school-going CLHIV participated in physical education and organized after-school sport respectively, compared to 64% ($p = 0.0003$; and $p = <0.01$, respectively) of their HIV-negative counterparts [56]. It has also been shown that children and adolescents with HIV spend less time in 5 and 10 min bouts of moderate to vigorous physical activity compared to HIV negative controls, indicating lower aerobic fitness [57], which in turn impacts on physical activity and functioning. Improved physical activity in children, adolescents and young adults living with HIV, is linked to improved cognitive performance, lower levels of total body fat, dyslipidemia and inflammatory markers [58,59].

Limitations

A limitation of this scoping review is that some studies which may have been of relevance were not able to be included due to them including younger age ranges as well as adolescents. The age range determined for the review was based on the definition of adolescence from UNICEF and the World Health Organization (ages 10 to 19 years [27,28]) however some studies included younger children in their sample and thus could not be included.

Research opportunities and clinical recommendations

Based on the age limitations of this study, a further scoping review that includes children from ages 7 upwards would be of interest. Additionally, clinical research to evaluate the long terms needs of PHIVA is recommended, with a specific focus on physical health and functioning since this data is still scant. Additionally, it would be beneficial to have further clinical research that included HIV-negative comparison groups. As the population of PHIVA age into later adolescence and adulthood it would be of interest to note which of the physical sequelae persist. Clinically, this scoping review highlights the necessity of a model of care that is specific to PHIVA to address their unique monitoring and intervention needs.

Conclusion

With the exception of the results from two studies [30, 36] this scoping review showed that PHIVA face significant physical challenges relating to stunting, wasting and decreased physical health and functioning. Early and comprehensive access to ART helps to limit these physical sequelae [14, 35] but does not prevent it completely. HIV continues to be a global challenge and all aspects of physical sequelae in PHIVA need to be considered.

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Disclosure statement

The authors have no conflict of interest to declare.

Ethics

The scoping review did not involve human participants thus no ethical clearance certificate was required.

Patient consent statement

The scoping review did not involve human participants thus no patient consent was required.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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4.3 Conclusion

This chapter was comprised of publications of the scoping review protocol and the scoping review, identifying and describing the physical sequelae of perinatal HIV in adolescents. The following chapter is presented as a publication exploring the perceived challenges that PHIVA face.

Chapter 5 Phase one: qualitative study

5.1 Publication details

Chapter 5 is presented as an article published in *Vulnerable Children and Youth Studies*, an interdisciplinary journal addressing research, policy and care for areas of vulnerability in childhood. This was a qualitative study that aimed to establish the perceived challenges that PHIVA face, through interviews with the adolescents. Table 5.1 contains the details of the publication.

Table 5.1 Publication specifics of the qualitative study

Title of publication	The perceived challenges of perinatal HIV in adolescents: a qualitative study
Authors	Nicolette Comley-White; Joanne Potterton; Veronica Ntsiea
Journal name	*Vulnerable Children and Youth Studies*
ISSN	1745-0136
Impact factor	1.493
Year	2021
Volume (issue)	16(4)
Pages	320-333
DOI number	10.1080/17450128.2021.1891358

5.2 Author contributions

Table 5.2 presents the author contributions, as defined by Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019), the full detail of which is in Appendix 1.

Table 5.2 Author contributions for the qualitative study

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Formal analysis	√	√	
Investigation	√		
Resources	√		
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Project administration	√		
Funding acquisition	√	√	√

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5.4 Associated documentation

The documentation for this phase of data collection is available as the following appendices:

- Appendix 5: Information letter for phase one
- Appendix 6: Assent and consent for phase one participation and audio recording
- Appendix 7: Interview schedule

5.5 Published article: The perceived challenges of perinatal HIV in adolescents: a qualitative study

VULNERABLE CHILDREN AND YOUTH STUDIES
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The perceived challenges of perinatal HIV in adolescents: a qualitative study

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ABSTRACT

As access to antiretroviral therapy has improved, so the population of perinatally HIV-infected adolescents (PHIVA) has grown. Data is emerging showing that this distinctive population faces increased risk of physical and psychosocial challenges, but there is limited research on what their experiences and perceptions are. This study aimed to explore the perceived challenges that PHIVA have.

Adolescents with perinatal HIV participated in semi-structured individual interviews. Clinical data was collected from their files. Substantive statements from the transcribed interviews were aligned with deductive codes, and then further explored through inductive analysis.

Data saturation was reached at 19 interviews. The mean age of the participants was 13.1 (SD ±2.2) years and the majority were female (63.2%). All of the participants were virally suppressed and the mean CD4 percentage was 40.5 (SD ± 6.7).

The most common codes were poor endurance (n = 10; 52.6%), pain (n = 10; 52.6%) and fatigue (n = 7; 36.8%), with only one participant not experiencing any challenges. Other codes were decreased community participation, poor muscle strength and/or motor skills; emotional difficulties; cognitive issues and other health issues. Together these codes formed the categories of physical challenges, psychosocial challenges, and other health issues, leading to the theme 'living life as an adolescent with perinatally acquired HIV'.

Despite the full sample of PHIVA being virally suppressed, there were still noteworthy challenges that they experienced, with poor endurance, pain and fatigue being the most common. This potentially impacts on their community participation and their quality of life. Since not all PHIVA are as well managed as this group, one would expect even greater challenges in other PHIVA. This study highlights the importance of healthcare providers performing a comprehensive assessment of a PHIVA's health, thus tailoring a model of care specific to their needs.

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Introduction

HIV continues to be a major health concern in children and adolescents globally. As access to antiretroviral therapy (ART) continues to improve, the number of adolescents with vertically transmitted HIV grows, producing a unique population (Sohn & Hazra, 2013). Perinatally HIV-infected adolescents (PHIVA) have spent their lifetime living with a virus that crosses the blood-brain barrier causing known neurocognitive complications (Strazza et al., 2011). Many PHIVA have also taken ART for a substantial period, which presents its own challenges in terms of neurotoxicity and other side effects (Abers et al., 2014; Shah et al., 2016; Underwood et al., 2015).

Quantitative data is emerging, showing that PHIVA are at risk of decreased bone mineral density (Cruz, 2015; DiMeglio et al., 2013; Puthanakit & Siberry, 2013); delayed pubertal onset and sexual maturation (Bellavia et al., 2017; Cruz, 2015); stunted growth (Bunupuradah et al., 2016; Cruz, 2015; Jesson et al., 2019); and neurocognitive delays and mental health challenges (Lowenthal et al., 2014; Smith & Wilkins, 2015; Willen et al., 2017). Furthermore, qualitative studies have explored the challenges that PHIVA face in terms of psychosocial wellbeing, adherence and disclosure (Friedman Nestadt et al., 2018; Madiba, 2016; Ramaiya et al., 2016) but there is very little research (either qualitative or quantitative) on the sequelae that PHIVA face and their experiences thereof.

Thus, this study aimed to explore the perceived challenges that PHIVA have.

Materials and methods

Design

This study applied a qualitative design, with semi-structured individual interviews.

Participant selection and study site

Participants were adolescents attending a large HIV clinic and research unit in Johannesburg, South Africa, as part of a cohort study looking at the chronic effects of perinatal HIV: the childhood HAART alterations in normal growth, genes and AGing evaluation study (CHANGES) (M120871). Adolescence is defined as ages 10–19 years (UNICEF, 2016; World Health Organization, 2014) and can be divided into early (10–15 years), middle (14–17 years) and late (16–19 years) adolescence (World Health Organization, 2010). For the purposes of this study, early and middle adolescence was defined as 10 to 14 years and 15 to 17 years, respectively. This study forms part of a larger study, in which the appropriate outcome measures required have an upper age limit of 16 years, thus only participants in early and middle adolescence were included. Participants also needed to have a diagnosis of perinatally acquired HIV and were excluded if they did not have a parent/guardian available to give consent; if they had physical/cognitive impairments that prevented them from participating in the interview process or that were not related to HIV.

Procedure

Purposive sampling was used to identify participants in the clinic that met the age criteria, and to ensure that both males and females were represented. They were invited to participate and were interviewed in English in a private room. All participants were aware of their HIV status.

The principal investigator (PI) used a semi-structured interview schedule, with appropriate probes to establish what the adolescents perceived to be challenges in their health and physical status and how this impacted on their activities and community participation. An hour was allocated per interview and refreshments were provided. The participants were not reimbursed for their participation and the interviews were on the day that they attended the clinic. Clinical data was collected from participants' files.

Ethical considerations

The Human Research Ethics committee of the University of the Witwatersrand granted ethical clearance (M180226). Consent and assent for participation and audio recording was obtained from the parents/guardians and participants and all data was kept confidential.

Data analysis

The interviews were recorded using the AudioNote application, transcribed verbatim, anonymised (by removing all identifiers) and crosschecked for accuracy by the PI. At the end of each interview, the PI took field notes, capturing the essence of the interview (Gill et al., 2008). Manual coding was done independently by two investigators (NC-W and JP), who then discussed any discrepancies and reached a consensus on the codes. This process was done twice to ensure the validity of the data analysis through triangulation (Bengtsson, 2016). Substantive statements were identified and aligned with codes that had been developed deductively and then explored with inductive analysis. The codes were captured in a codebook, along with their definitions. Manifest analysis was used to quantify the content (Bengtsson, 2016). Based on the codes, categories were developed which lead to an overall theme (Erlingsson & Brysiewicz, 2017).

Results

Demographic information

After 19 interviews data saturation was reached. Eleven (57.9%) of the participants were in early adolescence. The mean age of the group was 13.1 (SD ±2.2) years and the majority were female (63.2%). Table 1 shows the descriptive information of the study sample.

The clinical data collected from the participants' files are presented in Table 2. All of the participants were virally suppressed [a viral load of less than 50 copies/ml (UNAIDS, 2016)] as per their latest blood test results. The mean age of initiation of ART was 1 year 9.9 months (SD ± 1 year 2.3 months) and the mean CD4 percentage was 40.5 (SD ± 6.7).

The medical history noted a period of decreased adherence for six of the 19 participants (31.6%), although all participants currently had good adherence to their

Table 1. Description of the participants (n = 19)

Demographic data	n = 19
Male	7 (36.8%)
Female	12 (63.2%)
Early adolescence (10–14 years)	11 (57.9%)
Middle adolescence (15–16 years)	8 (42.1%)
Mean age	13.1 (SD ±2.2) years

Table 2. Clinical data of the participants (n = 19)

Clinical data	n	Values
Mean age of HIV diagnosis	n = 15 (4 incomplete records)	1 year 5.9 months (SD ± 1 year 3.4 months)
Mean age of ART initiation	n = 19	1 year 9.9 months (SD ± 1 year 2.3 months)
Mean CD4 count	n = 14 (5 incomplete records)	999.5 (SD±281.8)
Mean CD4 percentage	n = 14 (5 incomplete records)	40.5 (SD±6.7)
Viral load < 50 copies/ml	n = 19	100%

Table 3. Previous comorbidities recorded in the medical file

Comorbidity	n = 19 (%)
Tuberculosis	5 (26.3)
Mental health challenges	2 (10.5)
Developmental delay in early childhood	1 (5.3%)
Lymphadenopathy	1 (5.3%)
Peripheral neuropathy	1 (5.3%)
Hypothyroidism	1 (5.3%)
Gynecomastia	1 (5.3%)
Pneumonia	1 (5.3%)
Meningitis	1 (5.3%)
Epilepsy	1 (5.3%)

medication. Previous comorbidities noted in the medical history are presented in Table 3, with tuberculosis being the most common (n = 5; 26.3%).

Frequency of codes of perceived challenges of perinatal HIV in adolescence

Table 4 shows the frequency of codes identified in the data. The most common codes were poor endurance (n = 10; 52.6%), pain (n = 10; 52.6%) and fatigue (n = 7; 36.8%). Only one (5.3%) participant did not indicate any challenges whatsoever.

Although it was not coded specifically, the researchers found it noteworthy that 11 of the 19 participants (57.9%) reported that they did not do any official sports at school,

Table 4. Frequency of codes of perceived challenges of perinatal HIV in adolescence

Code	Frequency n = 19 (%)
Poor endurance	10 (52.6%)
Pain	10 (52.6%)
Fatigue	7 (36.8%)
Decreased community participation	4 (21.1%)
Poor muscle strength and/or motor skills	3 (15.8%)
Emotional issues (difficulty with ART adherence, status disclosure and insight into the condition)	2 (10.5%)
Other health issues (dizziness, nausea)	2 (10.5%)
Cognitive issues (forgetfulness)	1 (5.3%)

although all of them did indicate some physical activity in the form of walking to school and/or playing with their friends in the community.

Poor endurance

Endurance problems were a challenge for the majority (52.6%) of the adolescents. A decrease in endurance manifested in comments around participants' inability to manage their sporting activities and not being able keep up with their friends during social physical activities. Adolescents spoke about how, for example, they are not able to play a full soccer match, to skip as much as their friends or to keep up in races.

> 'I'm resting alone [i.e. his friends don't need to rest as much as he does]. My coach knows my situation [about his HIV positive status].'
>
> (Male, age 15)
>
> 'I'm telling coach that I'm tired then she puts another player in my place. I cannot play inside [any other position on the field], I can play only goalkeeper.'
>
> (Male, age 10)

Pain

Participants spoke about pain in varying presentations. Each participant that mentioned pain spoke about how it affected their ability to carry out their activities of daily living, thus potentially influencing their participatory levels.

> 'Like every day [for] about an hour. I just lie down and sleep [including during school time].' [Referring to abdominal pains]
>
> (Female, age 14)
>
> 'Sometimes when I walk too much I get a pain here. In my chest. Even if I don't walk, sometimes it comes.'
>
> (Female, age 15)

Fatigue

Several participants reported feeling fatigued in their day-to-day life. This was expressed as a feeling of extreme tiredness and not feeling like they ever have enough rest.

> 'Sometimes when I wake up, I want to still stay in the bed. I still get tired.'
>
> (Male, age 14)
>
> 'Maybe I will wake up [at] 12 o'clock or 1 o'clock.' [When asked about waking up over the weekends]
>
> (Male, age 15)

Decreased community participation

Although the participants were not asked directly about their participatory levels, some volunteered information about what they do, or do not do, in terms of socialising and participating within their communities.

> 'I'm just sitting at my home. I don't have a lot of friends. Sometimes my friends just tell me that I need to go out, but I just, before I answer them, I just think about my health, because I know my status, but they don't know, so I just say "no, I'm not that kind of person, ok?"'
>
> (Female, age 15)

Poor muscle strength and/or motor skills

The participants were asked questions around how strong they feel, if they wished to improve in anything or if there was something in particular that they struggled to do, especially compared to their friends. Their responses reflected that some of them struggle with feeling weak and/or clumsy.

> 'When I run sometimes I trip myself . . . even on the smooth [ground].'
>
> (Female, age 15)
>
> 'They [friends] are stronger than me.'
>
> (Female, age 15)
>
> 'I would like to improve my fastness because I am a bit slow.'
>
> (Female, age 12)

Emotional issues

Some of the participants discussed challenges that they faced with ART adherence and with difficulties around disclosing their status. These challenges form part of the emotional wellbeing of adolescents and also speak to their insight into being HIV positive and the role of their ART.

> 'When I see my CD4 is low anything can happen at the moment. I can pass on now or something like that. I never used to take it [ART] much but now I take it recently . . .. My body feels more better . . . like I don't get sick and things like that. When my CD4 count was low I can feel the difference.' [When asked about his health now that he is taking ART again.]
>
> (Male, age 16)
>
> 'I'm struggling with telling my friends about my status. I'm scared they going to judge me.'
>
> (Male, age 16)

Other health issues

Some participants raised other challenges that they face, pertaining to forgetfulness (cognitive challenges), dizziness and nausea. Although these fell out of the scope of this study, it is still worthwhile to note as challenges in the life of an adolescent with perinatal HIV.

> 'Whenever I drink my pills [ART] . . ., whenever I am sleepy before I drink my pills I get drowsy and I have to wait two more hours then the pills have settled then I eventually sleep. Because when I drink it at that time, I'll be numb, I just want to sit down. And do nothing.' [This happens every day]
>
> (Female, age 15)
>
> [When asked if there was anything that she would like to improve with her health] 'I've got a problem of forgetting things, being told something, I will be like, I've forgotten, I totally forgotten.'
>
> (Female, age 15)

Emergence of categories and a theme of perceived challenges of perinatal HIV in adolescence

By grouping the codes, the investigators formed three categories: physical challenges, psychosocial challenges and other health issues. Together these showed the theme of 'living life as an adolescent with perinatally acquired HIV'. Figure 1 shows the formation of the categories and theme from the codes.

Discussion

This study explored the challenges that young adolescents with perinatally acquired HIV experience. All of the participants were virally suppressed and had good CD4 percentage counts. Although inadvertent, this is a positive finding since a review of the literature shows that in South African PHIVA viral suppression ranges from 69% to 81% (Anderson et al., 2020). The viral suppression and CD4 percentage of this study's sample indicates that they were well managed and currently adherent to their ART. This is expected since the clinic is a large research site and participants are followed up regularly as part of a larger study. This is certainly not the case for all PHIVA (Koenig et al., 2011) and so one would expect even greater challenges in those PHIVA who do not have regular, controlled access to ART and monitoring in a well-managed, urban HIV clinic. Despite their viral suppression, they still faced significant challenges, both physical and psychosocial, with only one participant not raising any challenges at all.

Physical challenges

The majority of the study participants (52.6%) had challenges with endurance. This manifested as struggling to keep up with their friends in sporting and recreational activities. Endurance is decreased in adults with HIV (Chisati & Vasseljen, 2015; Gomes-

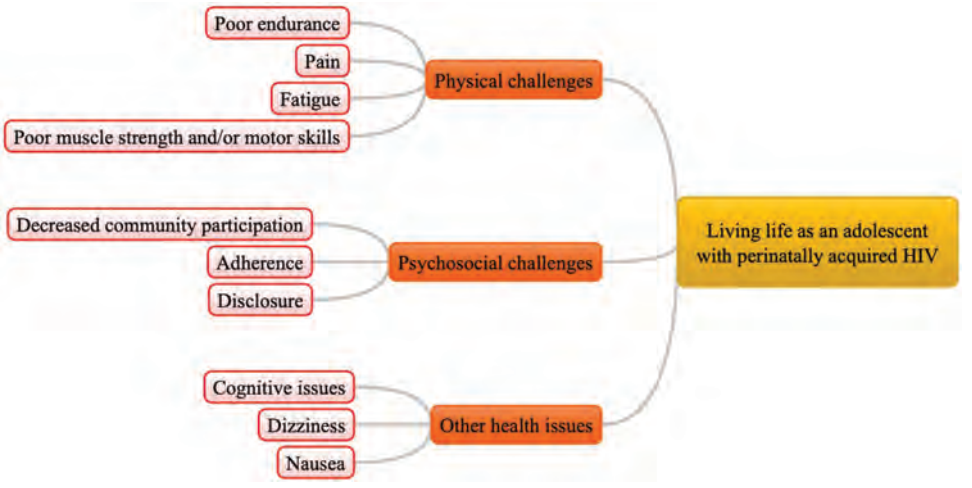

Figure 1. Establishing the codes, categories and theme of perceived challenges of perinatal HIV in adolescence.

