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Trend and predictors for early infant diagnosis by PCR among HIV-exposed infants in Dar es Salaam region, Tanzania, 2014-2016

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Background
Early infant diagnosis (EID) of HIV and timely initiation of antiretroviral therapy reduces morbidity and mortality in HIV-infected infants and children. Although the WHO had a global target for 2018 that 90% of HIV-exposed infants (HEI) should be tested by the age of 8 weeks, by 2015 only half were being tested. This study describes trends and predictors for HIV first testing in HEI in Dar es Salaam, Tanzania, from 2014 to 2016.

Methods
We conducted a cross-sectional study of HEI attending HIV services using secondary data collected at health facilities and collated at the national level. We estimated odds ratios and 95% confidence intervals for factors affecting uptake of HIV testing.

Results
Of 12,117 HEI, the proportion tested for HIV by age 8 weeks increased from 53.2% in 2014 to 69.2% in 2016; 2.3% were HIV-positive. Replacement feeding (aOR=2.94, 95% CI 2.31 – 3.74) and receiving nevirapine prophylaxis (aOR=1.55, 95% CI 1.28-1.88) were predictors for EID testing uptake. HEI born to mothers with WHO stage II (aOR=0.53, 95% CI 0.41 – 0.67), stage III (aOR=0.64, 95% CI; 0.52 – 0.79) and stage IV (aOR=0.58, 95% CI 0.34 – 0.99) were less likely to be tested than those born to mothers with WHO stage I disease progression.

Conclusion
There was an increasing trend in the uptake of HIV testing of infants at age 8 weeks during the study period. However, it is still below the global target. Efforts to promote EID testing are still needed.

Keywords: HIV early infant diagnosis, perinatal transmission, Tanzania

INTRODUCTION

In 2010, the World Health Organization (WHO) published a strategic vision for prevention of mother-to-child transmission (PMTCT) of HIV, which aimed to reduce the rate of mother-to-child transmission (MTCT) to 5% or less among breastfeeding women, and to 2% or less among non-breastfeeding women by 2015, consistent with United Nations General Assembly Special Session (UNGASS) and Millennium Development Goals (WHO, 2010). Without antiretroviral therapy (ART), one third of all HIV-infected children are likely to die during the first 18 months of life and half before they reach 24 months (UNAIDS, 2016). In Tanzania, the prevalence of HIV was 5.6% among pregnant women attending antenatal care in 2011 (Manyahi et al.,

2017). According to the UNAIDS progress report on the global plan for 21 priority countries, the estimated prevalence of HIV among HIV-exposed infants (HEI) at 6 weeks of age was 3% in 2014 (UNAIDS, 2015).

Testing HIV-exposed infants (HEI) early (within 4-6 weeks) is referred to as early infant diagnosis (EID), and it enables the timely initiation of ART and dramatically reduces morbidity and mortality in those infants found to be HIV-infected (Aledort et al.,2006; National PMTCT Guideline, 2013). Tanzania adopted the WHO guideline for EID in 2013, which recommends a first HIV test with DNA PCR for exposed children at 4 to 6 weeks postpartum or soon thereafter (National PMTCT guideline, 2013). In the same year, Tanzania published a national target to ensure that by 2018, 90% of all HEI were tested between 4 to 8 weeks of age and received their results within 4 weeks (TACAIDS, 2013). Since then, services to prevent MTCT, including EID testing, have been integrated into routine reproductive and child health services alongside routine childhood immunisation. The integration of services aims to increase accessibility and thereby promote the uptake of testing, whilst also providing the opportunity to provide health education to mothers and caregivers (National PMTCT guideline, 2013).

