Southern African Journal of Infectious Diseases
ISSN: (Online) 2313-1810, (Print) 2312-0053

Retention in care of infants diagnosed with HIV at birth: Beyond the diagnostic strategy

Authors:
Michael J. Christie[1]
Nicolette M. du Plessis[1]

Affiliations:
[1]Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Corresponding author:
Michael Christie,
michael.christie@up.ac.za

Dates:
Received: 16 Oct. 2023
Accepted: 17 Jan. 2024
Published: 30 Mar. 2024

How to cite this article:
Christie MJ, du Plessis NM. Retention in care of infants diagnosed with HIV at birth: Beyond the diagnostic strategy. S Afr J Infect Dis. 2024;39(1), a589. https://doi.org/10.4102/sajid.v39i1.589

Background: Birth HIV point-of-care (POC) tests curtail analytical testing issues and expedite diagnosis, potentially allowing for earlier mother-infant pair engagement and improved outcomes. Many children are lost post antiretroviral therapy (ART) initiation within the first 6 months of follow-up.

Objectives: We compared 6-month retention in care, HIV viral load (VL) suppression and mortality among infants diagnosed with HIV at birth, using laboratory-based versus POC HIV PCR testing.

Method: From 2018 to 2019, infants exposed to HIV underwent birth HIV PCR POC testing at Kalafong Provincial Tertiary Hospital in Tshwane District. Their outcomes were compared to a historical control born between 2014 and 2016, who exclusively underwent laboratory-based HIV PCR testing. Both groups received comparable HIV care following national guidelines.

Results: Fifty-seven infants were studied (POC: 27; Control: 30). The POC turnaround time was significantly shorter (POC: 15.5 h [IQR: 4.3–24.7], Control: 68.3 h [IQR 46.0–93.9]; $p = < 0.0001$). Both populations had the same elapsed time from HIV diagnosis to ART initiation (median: 13 days, POC: IQR 8–21 days; Control: IQR 9–36 days). Six infants were never initiated (POC: 2 [7%]; Control: 4 [13%]). At 6 months, overall care retention was 72% (41/57), higher among the Control group (Control 23/30, 77%; POC: 18/27, 67%). HIV viral suppression at 6 months was higher among the POC group (POC: 14/18, 78%; Control: 9/19, 47%, $p = 0.09$). No deaths were reported.

Conclusion: Poor care retention at 6 months post ART initiation is concerning. Initial mother-infant visits should be effectively utilised to assess and manage potential risk factors for loss of follow-up.

Contribution: This study highlights the ongoing need to find workable solutions to improve retention in care, thereby ensuring the benefits of expedited HIV diagnosis and ART initiation.

Keywords: HIV; infant; point-of-care; loss to follow-up; diagnostics.

Introduction

Expeditious HIV diagnosis and antiretroviral therapy (ART) initiation are crucial in managing children living with HIV (CLHIV). Mortality rates in untreated infants with perinatal HIV peak at 2–3 months of age, reaching 35% at 12 months.[1,2] If ART is initiated before 12 weeks of age, mortality is reduced.[3] Prompt ART initiation also reduces HIV viral reservoir size, improves virological control, immunological function and growth.[4,5,6,7,8,9,10,11)] Since 2010, the South African National Department of Health (NDoH) HIV guidelines evolved to incorporate this body of evidence. Guidelines recommended lifelong ART for all children living with HIV <1 year of age and pregnant and breast-feeding women living with HIV (so-called 'Option B+') in 2010 and 2013, respectively.[12,13] In 2015, updated guidelines recommended universal HIV polymerase chain reaction (PCR) testing at birth and 10 weeks for all HIV-exposed infants at birth.[14] This was a change from the previous 2013 guidelines of testing at 6 weeks.[13] Consequently, the Early Infant Diagnosis (EID) programme led to improved testing coverage and earlier infant diagnosis.[15,16]

In 2017, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set out the 90-90-90 targets, stating that by 2020 90% of all people would know their HIV status, of these 90% would be on ART, of whom 90% would be virally suppressed (i.e.: 90-90-90).[17] By 2018, the South African EID coverage was at 88.7% with 14 000 children (0–14 years) newly diagnosed with HIV. HIV was confirmed in 76% of children living with HIV, of whom 63% were on ART with 46% being virally suppressed.[18]