Neto et al., 2018) as well as in HIV positive children (Sanyahumbi et al., 2017; Walker, 2015). Adolescents with HIV can present with aerobic impairment and decreased physical fitness (Somarriba et al., 2013). Potential reasons for this could be due to the multiple cardiac/cardiopulmonary complications that perinatally acquired HIV can present within adolescence (Githinji et al., 2019; Lipshultz et al., 2013); or overall deconditioning which could be as a result of decreased physical activity in children and adolescents with HIV (Macdonald et al., 2017; Tanaka et al., 2015).

Decreased physical activity was reported in this study, with the majority of the participants (57.9%) stating that they did not do any school sports. In a study done in the same geographical area, it was found that significantly fewer children with HIV participated in physical education and after-school organised activities compared to their HIV negative counterparts (Wong et al., 2016). The decreased levels of physical activity would influence the participants' endurance as well as their muscle strength and motor skills, which the participants of this study identified as a challenge.

HIV infection negatively influences muscle strength in both adults and children (Gomes-Neto et al., 2018; Grinspoon & Mulligan, 2003), with muscle power deficits still being apparent in PHIVA (Macdonald et al., 2017). Muscle wasting in people living with HIV can be attributed to abnormal protein metabolism, insufficient nutritional intake, malabsorptive disorders, metabolic changes, hypogonadism and excessive cytokine production (Grinspoon & Mulligan, 2003; Hsu et al., 2005). Myopathy could also be a cause of muscle weakness in people with HIV, due to the virus itself and/or as a side effect of ART (Chu et al., 2017; Kiselnik et al., 2015).

Another common physical challenge that the participants raised was fatigue confirming findings from another South African study in which 24.6% of adolescents with HIV experienced clinically significant fatigue (Coetzee et al., 2019). The aetiology of fatigue in HIV is multifaceted and not well understood (Coetzee et al., 2019; Potterton, 2016).

Fatigue severity can be a predictor of quality of life in HIV (Voss, 2005) and is strongly associated with depression and anxiety (Jong et al., 2010). Adolescents with HIV have reported that fatigue has a substantial impact on their ability to concentrate at school and maintain social participation (Loades et al., 2018). They reported experiencing fatigue that was not improved by sleep, as was similar in this study ('When I sleep and when I wake up it's like I'm lazy to wake up and I can't.' Male, age 14).

Lastly, pain was one of the codes making up the category of physical challenges. The participants who discussed pain did so in terms of activity limitations. It is well established that pain impacts a person's activities of daily living and function in people living with HIV (Lawson et al., 2014; Parker et al., 2014). In a systematic review on pain in adults living with HIV/AIDS a point prevalence of 54% to 83% was reported, and pain was shown to be a multifactorial impairment (Parker et al., 2014). The participants of this study spoke about pain in general terms, and not as a specific injury, highlighting the multifactorial complexity of HIV-associated pain.

Psychosocial challenges

The psychosocial challenges that arose were with regard to decreased community participation, adherence and disclosure. Participation restrictions are a complex component of daily living, influenced by many factors including the stigma associated with HIV (Audet et al., 2013). Stigma is a central issue for adolescents with HIV (Ayres et al., 2006) and many people living with HIV struggle with disclosing their status to their communities. As was seen in this study, PHIVA are scared of being judged by their friends, and this has further impact on a person's participation levels, especially if they disclose their status and face segregation because of it.

Participation restrictions can also be affected by fatigue (Loades et al., 2018) and pain (Katz, 2002). It is apparent from the literature and the experiences of this study's participants that participation restrictions are multifactorial for PHIVA. Decreased participation in people with HIV is intertwined with depression and other mental health challenges (Rusch et al., 2004). Thus in this vulnerable population, who are already prone to mental health problems (Lowenthal et al., 2014;) and who often face significant life events such as bereavement, healthcare workers need to be extra vigilant in trying to address the impairments and limitations that PHIVA face.

Other health issues

Additional codes that were noteworthy but fell out of the scope of this study were issues around cognition, dizziness and nausea. Dizziness and nausea are very common side effects of ART in adolescents (Tukei et al., 2012) and can influence a person's participation and quality of life. Furthermore, cognitive issues have been shown to be prevalent sequelae of perinatal HIV in adolescents (Ene et al., 2014; Willen et al., 2017) and can potentially be compounded by the other challenges that PHIVA face, such as fatigue and decreased participation.

Limitations and recommendations

The sample for this study was from a single clinic in Johannesburg, South Africa, and thus the results of the study are not generalizable to all PHIVA. Additionally, the upper age limit of this study was 16 years and older PHIVA would perhaps have different challenges to share. Likewise, participants who could not consent to participation due to a caregiver not being present might have had varied experiences of living with perinatal HIV. Recommendations for future research would be to broaden the study to a wider geographical and sociodemographic range. The clinical recommendation to healthcare providers is to ensure comprehensive assessments of all PHIVA, thereby establishing what their individual challenges are and tailoring an accurate model of care for them.

Conclusion

This qualitative research offered insight into individual experiences of living life as an adolescent with perinatally acquired HIV. The two key categories that emerged were physical challenges and psychosocial challenges, with fatigue, poor endurance, pain and participation restrictions being significant components. These two categories, along with a third category of other health issues, formed the theme of 'Living life as an adolescent with perinatally acquired HIV'. For effective health management of PHIVA all challenges that the adolescent may face need to be considered.

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5.6 Conclusion

This chapter presented the findings of a qualitative study exploring the perceived physical sequelae in PHIVA, which was published in *Vulnerable Children and Youth Studies*. The following chapter presents the two manuscripts arising from the second phase of this study.

Chapter 6 Phase two: quantitative study

Chapter 6 presents the results from the second phase of this study: the quantitative, cross-sectional analysis of physical sequelae in PHIVA, with an HIV-negative comparison group. This study generated a substantial amount of data and the decision was made to divide the results between two manuscripts so as to not lose any of the value of the findings. Both manuscripts have been submitted to journals and are currently under review.

6.1 Disability, fatigue and peripheral neuropathy

6.1.1 Manuscript details

The first manuscript of this chapter presents the results for the outcome measures assessing disability, fatigue and peripheral neuropathy in PHIVA compared to HIV-negative peers. The key finding of this study is that PHIVA have significantly greater levels of fatigue intensity and disability compared to their peers.

The manuscript was submitted to *Vulnerable Children and Youth Studies*, a multidisciplinary journal addressing health and wellbeing in children and youth, and is currently under review. This chapter presents the manuscript as per the requirements of the journal submission guidelines. Details of the manuscript are presented in Table 6.1.

Table 6.1 Manuscript specifics of the first quantitative study

Title of manuscript	Disability and fatigue in adolescents with perinatal HIV
Authors	Nicolette Comley-White; Joanne Potterton; Veronica Ntsiea
Journal name	*Vulnerable Children and Youth Studies*
ISSN	1745-0136
Impact factor	1.493
Year	2022
Status	Under review

6.1.2 Author contributions

The author contributions as described by Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019) are presented in Table 6.2, with further detail on the definitions available in Appendix 1.

Table 6.2 Author contributions for the first quantitative study

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Formal analysis	√		
Investigation	√		
Resources	√	√	
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Project administration	√		
Funding acquisition	√	√	√

6.1.3 Manuscript under review: Disability and fatigue in adolescents with perinatal HIV

Disability and fatigue in adolescents with perinatal HIV

Journal:	*AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies*
Manuscript ID	VCY-2022-01-0093
Journal Selection:	Vulnerable Children & Youth Studies
Keywords:	HIV, perinatal, adolescence, disability, fatigue

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Disability and fatigue in adolescents with perinatal HIV

Abstract

Perinatally HIV-infected adolescents (PHIVA) experience many physical sequelae but little is known about their levels of disability, fatigue or peripheral neuropathy. This study aimed to determine these sequelae through a cross-sectional analysis in a population of PHIVA and HIV-negative adolescents. Outcome measures used were the HIV-related Fatigue Scale, World Health Organization Disability Assessment Schedule 2.0 and the Brief Peripheral Neuropathy Screen. Of the 249 participants assessed, 59% (n=147) were PHIVA, and the mean age of the participants was 12 years. Clinical data for the PHIVA group showed that the majority (87.1%) were virally suppressed. When compared to the HIV-negative group PHIVA presented with significantly greater levels of fatigue intensity [1.2(SD±0.5) vs. 1.5(SD±0.9) p=0.022] and disability [9.2(±6.8) vs. 11.5(±8.9) p=0.023], with specific limitations in mobility, self-care and participation. In conclusion, PHIVA face challenges with disability and fatigue highlighting the necessity of comprehensive management for this population.

Key words: HIV; perinatal; adolescence; disability; fatigue

Word count: 2305

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Introduction

The human immunodeficiency virus (HIV) continues to be a global health challenge across the age spectrum, with 37.7 million people living with HIV in 2020, of which 1.7 million are children (UNAIDS, 2021). With increasing access to antiretroviral therapy (ART), children with HIV (CLHIV) have lower rates of mortality and so the number of perinatally-HIV infected adolescents (PHIVA) is expanding, presenting a population living with chronic illness (Fairlie et al., 2014; Sohn & Hazra, 2013).

It is well established that perinatal HIV negatively impacts on a child's growth and development (Strehlau et al., 2019; Whitehead et al., 2014), in turn impacting on physical (Arbeitman et al., 2014; Bellavia et al., 2017; Ferrand et al., 2012; Jesson et al., 2019; Martins et al., 2017), neurocognitive and mental health (Laughton et al., 2013; Lowenthal et al., 2014; Smith & Wilkins, 2015; Willen et al., 2017) outcomes in adolescence. Other sequelae of HIV faced in childhood include peripheral neuropathy (Amiji et al., 2021; Benjamin et al., 2015; Esteban et al., 2009; Peters et al., 2014), disability, participation restrictions and decreased socialization (Maddocks et al., 2021; Rukuni et al., 2018). Qualitatively, PHIVA have expressed challenges with participation and fatigue (Comley-White et al., 2021) but little is known about the role that many of these sequelae play in the lives of PHIVA. Thus the aim of this study was to establish the level of disability, fatigue and peripheral neuropathy in adolescents with perinatal HIV.

Materials and methods

Study Design

This study was a cross-sectional analysis of PHIVA with a comparison group of HIV-negative adolescents from similar age- and socio-demographic backgrounds, and formed part

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of a larger study whose aim was to develop a model of care for PHIVA (Comley-White et al., 2019).

Setting and Participants

Data was collected from a cohort of children who had been followed from birth as part of the Childhood HAART Alterations in Normal Growth, Genes and AGing Evaluation Study (CHANGES) based at a large, urban paediatric HIV research and services clinic in Johannesburg, South Africa. The HIV-negative participants were accessed through the research unit's database of family and community members of the PHIVA and thus were from the same socioeconomic and geographical background as the PHIVA.

Adolescence is defined as 10 to 19 years (UNICEF, 2016; World Health Organization, 2014) and the children included in this study fell into the early and middle phases of adolescence, with a maximum age of 16 years. The exclusion criteria were: if HIV was acquired horizontally; if the participants had any cognitive/physical impairments that prevented them from taking part in the assessment process or that were not related to HIV (for example, a traumatic brain injury).

Procedure and instrumentation

Participants were informed telephonically about the study and invited to participate. If they accepted then a date was booked for their assessment at the study site. Upon arrival parental consent and child assent was obtained. The clinical counsellor, principal investigator and a research assistant (the latter two being physiotherapists) collected data on the participants' disability (in the domains of cognition, mobility, self-care, getting along, life activities and participation), fatigue and peripheral neuropathy using the World Health Organization Disability Assessment Schedule (WHODAS-2 Children and Youth), HIV-related fatigue

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scale and brief peripheral neuropathy screen, respectively. Height and weight were measured and clinical and demographic data were recorded from the participants' files.

Ethical considerations

Ethical clearance was granted by The Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M180226) and all ethical requirements were observed.

Data Analysis

Frequencies, means and standard deviations were used to describe the demographic and clinical data. Body mass index (BMI)-for-age z-scores (BAZ) and height-for-age z-scores (HAZ) were calculated using World Health Organization reference data (de Onis, 2007; World Health Organization, 2021). Wasted was defined as BMI-for-age <-2 standard deviations (SD) and stunted was defined as height-for-age <-2 SD (World Health Organization, 2008).

Normality tests were run for all variables and data were normally distributed, with exception of the fatigue intensity and the WHODAS-2 subsections for cognition and self-care. To compare the two groups, independent sample t tests were used except for the non-normative data that had Mann-Whitney U tests applied. Statistical significance was set at $p<0.05$ (Vexler & Hutson, 2018). Any potential influence of clinical variables on the outcome measures was established with multivariate regression analyses.

During data capturing and cleaning any data from incomplete records were removed. This occurred infrequently but the sample size for each of the affected outcome measures needed to be adjusted on analysis and is indicated in the results' tables.

Results

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Demographic and clinical information

This cross-sectional study analyzed 249 adolescents, of which 59% (n=147) were PHIVA and 41% (n=102) were HIV-negative. The two groups had the same mean age. Table 1 presents the demographic information for the study population.

[Table 1 near here]

Table 2 presents the PHIVA clinical data. The mean age of HIV diagnosis was 4.7 months (SD±5.9) and ART was initiated at a mean age of 8.5 months (SD±6.6 months). The majority (87.1%) of the participants had viral loads <200 copies/ml and a mean CD4% of 38.3 (SD±7.1).

[Table 2 near here]

Anthropometry

The PHIVA group versus the HIV-negative group presented with statistically significant lower height (p<0.001), weight (p<0.001) and BMI (p=0.004). Significantly more PHIVA presented with stunting and wasting compared the HIV-negative group (23.1% vs. 2.9% and 6.8% vs. 4.9% respectively; p=0.036). Table 3 presents further data on the anthropometry of the participants.

[Table 3 near here]

Disability

For disability the WHODAS-2 results showed that the PHIVA participants scored significantly higher (i.e. greater difficulty level) for the overall score (p=0.023), with significant differences in the sub-scores of Getting Around (p=0.014), Self-Care (p=0.047) and Participation in Society (p<0.001). Table 4 presents further details on the WHODAS-2 results.

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[Table 4 near here]

Fatigue

Table 5 presents the results of fatigue intensity in the participants. The PHIVA groups had significantly greater fatigue intensity compared to the HIV negative adolescents (p=0.022).

[Table 5 near here]

Peripheral neuropathy

While the PHIVA group consistently had a higher percentage of participants presenting with signs of peripheral neuropathy there were no significant differences between the two groups, with the exception of decreased unilateral vibration sense in the lower limb (p=0.006). Table 6 presents further detail on this.

[Table 6 near here]

Clinical predictors

A multivariate linear regression model was used to investigate the relationship between the clinical variables (age, sex, height, weight, BMI, viral suppression, current CD4%, age of HIV diagnosis and age of ART initiation) and the outcome measures. The combination of all of the clinical variables into a regression model as a whole was only significant for prediction of fatigue intensity (R^2=0.171; p=0.030), and the age of HIV diagnosis specifically was a significant predictor of fatigue intensity (p=0.010).

Discussion

The aim of this study was to determine the level of disability, fatigue and peripheral neuropathy in PHIVA compared to HIV-negative adolescents. The study found that PHIVA

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have significant levels of disability and fatigue, despite regular access to healthcare, early diagnosis of HIV, early ART initiation and high levels of viral suppression.

The PHIVA group presented with significantly lower weight ($p<0.001$), height ($p<0.001$) and BMI ($p=0.004$) and were significantly more wasted ($p=0.036$) and stunted ($p=0.036$). These findings are similar to those in other studies with PHIVA (Arbeitman et al., 2014; Jesson et al., 2019; Williams & Jesson, 2018) and are indicative of the long-term effects that perinatal HIV has on growth.

Disability

In this study PHIVA experienced an overall greater level of disability than the comparison group. Children living with HIV (CLHIV) frequently experience disability and decreased participation (Maddocks et al., 2021; Rukuni et al., 2018) and these results highlight the continuance of disability through to adolescence.

On analysis of the sub-scores on the WHODAS-2 it was found that the PHIVA participants had significant more difficulty in Getting Around, Self-care and Participation in Society. The Getting Around sub-score addresses activities such as standing for a period of time, walking long distances and getting up from sitting, thus this speaks to their level of physical disability and potential inability to manage day to day activities. The increased levels of fatigue that were also apparent in these participants would impact on these sub-scores of WHODAS-2.

For the Self-care component, activities of daily living (ADLs) are addressed. Adults with HIV have reported decreased self-care activities which are associated with cognitive impairment (Laverick et al., 2017) and although ART decreases dependence in ADLs (Kakinami et al., 2011) living with a chronic illness impacts significantly on ADLs and quality of life (QOL) for adolescents (Sawyer et al., 2007).

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The Participation in Society sub-score addresses involvement in activities such as attending social events and parties. A qualitative study found that decreased community participation was a common problem experienced by PHIVA (Comley-White et al., 2021). Decreased participation in people with HIV is a multi-factorial challenge that can be affected by stigma (Audet et al., 2013), mental health impairments (Rusch et al., 2004) and fatigue (Loades et al., 2018). Participation in society is not the only aspect that can be a challenge for PHIVA, but also within the home context since PHIVA can also struggle significantly with maintaining family functioning and the associated relationships (Louthrenoo et al., 2014). Participation can also refer to interaction with friends and in play-based activities. While the frequency of play decreases with age and thus may become less significant in adolescence it is still important to consider. Levels of play outdoors are significantly decreased in CLHIV compared to healthy children (Munambah et al., 2021) and this can impact on participation and motor development (Meissner et al., 2017; Pellegrini & Smith, 1998).

Fatigue

Fatigue was also a significant finding in this study, with PHIVA experiencing a significantly greater intensity than the comparison group. Although fatigue in paediatric HIV is not extensively researched it is a common and difficult symptom in adult HIV (Potterton, 2016). Proposed contributors to fatigue in HIV are the metabolic and hematologic changes associated with the virus and treatment; physiological factors such as anemia; psychological factors like anxiety and depression; and behavioral factors such as decreased physical activity and poor sleep hygiene (Perazzo et al., 2017).

In contrast to the findings of this study, ter Haar et al. (2021) found that their sample of PHIVA did not experience greater fatigue than adolescents with chronic disease, HIV-negative controls or the general Dutch population, however it should be noted that they had a

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small sample size (14 PHIVA) and used the Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale which, although designed to measure fatigue in chronic conditions, is not specific to HIV, unlike the scale used in our study. Although they did not find significant differences in fatigue levels they did establish that fatigue in PHIVA was associated with lower health-related QOL.

Loades et al. (2018) explored the experiences of fatigue in South African adolescents with HIV, showing that they encountered difficulties with concentrating at school, social interaction and participation. This is in line with the findings of our study which showed significantly less participation in society for PHIVA. A longitudinal study that followed HIV-positive adults with fatigue over a three year period found that fatigue did not spontaneously remit, highlighting the necessity for interventions targeted at managing fatigue in HIV (Barroso et al., 2015).

The multivariate regression analysis established a predictive relationship between the overall clinical presentation of PHIVA and their fatigue intensity, specifically with regards to their age of HIV diagnosis. This predictive factor thus forms a key part of patient management in the clinical setting, reiterating the importance of assessing fatigue in PHIVA.

Peripheral neuropathy

Peripheral neuropathy was not an apparent impairment in this study. Although significantly more PHIVA did experience decreased vibration sense in the right lower limb (p=0.006) no other signs of peripheral neuropathy were established. Since this study sample had good healthcare access and regular monitoring it is likely that any previous early signs of peripheral neuropathy were identified and mitigated through a change in ART management.