Globally, the uptake of HIV testing at 4 to 6 weeks remains low. In 2015, only half (50%) of HEI were reported to have been tested by 8 weeks old (UNICEF, 2015). Whilst uptake of EID has been increasing in some countries, such as South Africa where it increased from 31.4% in 2008 to 54.7% in 2010 (Sherman et al., 2014) and Thailand where it increased from 35.2% in 2008 to 50.5% in 2011 (Naiwatanakul et al., 2016), rates remain below global targets. A study conducted in Tanzania in 2013 found a decreasing trend in the median age at first DBS test (Chiduo et al., 2013). Various factors have been reported to influence uptake of EID services. These include infant feeding options, knowledge of caregivers on when EID should be done, stigma and fear of disclosure of mothers' status, travel distance to health facilities, out-of-pocket costs at the health facility, and long waiting times (Hassan et al., 2012; Cook et al., 2012; Ramaiya et al.,2016). This study builds on the limited information in Tanzania on the proportion of HEI tested by EID by PCR, and advances our understanding of what variables predict optimal uptake of EID. It also improves our understanding of the current intervention progress to achieve the WHO targets, reduce MTCT to less than 2%, and identify the gaps in the programmes which are prohibiting the achievement of the testing targets. This study aimed to describe the trend and predictors for EID testing of HEI in Dar es Salaam from 2014 to 2016.

METHODS

Study design and setting

We designed a cross-sectional study using secondary data routinely collected at health facilities and collated at the national level by the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC). Data on all HEI infants born to HIV-infected mothers attending HIV services in the Dar es Salaam region between January 2014 and December 2016 were used in the study. Dar es Salaam region is the largest city in Tanzania, with a population of over 4.4 million people (National Bureau of Statistics, 2013) and 248 health facilities providing PMTCT services. Management and Development for Health (MDH) manages 192 of the 248 PMTCT facilities and collects and collates electronic data for patient monitoring.

Study population

All HIV-infected mothers and their exposed infants up to 18 months of age registered at the 192 MDH-supported facilities were included in the study. Participants were excluded if they were missing dates of birth. All patients received the national recommended counselling prior to HIV testing of the infant, with information on the benefits for the infant including free ART treatment for infants who test HIV-positive.

Data sources

The study data were extracted from the MDH electronic patient-level database at the 192 PMTCT facilities. The electronic database contained data for the mother and the HEI who each had unique identifying numbers, with a link between mother and infant pairs. The information from the mother's treatment card and child's HEI diagnostic card were extracted from the patient-level electronic database. We also extracted potential predictor variables including mother's age, marital status, date started on ART, CD4 count, and WHO stage, and the HEI's date of birth, birth weight, sex, type of prophylaxis given, cotrimoxazole initiation, and the date when HIV test results were reported.

Study variables

The main outcome variable was uptake of EID. EID was defined as a DNA PCR HIV test that was performed within eight weeks following birth. HIV infection was defined as a positive HIV test result using DNA PCR.

Data analysis

We performed data analysis using STATA (StataCorp. College Station, Texas 77845 USA) version 13.0. We summarised descriptive statistics using frequencies for categorical variables and central tendency and dispersion for continuous variables. We calculated odds ratios (OR) and 95% confidence interval (CI) for the factors affecting uptake of HIV testing using a multivariable logistic regression model. Adjusted odds ratios (aOR) and 95% CI are shown for all predictors included in the final model with a p-value of less than 5%, which was considered statistically significant.

Ethical considerations

We obtained ethical clearance (989) from Kilimanjaro Christian Medical University College and permission from the MoHCDGEC and MDH to use the data of Dar es Salaam region. To ensure anonymity, only identity numbers were used to represent the subjects.

RESULTS

Characteristics of the study participants

A total of 12,417 HEI were enrolled into the PMTCT programme in the health facilities managed by MDH during the period of 2014-2016. Of these, 300 were missing date of birth and excluded from the analysis (Figure 1). Of the total sample of 12,117 HEI over the four years, 2,030 (17%) had tested for antibody at first test (aged above 9 months) and 10,087 (83%) received a DNA PCR HIV test. Of the 10,087, 2,347 did not have the HIV results recorded in the database and were excluded from prevalence calculations. Out of 7,740 with a DNA PCR test result, 177 (2.3%) were HIV-positive.

The characteristics of the 12,117 infants are presented in Table 1. More than half (6,345; 52.3%) were female; the median age was 1.4 (IQR 1.7-3.1) months. 7,670 (63.3%) of the infants initiated nevirapine syrup; 9,883 (81.5%) received cotrimoxazole treatment; and 1,806 (14.9%) were on replacement feeding. Maternal characteristics of the study participants are shown in Table 2. The mothers' mean age was 30.8 (SD, 6.0) years; 6,925 (57.2%) were between 25 and 35 years. Only 1,102 (9.1%) had been on ART for more than 3 years; 7,394 (61.0%) were in WHO stage 1 at the time of enrolment into EID care. The mothers' median CD4 was 548 cells/μL (IQR, 382-655) with 6.4% (774) having CD4 cell count less than 200 cells/μL.