Globally, the standard of care for diagnosing HIV in infants is laboratory-based HIV PCR tests. However, to curtail laboratory-based pre- and post-analytical testing issues, HIV PCR Point-of-Care tests (POCT) were developed, validated,[19,20,21,22] and shown to be beneficial in reducing cost, and result turn-around time (TAT) (<24 hours), and improving time to ART initiation and life expectancy.[23,24,25]

Regardless of the testing modality, success of an HIV programme depends on retaining patients in care.[26] Keeping children living with HIV in care remains a global challenge: 5% – 29% of children living with HIV are not retained in care by 12 months post ART initiation, with most lost within the first 6 months of follow-up.[27,28] This study aimed to describe retention in care rates at age 6-months of two historical infant cohorts after HIV birth diagnosis using two EID testing modalities: the first using POCT and the second using a centralised laboratory-based testing. We hypothesised that POCT would allow for earlier engagement with the mother–infant pair and improve retention in care.

Materials and methods

Study design

A secondary, descriptive analysis was done using data from two previous studies conducted at Kalafong Provincial Tertiary Hospital (KPTH) in Tshwane District, South Africa.[29,30]

The point-of-care (POC) group formed part of a prospective, implementation study for EID POC HIV PCR testing. Infants exposed to HIV at birth were enrolled between 01 July 2018 and 30 June 2019 and received POC HIV PCR testing. Infants with positive POC HIV PCR test results received an additional confirmatory POC HIV PCR and laboratory-based HIV PCR test and were managed by the paediatric immunology clinic at KPTH.[30] The control group formed part of a study to assess the feasibility of using models for targeted birth HIV PCR testing in infants at high risk for HIV vertical transmission, between 01 August 2014 and 31 December 2016. Infants with positive HIV PCR results received confirmatory laboratory-based HIV PCR tests and were managed at the same clinic.[29]

The following outcomes were compared: result return before discharge, TAT and agreement between POC results and laboratory results.

The POC HIV PCR test utilised whole blood sampled within 72-h post-delivery and tested on-site using the Cepheid Xpert® HIV-1 Qualitative assay (Cepheid, Sunnyvale, CA). Laboratory-based HIV PCR tests were conducted using whole blood sampled within 72-h post-delivery and tested at the National Health Laboratory Service (NHLS) laboratory using COBAS® TaqMan® HIV-1 Qualitative Test Version 2·0 (Roche Molecular Systems, Inc., Branchburg, NJ). Confirmatory laboratory-based HIV PCR testing was performed for all neonates, and an HIV-positive status was assigned to neonates with an 'HIV-detected' confirmatory result.

Study setting

In 2017, an estimated 6850 children living with HIV resided within Tshwane District; of whom 52% were receiving ART.[31,32] At KPTH, children living with HIV are managed at the on-site, multi-disciplinary paediatric immunology clinic. The clinic is staffed by nurses and doctors and assisted by dieticians, occupational therapists and social workers. It is overseen by two paediatric infectious disease specialists.

Study population

All infants born at KPTH and diagnosed with HIV through either laboratory-based or POC HIV PCR tests, irrespective of gestational age, comorbid conditions and birth weight, were included in the analysis. Infants not receiving a POCT or laboratory-based HIV PCR test ≤ 72 h of life were excluded. Infants kept in hospital were classified as either asymptomatic or symptomatic.