Peripheral neuropathy has been found to be a problem in both adult (Kaku & Simpson, 2014) and pediatric (Amiji et al., 2021; Benjamin et al., 2015; Esteban et al., 2009; Peters et al.,

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2014) HIV populations, causing severe pain, impaired function and decreased QOL (Biraguma & Rhoda, 2012; Dudley et al., 2019; Navis et al., 2018; Nicholas et al., 2007; Saylor et al., 2017). Although the PHIVA in this study did not present with significant peripheral neuropathy it is still a problematic sequelae of HIV in many populations and patients should have regular screening and early intervention.

Limitations and recommendations

The participants of this study were sourced from one site thus limiting the generalizability of the findings. Furthermore, the study site formed part of a research unit and the participants received regular follow-up and good management thus the sequelae found in this study may be greater in the general PHIVA population who mostly do not have the equivalent access to healthcare. Lastly, many of the comparison participants were siblings of the HIV-positive participants and may have been HIV-exposed uninfected (HEU) in utero which has also been shown to impact on growth and neurodevelopment (Wedderburn et al., 2019). With these limitations considered, it would be of clinical value for this study design to be replicated in other populations of PHIVA in different geographical and sociodemographic settings. Furthermore, it is recommended that PHIVA are regularly assessed for fatigue and disability and that healthcare professionals working with this population of youth structure their care to address the impairments, activity limitations and participation restrictions that arise.

Conclusion

Despite good medical management and high levels of viral suppression, many adolescents living with perinatal HIV encounter significant levels of disability and fatigue. This can affect their community participation and general well-being and thus it is imperative to address these areas when managing PHIVA.

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Declaration of interest

The authors have no conflict of interest to declare.

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Tables

Table 1: Demographic data of the study population (n=249)

	HIV positive adolescents n=147	**HIV negative adolescents n=102**	**P**
Female, n (%)	74 (50.3)	42 (41.2)	0.154
Male, n (%)	73 (49.7)	60 (58.8)	0.154
Age in years, mean (SD)	12 (±2)	12 (±1)	0.91
Minimum age	10 years 0 months	10 years 0 months	-
Maximum age	15 years 12 months	16 years 11 months	-

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Table 2. Clinical data of the HIV positive participants (n =147)

Clinical data	**Values**
Age in months at HIV diagnosis, mean (SD)	4.7 (±5.9)
n=107	
Age in months at antiretroviral therapy initiation, mean (SD)	8.5 (±6.6)
n=147	
CD4 percentage, mean (SD)	38.3 (±7.1)
n=145	
CD4 count in cells/mm^3, mean (SD)	1011.6 (±305.7)
n=147	
Participants with viral load > 200 copies/ml, n (%)	19 (12.9%)
n=147	
Participants with viral load < 200 copies/ml, n (%)	128 (87.1%)
n=147	

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Table 3: Anthropometric results for the study population (n=249)

	HIV positive adolescents n=147	**HIV negative adolescents** n=102	**P value**
Height in meters, mean (SD)	1.4 (±0.1)	1.5 (±0.1)	**<0.001**
Weight in kilograms, mean (SD)	36.8 (±10.2)	42.8 (±13.2)	**<0.001**
BMI, mean (SD)	17.9 (±3.2)	19.3 (±4.3)	**0.004**
HAZ, mean (SD)	-1.1 (±1.1)	-0.3 (±1.0)	0.246
BAZ, mean (SD)	-0.3 (±1.2)	0.3 (±1.4)	0.236
Stunted, n (%)	34 (23.1)	3 (2.9)	**0.036**
Wasted, n (%)	10 (6.8)	5 (4.9)	**0.036**

HAZ= height-for-age z-score; BMI= body mass index: BAZ= BMI-for-age z-score; stunted=<-2SD; wasted=<-2SD

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Table 4: WHODAS-2 results for the study population (n=249)

	HIV positive adolescents n=147	**HIV negative adolescents** n=102	**P value**
WHODAS: Understanding and Communicating, mean (SD)	1.7 (±2.4)	1.3 (±2.0)	0.281
WHODAS: Getting Around, mean (SD)	1.1 (±1.8)	0.6 (±1.1)	**0.014**
WHODAS: Self-care, mean (SD)	0.5 (±1.2)	0.3 (±0.9)	**0.047**
WHODAS: Getting Along with People, mean (SD)	1.8 (±2.0)	1.8 (±2.1)	0.906
WHODAS: Home Life Activities, mean (SD)	1.6 (±2.8)	2.0 (±2.7)	0.282
WHODAS: School Life Activities, mean (SD)	1.9 (±3.0)	1.7 (±2.6)	0.712
WHODAS: Participation in Society, mean (SD)	2.9 (±3.0)	1.4 (±1.8)	**<0.001**
WHODAS: Total Score, mean (SD)	11.5 (±8.9)	9.2 (±6.8)	**0.023**

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Table 5: Fatigue intensity results for the study population (n=249)

	HIV positive adolescents n=147	**HIV negative adolescents** n=101 (1 incomplete record)	**P value**
Fatigue intensity, mean (SD)	1.5 (±0.9)	1.2 (±0.5)	**0.022**

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Table 6: Brief Peripheral neuropathy screen results for the study population (n=249)

	HIV positive adolescents n=145 (2 incomplete records)	**HIV negative adolescents** n=102	**P value**
Subjective reporting of history of symptoms, n (%)	9 (6.2)	4 (3.9)	0.443
Vibration sense deficit right lower limb, n (%)	19 (13.1)	3 (2.9)	**0.006**
Vibration sense deficit left lower limb, n (%)	18 (12.4)	6 (5.9)	0.094
Ankle reflex absent right lower limb, n (%)	3 (2.1)	1 (1.0)	0.395
Ankle reflex absent left lower limb, n (%)	3 (2.1)	0 (0.0)	0.170
Pin prick sense deficit right lower limb (3 incomplete records for HIV positive group)	0 (0.0)	0 (0.0)	n/a*
Pin prick sense deficit left lower limb (3 incomplete records for HIV positive group)	0 (0.0)	0 (0.0)	n/a*

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*n/a= not applicable; pinprick sensitivity is a constant (i.e. both groups had pin-prick sensation intact)

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6.2 Muscle strength, endurance and motor performance

6.2.1 Manuscript details

The second manuscript of Chapter 6 presents the results of the assessment of muscle strength, endurance and motor performance in PHIVA, compared to an HIV-negative group of adolescents. Although the PHIVA performed poorly across all three outcomes, motor performance was significantly affected.

The manuscript was submitted to *AIDS Care*, a journal for medical research in HIV/AIDS, and is currently under review. The manuscript is presented in this chapter as per the journal guidelines for submission. Table 6.3 presents details on the manuscript.

Table 6.3 Manuscript specifics of the second quantitative study

Title of manuscript	Physical functioning in adolescents with perinatal HIV
Authors	Nicolette Comley-White; Veronica Ntsiea; Joanne Potterton
Journal name	*AIDS Care*
ISSN	1360-0451
Impact factor	2.320
Year	2021
Status	Under review

6.2.2 Author contributions

Table 6.4 details the author contributions to the manuscript, based on the terminology of Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019), with further detail on the definitions available in Appendix 1.

Table 6.4 Author contributions for the second quantitative study

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Formal analysis	√		
Investigation	√		
Resources	√	√	
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Project administration	√		
Funding acquisition	√	√	√

6.2.3 Manuscript under review: Physical functioning in adolescents with perinatal HIV

Physical functioning in adolescents with perinatal HIV

Journal:	*AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies*
Manuscript ID	AC-2021-12-1613
Journal Selection:	AIDS Care
Keywords:	HIV, physical functioning, muscle strength, endurance, growth

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Physical functioning in adolescents with perinatal HIV

Perinatal HIV impacts on growth and development in childhood, with physical impairments such as growth limitations, decreased physical activity, reduced exercise tolerance and cardiopulmonary dysfunction continuing into adolescence. There is limited data on other physical functioning domains in perinatally HIV-infected adolescents (PHIVA) thus the aim of this study was to establish the physical sequelae of perinatal HIV in adolescents. This cross-sectional study compared PHIVA with HIV-negative adolescents, assessing anthropometry, muscle strength, endurance and motor performance. All ethical considerations were adhered to. The study included 147 PHIVA and 102 HIV-negative adolescents, aged 10-16 years. The majority (87.1%) of PHIVA were virally suppressed however, they still showed significant deficits in height ($p<0.001$), weight ($p<0.001$) and BMI ($p=0.004$). Both groups performed poorly in muscle strength and endurance but did not differ significantly. In motor performance, the PHIVA scored significantly lower for manual dexterity and balance, with significantly more PHIVA with motor difficulty. A regression analysis showed that viral suppression predicted muscle strength ($p=0.032$) and age positively predicted endurance ($p=0.044$) and negatively predicated aiming and catching ($p=0.009$). In conclusion, PHIVA face growth deficits and challenges with motor performance, especially with manual dexterity and balance.

Keywords: HIV; physical functioning; muscle strength; endurance; growth; adolescence.

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Introduction

Despite great strides in HIV-related healthcare the disease continues to be a global burden, both in adult and childhood populations (Pandey & Galvani, 2019). In 2019 there were an estimated 1.7 million adolescents living with HIV (UNICEF, 2020a) and as access to antiretroviral therapy (ART) continues to expand so this population increases, shifting paediatric HIV management to that of a chronic disease (Fairlie et al., 2014; Sohn & Hazra, 2013).

Due to the nature of the virus itself, as well as the toxicity of drug therapy, children and adolescents are particularly vulnerable to adverse effects as they go through critical periods of growth and development (Flynn & Abrams, 2019). Research is showing that perinatally HIV-infected adolescents (PHIVA) face neurocognitive dysfunction and mental health issues (Laughton et al., 2013; Lowenthal et al., 2014; Smith & Wilkins, 2015; Willen et al., 2017), as well as physical sequelae such as growth impairment (Arbeitman et al., 2014; Jesson et al., 2019), decreased physical activity (Martins et al., 2017) reduced exercise tolerance (Ferrand et al., 2012) and impaired cardiopulmonary health (Miller et al., 2013). Adolescents themselves have expressed that they experience physical difficulties, with poor endurance, pain and fatigue being the most common complaints (Comley-White et al., 2021).

With the increasing number of PHIVA there is progressively more research that is becoming available on the long-term effects of perinatal HIV, however, there are still many gaps in the clinical knowledge. While it is well-established that children with perinatal HIV are negatively impacted in growth and development (Strehlau et al., 2019; Whitehead et al., 2014) there are areas of concern in PHIVA that need further

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investigation. Thus the aim of this study was to establish the physical sequelae of perinatal HIV in adolescents.

Materials and methods

Design

This study used a cross-sectional design, comparing data between PHIVA and a comparison group of HIV-uninfected adolescents, forming one of the phases of a larger study used for the development of a model of care for PHIVA. Further details on the methodology of this larger study have been published elsewhere (Comley-White et al., 2019).

Study site and participant selection

The study site was a large, urban HIV clinic and research unit in Johannesburg, South Africa. Data was collected from a longitudinal cohort of PHIVA that were followed through childhood as part of the Childhood HAART Alterations in Normal Growth, Genes and AGing Evaluation Study (CHANGES). The HIV-uninfected participants were accessed via a database that forms part of the CHANGES study. These adolescents are HIV negative family members, friends or community members of the PHIVA cohort, and as such are from a similar sociodemographic background as the PHIVA participants.

Adolescence is defined as 10 to 19 years (UNICEF, 2016; World Health Organization, 2014) and all of the CHANGES children were in the early and middle phases of adolescence, with a cut-off age of 16 years. Participants were excluded if 1) they had any cognitive/physical impairments that prevented them from taking part in the

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assessment process or that were not related to HIV (for example, a traumatic brain injury); 2) if the mode of transmission for the PHIVA group was not vertically acquired.

Procedure and instrumentation

Suitable adolescents were identified from the clinic's data base and contacted telephonically with information about the study and an invitation to participate. Upon arrival at the study site, the clinic counsellor obtained participant assent and parental consent. Clinical and demographic data were collected from the participants' files and the following variables were assessed by the principal investigator and a research assistant (both of whom were physiotherapists): height, weight, muscle strength, endurance and motor performance. The standing broad jump and the shuttle run test were used to assess muscle strength and endurance, respectively, and the Movement Assessment Battery for Children- Second Edition (MABC-2) evaluated motor performance.

Ethical considerations

The Human Research Ethics Committee (Medical) of the University of the Witwatersrand granted ethical clearance (M180226) and all ethical requirements were adhered to.

Data analysis

The demographic data were described with frequencies, means and standard deviations. Height-for-age z-scores (HAZ) and body mass index (BMI)-for-age z-scores (BAZ) were calculated using World Health Organization reference data (de Onis, 2007; World Health Organization, 2021). Weight-for-age reference data are not available for children over 10 years old since pubertal growth spurts can distort the relativity of height to body

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mass (World Health Organization, 2021). Stunted was defined as height-for-age <-2 standard deviations (SD) and wasted was defined as BMI-for-age <-2SD (World Health Organization, 2008).

Normality tests were run for all variables and data were normally distributed, with exception of the final standard score of the MABC-2. To compare the two groups, independent sample t tests were used except for the non-normative data that had Mann-Whitney U tests applied. Statistical significance was set at $p<0.05$ (Vexler & Hutson, 2018). Multivariate linear regression analyses were run to analyse the influence of the clinical variables on the outcome measures.

Data for the MABC-2 were analysed to show the standard score means and standard deviations for each component, as well as the frequency and percentages of the participants whose standard score results placed them in the red, amber or green zones. These zones are indicative of significant motor difficulty, at risk of motor difficulty and no motor difficulty, respectively.

At the time of data cleaning and analysis it was observed that there were sporadic data collection forms with information incomplete. The sample size for each of these outcome measures was adjusted on analysis and is reflected in the tables of results.

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Results

Demographic and clinical information

The study included 249 participants, of which 59% (n=147) were PHIVA and 41% (n=102) were the HIV-negative comparison group. The mean age for the two groups was the same. Table 1 presents the demographic information for the study population.

Insert Table 1 here

Clinical data for the PHIVA group is presented in Table 2. The mean age at which the participants' HIV diagnosis was made was 4.7 months (SD±5.9) and the mean age at ART initiation was 8.5 months (SD±6.6 months). At the time of assessment, the group had a mean CD4% of 38.3 (SD±7.1) and the majority (87.1%) of the participants had viral loads <200 copies/ml.

Insert Table 2 here

Anthropometry

The PHIVA group presented with statistically significant lower weight ($p<0.001$), height ($p<0.001$) and BMI ($p=0.004$) when compared to the HIV negative adolescents. Although the mean HAZ and BAZ results for each group were within acceptable ranges (i.e. >-2SD), the PHIVA group scored lower for both variables ($p=0.246$ and $p=0.236$, respectively) and significantly more PHIVA were stunted and wasted compared to the HIV negative adolescents (23.1% vs. 2.9% and 6.8% vs. 4.9% respectively; $p=0.036$). Further data on the anthropometric results are presented in Table 3.

Insert Table 3 here

Muscle strength and endurance

The two groups did not differ significantly in their muscle strength or endurance. Table 4 presents the results of the muscle strength and endurance assessments.

Insert Table 4 here

Motor performance

On the MABC-2 the PHIVA performed worse than the HIV-negative group, however the difference in the final standard score was not statistically significant ($p=0.144$). Despite this, there are important differences on the subscales. The PHIVA

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group performed significantly worse than the comparison group for manual dexterity (p=0.021) and balance (p=0.020) standard score means. Furthermore, an analysis of the frequencies of participants scoring in the red (i.e. significant motor difficulty), amber (i.e. at risk of motor difficulty) and green (i.e. no motor difficulty) zones showed that significantly more PHIVA than HIV-negative participants were in the red zone for the final MABC-2 scores (13.2% vs. 4.1%, p=0.054). Although not reaching statistical significance, it is noteworthy that there were more PHIVA than HIV negative participants who scored in the red zones for manual dexterity (15.8% vs. 11.1%, p=0.064), and balance (6.3% vs 4.0%, p=0.082); and in the amber zones for manual dexterity (9.6% vs. 3.0%, p=0.064), aiming and catching (6.8% vs. 3.0%, p=0.306) and balance (4.2% vs. 0.0%, p=0.082), Table 5 presents further results on the participants' motor performance.

Insert Table 5 here

Clinical predictors

A multivariate linear regression model was used to analyse the influence of the clinical variables of age, sex, height, weight, BMI, viral suppression, current CD4%, age of HIV diagnosis and age of ART initiation on the outcome variables, namely muscle strength, endurance and motor performance. Once the assumptions of multivariate normality, linearity, freedom from extreme values and multi-collinearity were cleared, the regression analysis was performed.

The regression model as a whole (i.e. a combination of all of the clinical variables) was significant for muscle strength (R^2=0.193; p=0.14) and endurance (R^2=0.213; p=0.006) however the model was not significant for predicting motor performance (p=0.886). Table 6 presents the results of investigating each clinical

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variable individually to establish the independent variables prediction of the dependent variables.

Insert Table 6 here

For the individual clinical variables, only viral suppression statistically significantly predicted muscle strength (p=0.032) while age significantly predicted the endurance (p=0.044). Finally, although the model was not a good fit for motor performance, age was the only variable that was statistically significant in predicting aiming and catching (p=0.009), however it was a negative prediction (while the former two were positive predictions).

Discussion

This study aimed to establish the physical sequelae of perinatal HIV in adolescents through a cross-sectional analysis of PHIVA and an HIV-negative comparison group. The results of this study shows that there are significant physical sequelae that PHIVA face with regards to stunting, wasting and motor performance.

Despite the PHIVA population of this study having early diagnosis (mean age: 4.7 months, SD±5.9), early ART initiation (mean age: 8.5 months, SD±6.6 months) and majority viral suppression (87.1%), they still presented with multiple physical challenges. This is a concerning finding, especially since this sample of PHIVA were well-managed, with regular follow-up appointments and access to health care via a large, urban HIV research unit. With many PHIVA not accessing regular health care in sub-Saharan Africa (Eba & Lim, 2017; Sam-Agudu et al., 2016) [where more than 88% of children and adolescents with HIV live (UNICEF, 2020b)], these sequelae are potentially even more prevalent. A review of long-term virologic outcomes in PHIVA

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living in low- and middle-income countries found that the median age of ART initiation was 4 to 9 years and that viral suppression ranged from 53% to 68%, and specifically in South Africa, it was 5 to 11 years and 69% to 81%, respectively (Anderson et al., 2020). Anderson et al.'s (2020) values are substantially poorer than the viral suppression frequency (87.1%) and mean age of ART initiation (8.5 months, SD±6.6 months) for this study's population thus indicating the potentially greater prevalence of physical sequelae in other PHIVA. This highlights the necessity of regular healthcare monitoring and access to early diagnosis and ART initiation.

Anthropometry

The PHIVA group had significantly lower height ($p<0.001$), weight ($p<0.001$) and BMI ($p=0.004$) compared to the HIV-negative adolescents, and they were significantly more stunted ($p=0.036$) and wasted ($p=0.036$). Perinatal HIV inhibits growth and development in children (Cruz & Cardoso, 2015; Williams & Jesson, 2018) and Jesson et al. (2019) found that a lower CD4 count and later ART initiation were associated with poorer growth in PHIVA. This study highlights that despite early diagnosis, ART initiation and regular follow-up growth deficits continue into adolescence.