Table 1: Characteristics of HIV-exposed infants, Dar es Salaam, Tanzania, 2014-2016 (N=12,117)

Variable	Total	2014	2015	2016
	N (%)	N (%)	N (%)	N (%)
	12,117	4,660	4,037	3,420
Sex				
Female	6,345 (52.3)	2,341 (50.2)	2,146 (53.2)	1,858 (54.3)
Male	5,772 (47.7)	2,319 (49.8)	1,891 (46.8)	1,562 (45.7)
Age of child at test (months)				
<2	7,160 (59.1)	2,481 (53.2)	2,313 (57.3)	2,366 (69.2)
≥2-18	4,957 (40.9)	2,179 (46.8)	1,724 (42.7)	1,054 (30.8)
Median age (Range)	1.4 (1.7 - 3.1)			
Birth weight of infant (kg)				
< 2.5	3,224 (26.6)	1,126 (24.2)	1,540 (16.3)	558 (16.3)
2.5 and above	8,622 (71.2)	3,463 (74.3)	2,439 (60.4)	2,720 (79.5)
Missing	271 (2.2)	71 (1.5)	58 (1.4)	142 (4.2)
Median birth weight (Range)	2.70 (2.4 - 3.3)			
Feeding practice at testing				
Exclusive breast feeding	6,149 (50.7)	1,790 (38.4)	1,766 (43.8)	2,593 (75.8)
Mixed feeding	1,753 (14.5)	764 (16.4)	816 (20.2)	173 (5.1)
Replacement feeding	1,806 (14.9)	838 (18.0)	732 (18.1)	236 (6.9)
Missing	2,409 (19.9)	1,268 (27.2)	723 (17.9)	418 (12.2)
Nevirapine				
No	1,606 (13.3)	693 (14.9)	715 (17.7)	198 (5.8)
Yes	7,670 (63.3)	2,923 (62.7)	2,518 (62.4)	2,229 (65.2)
Missing	2,841 (23.4)	1,044 (22.4)	804 (19.9)	993 (29.0)
Cotrimoxazole				
No	1,148 (9.5)	460 (9.9)	418 (10.4)	270 (7.9)
Yes	9,883 (81.5)	3,907 (83.8)	3,195 (79.1)	2,781 (81.3)
Missing	1,086 (9.0)	293 (6.3)	424 (10.5)	369 (10.8)

Trend in the uptake of early infant diagnosis among HEI

Of the 12,117 infants and children in our study population, 7,160 (59.1%) children tested for DNA PCR at less than 8 weeks age. The proportion of HEI testing before 8 weeks of age increased over time from 53.2% (2,481/4,660) in 2014 to 57.3% (2,314/4,037) in 2015 and 69.2% (2,366/3,420) in 2016 (Table 3).

Predictors associated with uptake of EID at less than 8 weeks of age

The factors associated with uptake of EID in crude and adjusted analyses are shown in Table 3. The unadjusted analysis shows that male infants had lower odds (OR=0.91, 95% CI 0.88 – 0.98) of being tested within 8 weeks compared to female infants. Infants who had not been exclusively breastfed had lower odds

(OR=0.63, 95% CI 0.57 – 0.70) of HIV testing compared to infants who were exclusively breastfed. Infants born to mothers with higher WHO stages were less likely to be tested when compared to those who were born to mothers with WHO stage 1 [(OR=0.24, 95% CI 0.21 – 0.26), (OR=0.61, 95% CI 0.55 – 0.68), (OR=0.55, 95% CI 0.43 – 0.71) for WHO stage 2, 3 and 4, respectively]. Infants weighing more than 2.5 kg at birth had higher odds (OR=1.18, 95% CI 1.09 – 1.28) of being tested compared to their counterparts who were born at <2.5kg. Infants born to mothers aged above 35 years had higher odds (OR=1.18, 95% CI 1.06 – 1.32) of being tested compared to those who were born to mothers age less than 25 years. Furthermore, infants born to mothers who were married had higher odds (OR= 1.19, 95% CI 1.08 – 1.31) of being tested compared to those born to unmarried mothers.