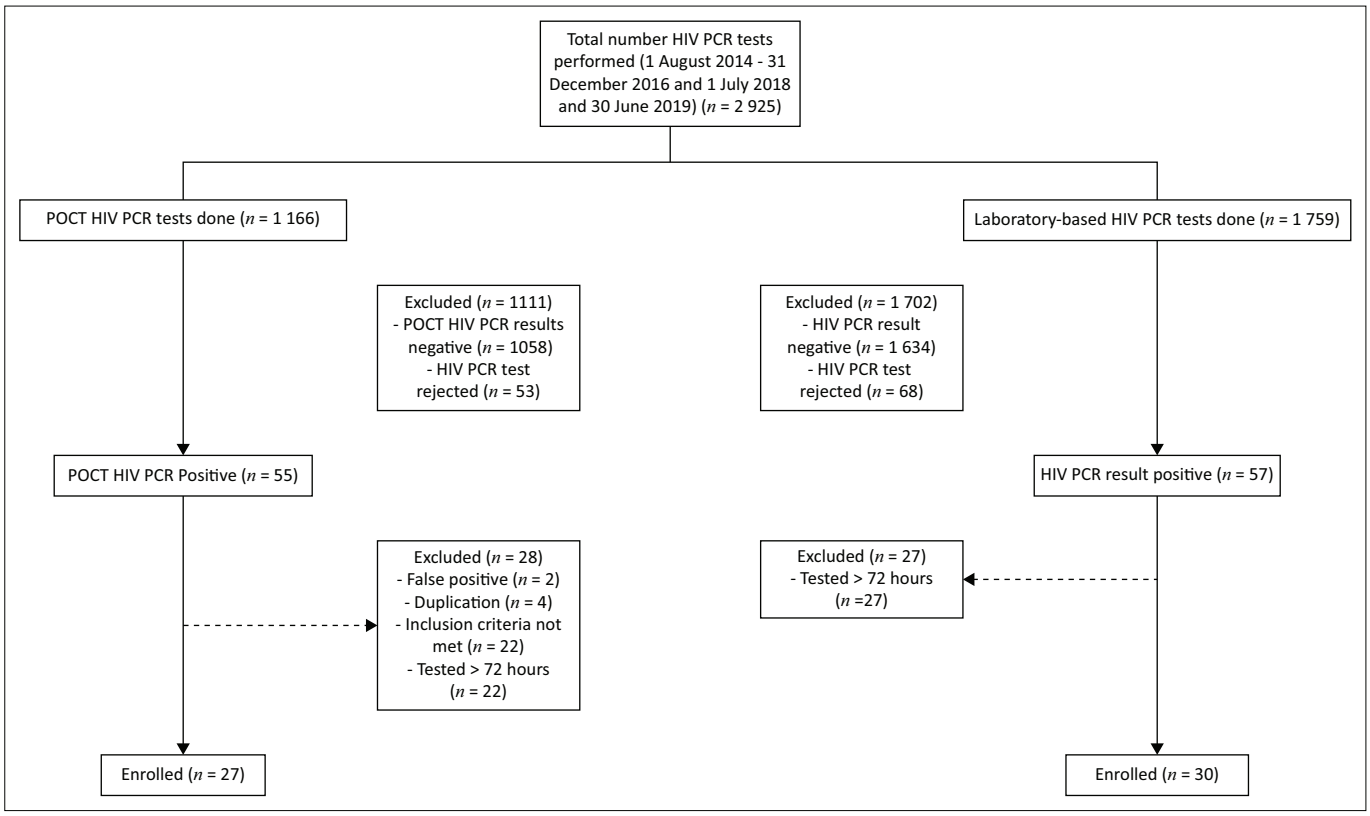
Definitions

Symptomatic infants were defined as requiring any medical care and intervention. Asymptomatic infants were clinically well, did not require any medical care or intervention and were only kept in hospital for social reasons. Antiretroviral initiation was considered delayed if initiated >7 days after diagnosis. Loss to follow-up (LTFU) was loss of patients from care at KPTH, at any point during the study period, for >90 days after the last scheduled appointment.[33] HIV viral suppression was defined as a viral load (VL) below detectable limits (lower than detectable [LDL]).[13,14] All patients at 6-months of age who were still in care at KPTH or had a 6-month HIV VL result available on the NHLS database were defined as retained in care. For patients no longer in care at KPTH, the NHLS TrakCare database was used to search for HIV VL results during the follow-up period; this served as a proxy for evidence of contact at healthcare facilities other than KPTH. The interval used in this study to define the 6-month HIV VL was any HIV VL test done between 5 and 7 months of age.

Both groups were managed in accordance with NDoH guidelines in which all children < 5 years were eligible for ART.[13,14,34] Follow-up occurred at monthly intervals.

Data analysis

Collected data were exported to an Excel 365 workbook (Microsoft, USA) for analysis. The following maternal parameters were recorded: maternal age, nationality, duration of ART, maternal HIV VL result at delivery (HIV-1 RNA copies/mL). Infant parameters at birth included gender, gestational age, birth weight, baseline CD4 percentage, time elapsed from diagnosis to ART initiation, duration of hospital stay and reasons thereof. Six-month infant outcomes were LTFU, HIV-related mortality, retention in care and HIV VL suppression. At 6 months, the



HIV, human immunodeficiency virus; PCR, polymerase chain reaction; POCT, point-of-care test.