Stunting in childhood impacts on pubertal development and it has been well established that pubertal delay occurs in PHIVA (Bellavia et al., 2017; Cruz & Cardoso, 2015; Ferrand et al., 2012; Iloh et al., 2017; Williams & Jesson, 2018). Stunting also has a long-term impact on cognition, academic and economic performance, and maternal reproductive function (Crookston et al., 2011; Dewey & Begum, 2011). Wasting is associated with chronic infections, inflammation and higher levels of morbidity and mortality (Harding et al., 2018). These deleterious effects of stunting and wasting are an indication of the need for regular monitoring of PHIVA in terms of growth, pubertal development, academic performance and cognition.

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Muscle strength and endurance

Although there were no differences between the two groups for muscle strength and endurance both performed below the expected norms for their ages (Hardy et al., 2018; Saint-Maurice et al., 2015; Tomkinson et al., 2017). This could be due to the general decreased levels of physical activity that this group of children may be experiencing. One needs to consider that this population is based in a low socio-economic environment and general access to school sport, extra-mural activities and club sports would potentially be limited.

Research in CLHIV has shown mixed results on muscle strength, power and endurance. Potterton et al. (2021) and Ramos et al. (2012) found no differences in the muscle strength of CLHIV and HIV-negative participants, however in Ramos et al.'s (2021) study anaerobic power was significantly lower in CLHIV and Somarriba et al. (2013) found significantly decreased lower extremity muscle strength in their population of 7 to 20 year old participants living with HIV. Although small, deficits in muscle power have been found in another study looking at perinatal HIV in children aged 8 to 25 years (Macdonald et al., 2017) but further research in this area is lacking.

In our study, although they did not differ significantly, both groups of adolescents performed overall poorly in endurance. Chisati and Vasseljen, (2015) assessed aerobic endurance in Malawian young adults with HIV, and found that they had significantly lower endurance compared to the HIV-negative group. Similarly, an assessment of Malawian children and adolescents with perinatal HIV (aged 5 to 18 years) using the six minute walk test (6MWT) showed that the HIV-positive group walked significantly shorter distances than the HIV-negative comparison group ($p=0.015$) (Sims Sanyahumbi et al., 2017). Other studies present contrasting findings: a

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South African cohort of well-managed CLHIV with early ART initiation did not differ significantly from their HIV-negative peers on the 6MWT (Potterton, Strehlau, Shiau, Comley-White, Kuhn, Yin, et al., 2021 *in press)*, nor did another South African cohort of PHIVA compared to an age-matched HIV-negative group (Githinji et al., 2019). It should be noted, however, that the 6MWT is an assessment of submaximal endurance and thus is not necessarily sensitive enough to detect mild cardiopulmonary deficits (Githinji et al., 2019).

Other studies have used VO_{2peak} as an outcome measure showing decreased endurance in HIV-positive adolescents (Cade et al., 2002; de Lima et al., 2017; Keyser et al., 2000; Somarriba et al., 2013) and Githinji et al., (2017) assessed lung function in 515 South African PHIVA and found significant lung dysfunction compared to HIV-negative adolescents, thus indicating significant functional aerobic impairment and cardiorespiratory insufficiency for this population. Aerobic and cardiorespiratory impairments are part of the multifactorial nature of decreased endurance. In addition to the potential low levels of physical activity found in PHIVA, impairments such as moderate to severe dyspnea have been reported 34.4% of a PHIVA population (Mwalukomo et al., 2016).

Motor performance

The PHIVA group did poorly in motor performance, with significantly lower performance in the standard score for manual dexterity (0.021) and balance (p=0.020), and with significantly more PHIVA than HIV-negative adolescents scoring in the red and amber zones for the total MABC-2 score (p=0.054), thus highlighting the risk of poor motor performance in PHIVA.

Studies have shown a decline in motor function over time in adults living with HIV (Elicer et al., 2018) and that CLHIV face developmental delay (Baillieu &

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Potterton, 2008; Ruel et al., 2012; Strehlau et al., 2019) but research is lacking in PHIVA. Willen et al. (2017) investigated neurocognitive outcomes in perinatally infected young adults (aged 18-24 years) and found executive dysfunction, with motor speed being significantly worse in the HIV-infected participants. Similarly, Horvath et al. (2018) found accelerated epigenetic ageing in a group of South African PHIVA which correlated with poorer cognitive functioning, including processing speed. Neurocognitive dysfunction can be caused by delayed cortical maturation and atrophy of the motor cortex that occurs in PHIVA (Yu et al., 2019).

Poor manual dexterity has negative implications for a child's school performance, with handwriting and activities of daily living, such as playing, being affected (Gaul & Issartel, 2016; Mathisen, 2016). Children and adolescents with perinatal HIV already face neurocognitive dysfunction and poor academic performance (Phillips et al., 2021; van Opstal et al., 2021) and thus decreased manual dexterity can further disadvantage the adolescent academically.

Balance is important in all daily functioning activities such as mobility, fall prevention and quality of life (Kovács et al., 2013; Schwartz et al., 2012; Surgent et al., 2019). Balance in younger CLHIV and PHIVA has been found to be negatively affected (da Silva Pontes et al., 2019; Debeaudrap et al., 2018; Medeiros et al., 2022).

Clinical predictors

Although the multivariate regression analysis did not reveal multiple significant predictive factors, it is still of value to consider that the overall clinical picture of PHIVA can be used to predict their endurance and muscle strength, more specifically in terms of age (B=28.239) and viral suppression (B=13.312), respectively. Further studies involving these variables could be used to create a predictive model for physical functioning in PHIVA, especially since such a model is not currently available.

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Viral load has an inverse relation to physical activity (Bopp et al., 2004) and physical functioning (Nieves-Lugo et al., 2017), resulting in a poorer health-related quality of life in people with HIV (Call et al., 2000), thus it is fitting that this study found viral suppression to be predictive of muscle strength, a component of physical health. Another study in South Africa found that BMI and Tanner staging were positively associated with muscle strength in CLHIV (Potterton, Strehlau, Shiau, Comley-White, Kuhn, & Arpadi, 2021) however our study did not assess Tanner staging nor did the authors find BMI to be a predictive factor. This may be because the participants in the study by Potterton et al. (2021) were younger (age 5 to 11 years) than the current study's participants and thus the results cannot be a direct comparison.

This study found age to have a negative prediction on the aiming and catching component of the MABC-2 (B=-0.892). Since PHIVA show smaller increases in physical activity levels with age when compared to HIV-negative peers (Dirajlal-Fargo et al., 2021) it can be expected that with age the skill of aiming and catching would decrease, i.e. as their physical activity levels are lower.

Limitations and recommendations

The participants of this study were accessed from only one clinical site, thus the results are not generalisable to all PHIVA. Furthermore, the HIV-negative participants were mostly siblings of the PHIVA participants and thus may have been HIV-exposed uninfected (HEU) adolescents. Studies are showing that many HEU children still face growth and neurodevelopmental sequelae (Wedderburn et al., 2019) and thus the negative outcomes of this study's PHIVA may be even greater when compared to HIV-unexposed uninfected (HUU) adolescents. Future recommendations for research would be to replicate this study using HUU adolescents as a comparative group and to

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investigate the same outcome measures in PHIVA who are not as well managed medically as this group.

An additional recommendation is for research on endurance in PHIVA using the shuttle run test. To the best of the authors' knowledge, no other studies have used the shuttle run test to assess endurance in PHIVA and future research would be beneficial, both in the PHIVA population and the general South African adolescent population.

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Conclusion

This study aimed to establish the physical sequelae of perinatal HIV in adolescents. The results showed that PHIVA have significant sequelae in height, weight and motor performance. It is of particular concern that these deficits are apparent in PHIVA who are mostly virally suppressed and well managed medically, highlighting the clinical concern for PHIVA across the rest of the globe who do not necessarily have sufficient access to health care and regular monitoring. A population-specific model of care and regular screening of physical sequelae in PHIVA is recommended for clinical practice to try and mitigate these deficits.

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Declaration of interest

The authors have no conflict of interest to declare.

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For Peer Review Only

Tables

Table 1: Demographic data of the study population (n=249)

	HIV negative adolescents n=102	**HIV positive adolescents** n=147	**P value**
Male, n (%)	60 (58.8)	73 (49.7)	0.154
Female, n (%)	42 (41.2)	74 (50.3)	0.154
Age in years, mean (SD)	12 (±1)	12 (±2)	0.91
Minimum age	10 years 0 months	10 years 0 months	-
Maximum age	16 years 11 months	15 years 12 months	-

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Table 2. Clinical data of the HIV positive participants

Clinical data	**Values**
Mean age at HIV diagnosis, months (n=107)	4.7 (SD±5.9)
Mean age at ART initiation, months (n=147)	8.5 (SD±6.6)
Mean CD4 count, cells/mm^3 (n=147)	1011.6 (SD±305.7)
Mean CD4 percentage (n=145)	38.3 (SD±7.1)
Number of participants with viral load < 200 copies/ml (n=147)	128 (87.1%)
Number of participants with viral load > 200 copies/ml	19 (12.9%)

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Table 3: Anthropometric results for the study population (n=249)

	HIV negative adolescents n=102	**HIV positive adolescents** n=147	**P value**
Weight in kilograms, mean (SD)	42.8 (±13.2)	36.8 (±10.2)	**<0.001**
Height in meters, mean (SD)	1.5 (±0.1)	1.4 (±0.1)	**<0.001**
BMI, mean (SD)	19.3 (±4.3)	17.9 (±3.2)	**0.004**
HAZ, mean (SD)	-0.3 (±1.0)	-1.1 (±1.1)	0.246
BAZ, mean (SD)	0.3 (±1.4)	-0.3 (±1.2)	0.236
Stunted, n (%)	3 (2.9)	34 (23.1)	**0.036**
Wasted, n (%)	5 (4.9)	10 (6.8)	**0.036**

HAZ= height-for-age z-score; BMI= body mass index: BAZ= BMI-for-age z-score; stunted=<-2SD; wasted=<-2SD

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Table 4: Muscle strength and endurance results for the study population (n=249)

	HIV negative adolescents n=102	**HIV positive adolescents** n=145 (2 incomplete records)	**P value**
Muscle strength: standing broad jump in meters, mean (SD)	120.3 (±21.5)	121.5 (±25.5)	0.716
Endurance: shuttle run test in meters, mean (SD)	277.0 (±132.1)	298.3 (±137.7)	0.225

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Table 5: Motor performance results for the study population (n=249)

	HIV negative adolescents n=102	**HIV positive adolescents n=147**	**P value**
	MABC-2: manual dexterity		
Complete records, n (%)	99 (97.1)	146 (99.3)	-
Standard score, mean (SD)	9.0 (±2.6)	8.2 (±2.7)	**0.021**
Red zone, n (%)	11 (11.1)	23 (15.8)	0.064
Amber zone, n (%)	3 (3.0)	14 (9.6)	
Green zone, n (%)	85 (85.9)	109 (74.7)	
	MABC-2: aiming and catching		
Complete records, n (%)	99 (97.1)	146 (99.3)	-
Standard score, mean (SD)	10.2 (±3.7)	10.0 ± (3.3)	0.573
Red zone, n (%)	14 (14.1)	15 (10.3)	0.306
Amber zone, n (%)	3 (3.0)	10 (6.8)	
Green zone, n (%)	82 (82.8)	121 (82.9)	
	MABC-2: balance		
Complete records, n (%)	100 (98.0)	144 (98.0)	-
Standard score, mean (SD)	11.87 (±2.7)	10.95 (±3.2)	**0.020**
Red zone, n (%)	4 (4.0)	9 (6.3)	0.082
Amber zone, n (%)	0 (0.0)	6 (4.2)	
Green zone, n (%)	96 (96.0)	129 (89.6)	
	MABC-2: total		
Complete records, n (%)	98 (96.1)	144 (98.0)	-
Standard score, mean (SD)	10.3 (±3.0)	9.95 (±6.7)	0.144
Red zone, n (%)	4 (4.1)	19 (13.2)	**0.054**

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Amber zone, n (%)	5 (5.1)	5 (3.5)
Green zone, n (%)	89 (90.8)	120 (83.3)

MABC-2: Movement Assessment Battery for Children- Second Edition

Table 6: Regression analysis results reaching statistical significance for individual clinical variables

Dependent variable	**Independent variable**	**Unstandardized B coefficient**	**T score**	**P value**
Muscle strength	Viral suppression	13.312	2.176	0.032
Endurance	Age	28.239	2.042	0.044
Aiming and catching	Age	-0.892	-2.667	0.009

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6.3 Associated documentation

The documentation for the second phase of data collection, as well as a description of the outcome measures, is available in the following appendices:

- Appendix 8: Information letter for phase two
- Appendix 9: Assent and consent for phase two participation
- Appendix 10: Description of the outcomes measures

6.4 Amendments to the original study protocol

The original sample size calculation for the phase two study (as seen in Chapter 3) required 154 participants per group, with a 95% confidence level. This calculation was based upon the number of available PHIVA on the clinic database however once data collection commenced there were a substantial number of PHIVA and HIV-negative adolescents who were no longer active on the database. The researcher and research assistants utilised every option that they could to contact the potential participants but data collection had to be ceased at 147 PHIVA and 102 HIV-negative controls. With 147 PHIVA, the sample size had a confidence level of 93.5% which is still considered an acceptable percentage (Yang et al., 2019). Although the study was not able to recruit the same number of HIV-negative adolescents as PHIVA, the comparison group was still well-matched for age and sex ($p=0.91$ and $p=0.154$, respectively). Additionally, the comparison group were community members, siblings or other family members of the HIV-positive participants thus they came from a similar background, making them suitable for comparison.

In the proposal of the study, one of the outcome measures that was incorporated was the Pediatric Quality of Life Inventory (PedsQL), along with the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). However, during the pilot study it was noted that many of the questions on the PedsQL were similar to that of the WHODAS 2.0 and participants were becoming irritated answering what appeared to them to be the same questions twice. The data collection session was already somewhat protracted and the decision was made to remove the PedsQL from the data collection procedure so as to make the session more time-efficient. While the WHODAS 2.0 is described as a disability assessment tool it has also been used in studies assessing QOL (Thomas et al., 2014; Üstün et al., 2010).

6.5 Conclusion

This chapter presented the results of the second phase of data collection, a quantitative analysis of the physical sequelae of PHIVA. The results of this phase, along with the phase one results and the scoping review, were used to develop a MoC for PHIVA, as presented in the following chapter.

Chapter 7 Phase three: Development of a model of care

7.1 Manuscript details

Chapter 7 is presented as a manuscript submitted to *Children and Youth Services Review* which is currently under review. The manuscript is included in this chapter following the submission guidelines of the journal. *Children and Youth Services Review* is a multidisciplinary journal addressing the health and welfare of youth. Details of the manuscript are provided in Table 7.1.

Table 7.1 Manuscript specifics of the model of care study

Title of manuscript	An inter-professional model of care for adolescents with perinatal HIV
Authors	Nicolette Comley-White; Veronica Ntsiea; Joanne Potterton
Journal name	*Children and Youth Services Review*
ISSN	0190-7409
Impact factor	2.393
Year	2022
Status	Under review

7.2 Author contributions

In Table 7.2 the author contributions are presented according to the terminology set out in Contributor Roles Taxonomy (CRediT) (Allen, O'Connell and Kiermer, 2019). Appendix 1 contains further detail on the definitions of the terminology.

Table 7.2 Author contributions for the model of care study

	Comley-White	Potterton	Ntsiea
Conceptualisation	√	√	√
Methodology	√	√	√
Formal analysis	√		
Investigation	√		
Resources	√		
Writing- original draft	√		
Writing- reviewing and editing	√	√	√
Visualisation	√	√	√
Supervision		√	√
Project administration	√		
Funding acquisition	√	√	√

7.3 Associated documentation

- Appendix 11: Information letter for phase three
- Appendix 12: Assent and consent for phase three participation

7.4 Manuscript under review: An inter-professional model of care for adolescents with perinatal HIV

Children and Youth Services Review

An inter-professional model of care for adolescents with perinatal HIV

--Manuscript Draft--

Manuscript Number:	CYSR-D-22-00350
Article Type:	Research paper
Section/Category:	Children and Youth Services Review, General
Keywords:	Youth; vertical transmission; healthcare; HIV; adolescence
Corresponding Author:	Nicolette Comley-White University of the Witwatersrand Johannesburg-Braamfontein, SOUTH AFRICA
First Author:	Nicolette Comley-White
Order of Authors:	Nicolette Comley-White
	Veronica Ntsiea
	Joanne Potterton
Abstract:	Objective The number of perinatally HIV-infected adolescents (PHIVA) is increasing however many healthcare systems are not prepared for this population and their health challenges, specifically a model of care (MoC) is lacking. Thus the objective of this study was to develop and propose a MoC for PHIVA. Methods Through a qualitative study design, a MoC was developed and ratified with two focus groups, consisting of PHIVA and healthcare professionals. Results Seven participants were included in each focus group and the following themes were developed: relatable attributes; missing components; implementation and suggestions. Changes were made to the drafts of the MoC in response to the focus group results, leading to the finalisation of a MoC for PHIVA. The MoC focused on the importance of inter-professional healthcare and addressed the physical sequelae that PHIVA are likely to encounter. A schematic of the MoC was created for the use in general public education. Conclusion It is important the healthcare facilities are equipped to handle the specific needs of PHIVA. The inter-professional MoC developed in this study helps to address the requirements of this population.
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An inter-professional model of care for adolescents with perinatal HIV

Abstract

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Methods

Through a qualitative study design, a MoC was developed and ratified with two focus groups, consisting of PHIVA and healthcare professionals.

Results

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Key words:

Youth; vertical transmission; healthcare; HIV; adolescence

An inter-professional model of care for adolescents with perinatal HIV

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Declarations

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Conflict of interest: The authors have no conflict of interest to declare

Ethics approval: Approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M180226). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions: **N Comley-White:** conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; writing- original draft. **V Ntsiea**: conceptualization; methodology; supervision; funding acquisition; writing- review and editing. **J Potterton**: conceptualization; methodology; supervision; funding acquisition; writing- review and editing.

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Conclusion

It is important the healthcare facilities are equipped to handle the specific needs of PHIVA. The inter-professional MoC developed in this study helps to address the requirements of this population.

Key words:

Youth; vertical transmission; healthcare; HIV; adolescence

Abbreviations PHIVA: perinatally HIV-infected adolescents; MoC: model of care; ART: antiretroviral therapy; IPG: inter-professional group; ICF: International Classification of Functioning, Disability and Health

1. Introduction

Approximately 2.8 million children live with HIV, of which 1.8 million are adolescents (UNAIDS, 2021). As antiretroviral therapy (ART) rollout and efficacy improves, so the population of children with perinatal HIV living into adolescence grows. These perinatally HIV-infected adolescents (PHIVA) present a novel health challenge (Laughton et al., 2013), with their entire developmental and growth period being influenced by the neurotoxic virus, as well as the effects of long-term ART usage. There are emerging physical challenges that PHIVA face, specifically with regards to growth failure, delayed puberty, cardiac and lung dysfunction, and bone and renal disease (Cruz & Cardoso, 2015; Lowenthal et al., 2014).

While there are models of care (MoC) available for people living with HIV, there are minimal MoCs specific to PHIVA. A review found four MoCs used in Africa for transition of adolescents to adult care but these models were not specifically for perinatal HIV, and their focus was on transition and ART adherence (Dahourou et al., 2017). Despite the growth of this unique population, many health care systems lack preparedness to deal with PHIVA and their specific challenges (Anderson et al., 2020), highlighting the need of a model that caters for PHIVA and the potential physical sequelae. Thus the aim of this study was to develop and propose a MoC for PHIVA.