Table 2: Characteristics of HIV-infected mothers, Dar es Salaam, Tanzania, 2014-2016 (N=12,117)

Variable	Total	2014	2015	2016
	N (%)	N (%)	N (%)	N (%)
	12,117	4,660	4,037	3,420
Age of mother (years)				
Less 25	2,208 (18.2)	939 (20.2)	756 (18.7)	2,207 (18.2)
25-35	6,925 (57.2)	2,741 (58.8)	2,286 (56.6)	6,925 (57.2)
35-above	2,984 (24.6)	980 (21.0)	995 (24.7)	1,009 (29.5)
Mean age (SD)	30.8 (6.0)			
Marital status				
Single/cohabiting	2,355 (16.4)	928 (19.9)	873 (21.6)	554 (16.2)
Divorced/widowed	625 (5.2)	206 (4.4)	224 (5.6)	195 (5.7)
Married	4,511 (37.2)	1,951 (41.9)	1,595 (39.5)	965 (28.2)
Missing	4,626 (38.2)	1,575 (33.8)	1,345 (33.3)	1,706 (49.9)
Duration on ART (years)				
<1	2,813 (23.2)	1,666 (35.8)	822 (20.4)	325 (9.5)
1-3	4,480 (37.0)	1,591 (34.1)	1,579 (39.1)	1,310 (38.3)
>3	1,102 (9.1)	290 (6.2)	380 (9.4)	4332 (12.6)
Missing	3,722 (30.7)	1,113 (23.9)	1,256 (31.1)	1,353 (39.6)
Median duration on ART (years)				
WHO stage				
1	7,394 (61.0)	2,746 (58.9)	2,435 (60.3)	2,213 (64.7)
2	1,898 (15.7)	776 (16.7)	680 (16.8)	680 (442)
3	1,643 (13.6)	673 (14.4)	639 (15.8)	331 (9.7)
4	254 (2.1)	112 (2.4)	88 (2.2)	54 (1.6)
Missing	928 (7.7)	353 (7.6)	195 (4.8)	380 (11.1)
CD4 count (cells/L)				
≤200	774 (6.4)	282 (6.1)	267 (6.6)	225 (6.6)
200-500	3,244 (26.7)	1,228 (26.4)	1,240 (30.7)	776 (22.7)
>500	5,933 (49.0)	2,325 (49.9)	1,877 (46.5)	1,731 (50.6)
Missing	2,166 (17.9)	825 (17.7)	653 (16.2)	688 (20.1)

In multivariate analysis, replacement feeding (aOR=2.94, 95% CI 2.31 – 3.74), nevirapine prophylaxis (aOR=1.55, 95% CI 1.28-1.88) and maternal WHO stage 1 were found to be independently associated with EID before 8 weeks of age. Infants born to mothers with higher WHO stages of disease had lower odds for HIV testing compared to those born to mothers with WHO stage 1 of disease; stage 2 (aOR=0.53, 95% CI 0.41 – 0.67), stage 3 (aOR=0.64, 95% CI; 0.52 – 0.79), stage 4 (aOR=0.58, 95% CI 0.34 – 0.99).

DISCUSSION

We found that the coverage of EID at less than 8 weeks of age in Dar es Salaam, Tanzania, increased over the three-year period 2014 to 2016 from 53.2% to 69.2%.

