University of the Witwatersrand

Submission of research report for MMed (Paediatrics)

The impact of caregiver mortality on treatment outcomes for 2021 in children and adolescents living with HIV at Empilweni clinic in Johannesburg – an observational cohort study

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Declaration of original work:

I, Dr Josephine Keal, solemnly declare that the contents of this paper, titled " The impact of caregiver mortality on treatment outcomes for 2021 in children and adolescents living with HIV at Empilweni clinic in Johannesburg – an observational cohort study" submitted in fulfilment of the requirements for the Masters of Medicine in Paediatrics and Child Health, are entirely my original work.

I affirm that the ideas presented, the data collected, the analyses conducted, and the conclusions drawn within this paper are the result of my own scholarly inquiry and intellectual effort. Any sources of information or inspiration that have been used in the preparation of this paper have been properly acknowledged through citations and references

I further declare that this paper has not been previously submitted, in whole or in part, for any other academic qualification, and it has not been plagiarized from any other source. All external contributions, whether through collaboration or consultation, have been appropriately credited.

I acknowledge that any attempt to misrepresent the originality of this work would constitute a breach of academic integrity and could result in disciplinary action

Name, Surname and Signature: Dr Josephine Keal

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Date: 07/10/2024

Dedication:

To my parents. For your time, care and support over the past four years and throughout my life.

Acknowledgements:

I would like to thank my supervisor, Prof Karl-Günter Technau whose guidance and encouragement were invaluable throughout my journey towards achieving my Masters in Medicine (MMed) in Paediatrics. He provided me with the support and mentorship necessary for the successful completion of this degree, as well as regular reminders and opportunity to prioritise what is really important.

I am also immensely thankful to my fellow authors and colleagues who collaborated with me on the research paper. Their contributions and insights were instrumental in the final paper.

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Title: Care for the caregiver: how caregiver mortality affects treatment outcomes – an observational cohort study

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Abstract

Introduction:

Despite improvements in HIV management, children and adolescents living with HIV remain vulnerable. Caregiver mortality in a large paediatric and adolescent HIV clinic in Johannesburg are described and the effect of the death of a caregiver on children and adolescents' HIV treatment outcomes was investigated.

Methods:

In this secondary retrospective analysis on longitudinal data we included children or adolescents attending clinic between 01 January to 31 December 2021. Data were divided into those with documented primary caregiver mortality and those without (ever documented including before enrolment into care). Viral load, treatment regimens, CD4, and anthropometry were analysed for the year 2021.

Results:

Caregiver vital status was recorded in 1171 (93%) of the 1260 patients attending clinic in 2021. In 115 children or adolescents (10%) we found a documented death of caregiver(s). Amongst 1120 mothers, 100 (9%) had died; of 460 fathers, 18 (4%) had died and one (1%) of 100 other caregivers had died. A large number (n=54 [45%]) of the 119 deaths occurred between 2016 and 2021 and 66 (69%) after the child/adolescent's enrolment in the clinic. In 2021, stunting and wasting were seen significantly more in the participants who had a caregiver death than those who had not (p=0.01 and 0.02 respectively). No significant difference was seen between the groups for the viral load, treatment regimens and CD4 counts.

Conclusion:

Caregiver death was incompletely captured in the clinic database, suggesting that clinicians were unaware of the death of a caregiver. Children experiencing the death of a caregiver were more likely to be malnourished. We propose increased attention on wellbeing of caregivers in paediatric HIV services.

Key words: HIV/AIDS , Caregiver, mortality, orphan.

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Statements and Declarations:

There are no competing interests, financial or non-financial, that are directly or indirectly related to the work submitted for publication to disclose.

Introduction:

There have been significant advancements in paediatric and adolescent human immunodeficiency virus (HIV) care since the roll-out of antiretroviral therapy (ART), especially so in sub-Saharan Africa.[1] However, progress in paediatric HIV care continues to lag behind adults, with 77% of eligible adults receiving ART globally, compared with 57% of children in 2022.[2] South Africa now has the largest ART programme in the world, providing treatment to roughly 5.7 million people.[3] Despite this success, according to The Joint United Nations Programme on HIV and Acquired Immunodeficiency Syndrome (*UNAIDS*) only 54% of children known to be living with HIV in South Africa were on ART in 2022.[4]

In 2022 HIV/AIDS related disease resulted in 13.9 million children being orphaned globally.[5] The after-effects of HIV-associated mortality in the 1990's and early 2000's are still being felt. In 2020 there were 2.9 million recorded orphans in total in South Africa. This is equivalent to approximately 14% of all children and adolescents living in South Africa.[6] An orphan is defined as a child or adolescent who has experienced the death of either their biological mother or father or both. Paternal orphans (biological father demised) make up 61% of orphans in South Africa in 2020.[6] The total number of orphans increased by over a million between 2002 and 2009 in South Africa and was largely attributed to deaths related to the HIV/AIDS pandemic, after which the trend was reversed.[7] Improved access to antiretrovirals resulted in orphan numbers dropping to lower than 2002 levels by 2017.[7] There has been a 70% decrease in the number of people dying of HIV each year in South Africa since 2010 but despite this improvement, it was estimated that there were 720 000 orphans (between the ages of 0-17 years) in 2022 due to one of their parents dying from AIDS.[7]

Adherence to prescribed treatment regimens is a necessity for effective long-term therapy on ART. Recent studies suggest that adherence levels need to range from 70-90% for treatment regimens to be effective.[8] Children and adolescents living with HIV have unique barriers to achieving optimal adherence as they are often placed on ART from a very young age, and face the prospect of being on treatment for life.[9] The majority (90%) of children and adolescents living with HIV reside in sub-Saharan Africa.[1] Therefore, in addition to the challenges faced with pill burden, tolerability and acceptance of a diagnosis of HIV infection, these children are faced with the myriad of daily struggles associated with living in a lower middle-income setting. A primary caregiver is defined by the South African Social Security Agency as the person responsible for a child's daily needs and well-being. [10] Caregivers living with HIV battle with their own adherence, acceptance and social challenges and it is not uncommon for caregivers to die from HIV/AIDS-associated illness.[11] The death of a primary caregiver can equate to the loss of a provider for the child and as a result; food security, shelter and other basic needs may be compromised. The psychological trauma of the death of a primary caregiver also negatively impacts on the overall well-being of the child and the child is more vulnerable to abuse and neglect.[11]

In Sub-Saharan Africa, up to 50% of children orphaned from HIV/AIDS who are living with HIV are now adolescents.[12] These children and adolescents are often cared for by HIV uninfected extended family members. Data suggest that caregivers of orphaned children and adolescents may stigmatise or discriminate against these children due to their HIV status, and this may result in poorer clinical outcomes.[12]

With the above in mind, this study aimed to evaluate and describe a paediatric population attending a specialised HIV clinic in Johannesburg focusing on the primary caregivers of these patients. Particularly, this study analysed how the death of a caregiver impacted

treatment outcomes such as viral load suppression rates, treatment regimens, CD4 counts and anthropological measurements to assess the health and the wellbeing of the children and adolescents included.

Methods:

We performed a secondary retrospective analysis on longitudinal data collected during routine clinical visits from the clinical visit database at a paediatric and adolescent HIV clinic, Empilweni Services and Research Unit (ESRU). The clinic is based at Rahima Moosa Mother and Child Hospital (RMMCH), in Johannesburg, South Africa. This study focussed on all children and adolescents under 20 years of age who attended the clinic between the 1st of January 2021 to 31st of December 2021 irrespective of their original enrolment date into the clinic. The cut-off age of 20 was chosen to include all adolescents attending the clinic. Children and adolescents may have been enrolled prior to and including 2021. Data were collected on this cohort from inception of the clinic in 1998 to the end of 2021. The database is hosted on the University of the Witwatersrand REDCAP platform.[13]

The ESRU clinic is a large paediatric HIV clinic in South Africa, with over 1400 children in active care and about 5000 managed in total since its opening in 1998. It is located in RMMCH, which is an urban academic hospital specialising in obstetrics and gynaecology, paediatric and neonatal services in Johannesburg, South Africa.