2. Methods

2.1 Study design

This study used a qualitative design with focus groups to propose a MoC for PHIVA as the final phase of a larger, mixed-methods study. Details of the methodology of the larger study have been published elsewhere (Comley-White et al., 2019) as well as the results of the different phases of the overall study, which included a cross-sectional analysis of the physical sequelae in PHIVA (Comley-White, Ntsiea, et al., 2022; Comley-White, Potterton, et al., 2022a), a qualitative analysis of their perceived physical challenges (Comley-White et al., 2021a) and a scoping review of the literature pertaining to physical sequelae in PHIVA (Comley-White et al., 2021b; Comley-White, Potterton, et al., 2022b).

2.2 Participant selection and study site

Based on the outcomes of the preceding studies, a MoC was drafted and proposed to two focus groups: one group of PHIVA and one inter-professional group (IPG) of healthcare providers working in the paediatric and adolescent HIV field.

Files and the booking diary of a large, urban HIV clinic in Johannesburg, South Africa were screened for potential participants who had perinatally acquired HIV and were aged 10 to 16 years. Following the screening procedure, potential participants were telephonically invited to participate in the study. The focus group was held face to face in a private room of the clinic. All COVID-19 precautions were adhered to.

For the IPG, purposive snowball sampling was used to identify a variety of healthcare professionals that work with adolescents with HIV across multiple clinical sites. This was done to ensure that there was a sufficient variety of input and clinical experience available for the focus group. The focus group was done online through video conferencing software to allow participants to attend from across South Africa.

2.3 Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (certificate M180226) and all participants and guardians gave the required informed assent and consent for participation and audio-recording.

2.4 Procedure

2.4.1 Development of the model of care

The MoC was developed following the study objectives laid out by Chetty and Hanass-Hancock during their development of a MoC for rehabilitation of people living with HIV in South Africa (Chetty & Hanass-Hancock, 2014). These steps entail a review of the literature [i.e. the prior scoping review (Comley-White et al., 2021b; Comley-White, Potterton, et al., 2022b)]; exploring the perceptions of the stakeholders [i.e. the qualitative interviews done previously with PHIVA (Comley-White et al., 2021a)]; identifying criteria to be included in the model ([i.e. data from the preceding cross-sectional and qualitative studies (Comley-White et al., 2021a; Comley-White, Ntsiea, et al., 2022; Comley-White, Potterton, et al., 2022a)]; and development and appraisal of the model (i.e. the focus groups of this study) (Chetty & Hanass-Hancock, 2014). This procedure is similar to other steps described in literature, which involves a review of the literature; qualitative gathering of information from involved parties; and populating the model (Davidson et al., 2006; Staniszewska et al., 2012).

The International Classification of Functioning, Disability and Health (ICF) is a common tool used to discuss disability (Kostajsek, 2011) and it was used as a conceptual framework for the basis of the

MoC. Figure 1 presents the initial draft of the MoC based on the physical impairments established in the preceding studies.

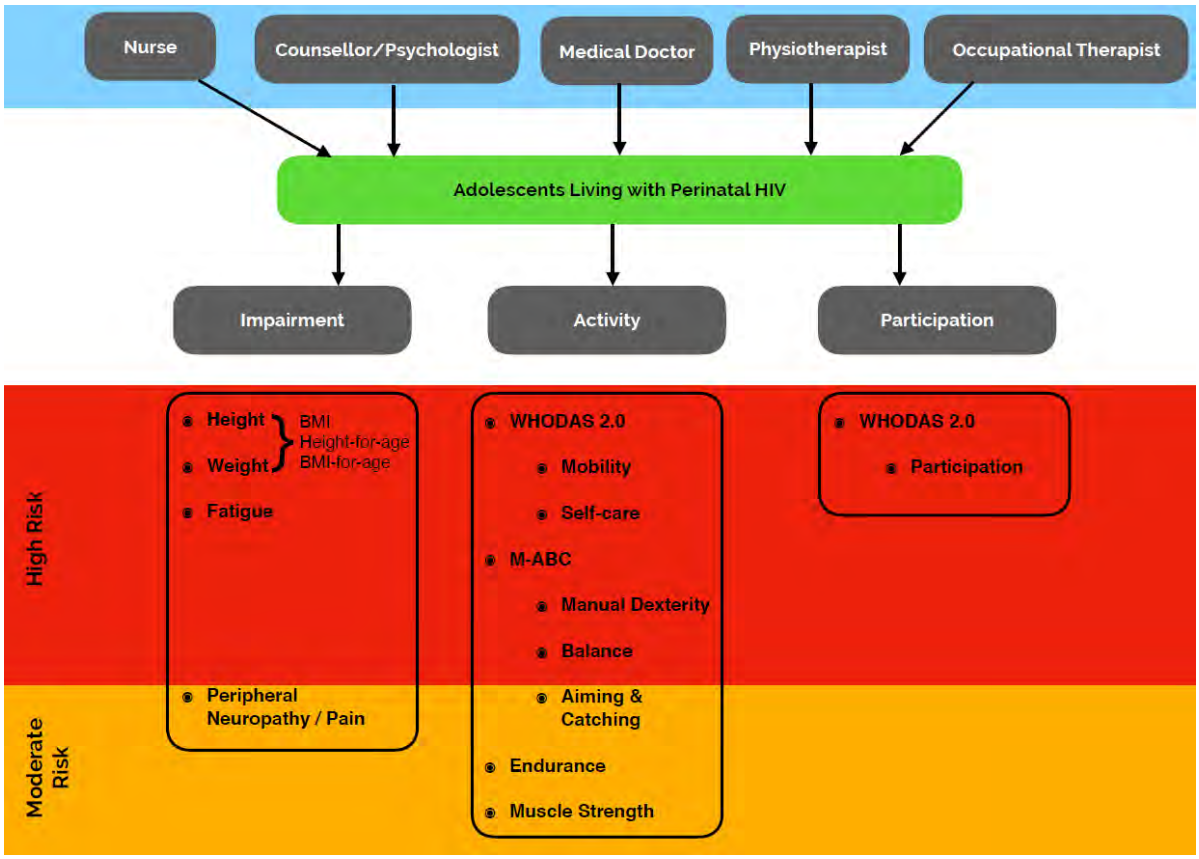

Figure 1. First draft of the inter-professional model of care for PHIVA

2.4.2 Focus groups

For both focus groups, following an icebreaker activity, the principal investigator (PI) presented a brief overview of the development of the MoC and then shared the MoC with the participants. The participants were given time to reflect upon the MoC and then shared their opinions on what they felt were positive attributes of the MoC and what they believed was missing from it. The PI asked probing questions and facilitated the free-flow of discussion and idea-sharing. For the PHIVA group a clinic counsellor was present for recruitment and data collection, and she was an important asset in the study because she was familiar with the adolescents, their caregivers and the logistics of the clinic.

2.5 Data analysis

The focus groups were audio-recorded and transcribed verbatim. Identifiers were removed from the transcriptions and the PI cross-checked them for accuracy. Field notes captured by the PI

summarised the focus group's input and were an added component of data collection (Gill et al., 2008). The transcriptions were analysed thematically and from these themes, adjustments to the proposed MoC were made, resulting in a final tool.

3. Results

3.1 Demographic and clinical information

Seven adolescents participated in the PHIVA group and seven healthcare professionals participated in the IPG. Details on the PHIVA group and IPG are presented in Table 1 and Table 2, respectively.

Table 1. Description of the adolescent focus group (n=7)

Variable	**n=7**
Male	2 (28.6%)
Female	5 (71.4%)
Mean age	12y4m (SD±1y2m)
Mean age at HIV diagnosis	3y7m (SD±2y2m)
Mean age of ART initiation	3y7m (SD±3y3m)
Mean CD4 percentage	34.8 (SD±6)
Viral load <500 copies/ml	7 (100%)

HIV: human immunodeficiency virus; ART: antiretroviral therapy

Table 2. Description of the inter-professional focus group (n=7)

Variable	**n=7**
Male	1 (14.3%)
Female	6 (85.7%)
Mean age, years	43 (SD±13)
Clinical profession:	
Physiotherapist	2
Medical doctor	1
Nurse	1
Occupational therapist	1
Counsellor	1

Clinical psychologist	1
Mean years of experience with adolescents	13 (SD±6)

3.2 Model of care

Following the presentation of the draft of the MoC (Figure 1) and discussion around it the resulting themes were developed: relatable attributes; missing components; implementation and suggestions. The two focus groups viewed the MoC from different perspectives (patient versus healthcare professional) and there were many areas of agreement. Table 3 presents the codes and themes from the focus group sessions.

Table 3. Codes and themes derived from the adolescent and inter-professional focus groups

Themes	**Inter-professional group**	**Adolescent group**
Relatable attributes	• Mental health challenges frequently encountered • Similar activity limitations on the MoC observed clinically	• Weight challenges • Impairments with aiming
Missing components	• Mental health • Social worker • Dietician • Cognitive and school performance	• Mental health • Social worker
Implementation and suggestions	• Screening as an inter-professional team • Use of support groups (age appropriate) • Bidirectional referral • Continuity of care	• Clarify presentation of pain specific to PHIVA • Use of groups

PHIVA: perinatally HIV-infected adolescents

3.2.1 Adolescent focus group

The strongest code to come out from the PHIVA group was mental health. The participants spoke about challenges with mental health, especially in regards to depression, anxiety and coping with peer pressure, and this was seen as a missing component on the MoC draft.

> *"What's missing here is two things that almost every teenager goes through: it is anxiety and depression…. And peer pressure." –female, age 14*

Another missing component was the role of the social worker within the healthcare professional input. Many of the participants discussed seeing a social worker during their clinic visits and felt that it should be reflected in this MoC. They also had not attended support groups which could be a component of implementation. When the PHIVA were asked what they could relate to on the MoC, they discussed having dissatisfaction with being underweight (*"I struggle with the weight… too little"*), and one participant said that he was struggling with aiming when playing sport. Pain was discussed but in broad terms (relating to menstrual pain), highlighting the necessity of clarifying types of pain in PHIVA on the MoC.

3.2.2 Inter-professional focus group

Following the PHIVA focus group, the MoC draft was updated with comments on the missing information about social workers, mental health and pain presentation. The updated MoC (Figure 2) was used for the inter-professional focus group.

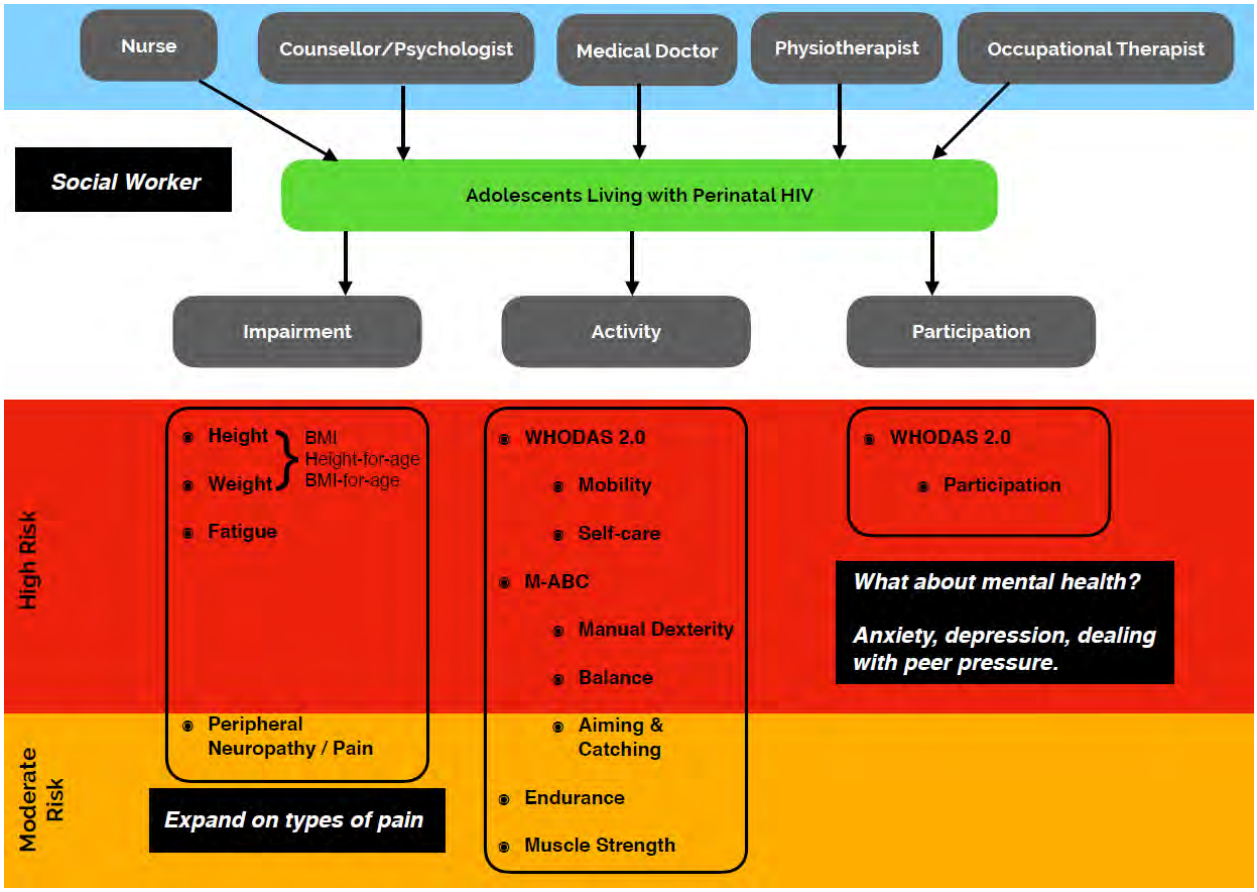

Figure 2. Second draft of the inter-professional model of care for PHIVA

The first point of discussion from the IPG was about what was seen as relatable items i.e. what they experienced within their clinical work. Mental health challenges in PHIVA was the primary code, with all seven participants verbalising their experiences of it within this population. The discussion expanded upon how mental health in PHIVA impacts on treatment adherence, risky behaviour and substance abuse. Additionally, it is affected by one's acceptance within a community and the influence of peer pressure and depression. Lastly, the role of mental health and school achievement was discussed, and how when PHIVA are not performing academically and are held back at school it impacts on their mental health and well-being.

> *"I really do see so many mental health problems… the impact of that on treatment adherence, never mind risk behaviour, is enormous."- Psychologist*

Additional relatable items on the MoC pertained to activity limitations. A physiotherapist discussed how in her work she encounters impairments specifically with self-care and mobility in PHIVA, as well as problems with fine motor control. These challenges were reiterated by the medical doctor in the group who discussed how PHIVA in the clinic often present with lower levels of functioning

causing problems with self-care, such as not managing their appointment dates, medication schedules; sexual health etcetera.

Following the discussion around relatable items on the MoC, the focus group discussed what could be missing from it. Mental health had already been discussed in detail as a crucial part of the MoC, and additional suggestions were made to include a dietician and social worker to the team. The participants reported social workers working with groups of PHIVA in their clinics, and with regards to the dietician, input was given on the need to refer PHIVA with poor eating habits (interlinked with mental health impairments) and poor nutritional statuses to a dietician. Lastly, cognitive and school performance were highlighted as an important component to consider in the MoC.

> *"…it also adds to their [PHIVA] mental health and anxiety when they start failing various grades at school. There is a lot of peer pressure and the adolescents in our clinic do very badly when they have to be kept back a year."- Medical doctor*

The last aspect of the focus group was a discussion on suggestions and implementation ideas for the MoC. A frequent code was the need for screening of PHIVA when they come to the clinic. It was noted that many PHIVA with additional impairments or activity limitations are only referred to other inter-professional team members very late in their presentation or when there is an obvious disability. The occupational therapist stated that *"the referral is based on when the patient mentions it, and how urgent and affecting it is to them*". Suggestions were made for regular screening within the clinics, especially if there are adolescent groups, and that the screening can be done by any of the inter-professional team member if they have had sufficient training.

> *"Ideally it would be nice to have the whole multidisciplinary team but if not, I think just having a good understanding of what the roles are of the whole team so that you can develop really good referral structures"- Physiotherapist*

> *"In a very busy clinic, quick screening tools which can be done by counsellors or nurses or even self-completed by the patients would help identify children who may be presenting with the need for an increased level of intervention."- Medical doctor*

Referral structures and the necessity of referral was also a strong code within implementation. The psychologist discussed the role of referrals between the clinic and community organisations, working in both directions and not just a down-referral to community structures: *"… the importance of bidirectional referrals. So that one can access the services that are being offered by community-based organisations within the community. So that between visits the young person has the support that they need".* One of the challenges raised with regards to screening and referrals is that often

the clinics have a high staff-turnover, resulting in a lack of commitment in addressing additional problems, and this continuity of care was echoed by the physiotherapist who expressed *"it really comes down to having a multidisciplinary team that is passionate about it [screening PHIVA], and doing screening days, and really building good referral structures across everyone"*.

Lastly, the role of support groups was discussed. Most of the clinical settings from the focus group participants used groups for their PHIVA management and the suggestions were given with regards to screening PHIVA and the importance of the peer support that the groups offered. It is important that groups are age-band specific and not all adolescents (aged 10 to 24 years) are convened together.

> *"Our doctor…has put them [PHIVA] into a club setting, and within that club setting they get training as well as social connection and support group with other adolescents, which has worked really well. … It definitely has to have one person spearheading it, otherwise it kind of gets lost." – Occupational therapist*

3.2.3 Finalisation of the model of care

Final additions and changes were made to the MoC, based on the results of the focus group data analysis. The need to expand on the potential types of pain experienced by PHIVA was addressed through examples of pain found in the preceding studies (Comley-White et al., 2021a; Comley-White, Potterton, et al., 2022a, 2022b). Figure 3 presents the final MoC that can be used to guide clinicians in screening, referrals and interaction within the inter-professional team. Finally, a simplified schematic of the MoC was developed and is depicted in Figure 4.