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Table 3: Crude and adjusted predictors associated with EID testing at less than 8 weeks, Dar es Salaam, Tanzania, 2014-2016 (N= 12,117)

		Number tested within 8 weeks		
Variable	Total	(%)	OR [95% CI]	aOR [95% CI]
Year				
2014	4,660	2,481 (53.2)	1	1
2015	4,037	2,314 (57.3)	1.18 [1.08 – 1.28]	0.95 [0.79 – 1.16]
2016	3,420	2,366 (69.2)	1.97 [1.79 – 2.16]	1.04 [0.84 – 1.30]
Sex				
Female	6,345	3,819 (53.3)	1	1
Male	5,772	3,341 (46.7)	0.91 [0.88 – 0.98]	0.96 [0.82 – 1.13]
Birth weight of infant (kg)				
< 2.5	3,224	1,793 (25.9)	1	1
2.5 and above	8,622	5,142 (74.1)	1.18 [1.09 – 1.28]	1.14 [0.96 – 1.34]
Feeding practice at testing				
Exclusive breast feeding	6,149	3,997 (65.4)	1	1
Mixed feeding	1,753	945 (15.4)	0.63 [0.57 – 0.70]	0.87 [0.71 – 1.05]
Replacement feeding	1,806	1,173 (19.2)	0.99 [0.89 – 1.11]	2.94 [2.31 – 3.74]
Nevirapine prophylaxis				
No	1,606	1,016 (18.6)	1	1
Yes	7,670	4,436 (81.4)	0.79 [0.71 – 0.89]	1.55 [1.28 – 1.88]
Age of mother (years)				
Less than 25	2,208	1,265 (17.7)	1	1
25-35	6,925	4,065 (56.8)	1.06 [0.96 – 1.17]	1.12 [0.90 – 1.39]
Above 35	2,984	1,830 (25.5)	1.18 [1.06 – 1.32]	1.13 [0.88 – 1.45]
Marital status				
Single/cohabiting	2,355	1,255 (30.0)	1	1
Divorced/widowed	625	336 (8.0)	1.02 [0.85 – 1.22]	0.93 [0.64 – 1.36]
Married	4,511	2,597 (62.0)	1.19 [1.08 – 1.31]	0.88 [0.74 – 1.05]
Duration of mothers on ART (years)				
<1	2,813	1,759 (34.4)	1	1
1-3	4,480	2,685 (52.5)	0.90 [0.81 – 0.98]	0.89 [0.75 – 1.07]
>3	1,102	667 (13.1)	0.92 [0.796 – 1.05]	0.87 [0.67 – 1.13]
WHO stage				
1	7,394	4,877 (75.1)	1	1
2	1,898	599 (9.2)	0.24 [0.21 – 0.26]	0.53 [0.41 – 0.67]
3	1,643	892 (13.7)	0.61 [0.55 – 0.68]	0.64 [0.52 – 0.79]
4	254	131 (2.0)	0.55 [0.43 – 0.71]	0.58 [0.34 – 0.99]
CD4 count (cells/µL)				
≤200	774	486 (8.1)	1	1
200-500	3,244	1,986 (33.3)	0.94 [0.79 – 1.10]	0.93 [0.67 – 1.29]
>500	5,933	3,496 (58.6)	0.85 [0.72 – 0.99]	0.97 [0.70 – 1.33]

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The uptake of EID was associated with infant feeding practice at time of testing, infant nevirapine prophylaxis and lower maternal WHO stage. The study found an overall HIV prevalence of 2.3% in HEI. This study highlights the positive steps that the PMTCT programme in Dar es Salaam is making to reach national and international targets to eliminate MTCT of HIV.

Our findings of increasing EID at 8 weeks of age are consistent with studies from South Africa in 2014 and Thailand in 2016 that showed an increasing trend (Sherman et al., 2014; Naiwatanakul et al., 2016). The findings are also consistent with findings from a study in Ethiopia which found 66.7% of the exposed infants had EID at 8 weeks of age (Olana et al., 2016). Chiduo and colleagues from Tanzania in 2013 also found an increasing trend of EID from 77.2% in 2009 to 97.8% in 2011. However, this study captured infant testing up to 18 months of age (Chiduo et al., 2013), and further highlighted the missed opportunity for testing and subsequently treating HIV-positive infants below 18 months of age. While the increasing trend in the uptake of EID is clearly positive for the three-year period, efforts to reach the national target of 90% coverage for those under 8 weeks of age by 2018 were not realised (TACAIDS, 2013).