Daily, the clinic manages neonates, children and adolescents living with HIV, as well as neonates that are exposed but uninfected. On average each patient will visit the clinic four times in a year. Management includes initiation of treatment naïve patients onto first line ART, regular follow-up appointments for patients established on ART, and management of patients with assumed and confirmed ART drug resistance in establishing a new ART regimen and dealing with any adherence issues. On entry into the clinic the patient's

demographics are recorded as well as the primary caregiver's information. The information collected on the primary caregiver includes: relationship to patient (biological mother or father, extended family member, institution employee, other.) age, national identity number or passport number (if available), HIV status and treatment regimen and details of any other children they may have. At each follow-up visit, patients are seen by doctors, and counsellors. Phlebotomy staff are available for taking the relevant and necessary blood tests. All results are recorded in a flow sheet in the patient files. National guidelines advise viral loads (VL) to be taken three months post initiation of ART, six months after that if suppressed (VL<50), and then annually from there on, if the VL remains suppressed.[14] Mental health screening is performed at each routine visit, and a more rigorous screening approach is taken with all adolescent patients.[15] Until a recent change in hospital policy, caregivers of children receiving treatment at the clinic were unable to receive their own ART treatment at RMMCH; making a family-centred approach to care very difficult. Caregiver and escort (if child is accompanied by someone other than their primary caregiver) information are updated at each visit. Data are routinely collected and updated from patient hospital records and entered into the database after each visit to the clinic.

The following data were included and were extracted from the existing database.
For caregivers we recorded the demographic characteristics (caregiver age and relationship to the child/adolescent) as well as their vital status at the time of the child's entry to the clinic and during subsequent visits up to the end of 2021. We noted any event of death in a primary caregiver. We recorded the current primary caregiver (parent or other caregiver in the absence of the biological parents) who accompanied the children and adolescents. The reported relationship between the primary caregiver and the study participant included biological mother and father, extended family members (grandparent, aunt/uncle, sibling),

adoptive or foster parents or an institution (represented by an employee). For the children and adolescents who were included in the study we included the age of the child/adolescent at entry into the clinic, the mode of entry (via routine testing as part of the prevention of mother-to-child-transmission [PMTCT] programme or through in- or outpatient child services) and the participants age in 2021. Other patient variables assessed included VL suppression rates, between 01/01/2021 and 31/12/2021, categorised as <50 RNA copies/mL, 50 to <1000 RNA copies/mL, and ≥1000 RNA copies/mL. ART regimens in 2021 were divided into categories; Integrase strand transfer inhibitors (INSTI), Protease Inhibitors (PI), Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based. We also assessed World Health Organisation (WHO) clinical stage at entry, nadir CD4 T-lymphocyte counts and anthropometry (Weight for age, Height for age and weight for height (WHZ) Z scores in those less than 5 years, body mass index (BMI) Z scores > 5 years) at first ever visit and 2021, ART start date and clinic visits through 2021.

The cohort was described in terms of numbers of deaths amongst caregivers, specifically mothers, fathers and other primary caregivers, the nature of how the death was captured: whether in the standard hospital record or ascertained through the national death registry (see below). The timing of these deaths were described in terms of year categories (2005 and before, 2006-2010, 2011-2015, 2016 to 2021) and timing with relation to entry of the child to the clinic as well as age of the child and caregiver at the time of the caregiver's death. Data were separated into those with a documented primary caregiver mortality and those without, to assess whether there were any differences noted in the two groups with regard to entry into the clinic or outcomes in 2021. Continuous variables were described using medians and interquartile ranges (IQR). Percentages and frequencies were used to describe categorical variables and these were compared using Chi-Square or the Fisher exact tests, depending on

the numbers. The student's t-test were used to compare continuous variables which are normally distributed, or the Wilcoxon test if they are not normally distributed variables.

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (M220516). The cohort is prospectively captured under the protocol since 2007 – "Cohort Study of HIV-infected and exposed Children receiving care at Rahima Moosa Mother and Child Hospital supported by the Empilweni Services and Research Unit and participation in the International epidemiological Databases to Evaluate AIDS (IeDEA) Collaboration" (M170778 – M220559). The ethics clearance includes the process to annually match data to the national death registry via a trusted third party (Medical Research Council), who has the mandate to handle national death registry data in the context of research. All data was kept in a password protected de-identified spreadsheet. Only the researcher and supervisor had access to this spreadsheet. All patients/caregivers entering the clinic have been invited since 2007 to consider a data sharing permission.

Results:

A total of 1518 children and adolescents attended the clinic during the study period. For 89 (6%) patients there was no caregiver recorded in the clinic data system and they were therefore excluded from the study. After exclusions (Figure 1) 1171 patients were included in the study. Caregiver status at entry to the clinic included 1120 (96%) mothers, 460 (39%) fathers and 100 (7%) other caregivers including 28 grandmothers, 48 other family members (aunts, uncles and siblings), 11 adoptive or foster parents and 13 other caregivers. In those cases where a biological mother was the documented primary caregiver, only 37% had a biological father who was an additional or secondary caregiver.

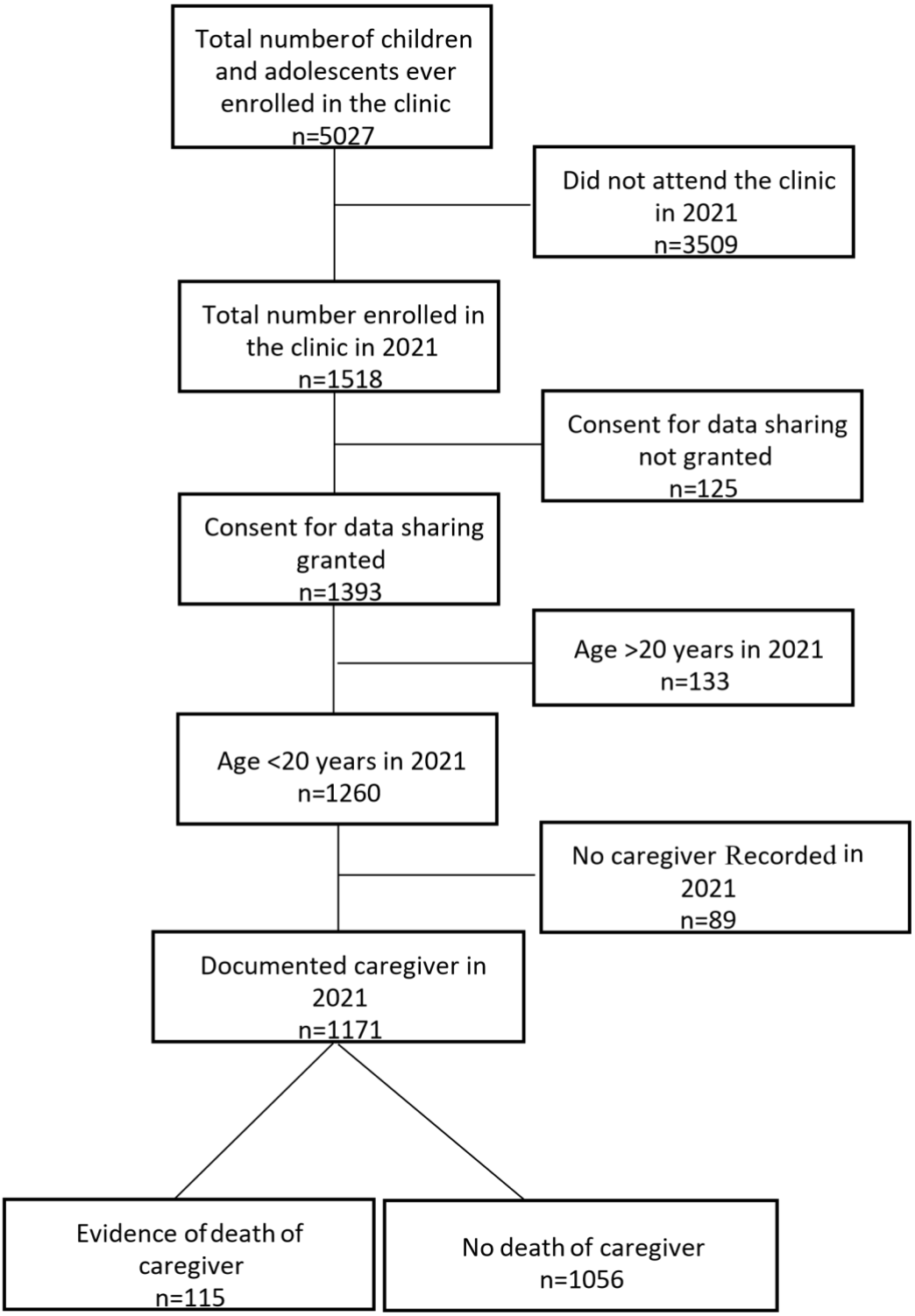

Figure 1: A flow diagram showing the process of screening potential participants attending a specialised paediatric an adolescent HIV including the vital status of their caregiver in 2021