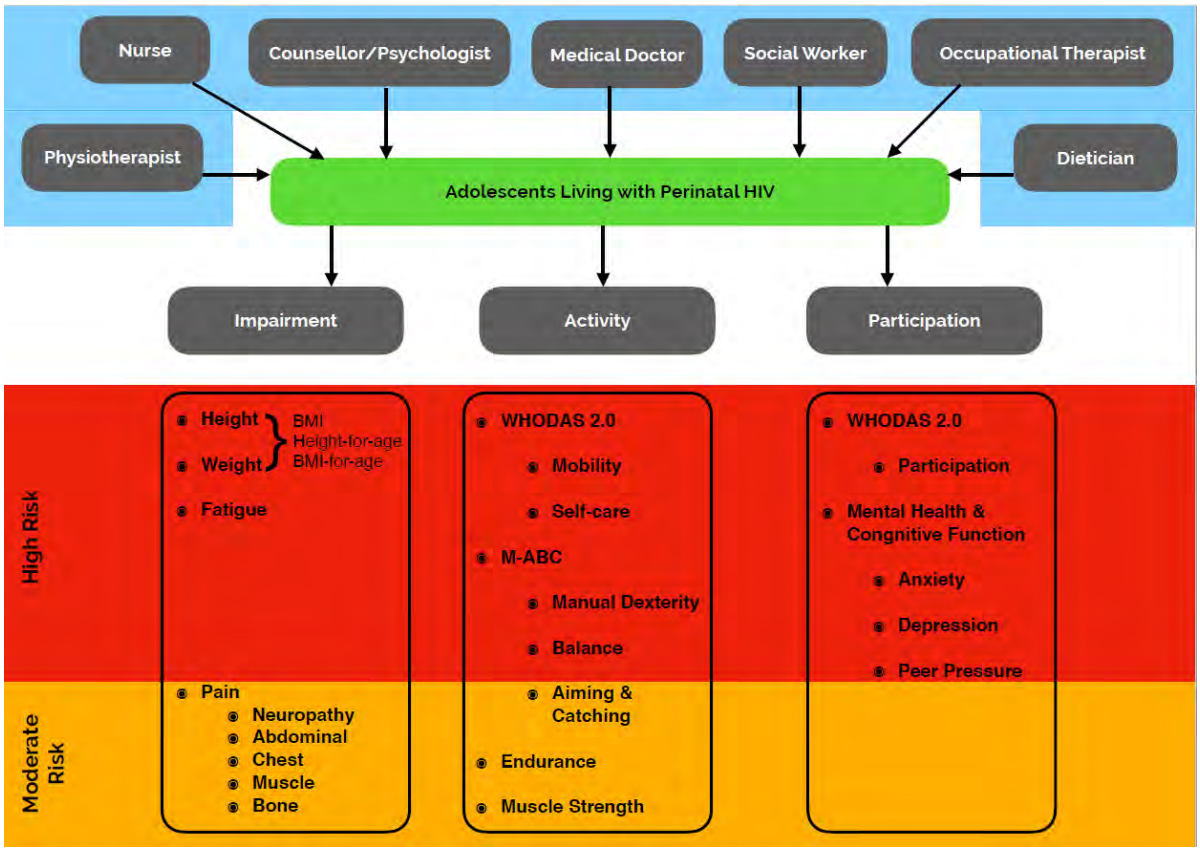

Figure 3. Final version of the inter-professional model of care for PHIVA

Figure 4: Schematic of the inter-professional model of care for PHIVA

4. Discussion

This study sought to develop a MoC for PHIVA, the initial draft of which was based on results from preceding studies. The MoC drafts were presented to two focus groups (PHIVA and healthcare professionals) and adjustments were made, resulting in a final inter-professional MoC for PHIVA.

4.1 Changes to the initial model of care

Based on the focus group input, the following changes were made to the MoC draft: dietician and social worker were added as part of the inter-professional team; mental health and cognitive functioning were additional impairments; and a list of pain examples was given.

Mental health challenges and cognitive health dysfunction are important sequelae of perinatal HIV and have significant effects on adolescents (Flynn & Abrams, 2019; Frigati et al., 2020). Some of the most common areas of neurocognitive dysfunction in PHIVA are cognitive and achievement scores, visual recognition memory, intelligence and executive dysfunction, with scores significantly lower

than in HIV-negative adolescents (Garvie et al., 2014; Hoare et al., 2018; Laughton et al., 2013; Nichols et al., 2016; Van den Hof et al., 2019). Mental health challenges that PHIVA frequently face are depression, suicidal tendency, anxiety, anger, and attention deficit hyperactivity disorder (Dessauvagie et al., 2020; Hoare et al., 2019; West et al., 2019). In drafting the MoC, the initial decision was made not to include mental health and neurocognitive dysfunction because it lay outside the scope of *physical* sequelae for PHIVA. While these two items are not necessarily physical outcomes in themselves, they are still strongly linked to physical sequelae and thus they were included in the final MoC, following the focus group feedback that highlighted their importance.

The relationship of physical outcomes with mental health and neurocognitive dysfunction is multifactorial. Cognitive impairment is strongly correlated with functional impairment, such as interpersonal relationships (Phillips et al., 2021), and a study of multisystem impairments in PHIVA found that of those who had neurocognitive impairment, nearly 60% had additional system impairments (e.g. renal, cardiac) (Frigati et al., 2019). Furthermore, mental health challenges impact negatively on quality of life and ART adherence, which in turn impacts on physical well-being.

A recent scoping review of physical sequelae in PHIVA found pain to be a component, specifically chest pain (Comley-White, Potterton, et al., 2022b). Qualitatively, PHIVA also have complained of chest pain, as well as abdominal pain (Comley-White et al., 2021a), and muscle aches have also been reported in PHIVA (Rosso et al., 2012). A point prevalence of pain in adults with HIV ranged from 54% to 83%, with multifactorial causes (Parker et al., 2014) but there is little literature available on the prevalence of other pain in PHIVA. Other studies in children with perinatal HIV have shown reports of generalised pain, abdominal pain, neuropathic pain and bone pain (Fortuny et al., 2015; Serchuck LK et al., 2010), highlighting the necessity for pain screening to be an important component of the MoC.

4.2 Implementation of a model of care

Suggestions made for the implementation of the MoC focussed predominantly around the importance of screening and referrals within the inter-professional team. The inter-professional team is a key player in the management of PHIVA, and although a paediatrician is adequately trained for adolescent health, an integrated inter-professional team is the ideal situation, and should include social workers, nurses, mental health professionals and counsellors (Cruz & Cardoso, 2015; Fairlie et al., 2014). The results of this study show that the inter-professional team can be expanded beyond these disciplines listed in the literature, to include occupational therapists, physiotherapists and dieticians.

A prevalence study of children with HIV at a clinic in South Africa found that of the children presenting with disability, only 46% had been referred to the relevant inter-professional team member (Brassell & Potterton, 2019). Despite the study being based at a busy urban research and services clinic, many children with disabilities were not accessing the services that they required and this is a cause for concern, especially when one considers children and adolescents receiving HIV care in less structured settings. One of the barriers to care in children with HIV is poor multi-disciplinary team functioning, with recommendations made for ongoing training of healthcare workers (Maddocks et al., 2021).

Additional recommendations for PHIVA care include screening for chronic complications of perinatal HIV, peer-led support groups, strategies to manage stigma and sufficient screening and management of mental health (Lowenthal et al., 2014). These components have been factored into the MoC developed in this study, with the idea that clinics and interprofessional team members working with PHIVA will be able to use the MoC as a guideline tool for sufficient screening and bidirectional referral. While the jargon of the MoC is appropriate for medical professionals, it is not PHIVA-friendly and thus the schematic (Figure 4) was developed, with potential use for general public education.

4.3 Limitations and recommendations

A limitation of this study was that, due to study logistics, the PHIVA group was comprised of participants from one study site and thus are not fully representative of this population. The authors attempted to mitigate the homogeneity of the participants by ensuring that the IPG covered a wider background. Future recommendations for research would be to investigate the types of pain in PHIVA to create a more specific screening tool.

4.4 Conclusion

This study aimed to establish an inter-professional MoC for PHIVA. Through two focus groups a final tool was developed that highlights the necessity of inter-professional screening and referral, with a focus on the physical sequelae of perinatal HIV, as well as the mental health. With the growing population of PHIVA, who present with unique healthcare challenges, it is imperative that medical facilities are adequately equipped to cater for this population.

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7.5 Conclusion

The process of developing a MoC for PHIVA was presented in this chapter in the format of a manuscript submitted to *Children and Youth Services Review*. This chapter was the final phase of the study, and the following chapter presents the integrative discussion, drawing the study together.

Chapter 8 Integrative discussion

8.1 Introduction

Chapter 8 will present a summary of the studies comprising this thesis, with a discussion linking the results together in relation to the overall objectives of the study. The strengths of the study, along with its limitations, will be presented, and clinical and research recommendations emanating from the results will be made.

This study was a mixed-methods study comprising of three phases of data collection and a scoping review. In summary, the objectives of the study were to determine the physical challenges that PHIVA face (first phase: qualitative study and scoping review); to determine their physical functioning (second phase: cross-sectional quantitative study); and finally to propose a model of care for PHIVA which would address the needs identified in phases one and two (third phase: qualitative study).

8.2 Discussion

The increasing success of ART access globally has led to a greater population of children with perinatal HIV growing into adolescence, bringing about new and unique health challenges (Laughton et al., 2013; Lowenthal et al., 2014). While the literature shows a strong theme of neurocognitive dysfunction in PHIVA (Flynn and Abrams, 2019; Frigati et al., 2020; Laughton et al., 2013; Willen et al., 2017) there is not a lot known about the physical challenges that they face. Thus the first two phases of this study set about determining what the impairments, activity limitations and participation restrictions could be in this population. In conjunction with the cross-sectional studies, a scoping review was undertaken.

8.2.1 Conceptual framework

It is important that HIV is not only viewed within a biomedical model approach but also how it affects lives more broadly, with an emphasis on disability and rehabilitation, and not just as a medical concern (Nixon et al., 2011). There is a plethora of conceptual frameworks used in HIV healthcare, for example to address adherence, pain, rehabilitation, to name a few (Judd et al., 2020; Merlin et al., 2014; Worthington et al.,

2005). The ICF is a conceptual framework model that is widely used in healthcare and disability (Kostajsek, 2011; Mitra and Shakespeare, 2019) and specifically within HIV (Giannattasio et al., 2011; Myezwa et al., 2011; Myezwa et al., 2009; Stevens et al., 2021; Van As et al., 2009) thus it was used as the conceptual framework for this study. The domains of impairment, activity limitations and participation restrictions were used to guide all of the phases of data collection and the development of the model of care, and to ensure that the healthcare of PHIVA was being viewed across all three domains and not just at an impairment level.

8.2.2 Scoping review findings

A scoping review - presented in Chapter 4 – aimed to identify and describe the physical sequelae of PHIVA reported in the literature. The review included eight studies that addressed the physical sequelae of perinatal HIV in adolescence. The key problems found pertained to stunting, wasting, low BMI, delayed puberty, decreased physical functioning and activity levels, reduced exercise tolerance and lung functioning, and pain. The most frequently reported impairments were poor growth, underweight and reduced BMI; and although there were study results for the physical health and functioning criteria, these results were less detailed and in fewer of the scoping review articles. This highlights that the impairments and limitations of physical functioning in PHIVA is an emerging field that requires further study.

The majority of the studies included in the scoping review lacked a comparison group. Only two of the eight studies had an HIV-negative group. While it is important to be able to compare findings to the normative data of a country (or globally) it is equally important to consider that there may be factors other than HIV status that could impact on the physical sequelae assessed in these studies. Socio-economic background, ethnic-specific genetics, and cultural beliefs and practices are just a few of the components that can influence the physical functioning and wellbeing of an adolescent and thus it is of value in any research of PHIVA to include an HIV-negative comparison group from a similar background as the HIV-positive adolescents. The lack of comparative groups in the available literature of the scoping review highlighted the necessity of ensuring that this study included an HIV-negative group in the quantitative cross-sectional phase of data collection.

The scoping review was limited to studies that included participants from 10 to 19 years of age. While this limit followed the definition of adolescence (UNICEF, 2016; World Health Organization, 2014) it is important to consider that some other studies include participants of slightly lower and/or higher ages thus not all physical sequelae studies would have been included in the scoping review. For example, a systematic review by Githinji et al. (2018) assessed lung function in perinatally infected children and adolescents, with an age range of 0 to 24 years, showing a high prevalence of lung function impairment. Similarly, de Lima et al. (2019) found that the PHIVA in their study presented with high blood pressure, adiposity and cholesterol levels, however their age range was 8 to 15 years. The findings of these two studies reinforce those of the scoping review results, showing the prevalence of impairments in children and young adults beyond the defined age used for the inclusion criteria of the scoping review.

The scoping review in this study was an integral component of the development of the model of care. One of the steps described in the literature for the development of models of care is to review the literature (Chetty and Hanass-Hancock, 2014; Davidson et al., 2006; Staniszewska et al., 2012). The results of the scoping review reinforced the findings of the other phases of this study, as well as addressed any potential gaps in the qualitative and quantitative findings.

8.2.3 Qualitative analysis of the physical sequelae of perinatal HIV in adolescents

When Chetty and Hanass-Hancock (2014) developed a model of care for people living with HIV in South Africa, one of their study objectives was to explore the perceptions of the stakeholders, which included the service users (i.e. people living with HIV). It is essential that youth are engaged in the development of policies and research that pertains to them, in order for the programmes to be successful (Oliveras Rodriguez, 2017). When planning the development of the model of care for PHIVA, the decision was made to include the input of PHIVA and thus the first phase of data collection was a qualitative study – presented in Chapter 5 – exploring the perceived challenges that PHIVA have.

After 19 interviews with PHIVA in early and middle adolescence, data saturation was reached. The main findings of the study showed that decreased endurance, pain and fatigue were the most prevalent impairments and activity limitations, while decreased community participation, decreased muscle strength and/or motor skill, and emotional

and cognitive challenges were also frequent sequelae that the PHIVA reported. Of the study participants, only one did not encounter any challenges and all participants were virally suppressed.

There has been extensive qualitative research in the PHIVA population with regards to transitioning to adult care, adherence to ART, retention in care and status disclosure (Cluver et al., 2015; Enane et al., 2020; Fair, Goldstein and Dizney, 2015; Fields et al., 2017; Madiba and Josiah, 2019; Maseko and Madiba, 2020; Zanoni et al., 2019), however there is a scarcity of qualitative research that pertains to the activity limitations and participation restrictions of living with perinatal HIV in adolescence, and none (to the author's knowledge) that speaks to their experiences of physical impairments or functioning. Mutumba et al. (2015) explored the psychosocial challenges experienced by PHIVA in Uganda and found that stigma was the main stressor for this population, and that they also expressed challenges in other psychosocial domains such as feelings of isolation, emotional distress, and relationship problems (Mutumba et al., 2015). Similarly, a study of Ghanaian PHIVA determined the qualitative barriers to- and enhancement of- their QOL, finding that limited resources, difficulties with family and poor health were some of the barriers to QOL (Enimil et al., 2016). Further qualitative research into the experiences of PHIVA and their physical wellbeing is strongly recommended as this appears to be an underexplored field of healthcare.

One of the key challenges expressed by the adolescents in the interviews of this study was that they struggled with endurance when playing sport or with their friends. While the 6 minute walk test is a commonly used outcome measure for endurance, it is in fact more sensitive to submaximal endurance and was not sensitive enough to pick up on potential differences in cardiopulmonary dysfunction, nor endurance, between CLHIV and their HIV-negative peers in a South African study (Githinji et al., 2019; Potterton et al., 2022). During the planning phase of this study, the outcome measure proposed for assessing endurance was the 6 minute walk test, however, following the results of the phase one study, in conjunction with the review of literature, it was decided to rather use the shuttle run test, which is a more physically challenging outcome measure. Thus the phase one results informed the planning of the phase two study.

8.2.4 Quantitative analysis of the physical sequelae of perinatal HIV in adolescents

The second phase was the largest phase of this study, with 147 PHIVA and 102 HIV-negative adolescents being assessed for height, weight, BMI, motor performance, peripheral neuropathy, fatigue, disability, endurance and muscle strength. Due to the amount of data collected, the results were written up as two separate publications, as presented in Chapter 6.

The phase two cross-sectional study found that the PHIVA group had significant impairment in their height ($p<0.001$), weight ($p<0.001$), BMI ($p=0.004$), manual dexterity ($p=0.021$), balance ($p=0.020$), fatigue intensity ($p=0.022$) and disability levels ($p=0.023$) (specifically with mobility, self-care and participation in society) compared to the HIV-negative group; and their muscle strength and endurance was lower than expected for their ages (Hardy et al., 2018; Saint-Maurice et al., 2015; Tomkinson et al., 2017). Although more PHIVA than HIV-negative participants presented with signs of peripheral neuropathy the differences between the two groups were not significant. These findings overall are a clear indication of the significant level of impairments, activity limitations and participation restrictions that PHIVA face.

It is important to note that the adolescents in this study are a well-managed group who, being part of a research unit, have regular access to healthcare, close monitoring and follow-up. In many cases their transport to the clinic is subsidised, if they miss appointments there are follow-up phone calls and their data is managed in a well-structured system. Additionally, they all had an early HIV-diagnosis and ART-initiation age [mean ages of 4.7 (±5.9) and 8.5 (±6.6) months, respectively] and the majority (87.1%) were virally suppressed. Despite the excellent healthcare that they have received there is still such a high prevalence of physical sequelae which is concerning because many PHIVA elsewhere do not necessarily receive the same level of management (Eba and Lim, 2017; Sam-Agudu, Folayan and Ezeanolue, 2016), nor do they initiate ART so early in life. A review of virologic outcomes in PHIVA found that in South Africa the median age for ART initiation was five to 11 years (Anderson, Muloiwa and Davies, 2020), far older than this study's PHIVA participants. Starting ART later in life is associated with stunting and low bone mineral density in PHIVA (Gregson et al., 2019; Jesson et al., 2019), while early ART initiation is associated with lower viral reservoir, HIV-seronegativity and better immunological function (Alvarez et al., 2017; Doria et al., 2021; Rinaldi et al., 2020; Wirotpaisankul et al., 2020).

Of all of the impairments assessed, peripheral neuropathy was the least prevalent. Although some PHIVA did present with signs of peripheral neuropathy, the findings did not reach significance. Peripheral neuropathy as a side-effect of ART is well established, particularly with the use of stavudine (Fortuin-de Smidt et al., 2017; Peters et al., 2014). While stavudine has been phased out of treatment (in favour of abavavir or zidovudine) there are still children and adolescents with perinatal HIV presenting with peripheral neuropathy. A recent study with Tanzanian HIV-positive children aged five to 18 years found a prevalence of 14.1% of peripheral neuropathy, with high viral load being a predictor (Amiji et al., 2021). The low rate of peripheral neuropathy in the PHIVA of our study can potentially be attributed to the fact that the majority (87.1%) of them were virally suppressed, and due to the close monitoring and evaluation that they receive at their clinic it is likely that early signs were noted and ART regimens amended. It is advisable that PHIVA continue to be monitored for signs of peripheral neuropathy since it is a debilitating side-effect, impacting negatively on QOL, function and pain (Biraguma and Rhoda, 2012; Dudley et al., 2019; Navis et al., 2018; Nicholas et al., 2007; Saylor et al., 2017).

8.2.5 Incorporating the phases' results to design a model of care

In order to create a comprehensive MoC for PHIVA, the results of the qualitative study, the quantitative study and the scoping review needed to be integrated and analysed in conjunction with each other. Variations of the steps involved in developing a MoC are well described in the literature (Davidson et al., 2006; Agency for Clinical Innovation, 2013; Staniszewska et al., 2012) however for this study the most appropriate procedure was laid out by Chetty and Hanass-Hancock (2014) in their study objectives for developing a MoC for rehabilitation of people living with HIV in South Africa. This involved reviewing current literature (Chapter 4); exploring perceptions of service users (Chapters 5 and 7); and identifying criteria to be included in the MoC and developing the MoC (Chapter 7) (Chetty and Hanass-Hancock, 2014).