FIGURE 1: Consolidated consort diagram for the POCT group study period from 01 July 2018 to 30 June 2019 and the Control group study period from 01 August 2014 to 31 December 2016.

proportion of live infants in the two groups in care at KPTH or had an HIV VL test result available on the NHLS TrakCare database were compared. Descriptive statistics were used to describe baseline characteristics. Categorical data were summarised by using proportions. Median and inter-quartile range were used for skewed variables. Chi-square, fisher exact tests and Wilcoxon signed-rank test were used to test significance.

Ethical considerations

The University of the Witwatersrand Human Subjects Research Ethics Committee (M1711115) and the University of Pretoria Research Ethics Committee (285/2014, 50/2018) approved the primary studies.[29,30] Ethical approval was obtained for this study from the University of Pretoria Research Ethics Committee (244/2019). Approval was obtained from KPTH management to access the patient files and collected data were anonymised.

Results

A total of 1166 HIV PCR POC tests were performed from 01 July 2018 to 30 June 2019. Of these, 55 tests (4.7%) were positive, 28 patients were excluded, and 27 neonates were subsequently enrolled. In the historical control group, 1759 infants with laboratory-based HIV PCR tests, 57 infants (3.2%) were positive, with 30 infants meeting the inclusion criteria. In both groups, delayed testing (>72 h of age) was the main reason for exclusion (Figure 1).

Neonate characteristics

Compared to the historical control group, infants within the POC group tended to be more premature (median gestation 36 weeks versus 40 weeks, $p = 0.06$), and hospitalised (19/27, 70% vs. 15/30, 50%, $p = 0.18$). Median birth weights in both groups were similar (POC: 2 585g [interquartile range {IQR}: 2325 g – 3335 g], Control: 2700 g [IQR: 2280g – 3100g]). Of the 19 POC infants kept in hospital, 9 infants (9/19, 47%) were asymptomatic and kept for maternal pre-ART counselling and ART initiation, and 10 infants (10/19, 53%) were symptomatic. Fifteen infants in the control group were kept in hospital, 10 infants were symptomatic (10/15, 67%) and five infants (5/15, 33%) were asymptomatic and kept for either ART initiation ($n = 4/15$ 27%) or maternal reasons ($n = 1$). Reported TAT in the POC group was significantly lower than the control group (POC: 15.5 h [IQR: 4.3–24.7 h], Control: 68.3 h [IQR 46.0–93.9 h]; $p \leq 0.0001$). The median time from HIV diagnosis to ART initiation was similar in both groups (13 days). Six infants were never initiated (POC: 2/27, 7%; Control: 4/30, 13%) (Table 1).

The documented reasons for delayed initiation (>7 days) in the POC group were indeterminant HIV PCR result (1/27, 4%), pre-ART counselling (7/27, 26%), concomitant disease (6/27, 22%) and LTFU after being discharged post-delivery (3/27, 11%). The documented reasons for delayed ART initiation within the control group were prolonged result TAT (12/30, 40%), indeterminate HIV PCR results (2/30, 6.7%) and concomitant disease (3/30, 10%).

TABLE 1: Baseline characteristics of Mother–Infant Pair at delivery at Kalafong Provincial Tertiary hospital between 01 July 2018 and 30 June 2019 (POCT group) and 01 August 2014 and 31 December 2016 (Control group).

Variable	POCT group (n = 27)				Control group (n = 30)				p†
	n	%	Median	IQR	n	%	Median	IQR	
Infant characteristics									
Child gender									
Male	17	63	-	-	17	57	-	-	0.78
Female	10	37	-	-	13	43	-	-	-
Gestation (weeks)‡									
Term (≥ 37)	14	56	36	35–40	24	86	40	37–40	0.06
Preterm (< 37)	11	44	-	-	4	14	-	-	-
Birth weight (grams)‡									
< 2500	9	35	2585	2325–3335	8	31	2700	2280–3100	0.42
≥ 2500	17	65	-	-	18	69	-	-	-
Reported TAT for HIV test results (hours)	-	-	15.5	4.3–24.7	-	-	68.3	46.0–93.9	< 0.0001¶
Time elapsed from diagnosis to initiation (days)									
≤ 7	4	15	13	8–21	4	13	12.5	9–36	0.83
8 – 28	16	59	-	-	15	50	-	-	-
> 28	5	19	-	-	7	24	-	-	-
Never initiated	2	7	-	-	4	13	-	-	-
Baseline CD4 (%)‡									
< 15	1	5	34.7	27.0–48.9	1	4	38.7	25.3–52.0	0.99
≥ 15	19	95	-	-	25	96	-	-	-
Infant kept in hospital									
Yes	19	70	-	-	15	50	-	-	0.18
No	8	30	-	-	15	50	-	-	-
Maternal characteristics									
Age (years)‡			29	26–33			28	23–33	-
≤ 18	2	9	-	-	3	12	-	-	0.93
> 18	21	91	-	-	23	88	-	-	-
Citizenship‡			-	-					
RSA citizen	12	52	-	-	18	72	-	-	0.23
Non-RSA citizen	11	48	-	-	7	28	-	-	-
ART duration‡			-	-					
< 3 months	9	39	-	-	10	34	-	-	0.78
≥ 3 months	14	61	-	-	19	66	-	-	-
Maternal HIV VL at delivery (HIV-1 RNA copies/mL)‡									
log(copies/mL)									
< 1000	5	25	4.37	3.3–5.02	5	19	4.1	3.61–4.85	0.72
≥ 1000	15	75	-	-	22	81	-	-	-