There were 115 (10%) children or adolescents with a documented death of caregiver(s) (Figure 1). Amongst 1120 mothers, 100 (9%) had died; of 460 fathers, 18 (4%) had died and one (1%) of 100 other caregivers had died. There were four children or adolescents who experienced the death of two caregivers. In three cases both parents had died, and in one case the mother and another caregiver (other than the father) had died.

Out of the 1120 mothers, 1037 had a documented date of birth and their age in 2021 could be calculated. The median age of caregivers who were mothers attending the clinic in 2021 was 39.6 years (IQR: 34-44 Table 1). For 66 of the 100 mothers who died, both the date of birth and death were known and the median age at death was 35.2 years (30-40). Of the 460 fathers, 314 (68%) had a documented date of birth and their age in 2021 was 44.3 years (3849). Ten of the 18 fathers who had died had both date of birth and date of death and were 43.2 years (33-52) at the time of death.

For 78 of the 100 mothers who died the year of death was known and 44 (56%) of these deaths occurred between 2016 and 2021. Similarly, out of 13 of the 18 fathers with known year of death, 9 (69%) died between 2016 and 2021. Out of 44 mothers who died between the years 2016-2021, 35 (80%) died while their child was enrolled at the clinic. Similarly 7 (78%) of the 9 fathers who died between 2016 and 2021 had a child enrolled at the clinic. Overall, there were significantly more deaths (43/54 [80%]) that occurred while the patient was enrolled from 2016 to 2021 compared to before 2016 where 20/38 (53%) died after the child had already been enrolled (p=0.023).

Table 1: Ages of caregiver and children and relation to clinic entry in cases with caregiver death

	All	Mother	Father	Other
Total	119	100	18	1
Median age of child (years) at time of death (IQR)	6.9 (3.5-11.7) N=95	6.1 (3.1-10.3) N=81	10.6 (5.113.5) N=13	12.7 N=1
Median age of caregiver (years) at time of death (IQR)	35.3 (30.241.7) N=77	35.2 (29.939.2) N=66	43.2 (32.752.1) N=10	65.4 N=1
Death in relation to entry into clinic N (%)				
After entry	66 (69)	57 (70)	8 (62)	1 (100%)
Same year as entry	10 (11)	8 (10)	2 (15)	0
Before entry	19 (20)	16 (20)	3 (23)	0
Unknown	24 (20)	19 (20)	5 (28)	0
Year of death N(%)				
2005 and earlier	2 (2)	2 (2)	0	0
2006-2010	13 (11)	13 (13)	0	0
2011-2015	23 (19)	19 (19)	4 (22)	0
2016-2021	54 (45)	44 (44)	9 (50)	1 (100)
Unknown	27 (23)	22 (22)	5 (28)	0

IQR: Inter-quartile range

The clinic database as well as the national death registry were cross-referenced to attain the total number of deaths of caregivers per study participants. The clinic data recorded 87 deaths in caregivers who were mothers. When looking at the National Death Registry (NDR) a total of 40 (40%) maternal deaths were captured. Twenty-seven (27%) of these were captured in both databases, 13 (13%) were only captured on the NDR. Of the 18 deaths of fathers captured, 14 (78%) were captured in the clinic database. Five (28%) were captured in the national death registry and only one (6%) was captured in both databases. One death was recorded in a primary caregiver other than a mother or father, and it was noted in both databases.

The majority of the deaths occurred between 2016-2021. With 20 (20%) occurring in 2019.

There is a steady increase in the age of the child when the caregiver died from 2006-2021. The mean age of the child at the time of the death of the caregiver in 2005 was 2.0 years (1.5-2.0), versus 2016-2021 where it was 9.2 years (5-13; p<0.0001 Wilcoxon test).

Table 2 shows the comparison between children and adolescents attending clinic in 2021 who had (n=115) and had not experienced the death of a caregiver (n=1056). The table addresses both characteristics at entry into HIV care as well as characteristics in 2021.

Table 2: Characteristics of patients attending the clinic in 2021

Characteristics	Total	Caregiver Mortality	No caregiver mortality	P value
Total	1171	115 (10)	1056 (90)	
Demographics and characteristics at entry to HIV services				
Female sex	579 (49)	54 (47)	525 (49)	0.80
Entry into clinic				
PMTCT	133 (11)	4 (3)	129 (12)	0.0095
Inpatient	492 (42)	49 (43)	443 (42)	
Outpatient	526 (45)	62 (54)	464 (44)	
Not known	20 (2)	0 (0)	19 (2)	
Median age in years at first visit (IQR)	2.3 (0.6-5.5)	3.0 (1.0-6.4)	2.1 (0.5-5.2)	0.026
Median weight for age zScore§ (IQR)	-1.6 (-2.6- -0.6)	-1.8 (-2.8- -0.7)	-1.5 (-2.6- -0.6)	0.26
Median height for age zScore§ (IQR)	-1.8 (-2.8- -0.7)	-2.0 (-3.0- -0.9)	-1.7 (-2.8- -0.7)	0.10
Median body mass index for age z-Score§ (IQR)	-0.6 (-1.6- 0.4)	-0.8 (-1.6-0.25)	-0.6 (-1.6-0.3)	0.27
Median nadir CD4 count (IQR)¶	500(302-722)	502 (345-719)	512 (310-731)	0.37
Median nadir CD4 % (IQR)	26(15-35)	27 (16.4-34.0)	27 (15.4-35.0)	0.13
WHO stage Not documented	443(55)	45(52)	398(56)	0.09
WHO stage 1	130 (16)	11(13)	119(17)	
WHO stage 2	44 (5)	1(1)	43(6)	
WHO stage 3	133 (17)	19(22)	114(16)	
WHO stage 4	51 (6)	10(12)	41(6)	
Ever had tuberculosis	398 (34)	50(43)	348(33)	0.08
Antiretroviral treatment				

On ART at first visit (%)	330 (29)	33 (31)	297 (29)	0.68
Median age (years) at ART start (IQR)	1.6 (0.4-4.3)	2.1 (0.6-6.3)	1.4 (0.4-4.0)	0.016
Characteristics in 2021				
Median age in years in 2021 (IQR)	13.9 (9.6-16.6)	14.5 (10.6-16.9)	13.5 (9.0-16.2)	0.013
Age group				
0-<5 years	125 (11)	4 (3)	121 (11)	0.038
5-<10 years	200 (17)	20 (10)	180 (17)	
10-<15 years	410 (35)	39 (34)	371 (35)	
15-<20 years	436 (37)	52 (45)	384 (36)	
Viral load (copies/ml) in 2021				
0-<50	882 (75)	91 (79)	791 (75)	0.61
50-1000	150 (13)	14(12)	136(13)	
>1000	86 (8)	10(9)	121(12)	
Regimen in 2021				
INSTI_based	913 (83)	96(83)	817(78)	0.19
NNRTI_based	16(1.2)	3(3)	13(1)	
Other/unknown	23(2)	2(2)	21(2)	
PI_Based	216(18)	14(12)	202(19)	
Anthropometric measures in 2021				
Weight for age z-Score < -2	51(18)	6 (27)	45 (17)	0.21
Height for age z-Score < -2	212 (22)	31(31)	181(21)	0.02
Body mass index for age zScore <-2	79 (8)	15 (15)	64 (7)	0.01

IQR: Inter-quartile range. WHO: World Health Organisation. All data reflected as n (%) unless otherwise indicated. § Z-Scores calculated according to the WHO 2007 standard calculated through the SAS. ¶ CD4 count measured in µl/ml

At entry into the clinic the most notable differences are that children and adolescents who had experienced a caregiver mortality were slightly older (3.0 years vs. 2.1 years p=0.026). A smaller proportion of children and adolescents who experienced caregiver mortality (3% vs 12%) entered the clinic via prevention of mother-to-child transmission services (which implies testing during routine immunisation or birth visit as opposed to sick child visits).