A MoC ensures that healthcare professionals work towards a collective goal (Davidson et al., 2006), in this case, the physical health and wellbeing of PHIVA. Thus the involvement of a variety of healthcare workers was a central consideration when creating the focus group to ratify the MoC. Additionally, the input and involvement of the PHIVA themselves was an important part in the development of the MoC, as youth

engagement is critical in ensuring the success of health programmes targeted towards them (Oliveras Rodriguez, 2017). Originally, the plan was for the MoC to be presented to a group of healthcare professionals and a group of PHIVA for consensus via the nominal group technique (as described in Chapter 3) however when the time came for the actual development of the MoC it became apparent that a nominal group technique was not the most appropriate method but that the traditional, interactive focus group would be better suited. With a nominal group technique items are ranked and voted upon so as to create an order of importance while the interactive focus group is an efficient method for obtaining experts' opinions (Sutton and Arnold, 2013). For the MoC the impairments' value had already been determined through the scoping review, qualitative phase one study and quantitative phase two study and thus ranking the items with a nominal group technique was not indicated and the interactive focus group was more relevant.

The results of the scoping review and the different phases of data collection yielded various impairments to be addressed by the MoC. While not all items were found repeatedly in each phase of data collection, there was strong overlap between most of them. For example, decreased participation and fatigue were significant findings in phase one and two but not apparent in the scoping review, while significantly lower height, weight and BMI were established in phase two and the scoping review, but participants did not comment on it in phase one. Table 8.1 gives an overview of where each of the impairments were identified. In designing the model of care, all of the impairments were incorporated but were stratified as either high risk or moderate risk, depending on how strongly they came through in the different forms of data collection. Figure 8.1 presents the model of care.

Table 8.1 Summary of results from data collection and scoping review

Impairment	Phase one (qualitative study)	Phase two (quantitative study)	Scoping review
Height, weight, BMI	x	√	√
Fatigue	√	√	x
Endurance	√	√*	√
Muscle strength	√	√*	x
Motor performance	√	√	x
Pain	√	√*	√
Disability (including participation)	√	√	x

*performed poorly but not significantly more so than the comparison group

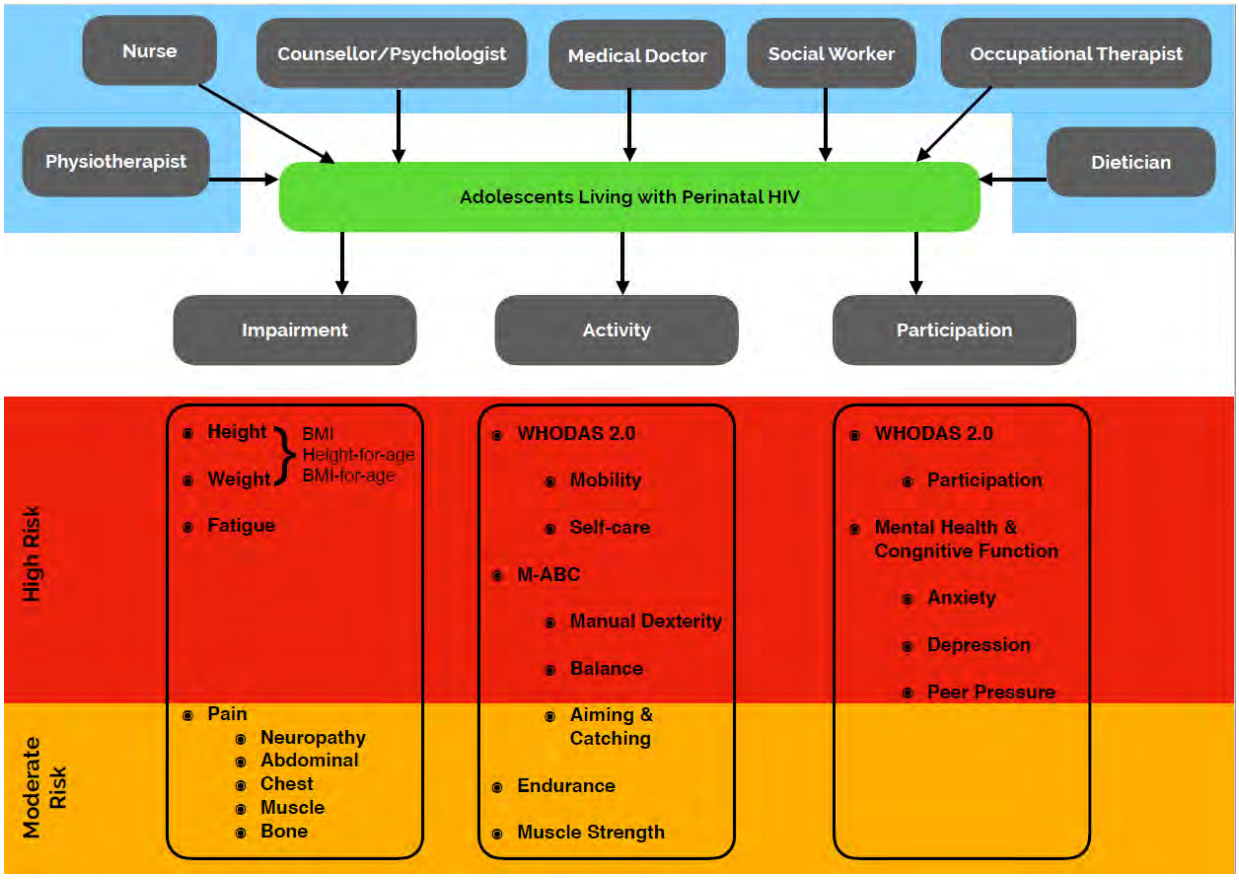

Figure 8.1 Model of care for adolescents living with perinatal HIV

While Figure 8.1 gives a detailed presentation of sequelae in PHIVA, it is not particularly adolescent-friendly as it predominantly uses medical jargon. It is important

that adolescent HIV clinics offer adolescent-friendly services (Falcão et al., 2021) and adolescent-friendly services have been shown to be a facilitator of HIV care in South African adolescents (Zanoni et al., 2019). A simplified schematic was designed and is presented in Figure 8.2. This schematic can be placed on clinic walls, used in healthcare pamphlets and general public education, with the idea of creating awareness of the sequelae that PHIVA may encounter.

Figure 8.2 Schematic of a model of care for adolescents living with perinatal HIV

8.3 Strengths and limitations of the study

8.3.1 Strengths of the study

This study had a number of elements that strengthened it. First of which was the mixed-methods design that included qualitative components (first and third phase) reflecting the PHIVA experiences and input. Adding the adolescent's voice to healthcare is an important step in ensuring that the end-product (i.e. the MoC) is relevant and applicable

(Oliveras Rodriguez, 2017). The results of the interviews with PHIVA in phase one were used to inform and confirm the phase two outcome measures, and also reinforced findings in the scoping review, adding further validity to the results.

Secondly, for the phase two quantitative study there was an HIV-negative comparison group that was well matched for age and sex. As seen in the scoping review, many studies do not use a matched comparison group when doing a cross-sectional study of PHIVA, instead they use national or international norms, or merely describe the PHIVA's presentation without any normative/comparison values. Often it is logistically challenging to find the comparison participants, and particularly to confirm their HIV-negative status. This study was based at a research unit who had a well-established comparison cohort with participants who could be invited to participate, strengthening the findings of the study.

Another strength of the study was the varied background of the participants in the inter-professional focus group of phase three. While the original study proposal planned to source participants from the research unit used in the prior phases of data collection, the advent of the coronavirus pandemic required that the group meet via online conferencing software. This then allowed focus group participants to join from outside of the province, and thus the clinical background and experience of the participants was more diverse than what it would have been if the focus group was limited to face to face interaction.

8.3.2 Limitations of the study

As is the nature of healthcare research there were some limitations to the study, the first of which is that the source of PHIVA for the three phases of data collection was from one site thus the results of this study are not generalizable to the full population of PHIVA. This study explored quantitative and qualitative components of physical sequelae in PHIVA that have not been established before and thus provided what will hopefully be the starting point for other studies in different PHIVA populations globally.

The second limitation of the study is that due to the requirements of most of the phase two outcome measures PHIVA were excluded if they had significant cognitive and/or physical disabilities that prevented them taking part in the assessments. While this was a logistical requirement (i.e., a participant would not be able to be assessed on the

shuttle run test, broad standing jump or components of the MABC-2 if they have a lower limb impairment), it resulted in the exclusion of some potential participants thus giving a more positive outcome than what may be the lived experiences of PHIVA. For example, two PHIVA were excluded from phase two due to significant cognitive impairment and physical disability that prevented them from completing the assessments, yet these are important disabilities that should be reflected in prevalence studies of physical sequelae in PHIVA, however it was beyond the scope of this study. Again, this study is the starting point of determining the physical sequelae of perinatal HIV in adolescence and thus the findings are still of value, even if they did not include the PHIVA with greater levels of disability.

Interviews conducted in a language other than the participant's home language could have limited how easily they communicated, even though an interpreter was available or if the participant spoke English as a second or third language. This made establishing rapport more challenging however the researcher attempted to overcome as far as possible with ice-breaking questions and trying to put the participant at ease.

Lastly, the HIV-negative comparison group in the second phase of the study were comprised mostly of siblings and other family members of the PHIVA group. Although they were HIV-negative there was no differentiation between those who were potentially HEU and those who were HUU. Research is showing that many HEU children have growth and neurodevelopmental impairments (Wedderburn et al., 2019) and thus the results of the PHIVA may be even more striking when compared to only HUU adolescents.

8.4 Recommendations

Based on the limitations of the study, as well as the lessons learnt during the research process and from the results of the study, there are a number of research and clinical recommendations to be made.

8.4.1 Research recommendations

Future studies into the physical sequelae of PHIVA are recommended in the following areas:

- To replicate the phase one and two studies with PHIVA from other geographical and socioeconomic backgrounds, but especially within SSA where more than 88% of children and adolescents with HIV live (UNICEF, 2020). The participants of this study were well-managed and the majority had viral suppression. It is important to know what the health profile is of PHIVA who do not have the support and access to healthcare that this group did.
- It would also be interesting to establish what the physical sequelae are in older PHIVA and young adults living with perinatal HIV. Due to the age restrictions of the outcome measures in this study participants were only included up to the age of 16. Future research could assess the physical functioning in older participants with age-appropriate outcome measures to ascertain if the impairments found in this age group continued through to older ages.
- The scoping review showed that there is very little data available on the physical functioning of PHIVA. Most research reflects anthropometric and/or neurocognitive impairments and so future research should aim to explore more information on PHIVA's endurance, muscle strength, motor skills, fatigue and pain.
- When analysing the data for the second phase, the researcher was unable to locate normative data for the shuttle run test in South African youth, or in international PHIVA, and so it would be beneficial for future research to be done in this area.
- As discussed in the limitations of this study, the comparison group may have had HEU participants who could also have potential physical sequelae of HIV thus future studies investigating the physical sequelae of perinatal HIV should use a comparison group comprised of only HUU youth.
- Lastly, further research is required into the prevalence of severe disability in PHIVA. This study excluded potential participants who could not physically and/or cognitively participate in the outcome measures used in phase two thus it is unknown what the prevalence of disability in this population is.
- One needs to consider that HIV is not the only factor affecting these adolescents. The fact that muscle strength and endurance were below international norms for the comparison group of the second phase suggests that they may have other issues. The health and physical wellbeing of children/ adolescents in resource limited communities in South Africa warrants further investigation.

8.4.2 Clinical recommendations

This study has highlighted important physical sequelae in PHIVA and subsequently a MoC has been developed for this unique population. Based on this, the following clinical recommendations are made:

- The inter-professional team working with PHIVA are encouraged to use the MoC developed in this study as a framework upon which to base their screening, assessment and referrals. The phase three inter-professional focus group highlighted the necessity of healthcare providers needing to work together in the PHIVA clinic, to be aware of each other's roles and to refer as soon as needed to the relevant team member. Regular, full assessment across all domains for all PHIVA in an HIV clinic is not practically feasible, however regular screening days can be implemented. The items to be screened for can be based on the MoC, using it as a guide.
- The simplified schematic of the MoC can be distributed to PHIVA and caregivers in the form of information pamphlets or posters on the clinic walls with the aim of raising awareness of some of the challenges encountered by PHIVA.
- The scoping review of this study highlighted the necessity of early ART initiation in CLHIV and so this, along with early screening and intervention, is clinically recommended. Preventing physical sequelae, or at least intervening early with rehabilitation, could potentially lessen the impact of these sequelae in adolescence.
- Adolescent care should be youth-friendly, with consideration given to their unique health needs and practical requirements, for example, access to clinics over weekends so as not to miss school activities during the week.
- This results of this research speak to the second and third goal of South Africa's National Strategic Plan for HIV, 2017-2022, i.e. to decrease HIV morbidity and to reach vulnerable populations through targeted interventions, respectively (SANAC, 2017). With comprehensive screening based on the MoC and increased referral to the necessary health services, the implementation of the results of this study play an important role in reaching the goals of the National Strategic Plan.

8.5 Conclusion

This chapter gave a synopsis of the results found in the scoping review and phases one to three of the study, with a discussion linking the phases together to develop a model of care for PHIVA. The strengths, limitations and recommendations of this study were presented. The following chapter will conclude this study.

Chapter 9 Conclusion

Globally, HIV remains a health challenge and with the advent of ART there is a growing population of adolescents living with perinatal HIV. They face significant neurocognitive and physical problems, even with early ART initiation and good management. Despite their specific health needs and physical challenges, there is limited knowledge and a paucity of healthcare options available for this population and thus this study aimed to determine the physical sequelae of perinatal HIV in adolescence (qualitatively and quantitatively) and to develop a MoC for PHIVA.

The study involved three phases of data collection which were based at an HIV research and services clinic in Johannesburg, South Africa. Additionally, a scoping review was done to explore the available literature on the physical sequelae of perinatal HIV in adolescents.

The first phase of data collection, a qualitative study, comprised of 19 adolescents who were interviewed individually, exploring their perceptions on their physical health. The resultant categories showed that PHIVA have challenges with physical, psychosocial and other health issues. They specifically struggled with decreased endurance, fatigue and pain; as well as decreased community participation, muscle strength and/or motor skills, and emotional and cognitive impairments. This group of participants initiated ART early and were all virally suppressed, yet they still reported substantial impairments, activity limitations and participation restrictions.

The second phase of data collection, a cross-sectional analysis of 147 PHIVA and 102 HIV-negative peers, assessed anthropometry, muscle strength, endurance, motor performance, fatigue, disability level and peripheral neuropathy. The results showed that in comparison to their peers, PHIVA have significantly impaired height, weight, BMI, manual dexterity, balance, fatigue intensity and disability levels. Although muscle strength and endurance were not significantly different to the comparison group, it is important to note that both groups performed lower than the expected norms for those outcome measures. The PHIVA in this phase of data collection had also initiated ART at a young age and the majority were virally suppressed, highlighting the prevalence of physical dysfunction in PHIVA even with good management.

A scoping review was performed, with the aim of describing what was currently known about physical sequelae in PHIVA. After screening 1291 citations, the review included eight studies whose results were grouped into anthropometric findings and physical health and functioning. The findings of the review showed that PHIVA have poor anthropometric outcomes and decreased physical functioning in terms of exercise tolerance, physical activity and pain.

The results of the scoping review and two phases of data collection were used to develop a MoC that was validated through focus groups with PHIVA and healthcare providers. The final MoC is a reflection of the physical challenges that PHIVA face in terms of impairments, activity limitations and participation restrictions; and the key players in the inter-professional management needed for PHIVA. The MoC is intended as a tool to create awareness of the multifaceted physical sequelae that PHIVA may have and to encourage the inter-professional screening and referral process. A schematic of the MoC was also created for the use within clinics, educational pamphlets and community programmes.

In conclusion, PMTCT has made a significant impact on decreasing the number of perinatal infections globally, however there are still a substantial number of CLHIV who are ageing into adolescence. This study has determined the physical sequelae of perinatal HIV in adolescence, assessed both clinically and from the adolescent's perspective, which was used to create a MoC for this distinctive population. The results of this study will provide a background for screening and care that will hopefully allow for earlier intervention and rehabilitation, thus improving the quality of life for PHIVA.

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Appendices

Appendix 1: Contributor Roles Taxonomy (CRediT)

Allen et al., (2019)

Term	Definition
Conceptualisation	Ideas; formulation or evolution of overarching research goals and aims
Methodology	Development or design of methodology; creation of models
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components
Validation	Verification, whether as a part of the activity or separate, of the overall replication/ reproducibility of results/experiments and other research outputs
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesise study data
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse
Writing - Original Draft	Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)
Writing - Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or post-publication stages
Visualisation	Preparation, creation and/or presentation of the published work, specifically visualisation/ data presentation
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team
Project administration	Management and coordination responsibility for the research activity planning and execution
Funding acquisition	Acquisition of the financial support for the project leading to this publication

Appendix 2: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms N Comley-White

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180226

NAME: (Principal Investigator)	Ms N Comley-White
DEPARTMENT:	School of Therapeutic Sciences Department of Physiotherapy Medical School University
PROJECT TITLE:	The physical sequelae of perinatally acquired HIV in adolescents
DATE CONSIDERED:	23/02/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professors V Ntsiea and J Potterton
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/06/2018

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

DECLARATION OF INVESTIGATORS

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

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

1/3/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3: Letter of permission from hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

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

MS. NICOLETTE COMLEY-WHITE
Physiotherapy Department
University of the Witwatersrand

Dear Ms. Comley-White,

RE: THE PHYSICAL SEQUELAE OF PERINATALLY ACQUIRED HIV IN ADOLESCENTS

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

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

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

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

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

Yours sincerely,

DR F BENSON
CLINICAL EXECUTIVE
2018:05:29

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

Appendix 4: Letter of permission from research site

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

Private Bag X20, Newclare, Johannesburg, South Africa, 2112
• Tel: +27(0)11 470 9214 •

WITS UNIVERSITY

11 April 2018

Dear Nicky

Following up on the discussions we have had regarding your PhD project entitled: The physical sequelae of perinatally acquired HIV in adolescents, I am pleased to grant you permission to conduct your research at ESRU. I am confident that your research questions will provide useful new insights and I support your investigations.

In order for you to write publications and analyse your data you will need to incorporate clinical and laboratory data which has already been collected as part of the CHANGES study (M120871). As one of the principal investigators of the CHANGES trial I grant you permission to access information on the CHANGES database and confirmed that permission has been granted by the other principal investigators of the CHANGES study. I ask that you utilise the primary study databases in order to maintain consistency across publications. If you need assistance from me or my team in compiling data sets, we will be happy to assist you.

I wish you everything of the best with your PhD.

Yours sincerely

Dr Renate Strehlau

DCH, DipHIV, MSc,
Deputy Director, ESRU
Renate.strehlau@wits.ac.za
082 321 8976

Appendix 5: Information letter for phase one

INFORMATION LETTER

Study title: **The physical sequelae of perinatally acquired HIV in adolescents.**

Hello,

My name is Nicolette Comley-White and I am a physiotherapist at the University of Witwatersrand. I am doing research on what are some of the physical challenges that adolescents who were born with HIV may be facing. Research is just the process to learn the answer to a question and to do this I am asking for your permission to include your child in a research study.

With your permission, I would like to chat with your child for about an hour to find out what they feel is physically difficult for them. Depending on the challenges that they have we might discuss issues around tiredness, weakness, pain or anything else that they raise as a problem for them. We will sit in a private room and you are welcome to sit with us. To make it easier for me to listen and to remember what we talk about I will record the conversation and type it out later (with all of the names of people and places removed). If at any time you or your child are not comfortable with the conversation we can stop immediately, with no negative consequences. I would also like to be able to read through your child's hospital file and results to learn about their medical history which might provide more information for my research.

The results of the interview will be used in a larger study that will propose a model of care for adolescents who were born with HIV.