Infants of mothers who were on replacement feeding and nevirapine prophylaxis were more likely to undergo EID, and they may represent mothers who were better engaged in care. In Tanzania, EID services (as part of PMTCT) were integrated into reproductive and child health clinics in 2013 (National PMTCT Guideline, 2013). Further research is needed to understand how this integration is taking place in practice and to highlight the potential gaps. In this setting, post-natal reproductive and child health clinics are already time-consuming and often require mother and baby pairs to wait long hours, visit multiple providers and receive various services. The integration of EID into this service makes sense logistically but may overburden the mothers (Ramaiya et al., 2016). It is likely that additional efforts are needed to reach the "harder to reach" mothers and infants. The predictors of uptake of EID in this study included replacement feeding, the HEI taking nevirapine and the mother having a lower WHO stage at enrolment. The first two factors may be indicative of mothers who know their child is at risk, have taken steps to reduce this risk, and are already engaged in care. Women who have not yet reached this stage may need additional support to enable them to also increase their uptake of these services.

Our study was not able to identify some predictors highlighted in other studies (for example travel distances, out-of-pocket costs at the health facility and long waiting times), and we report some differences in findings. This study used secondary data routinely collected in health facilities and the analysis was therefore restricted to the variables collected as part of the routine data. A study by Izudi found that increased maternal age was independently associated with EID. We also report that older mothers were more likely to test on time; however, this was not statistically significant. It is possible that younger women are more likely to drop out of care due to psychosocial and mental challenges (Ramaiya et al., 2016; Izudi et al., 2017). Findings from studies in South Africa, Uganda and Kenya found that maternal knowledge about EID was independently associated with timely EID testing (Woldesenbet et al., 2015; Goggin et al., 2016; Izudi et al., 2017). Moreover, stigma, discrimination and lack of education were associated with low EID uptake (Woldesenbet et al., 2015; Goggin et al., 2016).

In our study, a high number of participants had missing information for the date of birth and HIV status of the child. These missing data could result from a recording issue at the health facility, such as not recording measurements and test results or not updating registers in time for collation at the national level. The missing data could also be due to errors in administering the HIV test or to clients moving between facilities pre- or post-testing. Prior to 2014, individual-level electronic EID data in routine care was virtually non-existent; the shift to individual-level electronic data collection may have impacted data quality, including providers' omissions or errors in data entry. Without accurate data, it is not possible to evaluate the PMTCT programme success, nor effectively target activities to increase EID uptake and reduce transmission rates.

The use of routine data enabled the study to obtain a large number of study participants from all facilities managed by MDH in the study area. The large sample increased the generalisability of the results and the ensured the study was adequately powered to assess the uptake and predictors of testing with precision. However, the study also had several limitations; in addition to challenges of using routine data that have already been mentioned, the study included only women who registered their baby at PMTCT and where the baby was tested. Women who were HIV-infected and did not bring their children to be tested were not included in the analysis, potentially resulting in an overestimation of the uptake of testing. All facilities used by the study were operated by MDH and were not randomly sampled. This may have biased selection, and hence the estimates obtained might not be true representations for the region. Moreover, because the study used existing data, we were not able to measure associations with variables identified as significant by other studies. Finally, a large proportion of tested infants had missing test results, which may have resulted in an incorrect estimation of uptake.

CONCLUSION

We found that there was an increasing trend over three years in the uptake of EID test at less than 8 weeks of age. However, the proportion of infants testing fell below the national target,

and more efforts are needed to ensure a 90% testing coverage at 8 weeks of age. The sub-optimal uptake may undermine efforts to reduce HIV/AIDS-related morbidities and mortality among children, as the majority of children are diagnosed at a late age (missed opportunity for early diagnosis) and hence delayed initiation of treatment. Infants who were initiated on nevirapine were more likey to test for EID, and this calls for advocating caretakers to take their infants to post-natal services.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

MM designed the study, participated in statistical data analysis and wrote the manuscript. PN and BJL participated in statistical data analysis; JT participated in designing the study, and advised on the analysis; GL and LM participated in conception of the study; SM and MJM participated in conception and study design; JR participated in study design, reviewed the manuscript for intellectual content, and statistical analysis. All authors reviewed the manuscript and read and approved the final manuscript.

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Figure 1: Flow chart of HIV testing results for HIV-exposed infants enrolled in Dar es Salaam from January 2014 to December 2016.