The cohort who had experienced the death of a caregiver(s) were not significantly more underweight for age in 2021 than the cohort who had not experienced a death of a caregiver(s). Stunting was significantly higher in the cohort who had a caregiver death ($p = 0.01$) and a higher rate of wasting was seen in the participants who had a caregiver die than those who had not ($p = 0.02$).

There was no statistically significant difference between the two groups for rates of viral load suppression, nadir CD4 count, ever having had TB and ART regimen in 2021.

Discussion:

Our study showed that nearly 10% of the clinic population in 2021 had experienced the death of a primary caregiver, and most deaths occurred while the child was in care at the clinic. Children, and to some degree adolescents, are dependent on the commitment and reliability of their caregiver to ensure adherence to their ART.[16] With the improvements in ART, HIV has now changed into a chronic condition. Chronic medical conditions have their unique challenges for the caregivers of children living with them.[17] In a cross-sectional study done in Uganda in 2021 the burden of being a caregiver of a child living with HIV was discussed.[11] Care burden refers to the emotional, physical, financial, and social toll that caring for a child with a chronic illness encompasses. It was found that care burden is common among the caregivers of children living with HIV in the study sample population. The recommendation was to implement social and spiritual support systems that would help to support caregivers with their unique struggles experienced while caring for orphaned children living with HIV.[11]

The health of the parent(s) or caregivers is integral to the health of the child. We noted that the caregiver death was incompletely captured and documented in the clinic database as 13% of the maternal deaths and 5% of the paternal deaths were only noted in the national death registry and not in the clinical notes or database; suggesting that the clinicians were unaware of the death. The year with the highest number of deaths was 2019 with 20% occurring in this year. The reason for this high number is unclear but could be related to increased awareness due to a mental health screening process being added to the clinic at this time. During the time of death of a caregiver, there is an element of social disruption as a newly allocated caregiver would have to take over these responsibilities. What is often overlooked is the bereavement process that the child needs to go through with the death of a primary caregiver, and how that may influence their adherence to ART. The death of a caregiver should prompt interventions to protect the child/adolescent from other adverse outcomes that may be secondary to the death of a caregiver.

In research done on the outcomes of children and adolescents orphaned by HIV, it has been shown that they have increased mortality and morbidity, regardless of their own HIV status.[16] The cohort who had a primary caregiver death had significantly higher rates of wasting and stunting, suggesting chronic illness and /or malnutrition. Possible reasons for this could be worsening food insecurity (resulting in malnutrition) or poor adherence to ART (resulting in chronic illness), both of which could be due to the death of a primary caregiver and breadwinner. A cross-sectional study done in 2020 showed there was a direct correlation between improved quality of life and being a part of a nuclear family (family of two parents and their children). [17] The death of one or both parents is associated with an increased risk of short and long term mental health problems.[12]

There was no difference in virological outcomes between the two cohorts, implying that the increase in wasting and stunting rates that was seen, was likely due to socioeconomic issues rather than due to adherence issues. Addressing quality of life and mental health research in relation to the death of a caregiver needs to be investigated in the future.

The majority of both maternal (67%) and paternal (80%) deaths occurred in the last five years of the observation period. This is counterintuitive and in stark contrast to the decline in orphanhood observed in society.[7] This raises concern for treatment fatigue and missed opportunities in addressing the health issues of the parents as the majority of the caregivers were attending the clinic with their child(ren) at the time of their demise, supporting the need for a family-centred approach to HIV care.[18] Preventing deaths amongst caregivers who are potentially even attending clinic with their child should be prioritised. Screening for treatment interruption, mental health issues as well as other health screens (e.g. PAP smears, screening for diabetes and high blood pressure) could be easily offered and have been started at our clinic. It will be important to monitor the trend in the future to assess whether these interventions have helped.

Within the cohort who had a primary caregiver death, children were slightly older at entry into the clinic. They were therefore less likely to be diagnosed through routine HIV testing offered during PMTCT services. This suggests that children may not have had the same access to routine early infant HIV diagnosis. The median age at starting ART was nine months later in the group of children who had a caregiver death. This delay is significant for children where the risk of mortality in the first years of life is around 50% in the absence of ART.[19] There may be different reasons for this later ART start. Mothers who struggled with acceptance of their own diagnosis or treatment may have been at risk of not accessing

PMTCT services, as well as being at risk of poorer outcomes for themselves. Alternatively the maternal HIV results may have been kept secret and may not have been known until the mother died and the child came into the care of a different caregiver. Our data did not allow us to understand this in greater detail and more in-depth analyses of the journeys of children whose parents, particularly whose mothers, died may help to understand this better. In a study done in 2015, childhood mortality was shown to rise 7-11 months before to the mother's death.[20] This is likely due to the mother being ill and being unable to provide adequately for the child, however once the mother or primary caregiver has passed away another caregiver steps in and fulfils that role.

Speaking about the death of biological parents and other caregivers comes with its own challenges. Dealing with the death and bereavement in children and adolescents is not easy, whether the death happened long ago or recently.[21] The death of a primary caregiver should be seen as a defining event in a child or adolescent's life and should immediately trigger a higher level of awareness and caution about potential long term clinical and psychosocial problems. As part of routine history-taking, the health of the primary caregiver and family should be enquired about and documented at each visit. The first step, however, is to quantify the problem and create more awareness.

The health of a child is dependent on the support and stability of a healthy caregiver. More stringent screening tools need to be put in place to intervene and help caregivers who are ill, and to create a stronger system of documenting deaths. In the event of a death, support networks and structures need to be put into place to help the children or adolescents grieve and cope with the loss. We see that the effects of a caregivers' death are not short-lived but rather translate to chronic issues such as stunting and a wasting. There is a small portion in

the Integrated management of childhood illness (IMCI) booklet that asks about maternal health when the child visits the clinic.[22]. According to the WHO, IMCI is an integrated approach focusing on the health and well-being of children with the intention to reduce preventable mortality, decrease illness and disability, and promote healthy growth and development of children under five years of age. We would argue that policy should be moving towards treating the primary caregiver and the child as a unit and screening the dyad at every routine clinic visit as well as any presentation for medical care. In addition, parents and children should ideally be able to access their HIV care and other primary health care needs in the same clinic on the same day.

Strengths of the study included a large sample size as well as a long study period. The study also pooled data from multiple sources to try get the most accurate representation of caregiver mortality. The weaknesses are that it was a single-centre study and only looked at those children and adolescents attending the clinic in 2021. There was a large amount of missing data, as well as a number of confounders that could have contributed to the child's overall well-being. As this was a retrospective study it was challenging to identify a specific outcome related to caregiver mortality in a cohort of children and adolescents who had been in care for various durations. This made it difficult to do a multivariate analysis. The study also highlighted the incomplete documentation of caregiver health and mortality, and it is possible that deaths were missed. The National death registry (NDR) uses South African identity numbers, therefore the data gathered using the NDR will have significant omissions as caregivers without identify numbers or caregivers who are foreign nationals would not have been captured on this system.