Participation is voluntary and your child may withdraw at any time should he/she wish to do so. Your child may discontinue participation at any time without penalty or loss of benefits to which s/he is entitled.

Risks

There are no risks involved.

Benefits

The study will help us to find out if there are physical challenges that your child has and how we can help them.

Confidentiality

All efforts will be made to keep personal information private. Absolute confidentiality cannot be guaranteed. Organisations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the University of Witwatersrand Human Research Ethics Committee.

Distress protocol

Should the interview be in any way upsetting to you/your child, you/your child will be referred to a councillor within ESRU.

Kind regards,

Nicolette

Contact details of researcher (for any questions or comments about the study):

Mrs Nicolette Comley-White, Physiotherapist
Department of Physiotherapy
University of the Witwatersrand
011 717 3702
082 393 0834

Contact details of REC administrator and chair (for reporting of complaints/problems):

Prof Clement Penny
Clement.penny@wits.ac.za 011 717 1234

Appendix 6: Assent and consent for phase one participation and audio recording

CONSENT FOR PARTICIPATION

I, the undersigned, _____, acknowledge that I read the information sheet and hereby give permission that my son/ daughter,

_____, may participate in the study as described
(Full name and Surname)

above.

Signatures:

Parent or Guardian: _____

Researcher: _____

Witness: _____

Date: _____

VERBAL ASSENT FOR PARTICIPATION

Hi, my name is Nicolette. I am busy with a project for the university. Please can I spend about an hour chatting with you to find out if you have any physical difficulties or things that you find hard to do? Depending on the challenges that you have we might discuss issues around tiredness, weakness, pain or anything else that you raise as a problem. We will sit in a private room and if you would like to then you can have your parent/guardian with you. I would also like to read your hospital file and results to learn about your medical history which might provide more information for my research.

If you feel that you do not want to, or become uncomfortable with the conversation, then you can stop.

This letter says that I explained what you will be doing and that you either agree or may refuse to help me.

Signatures:

Participant: _____

Researcher: _____

Witness: _____

Date: _____

CONSENT FOR AUDIO RECORDING

I agree that Nicolette Comley-White may audio record the interview with my child and that she will take out any names and places that we talk about when the interview is typed up.

Signatures:

Parent or Guardian: _____

Researcher: _____

Witness: _____

Date: _____

VERBAL ASSENT FOR AUDIO RECORDING

Hi, my name is Nicolette. I am busy with a project for the university. Please can record to conversation that I have with you about what physical challenges you may have? The recording is so that I can listen better to you and have a reminder later about what we spoke about.

If you feel that you do not want to, or become uncomfortable with the conversation, then you can stop.

This letter says that I explained what you will be doing and that you either agree or may refuse to help me.

Signatures:

Participant: _____

Researcher: _____

Witness: _____

Date: _____

Appendix 7: Interview schedule

Interview schedule: phase one

Following an introduction of themselves and what the study is about, the researcher will ask questions in an open and friendly manner, allowing the participants to express their own opinions and views. The questions are broad and open-ended and the interview process is fluid. Some of the questions that will be used, but not limited to, are as follows:

- Tell me a little bit about yourself, how old you are, what you enjoy doing, do you play any sport? [The researcher will spend approximately five to ten minutes chatting with the adolescent generally].
- Since we are here to discuss the physical difficulties that you may be facing, can you tell me if there is anything that you find difficult to do during the day/at school/at home/with friends. Perhaps you feel too weak to do something? Or too tired? Or too sore?
- Is there anything that you see that your friends/siblings/cousins doing that you find difficult to do?
- Do you ever find that you can't take part in things at school/home that you would like to do because your body feels like it can't manage it?
- Of the things that you struggle to do, can you think why it is hard?
- Do you feel like your body is healthy? Why? What would you want to improve on?

Appendix 8: Information letter for phase two

INFORMATION LETTER

Study title: **The physical sequelae of perinatally acquired HIV in adolescents.**

Hello,

My name is Nicolette Comley-White and I am a physiotherapist at the University of Witwatersrand. I am doing research on what are some of the physical challenges that adolescents may be facing. Research is just the process to learn the answer to a question and to do this I am asking for your permission to include your child in a research study. By answering questions with this research we hope to learn more about the physical challenges faced by adolescents in areas such as tiredness, pain, muscle strength, disability, quality of life and motor development.

With your permission, I would like to spend about two hours with your child asking them to do a few activities like walking; jumping; playing; answering questions about their day to day life; checking their reflexes and how well they can feel; checking their heart rate. If at any time you or your child are not comfortable we can stop immediately, with no negative consequences. I would also like to be able to read through your child's hospital file and results to learn about their medical history which might provide more information for my research.

The results of the study will be used in a larger study that will propose a model of care for adolescents who were born with HIV.

Participation is voluntary and your child may withdraw at any time should he/she wish to do so. Your child may discontinue participation at any time without penalty or loss of benefits to which s/he is entitled.

Risks

There are no risks involved.

Benefits

The study will help us to find out if there are physical challenges that your child has and how we can help them.

Confidentiality

All efforts will be made to keep personal information private. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organisations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the University of Witwatersrand Human Research Ethics Committee.

Distress protocol

Should the interview be in any way upsetting to you/your child, you/your child will be referred to a councillor within ESRU.

Kind regards,

Nicolette

Contact details of researcher (for any questions or comments about the study):

Mrs Nicolette Comley-White, Physiotherapist
Department of Physiotherapy
University of the Witwatersrand
011 717 3702
082 393 0834

Contact details of Human Research Ethics Committee administrator and chair (for reporting of complaints/problems):

Prof Clement Penny
Clement.penny@wits.ac.za 011 717 1234

Appendix 9: Assent and consent for phase two participation

CONSENT FOR PARTICIPATION

I, the undersigned, _____, acknowledge that I read the information sheet and hereby give permission that my son/ daughter,

_____, may participate in the study as described
(Full name and Surname)

above.

Signatures:

Parent or Guardian: _____

Researcher: _____

Witness: _____

Date: _____

VERBAL ASSENT FOR PARTICIPATION

Hi, my name is Nicolette. I am busy with a project for the university. Please can I spend about two hours doing some activities with you to find out if you have any physical difficulties or things that you find hard to do? We will look at things such as tiredness, pain, muscle strength, disability, quality of life and motor development. We will sit in a separate room and if you would like to then you can have your parent/guardian with you. . I would also like to read your hospital file and results to learn about your medical history which might provide more information for my research.

The activities that I will ask you to do include walking; jumping; playing; answering questions about your day to day life; checking your reflexes and how well you can feel; checking your heart rate.

If you feel that you do not want to, or become uncomfortable with the session, then you can stop.

This letter says that I explained what you will be doing and that you either agree or may refuse to help me.

Thank you for your help.

Signatures:

Participant: _____

Researcher: _____

Witness: _____

Date: _____

Appendix 10: Description of the outcomes measures

Table 11.1 presents a description of the outcome measures used in the phase two study.

Table 11.1 Description of outcome measures for phase two

Variable assessed	Outcome measure	Explanation	Psychometric properties
Endurance	Shuttle run test	A multi-stage fitness test that requires a person to run as fast as they can between two marks 20m apart within specified increments of time (Léger et al., 1988).	-Test-retest reliability coefficient: 0.89 (Léger et al., 1988). -Validity coefficient: 0.84 (Léger and Lambert, 1982)
Muscle strength	Broad standing jump	A general index test used in youth for muscle fitness. It involves the participant jumping with their feet together from a starting line and the distance of the jump is measured (Castro-Pinero et al., 2010).	-Strongly associated with lower body muscle strength tests: R^2=0.829–0.864 (Castro-Pinero et al., 2010). -Test-retest reliability coefficient: 0.90-0.96 (Rahman, 2021).
Motor performance	Movement assessment battery for children- second edition (Movement ABC-2)	A tool to measure motor impairment in children and adolescents across three domains:	-Inter-rater reliability coefficient: 0.94 to 1.0 (Henderson, Sugden and Barnett, 2007).

		manual dexterity, balance, and aiming and catching (Brown and Lalor, 2009).	–Test-retest reliability coefficient: 0.97 (Wuang, Su and Su, 2012). -Internal consistency coefficient: 0.90 (Wuang, Su and Su, 2012).
Disability	World Health Organization disability assessment schedule for children (WHODAS-Child)	A 36-item tool based on the ICF that youth use to rate their difficulty in different domains of daily living (Scorza et al., 2013).	-Test-retest reliability coefficient: 0.83 (Scorza et al., 2013). -Inter-rater reliability coefficient: 0.88 (Scorza et al., 2013).
Peripheral neuropathy	Brief peripheral neuropathy screen	A simple and quick tool to assess for peripheral neuropathy in HIV (Cherry et al., 2005).	-Specificity and correct diagnostic rate: 88% and 78%, respectively (Ellis et al., 2005).
Fatigue	HIV-related fatigue scale	A 56-item tool to establish fatigue in people living with HIV (Barroso et al., 2014).	-Content validity (Barroso and Lynn, 2002). -Internal consistency coefficient: 0.94 (Barroso and Lynn, 2002).

Appendix 11: Information letters for phase three

INFORMATION LETTER: adolescents

Study title: **The physical sequelae of perinatally acquired HIV in adolescents.**

Hello,

My name is Nicolette Comley-White and I am a physiotherapist at the University of Witwatersrand. I am doing research on what are some of the physical challenges that adolescents who were born with HIV may be facing, and how we can structure health care for them. Research is just the process to learn the answer to a question and to do this I am asking for your permission to include your child in a research study.

During the previous months we have been looking at problems in adolescence such as tiredness, weakness, pain, disability, quality of life and motor development. Based on this information we have put together a health care structure and some ideas about how best to help the adolescents.

With your permission, I would like to chat with your child in a group for about an hour to find out what they think about some ideas we have about health care for them. We will sit in a private room and you are welcome to sit with us. To make it easier for me to listen and to remember what we talk about I will record the conversation and type it out later (with all of the names of people and places removed). If at any time you or your child are not comfortable with the conversation we can stop immediately, with no negative consequences. I would also like to be able to read through your child's hospital file and results to learn about their medical history which might provide more information for my research.

Participation is voluntary and your child may withdraw at any time should he/she wish to do so. Your child may discontinue participation at any time without penalty or loss of benefits to which s/he is entitled.

Risks

There are no risks involved.

Benefits

The study will help us to further find out how we can best help adolescents with HIV.

Confidentiality

All efforts will be made to keep personal information private. Due to the nature of group discussions the conversations are not confidential, however the recording and transcriptions (the typed out discussion) will be anonymous and the information will be kept confidential thereafter. Personal information may be disclosed if required by law. Organisations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the University of Witwatersrand Human Research Ethics Committee.

Distress protocol

Should the interview be in any way upsetting to you/your child, you/your child will be referred to a councillor within ESRU.

Kind regards,

Nicolette

Contact details of researcher (for any questions or comments about the study):

Mrs Nicolette Comley-White, Physiotherapist
Department of Physiotherapy
University of the Witwatersrand
011 717 3702
082 393 0834

Contact details of REC administrator and chair (for reporting of complaints/problems):

Prof Clement Penny
Clement.penny@wits.ac.za 011 717 1234

INFORMATION LETTER: clinical experts

Study title: **The physical sequelae of perinatally acquired HIV in adolescents.**

Hello,

My name is Nicolette Comley-White and I am a physiotherapist at the University of Witwatersrand. I have been doing research on what are some of the physical challenges that adolescents who were born with HIV may be facing (looking at muscle strength, endurance, fatigue, pain, disability, quality of life and motor development). Based on the results I have structured a model of care for adolescents with perinatally acquired HIV.

Based on your clinical expertise I would like to invite you to join a group of clinicians with whom I will be discussing the model of care. The group session will take approximately an hour and you will be asked to share your thoughts and suggestions. The session will be audio-recorded and transcribed (with identifying factors removed) for analysis at a later stage.

Participation is voluntary and you may withdraw at any time should you wish to do so without any negative consequences.

Risks

There are no risks involved.

Benefits

The study will help us to further find out how we can best help adolescents with HIV.

Confidentiality

All efforts will be made to keep personal information private. Due to the nature of group discussions the conversations are not confidential, however the recording and transcriptions will be anonymised and the information will be kept confidential thereafter. Personal information may be disclosed if required by law. Organisations that may inspect and/or copy your research records for quality assurance and data

analysis include groups such as the University of Witwatersrand Human Research Ethics Committee.

Kind regards,
Nicolette

Contact details of researcher (for any questions or comments about the study):
Mrs Nicolette Comley-White, Physiotherapist
Department of Physiotherapy
University of the Witwatersrand
011 717 3702
082 393 0834

Contact details of REC administrator and chair (for reporting of complaints/problems):

Prof Clement Penny
Clement.penny@wits.ac.za 011 717 1234

Appendix 12: Assent and consent for phase three participation

CONSENT FOR PARTICIPATION

I, the undersigned, _____, acknowledge that I read the information sheet and hereby give permission that I/my son/my daughter,

_____, may participate in the study as described
(Full name and Surname)

above.

Signatures:

Parent/Guardian/Participant: _____

Researcher: _____

Witness: _____

Date: _____

VERBAL ASSENT FOR PARTICIPATION

Hi, my name is Nicolette. I am busy with a project for the university. Please can I spend about an hour chatting with you in a group to find out what you think of some ideas that I have had for health care for adolescents?

During the previous months we have been looking at problems in adolescence such as tiredness, weakness, pain, disability, quality of life and motor development. Based on this information we have put together a health care structure and some ideas about how best to help the adolescents.

We will sit in a private room and if you would like to then you can have your parent/guardian with you. If you feel that you do not want to, or become uncomfortable with the conversation, then you can stop. All efforts will be made to keep personal information private. Due to the nature of group discussions the conversations are not confidential, however the recording and transcriptions (the typed out discussion) will be anonymous and the information will be kept confidential thereafter.

This letter says that I explained what you will be doing and that you either agree or may refuse to help me.

Signatures:

Participant: _____

Researcher: _____

Witness: _____

Date: _____

CONSENT FOR AUDIO RECORDING

I agree that Nicolette Comley-White may audio record the interview with my child/me and that she will take out any names and places that we talk about when the interview is typed up.

Signatures:

Parent/Guardian/Participant: _____

Researcher: _____

Witness: _____

Date: _____

VERBAL ASSENT FOR AUDIO RECORDING

Hi, my name is Nicolette. I am busy with a project for the university. Please can I record the conversation that I have with you about the health care suggestions that I have? The recording is so that I can listen better to you and have a reminder later about what we spoke about.

If you feel that you do not want to, or become uncomfortable with the conversation, then you can stop.

This letter says that I explained what you will be doing and that you either agree or may refuse to help me.

Signatures:

Participant: _____

Researcher: _____

Witness: _____

Date: _____

Appendix 13: Declaration by students and co-authors agreement for published papers submitted for examination purposes

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Nicolette Comley-White, student number 0400842T, declare that this thesis is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my thesis.

Signature of Student …… **Date**……13 March 2022……..

Name of Primary Supervisor……Prof Joanne Potterton……

Signature of Primary Supervisor ……**Date**…… 14 March 2022

Name of Co-supervisor: Associate Prof Veronica Ntsiea……

Signature of Co-supervisor ……**Date**…… 15 March 2022

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of her thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for her degree purposes.

Article 1: Title: The physical sequelae of perinatally acquired HIV in adolescents: a research proposal

Journal name, year, volume and page numbers: *BMC Research notes*, 2019, 12:62

Authors	Name	Signature	Date
1st author	Nicolette Comley-White		13 March 2022
2nd author	Joanne Potterton		14 March 2022
3rd author	Veronica Ntsiea		15 March 2022

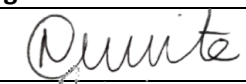
Comments by primary supervisor:

This publication is a result of original work conducted by the candidate, Nicolette Comley-White, supervised by Prof Joanne Potterton and Associate Prof Veronica Ntsiea.

……

Article 2: Title: Physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review protocol

Journal name, year, volume and page numbers: *JBI Evidence Synthesis,* 2021, 19(11): 3149-3154

Authors	Name	Signature	Date
1st author	Nicolette Comley-White		13 March 2022
2nd author	Joanne Potterton		14 March 2022
3rd author	Veronica Ntsiea		15 March 2022

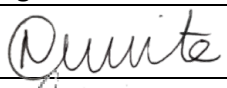
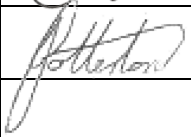
Comments by primary supervisor:

This publication is a result of original work conducted by the candidate, Nicolette Comley-White, supervised by Prof Joanne Potterton and Associate Prof Veronica Ntsiea.

……

Article 3: Title: The physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review

Journal name, year, volume and page numbers: *Physical Therapy Reviews*, 2022, online

Authors	Name	Signature	Date
1st author	Nicolette Comley-White		13 March 2022
2nd author	Joanne Potterton		14 March 2022
3rd author	Veronica Ntsiea		15 March 2022

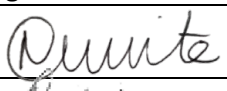
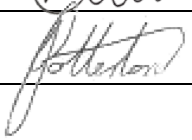
Comments by primary supervisor:

This publication is a result of original work conducted by the candidate, Nicolette Comley-White, supervised by Prof Joanne Potterton and Associate Prof Veronica Ntsiea.

……

Article 4: Title: The perceived challenges of perinatal HIV in adolescents: a qualitative study

Journal name, year, volume and page numbers: *Vulnerable Children and Youth Studies,* 2021, 16(4):320-333

Authors	Name	Signature	Date
1st author	Nicolette Comley-White		13 March 2022
2nd author	Joanne Potterton		14 March 2022
3rd author	Veronica Ntsiea		15 March 2022

Comments by primary supervisor:

This publication is a result of original work conducted by the candidate, Nicolette Comley-White, supervised by Prof Joanne Potterton and Associate Prof Veronica Ntsiea.

……

Appendix 14: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

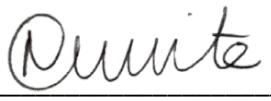
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Nicolette Comley-White (Student number: 0400842T) am a student registered for the degree of Doctor of Philosophy in the academic year 2022.

I hereby declare the following:

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

Signature:  Date: 13 March 2022

Appendix 15: Turnitin Similarity Report

A Turnitin similarity report gives an indication of the originality of an author's work and it is a requirement of the University of the Witwatersrand when submitting a thesis for examination. For this thesis, Chapters 1, 2, 8 and 9 were submitted to Turnitin, generating a similarity index of 13%, which is within the acceptable norms. The similarity index report is presented below.

The supervisors of this thesis have seen and acknowledge the turnitin report.

Supervisor 1

Name: Prof Joanne Potterton

Signature:_____

Date: 14 March 2022

Supervisor 2

Name: Associate Professor Veronica Ntsiea

Signature:_____

Date: 15 March 2022

PhD thesis

ORIGINALITY REPORT

13%	9%	11%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	4%
2	Nicolette Comley-White, Joanne Potterton, Veronica Ntsiea. "The perceived challenges of perinatal HIV in adolescents: a qualitative study", Vulnerable Children and Youth Studies, 2021 Publication	1%
3	Nicolette Comley-White, Joanne Potterton, Veronica Ntsiea. "The physical sequelae of growing into adolescence with perinatally acquired HIV: a scoping review", Physical Therapy Reviews, 2022 Publication	1%
4	bmcresnotes.biomedcentral.com Internet Source	<1%
5	eprints.kingston.ac.uk Internet Source	<1%
6	www.science.gov Internet Source	<1%