POCT, point-of-care test; IQR, interquartile range; CD4, cluster of differentiation; RSA, Republic of South Africa; ART, antiretroviral therapy; HIV, human immunodeficiency virus; VL, viral load; RNA, ribonucleic acid; TAT, turnaround time.

†, Chi square/Fischer's exact test utilised unless otherwise specified.

‡, Percentages and p-values were calculated using the known data; missing data was omitted from the calculations.

¶, Wllcoxon Signed-Rank Test.

Significant difference shown if $p < 0.05$.

Maternal characteristics

Maternal ART duration was mostly ≥3 months (POC: 14/27, 52%; Control: 19/30, 66%); however, most mothers had an unsuppressed HIV VL result at delivery (POC: 15/27, 55%; Control 22/30, 73%) (Table 1).

Follow up data

Overall retention in care at 6 months was 72% (41/57); 22 patients were LTFU at some point during the study period (POC: 11/27, 41%; Control: 11/30, 37%). By 6 months, more patients within the control group remained in care (Control: 23/30, 77%; POC: 18/27, 67%; p = 0.55) (Table 2). Twelve of the initially hospitalised infants were LTFU (POC: 6; Control: 6). HIV viral suppression at 6 months tended to be higher among the POC group (POC: 14/18, 78%; Control: 9/19, 47%, p = 0.09) (Table 2). No known deaths occurred over the study period in both groups; however, 16 patients (POC: 9; Control: 7) never returned to care (Table 2).

Discussion

Early diagnosis is a crucial step in the care cascade of infants with perinatal HIV. Expedited ART initiation reduces mortality, lessens HIV viral reservoirs, improves growth parameters and reduces neurodevelopmental compromise and hospitalisation.[3,4,5,7,10,35,36] Although the sample size was small, in this secondary analysis, POCT significantly reduced TAT ($p \leq 0.0001$). Between the two groups, the time elapsed from diagnosis to ART initiation and the number of infants

TABLE 2: Outcomes of the point-of-care test group and control group at 6 months of age.

Outcome	Total		POCT group		Control group		*p*†
	n	%	*n*	%	*n*	%	
HIV positive at enrolment	57	-	27	-	30	-	-
Lost to follow-up‡	22/57	39	11	41	11	37	0.79
Returned to care	6/22	27	2/11	18	4/11	36	0.63
Never returned to care	16/22	73	9/11	82	7/11	64	
Retained in care at 6 months¶	41/57	72	18/27	67	23/30	77	0.55
HIV viral load available at 6 months (copies/ml)	37	-	18	-	19	-	-
< 1000	23/37	62	14/18	78	9/19	47	0.09
≥ 1000	14/37	38	4/18	22	10/19	53	-
Recorded mortality	0	-	0	-	0	-	-

POCT, point-of-care test; HIV, human immunodeficiency virus; ml, millilitre; KPTH, Kalafong Provincial Tertiary Hospital; NHLS, National Health Laboratory Service.
‡, Lost to follow-up was defined as loss of patient from care at KPTH, at any point during the study period, for >90 days after the last scheduled appointment.
¶, Retained in care at 6 months defined as in care at KPTH or those who had a 6-month HIV viral load result available on the NHLS database.
†, Fischer's exact test, significant difference shown if $p < 0.05$.

kept in hospital were not statistically different, while in hospital the reduced TAT created an opportunity for maternal pre-ART counselling and support prior to infant ART initiation. However, this counselling opportunity did not translate into improved retention at 6 months: retention in care remained poor irrespective of the testing modality. Retention in care rates for both groups were comparable to previously reported rates of approximately 70%.[28,37]