This study was unique in looking at the effects of the death of any primary caregiver, not just the mother. In South Africa this is particularly important as many children are raised by extended family members or other primary caregivers. The study also looked at chronic clinical outcomes such as stunting and wasting rather than mortality outcomes alone. Many children in South Africa come from backgrounds where their biological parents, for numerous reasons, are not their primary caregiver. The death of an extended family member or grandparent acting as a primary caregiver may have as profound an effect on a child's health and wellbeing as the death of a biological parent. This may be easily overlooked if not enquired about in enough detail in our setting. There was only one documented death of a non-biological parent primary caregiver in our study. The documentation of these deaths may be a potential weakness in our study and something to enquire further about.

There is room for further investigation into how caregiver mortality affects other aspects of child and adolescent wellbeing including but not limited to mental health, developmental milestones and school or academic performance. There is a need for increased surveillance of mothers' and caregivers' health when children are admitted to hospital, to screen maternal and caregiver health and identify and address issues before discharging the child back into their care. This study hopes to highlight the importance of seeing the caregiver and child as a dyad rather than treating the child in isolation. Documentation of the death of a caregiver is equally important, so that clinicians are sensitised to screen for potential issues that may arise in ongoing care of the child.

Author contributions:

The contributions of each author to the research and preparation of the manuscript are as follows:

1. Dr Josephine Keal
    - Conceptualisation of the study
    - Designing the research methodology
    - Data collection, analysis, and interpretation
    - Drafting and revising the manuscript
    - Final approval of version to be published

2. Dr Gillian Sorour
    - Contributing to the writing and editing process
    - Reviewing and providing critical feedback on the manuscript
    - Approval of the final version for publication

3. Dr Nicola van Dongen
    - Contributing to the writing and editing process
    - Reviewing and providing critical feedback on the manuscript
    - Approval of the final version for publication

4. Dr Thalia Ferreria
    - Contributing to the writing and editing process
    - Reviewing and providing critical feedback on the manuscript
    - Approval of the final version for publication

5. Associate Professor Karl-Günter Technau

    - Conceptualisation of the study
    - Designing the research methodology
    - Participation in data acquisition or analysis
    - Reviewing and providing valuable input during manuscript preparation.
    - Final approval of version to be published

We confirm that all the authors have reviewed and agreed upon the final version of the manuscript submitted for publication. Additionally, we attest that all individuals who have made substantial contributions to the work have been included as authors, and all authors share accountability for the accuracy and integrity of the research presented in the manuscript

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AIDS and Behavior

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The impact of caregiver mortality on treatment outcomes for 2021 in children and adolescents living with HIV at Empilweni clinic in Johannesburg – an observational cohort study

Student: Dr Josephine Keal

Student no.: 436961

Degree: Master of Medicine in Paediatrics
Research Protocol

Supervisor: Assoc. Prof. Karl-Günter Technau

Summary:

With global improvements to HIV services and care, paediatric and adolescent populations are emerging as vulnerable and high-risk groups. Adherence to prescribed treatment regimens is a necessity for effective long-term therapy. Recent studies suggest that adherence levels need to range from 70-90% for treatment regimens to be effective. Caregivers play an integral role in ensuring adherence to treatment. Children and adolescents living with HIV are often dependent on a caregiver to help with administration and adherence of doses. Many children and adolescents living with HIV have had to endure the loss of a parent or other primary caregiver. The loss of a primary care giver can equate to the loss of a provider for the child and as a result, food security, shelter and other basic needs may be compromised. There is evidence to suggest that maternal mortality has a direct impact on child health and wellbeing. This descriptive study is a secondary data analysis of a prospectively collected data set and aims to describe a paediatric and adolescent cohort at a clinic in Johannesburg, in terms of the nature and vital status of their primary caregiver. The study investigates how caregiver mortality affects adherence to treatment regimens. Viral load suppression and what line of antiretroviral therapy the child is on will be analysed. The objectives are: 1) to describe the nature of the registered primary caregiver for a cohort of children and adolescents attending Empilweni HIV clinic in Johannesburg for the year 2021 2) to

assess the impact of caregiver mortality on paediatric and adolescent clinical outcomes.

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List of Abbreviations

AIDS: Acquired Immunodeficiency syndrome

ART: Antiretroviral therapy

BMI: Body mass index

ESRU: Empilweni Services and Research Unit

HIV: Human Immunodeficiency Virus

HIV OVC: Orphans and vulnerable children affected by HIV/AIDS

TB: Mycobacterium Tuberculosis

RMMCH: Rahima Moosa Mother and Child Hospital

WAZ: Weight for age Z score

WHZ: Weight for height Z score

WFL: Weight for length Z Score

WHO: World Health Organisation

1.0 Introduction

There has been significant progress in paediatric and adolescent human immunodeficiency virus (HIV) care since the roll-out of antiretroviral therapy (ART) globally, but especially in sub-Saharan Africa. A steady decline in the number of new paediatric infections and Acquired Immunodeficiency Syndrome (AIDS) related deaths between 2016 and 2020 was observed.(1) However, despite this progress East and Southern Africa has over half of the total number of HIV infected people in the world (2), and South Africa had more than one quarter of the region's new infections, in 2018.(2) HIV/AIDS related disease has resulted in 17.8 million children being orphaned globally. In South Africa more than half of the 3.9 million recorded orphans lost one or both of their parents due to HIV/AIDS.(2)

The international burden of children and adolescents living with HIV is substantial. Advances in paediatric HIV care continue to lag behind adult HIV care, with 54% of adults eligible for ART receiving ART globally, compared with 43% of children in 2016.(3) South Africa now has the largest ART programme in the world, providing treatment to roughly 4.8 million people.(3) Despite this success, 2019 statistics in South Africa reported that only 47% of children known to be living with HIV were on . (ART.(3)

Many children and adolescents living with HIV are still not virologically suppressed, even after being initiated on appropriate therapy.(3) Adherence to correct treatment

regimens and attending clinical visits regularly are challenges that clinicians have identified in this population. Early diagnosis and access to care is a vital part in preventing premature death in HIV infected neonates and children.(4) Adherence to prescribed treatment regimens is a necessity for effective long term therapy. Recent studies suggest that adherence levels need to range from 70-90% in order for treatment regimens to be effective.(5)

Caregivers play an integral role in ensuring adherence to treatment. Children and adolescents living with HIV are often dependent on a caregiver to help with administration and adherence of doses.(6) The loss of a primary caregiver can equate to the loss of a provider for the child and as a result, food security, shelter and other basic needs may be compromised. Losing a parent causes ongoing trauma on many levels. Grandparents and extended family often must assist with continuing care for orphaned children. In a study done in South Africa in 2015, it was found that maternal mortality resulted in an increased risk of morbidity and mortality for her children.(7) A maternal death due to HIV/AIDS or tuberculosis (TB) further raised the risk of mortality for her children, and they were more likely to die due to HIV/AIDS or TB, relative to other causes.(7)

Many children in South Africa come from backgrounds where their biological parents, for numerous reasons, are not their primary caregivers. A child or adolescent may face the loss of a primary caregiver other than a parent, and there is a paucity of data on the effect on children when a primary caregiver other than a mother demises. Children and adolescents may face the death of a primary caregiver at

various time points, it may occur at a very young age, before or after their own diagnosis of HIV or later during ART treatment.

With the above in mind, this study is aimed to describe a paediatric cohort in an HIV clinic based in Johannesburg, in terms of the relationship to the primary caregiver, the age of the primary caregiver at entry into the cohort, and what the effects on treatment outcomes are with a primary caregiver passing away.

2.0 Literature Review

2.1 Adolescent and paediatric specific barriers to adherence

Research suggests that in order for ART to be effective, a high degree of adherence is required in order to achieve viral suppression.(8) Children and adolescents living with HIV have unique barriers to achieving optimal adherence as they are often placed on treatment regimens from a very young age, and face the prospect of being on treatment for life.(8) The majority of children and adolescents living with HIV reside in sub-Saharan Africa,(9) therefore in addition to the challenges faced with pill burden, taste and acceptance of a diagnosis of HIV infection, these children are faced with the myriad daily struggles associated with living in a low income setting. Poor adherence and high viraemia may result in viral mutations that are resistant to first-line ART, and the child or adolescent being escalated to second or even thirdline treatment. Second-line ART was defined as the regimen used for treatment of patients living with HIV who failed a first-line regimen, third-line for those who fail second-line. In South Africa first-line ART is nucleoside/nucleotide reverse

transcriptase inhibitor based regimen, second-line Protease Inhibitor based and third-line designed in collaboration with the Third-line ART committee.(8)

A meta-analysis done in 2016 on patient reported barriers to adherence found that the most common barriers included forgetting to take the treatment, not being at home, or an altered routine.(10) Depression was noted as a challenge by up to 15% of the participants.(10)

Mental health is a well-known trial for children and adolescents living with HIV, however there is a paucity of data regarding the impact of mental health on adherence and clinical outcomes.(11) Some challenges that have been identified include a lack of screening process, inadequate data on how to correctly manage mental health issues, and the generally poor health care frameworks that exist in low income countries.(11) In addition to acknowledging and accepting their own status, many children and adolescents living with HIV have lost parents or caregivers to the virus. This creates social disruption in that the child or adolescent is now cared for by someone else, but what is often overlooked is the bereavement process that the child needs to go through with the loss of a primary caregiver, and how that may influence their adherence to therapy. The loss of one or both parents is associated with increased risk of short and long term mental health problems.(12)

A review done in 2016 on adolescents found that they had poorer ART treatment outcomes than adults from the same areas.(10) Stigma and disclosure issues continue to be the main barriers to adherence among adolescents.(13) A review done in 2016 on stigma in paediatric populations living with HIV suggests that it

remains a major barrier to adherence for both the families and children/ adolescents living with HIV.(13)

While the rising numbers of adolescents living with HIV can be somewhat attributed to children living with HIV surviving into adolescence, there is also a group of adolescents and young adults that acquire infection through high risk behaviors (14)(15).

2.2 Primary caregivers in paediatric and adolescent HIV

Paediatric and adolescent HIV services are often difficult to navigate, as clinicians, nurses and counsellors are not only treating the patient, but the primary caregiver as well. If there is little or no buy-in from the primary caregiver in terms of adherence and faith in the treatment, it is unlikely that ART programmes will have success in achieving viral suppression in patients attending those services.(6)

In a study done in 2012 looking at barriers to adherence identified by children living with HIV as well as their caregivers, it was identified that there was a poor correlation between what the child/youth identified as potential barriers compared to their caregiver. The conclusion drawn was that there needs to be interventions involving both the child and caregiver in order to achieve better adherence.(10)

In South Africa the regimens available for younger children are unpalatable, with a high pill burden. Moves have been made to create simpler, better tolerated formulations, but we are still far away from an ideal regimen.(16)

Children, and to some degree adolescents, are therefore largely dependent on the commitment and reliability of their caregiver to ensure adherence to their ART. With the improvements in ART, HIV has now changed into a chronic condition for children and adolescents living with HIV. Chronic medical conditions have their own unique challenges for the caregivers of children living with them.(17) In a cross sectional study done in Uganda in 2021 the burden of being a caregiver of a child living with HIV was discussed.(17) Care burden refers to the emotional, physical, financial and social toll that caring for a child with a chronic illness encompasses.(17) It was found that care burden is common among the caregivers of children living with HIV in the study sample population. The recommendation was to implement systems that will help support caregivers with their unique struggles at the diagnosis of their child.(17)

2.3 Orphans living with HIV

The after-effects of the high mortality rate secondary to HIV in the late 1990's through early 2000's are still being felt. Many children and adolescents lost their parents/ primary caregivers to HIV/AIDS as there were very limited treatment options available and the disease was poorly understood.(18) Unfortunately, this mortality has not yet abated. While there has been significant loss of caregivers early on, many children and adolescents are still experiencing this loss. Caregivers living with HIV battle with their own adherence, acceptance and social challenges and it is not uncommon to hear about the recent loss of a caregiver due to illness. (18)

Up to 50% of children orphaned from HIV/AIDS who are living with HIV are now in adolescence.(19) These children and adolescents are often cared for by HIV negative extended family members. Data suggest that caregivers of orphaned

children and adolescents may stigmatise or discriminate against these children due to their positive status, and this may result in poorer clinical outcomes.(19)

Orphans living with HIV fall into the larger group of orphans and vulnerable children affected by HIV/AIDS (HIV OVC). “This includes children who are HIV positive, living without adequate adult support (e.g., in a household with chronically ill parents, a household that has experienced a recent death from chronic illness, a household headed by a grandparent, and/or a household headed by a child), living outside of family care (e.g., in residential care or on the streets), or are marginalized, stigmatized, or discriminated against”(20)

There has been research into the outcomes of children and adolescents orphaned by HIV. They have increased mortality and morbidity, regardless of their own HIV status.(20) With the high number of orphaned children, it often falls upon a family member to take up the role of primary care giver. A cross sectional study done in 2020 showed that there is a direct correlation with improved quality of life and a nuclear family member being involved in care.(6)

Speaking about loss of biological parents and other caregivers comes with its own challenges, dealing with loss and bereavement in children and adolescents is not easy, whether the loss happened long ago or recently. (13) A first step, however, is to quantify the problem and create more awareness.

3.0 Aims and Objectives

3.1 Problem Statement

Adherence to ART remains an ongoing challenge in paediatric HIV clinical services. Children and adolescents living with HIV are largely dependent on a caregiver for treatment administration and to ensure adherence. With one or both parents deceased, orphans living with HIV are often cared for by extended family members or siblings, who themselves face numerous challenges. Does the death of a primary caregiver (the person who provides most of the care or guardianship) of children and adolescents living with HIV have an impact on clinical outcomes?

3.2 AIM

To investigate whether death of primary caregiver has an effect on clinical outcomes, this study aims to describe a paediatric and adolescent cohort at a clinic in Johannesburg. The study will look at the relationship to the recorded primary caregiver, the vital status of the recorded primary caregiver, and to investigate if the death of a primary caregiver has occurred, what effect there is on clinical outcomes over the period of observation, from 01 January 2021 to 31 December 2021.

3.3 OBJECTIVES

1. To describe the demographic characteristics of primary caregivers who accompany children and adolescents actively attending an HIV clinic in Johannesburg during 2021. Children and adolescents may have been enrolled prior to and including 2021.
    a. Age of primary caregivers at entry into the clinic, and participant age in

2021.

b. The relationship between the primary caregiver and the study participant: mother, father, extended family member (grandparent, aunt/uncle, sibling), institution, employee, other.

   Documented mortality of a biological parent at date of entry into the clinic, or documented mortality of a registered primary caregiver up until and including 2021.

2. To assess the association of caregiver mortality on treatment outcomes for all children and adolescents receiving care at an HIV clinic in Johannesburg for the year of 2021, namely:
   a. Viral load suppression rates, between 01/01/2021 and 31/12/2021, categorised as <50RNA copies/mL, 50 to <1000 RNA copies/mL, and ≥1000 RNA RNA copies/mL, and comparing absolute values.
   b. ART regimen divided into categories; first line, second line, third line, as per national ART guidelines.
   c. CD4 T-lymphocyte counts: categorised according to percentage (<15%, 15-<25%, ≥25%) for children under 5 years of age, and absolute counts (<200, 200-<500, ≥500) for those older than 5 years of age.
   d. Anthropometry (Weight for height (WHZ) Z scores in those less than 5 years, BMI Z scores > 5 years) at first ever visit, ART start and visits through 2021.