Our study was conducted in an academic hospital with admission capacity for mothers and infant pairs, thus ensuring early linkage to care and pre-ART counselling and support. This contrasts with many South African maternal obstetric units (MOU), situated in peripheral areas, where most deliveries occur. At these facilities, mothers are discharged after 6 h post normal vaginal delivery,[38] and resources are unavailable to retain the mother–infant pair beyond the stipulated 6 h. Although POC is effective in peripheral settings to reduce TAT and improve ART initiation,[39] children living with HIV in these areas are at a higher risk of LTFU.[40] Purported risk factors for LTFU include caregiver (poor living conditions, lack of transportation, low caregiver education levels, social stigma, HIV status denial, seeking alternate faith-based or traditional treatment) and health system-related (fragmented HIV services, poor healthcare worker knowledge and support, lack of medication, waiting times, clinic distances) issues.[26,27,40,41]

Despite ART delayed initiation for some POC infants (>7 days) because of maternal pre-ART counselling (7/27, 26%), POC HIV PCR tests still proved marginally beneficial in improving ART initiation rates (POC: 93% vs. Control: 87%) and time from HIV diagnosis to ART initiation – most patients were initiated within 28 days (POC: 74% vs. Control: 63%). This benefit was observed in similar African studies.[25,42] This study does highlight that if EID HIV diagnosis occurs in isolation, we will struggle to achieve the updated UNAIDS goals of 95-95-95. The first 6 months after diagnosing HIV is a particularly vulnerable period and action should be taken early to ensure patients are retained in care and offered adequate support. Every mother–infant pair living with HIV should be categorised as high risk and managed accordingly. Any healthcare contact, particularly the initial visits, should be utilised to assess for any barriers to adherence (caregiver and health system related), to offer counselling and support and to address any maternal needs.[27,43] The family-centred care model can improve retention by providing coordinated care that addresses the health and social needs of all members of the family.[44] Improved linkage to integrated HIV services after diagnosis, capturing correct patient contact details, telephonic appointment reminders, improved identification of patients who have missed appointments and better referral and case-finding procedures can further aid in improving retention in care.[26,27,28] Continued research is warranted to identify factors to improve care retention and ART compliance in different settings.

This study has several limitations. The small cohort enrolled limited the study's power to provide statistically significant outcomes. As utilised data came from different time periods, the variations between the study population's baseline characteristics and management may have introduced biases. The low number of infants diagnosed with HIV bears witness to the ongoing effectiveness of the vertical transmission prevention programme. The group of patients initially categorised as LTFU and never returned to care underscores important considerations in accurately determining retention: results may not have been correctly retrieved as no unique national health-system identifier exists; patients may be enrolled in care at another facility under an alternate name and may also have been misclassified as LTFU rather than deceased if unrecorded deaths occurred. The latter is concerning: no deaths were reported in the study despite high infant mortality rates in the first few months of life among untreated infants living with HIV.[1,2]

Conclusion

Retention rates of children living with HIV after ART initiation are an ongoing concern in our community and outweighs EID modality in our setting. As most patients are LTFU within the first 6-month post ART initiation, the initial visits should be effectively utilised to manage potential risk factors for LTFU. If workable solutions to improve retention are not implemented, possible gains of expedited diagnosis and ART initiation will be diminished. Ongoing research is warranted to determine factors at primary healthcare level to improve retention in care.

Acknowledgements

The authors would like to thank the dedicated and hard-working staff of the paediatric immunology clinic and Department of Paediatrics and Child Health at KPTH for their support and assistance, as well as Drs A. Haeri Mazanderani and F. Moyo and Professor G. Sherman for the initial conceptualisation and data analysis.

Competing interests

The authors have declared that no competing interest exists.

Authors' contributions

M.J.C. and N.M.D.P. conceived the study design, acquired the data and interpreted the data. M.J.C. wrote the article. N.M.D.P. provided critical revision and final approval.

Funding information

The authors received no financial support for the research, authorship, and/or publication of this article.

Data availability

All relevant data are presented within the manuscript. Additional data are available at the University of Pretoria Research Data Repository (Figshare) URL: https://researchdata.up.ac.za/account/home#/activity DOI: 10.25403/UPresearchdata.23260928.

Disclaimer

The views expressed in the submitted article are the views of the authors and not an official position of the institution or funder.

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