4.0 Study Design and Methods

4.1 Study Design:

Prospective longitudinal data collected during routine clinical visits from the clinical visit database at a paediatric and adolescent HIV clinic in Johannesburg, South Africa will be used. Data were collected at Rahima Moosa Mother and Child Hospital (RMMCH) from the 01 January 2021 to 31 December 2021 for the outcomes during 2021 and from inception of the clinic to the end of 2021 for the caregiver status and events of caregiver mortality. This is an urban academic hospital specialising in maternal, paediatric and neonatal patient services in Johannesburg, South Africa. This study will be a retrospective secondary data analysis from the prospectively collected data.

The Empilweni Services and Research unit (ESRU) clinic is one of the larger paediatric HIV clinics in South Africa, with over 1400 children in active care and ~5000 children ever seen since 1998. Daily, the clinic manages neonates, children and adolescents living with HIV, as well as neonates that are exposed but uninfected. Management includes initiation of treatment naïve patients onto first line ART, regular follow-up appointments, and management of those requiring 2nd or 3rd line treatment. On average each patient will visit the clinic four times in a year. On entry into the clinic, a demographics sheet is completed with all primary caregiver's information (Appendix 1). At each follow up visit, patients are seen by doctors, and counsellors. Phlebotomy staff are available for taking the relevant and necessary blood tests. All results are recorded in a flow sheet in the patient files (Appendix 2).

Caregiver and escort information are updated at each visit. All patients/caregivers entering the clinic have been invited since 2007 to consider a data sharing permission (Appendix 3). The cohort is prospectively captured under the protocol,

Cohort Study of HIV-infected and exposed Children receiving care at Rahima Moosa Mother and Child Hospital supported by the Empilweni Services and Research Unit and participation in the International epidemiological Databases to Evaluate AIDS (IeDEA) Collaboration (M170778) which includes annual correlation with the national death registry.

4.2 Participants

Inclusion criteria

All children and adolescents, enrolled prior to 2021 and including 2021, in care at Empilweni clinic and attending clinical visits between 01 January 2021 and 31 December 2021.

Exclusion Criteria:

Children/adolescents being cared for at RMMCH who refuse/whose parents refuse consent for the use of routine data for research purposes.

4.3 Study Procedures

The following data will be requested as a de-identified extract from the existing database for each patient fulfilling the inclusion criteria. The estimated sample size is ~1400 patients, with at least 10% anticipated occurrence of primary caregiver mortality.

Table 1 Requested Data extract:

Raw data	Calculated	Categories
Age	Continuous	
Gender		Female, Male
Year of first entry	Continuous	
Year of ART start	Continuous	
Relationship to primary caregiver at first ever visit, age of primary caregiver		Mother, father, extended family member (grandparent, aunt/uncle, sibling), institution, employee, other.
Vital status of biological parents at first ever visit, documented mortality of registered caregiver from entry until 2021		Demised • Maternal orphan • Paternal orphan • Both Alive
Viral loads 2021	Highest, lowest, last	<50, 50-1000, >1000 RNA copies/mL
Treatment regimen		1st line, 2nd line, 3rd line
Latest CD4 count 2021		CD4 level: under 5 years (<15%, 15-25% >25%), over 5 years absolute CD4 count (<100, 100-200, >200)
Weight and length at first visit and in 2021	Z-Scores for weight, height, body mass index, weight for age	<-3/>-3<-2/ >-2 z scores for age

4.4 Data Collection

Data are routinely collected from patient hospital records and entered into the database. The database is hosted on the University of the Witwatersrand REDCAP platform. (22) Application to the electronic gatekeeper of the database will be made for data to be extracted. Data will be received in a de-identified format.

4.5 Data Management

The dataset will be reviewed and cleaned to check for missing and incorrect values. Outliers will also be identified. In cases of concern, files will be reviewed to verify entries, should data transcription errors have occurred during routine capture. Once an anonymised clean final dataset is agreed upon, all data will be kept in a password protected de-identified spreadsheet. Only the researcher and supervisor will have access to this spreadsheet.

4.6 Data Analyses – Per Objective

Objective 1

a) Age of caregiver on entry into care,
b) Relationship of caregiver at entry: parent (both, one, none), family member (grandmother, aunt, other family member), institution employee, self (i.e. no escort), other or unknown.
c) Incident mortality of primary caregiver.

The data collected will be described using standard statistical methods. Continuous variables will be analysed through mean and standard deviation or median and interquartile range. Percentages and frequencies will be used to describe categorical variables.

Objective 2

Data will be separated into those with a documented primary caregiver mortality and those without. Viral loads for the year of 2021, viral load regimens, CD4 percentages and counts, and anthropometry will be described using the same statistical methods described above, and compared using Chi-Square or the Fisher exact test to compare categorical variables, depending on the numbers. The student's t-test will be used to compare continuous variables which are normally distributed, or the Wilcoxon test if they are not normally distributed variables. Logistic regression modelling could also be used. This will be a multivariable regression to look at the association between clinical outcomes and caregiver vital status, adjusting for other variables collected.

5.0 Ethical considerations:

Upon attending the Empilweni clinic, parents/guardians of participants younger than 18 years as well as the participants older than 18 years are invited to sign a data sharing consent form (Appendix 3), which allows for data to be used for research purposes. Data will be anonymised using a numbering system and kept in a password protected spreadsheet. There is prior ethics approval of the Empilweni database in terms of research (University of the Witwatersrand HREC protocol M170778 – Appendix 4). Permission to receive de-identified data of the above fields in the Empilweni database has been requested from the electronic gatekeeper, Matron Lesley Rose, and access has been provided by the Principal Investigator (Appendix 5,6). Institutional permissions to conduct research at RMMCH will be sought from the hospital CEO and an application for this study will be made to the University of Witwatersrand Faculty Graduate Studies Committee and the Human

Research Ethics committee of the University of the Witwatersrand.

All costs incurred during this study (e.g. travel expenses, printing and stationery) will be self-funded, and are estimated at R1800

6.0 Gantt Chart:

7.0 Limitations:

This study will have limitations regarding the capturing of the data, Empilweni it is not a research driven clinic, therefore the data may be incomplete and may include errors. Another potential limitation is the accuracy of the recorded caregiver of the child/adolescent. If the primary caregiver had changed and these details have not been reflected in the database, it may impact on the accuracy of the analytic endpoints of the study.

8.0 Expected outcomes:

Study findings will be shared with the hospital and department of paediatrics. Findings will be written up for presentation at conferences and publication in peer reviewed journals. The project hopes to create awareness around caregiver

dynamics, and to encourage staff to face the issue of loss of a caregiver on the wellbeing of clinic attendees more consciously.

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9.0 Appendices

9.1 Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr J Keal

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220516

NAME: (Principal Investigator)	Dr J Keal
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Empilweni Services and Research Unit Medical School University
PROJECT TITLE:	*The impact of caregiver mortality on treatment outcomes in children and adolescents living with HIV at a Johannesburg clinic in 2021 – an observational cohort study*
DATE CONSIDERED:	2022/05/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor K-G Technau
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/07/14

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

DECLARATION OF INVESTIGATORS

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

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

Signature of Principal Investigator — Date: 29/07/2022

9.2 Faculty protocol approval letter

2092
South Africa

Dear Miss Josephine Keal

Master of Medicine in Paediatrics: Approval of Title

Private
Bag 3
Wits, 2050
Fax:
02711717
2119
Tel: 02711
7172076

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

26 April
2022
Person No:
436961
PAG

Miss JI Keal
47 A 5th Avenue
Melville

We have pleasure in advising that your proposal entitled *The impact of caregiver mortality on treatment outcomes in children and adolescents living with HIV at a Johannesburg clinic in 2021 - an observational cohort study* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

9.3 Demographics sheet

Demographic Details - adjust Phone numbers/address as time goes on			
Child / Adolescent			
Name and Surname			
Date of Birth (dd/mm/yyyy)	_____		
Child's ID Number	SA National ID Number:	RTHB identifier if available:	
Gender	Male / Female		
Phone Number	add international dialing code if not national number		
Addresses as of First Visit to Clinic - add new addresses as time goes on			
Address and Phone number where child lives		**Date:**	
		With who?	
Address and Phone number where child lives		**Date:**	
		With who?	
Address and Phone number where child lives		**Date:**	
		With who?	
Mother			
Name			
DOB	...../...../.....	**ID**	_ _ _ _ _ _ _ _ _ _ _ _ _ note passport/assylum if not SA citize
Phone Number	add international dialing code if not national number		
Alternative Phone Number	.....This phone belongs to		
HIV Status	Pos / Neg / Unknown On ART since _____ at _____clinic / Not on ART		
Vital Status	Alive / Deceased / Unk Date of Death:		
Father			
Name			
DOB	...../...../.....	**ID**	_ _ _ _ _ _ _ _ _ _ _ _ _ note passport/assylum if not SA citize
Phone Number	add international dialing code if not national number		
Alternative Phone Number	.....This phone belongs to		
HIV Status	Pos / Neg / Unknown On ART since _____ at _____clinic / Not on ART		
Vital Status	Alive / Deceased / Unk Date of Death:		
Other Primary Caregiver (including institution)			
Name			
DOB	...../...../.....	**ID**	_ _ _ _ _ _ _ _ _ _ _ _ _ note passport/assylum if not SA citize
Relationship	Granny / Other Family / Foster / Adoptive / Institution / Self / Other		
Phone Number	add international dialing code if not national number		
Alternative Phone Number	.....This phone belongs to		
HIV Status	Pos / Neg / Unknown On ART since _____ at _____clinic / Not on ART		
Vital Status	Alive / Deceased / Unk Date of Death:		
Sibling 1 of ..... siblings, recommend testing if not yet tested			
Name			
Year of Birth			
HIV Result	Pos / Neg / Unknown If pos: On HAART / Not on HAART		
Sibling 2			
Name			
Year of Birth			
HIV Result	Pos / Neg / Unknown If pos: On HAART / Not on HAART		
Sibling 3			
Name			
Year of Birth			
HIV Result	Pos / Neg / Unknown If pos: On HAART / Not on HAART		
Note significant events in life of child:			

Clinical Details	
First Visit Date (dd/mm/yyyy)	
Referred from	Inpatient Service /Outpatient Service /Infant Test part of PMTCT protocol /Other …
Mode of HIV transmission	Mother to Child / Not Mother to child :_____
Birth and Prenatal Care	
Antenatal care	Booked at _____ clinic at _____ weeks of pregnancy / Unbooked / Unknown
Parity/ Gravidity/ Children alive	At the time of delivering this baby Parity _____ / Gravidity _____ / Live children_____
Place of Birth	Name of site: _____ = Hospital / MOU / Other
Birth Measures	wt:_____kg / Ht: _____cm / HC: _____cm
Mode of delivery	NVD / C/S Reason: / Assisted / Unknown
Gestation at birth	weeks: Premature / Term / Post dates / Unknown
RTHB	Up to date? Yes / No / Unknown Notes:
PMTCT and Feeding	
Feeding History	Breatsfed: Yes Until _____ / Never Breastfed / Unknown
Infant PMTCT	
Mother PMTCT	
HIV diagnosis date of mother	_____ / _____ / _____ Timing: Before / During / After Pregnancy
ART start date of mother	_____ / _____ / _____ Regimen: Clinic Name:
Child Diagnosis and ART	
Date of first diagnosis	_____ / _____ / _____ Test: PCR / Rapid / ELISA
Where was the test done	Barcode:
Was child on ART at First Visit?	Yes at _____ Clinic / No
First ART start DATE of CHILD	_____ / _____ / _____ WHO Stage at INITIATION: I / II / III / IV / Unknown
Any prior ART exposure?	
Medical History at the time of First VISIT to clinic	
TB	Never / Current _____ date started / Unknown
Number of past admissions	
Other	
Diagnoses / Adverse EVENTS	
Event and method of diagnosis	
Date of first diagnosis	
Notes	
Diagnoses / Adverse EVENTS	
Event and method of diagnosis	
Date of first diagnosis	
Notes	
Diagnoses / Adverse EVENTS	
Event and method of diagnosis	
Date of first diagnosis	
Notes	
Diagnoses / Adverse EVENTS	
Event and method of diagnosis	
Date of first diagnosis	
Notes	
Comments:	

9.4Results flow sheet

Name:_____						Hosp No:_____		
Date								
Age								
Weight (kg)								
Height (cm)								
BMI ≥5years								
MUAC (cm) <5years								
Head Circ <2 years								
BP								
Urine Dipstix								
Co-Trimoxazole								
MVTs								
INH								
TB Meds:								
HAART:								
Other:								
Bloods: CD4 count								
CD4 %								
POC Viral Load								
Viral Load								
WBC								
Hb								
MCV								
PLTs								
RDW								
Neutrophils (Abs)								
Creatinine								
TB investigations								
Cholesterol / Trigs								
Other								
Lab stickers (Barcodes)								
TCB								

9.5 Data sharing consent

CONSENT FORM: USE OF CLINICAL INFORMATION

Dear Guardian, Parent and Patient,

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

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

We are part of an international collaboration called IeDEA that aims to improve our knowledge about HIV/AIDS by sharing information with other sites and doing scientific analysis. We share our routine clinic information (e.g. weight and height measurements, blood test results and treatment details which are all routinely collected) with IeDEA regularly but do not include your name or any identifying details.

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

As other projects using routinely collected data arise we would like to obtain your consent to use information from your file/your child's file for the purpose of research, subject to the aforementioned conditions. If research arises that needs more detailed information we will approach you for further specific consent first. If you choose not to give consent, this will not compromise your treatment/your child's treatment in any way. If at any time you choose to withdraw consent you are free to do so and will not be prejudiced in any way. For any concerns about the approval processes followed at the University of the Witwatersrand please contact the Human Research Ethics Committee: Ms Zanele Ndlovu (Administrative Officer) 011 717 2700, (15) or Mr Rhulani Mkansi (Administrative Officer) 011 717 2656, Rhulani.mkansi@wits.ac.za .

PATIENT NAME:…….

A.

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

GUARDIAN NAME and RELATION:.....

SIGNATURE:…….. DATE:.....

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

B.

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

GUARDIAN NAME and RELATION:……..

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

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

9.5 HREC Certificate

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

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

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

Dear Professor Technau

Re: Protocol Ref No: Ml 70778
Grant Number: IJ01A1069924
Protocol Title: Cohort study of HIV-infected and exposed children receiving care at Rahima Moosa Mother and Child Hospital, supported by Empilweni Services and Research Unit (IeDEA-SA)
Principal Investigator: Professor K-G Technau (Overall PI's Professors Egger and Davies)

Thank you for your letter of 27/06/2020.

I confirm that the annual progress report provided in your letter is satisfactory and therefore that Clearance Certificate No. Ml 70778 remains valid until 4 September 2022, subject to continued satisfactory progress.

Thank you for keeping us informed.

Yours Sincerely

.....

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

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medica

9.6 PI permission

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

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

15th February 2022

Dear Dr Keal

Re: Proposed MMed Project titled:
The impact of caregiver mortality on treatment outcomes in children and adolescents living with HIV in Johannesburg – an observational cohort study.

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

Yours sincerely

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

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GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries: Mrs Lesley Rose
Directorate: Nursing
Tel: 011 470 9033
Email: Lesley.Rose@gauteng.gov.za
Date: 18 February 2022

Dear Dr Josephine Keal

Student Number: 436961

Title: The impact of caregiver mortality on treatment outcomes in children and adolescents living with HIV in Johannesburg – an observational cohort study

Re: Permission granted to access the data base at the HIV Clinic Rahima Moosa Mother and Child Hospital

Permission is granted to access the data base for the collection of your data for the above mentioned Study. Please liaise with the data team for convenient times to access the data base to avoid work piling up and conflict. Good luck with your project

Yours sincerely,

Ms. Lesley Rose

RN, ADM, BA (CUR) UNISA

Gatekeeper Empilweni Clinic

Deputy Manager, Nursing

Rahima Moosa Mother and Child Hospital